Photobromination of Carbohydrate Derivatives. Part 5.[1] Preparation and Reactions of (5*S*)-1,2,3,4-Tetra-*O*-acetyl-5-bromo-β-D-xylopyranose; a New Type of ' Double-Headed ' Nucleoside

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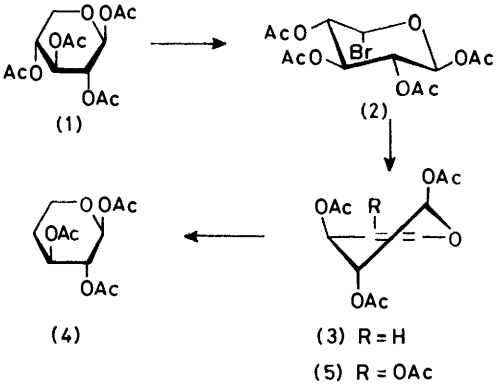
Photobromination of tetra-*O*-acetyl-β-D-xylopyranose gives a crystalline product (2) with bromine replacing the axial hydrogen atom at C-5. Nucleophilic displacement of the bromine afforded compounds with inverted stereochemistry at this centre, the methoxy-product (9) undergoing displacement of acetoxy-group from C-1 on treatment with hydrogen bromide and giving the 5-methoxyglycosyl bromide ester (10). Elimination reactions of the bromides (2) and (10) were studied, and the derived ' glycal ' compounds (3) and (12) afford routes to 4-deoxy-L-*threo*-pentose and its enantiomer, respectively. Attempts to prepare new types of crown ethers by way of a di-*O*-glycosylethane-1,2-diol derivative (15) were not successful, but a novel type of ' double-headed ' nucleoside (22) was obtained from the initial bromide (2).

PREVIOUS reports in this series have described the substitution of bromine at C-5 of D-glucopyranose [2,3] and D-glucopyranuronate [4] esters by use of *N*-bromosuccinimide or bromine in carbon tetrachloride solution under bright light. Not all glucopyranose compounds react at this centre, however, and we have encountered two instances [1,5] of glucopyranoside derivatives which have led to carbonyl-containing products derived apparently following free-radical abstraction of hydrogen from their anomeric centres. The reaction applied to tetra-*O*-acetyl-β-D-xylopyranose is now shown to give as the main product the bromide formed by substitution of the axial hydrogen atom at C-5, and thus access has been gained to a pentopyranose derivative with displaceable groups at both positions 1 and 5. Elimination and substitution reactions have been studied, and the compound has given access to a new type of ' double-headed ' nucleoside.

Photobromination of tetra-*O*-acetyl-β-D-xylopyranose (1) with bromine (the reagent which is more effective with penta-*O*-benzoyl-β-D-glucopyranose [3]) gave a complex set of products, but with *N*-bromosuccinimide it afforded mainly one, which was chromatographically more mobile than the starting material. Direct crystallisation gave this compound (2) in 46% yield, and it was shown by ^{1}H n.m.r. spectroscopy to make up substantial proportions of the non-crystalline fraction. However, it proved to be difficult to purify, even after several recrystallisations containing small amounts of starting material which, for the purposes of obtaining an analytically pure sample of the bromide, had to be removed by a rebromination process. By ^{1}H n.m.r. spectroscopy the product was shown to retain the pyranoid ring in the $^4C_1$ conformation ($J_{1,2}$ 8.5, $J_{2,3} = J_{3,4} = 9.5$ Hz), and to have undergone substitution of the axial proton at C-5 ($J_{4,5}$ 4.5 Hz). Consistent with the generation of an asymmetric centre at this position with the *S*-configuration, the product ($[\alpha]_D$ −117°) was more laevorotatory than the starting material ($[\alpha]_D$ −25°); [1-4] in carbohydrate terminology a β-D-anomeric centre was generated, and this would be expected to make a negative contribution to the optical rotation of the compound.[6] Although it was not determined which of the hydrogen atoms was removed during the substitution process, it would be anticipated that a free radical would be produced more readily by loss of the axial atom,[7] and that it might exist in such a form that attack from the axial direction would be favoured.[8] In the ^{1}H n.m.r. spectrum of the bromo-derivative (2) H-5 resonated at δ 6.42 (H-1 for tri-*O*-acetyl-α-D-xylopyranosyl bromide, δ 6.58), H-2 and H-4 were largely unaffected by the substitution, but H-1 and H-3, having the *syn*-diaxial relationship with the halogen atom, were both deshielded by *ca.* 0.5 p.p.m. as expected.[1-4]

Since the bromide (2) is a 5-substituted acylated glycopyranosyl bromide it was subjected to reactions which are typical of glycosyl halide esters, and with zinc and acetic acid it gave the 5-substituted glycal (3) which, on hydrogenation, afforded 1,2,3-tri-*O*-acetyl-4-deoxy-α-L-*threo*-pentose (4), so that the bromination–elimination–reduction sequence (Scheme 1) provides

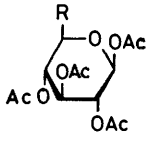


SCHEME 1

a convenient route to this compound and hence access to the unknown 4-deoxypentose. When treated with 1,5-diazabicyclo[5,4,0]undec-5-ene (DBU) in *NN*-dimethylformamide the bromide (2) underwent dehydrobromination to afford the 5-substituted ' hydroxy-

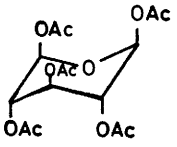
glycal ' ester (5) which, like the glycal (3), adopted the $^1H_2$ conformation as shown (small $J_{1,2}$ values) with favourable factors derived from both the anomeric[9] and allylic effects.[10] Neither of the alkenes (3) or (5) could be induced to react cleanly with ethanol in the presence of boron trifluoride or to undergo intramolecular isomerisation by heating to give allylically rearranged products, and since esterified glycals and 2-hydroxyglycals readily undergo such reactions,[11] it is concluded that the acetoxy-groups at C-1 hinder the processes by diminishing the stabilisation by the ring oxygen atoms of the allylic carbonium ions formed by cleavage of the C–O bonds at C-3.

In the same way as the ester group at C-1 inhibited allylic rearrangement reactions of compounds (3) and (5), it also inhibited the unshared electrons of ring oxygen participating in the ionisation of the bromide (2) which therefore is not so susceptible to nucleophilic displacement reactions as is tri-*O*-acetyl-α-D-xylopyranosyl bromide [the enantiomer of compound (2) without the acetoxy-group at C-1]. Under conditions in which the half-life of this latter compound in 5% v/v pyridine–methanol was 10 min, compound (2) had a half life of 920 min. Consistent with this, the bromide (2) is much less susceptible to degradation than is tri-*O*-acetyl-α-D-xylopyranosyl bromide and can be kept indefinitely at low temperatures and for considerable periods at room temperature. Nevertheless, it is susceptible to reactions which nucleophilically displace the bromine, and with acetic acid, acetic anhydride, and silver acetate acetolysis occurred as expected with inversion of configuration to give the symmetrical penta-acetate (6). Similarly, the thioacetate (7), the chirality of which arises only from the asymmetry generated by different atoms bonded to C-1 and C-5, the azide (8), and the methoxy-compound (9) were produced by nucleophilic



R
(6) OAc
(7) SAc
(8) N_3
(9) OMe

substitution reactions. All the products (6)—(9) were appreciably more dextrorotatory than their precursor (2), and all showed (in DMSO) $J_{1,2}$ and $J_{4,5}$ values near 7 Hz indicating that they existed predominantly in the $^4C_1$ conformation with all the bulky groups equatorially disposed. Similar coupling constants were observed in chloroform solution except for the penta-acetate (6) which had $J_{1,2}$ and $J_{4,5}$ of 3 Hz indicating that this compound had undergone conformational inversion and existed with all the ester groups axial. Since the conformational equilibrium for tetra-*O*-acetyl-β-D-xylopyranose (in acetone) contains *ca.* 25% of the ' all-axial ' chair form,[12] and since this form of the penta-acetate (6) would have both anomeric acetoxy-groups favourably disposed, and, furthermore, because *syn*-related axial acetoxy-groups do not give rise to large interaction energies,[13] it is not altogether unexpected that the conformation of compound (6) in chloroform solution is as depicted.



(6)

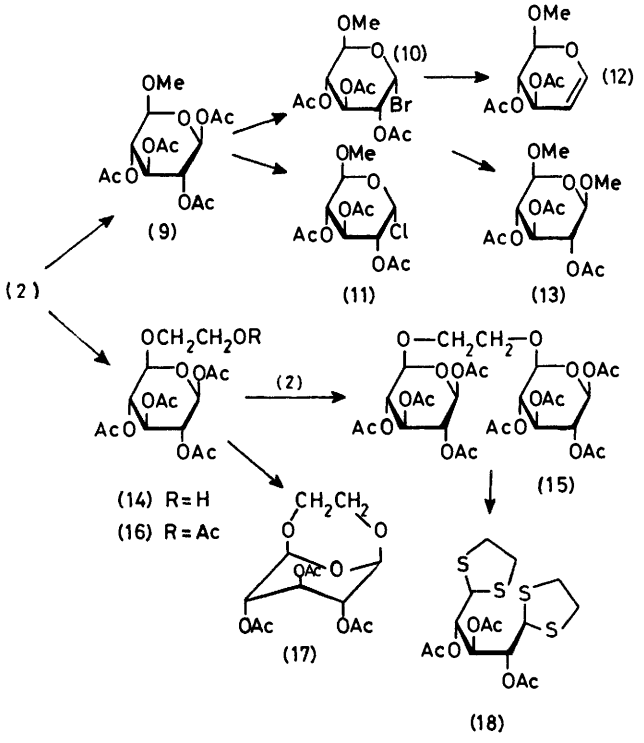
The availability of the methoxy-compound (9) which possesses both glycosidic and glycosyl ester functionalities allowed an investigation of the relative leaving properties of methoxy- and acetoxy-groups, and when treated with hydrogen bromide in acetic acid compound (9) gave the methoxyglycosyl bromide (10) almost exclusively (^{1}H n.m.r.; 38% isolated crystalline) and, likewise, the chloride (11) was produced when the methoxyacetate (9) was treated with titanium tetrachloride in chloroform solution. The former bromide was intermediate between tri-*O*-acetyl-α-D-xylopyranosyl bromide and compound (2) in ease of displacement of bromide during methanolysis (see above) as would be expected on inductive grounds. Treatment with zinc and acetic acid afforded the 4,5-unsaturated glycoside (12), hydrogenation of which would provide a route to 4-deoxy-D-*threo*-pentose and its methyl α-pyranoside. Methanolysis of the bromomethoxy-compound (10) gave the achiral dimethoxy-derivative (13) as expected.

With the knowledge that the anomeric acyloxy-group of 5-alkoxyglycopyranosyl esters could be specifically displaced, efforts were turned to the preparation of the dimeric compound (15) in the hope that bridging of the esterified anomeric centres could then be effected to give macrocyclic products related to chiral crown ethers which are currently of great interest.[14] To this end the bromide (2) was treated with ethane-1,2-diol in the presence of mercury(II) cyanide to give the crystalline hydroxyethoxy-derivative (14) in 46% yield. This had a ^{1}H n.m.r. spectrum entirely analogous to that of the methoxy-compound (9), and when treated with the bromide (2), gave the disubstituted compound (15) in 33% yield and a by-product which was the acetate (16) of the intermediate (14) and which may have been produced by rearrangement of an ortho-ester intermediate or by competitive attack by the alcohol at the ester carbonyl group at C-1 of the glycosylating agent (Scheme 3).

When the monosubstituted ethylene glycol (14) was then treated in chloroform solution with boron trifluoride–ether no macrocyclic product was observed. Instead, intramolecular displacement took place to give the crystalline bicyclic product (17), obtained in

54% yield. Small coupling between H-1 and -2 and H-4 and -5 indicated that the compound adopted the illustrated conformation as is required by the constraints of the 7-membered ring.

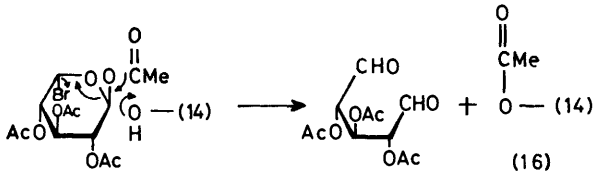
In a further attempt to produce a macrocyclic com-



SCHEME 2

pound, the diglycoside (15) was treated with ethane-1,2-diol, boron trifluoride–ether, and sodium tetrafluoroborate in the hope that a template effect would provide a 14-crown-6 derivative, and since no discrete product was obtained, the experiment was repeated with ethane-1,2-dithiol, but the only product isolated in this case was the bisdithioacetal (18) formed by thioacetal formation from each potential aldehydic centre of the monomeric carbohydrate components of the dimer (15). The same compound was obtainable from the penta-acetate (6) which further exemplifies the propensity of thiols to form dithioacetals.

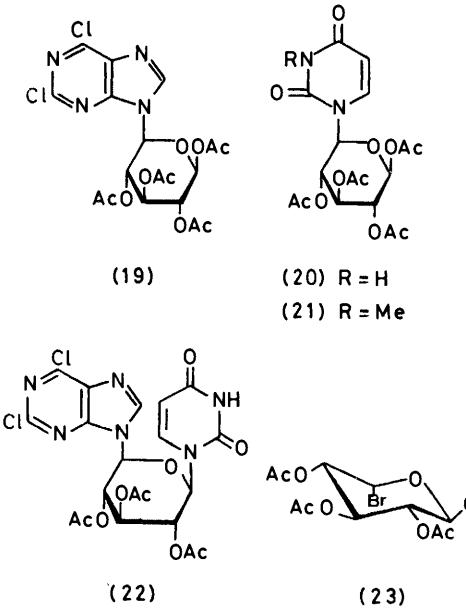
'Double-headed' nucleosides are monosaccharide



SCHEME 3

derivatives containing two heterocyclic bases, and those which have been synthesised to date have one base bonded glycosidically in the usual way and the other attached through nitrogen to C-5 of pentofuranosyl rings.[15] The availability of the bromide (2) led us to investigate the preparation of a new type of such compound: those having bases linked glycosidically to both C-1 and C-5 of pyranosyl rings. Separate treatment of the bromide (2) with bis-(2,6-dichloropurinyl)-mercury in xylene [16] and bis(trimethylsilyl)uracil in nitromethane in the presence of mercury(II) cyanide [17] afforded the novel crystalline nucleoside analogues (19) and (20) in 32 and 60% yield, respectively. These gave ^{1}H n.m.r. spectra consistent with the assigned structures. Signals for H-1 and H-5 were unresolved in chloroform solution, but when measured in deuteriated dimethyl sulphoxide [compound (19)] and acetone [compound (20)] were seen as doublets with $J_{1,2}$ and $J_{4,5}$ values of 8—9 Hz signifying that the nucleosides had been produced, like compounds (6)—(9), by reactions which proceeded with inversion of stereochemistry at C-5. Consistent with this, they were much more dextrorotatory than was the bromide (2). The positions of bonding of the bases were assigned from ultraviolet data [compound (19), $\lambda_{max.}$ 274 nm (ε 8 100); [18] compound (20), $\lambda_{max.}$ 254 nm, (ε 8 900) [17,19]], and are consistent with expectations based on the methods of synthesis.[16,17]

After unsuccessful efforts to condense the purine derivatives (19) with nucleoside bases in the presence



of titanium tetrachloride, it was treated with dichloromethyl methyl ether in the presence of boron trifluoride–ether [20] to give a chromatographically more mobile product which was assumed to be the β-glycosyl chloride derivative (see below). This, without isolation, was then treated with bis(trimethylsilyl)uracil in the presence of mercury(II) cyanide and gave the 'double-headed' nucleoside (22) as a high melting, crystalline product in 30% yield. It is noteworthy that several 'double-headed' nucleoside derivatives based on 1,5-disubstituted D-ribofuranose also melt near 300 °C.[15] The ^{1}H n.m.r. spectrum of compound (22) showed the

characteristic singlet for H-8 of the purine moiety, the pair of doublets derived from H-5 and H-6, and a broad singlet for NH of the pyrimidine ring, as well as the expected resonances of the sugar component. $J_{1,2}$ and $J_{4,5}$ values of 8.5 and 9 Hz reveal the configurations at the glycosidic centres.

It should be possible to synthesise the enantiomer of compound (22), *i.e.* the nucleoside with the positions of the bases reversed, by condensation of the uracil nucleoside (20) with dichloropurine. However, preliminary experiments indicate that complications, conceivably based on the possibility that the carbonyl oxygen atom at C-2 of the base could take part in competing reactions at the anomeric centre, are involved. To eliminate this problem compound (20) was methylated to give the *N*-methyl derivative (21), but this did not react cleanly with bis-(2,6-dichloropurinyl)mercury after treatment with dichloromethyl methyl ether and boron trifluoride–ether.

That β-glycosyl chlorides are produced in this series by use of dichloromethyl methyl ether and boron trifluoride–ether was confirmed by the production of the novel, crystalline bromochloro-derivative (23) in 44% yield from the initial bromide (2) by use of these reagents. The ^{1}H n.m.r. spectrum clearly revealed the structure, the spectrum being similar to that of the starting material except that the broad doublet for H-1 was shielded by 0.8 p.p.m.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured at 60 MHz for solutions in deuteriochloroform with tetramethylsilane as internal reference on a Perkin-Elmer–Hitachi R 20 instrument, unless otherwise stated. Optical rotations were recorded for solutions in chloroform within the concentration range 1—3% unless otherwise stated.

(5*S*)-1,2,3,4-*Tetra*-O-*acetyl*-5-*bromo*-β-D-*xylopyranose* (2).—A suspension of tetra-*O*-acetyl-β-D-xylopyranose (10 g) and *N*-bromosuccinimide (26.4 g, 5 mol. equiv.) in dry carbon tetrachloride (250 ml) was heated under reflux over two 275-W heat lamps for 5 h. After cooling, the solids and solvent were removed and the residue was taken up in chloroform, washed with water (×2), and dried. Evaporation gave a yellow syrup which was dissolved in ether (10 ml) and stored at 4 °C for 2 days to give the crystalline *5-bromide* which was crushed under ether–light petroleum (1 : 1 v/v) and then washed with this solvent. This product (5.7 g, 46%) was shown by n.m.r. spectroscopy to be substantially pure and was used for synthetic purposes. An analytical sample was produced by resubjection to bromination followed by recrystallisation (×6) from methanol and had m.p. 135—140 °C, $[\alpha]_D$ −117° (Found: C, 39.2; H, 4.5. $C_{13}H_{17}BrO_9$ requires C, 39.3; H, 4.3%); δ 2.01 (6 H, s, 2 Ac), 2.07 (6 H, s, 2 Ac), 4.81 (1 H, dd, $J_{3,4}$ 9.5, $J_{4,5}$ 4.5 Hz, H-4), 5.11 (1 H, t, $J_{1,2}$ 8.5, $J_{2,3}$ 9.5 Hz, H-2), 5.55 (1 H, t, H-3), 6.16 (1 H, d, H-1), and 6.42 (1 H, d, H-5).

1,2,3-*Tri*-O-*acetyl*-4-*deoxy*-α-L-threo-*pent*-4-*enopyranose* (3).—Copper(II) sulphate (0.2 g) in water (1 ml) followed by zinc dust (2 g) were added to a solution of sodium acetate (2 g) in aqueous acetic acid (12 ml, 2 : 3 v/v) at 0 °C, and when the blue colour of the solution had faded a solution of the 5-bromo-compound (2) (1.0 g) in acetic acid (15 ml) was added and the mixture was stirred at 0 °C for 1 h and then at room temperature for 4 h. The solids were removed, chloroform was added to the filtrate, and the organic phase was washed with water (×2), saturated aqueous sodium hydrogencarbonate solution, and water, and then dried. Removal of the solvent gave a syrup which, on trituration with ether–light petroleum, gave the 4-*deoxyalkene* (0.3 g, 46%), m.p. 97—98 °C (from ether–light petroleum), $[\alpha]_D$ +18° (Found: C, 51.2; H, 5.8. $C_{11}H_{14}O_7$ requires C, 51.2; H, 5.4%); $\nu_{max.}$ 1 655s cm^{-1} (C=C); δ 2.02 (3 H, s, Ac), 2.07 (6 H, s, 2 Ac), 4.8—5.1 (3 H, m, H-2, -3, and -4), 6.07 (1 H, d with virtual coupling, $J_{1,2}$ 3 Hz, H-1), and 6.32 (1 H, d with virtual coupling, $J_{4,5}$ 4.5 Hz, H-5). The mother-liquors consisted mainly of this same product (n.m.r.).

Tri-O-*acetyl*-4-*deoxy*-α-L-threo-*pentopyranose* (4).—Hydrogenation of the 4-enose derivative (3) (0.5 g) in ethyl acetate (20 ml) occurred smoothly in the presence of palladium–charcoal (1 g, 5%) to give the crystalline 4-*deoxy-compound* (0.36 g, 71%), m.p. 94—95 °C (from ether–light petroleum), $[\alpha]_D$ −3.5° (Found: C, 50.9; H, 6.4. $C_{11}H_{16}O_7$ requires C, 50.8; H, 6.2%); δ 1.9—2.4 (2 H, m, H-4, and -4′), 2.01 (6 H, s, 2 Ac), 2.05 (3 H, s, Ac), 3.4—4.2 (2 H, m, H-5, and -5′), 4.7—5.1 (2 H, m, H-2, and -3), and 5.55 (1 H, d, $J_{1,2}$ 6 Hz, H-1).

1,2,3,4-*Tetra*-O-*acetyl*-α-L-threo-*pent*-4-*enopyranose* (5).—A solution of 1,5-diazabicyclo[5,4,0]undec-5-ene (0.5 g) in *NN*-dimethylformamide (15 ml) was added over 1 h to the 5-bromide (2) (1.0 g) in the same solvent (10 ml) at 0 °C. After the solution had been stirred at this temperature for a further 1.5 h, more of the base (0.1 g in 1 ml solution) was added. After 1 h, water was added and the mixture was extracted with chloroform. The extracts were washed with water (×4) and dried and taken to a syrup which on trituration with ethanol afforded the 4-*ene* (0.36 g, 45%), m.p. 113—114 °C (from ethanol), $[\alpha]_D$ +7° (Found: C, 49.5; H, 5.2. $C_{13}H_{16}O_9$ requires C, 49.4; H, 5.1%); $\nu_{max.}$ 1 690w cm^{-1}, (C=C); δ 2.05 (3 H, s, Ac), 2.10 (9 H, s, 3 Ac), 5.06 (1 H, t, $J_{1,2} = J_{2,3}$ = 2.5 Hz, H-2), 5.35br (1 H, s, H-3), 6.10 (1 H, dd, $J_{1,3}$ 1 Hz, H-1), and 6.50 (1 H, s, H-5). The mother-liquors (0.2 g) contained this product as a major component (n.m.r.).

(5R)-5-*Acetoxy*-1,2,3,4-*tetra*-O-*acetyl*-β-D-*xylopyranose* (6).—Silver acetate (0.5 g) was added to a solution of the 5-bromo-compound (2) (1.0 g) in acetic acid–acetic anhydride (15 ml; 2 : 1 v/v) and the mixture was stirred at 50 °C for 0.5 h. After removal of the solids and solvent the residue was taken up in chloroform, washed with saturated aqueous sodium hydrogencarbonate, then water, and dried before the solvent was removed to give a semi-crystalline residue which on trituration with ethanol gave the *penta-acetate* (0.55 g, 58%), m.p. 155—157 °C (from ethanol), $[\alpha]_D$ 0° (Found: C, 47.9; H, 5.4. $C_{15}H_{20}O_{11}$ requires C, 47.9; H, 5.4%); δ 2.02 (3 H, s, Ac), 2.07 (6 H, s, 2 Ac), 2.12 (6 H, s, 2 Ac), 5.15—5.4 (3 H, m, H-2, -3, and -4), 6.03 (2 H, d, $J_{1,2} = J_{4,5}$ = 3 Hz, H-1 and -5); δ([$^2H_6$]-DMSO) 1.95 (3 H, s, Ac), 1.99 (6 H, s, 2 Ac), 2.03 (6 H, s, 2 Ac), 4.98 (2 H, dd, $J_{1,2} = J_{4,5}$ = 7, $J_{2,3} = J_{3,4}$ = 8 Hz, H-2 and -4), 5.44 (1 H, t, H-3), and 6.07 (2 H, d, H-1,5).

(5R)-1,2,3,4-*Tetra*-O-*acetyl*-5-*acetylthio*-β-D-*xylopyranose* (7).—Thioacetic acid (0.35 g) and potassium hydroxide (0.21 g) in ethanol (7.5 ml) were added to the 5-bromo-compound (2) (1.0 g) in chloroform (7.5 ml) and the solution was heated under reflux under nitrogen for 1 h. Chloroform was added and the mixture was extracted with water, saturated aqueous sodium hydrogencarbonate, and again with water. The organic phase was dried and treated with

activated charcoal and the solvent was removed to leave a syrup which gave on trituration with ethanol the crystalline *thio-compound* (0.23 g, 23%), m.p. 146—147 °C (from ethanol), $[\alpha]_D$ −13° (Found: C, 45.9; H, 5.2; S, 8.2. $C_{15}H_{20}O_{10}S$ requires C, 45.9; H, 5.1; S, 8.2%); δ([$^2H_6$]DMSO) 1.92 (3 H, s, OAc), 1.98 (6 H, s, 2 OAc), 2.07 (3 H, s, OAc), 2.33 (3 H, s, SAc), 4.92 (1 H, dd, $J_{1,2}$ 7.5, $J_{2,3}$ 9 Hz, H-2), 5.00 (1 H, t, $J_{3,4} = J_{4,5}$ = 9 Hz, H-4), 5.45 (1 H, t, H-3), 5.62 (1 H, d, H-5), and 6.00 (1 H, d, H-1).

(5S)-*Tetra*-O-*acetyl*-5-*azido*-β-D-*xylopyranose* (8).—Sodium azide (1.3 g, 1.5 mol. equiv.) was added to a solution of the bromide (2) (4.65 g) in *NN*-dimethylformamide (35 ml) and, after stirring for 2 h, dichloromethane was added. The solution was washed with water (×3), dried, and evaporated to give a dark syrup (2.8 g) which was chromatographed on silica gel to give a syrup (1.9 g) from which on trituration with ether–light petroleum crystallised the *azido-compound* (1.1 g, 26%), m.p. 150—152 °C (from methanol), $[\alpha]_D$ +33° (Found: C, 43.3; H, 4.6; N, 11.9. $C_{13}H_{17}N_3O_9$ requires C, 43.5; H, 4.7; N, 11.7%); δ 2.01, 2.06, and 2.12 (12 H, 3s, 4 Ac), 4.8—5.25 (4 H, m, H-2, -3, -4, and -5), and 5.84 (1 H, d with virtual coupling, $J_{1,2}$ 7 Hz, H-1).

(5S)-1,2,3,4-*Tetra*-O-*acetyl*-5-*methoxy*-β-D-*xylopyranose* (9).—Silver oxide (2 g) was added to a solution of the 5-bromo-compound (2) (2.0 g) in methanol (20 ml) and dichloromethane (20 ml) and the mixture was stirred at room temperature for 1 h. The solids and solvent were removed to leave a syrup which gave the *methoxy-compound* (1.6 g, 91%) on trituration with aqueous methanol, m.p. 117—119 °C [from aqueous methanol (20 ml; 1 : 1 v/v)], $[\alpha]_D$ +16° (Found: C, 48.2; H, 5.9. $C_{14}H_{20}O_{10}$ requires C, 48.3; H, 5.8%); δ 1.99 (6 H, s, 2 Ac), 2.02 (3 H, s, Ac), 2.06 (3 H, s, Ac), 3.41 (3 H, s, Me), 4.57 (1 H, α with virtual coupling, $J_{4,5}$ 5.5 Hz, H-5), 4.8—5.4 (3 H, m, H-2, -3, and -4), 5.80 (1 H, d with virtual coupling, $J_{1,2}$ 6.5 Hz, H-1).

(5S)-2,3,4-*Tri*-O-*acetyl*-5-*methoxy*-α-D-*xylopyranosyl Bromide* (10).—The methoxytetra-acetate (9) (0.5 g) was allowed to stand for 1 h in chloroform (15 ml) containing hydrogen bromide in acetic acid (1.0 ml; 45% w/v). The solution was washed with water, saturated aqueous sodium hydrogencarbonate, and then water before being dried. Removal of the solvent left a syrup which was triturated with ether–light petroleum to give the glycosyl bromide (0.21 g, 38%), m.p. 94—95 °C (from ether–light petroleum), $[\alpha]_D$ +206°, δ 2.00, 2.04, and 2.06 (9 H, 3 s, 3 Ac), 3.45 (3 H, s, Me), 4.78 (1 H, dd, $J_{1,2}$ 4.5, $J_{2,3}$ 9 Hz, H-2), 4.85 (1 H, d, $J_{4,5}$ 7.5 Hz, H-5), 5.02 (1 H, dd, $J_{3,4}$ 10 Hz, H-4), 5.50 (1 H, t with virtual coupling, H-3), and 6.51 (1 H, d, H-1). The compound decomposed before elemental analysis could be carried out.

(5S)-2,3,4-*Tri*-O-*acetyl*-5-*methoxy*-α-D-*xylopyranosyl Chloride* (11).—After a solution of the methoxytetra-acetate (9) (1.0 g) in chloroform (10 ml) containing titanium tetrachloride (0.5 g) had been allowed to stand for 0.5 h it was washed with saturated aqueous sodium hydrogencarbonate and water and then dried. Removal of the solvent left a syrup which was triturated with ether–light petroleum to give the *glycosyl chloride* (0.38 g, 41%). Recrystallised from this solvent it had m.p. 46—52° then 89—91 °C, $[\alpha]_D$ +172° (Found: C, 44.1; H, 5.2; Cl, 11.2. $C_{12}H_{17}ClO_8$ requires C, 44.4; H, 5.2; Cl, 10.9%); δ 2.02, 2.04, and 2.08 (9 H, 3 s, 3 Ac), 3.47 (3 H, s, OMe), 4.8—5.2 (3 H, m, H-2, -4, and -5), 5.48 (1 H, dt, $J_{2,3} = J_{3,4}$ = 10 Hz, further splitting of 4.5 Hz due to virtual coupling, H-3), and 6.23 (1 H, d, $J_{1,2}$ 4 Hz, H-1).

Methyl 2,3-*Di*-O-*acetyl*-4-*deoxy*-α-D-threo-*pent*-4-*enopyranoside* (12).—Copper(II) sulphate (0.12 g) in water (1 ml) and zinc dust (1.2 g) were added to a solution of sodium acetate (1.2 g) in aqueous acetic acid (16 ml; 1 : 1 v/v) at 0 °C followed by a solution of the 5-methoxyglycosyl bromide (10) (0.6 g) in acetic acid (15 ml) and the mixture was stirred at 0 °C for 1.5 h and then at room temperature for 0.5 h. The solids were removed and chloroform was added to the filtrate which was washed with water, saturated aqueous sodium hydrogencarbonate, and again with water, and dried. Removal of the solvent gave a syrup which was chromatographed on silica gel to give the *alkene* (0.24 g, 64%), $[\alpha]_D$ −23° (Found: C, 52.2; H, 6.2. $C_{10}H_{14}O_6$ requires 52.2; 6.1%); $\nu_{max.}$ 1 658s cm^{-1} (C=C); δ 2.05 (3 H, s, Ac), 2.08 (3 H, s, Ac), 3.45 (3 H, s, Me), 4.8—5.25 (4 H, m, H-1, -2, -3, and -4), and 6.35 (1 H, d, $J_{4,5}$ 6 Hz, H-5).

Methyl (5S)-2,3,4-*Tri*-O-*acetyl*-5-*methoxy*-β-D-*xylopyranoside* (13).—The 5-methoxyxylopyranosyl bromide (10) (0.2 g) in methanol–chloroform (5 ml; 4 : 1 v/v) was stirred with silver oxide (0.2 g) for 0.5 h and the solution was then treated with activated charcoal. Removal of the solvent gave a residue which afforded on trituration with methanol–water (4 : 1 v/v) the crystalline *dimethoxy-compound* (0.13 g, 75%), m.p. 133—134 °C [from methanol–water (4 : 1 v/v)], $[\alpha]_D$ 0° (Found: C, 48.5; H, 6.5. $C_{13}H_{20}O_9$ requires C, 48.8; H, 6.3%); δ 1.99 (3 H, s, Ac), 2.01 (6 H, s, 2 Ac), 3.44 (6 H, s, 2 Me), 4.51 (2 H, d with virtual coupling, $J_{1,2} = J_{4,5}$ = 5 Hz, H-1 and -5), 4.9—5.1 (3 H, m, H-2, -3, and -4).

(5S)-1,2,3,4-*Tetra*-O-*acetyl*-5-(2-*hydroxyethoxy*)-β-D-*xylopyranose* (14).—Ethanediol (2 ml) and mercury(II) cyanide (1.0 g) were added to a solution of the 5-bromoxylose derivative (2) (1.0 g) in acetonitrile (10 ml) and the mixture was stirred for 6 h. Chloroform was added and washing was effected with saturated aqueous sodium hydrogencarbonate and water. The chloroform solution was dried and the solvent removed to give a solid residue (0.7 g) which afforded on trituration with ethanol–light petroleum the *hydroxyethyl compound* (0.44 g, 46%), m.p. 126—127 °C (from ethanol–light petroleum), $[\alpha]_D$ +7° (Found: C, 47.7; H, 5.9. $C_{15}H_{22}O_{11}$ requires C, 47.6; H, 5.8%); δ 2.0—2.1 (12 H, 4s, 4 Ac), 2.48 (1 H, s, OH), 3.70 (4 H, s, 2 CH_2), 4.78 (1 H, d with virtual coupling, $J_{4,5}$ 5 Hz, H-5), 4.9—5.4 (3 H, m, H-2, -3, and -4), 5.81 (1 H, d with virtual coupling, $J_{1,2}$ 6 Hz, H-1).

(5S)-5-(2-*Acetoxyethoxy*)-1,2,3,4-*tetra*-O-*acetyl*-β-D-*xylopyranose* (16).—The 2-hydroxyethoxy-compound (14) (0.5 g) was acetylated under standard conditions using acetic anhydride and pyridine to give the crystalline acetate (0.44 g, 80%) which, recrystallised (×4) from ethanol, had m.p. 100—101 °C, $[\alpha]_D$ +15° (Found: C, 48.3; H, 5.8. $C_{17}H_{24}O_{12}$ requires C, 48.6; H, 5.7%); δ 2.00—2.12 (15 H, 4s, 5 Ac), 3.6—3.9 (2 H, m, CH_2–O–C-5), 4.0—4.3 (2 H, m, CH_2-OAc), 4.70 (1 H, d with virtual coupling, $J_{4,5}$ 5 Hz, H-5), 4.9—5.4 (3 H, m, H-2, -3, and -4), 5.80 (1 H, d with virtual coupling, $J_{1,2}$ 6 Hz, H-1).

5,5′-*Ethylenedioxybis*-[(5S)-1,2,3,4-*tetra*-O-*acetyl*-β-D-*xylopyranose*] (15).—A solution of the 5-bromoxylose compound (2) (2.2 g) and the 2-hydroxyethoxy-compound (14) (2.2 g, 1.05 mol. equiv.) in nitromethane (30 ml) was stirred with mercury(II) cyanide (1.4 g, 1.0 mol. equiv.) for 6 h. A similar quantity of the bromide was added and stirring was continued for 16 h, after which benzene was added and the mixture was washed with saturated aqueous

sodium hydrogencarbonate and water and the organic phase was dried and taken to a syrup (4.9 g). Trituration with ethanol gave a crystalline product (1.75 g) which on recrystallisation from ethanol afforded the *diglycoside* (1.34 g, 33%), m.p. 160—164 °C. Further recrystallisation (×4) from the same solvent gave a m.p. of 166—168 °C, $[\alpha]_D$ +34° (Found: C, 48.4; H, 5.6. $C_{28}H_{38}O_{20}$ requires C, 48.4; H, 5.5%); δ 2.0—2.1 (24 H, 3s, 8 Ac), 3.73br (4 H, s, 2 CH_2), 4.73 (2 H, d with virtual coupling, $J_{4,5} = J_{4',5'} =$ 5 Hz, H-5 and -5'), 4.9—5.3 (6 H, m, H-2, -2', -3, -3', -4, and -4'), and 5.77 (2 H, d with virtual coupling, $J_{1,2} = J_{1',2'} = 6$ Hz, H-1, and -1'). Chromatography of the non-crystalline products gave the acetate (16) (0.25 g, 10%), m.p. 100—101 °C, identical (^{1}H n.m.r.) with the product of acetylation of the hydroxyethoxy-compound.

(5S)-2,3,4-*Tri*-O-*acetyl*-1,5-O-*ethylene*-5-*hydroxy*-β-D-*xylopyranoside* (17).—The hydroxyethoxy-compound (14) (0.4 g) was allowed to stand for 1 h in dry chloroform (10 ml) containing boron trifluoride–ether (0.15 g), and the solution was then washed with saturated aqueous sodium hydrogencarbonate and water. After drying, the solvent was removed to give a syrup (0.3 g) which afforded after chromatography on silica gel the crystalline *bicyclic product* (0.18 g, 54%), m.p. 123—124 °C (from ether–light petroleum), $[\alpha]_D$ 0° (Found: C, 49.1; H, 5.8. $C_{13}H_{18}O_9$ requires C, 49.1; H, 5.7%); δ 2.02 (9 H, s, 3 Ac), 3.88 (4 H, s, $2CH_2$), 4.95 (2 H, d, $J_{1,2} = J_{4,5} = 3$ Hz), and 5.2—5.5 (3 H, m, H-2, -3, and -4).

2,3,4-*Tri*-O-*acetyl*-xylo-*pentodialdose Bis*(*ethylene dithioacetal*) (18).—A solution of the penta-acetate (6) (1.0 g) in chloroform (40 ml) containing ethane-1,2-dithiol (0.52 g, 2.1 mol. equiv.) and boron trifluoride–ether (0.38 g) was allowed to stand at room temperature for 21 h and then washed with saturated aqueous sodium hydrogencarbonate and water and then dried. Removal of the solvent left a syrup which was resolved on a column of silica gel to give the *bis-acetal* (18) (0.63 g, 56%), m.p. 103—104 °C, (from ethanol), $[\alpha]_D$ 0° (Found: C, 42.2; H, 5.1; S, 29.9. $C_{15}H_{22}O_6S_4$ requires C, 42.2; H, 5.2; S, 30.1%); δ 2.07—2.10 (9 H, 3s, 3 Ac), 5.17 (8 H, s, $4CH_2$), 4.52 (2 H, d, $J_{1,2'} = J_{4,5} = 8$ Hz, H-1,5), 4.97 (2 H, dd, $J_{2,3'} = J_{3,4} = 3.5$ Hz, H-2, and -4), and 5.52 (1 H, t, H-3). When a solution of the diglycoside (15) (0.45 g) in chloroform (18 ml) containing ethane-1,2-dithiol (0.061 g, 1.0 mol. equiv.) and boron trifluoride–ether (0.092 g, 1.0 mol. equiv.) was allowed to stand for 1.5 h, the bis-acetal (18) was observed (t.l.c.) to have become the major discrete component of the reaction mixture. Conventional processing and resolution of the syrupy product on silica gel gave the title compound (18) (0.06 g, 21% based on the thiol). Recrystallised from ethanol it had m.p. and mixed m.p. 103—104 °C, and gave a ^{1}H n.m.r. spectrum identical to that of the authentic material.

9-[(5S)-5-*Acetoxy*-2,3,4-*tri*-O-*acetyl*-β-L-*xylopyranosyl*]-2,6-*dichloropurine* (19).—A suspension of bis-(2,6-dichloropurinyl)mercury(II) [16] (4.5 g) on Celite (4.5 g) was heated under reflux in xylene (100 ml) for 15 min with removal of traces of water. The bromo-compound (2) (6.0 g, 1.94 mol. equiv.) was added and refluxing was continued for 20 min. Removal of the solids and solvent gave a syrup which was extracted into chloroform and washed with aqueous sodium iodide and water. After drying, the solvent was removed, the residue (8.6 g) was redissolved in chloroform (30 ml) and the *purine nucleoside derivative* (2.45 g, 32%) crystallised after addition of light petroleum. Recrystallised from ethyl acetate–light petroleum, then chloroform–light petroleum, it had m.p. 226—228 °C, $[\alpha]_D$ +22° (Found: C, 42.5; H, 3.7; Cl, 14.2; N, 11.0. $C_{18}H_{18}Cl_2N_4O_9$ requires C, 42.7; H, 3.6; Cl, 14.1; N, 11.1%); δ([$^2H_6$]DMSO) 1.73 [3 H, s, Ac-4)], 1.98, 2.04, and 2.07 (9 H, 3 s, 3 Ac), 5.27 (1 H, t, $J_{1,2} = J_{2,3} = 8.5$ Hz, H-2), 5.55—6.00 (2 H, m, H-3, and -4), 6.30 (1 H, d, H-1), 6.52 (1 H, d with virtual coupling, $J_{4,5}$ 9 Hz, H-5), and 8.98 (1 H, s, purine H-8).

1-[(5S)-5-*Acetoxy*-2,3,4-*tri*-O-*acetyl*-β-L-*xylopyranosyl*]-*uracil* (20).—Bis(trimethylsilyl)uracil [17] (3.5 g) and mercury(II) cyanide (1.9 g, 0.6 mol. equiv.) were added to a solution of the bromide (2) (5.0 g, 0.9 mol. equiv.) in dry nitromethane (30 ml) in the presence of 4A molecular sieve and the mixture was stirred for 24 h. Further mercury(II) cyanide (1 g) was added and stirring was continued for 24 h when benzene (50 ml) was added, the solids were removed and the filtrate was washed with aqueous sodium hydrogencarbonate, dried, and taken to a syrup which, on trituration with ether gave the *pyrimidine nucleoside* derivative (3.21 g, 60%), m.p. 213—215 °C [from ethanol (×3)], $[\alpha]_D$ −3.1° (Found: C, 46.6; H, 5.0; N, 6.3. $C_{17}H_{20}N_2O_{11}\cdot 0.5\ H_2O$ requires C, 46.7; H, 4.8; N, 6.4%); δ[$(CD_3)_2CO$] 1.93, 1.96, 2.00, and 2.07 (12 H, 4s, 4Ac), 5.23 (1 H, t, *J* 10 Hz, H-2 or 4), 5.37 (1 H, t, *J* 10 Hz, H-2 or 4), 5.66 (1 H, t, *J* H-3), 5.70 (1 H, d, $J_{5,6}$ 8.5 Hz, uracil H-5), 6.16 (1 H, d, *J* 8 Hz, H-1), 6.20 (1 H, d, *J* 9 Hz, H-5), 7.80 (1 H, d, uracil H-6), and 10.0br (1 H, s, NH).

1-[(5S)-5-*Acetoxy*-2,3,4-*tri*-O-*acetyl*-β-L-*xylopyranosyl*]-3-N-*methyluracil* (21).—A freshly prepared solution of diazomethane in ether (50 ml) was added to the nucleoside (20) (1 g) in 1,2-dichloroethane (10 ml) and the solution was kept at 4 °C for 8 h. The solvent was removed and the residue was purified on a column of silica gel to give the N-*methyl derivative* (0.8 g, 77%), m.p. 148—149 °C (from chloroform–light petroleum, $[\alpha]_D$ +1° (Found: C, 49.2; H, 5.3; N, 6.0. $C_{18}H_{22}N_2O_{11}$ requires C, 48.9; H, 5.0; N, 6.3%); δ 1.95, 1.99, 2.01, and 2.08 (12 H, 4 s, 4 Ac), 3.27 (3 H, s, Me), 4.8—5.6 (3 H, m, H-2, -3, and -4), 5.77 (1 H, d, $J_{5,6}$ 8.5 Hz, uracil H-5), 5.96 (1 H, d, $J_{4,5}$ 9 Hz, H-5), 6.11 (1 H, d, $J_{1,2}$ 9 Hz, H-1), and 7.25 (1 H, d, uracil H-6).

1-[(5S)-2,3,4-*Tri*-O-*acetyl*-5-(2,6-*dichloropurin*-9-yl)-β-D-*xylopyranosyl*]*uracil* (22).—A solution of the purine derivative (19) (1.42 g) in 1,2-dichloroethane (30 ml) containing boron trifluoride–ether (1.2 g, 3 mol. equiv.) and dichloromethyl methyl ether (0.96 g, 3 mol. equiv.) was heated under reflux for 5.5 h by which time the starting material had been converted to an ultraviolet-absorbing, chromotographically more mobile product. The solution, after cooling, was washed with saturated aqueous sodium hydrogencarbonate and then with water before being dried. The residue (1.26 g) was dissolved in dry nitromethane (15 ml), and after the solution had been stirred with 4A molecular sieve for 0.5 h, bis(trimethylsilyl)uracil (1.0 g, 1.5 mol. equiv.) and mercury(II) cyanide (1.0 g, 1.5 mol. equiv.) were added and the mixture was allowed to stand at 20 °C for 7 days with occasional stirring. Chloroform (100 ml) was added before washing with saturated aqueous sodium hydrogencarbonate and then water. After drying, the solvent was removed to give a dark residue (1.25 g) which was chromatographed on silica gel to give the '*double-headed*' *nucleoside* derivative as a microcrystalline solid (0.47 g, 30%). Recrystallised from ethyl acetate–light petroleum and then ethanol it had m.p. 299—302 °C (decomp.), $[\alpha]_D$ +19° (*c*, 1 in EtOAc) (Found: C, 43.0; H,

3.5; Cl, 12.8; N, 15.3. $C_{20}H_{18}Cl_2N_6O_9$ requires C, 43.1; H, 3.3; Cl, 12.7; N, 15.0%); δ[$(CD_3)_2CO$] 1.78 [3 H, s, Ac-4], 2.03 (6 H, s, 2 Ac), 5.5—6.15 (4 H, m, H-2, -3, and -4, and uracil H-5; d, 8.5 Hz at 5.72 probably uracil H-5), 6.55 (1 H, d, *J* 8.5 Hz, H-1 or -5), 6.59 (1 H, d, *J* 9 Hz, H-5 or -1), 7.90 (1 H, $J_{5,6}$ 8.5 Hz, uracil H-6), 8.78 (1 H, s, purine H-8), and 10.15br (1 H, s, NH).

(5S)-2,3,4-*Tri*-O-*acetyl*-5-*bromo*-β-D-*xylopyranosyl Chloride* (23).—The bromide (2) (3.0 g) in 1,2-dichloroethane (50 ml) containing boron trifluoride–ether (2.15 g, 2 mol. equiv.) and dichloromethyl methyl ether (1.8 g, 2 mol. equiv.) was heated under reflux for 4 h. The black solution was washed with saturated sodium hydrogencarbonate, then with water and dried. Removal of the solvent left a dark residue (2.3 g) which was fractionated on a column of silica gel to give the crystalline *bromochloride* (1.24 g, 44%), m.p. 120—122 °C (from chloroform–light petroleum (×3), $[\alpha]_D$ −202° (Found: C, 35.1; H, 3.7; Br, 21.1; Cl, 9.4. $C_{11}H_{14}BrClO_7$ requires C, 35.3; H, 3.8; Br, 21.4, Cl, 9.5%); δ 2.00 (3 H, s, Ac), 2.07 (6 H, s, 2 Ac), 4.85 (1 H, dd, $J_{4,5}$ 4 Hz, $J_{3,4}$ 9 Hz, H-4), 5.12 (1 H, t, $J_{1,2}$ 9 Hz, H-2), 5.40 (1 H, d, H-1), 5.61 (1 H, t, $J_{2,3}$ 9 Hz, H-3), and 6.48 (1 H, d, H-5).

The authors thank the New Zealand University Grants Committee for the award of a Postgraduate Scholarship (to P. C. T.) and Dr. R. H. Furneaux for his general assistance,

[0/098 *Received*, 17*th January*, 1980]

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