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SUGARS WITH POTENTIAL ANTIVIRAL ACTIVITY—III

THE ISOLATION OF THE ANOMERIC 6-BENZAMIDO-9(1′,2′:5′,6′-DI-O-ISOPROPYLIDENE-D-MANNOFURANOSYL) PURINES SOME (1′,5′-DIALDOFURANOSYL) NUCLEOSIDES AND RELATED COMPOUNDS*

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Abstract—The reaction of 1,2:5,6-di-O-isopropylidene α-D-mannofuranosyl chloride with chloromercuri-6-benzamidopurine gives a mixture of α- and β-isomers in the ratio 39α:14β. Both isomers have been isolated as pure crystalline compounds. Some further extensions of the reaction are described, together with attempts to make nucleosides containing free aldehydo- groups.

RECENTLY[1] we described the synthesis of 9-D-mannofuranosyl adenine by a one step procedure from 2,3:5,6-di-O-isopropylideneα-D-mannofuranose.

Analytical examination showed this to be a simple anomer, and no indication was found of a second anomer. However, although condensation of glycosyl halides bearing an ester group in the $C_{(2)}$ position normally results in the production of only one isomer (that having the *trans* arrangement of the $C_{(1')}$ and $C_{(2')}$ substituents),[2] when, as in this particular case, no $C_{(2')}$ ester group is present, the trans-rule is inoperable,[2] and the question arose whether only one isomer was actually formed, or whether the second isomer was lost in the isolation of the product.

When reaction of 2,3:5,6-di-O-isopropylideneα-D-mannofuranose with triphenyl phosphine in carbon tetrachloride was repeated, using slightly modified conditions, the 2,3:5,6-di-O-isopropylideneα-D-mannofuranosyl chloride (I) was isolated in 67% yield, the proton magnetic resonance spectrum (PMR) and the molecular rotation‡ being in agreement with the α-configuration previously assigned.[1] We have found that the triarylphosphine in this reaction may be replaced by trialkylphosphines or phosphorous tris-(*N*,*N*-dialkyl)amides with equally good results, and that a variety of other polyhalo-compounds may replace carbon tetrachloride with formation of the corresponding halides.[3]§

2,3:5,6-Di-O-isopropylideneα-D-mannofuranosylchloride was allowed to react with chloromercuri-6-benzamidopurine as previously described, but with the

* This work is mainly abstracted from Research Reports (by T.J.N.), Loughborough University, 196 5, 1966 and a Ph.D. Thesis (T.J.N.), Loughborough University, 1967. An outline summary has also appeared in the *Loughborough University Chemical Society Journal.*

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‡ The value reported in Ref 1 should read $[\alpha]_D^{19.5}$ +72·5° (c 8·3 acetone), not +2·75°.

§ The use of phosphorous tris (di-*N*-alkyl)amides has a further advantage in the isolation of products, where the alkyl halide produced is water stable. In the present case the halide must be used *in situ* before washing out the tris (di-*N*-alkyl) phosphoric amide with water.

omission of the hydrolytic stages. A yellow syrup was obtained which was shown to consist of two major and at least nine minor components. The two major components (60% total) were isolated by preparative layer chromatography.

The faster moving component was shown to be 6-benzamido-9-(2',3':5',6'-di-O-isopropylideneα-D-mannofuranosyl)purine (II) while the slower moving component was the β-anomer, (III). The ratio α:β was found to be 39:14 assuming quantitative isolation. Both anomers were obtained as crystalline solids which analysed correctly for the expected structures, having IR and PMR spectra in accord with these structures. The anomeric structures could be clearly distinguished by PMR spectroscopy, since they showed considerable differences in the resonance positions and patterns of the signals from the protons in the sugar moiety.

Thus, in the spectrum of II (Fig. 1) $H_{(1')}$ appears as a sharp singlet at 4·10 τ, from

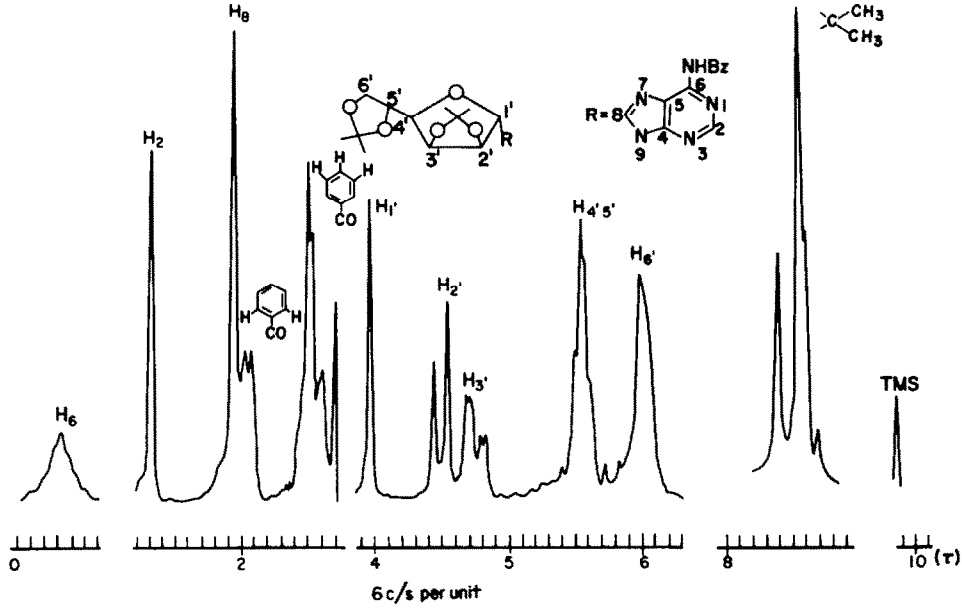


FIG. 1. ^{1}H NMR spectrum of 6-benzamido-9-(2',3':5',6'-di-O-isopropylideneβ-D-mannofuranosyl) adenine.

which it may be concluded that a *trans* arrangement exists between $H_{(1')}$ and $H_{(2')}$ ($\phi_{1'2'}$ approximating to a right angle)[4] confirming the α-configuration. The doublet ($J_{2',3'} = 6$ c/s) at 4·62 τ may be assigned to $H_{(2')}$, this being *cis* to, and forming an AB system* with, $H_{(3')}$ (4·88 τ : $J_{3',4'} = 1{\cdot}7$ c/s). In contrast, an examination of the resonance positions of the sugar protons in the spectrum of the β-compound (III; Fig. 2) reveals that only the signal for the anomeric proton is below 5·0 τ. This proton appears as a doublet ($J_{1'2'} = 2{\cdot}7$ c/s) as is to be expected for a *cis* relation with $H_{(2')}$ at 3·89 τ.

Examination of models indicates that the appearance of the $H_{(2')}$ and $H_{(3')}$ resonances at lower field in the α-anomer may be ascribed to anisotropic deshielding by the purine nucleus. That $H_{(4')}$ is not likewise deshielded is almost certainly due to

* We adopt here the nomenclature of Pople, Schneider and Bernstein, *High Resolution Magnetic Resonance* McGraw Hill, New York (1959).

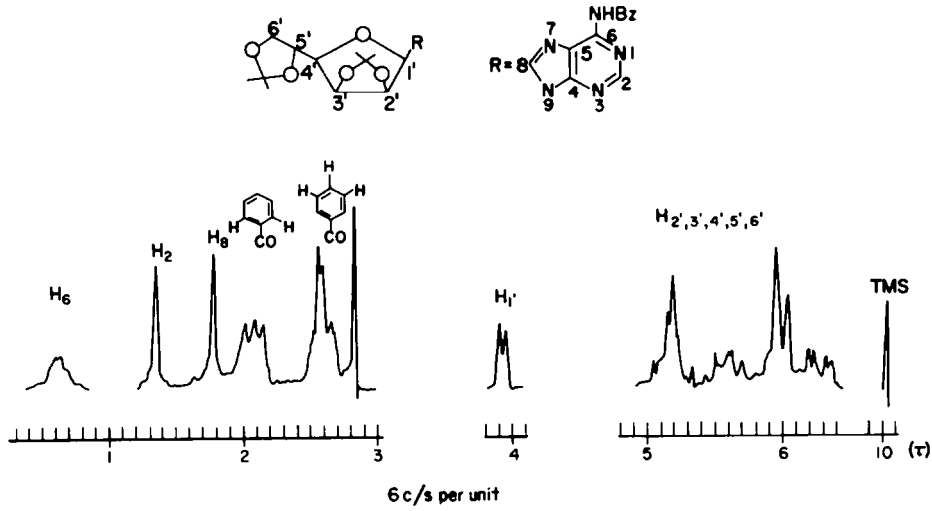


FIG. 2. ^{1}H NMR spectrum of 6-benzamido-9-(2',3':5',6'-di-O-isopropylidene-α-D-mannofuranosyl) adenine.

slight twisting of the sugar-ring with resultant movement of this proton towards an "equatorial" position. In agreement with this is the surprisingly low coupling constant observed between $H_{(4')}$ and its *cis* neighbour, $H_{(3')}$. In the β-compound anisotropic deshielding of the corresponding protons cannot occur. It is interesting to note that in the latter anomer one favoured conformation of the purine nucleus permits interactions between the oxygen atom attached to the $C_{(2)}$ atom and the $H_{(8)}$ proton. This should result in deshielding of $H_{(8)}$ relative to the situation in the α-anomer. A singlet resonance occurs at 2·08 $^\tau$ in the spectrum of compound (II), whilst the spectrum of compound (III) shows a corresponding resonance 31 c/s downfield. These signals may therefore be attributed to $H_{(8)}$.

During the course of this work Lerner and Kohn[5] described the reaction of 2,3:5,6-di-O-isopropylidene-α?-D-mannofuranose with thionyl chloride, followed by the condensation of the glycosyl chloride with chloromercuri-6-benzamidopurine using Davoll and Lowy's technique.[6] They claimed to have isolated only the α-product, but no proof of the anomeric purity of the product, or of the anomeric configuration of product or glycosyl halide, was offered. Since thionyl chloride often reacts with alcohols with retention of configuration (via an S_Ni mechanism,)[7] the mannosyl chloride obtained by these workers probably had the same (α) configuration as that obtained by us. We assume that the mannofuranosyl-adenine obtained by these workers had the α-configuration also.

One possible explanation for the observed results is that reaction proceeds by competing processes, one involving a cyclic transition state, e.g. (IV), the other being a normal S_N2 process, this latter being somewhat less favoured owing to the steric hindrance afforded by the isopropylidene group.

We have applied this reaction to the synthesis of some other mannofuranosyl purines and pyrimidines. Thus reaction of the mannosyl chloride (I) prepared *in situ* was attempted with the mercuri-salts of thymine (V) theophylline (VI), and of (2,6-*N*,*O*-dibenzoyl)guanine (VII). In addition a number of variations in treatment of

the mannosyl chloride mixture were examined in attempts to improve the reaction, but with little observed difference in yield.

When dithymylmercury (V) was reacted with the glycosyl halide, a variety of materials resulted, preparative layer chromatography showing the presence of six components. One major component, isolated in crystalline form, was identified by spectroscopy and elemental analysis as 1,4-anhydro-2,3:5,6-di-O-isopropylidene-D-mannitol, (VIII). This reduction product of the glycosyl halide may possibly arise by formation and breakdown of an intermediate mercuri-chloride, and this point is being examined. A second portion of material appeared to be the required β-nucleoside (IX) since the anomeric proton appeared as a doublet ($J_{H_1'H_2'}$ = 6 c/s) at 4·7 τ. (H_4 also appears as a singlet at 1·85 τ), whilst a third fraction was the α-nucleoside (X) (singlet anomeric proton, H_4 at 2·2 τ). The ratio of α:β in this case was approximately 27:20.

Theophylline mercurichloride (VI) was reacted with the halide (I), and the mixture again subjected to PLC. Eight fractions were obtained, but while two appeared to be mainly the required α and β materials (XVIII), they were difficult to purify properly, and were treated further as described below. Reaction of (2,6-*N*,*O*-dibenzoyl guanine) mercurichloride (VII) with the halide also produced a complex mixture (XIX), difficult to purify, and the further treatment of this is also described below.

In developing routes to nucleosides of higher sugars, we required as intermediates nucleosides containing aldehydo-or keto- groups. Pfitzner and Moffat[8] in a preliminary communication described the use of the DMSO–DCC reagent (the Pfitzner–Moffat reagent), and the oxidation of 3'-O-acetyl thymidine, 2',3'-O-isopropylideneuridine, and 2',3'-O-isopropylidene adenosine was stated to lead to the corresponding 5'-aldehydo compounds. In a later fuller paper[9] the oxidation of 3'-O-acetyl thymidine was detailed, but it appears that the product was not obtained in a pure state.

We examined the use of the reagent in the oxidation of 2',3'-O-isopropylidene adenosine and 2',3'-O-isopropylidene guanosine. We also examined the use of DMSO-acetic anhydride which was found to be of use in some cases.[10] When 2',3'-O-isopropylideneadenosine was reacted with DMSO plus acetic anhydride under mild conditions the only materials isolated were 2',3'-O-isopropylidene-5'-O-acetal adenosine, and a number of breakdown products of the nucleoside. No aldehydo compound was found. 2',3'-O-Isopropylidene guanosine behaved in a similar manner. The oxidation of this latter material with DMSO containing dicyclohexylcarbodiimide and phosphoric acid was carried out at room temperature for 4 hr. A number of fractions were isolated but in none could an aldehyde group be detected by either PMR or IR spectroscopy, nor was material obtained which gave a positive Brady reaction.

An alternative route seemed desirable. Silver II picolinate has been shown in these laboratories to oxidize alcohols smoothly to aldehydes or ketones,[11] and appears reasonably effective in the sugar series. However, it also oxidizes phenolic and amino groups,[12] and since both were present in the compounds under examination, attack upon these was possible. Oxidation of both 2',3'-O-isopropylidene adenosine and 2',3'-O-isopropylidene guanosine proceeded rapidly, but in each case by attack upon base rather than sugar moiety. Experiments with suitably protected materials seem more promising.[12]

The removal of an isopropylidene protecting group by dilute acid proceeds more

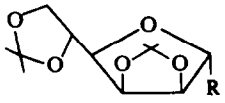
readily for acyclic than for fused rings,[13] and advantage of this has been taken in a number of cases in the sugar field to obtain selective removal of one protecting group. In the case of the di-isopropylidene derivatives synthesised above, preferential removal of the 5',6'-O-isopropylidene residue would expose the $C_{5'}$ and $C_{6'}$ hydroxyl groups, (XI), which could then by periodate oxidation presumably be converted into the corresponding 1',5'-pentodialdo compounds (XII).

Compound IX was hydrolysed by 70% aqueous acid at 50° for 150 min and by fractionation of the syrupy mixture of products a poor yield of (2',3'-*O*-isopropylidene-β-D-mannofuranosyl) thymine (XIII) was obtained, having IR and PMR spectra in agreement with this structure. This material consumed approximately 1 mol. of periodate, formaldehyde being produced, together with an off-white low-melting solid, which showed an aldehyde signal in the PMR (0·15 τ) and had other PMR and IR spectral characteristics in agreement with the expected compound, viz.: (2',3'-*O*-isopropylidene-1',5'-pentodialdofuranosyl) thymine (XIV).

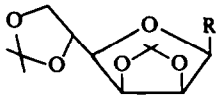
When compound (X) was hydrolysed under similar conditions a small amount of (2',3'-*O*-isopropylidene-α-D-mannofuranosyl)-thymine, (XV), was formed, but the amount obtained was not sufficient for further reaction.

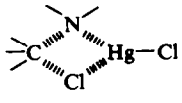
The crude theophylline derivatives were subjected to similar hydrolysis, and, with some difficulty, (2',3'-*O*-isopropylidene-β-D-mannofuranosyl)-theophylline (XVI) was obtained, the β-configuration following from the H_1 signal, which appears as a doublet at about 3·75 τ. The treatment of this material with aqueous sodium metaperiodate (1 mol.) gave formaldehyde and an oil which, whilst giving a positive Brady test, was obtained in too small amount to be positively identified as the required aldehyde compound. In further experiments material showing essentially the required PMR spectrum (including an aldehyde proton at 0·2 τ) was obtained, contaminated by further material, but the purification of this material was not accomplished.

The hydrolysis of the crude mixture from the dibenzoyl guanine reaction was then attempted, using the conditions described above. Isolation of the product proved easier in this case, but examination of the IR and PMR spectra showed complete absence of isopropylidene residues, the presence of one amide and four other proton signals, all removed on treatment with D_2O, and the remaining spectral and physical characteristics, indicated the material to be 2,6-*N*,*O*-dibenzoyl-(D-mannofuranosyl) guanine (XVII). Further experiments are under way to improve these preparations, and to obtain the 1',5'-*ribo*pentodialdo compounds, via the corresponding allose derivatives.

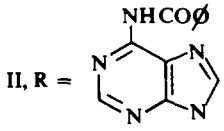


I, R = Cl



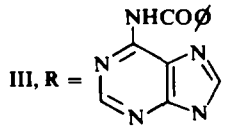


IV

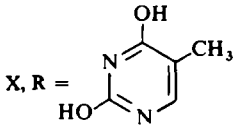


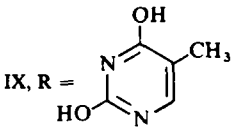
II, R =

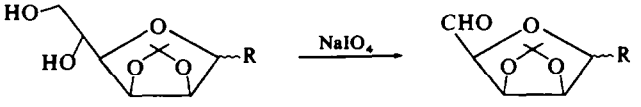
VIII, R = H



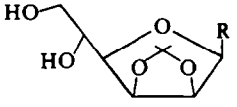
III, R =

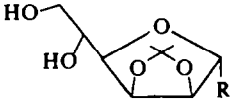

X, R =

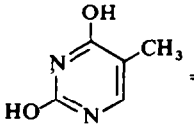

IX, R =


XI, R = Base

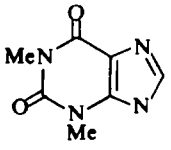
XII, R = Base

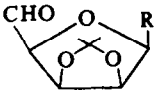


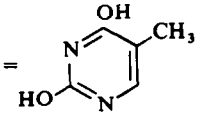


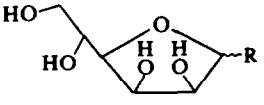

XIII, R = = R, XV

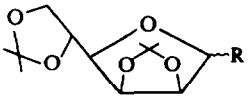
XVI,

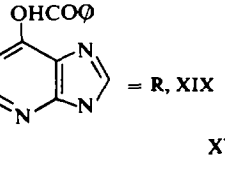

R =

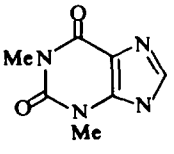



XIV, R =






XVII, R = = R, XIX


XVIII, R =

EXPERIMENTAL

IR spectra were measured using Perkin–Elmer 237 and 257 spectrophotometers. Optical rotations measured using a Bendix N.P.L. Automatic Polarimeter, PMR Spectra measured on a Perkin–Elmer R 10 (60 M) spectrometer usually in $CDCl_3$ at 34° using TMS as internal standard. PLC on Kieselgel HF 254 support eluted with either (A) benzene–methanol 9:1, or (B) benzene–methanol 19:1. Carbon tetrachloride, stored over calcium chloride, was distilled before use, rejecting the first ~20% distillate.

Triphenylphosphine was kept *in vacuo* over phosphorus pentoxide. Other materials were purified commercial samples.

2,3:5,6-*Di*-O-*isopropylidene*α-D-*mannofuranosyl chloride.* (I) To a solution of 2,3:5,6-d-O-isopropylidene α-D-mannofuranose (5·2 g) in carbon tetrachloride (25 ml) was added triphenylphosphine (5·25 g) and the mixture was heated under reflux with exclusion of water. Triphenylphosphine oxide commenced to separate soon afterwards and after 45 min anhydrous lead carbonate (0·5 g) and powdered anhydrous charcoal was added. The mixture was concentrated after filtration through dry kieselguhr, and the residue was extracted with anhydrous 80–100° petrol. The combined extracts were filtered, concentrated to a syrup, and the syrup distilled in a short-path distillation apparatus under vacuum, giving 2,3:5,6-di-O-isopropylidene α-D-mannofuranosyl chloride, (I), (3·75 g, 67%), $n_D^{26\cdot5}$ 1·4649, $[\alpha]_D^{26\cdot5}$ +76·4° (*c* 2·16 in acetone).

6-*Benzamido*-9-(2′,3′;5′,6′-*d*i-O-*isopropylidene*-D-*mannofuranosyl*) *purines,* α *and* β *forms,* (II, III). A suspension of Celite (4·8 g) and chloromercuri-6-benzamido purine (4·75 g) in sodium dried, redistilled xylene (200 ml) was partially distilled under reduced pressure. When the volume was reduced to about 150 ml, 2,3;5,6-di-O-isopropylidene α-D-mannofuranosyl chloride (I), (2·79 g), contained in dry xylene, was added. The mixture was stirred for 15 hr at 120°C under an atmosphere of nitrogen. Charcoal was added, the hot mixture was filtered, the residues were washed with chloroform, and the combined filtrate and washings were evaporated, using a rotary evaporator, to small bulk. The residues were dissolved in chloroform (150 ml) and the solution again filtered, washed in succession with 30% aq. KI solution, (3 × 50 ml), and water (50 ml), dried over sodium sulphate, and concentrated to a syrup (5·85 g).

Analytical TLC of the syrup on Keiselgel PF 254 eluted with solvent (B), with two further repetitive elutions, showed two major components, with at least eight minor constituents. Using the same conditions portions of syrup were subjected to PLC (on 3 × 100 × 20 cm plates). The two major bands were removed in turn, and each component was separated from siliceous material by extraction with methanol evaporation of the solvent, and extraction with chloroform. In each case the chloroform extracts were dried, concentrated *in vacuo*, and the residue recrystallized from 60–80° petrol–ether mixture. In a typical experiment the faster running component had R_f 0·65, and was 6-benzamido-9-(2′,3′;5′,6′-di-O-isopropylidene α-D-mannofuranosyl) purine (II) (38·7 mg), m.p. 113–115, $[\alpha]_D^{21}$ +62° (c, 1 in $CHCl_3$), as confirmed by its PMR spectrum (Fig. 1). (Found: C, 57·7; H, 5·9; N, 14·4. $C_{24}H_{27}H_5O_6 \cdot H_2O$ requires: C, 57·7; H, 5·8; N, 14·0%).

The slower moving component was (R_f 0·48) 6-benzamido-9-(2′,3′:5′,6′-di-O-isopropylidene β-D-mannofuranosyl) purine, (III), (13·6 mg) m.p. 114–115°, $[\alpha]_D^{21}$ −4° (c, 0·9 in $CHCl_3$) again confirmed by its PMR spectrum (Fig. 2). (Found: C, 57·5; H, 5·8. $C_{24}H_{27}N_5O_6 \cdot H_2O$ requires: C, 57·7; H, 5·8%).

PMR spectral assignments. (in $CDCl_3$, TMS internal standard).

Compound II—$H_{1'}$ appears as a singlet at 4·10 τ. The doublet at 4·62 τ was assigned to $H_{2'}$ coupled up field to $H_{3'}$ (4·88 τ, $J_{2'3'}$ = 6·0 c/s). The coupling constant $J_{3'4'}$ is low (1·7 c/s approx.). $H_{4'}$ and $H_{5'}$ appear largely as a broad singlet centred at 5·68 τ, and the $H_{6'}$ protons are another broad signal at about 6·13 τ. The isopropylidene methyls are at highest field (8·55–8·78 τ, overlapped. The two protons of the purine nucleus occur as singlets at 1·45 τ and 2·08 τ, the latter, probably H_8, being overlapped with the ortho protons (1·95–2·28 τ) of the benzoyl phenyl group. The remaining aromatic protons are at 2·5–2·8 τ The broad one-proton singlet at 0·45 τ, removed by treatment with D_2O, is the amide proton.

Compound III—$H_{1'}$ (3·89 τ) appears as a doublet ($J_{1'2'}$ = 2·7 c/s). The isopropylidene methyls are at high field (8·5–8·8 τ), the remaining protons of the sugar moiety occur in the range 4·98–6·36 τ, and have the correct integration and the distribution pattern expected for the hexofuranosyl system. H_2 and H_8 in the purine are singlets at 1·31 and 1·56 τ. The ortho protons of the phenyl group, deshielded by the amide C=O, are at 1·90–2·18 τ. The remaining aromatic protons are at 2·40–2·75 τ. One exchangeable low field proton is the amide proton.

Attempted oxidation of 2′3′-O-*isopropylidene guanosine.* Using the conditions described by Pfitzner and Moffat[8,9] the nucleoside (1·6 g) was reacted at room temperature for 4 hr. After removal of solid dicyclohexylurea and of solvent the oily residue was examined by PMR. Some aldehyde was present as

indicated by a signal at low field. The residue was extracted with chloroform, and the insoluble material, which gave no low field signal, separated. The filtrate was evaporated to give an oil which was subjected to PLC (solvent A). Four fractions were obtained, two of which showed no low field signal in the PMR. In a third fraction, which proved difficult to examine since it was relatively insoluble, proton signals were noted in CD_3SOCD_3 at 1·8, doublet, 2·1 singlet, 3·8, (all one-proton signals), 4·4–5·6 (four protons) and 8·5 (six protons). It is unlikely that an aldenyde proton will occur at such a high tau value as 1·8 $^{\tau}$, and this material was not further examined. The final fraction showed a singlet resonance at 1·15 $^{\tau}$, but no lower signals, and again was not examined further.

2′,3′;5′,6′-*Di*-O-*isopropylidene*α-D-*mannofuranosyl thymine* (X) *and its* β (IX). Dithymyl mercury was prepared and the mannosyl chloride preparation was carried out to the point of extraction with 80–100° petrol. The mercury salt was then reacted under similar conditions to those described above. After several fractionations of the syrupy product the syrup was finally subjected to PLC. Seven fractions were present.

Fraction 6. (R_f = 0·91) (140 mg) was 1,4-anhydro-2,3;5,6-di-O-isopropylidene-D-mannitol (VIII) which showed no bands in the IR in the OH, NH, or the C=O regions, but showed signals in the PMR in $CDCl_3$ at 8·55, 8·65 and 8·68 $^{\tau}$ (6, 3 and 3 protons, slightly overlapped singlets) and in the range 4·75 to 6·2 $^{\tau}$ (8 protons) not readily analysed by first order methods. Found: C, 59·33; H, 8·07. $C_{12}H_{20}O_5$ requires: C, 59·01; H, 8·19%.

Fraction 4. (R_f = 0·75) was 2′,3′;5′,6′-di-O-isopropylideneβ-D-mannofuranosyl thymine (IX) (200 mg) m.p. 104–106°, showing signals in its PMR spectrum in $CDCl_3$ at 1·85 $^{\tau}$ (H_4, 1 proton singlet), 3·7 $^{\tau}$ ($H_{1'}$, $J_{1',2'}$ = 6 c/s, 1 proton doublet), 8·52–8·65 (12 protons) 5·0–6·2 $^{\tau}$ (6 protons, complex).

Fraction 5. (R_f = 0·83) was 2′,3′;5′,6′-di-O-isopropylideneα-D-mannofuranosyl thymine (X) (270 mg) m.p. 168–170° showing signals in its PMR in $CDCl_3$ at 2·2 $^{\tau}$ (H_4 1 proton singlet) 3·6 $^{\tau}$ (1 proton singlet) 8·5–8·7 $^{\tau}$ (6 proton singlet and two 3 proton singlets somewhat overlapped) 4·7–6·2 $^{\tau}$ (6 protons, complex).

2′,3′;5′,6′-*Di*-O-*isopropylidene*-D-*mannofuranosyl theophylline* (αβ *mixture*). (XVIII). Using similar conditions the theophylline mercuri salt was made and reacted with the chlorosugar. Attempts to fractionate the product were only partially successful, and two fractions which appeared to contain nucleoside were combined for hydrolysis as described below.

2,6-N,O-*Dibenzoyl* (2′,3′;5′,6′-*di*-O-*isopropylidene*-D-*mannofuranosyl*) *guanine* (αβ *mixture*), (XIX). By similar methods the reaction of the mercury salt, VII, and the chloride, I, yielded a mixture which proved difficult to fractionate and the partially purified material was hydrolysed as described below.

(2′,3′-O-*Isopropylidene*α-D-*mannofuranosyl*) *thymine*, (XIII). A solution of (2′,3′;5′,6′-di-O-isopropylideneβ-D-mannofuranosyl) thymine (IX) (0·2 g) in 70% aqueous acetic acid was kept at 50° for 150 min. Solvent was removed at the pump, ethanol was added, and again removed under vacuum. This process was repeated, then toluene was added and also removed under vacuum. The oily residue could not be persuaded to crystallize. It behaved as a single spot on TLC in a number of solvents. It showed strong broad absorption at 3400 cm^{-1} in its IR spectrum, together with a band at 1660 cm^{-1} with shoulders at 1680 and 1695 cm^{-1}. Its PMR spectrum in $CDCl_3$ showed signals at 8·55 and 8·65 $^{\tau}$ (2 three proton singlets), had three protons replaceable by treatment with D_2O; a one proton doublet at 3·7 $^{\tau}$ was in agreement with a β-confiiguration. The remaining signals from the sugar moiety integrated correctly but were insufficiently resolved for complete analysis.

(2′,3′-O-*Isopropylidene*-1′,5′-*lyxopentodialdofuranosyl*) *thymine* (XIV). The diol from the previous experiment was dissolved in the minimum amount of methanol, and the solution was added with stirring to a solution of sodium metaperiodate (0·7 g) in water (20 ml). The mixture was kept with stirring for 2·5 hr. Formaldehyde (detected in the usual way) was set free (0·78 mol). The solution was poured into ethanol, the solid was separated and the solution evaporated (rotary evaporator) to dryness. The residue was extracted with hot absolute ethanol, and the cooled solution filtered. The filtrate was evaporated and the residue recrystallized with difficulty to give the title compound (0·064 g) m.p. 53–54°. This showed bands in the IR at 1703 cm^{-1}, 1660 cm^{-1} (shoulders at 1680, 1695 cm^{-1}. The NMR spectrum (in methanol) showed a one-proton signal at 0·15 $^{\tau}$, confirming aldehyde.

(2′,3′-O-*Isopropylidene*α-D-*mannofuranosyl*) *thymine* (XV). When compound (X) was treated under similar conditions to those given above, a very low yield of the title compound was obtained, m.p. 191–192°, (0·022 g).

2,6-N,O-*Dibenzoyl* (α-D-*mannofuranosyl*) *guanine* (XVII). The crude mixture of isopropylidene compounds was hydrolysed with acetic acid as above for 2·5 hr and worked up as usual. The product (0·029 g), m.p. 240–241°, showed no PMR signal in CD_3SOCD_3 at 8·5–9 $^{\tau}$, and had five protons exchangeable with

D_2O (at 0·4 and 3·6 τ) a singlet proton (H_8) plus ten aromatic protons in the range 1·7–3 τ, a singlet at 4·05 τ, and a five-proton complex from 5·0 to 5·8 τ. The IR showed bands in the region 1625–1710 cm^{-1} and a broad absorption at 3300 cm^{-1}.

(*2',3'-O-Isopropylidene*β-D-*mannofuranosyl*) *theophylline* (XVI). This material, obtained from the crude di-isopropylidene compounds by hydrolysis, followed by fractionation on silica, and PLC using several different systems, was a semi-solid oil which showed bands at 3400 cm^{-1} (broad), 1700 cm^{-1}, and 1655 cm^{-1} (several shoulders) in the IR, and gave signals in its PMR spectrum in CD_3COCD_3 at 1·7 τ (singlet, 1 proton), 3·75 τ (doublet, $J_{1'2'}$ = 5·8 c/s), 8·5 and 8·6 τ (2 singlets, 6 protons), 4·75–6·5 τ (multiplets, twelve protons, incl. 3-proton singlets at 6·45 and 6·32 τ, plus two additional protons removed by treatment with D_2O).

When this material was treated with sodium periodate at 5°C, for 30 min, formaldehyde was obtained (0·73 mol) and a small amount of material giving a positive Brady test. When a further portion was reacted a pale yellow solid was obtained (175 mg) which was obviously impure, since it showed OH bands (weak) in the IR at 3300 cm^{-1}, and whilst its PMR spectrum contained the expected signals at 0·8, 1·8, 3·9, 4·9–6 and 8·5–8·7 τ, various other signals were present, and the integrated signals were not in proportion.

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