STUDIES IN THE SYNTHESIS OF GLYCOSIDES

A THESIS

SUBMITTED TO

THE SHIVAJI UNIVERSITY

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MASTER OF SCIENCE

BY

Mrs. V. S. BHAT

NATIONAL CHEMICAL LABORATORY

POONA - 8

1975

ACKNOWLEDGEMENTS

I am deeply indebted to Dr. J.L. Bose, Scientist E, National Chemical Laboratory, Poona, for his inspiring guidance throughout the course of this work.

My thanks are also due to Mrs. Bharati Sinha, Mr. A.B. Landge, Dr. T.R. Ingle and Mr. R.K. Irani for fruitful discussions.

Services from the Micro-analytical Section of this Laboratory are gratefully acknowledged.

Finally, my thanks are due to the Director, National Chemical Laboratory, Poona, for kindly allowing me to submit this work in the form of a thesis.

S Bhat

(Mrs) V. S. Bhat

NCL, Poona 8

November 1975

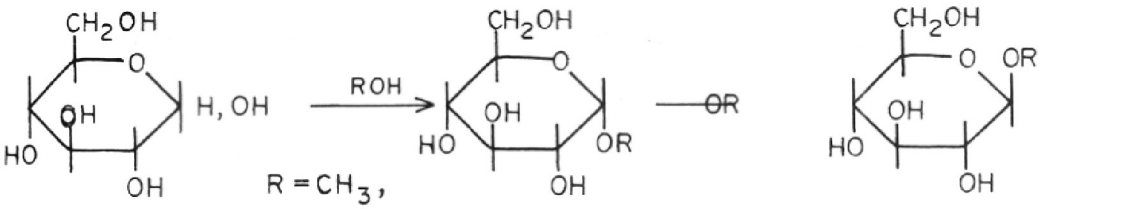
C O N T E N T S

CHAPTER I

I N T R O D U C T I O N

INTRODUCTION

Glycosides are acetal derivatives of sugars in which the hydrogen of the hemiacetal hydroxyl group is replaced by an alkyl or an aryl group. Thus, the hemiacetal hydroxyl group of a monosaccharide such as D-glucopyranose can react, under certain conditions, with an alcoholic or a phenolic hydroxyl group of another organic molecule, such as methanol or phenol, to give the corresponding glucosides in either of the anomeric α- or β-configurations (Fig.1).



D – gluco – pyranose

Methyl (or phenyl) α – D – glucopyranoside

Methyl (or phenyl) β – D – glucopyranoside

FIG. 1.

Disaccharides or oligosaccharides can also react similarly to give the corresponding glycosides. Thio-alcohols or thiophenols can also take part in this reaction to give the corresponding thioglycosides.

Glycosides are widely distributed in the plant kingdom but only to a limited extent in animals. In plants, they range from the most prominent and attractive anthocyanin pigments of flowers to the cardiac glycoside drugs of the Digitalis species. In animals, they are limited to the

cerebrosides, glycolipids and gangliosides found in the brain, spleen and nerve tissues of animals.

Numerous conjectures have been made about the functions of glycosides in plants. Glycosides may serve as a reserve deposit for sugars, particularly in seeds. They may also control the osmotic pressure of the cells of plants. Glycosidation may be a natural process for stabilization of labile aglycones and also for removal of toxic organic compounds as end products of metabolic processes. Apart from anthocyanins which constitute the pigments of flowers, many important natural colouring matters belonging to the flavonoid, anthraquinonoid and the carotenoid groups occur as glycosides.

Several natural as well as synthetic glycosides have found many important uses. Rutin (Fig.2), the rutinoside (β-L-rhamnosido-6-D-glucoside) of the flavonol quercetin, is an important drug used for reducing capillary fragility and permeability. The glycosides of Strophanthus and Digitalis species have proved to be of considerable therapeutic value in cases of impaired heart functions by increasing the intensity of heart-beat and decreasing the rate. The important antibiotic streptomycin is composed of three glycosidically linked sugar derivatives, streptidine, streptose and N-methyl-L-glucosamine. Many saponins, which are glycosides of triterpenoids and similar substances have

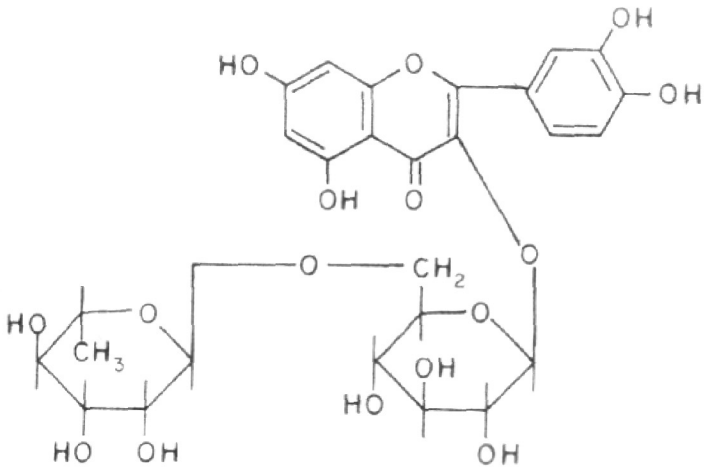
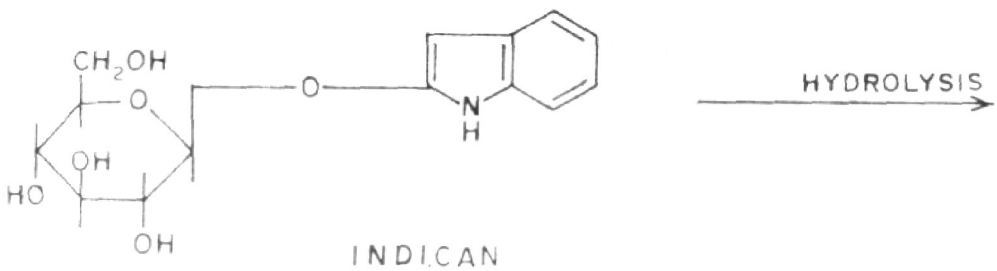
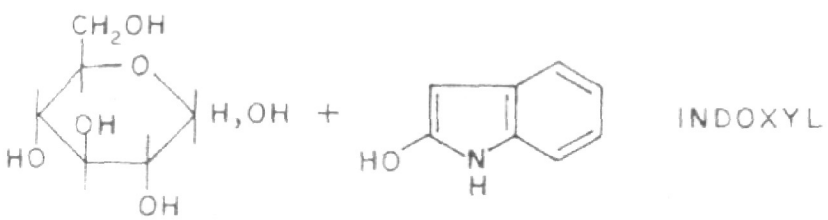


FIG · 2



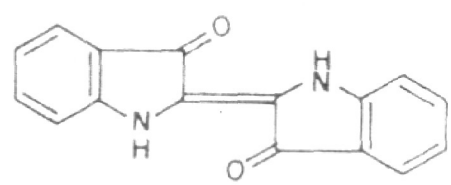
INDICAN



GLUCOSE

INDOXYL

OXIDATION



FIG·3

INDIGO BLUE

been found to possess important antimicrobial and antimycolic properties[1].

It is interesting to note that a glucoside plays an important part in the ancient Indian process of preparation of the famous dye, indigo blue, from plants belonging to the genus Indigofera. Marco Polo who visited India in the thirteenth century described the method in use at that time. The dyestuff indigo blue does not occur as such in the plant. On steeping the plant in water at 50°, the soluble glucoside indican (2-O-β-D-glucoside of indoxyl) present in the plant dissolves in water and gets hydrolysed to D-glucose and indoxyl by the natural enzymes present or by the added acids. Aeration of the solution oxidises indoxyl which then dimerises to give the insoluble indigo blue. The reactions taking place in the aqueous solution are given in Fig.3.

Many synthetic glycosides are useful for various important biochemical studies. Synthetic α-methylglucoside is now a commercial product[2] in use for the preparation of surface active agents and tetrahydrophthalic anhydride resins.

The glycosides are synthesised in nature probably by an enzymic process. This process, however, has not been duplicated in the laboratory so far.

The first ever chemical synthesis of glycosides was achieved by Michael[3] in 1879. By reacting tetra-O-acetyl-α-D-glucopyranosyl chloride with potassium phenate he obtained phenyl tetra-O-acetyl-β-D-glucopyranoside. In view of the growing importance of glycosides in various fields such as genetics, affinity chromatography for the separation of certain enzymes and proteins and also as drugs, several other synthetic methods have been developed for the preparation of various glycosides. Of these methods those of general applicability are described briefly in the following paragraphs:

(1) Glycosidation with free sugars

Fischer[4] successfully carried out glycosidation of lower alcohols with free sugars. In this process of glycosidation a suspension of the sugar (mono-, di- or oligosaccharide) in the anhydrous alcohol (aglycone) is treated with dry hydrogen chloride. Thus, D-glucose and methanol give methyl α-D-glucoside by this process. The di- and oligosaccharides get partially alcoholysed during this process. Cation exchange resins in the H^+ form can also be used in this reaction instead of hydrogen chloride. Bishop and Cooper[5] have shown that this reaction proceeds through the following stages finally giving the glycosides in the α pyranoside form (Fig.4).

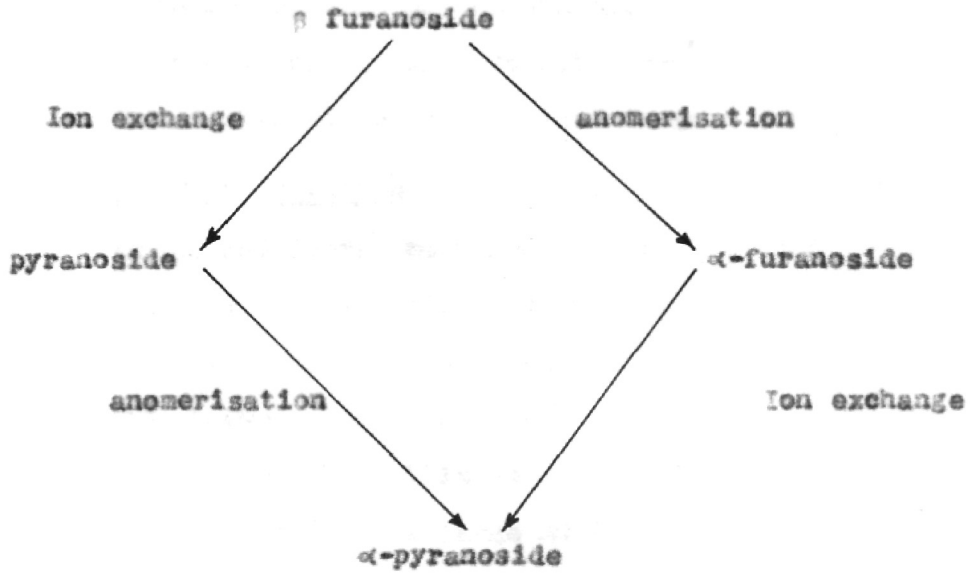


Fig.4

2) Glycosidation with O-acylglycosyl halides

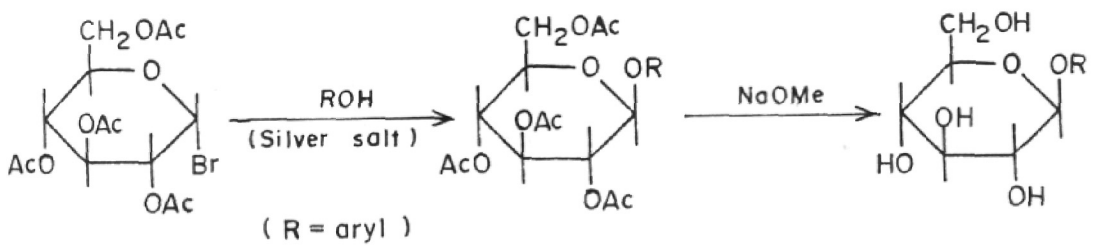
(A) Michael's method

As mentioned earlier, this was the first method developed for the synthesis of aryl glycosides. In the original method in which tetra-O-acetylglycosyl chloride and potassium phenate were used as the reactants, the acetyl groups of the sugar got simultaneously hydrolysed under the conditions of the reaction resulting in the formation of the free glycoside directly in low yields. The utility of this method was increased later by using the more reactive tetra-O-acetyl-α-D-glycopyranosyl bromides and carrying out the reaction in an alkaline

aqueous-acetonic solution of the phenol. Under these conditions, the acetyl groups are not hydrolysed and the acetylated glycosides are obtained in good yields.

(B) Koenigs-Knorr's method

Koenigs and Knorr[6] modified Michael's method of glycosidation by using silver compounds, such as, silver oxide or silver carbonate as the acid acceptor in the reaction between acetyl glycosyl bromides (or chlorides) and phenols or alcohols. This method has been extensively used for the synthesis of a large number of glycosides. The resulting acetylated glycosides can be quantitatively deacetylated by Zemplen's method[7], using catalytic quantities of sodium methoxide in absolute methanol. Walden inversion always occurs in this reaction. Since tetra-O-acetyl-α-glycosyl halides are available as the comparatively more stable anomers, this reaction is suitable usually for the preparation of β-anomeric glycosides (Fig.5).



Tetra-O-acetyl-α-D glucopyranosyl bromide

Aryl tetra-O-acetyl β-D-glucopyranoside

Aryl β-D-glucopyranoside

FIG. 5.

An elegant modification of this method was introduced by Zemplen[8]. In this method, the costly silver salts used as acid acceptors were replaced by cheaper mercury salts. Moreover, this modification had an added advantage in that no Walden inversion took place particularly when the reaction was carried out in an inert solvent. This modification is particularly of value for the preparation of the difficultly accessible α-anomeric glycosides.

(3) Glycosidation with dialkyl or diaryl alkyl thioacetals

Pacsu[9] successfully used dialkyl or diaryl alkyl thioacetals of monosaccharides for the glycosidation of alcohols in the presence of mercury (II) chloride as a catalyst. By changing the reaction temperature and by using yellow mercuric oxide as an additional catalyst, it is possible to prepare the alkyl glycosides in either of the pyranoside or the furanoside form and in the α- or β-configuration (Fig.6).

(4) Glycosidation with Ortho esters

Kochetkov et al.[10] reacted 1,2 ortho-ester sugar acetates with an aliphatic alcohol in the presence of mercuric bromide and traces of p-toluene sulphonic acid as catalysts in nitromethane medium to obtain the corresponding β-glycosides. They prepared successfully disaccharides and oligo-saccharides using a second sugar molecule as the

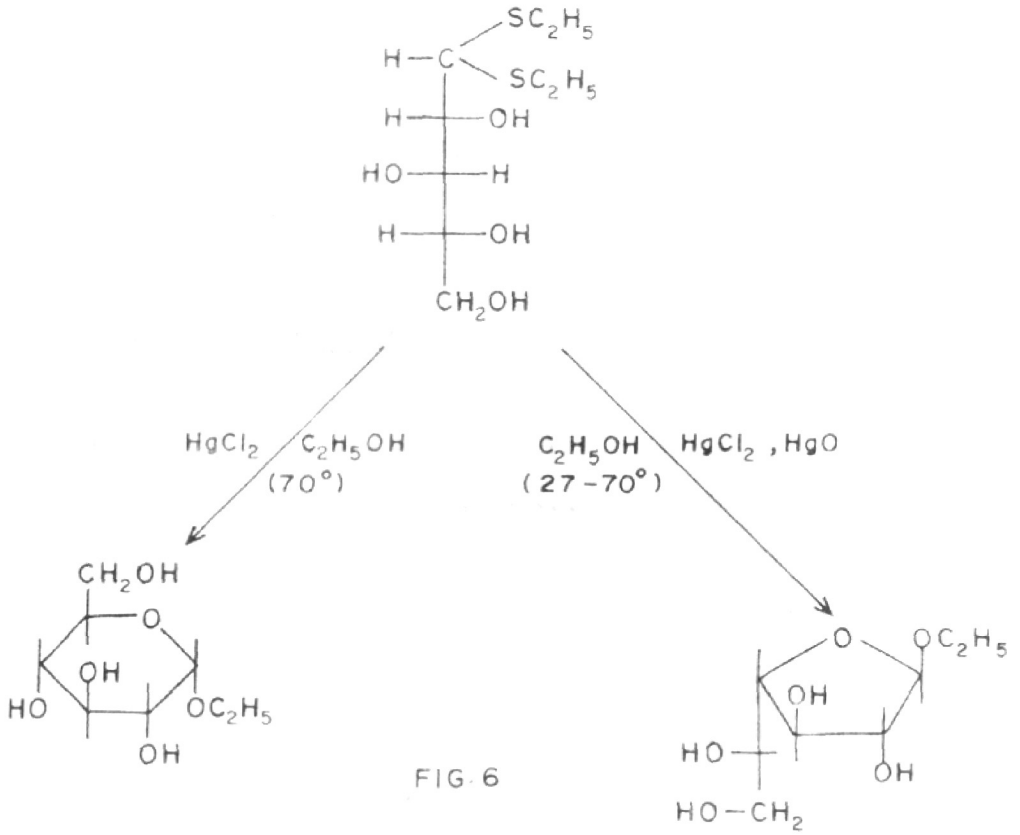
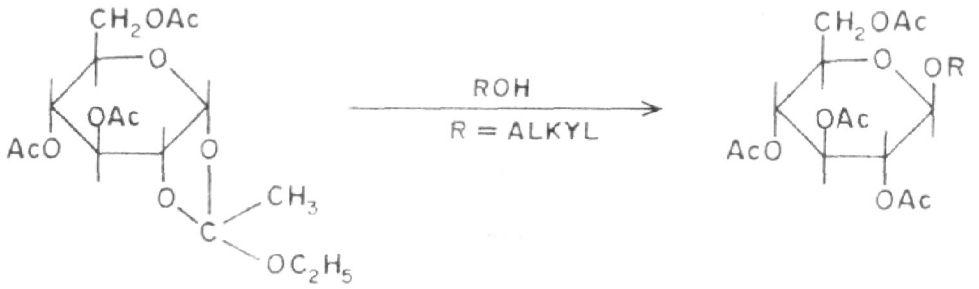


FIG 6



TRI-O-ACETYL α-D-GLUCOPYRANOSE
1,2 ETHYL ORTHOESTER

ALKYL TETRA-O-ACETYL
-β-D-GLUCOPYRANOSIDE

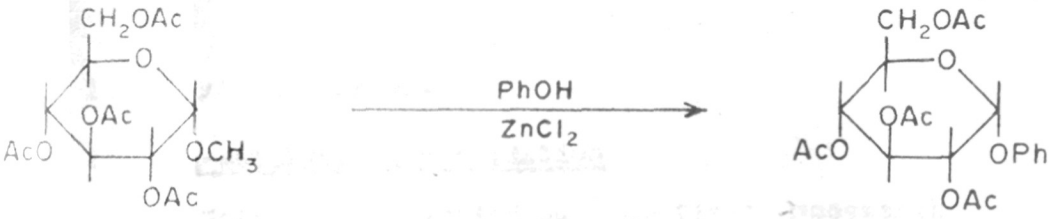
FIG 7

aliphatic alcohol moiety. They also found that different types of sugars such as hexoses, pentoses or disaccharides exhibit the same reactivity towards glycosidation in this reaction (Fig.7).

(5) Trans-glycosidation

In this method the aliphatic aglycone part of a glycoside is exchanged with a different aliphatic or aromatic aglycone to obtain the corresponding alkyl or aryl glycoside. The exchange may take place with or without a change in the configuration depending on the reaction conditions. Thus methyl tetra-O-acetyl-α-D-glucopyranoside on reacting with phenol in the presence of zinc chloride gives phenyl tetra-O-acetyl-α-D-glucopyranoside[11] (Fig.8).

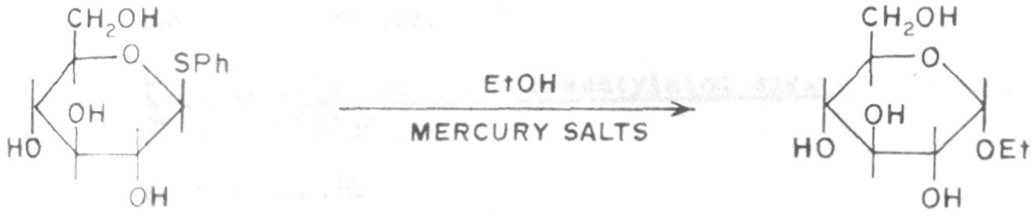
Recently Ferrier et al.[12] have developed an elegant method of transglycosidation using the stable phenyl α- or β-D-thioglucoside as the starting material. Treatment of either of these thioglucosides with an alcohol in the presence of mercuric salts leads to the formation of the corresponding glycosides in excellent yields with an inverted anomeric configuration. Whereas β-glycosides were found to be formed stereospecifically the α-glycosides contained about 6% of the β-anomer. Thus phenyl β-D-thio-glucoside on treatment with dry ethanol with mercuric chloride and mercuric oxide gave ethyl α-D-glucopyranoside



METHYL TETRA-O-ACETYL -α-D-GLUCOPYRANOSIDE

PHENYL TETRA-O-ACETYL-α-D-GLUCOPYRANOSIDE

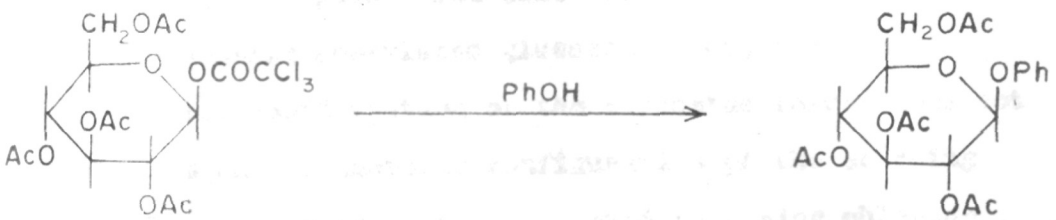
FIG·8



PHENYL-β-D-THIOGLUCO-PYRANOSIDE

ETHYL-α-D-GLUCOPYRANOSIDE

FIG·9



1-O-TRICHLOROACETYL-2,3,4,6-TETRA-O-ACETYL β-D-GLUCOPYRANOSE

PHENYL TETRA-O-ACETYL-β-D-GLUCOPYRANOSIDE

FIG·10

in 67% yield (Fig.9).

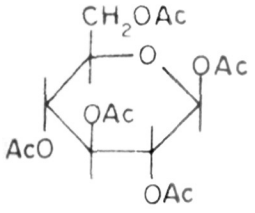
(6) Non-catalytic glycosidation

Helferich[13] carried out the first successful non-catalytic synthesis of a glycoside by heating 1-O-trichloroacetyl 2,3,4,6-tetra-O-acetyl β-D-glucopyranose with phenol without any catalyst to obtain the corresponding phenyl tetra-O-acetyl-α-D-glucopyranoside. In this reaction, the trichloroacetyl group was replaced by phenyl group without inversion (Fig.10).

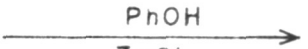
(7) Glycosidation with fully acetylated sugars catalysed by Lewis acids

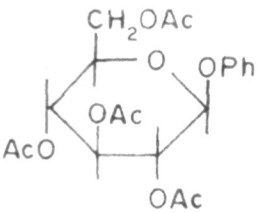
(A) Zinc chloride

Helferich et al.[14-17] used anhydrous zinc chloride for the first time as a condensing agent in the glycosidation of phenols with fully acetylated sugars in the absence of a solvent. The formation of the α-anomers is favoured at higher reaction temperatures (120-140°) and longer periods of heating. Thus, penta-O-acetyl-β-D-glucopyranose on heating with phenol and zinc chloride gives a mixture of the two anomeric acetylated glucosides (Fig.11). The anomeric configuration of the glycoside formed does not depend on the anomeric configuration of the starting acetylated sugar. It is believed that zinc chloride first produces the β-anomeric glycosides which then anomerise to the α form. The synthesis of phenyl and p-nitrophenyl

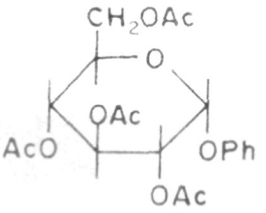


PENTA-O-ACETYL
β-D-GLUCOPYRANOSE





PHENYL TETRA-O-ACETYL
β-D-GLUCOPYRANOSIDE



PHENYL TETRA-O-ACETYL α-D-
GLUCOPYRANOSIDE

FIG. 11

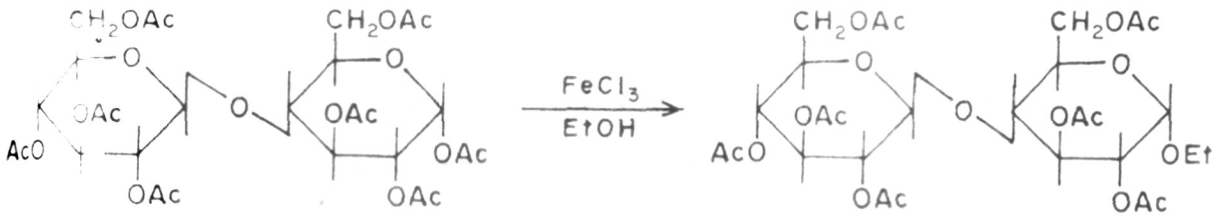


FIG. 12

tetra-O-acetyl-α-D-glucopyranosides makes use of a nitrogen atmosphere and a lower reaction temperature (120°).

(B) p-Toluenesulphonic acid

Aryl β-D-glycosides have been successfully synthesised by the reaction of phenols with fully acetylated sugars in the form of a melt using p-toluenesulphonic acid as the catalyst. This method often gives good yields of the glycosides at lower reaction temperatures (100-120°) and shorter reaction periods. A number of acetylated-β-D-xylopyranosides of various substituted phenols have been synthesised by this method[18].

(C) Titanium tetrachloride

Anhydrous titanium tetrachloride was used by Karaswa et al.[19] for the condensation of phenols with fully acetylated sugars to give acetylated β-anomeric glycosides.

(D) Ferric chloride

Anhydrous ferric chloride[20] has been used as the condensing agent by Zemplen for the preparation of ethyl hepta-O-acetyl-α-D-cellobioside from octa-O-acetyl-α-D-cellobiose (Fig.12). It was postulated that ferric chloride first forms a complex with the fully acetylated sugar which finally yields the glycoside.

(E) Anhydrous aluminium chloride

Anhydrous aluminium chloride[21] has been used as a

condensing agent for the glycosidation of phenols with glucose-β-D-pentaacetate. The mixture on fusion is reported to give both the anomeric glycosides and only the β-anomer was actually isolated.

(F) Boron trifluoride

Bretschneider and Befank[22] used a trace of boron trifluoride for the condensation between penta-O-acetyl-β-D-glucopyranose and phenol in benzene medium at the room temperature. Only the formation of β-anomeric glycoside was reported in this reaction.

(G) Stannic chloride

Stannic chloride was first used by Lemieux and Shyluk[23] to prepare methyl- and phenyl- tetra-O-acetyl-β-D-glucopyranoside by condensing penta-O-acetyl-β-D-glucopyranose with methanol or phenol respectively in benzene medium. Bose *et al.* of this laboratory have made exhaustive studies of this reaction[24] and have observed the formation of both of the anomeric glycosides. They also established conditions for obtaining either of the anomeric glycosides as the major product in these reactions[25]. This reaction has been discussed in greater details in Chapter II of this thesis.

(H) Phosphorous oxychloride

Bembry and Powell[26] used moist phosphorous oxychloride

as a catalyst for glycosidation of phenols with acetylated sugars in benzene medium and obtained acetylated aryl β-D-glycosides. This reaction has been studied in details by us and will be discussed in Chapter IV of this thesis.

REFERENCES

1 Cucu, V and Gucu L., Farmacia 19, 1971, 641.

2 Manufactured by M/s. Corn Products Ltd., New York.

3 Michael, A., Amer. Chem. J. 1, 1879, 305.

4 Fischer, E., Ber. 26, 1893, 2400.

5 Bishop, C.T., and Cooper, F.P., Canad. J. Chem. 41, 1963, 2743.

6 Koenigs, W. and Knorr, E., Ber. 34, 1901, 957.

7 Zemplen, G., Ber. 60, 1927, 1555.

8 Zemplen, G. and Gerecs A., Ber. 63, 1930, 2720.

9 Pacsu, E., Ber. 58, 1925, 509.

10 Kochetkov, N.K., Kharlin, A.J., Bodkov, A.F., Tetrahedron letters, 1964, 289.

11 Hudson, C.S., Montgomery, E.M. and Richtmyer, N.K., J. Am. Chem. Soc. 64, 1942, 690.

12 Ferrier, R.J., Hay, R.W. and Vethavisarar, N., Carbohyd.Res. 27, 1973, 55.

13 Helferich, B. and Gootz, R., Ber. 62, 1929, 2788.

14 Helferich, B. and Reischal, W., Ann. 535, 1938, 278.

15 Helferich, B. and Streeck, R., Ber. 69, 1936, 1111.

16 Helferich, B. and Phillip, F., Ann. 519, 1934, 218.

17 Helferich, B. and Winkler, S., Ber. 62, 1933, 1556.

18 Debruyene, C.K. and Vanvisneuel acle F., Carbohyd. Res. 4, 1967, 102.

19 Karaswa, I., and Onishi, R., C.A. 63, 5729[e]
J. Agr. Chem. Soc. (Japan) 33, 1961, 707.

20 Zemplen, G., Ber. 62, 1929, 985.

21 Huad, C.D. and Bonner, W.A., J. Org. Chem. 11, 1946, 50.

22 Bretschneider, Berank, H., Monatsch, 80, 1949, 262.

23 Lemieux, R.U. and Shyluk, W.P., Canad. J. Chem. 31, 1953, 528.

24 Bose, J.L. and Ingle, T.R., Chem. and Ind. (London), 1967, 1451; Carbohyd. Res. 12, 1970, 459.

25 Audichya, T.D., Ingle,T.R. and Bose, J.L., Indian J.Chem. 9, 1971, 315.

26 Bembry, T.H. and Powell, G., J. Am. Chem. Soc. 64, 1942, 2419.

CHAPTER II

STANNIC CHLORIDE CATALYSED SYNTHESIS OF ALKYL GLYCOSIDES

STANNIC CHLORIDE CATALYSED SYNTHESIS OF ALKYL GLYCOSIDES

INTRODUCTION

The preparation of α-anomeric glycosides has always been a difficult task, except for those derived from 1,2-trans oriented sugars like α-D-mannopyranose. No method of general applicability has been described in literature for the preparation of these glycosides. The method developed by Helferich and co-workers[1] for the synthesis of aryl α-glycosides cannot be employed for the synthesis of alkyl α-glycosides.

Methods of Synthesis of alkyl α-glycosides

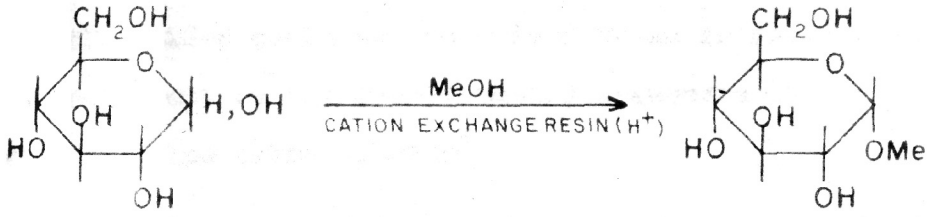
A survey of literature reveals that although several methods have been proposed for the synthesis of alkyl α-anomeric glycosides, none are of general applicability. Some of the methods available for the preparation of alkyl α-glycosides and their drawbacks are discussed in the following paragraphs.

Emil Fischer[2] developed a method for the preparation of alkyl α-glycosides by heating a sugar with an excess of an alcohol like methanol or ethanol in the presence of small amounts of an acidic catalyst like hydrogen chloride. This well-known method gives an equilibrium mixture of the anomeric glycosides in the furanose and pyranose forms.

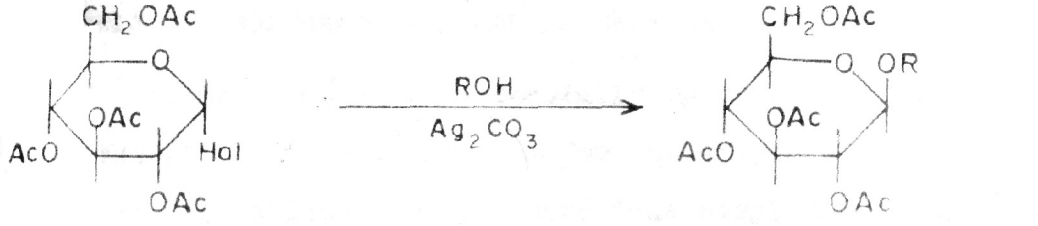
Under comparatively more drastic reaction conditions, the pyranosides predominate when equilibrium is established. This method is, therefore, suitable for the preparation of alkyl α-glycosides, but satisfactory results are obtained only with the lower aliphatic alcohols. In this method, the acidic catalyst, mainly hydrogen chloride, can be replaced by a cation exchange resin in the H^+ form. By using this procedure, it has been possible to develop a continuous commercial process for the manufacture of methyl α-D-glucopyranoside (I).

The Koenigs-Knorr method[2A] in which the stable O-acetyl-α-glycosyl halides (II) are used as the glycosidation reagent in the presence of an excess of silver carbonate or oxide, gives acetylated β-anomeric glycosides (III) with alcohols or phenols as the reaction is accompanied by a Walden inversion at C-1 (in the case of 1,2-cis oriented sugar derivatives). The O-acetyl-β-glycosyl halides are highly unstable and, therefore, cannot be used generally for the synthesis of acetylated α-anomeric glycosides. Except in very special cases this method is therefore not suitable for the synthesis of α-anomeric glycosides.

Paesu[3] converted diethyl dithioacetals of monosaccharides (IV) to alkyl α-glycosides (V) by reacting the former with the appropriate alcohol in the presence of mercuric chloride. He also found that acetylated alkyl

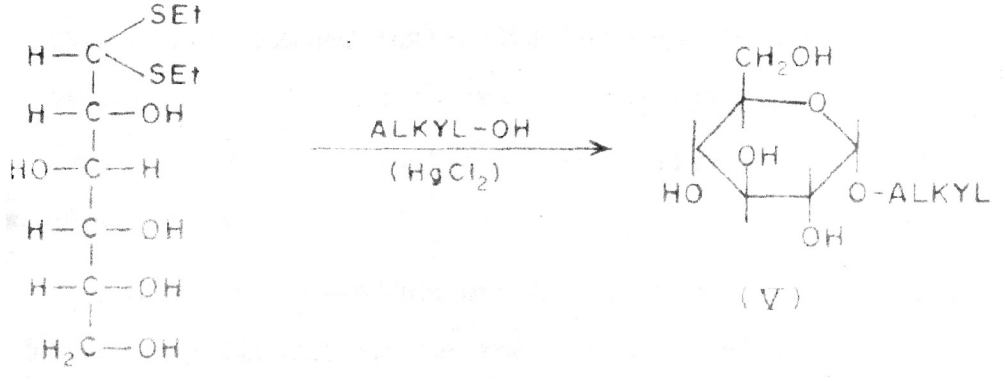


D-GLUCOPYRANOSE (I)

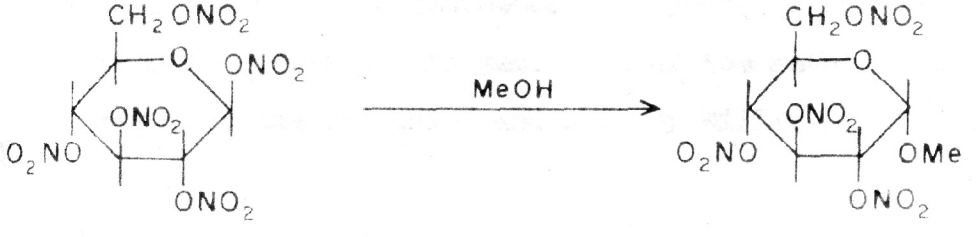


R= ALKYL or ARYL

(II) (III)



(IV) (V)



(VI) (VII)

β-D-glycosides could be anomerised by an intramolecular rearrangement to the corresponding α-anomers by heating them with titanium tetrachloride[4].

Another method developed by Wolfrom and Gilliam[5] for the preparation of alkyl α-D-glycopyranosides consists in anomeric displacement of the 1-nitro group in a compound like β-D-glucopyranose pentanitrate (VI) by a methyl group to yield the corresponding methyl α-D-glucoside (VII).

Enzymes were used successfully by Bourquelot and co-workers[6] as early as in 1913 for the preparation of alkyl α-D-glycosides. They showed that alkyl α-D-glycosides could be prepared by the action of the enzyme α-glycosidase present in yeast on a dilute alcoholic solution of certain reducing sugars. Manners et al.[7] synthesised several α-linked disaccharides containing the α-D-glucosyl residue, by the action of the enzyme from Tetrahymena pyriformis on phenyl α-D-glucopyranoside in the presence of a second monosaccharide.

All of these methods synthetic or enzymic, are only of limited applicability for the synthesis of alkyl α-D-glycosides.

In most of the syntheses α-anomeric glycosides, the β-anomer is invariably formed. One of the methods advocated by Helferich and Johannis[8] and also by Miller et al.[9] is

by preferential enzymic hydrolysis of the β-anomeric glycoside from the mixture of the anomers leaving behind the pure α-anomer. Several pure alkyl α-glycosides have been prepared by this procedure.

A method, which could be of general applicability for the synthesis of alkyl α-glycosides, therefore, would be of considerable importance, even if the product obtained contained some of the β-anomer. The pure α-anomer could be obtained from the mixture of the free glycosides by preferential enzymic hydrolysis of the β-anomer or from the mixture of the acetylated glycosides by chromatographic separation on a silica gel column.

It has already been mentioned in the earlier chapter that Lemieux and Shyluk[10] obtained exclusively the acetylated β-anomeric glucosides in the stannic chloride catalysed glucosidation of phenol and methanol with penta-O-acetyl-β-D-glucopyranose using benzene as a diluent. They attributed the exclusive formation of the β-anomer in this reaction, to the preponderance of the stable ion(VIII)formed as a result of anchimeric assistance of the acetoxy group at C-2. Bose et al.[11] later established that α-anomers are also formed in the glycosidation of phenols by this method. They have recently suggested the possible mechanism of this glycosidation reaction on the basis of experimental evidence[12].

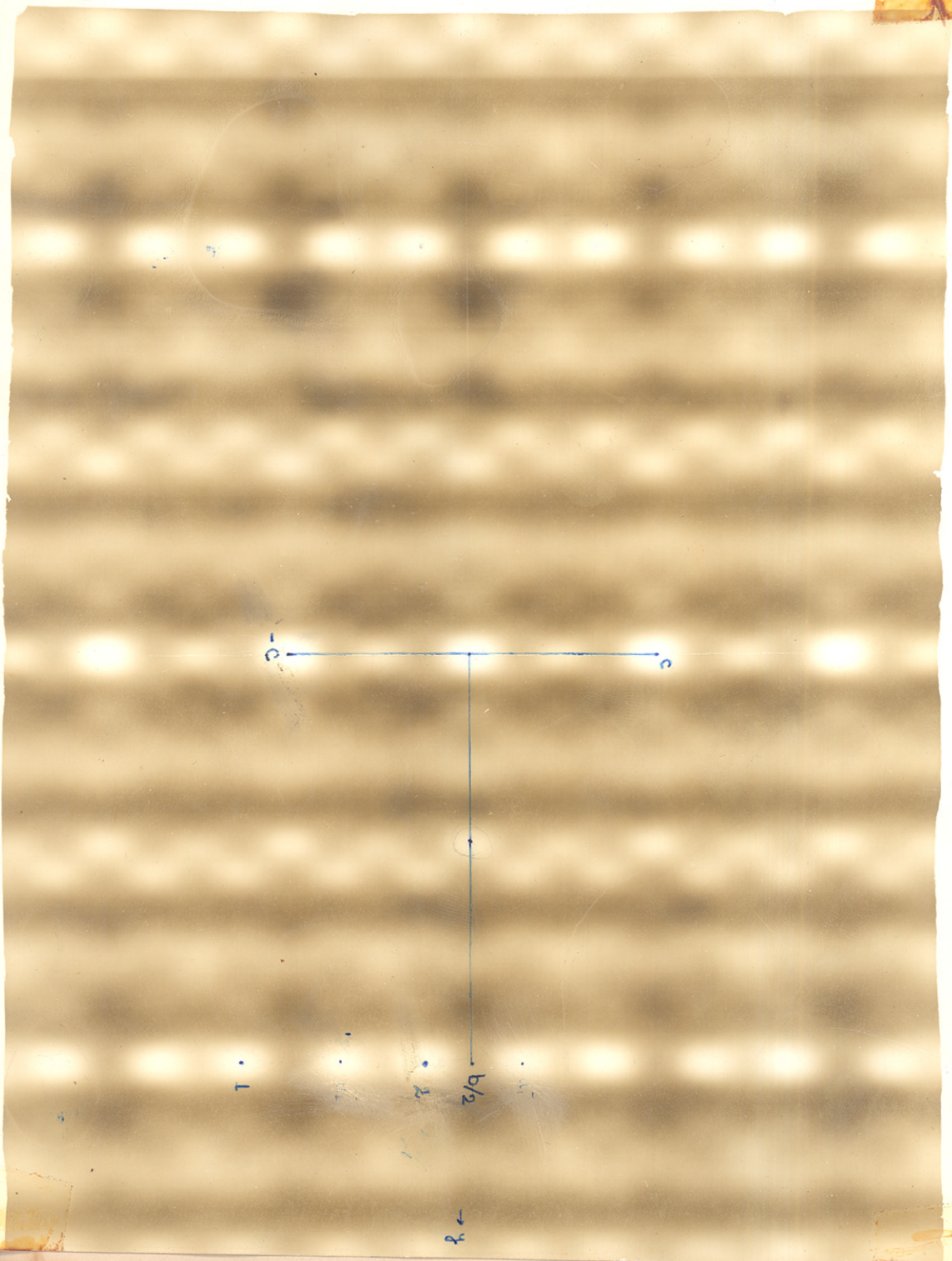


FIGURE III-4 : (100) PATTERSON MAP

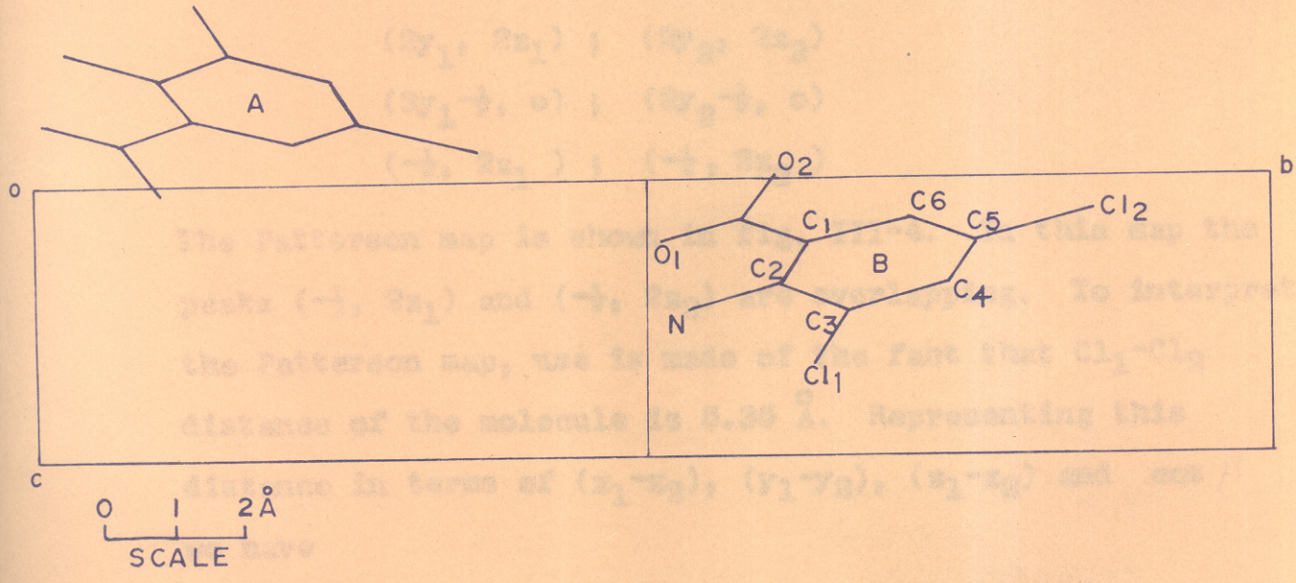
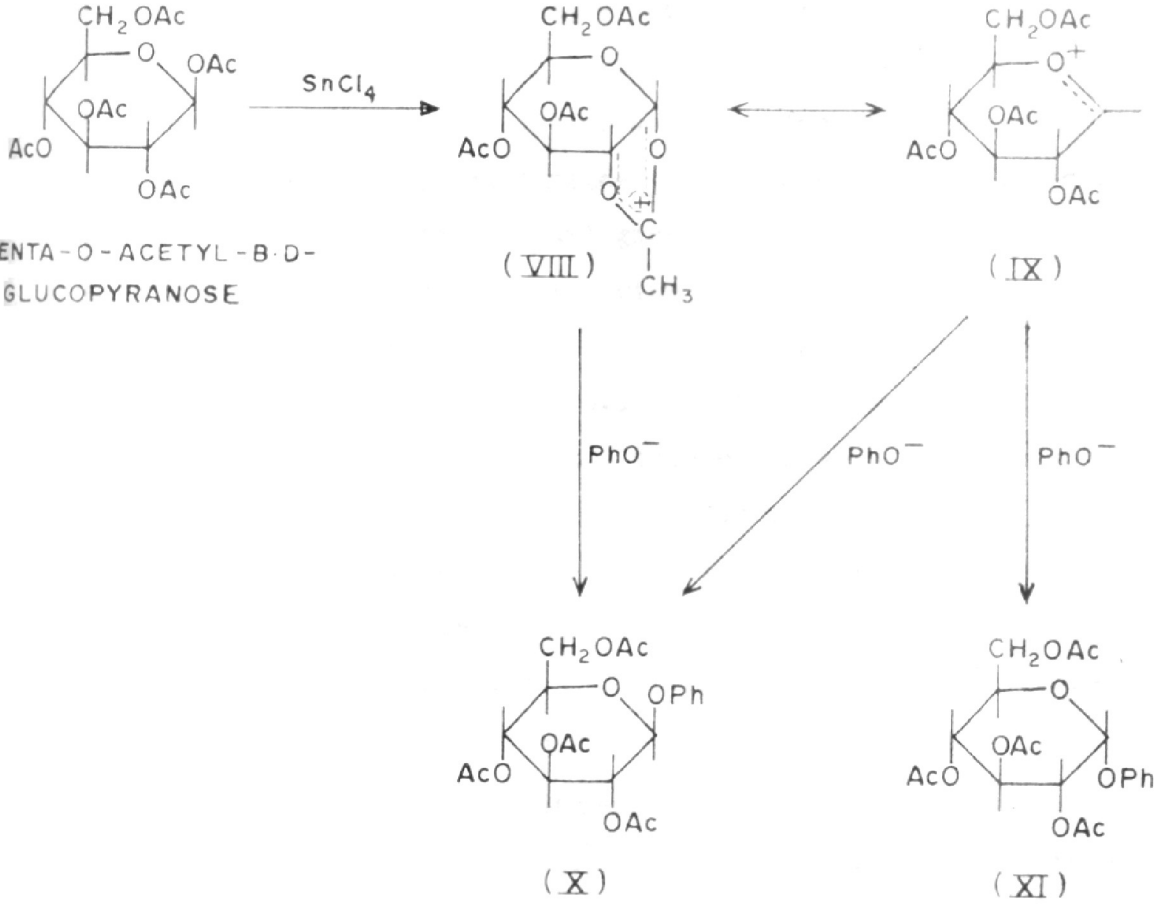


Fig. III-5, SYMMETRY RELATED ATOMS IN THE UNIT CELL (100)

One of the pathways suggested by Bose et al. for the formation of the α-anomer in this process, is through $SnCl_4$-catalysed anomerisation of the β-anomer, formed initially through the ion(VIII) by an intermolecular pathway in the presence of the added phenolic aglycone, whereas it had been established earlier that acid-catalysed anomerisation of acetylated alkyl glycosides takes place by an intramolecular process in which addition of the alcoholic aglycone is not necessary[13]. The formation of the α-anomer being an irreversible process, leads to a gradual accumulation of this stable anomer at the expense of the β-anomer.

Acid-catalysed anomerisation, however, is a relatively slow process and, therefore, cannot explain the appearance of appreciable quantities of the α-anomer at the early stages of the reaction as revealed by TLC studies. Therefore, an additional pathway for the early formation of the α-anomer has also been suggested by Bose et al.[12]. This involved the formation of the stabilized oxonium ion(IX) resulting from the elimination of the acetoxy anion at C-1. This ion (IX) may be regarded as the resonance hybrid of the ion (VIII). Ion (IX), on attack by a phenoxy anion has equal chances of conversion to either of the anomeric acetylated phenyl-D-glucosides (X) or (XI). In contrast, ion (VIII)


CH2OAc
OAc
AcO
OAc
SnCl4
PENTA-O-ACETYL-B-D-
GLUCOPYRANOSE
(VIII)
(IX)
PhO⁻
PhO⁻
PhO⁻
OPh
(X)
(XI)

would only give the β-anomer (X). Bose and co-workers[14] also observed that in this reaction, use of lesser quantities of the diluent (benzene) leads to a progressive increase in the relative quantity of the α-anomer formed. Thus, in a reaction with 10 millimoles of the acetylated sugar addition of only 5 ml of the diluent gives a reaction product containing mainly the α-anomer with little or none of the β-anomer. Under these conditions some degradation products are also formed. The formation of the anomer in large quantities under these conditions can probably be explained by the increase in the concentration of the reagents and catalyst by use of less of the diluent, which favours the anomerisation process. On the other hand, if the same reaction is carried out under dilute conditions using 50-300 ml of benzene more and more of the β-anomer is formed.

All these observations were made with respect to formation of acetylated aryl glycosides only. It was thought of interest to find out how far these observations apply for acetylated alkyl glycosides. In the course of the present work for the synthesis of the anomeric acetylated alkyl and arylalkyl glycosides encouraging results were obtained initially and the work was followed up exhaustively. The present chapter gives an account of the work carried out on the synthesis of acetylated alkyl α-D-glycosides. Conditions were also established for obtaining the β-anomers

in good yields.

The intramolecular nature of the anomerisation process of acetylated β-anomeric glycosides would indicate that only one mole of the alcoholic aglycone should be enough unlike that in the case of synthesis of acetylated aryl glycosides where the use of at least two moles of the phenol is necessary. But, in view of the recent finding of Sinha and Bose[15] that acetates of the aglycones are formed as by-products in this glycosidation reaction, the alcoholic aglycone was used in excess (2 moles) in all the reactions carried out in the course of the present work.

The conditions favourable for the synthesis of either of anomeric acetylated alkyl glycosides in reasonably good yields were established initially by TLC studies of several probing small scale reactions using various aliphatic alcohols. In the course of these studies, it was observed that the optimum periods required for completion of these reactions were not much different in either the dilute or the concentrated conditions. For example, most of the reactions showed optimum yields on an average between 13 to 18 minutes at the boiling water bath temperature. The small difference is likely to be the result of the slight differences in the relative reactivities of the aliphatic alcohols in relation to their chain lengths. The optimum

period of reaction for each alcohol was first established by a small scale probing experiment before the main reactions were carried out.

Aliquots of the probing reaction mixture were taken out at various intervals and examined by TLC. The eye estimates of the relative intensities of the spots of the anomeric acetylated glycosides and unreacted sugar acetate were found to be very near to the values obtained by densitometry. The reaction was usually stopped as soon as the spot for sugar acetate disappeared or even earlier if the period required for this to happen was long enough to cause degradation of the products causing reduction in overall yields of the acetylated glycosides.

The procedure was applied successfully for the preparation of the α- and β-anomers of methyl, n-butyl, n-hexyl and cetyl glycopyranosides. Though degradation products are formed in the reaction, the tetraacetates of the anomeric glycosides were obtained in reasonably good yields. The free glycosides were obtained from the pure acetates by Zemplen's method[16] as modified by Leaback[17] in almost quantitative yields. The completion of the deacetylation process was confirmed by TLC before working up the product.

The acetates of the α- and β-anomeric alkyl glycosides

and the corresponding free glycosides prepared in the course of the present work are listed in Tables (I) and (II) respectively.

TABLE 1

ALKYL TETRA-O-ACETYL GLYCOPYRANOSIDES PREPARED BY STANNIC CHLORIDE CATALYSED GLYCOSIDATION OF ALIPHATIC ALCOHOLS

Sl.No.	Aglycone part	m.p. °C	$[\alpha]_D$	Mol. formula	Analytical values FOUND % C	FOUND H	REQUIRED % C	REQUIRED H
				α-D-glucopyranosides				
1	Methyl	99-101 (101)	+140.3 (+134.4)	$C_{15}H_{22}O_{10}$	50.02	6.19	49.72	6.12[18]
2	*n-Butyl	syrup	+123.2	$C_{18}H_{28}O_{10}$	53.84	7.05	53.46	6.93
3	n-Hexyl	60-61 (61)	+118.8 (116.6)	$C_{20}H_{32}O_{10}$	55.46	7.51	55.54	7.46[19]
4	*Cetyl	48-49	119	$C_{30}H_{52}O_{10}$	63.19	9.32	62.94	9.09
				α-D-galactopyranosides				
5	Methyl	86-88 (86-87)	+139.4 (+132.5)	$C_{15}H_{22}O_{10}$	50.47	6.19	49.72	6.12[20]
				β-D-glucopyranosides				
6	Methyl	103-104 (104-105)	-21.5 (-22.1)	$C_{15}H_{22}O_{10}$	49.96	6.18	49.72	6.12[18]
7	n-Butyl	66-67 (65-66)	-26 (-26.8)	$C_{18}H_{28}O_{10}$	53.83	7.34	53.46	6.93[21]

....Contd.

TABLE 1 (Contd.)

Sl.No.	Aglycone part	m.p. °C	$[\alpha]_D$	Mol. formula	Analytical values			
					FOUND		REQUIRED	
					% C	H	% C	H
8	n-Hexyl	50-52 (51-52)	-24.6 (-22.4)	$C_{20}H_{32}O_{10}$	55.49	7.91	55.54	7.46[22]
9	Cetyl	74 (71-73)	-18 (-20.3)	$C_{30}H_{52}O_{10}$	63.04	9.19	62.94	9.09[23]
				β-D-galactopyranoside				
10	Methyl	94-96 (94)	-12.2 (-14.05)	$C_{15}H_{22}O_{10}$	49.83	5.39	49.72	6.12[24]

*New compounds

+Literature values are given in parenthesis.

TABLE 2

ALKYL GLYCOPYRANOSIDES PREPARED BY ZEMPLEN'S DEACETYLATION OF THE CORRESPONDING ACETYLATED ALKYL GLYCOSIDES (TABLE 1)

Sl.No.	Aglycone part	m.p. °C	$[\alpha]_D$	Mol. formula	Analytical values				Ref.
					FOUND		REQUIRED		
					% C	H	% C	H	
				α-D-glucopyranosides					
1	Methyl	164-166 (165-166)	+155.7 (+158.2)	$C_7H_{14}O_6$	43.96	7.67	43.29	7.27	18
2	n-Butyl	83-85 (86-87)	+136 (+135.4)	$C_{10}H_{20}O_6$	51.12	8.86	50.84	8.47	25
3	*n-Hexyl	68-70	+146.6	$C_{12}H_{24}O_6$ 1/2 H_2O	52.73	9.00	52.70	9.10	
4	*Cetyl	92	+84	$C_{22}H_{44}O_6$	65.00	11.06	65.34	10.90	
				α-D-galactopyranosides					
5	Methyl	107-109 (111)	+171.4 (+178.8)	$C_7H_{14}O_6$ H_2O	39.77	7.78	39.62	7.60	26
				β-D-glucopyranosides					
6	Methyl	108-109 (108-110)	-36 (-34.2)	$C_7H_{14}O_6$ 1/2 H_2O	41.26	7.46	41.38	7.39	18
7	n-Butyl	70-72 (68-69)	-33.9 (-36.9)	$C_{10}H_{20}O_6$	50.29	8.86	50.84	8.47	21
8	n-Hexyl	Syrup (90-92)	-26 (-34.5)	$C_{12}H_{24}O_6$	54.71	9.22	54.54	9.09	27

...Contd.

TABLE 2 (Contd.)

Sl.No.	Aglycone part	m.p. ^{o}C	$[\alpha]_D$	Mol. formula	Analytical values				Ref.
					FOUND		REQUIRED		
					% C	H	% C	H	
9	Cetyl	145-155 (110-145)	-21 (-22)	$C_{22}H_{44}O_6$	65.66	11.05	65.34	10.90	23
				β-D-galactopyranosides					
10	Methyl	178-180 (178-180)	-20 (+0.7)	$C_7H_{14}O_6$	42.88	7.19	43.29	7.27	28

*New compounds

+Literature values are given in parenthesis.

E X P E R I M E N T A L

General

All glycosidation reactions were carried out under anhydrous conditions and all evaporations of solvents were carried out under reduced pressure. Melting points were recorded on a Kofler block and uncorrected values are given. Optical rotations were determined with a Perkin-Elmer automatic Polarimeter, model 141. Densitometric studies were made with a Densitometer Model 52C of Photovolt Corporation fitted with automatic recorder, model 42B.

Thin-layer chromatography and Column Chromatography

Thin-layer chromatographic plates were prepared using silica gel G (E. Merck, Darmstadt) in the form of a slurry in water (1:2 w/v). The slurry was spread on glass plates (15 x 10 cm) with the help of an applicator. The plates were first dried in air and then activated by heating in an oven at 110° for 1 hr and were then cooled and preserved in a desiccator. Thin-layer chromatography was carried out in closed rectangular glass vessels containing the solvent system acetone-pet. ether (60-65°) (1:3 v/v). Developments were usually made up to the 10 cm mark from the base line but in cases of poor separations multiple developments were carried out upto the same mark, after drying the plates at the room temperature after each development. The spots

were visualised by spraying with sulphuric acid in methanol (10%) and heating in an oven at 110°. When necessary, the spots were temporarily visualised by putting the developed plates after air-drying in an iodine chamber. The mobilities of the anomeric acetylated glycosides and the starting acetylated sugar were found to be always in the following order:

acetylated α-D-glucoside > acetylated β-D-glycoside > acetylated sugar

Column chromatographic separations were made on column chromatography grade silica gel (prepared by Fine Chemicals Project of this laboratory). The columns were eluted with pet. ether (60-65°) containing gradually increasing quantities of acetone.

Reagents

Throughout this work pet. ether refers to the fraction having b.p. 60-65°. Pet. ether and acetone were distilled over potassium permanganate and dried over anhydrous potassium carbonate. Benzene used as a diluent in the glycosidation reactions was made thiophene free and then dried over sodium. Stannic chloride used as catalyst was anhydrous (fuming) and reagent grade. All solvents used for crystallisation were pure and redistilled. Absolute methanol was prepared from the usual 'absolute' methanol of commerce by treatment with magnesium and iodine following the standard procedure[29].

Penta-O-acetyl-β-D-glucopyranose and -galactopyranose were prepared by standard procedures[30,31] and their purity was checked by m.p. and TLC.

Probing experiments

All reactions were initially probed under the conditions established earlier for the synthesis of either of the anomeric acetylated aryl D-glycosides[14], to determine the optimum period for which a particular reaction should be carried out. These studies were made with 2 to 5 millimoles of the acetylated sugar and the progress of the reaction was followed by TLC. The laboratory-scale syntheses were then carried out under these optimum conditions.

Methyl 2,3,4,6-tetra O-acetyl-α-D-glucopyranoside

Dry methanol (0.8 ml, 20 m.moles) and stannic chloride (1.1 ml, 10 m.moles) were added to a stirred suspension of penta-O-acetyl-β-D-glucopyranose (3.9 g, 10 m.moles) and benzene (5 ml). The mixture was heated on a boiling water-bath with stirring for 15 minutes and cooled. The reaction products were then dissolved in benzene (150 ml) and the benzene solution was stirred with ice and water to decompose excess of stannic chloride. The benzene layer was separated, the aqueous layer was extracted with benzene (25 ml x 2) and the benzene extract was taken up with main benzene solution and washed in a separating funnel successively with water (25 x 2 ml), saturated aqueous sodium bicarbonate solution

(25 x 3 ml) and water (25 ml) and then dried over anhydrous sodium sulphate. The syrup obtained on removal of benzene showed mainly the α-anomer on TLC. It crystallised from methanol in colourless prisms m.p. 99-101°, $[\alpha]_D^{22}$ +140.3° (c, 1.0, $CHCl_3$). The yield of the pure material was 0.35 g (9.7%). Lit. m.p. 101°; $[\alpha]_D$ +134.4 ($CHCl_3$).

Found: C, 50.02; H, 6.19.

Calculated for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12%.

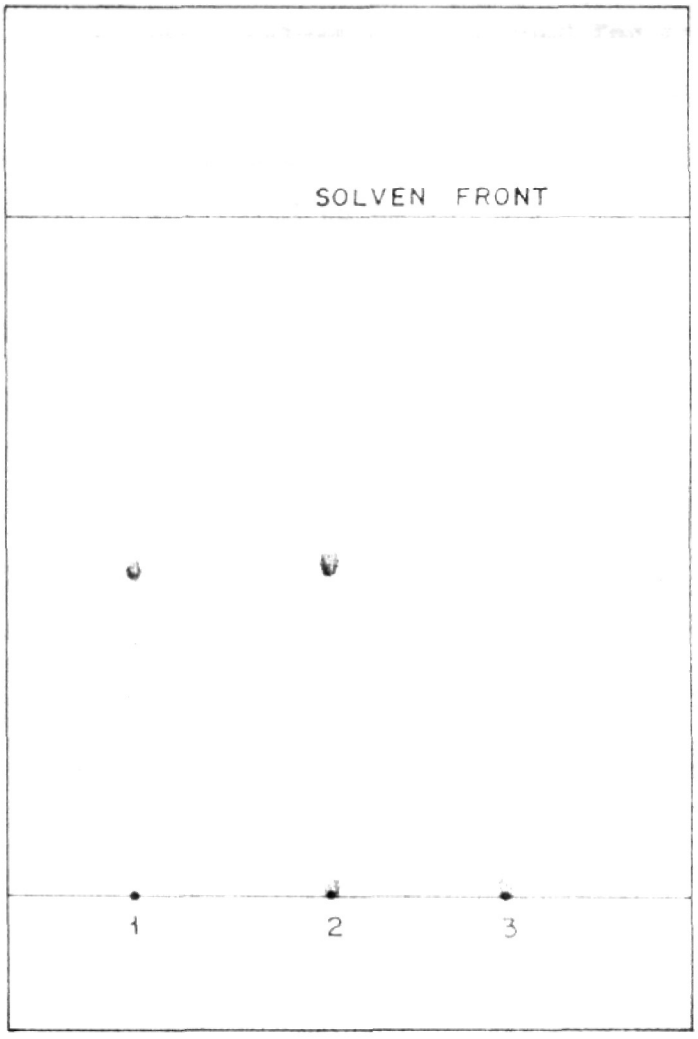
Methyl α-D-glucopyranoside

A solution of sodium methoxide (in absolute methanol 0.1 ml, 1%) was added to methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (0.225 g) and the mixture was shaken from time to time and left at the room temperature. After 1 hr TLC showed that the deacetylation was complete (TLC plate 1). The solution was then shaken with methanol - washed Amberlite IR-120 (H^+) resin (0.1 ml) and the resin was filtered off immediately after the solution became neutral. The residue obtained after removal of methanol from the filtrate, crystallised from ethanol in colourless prisms, m.p. 164-166°, $[\alpha]_D^{30}$ +155.7° (c, 1.0, H_2O). The yield was almost quantitative. Lit. m.p. 165-166°; $[\alpha]_D$ +158.2° (H_2O).

Found: C, 43.96; H, 7.67;

Calculated for $C_7H_{14}O_6$: C, 43.29; H, 7.27%.

T. L. C. PLATE 1



DEACETYLATION OF METHYL 2,3,4,6 TETRA-O-ACETYL-α-D-GLUCOPYRANOSIDE

1) METHYL 2,3,4,6 TETRA-O-ACETYL-α-D-GLUCOPYRANOSIDE

2) REACTION MIXTURE AFTER 15 MINUTES

3) REACTION MIXTURE AFTER 1 HOUR

Methyl 2,3,4,6-tetra-O.acetyl-β-D-glucopyranoside

This reaction was carried out with the same quantities of the reactants and catalyst as mentioned for the preparation of the α-anomer, except that a larger quantity of benzene (50 ml) was used as a diluent in the reaction. The optimum time of reaction was found to be 15 min. in this case also. The reaction product was worked out in the same manner as described earlier. The crude acetylated glucoside crystallised from methanol in colourless needles, m.p. 103-104°, $[\alpha]_D^{22}$ -21.5° (c, 1.0, $CHCl_3$). The yield of the pure material was 1.04 g (28.73%). Lit. m.p. 104-105°; $[\alpha]_D$ -26.8° ($CHCl_3$).

Found: C, 49.96; H, 6.18;

Calculated for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12%.

Methyl β-D-glucopyranoside

A solution of the above acetylated glucoside (0.247 g) was deacetylated in absolute methanolic solution with catalytic amounts of sodium methoxide in methanol as described earlier. In this case also the deacetylation was complete in 1 hr. The crude deacetylated product crystallised from methanol as a hemihydrate in colourless needles, m.p. 108-109°, $[\alpha]_D^{25}$ -36.0° (c, 1.0, EtOH). Lit. m.p. 108-110°; $[\alpha]_D$ -34.2° (EtOH). The yield was almost quantitative.

Found: C, 41.26; H, 7.46.

Calculated for $C_7H_{14}O_6$, 1/2 H_2O, C, 41.38; H, 7.39%.

n-Butyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside

n-Butanol (0.375 ml, 10 m.moles) and stannic chloride (0.55 ml, 5 m.moles) were added to a stirred mixture of penta-O-acetyl-β-D-glucopyranose (1.95 g, 5 m.moles) and benzene (2.5 ml). The reaction mixture was heated on a boiling water bath under stirring for 16 min. At this stage, TLC showed that the anomeric glycosides were formed in the proportion of α:β :: 3:1. Some unreacted glucose pentaacetate (a mixture of the anomers) were also seen on the plate. The reaction was stopped at this stage although it was not completed since heating for a further period caused considerable degradation of the glycosides already formed which would lead to a decrease in the overall yields (TLC, plate 2).

The reaction product was worked up in the same manner as described earlier for methyl tetra-O-acetyl-α-D-glucopyranoside. The crude product containing the acetylated anomeric glycosides and anomeric glucose pentaacetates along with degradation products was chromatographed on a silica gel column (65 cm) in a tube (85 x 2.3 cm). The silica gel was packed in a pet.ether slurry and the crude product dissolved in acetone-pet. ether (1:1) was applied at the top of the column and eluted with pet. ether containing increasing quantities of acetone. Fractions were collected as shown in Table 3. Each fraction was examined by TLC and combined accordingly. The combined fractions containing the pure

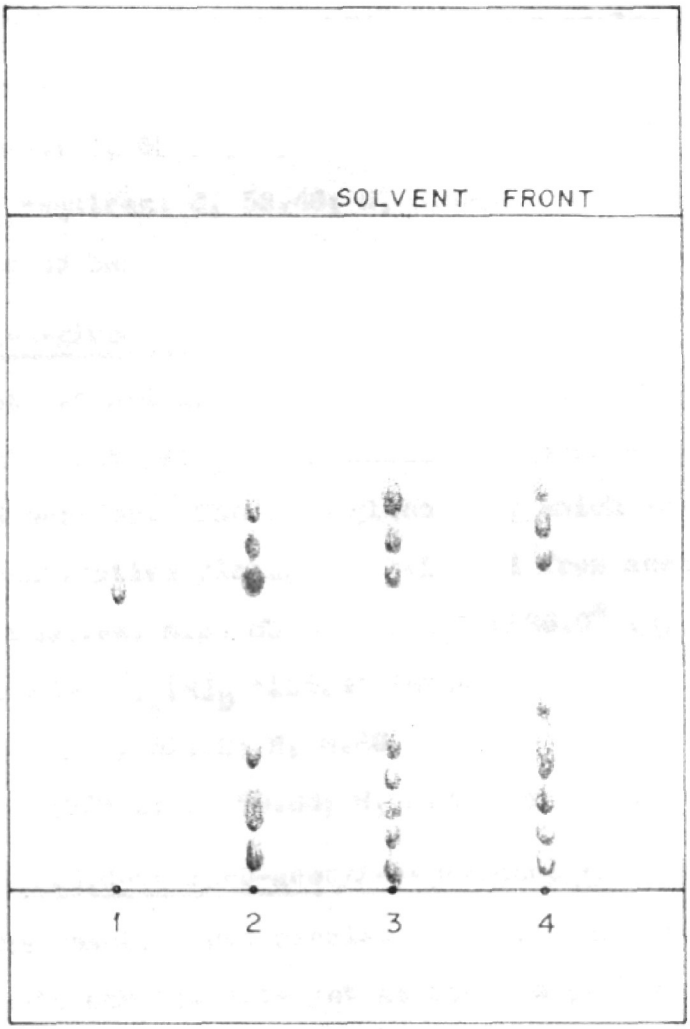
TABLE 3

COLUMN CHROMATOGRAPHIC SEPARATION OF n-BUTYL 2,3,4,6-TETRA-O-ACETYL-α-D-GLUCOPYRANOSIDE

Wt. of silica gel used .. 50 g Silica gel column length .. 65 cm Inner dia. of the column. 2.3 cm

Eluted fraction No.	Eluting solvent	Vol. of eluate (ml)	TLC picture	Weight (g)
1 - 3	Pet. ether	3 x 50	fast moving products traces.	-
4 - 7	Pet.ether-acetone (95:5)	4 x 100	n-butanol	-
8 - 13	Pet. ether-acetone (32.5: 7.5)	6 x 50	α	0.417
14 - 23	Pet. ether-acetone (90:10)	10 x 50	α + β (10:90)	0.125
24 - 28	""	5 x 50	β (traces)	-

T.L.C. PLATE 2



PROBING REACTION FOR THE PREPARATION OF n-BUTYL-2,3,4,6 TETRA-O-ACETYL-α-D-GLUCOPYRANOSIDE

1) PENTA-O-ACETYL-B-D-GLUCOPYRANOSE

2) REACTION MIXTURE AFTER 10 MINUTES HEATING

3) REACTION MIXTURE AFTER 16 MINUTES HEATING

4) REACTION MIXTURE AFTER 20 MINUTES HEATING

α-anomer was evaporated to a syrup and weighed. The yield was 0.417 g (28.9%). The product could not be crystallised. It had $[\alpha]_D^{25}$ +123.2° (c,1, EtOH). It was analysed as a syrup after drying in a vacuum desiccator over phosphorus pentoxide.

Found: C, 53.84; H, 7.05.

$C_{18}H_{28}O_{10}$ requires: C, 53.46; H, 6.93%.

This compound has not been reported in literature.

n-Butyl α-D-glucopyranoside

The tetra-O-acetyl derivative (syrup 0.3 g) was deacetylated with sodium methoxide in absolute methanol as described earlier. The free glucoside, which was obtained in almost quantitative yield, crystallised from acetone-pet.ether in small needles, m.p. 83-85°. $[\alpha]_D^{25}$ +136.0° (c, 0.5, EtOH). Lit. m.p. 86-87°; $[\alpha]_D$ +135.4° (EtOH).

Found: C, 51.12; H, 8.86.

$C_{10}H_{20}O_6$ requires: C, 50.84; H, 8.47 per cent.

n-Butyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

The reaction was carried out with the same quantities of reactants and the catalyst as for the preparation of the α-anomer. The volume of benzene used was 25 ml and period of heating was 16 min. TLC picture at this stage showed β:α :: 95:5 and some unreacted glucose pentaacetate. The reaction mixture was worked out in the same manner as described earlier and the crude reaction product was chromatographed on a silica gel

column (50 g of silica gel, 65 cm column length). The results of column chromatography are shown in Table 4. The yield of the pure β-anomer was 0.696 g (35.5%). The product crystallised from acetone-pet. ether in colourless prismatic needles, m.p. 66-67°. $[\alpha]_D^{25}$ -26.0° (c, 1.0, EtOH). Lit. m.p. 65-66°; $[\alpha]_D$ -26.8° (EtOH).

Found: C, 53.83; H, 7.34.

Calculated for $C_{18}H_{28}O_{10}$: C, 53.46; H, 6.93%.

n-Butyl β-D-glucopyranoside

The tetra-O-acetyl derivative (0.2 g) was deacetylated with sodium methoxide in methanol as described earlier. The yield was almost quantitative. The crude product crystallised from acetone in small colourless needles, m.p. 70-72°, $[\alpha]_D^{24}$ -33.9° (c, 0.5, EtOH). Lit. m.p. 68-69°. $[\alpha]_D$ -36.9° (EtOH).

Found: C, 50.29; H, 8.86.

Calculated for $C_{10}H_{20}O_6$: C, 50.84; H, 8.47%.

n-Hexyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside

The reaction was carried out with the same molar quantities of the reactants, catalyst and the diluent as for the preparation of methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside. The time for which the reaction was carried out on a boiling water bath was 16 min. The crude product, obtained by working up the reaction mixture as usual, crystallised from pet. ether in colourless short needles,

TABLE 4

COLUMN CHROMATOGRAPHIC SEPARATION OF n-BUTYL 2,3,4,6-TETRA-O-ACETYL-β-D-GLUCOPYRANOSIDE

Eluted fraction No.	Eluting solvent	Vol. of eluate (ml)	TLC picture	Wt.(g)
1 - 3	Pet. ether	3 x 50	fast moving products (traces)	-
4 - 5	Pet.ether-acetone (95:5)	2 x 80	fast moving products	-
6 - 7	Pet. ether-acetone (95:5)	2 x 80	fast moving products + α (traces)	-
8 - 13	Pet. ether-acetone (92:8)	6 x 50	β	0.696
14 - 16	Pet. ether-acetone (90:10)	3 x 50	β + glucose pentaacetate	0.06 g

m.p. 60-61°, $[\alpha]_D^{25}$ 118.8° (c, 1.0, $CHCl_3$). Lit. m.p. 61°. $[\alpha]_D$ 166.6° ($CHCl_3$). The yield was 0.95 g (36.0%).

Found: C, 55.46; H, 7.51.

Calculated for $C_{20}H_{32}O_{10}$: C, 55.54; H, 7.46%.

n-Hexyl α-D-glucopyranoside

The tetra-O-acetyl derivative (0.5 g) was deacetylated and worked up in the usual manner. The yield was good. The crude product crystallised as a hemihydrate from pet.ether at -10° in clusters of tiny colourless needles, m.p. 68-70°, $[\alpha]_D^{33}$ 146.6° (c, 1.0, EtOH). This product has not been reported in literature.

Found: C, 52.73; H, 9.00.

$C_{12}H_{24}O_6$, 1/2 H_2O requires: C, 52.70; H, 9.10 per cent.

n-Hexyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

The reaction was carried out with the same molar quantities of the reactants and the catalyst as for the preparation of methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside. The diluent (benzene) used in this reaction was 50 ml. The period of heating on a boiling water bath was 16 min. The crude product, obtained on working up the reaction mixture as usual, crystallised from acetone-pet. ether in needles, m.p. 50-52°, $[\alpha]_D^{24}$ -24.6° (c, 1.2, $CHCl_3$). Lit. m.p. 51-52°. $[\alpha]_D$ -22.4° ($CHCl_3$). The yield was 1.7 g (39.3%).

Found: C, 55.49; H, 7.91.

Calculated for $C_{20}H_{32}O_{10}$: C, 55.54; H, 7.46%.

n-Hexyl β-D-glucopyranoside

The tetra-O-acetyl derivative on deacetylation and working up in the usual manner gave the free glycoside in almost quantitative yield. It was obtained in the form of syrup which failed to crystallise. $[\alpha]_D^{34}$ -26.0° (c, 2.0, EtOH).

Found: C, 54.71; H, 9.22.

Required for $C_{12}H_{24}O_6$, H_2O: C, 54.54; H, 9.09%.

The product is described in literature as crystalline (without water of crystallisation) m.p. 30-32°, $[\alpha]_D$ 34.5° (water).

Cetyl 2,3,4,6 tetra-O-acetyl-α-D-glucopyranoside

The reaction was carried out as usual with penta-O-acetyl-β-D-glucopyranose (10 m. moles). The period of heating on a boiling water bath was 18 min. in this case. The crude product obtained by working up the reaction mixture in the usual way was 6.2 g and consisted of a mixture of unreacted cetyl alcohol (iodine chamber), the acetates of the anomeric cetyl glucosides (α:β:: 5:2), traces of unreacted glucose pentaacetate and some fast and slow-moving spots (TLC plate 3). The product was chromatographed on a silica gel column (silica gel 50 g, column length 65 cm). The results of column chromatography is shown in Table 5. The yield of the pure α-anomer fraction was 1.24 g (21.6%) (some more was in the mixture). The pure acetylated α-anomer crystallised from pet. ether in colourless needles m.p. 48-49°, $[\alpha]_D^{30}$ +119° (c, 1.0, EtOH). This compound has not been reported in

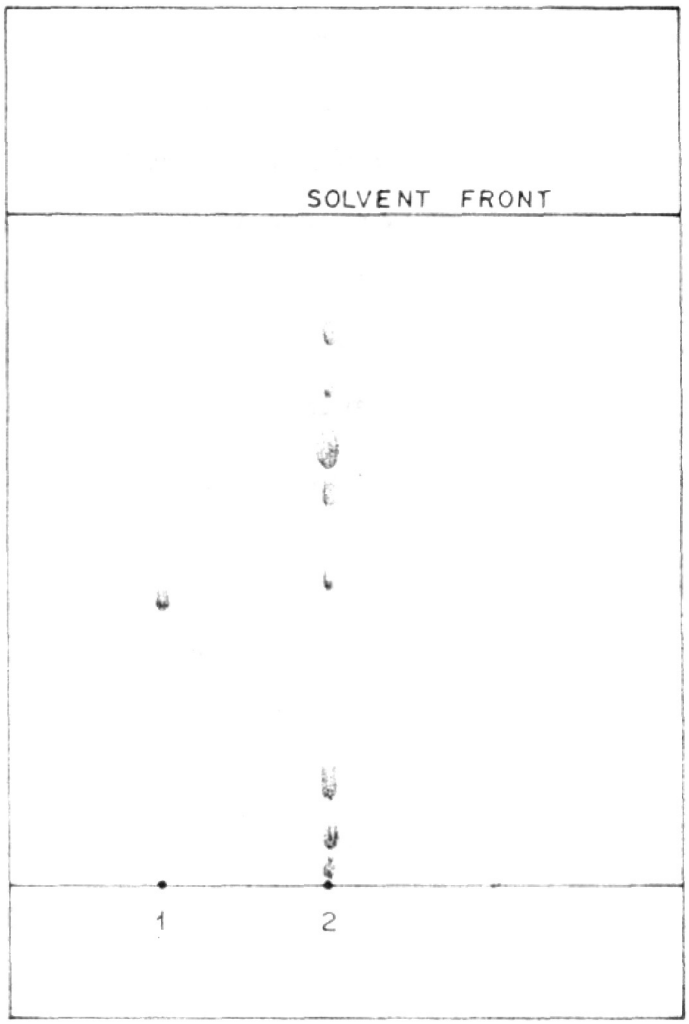
TABLE 5

COLUMN CHROMATOGRAPHIC SEPARATION OF CETYL 2,3,4,6 TETRA-O-ACETYL α-D-GLUCOPYRANOSIDE

Eluted fraction No.	Eluting solvent	Vol. of eluate (ml)	TLC picture	Wt.(g)
1 - 2	Pet.ether - acetone (95:5)	2 x 250	no spot	-
3 - 4	Pet.ether-acetone (90:10)	2 x 50	fast moving compound.	0.04
5 - 9	" "	2 x 25	cetyl alcohol and α-glucoside (90:10)	0.05
10 - 20	" "	11 x 50	α-glucoside	1.24
21 - 22	" "	2 x 50	α- and β-glucosides (1:1)	0.02
23 - 25	" "	2 x 100	β-glucoside and glucose penta-acetate (90:10)	0.35

The slower moving decomposition products were not eluted out.

T.L.C. PLATE 3



PREPARATION OF CETYL 2,3,4,6 TETRA-O-ACETYL-α-D-GLUCOPYRANOSIDE

1) PENTA-O-ACETYL-β-D-GLUCOPYRANOSE

2) REACTION MIXTURE AFTER 18 MINUTES

Cetyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside

The reaction was carried out as usual with 10 m.moles of penta-O-acetyl-α-D-glucopyranose using 50 ml of benzene as diluent. The reaction mixture was heated on a boiling water bath for 18 min. The reaction product was worked out as usual. The crude product (6.22 g) containing fast moving products, unreacted cetyl alcohol, the anomeric acetylated glucosides (α:β:: 3:7), the unreacted glucose pentaacetate and some slow moving degradation products was chromatographed on a silica gel column (silica gel 50 g, column length 65 cm). The crude product, dissolved in 1:1 acetone-pet. ether (7 ml) was applied at the top of the column and eluted with increasing concentrations of acetone in pet. ether. The results of the column chromatography are shown in Table 6. The yield of the pure α-anomer fraction from the column was 1.25 g (21.8%). The pure acetylated α-anomer crystallised from pet. ether in colourless long needles, m.p. 74°, $[\alpha]_D^{25}$ -18° (c, 0.5, EtOH). Lit. m.p. 71.73°. $[\alpha]_D$ -20.9° (EtOH).

Found: C, 63.04; H, 9.19.

Calculated for $C_{30}H_{52}O_{10}$: C, 62.94; H, 9.09%.

Cetyl β-D-glucopyranoside

The tetra-O-acetyl derivative (0.12 g) was deacetylated in the usual manner and the crude deacetylated product was obtained in good yields. It crystallised from methanol in colourless prisms. The crystals soften at 88° and melts between 145° and 155°. (Lit.[23] softens at 78° and melts between

Cetyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside

The reaction was carried out as usual with 10 m.moles of penta-O-acetyl-α-D-glucopyranose using 50 ml of benzene as diluent. The reaction mixture was heated on a boiling water bath for 18 min. The reaction product was worked out as usual. The crude product (6.22 g) containing fast moving products, unreacted cetyl alcohol, the anomeric acetylated glucosides (α:β:: 3:7), the unreacted glucose pentaacetate and some slow moving degradation products was chromatographed on a silica gel column (silica gel 50 g, column length 65 cm). The crude product, dissolved in 1:1 acetone-pet. ether (7 ml) was applied at the top of the column and eluted with increasing concentrations of acetone in pet. ether. The results of the column chromatography are shown in Table 6. The yield of the pure α-anomer fraction from the column was 1.25 g (21.8%). The pure acetylated α-anomer crystallised from pet. ether in colourless long needles, m.p. 74°, $[\alpha]_D^{25}$ -18° (c, 0.5, EtOH). Lit. m.p. 71.73°. $[\alpha]_D$ -20.9° (EtOH).

Found: C, 63.04; H, 9.19.

Calculated for $C_{30}H_{52}O_{10}$: C, 62.94; H, 9.09%.

Cetyl β-D-glucopyranoside

The tetra-O-acetyl derivative (0.12 g) was deacetylated in the usual manner and the crude deacetylated product was obtained in good yields. It crystallised from methanol in colourless prisms. The crystals soften at 88° and melts between 145° and 155°. (Lit.[23] softens at 78° and melts between

TABLE 6

COLUMN CHROMATOGRAPHIC SEPARATION OF CETYL 2,3,4,6-TETRA-O-ACETYL-β-D-GLUCOPYRANOSIDE

Eluted fraction No.	Eluting solvent	Vol. of eluate (ml)	TLC picture	Wt.(g)
1 - 6	Pet.ether-acetone (95:5)	6 x 100	No spot	-
7 - 9	Pet.ether-acetone (90:10)	3 x 50	fast moving spots	0.05
10	"	1 x 30	cetyl alcohol	0.036
11 - 15	"	5 x 25	α-glucoside	0.25
16	"	1 x 25	α + β-glucosides (20:80)	0.30
17 - 22	"	6 x 75	β-glucoside	1.25
23 - 25	Pet.ether-acetone (85:15)	3 x 50	glucose penta-acetate	Traces

110° and 145°), Lit. $[\alpha]_D$ -22° (EtOH), $[\alpha]_D^{25}$ -21.0° (c, 1.0, EtOH).

Found: C, 65.66; H, 11.05.

Calculated for $C_{22}H_{44}O_6$: C, 65.34; H, 10.90%.

Methyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside

This reaction was carried out with penta-O-acetyl-β-D-galactopyranose (3.9 g, 10 m.moles) and corresponding quantities of methanol and $SnCl_4$ as mentioned in the earlier reactions. Benzene (5 ml) was used as a diluent. The reaction was carried out for 15 min. and the products were worked out as usual. The crude product crystallised from acetone-pet. ether in colourless needles m.p. 86-88°, $[\alpha]_D^{30}$ +139.4° (c, 0.36, $CHCl_3$). Lit. m.p. 86-87°; $[\alpha]_D$ +132.5° ($CHCl_3$). The yield was 0.76 g (20.9%).

Found: C, 50.47; H, 6.19.

Calculated for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12%.

Methyl α-D-galactopyranoside

The tetra-O-acetyl derivative (0.4 g) was deacetylated in the usual manner. The crude free glycoside obtained in excellent yields crystallised from methanol as a monohydrate in prisms, m.p. 107-109°, $[\alpha]_D^{30}$ 171.4° (c, 0.1, EtOH). Lit. m.p. 111° (hydrate), $[\alpha]_D$ 175.5° (EtOH).

Found: C, 39.77; H, 7.78.

Calculated for $C_7H_{14}O_6$, H_2O, C, 39.62; 7.60%.

Methyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside

The reaction was carried out with penta-O-acetyl-β-D-galactopyranose (3.9 g, 10 m.moles) under dilute conditions (benzene 50 ml). The crude product, obtained by working up the reaction mixture in the usual manner, crystallised from acetone-pet.ether in colourless needles, m.p. 94-96°, $[\alpha]_D^{30}$ -12.2°; (c, 0.5, $CHCl_3$). Lit. m.p. 94°; $[\alpha]_D$ -14.05° ($CHCl_3$). The yield was 0.612 g (16.8%).

Found: C, 49.83; H, 5.39.

Calculated for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12%.

Methyl β-D-galactopyranoside

The tetra-O-acetyl derivative (0.4 g) was deacetylated in the usual way. On crystallisation of the crude product from ethanol the pure free galactoside was obtained in needles, m.p. 178-80°, $[\alpha]_D^{20}$ -20.0° (c, 0.2, EtOH). Lit. m.p. 178-180°, $[\alpha]_D$ +0.7° (H_2O).

Found: C, 42.88; H, 7.19.

Calculated for $C_7H_{14}O_6$: C, 43.29; H, 7.27%.

REFERENCES

1 Helferich, B and Schmitz-Hillebrecht, E, Ber. 66 (1933),378.

2 Fischer, E, Ber. 26 (1893), 2400.

2A Koenigs, W. and Knorr, Ber. 34 (1901), 957.

3 Pacsu, E, Ber. 58 (1925), 509.

4 Pacsu, E, Ber. 61 (1928), 137, 1508.

5 Wolfrom, M.L., and Gillman, I.C., J. Org. Chem. 26 (1961), 3564.

6 Bourquelot, E and Verdon E, J. Pharm. Chim. 8 (1913), 19; C.A. 8(1914), 1131.

7 Manners, D.J., Pennie, I.R. and Stark, J.R., Carbohyd. Res. 7 (1968), 2911.

8 Helferich, B., and Johannis, J., Ann. 632(1910), 121.

9 Miller, J.M. and Wing, R.E., Carbohyd. Res. 10(1969), 448.

10 Lemieux, R.U. and Shyluk, W.P., Canad. J. Chem. 31(1953), 528.

11 Bose, J.L. and Ingle, T.R., Chem. Ind. (1967), 451.

12 Audichya, T.D., Ingle, T.R. and Bose, J.L., Ind. J. Chem. (In press).

13 Lemieux, R.U., Brice, C and Huber G., Canad. J.Chem. 33 (1955), 134.

14 Audichya, T.D., Ingle T.R., and Bose J.L., Indian J. Chem. 9 (1971), 315.

15 (Mrs) Sinha (nee Bose) Bharati and Bose J.L., Unpublished work.

16 Zemplen, G. and Pacsu, E., Ber. 62(1929), 1613.

17 Leeback D.H., J. Chem. Soc. (1960), 3166.

18 Isbell, H.S., J. Research Natl. Bur Standards 8(1932), 1.

19 Pacsu, E., J. Am. Chem. Soc. 52(1930), 2563.

20 Micheel, F, and Littmann, O., Ann. 466(1928), 115.

21 Kreider L.C. and Friesen, E., J.Am. Chem. Soc. 64(1942), 1482.

22 Noller, C.R. and Rockwell, W.C., J. Am. Chem. Soc. 60(1938), 2076.

23 Fischer, E. and Helferich, B., Ann. 383 (1911), 68-69.

24 Bourquelot E., Ann. Chem.[9], 7(1917), 218.

25 Pigmann W.W. and Laffre, R.O., J. Am.Chem. Soc. 73(1951), 4884.

26 Pacsu, E. and Ticharich, N., Ber. 62(1929), 3008.

27 Pigmann, W.W. and Richtmyer, N.K., J.Am.Chem.Soc. 64(1942), 369.

28 Miller, E., Ber. 64(1931), 1820.

29 Vogel, A.I.,"Rractical Organic Chemistry" III Edition, 1957, 169-170, Longmans Green and Co.

30 Vogel, A.I., "Practical Organic Chemistry" III Edition, 1957, 452, Longmans Green and Co.

31 Whistler, R.L. and Wolfrom, M.L., "Methods in Carbohydrate Chemistry" Vol.1, 1963, 122, Academic Press Inc. New York.

CHAPTER III

STANNIC CHLORIDE CATALYSED SYNTHESIS OF ARYL ALKYL GLYCOSIDES

STANNIC CHLORIDE CATALYSED SYNTHESIS OF ARYL ALKYL GLYCOSIDES

INTRODUCTION

Aryl alkyl alcohols like phenyl ethyl and phenyl propyl alcohols are able to inhibit the production of DNA viruses but not the reproduction of RNA viruses in tissue culture. Both phenyl ethyl- and phenyl propyl alcohols have high toxicity for tissue culture and, therefore these alcohols cannot be administered directly for these studies. It has been found recently[1] that certain glycosides and glucuronides of these aryl alkyl alcohols possess lower toxicity than that of the free alcohols. The use of the virus-inhibiting aryl alkyl alcohols in the form of their glycosides has made it possible for the active component alcohols to be brought into the cell in a non-toxic form to be liberated by hydrolysis *in situ* by the cell enzymes.

In view of these recent observations about the useful applications of glycosides of aryl alkyl alcohols and also in view of the successful use of anhydrous stannic chloride as a catalyst for the glycosidation of aliphatic alcohols to obtain either of the anomeric glycosides depending on the conditions of reaction as detailed in Chapter II, we were encouraged to extend the use of this reagent for the glycosidation of aryl alkyl alcohols. In this Chapter, an account is given of successful syntheses of

six pairs of anomeric acetylated aryl alkyl glycosides in good yields. Of these twelve acetylated aryl alkyl glycosides five are new compounds. These glycosides are listed in Table I.

All of these acetylated glycosides were deacetylated by Zemplen's method to obtain the corresponding free aryl alkyl glycosides in almost quantitative yields. Six of these free aryl alkyl glycosides are new. The three hemihydrates of benzyl β-D-glucopyranoside, benzyl β-D-galactopyranoside and phenylpropyl β-D-galactopyranoside obtained in the course of this work are also new compounds and have not been described in literature. These free aryl alkyl glycosides are listed in Table II.

Among the aryl alkyl alcohols used in these experiments, benzyl and phenyl ethyl alcohols were chemically pure products (E.Merck) and were further purified by distillation under reduced pressure. Phenyl propyl alcohol was prepared by the reduction of cinnamyl alcohol with sodium and ethanol[5].

These studies have thus established the versatility of anhydrous stannic chloride as a catalyst for the glycosidation of not only phenols, but also of aliphatic and aryl alkyl alcohols. Moreover, either of the anomers in all these cases can be obtained as the major product by selecting proper conditions as detailed in the experimental part.

Aryl alkyl tetra-O-acetyl-D-glycopyranosides

Sl.No.	Aglycone part	m.p. °C	$[\alpha]_D$	Mol. formula	Analytical values Found % C	Found H	Required % C	Required H	Ref.
			α-D-gluconpyranosides						
1	Benzyl	112 (111)	+140 (+143)	$C_{21}H_{26}O_{10}$	57.89	6.12	57.53	5.94	2
2	*Phenylethyl	126	+133.0	$C_{22}H_{28}O_{10}$	58.52	6.32	58.41	6.19	-
3	*Phenylpropyl	50-51	+129.3	$C_{23}H_{30}O_{10}$	59.24	6.54	59.23	6.43	-
			α-D-galactopyranosides						
4	*Benzyl	107	+166	$C_{21}H_{26}O_{10}$	57.37	5.99	57.53	5.94	-
5	*Phenylethyl	94	+147.74	$C_{22}H_{28}O_{10}$	58.60	6.32	58.41	6.19	-
6	*Phenylpropyl	134-35	+150	$C_{23}H_{30}O_{10}$	59.43	6.63	59.23	6.43	-

*New compound

Lit. m.p. and $[\alpha]_D$ values are given in parenthesis.

TABLE 1 (Contd.)

Sl.No.	Aglycone part	m.p. °C	$[\alpha]_D$	Mol. formula	Analytical values Found % C	Found H	Required % C	Required H	Ref.
			β-D-glucopyranosides						
7	Benzyl	101 (96-101)	-48 (-48)	$C_{21}H_{26}O_{10}$	57.92	6.11	57.53	5.94	2
8	Phenylethyl	73-74 (72-73)	-18 (-19.2)	$C_{22}H_{28}O_{10}$	58.66	6.32	58.41	6.19	3
9	Phenylpropyl	81-82 (79-80)	-20.3 (-13.1)	$C_{23}H_{30}O_{10}$	58.98	6.62	59.23	6.43	3
			β-D-galactopyranosides						
10	*Benzyl	syrup	-32.0	$C_{21}H_{26}O_{10}$	57.59	6.20	57.53	5.94	-
11	*Phenylethyl	88-89	-26.4	$C_{22}H_{28}O_{10}$	58.66	6.27	58.41	6.19	-
12	*Phenylpropyl	syrup	-24.7	$C_{23}H_{30}O_{10}$	58.98	7.01	59.23	6.43	-

*New compound.

Lit. m.p. and $[\alpha]_D$ values are given in paranthesis.

TABLE 2

Aryl alkyl-D-glycopyranosides

Sl.No.	Aglycone part	m.p. °C	$[\alpha]_D$	Mol. formula	Analytical values Found % C	Found H	Required % C	Required H	Ref.
				α-D-glucopyranosides					
1	Benzyl	124 (122)	138 (+131)	$C_{13}H_{18}O_6$	57.40	7.00	57.78	6.67	2
2	*Phenylethyl	65	+164	$C_{14}H_{20}O_6H_2O$	55.68	7.40	55.63	7.28	-
3	*Phenylpropyl	syrup	+88.28	$C_{15}H_{22}O_6$	60.42	8.01	60.40	7.38	-
				α-D-galactopyranosides					
4	*Benzyl	syrup	+135.6	$C_{13}H_{18}O_6$	57.33	7.02	57.78	6.67	-
5	*Phenylethyl	syrup	+53.71	$C_{14}H_{20}O_6$, 1/2 H_2O	57.60	7.51	57.92	7.21	-
6	*Phenylpropyl	75-77	+143	$C_{15}H_{22}O_6$	60.00	7.64	60.40	7.38	-

*New compound

Literature m.p. and $[\alpha]_D$ are given in parathesis.

TABLE 2 (Contd.)

Sl.No.	Aglycone part	m.p. °C	$[\alpha]_D$	Mol. formula	Analytical values Found % C	Found H	Required % C	Required H	Ref.
				α-D-glucopyranosides					
1	Benzyl	124 (123-125)	-52 (-55.8)	$C_{13}H_{18}O_6$	57.40	7.00	57.78	6.67	2
	*Benzyl (hemihydrate)	94		$C_{13}H_{18}O_6$, 1/2 H_2O	56.62	6.80	56.59	6.81	-
2	Phenylethyl	121-122 (120-122)	-34 (-36.0)	$C_{14}H_{20}O_6$	58.68	7.10	59.16	7.04	1
3	Phenylpropyl	99-100 (100-107)	-24.57 (-27.3)	$C_{15}H_{22}O_6$	60.55	7.61	60.40	7.38	-
				α-D-galactopyranosides					
4	*Benzyl hemihydrate	85-90	-91.3	$C_{13}H_{18}O_6$, 1/2 H_2O	55.56	7.01	55.91	6.81	-
	Benzyl (anhydrous)	(119)	(-29.5)	$C_{13}H_{18}O_6$					4
5	*Phenylethyl	107-108	-33.94	$C_{14}H_{20}O_6$	58.49	7.22	59.16	7.04	-
6	*Phenylpropyl	syrup	-5.3	$C_{15}H_{22}O_6$, 1/2 H_2O	58.90	7.19	58.68	7.49	-
	Phenylpropyl (anhydrous)	120-122	-6.4	$C_{15}H_{22}O_6$					1

*New compound.
Literature m.p. and $[\alpha]_D$ values are given in paranthesis.

E X P E R I M E N T A L

Benzyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside

Penta-O-acetyl-β-D-glucopyranose (3.9 g, 10 m.moles) was stirred in benzene (2.5 ml) and to this mixture was added stannic chloride (1.1 ml, 10 m.moles) and benzyl alcohol (2.0 ml, 20 m.moles). The mixture was heated on a boiling water bath under reflux for 15 min. under stirring. The reaction mixture was then cooled, diluted with benzene (100 ml) and then stirred with ice and water to decompose excess of stannic chloride. The benzene layer was separated and the aqueous layer was washed with benzene (2 x 25 ml) and taken up with the main benzene layer. The total benzene solution was washed successively with water, sodium bicarbonate solution (5%) and water, and was then dried over anhydrous sodium sulphate. The syrupy material obtained on stripping of the solvent was chromatographed on a silica gel column as detailed in Table 3. The acetylated α-glucoside fraction obtained from the column (1.51 g) was crystallised from dilute methanol, when the pure product was obtained in colourless prismatic needles, m.p. 112°, $[\alpha]_D^{29}$ 140.0° (c, 0.5, MeOH), lit.[2] m.p. 111°, $[\alpha]_D$ +143° ($CHCl_3$). The yield was 1.51 g (38.8%).

Found: C, 57.89; H, 6.12. Required for $C_{21}H_{26}O_{10}$, C, 57.53; H, 5.94 per cent.

TABLE 3

Column Chromatographic separation of benzyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside.

Wt. of silica gel .. 80 g
Length of silica gel column .. 66 cm
Inner diameter of the column .. 2.5 cm.

Eluted fraction Nos.	Eluting solvent (Acetone: Pet.ether)	Volume of eluate (ml)	TLC data	Wt.(g)
1 - 11	5:95	11 x 50	fast moving compound	-
12 - 17	10:90	6 x 50	α-anomer	1.51
18 - 19	"	2 x 50	α + β (1:1)	-
20 - 21	"	2 x 50	β-anomer	-
22 - 23	"	2 x 50	no spot	-

Benzyl α-D-glucopyranoside

The tetra-O-acetyl derivative (0.15 g) was deacetylated with catalytic amounts of sodium methoxide in absolute methanol. The completion of deacetylation (2 hr) was followed by TLC. The solution was then decationised with a small quantity of Amberlite IR-120 (H^+) and filtered as soon as its alkalinity disappeared. The syrup obtained on removal of methanol crystallised from ether-pet.ether containing a little methanol to give the pure glucoside in colourless long needles, m.p. 124°, $[\alpha]_D^{25}$ +138° (c, 0.5, EtOH). Lit.[1] gives m.p. 122°, $[\alpha]_D^{35}$ +131°. The yield was almost quantitative.

Found: C, 57.40; H, 7.00. Calculated for $C_{13}H_{18}O_6$, C, 57.78; H, 6.67per cent.

Benzyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

The β-anomer was prepared with the same quantities of reactants and the catalyst using more of benzene (50 ml) as the diluent. The optimum period of reaction was 15 min. (under reflux) in this case also. The crude product, obtained in the usual manner was chromatographed on a silica gel column as detailed in Table 4. The chromatographed acetylated β-D-glucoside fraction (1.72 g), crystallised from ether-pet. ether to give the pure product in colourless needles, m.p. 101°, $[\alpha]_D^{28}$ -48.0° (c, 0.5, EtOH). Lit.[2] gives m.p. 96-101°, $[\alpha]_D$ -48° (EtOH). The yield was 38.8%.

TABLE 4

Column chromatographic separation of benzyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

Column data: same as in Table 3.

Eluted fraction Nos.	Eluting solvent (acetone:pet.ether)	Volume of eluate (ml)	TLC data	Wt.(g)
1 - 7	5 : 95	7 x 50	No spot	-
8 - 9	8 : 92	2 x 50	α + β	-
10 - 19	10 : 90	10 x 50	β	1.72
20 - 21	10 : 90	2 x 50	no spot	-

Found: C, 57.92; H, 6.11; Calculated for $C_{21}H_{26}O_{10}$, C, 57.53; H, 5.94 per cent.

Benzyl α-D-glucopyranoside

The tetra-O-acetyl derivative (0.15 g) was deacetylated in the usual manner. The syrup obtained on removal of methanol crystallised from ether in soft colourless needles m.p. 124° (softens earlier), $[\alpha]_D^{35}$ -52° (c, 0.5, EtOH). Literature[2] gives m.p. 123-125°, $[\alpha]_D^{20}$ -55.8° (H_2O). The yield was almost quantitative.

Found: C, 57.40; H, 7.00. Calculated for $C_{13}H_{18}O_6$, C, 57.78; H, 6.67 per cent.

A part of the syrup was crystallised from methanol-ether-pet.ether when a hemihydrate of the glycoside was obtained in colourless long slender needles, m.p. 94°.

Found: C, 56.62; H, 6.80. $C_{13}H_{18}O_6$ 1/2 H_2O requires: C, 56.59; H, 6.81 per cent.

This compound has not been described in literature.

Phenyl ethyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside

This reaction was carried out with the same quantities of the reactants, catalyst and diluent as described in the synthesis of benzyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside described earlier except that more of benzene (5 ml) was used here. Period of heating was 15 min. in this case also. The crude reaction product obtained by working up of the reaction mixture, crystallised in colourless prismatic needles

from methanol, m.p. 126°C, $[\alpha]_D^{26}$ +133° (c, 0.5, EtOH). The yield was 1.81 g (39.9%).

Found: C, 58.52; H, 6.32. $C_{22}H_{28}O_{10}$ requires: C, 58.41; H, 6.19 per cent.

This compound has not been reported in literature.

Phenyl ethyl α-D-glucopyranoside

The tetra-O-acetyl derivative (0.2 g) was deacetylated in the usual manner to obtain the free glycoside almost quantitatively. It crystallised from acetone-pet. ether as a monohydrate, in long needles, m.p. 65°, $[\alpha]_D^{24}$ +164° (c, 0.5, EtOH).

Found: C, 55.68; H, 7.40. $C_{14}H_{20}O_6$, H_2O requires: C, 55.63; H, 7.28 per cent.

This compound has not been described in literature.

Phenyl ethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

This reaction was carried out with the same quantities of the reactants, and catalyst and under the same conditions as described in the case of benzyl tetra-O-acetyl-β-D-glucopyranoside except that more of benzene (175 ml) was used. The crude product showed the presence of a substantial quantity of the α-anomer. It was chromatographed on a silica gel column as described in Table 5. The pure acetylated-β-glucoside fraction obtained from the column (1.13 g) was crystallised from a mixture of ether and pet. ether to obtain the pure acetylated glucoside in colourless prismatic rods,

TABLE 5

Column chromatographic separation of phenylethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

Column data: Same as in Table 3

Eluted fraction Nos.	Eluting solvents (acetone: Pet.ether)	Volume of eluate (ml)	TLC data	Wt.(g)
1 - 4	5 : 95	4 x 50	no spot	-
5 - 8	10 : 90	4 x 100	α	0.35
9 - 12	20 : 80	4 x 50	α + β (1:1)	0.31
13 - 16	20 : 80	4 x 100	β	1.13
17 - 18	20 : 80	2 x 100	no spot	-

m.p. 73-74°, $[\alpha]_D$ -18° (c, 0.4, $CHCl_3$). Lit.[3] gives m.p. 72-73°, $[\alpha]_D$ -19.2° ($CHCl_3$). The yield of the material was 24.8%.

Found: C, 58.66; H, 6.32. Calculated for $C_{22}H_{28}O_{10}$: C, 58.41; H, 6.19 per cent.

Phenyl ethyl β-D-glucopyranoside

The tetra-O-acetyl derivative (0.25 g) was deacetylated by Zemplen's method. The yield was good. The deacetylated product crystallised from acetone-pet.ether in colourless fine needles, m.p. 121-122°, $[\alpha]_D^{33}$ -34° (c, 0.5, H_2O). Lit.[1] gives m.p. 120-122°, $[\alpha]_D^{22}$ -36° (H_2O).

Found: C, 58.68; H, 7.10. Calculated for $C_{14}H_{20}O_6$: C, 59.16; H, 7.04 per cent.

Phenyl propyl alcohol

Freshly cut sodium (40 g) and porcelain beads (20 g) were placed in a two-necked round-bottomed flask fitted with a reflux condenser and a guard tube, and a stoppered dropping funnel fitted with a pressure equalizer tube containing a solution of cinnamyl alcohol (50 g) in ethanol (250 ml). The flask was heated in an oil bath placed on a hot plate until the sodium melted. The ethanolic solution of cinnamyl alcohol was then added carefully dropwise over the molten sodium in the course of 1 hr. After the addition was complete the mixture was refluxed for 4 hr and cooled and an excess of a mixture of ethanol and water (1:1 v/v) was added. The mixture was then steam-distilled to remove ethanol and

phenyl propyl alcohol. The aqueous distillate was extracted with benzene (3 x 100 ml) and the benzene layer was dried over anhydrous sodium sulphate. The residual liquid obtained after stripping off ethanol and benzene was distilled under reduced pressure (5 mm) and the fraction b.p. 115-120° was collected. The yield was 30 g.

Phenyl propyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside

This reaction was carried out under concentrated conditions under the same conditions as described for the preparation of acetylated benzyl α-D-glucoside. But in view of low yields, the reaction was scaled up to double the molar quantities used in the other experiment. The time of refluxing was the same (15 minutes). The crude product containing some fast moving spots and the β-anomer was subjected to silica gel column chromatography to isolate the pure α-glycoside fraction. The column chromatographic data is given in Table 6.

The acetylated α-glucoside fraction obtained from column chromatography (0.48 g) was crystallised from pet.ether when the pure material was obtained in colourless fine needles, m.p. 50-51°, $[\alpha]_D$ +129.3°. The yield was 12.1%.

Found: C, 59.24; H, 6.54. $C_{23}H_{30}O_{10}$ requires: C, 59.23; H, 6.43 per cent.

This compound has not been described in literature.

TABLE 6

Column chromatographic separation of phenylpropyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside

Column data: Same as in Table 3.

Eluted fraction Nos.	Eluting solvent (acetone: pet.ether)	Volume of eluate (ml)	TLC data	Wt.(g)
1 - 2	2 : 98	2 x 250	no spot	-
3 - 4	3 : 97	2 x 250	phenyl ethyl alcohol (iodine-chamber)	-
5 - 6	4 : 96	2 x 250	fast-moving product	-
7 - 50	5 : 95	44 x 25	no spot. fast moving.	-
51 - 60	5 : 95	10 x 25	fast moving + α (traces)	0.052
61 - 100	5 : 95	40 x 25	α	0.481
101 - 111	5 : 95	11 x 25	α + traces of β	0.044

The column was not eluted further.

Phenyl propyl α-D-glucopyranoside

The tetra-O-acetyl derivative (0.19 g) was deacetylated in the usual manner. The crude deacetylated product, obtained in good yield, could not be crystallised. It was obtained as a syrup, $[\alpha]_D^{24}$ +88.28°.

Found: C, 60.42; H, 8.01. $C_{15}H_{22}O_6$ requires: C, 60.40; H, 7.38 per cent.

This compound has not been described in literature.

Phenyl propyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

Penta-O-acetyl-β-D-glucopyranose (3.9 g, 10 m.moles) was dissolved in benzene (175 ml). To the stirred solution was added phenylpropyl alcohol (2.7 g, 20 m.moles) followed by stannic chloride (1.1 ml, 10 m.moles). The reaction mixture was refluxed on the water bath for 30 minutes. The optimum conditions for the preparation of this glycoside was arrived at earlier by TLC study of small scale probing experiments.

The reaction product was worked up as usual. TLC showed the proportion of α:β as 1:4. The product was subjected to silica gel column chromatography for the isolation of the pure β-anomeric glycoside. This is detailed in Table 7.

The chromatographed β-anomer (0.8 g) crystallised from pet.ether-ether in colourless prismatic needles, m.p. 81-82°; $[\alpha]_D^{30}$ -20.3° (c, 1, EtOH). The yield of the product was 20%. Lit.[3] gives m.p. 79-80°, $[\alpha]_D$ -13.1° ($CHCl_3$).

TABLE 7

Column chromatographic separation of phenylpropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

Column data: Same as in Table 3.

Eluted fraction No.	Eluting Solvent (acetone: pet.ether)	Volume of eluate (ml)	TLC data	Wt.g
1 - 50	5 : 95	50 x 5	fast moving spots	-
51 - 75	5 : 95	25 x 5	α	0.18
76 - 100	5 : 95	25 x 5	β	0.796
101 - 105	5 : 95	5 x 5	no spot	-

Found: C, 59.98; H, 6.62. Calculated for $C_{23}H_{30}O_{10}$, C, 59.23; H, 6.43 per cent.

Phenylpropyl β-D-glucopyranoside

The tetra-O-acetyl derivative (0.16 g) was deacetylated by Zemplen's method. The deacetylated product crystallised from acetone-pet.ether in colourless prisms, m.p. 99-100°, $[\alpha]_D^{28}$ -24.57° (c, 0.4, EtOH). Lit.[3] gives m.p. 100-107°, $[\alpha]_D$ -27.3° (H_2O).

Found: C, 60.55; H, 7.61. Calculated for $C_{15}H_{22}O_6$: C, 60.40; H, 7.38 per cent.

Benzyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside

This reaction was carried out with penta-O-acetyl-β-D-galactopyranose (3.9 g, 10 m.moles) in the same manner and with the same proportion of the other reagents as described for the corresponding glucoside analogue. The crude product showed on TLC, some fast moving compounds and the β-anomer as well as traces of unreacted glucose penta-acetate. It was subjected to column chromatography the results of which are detailed in Table 8. The pure acetylated α-galactoside fraction crystallised from ether-pet.ether mixture in rectangular plates m.p. 107°, $[\alpha]_D^{28}$ +165° (c, 0.2 EtOH). This galactoside has not been described in literature. The yield of the pure product was 32%.

Found: C, 57.37; H, 5.99. $C_{21}H_{26}O_{10}$ requires: C, 57.53; H, 5.94 per cent.

TABLE 8

Column chromatographic separation of benzyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside

Column data: Same as in Table 3

Eluted fraction No.	Eluting solvent (acetone: pet. ether)	Volume of eluate (ml)	TLC data	Wt.(g)
1 - 7	5 : 95	7 x 50	fast moving products	-
8 - 9	10 : 90	2 x 50	Fast moving products + α (traces)	-
10 - 15	10 : 90	6 x 50	α	1.411
16	10 : 90	1 x 50	α and β (80:20)	0.013
17 -20	10 : 90	4 x 50	β	0.135
21 - 22	10 : 90	2 x 50	galactose pentaacetate	-

Benzyl α-D-galactopyranoside

The tetra-O-acetyl derivative (0.15 g) was deacetylated in the usual manner. The free galactoside was obtained as a syrup, $[\alpha]_D^{28}$ +135.6° (c, 0.2, EtOH) which could not be crystallised. The yield was almost quantitative. This product has not been described in literature.

Found: C, 57.33; H, 7.02. $C_{13}H_{18}O_6$ requires: C, 57.78; H, 6.67 per cent.

Benzyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside

This reaction was carried out with the same molar proportions of the reactants and under the same conditions as described for the corresponding α-anomer except for the quantity of the diluent benzene used (50 ml). Since the crude product contained the α-anomer and unreacted penta-acetate and other impurities, it was chromatographed as detailed in Table 9.

The pure β-fraction was obtained from the column as a syrup $[\alpha]_D^{30}$ -32.0° (c, 0.2, EtOH). The yield of the product was 35%. It could not be crystallised. Although the free glycoside has been described in literature (loc. cit), the tetra-O-acetyl derivative has not been described so far.

Found: C, 57.59; H, 6.20. $C_{21}H_{26}O_{10}$ requires: C, 57.53; H, 5.94 per cent.

Benzyl β-D-galactopyranoside

The tetra-O-acetyl derivative (0.15 g) was deacetylated

TABLE 9

Column chromatographic separation of benzyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside

Column data: Same as in Table 3.

Eluted fraction Nos.	Eluting Solvent (acetone: pet.ether)	Volume of eluate (ml)	TLC data	Wt.(g)
1 - 3	5 : 95	3 x 50	no spot	-
4 - 13	10 : 90	10 x 70	fast moving compounds	-
14 - 15	15 : 85	2 x 50	" "	-
16 - 18	15 : 85	3 x 50	α	0.16
19 - 25	20 : 80	7 x 50	β	1.531
26 - 28	20 : 80	2 x 50	β + penta-acetate (traces)	-

in the usual manner. The pure product from chromatographic column crystallised from methanol acetone mixture in colourless slender needles, m.p. 85-90°, $[\alpha]_D^{30}$ -91.3° (c, 0.24, EtOH). The product was found to be a hemihydrate which has not been described in literature. Lit.[4] describes the unhydrated galactoside, m.p. 119°, $[\alpha]_D$ -29.5° (water).

Found: C, 55.56; H, 7.01. $C_{13}H_{18}O_6$, 1/2 H_2O requires: C, 55.91; H, 6.81 per cent.

Phenyl ethyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside

This reaction was carried out under the α-condition with the same molar proportion of the starting materials as described for the benzyl analogue. In this case also reaction mixture was refluxed on a boiling water bath for 15 minutes. The reaction product obtained was subjected to column chromatography as described in Table 10. The pure α-anomer obtained from the column crystallised from ethanol in colourless prisms m.p. 94°, $[\alpha]_D^{29}$ +147.74° (c, 0.2, EtOH). The yield was 44.2%. This galactoside has not been described in literature.

Found: C, 58.60; H, 6.22. $C_{22}H_{28}O_{10}$ requires: C, 58.41; H, 6.19 per cent.

Phenyl ethyl α-D-galactopyranoside

The free galactoside was obtained in almost quantitative yields by deacetylation of the tetra-O-acetyl derivative (0.25 g) by Zemplen's method as a syrup, $[\alpha]_D^{28}$ +53.71 (c,

TABLE 10

Column chromatographic separation of phenylethyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside

Column data: Same as in Table 3

Eluted fraction Nos.	Eluting solvent (acetone: pet.ether)	Volume of eluate (ml)	TLC data	Wt.(g)
1 - 9	10 : 90	9 x 25	traces of fast moving product.	-
10 - 11	10 : 90	2 x 25	fast moving product+ α	-
12 - 15	10 : 90	4 x 25	α	2.0
16 - 19	15 : 85	4 x 25	α + β (1:1)	-
20 - 23	15 : 85	4 x 25	β	-

0.19, EtOH). The product could not be crystallised. This product is not reported in literature. It analysed for a monohydrate.

Found: C, 57.60; H, 7.51. $C_{14}H_{20}O_6$, H_2O requires: C, 57.92; H, 7.21 per cent.

Phenyl ethyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside

The same molar proportions of reactants were used in this as for the α-anomer except for the diluent benzene (50 ml). The time of reflux in this case also was 15 minutes. The crude reaction product was chromatographed on a silica gel column as detailed in Table 11. The chromatographed β-fraction crystallised from ether-pet. ether in colourless long prismatic needles, m.p. 88-89°, $[\alpha]_D^{30}$ -26.4° (c, 2.5, EtOH). The yield was 39.3%. This galactoside is not reported in literature.

Found: C, 58.66; H, 6.27. $C_{22}H_{28}O_{10}$ requires: C, 58.41; H, 6.19 per cent.

Phenylethyl β-D-galactopyranoside

The crude free galactoside, obtained on deacetylation of the tetra-O-acetyl derivative (0.175 g) in the usual manner in good yields, crystallised from acetone-pet. ether in colourless fine needles, m.p. 107-108°, $[\alpha]_D^{24}$ -33.94° (c, 0.165, EtOH). This galactoside has not been described in literature.

Found: C, 58.49; H, 7.22. $C_{14}H_{20}O_6$ requires: C, 59.16; H, 7.04 per cent.

TABLE 11

Column chromatographic separation of phenylethyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside

Column data: Same as in Table 3

Eluted fraction Nos.	Eluting solvent (acetone: pet.ether)	Volume of eluate (ml)	TLC data	Wt. (g)
1 - 10	10 : 90	10 x 25	no spot	-
11 - 13	10 : 90	3 x 25	fast moving compounds + α	0.201
14 - 16	10 : 90	3 x 50	α	0.095
17 - 29	10 : 90	13 x 50	α + β (1:1)	0.050
30 - 39	15 : 85	10 x 50	β	1.769
40	15 : 85	1 x 50	pentaacetate	-

Phenylpropyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside

This product was prepared with the same molar proportion of reactants and under the same conditions as described for the phenylethyl-α-analogue. The crude product, obtained as a syrup on working up the reaction mixture in the usual manner, was subjected to column chromatography on silica gel as described in Table 12. The chromatographically pure α fraction crystallised from ether-pet.ether in colourless needles, m.p. 134-135°, $[\alpha]_D^{25}$ +150° (c, 0.2, $CHCl_3$). The yield was 49%. This galactoside has not been reported in literature.

Found: C, 59.43; H, 6.63. $C_{23}H_{30}O_{10}$ requires: C, 59.23; H, 6.43 per cent.

Phenylpropyl α-D-galactopyranoside

The crude free galactoside, obtained in good yields by Zemplen deacetylation of the tetra-O-acetyl derivative (0.2 g), crystallised from acetone-pet.ether in colourless rectangular plates, m.p. 75-77°, $[\alpha]_D^{35}$ +143° (c, 1.0, EtOH). This galactoside has not been described in literature.

Found: C, 60.00; H, 7.64. $C_{15}H_{22}O_6$ requires: C, 60.40; H, 7.38 per cent.

Phenylpropyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside

This reaction was carried out exactly as in the case of the benzyl analogue under the β-condition. The crude reaction product obtained in the usual manner was subjected

Column chromatographic separation of phenylpropyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside

Column data: Same as in Table 3

Eluted fraction Nos.	Eluting Solvent (acetone-pet.ether)	Volume of eluate (ml)	TLC data	Wt.(g)
1 - 5	5 : 95	5 x 50	no spot	-
6 - 8	10 : 90	3 x 50	fast moving product.	-
9 - 16	10 : 90	8 x 50	α	2.293
17	10 : 90	1 x 50	α + β (1:3)	0.032
18 - 20	10 : 90	3 x 50	β	0.216
21	10 : 90	1 x 50	pentaacetate (traces)	-

to column chromatography as detailed in Table 13. The chromatographed β-anomer (yield 43%) was obtained as syrup which could not be crystallised. It gave $[\alpha]_D^{25}$ -24.7° (c, 0.5, EtOH).

Found: C, 58.98; H, 7.01; $C_{23}H_{30}O_{10}$ requires: C, 59.23; H, 6.43 per cent.

Phenylpropyl β-D-galactopyranoside

The free glycoside was obtained as a syrup by Zemplen deacetylation of the tetra-O-acetyl derivative (0.150 g). The syrup, giving $[\alpha]_D^{25}$ -5.3° (c, 0.13, EtOH), could not be crystallised. This glycoside analysed for a hemihydrate.

Found: C, 58.90; H, 7.19. $C_{15}H_{22}O_6$ 1/2 H_2O requires: C, 58.68; H, 7.49 per cent.

This glycoside has been recently prepared by the Koenigs-Knorr reaction by Weil *et al.*[1] in a crystalline form (anhydrous) m.p. 100-102°, $[\alpha]_{546}^{22}$ -6.4° (H_2O). But the intermediate tetra-O-acetyl derivative was not characterized and was directly deacetylated to obtain the free galactoside.

TABLE 13

Column chromatic separation of phenylpropyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside

Column data: Same as in Table 3

Eluted fraction Nos.	Eluting solvent (acetone: pet.ether)	Volume of eluate (ml)	TLC data	Wt.(g)
1 - 5	5 : 95	5 x 50	no spot	-
6 - 7	10 : 90	2 x 50	fast moving compound	-
7 - 9	10 : 90	2 x 50	α	0.201
10	10 : 90	1 x 50	α + β (1:1)	0.10
11 - 18	10 : 90	8 x 50	β	2.251
19	10 : 90	1 x 50	no spot	-

REFERENCES

1 Weil, R., Maass, G., Wallenfels, K. and Haas, R., Biochem. Pharm., 17(1968), 1909.

2 Helferich, B. and Gootz, R., Ber., 62(1929), 2788.

3 Richtmyer, N.K., J. Am. Chem. Soc. 56(1934), 1636.

4 Helferich, B. and Poick, A., Ann. 586(1954), 239.

5 Gray, W.H., J. Chem. Soc., 127(1925), 1150.

CHAPTER IV

PHOSPHOROUS OXYCHLORIDE CATALYSED SYNTHESIS OF GLYCOSIDES

PHOSPHORUS OXYCHLORIDE CATALYSED SYNTHESIS OF GLYCOSIDES

INTRODUCTION

A brief mention was made in the first chapter of the use of phosphorus oxychloride as a condensing agent for the synthesis of glycosides. The use of this reagent was reported in one publication by Bembry and Powell[1] in 1942, for the synthesis of the β-anomers of five acetylated aryl D-glycosides. These authors observed that pure phosphorus oxychloride was an unsatisfactory reagent and recommended that it should be mixed with water (1% v/v) to make an effective catalyst for the glycosidation reactions. No further work was reported so far on the use of this reagent for glycosidation.

Stannic chloride was initially used by Lemieux and Shyluk[2] for the synthesis of the β-anomers of one alkyl and one aryl glycoside. Bose et al.[3] established later that stannic chloride can be used for the synthesis of α-anomeric acetylated glycosides as well, and prepared a large number of acetylated α- and β- D-glycosides and thioglycosides by using this reagent. The use of this reagent was extended further for the synthesis of α- and β-anomeric alkyl and aryl alkyl glycosides as presented in Chapters II and III respectively of this thesis. In view

of the similarity of stannic chloride and phosphorus oxychloride and the known but limited use of the latter reagent for the synthesis of a few aryl glycosides it was considered of great interest to investigate the possibility of a wider use of this reagent for the synthesis of not only aryl but also alkyl and aryl alkyl glycosides in both the β- and the α-configuration. The present chapter gives an account of the results of these investigations.

Moisture content of phosphorus oxychloride in relation to its effectiveness as a catalyst for the glycosidation reaction

At the initial stage, it was considered necessary to establish the validity or otherwise of the conclusions reached by Bembry and Powell[1] about the necessity of using $POCl_3$ treated with water (1% v/v) to make it an effective catalyst for the glycosidation reaction. As a result of a comparative study of the glycosidation of phenol with penta-O-acetyl-β-D-glucopyranose, catalysed by (1) dry $POCl_3$ (2) $POCl_3$ treated with water (1% v/v) (3) $POCl_3$ treated with water (5% v/v), carried out under the conditions described by Bembry and Powell as detailed in the experimental part, we arrived at the following conclusions:

1. Dry $POCl_3$ gives the same yields of the glycosides as $POCl_3$ treated with 1% and 5% water. The latter are actually mixtures of $POCl_3$ with orthophosphoric

acid formed by reaction between $POCl_3$ and water.

2. In all these reactions both of the anomeric acetylated glycosides were formed. The proportion of β:α was 3:1 approximately.

3. A good part of the penta-O-acetyl-β-D-glucopyranose was converted to the α-anomer in this process.

In view of these observations we used dry $POCl_3$ in all our subsequent experiments on optimization.

<u>A comparative study of the catalytic action of phosphorus oxychloride and stannic chloride in the glucosidation of p-cresol</u>

The similarity of the two glycosidation catalysts, stannic chloride and phosphorus oxychloride on the one hand and our experience on the use of former reagent in the synthesis of alkyl and aryl alkyl glycosides on the other, initiated us to make a comparative study of the catalytic effect of these two reagents on a selected glycosidation reaction, namely, that between p-cresol and penta-O-acetyl-β-D-glucopyranose, in the presence of an excess of benzene as a diluent. From a comparative TLC study of the products of reaction taken out at various intervals the following conclusions were arrived at:

1. Glycosidation with $POCl_3$ although a slower process is cleaner than that with $SnCl_4$ anf gives much lesser

quantities of the degradation products or by-products, even when compared at the level of equal yields of the acetylated glycosides.

2. The relative rate of formation of the α-anomer is slower with $POCl_3$ than with $SnCl_4$. As a result, at the level of equal yields of total acetylated glycosides in the two reactions, the ratio of β:α is greater in the $POCl_3$ catalysed reactions. This leads to the conclusion that unlike in $SnCl_4$ catalysed glycosidation, the α-anomer is formed in $POCl_3$ catalysed reactions almost entirely by the process of anomerisation.

Phosphorus oxychloride catalysed anomerisation reactions

Several alkyl α-D-glycosides have been successfully prepared by anomerisation of the β-anomers with suitable acidic catalysts[4,5]. These anomerisations have been shown to proceed through an intramolecular mechanism and do not require the presence of added alcoholic aglycones[6]. It is, however, well-known that aryl β-D-glucopyranosides are highly resistant to acid-catalysed anomerisations[2]. Methods successfully employed for the preparation of some alkyl α-D-glycosides were not useful for the preparation of aryl α-D-glycosides[7].

It was established by Bose *et al.*[8] that anhydrous

stannic chloride is a suitable reagent for the anomerisation of acetylated aryl β-D-glycosides in the presence of added phenolic aglycones. On the basis of experimental evidence the same authors[9] have recently suggested an intermolecular mechanism for the anomerisation process of the acetylated aryl glycosides.

In view of the great similarity between the catalytic action of stannic chloride and phosphorus oxychloride for glycosidation reactions, and in view of the anomerisation process observed during $POCl_3$ catalysed glycosidation reactions as indicated earlier in this Chapter, it was thought of interest to make a detailed study of some $POCl_3$-catalysed anomerisations. The following important conclusions were arrived at as a result of TLC study of a number of small scale $POCl_3$ catalysed anomerisation reactions as summarised in Table 1.

TABLE 1

Phosphorus oxychloride catalysed anomerisation reactions

Conditions of reaction: The compound to be anomerised (1 m.mol), phenolic aglycone, when added (1 m.mol), $POCl_3$ (15 m.mol), heated on a boiling water bath for 3 hr.

Sl.No.	Compound anomerised	Products obtained	
1	Penta-O-acetyl-β-D-glucopyranose	Penta-O-acetyl-α-D-glucopyranose	Small amounts of degradation products.

...contd.

TABLE 1 (Contd.)

Sl.No.	Compound anomerised	Products obtained	
2	Penta-O-acetyl-α-D-glucopyranose	unreacted 2	Small amounts of degradation products
3	n-Butyl tetra-O-acetyl β-D-glucopyranoside	n-Butyl-tetra-O-acetyl-α-D-glucopyranoside.	" "
4	n-Butyl tetra-O-acetyl-α-D-glucopyranoside	Unreacted 4	" "
5	Phenyl tetra-O-acetyl-β-D-glucopyranoside	Unreacted 5	" "
6	Phenyl tetra-O-acetyl-β-D-glucopyranoside + phenol.	Phenyl tetra-O-acetyl-α-D-glucopyranoside	" "
7	Phenyl tetra-O-acetyl-α-D-glucopyranoside + phenol.	Unreacted 7	" "

The following important conclusions were arrived at as a result of these TLC studies:

1. The stable α-anomers do not anomerise at all under these conditions.
2. Penta-O-acetyl-β-D-glycopyranoses can be completely converted to the α-anomers.
3. Alkyl tetra-O-acetyl-β-D-glycopyranosides can be completely converted to the α-anomers even in the absence of the added alcoholic aglycone.
4. Aryl tetra-O-acetyl-β-D-glycopyranosides can be

completely converted to the α-anomers only in the presence of added phenolic aglycone. In the absence of added phenolic aglycones no anomerisation takes place.

From these experiments it has been established that $POCl_3$ catalysed anomerisation is an excellent method for the preparation of acetylated α-anomeric glycosides from the easily available β-anomers, in good yields. This was substantiated by a laboratory-scale preparation of phenyl tetra-O-acetyl-α-D-glucopyranoside from the β-anomer in 60% yields as described in the experimental section. The reaction was carried out at 55° for 6 hr to reduce the quantity of degradation products formed.

Phosphorus oxychloride - a potential reagent for glycosidation

These preliminary studies indicated that phosphorus oxychloride is a potentially attractive catalyst for the preparation of the anomeric acetylated aryl glycosides. It was also observed that under more concentrated conditions using lesser quantities of the diluent (benzene), it was possible to enhance the rate of anomerization leading to the formation of progressive amounts of the α-anomer at the expense of the β-anomer. Finally, the conditions established for the preparation of the α- and β-anomeric acetylated aryl glycosides using $POCl_3$ as the condensing agent were successfully employed for the preparation of a number of α- and β-anomeric

acetylated alkyl and aryl alkyl glycosides.

Phenol and penta-O-acetyl-α-D-glucopyranose were selected as reactants to study the following parameters of the phosphorus oxychloride catalysed glycosidation reaction:

(1) effect of molarity of $POCl_3$

(2) effect of molarity of phenol

(3) effect of dilution with benzene.

Effect of molarity of phosphorus oxychloride and duration of reaction in the glucosidation of phenol with penta-O-acetyl-α-D-glucopyranose

These reactions were studied using two mols (5 millimols) of the phenol per mol (2.5 millimols) of the acetylated sugar. This proportion of the reactants was chosen in view of the results of earlier studies in the stannic chloride catalysed glycosidation reactions, in the course of which it was established that part of the phenolic aglycone got acetylated and could not take part in the reaction[10]. Although Bembry and Powell[1] used only 1/3 mol of $POCl_3$, we maintained the molarity of $POCl_3$ at higher levels of 5, 10 and 15 to increase the reaction rates. The effect of the duration of reaction at the levels of 1,3,5 and 7 hr were also studied for each of these molarities of $POCl_3$. The quantity of benzene used as a diluent in all these reactions was 50 ml.

The results of these studies as shown in Tables 2 to 5 were compiled from eye-estimates of the relative intensities of the TLC spots for different products obtained from each reaction. Some of these TLC plates were also scanned by a recording densitometer and the eye-estimates proved to be quite accurate.

TABLE 2

Period of reaction: 1 hr

Mols of $POCl_3$	α (Rf 0.62)	β (Rf 0.56)	Unreacted glucose pentaacetates (anomerised)	
			α Rf 0.50	β Rf 0.48
5	10	55	30	
10	15	60	25	
15	15	75	10	

About 5% of the total visible products on TLC represented the by products having Rf values of 0.37, 0.71 and 0.80 respectively.

TABLE 3

Period of reaction: 3 hr

Mols of $POCl_3$	α	β	Unreacted glucose pentaacetates (anomerised)
5	10	60	25
10	15	65	10
15	20	65	5

About 5 to 10% of the visible products on TLC represented the by-products of the reaction.

TABLE 4

Period of reaction: 5 hr

Mols of $POCl_3$	α	β	Unreacted glucose pentaacetates (anomerised)
5	10	75	5
10	15	70	5
15	20	70	Traces

About 10% of the visible products on TLC represented the by-products of the reaction.

TABLE 5

Period of reaction: 7 hr

Mols of $POCl_3$	α	β	Unreacted glucose pentaacetates (anomerised)
5	10	80	Traces
10	20	70	Traces
15	25	60	Traces

About 10 to 15% of the visible products on TLC represented the by-products of the reaction.

The following conclusions were arrived at from these studies:

(1) The amount of undesirable by-products formed increases with increased period of reaction and to a limited extent with increased molarity of $POCl_3$.

(2) Penta-O-acetyl-β-D-glucopyranose gets anomerized.

(3) The reactions carried out for longer periods give darker reaction mixtures and the separation of the required products becomes more difficult.

(4) It is better to use 15 mols of $POCl_3$ for a shorter period even if some quantity of the sugar acetate remains unreacted. The separation of the latter poses no problem.

Effect of molarity of phenol and duration of reaction in the glucosidation of phenol with penta-O-acetyl-β-D-glucopyranose

These experiments were carried out with 1 mol of penta-O-acetyl-β-D-glucopyranose, 15 mols of $POCl_3$ and 1,2 and 4 mols of phenol. Actual quantities used were penta-O-acetyl-β-D-glucopyranose (2.5 millimols), phenol (2.5, 5 and 10 millimols), $POCl_3$ (37.5 millimols) and benzene (50 ml). Probing experiments using 5 mols (12.5 millimols) of phenol did not show any improvement over those using 4 mols of phenol. The results of these experiments (proportion of the products) are given in Tables 6 to 8.

TABLE 6

Period of reaction : 20 minutes

Mols. of phenol	∝	β	Unreacted glucose pentaacetate
1	15	65	20
2	15	70	15
4	15	80	5

Practically no degradation products or by-products were seen on the TLC plates.

TABLE 7

Period of reaction: 40 minutes

Mols of phenol	∝	β	Unreacted glucose pentaacetate
1	20	70	10
2	20	75	5
4	25	75	Traces

Practically no degradation products or by-products were seen on the TLC plates.

TABLE 8

Period of reaction: 1.5 hr

Mols of phenol	∝	β	Unreacted glucose pentaacetate
1	20	70	5
2	25	65	5
4	30	65	Traces

About 5% of degradation products and by-products were visible on the TLC plates.

These results reveal that the use of 15 mols of $POCl_3$ and 4 mols of phenol give excellent yields of the acetylated glucosides in a short time of 20 to 40 minutes with more or less complete disappearance of glucose pentaacetate.

Effect of dilution with benzene: Optimum conditions for the synthesis of acetylated β- and ∝-anomeric glycosides

Another important aspect of optimisation remained to be studied was the effect of dilution of the reaction mixture with benzene. It has been already observed in stannic chloride catalysed glycosidation reactions[11] that use of more of the diluent (benzene) leads to a favourable β / ∝ anomeric ratio, whereas use of small quantities of the diluent makes the ∝ / β anomeric ratio large.

It has been already established by us as described earlier in this chapter that good yields of acetylated β-anomeric aryl glucosides were obtained by using 15 mols of $POCl_3$, 4 mols of phenol, 200 ml of benzene per mol of the acetylated sugar, the reaction being carried out at the boiling water bath temperature for a period of 20 minutes to 1 hr depending on the reactivity of phenol. The same optimum conditions with marginal adjustments were found to hold good for the synthesis of β-anomers of acetylated alkyl and aryl alkyl glycosides as well.

When the diluent (benzene) was completely absent from the reaction mixture keeping the other conditions same, a very good α / β anomeric ratio of 9 : 1 was obtained in 40 minutes in the synthesis of phenyl tetra-O-acetyl D-glucopyranoside. With marginal adjustments, these conditions were employed as optimum for the synthesis of α-anomers of acetylated aryl, alkyl and aryl alkyl glycosides in the course of the work presented in this Chapter.

Table 9, gives a list of eleven acetylated aryl, alkyl and arylalkyl β and α-anomeric D-glucopyranosides including one pair of thioglucosides synthesised by $POCl_3$-catalysed reactions under the optimum conditions established in the course of the work presented in this Chapter. The corresponding free (deacetylated) glycosides were not prepared as most of them have already been prepared by us and by other

workers earlier.

The work presented in this chapter, therefore, has established phosphorus oxychloride as an excellent new reagent for the synthesis of either of the β- or α-anomer of acetylated aryl, alkyl and aryl alkyl glycosides and thioglycosides. This reagent has also been proved to be of value for the anomerisation of acetylated β-anomeric glycosides for the preparation of the corresponding α-anomers.

TABLE 9

Tetra-O-acetyl-β-D-glucopyranosides prepared by phosphorus oxychloride reaction.

Sl.No.	Glycoside	m.p. °C	$[\alpha]_D$	Mol. formula	Analytical values				Ref.
					% C Found	H Found	%C Required	H Required	
1	Phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside	126 (125-126)	-23.9 (-22.5)	$C_{20}H_{24}O_{10}$	56.54	5.78	56.59	5.66	11
2	p-Phenyl phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.	156 (155)	-16.8 (-12.3)	$C_{26}H_{28}O_{10}$	62.70	5.84	62.40	5.64	11
3	*m-Methoxy phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.	135	-28.6	$C_{21}H_{26}O_{11}$	55.37	5.82	55.51	5.73	-
4	Phenyl 2,3,4,6-tetra-O-acetyl-β-D-thioglucopyranoside.	119 (118)	-41.3 (-40.1)	$C_{20}H_{24}O_9S$	54.58	5.53	54.54	5.45	12
5	Cetyl 2,3,4,6 tetra-O-acetyl-β-D-glucopyranoside	74 (71-73)	-18.6 (-20.9)	$C_{30}H_{52}O_{10}$	62.76	9.11	62.94	9.09	13
6	Phenyl ethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.	73-74 (72-73)	-21.5 (-19.2)	$C_{22}H_{28}O_{10}$	58.83	6.30	58.41	6.19	14

Literature values are given in parenthesis.

*New product.

Tetra-O-acetyl α-D-glucopyranosides prepared by phosphorus oxychloride catalyst reaction.

Sl.No.	Glycoside	m.p. °C	$[\alpha]_D$	Mol. formula	Analysis Found % C	Found H	Required C	Required H	Ref.
1	Phenyl 2,3,4,6-tetra-O-acetyl-α-D-gluco-pyranoside	114 (114)	+162.2 (+168)	$C_{20}H_{24}O_{10}$	56.80	5.91	56.59	5.66	11
2	p-Phenyl phenyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside	167-168 (169-70)	+190.8 (+198.55)	$C_{26}H_{28}O_{10}$	62.81	5.86	62.40	5.64	11
3	Phenyl 2,3,4,6-tetra-O-acetyl-α-D-thio-glucopyranoside	92-93 (85-86)	+8.5 (+6.2)	$C_{20}H_{24}O_9S$	54.53	5.49	54.54	5.45	12
4	*Cetyl 2,3,4,6 tetra-O-acetyl-α-D-glucopyra-noside.	48-49	+117.8	$C_{30}H_{52}O_{10}$	63.15	9.21	62.94	9.09	-
5	*Phenylethyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside.	126	+133.5	$C_{22}H_{28}O_{10}$	58.13	6.31	58.41	6.19	-

Literature values are given in parenthesis.

*New products.

E X P E R I M E N T A L

Effect of addition of water to phosphorus oxychloride on its efficiency as a catalyst for glycosidation reactions

The reagents to be used as catalyst were prepared by adding 0.5 and 2.5 ml of water dropwise to 50 ml of dry $POCl_3$ under anhydrous conditions. The mixture was cooled in ice and water as the reaction was highly exothermic.

Three glycosidation reactions were carried out using (i) dry $POCl_3$ (ii) $POCl_3$ with 1% water (v/v) and (iii) $POCl_3$ with 5% water (v/v) as follows:

A mixture of penta-O-acetyl-β-D-glucopyranose (3.9 g, 10 m.moles), phenol (0.94 g, 10 m.moles), the phosphorus oxychloride reagent (0.2 ml, 3.3 m.moles) and benzene (200 ml) was refluxed on a boiling water bath for 3 hr. After this period, $POCl_3$ and benzene ware distilled off from the reaction mixture under reduced pressure and the residual thick liquid was added to a saturated sodium bicarbonate solution under stirring to decompose the residual phosphorus oxychloride and neutralise orthophosphoric acid. After shaking further in a mechanical shaker for 1 hr. the mixture was extracted with benzene (3 x 50 ml). The combined benzene extract was washed with sodium hydroxide (20 x 3 ml, 1%) and then with water (20 x 3 ml). The neutral benzene solution was dried over anhydrous sodium sulphate and the solvent was

stripped off under reduced pressure. The resulting thick liquid was dissolved in a mixture of acetone and pet. ether and applied to a column of silica gel (100 g) and the individual compounds eluted with pet. ether containing increasing quantities of acetone (5 - 15%). The yields of the α- and β-anomeric phenyl tetra-O-acetyl-D-glucopyranosides as well as the quantities of unreacted penta-O-acetyl-β-D-glucopyranose and anomerised α-anomer are given in Table 10.

TABLE 10

Sl.No.	$POCl_3$	Yields of acetylated glycosides (g)		Recovered glucose pentaacetate (g) anomerised	
		α	β	α	β
1	dry	0.24	0.76	1.26	0.33
2	contg. 1% water	0.23	0.72	1.24	0.36
3	contg. 5% water	0.26	0.80	1.34	0.30

All these pure chromatographic fractions were separately crystallised and identified.

A comparative TLC study of phosphorus oxychloride and stannic chloride catalysed glycosidation of p-cresol with penta-O-acetyl-β-D-glucopyranose.

These reactions were carried out on a small scale. In each reaction a mixture of penta-O-acetyl-β-D-glucopyranose

(2.5 m.mol), p-cresol (5 m. mol), stannic chloride (2.5 m.mol) or phosphorus oxychloride (12.5 m.mol) and benzene (50 ml) was refluxed on a boiling water bath. Aliquots were taken out from each reaction mixture after 15 minutes, 30 minutes, 1 hr and 1.5 hr. After decomposition with water, neutralization and extraction with benzene the products were studied by TLC. The conclusions arrived at as a result of these studies have already been described in the theoretical part.

Phosphorus oxychloride catalysed anomerization reactions

The anomerisations were carried out by refluxing a mixture of the acetylated glycosides or the sugar pentaacetates (0.5 m.mol), $POCl_3$ (7.5 m.mol) and benzene (10 ml) on a boiling waterbath for 3 hr. The results as observed on TLC and the conclusions arrived at have already been discussed in the theoretical part.

Preparation of phenyl tetra-O-acetyl-α-D-glucopyranoside by phosphorus oxychloride catalysed anomerisation of phenyl tetra-O-acetyl-β-D-glucopyranoside

A mixture of penta-O-acetyl-β-D-glucopyranoside (3.9 g, 10 m.mol), phenol (0.94 g, 10 m.mol) and $POCl_3$ (8.4 ml, 15 m.mol) were heated without any diluent at 55° for 5 hr with occasional shaking. An aliquot of the reaction mixture at this stage showed the proportion of α:β as 9 : 1. The reaction mixture was worked up in the manner described earlier and the crude reaction product was subjected to column chromatography on

silica gel (100 g). Elution with pet. ether containing increasing proportions of acetone gave 2.56 g (60.1%) of the pure α-fraction (TLC). The product crystallised from acetone-pet. ether in colourless needles, m.p. 114°, $[\alpha]_D$ +163° (c, 0.1, EtOH). It did not depress the m.p. of an authentic sample of phenyl tetra-O-acetyl-α-D-glucopyranoside, m.p. 114°, with which it had identical mobility on TLC.

Phenyl tetra-O-acetyl-β-D-glucopyranoside

A mixture of penta-O-acetyl-β-D-glucopyranose (3.9 g, 10 m.moles), phenol (3.76 g, 40 m.moles), $POCl_3$ (8.4 ml, 150 m.moles) and benzene (200 ml) was refluxed on a boiling water bath for 40 minutes. At this stage TLC showed practically no unreacted pentaacetate. The reaction mixture was worked up as described in an earlier experiment. The crude reaction product was subjected to column chromatography on silica gel (Table 11). The acetylated β-glycoside fraction (2.63 g, 63%) crystallised from acetone-pet. ether in colourless needles, m.p. 126°, $[\alpha]_D^{25}$ -23.9° (c, 0.26, EtOH).

Found: C, 56.54; H, 5.78. Calculated for $C_{20}H_{24}O_{10}$: C, 56.59; H, 5.66%.

TABLE 11

Column chromatographic separation of phenyl tetra-O-acetyl-β-D-glucopyranoside.

Wt. of silica gel used .. 100 g
Silica gel column length.. 75 cm.
Inner diameter of the column 2.5 cm

TABLE 11 (Contd.)

Eluted fraction Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture	Wt.(g)
1 - 6	Pet.ether-acetone (95:5)	6 x 50	Fast moving products	-
7 - 10	" " (8:92)	3 x 50	α	0.86
11-	" " (10:90)	1 x 50	α + β	0.02
12- 21	" " (10:90)	10x 50	β	2.63

p-Phenyl phenyl tetra-O-acetyl-β-D-glucopyranoside

The molar proportions of the reactants were the same as in the earlier experiment. The optimum time of refluxing in this case was 40 minutes (as established earlier by a small scale probing experiment). The crude product obtained in the usual manner described earlier was subjected to column chromatography on silica gel as detailed in Table 12. Some p-phenyl phenol acetate was isolated in crystalline state and identified. The pure acetylated β-glucoside fraction (3.23 g, 65.4%) crystallised from acetone-pet. ether in colourless needles m.p. 156°, $[\alpha]_D^{25}$ -16.8° (c, 0.28, EtOH).

Found: C, 62.70; H, 5.84; Calculated for $C_{26}H_{28}O_{10}$: C, 62.40; H, 5.64%.

TABLE 12

Column chromatographic separation of p-phenyl phenyl tetra-O-acetyl-β-D-glucopyranoside.

Column data: Same as in Table 11.

Eluted Fr.Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture (Iodine chamber)	Wt.(g)
1 - 8	Pet.ether	8 x 50	p-phenyl phenol	traces
9 - 16	Pet.ether-acetone (95:5)	8 x 50	p-phenyl phenol acetate	1.55
17	"" (92:8)	1 x 100	α	0.81
18 - 21	"" ""	3 x 50	α + β	0.25
22 - 30	"" (90:10)	9 x 50	β	3.23
30 - 31	"" ""	2 x 50	-	-

m-Methoxyphenyl tetra-O-acetyl-β-D-glucopyranoside: A mixture of Penta-O-acetyl β-D-glucopyranose (1.95 g, 5 m. moles), resorcinol monomethyl ether (2.5 ml, 20 m.moles), $POCl_3$ (4.2 ml, 75 m.moles) and benzene (100 ml) was refluxed on a boiling water bath for 30 minutes. TLC at this stage showed that the pentaacetate spot had disappeared completely. The reaction mixture was worked up as usual and the crude product was subjected to column chromatography on silica gel (Table 13). The pure acetylated β-glucoside fraction (0.7 g, 30%) crystallised

from acetone-pet.ether in colourless prismatic rods, m.p. 135° (softens at 130°), $[\alpha]_D^{24}$ -28.6° (c, 0.23, EtOH). This compound has not been reported in literature.

Found: C, 55.37; H, 5.82. $C_{21}H_{26}O_{11}$ requires: C, 55.51; H, 5.73%.

TABLE 13

Column chromatographic separation of m-methoxy-phenyl tetra-O-acetyl-β-D-gluco-pyranoside.

Wt. of silica gel .. 50 g
Silica gel column length 40 cm
Inner diameter of the column 1.2 cm

Eluted fraction Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture	Wt.(g)
1 - 4	Pet.ether-acetone (95:5)	4 x 50	Fast moving substance	-
5 - 8	" " (92:8)	4 x 50	α	0.22
9	" " (90:10)	1 x 50	α + β	0.02
10 - 17	" "	8 x 50	β	0.70
18 - 19	" "	2 x 50	-	-

Thiophenyl tetra-O-acetyl-β-D-glucopyranoside

The molar proportion of the reactants and the diluent are the same as for the earlier experiment described for the

preparation of phenyl tetra-O-acetyl β-D-glucopyranoside. The time of heating was 40 minutes. The crude reaction product was subjected to column chromatography (Table 14). The pure α-fraction 1.04 g (24%) crystallised from pet.ether in colourless needles, m.p. 119°, $[\alpha]_D^{24}$ -41.3° (c, 0.32, EtOH).

Found: C, 54.58; H, 5.53. Calculated for $C_{20}H_{24}O_9S$: C, 54.54; H, 5.45%.

TABLE 14

Column chromatographic separation of thiophenyl tetra-O-acetyl-α-D-glucopyranoside

Column data: Same as in Table 11

Eluted fraction Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture	Wt.(g)
1 - 7	Pet.ether-acetone (5:5)	7 x 50	fast moving product	-
8 - 14	" "	7 x 50	α	0.39
15- 22	" "	8 x 50	β	1.04
23- 24	" "	2 x 50	-	-

Cetyl tetra-O-acetyl-β-D-glucopyranoside

The molar proportions of the reactants and the diluent were the same as in earlier experiments. The time of heating was 20 minutes. The crude reaction product was column chromatographed on silica gel (Table 15). The pure

β-fraction (3.54 g, 61.8%) crystallised from pet. ether in colourless long slender needles, m.p. 74°, $[\alpha]_D^{24}$ -18.6° (c, 0.5, EtOH).

Found: C, 62.76; H, 9.11. Calculated for $C_{30}H_{52}O_{10}$: C, 62.94; H, 9.09%.

TABLE 15

Column chromatographic separation of cetyl tetra-O-acetyl-β-D-glucopyranoside

Column data: Same as in Table 11.

Eluted fraction Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture (Iodine chamber)	Wt.(g)
1 - 5	Pet.ether-acetone (95:5)	5 x 50	-	-
6 - 8	" " (90:10)	3 x 50	Cetyl alcohol + fast moving	-
9 - 10	" "	2 x 50	-	-
11- 15	" "	5 x 50	α	1.13
16	" "	1 x 50	α + β	0.03
17- 26	" "	10x 50	β	3.54
27	" "	1 x 50	-	-

Phenyl ethyl tetra-O-acetyl-β-D-glucopyranoside

This reaction was carried out with the same molar proportions of reactants and catalyst and the same volume of

the diluent as the preparation of phenyl tetra-O-acetyl-β-D-glucopyranose. The crude reaction product was subjected to column chromatography on silica gel (Table 16). The pure acetylated β-glucoside fraction (0.98 g, 21.7%) crystallised from acetone-pet.ether in colourless needles, m.p. 73-74°, $[\alpha]_D^{24}$ -21.5° (c, 0.2, EtOH).

Found: C, 58.83; H, 6.30. Calculated for $C_{22}H_{28}O_{10}$: C, 58.41; H, 6.19%.

TABLE 16

Column chromatographic separation of phenyl ethyl tetra-O-acetyl-β-D-glucopyranoside

Column data: Same as in Table 11.

Eluted fraction Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture (Iodine chamber)	Wt.(g)
1 - 5	Pet.ether-acetone (95:5)	5 x 100	Phenyl ethyl alcohol	-
6 - 10	" " (90:10)	5 x 100	fast moving product	-
11	" "	1 x 100	fast moving product + α	0.06
12- 18	" "	7 x 50	α	0.13
19	" "	1 x 100	α + β	0.39
20- 30	" "	11x 100	β	0.98
31- 32	" "	2 x 50	-	-

Phenyl tetra-O-acetyl-α-D-glucopyranoside

A mixture of penta-O-acetyl-β-D-glucopyranose (3.9 g, 10 m.moles), phenol (3.76 g, 40 m.moles), phosphorus oxychloride (8.4 ml, 150 m.moles) is kept at the room temperature (average 25°) for 140 hr with occasional shaking. The reaction mixture was decomposed with ice-water after removal of phosphorus oxychloride under reduced pressure, and worked up as usual. The crude reaction product was subjected to column chromatography on silica gel (Table 17). The crude acetylated α-D-glucoside (0.99 g, 23.4%) crystallised from ethanol in colourless needles, m.p. 113°, $[\alpha]_D^{27}$ +162.2° (c, 0.3, EtOH).

Found: C, 56.80; H, 5.91. Calculated for $C_{20}H_{24}O_{10}$: C, 56.59; H, 5.66%.

TABLE 17

Column chromatographic separation of phenyl tetra-O-acetyl-α-D-glucopyranoside

Column data: Same as in Table 11.

Eluted fraction Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture (Iodine chamber)	Wt.(g)
1 - 6	Pet.ether-acetone (95:5)	6 x 50	phenol + fast moving product	-
7	" (90:10)	1 x 100	Fast moving product + α	0.02
8 - 11	" "	4 x 100	α	0.99
12- 14	" "	3 x 100	α + β	0.09
15- 21	" "	7 x 100	β	0.10
22- 29	" "	8 x 100	β + pentaacetate	0.02
30- 31	" "	2 x 100	-	-

p-Phenyl phenyl tetra-O-acetyl-α-D-glucopyranoside

The molar proportions of reactants for this reaction were the same as acetylated phenyl-α-D-glucoside. The mixture, in this case, was heated on a boiling water bath for 40 minutes and worked up as described in the earlier experiment. The crude reaction product was column chromatographed on silica gel (Table 18). The pure acetylated α-D-glucoside fraction (2.28 g, 45.6%) crystallised from ethanol in colourless needles, m.p. 167-168°, $[\alpha]_D^{25}$ +190.8° (c, 0.2, EtOH).

Found: C, 62.81; H, 5.86. Calculated for $C_{26}H_{28}O_{10}$: C, 62.40; H, 5.64%.

TABLE 18

Column chromatographic separation of p-phenyl phenyl tetra-O-acetyl-α-D-glucopyranoside.

Column data: Same as in Table 11.

Eluted fraction Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture (iodine chamber)	Wt.(g)
1 - 3	Pet.ether-acetone (95:5)	3 x 50	p-phenyl phenyl acetate	1.47
4 - 20	" "	17 x50	fast moving product	-
21- 28	" (92:8)	8 x 50	"	
29- 31	" "	3 x 50	fast moving product + α	0.11
32- 47	" "	16x 50	α	2.28
48- 55	" (90:10)	8 x 50	α + β	0.09
56- 62	" "	7 x 50	β	0.05
63- 64	" "	2 x 50	-	-

Phenyl tetra-O-acetyl-α-D-thioglucopyranoside

This reaction was carried out with the same molar proportion of the reactants as in the earlier experiments. The quantity of thiophenol (distilled) used was 4.49 g (40 m.mols). The reaction mixture was heated on a boiling water bath with occasional shaking for 30 minutes. The crude reaction product obtained in the usual manner was subjected to column chromatography on silica gel (Table 19). The pure acetylated α-D-thioglucoside fraction (1.23 g, 27.8%) crystallised from pet. ether in colourless needles, m.p. 92-93°, $[\alpha]_D^{25}$ +8.5° (c, 0.5, EtOH).

Found: C, 54.53; H, 5.49. Calculated for $C_{20}H_{24}O_9S$: C, 54.54; H, 5.45%.

TABLE 19

Column chromatographic separation of phenyl tetra-O-acetyl-α-D-thioglucopyranoside.

Column data: Same as in Table 11.

Eluted fraction Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture (iodine chamber)	Wt.(g)
1 - 5	Pet.ether-acetone (95:5)	5 x 50	thiophenol	-
6 - 15	" (90:10)	10x 50	α	1.23
16- 18	" "	3 x 50	α + β	0.08
19- 25	" "	7 x 50	β	0.19
26- 27	" "	2 x 50	-	-

Cetyl tetra-O-acetyl-α-D-glucopyranoside

The molar proportions were the same as for the preparation of the other acetylated α-glucosides. Quantity of cetyl alcohol used was 4.84 g (40 m.mols). The reaction mixture was heated on a boiling water bath for 20 minutes and the reaction mixture was worked up as usual. The crude product was column chromatographed on silica gel (Table 20). The pure acetylated α-glucoside fraction (2.29 g, 40.0%) crystallised from pet. ether in colourless needles, m.p. 48-49°, $[\alpha]_D^{25}$ +117.8° (c, 0.2, EtOH).

This is a new compound but already prepared by us as described in Chapter II of this thesis.

Found: C, 63.15; H, 9.21. $C_{30}H_{52}O_{10}$ requires: C, 62.94; H, 9.09%.

TABLE 20

Column chromatographic separation of cetyl tetra-O-acetyl-α-D-glucopyranoside.

Column data: Same as in Table 11.

Eluted fraction Nos.	Eluting solvent	Vol. of eluate (ml)	TLC picture (Iodine chamber)	Wt. (g)
1 - 6	Pet. ether-acetone (95:5)	6 x 50	-	-
7 - 9	" (90:10)	3 x 50	Cetyl alcohol	-
10	" "	1 x 50	-	
11 - 16	" "	6 x 50	α	2.29
17	" "	1 x 50	α + β	0.04
18 - 20	" "	3 x 50	β	0.45

Phenylethyl tetra-O-acetyl-α-D-glucopyranoside

This reaction was carried out with the same molar proportions of the reactants as in the previous reaction for α. The reaction mixture was heated for 30 minutes on a boiling water-bath with occasional shaking. The crude reaction product obtained by working up of the reaction mixture in the usual manner was fractionated by column chromatography on silica gel (Table 21). The pure acetylated α-glucoside fraction (0.97g, 21.2%) crystallised from dil. methanol in colourless prismatic needles, m.p. 126°, $[\alpha]_D^{25}$ +133.5° (c, 0.2, EtOH). This glycoside is also a new product but already prepared by us as described in Chapter III of this thesis.

Found: C, 58.13; H, 6.31. $C_{22}H_{28}O_{10}$ requires: C, 58.41; H, 6.19%.

TABLE 21

Column chromatogfaphic separation of phenylethyl tetra-O-acetyl-α-D-glucopyranoside

Column data: Same as in Table 11

Eluted fraction Nos.	Eluting solvent	Vol.of eluate (ml)	TLC picture (iodine chamber)	Wt.(g)
1 - 5	Pet.ether-acetone (95:5)	5 x 50	Phenyl ethyl alcohol	-
6 - 10	" (90:10)	5 x 50	fast moving product	-
11- 20	" "	10x 50	α	0.97
21	" "	1 x 50	α + β	-
22- 26	" "	5 x 50	β	0.11
27- 28	" "	2 x 50	-	-

REFERENCES

1 Bembry, T.H. and Powell, G., J. Am. Chem. Soc., 64(1942), 2419.

2 Lemieux, R.U. and Shyluk, W.P., Can. J. Chem., 31(1953),528.

3 Bose, J.L. and Ingle, T.R., Chem. and Ind. (1967), 1451. Carbohydrate Res., 12(1970), 459.

4 Capon, B., Chem. Rev., 69(1969), 407.

5 Conchie, J., Levvy, A and March, C.A., Adv. Carbohyd. Chem. 12(1957), 157.

6 Lemieux, R.U., Adv. Carbohyd. Chem., 9(1954), 1.

7 Montgomery, E.M., Richtmeyer, N.K. and Hudson, C.S., J. Am. Chem. Soc., 64(1942), 690.

8 Audichya, T.D., Ingle, T.R. and Bose J.L., Indian J.Chem. (In press), 11(1973), 704.

9 Audichya, T.D., Ingle, T.R. and Bose J.L., Indian J. Chem. in press.

10 Mrs Sinha (nee Bose), Bharati and Bose, J.L., Unpublished work.

11 Audichya, T.D., Ingle, T.R. and Bose, J.L., Indian J.Chem. 9(1971), 315.

12 Landge, A.B., Ingle, T.R. and Bose, J.L., Indian J. Chem. 7(1969), 1200.

13 Fischer, E. and Helferich, B., Ann., 383 (1911), 68.

14 Richtmyer, N.K., J. Am. Chem. Soc., 56(1934), 1636.

S U M M A R Y

SUMMARY

CHAPTER I - Introduction

This introductory chapter gives an account of the occurrence and role of glycosides in nature. It also briefly describes the usefulness of some of the natural and synthetic glycosides. This is followed up by a survey of various important synthetic methods available for the preparation of various glycosides indicating the drawbacks of some of these methods. As an introduction to the work presented in this thesis, a brief account of the earlier work on synthesis of glycosides using anhydrous stannic chloride and phosphorus oxychloride as catalysts is also included in this Chapter.

CHAPTER II - Synthesis of alkyl glycosides

Anhydrous stannic chloride has been extensively used in recent years by Bose *et al.* for the synthesis of both of the anomers of various acetylated aryl D-glycosides and thioglycosides. Except for the synthesis of only one acetylated alkyl β-D-glycoside in 1953 by Lemieux *et al.* no further work has been reported so far in literature for the synthesis of acetylated alkyl glycosides. This chapter gives an account of successful synthesis of ten α and β-anomers of acetylated alkyl glycopyranosides, some of them new, using this reagent. In the course of this work optimum conditions were also

established for the synthesis of the β- as well as the α-anomers. All of these acetylated glycosides were successfully deacetylated to the free glycosides by using Zemplen's method. In all ten acetylated and ten free alkyl glycosides have been prepared. Stannic chloride has thus been established as a valuable catalyst for the synthesis of alkyl α- and β-anomeric glycosides.

CHAPTER III - Stannic chloride catalysed synthesis of aryl alkyl glycosides

Some aryl alkyl glycosides are useful for biochemical studies. No aryl alkyl glycosides have been prepared so far by using stannic chloride as a catalyst. The present Chapter gives an account of successful synthesis of 12 acetylated aryl alkyl α- and β-glycosides for which optimum conditions were established. All of these glycosides were successfully deacetylated by Zemplen's method.

Thus stannic chloride has been established as a versatile catalyst for the preparation of all types of glycosides.

CHAPTER IV - Phosphorus oxychloride catalysed synthesis of glycosides

Bembry and Powell published a paper in 1942 in which they described the use of moist phosphorus oxychloride as a catalyst for the synthesis of a few acetylated aryl glycosides. No further work has been reported so far on any further use of this reagent for glycosidation.

In view of the successful use of stannic chloride as a catalyst for the synthesis of anomeric acetylated glycosides and a similarity of stannic chloride and phosphorus oxychloride it was considered of interest to investigate the usefulness of this reagent for the synthesis of not only the acetylated aryl β-D-glycosides but also of acetylated alkyl and aryl alkyl β-D-glycosides and of the corresponding α-anomers.

As a result of these studies it has been established that phosphorus oxychloride is an excellent catalyst for the synthesis of acetylated aryl, alkyl and aryl alkyl β-D-glycosides. Conditions were also established for the synthesis of the acetylated α-anomeric glycosides also with this reagent. Optimum conditions for obtaining the acetylated α and β-anomeric glycosides in good yields were also established. A pair of anomeric acetylated aryl D-thioglucosides were also successfully prepared using this reagent. A total of eleven acetylated glycosides were synthesised by this method. It was also proved that contrary to the observation of Bembry and Powell, the addition of water to phosphorus oxychloride do not bring about any advantage and, therefore, the dry reagent has been used throughout this work.

Phosphorus oxychloride has been also found to be a good reagent for anomerisation of the acetylated β-anomeric glycosides. This method can be used for the preparation of

the difficultly accessible α-anomers starting from more easily available β-anomers.