Tetrahedron, 1967, Vol. 23, pp. 1369 to 1378. Pergamon Press Ltd. Printed in Northern Ireland

SELECTIVE ACYLATION OF PYRANOSIDES—I.

BENZOYLATION OF METHYL α-D-GLYCOPYRANOSIDES OF MANNOSE, GLUCOSE AND GALACTOSE[1]

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(*Received* 7 *July* 1966; *accepted for publication* 19 *August* 1966)

Abstract—Selective tribenzoylation of methyl α-D-glucopyranoside, methyl α-D-mannopyranoside and methyl α-D-galactopyranoside gives the 2,3,6-tri-O-benzoates in good yield (> 50%); the glucoside gives in addition the 2,4,6-tri-O-benzoate in substantial yield (19% isolated). Selective dibenzoylation of methyl α-D-mannopyranoside and methyl α-D-glucopyranoside gives the 3,6- and 2,6-di-O-benzoates respectively, whereas the corresponding galactopyranoside showed low selectivity. The order of reactivity of the secondary OH groups has been deduced from the results and is different for each glycoside, being 2-OH > 3-OH > 4-OH for the glucoside, 3-OH > 2-OH > 4-OH for the mannoside, and 2-OH, 3-OH > 4-OH for the galactoside. Possible reasons for these differences in reactivity are discussed. PMR spectroscopy is shown to be a useful method for determining the structures of glycoside diesters.

SURPRISINGLY little systematic work[2–5] has been reported on the selective esterification of carbohydrates. The relative reactivity of OH groups in carbohydrates, in addition to being of theoretical interest, has practical utility[6] and the more versatile use of selective acylation warranted further investigation. Accordingly we have investigated the selective benzoylation of some glycopyranosides. Reaction of methyl α-D-galactopyranoside (I) monohydrate with 4·2 molar equiv of benzoyl chloride in pyridine at −30° gave, in 65% yield, a tribenzoate which was identical with methyl 2,3,6-tri-O-benzoyl-α-D-galactopyranoside (III) prepared by Reist *et al.*[7] Catalytic debenzoylation of the mother liquid resulted in the recovery of methyl α-D-galactopyranoside in 28% yield, making the effective yield of tribenzoate 90%. The method thus represents a marked improvement on the previous four-step syntheses[7] (overall yield 25–42%). The tribenzoate gave a methanesulphonate derivative which was isolated in two dimorhic crystalline forms, and which was shown to be methyl 2,3,6-tri-O-benzoyl-4-O-methanesulphonyl-α-D-galactopyranoside by the nucleophilic displacement of Reist *et al.*,[8,9] who have also recently described[9] a similar synthesis

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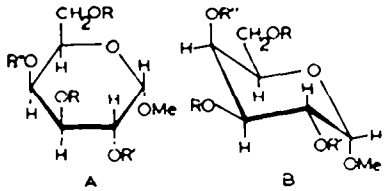
[1] Part of this work has been published in preliminary form, *Chem. Comm.*, 1[illegible]4 (1965).
[2] J. F. Mahoney and C. B. Purves, *J. Amer. Chem. Soc.* **64**, 9 (1942); T. S. Gardner and C. B. Purves, *Ibid.* 1539 (1942).
[3] R. W. Jeanloz and D. A. Jeanloz, *J. Amer. Chem. Soc.* **79**, 2579, (1957).
[4] R. W. Jeanloz, A. M. C. Rapin and S. I. Hakamori, *J. Org. Chem.* **26**, 3939 (1961).
[5] P. J. Garegg, *Acta. Chem. Scand.* **16**, 1849 (1962).
[6] See e.g. J. M. Sugihara, *Adv. Carbohydrate Chem.* **8**, 1 (1953).
[7] E. J. Reist, R. R. Spencer, B. R. Baker and L. Goodman, *Chem. & Ind.* 1794 (1962).
[8] E. J. Reist, R. R. Spencer and B. R. Baker, *J. Org. Chem.* **24**, 1618 (1959).
[9] E. J. Reist, R. R. Spencer, D. F. Calkins, B. R. Baker and L. Goodman, *J. Org. Chem.* **30**, 2312 (1965).

of the tribenzoate by partial benzoylation of anhydrous methyl α-D-galactopyranoside.

Axial OH groups are known[10] to undergo acylation less rapidly than equatorial OH groups, and the formation of the 2,3,6-tribenzoate (III), in which the 4-OH group is axial in the preferred conformation (IIIB), may thus be rationalised. However, this simple rule may not be expected invariably to apply to complex molecules such as pyranosides.

In separate experiments the mother liquors remaining after the crystallization of the galactoside tribenzoate were not debenzoylated, but were fractionated on a column of silica gel. This afforded a crystalline dibenzoate in 6% yield, a further 13% of the 2,3,6-tribenzoate, and a small amount (2%) of the 2,3,4,6-tetrabenzoate. The dibenzoate was shown to be the 3,6-isomer (II) by PMR spectroscopy. The signal of a ring proton attached to the same carbon atom as a BzO group occurs to



I: R = R' = R'' = H
II: R = PhCO, R' = R'' = H
III: R = R' = PhCO, R'' = H
IV: R = R' = PhCO, R'' = $MeSO_2$

low field of the other ring protons (with the possible exception of the anomeric proton) because of the deshielding effect of the ester group.[11] One such low-field signal was observed (at τ 4·70) for the dibenzoate. The signal was a quartet with spacings of 10·0 and 2·9 c/s. The H_1 doublet at τ 5·16 had a spacing of 3·6 c/s, and the quartet at τ 4·70 must therefore correspond to H_3*, for which $J_{2,3}$ is 10·0 (axial-axial coupling) and $J_{3,4}$ is 2·9 c/s (axial-equatorial coupling). H_4 would experience two small (equatorial-axial) couplings with H_3 and H_5 in the chair conformation corresponding to IB. The structure of the dibenzoate is therefore methyl 3,6-di-O-benzoyl-α-D-galactopyranoside. The 2,6-isomer is also excluded by the lack of an acid-catalysed reaction with acetone to give the 3,4-ketal.

Preliminary experiments on the reaction of methyl α-D-galactopyranoside with two equivalents of benzoyl chloride have indicated low selectivity. The product was shown by TLC to contain at least four main products amongst which the 2,3,6-tribenzoate predominated. Fractionation of the crude product by TLC gave the 2,3,6-tribenzoate, the 3,6-dibenzoate and two impure syrupy compounds which were not characterized.

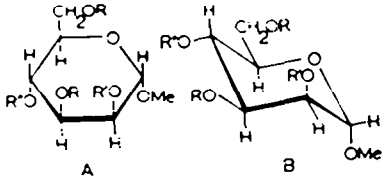
Selective benzoylation of methyl α-D-mannopyranoside (VA, conformation VB) with 3·1 molar equivs of benzoyl chloride gave as major product a tribenzoate which was isolated in 56% yield as a crystalline monohydrate after column chromatography. The derived methanesulphonate ester was resistant to nucleophilic displacement by

* This deduction was confirmed by the asymmetry of the H_1 doublet which showed that H_1 was coupled to a proton to high field.

[10] See e.g. E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.* **79**, 5986 (1957).

[11] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* p. 55. Pergamon, London (1963).

benzoate in N,N-dimethylformamide, therefore other means of structural elucidation were used. Reaction of the tribenzoate with 2,3-dihydro-4-H-pyran in the presence of *p*-toluenesulphonic acid gave a crystalline mixture of the two diastereoisomeric tetrahydropyranyl ethers which was catalytically debenzoylated with sodium methoxide. Methylation followed by mild acid hydrolysis gave a methyl tri-O-methyl-α-D-mannopyranoside in 53% overall yield from the tribenzoate. Acid hydrolysis then gave syrupy 2,3,6-tri-O-methyl-D-mannose, characterized as the crystalline di-*p*-nitrobenzoate.[13] The structure of the tribenzoate is therefore methyl 2,3,6-tri-O-benzoyl-α-D-mannopyranoside (VII).



A B

V. R = R' = R'' = H
VI. R = PhCO, R' = R'' = H
VII. R = R'' = PhCO, R' = H
VIII. R = R'' = PhCO, R' = $MeSO_2$

A crystalline dibenzoate was also isolated in 26% yield from the mannoside reaction product; the 3,6-dibenzoate structure (VI) was assigned on the basis of the compound's resistance to periodate oxidation and the assumption that one of the benzoate groups was located at C_6 due to the greater reactivity of the primary 6-OH group. This structure was unequivocally confirmed by PMR spectroscopy in an exactly similar manner to that described for the galactoside 3,6-dibenzoate. With acetone as solvent the H_1 doublet was not completely resolved. However when pyridine was used as solvent the H_1 doublet at τ 4·99 was resolved and had a spacing of 1·6 c/s. As in the case of the galactoside dibenzoate a quartet was present at low field (τ 4·15) with spacings of 9·1 and 3·2 c/s (Table 1). This quartet was assigned to H_3 and the dibenzoate was identified as the 3,6-isomer (VI) for which $J_{1,2}$ is 1·6, $J_{2,3}$ is 3·2 (axial-equatorial coupling) and $J_{3,4}$ is 9·1 c/s (axial-axial coupling). The data is consistent with the chair conformation (VIB) of the dibenzoate, and the low value for $J_{1,2}$ falls within the range (0·6–1·7 c/s) which is characteristic for $J_{1,2}$ in derivatives of α-D-mannopyranose (and α-D-altropyranose) having the same (C1) chair conformation.[13] The dibenzoate gave a crystalline diacetate, the acetoxy proton resonances of which occurred at τ 8·07 and 7·93, values typical of an equatorial and an axial acetoxyl respectively.[14] However the latter evidence alone is not considered unequivocal since the diamagnetic anisotropy of the benzene rigns may influence the acetoxy signals. The 3,6-dibenzoate was also isolated in 62% yield by selective benzoylation of the mannoside (V) with two molar equivalents of benzoyl chloride.

Similar reaction of methyl α-D-glucopyranoside (IXA, conformation IXB) with 3·1 molar equivs of benzoyl chloride gave a product which contained predominantly two tribenzoates. The 2,3,6-tribenzoate (XI), which was the major product, was

[13] P. A. Rebers and F. Smith, *J. Amer. Chem. Soc.* **76**, 6097 (1954).
[13] B. Coxon, *Tetrahedron* **21**, 3481 (1965).
[14] L. D. Hall, *Adv. Carbohydrate Chem.* **19**, 67 (1964).

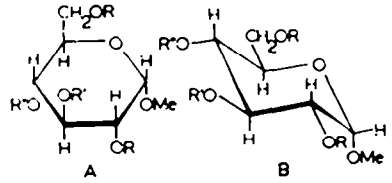
TABLE 1. PMR DATA FOR GLYCOSIDE DIBENZOATES

Compound	Chemical shift (τ-values)					First order coupling constant*			Solvent
	H_1	H_2	H_3	unidentified protons	OCH_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	
Methyl α-D-galacto-pyranoside 3,6-dibenzoate	5·16 (d)	—	4·70 (q)	5·4–5·9 (cm) 6·34 (bs) 6·49 (bs)	6·56 (s)	3·6	10·0	2·9	acetone
Methyl α-D-manno-pyranoside 3,6 dibenzoate	—	—	4·61 (q)	5·2–5·9 (cm)	6·54 (s)	—	3·1	9·1	acetone
	4·99 (d)	—	4·15 (q)	5·03–5·83 (cm)	6·67	1·6	3·2	9·1	pyridine
Methyl α-D-gluco-pyranoside 2,6-dibenzoate	4·63 (d)	4·39 (q)	—	4·7–5·9 (cm)	6·58 (s)	3·8	9·7	—	pyridine

* = cycles/second

s = singlet q = quartet
bs = broad singlet cm = complex multiplet
d = doublet

isolated in 13% yield after seeding with authentic material, and fractionation of the mother liquor on silica gel effected a partial separation of the two tribenzoates. The second tribenzoate, although not crystallized,* was characterized as the 2,4,6-isomer[15] (XII) by conversion to the known tosylate[15] derivative. The 2,3,6- and 2,4,6-tribenzoates were formed in 67 ± 5% and 28 ± 5% yield respectively, and were isolated pure in 48% and 19% yields respectively.



A B

X: R = R' = R'' = H
XI: R = PhCO, R' = R'' = H
XII: R = R'' = PhCO, R' = H
XIII: R = R' = PhCO, R'' = H
XIV: R = R' = R'' = PhCO

Methyl 2,6-di-O-benzoyl-α-D-glucopyranoside (X) was prepared[16] in 50% yield by dibenzoylation of methyl α-D-glucopyranoside, and the PMR spectrum of the dibenzoate in pyridine was consistent with its structure. The H_2 quartet at τ 4·39 had spacings of 3·8 and 9·7 c/s, and the H_1 doublet at τ 4·63 had a spacing of 3·9 c/s. The asymmetry of the H_1 doublet also showed that H_1 was coupled to a proton to low field. Hence $J_{1,2}$ and $J_{2,3}$ were 3·8 and 9·7 c/s respectively, values consistent

* see Experimental.

[15] J. J. Willard, J. S. Brimacombe and R. P. Brueton, *Canad. J. Chem.* **42**, 2560 (1964).

[16] T. Lieser and R. Schweizer, *Liebigs Ann.* **519**, 271 (1935); *Naturwiss* **23**, 131 (1935).

with the equatorial-axial-axial orientation of H_1, H_2 and H_3 in the C1 chair conformation (XB) of the dibenzoate.

From the results it is possible to predict the order of reactivity of the secondary OH groups of methyl-α-D-glucopyranoside and methyl α-D-mannopyranoside towards benzoyl chloride. It must be stressed however that this order does not necessarily apply to benzoic anhydride and other acylating agents since it has been shown that the products of selective acylation vary with acylating agent and catalyst.[3,5]

It is well known[6] that the primary OH group of carbohydrates is more reactive towards esterifying agents than the secondary OH groups, a fact which permits the easy preparation of many compounds with terminal ester groups. Methyl α-D glucopyranoside gives the 2,6-dibenzoate as major product upon dibenzoylation, and so the 2-OH group is the most reactive of the secondary OH groups; this has been attributed[6] to an activating effect of the anomeric centre. In the 2,6-dibenzoate (X) the 3-OH group experiences gauche interactions with a BzO group and a OH group,* whereas the 4-OH group is adjacent to the somewhat larger 5-benzoyloxymethyl group and a OH group and is therefore more sterically hindered.† The preponderance of the 2,3,6-tribenzoate (67%) over the 2,4,6-isomer (28%) is consistent with these arguments, and the order of reactivity of the secondary OH groups is therefore 2-OH > 3-OH > 4-OH.

The isolation of the 3,6-dibenzoate in good yield upon dibenzoylation of methyl α-D-mannopyranoside (V) shows that the 3-OH group is the most reactive of the secondary OH groups in this glycoside, and therefore the activation, if any, of the 2-OH group by the anomeric centre is overcome by its unfavourable axial disposition (see VB).

In agreement with this Aspinall and Zweifel[19] have found that the equatorial 3-OH group in methyl 4,6-O-ethylidene-α-D-mannopyranoside is sulphonylated more rapidly than the axial 2-OH group.

The isolation of the 2,3,6-tribenzoate in good yield upon tribenzoylation of methyl α-D-mannopyranoside (V) clearly shows that the 4-OH group is the least reactive, and the order of reactivity of the secondary OH groups in V is 3-OH > 2-OH > 4-OH. The greater reactivity of the 2-OH group compared with the 4-OH group is difficult to rationalise, and shows that the 2-OH group experiences less unfavourable interactions and/or more activation, possibly by the anomeric group, than the 4-OH group.

The exact order of reactivity of the secondary OH groups of methyl α-D-galactopyranoside cannot be predicted from our results because of the low selectivity towards dibenzoylation. However the high selectivity towards tribenzoylation demonstrates quite clearly that the axial 4-OH group is least reactive, as may be predicted on conformational grounds. The order of reactivity of the secondary OH groups in

* The interaction between two gauche OH groups has been estimated[17] to be 0·45 kcal/mol^{-1}; dipolar repulsions between bulky polar groups might be expected to be even larger, and a value of 1·8 kcal/mol^{-1} has been estimated[18] for the gauche interaction between two *p*-toluenesulphonyloxy groups.

† Strictly speaking interactions in the transition state should be considered. For present purposes it is assumed that such interactions are similar to those in the ground state.

[17] S. J. Angyal and D. J. McHugh, *Chem. & Ind.* 1147, (1956).

[18] R. U. Lemieux and J. W. Lown, *Canad. J. Chem.* **42**, 893 (1964).

[19] G. O. Aspinall and G. Zweifel, *J. Chem. Soc.* 2271 (1957).

methyl α-D-galactopyranoside may therefore be described as 2-OH and 3-OH > 4-OH. It is interesting to note that the 4-OH group in methyl α- and β-D-galactopyranoside is also least reactive towards methylation.[20]

The possibility that benzoyl migration may occur and exercise thermodynamic control over the reaction products is considered unlikely since no isomerization of methyl α-D-glucopyranoside 2,3,6-tribenzoate to the 2,4,6-tribenzoate takes place in pyridine saturated with pyridine hydrochloride at room temperature during 2 days, although both products occur in the tribenzoylation reaction product. Acetate ester groups have been shown to migrate in anhydrous pyridine, but only at elevated temperatures (120°).[21]

Also similar results have been observed in selective sulphonylation, for example methyl α-D-galactopyranoside and methyl α-D-mannopyranoside both give the 2,3,6-tri-O-methanesulphonates as major products.[22] There is no evidence for migration of sulphonate esters in pyridine.

Among the many factors which may influence the rate of benzoylation is hydrogen bonding. Correlations have been noted between (enhanced) rates of esterification (in pyridine) and intramolecular hydrogen bonding (in CCl_4).[23] It is unlikely* that intramolecular hydrogen-bonding would persist in pyridine, which forms strong intermolecular hydrogen-bonds with alcohols,[25] but if hydrogen-bonding to pyridine is sterically hindered in the transition state then intramolecular hydrogen-bonding to a suitably disposed acceptor could conceivably assume importance. However, the possibilities for intramolecular hydrogen-bonding in methyl glycosides and intermediates such as VI are diverse and there appear to be no convincing correlations.

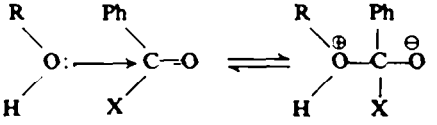
The above results together with those of earlier workers[19,26] disprove the generalization[6,27,28] that the 2-OH group in aldoses and aldosides is more reactive than the other secondary OH groups. The configuration of the anomeric centre also influences such reactions, for example methyl 4,6-O-benzylidene-α-D-glucopyranoside reacts with benzylthiochloroformate to give mainly the 2-ester, whereas the β-anomer gives mainly the 2,3-diester.[15,29] Similar results[30] have been obtained for sulphonylation. Methyl β-D-glucopyranoside has been stated[6,27] to give the 2,6-dibenzoate but the literature references given[16] describe the preparation of only the α-anomer of the 2,6-dibenzoate *by selective benzoylation*. Dimolar benzoylation of methyl β-D-glucopyranoside in fact gives a product containing at least four major

* IR measurements on pyridine solutions of free sugars provide no evidence for intramolecular hydrogen bonds.[24]

[20] N. R. Williams and R. W. Jeanloz, *J. Org. Chem.* **29**, 3434 (1964).
[21] S. J. Angyal, P. T. Gilham and G. J. H. Melrose, *J. Chem. Soc.* 5252 (1965).
[22] R. C. Chalk, D. H. Ball and L. Long, Jr., *J. Org. Chem.* **31**, 1509 (1966). We are grateful to the authors for sending a copy of their manuscript before publication.
[23] K. W. Buck, A. B. Foster, A. R. Perry and J. M. Webber, *J. Chem. Soc.* 4171 (1963); R. J. Ferrier, D. Prasad, A. Rudoswki and I. Sangster, *Ibid.* 3330 (1964).
[24] M. A. Kabayama and D. Patterson, *Canad. J. Chem.* **36**, 563 (1958).
[25] G. C. Pimentel and A. L. McClellan, *The Hydrogen Bond* p. 91. Freeman (1960).
[26] R. W. Jeanloz and D. A. Jeanloz, *J. Amer. Chem. Soc.* **80**, 5692 (1958).
[27] J. Compton, *J. Amer. Chem. Soc.* **60**, 395 (1938).
[28] A. K. Mitra, D. H. Ball and L. Long Jr., *J. Org. Chem.* **27**, 160 (1962).
[29] J. J. Willard, J. Sadowski and W. Vitale, *Canad. J. Chem.* **41**, 1223 (1963).
[30] J. C. P. Schwarz, private communication.

products.[31] The preferential esterification of the 2-OH group in 1,5-anhydro-4,6-O-benzylidene-D-glucitol has been erroneously interpreted to mean that the substituent at C_1 does not influence the reactivity of the 2-OH group.[32] It may be noted that the 2-OH group in the glucitol derivative is the least sterically hindered.

In the above discussion the electronic effect of a BzO group on a neighbouring OH group has not been considered. The effect cannot be predicted without a knowledge of the mechanism of benzoylation. The electron withdrawing effect of an ester group may be expected to decrease the availability of the lone pair electrons of the hydroxyl oxygen, and this would decrease the rate of reaction *if* the rate-determining step involves nucleophilic attack of the alcohol on the acylating agent, e.g. (1)*



(1)

This would be contrary to a previous suggestion that a vicinal ester group activates a OH group,[15] and would also lead to the prediction that the 2-OH group would be *deactivated* by the electron-withdrawing effect of the anomeric centre.† Clearly, more detailed studies, including the elucidation of the mechanism of benzoylation in pyridine are necessary to evaluate these effects.

The synthesis of 2,3,6-tri-O-methyl-D-mannose, prepared for the first time from D-mannose, provides an example of one of the many possible synthetic applications of the benzoates described above. Methyl 2,3,6-tri-O-benzoyl-4-O-methanesulphonyl-α-D-galactopyranoside (IV) is an intermediate in the synthesis of 4-amino-4-deoxy-D-glucose,[7,8] a class of compounds which has recently assumed importance with the discovery of related 4-amino-4,6-dideoxy hexoses in nature.[33]

It is interesting to note the resistance of methyl 2,3,6-tri-O-benzoyl-4-O-methanesulphonyl-α-D-mannopyranoside (VIII) to nucleophilic displacement. This may be attributed to the presence of an axial 2-BzO group, which may hinder the approach of the nucleophile at position 4 and/or may cause severe non-bonded interactions in the transition state.[34] A similar argument has been suggested to account for the fact that the β-anomer but not the α-anomer of 3-O-*p*-toluenesulphonyl-D-glucopyranose tetrabenzoate reacts with sodium benzoate in N,N-dimethylformamide.[35] Similar reasoning has also accounted for the lack of reactivity of some chlorosulphate esters of glycosides.[36]

EXPERIMENTAL

Solns were concentrated under reduced press. M.ps: on a Kofler micro-hot-stage apparatus. Optical rotations were measured at 24 ± 1° unless otherwise stated. IR spectra: on a Unicam SP 200

* Although the mechanism of benzoylation in pyridine is not known it is more likely that the unionised (aliphatic) alcohol is involved rather than its anion (R—O⁻).

† Our earlier statement[1] that the enhanced reactivity of the 2-OH group in methyl α-D-glucoside may be attributed to the electron-withdrawing effect of the anomeric center should be amended to "the enhanced reactivity . . . may be due to some activation by the anomeric center."

[31] J. M. Williams, unpublished work.

[32] F. H. Newth, *J. Chem. Soc.* 2717 (1959).

[33] C. L. Stevens *et al.*, *J. Amer. Chem. Soc.* **85**, 3061 (1963); **86**, 2937 (1964).

[34] E. L. Eliel, N. L. Allinger, S. J. Agyal and G. A. Morrison, *Conformational Analysis* p. 88, Interscience, New York, London, Sydney (1965).

[35] N. A. Hughes and P. R. H. Speakman, *J. Chem. Soc.* 2236 (1965).

[36] H. J. Jennings and J. K. N. Jones, *Canad. J. Chem.* **43**, 2372; 3018 (1965).

spectrophotometer, and the spectrum of each new compound was consistent with its proposed structure. PMR spectra: on a Varian A-60 or a Perkin–Elmer R10 spectrometer at normal operating temp using the solvent stated. TLC: on layers of silica gel G (Merck) deposited on either 20 cm × 5 cm plates or microscope slides; for detection of compds the plates were sprayed with 5% v/v H_2SO_4 in EtOH followed by heating at 120° for *ca.* 10 min. Column chromatography was carried out using Davison silica gel, grade 950, 60–200 mesh. Pyridine was dried by distillation (twice) from P_2O_5 and was stored over solid KOH.

Selective benzoylation. A magnetically-stirred soln of the glycoside in anhyd pyridine was cooled by means of a solid CO_2 acetone bath at −40° unless otherwise stated. Benzoyl chloride was added dropwise (10–30 min), with exclusion of moisture; the bath temp was kept below −20° for 2 hr and was then allowed to increase to room temp slowly (4–12 hr). After 36–48 hr most of the pyridine was removed by evaporation below 40° and the residue was dissolved in Chf. The Chf soln was washed successively with dil HClaq, 5% $NaHCO_3$aq, and water, and was then dried ($MgSO_4$). Removal of the desiccant and solvent gave the crude product.

Trimolar benzoylation of methyl α-D-*galactopyranoside.* Treatment of I monohydrate (14·84 g, 0·07 mole) in pyridine (450 ml) with benzoyl chloride (33·9 ml, 4·2 equivs) at −30° gave a product which was shown by TLC to contain at least one major and four minor components. The syrupy product crystallized and recrystallization from EtOH (60 ml) gave III (22·35 g), m.p. 139–140°, (lit.[7] m.p. 135·5–137°) $[\alpha]_D^{27}$ +123° (*c*, 0·92 in Chf). Recrystallization of subsequent crops from aqueous EtOH gave 0·83 g, m.p. 139–140°, total yield 23·18 g, 65%. (Found: C, 66·24; H, 5·38. Calc. for $C_{28}H_{26}O_9$: C, 66·39; H, 5·18%.) The tribenzoate was identical with an authentic sample[7] (mixed m.p. and IR spectra). Optimum conditions for tribenzoate formation were not established, but experiments using 4·0 and 4·1 molar equivs of benzoyl chloride gave lower yields.*

The mother liquor was dissolved in dry MeOH (200 ml) and metallic Na (ca. 500 mg) was added. After 3 days at room temp Na ions were removed with Amberlite IR 120 (H form) resin, and concentration of the soln gave a residue from which methyl benzoate was removed by partition between water and ether. Concentration of the aqueous layer and recrystallization of the residue from EtOH gave methyl α-D-galactopyranoside monohydrate (4·15 g, 28% recovery).

Alternatively, fractionation of the combined mother liquors from several preparations† on silica gel using benzene–ether as solvent gave the following compounds:- methyl α-D-galactopyranoside 2,3,4,6-tetra-O-benzoate (2%) m.p. 117–119°, $[\alpha]_D$ +151° (*c*, 1·216 in Chf), (Found: C, 68·9; H, 5·1. $C_{48}H_{40}O_{10}$ requires: C, 68·8; H, 4·95%); methyl α-D-galactopyranoside 2,3,6-tri-O-benzoate (13%), and a methyl *di*-O-*benzoyl*-α-D-*galactopyranoside* (6%) m.p. 145–146°, $[\alpha]_D$ +103° (*c*, 0·965 in Chf) (Found: C, 62·7; H, 5·75. $C_{21}H_{22}O_8$ requires: C, 62·65; H, 5·5%). The dibenzoate did not react with anhyd acetone in the presence of anhyd $CuSO_4$ or conc. H_2SO_4 or both. The 3,6-*dibenzoate* structure was assigned on the basis of PMR data (Table 1).

Dimolar benzoylation of methyl α-D-*galactopyranoside.* Treatment of methyl α-D-galactopyranoside monohydrate (636 mg, 3 mmole) in pyridine (20 ml) with benzoyl chloride (1·07 ml, 3·1 equivs) gave a product in which the 2,3,6-tri-O-benzoate predominated. At least 4 other products were shown to be present by TLC and one of these was lost during the partition work-up. Part (7%) of the 2,3,6-tri-O-benzoate was isolated by fractional crystallization. A portion of the mother liquor was then fractionated on thin layer plates (20 cm × 20 cm, detection by iodine vapour) and the 3 main bands, designated 1, 2 and 3 in order of increasing R_F were eluted with acetone or chf. Band 3 gave the 2,3,6-tribenzoate (34 mg, m.p. 139–140·5°); band 2 gave the 3,6-dibenzoate (19 mg, m.p. 144·5–145·5°) the mother liquor from which gave a syrup (ca. 43 mg) which contained a compound having the same R_F as the 3,6-dibenzoate and a second compound evidently formed by decomposition; band 1 gave a syrup (ca. 36 mg) which was found, after unsuccessful attempts at crystallization, to contain 3 compounds again as a result of decomposition.

Methyl 2,3,6-*tri*-O-*benzoyl*-4-O-*methanesulphonyl*-α-D-*galactopyranoside.* The tribenzoate (III 2·53 g, 5 mmole) in cold pyridine (30 ml) was treated with methanesulphonyl chloride (0·42 ml, 5·5 mmole). After 42 hr at room temp the reaction mixture was treated with a few drops of water, and then poured into ice-cold water (100 ml). The product was isolated by chf extraction in the usual way. The syrupy product crystallized after several weeks, yield 2·57 g, m.p. 114–117°. Recrystallization

* Preparation of the tribenzoate (recently reported[8]) has also been accomplished by benzoylation of methyl α-D-galactopyranoside with 3·5 equivs of benzoyl chloride at 0°.

† In which 4·0 and 4·1 equivs of benzoyl chloride were used.

from ether–pet. ether (80–100) gave 2·27 g, m.p. 121–125°, $[\alpha]_D$ +104 ± 2° (*c*, 1·02 in Chf). (Found: C, 59·9; H, 5·1. Calc. for $C_{20}H_{32}O_{11}S$: C, 59·6; H, 4·85%.) The IR spectrum of the methanesulphonate in Chf soln was identical with that of the higher-melting (m.p. 141–142°) form isolated by Reist *et al.*[7] The The lower-melting dimorphic form was converted into the higher-melting form (m.p. 143–144°, $[\alpha]_D$ +102 ± 2° *c*, 0·717 Chf) by recrystallization using seeds of the latter. In all subsequent preparations the higher-melting form was isolated.

Reaction of methyl 2,3,6-*tri*-O-*benzoyl*-4-O-*methanesulphonyl*-α-D-*galactopyranoside with sodium benzoate.* The methanesulphonate (117 mg, 0·2 mmole) in NN-dimethylformamide (2 ml) was heated with sodium benzoate (45 mg, 1·5 equivs) for 15 hr at 150°. The dark brown reaction mixture was diluted with chf (10 ml), treated with charcoal and filtered through celite. The filtrate was washed with water (3 × 10 ml) and the Chf layer was dried ($MgSO_4$). Removal of desiccant and solvent followed by crystallization from EtOH gave XIV (67 mg, m.p. 99–103°). Recrystallization from ether–pet. ether (100–120) gave 63 mg (52%), m.p. 105–107°, undepressed on admixture with an authentic specimen.

Trimolar benzoylation of methyl α-D-*mannopyranoside.* Treatment of V, (9·7 g, 0·05 mole) in pyridine (400 ml) with benzoyl chloride (17·9 ml, 0·155 mole) gave a product which was shown to contain one major and at least three other products. Attempts to crystallize the crude product were unsuccessful and fractionation on silica gel (1 Kg), using benzene–ether as solvent, gave the following compounds:- 2,3,4,6-tetra-O-benzoate (1·05 g, 3%) m.p. 134–135° (from EtOH), $[\alpha]_D$ −68° (*c*, 0·88 in Chf) (lit.[37] m.p. 134–135°, $[\alpha]_D$ −66°); a syrupy *tri*-O-*benzoate* (14·5 g, 57%, $[\alpha]_D$ −6·5° *c*, 0·93 in Chf) which crystallized as a *monohydrate* from 80% aqueous EtOH, m.p. 67–69°, $[\alpha]_D^{27}$ −21° (*c*, 0·89 in Me_2CO). (Found: C, 64·2; H, 5·35. $C_{28}H_{26}O_9 \cdot H_2O$ requires: C, 64·1; H, 5·4%); and a dibenzoate (5·3 g, 26%) m.p. 145–145·5° (from ether–pet. ether), $[\alpha]_D$ +61·6° (*c*, 1·38 in Chf). (Found: C, 62·75; H, 5·60. $C_{21}H_{22}O_6$ requires: C, 62·65; H, 5·5.) The dibenzoate was not oxidized by sodium metaperiodate in 50% EtOHaq; methyl α-D-glucopyranoside was used as control and the reaction was followed spectrophotometrically.[38*] This evidence, together with PMR data (Table 1), showed that the dibenzoate was the 3,6-*isomer* (VI).

Methyl 2,4-*di*-O-*acetyl*-3,6-*di*-O-*benzoyl*-α-D-*mannopyranoside.* The dibenzoate (220 mg) in dry pyridine was treated with an excess of Ac_2O (1 ml). After 5 days the reaction mixture was poured into cold water to give a quantitative yield of the *diacetate*, m.p. 129–131°. Recrystallization from Chf–pet. ether (80–100°) gave needles (253 mg, 95%) m.p. 130–131°, $[\alpha]_D$ +29° (*c*, 1·095 in Chf). (Found: C, 61·7; H, 5·5. $C_{24}H_{26}O_{10}$ requires: C, 61·75; H, 5·4%.) A 20% soln in Chf showed τ 7·93 and 8·07 (singlets, —CO·CH_3).

Proof of structure of mannoside tribenzoate. The tribenzoate monohydrate (1·048 g, 2 mmole) was dissolved in Chf (5 ml) and water was removed by the addition of $MgSO_4$ (ca. 0·3 g). After 10 min the desiccant was filtered off and washed with Chf. To the filtrate was added an excess of 2,3-dihydro-4H-pyran (0·7 ml, ca. 8 mmoles) and *p*-toluenesulphonic acid (ca 10 mg). TLC showed that ether formation was complete in 5–10 min. After 30 min the soln was washed with 10% NaOHaq (6 ml), water, then dried ($MgSO_4$). Removal of desiccant, concentration and addition of pet. ether (100–120) gave, after 2 days, large colourless elongated prisms of the *tetrahydropyranyl ether* (1·045 g, 89%) m.p. 135–139°. Recrystallization from different solvents gave several fractions, presumably containing different proportions of diastereoisomers, having different m.ps ranging from 114 to 143°. The analytical sample had m.p. 131–133°. (Found: C, 66·7; H, 5·75. $C_{33}H_{34}O_{10}$ requires: C, 67·1; H, 5·8%.) The rotation sample had m.p. 135–141°, $[\alpha]_D$ −54° (*c*, 0·67 in Chf).

The tetrahydropyranyl ether (400 mg, m.p. 126–130°) was dissolved in MeOH (10 ml) and Chf (3 ml), and 4 ml of a methanolic soln containing ca. 20 mg of MeONa was added. The debenzoylation was followed by TLC, and after 3 days the soln was concentrated to dryness. The dried residue was dissolved in a mixture of acetone (10 ml), MeI (10 ml) and MeOH (5 ml). Dry Ag_2O (3 × 1 g) was added at hourly intervals to the stirred soln, and after 24 hr the mixture was filtered. The residue was washed with acetone and MeOH, and filtrate and washings were concentrated to a syrup which was remethylated in acetone and excess MeI using ca. 1 g of Ag_2O over 2 days. Filtration and extraction of the solids with acetone followed by concentration gave a pale yellow oil (351 mg), which was dissolved

* The concentration of dibenzoate was such that its absorption was low enough to permit the detection of a change in the absorption of periodate ion.

[37] W. T. Haskins, R. M. Hann and C. S. Hudson, *J. Amer. Chem. Soc.* **68**, 628 (1946).

[38] G. O. Aspinall and R. J. Ferrier, *Chem. and Ind.* 1216 (1957).

in acetone (3 ml) and 0·5 N HCl (10 ml). After standing overnight the soln was neutralized with Amberlite IR 45 (OH) resin and concentrated to give crude syrupy methyl tri-O-methyl-α-D-mannopyranoside (139 mg). Acetone condensation products were removed by fractionation on silica gel (23 g); yield of trimethyl ether was 94 mg (59%, based on the tetrahydropyranyl ether). The glycoside was hydrolysed by the action of 2N HCl (4 ml) at 100° for 2 hr. Neutralization (IR 45 OH) followed by concentration gave the syrupy tri-O-methyl D-mannose (55 mg) which did not crystallize when seeded with authentic 3,4,6-tri-O-methyl-D-mannose. The trimethyl ether (53 mg) was dissolved in dry pyridine (2 ml) and treated with *p*-nitrobenzoyl chloride (105 mg, ca, 2·2 equivs, m.p. 72–73°). After 24 hr the mixture was poured into cold water (7 ml) and the crystalline product was filtered off after 1 hr at 5°, yield 110 mg, m.p. 162–180°. Recrystallization from EtOH gave pale yellow needles of 2,3,6-tri-O-methyl-1,4-di-O-*p*-nitrobenzoyl-α-D-mannopyranose, 73 mg (63%) m.p. and mixed m.p. 188–190, $[\alpha]_D^{27}$ +37° (*c*, 0·425 in Chf), lit.[39] + 33°.

Methyl 2,3,6-tri-O-benzoyl-4-O-methanesulphonyl-α-D-mannopyranoside. The syrupy VII (5·15 g) was dissolved in dry pyridine (70 ml) and the soln was cooled in iced-water. Methanesulphonyl chloride (0·85 ml), 1·1 equiv) was added with stirring. After 48 hr a few drops of water were added and the reaction mixture was poured into cold water (700 ml). The resulting solid was filtered off after 16 hr at +5°, and was washed with water, yield 5·15 g, 87%, m.p. 178–183°. Recrystallization from EtOH was accomplished with little loss and gave the *methanesulphonate* (VIII) m.p. 185–186°, $[\alpha]_D$ −53° (*c*, 1·17 in Chf). (Found: C, 59·3; H, 5·05; S, 5·4. $C_{28}H_{28}O_{11}S$ requires: C, 59·6; H, 4·85; S, 5·5%.) The methanesulphonate was resistant to nucleophilic displacement by sodium benzoate in N,N-dimethylformamide at 150° during 60 hr.

Dimolar benzoylation of methyl α-D-mannopyranoside. Treatment of methyl α-D-mannopyranoside 0·97 g, 5 mmole in pyridine (50 ml) with benzoyl chloride (1·27 ml, 11 mmole gave a product in which a dibenzoate predominated. Crystallization from Chf–pet. ether (40–60) gave VI, 1·25 g (62%), m.p. 142–144°), identical with that obtained from the tribenzoylation.

Trimolar benzoylation of methyl α-D-glucopyranoside. Treatment of IX (3·88 g, 20 mmoles) in pyridine (150 ml) with benzoyl chloride (7·14 ml, 62 mmole, 3·1 equiv) gave a product which contained two major components. Compound XI was isolated (1·31 g, 13%) from Chf–pet. ether (80–100) after seeding with authentic material. The mother liquor (one tenth aliquot) was fractionated on silica gel (160 g) to give a syrupy tribenzoate A (0·189 g, 19% $[\alpha]_D$ +98° *c*, 0·50 in Chf), a mixture of A and the 2,3,6-tribenzoate (0·241 g, 24%), and the 2,3,6-tribenzoate (0·400 g, 40%). The latter had m.p. 82–93° when crystallized from Chf–pet. ether, and m.p. 129–130° when crystallized from MeOH; $[\alpha]_D$ +141° (*c*, 0·697 in Chf). Bell[40] quotes m.p. 132–133°, $[\alpha]_D$ +141°. Several crystalline forms of the 2,3,6-tribenzoate have been observed.[41] Tribenzoate A did not crystallize when seeded with the 2,4,6-tribenzoate[18] ($[\alpha]_D$ +94·9° in Chf); the seeds were impure (TLC) and could not be recrystallized. The IR spectrum of tribenzoate A (in Chf) was almost completely superimposable on that of the impure 2,4,6-tribenzoate. Tribenzoate A (55 mg) was converted into the *p*-toluenesulphonate deriv by treatment with dry pyridine (2 ml) and *p*-toluenesulphonyl chloride (50 mg) for 2 weeks at room temp. The reaction mixture was poured into cold water, and the product (60 mg, m.p. 145–160°) was isolated after Chf extraction. Recrystallization from Chf–pet. ether (80–100) gave methyl 2,4,6-tri-*O*-benzoyl-3-*p*-toluenesulphonyl-α-D-glucopyranoside, 38 mg, m.p. 165–167°, undepressed on admixture with an authentic sample.[18] The IR spectra of product and authentic sample were identical. The mixture of tribenzoates isolated after column chromatography was estimated (visually by TLC) to contain the 2,3,6- and 2,4,6-tribenzoates in the ratio 60 ± 20: 40 ± 20, therefore these tribenzoates are formed in 67 ± 5% and 28 ± 5% yields respectively.

Dimolar benzoylation of methyl α-D-glucopyranoside. Compound X was prepared, with slight modification of the method of Lieser and Schweizer,[16] in 50% yield, m.p. 143–143·5° (lit. 144°).

Acknowledgement—Part of this work was financed by the Medical Research Council whose support is gratefully acknowledged. We are also grateful to Dr. L. Hough for his advice and encouragement. We are indebted to the following persons for their kind donation of authentic samples:- J. G. Buchanan, G. O. Aspinall, L. Goodman and J. J. Willard. We also thank Dr. F. J. Hopton for the determination of a PMR spectrum.

[39] P. A. Rebers and F. Smith, *J. Amer. Chem. Soc.* **76**, 6097 (1954).
[40] D. J. Bell, *J. Chem. Soc.* 1076 (1933).
[41] J. G. Buchanan, private communication.