# Photobromination of Carbohydrate Derivatives. Part 7.[1] Reaction of Furanose Derivatives with Bromine: 4'-Bromo- and 4'-Fluoro-aldofuranose and -nucleoside Esters

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Photobromination of 1-O-acetyl-2,3,5,6-tetra-O-benzoyl-β-D-glucose or -D-galactose with bromine gives the same mixture of 4-monobrominated compounds from which the D-*galacto*-epimer can be isolated in *ca.* 70% yield. 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribose similarly gives the 4-bromo-products; the D-*ribo*-isomer was isolated and the corresponding halogenated derivative was obtained from pentabenzoyladenosine. In each of these series 4-fluoro-analogues were obtained from the initial bromides.

In previous reports in this series radical brominations of a range of aldopyranosyl compounds have been described by which the halogen can be introduced into their sugar rings at positions adjacent to the ring oxygen atom. Early studies showed that pyranoid uronic acid derivatives can efficiently take part in the reaction to give 5-bromo-derivatives,[2] and other workers have now established that ketonic groups or their O-substituted oximes within the sugar rings,[3] or C-nitrile groups attached to them,[3,4] can activate α-related ring carbon atoms towards homolytic bromination. In this way, bromine has been introduced to give glycopyranosyl bromide derivatives by use of the carbonyl group at C-2 or the nitrile substituent at C-1. We had earlier noted that under photobromination conditions 1-H can be abstracted from both alkyl pyranoside[5] and aryl 1-thiopyranoside esters,[6] and that various reactions can ensue. For the bromination reaction to occur with good selectivity at C-5 we have concluded that the anomeric centre should bear a substituent which is less able to stabilise radicals at this position than is an alkoxy group and which, also, should preferably occupy the equatorial site. In such cases strong radical-stabilising groups are not required adjacent to C-5 as is evidenced by the findings that penta-O-acyl-β-D-glucopyranose,[7,8] tetra-O-acetyl-β-D-xylopyranose,[9] and aryl β-D-glucopyranoside esters[5] undergo efficient bromination at this position.

Since hydrogen abstraction from the ether carbon atoms of tetrahydrofuran is favoured relative to abstraction from these positions of tetrahydropyran,[10] bromination of furanose derivatives should occur relatively readily under radical conditions. Tri-O-acetyl-1,6-anhydro-β-D-glucopyranose (and a disaccharide derivative containing a 1,6-anhydro-D-glucopyranose unit[11]), in which C-5 is a ring junction atom, undergoes substitution at C-6[1] to provide the only examples so far reported of such a reaction within a 5-membered ring of a sugar derivative. We now report a study of the photobromination of some furanosyl compounds, using bromine as radical source and carried out with the hope of obtaining 4-bromo-products. To this end, we initially selected for examination compounds with ester groups at C-1 (see above). Such bromides were of interest as potential precursors of 4-enofuranose derivatives from which functionalised cyclopentanes could perhaps be made[12] following the precedent that, on treatment with mercury(II) salts in aqueous media, 6-deoxyhex-5-enopyranosyl derivatives are efficiently converted into cyclohexanones.[13] Secondly, the characterisation of the potent antitrypanosomal agent nucleocidin[14] as a 4'-fluoroadenosine derivative has raised interest in 4-substituted aldofuranose compounds, the great majority of which have been made by addition reactions applied either to ald-3-enofuranose[15] or ald-4-enofuranose[16]

derivatives. One example has been reported of a carbon substituent having been introduced at C-4 of a furanoid compound by a sigmatropic rearrangement process,[17] but the only direct substitutions to have been effected involve compounds having a carbonyl group at C-5.[18]

Photobromination of 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose and 3,5,6-tri-O-benzoyl-1,2-O-isopropylidene-α-D-glucofuranose gave several products, [1]H n.m.r. examination of which indicated that at least some bromination had occurred at C-1. When, however, the reaction was applied to 1,2-di-O-acetyl-3,5,6-tri-O-benzoyl-β-D-glucose (1) substantially only one product was formed and the [1]H n.m.r. spectrum was consistent with its having been produced by substitution of bromine at C-4. While this pentaester was inconvenient to prepare, being a syrup and difficult to separate from its α-anomer with which it was produced on acetolysis of the corresponding 1,2-O-isopropylidene acetal, the tetrabenzoyl-glycosyl acetate (2) was obtainable in high yield by adaptation of a procedure reported by Wolfrom and Groebke.[19] Rather than make this compound from ethyl 2,3,5,6-tetra-O-benzoyl-1-thio-α-D-glucofuranoside by way of the glycosyl chloride, we used solvolysis in acetic acid and mercury(II) acetate to activate the ethylthio group[20] and obtained the required ester almost quantitatively.[21]

Treatment of the tetra-O-benzoyl β-acetate (2) in refluxing carbon tetrachloride with bromine under a heat lamp caused rapid conversion into one major product which was isolated as a pure microcrystalline solid in 72% yield following purification on a column of silica gel. N.m.r. spectroscopy (both ^{1}H and ^{13}C) and elemental analysis indicated that a bromine atom had replaced 4-H of the starting material, and the compound was assigned the D-*galacto*-configuration (5) by comparative n.m.r. methods (see below). Examination of the unfractionated reaction products showed that a second bromo-compound was present (Scheme 1), and from its [1]H n.m.r. features (Table 1, obtained from the spectrum of the mixture) it was assigned the 4-bromo-D-*gluco*-structure (6).

In the pyranose series it was concluded that discrete carbohydrate radical intermediates were involved in the photobromination reactions since penta-O-acetyl-β-D-glucopyranose gave the same 5-bromide as did its 5-epimer.[7] To see whether the same applied in the present case the D-*galacto*-isomer (3) of compound (2) was subjected to the reaction and it afforded the same products (5) and (6) in the same proportions. Compounds (5) and (6) as produced from the esters (2) and (3) might, however, represent the same equilibrated mixture derived from different initial products, and to investigate this possibility compound (5) was heated with tetra-n-butylammonium bromide in carbon tetrachloride and

**Table 1.** [1]H N.m.r. parameters for 4-halogenoaldofuranose esters



(2) X = H
(7) X = F
(6) X = Br
(19) X = Cl

(3) X = H
(8) X = F
(5) X = Br
(20) X = Cl

(9) X = H
(15) X = F
(11) X = Br

(14) X = F
(12) X = Br

| Compound | Chemical shifts ($\delta$; $CDCl_3$)[a] | | | | | | | | Observed coupling constants (Hz) | |
| | 1-H | 2-H | 3-H | 5-H | 5'-H | 6-H | 6'-H | Ac | $J_{1,2}$ | $J_{2,3}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| (2) | 6.44 | 5.59 | 5.93 | 5.8 | | 5.0 | 4.62 | 2.18 | 0 | 0.9 |
| (7) | 6.69 | 5.47 | 5.88 | 6.10 | | 5.02 | 4.72 | 2.16 | 0 | 0 |
| (6) | 6.70 | 5.45 | 6.28 | 6.29 | | 5.07 | 4.84 | 2.20 | 1.5 | 0.5 |
| (19) | 6.71 | 5.47 | 6.12 | 6.22 | | 5.07 | 4.82 | 2.19 | 1.1 | 0.5 |
| (3) | 6.53 | 5.62 | 5.73 | 6.04 | | 4.7 | 4.7 | 2.17 | 0 | 0 |
| (8) | 6.56 | 5.82 | 6.11 | | | | | 2.21 | 2.2 | 4.7 |
| (5) | 6.59 | 5.98 | 6.09 | 6.06 | | 5.18 | 4.79 | 2.23 | 2.4 | 6.0 |
| (20) | 6.57 | 5.96 | 6.22 | 6.01 | | 5.13 | 4.76 | 2.23 | 2.7 | 5.7 |
| (9) | 6.46 | 5.79 | 5.93 | 4.8 | 4.50 | | | 1.98 | 0.8 | 4.9 |
| (15) | 6.61 | 5.78 | 6.00 | 4.78 | 4.53 | | | 1.98 | 0 | 5.3 |
| (11) | 6.57 | 5.84 | 6.01 | 5.20 | 4.63 | | | 1.84 | 0 | 5.4 |
| (14) | 6.66 | 5.91 | 6.19 | 4.85 | 4.65 | | | 2.19 | 3.0 | 5.1 |
| (12) | 6.74 | 6.28 | 6.49 | 4.98 | 4.83 | | | 2.21 | 3.9 | 4.9 |

[a] Although all the given data were obtained from spectra measured in deuteriochloroform, assignments were on several occasions assisted by re-examination in perdeuterioacetone in which resolutions of signals were freqeuently better. Resonances for the ester groups were observed as expected.

gave a mixture, shown by [1]H n.m.r. spectroscopy, to contain 74% starting material and 26% of the D-*gluco*-isomer (6). Equilibration therefore could have occurred subsequent to photobromination. When the pentaesters were brominated in the presence of potassium carbonate to remove hydrogen bromide the products in each case were shown ([1]H n.m.r.) to be the two bromides in the ratio 82:18. It is therefore concluded that the epimeric starting materials both gave mainly compound (5) as initial product by way of a common radical intermediate. It was not established whether the first D-*gluco*-bromide formed was derived from the analogous D-*gluco*-radical or by some isomerisation of the *galacto*-product (5).
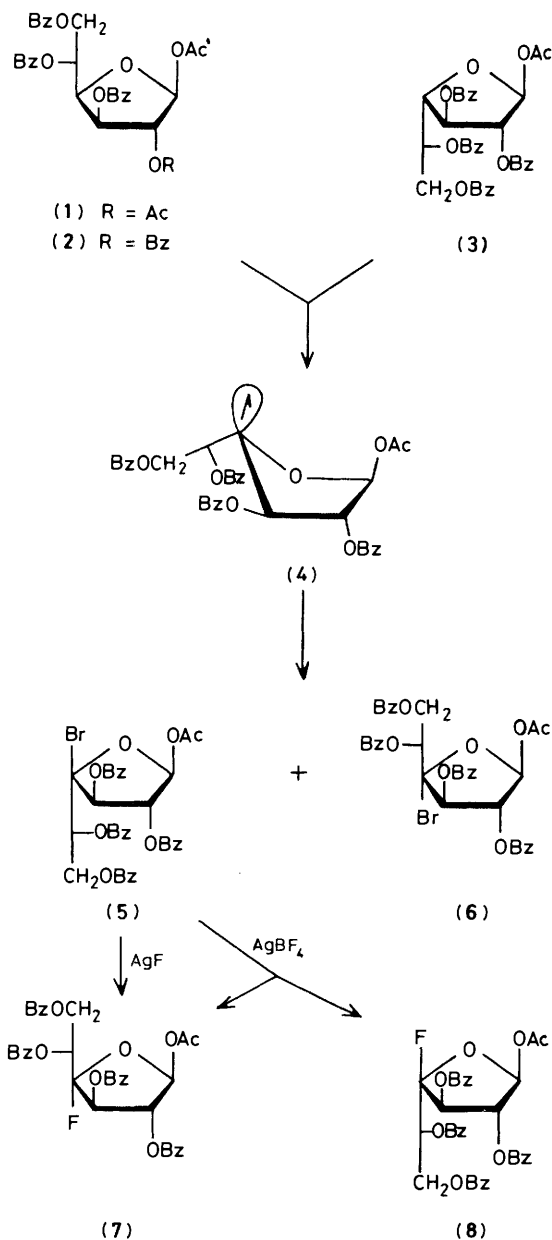
It is proposed that the intermediate is the pyramidal species (4) which, in the D-*galacto*-configuration and the illustrated conformation ($^4E$), is stereoelectronically favoured at the radical centre[10,22] and, furthermore, the large ring substituents at C-3 and C-4 are both *trans*-related and suitably *quasi*-equatorial. The coupling constants $J_{1,2}$ and $J_{2,3}$ (Table 1) for the main reaction product (5) indicate that it also adopts this envelope conformation. Alternatively, the less stable radical with the D-*gluco*-configuration would, for stereoelectronic reasons, favour the $E_4$ ring shape, but now the C-3 substituent is *quasi*-axial and C-3, C-4 groups are unfavourably *cis*-related. It is again noteworthy that the brominated product (6) adopts the same conformation as is probably favoured by its predecessor radical.

A most convenient feature of the mixture of bromides (5) and (6) was that the latter hydrolysed specifically during chromatography on a silica gel column—presumably because of neighbouring group assistance by the ester group at C-3—and therefore the pure D-*galacto*-isomer (5) was readily

obtainable by column chromatography as a syrup which occasionally transformed into a microcrystalline solid.

Attention was then turned to 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (9) which, on a small scale and in a water-cooled photoreactor and in the presence of potassium carbonate, gave the D-*ribo*-product (11) exclusively. However when either the reaction was carried out on a larger scale or without cooling of the solvent, mixtures of this and the L-*lyxo*-isomer (12) were obtained in the ratio 55:45 (Scheme 2) which was found in equilibration studies to be near the equilibrated ratio. This suggests that the *ribo*-compound was formed under kinetic control and that isomerisation to the L-*lyxo*-epimer ensued. The initial formation of the D-*ribo*-compound can be accounted for by invoking the intermediacy of the radical (10) in the $^3T_4$ conformation in which the uncoupled electron occupies a suitable *quasi*-axial orbital[10,22] and non-bonded interactions between 2-O, 3-O, and 3-O, C-5 are minimised. The proton–proton coupling constants $J_{1,2}$ and $J_{2,3}$ (Table 1) indicate the product (11) also adopts a similar conformation (11a)[23] which permits the electronegative atom and the carbon-bonded substituent at C-4 to occupy their preferred *quasi*-axial and *quasi*-equatorial sites, respectively. Likewise, the L-*lyxo*-bromide (12) adopts a conformation close to $^4T_3$, (12a), having these groups in the same orientations.

When a mixture of the epimeric bromides (11) and (12) was passed through a column of silica gel under flash chromatography conditions[12] only the former was eluted (50%) and, as happened in the case of the hexose derivatives (5) and (6), the isomer with the ester group at C-3 *trans*-related to the bromine atom underwent hydrolysis. A compound having ^{1}H and [13]C n.m.r. spectral characteristics consistent with those expected for the anticipated hydrolysis product—2,3,5-tri-*O*-
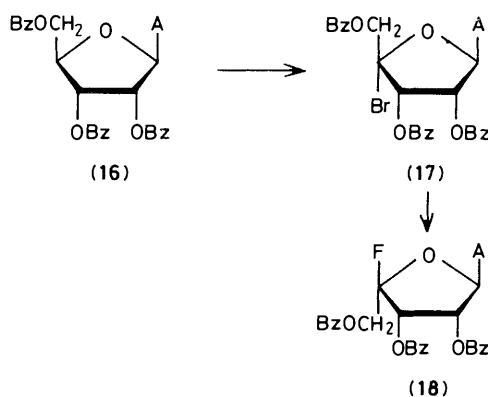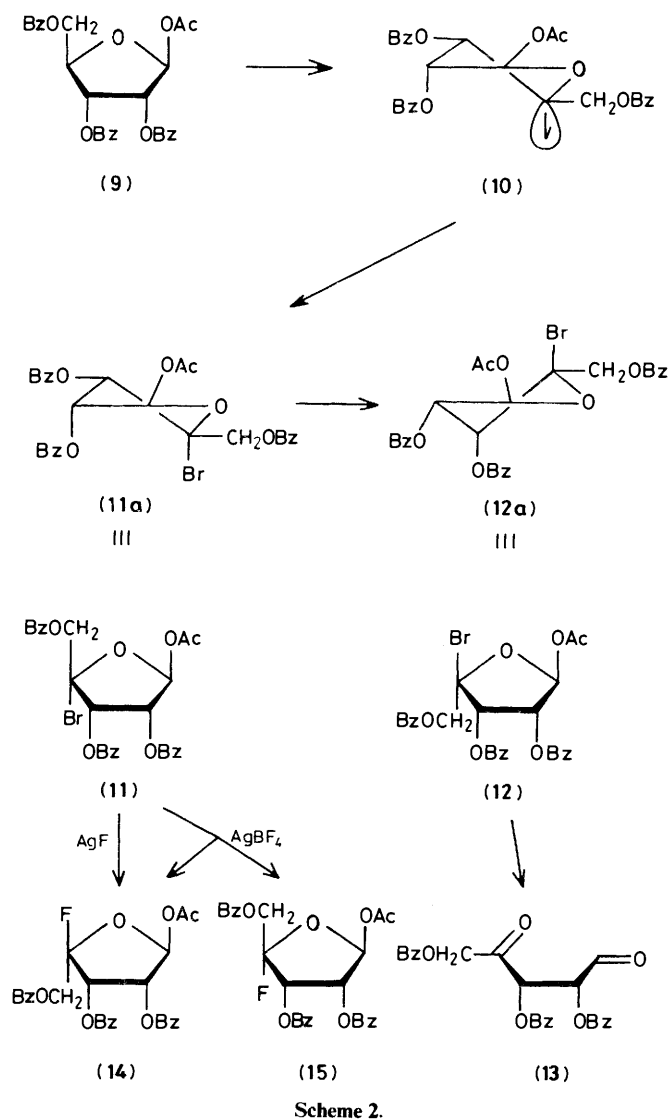
BzOCH₂ / BzO / OAc' / OBz / OR

(1) R = Ac
(2) R = Bz

O / OAc / OBz / OBz / CH₂OBz

(3)

BzOCH₂ / BzO / OBz / O

(4)

Br / O / OAc / OBz / OBz / OBz / CH₂OBz

(5)

+

BzOCH₂ / BzO / O / OAc / OBz / Br / OBz

(6)

BzOCH₂ / BzO / O / OAc / OBz / F / OBz

AgF

AgBF₄

(7)

F / O / OAc / OBz / OBz / OBz / CH₂OBz

(8)

**Scheme 1.** Bz = benzoyl

BzOCH₂ / O / OAc / OBz / OBz

(9)

BzO / OAc / BzO / O / CH₂OBz

(10)

BzO / OAc / BzO / O / CH₂OBz / Br

(11a)
III

AcO / Br / CH₂OBz / BzO / O / OBz

(12a)
III

BzOCH₂ / O / OAc / Br / OBz / OBz

(11)

Br / O / OAc / BzOCH₂ / OBz / OBz

(12)

AgF

AgBF₄

F / O / OAc / BzOCH₂ / OBz / OBz

(14)

BzOCH₂ / O / OAc / F / OBz / OBz

(15)

BzOH₂C / O / O / OBz / OBz

(13)

**Scheme 2.**

BzOCH₂ / O / A / OBz / OBz

(16)

BzOCH₂ / O / A / Br / OBz / OBz

(17)

F / O / A / BzOCH₂ / OBz / OBz

(18)

**Scheme 3.** A = 1,N-Dibenzoyladenin-9-yl. The positions of the benzoyl groups are taken by analogy but do not appear to have been rigorously established (see ref. 34)

benzoyl-D-erythro-pentos-4-ulose (13)—was also isolated (33%).

Photobromination of the adenosine derivative (16) gave a complex mixture of products from which the unstable 4'-bromo-D-ribo-derivative (17) was isolated in 14% yield as a syrup (Scheme 3). A second product with a similar ¹H n.m.r. spectrum was tentatively characterised as the 4',8-dibromo-analogue, the second bromine atom being assigned to C-8 because of the preference for radical substitution at this position shown by adenosine esters.[25] A significantly better yield of the monobromide was subsequently obtained using N-bromosuccinimide as brominating agent.[26]

The epimerisations of the 4-bromo-compounds which were effected by use of bromide ions and the observed substitution reactions which occurred with amide nitrogen nucleophiles[26] suggested the possibility of carrying out formal nucleophilic displacements—particularly with fluoride ions because of the relationship of the possible products with nucleocidin.[14]

Accordingly, the D-galacto-bromide (5) was treated with silver fluoride in suspension in acetonitrile and gave the syrupy D-gluco-fluoride (7) (which was difficult to dry and analysed as a monohydrate) in good yield in accord with observations that 1,2-cis-related acylated glycosyl bromides react, under these

**Table 2.** $^{13}$C N.m.r. parameters for 4-halogenofuranose esters[a]

| Compound | Chemical shifts ($\delta$/p.p.m.) | | | | | | $^{13}$C, $^{19}$F Coupling constants (Hz) | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | $J_{C\ 1,F}$ | $J_{C\ 2,F}$ | $J_{C\ 3,F}$ | $J_{C\ 4,F}$ | $J_{C\ 5,F}$ |
| (2)[b] | 99.6 | 81.0 | 74.8 | 81.0 | 70.5 | 64.6 | | | | | |
| (7)[b] | 102.0 | 79.0 | 77.2 | 120.7 | 70.6 | 62.5 | 0 | 0 | 41.2 | 232.1 | 26.4 |
| (19)[b] | 102.5 | 81.7 | 80.4 | 109.2 | 71.8 | 64.0 | | | | | |
| (3)[b] | 100.1 | 82.2 | 78.1 | 84.4 | 71.4 | 64.3 | | | | | |
| (8)[c] | 98.8 | 79.7 | 75.5 | | 70.1 | 62.2 | 2.2 | 0 | 21.1 | | 35.7 |
| (5)[b] | 99.6 | 80.7 | 76.9 | 104.3 | 75.3 | 63.9 | | | | | |
| (9)[c] | 98.6 | 75.2 | 71.7 | 80.2 | 63.9 | | | | | | |
| (15)[c] | 98.3 | 73.1 | 70.1 | 114.4 | 62.8 | | 0 | 0 | 18.0 | 237.5 | 44.4 |
| (11)[c] | 99.2 | 73.5 | 70.8 | 100.8 | 67.1 | | | | | | |
| (14)[c] | 99.4 | 74.9 | 74.6 | 118.2 | 62.4 | | 2.5 | 0 | 42.0 | 232.7 | 30.2 |
| (12)[c] | 99.6 | 78.9 | 75.0 | 100.1 | 66.4 | | | | | | |

[a] The signals for the ester carbon atoms were observed as expected. [b] Measured in perdeuterioacetone. [c] Measured in deuteriochloroform.

conditions, with inversion of configuration.[27] With silver tetrafluoroborate in diethyl ether the mixed epimers (7) and (8) were produced (in the ratio 3:1) in agreement with literature precedent.[28] These could not be separated by chromatography, but with the pure D-*gluco*-compound available it was possible to obtain the $^1$H and $^{13}$C n.m.r. spectra of the minor isomer by application of subtraction methods to the spectra of mixtures.

In similar fashion the 4-bromo-D-ribofuranose derivative (11) gave the L-*lyxo*-fluoride (14) on treatment with silver fluoride suspended in acetonitrile, whereas a mixture of this compound and its epimer (15) (ratio 4:3) was produced with silver tetrafluoroborate. Similar results were obtained when an unfractionated mixture of the D-*ribo*- and L-*lyxo*-bromide (11) and (12) were treated with silver tetrafluoroborate. Both fluorides (14) and (15) were obtained crystalline following flash column chromatography, the latter compound being, in this case, adequately stable under the conditions of the separation. The nucleoside bromide (17) gave the crystalline *lyxo*-fluoride (18) after treatment with silver fluoride. Related 4-fluoronucleoside derivatives have been reported previously following studies related to nucleocidin.[16d,e]

With the 4-fluoro-compounds it was possible to obtain their configurations by use of $^1$H, $^{19}$F coupling constants, and the bromo-analogues and also the chloro-derivatives (19) and (20), which were obtained in subsequent work,[26] were characterised by comparative $^1$H and $^{13}$C n.m.r. methods. From studies of closely related glycosyl fluoride esters[16b,29] it is possible to predict that, in the present series, coupling constants for fluorine with *cis*-related protons 3-H, 2-H, and 1-H would be within the ranges 2.5—7, 0—2.4, and 0—1.5 Hz, whereas these ranges for *trans*-related pairs of atoms would be very different: 12—20.6, 0—0.7, and 2.5—7.9 Hz, respectively. Compounds (7) and (8) gave $J_{3-H,F}$, $J_{2-H,F}$, and $J_{1-H,F}$ values of 7.3, 0, and 0 Hz [for (7)] and 15.2, 0, and 4.0 Hz [for (8)], which therefore clearly identify them as the D-*gluco* and D-*galacto* isomers. Likewise, the pentose compounds (14) and (15) gave corresponding values of 8.0, 1.0, and 3.9 Hz [(14)] and 17.3, 0.8, and 0 Hz [(15)], and are therefore the L-*lyxo* and D-*ribo* fluorides. These coupling constants for the fluorinated nucleoside (18) were 5.1, 2.4, and 3.7 Hz and it is therefore assigned the L-*lyxo*-configuration. $^{13}$C, $^{19}$F Coupling constants (Table 2) also reveal a generalisation which is of value in configurational analysis: when the ester substituent on the ring atom adjacent to the fluorinated atom is *cis* to the halogen the $^2J_{C,F}$ values are *ca.* 20 Hz, whereas this value is doubled for the *trans*-related compounds. This also applies with the acetylated D-fructofuranosyl fluorides.[29b] The fluorides, bromides, and chlorides assigned the D-*gluco*-configuration have 1-H resonances deshielded by *ca.* 0.3 p.p.m.

relative to 1-H of both 1-O-acetyltetra-O-benzoyl-β-D-glucofuranose (2) and their D-*galacto*-epimers (Table 1). Likewise, compounds (8), (5), and (20) have 2-H deshielded by approximately this amount relative to the corresponding hydrogen atoms of 1-O-acetyltetra-O-benzyl-β-D-galactofuranose (3) and the D-*gluco*-compounds (7), (6), and (19). With the pentose derivatives this deshielding influence is observable for 2-H, but not for 1-H, but in these cases the acetyl resonances offer another parameter for comparison, the D-*ribo*-compounds giving this signal about 0.2 p.p.m. upfield from the position of this resonance for the L-*lyxo*-compounds. The coupling constants $J_{1,2}$ and $J_{2,3}$ supply further data in support of the assignments, the halogenated D-*gluco*-compounds having both values $\geqslant 1.5$ Hz while the D-*galacto*-epimers show couplings of 2.2—2.7 and 4.7—6.0 Hz, respectively. Likewise, the pentose derivatives afford consistent values: 0—0.8 Hz and 4.9—5.4 Hz for the D-*ribo*- and 3.0—3.9 and 4.9—5.1 Hz for the L-*lyxo*-halides.

In Table 2 the $^{13}$C n.m.r. parameters of the 4-halogenated compounds are given. These show many effects observed previously with furanose derivatives,[30] but are less helpful than the proton spectra for assigning configuration at C-4. Nevertheless, it is noted that in those halogenated compounds which have the halogen substituents at C-4 *trans*-related to 3-O [compounds (8), (14), and (12)] their C-5 resonances appear upfield relative to the resonances of their C-4 epimers [compounds (7), (15), and (11)] as expected.[30]

With the nucleoside derivatives (17) and (18) the latter was readily characterised by consideration of $^1$H, $^{19}$F coupling constants (see above) and the former is assigned the D-*ribo*-structure since 1-H was deshielded relative to this resonance in the unbrominated material whereas 2-H was not. In addition, $J_{1,2}$ and $J_{2,3}$ values of 2.5 and 7.2 Hz indicate the $E_4$ conformation for the furanose ring as expected for 4-halogeno-D-ribofuranoses.

No detailed study of the optical rotations of the 4-halogenated compounds was undertaken, but it was observed that the D-*ribo* and L-*lyxo* 4-fluoropentose esters (15) and (14), with $[\alpha]_D$ values of $+60°$ and $+18°$, respectively, represent, if they are considered as glycosyl fluorides, a further exception to Hudson's Isorotation Rules.[31] It is noted that the related tri-O-benzoyl-α- and -β-D-ribofuranosyl fluoride likewise are exceptional.[32]

## Experimental

Unless otherwise indicated n.m.r. spectra were measured in deuteriochloroform using a Varian FT 80A instrument, and

optical rotations were determined in chloroform within the concentration range of 0.5—1.5%. The benzoylated glyco-furanosyl acetates (2), (3), and (9) were prepared by solvolysis of the corresponding S-ethyl 1-thioglycoside benzoates in acetic acid in the presence of mercury(II) acetate.[21] Solutions were dried over magnesium sulphate. Light petroleum refers to that fraction boiling in the range 60—80 °C.

1,2-*Di*-O-*acetyl*-3,5,6-*tri*-O-*benzoyl*-β-D-*glucofuranose* (1).— 3,5,6-Tri-O-benzoyl-1,2-O-isopropylidene-α-D-glucose[33] (4.00 g) was dissolved in a mixture of glacial acetic acid (37 ml) and acetic anhydride (4.2 ml) and the solution was cooled to 0 °C in an ice–water bath. Concentrated sulphuric acid (2.2 ml) was added to the stirred solution and the mixture was left at room temperature for 18 h. After being poured into ice–water it was extracted with chloroform (×2) and the combined extracts were washed in turn with water, saturated aqueous sodium hydrogen carbonate, and water and then dried. Removal of the solvent under reduced pressure yielded the anomeric 1,2-diacetates as a syrup (4.31 g, 99%) which was homogeneous by t.l.c. The β and α anomers were shown by $^1$H n.m.r. spectroscopy to be present in a ratio of *ca.* 3:1.

Application of column chromatography to the mixture resulted in partial separation of the anomers and provided a sample (0.17 g) of pure β-*anomer* (1) as a syrup which was further purified by preparative t.l.c. and then had $[\alpha]_D$ −81° (Found: C, 64.9; H, 5.2. $C_{31}H_{28}O_{11}$ requires C, 64.6; H, 4.9%); δ 2.20 (6 H, s, OAc), 4.53 (1 H, dd, $J_{5,6}$ 5.1, $J_{6,6'}$ 12.5 Hz, 6-H), 4.92 (1 H, dd, $J_{3,4}$ 4.5, $J_{4,5}$ 9.0 Hz, 4-H), 4.95 (1 H, dd, $J_{5,6'}$ 2.4 Hz, 6′-H), 5.30 (1 H, s, 2-H), 5.74 (1 H, d, 3-H), 5.76 (1 H, m, 5-H), 6.22 (1 H, s, 1-H), and 7.0—8.0 (15 H, m, Ph).

1-O-*Acetyl*-2,3,5,6-*tetra*-O-*benzoyl*-4-*bromo*-β-D-*galactofuranose* (5).—The D-*gluco*-β-acetate (2)[21] (1.50 g) was dissolved in dry carbon tetrachloride (60 ml) and dry nitrogen gas was bubbled through the solution for 5 min. Bromine (1.50 g) was added and the mixture was heated under reflux over a 275 W heat-lamp for 1 h. Evaporation of the solvent left a pale yellow syrup which was purified on a column of silica gel eluted with light petroleum–ethyl acetate to yield the D-galacto-*bromide* (5) (1.21 g, 72%) as a microcrystalline solid, m.p. 58—61 °C; $[\alpha]_D$ +19° (Found: C, 60.3; H, 4.2; Br, 12.0. $C_{36}H_{29}BrO_{11}$ requires C, 60.3; H, 4.1; Br, 11.1%). N.m.r. data are given in Tables 1 and 2.

$^1$H *N.m.r. Investigation of the Crude Product Mixtures resulting from Photobrominations of the* β-*Acetates* (2) *and* (3) *with Bromine.*—Separate mixtures of one of the acetates (0.15 g), anhydrous potassium carbonate (0.75 g), and bromine (0.19 g) were heated under reflux in carbon tetrachloride (7.5 ml) over a 275 W heat-lamp for 16 min. After filtration and evaporation of the solvent under reduced pressure, the $^1$H n.m.r. spectra of the crude bromination mixtures (0.17 g, 100%) revealed that they both consisted of the D-*galacto*-bromide (5) and the D-*gluco*-bromide (6) in the ratio 4.6:1. The $^1$H n.m.r. features of the latter product were determined from the mixture and are given in Table 1.

*Reaction of the* D-galacto-*Bromide* (5) *with Tetra-n-butyl-ammonium Bromide.*—The D-*galacto*-bromide (0.03 g) and tetra-n-butylammonium bromide (0.02 g, 1.0 mol equiv.) were heated under reflux in carbon tetrachloride (1.5 ml) for 1 h after which time the mixture was diluted with the same solvent (15 ml), washed with water (2 × 15 ml), and dried, and the solvent was removed under reduced pressure. $^1$H N.m.r. spectroscopy indicated that the residue (0.03 g) was composed of the D-*galacto*- and the D-*gluco*-bromide (5) and (6) in the ratio 2.8:1.

1-O-*Acetyl*-2,3,5-*tri*-O-*benzoyl*-4-*bromo*-β-D-*ribofuranose* (11).—The D-*ribo*-β-acetate (9) (1.00 g), anhydrous barium

carbonate (3.0 g), and bromine (0.8 g) were heated and stirred in carbon tetrachloride (50 ml) over two 275 W heat-lamps for 0.3 h, after which time the mixture was filtered and the solvent was removed under reduced pressure. The product mixture, containing two main components, was fractionated by flash chromatography[24] and gave the D-*ribo*-bromide (11) (0.57 g, 49%) in the first fraction, $[\alpha]_D$ +20.5° [Found: ionisable Br (silver bromide precipitated from aqueous acetone at room temperature and weighed) 11.7. $C_{28}H_{23}BrO_9$ requires Br, 13.7%]. N.m.r. data are given in Tables 1 and 2.

The less mobile fraction (0.30 g, 33%) was tentatively identified as 2,3,5-tri-O-benzoyl-D-*erythro*-pentos-4-ulose (13), $[\alpha]_D$ +42.1°; $\delta_H$ 5.12 (1 H, d, $J_{5,5'}$ 17.5 Hz, 5-H), 5.46 (1 H, d, 5′-H), 6.05 and 6.33 (2 H, 2 d, $J_{2,3}$ 2.8 Hz, 2- and 3-H), 7.2—8.2 (15 H, m, Ph), and 9.74 (1 H, s, 1-H); $\delta_C$ 67.1 (C-5), 76.4 and 77.4 (C-2 and -3), 194.4 (C-1), and 198.0 p.p.m. (C-4).

$^1$H *N.m.r. Investigation of the Reaction of the* D-ribo-β-*Acetate* (9) *with Bromine under Light.*—(a) *Photobromination at room temperature.* The D-*ribo*-β-acetate (0.04 g), anhydrous potassium carbonate (0.20 g), and bromine (0.09 g) were stirred in carbon tetrachloride (3 ml) in a cold-water-jacketted reaction vessel and the mixture was irradiated with a 275 W heat-lamp. After 0.75 h, further bromine (0.10 g) was added and the mixture was photolysed for a further 4 h before it was filtered and the solvent was removed under reduced pressure. $^1$H N.m.r. spectroscopy revealed that the residue consisted solely of the D-*ribo*-bromide (11).

(b) *Photobromination at* 80 °C. The D-*ribo*-β-acetate (9) (0.20 g), anhydrous potassium carbonate (1.18 g), and bromine (0.14 g) were heated under reflux and stirred in carbon tetrachloride (10 ml) over a 275 W heat-lamp for 0.25 h. The mixture was then filtered and the solvent was removed under reduced pressure to give a syrup which was examined by $^1$H n.m.r. spectroscopy. This indicated that the D-*ribo*-bromide (11) and the L-*lyxo*-bromide (12) were present in the ratio 55:45.

*Reaction of the* D-ribo-*Bromide* (11) *with Tetra-n-butyl-ammonium Bromide.*—The D-*ribo*-bromide (0.03 g) and tetra-n-butylammonium bromide (0.02 g, 1.2 mol equiv.) were dissolved in carbon tetrachloride (1.5 ml) and the mixture was heated under reflux for 1 h. After dilution with the same solvent, the solution was washed with water (2 × 10 ml) and dried before the solvent was removed under reduced pressure. A $^1$H n.m.r. spectrum of the reaction mixture indicated that it was composed of the D-*ribo* and the L-*lyxo* bromides (11) and (12) in the ratio 73:27.

1,N-*Dibenzoyl*-2′,3′,5′-*tri*-O-*benzoyl*-4′-*bromoadenosine* (*Imine Tautomer*) (17).—Adenosine pentabenzoate (16)[34] (0.40 g), anhydrous potassium carbonate (2.0 g), and bromine (0.30 g) were heated under reflux in carbon tetrachloride (40 ml) over a 275 W heat-lamp for 0.5 h. Further bromine (0.10 g) was added and the mixture was photolysed for a further 1.3 h, after which time chloroform (50 ml) was added. The reaction mixture was washed with dilute aqueous sodium thiosulphate (100 ml), dried, and the solvent was removed under reduced pressure. The complex product mixture was fractionated by flash chroma-tography to give the somewhat unstable adenosine-4′-yl bromide (17) (0.06 g, 14%), $[\alpha]_D$ −81.8° (Found: Br, 8.5. $C_{45}H_{33}BrN_5O_9$ requires Br, 9.2%); $\delta_H$ 4.85 and 5.16 (2 H, 2 d, $J$ 12.4 Hz, 5′-$H_2$), 6.34 (1 H, dd, $J_{1',2'}$ 2.5, $J_{2',3'}$ 7.2 Hz, 2′-H), 6.49 (1 H, d, 1′-H), 6.63 (1 H, d, 3′-H), and 7.0—8.2 (27 H, ArH); $\delta_C$ (*inter alia*) 65.9 (C-5′), 71.2 and 72.2 (C-2′ and -3′), 90.8 (C-1′), 102.1 (C-4), 164.5, 165.1, and 165.4 (O–C=O), and 172.0 and 172.0 p.p.m. (N–C=O).

A second product gave a very similar proton spectrum. Bromine was therefore present at C-4′, and the absence of one

aromatic proton resonance indicated that a second atom had been introduced into the purine ring.

1-*O*-*Acetyl*-2,3,5,6-*tetra*-*O*-*benzoyl*-4-*fluoro*-β-D-*glucofuran-ose* (**7**).—A solution of the D-*galacto*-bromide (**5**) (0.24 g) in dry acetonitrile (1 ml) was added at 0 °C under nitrogen to a stirred suspension of silver fluoride (0.25 g) in the same solvent (0.5 ml). After being stirred overnight at room temperature the reaction mixture was filtered and, after removal of the solvent under reduced pressure, the product was purified by flash chromatography. This gave the syrupy 4-*fluoride* (**7**) as a monohydrate (0.16 g, 72%), [α]$_D$ +6.6° (Found: C, 64.6; H, 4.6; F, 2.6. $C_{36}H_{29}FO_{11} \cdot H_2O$ requires C, 64.1; H, 4.6; F, 2.8%). N.m.r. data are given in Tables 1 and 2.

*Reaction of the* D-galacto-*Bromide* (**5**) *with Silver Tetrafluoro-borate*.—Silver fluoride (0.14 g) was dissolved in a solution of boron trifluoride–diethyl ether (0.5 ml) in diethyl ether (5 ml) under an atmosphere of dry nitrogen, and to this stirred mixture was added a solution of the D-*galacto*-bromide (0.60 g) in the same solvent (3 ml) at −15 °C. After 5 min at room temperature, saturated aqueous sodium hydrogen carbonate (50 ml) was added to the reaction mixture which was then filtered. The aqeuous phase was extracted with diethyl ether (2 × 20 ml), and the combined organic phases were washed with saturated aqueous sodium chloride (60 ml) and dried. After removal of the solvent under reduced pressure, the product mixture was flash chromatographed and gave the D-*gluco*-fluoride (**7**) and the D-*galacto*-fluoride (**8**) (0.38 g, 68%) in the approximate ratio 3:1 (as determined by $^1$H n.m.r. spectroscopy).

1-*O*-*Acetyl*-2,3,5-*tri*-*O*-*benzoyl*-4-*fluoro*-α-L-*lyxofuranose* (**14**).—To a stirred suspension of silver fluoride (0.17 g) in acetonitrile (5 ml), at 0 °C under dry nitrogen, was added a solution of the D-*ribo*-bromide (**11**) in the same solvent (3 ml). The mixture was stirred at this temperature for 1 h before being filtered and the solvent removed under reduced pressure. The residue was dissolved in chloroform (10 ml) and the solution was shaken with saturated aqueous sodium chloride (10 ml) which, after separation and filtration, was extracted with chloroform (2 × 10 ml). After the combined organic phases had been dried, the solvent was removed and the crude product was purified by preparative t.l.c. This gave the L-lyxo-*fluoride* (**14**) (0.08 g, 53%) which crystallised upon the addition of methanol and, after recrystallisation from the same solvent, had m.p. 89—90 °C, [α]$_D$ +17.6° (Found: C, 64.3; H, 4.5; F, 3.7. $C_{28}H_{23}FO_9$ requires C, 64.4; H, 4.4; F, 3.6%). N.m.r. data are given in Tables 1 and 2.

1-*O*-*Acetyl*-2,3,5-*tri*-*O*-*benzoyl*-4-*fluoro*-α-L-*lyxofuranose* (**14**) *and* 1-*O*-*Acetyl*-2,3,5-*tri*-*O*-*benzoyl*-4-*fluoro*-β-D-*ribofuranose* (**15**).—(a) *From a mixture of the* D-ribo- *and the* L-lyxo-*bromide* (**11**) *and* (**12**). The D-*ribo*-β-acetate (**9**) (1.50 g) and bromine were heated under reflux in carbon tetrachloride (90 ml) over a 275 W heat-lamp for 0.75 h. The reaction mixture was then washed in turn with dilute aqueous sodium thiosulphate (100 ml) and saturated aqueous sodium hydrogen carbonate (100 ml), and was dried before the solvent was removed under reduced pressure. The mixture of the bromides (**11**) and (**12**) so obtained was dissolved in diethyl ether (5 ml). This was added, at 0 °C under nitrogen, to a stirred solution of silver fluoride (0.53 g) in diethyl ether (100 ml) containing boron trifluoride–diethyl ether (0.75 ml). After 0.17 h, saturated aqueous sodium hydrogen carbonate (30 ml) was added to the mixture which was then filtered. The organic phase was washed with saturated aqueous sodium hydrogen carbonate (100 ml), dried, and, after removal of the solvent under reduced pressure, the crude product

mixture was fractionated by flash chromatography. In the first fraction was the pure L-*lyxo*-fluoride (**14**) (0.38 g, 24%), which was identical by t.l.c. and $^1$H n.m.r. spectroscopy with the previous sample of this compound, while the second fraction (0.43 g) contained a 57:43 mixture of this fluoride (**14**) (total yield 0.63 g, 40%) and the D-*ribo*-fluoride (**15**). The final fraction contained the pure D-ribo-*fluoride* (**15**) (0.33 g, 21%; total yield 0.51 g, 33%) which crystallised from methanol and, after recrystallisation from the same solvent, had m.p. 93—94 °C, [α]$_D$ +59.6° (Found: C, 64.2; H, 4.7; F, 3.7. $C_{28}H_{23}FO_9$ requires C, 64.4; H, 4.4; F, 3.6%). N.m.r. data are given in Tables 1 and 2.

(b) *From the* D-ribo-*bromide* (**11**). Silver fluoride (0.05 g) was dissolved in a solution of boron trifluoride–diethyl ether (0.25 ml) in diethyl ether (5 ml) under dry nitrogen. To this stirred solution was added, at 0 °C, a solution of the D-*ribo*-bromide (0.176 g) in the same solvent (5 ml), and after 0.3 h the reaction was quenched with saturated aqueous sodium hydrogen carbonate (15 ml). The aqueous phase was extracted with diethyl ether (15 ml) and with ethyl acetate (5 ml), and the combined extracts were washed with saturated aqueous sodium chloride solution (30 ml) and dried. After removal of the solvent under reduced pressure, the product mixture was chromatographed on a preparative t.l.c. plate, from which three fractions were removed. In the most mobile fraction was the L-*lyxo*-fluoride (**14**) (0.040 g, 25%), which had identical t.l.c. and $^1$H n.m.r. characteristics with the material prepared previously, and the second fraction (0.041 g, 26%) was also found to contain this fluoride together with the D-*ribo*-fluoride (**15**), in the ratio 42:58 (as determined by $^1$H n.m.r. spectroscopy). The total yield of the L-*lyxo*-fluoride (**14**) was accordingly 0.057 g (36%). From the final fraction was obtained the D-*ribo*-fluoride (**15**) (0.017 g, 11%; total 26%) which had identical t.l.c. and $^1$H n.m.r. characteristics with the previous sample.

1,N-*Dibenzoyl*-9-(2′,3′,5′-*tri*-*O*-*benzoyl*-4-*fluoro*-α-L-*lyxofur-anosyl*)*adenine* (*Imine Tautomer*) (**18**).—To a stirred suspension of silver fluoride (0.22 g) in acetonitrile (1 ml), at 0 °C under nitrogen, was added a solution of the adenosin-4′-yl bromide (**17**) (0.22 g) in the same solvent (2 ml). After 1 h methylene dichloride (6 ml) was added, and the mixture was filtered before evaporation of the solvent under reduced pressure. The resulting syrup was purified by preparative t.l.c. and gave the 4′-*fluoride* (**18**) (0.07 g, 31%), which crystallised from methanol. After recrystallisation from the same solvent, it had m.p. 171—173 °C [α]$_D$ −93.0° (Found: C, 66.9; H, 4.3; F, 2.3; N, 8.5. $C_{45}H_{33}FN_5O_9$ requires C, 67.1; H, 4.0; F, 2.4; N, 8.7%); $\delta_H$ 4.70 (1 H, dd, $J_{5'(1),5'(2)}$ 12.5, $J_{5'.F}$ 17.9 Hz, 5′H), 4.92 (1 H, t, $J_{5'.F}$ ca. 12 Hz, 5′-H), 6.35 (1 H, dd, $J_{1'.2'}$ 4.6, $J_{1'.F}$ 3.7 Hz, 1′-H), 6.50 (1 H, ddd, $J_{2'.3'}$ 6.1, $J_{2'.F}$ 2.4 Hz, 2′-H), 6.9 5 (1 H, dd, $J_{3'.F}$ 5.1 Hz, 3′-H), and 7.1—8.6 (27 H, ArH); $\delta_C$ (*Inter alia*) 61.6 (d, $J_{5'.F}$ 29.8 Hz, C-5′), 73.6 (d, $J_{3'.F}$ 41.8 Hz, C-3′), 74.3 (s, C-2′), 87.1 (d, $J_{1'.F}$ 1.4 Hz, C-1′), and 118.3 p.p.m. (d, $J_{4'.F}$ 230.8 Hz, C-4′).

## Acknowledgements

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