Carbohydrate Orthoesters. Part II.[1] Acid-catalysed Ethanolysis of 1-*O*-(1,1-Diethoxyethyl)-2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose †

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Ethanolysis of 1-*O*-(1,1-diethoxyethyl)-2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose catalysed by 2,6-dichlorobenzoic acid yielded ethyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranosides (36·6%; β:α ratio 29·5:1) and 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose (63·3%) by parallel first-order reactions. With added salt (0·06N-lithium toluene-*p*-sulphonate) the glucosidic products predominated (65·2%), but the selectivity for β-glucoside formation was much less (β:α ratio 2·1:1). Mechanisms for the reaction are discussed.

In a review of acid-catalysed methanolyses of carbohydrate 1,2-(alkyl orthoacetates) (I), Pacsu [2] postulated an acyclic 2-(dialkyl orthoacetate) (II) as the intermediate responsible for the observed formation of glycoses with unsubstituted C-1 and C-2 hydroxy-groups (III). Later, Perlin [3] extended this concept to include either acyclic 1- (IV) or 2-(dialkyl orthoacetates) (II) as intermediates in the formation of 3,4,6-tri-*O*-acetyl-D-glycopyranoses in acid-catalysed methanolyses of peracetylated β-D-mannopyranose and α-D-glucopyranose 1,2-(alkyl orthoacetates).

We considered that compounds of type (IV), in addition to yielding glycoses, could potentially form 2-hydroxyglycosides (V) in acid-catalysed alcoholyses. 2-Hydroxyglycosides are major products of acid-catalysed

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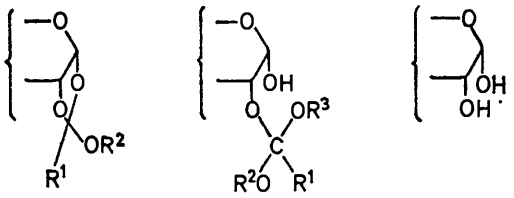
[1] L. R. Schroeder, D. P. Hultman, and D. C. Johnson, *J.C.S. Perkin II*, 1972, 1063 is regarded as Part I.

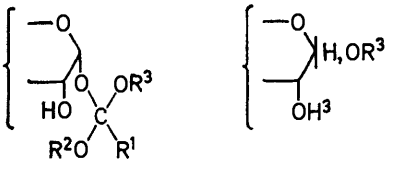
[2] E. Pacsu, *Adv. Carbohydrate Chem.*, 1945, **1**, 77.

[3] A. S. Perlin, *Canad. J. Chem.*, 1963, **41**, 555.

methanolyses [3] and ethanolyses [4] of peracetylated and permethylated α-D-glucopyranose 1,2-(alkyl orthoacetates), respectively, and a mechanism has been proposed to account for their formation.[3] However,



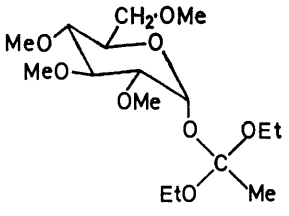
(I) (II) (III)



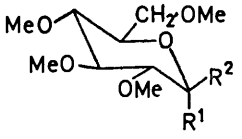
(IV) (V)

to our knowledge, the potential of 1-(dialkyl orthoacetates) (IV) to form glycosides in acid-catalysed alcoholyses and hence their potential as precursors of 2-hydroxyglycosides (V) in acid-catalysed alcoholyses of carbohydrate 1,2-(alkyl orthoacetates) (I) has not been investigated.

We report here the results of a study of acid-catalysed ethanolyses of a model for system (IV), 1-*O*-(1,1-diethoxyethyl)-2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose (VI).



(VI)



(VII) R^1 = H, R^2 = OEt
(VIII) R^1 = OEt, R^2 = H
(IX) R^1 = OH, R^2 = H
(X) R^1 = H, R^2 = OH
(XI) R^1 = OAc, R^2 = H

RESULTS AND DISCUSSION

Reaction Analyses.—The analytical procedures employed permitted identification and quantitative measurement of both unchanged orthoester (VI) and its ethanolysis products: ethyl tetra-*O*-methyl-β-D-glucopyranoside (VII), ethyl tetra-*O*-methyl-α-D-glucopyranoside (VIII), and 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose (IX). Quantitative g.l.c. analyses as a function of time accounted for an average of 97·9% ($\sigma \pm 3{\cdot}0\%$) of the carbohydrates in the system. N.m.r. analysis established the anomeric configuration of the reducing sugar (IX).

In the g.l.c. analytical procedure, unchanged orthoester (VI), too unstable for direct g.l.c. analysis, was estimated by hydrolysis of the mixture to give the α-D-glucopyranose (IX), tetra-*O*-methyl-β-D-glucopyranose (X), and 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose (XI). The concentration of (VI) was then calculated from the mole fraction of (XI) generated from (VI) by hydrolysis under these conditions.

The α-configuration of the reducing sugar [*i.e.* (IX)] formed in the ethanolysis of (VI) was ascertained by n.m.r. analysis of a mixture formed by [$^2H_6$]ethanolysis catalysed by 2,4,6-trinitrophenol. The signal for the anomeric proton of compound (IX) (δ 5·23 p.p.m.) was apparent; no signal for the anomeric proton of the β-anomer (X) (δ *ca.* 4·4—4·5 p.p.m.) was evident. However, in the analytical g.l.c. procedure compound (IX), because of mutarotation at various stages in the procedure and a final propanoylation, was estimated as a mixture of the *O*-propanoyl derivatives of (IX) and (X). The concentration of (IX) formed *via* ethanolysis was obtained by correcting the measured amount of (IX) and (X) for the amounts of these products attributable to hydrolysis of unchanged orthoester (VI).

The anomeric glycosides (VII) and (VIII) were adequately resolved for individual analysis in the g.l.c. procedure. However, the measured amount of the β-anomer (VII) had to be corrected for (VII) present initially as an impurity in the orthoester (VI).

Ethyl acetate was identified as a reaction product by its characteristic acetyl methyl resonance (δ 2·00 p.p.m.) in the mixture from [$^2H_6$]ethanolysis of (VI). 1,1,1-Triethoxyethane was identified as a product by its characteristic ' popcorn-like ' odour.

The disappearance of orthoester and appearance of carbohydrate products were adequately described by parallel first-order kinetics as shown in Figure 1. The disappearance of orthoester (VI) followed equation (1), and the appearance of products (VII)—(IX) was governed by equation (2).*

$$\ln X_{r,t} = -k_r t \quad (1)$$

$$\ln (X_{i,\infty} - X_{i,t}) = -k_r t + \ln X_{i,\infty} \quad (2)$$

where $X_{r,t}$ = mole fraction of reactant at time t, $X_{i,t}$ = mole fraction of product i at time t, $X_{i,\infty} = X_{i,t}$ at completion (the relative proportion of product i formed), $k_r = \Sigma k_i$ = first-order specific rate constant for reactant disappearance, and k_i = first-order specific rate constant for formation of product i.

* Frost and Pearson [5] have described the mathematics of parallel first-order kinetics. The equations given here are simplifications based on the fact that the term $k_t/\Sigma k_t$ is the mole fraction of the products accounted for by product i.

[4] D. P. Hultman, Doctoral Dissertation, The Institute of Paper Chemistry, Appleton, Wisconsin, 1970.

[5] A. A. Frost and R. G. Pearson, ' Kinetics and Mechanism,' 2nd edn., Wiley, New York, 1961.

The Table summarises the analyses of ethanolyses of the orthoester (VI) with and without added salt. The

Rate constants and product mole fractions for ethanolyses at 25·0°

DCB [a]	LiOTs [b]	Product mole fraction ($X_{t,\infty}$) (VII)	(VIII)	(IX)	10^4k_r/s^{-1} [c]
0·00525N		0·354	0·012	0·633	7·1
0·00522N	0·063N	0·440	0·212	0·348	65 [d]

[a] 2,6-Dichlorobenzoic acid. [b] Lithium toluene-*p*-sulphonate. [c] Minimum values; see text. [d] Rate constant estimated from $X_{i,t}$ and $X_{r,t}$ values at 2·7 min.

specific rate constants, k_r, should be considered minimum values since the method of preparing (VI) may leave traces of pyridine (employed in the chromatography

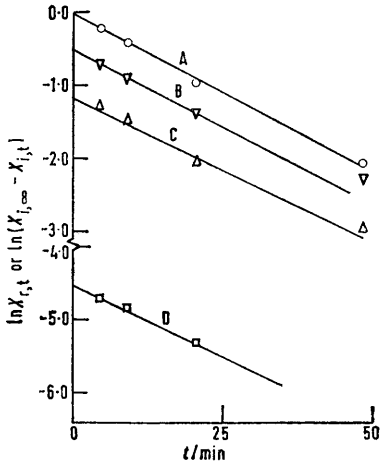


FIGURE 1 Parallel first-order kinetic plot of 1-*O*-(1,1-diethoxyethyl)-2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose ethanolysis data: A, orthoester (VI); B, α-OH (IX) ($X_{t,\infty}$ 0·633); C, β-OEt (VII) ($X_{t,\infty}$ 0·354); D, α-OEt (VIII) ($X_{t,\infty}$ 0·012)

eluant) as a contaminant. The buffering effect of traces of pyridine on the 2,6-dichlorobenzoic acid catalyst could be drastic.[4] However, even allowing for this possible complication, the ethanolysis of (VI) proceeds over 20 times faster than ethanolysis of the cyclic 1,2-orthoester, 3,4,6-tri-*O*-methyl-1,2-*O*-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose under the same conditions.[4,6]

Although the major product of ethanolysis of the orthoester (VI), in the absence of salt, is the α-reducing sugar (IX) (63·3%), glucosidic products, (VII) and (VIII), account for a significant proportion (36·6%) of the reacted orthoester. Thus, it seems that analogues of (VI) [*i.e.* (IV)] could be intermediates for formation of 2-hydroxyglycosides (V) as well as reducing sugars (III) in acid-catalysed alcoholyses of carbohydrate 1,2-(alkyl orthoacetates) (I).

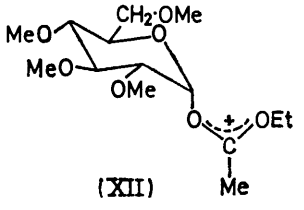
Addition of salt (0·063N-lithium toluene-*p*-sulphonate) resulted in an approximately nine-fold increase in the rate of ethanolysis of (VI) (Table). The primary reason for this is probably increased dissociation of the weak acid catalyst, *i.e.* a secondary salt effect, although a positive primary salt effect would also be expected for the acid-catalysed reaction.[7]

Salt addition also drastically changed the product distribution (Table). With the salt present glycosides (VII) and (VIII) accounted for 65·2% of the products; without salt the figure was only 36·6%. In addition, the anomeric ratio of the glycosides changed drastically with salt addition. With salt present the ratio of the β-glucoside (VIII) to the α-glucoside (VIII) was *ca.* 2·1 : 1; without salt the ratio was 29·5 : 1.

Reaction Mechanism.—Compound (VI) can be envisaged as containing both an orthoester and an acetal system which have one oxygen atom in common. Most acid-catalysed hydrolyses of acetals and orthoesters proceed with cleavage of the carbonyl carbon–oxygen bond to yield intermediate carboxonium ions.[8] The probable intermediate in acid-catalysed [$^2H_6$]ethanolyses of alkyl orthoacetates is the 1,1-dialkoxyethyl cation.[9] By analogy, acid-catalysed reactions of compound (VI) could occur by protonation of any one of the four acetal or orthoester oxygen atoms and subsequent or simultaneous carbon–oxygen bond cleavage to yield an intermediate carboxonium ion. However, we consider that the observed products (VII)—(IX) of the acid-catalysed ethanolysis of (VI) result only from reactions initiated at the oxygen atom common to the acetal and orthoester systems, *i.e.* the C-1 oxygen atom.

Reactions initiated by transfer of a proton to the pyranose ring oxygen atom would not be important in ethanolyses of (VI). This type of reaction is analogous to a pathway theoretically possible for acid-catalysed anomerisation or transglycosidation of glycopyranosides. Since the ethanolysis of (VI) is much faster than such reactions,[10] reactions initiated at the pyranose ring oxygen atom must not be important.

Protonation of either of the two ethoxy-oxygen atoms in the 1-*O*-(1,1-diethoxyethyl) substituent of (VI) would ultimately result in formation of the carboxonium ion (XII), which would be expected to re-form (VI) rapidly.* Thus, while the formation of (XII) probably occurs, it does not result in the final products.



(XII)

Reactions initiated by protonation at the C-1 oxygen atom can account for all of the products. However,

* Fragmentation of (XII) to form the less stable 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl cation and ethyl acetate, even with the attendant favourable entropy increase, is considered unlikely. However, this fragmentation would provide an additional mode of glycoside formation.

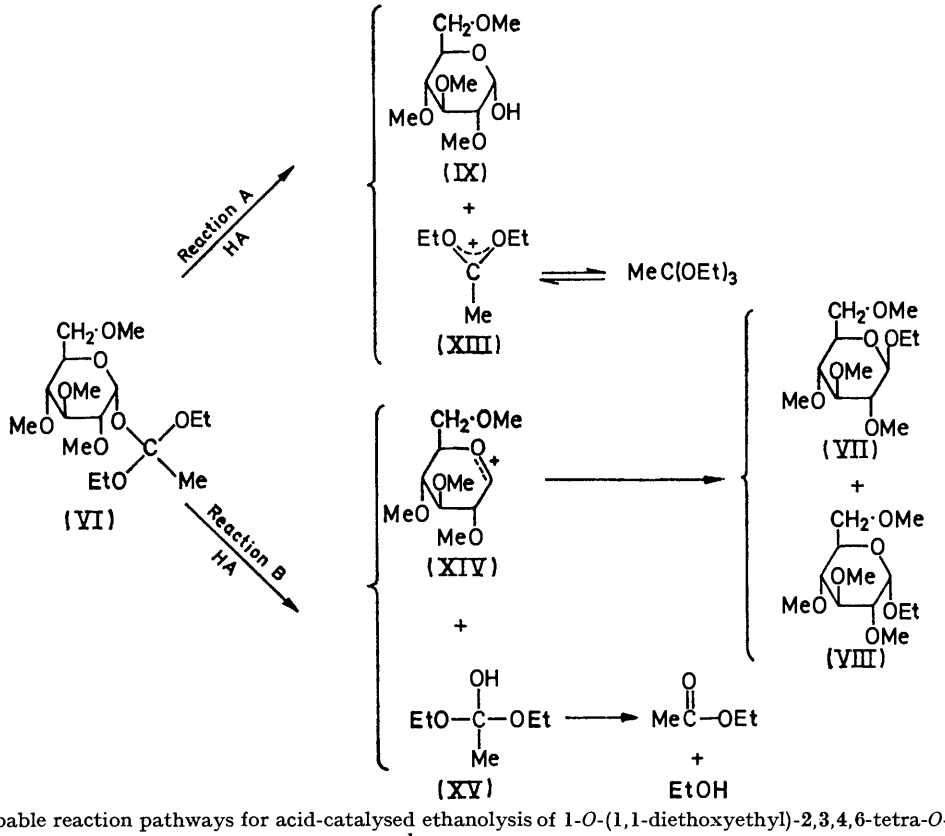
[6] D. P. Hultman, and L. R. Schroeder, in preparation.
[7] R. P. Bell, 'Acid-base Catalysis,' O.U.P., London, 1941 (reprinted 1949).
[8] E. H. Cordes, *Progr. Phys. Org. Chem.*, 1967, **4**, 1.
[9] L. R. Schroeder, *J. Chem. Soc.* (*B*), 1970, 1789.
[10] L. R. Schroeder, J. W. Green, and D. C. Johnson, *J. Chem. Soc.* (*B*), 1966, 447.

the present data do not allow a decision as to whether formation of the carboxonium ion from the conjugate acid (*A*-1 mechanism) or proton transfer to the oxygen atom (S_E2 mechanism) is the rate-determining step. This is not important for the following discussion since the two reactions which dictate the product distribution are initiated at the same oxygen atom.

As envisioned earlier by Perlin [3] for analogous systems, the orthoester (VI) can react as a typical alkyl orthoacetate in the acidic system by cleavage of the C-1 oxygen–orthoester carbon bond to yield the α-glycose (IX) and the 1,1-diethoxyethyl cation (XIII) (Scheme, reaction A). The ion (XIII) subsequently reacts with ethanol to form triethyl orthoacetate.

However, compound (VI) can also undergo a reaction characteristic of an acetal. With transfer of a proton to the C-1 oxygen atom, bond cleavage can also occur between the C-1 oxygen atom and C-1 to yield the 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl cation (XIV) and 1,1-diethoxyethanol (XV) (Scheme reaction B). Compound (XIV) reacts with ethanol to form glycosides (VII) and (VIII) while (XV) rapidly forms ethanol and ethyl acetate. Preferential formation of the β-glucopyranoside (Table) can be attributed to the high reactivity of the glucopyranosyl cation (XIV) resulting in reaction with ethanol in most cases before the leaving group (XV) is far from the reaction centre.

The question arises as to why transfer of a proton to the C-1 oxygen atom of (VI) can initiate carbon–oxygen bond cleavage on either side of the oxygen atom. On the basis solely of the stabilities of the intermediate carboxonium ions it would be anticipated that bond cleavage between O-1 and the orthoester carbon atom (reaction A) would be the only important reaction, *i.e.* ion (XIII) is much more stable than ion (XIV). However, the transition state free energies for the two reactions are related to both the ability of the system to delocalise the positive charge developing on the carbon atom (indicated by the stability of the resultant carbonium ion) and the ability of the oxygen atom of the



SCHEME Probable reaction pathways for acid-catalysed ethanolysis of 1-*O*-(1,1-diethoxyethyl)-2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose

fragmenting neutral species to accept the pair of electrons from the cleaving bond ('leaving ability'). The relative 'leaving abilities' of the two species (IX) and (XV) (Scheme) can be roughly correlated with their basicities; the species which is the weaker base would be the better leaving group. The hydroxylic oxygen atom of (XV), being geminal to two electronegative oxygen atoms, should be considerably less basic than the hydroxylic oxygen atom of (IX), which is geminal to only one oxygen atom. Species (XV) should therefore be a much better leaving group than (IX). Of the two reactions, bond cleavage between O-1 and the orthoester carbon atom (reaction A) utilises the more stable carbonium ion (XIII), whereas bond cleavage between O-1 and C-1 (reaction B) utilises the better leaving group (XV). Thus, the 'leaving ability' of (XV) can be

thought to decrease the transition state free energy of carbon–oxygen bond cleavage of the acetal system of (VI) to the extent that it can compete effectively with carbon–oxygen bond cleavage of the orthoester system.

The effect of added salt on the product distribution in acid-catalysed ethanolysis of (VI) (Table) is consistent with the proposed reaction pathways (Scheme). Increased ionic strength should effect increased stabilisation of the carboxonium ions (XIII) and (XIV). However, the magnitude of the effect would be expected to be different for the two transition states. In the transition state for formation of the glucopyranosyl cation (XIV), the developing positive charge is less delocalised than in the transition state leading to the 1,1-diethoxyethyl cation (XIII). The transition state leading to (XIV) should therefore experience more additional stabilisation with an increase in ionic strength than the transition state for formation of (XIII). Thus, it is not surprising that the proportion of glucosidic products, which form *via* (XIV), increased when a salt was added.

The decrease in stereoselectivity for β-glucoside formation with increased ionic strength (Table) can be attributed to enhanced stability of the glucopyranosyl cation (XIV). The longer average lifetime of (XIV) allows the leaving group (XV) to move farther away from the reaction centre before reaction with ethanol occurs. Thus, ' shielding ' of the α-side of (XIV) is decreased relative to ethanolysis without added salt.

EXPERIMENTAL

Analytical Methods.—M.p.s, optical rotations, elemental analyses, and n.m.r. spectra were determined as described previously.[1] A Varian Aerograph model 1200–1 gas chromatograph equipped with a hydrogen flame ionisation detector was used for g.l.c. Chromatographic response was recorded and integrated with a Honeywell Electronic 16 recorder equipped with a model 227 Disc integrator. The column (5% SE-30 on 60—80 mesh Chromosorb W, 10 ft × 0·125 in o.d., stainless steel) was rigged for on-column injection. Analyses were performed under the following conditions: column, 130 ⟶ 162° programmed at 1° min^{-1}; injector, 205°; detector, 265°; nitrogen (carrier gas), 45 lb in^{-2}.

Methyl 2,3,4,6-*Tetra*-O-*methyl*-β-D-*glucopyranoside* (XVI).—Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[11] (74 g) and powdered sodium hydroxide (210 g) were added to tetrahydrofuran (1150 ml) in a water-bath at room temperature. Dimethyl sulphate (170 ml) was added dropwise during 10 h to the vigorously stirred mixture. After an additional 10 h water (500 ml) was added, and the mixture was heated (75°) for 1—2 h with stirring to decompose residual dimethyl sulphate and remove the tetrahydrofuran. The cooled solution was extracted with chloroform (1 × 750 ml; 1 × 250 ml). The extracts were washed with water (1 × 200 ml) and concentrated *in vacuo* to a yellow oil (50 g, 97%) which crystallised at −15° overnight. Recrystallisation once from diethyl ether and subsequent sublimation (*ca.* 0·05 mmHg; 36°) yielded the product (XVI), m.p. 37·5—39°, $[\alpha]_D^{25}$ −19·4° (*c* 1 in H_2O) {lit.,[12] m.p. 40—41°, $[\alpha]_D^{25}$ −17° (*c* 4 in H_2O)}.

Ethyl 2,3,4,6-*Tetra*-O-*methyl*-β-D-*glucopyranoside* (VII).—Methylation of ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[11] (42 g) as described for (XVI) yielded an oil (30 g, 85%). The oil was distilled at reduced pressure (*ca.* 0·05 mmHg) through a 15 cm Vigreux column. A middle fraction of 10 ml was retained. The purified *oil* could be crystallised by refrigeration and had $[\alpha]_D^{30}$ −18·7° (*c* 2·9 in EtOH). G.l.c. analysis indicated a minor impurity (*ca.* 1%) (Found: C, 54·8; H, 9·0. $C_{12}H_{24}O_6$ requires C, 54·5; H, 9·2%).

Ethyl 2,3,4,6-*Tetra*-O-*methyl*-α,β-D-*glucopyranoside* [(VII) *and* (VIII)].—A mixture of glucose (30 g), ethanol (300 ml), and acetyl chloride (15 ml) was refluxed for 24 h, cooled, neutralised with solid sodium carbonate, filtered, and concentrated *in vacuo*. The resultant syrup was acetylated with acetic anhydride (100 ml) and pyridine (150 ml) for 24 h and worked up to yield a syrup (56 g). Methylation as described for (XVI) yielded an oil (38 g), which was distilled through a 15 cm Vigreux column at reduced pressure (*ca.* 0·05 mmHg).* A 10 ml fraction (after 1 ml of forerun) had $[\alpha]_D^{30}$ +92·5 (*c* 2·7 in EtOH) (Found: C, 54·7; H, 8·9. Calc. for $C_{12}H_{24}O_6$: C, 54·5; H, 9·2%). G.l.c. analysis indicated the α-anomer was the major component (*ca.* 65%) of the anomeric mixture.

2,3,4,6-*Tetra*-O-*methyl*-α-D-*glucopyranose* (IX).—Acid-catalysed hydrolysis of compound (VII), (VIII), or (XVI) gave the glucopyranose (IX). A typical preparation is described.

Methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside (30 g) in 0·5N-hydrochloric acid (300 ml) was refluxed for 48 h. The solution was cooled, neutralised ($NaHCO_3$), and concentrated *in vacuo* to dryness. The resulting mixture of salts and oil was extracted with chloroform (500 ml). Addition of charcoal, filtration through Celite, and concentration *in vacuo* yielded an oil which crystallised spontaneously. After one crystallisation from light petroleum (b.p. 60—110°), the yield was 20 g (70%). Two recrystallisations from light petroleum gave the sugar (IX), m.p. 94—97°, $[\alpha]_D^{30}$ +106° ⟶ 78·5° (*c* 2·8 in H_2O) {lit.,[13] m.p. 98° $[\alpha]_D^{30}$ +79·4° (equilibrium, H_2O)}.

1-O-*Acetyl*-2,3,4,6-*tetra*-O-*methyl*-D-*glucose* (XI).—Compound (IX) (3 g) was treated with pyridine (12 ml) and acetic anhydride (6 ml) at 0° for 16 h. The resultant solution was stirred with ice–water (100 ml) for 0·5 h and extracted with chloroform (2 × 100 ml). The extracts were washed with N-sulphuric acid, saturated sodium hydrogen carbonate solution, and water, decolourised, filtered (Celite), and concentrated at *ca.* 15—20 mmHg) to an oil. Residual chloroform was removed at *ca.* 0·05 mmHg (room temp., 3 h). The oil had $[\alpha]_D^{21}$ +107° (*c* 1·9 in EtOH) (Found: C, 51·9; H, 8·0. Calc. for $C_{12}H_{22}O_7$: C, 51·8; H, 8·0%). G.l.c., which did not resolve the α- and β-anomers, showed no impurities. N.m.r. analysis indicated that the mixture contained at least 85% of the α-anomer.

1-O-(1,1-*Diethoxyethyl*)-2,3,4,6-*tetra*-O-*methyl*-α-D-*glucopyranose* (VI).—Compound (IX) (5 g), 1,1,1-triethoxyethane (50 ml), and 2,6-dichlorobenzoic acid (0·5 g) were heated at reduced pressure in a distillation apparatus fitted with a 15 cm Vigreux column. In a total time of 30 min and at a maximum head temperature of 94°, the following distillates

* The α-anomer is less volatile than the β-anomer.

[11] L. R. Schroeder and J. W. Green, *J. Chem. Soc.* (*C*), 1966, 530.

[12] C. C. Barker, E. L. Hirst, and J. K. N. Jones, *J. Chem. Soc.*, 1946, 783.

[13] E. S. West and R. F. Holden, *Org. Synth.*, 1940, **20**, 97.

were collected: 1·4 ml (200 mmHg) and 3 ml (105 mmHg). The mixture was cooled, diluted with absolute chloroform (50 ml), washed with 0·1N-sodium hydroxide (2 × 100 ml) and water (100 ml), dried (Na_2SO_4), and concentrated *in vacuo* after addition of several drops of pyridine. The resultant oil (6·5 g) was purified by dry-packed column chromatography on alumina [156 g, Mallinckrodt AluminAR CC-10, 25 mm i.d. column; elution with di-isopropyl ether–pyridine (10 : 1 v/v)]. Fractions 4—8 (15 ml fractions) were combined and concentrated to an oil (2·1 g), which was subjected to a second column chromatographic purification under the same conditions. Fractions 4—6 of the second purification yielded the orthoester (VI) (1·4 g) $[\alpha]_D^{25}$ +115° (*c* 4·1 in $CHCl_3$), which was stored at 0° in a vacuum desiccator (NaOH). The final product contained 2·4 mole % of compound (VII) as an impurity, as shown by hydrolysis, propanoylation (propanoic anhydride–pyridine), and g.l.c. analysis.

The α-configuration of (VI) was indicated by the large positive specific optical rotation and the small coupling constant for H-1 [$J_{1,2}$ 3·5 Hz; δ ($CDCl_3$) 5·37 p.p.m.]. The presence of the 1-*O*-(1,1-diethoxyethyl) substituent was verified by the relative integrals of the MeC≤ singlet (δ 1·52 p.p.m.; 3H) and the *Me*CH_2·O triplet (δ 1·17 p.p.m.; 6H).

Isopropyl 3,4,6-*Tri*-O-*methyl*-β-D-*glucopyranoside* (XVII). —Crude 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide [prepared [1] from 1,2-di-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranose (10 g)] was treated with absolute propan-2-ol in a Koenigs–Knorr reaction employing mercuric salts.[11] The product mixture was dissolved in acetone (25 ml), diluted with 0·5N-sodium hydroxide (200 ml), heated on a steam-bath (30 min), cooled, and extracted with chloroform (4 × 125 ml). The combined extracts were washed with water (6 × 150 ml) and concentrated *in vacuo* to an oil. Crystallisation from light petroleum (b.p. 60—110°) yielded the glucopyranoside (XVII) (3·6 g, 42% based on 1,2-di-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranose). One recrystallisation from light petroleum (b.p. 60—110°) yielded *needles*, m.p. 33·5—36°, $[\alpha]_D^{30}$ −27° (*c* 1·0 in $CHCl_3$) (Found: C, 54·3; H, 9·1. $C_{12}H_{24}O_6$ requires C, 54·5; H, 9·2%).

The β-configuration of (XVII) was indicated by the negative specific optical rotation and the magnitude of the coupling constant for H-1 [$J_{1,2}$ 7·0 Hz, δ ($CDCl_3$) 4·27 p.p.m.]. The presence of the isopropoxy-group was substantiated by a doublet of doublets for the nonequivalent methyl groups (δ 1·19 and 1·26 p.p.m., *J ca.* 6 Hz). The unsubstituted C-2 hydroxy-group produced a doublet (δ 2·52 p.p.m., *J ca.* 2 Hz) which disappeared on addition of deuterium oxide.

Solvents and Reagents.—Ethanol was dried by refluxing with magnesium and iodine.[14] Propan-2-ol was dried under reflux with sodium (5 g l^{-1}). Both alcohols were fractionally distilled (40 cm Vigreux column) with the exclusion of moisture into receivers previously dried by storage over potassium hydroxide or by rinsing with fresh distillate. Ethanol used in solvolyses was subjected to the drying procedure twice, the second time just prior to use.

2,6-Dichlorobenzoic acid was prepared from 2,6-dichlorotoluene [4,15] with final purification by sublimation; m.p. 143—144°.

Lithium toluene-*p*-sulphonate was prepared by neutralising an aqueous solution of toluene-*p*-sulphonic acid with lithium carbonate. The salt crystallised on evaporation of the water and was dried *in vacuo* at 100° for 48 h. An aqueous 5% solution of the salt was neutral.

Ethanolyses.—Solution preparation. All glassware used in solution preparation was dried by extended storage (KOH) in a desiccator.

A stock catalyst solution was prepared by weighing 2,6-dichlorobenzoic acid into a volumetric flask and diluting with anhydrous ethanol at 25·0°. The concentration of the catalyst solution was greater than ten times the final acid concentration required in the ethanolysis. For the ethanolysis with added lithium toluene-*p*-sulphonate, the catalyst solution was prepared with the appropriate amounts of both lithium toluene-*p*-sulphonate and 2,6-dichlorobenzoic acid.

The orthoester (VI) was transferred to a tared volumetric flask. The pyridine used as a stabiliser in the orthoester was removed *in vacuo* (*ca.* 0·05 mmHg, room temp., 3 h) and the weight of orthoester determined. The orthoester, anhydrous ethanol, and the catalyst solution were kept for 20 min in a bath at 25·0°. Anhydrous ethanol was added to the flask containing the orthoester to make up about 80% of the final intended volume. The orthoester was dissolved by swirling and sufficient catalyst solution to give the desired concentration on final dilution was added. Zero time was taken to be that time at which one-half of the required acid catalyst had been added. The solution was diluted to the required volume with anhydrous ethanol, a sampling apparatus (Figure 2) was attached to the flask, and sampling was begun.

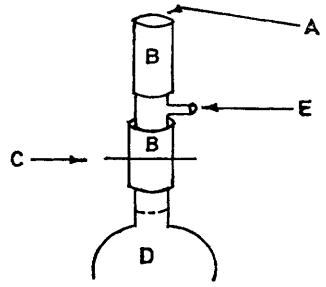


FIGURE 2 Sampling apparatus: A, pipette drying chamber; B, rubber tube; C, clamp; D, flask; E, air (*ca.* 500 ml min^{-1}) dried by passing over 20 × 1 in column of fresh KOH pellets

Sampling. Contamination by water (atmospheric and adsorbed moisture on sampling pipettes) during sampling was minimised by use of the illustrated apparatus (Figure 2). To remove a sample for analysis, a pipette was placed in the rubber tube of the drying chamber and dry air was passed through the chamber for several minutes. The clamp was opened and the pipette was pushed down into the solution to withdraw a sample. The pipette was removed and the clamp closed until the next sample was taken.

Quantitative g.l.c. analysis. A sample (1 ml) of the ethanolysis solution [initially *ca* 6·0 × 10^{-2}M in (VI); 5·2 × 10^{-3}N in 2,6-dichlorobenzoic acid] was pipetted into a standard solution (2 ml) of (XVII) (*ca.* 1·5 × 10^{-2}M at 25°) in toluene–triethylamine (7 : 3 v/v). A portion of the resultant solution (1—2 ml) was concentrated to an oil *in vacuo* (45° bath) and a solution of Universal Indicator * (4 ml) in aqueous acetone was added. Sulphuric acid (N; 1 drop) was added and, after 3 min, sodium hydroxide

* Harleco Universal Wide Range Indicator (50 ml) was concentrated to dryness to remove the ethanol solvent and the residue was dissolved in acetone–water (2 l; 9 : 1 v/v).

[14] H. Lund and J. Bjerrum, *Ber.*, 1931, **64**, 210.

[15] J. F. Norris and A. E. Bearse, *J. Amer. Chem. Soc.*, 1940, **62**, 956.

(0·01N) was added (to pH 5—7). Buffer (0·4 ml; 0·1M-K_2HPO_4 and 0·1M-KH_2PO_4) was added and the solution was concentrated *in vacuo* to about 0·5 ml. Drying of the sample was completed by storing the open flask in a vacuum desiccator (*ca.* 20 mmHg) (KOH) for a minimum of 5 h.

The dried sample was treated with pyridine–propanoic anhydride (*ca.* 1·5 ml; 5 : 3 v/v) at room temperature with occasional swirling for 24 h. Water (12 ml) was added and, after 15 min, the solution was extracted with chloroform (3 × 15 ml). The extracts were washed with 2N-hydrochloric acid in saturated sodium chloride solution (6—7 ml), a saturated solution of sodium hydrogen carbonate in 10% sodium chloride (6—7 ml), and water (10 ml). After each washing the aqueous phase was back-extracted with a comparable volume of chloroform. The chloroform solutions were then combined for the next stage.

The resultant solution was concentrated *in vacuo* to an oil. In cases where the presence of residual propanoic acid was noted, it was removed as its aqueous azeotrope by adding several ml of water and reconcentrating. The oil was further dried (KOH) in a desiccator for several hours, dissolved in acetone (1—2 ml), and analysed by g.l.c.

Analysis of unchanged orthoester (VI) as its hydrolysis products, 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose (XI) and 2,3,4,6-tetra-*O*-methyl-D-glucopyranose [(IX) and (X)] by the foregoing procedure necessitated determining the ratio of (XI) to [(IX) and (X)] formed by hydrolysis of (VI) under these conditions. The orthoester (VI) (2 drops) was dissolved in toluene–triethylamine (2 ml; 7 : 3 v/v) and ethanolic 2,6-dichlorobenzoic acid (1 ml; 0·005N) was added. The sample was then treated as an ethanolysis sample. Alternatively, direct addition of (VI) to the acidic aqueous acetone hydrolysis solution in the analysis procedure yielded the same results; *i.e.* (XI) (48·3 mole %), (IX) and (X) (49·3 mole %), and (VII) (2·4 mole %) [present as an impurity in (VI)].

The response factors required for quantitative g.l.c. were determined by subjecting synthetic mixtures of the necessary compounds in ethanol to the analysis procedure. The response factors for the α- (VIII) and β-glucoside (VII) were assumed to be equal.

The g.l.c. retention times (min) were: (VII) 12·0, (VIII) 12·9, (IX) and (X) (monopropionates) 21·0 and 22·2, (XI) 16·8, and (XVII) (monopropionate) 29·7.

N.m.r. analysis. The orthoester (VI) (0·10 ml) was added to an n.m.r. sample tube containing absolute [$^2H_6$]ethanol (0·50 ml), tetramethylsilane (internal standard), and a small quantity of 2,4,6-trinitrophenol. The sample tube was shaken and the necessary spectra were determined at normal probe temperature.

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