Syntheses of the Two Epimeric 5'-Methylcytidines, their 5'-Phosphates and [5-^{3}H]-5'-Pyrophosphates, and the Two 5'-Methyldeoxycytidines. A Novel Cystosine Anhydro-nucleoside with Two Oxygen Bridges between the Base and the Sugar

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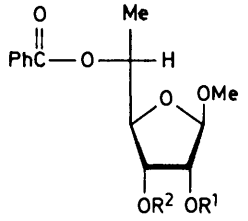
In a series of experiments the starting materials were methyl 2,3-*O*-isopropylidene-β-D-allo- and -α-L-talo-furanosides. These were converted in two steps into the corresponding 2,3,5-tri-*O*-benzoyl esters, (5) and (11), which were coupled with *N*-acetylbis(trimethylsilyl)cytosine in the presence of tin(IV) chloride, to the protected nucleosides (19) and (20). Alkaline methanolysis gave the free cytidine homologues, 1-(6-deoxy-β-D-allo- and -α-L-talo-furanosyl)cytosine (23) and (28), which were converted into the crystalline 5'-phosphates (24) and (29), and hence to the dilithium salts of the 5'-pyrophosphates, (25) and (30), by standard procedures. These were labelled at C-5 by bromination, followed by catalytic reduction in tritium gas. The same methyl furanoside starting materials were converted into the 3,5-dibenzoates, (3) and (9), by deacetalation followed by monobenzoylation by the stannylene procedure. Substitution of iodine *via* the 2-trifluoromethanesulphonates gave iodides which were reduced by tributylstannane to methyl 3,5-di-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*- and -α-L-*lyxo*-hexofuranosides (7) and (13). Coupling of these in the same way as above, followed by alkaline methanolysis, gave the two deoxycytidine homologues, 1-(2,6-dideoxy-β-D-*ribo*- and -α-L-*lyxo*-hexofuranosyl)cytosine, (16) and (17), together with their anomers (14) and (15). In another approach to these nucleosides, 4-*N*-acetyl-2',3'-*O*-isopropylidenecytidine was oxidized to the aldehyde (33) which was condensed with dimethylsulphoxonium methylide to a mixture of epoxides (34) and (35). Hydrogen bromide opening, followed by tributylstannane reduction, converted these epoxides into 4-*N*-acetyl-1-(2,3-*O*-isopropylidene-6-deoxy-β-D-allo- and -α-L-talo-furanosyl)cytosine (36) and (37). Treatment of the same mixture dissolved in tetrahydrofuran (THF) by boron trifluoride–ether gave 4-acetamido-1-(2,5'; 2,6'-*dianhydro*-2',3'-*O*-isopropylidene-α-L-talofuranosyl)-2*H*-pyrimidine (39), the first reported anhydro-nucleoside with two oxygen bridges between the base and the sugar, available in 18% overall yield from protected cytidine.

AMONG the vast number of non-natural nucleosides which have been synthesized, derivatives modified in the sugar ring show in most cases configurations drastically different from those of β-D-ribofuranose and 2-deoxy-β-D-*erythro*-pentofuranose. The cytosine nucleosides (or nucleotides) described below may be viewed on paper as products of the substitution by a methyl of one 5'-H in the natural derivatives. This homologation does not alter the configuration of functional groups. Besides, this modification is located as far as possible from the target of the ribonucleotide reductase enzymes.[1,2] For most of these, cytidine 5'-pyrophosphate is the most active substrate, but they can tolerate, at the expense of yields, some variations in the nature of the bases, and the replacement by sulphur of some pyrophosphate oxygen atoms.[3] They appear specifically to be of the β-D-ribofuranose configuration, but all nucleotides so far tested were modified very near 2'-OH. With this problem of specificity in mind, we have synthesized labelled pyrophosphates of the 5'-methylcytidines, and their assumed reduction products as unlabelled carriers. These would allow the assay of even partially purified enzymes, *e.g.* from tumours. While known coupling methods could be applied, the elaboration of a workable method for reduction at C-2 of a furanose sugar, and the direct homologation of cytidine, pose problems of chemical interest.

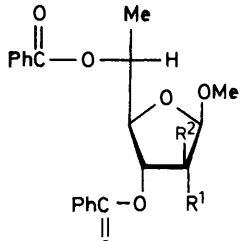
DISCUSSION

We shall deal first with the syntheses of the 2'-deoxy-nucleosides, 1-(2,6-dideoxy-β-D-*ribo*- and -α-L-*lyxo*-hexofuranosyl)cytosine (16) and (17). The reduction of nucleosides (23) and (28), now readily available (*see below*) was not considered, for there was little encouragement from known cytidine chemistry. Suitable, reducible cytidine derivatives would be 2',3'-*O*-thionocarbonates,[4] or products chlorinated at C-2'. However, the preparation of thionocarbonates seems impracticable, because of their probable ready conversion into 2,2'-*anhydro*-nucleosides,[5] and the known chloro-compounds have been so far obtained by indirect routes,[6,7] not from cytidine. So we selected a coupling procedure.

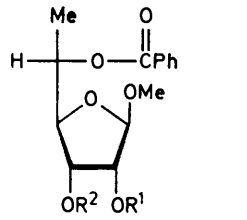
The starting materials were methyl 2,3-*O*-isopropylidene-β-D-allo- and -α-L-talo-furanoside, both easily prepared from L-rhamnose.[8] Benzoylation of the D-*allo*-acetal, followed by hydrolysis in 10% water in trifluoroacetic acid, gave the crystalline diol (1). Dropwise addition during 30 min of a toluene solution of its 2,3-*O*-thionocarbonate and αα'-azoisobutyronitrile (0.1% by weight) to a refluxing toluene solution of tributylstannane gave a 90% yield of reduced products (addition in the reverse order gave low and erratic results). However, the main product was the 3-deoxy-furanoside. Therefore we looked for methods of halogenation at position 2. The reaction of *N*-bromosuccinimide in carbon tetrachloride[9] with the benzylidene acetal (2) gave a mixture of three bromides which were directly reduced by tributylstannane. The main sugar obtained (18) (45%) was reduced at C-5: the ^{1}H n.m.r. spectrum indicated the presence of *C*-ethyl (a three-proton triplet and a two-proton multiplet at δ 0.95 and 1.50). Protons 1-H and 2-H appear not to be coupled, an



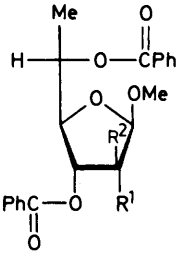
(1) $R^1 = R^2 = H$
(2) $R^1, R^2 = PhCH$
(3) $R^1 = H, R^2 = PhCO$
(4) $R^1 = PhCO, R^2 = H$
(5) $R^1 = R^2 = PhCO$



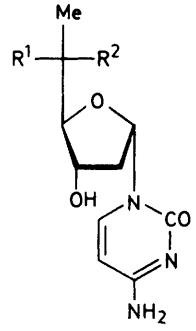
(6) $R^1 = H, R^2 = I$
(7) $R^1 = R^2 = H$



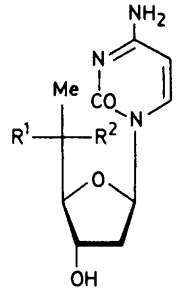
(8) $R^1 = R^2 = H$
(9) $R^1 = H, R^2 = PhCO$
(10) $R^1 = PhCO, R^2 = H$
(11) $R^1 = R^2 = PhCO$



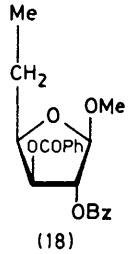
(12) $R^1 = H, R^2 = I$
(13) $R^1 = R^2 = H$



(14) $R^1 = OH$ $R^2 = H$
(15) $R^1 = H$ $R^2 = OH$

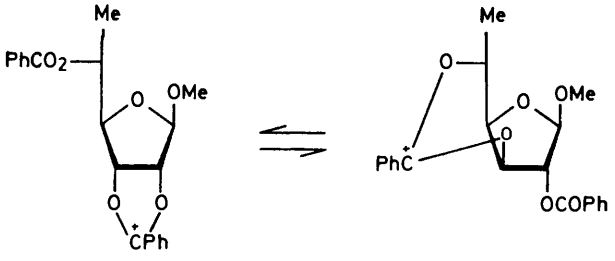


(16) $R^1 = OH$ $R^2 = H$
(17) $R^1 = H$ $R^2 = OH$



(18)

indication of a *trans*-arrangement of 1-H, 2-H, and 3-H, and hence a β-D-*xylo*-configuration, assuming no changes at C-1 and C-4. An equilibrium between the 2,3- and 3,5-oxonium ions, and preferential attack at C-5 may readily explain this result.



Iodination at C-2 was achieved in three steps. Monobenzoylation of diol (1) by the stannylene procedure under conditions described previously by one of us [10] was complete in 5 min at room temperature. Although there was t.l.c. evidence that the substitution was regiospecific at the beginning, the work-up gave a mixture of dibenzoates (3) and (4). These could be readily separated. The unwanted 2-benzoate was partially isomerized in refluxing toluene, to give more of the 3-benzoate, again separated. It was obtained finally in 78% yield after two such cycles. Identification of the position of benzoylation in dibenzoates (3) and (4) was made in the usual way, from the coupling constants of the protons *gem* to the ester functions. Attempted substitution with the triphenylphosphine–carbon tetrachloride reagent gave only traces of chlorinated product. This reagent had proved satisfactory for substitution at the 2-position of a β-D-ribofuranose,[11] but the outcome of the reaction seems highly dependent upon the configuration. However, esterification with trifluoromethanesulphonic anhydride, followed by displacement by tetrabutylammonium iodide, according to the procedure of Binkley and Hehemann,[12] gave in 82% overall yield the crystalline iodide (6). We adopt the 2-deoxy-2-iodo-D-*altro*-configuration, because the coupling constants ($J_{1,2}$ 4, $J_{2,3}$ 9 Hz) are compatible with a *cis–trans* arrangement of protons 1, 2, and 3. Tri-

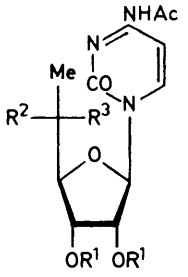
butylstannane reduction of iodide (6) was nearly quantitative, thus allowing a 50% overall yield of the 2-deoxyfuranoside (7) from diol (1).

Condensation of 1-*O*-acylfuranosides with *N*-acetylbis(trimethylsilyl)cytosine in the presence of tin(IV) chloride after the method of Niedballa and Vorbrüggen [13] is usually effective at room temperature. With the less reactive methyl furanoside (7), 4 h heating at 50 °C was necessary for completion. As there was no participation, an αβ-mixture of protected nucleosides was obtained in 75% yield. The free nucleosides, (14) and (16), obtained by alkaline methanolysis, were readily separated by chromatography on a Dowex 1 (OH^-) ion-exchange resin. The α-D (14) and β-D (16) configurations were respectively ascribed to the first and second eluted anomer for the following reasons: the second anomer had a higher optical rotation, and in its first-order, 250-MHz ^1H n.m.r. spectrum, the signal of 1′-H, a doublet of doublets ($J_{1',2'}$ 6, $J_{1',2''}$ 8 Hz), resembled closely the 1′-H unresolved triplet (W_H 13.5 Hz) of deoxycytidine. Conversely, the signal of 1′-H of the anomer eluted first, ($J_{1',2'}$ 2, $J_{1',2''}$ 7 Hz), was clearly analogous to the signal of 1′-H in ' α-deoxy-cytidine ', a pseudo-quartet (W_H 10.5 Hz).

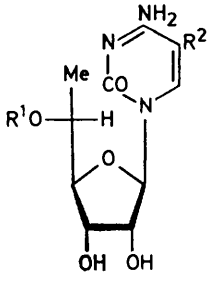
The synthesis of 1-(2,6-dideoxy-α-L-*lyxo*-hexofuranosyl)cytosine (17) was strictly parallel to that of its D-*ribo*-isomer, with almost identical yields at each step for all the compounds isolated, (8)—(13), (15), and (17). The thionocarbonate reduction method likewise gave an excess of unwanted 3-deoxy-furanoside. Identification of the two anomers (15) and (17) obtained in the synthesis rested on the same criteria as above. As the β-D-*ribo*- (16) and α-L-*lyxo*-anomers (17) have the same configuration up to C-5′, it is not surprising that they were both eluted second from the ion-exchange column.

The starting materials for the preparation of the cytidine homologue (23) and (28) were again the furanosides (1) and (8). The β-D-*allo*-derivative (1) was converted into the tribenzoate (5), which was coupled to *N*-acetylbis(trimethylsilyl)cytosine by the same method as above.[13] Slightly more vigorous conditions (2 h at 80 °C) were necessary in the present case. The protected nucleoside (19) was obtained in 82% yield, and methanolysed in alkaline conditions to the free, crystalline nucleoside, 1-(6-deoxy-β-D-allofuranosyl)cytosine (23).

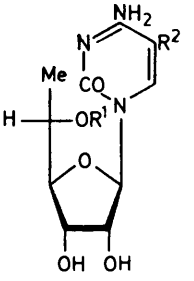
While there is now little doubt that participation in the reaction of the 2-*O*-benzoyl groups must lead to the exclusive formation of the β-D-furanoside, an independent proof for this was found in the conversion of (23) into the *N*-acetyl-1,3-*O*-isopropylidene derivative (21) which could also be prepared from cytidine. The



(19) R^1 = PhCO, R^2 = OCOPh, R^3 = H
(20) R^1 = PhCO, R^2 = H, R^3 = OCOPh
(21) R^1–R^1 = $>CMe_2$, R^2 = OH, R^3 = H
(22) R^1–R^1 = $>CMe_2$, R^2 = H, R^3 = OH



(23) R^1 = R^2 = H
(24) R^1 = PO_3H_2, R^2 = H
(25) R^1 = PO(OH)-OPO_3H_2, R^2 = H
(26) R^1 = PO(OH)-OPO_3H_2, R^2 = Br
(27) R^1 = PO(OH)-OPO_3H_2, R^2 = ^3H



(28) R^1 = R^2 = H
(29) R^1 = PO_3H_2, R^2 = H
(30) R^1 = PO(OH)-OPO_3H_2, R^2 = H
(31) R^1 = PO(OH)-OPO_3H_2, R^2 = Br
(32) R^1 = PO(OH)-OPO_3H_2, R^2 = ^3H

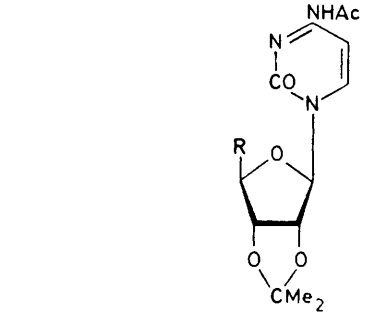
overall yield of nucleoside (23) from the starting materials was *ca.* 65%.*

For the preparation of the 5′-phosphate, the method of Yoshikawa *et al.*,[15] which rests on the selective phosphorylation of a primary alcohol, obviously cannot be used, and it was first necessary to protect the *cis*-diol system by acetalation to the isopropylidene derivative before esterification with β-cyanoethyl phosphate according to Tener.[16] The 5′-phosphate (24) was finally obtained in 70% yield as the pure, crystalline, anhydrous, free acid. The pyrophosphate (25) was prepared according to Michelson,[17] and isolated as the acetone-insoluble dilithium salt, which had the composition of a tetrahydrate, and a compatible u.v. spectrum in water and 0.1M HCl. Bromination of this pyrophosphate gave the 5-bromo-derivative (26), probably in nearly quantitative yield. This was checked by the disappearance in the ^{1}H n.m.r. spectrum of the signal of 5-H, and the $J_{5,6}$ coupling, and the shifting of $\lambda_{max.}$ to 300 nm, a wavelength characteristic of 5-halogenocytidines.[18] Without extensive purification, the bromonucleotide was catalytically reduced with tritium gas to the labelled analogue (27).

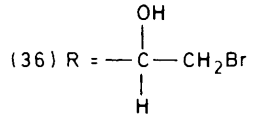
Starting from the methyl furanoside (8), the same reaction sequence, in the α-L-*talo*-series, gave successively compounds (11), (20), (28), (22), and (29)—(32), with similar yields at each step.

Homologation of cytidine was next investigated as a more direct route to nucleosides (23) and (28). 4-*N*-Acetyl-*O*-2′,3′-isopropylidenecytidine was oxidized as described for the 4-*N*-benzoyl analogue [19] to an aldehyde which was converted *in situ* into the crystalline *NN*′-diphenylimidazoline (34) to protect it during work-up. The aldehyde (33) obtained in 78% overall yield from protected cytidine, by acidic hydrolysis of the pure imidazoline, crystallized in the carbonyl form from water–THF solution, while its 4-*N*-benzoyl analogue gave a stable hydrate under the same conditions.[19] Reaction with dimethyloxosulphonium methylide [20] gave, together with decomposition products, a 1 : 1 epimeric mixture of epoxides (35) as estimated from the intensities of the well separated signals of 6′-H on the n.m.r. spectrum. Opening of the epoxide rings by hydrogen bromide gave a mixture of bromohydrins (36) and (37), which could be separated from each other, but not obtained pure because of their amorphous nature. However, in the ^{1}H n.m.r. spectrum in [$^2H_6$]dimethyl sulphoxide the shifting of the 6′-H protons to δ 3.36, and the presence of the doublet characteristic of a secondary alcohol was in agreement with the proposed structures. Tributylstannane reduction of bromohydrins (36) and (37) gave nucleosides respectively identical (m.p. and mixed m.p. and optical rotation) with the products of *N*-acetylation, (21) and (22), of 1-(6-deoxy-*O*-1,2-isopropylidene-β-D-allo- and -α-L-talo-furanosyl)cytidine.

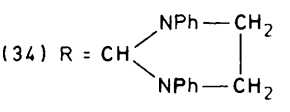
Attempted isomerization of the mixture of epoxides (35) to an aldehyde with boron trifluoride–ether in THF gave a most unexpected result. Two products were obtained after the usual work-up involving aqueous solutions. The minor one, which was the more polar on silica gel, showed u.v. and ^{1}H n.m.r. spectra compatible with structure (38), 4-*N*-acetyl-1-(2,3-*O*-isopropylidene-β-D-allofuranosyl)cytosine. Acidic hydrolysis gave a sugar which behaved as D-allose in three different paper chromatography systems (p.c.). The major



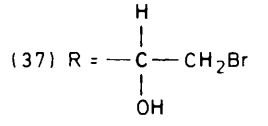
(33) R = CHO



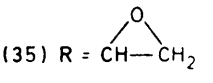
(36) R = —C(OH)(H)—CH$_2$Br



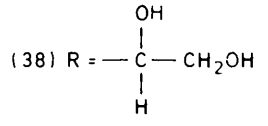
(34)



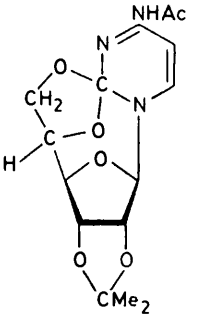
(37) R = —C(H)(OH)—CH$_2$Br



(35) R = CH(O)CH$_2$



(38) R = —C(OH)(H)—CH$_2$OH



(39)

product (65%) showed a u.v. spectrum with two maxima of near equal absorption, $\lambda_{max.}$ 239 and 306 nm, quite different from those of either 4-*N*-acetylcytidine derivatives or any known pyrimidine 2,5′-anhydronucleoside. The drastic alteration of the chromophore was confirmed by the ^{13}C n.m.r. spectrum, which is partially reported in the Table, together with data from the literature. The 38 p.p.m. shift of the signal of C-2 upfield from the average value for the other nucleosides [155 (±3) p.p.m.] is an indication of rehybridization from sp^2 to sp^3. The ^{1}H n.m.r. spectrum indicated that no C–H

* After completion of this work, we were aware of a synthesis of nucleoside (23) by coupling a 1-*O*-acetylfuranoside, but no data are available to us for comparison.[14]

TABLE

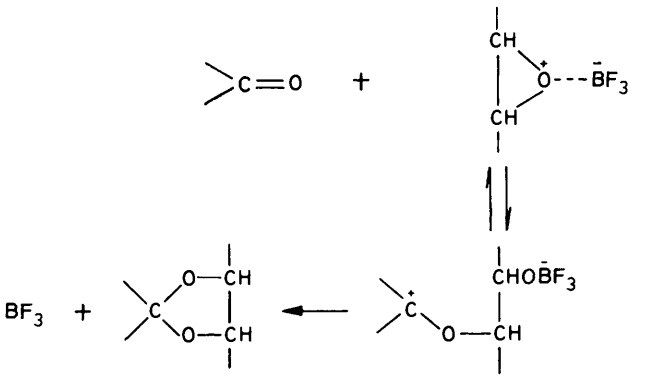
N.m.r. data for some carbons of pyrimidine nucleoside derivatives [a]

	C-4	C-2	C-6	C-5	C-1′	C-5′	C-6′
Cytidine [b]	166	156	142	96	90	62	
4-*N*-Acetylcytidine [c]	162	154	146	95	93	61	
(39) [d]	156	117	142	99	88	77	65
Uridine [b]	164	152	141	103	89	62	
2,5′-*anhydro*-isopropylideneuridine [b]	170	157	143	109	97	75	

[a] In δ from $SiMe_4$. [b] In benzene.[21] [c] In [$^2H_6$]dimethyl sulphoxide. [d] In $CDCl_3$.

proton had been lost in the reaction, but the shifting upfield of the pyrimidine protons, N–H, 5-H, and 6-H, again suggested modification (de-aromatisation) of this ring. A blurring of the 5-H doublet was also observed. The i.r. spectrum showed no OH absorption, and the product was resistant to acetylation under the usual conditions. Acidic hydrolysis gave a sugar which behaved as L-talose in three different p.c. systems. All this evidence pointed to the structure of the bis-*anhydro*-nucleoside (39). This was definitively established by a single-crystal *X*-ray structure determination of the structure.[22] Although a model of this structure seems fairly rigid, there are no angles with abnormal values. The exceptional stability of the isopropylidene ring in compound (39), which cannot be hydrolysed without complete breaking of the bonds between the base and the sugar, may be due to hindrance to *O*-protonation.

Compound (39), prepared in three steps from 4-*N*-acetyl-2′,3′-*O*-isopropylidenecytidine in 18% overall yield, is the first instance of an *anhydro*-nucleoside with two oxygen bridges. One possible mechanism of formation may be the attack by the carbonyl oxygen at one carbon of the activated epoxide, generating a carbocation ion at C-2 which links itself to the (formerly) epoxide oxygen atom at the next step. It may be significant that the two products (38) and (39) have opposite configurations at C-5′.



This novel reaction has not yet been described among the methods for acetalation of urea-type carbonyls,[23] and is the first reported one-step procedure.

EXPERIMENTAL

Unless otherwise stated, preparative chromatographic separations were performed on silica gel columns, with monitoring of the effluent by t.l.c. on silica gel. The eluant mixtures were: chloroform–methanol, 4 : 1 (A) 9 : 1 (B), 19 : 1 (C); ether–light petroleum, 1 : 1 (D), 1 : 2 (E), 1 : 4 (F); toluene–ether–light petroleum 8 : 1 : 3 (G). Ion-exchange columns were made from Dowex (X8, 100—200 mesh) resins. Except for compound (39), for which both ^1H and ^{13}C n.m.r. spectra are reported, δ values refer to ^1H n.m.r. chemical shifts in the given solvent, with $SiMe_4$ or sodium trimethylsilylpropane-1-sulphonate as internal standard. Compatible ^1H n.m.r. spectra were observed for all the structures described below, but only data deemed of interest are reported.

Methyl 5-O-*Benzyl*-6-*deoxy*-β-D-*allofuranoside* (1).—The crude benzoate prepared in the usual way from methyl 6-deoxy-β-D-allofuranoside (1.5 g) was dissolved in water–trifluoroacetic acid (1 : 9) (22 ml). The solution was kept for 5 min at room temperature, and then evaporated to dryness. Chromatography of the residue (chloroform) gave the benzoate (1) (1.72 g; 83%), m.p. 88 °C (from ether–hexane), $[\alpha]_D^{20}$ −85° (*c* 0.7 in CH_2Cl_2) (Found: C, 59.6; H, 6.4; O, 34.1. $C_{14}H_{18}O_6$ requires C, 59.6; H, 6.4; O, 34.0%).

Methyl 2,3-O-*Benzylidene*-5-O-*benzoyl*-6-*deoxy*-β-D-*allofuranoside* (2).—A mixture of furanoside (1) (0.88 g), zinc chloride (0.6 g) and benzaldehyde (30 ml) was shaken for 2 h at room temperature, and then poured into ice-water. The usual work-up gave a residue which was purified by chromatography (D) to give the acetal (2) as a syrup, b.p. 174 °C at 0.02 mmHg, $[\alpha]_D^{20}$ −38° (*c* 0.4 in CH_2Cl_2) (Found: C, 68.0; H, 6.0; O, 25.8. $C_{21}H_{22}O_6$ requires C, 68.1; H, 6.0; O, 25.9%).

Methyl 2,3-*Di*-O-*benzoyl*-5,6-*dideoxy*-β-D-xylo-*hexofuranoside* (18).—A solution of the acetal (2) (0.5 g) in carbon tetrachloride (5 ml) was refluxed for 4 h in the presence of *N*-bromosuccinimide (0.28 g) and barium carbonate (0.65 g). The solution was cooled, filtered, and evaporated to dryness. Chromatography of the residue (G) gave a syrup (0.5 g). A solution of this in toluene (15 ml) was refluxed for 2 h in the presence of tributylstannane (0.8 ml) and αα′-azo(isobutyronitrile) (16 mg), and then evaporated to dryness. Chromatography (G) first gave the furanoside (18) as a syrup (223 mg, 45%), b.p. 165 °C at 0.02 mmHg, $[\alpha]_D^{20}$ +49° (*c* 1.3 in CH_2Cl_2); δ($CDCl_3$) 0.95 (3 H, t, $J_{5,6}$ 7 Hz, C-Me), 1.5 (2 H, m, 5-H_2), 3.37 (3 H, s, OMe), 4.30 (1 H, dt, $J_{4,5}$ 6, $J_{3,4}$ 8 Hz, 4-H), 4.78 (1 H, s, 1-H), 5.3 (1 H, s, 2-H), 5.47 (1 H, d, $J_{3,4}$ 6 Hz, 3-H), and 7.3—8.1 (Ar-H) (Found: C, 67.9; H, 6.0; O, 25.6. $C_{21}H_{22}O_6$ requires C, 68.0; H, 6.0; O, 25.9%).

Methyl 3,5- *and* 2,5-*Di*-O-*benzoyl*-6-*deoxy*-β-D-*allofuranoside* (3) *and* (4).—A mixture of the diol (1) (564 mg) and dibutyltin oxide (500 mg) was refluxed in benzene, with azeotropic removal of water, for 4 h. The clear solution was concentrated to 10 ml, and cooled to room temperature. Benzoyl chloride (0.25 ml) was added. After 5 min, the solution was evaporated to dryness. Chromatography (D) of the residue gave in succession the dibenzoates (4) and (3). Isomerization of dibenzoate (4) in refluxing toluene (5 h) gave a mixture of (3) and (4) which was again separated with the same column. After one more cycle, the 3,5-*dibenzoate* (3) was obtained in a total yield of 0.6 g (78%) as a syrup, b.p. 190 °C at 0.02 mmHg, $[\alpha]_D^{20}$ +3° (*c* 2.2 in CH_2Cl_2); δ($CDCl_3$) 4.47 (1 H, d, $J_{2,3}$ 5 Hz, 2-H), 4.90 (1 H, s, 1-H), and 5.58 (1 H, dd, $J_{3,4}$ 6 Hz, 3-H) (Found: C, 65.4; H, 5.8; O, 28.7. $C_{21}H_{22}O_7$ requires C, 65.3; H, 5.7; O, 29.0%).

Continued elution gave the 2,5-*dibenzoate* (0.1 g; 13%), m.p. 138 °C (from ether–light petroleum), $[\alpha]_D^{20}$ −30° (*c* 0.5 in CH_2Cl_2); δ($CDCl_3$) 4.8 (1 H, dd, $J_{2,3}$ 5, $J_{3,4}$ 7 Hz, 3-H), 4.98 (1 H, s, 1-H), and 5.35 (1 H, d, 2-H) (Found: C, 65.2; H, 5.7; O, 28.7. $C_{21}H_{22}O_7$ requires C, 65.3; H, 5.7; O, 29.0%).

Methyl 3,5-*Di*-O-*benzoyl*-2,6-*dideoxy*-2-*iodo*-β-D-*altrofuranoside* (6).—A solution of trifluoromethanesulphonic anhydride (0.5 ml) in dry dichloromethane (10 ml) was added dropwise to a solution kept at −15 °C of dibenzoate (3) (0.74 g) and *sym*-collidine (1.2 ml) in dichloromethane (30 ml). After 1 h, the mixture was poured into saturated aqueous sodium hydrogencarbonate, the organic layer was washed with 1M hydrochloric acid and saturated aqueous sodium hydrogencarbonate, and evaporated to dryness. A solution of the residue (1.16 g) in benzene (30 ml) was refluxed for 24 h in the presence of tetrabutylammonium iodide (1.85 g), cooled, washed with aqueous saturated sodium thiosulphate and sodium hydrogencarbonate, and evaporated to dryness. Chromatography (F) of the residue gave the *iodide* (6) (82%), m.p. 80 °C (from cyclohexane), $[\alpha]_D^{20}$ −105° (*c* 0.5 in CH_2Cl_2); δ 4.3 (1 H, dd, $J_{1,2}$ 4, $J_{2,3}$ 9 Hz, 2-H), 4.85 (1 H, d, 1-H), and 6.11 (1 H, dd, $J_{3,4}$ 6 Hz, 3-H) (Found: C, 50.9; H, 4.3; O, 18.9; I, 25.4. $C_{21}H_{21}IO_6$ requires C, 50.8; H, 4.3; O, 19.3; I, 25.6%).

Methyl 3,5-*Di*-O-*benzoyl*-2,6-*dideoxy*-β-D-ribo-*hexofuranoside* (7).—A solution of iodide (6) (0.5 g), tributylstannane (0.4 ml), and αα′-azoisobutyronitrile (16 mg) in toluene (10 ml) was refluxed for 4 h, cooled to room temperature, and evaporated to dryness. Chromatography (F) of the residue gave the *reduced furanoside* (7) (0.34 g; 90%), b.p. 150 °C at 0.02 mmHg, $[\alpha]_D^{20}$ −26° (*c* 0.5 in CH_2Cl_2); δ($CDCl_3$) 2.26 (1 H, ddd, $J_{1.2'}$ 5, $J_{2.2'}$ 14, $J_{2',3}$ 5 Hz, 2′-H), 2.54 (1 H, ddd, $J_{1,2}$ 2.5, $J_{2,3}$ 7 Hz, 2-H), and 5.18 (1 H, dd, 1-H) (Found: C, 68.6; H, 6.0; O, 25.9. $C_{21}H_{22}O_6$ requires C, 68.1; H, 6.00; O, 25.9%).

Mixture of Anomeric 4-N-*Acetyl*-1-(3,5-*di*-O-*benzoyl*-2,6-*dideoxy*-D-ribo-*hexofuranosyl*)*cytidines*.—*N*-Acetylbis(trimethylsilyl)cytosine (356 mg) and tin(IV) chloride (0.23 ml) were added to a solution of furanoside (7) in 1,2-dichloroethane (30 ml). The mixture was stirred at 50 °C for 4 h, then poured into saturated aqueous sodium hydrogencarbonate. After filtration over a Celite bed, the organic layer was washed and evaporated to dryness. Chromatography (B) of the residue gave the mixture of anomeric protected nucleosides, as a foam (0.37 g; 75%) (Found: C, 63.4; H, 5.2; N, 8.4; O, 22.1. $C_{26}H_{25}N_3O_7$ requires C, 63.5; H, 5.1; N, 8.5; O, 22.8%).

1-(2,6-*Dideoxy*-α- *and* -β-D-ribo-*hexofuranosyl*)*cytosines* (14) *and* (16).—A solution of the above mixture (356 mg) in 0.05M sodium methoxide in methanol (10 ml) was kept overnight at room temperature. The free nucleosides were adsorbed by filtration through a Dowex 50 W (H^+) column which was washed with methanol and water. Elution with 1M ammonia gave the mixture of free nucleosides which were separated by repeated chromatography on a column (2.6 × 75 cm) of Dowex 1 (OH^-), with elution by 30% methanol in water. The α-D-*nucleoside* (14) was eluted first (0.1 g; 57%), m.p. 218 °C (from methanol), $[\alpha]_D^{20}$ −51° (*c* 0.8 in water); $\lambda_{max.}$ (H_2O) 272 (ε 10 000); $\lambda_{max.}$ (0.1M HCl) 280 nm (ε 15 000); δ(D_2O) 1.28 (3 H, d, $J_{5',Me}$ 6.5 Hz, 6′-Me), 2.16 (1 H, ddd, $J_{1'.2''}$ 2, $J_{2'.2''}$ 15, $J_{2''.3'}$ 2 Hz, 2″-H), 2.68 (1 H, ddd, $J_{1'.2'} = J_{2'.3'}$ = 7 Hz, 2′-H), and 4.54 (1 H, dd, $J_{3'.4'}$ 2 Hz, 3′-H) (Found: C, 49.6; H, 6.2; N, 17.3; O, 26.7. $C_{10}H_{15}N_3O_4$ requires C, 49.8; H, 6.3; N, 17.4; O, 26.5%).

Continued elution gave the β-D-*nucleoside* (16) (66 mg; 38%), m.p. 198 °C (from ethanol), $[\alpha]_D^{20}$ +4° (*c* 0.6 in H_2O) $\lambda_{max.}$ (H_2O) 272 (ε 9 800), $\lambda_{max.}$ (0.1M HCl) 280 nm (13 400); δ(D_2O) 1.28 (3 H, d, $J_{5',Me}$ 6.5 Hz, 6′-Me), 2.28 (1 H, ddd, $J_{1'.2'}$ 8, $J_{2'.2''}$ 14, $J_{2'.3'}$ 6 Hz, 2′-H), 2.40 (1 H, ddd, $J_{1'.2''}$ 6, $J_{2''.3'}$ 3 Hz, 2″-H), 3.86 (1 H, dd, $J_{3'.4'}$ 3, $J_{4'.5'}$ 4 Hz, 4′-H), 4.0 (1 H, dq, 5′-H), 4.55 (1 H, dd, 3′-H), 6.01 (1 H, d, $J_{5.6}$ 7.5 Hz, 5-H), 6.26 (1 H, dd, 1′-H), and 7.80 (1 H, d, 6-H) (Found: C, 49.5; H, 6.2; N, 16.9; O, 24.6. $C_{10}H_{15}N_3O_4$ requires C, 49.8; H, 6.3; N, 17.4; O, 26.5%).

Methyl 5-O-*Benzoyl*-6-α-L-*talofuranoside* (8).—A solution of methyl 5-*O*-benzoyl-2,3-*O*-isopropylidene-6-deoxy-α-L-talofuranoside (3.0 g) in 10% water in trifluoroacetic acid (30 ml) was kept for 5 min at room temperature and then evaporated to dryness. Chromatography of the residue (chloroform) gave the *free diol* (8) (2.2 g; 84%), m.p. 76 °C (from ether–hexane), $[\alpha]_D^{20}$ −44° (*c* 2.0 in CH_2Cl_2) (Found: C, 59.1; H, 6.4; O, 34.3. $C_{14}H_{18}O_6$ requires C, 59.6; H, 6.4; O, 34.0%).

Repetition of the above synthetic procedures in the L-*talo*-series gave the following derivatives.

Methyl 3,5-*di*-O-*benzoyl*-6-*deoxy*-α-L-*talofuranoside* (9), syrup (74%), b.p. 175 °C at 0.02 mmHg, $[\alpha]_D^{20}$ +5° (*c* 4.5 in CH_2Cl_2); δ($CDCl_3$) 4.40 (1 H, d, $J_{2,3}$ 4 Hz, 2-H), 4.90 (1 H, s, 1-H), and 5.40 (1 H, dd, $J_{3,4}$ 6 Hz, 3-H) (Found: C, 65.2; H, 5.9; O, 28.3. $C_{21}H_{22}O_7$ requires C, 65.3; H, 5.7; O, 29.0%).

Methyl 2,5-*di*-O-*benzoyl*-6-*deoxy*-α-L-*talofuranoside* (10), syrup, b.p. 170 °C at 0.02 mmHg, $[\alpha]_D^{20}$ −2° (*c* 3.5 in CH_2Cl_2); δ($CDCl_3$) 4.55 (1 H, dd, $J_{2,3}$ 4, $J_{3,4}$ 8 Hz, 3-H), 4.97 (1 H, s, 1-H), and 5.35 (1 H, d, 2-H) (Found: C, 65.2; H, 5.9; O, 29.1. $C_{21}H_{22}O_7$ requires C, 65.3; H, 5.7; O, 29.0%).

Methyl 3,5-*di*-O-*benzoyl*-2,6-*dideoxy*-2-*iodo*-α-L-*galactofuranoside* (12), syrup, b.p. 205 °C at 0.02 mmHg, $[\alpha]_D^{20}$ −77° (*c* 0.8 in CH_2Cl_2); δ($CDCl_3$) 4.35 (1 H, dd, $J_{1,2}$ 4, $J_{2,3}$ 9 Hz, 2-H), 4.90 (1 H, d, 1-H), and 6.01 (1 H, dd, $J_{3,4}$ 6 Hz, 3-H) (Found: C, 50.9; H, 4.4; O, 19.6; I, 25.8. $C_{21}H_{21}IO_6$ requires C, 50.8; H, 4.3; O, 19.3; I, 25.6%).

Methyl 3,5-*di*-O-*benzoyl*-2,6-*dideoxy*-α-L-lyxo-*hexofuranoside* (13), syrup (76%), b.p. 155 °C at 0.02 mmHg, $[\alpha]_D^{20}$ −27° (*c* 0.6 in CH_2Cl_2); δ($CDCl_3$) 2.28 (1 H, ddd, $J_{1.2'}$ 5.5, $J_{2'.3}$ 5.5, $J_{2,2'}$ 14 Hz, 2′-H), 2.58 (1 H, ddd, $J_{1.2}$ 2, $J_{2.3}$ 7 Hz, 2-H), 5.24 (1 H, dd, 1-H), and 5.60 (1 H, ddd, $J_{3.4}$ 5 Hz, 3-H) (Found: C, 68.1; H, 5.9; O, 26.1. $C_{21}H_{22}O_6$ requires C, 68.1; H, 6.0; O, 25.9%).

Mixture of anomeric 4-*N*-acetyl-1-(3,5-di-*O*-benzoyl-2,6-dideoxy-L-*lyxo*-hexofuranosyl)cytosine (70%) (Found: C, 63.3; H, 5.2; N, 8.3; O, 22.9. $C_{26}H_{25}N_3O_7$ requires C, 63.5; H, 5.1; N, 8.5; O, 22.8%).

1-(2,6-*Dideoxy*-α- *and* -β-L-lyxo-*hexofuranosyl*)*cytosine* (17) *and* (15).—The mixture obtained after alkaline methanolysis (94%) was resolved by chromatography on a Dowex 1 (OH^-) column (2.6 × 75 cm). Elution [methanol–water (3 : 7)] first gave the β-L-*nucleoside* (15) (97 mg, 58%), as a foam, $[\alpha]_D^{20}$ −43° (*c* 1.4 in H_2O); $\lambda_{max.}$ (H_2O) 272 (ε 7 700); $\lambda_{max.}$ (0.1M HCl) 280 nm (ε 11 000); δ(D_2O) 1.26 (3 H, d, $J_{5'.6'}$ 6.5 Hz, 6′-H), 2.14 (1 H, dt, $J_{1'.2'} = J_{2'.3'}$ = 2.5, $J_{2'.2''}$ 15 Hz, 2′-H), 2.74 (1 H, dt, $J_{1'.2''} = J_{2'.3''}$ = 7 Hz, 2″-H), 3.82 (1 H, dq, $J_{4'.5'}$ 6 Hz, 5′-H), 4.18 (1 H, dd, $J_{3'.4'}$ 2 Hz, 4′-H), 4.42 (1 H, m, 3′-H), 6.01 (1 H, d, $J_{5.6}$ 7.5 Hz, 5-H), 6.12 (1 H, dd, 1′-H), and 7.85 (1 H, d, 6-H) (Found: C, 48.0; H, 6.40; N, 16.8; O, 28.7. $C_{10}H_{15}N_3O_4{\cdot}0.5H_2O$ requires C, 48.0; H, 6.4; N, 16.8; O, 28.8%).

Continued elution gave the α-L-*nucleoside* (17) as a foam (47 mg, 28%), $[\alpha]_D^{20}$ +41° (*c* 1.0 in water); δ(D_2O) 2.28 (1 H, dt, $J_{1',2'} = J_{2',3'} = 7$, $J_{2',2''}$ 14 Hz, 2'-H), 2.40 (1 H, ddd, $J_{1',2''}$ 6.5, $J_{2'',3'}$ 4 Hz, 2''-H), 4.42 (1 H, ddd, $J_{3',4'}$ 4 Hz, 3'-H), and 6.26 (1 H, t, 1'-H) (Found: C, 47.0; H, 6.4; N, 16.5; O, 29.1. $C_{10}H_{15}N_3O_4 \cdot 0.75H_2O$ requires C, 47.1; H, 6.5; N, 16.5; O, 29.8%).

Methyl 2,3,5-*Tri*-O-*benzoyl*-6-*deoxy*-β-D-*allofuranoside* (5).—A solution of methyl 2,3-*O*-isopropylidene-6-deoxy-β-D-allofuranoside (5.5 g) in 10% water in trifluoroacetic acid (50 ml) was kept for 5 min at room temperature and then evaporated to dryness. Chromatography (A) of the residue gave the pure methyl glycoside (3.4 g), which was benzoylated in the usual way to the *tribenzoate* (5) (9.0 g; 86%), m.p. 97 °C (from ether–hexane), $[\alpha]_D^{20}$ +78° (*c* 1.4 in CH_2Cl_2) (Found: C, 68.4; H, 5.4; O, 26.0. $C_{28}H_{26}O_8$ requires C, 68.6; H, 5.3; O, 26.1%).

4-N-*Acetyl*-1-(2,3,5-*tri*-O-*benzoyl*-6-*deoxy*-β-D-*allofuranosyl*)*cytosine* (13).—A solution of (5) (3.3 g), *N*-acetylbis(trimethylsilyl)cytosine (2.6 g), and tin(IV) chloride (1.6 ml) in dry 1,2-dichloroethane was stirred at 80 °C for 2 h, and then poured into saturated aqueous sodium hydrogencarbonate. The suspension was filtered over a Celite bed, and the organic layer of the filtered solution was washed and evaporated to dryness. Chromatography (B) of the residue gave the *protected nucleoside* (13) as a foam (3.4 g, 83%), $[\alpha]_D^{20}$ −104° (*c* 2.3 in CH_2Cl_2) (Found: C, 64.5; H, 4.8; N, 6.9; O, 23.5. $C_{33}H_{29}N_3O_9$ requires C, 64.8; H, 4.8; N, 6.9; O, 23.5%).

1-(6-*Deoxy*-β-D-*allofuranosyl*)*cytosine* (23).—A solution of the protected nucleoside (13) (0.71 g) in 0.05M sodium methoxide in methanol (10 ml) was kept overnight at room temperature, and then run through a Dowex 50 W (H^+) column which was washed with methanol and water. Elution with 1M aqueous ammonia gave the *nucleoside* (23) (0.275 g; 92%), m.p. 243—246 °C (aqueous ethanol), $[\alpha]_D^{20}$ −39° (*c* 0.5 in H_2O); $\lambda_{max.}$ (H_2O) 272 (9 500); $\lambda_{max.}$ (0.1M HCl) 280 nm (ε 12 900), δ(D_2O) 1.28 (3 H, d, $J_{5',6'}$ 6.5 Hz, 6'-Me), 3.98 (1 H, dd, $J_{3',4'} = J_{4',5'} = 3.5$ Hz, 4'-H), 4.08 (1 H, dq, 5'-H), 4.32 (2 H, m, 2'-H, 3'-H), 5.90 (1 H, d, $J_{1',2'}$ 4.5 Hz, 1'-H), 6.04 (1 H, d, $J_{5,6}$ 7 Hz, 5-H), and 7.80 (1 H, d, 6-H) (Found: C, 46.5; H, 6.0; N, 16.1; O, 31.2. $C_{10}H_{15}N_3O_5$ requires C, 46.7; H, 5.9; N, 13.3; O, 31.1%).

1-(6-*Deoxy*-2,3-O-*isopropylidene*-β-D-*allofuranosyl*)*cytosine*.—A solution of the nucleoside (23) (257 mg) in dry acetone (20 ml) was stirred overnight in the presence of anhydrous toluene-*p*-sulphonic acid (1.7 g) and then poured dropwise into a suspension of Dowex-1 (HCO_3^-; 50—100 mesh; used in excess) in water (200 ml). Filtration and chromatographic purification [chloroform–methanol (17 : 3)] of the precipitate gave the isopropylidene acetal as a foam (290 mg).

1-(6-*Deoxy*-5-O-*phosphoryl*-β-D-*allofuranosyl*)*cytosine* (24).—The preceding acetal (297 mg), dicyclohexylcarbodiimide (832 mg), and β-cyanoethyl phosphate (2.2 mmol) were added in that order to dry pyridine. The solution was kept for two days at room temperature, and water was added. The mixture was stirred for 1 h, filtered, and evaporated to dryness. The residue was taken up in 7M aqueous ammonia, the solution heated at 70 °C for 2 h, and then evaporated to dryness. Trifluoroacetic acid–water (9 : 1) was added to the residue. The solution was kept at room temperature for 20 min, evaporated to dryness, and co-evaporated several times with methanol. The residue was dissolved in water (20 ml), and the solution refluxed for 30 min, cooled, and run through a Dowex 50 W (H^+) column (1.6 × 40 cm). Elution with 0.5M acetic acid gave the *nucleotide* (24) (240 mg; 70%), m.p. 264—266 °C (decomp.); $[\alpha]_D^{20}$ −8° (*c* 0.1 in H_2O); $\lambda_{max.}$ (H_2O) 275 (ε 11 000), $\lambda_{min.}$ 246 nm (5 500); $\lambda_{max.}$ (0.1M HCl) 280 (ε 14 300); $\lambda_{min.}$ 242 nm (ε 3 500) (Found: C, 35.7; H, 4.8; N, 12.4; O, 37.6; P, 9.3. $C_{10}H_{16}N_3O_8P$ requires C, 35.6; H, 4.8; N, 12.5; O, 37.9; P, 9.2%)

1-(6-*Deoxy*-5-O-*pyrophosphoryl*-β-D-*allofuranosyl*)*cytosine* (25).—Diphenyl chlorophosphonate (0.04 ml; 0.12 mmol) was added to a solution of the mono(methyl-tri-n-octylammonium) salt of phosphate (24) (0.15 mmol) in dry *NN*-dimethylformamide (0.3 ml). Dioxan (0.7 ml) and tri-n-butylamine were added immediately in that order. The clear solution was kept for 3 h at room temperature, evaporated to dryness, the residue extracted with ether, and the insoluble portion dissolved in dioxan. The dioxan solution was evaporated to dryness, and the residue was dissolved in a solution of tri-*n*-butylammonium orthophosphate (0.45 mmol) in pyridine (0.45 ml). The next day, the solution was evaporated to dryness and the residue was extracted with ether. The insoluble portion was dissolved in water–ethanol (1 : 1), and the solution was brought to pH 4. After 2 h, the pH was brought to 9, and the solution was put on the top of a DEAE Sephadex (A 25, HCO_3^-) column (1.6 × 35 cm). Elution with an aqueous triethylammonium hydrogencarbonate linear gradient (0—0.4M, 3 l) gave a major nucleotide, which was separated by evaporation of the solvent, followed by several co-evaporations with aqueous methanol. The triethylammonium salt thus obtained (75 mg; 75%) was dissolved in a minimum amount of water. Addition of a 1M lithium iodide solution in acetone precipitated the Li salt of (25); $\lambda_{max.}$ (H_2O) 272 (ε 8 900); $\lambda_{max.}$ (0.1M HCl) 280 nm (ε 12 200) (Found: N, 8.3; P, 12.3. $C_{10}H_{15}Li_2N_3O_{11}P_2.4H_2O$ requires N, 8.4; P, 12.4%).

[5-^{3}H]-1-(6-*Deoxy*-5-O-*pyrophosphoryl*-β-D-*allofuranosyl*)-*cytosine* (27).—To a solution of the triethylammonium salt pyrophosphate (25) (50 mg) in dry *NN*-dimethylformamide (1 ml), a 10% (v/v) solution of bromine in carbon tetrachloride was added to a persistent coloration (*ca.* 0.7 ml). Excess of bromine was destroyed by one drop of aniline, water was added (20 ml), and the solution was extracted with chloroform (3 × 20 ml). The aqueous phase was concentrated and put on the top of a DEAE Sephadex (A 25, HCO_3^-) column. Elution with a triethylammonium hydrogencarbonate gradient (0—0.4M, 3 l), and evaporation and co-evaporation with water of the main fractions gave the triethylammonium salt of the 5-bromonucleotide (26) (50 mg) which was converted into the lithium salt by running a solution through a Dowex 50 (Li^+) column, and freeze-drying; $\lambda_{max.}$ (0.1M HCl) 300 nm (ε *ca.* 8 000).

A solution of the bromonucleoside (26) (12 μmol; u.v. estimation) and ethyldi-isopropylamine (0.1 ml) in water (1.5 ml) in the presence of palladium–barium sulphate (29 mg) was shaken in an atmosphere of tritium gas for 4.5 h at room temperature and atmospheric pressure. After filtration and removal of labile tritium, the recovered activity was 286 mCi (80%). A 25-mCi aliquot was purified by p.l.c. on a PEI cellulose plate [irrigant: 0.5M LiCl–0.5M formic acid (1 : 1)]. Elution from the plate with 0.5M ammonium hydrogencarbonate (pH 8.6) was followed by chromatography on a DEAE Sephadex column (eluant, tetraethylammonium hydrogencarbonate). The recovered

[5-^{3}H]-*nucleotide* (22 mCi; 29 Ci mmol^{-1}) was diluted with a cold carrier to a specific activity of 184 mCi mmol^{-1} and stored dissolved in ethanol–water (1 : 1) at −20 °C.

Repetition of the above synthetic procedures in the L-*talo*-series gave the following derivatives.

Methyl 2,3,5-*tri*-O-*benzoyl*-6-*deoxy*-α-L-*talofuranoside* (11), glass (87%), b.p. 225 °C at 0.02 mmHg, $[\alpha]_D^{20}$ +55° (*c* 2.5 in CH_2Cl_2) (Found: C, 68.4; H, 5.3; O, 26.5. $C_{28}H_{26}O_8$ requires C, 68.6; H, 5.3; O, 26.1%).

4-N-*Acetyl*-1-(2,3,5-*tri*-O-*benzoyl*-6-*deoxy*-α-L-*talofuranosyl*)*cytosine* (20), foam (81%), $[\alpha]_D^{20}$ −52° (*c* 1.6 in CH_2Cl_2) (Found: C, 64.4; H, 4.8; N, 6.8; O, 23.1. $C_{33}H_{29}N_3O_9$ requires C, 64.8; H, 4.8; N, 6.9; O, 23.5%).

1-(6-*Deoxy*-α-L-*talofuranosyl*)*cytosine* (28), crystals (93%), m.p. 221—224 °C (from ethanol), $[\alpha]_D^{20}$ +38° (*c* 1 in H_2O); $\lambda_{max.}$ (H_2O) 272 nm (ε 9 400); $\lambda_{max.}$ (0.1M HCl) 280 nm (ε 12 900); δ(D_2O) 1.30 (3 H, d, $J_{5',6'}$ 7 Hz, 6'-Me), 3.90 (1 H, dd, $J_{3',4'} = J_{4',5'} = 5$ Hz, 4'-H), 4.03 (1 H, dq, 5'-H), 4.18 (1 H, dd, $J_{2',3'}$ 5 Hz, 3'-H), 4.30 (1 H, dd, 2'-H), 5.88 (1 H, d, $J_{1',2'}$ 4 Hz, 1'-H), 6.03 (1 H, d, $J_{5,6}$ 7.5 Hz, 5-H), and 7.84 (1 H, d, 6-H) (Found: C, 46.3; H, 5.8; N, 16.3; O, 30.9. $C_{10}H_{15}N_3O_5$ requires C, 46.7; H, 5.9; N, 16.3; O, 31.1%).

1-(6-*Deoxy*-2,3-O-*isopropylidene*-α-L-*talofuranosyl*)*cytosine*, foam (87%), $[\alpha]_D^{20}$ −19° (*c* 1.3 in CH_2Cl_2).

1-(6-*Deoxy*-5-O-*phosphoryl*-α-L-*talofuranosyl*)*cytosine* (29), crystals (70%), m.p. 222—226 °C (decomp.) (ethanol), $[\alpha]_D^{20}$ +9° (*c* 0.1 in H_2O); $\lambda_{max.}$ (H_2O) 275 nm (ε 9 400); $\lambda_{max.}$ (0.1M HCl) 280 nm (ε 12 600) (Found: C, 34.4; H, 4.9; N, 11.9; O, 38.5; P, 8.8. $C_{10}H_{16}N_3O_8P$ requires C, 34.7; H, 4.9; N, 12.1; O, 39.3; P, 8.9%).

1-(6-*Deoxy*-5-O-*pyrophosphoryl*-α-L-*talofuranosyl*)*cytosine* (25). Triethylammonium salt formed in 60% yield. Lithium salt, $\lambda_{max.}$ (H_2O) 273 nm (ε 9 000); $\lambda_{max.}$ (0.1M HCl) 280 nm (ε 12 000) (Found: N, 8.7; P, 12.6. $C_{10}H_{15}Li_2N_3O_{11}P_2 \cdot 3H_2O$ requires N, 8.7; P, 12.8%).

5-*Bromo*-1-(6-*deoxy*-5-*O*-*pyrophosphoryl*-α-L-*talofuranosyl*)*cytosine* (30), $\lambda_{max.}$ (0.1M HCl) 300 nm.

[5-^{3}H]-1-(6-*Deoxy*-5-O-*pyrophosphoryl*-α-L-*talofuranosyl*)-*cytosine* (32). The radioactive yield was 24%;[1] the pure nucleotide (12.8 mCi; 8.5 Ci mmol^{-1}), was diluted to 171 Ci mol^{-1}.

4-N-*Acetyl*-1-[5-*deoxy*-2,3-O-*isopropylidene*-5,5-(NN'-*diphenylethylenediamino*)-β-D-*ribofuranosyl*]*cytosine* (34).—A solution of 4-*N*-acetyl-2,3-*O*-isopropylidenecytidine (5 g) and dicyclohexylcarbodi-imide (4.8 g) in dimethyl sulphoxide (40 ml) was cooled to 0 °C, anhydrous pyridine (1.24 ml) and trifluoroacetic acid (0.58 ml) were added, and the mixture was kept overnight at room temperature. Water (10 ml) was then added, and the mixture was stirred for 30 min, filtered, and evaporated to dryness below 50 °C, using an oil pump. The residue was taken up in methanol (80 ml), 1,2-dianilinoethane (15.4 mmol) was added, followed by acetic acid (0.1 ml). After 1 h, collection of the precipitate (4.5 g; 57%) and chromatography of the mother-liquors [chloroform–methanol (9 : 1)] gave a total yield of 78% of *derivative* (34), m.p. 185 °C (methanol), $[\alpha]_D^{20}$ +39° (*c* 0.4 in methanol); $\lambda_{max.}$ (MeOH) 215 (ε 20 000), 250 (37 000), and 300 nm (10 000); δ($CDCl_3$) 4.50 (1 H, dd, $J_{3',4'}$ 6, $J_{4',5'}$ 4 Hz, 4'-H), 5.90 (1 H, d, 5'-H), and 5.92 (1 H, s, 1'-H) (Found: C, 64.1; H, 6.1; N, 13.2; O, 16.4. $C_{28}H_{31}O_5N_5$ requires C, 63.9; H, 6.1; N, 13.3; O, 16.7%).

4-N-*Acetyl*-1-(2,3-O-*isopropylidene*-β-D-ribo-*pentodialdo*-1,5-*furanosyl*)*cytosine* (33).—A suspension of Dowex 50 resin (50—100 mesh; H^+; 10 ml) was added to a solution of the protected aldehyde (34) (1.04 g) in water–THF (1 : 1) (100 ml). The suspension was stirred for 1 h at room temperature. Filtration, followed by concentration of the filtered solution, gave the *free aldehyde* (33) as a crystalline precipitate, m.p. 198—200 °C, $[\alpha]_D^{20}$ −12° (*c* 1.0 in MeOH); $\lambda_{max.}$ (EtOH) 213 (ε 12 000), 249 (10 000), and 275 nm (4 700); δ($CDCl_3$) 1.35, 1.52 (2 × 3 H, 2 s, CMe_2), 2.15 (3 H, s, NAc), 4.55 (1 H, s, 4'-H), 5.12 (1 H, d, $J_{2',3'}$ 6 Hz, 3'-H), 5.27 (1 H, d, 2'-H), 5.57 (1 H, s, 1'-H), 7.49 (1 H, d, $J_{5,6}$ 8 Hz, 5-H), 7.68 (1 H, d, 6-H), 9.32 (1 H, s, 5'-H), and 9.9 (1 H, s, NH) (Found: C, 51.8; H, 5.5; N, 12.9; O, 29.9. $C_{14}H_{17}N_3O_6$ requires C, 52.0; H, 5.3; N, 13.0; O, 29.7%).

A less pure sample of aldehyde (33) could be obtained by direct crystallization from ethyl acetate of the crude, underivatized oxidation product, as prepared in the preceding section (60%; traces of dicyclohexylcarbodi-imide).

Mixture of 4-N-*Acetyl*-1-(2,3-O-*isopropylidene*-5,6-*anhydro*-β-D-*allo*- *and* -α-L-*talo*-*furanosyl*)*cytosine* (35).—A solution of the aldehyde (33) (3.0 g) in dry THF (60 ml) was slowly added to a 0.67M solution of dimethyloxosulphonium methylide in THF (15.3 ml; prepared according to ref. 20) kept under nitrogen. After stirring for 2 h at 60 °C, the precipitate was completely dissolved. Evaporation to dryness followed by chromatography (C) of the residue gave the mixture of *epoxides* (35) (1.2 g; 38%), m.p. 192—194 °C (benzene–methyl cyanide); $\lambda_{max.}$ (MeOH) 250 (ε 16 000), and 300 nm (ε 6 900) (Found: C, 53.2; H, 5.5; N, 12.3; O, 28.7. $C_{15}H_{19}N_3O_6$ requires C, 53.4; H, 5.7; N, 12.5; O, 28.5%).

4-N-*Acetyl*-1-(2,3-O-*isopropylidene*-6-*bromo*-6-*deoxy*-β-D-*allo*- and -α-L-*talo*-*furanosyl*)*cytosine* (36) *and* (37).—A solution of the epoxides (35) (337 mg) in 6% hydrogen bromide in dimethylformamide (6 ml) was kept for 30 min at room temperature, neutralized with silver carbonate, filtered, and evaporated to dryness. Chromatography (C) of the residue first gave the L-*talo*-bromide (37), as a foam (190 mg; 45%), $[\alpha]_D^{20}$ +26° (*c* 0.9 in ethanol); δ([$^2H_6$]-DMSO) 3.46 (1 H, dd, $J_{6',6''}$ 10, $J_{5',6'}$ 7 Hz, 6'-H), 3.40 (1 H, dd, $J_{5',6''}$ 5.5 Hz, 6''-H), and 5.94 (1 H, d, $J_{5',OH}$ 5.5 Hz, OH).

Continued elution then gave the D-*allo*-bromide (36) (218 mg; 52%), $[\alpha]_D^{20}$ +8° (*c* 1.2 in ethanol; δ([$^2H_6$]DMSO) 3.40 (1 H, dd, $J_{6'6''}$ 11, $J_{5',6'}$ 5 Hz, 6'-H), 3.54 (1 H, dd, $J_{5',6''}$ 3 Hz, 6''-H), 5.79 (1 H, d, $J_{5',OH}$ 5 Hz, O-H).

4-N-*Acetyl*-1-(2,3-O-*isopropylidene*-6-*deoxy*-β-D-*allo*-*furanosyl*)*cytosine* (21).—(*a*) Acetic anhydride was added in portions (4 × 0.5 ml), at 1-h intervals, to a refluxing solution of nucleoside (23) (515 mg) in ethanol (20 ml). The solution was cooled and evaporated to dryness. A suspension of the residue in acetone (20 ml) in the presence of toluene-*p*-sulphonic acid (20 mmol) was kept for 2 h at room temperature, and then poured into a suspension of excess of Dowex 50 (50—100 mesh; HCO_3^-) in water (50 ml). The neutral solution was evaporated to dryness after filtration. Chromatography (B) of the residue gave the *protected nucleoside* (21) (545 mg; 80%), m.p. 228 °C (methyl cyanide), $[\alpha]_D^{20}$ −24° (*c* 1.1 in ethanol) (Found: C, 52.9; H, 6.1; N, 12.2; O, 28.3. $C_{15}H_{21}N_3O_6$ requires C, 53.1; H, 6.2; N, 12.4; O, 28.3%).

(*b*) A solution of the D-*allo*-bromide (36) (98 mg), tributylstannane (0.14 g), and azo(isobutyronitrile) (16 mg) in benzene (50 ml) was refluxed for 1 h, and then evaporated to dryness. Chromatography (B) of the residue gave the protected nucleoside (21) identical with the sample prepared

above, m.p. and mixed m.p. 226—228 °C, $[\alpha]_D^{20}$ −26° (*c* 1.2 in methanol), identical by t.l.c.

4-N-*Acetyl*-1-(2,3-O-*isopropylidene*-6-*deoxy*-α-L-*talofuranosyl*)*cytosine* (22).—(*a*) Tributylstannane reduction of the α-L-*talo*-bromide (37) gave the protected α-L-*talo*-*nucleoside* (22), m.p. 225—228 °C (methyl cyanide), $[\alpha]_D^{20}$ +21° (*c* 1.2 in ethanol) (Found: C, 52.7; H, 6.3; N, 12.2; O, 28.2. $C_{15}H_{21}N_3O_6$ requires C, 53.1; H, 6.2; N, 12.4; O, 28.3%).

(*b*) Derivatization as above of nucleoside (28) gave a protected nucleoside identical with (22) by t.l.c. (B), m.p. and mixed m.p. 221—223 °C, $[\alpha]_D^{20}$ +20° (*c* 0.8 in ethanol).

4-*Acetamido*-1-(2,5′;2,6′-dianhydro-2′,3′-O-*isopropylidene*-α-L-*talofuranosyl*)-2H-*pyrimidine* (39).—Boron trifluoride–ether (0.06 ml) was added to a solution of epoxides (35) (170 mg) in dry THF (5 ml). After 5 min at room temperature, t.l.c. (B) indicated the disappearance of the starting material. The solution was neutralized with saturated aqueous potassium hydrogencarbonate and extracted with ethyl acetate. Chromatography (B) of the extract first gave the anhydro-*nucleoside* (39) (0.11 g; 65%), m.p. 151—153 °C (acetone), $[\alpha]_D^{20}$ +31° (*c* 0.6 in CH_2Cl_2); $\lambda_{max.}$ (MeOH) 239 (ε 9 400) and 306 (9 000); $\lambda_{min.}$ (MeOH) 220 (5 700) and 270 nm (2 300); δ_H ($CDCl_3$) 1.33, 1.51 (2 × 3 H, 2 s, CMe_2), 2.11 (3 H, s, NAc), 4.15 (1 H, dd, $J_{6',6''}$ 7, $J_{5',6'}$ 2 Hz, 6′-H), 4.21 (1 H, dd, $J_{5',7''}$ 6 Hz, 6″-H), 4.42 (1 H, d, $J_{4',5'}$ 1.5 Hz, 4′-H), 4.62 (1 H, ddd, 5′-H), 4.78 (1 H, d, $J_{2',3'}$ 6 Hz, 2′-H), 4.91 (1 H, d, 3′-H), 5.21 (1 H, s, 1′-H), 6.46 (1 H, d, $J_{5,6}$ 7.5 Hz, 5-H), 6.95 (1 H, d, 6-H), and 7.82 (1 H, s, NH); δ_C (15.08 MHz, $CDCl_3$, $SiMe_4$) 24.64, 24.94 (2 q, isopropylidene Me), 26.28 (q, COMe), 65.80 (t, C-6′), 77.76 (d, C-5′), 81.65 (d, C-4′), 87.30 (d, C-3′), 88.08 (2 d, C-1′, C-2′), 99.19 (d, C-5), 112 (s, O–*C*Me_2–O), 117 (s, C-2), 142.36 (d, C-6), 156.57 (s, C-4), and 170.23 (s, NH–*C*–Me) (Found: C, 53.8; H, 5.8; O, 28.3. $C_{15}H_{19}N_3O_6$ requires C, 53.4; H, 5.7; O, 28.5%).

Hydrolysis by heating a solution of compound (39) in water, in the presence of Dowex 50 resin (50—100 mesh; H^+) for 1.5 h at 100 °C gave a sugar which behaved as talose in the following p.c. systems; H, ethyl acetate–pyridine–water (2 : 1 : 2). R_{Gal} 1.61; butanol–pyridine–water (3 : 1 : 1), R_{Gal} 1.81; and K, butanol–acetic acid–water (4 : 1 : 5), R_{Gal} 1.58.

Continued elution gave the nucleoside (38) (50 mg, 28%), m.p. 128—130 °C (from aqueous acetone), $[\alpha]_D^{20}$ −13° (*c* 0.6 in ethanol); $\lambda_{max.}$ (MeOH) 249 (ε 15 000) and 300 nm (6 600); δ[$(CD_3)_2SO$] 1.28, 1.48 (2 × 3 H, 2 s, CMe_2), 2.10 (3 H, s, NAc), 3.38 (2 H, m, 6′-H), 3.75 (1 H, m, 5′-H), 4.17 (1 H, dd, $J_{3',4''}$ 3, $J_{4',5'}$ 3.5 Hz, 4′-H), 4.70 (1 H, t, $J_{6',OH}$ 5 Hz, 6′-OH), 4.83 (1 H, dd, $J_{1',2'}$ 2, $J_{2',3'}$ 7 Hz, 2′-H), 4.90 (1 H, dd, 3′-H), 5.26 (1 H, d, $J_{5',OH}$ 5 Hz, 5′-OH), 5.85 (1 H, d, $J_{1',2'}$ 2 Hz, 1′-H), 7.19 (1 H, d, $J_{5,6}$ 7.5 Hz, 5-H), and 8.22 (1 H, d, 6-H).

Hydrolysis of (38) in the same way as (39) gave a sugar which behaved as allose in the three p.c. systems: H, (R_{Gal} 1.25); (R_{Gal} 1.42); and K, (R_{Gal} 1.27).

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