# THE CONFIGURATION OF GLYCOSIDIC LINKAGES IN OLIGOSACCHARIDES

## X. KÖNIGS–KNORR REACTIONS OF 3,5-DI-*O*-BENZOYL-ARABINO- AND -RIBO-FURANOSYL BROMIDES AND THEIR 2-SUBSTITUTED DERIVATIVES[1]

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ABSTRACT

The reactions of 3,5-di-*O*-benzoyl-L-arabinofuranosyl and -D-ribofuranosyl bromides and their 2-substituted 1,2-trans-derivatives (2-acetates, 2-benzoates, 2-*p*-nitrobenzoates, and 2-nitrates) with methanol and 1,2,3,4-tetra-*O*-acetyl-β-D-glucose have been studied. The products of these reactions, the occurrence of retention or inversion of configuration or ortho-ester formation, and the suitability of bromo derivatives for stereospecific synthesis of glycosidic linkages were considered. In general, the syntheses of oligosaccharides are more stereospecific than the corresponding formation of methyl glycosides. As in the α-D-mannopyranosyl bromide series, the reactions with tetra-*O*-acetyl-glucose give products with retention of configuration about C-1, presumably via an intermediate cyclic carbonium ion when there is an ester at C-2, but retention can take place also even when there is no convenient ester group at C-2 of the bromide. The participation of the C-2 substituent is particularly noteworthy in the condensations of the 2-acetate and 2-benzoate derivatives of 3,5-di-*O*-benzoyl-β-D-ribofuranosyl bromide with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose, which yield exclusively disaccharides of the orthoester type.

## INTRODUCTION

In a previous paper (1) various derivatives of α-D-mannopyranosyl bromide were used in condensation reactions with hydroxyl compounds under Königs–Knorr conditions. In some cases the configuration of the product was different from that expected on the basis of earlier work (summarized in refs. 2 and 3). For instance, 3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl bromide and its 2-*O*-benzyl derivative both gave disaccharides with an α-configuration on condensation with 1,2,3,4-tetra-*O*-acetyl-D-glucose. Previously, reactions examined in which a substituent in the 2-position could not participate by forming an intermediate cyclic carbonium ion (e.g. 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -D-galactopyranosyl bromides) have given products with the configuration opposite to that of the starting material. A qualitative and semi-quantitative study has now been made using 1-bromo derivatives of L-arabino- and D-ribo-furanose benzoates in which the bromo groups are also mainly trans to the C-2 substituent. The nature of the grouping at C-2 was varied and the configuration and structure of the products studied in two series of experiments. These reactions were carried out in the presence of silver oxide (*a*) with pure methanol and (*b*) with an excess of tetra-*O*-acetyl-D-glucose in chloroform in the presence of Drierite.

The current interest in nucleosides and nucleotides has focussed attention on stereospecific Königs–Knorr syntheses of pentofuranosyl glycosidic linkages. β-D-Ribofuranosyl derivatives have been prepared from 2,3,5-tri-*O*-acetyl-α-D-ribofuranosyl chloride (4) and bromide (configuration unknown) (5) and 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide (6, 7) whereas α-D-ribofuranosides can be derived from 5-*O*-benzoyl-2,3,-*O*-carbonyl-D-ribofuranosyl bromide (8). In the arabinofuranosyl series the α-configuration is readily attainable and has been synthesized by Wright and Khorana, who used 2,3,5-tri-*O*-benzoyl-α-D- and -L-arabinofuranosyl bromides (9) and a 2,3,5-tri-*O*-acetyl-L-arabinofuranosyl bromide (9) of uncertain configuration. β-D-Arabinofuranosides are of interest

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because of their natural occurrence in the nucleosides of sponges (10, 11). The Königs-Knorr synthesis of this type of linkage does not appear to have been carried out, although it has been formed by the inversion of the C-2 hydroxyl group of a D-ribofuranosyl uracil (12) and thymine (13, 14) derivatives. Although the conditions used above are different from those for disaccharide synthesis, it appeared that some of these bromides could be adapted for the preparation of α-L-arabinofuranosyl and β-D-ribofuranosyl disaccharides. Thus, the condensation of 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl bromide with 2,3,4-tri-*O*-acetyl-L-arabinose diethyl dithioacetal has now led to the synthesis of 5-*O*-α-L-arabinofuranosyl-L-arabinose, a structural component in sugar beet pentosan (15).

The use of substitutents on C-2 of a sugar bromide in order to control the configuration of the product has been demonstrated in the D-ribofuranose (8), the D-glucopyranose (16, 17, 18*a*), and the D-mannopyranose series (1), and use of this technique has now been utilized in the L-arabinofuranosyl and D-ribofuranosyl series. Convenient compounds for such starting materials in the preparation of 1-bromo derivatives of L-arabino- and D-ribo-furanose have been described by Fletcher and Ness (19, 20). These are 1,3,5-tri-*O*-benzoyl-β-L-arabinose and 1,3,5-tri-*O*-benzoyl-α-D-ribose, and from these compounds the 2-acetates (19, 21), 2-nitrates, and 2-*p*-nitrobenzoates can be prepared using conventional reactions. Treatment of these products with chloroform containing hydrogen bromide until constant rotation had been reached furnished the 1-bromo derivatives (Table I),

TABLE I

3,5-Di-*O*-benzoyl-L-arabino- and -D-ribo-furanosyl bromide derivatives and their reaction products with methanol and 1,2,3,4-tetra-*O*-acetyl-β-D-glucose

| 2-Substituted bromo derivatives | Specific rotations | Product from methanol | Product from 1,2,3,4-tetra-*O*-acetyl-β-D-glucose |
|---|---|---|---|
| 3,5-Di-*O*-benzoyl-L-arabinofuranose | | | |
| α-2-Acetate | −112° | Mainly orthoacetate* | α-Disaccharide* |
| | | α- and β-Glycoside | Trace of β |
| α-2-Benzoate | | Orthobenzoate | α-Disaccharide |
| | | α- and β-Glycoside (β > α) | Trace of β |
| α-2-*p*-Nitrobenzoate | −63° | Ortho-*p*-nitrobenzoate | α-Disaccharide |
| | | α- and β-Glycoside (β > α) | Trace of β |
| α-2-Nitrate | −65° | β-Glycoside | β-Disaccharide |
| | | | Trace of α |
| α-2-Hydroxyl | −103° | β-Glycoside | α and β-Disaccharide (39:61) |
| 3,5-Di-*O*-benzoyl-D-ribofuranose | | | |
| β-2-Acetate | −52° | Orthoacetate | Orthoester |
| | | α- and β-Glycoside | |
| β-2-Benzoate | −11° | Orthobenzoate | Orthoester |
| | | β-Glycoside | |
| β-2-*p*-Nitrobenzoate | +8° | Ortho-*p*-nitrobenzoate | β-Disaccharide |
| | | α- and β-Glycoside | Orthoester |
| β-2-Nitrate | −39° | α-Glycoside | α- and β-Disaccharide (32:68) |
| | | Trace of β | |
| α-2-Hydroxyl | +109° | α- and β-Glycoside | α- and β-Disaccharide (46:54) |

*In all these reactions some free arabinose (or ribose) was obtained on de-esterification. However, the purpose of the paper is to compare orthoester and α- and β-glycoside formation.

which were used immediately because of possible instability. From the specific rotations of the bromides it was concluded that all the L-arabinofuranose derivatives were predominantly α and the D-ribofuranose compounds β, with the notable exception of 3,5-di-*O*-benzoyl-D-ribofuranosyl bromide (20), which appeared to be α because of its marked difference in specific rotation from the rest of the series (Table I).

When the 2-benzoates, 2-*p*-nitrobenzoates, and 2-acetates of 3,5-di-*O*-benzoyl-L-arabinofuranosyl bromide and 3,5-di-*O*-benzoyl-D-ribofuranosyl bromide were treated in one series of experiments with methanol and in the other with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose (silver oxide being used in both cases as acid acceptor, with iodine present also in the arabinofuranosyl disaccharide syntheses) the course of reaction could be anticipated to some extent by taking into account participation, prior to glycoside formation, of the 2-substituted group via intermediate cyclic carbonium ions. In the L-arabinose series, methanol treatment of these bromides resulted in the formation of orthoester derivatives and methyl arabinofuranosides of which the β-anomer predominated. These results are essentially analogous to those obtained by Isbell and Frush when 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide was treated with methanol in the presence of silver carbonate (22) except that in this instance some methyl α-L-arabinofuranoside was formed in addition to the β-anomer. Also analogous were the results from the use of excess 1,2,3,4-tetra-*O*-acetyl-D-glucose as the nucleophilic reagent (1). The disaccharide formed after deacetylation was 6-*O*-α-L-arabinofuranosyl-D-glucose (characterized as the free sugar and its heptaacetate) with little of the β-anomer. However, mixtures of α- and β-disaccharides (39:61) were formed from 3,5-di-*O*-benzoyl-α-L-arabinofuranosyl bromide, in contrast to the product formed from 3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl bromide, which was mainly α in configuration (1). The possibility that the C-5 benzoyl group could participate in this reaction via a cyclic carbonium ion seems unlikely since on treatment with methanol the bromide yielded methyl β-L-arabinofuranoside and no 1,5-orthobenzoate.*

No orthoesters were obtained from the reaction of the arabinofuranosyl bromides with tetra-*O*-acetyl glucose, but their absence may have been due to the excess of acid which was found to be produced in early stages of the condensations. The Königs–Knorr condensations described in this paper were not carried out under optimum conditions in which the halide would be added slowly to an excess of the alcohol (23). Since some of the pentofuranosyl bromides were somewhat unstable, the mixture of alcohol and other components were added in one batch to a flask containing the bromide, immediately after its preparation. Such conditions were probably also responsible in all the condensations for a product in which gentiobiose and higher oligosaccharides could be detected after deacylation. In the case of the reaction using 3,5-di-*O*-benzoyl-α-L-arabinofuranosyl bromide, the disaccharide by-product was isolated and converted by de-esterification to gentiobiose. When 1,2,3,4-tetra-*O*-acetyl-β-D-glucose alone was treated with hydrogen bromide in chloroform, slow-moving spots corresponding to gentiobiose and higher oligosaccharides were noted on paper chromatograms after deacetylation. These results are similar to those described by Haq and Whelan (24), who produced 1,6-*O*-β-D-glucopyranose oligosaccharides by the self-condensation of 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl bromide. The yields of gentiobiose in the Königs–Knorr reactions in the L-arabinofuranose series appear to correspond to the reactivity of the starting halide towards alcohols. The 2-*p*-nitrobenzoyl and 2-*O*-nitro bromides gave little of the disaccharide by-product whereas the 2-benzoyl, 2-hydroxyl, and 2-acetyl bromides gave appreciable amounts.

Condensations using a 2-*O*-nitro halide have been reported by Wolfrom, Pittet, and Gillam (18), who prepared an α-disaccharide (contaminated with β) by the reaction of 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose. From a preparative point of view, 3,5-di-*O*-benzoyl-2-*O*-nitro-α-L-arabino-

*Similarly, no 1,5-orthobenzoate was formed from 3,5-di-O-benzoyl-α-D-ribofuranosyl bromide.

furanosyl bromide is similarly useful for synthesis of β-arabinofuranosides. Reaction of the 2-*O*-nitro bromide with methanol and 1,2,3,4-tetra-*O*-acetyl-β-D-glucose resulted in the formation of the methyl β-L-arabinofuranoside derivative and a β-disaccharide, respectively, and only traces of the α-anomers were formed. The latter result thus shows that the 2-nitrate group does not participate in the formation of an intermediate nitronium ion.

In the D-ribofuranosyl series the reactions with methanol and 1,2,3,4-tetra-*O*-acetyl-D-glucose gave mixtures of products (Table I), as would be expected on the basis of $S_N1$ mechanisms. Treatment of the bromides with tetra-*O*-acetyl-glucose gave mainly β-disaccharides, which were adulterated either with orthoester or α-disaccharide. In specific instances, such as the reaction of 3,5-di-*O*-benzoyl-2-*O*-nitro-β-D-ribofuranosyl bromide with methanol and 1,2,3,4-tetra-*O*-acetyl-β-D-glucose, some unexpected reactions took place. The methanol reaction gave complete inversion at C-1 whereas with tetra-*O*-acetyl-glucose there was much retention of configuration. This picture is similar to the condensation of 2-*O*-benzyl-3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide with methanol and tetra-*O*-acetyl-β-D-glucose, which has been considered in a previous paper (1).

Under certain conditions trans-1-bromides of sugars can be converted to products of the same configuration without the chemical participation of an ester group at C-2. 3,4,6-Tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucosyl chloride yields mainly the α-glycoside and does not, in contrast to trans-2-acetate derivatives, give a 1,2-orthotrichloroacetate on reaction with methanol (25). This has been explained by the reduction of nucleophilic activity of the carbonyl oxygen by the three chloro groups so that a cyclic carbonium ion intermediate is not possible (3). A more limited reduction of carbonyl participation could explain the differing reactions of the 2-acetyl, 2-benzoyl, and 2-*p*-nitrobenzoyl derivatives of 3,5-di-*O*-benzoyl-β-D-ribofuranosyl bromides with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose. The two former derivatives give orthoester products only whereas the 2-*p*-nitrobenzoate derivative gives rise to β-disaccharide also.

The reactions summarized in Table I can give rise to some overall generalizations. It appears that, in the five-membered ring, the ester group at C-2 can participate in the Königs–Knorr reaction by formation of cyclic carbonium ion intermediates to a greater extent than in the 6-membered series. The participation of C-2 is emphasized in the ribofuranosyl series since orthoester yield is very high in attempted ribofuranosyl disaccharide syntheses. This should not be surprising when the favorable stereochemistry of cis-carbon to oxygen bonds at C-1 and C-2 of the five-membered ring is considered. It can also be concluded that the reaction in disaccharide formation is more stereospecific than the corresponding methyl furanoside synthesis. This presumably is due to the size of the nucleophilic reagent, which could be a factor limiting the direction of approach of the tetra-*O*-acetyl glucose, in contrast to that of the smaller methanol molecule.

## EXPERIMENTAL

Evaporations were carried out under reduced pressure at 50° C (bath temperature and optical rotations were measured at 23° C).

*Preparation of 2-Substituted 1,3,5-Tri-O-benzoyl-β-L-arabinoses*

*(a) 2-p-Nitrobenzoate*

1,3,5-Tri-*O*-benzoyl-β-L-arabinose (1.40 g) was heated at 80° C for 1 hour in pyridine (20 ml) containing *p*-nitrobenzoyl chloride (1.40 g). The mixture was then added to aqueous sodium bicarbonate, shaken for an hour, and the precipitate which formed was filtered off. Two recrystallizations from ethyl acetate – hexane gave the 2-*p*-nitrobenzoate with m.p. 170–171° C and $[\alpha]_D$ +114° (*c*, 1.0, $CHCl_3$). Calculated for $C_{33}H_{25}O_{11}N$: C, 64.8%; H, 4.1%. Found: C, 64.6%; H, 4.2%.

*(b) 2-Nitrate*

1,3,5-Tri-*O*-benzoyl-β-L-arabinose (1.38 g) dissolved in acetic anhydride (10 ml) was added slowly to a mixture of acetic anhydride (8 ml) and fuming nitric acid (2 ml), cooled in an ice bath. After 30 minutes at 0° C and 15 minutes at room temperature, ice-cold aqueous sodium bicarbonate solution was added to destroy the reagent. Extraction with chloroform and evaporation of the extract yielded a solid which, on two recrystallizations from ethanol, yielded the 2-nitrate (1.06 g) with m.p. 99–100° C and $[\alpha]_D$ +58° (*c*, 0.5, $CHCl_3$). Calculated for $C_{26}H_{21}O_{10}N$: C, 61.5%; H, 4.2%; N, 2.8%. Found: C, 61.3%; H, 4.2%; N, 2.1%.

*Preparation of 2-Substituted 1,3,5-Tri-O-benzoyl-α-D-riboses*

*(a) 2-p-Nitrobenzoate*

1,3,5-Tri-*O*-benzoyl-α-D-ribose was *p*-nitrobenzoylated by the above method. Two recrystallizations from ethyl acetate – hexane yielded the 2-*p*-nitrobenzoate with m.p. 112–115° C and $[\alpha]_D$ +100° (*c*, 1.0, $CHCl_3$). Calculated for $C_{33}H_{25}O_{11}N$: C, 64.8%; H, 4.1%; N, 2.3%. Found: C, 64.8%; H, 4.2%; N, 2.2%.

*(b) 2-Nitrate*

1,3,5-Tri-*O*-benzoyl-α-D-ribose was converted to its sirupy 2-nitrate derivative using the nitration procedure described above. It had $[\alpha]_D$ +69° (*c*, 0.7, $H_2O$). Calculated for $C_{26}H_{21}O_{10}N$: N, 2.8%. Found: N, 2.2%.

*Bromination of 2-Substituted 1,3,5-Tri-O-benzoyl-β-L-arabinoses*

To purify the chloroform, it was washed with water, dried with calcium chloride, and distilled, and hydrogen bromide was bubbled through it for 2 minutes to yield an approximately 0.3 *N* solution. A 1% solution of each benzoate derivative in this solvent was prepared and its specific rotation followed. The solution was then evaporated (bath temperature 0° C), and residual hydrogen bromide removed by evaporation three times of chloroform solutions. The specific rotations recorded are as follows, the initial reading being measured in chloroform separately, and the final reading being the constant value reached:

| | | |
|---|---|---|
| (*a*) | 2-acetate | +60° → −112° (immediate), |
| (*b*) | 2-*p*-nitrobenzoate | +114° → −63° (7 minutes), |
| (*c*) | 2-nitrate | +58° → −65° (12 minutes), |
| (*d*) | 2-hydroxyl | +4° → −103° (immediate). |

*Bromination of 2-Substituted 1,3,5-Tri-O-benzoyl-α-D-riboses*

A similar bromination procedure was used, and the following specific rotations were measured:

| | | |
|---|---|---|
| (*a*) | 2-acetate | +74° → −52° (6 minutes), |
| (*b*) | 2-benzoate | +88° → −11° (9 minutes), |
| (*c*) | 2-*p*-nitrobenzoate | +100° → +8° (16 minutes), |
| (*d*) | 2-nitrate | +83° → −39° (2 hours), |
| (*e*) | 2-hydroxyl | +87° → +109° (immediate). |

*Reactions of Pentofuranosyl Bromides with Methanol*

The bromides prepared from the appropriate 1-benzoate derivative (0.50 g) were shaken for 1 hour in methanol (20 ml) containing an excess of silver oxide (2.5 g). The solutions were then filtered and evaporated. De-esterification, when necessary, was carried out in 30 hours using 0.1 *N* sodium methoxide in methanol (0.2 equivalents). Characterization of products was then carried out using paper chromatograms (sprays: *p*-anisidine hydrochloride (26) and ammoniacal silver nitrate (27); solvent: *n*-butanol–ethanol–water (40:11:19 v/v)). Orthoesters had $R_F$'s ~0.8 and methyl α-L-arabinofuranoside was characterized since it moved faster than its β-anomer, both glycosides having $R_F$'s ~0.4.

*(a) L-Arabinofuranosyl Series*

*(i) 2-Acetate derivative.*—The material appeared to be mainly the methyl orthoester. The reaction product had $[\alpha]_D$ +15° (*c*, 1.0, $CHCl_3$) and, after crystallization and two recrystallizations from hexane, had m.p. 120–121° C and $[\alpha]_D$ 0° (*c*, 2.3, $CHCl_3$). Calculated for $C_{22}H_{22}O_8$: C, 63.8%; H, 5.35%. Found: C, 63.9%; H, 5.4%. De-esterification did not give methyl arabinosides.

*(ii) 2-Benzoate derivative.*—The product had $[\alpha]_D$ −20° (*c*, 1.0, $CHCl_3$) and the de-esterified sample showed mainly orthoacetate, some methyl β-arabinoside, and only a small proportion of the α-anomer. Methyl 1,2-orthobenzoyl-L-arabinose was isolated by ethyl acetate extraction of an aqueous solution of the mixture which had been previously extracted with hexane to remove methyl benzoate. The product had no carbonyl absorption in the infrared and had $[\alpha]_D$ −5° (*c*, 2.1, $H_2O$). Treatment with 0.01 *N* sulphuric acid immediately changed this to +80° (*c*, 1.0) and the material (probably 2-*O*-benzoyl-L-arabinose) obtained after neutralization and evaporation had strong carbonyl absorption at 1710 $cm^{-1}$.

*(iii) 2-p-Nitrobenzoate derivative.*—The product had $[\alpha]_D$ +36° (*c*, 1.2, $CHCl_3$) and, on de-esterification, gave a similar picture on a paper chromatogram as the above 2-benzoate. 3,5-Di-*O*-benzoyl-1,2-methyl-ortho-*p*-nitrobenzoyl-L-arabinose crystallized, and two recrystallizations from ethyl acetate – hexane gave

material with m.p. 155–159° C and $[\alpha]_D$ +36° (*c*, 0.8, $CHCl_3$). Calculated for $C_{27}H_{23}O_{10}N$: C, 62.2%; H, 4.95%. Found: C, 61.8%; H, 4.8%. De-esterification gave material corresponding to a methyl ortho-*p* nitrobenzoate derivative on a paper chromatogram.

*(iv) 2-Nitrate derivative.*—The product, $[\alpha]_D$ +85° (*c*, 1.5, $CHCl_3$), crystallized, and two recrystallizations from hexane yielded methyl 3,5-di-*O*-benzoyl-2-*O*-nitro-β-L-arabinofuranoside with m.p. 98–99° C and $[\alpha]_D$ +85° (*c*, 0.8, $CHCl_3$). Calculated for $C_{20}H_{19}O_9N$: C, 57.55%; H, 4.6%; N, 3.4%. Found: C, 57.8%; H, 4.7%; N, 2.8%. The methyl glycoside (37 mg) was shaken in ethanol (10 cc) containing 5% palladium on charcoal (30 mg) under 2 atmospheres of hydrogen for 24 hours (28). After filtration and evaporation the product was de-esterified to yield methyl β-L-arabinofuranoside (identified on a paper chromatogram).

*(v) Hydroxyl derivative.*—The methyl glycoside derivative obtained appeared to be methyl 3,5-di-*O*-benzoyl-β-L-arabinofuranoside since only the β-L-glycoside was obtained on de-esterification.

*(b) D-Ribofuranosyl Series*

The products obtained in this series were sirupy and are summarized in Table I. The specific rotations of the products after treatment with methanol are as follows: 2-acetate +72° (*c*, 0.6, $CHCl_3$); 2-benzoate +90° (*c*, 0.9, $CHCl_3$); 2-*p*-nitrobenzoate +112° (*c*, 1.1, $CHCl_3$); 2-nitrate +69° (*c*, 0.7, $CHCl_3$); and 2-hydroxyl +39° (*c*, 0.8, $CHCl_3$). Methyl ribofuranosides were identified by their relative $R_F$ values (29).

*Reactions of L-Arabinofuranosyl Bromides with 1,2,3,4-Tetra-O-acetyl-β-D-glucose*

In these experiments 1.0 g of the appropriate bromide was mixed with silver oxide (1.0 g), iodine (0.25 g), and Drierite (5.0 g). Then a solution of 1,2,3,4-tetra-*O*-acetyl-β-D-glucose (4.0 g) in dry chloroform (16 ml) was added, and the mixture was shaken overnight. After filtration and evaporation the sirup was de-esterified with 0.2 equivalents of 0.1 *N* sodium methoxide in methanol over 3 hours. The product was then examined on paper chromatograms in the ethyl acetate – pyridine – water (10:4:3 v/v) solvent using aniline oxalate (30) as spray. 6-*O*-α-L-Arabinofuranosyl-D-glucose had $R_{Galactose}$ 1.2 whereas the β-anomer had $R_{Galactose}$ 1.0. In each addition some gentiobiose and higher homologues were detected and the disaccharide was isolated in the case of the condensation with 2-hydroxyl derivative. The products were fractionated on a cellulose column. *n*-Butanol saturated with water gave a partial separation of the arabinosyl glucosides and *n*-butanol–ethanol–water (4:1:1 v/v) eluted gentiobiose.

*(i) 2-O-Benzoyl derivative.*—The product was mainly 6-*O*-α-L-arabinofuranosyl-α-D-glucose (0.30 g) with spots corresponding to 1,6-*O*-β-glucopyranosyl oligosaccharides. The former was recrystallized twice from ethanol and had m.p. 163–165° C and $[\alpha]_D$ −15° → −40° (*c*, 1.0, $H_2O$; constant value, 18 hours). Calculated for $C_{11}H_{20}O_{10}$: C, 42.3%; H, 6.5%. Found: C, 42.3%; H, 6.4%. The sugar was α rather than β since on oxidation in aqueous sodium periodate the specific rotation of the solution changed to −77° (*c*, 0.6, $H_2O$) (31). The crude disaccharide (0.24 g) was heated in acetic anhydride (2 ml) containing sodium acetate (0.20 g) at 100° C overnight. The anhydride was destroyed with ice water and the mixture extracted with benzene. The solution was evaporated and the residue crystallized from ethanol–hexane. Recrystallization from the same solvent gave hepta-*O*-acetyl-6-*O*-α-L-arabinofuranosyl-β-D-glucose (0.17 g) with m.p. 108–109° C and $[\alpha]_D$ −20° (*c*, 2.0, $CHCl_3$). Calculated for $C_{25}H_{34}O_{17}$: C, 49.5%; H, 5.7%. Found: C, 49.45%; H, 5.7%. The acetate appeared to be β since its mother liquor had a specific rotation of −10° (*c*, 2.0, $CHCl_3$).

*(ii) 2-O-Acetyl derivative.*—In addition to 6-*O*-α-L-arabinofuranosyl-D-glucose (310 mg) spots corresponding to 1,6-*O*-β-D-glucopyranosyl oligosaccharides were obtained. The arabinosyl glucose was converted to its hepta-*O*-acetate, m.p. and mixed m.p. 106.5–108° C.

*(iii) 2-p-Nitrobenzoate derivative.*—The product in this case contained only a trace of glucose containing oligosaccharides and in the arabinofuranosyl glucose fraction the α-anomer predominated. The isolated 6-*O*-α-L-arabinofuranosyl-D-glucose (252 mg) was converted to the hepta-*O*-acetate, m.p. and mixed m.p. 107.5–109.5° C.

*(iv) 2-Nitrate derivative.*—Here the reaction mixture was filtered and evaporated and half of the residue taken up in benzene, which was then washed three times to remove tetra-*O*-acetyl-glucose. On evaporation, the sirup crystallized and after two recrystallizations from ethanol yielded 0.22 g of 6-*O*-β-(3,5-di-*O*-benzoyl-2-*O*-nitryl-L-arabinofuranosyl)-(1,2,3,4-tetra-*O*-acetyl-β-D-glucose) with m.p. 152–153° C and $[\alpha]_D$ +83° (*c*, 1.1, $CHCl_3$). Calculated for $C_{33}H_{35}O_{18}N$: C, 54.0%; H, 4.8%. Found: C, 54.0%; H, 4.8%.

Of this material 0.11 g was denitrated by shaking in ethanol (25 ml) containing 5% palladium charcoal (0.20 g) under 2 atmospheres of hydrogen overnight. After filtration of the catalyst this process was repeated. Refiltration and evaporation gave a product (45 mg) which did not crystallize on seeding with the starting material. The product had $[\alpha]_D$ +49° (*c*, 1.1, $CHCl_3$), and de-esterification gave 6-*O*-β-L-arabinofuranosyl-D-glucose (20 mg) with $[\alpha]_D$ +73° (*c*, 0.6, $H_2O$).

Repetition of this process on the crude Königs–Knorr product showed that only a trace of the 6-*O*-α-L-arabinofuranosyl-D-glucose derivative was present.

*(v) 2-Hydroxyl derivative.*—The product consisted of 6-*O*-α- and 6-*O*-β-L-arabinofuranosyl-D-glucose. An attempt was made to fractionate these on a cellulose column and two fractions were obtained, one (373 mg) with $[\alpha]_D$ +34° (*c*, 1.5, $H_2O$) and the other (79 mg) with $[\alpha]_D$ +8° (*c*, 1.3, $H_2O$). Based on the known specific rotations of the α- and β-disaccharide, the mixture consisted of 39% of the α- and 61% of the β-anomer.

Gentiobiose (310 mg) was also separated from its higher oligomer and was converted to its β-octaacetate derivative (32). Two recrystallizations from ethanol gave crystals with m.p. 200–202° C and $[\alpha]_D$ −5° (*c*, 1.2, $CHCl_3$). Calculated for $C_{28}H_{38}O_{19}$: C, 49.6%; H, 5.6%. Found: C, 49.6%; H, 5.65%. X-Ray diffraction patterns of this and a specimen of authentic gentiobiose, β-octaacetate, were identical.

*Action of Hydrogen Bromide in Chloroform on 1,2,3,4-Tetra-O-acetyl-β-D-glucose*

1,2,3,4-Tetra-*O*-acetyl-β-D-glucose (0.48 mmole) was treated with hydrogen bromide (0.96 mmole) in chloroform (5.4 ml) and the specific rotation followed.

| Time (minutes) | 0 | 2 | 4 | 5 | 6 | 10 |
|---|---|---|---|---|---|---|
| Specific rotation (in pure $CHCl_3$) | +11° | −26° | −32° | −39° | −43° | −46° |

The solution after 10 minutes was washed with aqueous sodium bicarbonate, then water, and evaporated. Deacetylation gave mainly glucose with a small proportion of material corresponding to gentiobiose.

*Reactions of* D-*Ribofuranosyl Bromides with 1,2,3,4-Tetra-O-acetyl-β-D-glucose*

The conditions used in this series of experiments were identical with those used in the L-arabinofuranosyl series, except that the relative proportion of silver oxide was increased fivefold and no iodine was used.

*(i) 2-O-Acetyl derivative.*—The product, after deacetylation, gave a yellow spot with $R_{Galactose}$ 0.8 on paper chromatograms (solvent: *n*-butanol–ethanol–water (40:11:19 v/v); spray: *p*-anisidine hydrochloride) and this disappeared on acidification with acetic acid. No normal disaccharide was present.

*(ii) 2-O-Benzoyl derivative.*—When a similar procedure as for the above 2-acetyl derivative was used a spot with $R_{Galactose}$ 0.9 was obtained, also corresponding to orthoester. No ribofuranosyl-glucose was present.

*(iii) 2-p-Nitrobenzoyl derivative.*—The product on de-esterification appeared to be a mixture of orthoester and a normal disaccharide. The disaccharide fraction had $R_{Galactose}$ 0.95 (and a trace at 0.90) in the ethyl acetate – pyridine – water (10:4:3 v/v) solvent, and on isolation from a cellulose column it (35 mg) had $[\alpha]_D$ 0° (*c*, 1.0, $H_2O$). Oxidation with aqueous sodium periodate changed its specific rotation to −94° (*c*, 0.6, $H_2O$; constant value 5 minutes), indicating a β-linkage. Acetylation of the 6-*O*-β-D-ribofuranosyl-D-glucose by the hot acetic anhydride – sodium acetate method (see earlier in experimental reaction for method) yielded a substance which crystallized, and after two recrystallizations from ethanol–hexane the waxy hepta-*O*-acetate had m.p. 108–110° C and $[\alpha]_D$ +3° (*c*, 1.5, $CHCl_3$). Calculated for $C_{25}H_{34}O_{17}$: C, 49.5%; H, 5.65%. Found: C, 49.6%; H, 5.7%.

*(iv) 2-Nitrate derivative.*—After denitration (as for denitration of the 2-nitrate of the corresponding L-arabinofuranose derivative) followed by de-esterification the mixture was fractionated on a cellulose column. The product (41 mg) had $[\alpha]_D$ +34° (*c*, 0.9, $H_2O$), and on oxidation with sodium periodate a value of −48° (*c*, 0.5, $H_2O$; constant value 1 hour) was obtained. This corresponds to 68% of 6-*O*-β-D-ribofuranosyl-D-glucose and 32% of the α-anomer (31).

*(v) 2-Hydroxyl derivative.*—After de-esterification paper chromatography showed an almost equal mixture of the β- and α-anomers ($R_{Galactose}$ 0.95 and 0.90 respectively). Column chromatography yielded two fractions, one (16 mg) with $[\alpha]_D$ +77° (*c*, 1.0, $H_2O$) (after periodate oxidation +54° (*c*, 0.6, $H_2O$)) consisting mainly of 6-*O*-α-D-ribofuranosyl-D-glucose, and the other (14 mg) had $[\alpha]_D$ +12° (*c*, 0.6, $H_2O$) (after periodate oxidation −88° (*c*, 0.3, $H_2O$)) and was mainly β-anomer. The combined fractions thus appear to consist of 54% of β- and 46% of α-disaccharide.

*Preparation of 5-O-α-L-Arabinofuranosyl-L-arabinose*

*5-O-α-L-Arabinofuranosyl-L-arabinose Diethyl Thioacetal*

Using the same Königs–Knorr conditions as for the preparation of the other L-arabinofuranosyl disaccharides 2,3,4-tri-*O*-benzoyl-α-L-arabinofuranosyl bromide (1.0 g) was treated with 2,3,4-tri-*O*-acetyl-L-arabinose diethyl thioacetal. The product, after de-esterification, was fractionated on a cellulose column. Benzene–ethanol–water (1000:50:1 v/v) eluted unchanged thioacetal and the (500:50:1 v/v) mixture gave the disaccharide thioacetal (0.41 g). The mercaptal was crystallized twice from ethyl acetate – hexane and had m.p. 56° C and $[\alpha]_D$ −62° (*c*, 1.3, $H_2O$). Calculated for $C_{19}H_{28}O_8S_2$: C, 43.3%; H, 7.3%. Found: C, 42.9%; H, 7.3%. Oxidation with sodium periodate gave a product with $[\alpha]_D$ −91° (*c*, 0.6, $H_2O$), thus indicating an α-L-configuration for the disaccharide linkage.

*5-O-α-L-Arabinofuranosyl-L-arabinose*

The disaccharide thioacetal (100 mg) was acetylated by the hot acetic anhydride – sodium acetate method (see earlier in experimental section for method) to yield the hexa-*O*-acetate (158 mg). This was dissolved in acetone (3 ml) and water (1.5 ml). Mercuric oxide (2.0 g) was added, followed by mercuric chloride (0.40 g) in acetone (4 ml), to the stirred mixture. After 30 minutes the solution was refluxed for 10 minutes, and then filtered and evaporated. The sirup was dissolved in chloroform, which was washed twice with water, dried ($MgSO_4$), filtered, and evaporated. The product was deacetylated and the disaccharide obtained was fractionated on a cellulose column (*n*-butanol 3/4 saturated with water as solvent) to yield the purified material (55 mg) with $[\alpha]_D$ −94° (*c*, 1.4, $H_2O$). A sample of disaccharide prepared from

sugar beet araban had $[\alpha]_D$ −72° (15). On sodium periodate oxidation the $[\alpha]_D$ changed to −76° (210 minutes; *c*, 0.9, $H_2O$) (expected value: −79° to −88° (31)), thus indicating that the 5-*O*-α-L-arabinofuranosyl-L-arabinose was not entirely pure.

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