companion paper, this issue.
(9) The nomenclature of these compounds presents some difficulties since the presence of the 4-hydroxymethyl group removes one chiral center from the molecule. Hence, they are properly named as 4-(hydroxymethyl)-D-*erythro*-pentofuranosyl derivatives. Simple, otherwise unsubstituted nucleoside derivatives such as **16** are referred to as, e.g., 4'-(hydroxymethyl)adenosine. We appreciate the advice of Dr. K. L. Loening of the Chemical Abstracts Service on this matter.
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4'-Substituted Nucleosides. 5.[1] Hydroxymethylation of Nucleoside 5'-Aldehydes

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Crossed aldol condensations between variously substituted nucleoside 5'-aldehydes and formaldehyde in the presence of aqueous sodium hydroxide lead, following rate-limiting Cannizzaro reduction, to the corresponding 4'-hydroxymethyl nucleoside derivatives. The speed and overall efficiency of the above reactions are improved by incorporating a borohydride reduction of the initial aldol product rather than relying upon the normal Cannizzaro reduction. Such reactions conducted with 2',3'-unsubstituted nucleoside 5'-aldehydes give mixtures of 4'-hydroxymethyl nucleosides epimeric at $C_{3'}$ presumably via a reverse aldol cleavage followed by recyclization. Hence, the use of base stable 2',3'-O protecting groups is recommended for these reactions. In the case of 2',3'-*O*-isopropylidene derivatives of N^6-benzoyladenosine and N^4-benzoylcytidine 5'-aldehydes, some exchange of the acetonide by a methylene group is observed and a mechanism is proposed. For extension to the 2'-deoxynucleoside series, the corresponding hydroxymethylation of 3'-*O*-benzylthymidine 5'-aldehyde followed by catalytic hydrogenolysis leads to 4'-(hydroxymethyl)thymidine. Syntheses of a number of new, variously protected nucleoside 5'-aldehydes are described.

The preparation and synthetic utility of nucleoside 5'-aldehydes[3] and the synthesis of 4'-substituted nucleosides[4] have been the focal point of two major programs in this laboratory during recent years. While 4',5'-unsaturated nucleosides have proved to be useful intermediates for the introduction of 4'-halo and 4'-alkoxy substituents,[4] they have not, as yet, provided a facile entry to compounds bearing $C_{4'}$ carbon–carbon linkages. For this purpose substitution at $C_{4'}$ of nucleoside 5'-aldehydes provides an attractive route, although we have previously noted the ease with which these compounds undergo base-promoted epimerization and elimination reactions.[5] Recently Secrist et al. have briefly reported the preparation of enol acetate and enamine derivatives of uridine 5'-aldehyde and their conversion to certain $C_{4'}$-alkylated substances.[6]

The present paper describes our studies on the preparation of 4'-hydroxymethyl nucleosides, **10** and **17**, via aldol condensation of nucleoside 5'-aldehydes with formaldehyde. In the accompanying paper[1] we consider the synthesis of related compounds via condensation of a versatile 4-(hydroxymethyl)pentofuranosyl derivative with a variety of heterocyclic bases. A preliminary account of both approaches has appeared.[7]

Both approaches to the synthesis of 4'-hydroxymethyl nucleosides are based upon early work by Schaffer, who has reported the condensation of 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose with formaldehyde in aqueous sodium hydroxide.[8] The initial aldol product formed in this reaction underwent Cannizzaro reduction with excess formaldehyde to give 4-(hydroxymethyl)-1,2-*O*-isopropylidene-β-L-*threo*-

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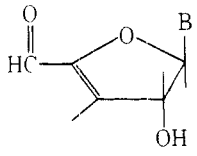
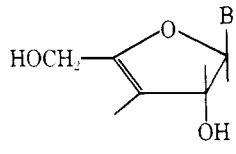
pentofuranose as the isolated product. Leland and Kotick[9] have subsequently condensed a suitable derivative of this sugar with N^6-benzoyladenine, leading to the preparation of 9-[4-(hydroxymethyl)-α-L-*threo*-pentofuranosyl]adenine (**11c**). Various aspects of this work are discussed in our companion paper.[1]

In view of the ease with which 2′,3′-acetals of nucleoside 5′-aldehydes undergo base-catalyzed elimination of the acetal group and epimerization at $C_{4'}$,[5] we initially considered that the mixed aldol condensation should be attempted using the weakest possible base. Reactions of aqueous dioxane or methanol solutions of the protected aldehydes **14a**[3c] and **14b**[3d] with potassium carbonate in either the presence or absence of excess formaldehyde, however, led predominantly to the olefins **1**[5] via elimination of the acetals. Borohydride reduction of the crude product from **14b** followed by debenzoylation gave a major product that was identical with an authentic sample of 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**2b**).[5,10] Similarly, **14a** was shown to give primarily **2a**



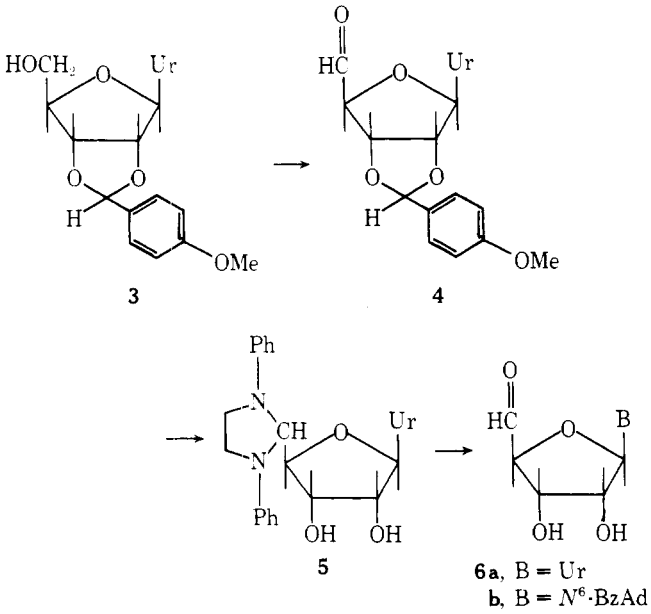
1a, B = Ur
b, B = N^6-BzAd



2a, B = Ur
b, B = Ad

following base treatment and borohydride reduction. These results convinced us that the mixed aldol condensation under these conditions was fruitless.

Since acetal elimination was the predominant reaction occurring with the aldehydes **14a** and **14b**, we chose to investigate comparable reactions using unprotected uridine 5′-aldehyde (**6a**). While **6a** was one of the first nucleoside aldehydes to be investigated,[11] its isolation in pure form has previously not been described. Oxidation of 2′,3′-*O*-anisylideneuridine (**3**)[12,13] using the dimethyl sulfoxide–dicyclohexylcarbodiimide (Me_2SO–DCC)[14] method followed by mild acidic hydrolysis of the anisylidene group gave **6a** that was isolated in an overall yield of 53% as its crystalline 1,3-diphenylimidazolidine derivative (**5**) by addition of *N,N′*-diphenylethylenediamine.[3c,d] Treatment of **5** with Dowex 50 (H^+) resin regenerated **6a** in essentially quantitative yield. This compound was also prepared by hydrolysis of the previously described 2′,3′-*O*-cyclohexylidene derivative **14a**[3c] with 90% trifluoroacetic acid. The dried products so obtained proved to be roughly equal mixtures of the aldehyde **6a** and its hydrate as judged by ^1H NMR in Me_2SO-d_6, while the spectrum in D_2O showed only the presence of the hydrate. While **6a** was perfectly suitable for subsequent reactions, acceptable elemental analyses could not be obtained. Any exposure to alcohols during the workup led to partial formation of hemiacetals as judged by NMR spectroscopy, and this seriously limited any efforts at the isolation of an analytically pure chemical entity. Attempts to complete the dehydration to the free aldehyde by azeotropic distillation with benzene, a method found suitable with more highly substituted derivatives (e.g., **24**), were not successful, perhaps due to the very low solubility of **6a** in nonpolar solvents.

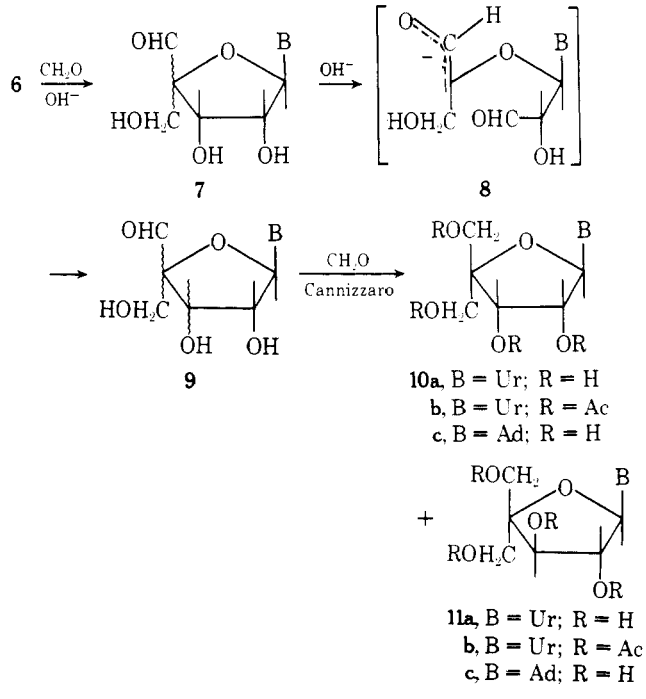


3 4 5

6a, B = Ur
b, B = N^6-BzAd

The prospect of β-elimination with **6a** was considered to be considerably less likely than for the acetal derivatives **14a** and **14b**, and any epimerization at $C_{4'}$ of the starting nucleoside 5′-aldehyde[5] need not be considered as the expected product, following Cannizzaro reduction, contains a nonasymmetric $C_{4'}$ carbon. Therefore, **6a** was reacted with an excess of 37% formaldehyde in 0.5 N sodium hydroxide at room temperature for 24 h to give, following isolation by preparative TLC, a more polar product in 62% yield. However, ^1H NMR analysis showed this to be a roughly equal mixture of two isomeric compounds that had widely different mobilities upon borate electrophoresis at pH 6.0 (mobilities of 1.50 and 0.25 relative to uridine). Following acetylation, two isomeric tetraacetates could be separated with some difficulty by preparative TLC and each was then hydrolyzed to the corresponding tetrol. The strong borate complexing ability of one of the isomers suggests either the formation of a bis adduct or of a tridentate complex similar to that from β-D-lyxofuranosyl nucleosides.[15] In either case this would be consistent with the isomer of greater electrophoretic mobility being the desired 1-[4-hydroxymethyl)-β-D-*erythro*-pentofuranosyl]uracil (**10a**, 4′-(hydroxymethyl)uridine). We consider the other isomer to be 1-[4-(hydroxymethyl)-α-L-*threo*-pentofuranosyl]uracil (**11a**), which presumably arises via a reverse aldol cleavage of the initial formaldehyde adduct **7** followed by recyclization to generate both $C_{3'}$ epimers (**9**, Scheme I). A similar epimerization was encountered during our condensations of formaldehyde with 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-

Scheme I



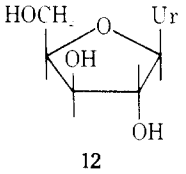
7 8 9

10a, B = Ur; R = H
b, B = Ur; R = Ac
c, B = Ad; R = H

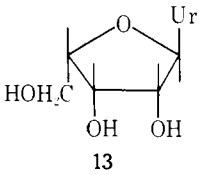
11a, B = Ur; R = H
b, B = Ur; R = Ac
c, B = Ad; R = H

furanose and its ribo isomer and is described in the accompanying paper.[1] Leland and Kotick[9] have also observed isomerization at C_3 during hydroxymethylation of the D-xylo aldehyde but have offered no explanation of this phenomenon.

In the above scheme it is suggested that the reverse aldol cleavage occurs on the initial formaldehyde adduct **7**. The possibility also exists that the nucleoside aldehyde **6** could undergo a similar epimerization at $C_{3'}$ and that formaldehyde addition and Cannizzaro reduction are subsequent steps. In an effort to cast some light on this question, we have examined the reaction of **6a** with aqueous sodium hydroxide in the absence of formaldehyde. To facilitate analysis of the reaction, aliquots were removed and directly reduced with sodium borohydride prior to examination by borate electrophoresis. Should epimerization at $C_{3'}$ occur via a reversible retro-aldol reaction, then a mixture of all four nucleosides with the D-ribo, D-xylo, L-arabino, and L-lyxo configuration, readily resolved by borate paper electrophoresis,[15] should be produced following sodium borohydride reduction. In contrast to the reaction in the presence of formaldehyde, the reaction of **6a** with sodium hydroxide alone led to rapid coloration, but even after 1 h of reaction (by which time virtually no uridine remained in a comparable reaction in the presence of formaldehyde) there was essentially no formation of the xylo isomer **12**. In



12

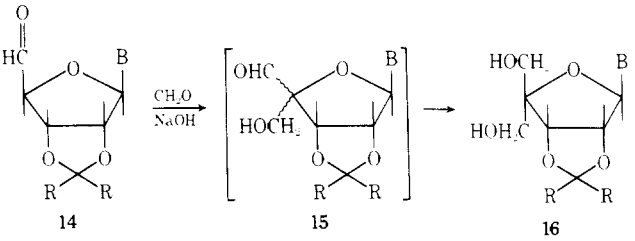


13

addition to regenerated uridine, several significant new products were formed with borate electrophoretic mobilities greater than that of uridine. One of these could well be 1-(α-L-*lyxo*-furanosyl)uracil (**13**)[5,16] arising by epimerization at $C_{4'}$, while others could possibly be aldol dimerization products of **6a**. Since the object of this experiment was only to investigate possible retro-aldol epimerization at $C_{3'}$, these other products were not further investigated. Presumably, in the presence of formaldehyde, the initial enolate is trapped, thus precluding aldol dimerization and other side reactions.

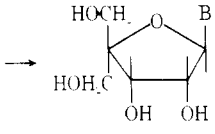
The results above, together with kinetic studies presented in Figure 1 (see later), show that the presence of a free hydroxyl group at $C_{3'}$ in a nucleoside aldehyde such as **6** is a source of complications during mixed aldol condensations with formaldehyde. Accordingly, we returned to investigations using 2′,3′-*O*-acetal derivatives. To our surprise we found that the reaction of **14a** with formaldehyde in aqueous dioxane containing sodium hydroxide rather than sodium carbonate led to the formation of a new product that was not formed in the absence of formaldehyde. Chromatography of the reaction mixture then led to the isolation of TLC- and NMR-homogeneous 2′,3′-*O*-cyclohexylidene-4′-(hydroxymethyl)uridine (**16a**) in a yield of 38%. This material, which could be obtained in crystalline form from methanol, gave a well-resolved ^1H NMR spectrum in Me_2SO-d_6 except that the signals for the two hydroxymethyl groups were superimposed and appeared as a four-proton multiplet at 3.55 ppm. The presence of the two primary hydroxyl groups was confirmed by the appearance of a pair of D_2O-exchangeable triplets at 4.58 and 5.12 ppm. The ^1H NMR spectrum reported for **6a** in our preliminary communication[7] was inadvertently that of the corresponding tetraol **10a**.

Cleavage of the cyclohexylidene acetal was accomplished by treatment of **16a** with 90% trifluoroacetic acid at room temperature, giving 4′-(hydroxymethyl)uridine (**10a**) as a homogeneous foam. Acetylation of this product gave a tetraacetate, **10b**, which was identical with the less polar isomer derived from unprotected uridine 5′-aldehyde as described above. At this point we can offer no convincing explanation for the radically different reaction paths observed during treatment of **14a** with formaldehyde and sodium hydroxide as opposed to potassium carbonate. Apparently the reversible reaction between **14a** and formaldehyde in the presence of



14 15 16

14-16a. B = Ur; R, R = $(CH_3)_2C$
b. B = N^6-BzAd; R = Me
c. B = N^4-BzCy; R = Me
d. B = OMe; R = Me

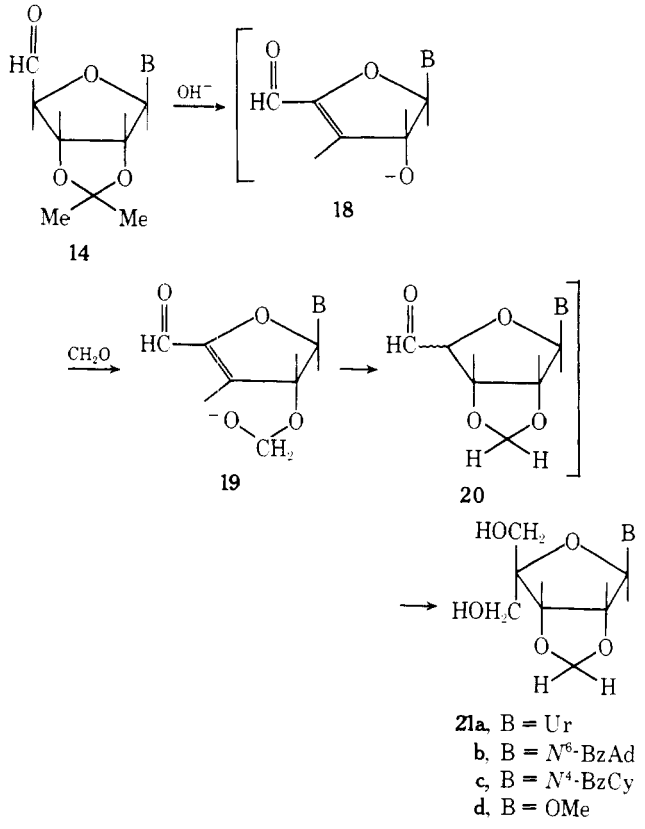


10a. B = Ur
c. B = Ad
17. B = Cy

sodium hydroxide is extremely rapid and the equilibrium is largely in favor of the intermediate **15**. The rate-limiting step of the overall process is the subsequent Cannizzaro reduction of **15** to the isolated product **16** (see later for experiments to support this).

Since the sodium hydroxide promoted hydroxymethylation of **14a** appeared to be a viable reaction, we attempted its extension to other nucleosides. The condensation of the hydrate of N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine 5′-aldehyde (**14b**)[3d] with formaldehyde and aqueous sodium hydroxide reached completion somewhat more rapidly than that with **14a**. Following chromatography, two new products with rather similar TLC mobilities were isolated. The less polar of these, isolated as a foam in 39% yield, proved to be the desired N^6-benzoyl-4′-(hydroxymethyl)-2′,3′-*O*-isopropylideneadenosine (**16b**). The absence of a $C_{4'}$ proton was confirmed by the appearance of $C_{3'}$ H as a sharp doublet at 5.19 ppm in $CDCl_3$ and the two hydroxymethyl groups appeared as overlapping signals centered at 4.83 ppm. Well-resolved signals for $C_{1'}$, $C_{2'}$, and $C_{3'}$ H, the purine ring protons, and the isopropylidene function ensured the homogeneity of the sample.

The slightly more polar product, isolated in 8.5% yield, showed an almost identical ^1H NMR spectrum with that of **16b** except for the absence of signals for the isopropylidene group. These were replaced by two one-proton singlets at 5.07 and 5.36 ppm, chemical shifts typical of a methylenedioxy group. This product is hence identified as N^6-benzoyl-4′-(hydroxymethyl)-2′,3′-*O*-methyleneadenosine (**21b**), an assignment that is supported by elemental analysis. We suggest that the methylene compound arises via a competitive reaction involving β-elimination of the acetonide, leading to an oxy anion (**18**), which is trapped by formaldehyde to give the intermediate **19** that undergoes conjugate addition to the unsaturated aldehyde. The resulting **20** can then undergo aldol condensation in the usual way, giving **21** after Cannizzaro reduction. We have not isolated the corresponding uridine derivative **21a** from reactions of **14a** with formaldehyde. Whether this is the consequence of differing propensities for elimination of the cyclohexylidene and isopropylidene func-



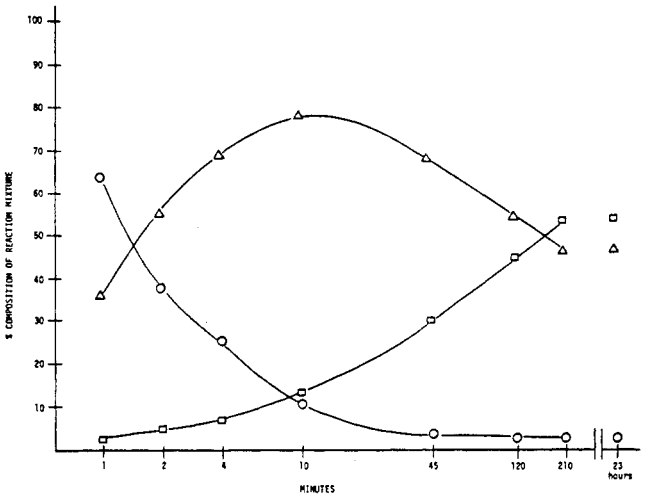


Figure 1. Variation of the composition of the reaction product of uridine 5′-aldehyde (**6a**) with formaldehyde. Samples were treated with sodium borohydride and then assayed using pH 6.0 borate paper electrophoresis.[15b] Zones corresponding to the mobility of uridine (○), **10a** (△), and **11a** (□) were eluted with 3 mL of 0.01 N HCl, and the optical density measured at 260 nm. All points except those at 3.50 and 23 h are an average of two determinations.

tions or of problems in chromatographic isolation remains to be explored.

It is interesting to note that the comparable reaction of methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdofuranose (**14d**) with formaldehyde is extremely fast, the aldol and Cannizzaro steps being complete within 30 min. ^{1}H NMR and VPC–mass spectral analyses of the product showed it to be a 9:1 mixture of the 2,3-*O*-isopropylidene and 2,3-*O*-methylene derivatives **16d** and **21d.** Both compounds were isolated in homogeneous form by chromatography on silicic acid. This reaction has previously been described by Leland and Kotick[9] without mention of the methylene derivative. We can offer no explanation for the rapidity of this reaction relative to those in the nucleoside series.

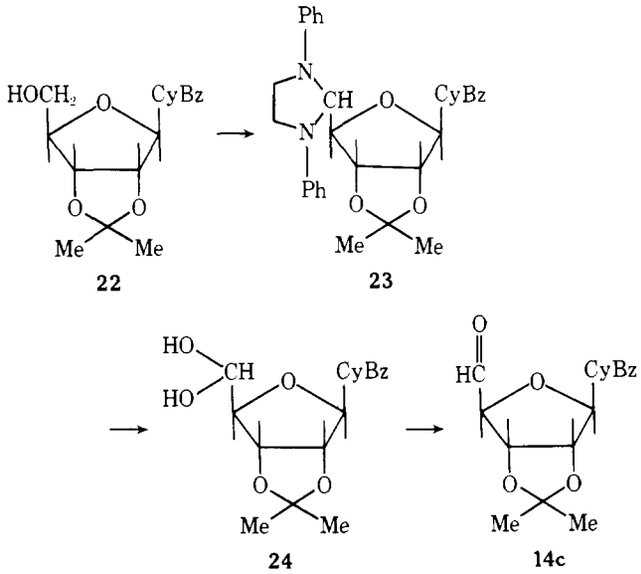
Several features of these reactions, including the lack of coloration in the presence of formaldehyde as opposed to the observed coloration in its absence, suggested that the aldol condensation[17a] was very rapid while the Cannizzaro reduction[17b] was relatively slow. In order to test this idea, a reaction, comparable to that above, between **14b,** formaldehyde, and sodium hydroxide was directly examined by TLC. After only 2 min at room temperature, the conversion of **14b** to a slightly more polar product seemed to be complete. After a total of 15 min, the mixture was neutralized with acetic acid and the organic solvent soluble products were reduced with sodium borohydride. Chromatography of the resulting products then led to the isolation of **16b** and **21b** in yields of 57 and 12%, respectively. It is interesting to note that the ratio of **16b** and **21b** is almost identical using either Cannizzaro or borohydride reduction. This shows that formation of the methylene derivative is also very rapid and supports the formation of both **16b** and **21b** from a common aldehyde enolate. In a similar fashion, reaction of **14a** with formaldehyde–aqueous sodium hydroxide for 5 min at 22 °C followed by sodium borohydride reduction gave **16a,** although in only 40% yield. In this experiment, as well as in the previous one carried out under Cannizzaro conditions, we were unable to isolate any of the corresponding 2′,3′-*O*-methylene derivative **21a.**

The observation above led us to hope that the aldol reaction with free uridine 5′-aldehyde (**6a**) could be quenched with sodium borohydride before retro-aldol epimerization of the initial product became extensive. The results of this study, represented in Figure 1, showed that, quite in contrast to the results with the 2′,3′-acetals (**14a** or **14b**), complete conversion to products required 45 min, at which time considerable amounts of the threo compound **11a** were observed. From Figure 1 it can be concluded that optimal formation of the erythro tetrol **10a** was achieved in 10 min.

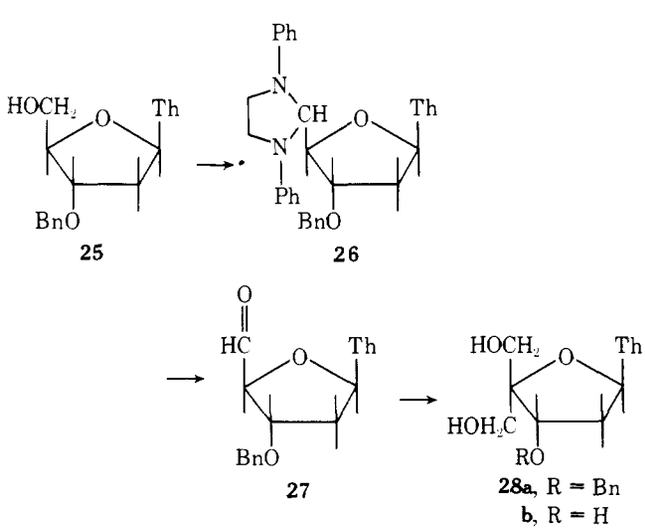
In a similar fashion, N^6-benzoyladenosine 5′-aldehyde (**6b**) was reacted with formaldehyde in 0.3 N sodium hydroxide solution for 2 h followed by the addition of excess sodium borohydride. Debenzoylation with methanolic ammonium hydroxide followed by chromatography on Dowex 1 (OH^-) resin[19] gave an almost complete separation of 4′-(hydroxymethyl)adenosine (**10c**) and the corresponding threo isomer **11c.** The structure of **11c** (29%) was confirmed by electrophoretic comparison[15] with its uridine counterpart **11a** and 9-β-D-xylofuranosyladenine, and by the identity of its physical properties with those reported by Leland and Kotick.[9] A sample of **10c** (38%) obtained in this way was still contaminated with 7% of **11c,** but the major component was electrophoretically identical with the compound obtained by sequential treatment of **16b** with 90% trifluoroacetic acid and methanolic ammonium hydroxide. In this way, 4′-(hydroxymethyl)adenosine (**10c**) was obtained as a crystalline hemihydrate and shown to be in all ways identical with the compound described in the accompanying paper via condensation of 6-chloropurine with 4′-(acetoxymethyl)-1,2,3,5-tetra-*O*-acetyl-D-*erythro*-pentofuranose followed by aminolysis.[1] It should be noted that very recently Rosenthal and Ratcliffe[18] have reported the preparation of **10c** and its α anomer via condensation of bis(trimethylsilyl)-N^6-benzoyladenine with a glycosyl bromide derived from apparently the same sugar we have used[1] but arrived at by an interesting photochemical pathway. The assignment of anomeric configuration to the compounds obtained in this way was based upon ^{1}H NMR and circular dichroism studies, but there appears to be a poor correlation between the reported data for the β isomer and that for **10c** prepared by either of our two routes. Thus, Rosenthal and Ratcliffe reported that the ^{1}H NMR signals for $C_{1'}$ H and $C_{3'}$ H (the only sugar protons reported) in methanol-d_4 appear as doublets at 6.41 ($J_{1',2'}$ = 2.5 Hz) and

5.79 ppm, respectively. In our hands these protons appear at 5.91 ($J_{1',2'}$ = 6.5 Hz) and 4.38 ppm in the same solvent. There is also a considerable discrepancy in the values of $[\alpha]^{23}_D$, ours being −45.5° (*c* 0.5, MeOH) and theirs being 1° (*c* 0.1, H_2O). Finally, the reported UV spectrum[18] has an extinction coefficient of 7860 at 258 nm, a figure that is extremely low for an adenosine derivative and must be regarded with suspicion. We feel that the identity of samples of **10c** prepared by both glycosidation of a purine moiety and transformation of an existing adenosine derivative leaves no ambiguity as to its structure.

In order to extend this work to the cytidine series and to the deoxynucleoside thymidine, it was necessary to prepare suitable nucleoside 5′-aldehyde derivatives. To this end N^4-benzoylcytidine[20] was converted into its 2′,3′-*O*-isopropylidene derivative (**22**) in 80% yield by treatment with acetone, dimethoxypropane, and perchloric acid, a considerably more facile procedure than that used by Holý and Pischel.[21] Oxidation of **22** was effected using the Me_2SO–DCC method[14] in the presence of pyridinium trifluoroacetate, and the resulting aldehyde was isolated as its crystalline 1,3-diphenylimidazolidine derivative (**23**) in 85% yield. Cleavage of the imidazolidine derivative using Dowex 50 (H^+) resin in aqueous tetrahydrofuran at room temperature then gave the crystalline aldehyde hydrate (**24**) that could be dehydrated to the crystalline free aldehyde **14c** by azeotropic distillation with benzene.



Along similar lines, 3′-*O*-benzylthymidine (**25**), prepared by a modification of the method of Griffin and Todd,[22] was oxidized using the Me_2SO–DCC method. Isolation of the aldehyde as its crystalline 1,3-diphenylimidazolidine derivative (**26**) was accomplished in 64% yield without need of chromatography. Unlike the case of **23**, regeneration of 3′-*O*-benzylthymidine 5′-aldehyde (**27**) from **26** was slow using Dowex 50 (H^+) resin, and even after 20 h under reflux in aqueous tetrahydrofuran a trace of **26** remained and appreciable amounts of thymine were produced. A similar slow deprotection using Dowex 50 (H^+) resin was previously noted during preparation of 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose.[23] On the other hand, treatment of **26** with a slight excess of *p*-toluenesulfonic acid monohydrate in methylene chloride–acetone at room temperature led to rapid hydrolysis. Following a simple partitioning workup, **27** was obtained as a foam in almost quantitative yield after drying in vacuo over phosphorus pentoxide. Both ^1H NMR spectroscopy and elemental analysis showed that this material was a 1:1 mixture of the free aldehyde (δ 9.65) and its hydrate. For the present purpose it was not necessary to further convert this to an anhydrous form.



Condensations of **14c** and **27** with formaldehyde and sodium hydroxide were carried out essentially as described for **14a** and **14b**. The reaction using **14c** was worked up after 5 min by sodium borohydride reduction and gave, after chromatography on a column of silicic acid, crystalline N^4-benzoyl-4′-(hydroxymethyl)-2′,3′-*O*-isopropylidenecytidine (**16c**) and the related 2′,3′-*O*-methylene nucleoside (**21c**) in yields of 42 and 10%. The same products were obtained in somewhat lower yields from a longer reaction (4 h) of **14c** under Cannizzaro reduction conditions. In this case there is a clear advantage in the use of sodium borohydride since considerable debenzoylation accompanied the lengthy reaction time required for completion of the Cannizzaro reduction. Deblocking of **16c** was achieved by sequential treatment with methanolic ammonium hydroxide and 90% trifluoroacetic acid, giving 4′-(hydroxymethyl)cytidine (**17**) as a TLC and NMR homogeneous precipitate in quantitative yield. Similarly, hydroxymethylation of **27** for 16 h gave crystalline **28a** in 40% yield, and subsequent debenzylation by catalytic hydrogenolysis afforded 4′-(hydroxymethyl)thymidine (**28b**).

All of the 4′-hydroxymethyl nucleosides described in this paper have been examined by conventional spectroscopic techniques that confirm the assigned structures. In particular, all of the 4′-hydroxymethyl compounds give ^1H NMR spectra which lack a $C_{4'}$ proton, with $C_{3'}$ hydrogens appearing as clear doublets. In most cases the $C_{5'}$ protons and the $C_{4'}$ hydroxymethyl groups appear as overlapping signals integrating for the expected four protons.

Clearly, the synthetic methods described in this paper, together with the approach outlined in the companion piece,[1] make 4′-hydroxymethyl derivatives of a wide range of nucleosides readily available. In our experience these compounds have shown little in the way of interesting biological activities. Further studies related to this work will be reported at a later date.[3e]

Experimental Section

General Methods. Thin-layer chromatography (TLC) was conducted using 0.25-mm layers of silica gel HF from Analtech Corp. and preparative TLC using 20 × 100 cm glass plates coated with a 0.75-mm layer of Merck silica gel GF. Merck silica gel with 0.05–0.20 mm particles was used for column chromatography. Elemental and other instrumental analyses, including 100-MHz ^1H NMR spectra, were obtained by the staff of the Analytical Laboratories of Syntex Research, to whom we are indebted. Melting points are corrected.

5′-Deoxy-5′,5′-(*N*,*N*′-Diphenylethylenediamino)uridine (5). Trifluoroacetic acid (0.2 mL, 2.5 mmol) was added to an ice-cooled solution of 2′,3′-*O*-anisylideneuridine (**3**; 1.84 g, 5 mmol), dicyclohexylcarbodiimide (3.1 g, 15 mmol), and pyridine (0.04 mL, 5 mmol) in anhydrous dimethyl sulfoxide (13 mL), and the resulting mixture

was stirred at 22 °C for 16 h. *N,N'*-Dicyclohexylurea was then filtered off and washed with ethyl acetate, and the combined filtrates were partitioned between ethyl acetate (100 mL) and water (100 mL). The organic phase was further washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. A solution of the residue in 80% acetic acid (50 mL) was stored at 37 °C for 16 h and then concentrated in vacuo. An aqueous solution (100 mL) of the residue was washed with chloroform (2 × 75 mL) and ethyl acetate (75 mL) and then evaporated to dryness, giving an off-white foam (1.30 g). This was dissolved in methanol (30 mL), *N,N'*-diphenylethylenediamine (1.1 g, 5.2 mmol) and glacial acetic acid (0.6 mL) were added, and the resulting solution was stored at 22 °C for 18 h. The crystalline product was collected by filtration, washed with methanol, and dried in vacuo, giving 1.24 g (53%) of **5** as a methanolate with mp 163–164 °C. An analytical sample from methanol had mp 164–165 °C: $[\alpha]^{25}_D$ 13.8° (*c* 0.2, *p*-dioxane); λ_{max} (MeOH) 253 nm (ε 38 600); ^{1}H NMR (Me_2SO-d_6) δ 3.17 (s, 3, CH_3OH), 3.63 (m, 4, NCH_2CH_2N), 4.0 (m, 2, $C_{2'}$ H, $C_{3'}$ H), 4.35 (dd, 1, $J_{4',5'}$ = 1 Hz, $J_{3',4'}$ = 6 Hz, $C_{4'}$ H), 5.49 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 5.71 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}$ H), 5.83 (br s, 1, $C_{5'}$ H), 6.85 and 7.25 (m, 10, Ph), 7.41 (d, 1, C_6 H).

Anal. Calcd for $C_{23}H_{24}N_4O_5 \cdot CH_3OH$ (468.50): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.70; H, 5.98; N, 11.87.

1-(β-D-*ribo*-Pentodialdo-1,4-furanosyl)uracil (6a). (a) From the 2',3'-Cyclohexylidene Derivative 14a.[3c] A solution of **14a** (510 mg, 1.5 mmol, of hydrate) in 9:1 trifluoroacetic acid–water (5 mL) was stored at 22 °C for 45 min and then diluted with water (50 mL).[24] The resulting solution was extracted with ethyl acetate (3 × 50 mL), and the aqueous phase was evaporated to dryness in vacuo. The residue was coevaporated with water and dried under high vacuum, giving 0.36 g (92%) of **6a** as an amorphous white foam that contained only traces of impurities by TLC ($CHCl_3$–MeOH, 4:1). Since the product readily formed hemiacetals in the presence of alcohols, no convenient method for chromatographic purification could be found. The ^{1}H NMR spectrum in D_2O showed the product to be essentially pure: δ 4.00 (dd, 1, $J_{3',4'}$ = 3 Hz, $J_{4',5'}$ = 4 Hz, $C_{4'}$ H), 4.4 (m, 2, $C_{2'}$ H, $C_{3'}$ H), 5.19 (d, 1, $J_{1',2'}$ = 4 Hz, $C_{1'}$ H), 5.90 (d, 1, $J_{5,6}$ = 8 Hz, C_6 H), 5.97 (d, 1, $C_{5'}$ H), 7.89 (d, 1, C_6 H). The ^{1}H NMR in Me_2SO-d_6 showed the product to be an almost equal mixture of free aldehyde and aldehyde hydrate: δ 9.60 (s, 0.5, $C_{5'}$ H), 7.80 and 7.84 (d, $J_{5,6}$ = 8 Hz, C_6H). While acceptable elemental analyses could not be obtained (C and N ~1% off), the compound was suitable for use in subsequent reactions.

(b) From the Imidazolidine Derivative 5a. A mixture of dry Dowex 50 (H^+) resin (8 g) and **5a** (0.88 g, 1.88 mmol) in 5:3 tetrahydrofuran–water (16 mL) was stirred at 22 °C for 1 h. The resin was removed by filtration, the filtrate was concentrated in vacuo, and the residue was dried at 0.003 mm Hg, giving 0.56 g (quantitative for trihydrate) of **6a** as a white foam that was chromatographically identical with that from (a).

N^6-Benzoyl-9-(β-D-*ribo*-pentodialdo-1,4-furanosyl)adenine (6b). A solution of **14b** (427 mg, 1 mmol, of hydrate) in 9:1 trifluoroacetic acid–water (5 mL) was stored at 22 °C for 10 min and then concentrated in vacuo. The residue was coevaporated twice with methanol and triturated with ether to give 220 mg (57%) of **6b.** Rapid dissolution of this material in hot water led to the crystallization of 135 mg of the hydrate of **6b,** mp 157–158 °C, which was then quite insoluble in water.

Anal. Calcd for $C_{17}H_{15}N_5O_5 \cdot H_2O$ (387.35): C, 52.71; H, 4.42; N, 18.08. Found: C, 52.80; H, 4.29; N, 17.55.

4'-(Acetoxymethyl)-2',3',5'-tri-*O*-acetyluridine (10b) and 1-[4-(Acetoxymethyl)-2,3,5-tri-*O*-acetyl-α-L-*threo*-pentofuranosyl]uracil (11b). Aqueous sodium hydroxide (2 mL of 1 N) was added at 0 °C to a solution of **6a** (regenerated from 468 mg, 1 mmol, of **5a**) and 37% aqueous formaldehyde (0.2 mL) in water (2 mL). After 24 h at 22 °C, the solution was passed through a Dowex 50 (H^+) column and the aqueous eluates were concentrated in vacuo. The residue was purified by preparative TLC using MeOH–$CHCl_3$ (1:3) to give 170 mg (62%) of a mixture of **10a** and **11a** by ^{1}H NMR analysis.

A portion (140 mg) of this mixture was dissolved in dry pyridine (5 mL), acetic anhydride (1 mL) was added, and the mixture was stored at 22 °C for 16 h. Methanol was then added with cooling, and the solution was concentrated in vacuo. A chloroform solution of the residue was washed with water, dried ($MgSO_4$), and concentrated to dryness in vacuo. The residue was separated by preparative TLC using 2:3 ethyl acetate–ether to give 60 mg (27%) of **10b** and 50 mg (22%) of the less polar threo isomer **11b.** The erythro isomer **10b** was identical in all respects with a sample prepared by acetylation of **10a** derived by hydrolysis of the 2',3'-*O*-cyclohexylidene derivative **16a. 10b:** $[\alpha]^{25}_D$ 3.5° (*c* 0.49, $CHCl_3$); λ_{max} (MeOH) 257 nm (ε 9500); ^{1}H NMR ($CDCl_3$) δ 2.07 and 2.13 (s, 12, $COCH_3$), 4.17, 4.22, 4.29, and 4.41 (d, 4, J_{gem} = 12 Hz, $C_{5'}$ H_2 and $C_{4'}$ CH_2), 5.48 (dd, 1, $C_{2'}$ H), 5.60 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}$ H), 5.76 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 6.03 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}$ H), 7.35 (d, 1, C_6 H), 9.25 (br s, 1, NH).

Anal. Calcd for $C_{18}H_{22}N_2O_{11}$ (442.31): C, 48.87; H, 5.01; N, 6.33. Found: C, 48.88; H, 5.32; N, 5.71.

11b: $[\alpha]^{25}_D$ −22.4° (*c* 0.51, $CHCl_3$); λ_{max} (MeOH) 257 nm (ε 9470); ^{1}H NMR ($CDCl_3$) δ 2.10 and 2.14 (s, 12, $COCH_3$), 4.02 and 4.52 (d, 1, J_{gem} = 12 Hz, $C_{5'}$ H_2), 4.29 (s, 2, $C_{4'}$ CH_2), 5.38 (dd, 1, $C_{2'}$ H), 5.64 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}$ H), 5.80 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 6.17 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}$ H), 7.56 (d, 1, C_6 H), 9.25 (br s, 1, NH).

Anal. Calcd for $C_{18}H_{22}N_2O_{11}$ (442.31): C, 48.87; H, 5.01; N, 6.33. Found: C, 48.79; H, 5.26; N, 5.75.

Small samples of **10b** and **11b** were treated with ammonium hydroxide and then analyzed by paper electrophoresis using a pH 6 borate buffer.[15] The less polar acetate **11b** gave a tetrol (**11a**) that had a mobility relative to uridine of 0.25 (M_{Ur} = 0.25), while the more polar acetate **10b** gave a tetrol with the same mobility as an authentic sample of **10a** (M_{Ur} = 1.5).

4'-(Hydroxymethyl)adenosine (10c) and 9-[4-(Hydroxymethyl)-α-L-*threo*-pentofuranosyl]adenine (11c) from 6b. Aqueous sodium hydroxide (1 mL of 2 N) was added to a suspension of **6b** (369 mg, 1 mmol) in 37% aqueous formaldehyde (0.2 mL) and water (5 mL). After storage at 22 °C for 2 h, the resulting solution was cooled to ~5 °C, sodium borohydride (50 mg) was added, and the mixture was kept at 22 °C for a further 30 min before being neutralized with carboxymethylcellulose (H^+). The resin was filtered off and washed well with 50% aqueous methanol, and the combined filtrates were concentrated to dryness. The residue was dissolved in 1:1 methanol–concentrated ammonium hydroxide (10 mL) and stored at 22 °C for 5 days. The solvents were removed in vacuo, giving 0.46 g of a white solid. An aqueous solution of this material (12 500 ODU_{257}) was applied to a Dowex 1 × 2 (OH^-)[19] column (42 × 2.5 cm) that was eluted with a linear gradient (8 L) of 0–80% methanol in water at a flow rate of 3 mL/min, giving two major peaks that partially overlapped. The first peak (4350 ODU_{257}, 29%, eluted at 58% MeOH) was concentrated in vacuo, and the residue was crystallized from ethanol, giving **11c** (67 mg, 23%) with mp 254–255 °C (lit.[9] mp 251–253 °C).

The second peak (5760 ODU_{257}, 38%, eluted at 68% MeOH) was concentrated in vacuo, giving 75 mg (25%) of a white solid that was shown by pH 6.0 borate electrophoresis[15] to be a 93:7 mixture of **10c** and **11c.** The electrophoretic mobility (M_{Ad} = 1.7) of **10c** was identical with that obtained via hydrolysis of **16b,** and that of **11c** (M_{Ad} = 0.1) was the same as that of a sample of 9-β-D-*xylo*-furanosyladenine kindly supplied by Dr. E. Acton. Crystallization of this material from water gave 35 mg of the hemihydrate of **10c,** mp 135–137 °C, that was still contaminated with a trace of the L-threo isomer **11c** but otherwise was identical with an authentic sample.[1]

2',3'-*O*-Cyclohexylidene-4'-(hydroxymethyl)uridine (16a). (a) Via Cannizzaro Reduction. Aqueous sodium hydroxide (10 mL of 2 N) was added to a stirred solution of **14a** (3.4 g, 10 mmol, of hydrate) and 37% aqueous formaldehyde (2 mL) in *p*-dioxane (20 mL). The resulting yellow solution was stirred at 22 °C for 16 h, neutralized to pH 7 with acetic acid, mixed with silica gel (30 g), and concentrated in vacuo to dryness. The residue was dried by successive coevaporation with ethanol and chloroform before it was suspended in 1:19 methanol–chloroform and added to a silica gel column (34 × 4.2 cm) prepared in the same solvent. The column was eluted with 1:9 methanol–chloroform to give 1.35 g (38%) of chromatographically homogeneous **16a** that was crystallized from methanol, giving 0.80 g (23%) of **16a** with mp 218–219 °C: $[\alpha]^{25}_D$ −48.0° (*c* 0.5, DMF); λ_{max} (MeOH) 260 nm (ε 10 620); ^{1}H NMR (Me_2SO-d_6) δ 1.5–1.7 (m, 10, CH_2), 3.55 (m, 4, $C_{5'}$ H_2 and $C_{4'}$ CH_2), 4.58 and 5.11 (t, 1, OH), 4.73 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}$ H), 4.85 (dd, 1, $J_{1',2'}$ = 4 Hz, $C_{2'}$ H), 5.63 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 5.89 (d, 1, $C_{1'}$ H), 7.91 (d, 1, C_6 H), 11.17 (br s, 1, NH).

Anal. Calcd for $C_{16}H_{22}N_2O_7$ (354.37): C, 54.23; H, 6.26; N, 7.91. Found: C, 54.13; H, 6.23; N, 7.83.

(b) Via Sodium Borohydride Reduction. 2',3'-*O*-Cyclohexylideneuridine 5'-aldehyde (**14a;** 1.7 g, 5 mmol) was reacted with formaldehyde as described above except that after 5 min of reaction the mixture was cooled to 5 °C and sodium borohydride (340 mg) was added. After 2 h the reaction mixture was neutralized with Dowex 50 (H^+) resin that was then removed by filtration. The combined filtrates were concentrated in vacuo, giving a yellow foam (1.82 g). Chromatography on silica gel as above gave 0.71 g (40%) of **16a,** identical in all respects with a sample prepared by method (a).

N^6-Benzoyl-4'-(hydroxymethyl)-2',3'-*O*-isopropylideneadenosine (16b). (a) Via Cannizzaro Reduction. Aqueous sodium hydroxide (10 mL of 2 N) was added to a stirred mixture of **14b** (4.27 g, 10 mmol, of hydrate), 37% aqueous formaldehyde (2.25 mL), and

p-dioxane (30 mL), and the resulting clear solution was stirred at 22 °C for 5.25 h. The solution was adjusted to pH 7 with acetic acid, diluted with water (100 mL), and extracted several times with chloroform. The combined organic phases were washed with aqueous sodium bicarbonate (50 mL) and water (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on a silica gel column (45 × 5.4 cm) prepared in chloroform and eluted with a gradient of chloroform (4 L) to 3:7 chloroform–acetone (4 L). The less polar product peak gave 1.72 g (39%) of **16b** as a chromatographically homogeneous foam that tenaciously bound solvent even after drying in vacuo at 60 °C: $[\alpha]^{25}_D$ −60.2° (*c* 1, MeOH); λ_{max} (MeOH) 280 nm (ε 19 940), 230 (12 820); ^1H NMR ($CDCl_3$) δ 1.39 and 1.66 (s, 3, Ip), 3.83 (m, 4, $C_{5'}$ H_2, $C_{4'}$ CH_2), 5.19 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}$ H), 5.37 (dd, 1, $J_{1',2'}$ = 5 Hz, $C_{2'}$ H), 5.98 (d, 1, $C_{1'}$ H), 7.55 and 8.0 (m, 5, Ph), 8.05 and 8.74 (s, 1, C_2 H, C_8 H).

Anal. Calcd for $C_{21}H_{23}N_5O_6 \cdot 0.1CHCl_3$ (453.39): C, 55.89; H, 5.13; N, 15.45. Found: C, 55.66; H, 5.44; N, 15.35.

The more polar material gave 0.35 g (8.5%) of the 2′,3′-*O*-methylene derivative **21b** that was shown by TLC to be slightly contaminated by the corresponding isopropylidene derivative **16b.** Preparative TLC on a sample of **21b** (75 mg) using 3:2 acetone–chloroform gave pure **21b** (38 mg) as a chromatographically homogeneous foam still retaining some chloroform: $[\alpha]^{25}_D$ −50.5° (*c* 1, MeOH); λ_{max} (MeOH) 280 nm (ε 17 870), 233 (11 120); ^1H NMR ($CDCl_3$) δ 3.83 (m, 4, $C_{5'}$ H_2, $C_{4'}$ CH_2), 4.93 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}$ H), 5.07 and 5.36 (s, 1, $H_2C(O)_2$), 5.37 (dd, 1, $J_{1',2'}$ = 4.5 Hz, $C_{2'}$ H), 5.98 (d, 1, $C_{1'}$ H), 7.5 and 8.0 (m, 5, Ph), 8.12 and 8.71 (s, 1, C_2 H, C_8 H).

Anal. Calcd for $C_{19}H_{19}N_5O_6 \cdot 0.4CHCl_3$ (489.22): C, 52.54; H, 4.62; N, 14.32. Found: C, 52.77; H, 4.77; N, 14.53.

(b) Via Sodium Borohydride Reduction. N^6-Benzoyl-2′,3′-*O*-isopropylideneadenosine 5′-aldehyde (**14b;** 0.43 g, 1 mmol) was reacted with formaldehyde as described above. After 2 min of reaction, TLC analysis using 1:3:16 *n*-butyl alcohol–acetone–chloroform showed that **14b** had been converted to a slightly more polar material, presumably **15b.** The reaction mixture was neutralized with acetic acid after 15 min, the solvents were removed in vacuo, and the residue was partitioned between chloroform (25 mL) and water (20 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow foam. Sodium borohydride (25 mg) was added at 0–5 °C to a solution of this material in ethanol (10 mL), and the mixture was stirred at 0–5 °C for a further 30 min before it was neutralized with acetic acid. The resulting solution was concentrated to dryness and the residue was partitioned between chloroform (25 mL) and water (10 mL). The organic phase was washed with aqueous sodium bicarbonate (10 mL) and water, dried ($MgSO_4$), and concentrated to dryness. Purification of the residue by preparative TLC, using 2:3:15 *n*-butyl alcohol–acetone–chloroform, gave 0.25 g of **16b** (57%) and 0.049 g of **21a** (12%) as chromatographically homogeneous foams, identical with those above.

Methyl 4-(Hydroxymethyl)-2,3-*O*-isopropylidene-β-D-*erythro*-pentofuranoside (16d). Aqueous sodium hydroxide (10 mL of 2 N) was added to a solution of **14d** (2.02 g, 10 mmol) and 37% aqueous formaldehyde (2.25 mL) in *p*-dioxane (30 mL). The solution was stirred at 22 °C for 16 h, although TLC analysis after 35 min indicated that the reaction was complete, and then neutralized with Dowex 50 (H^+) resin. The resin was filtered off, the filtrates were concentrated in vacuo, and the residue was partitioned between saturated brine and ethyl acetate. The aqueous phase was further extracted twice with ethyl acetate, and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo, giving 1.86 g of crude product. GLC analysis using a 4 ft × ⅛ in. 3% OV 101 column at 100 °C showed that this material consisted of two products in a ratio of roughly 9:1. GLC–MS analysis of this mixture then indicated that the major, less volatile compound was the 2,3-*O*-isopropylidene derivative **16d** (M^+ 234) and that the minor component was the 2,3-*O*-methylene derivative **21c** (M^+ 206).

The above product (1.86 g) was then chromatographed on a silica gel column (46 × 3.8 cm) that was eluted with a gradient of 1–6% methanol in chloroform (4 L), giving 1.11 g of pure **16d** and 0.33 g of a mixture of **16d** and **21c.** Crystallization of the major fraction from cyclohexane gave 0.99 g (42%) of **16d** with mp 97–98 °C (lit.[9] mp 94–96.5 °C): $[\alpha]^{25}_D$ −40.7° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 and 1.47 (s, 3, Ip), 3.38 (s, 3, OCH_3), 3.58, 3.63, 3.75, and 3.78 (d, 4, J_{gem} = 12 Hz, C_5 H_2, C_4 CH_2), 4.64 and 4.82 (d, 2, $J_{2,3}$ = 6 Hz, C_2 H, C_3 H), 4.96 (s, 1, C_1 H). The minor fraction was further purified by preparative TLC using 6% methanol in chloroform to give 160 mg of **16d** (total yield 56%) and 70 mg (3.4%) of **21d** as an oil: $[\alpha]^{25}_D$ − 50.5° (*c* 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.39 (s, 3, OCH_3), 3.59, 3.62, and 3.78 (d, 4, J_{gem} = 12 Hz, C_5 H_2, C_4 CH_2), 4.59 and 4.71 (d, 2, $J_{2,3}$ = 6 Hz, C_2 H, C_3 H), 4.92 and 4.99 (s, 2, $H_2C(O)_2$), 4.97 (s, 1, C_1 H).

Anal. Calcd for $C_8H_{14}O_6$ (206.20): C, 46.60; H, 6.84. Found: C, 46.10; H, 6.94.

4′-(Hydroxymethyl)uridine (10a). A solution of **16a** (0.65 g, 1.84 mmol) in 9:1 trifluoroacetic acid–water (6.5 mL) was stored at 22 °C for 15 min before being diluted with water (30 mL).[24] The resulting solution was extracted with ether (3 × 25 mL) and chloroform (2 × 25 mL) and was then concentrated to dryness in vacuo. The residue was purified by preparative TLC, using 1:3 methanol–chloroform, to give 0.37 g (74%) of **10a** as a chromatographically homogeneous white foam: $[\alpha]^{25}_D$ −12.1° (*c* 1, MeOH); λ_{max} (MeOH) 257 nm (ε 9440); ^1H NMR (MeOH-d_4) δ 3.55 (m, 4, $C_{5'}$ H_2, $C_{4'}$ CH_2), 3.62 and 3.75 (d, 2, J_{gem} = 11 Hz, $C_{4'}$ CH_2), 4.23 (d, 1, $J_{2',3'}$ = 5 Hz, $C_{3'}$ H), 4.31 (dd, 1, $C_{2'}$ H), 5.67 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 5.94 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}$ H), 7.92 (d, 1, C_6 H). While the purity of the sample was ensured by its NMR spectrum, **10a** was very hygroscopic and could not be obtained in crystalline form. Acceptable elemental analyses could not be obtained due to the presence of traces of silica gel. Acetylation of **10a** gave the tetraacetate **10b,** identical with that described above.

4′-(Hydroxymethyl)adenosine (10c). A solution of **16b** (0.5 g, 1.13 mmol) in 9:1 trifluoroacetic acid–water (5 mL) was stored at 22 °C for 10 min. The solution was then diluted with water (30 mL), extracted with ether (3 × 30 mL), and concentrated to dryness in vacuo, giving a white foam (0.53 g). A solution of this foam in 1:1 methanol–concentrated ammonium hydroxide (10 mL) was stored at 22 °C for 24 h and then concentrated to dryness in vacuo. The residue was purified by preparative TLC using 1:3 methanol–chloroform, and the product was recrystallized from water (2 mL), giving 170 mg (49%) of **10c** as a hemihydrate, mp 135–138 °C (sintering at 130 °C), identical with a previously obtained sample.[1]

N^4-Benzoyl-2′,3′-*O*-isopropylidenecytidine (22). Perchloric acid (10 mL, 70%) was added to a vigorously stirred suspension of N^4-benzoylcytidine (34.8 g, 0.1 mol) in a mixture of 2,2-dimethoxypropane (250 mL) and anhydrous acetone (1.5 L). After standing at 22 °C for 3 h, the reaction mixture was neutralized with ammonium hydroxide (~8.5 mL) and the solvents were removed in vacuo. The residue was partitioned between chloroform (2 L) and water (1 L), the aqueous layer was further extracted with chloroform, and the combined organic phases were washed with water, dried ($MgSO_4$), and concentrated to dryness. The residue was crystallized from chloroform–hexane, giving 30.8 g (80%) of **22** with mp 182–184 °C; a second crop (3.8 g, 10%) with mp 171–177 °C was also obtained (the literature[21] gives mp 182 °C).

N^4-Benzoyl-5′-deoxy-5′,5′-(*N,N′*-diphenylethylenediamino)-2′,3′-*O*-isopropylidenecytidine (23). Trifluoroacetic acid (4 mL, 50 mmol) was added dropwise to an ice water cooled solution of **22** (31 g, 80 mmol, dried by two coevaporations with pyridine), dicyclohexylcarbodiimide (49.6 g, 240 mmol), and pyridine (6.4 mL, 80 mmol) in dimethyl sulfoxide (200 mL), and the resulting mixture was stirred at 22 °C for 7 h. A solution of oxalic acid dihydrate (20.2 g, 160 mmol) in methanol (60 mL) was then carefully added, and the mixture was stirred at 22 °C for a further 1 h. *N,N′*-Dicyclohexylurea was filtered off and washed with methanol, and to the combined filtrates was added *N,N′*-diphenylethylenediamine (17 g, 80 mmol) and glacial acetic acid (9.6 mL) in methanol (60 mL). The resulting solution was stored for 16 h at 22 °C, neutralized by the addition of aqueous sodium bicarbonate, and partitioned between chloroform and water. The chloroform layer was washed three times with saturated brine, dried ($MgSO_4$), and concentrated to dryness, and the residue was treated with methanol (80 mL) to give in two crops 39.5 g (85%) of **23** that is sufficiently pure for the subsequent transformations. An analytical sample with mp 190–192 °C was prepared by recrystallization from methanol: $[\alpha]^{25}_D$ 18.7° (*c* 1, $CHCl_3$); λ_{max} (MeOH) 297 nm (ε 12 830), 254 (52 200); ^1H NMR ($CDCl_3$) δ 1.24 and 1.37 (s, 3, Ip), 3.7 (m, 4, NCH_2CH_2N), 4.49 (dd, 1, $J_{3',4'}$ = 5.5 Hz, $J_{4',5'}$ = 4 Hz, $C_{4'}$ H), 4.71 (dd, $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 6 Hz, $C_{2'}$ H), 4.94 (dd, 1, $C_{3'}$ H), 5.89 (d, 1, $C_{1'}$ H), 5.93 (d, 1, $C_{5'}$ H), 6.7–7.6 and 7.85 (m, 17, Ph, C_5 H, C_6 H).

Anal. Calcd for $C_{33}H_{33}N_5O_5$ (579.62): C, 68.38; H, 5.74; N, 12.08. Found: C, 68.12; H, 5.66; N, 11.88.

N^4-Benzoyl-1-(2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanosyl)cytosine (14c). A suspension of **23** (290 mg, 0.5 mmol) and dry Dowex 50 (H^+) resin (500 mg) in 1:1 water–tetrahydrofuran (20 mL) was stirred at 22 °C for 2.5 h. The resin was filtered off and washed with tetrahydrofuran, and the combined filtrates were concentrated in vacuo to a volume of about 10 mL and then cooled at 0 °C. The white precipitate was filtered off, washed with water, and dried in vacuo, giving 170 mg (84%) of the aldehyde hydrate **24.** An analytical sample of the monohydrate with mp 205–208 °C was prepared by crystallization from tetrahydrofuran–*n*-hexane: $[\alpha]^{25}_D$ −17.1° (*c* 0.3, MeOH); λ_{max} (MeOH) 304 nm (ε 9920), 259 (23 520); ^1H NMR (Me_2SO-d_6) δ 1.29 and 1.48 (s, 3, Ip), 4.06 (dd, 1, $J_{4',5'}$ = 4

Hz, $J_{3',4'}$ = 0.5 Hz, $C_{4'}$ H), 4.86 (br s, 2, $C_{2'}$ H, $C_{3'}$ H), 4.91 (ddd, 1, $C_{5'}$ H), 5.86 (br s, 1, $J_{1',2'} \simeq$ 0.5 Hz, $C_{1'}$ H), 6.21 and 6.27 (d, 1, $J_{5'H,OH}$ = 4 Hz, 2 × OH), 7.31 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 7.5 and 8.0 (m, 5, Bz), 8.35 (d, 1, C_6 H), 11.25 (br s, 1, NH).

Anal. Calcd for $C_{19}H_{21}N_3O_7$ (403.38): C, 56.57; H, 5.25; N, 10.42. Found: C, 56.54; H, 5.35; N, 10.28.

A suspension of the above hydrate (690 mg, 1.7 mmol) in benzene (120 mL) was heated under reflux using a Dean-Stark apparatus for 3.5 h. The solvent was then removed in vacuo, giving 650 mg (99%) of the aldehyde **14c** as a free-flowing white powder with mp 201–206 °C: ^{1}H NMR (Me_2SO-d_6) δ 1.30 and 1.45 (s, 3, Ip), 4.54 (s, 1, $C_{4'}$ H), 5.06 and 5.16 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{2'}$ H, $C_{3'}$ H), 5.91 (s, 1, $C_{1'}$ H), 7.33 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 7.5 and 8.0 (m, 5, Bz), 8.35 (d, 1, C_6 H), 9.22 (s, 1, $C_{5'}$ H), 11.30 (s, 1, NH).

Anal. Calcd for $C_{19}H_{19}N_3O_6$ (385.36): C, 59.21; H, 4.97; N, 10.90. Found: C, 59.31; H, 5.29; N, 11.00.

N^4-Benzoyl-4′-(hydroxymethyl)-2′,3′-*O*-isopropylidenecytidine (16c). Aqueous sodium hydroxide (10 mL of 2 N) was added to a stirred suspension of **14c** (3.85 g, 10 mmol) and 37% aqueous formaldehyde (2.3 mL) in *p*-dioxane (30 mL). The resulting solution was stirred at 22 °C for 5 min, neutralized with glacial acetic acid, and concentrated to dryness in vacuo, and the residue was partitioned between water and chloroform. The aqueous phase was further extracted three times with chloroform, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. A solution of the resulting foam (largely **15c**) in ethanol (100 mL) was cooled to 0 °C, sodium borohydride (250 mg) was added, and the mixture was stirred at 0 °C for 25 min. After neutralization with acetic acid, the reaction mixture was worked up by a partition process as above, giving 3.4 g of crude product. This was chromatographed on a silica gel column (250 g) that was eluted with a gradient (4 L) of 25–75% acetone in chloroform, giving 1.99 g (48%) of **16c** and 0.50 g (13%) of the more polar **21b.** The 2′,3′-*O*-isopropylidene derivative **16c** was crystallized from acetone–*n*-hexane, giving 1.74 g (42%) with mp 205–207 °C: $[\alpha]^{25}_D$ −27.7° (*c* 1, pyridine); λ_{max} (MeOH) 303 nm (ε 10 560), 259 (24 220); ^{1}H NMR (Me_2SO-d_6) δ 1.29 and 1.50 (s, 3, Ip), 3.6 (br m, 4, $C_{5'}$ H_2, $C_{4'}$ CH_2), 4.74 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}$ H), 4.89 (dd, 1, $J_{1',2'}$ = 3 Hz, $C_{2'}$ H), 4.70 and 5.13 (br t, 1, 2 × OH), 5.87 (d, 1, $C_{1'}$ H), 7.34 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 7.5 and 8.0 (m, 5, Bz), 8.37 (d, 1, C_6 H), 11.25 (br s, 1, NH).

Anal. Calcd for $C_{20}H_{23}N_3O_7$ (417.46): C, 57.55; H, 5.55; N, 10.07. Found: C, 57.36; H, 5.71; N, 9.88.

The 2′,3′-*O*-methylene derivative **21b** was further purified by preparative TLC using 1:1 acetone–chloroform to give 400 mg (10%) of pure **21b.** An analytical sample with mp 208–210 °C was prepared by crystallization from acetone–*n*-hexane: $[\alpha]^{25}_D$ − 28.6° (*c* 1, pyridine); λ_{max} (MeOH) 303 nm (ε10 700), 258 (24 720); ^{1}H NMR (Me_2SO-d_6) δ 3.62 (br m, 4, $C_{5'}$ H_2, $C_{4'}$ CH_2), 4.57 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{3'}$ H), 4.77 and 5.2 (br t, 1, 2 × OH), 4.93 (dd, 1, $J_{1',2'}$ = 2 Hz, $C_{2'}$ H), 5.02 and 5.14 (s, 1, $H_2C(O)_2$), 5.85 (d, 1, $C_{1'}$ H), 7.33 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 7.6 and 8.05 (m, 5, Bz), 8.34 (d, 1, C_6 H), 11.3 (br s, NH).

Anal. Calcd for $C_{18}H_{19}N_3O_7$ (389.37): C, 55.53; H, 4.92; N, 10.79. Found: C, 55.51; H, 5.03; N, 10.66.

4′-(Hydroxymethyl)cytidine (17). A suspension of **16c** (1.67 g, 4 mmol) in 1:1 methanol–concentrated ammonium hydroxide (80 mL) was stirred at 22 °C for 2 h, and the resulting clear solution was concentrated to dryness in vacuo. A solution of the residue in 9:1 trifluoroacetic acid–water (30 mL) was kept at 22 °C for 30 min before the solvents were removed in vacuo. The residue was dissolved in water, and the solution was passed through a Dowex 50 (H^+) column (200 mL) that was washed with water until a neutral eluate was obtained and then with 3% ammonium hydroxide solution to give, after evaporation, 1.15 g (quantitative) of **17** as an amorphous powder. An analytical sample was prepared by trituration with isopropyl alcohol: paper chromatography, R_f 0.2 (*n*-BuOH–HOAc–H_2O, 5:2:3) and 0.52 (*i*-PrOH–NH_4OH–H_2O, 7:1:2); $[\alpha]^{25}_D$ −16.2° (*c* 1, H_2O); λ_{max} (MeOH) 272 (ε 8040), 263 (7710); ^{1}H NMR (Me_2SO-d_6) δ 3.5 (br s, 4, $C_{5'}$ H_2, $C_{4'}$ CH_2), 4.10 (br m, 2, $C_{2'}$ H, $C_{3'}$ H), 5.73 (d, 1, $J_{5,6}$ = 8 Hz, C_5 H), 5.87 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}$ H), 7.18 (br s, 2, NH_2), 7.82 (d, 1, C_6 H).

Anal. Calcd for $C_{10}H_{15}N_3O_6 \cdot {}^1/_3(CH_3)_2CHOH$ (293.23): C, 45.06; H, 6.07; N, 14.33. Found: C, 45.03; H, 6.20; N, 14.01.

3′-*O*-Benzyl-5′-deoxy-5′,5′-(*N,N′*-diphenylethylenediamino)thymidine (26). Trifluoroacetic acid (0.29 mL, 3.6 mmol) was added to an ice water cooled solution of 3′-*O*-benzylthymidine[22] (**25;** 2.4 g, 7.25 mmol), dicyclohexylcarbodiimide (4.5 g, 21.7 mmol), and pyridine (0.58 mL 7.25 mmol) in anhydrous dimethyl sulfoxide. This mixture was stirred at 22 °C for 2 h, and then a solution of oxalic acid (1.8 g, 14.5 mmol) in methanol (10 mL) was carefully added. After a further 30 min, the mixture was filtered and the solid (DCU) was washed with methanol (3 × 5 mL). *N,N′*-Diphenylethylenediamine (1.55 g, 7.3 mmol) and glacial acetic acid (0.8 mL) were added to the combined filtrates, and the solution was stored at 22 °C for 4 h before it was poured into aqueous sodium bicarbonate (200 mL). The aqueous mixture was extracted with chloroform (2 × 100 mL) that was then washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated to dryness. The residue was crystallized from ethanol, giving 2.44 g (2 crops, 64%) of **26** with mp 171–173 °C: $[\alpha]^{25}_D$ 47.2° (*c* 1, $CHCl_3$); λ_{max} (MeOH) 253 nm (ε 37 270); ^{1}H NMR ($CDCl_3$) δ 1.57 (br s, 3, C_5 CH_3), 1.90 (dd, 1, $J_{2'a,2'b}$ = 13 Hz, $J_{2'a,3'} \simeq$ 0 Hz, $J_{1',2'a}$ = 6.5 Hz, $C_{2'a}$ H), 2.23 (m, 1, $C_{2'b}$ H), 3.07 (m, 4, NCH_2CH_2N), 4.17 (m, 1, C_3' H), 4.37 (s, 2, OCH_2Ph), 4.48 (dd, 1, $J_{4',5'}$ = 1 Hz, $J_{3',4'}$ = 4 Hz, $C_{4'}$ H), 5.71 (br s, 1, $C_{5'}$ H), 6.27 (dd, 1, $J_{1',2'a} = J_{1',2'b}$ = 6/5 Hz, $C_{1'}$ H), 6.75 and 7.25 (m, 16, $C_{6'}$ H, Ph), 8.95 (br s, 1, NH).

Anal. Calcd for $C_{31}H_{32}N_4O_4$ (524.63): C, 70.97; H, 6.15; N, 10.68. Found: C, 70.71; H, 6.32; N, 10.63.

1-(3-*O*-Benzyl-2-deoxy-β-D-*erythro*-pentodialdo-1,4-furanosyl)thymine (27). A solution of *p*-toluenesulfonic acid hydrate (1.71 g, 9 mmol) in acetone (50 mL) was added to an ice-cooled solution of **26** (1.58 g, 3 mmol) in methylene chloride (100 mL). The mixture was stirred at 22 °C for 1 h, and the white precipitate was filtered off and washed with methylene chloride (50 mL). The combined filtrates were washed with saturated sodium bicarbonate (50 mL) and water (50 mL), dried ($MgSO_4$), and concentrated in vacuo, giving 1.0 g (99%) of **27** as a white foam. An analytical sample was dried for 16 h at 0.001 mmHg over P_2O_5: $[\alpha]^{25}_D$ 18.1° (*c* 1, $CHCl_3$); λ_{max} (MeOH) 265 nm (ε 9530); ^{1}H NMR ($CDCl_3$) δ 1.92 (br s, 3, C_5 CH_3), 6.18 (dd, 1, $J_{1',2'a} = J_{1',2'b}$ = 6.5 Hz, $C_{1'}$ H), 9.65 (s, 0.5, $C_{5'}$ H); the rest of the spectrum was difficult to analyze since the sample was about a 50:50 mixture of the aldehyde **27** and its hydrate.

Anal. Calcd for $C_{17}H_{18}N_2O_5 \cdot 0.5H_2O$ (339.34): C, 60.17; H, 5.64; N, 8.26. Found: C, 60.39; H, 5.42; N, 8.08.

3′-*O*-Benzyl-4′-(hydroxymethyl)thymidine (28a). Aqueous sodium hydroxide (4.6 mL of 2 N) was added to a stirred solution of **27** (1.1 g, 3.2 mmol) and 37% aqueous formaldehyde (1.8 mL) in *p*-dioxane (9 mL). The resulting solution was stored at 22 °C for 16 h and then percolated through a Dowex 50 (H^+) column (20 mL) that was then washed with 1:1 *p*-dioxane–water. The eluate was concentrated in vacuo, and the residue was crystallized from 50% aqueous ethanol, giving 0.79 g (2 crops, 66%) of **28a** with mp 186–187 °C: $[\alpha]^{25}_D$ 41.6° (*c* 0.5, MeOH); λ_{max} (MeOH) 266 nm (ε 10 100); ^{1}H NMR (Me_2SO-d_6) δ 1.77 (s, 3, C_5 CH_3), 2.35 (m, 2, $C_{2'}$ H_2), 3.59 (br s, 4, $C_{5'}$ H_2, $C_{4'}$ CH_2), 4.31 (dd, 1, $J_{2'a,3'}$ = 4.5 Hz, $J_{2'b,3'}$ = 6 Hz, $C_{3'}$ H), 4.51 and 4.64 (d, 1, J_{gem} = 12 Hz, OCH_2Ph), 6.19 (dd, 1, $J_{1',2'a} = J_{1',2'b}$ = 6.5 Hz, $C_{1'}$ H), 7.4 (m, 5, Ph), 7.79 (br s, 1, C_6 H).

Anal. Calcd for $C_{18}H_{22}N_2O_6$ (362.38): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.89; H, 6.09; N, 7.74.

4′-(Hydroxymethyl)thymidine (28b). A mixture of **28a** (362 mg, 1 mmol), 5% palladium on barium sulfate (150 mg), and methanol (40 mL) was stirred at 22 °C for 16 h in an atmosphere of hydrogen. Four further quantities (50 mg) of catalyst were then added at 1-day intervals while the hydrogenolysis was continuing. After 5 days, the catalyst was removed by filtration through a Celite bed and the filtrates were concentrated to dryness. The residue was purified by preparative TLC, giving 0.22 g (81%) of **28b** as an amorphous solid: $[\alpha]^{25}_D$ 26.3° (*c* 0.5, MeOH); λ_{max} (MeOH) 267 nm (ε 9250); ^{1}H NMR (Me_2SO-d_6) δ 1.76 (br s, 3, C_5 CH_3), 2.16 (br m, 2, $C_{2'}$ H_2), 3.50 (m, 4, $C_{5'}$ H_2, $C_{4'}$ CH_2), 4.33 (dd, 1, $J_{2'a,3'} = J_{2'b,3'}$ = 6 Hz, $C_{3'}$ H), 6.19 (dd, 1, $J_{1',2'a} = J_{1',2'b}$ = 6.5 Hz, $C_{1'}$ H), 7.73 (br s, 1, C_6 H), 11.15 (br s, 1, NH).

Anal. Calcd for $C_{11}H_{16}N_2O_6$ (272.26): C, 48.53; H, 5.92; N, 10.29. Found: C, 48.43; H, 6.23; N, 9.79.

Registry No.—**3,** 53166-52-2; **4,** 68707-83-5; **5,** 68738-44-3; **6a,** 28370-56-1; **6a** hydrate, 68707-84-6; **6b,** 68707-85-7; **6b** hydrate, 68707-86-8; **10a,** 63592-91-6; **10b,** 63592-92-7; **10c,** 63070-09-7; **11a,** 63640-31-3; **11b,** 63592-93-8; **11c,** 55797-69-8; **14a,** 34311-30-3; **14b,** 43077-06-1; **14c,** 68707-87-9; **14d,** 33985-40-9; **16a,** 63592-89-2; **16b,** 63592-90-5; **16c,** 68707-88-0; **16d,** 55797-67-6; **17,** 68707-89-1; **21b,** 63592-94-9; **21c,** 68707-90-4; **21d,** 68707-91-5; **22,** 39946-94-6; **23,** 68707-92-6; **24,** 68707-93-7; **25,** 63593-01-1; **26,** 63592-96-1; **27,** 63593-08-8; **28a,** 63861-64-3; **28b,** 63861-63-2; *N,N′*-diphenylethylenediamine, 150-61-8; N^4-benzoylcytidine, 13089-48-0; 2,2-dimethoxypropane, 77-76-9.

References and Notes

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Nucleic Acid Related Compounds. 30. Transformations of Adenosine to the First 2',3'-Aziridine-Fused Nucleosides, 9-(2,3-Epimino-2,3-dideoxy-β-D-ribofuranosyl)adenine and 9-(2,3-Epimino-2,3-dideoxy-β-D-lyxofuranosyl)adenine[1,2]

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Treatment of the diastereomeric epoxides derived from adenosine, 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (1) and 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (8), with azide gave the resulting 3'-azido diastereomers, 9-(3-azido-3-deoxy-β-D-arabinofuranosyl)adenine (2) and 9-(3-azido-3-deoxy-β-D-xylofuranosyl)adenine (9), in good yields plus minor quantities of the 2'-azido substitution products. Selective protection of the 5'-hydroxyl function, mesylation or tosylation of the 2'-hydroxyl group, and reduction of the resulting *trans*-3'-azido-2'-sulfonate ester with intramolecular displacement–cyclization provided the respective fused-ring aziridine products, 9-(2,3-epimino-2,3-dideoxy-β-D-ribofuranosyl)adenine (7) and 9-(2,3-epimino-2,3-dideoxy-β-D-lyxofuranosyl)adenine (12). Unusual ultraviolet circular dichroism and ^{1}H NMR spectral properties of these bicyclo[3.1.0] sugar–nucleoside systems are discussed.

The 2',3'-anhydro (oxirane) function has been known and utilized synthetically in nucleoside chemistry for a number of years.[5] However, no examples of nucleosides functionalized as the corresponding 2',3'-dideoxy-2',3'-epimino (aziridine) system have been reported, although such goals have been alluded to.[6,7h] Only very recently has a *p*-chlorobenzoyloxy-substituted nucleoside–aziridine been proposed as the reaction product of a postulated azirene intermediate in the uridine series.[6b]

The unambiguous synthesis of a number of pyranosyl and furanosyl fused aziridines have been reported in the carbohydrate field.[7] These compounds have been investigated as potential chemotherapeutic agents as well as useful synthetic intermediates. Amino–sugar chemistry has not been explored extensively or systematically in the nucleoside area, despite the number and variety of nucleoside antibiotics that have an amino–sugar moiety.[8] Prior studies in this area have concentrated primarily on total syntheses of the natural products per se and closely related analogues.[8a,9]

We have been interested in the investigation of general methods for the modification of intact nucleosides and nucleoside antibiotics[10] that are not dependent upon specific structural features such as participation of the base. We now wish to report the synthesis of the two diastereomeric 2',3'-dideoxy-2',3'-epimino compounds from adenosine and some unusual spectral effects of these bicyclo[3.1.0] fused aziridine–furanosyl nucleosides. These provide the first examples of the parent nucleoside–aziridine system (which are of intrinsic interest by analogy with natural products such as the antitumor antibiotic[11] mitomycin C, whose biological activity is thought to be related to reactions of the activated fused-aziridine moiety[12]) and also serve as useful synthetic intermediates for conversion to a variety of new mono-, di-, and triamino sugar nucleosides.

Treatment of 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine[9b,13] (1) with lithium azide in hot DMF[9c] gave 9-(3-azido-3-deoxy-β-D-arabinofuranosyl)adenine (2) (see Scheme I) in ~80% yield plus a minor amount (~8%) of the 2'-azido-

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