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4′-Substituted Nucleosides. 4. Synthesis of Some 4′-Hydroxymethyl Nucleosides[1]

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Two complementary routes have been developed for the synthesis of 4-(acetoxymethyl)-1,2,3,5-tetra-*O*-acetyl-D-*erythro*-pentofuranose (**9**). The first of these involves a mixed aldol condensation between 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose and formaldehyde which gives, as its major product, 4-(hydroxymethyl)-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (**5a**). Inversion of configuration at C_3 is achieved via an oxidation–reduction sequence, and subsequent acetolysis furnishes **9**. A more efficient route to **9** involves a mixed aldol condensation between 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdofuranose (**12a**) and formaldehyde followed by debenzylation, acetylation, and acetolysis. The condensation of **9** with a number of purine and pyrimidine bases and their analogues led to the preparation of a variety of 4′-hydroxymethyl nucleosides that have been screened for potential biological activities.

Recent work from this Laboratory has led to the development of methods for the synthesis of ribonucleosides substituted at the 4′ position by fluoro,[1,3] methoxyl,[4,5] and azido[5] groups. Most of these aspects have been reviewed.[6] Nucleosides such as those above bearing electronegative substituents at $C_{4'}$ are frequently rather labile, particularly when the hydroxyl functions are all unsubstituted.[1,3-6] Hence, it was of interest to undertake the synthesis of nucleosides bearing stable carbon–carbon linked substituents at the $C_{4'}$ position. Such syntheses could, in principle, be carried out via addition reactions to the vinyl ether function of 4′,5′-unsaturated nucleosides, this method being the one used successfully for the preparation of the 4′-fluoro, -methoxy, and -azido compounds. Preliminary attempts to introduce, e.g., a 4′-cyano function by this route were not, however, overly promising.

An alternate approach for the introduction of 4′ substituents is based upon the reactions of nucleoside 5′-aldehydes, a subject that has been of interest to us for some years.[7] This approach has been carried on in parallel with that reported in the present paper and is described separately.[8c] This latter work did, indeed, lead to the preparation of several 4′-hydroxymethyl nucleosides via crossed aldol condensations between suitably protected nucleoside 5′-aldehydes and formaldehyde.[8b,c] As an alternative to this introduction of a $C_{4'}$

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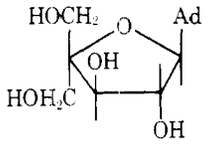
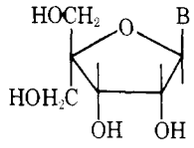
carbon linked substituent at the nucleoside level, it was of interest to develop a synthesis of an appropriate 4′-(hydroxymethyl)-D-ribofuranose derivative[9] that could subsequently be condensed with a variety of heterocyclic bases. In this paper we describe the synthesis of such an intermediate and its use in the preparation of a number of 4′-hydroxymethyl nucleosides. Preliminary accounts of this work have already appeared.[8a,10]

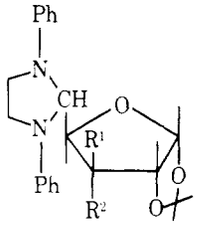
The essentials of the key step in the present work find their origin in an earlier study by Schaffer,[11] who showed that reaction of 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose (**4a**)[12] with formaldehyde and aqueous sodium hydroxide led to the isolation of 4-(hydroxymethyl)-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (**5a**). This product arose via an initial mixed aldol condensation followed by Cannizzaro reduction of the resulting hydroxy aldehyde. Following our own work reported in this paper, Leland and Kotick[13] have also briefly described this reaction and have converted **5a** into the corresponding pentaacetate, which has been condensed, via the glycosyl chloride, with N^6-benzoyladenine to form 9-[4-



1



2



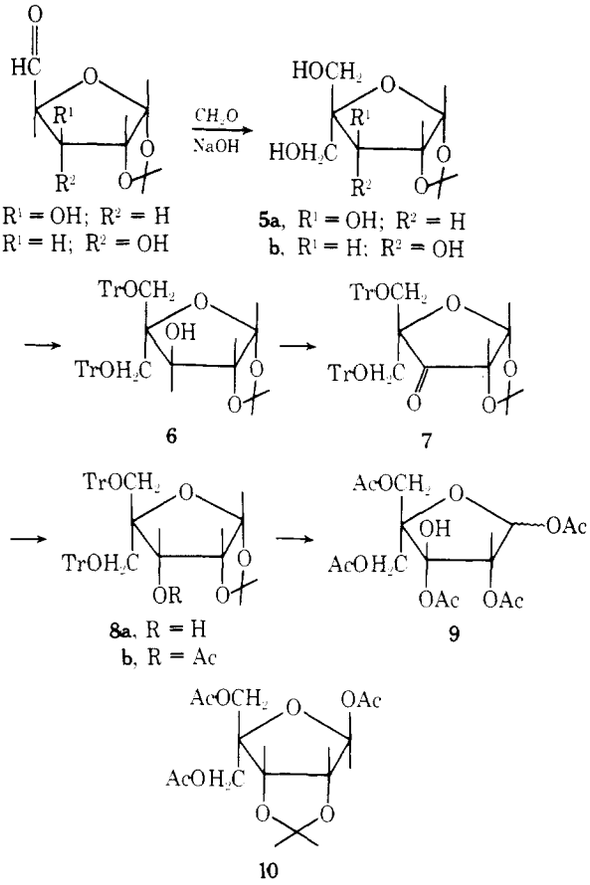
3a, $R^1 = OH$; $R^2 = H$
b, $R^1 = H$; $R^2 = OH$

(hydroxymethyl)-α-L-*threo*-pentofuranosyl]adenine (**1**).

In contrast with the work of Leland and Kotick,[13] our interest lay in the preparation of 4-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl nucleosides (**2**), which much more closely resemble the ribonucleosides in that they possess the normal cis (D-erythro) orientation of the 2′,3′-diol. Hence, our projected key intermediate was considered to be 4-(acetoxymethyl)-1,2,3,5-tetra-*O*-acetyl-D-*erythro*-pentofuranose (**9**), the synthesis of which has been approached in two different ways. In the first of these we undertook an inversion of the configuration at C_3 in the known β-L-threo compound **5a**.[11a] The synthetic route followed is outlined in Scheme I.

1,2-*O*-Isopropylidene-α-D-*xylo*-pentodialdofuranose (**4a**) was prepared by periodate oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose as described by Schaffer and Isbell.[12] As directly obtained, the crude aldehyde was found by TLC to give three spots, all giving a positive test with acidic 2,4-dinitrophenylhydrazine spray.[14] It is known that **4a** can be isolated as a crystalline dimer in roughly 70% yield. We have found that **4a** can also be readily isolated as its crystalline 1,3-diphenylimidazolidine derivative (**3a**) in an overall yield of 74% from 1,2-*O*-isopropylidene-α-D-glucofuranose by treatment of the crude oxidation product with *N,N′*-diphenylethylenediamine[15] in methanol containing acetic acid. We have previously found the 1,3-diphenylimidazolidine derivative to provide an expeditious method for the isolation and subsequent regeneration of aldehydes.[7c-e,16] For the present purposes it is not necessary to purify **4a** via **3a**, and direct treatment of crude **4a** with formaldehyde and sodium hydroxide led to the isolation of crystalline 4-(hydroxymethyl)-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (**5a**)

Scheme I



in 60% overall yield from 1,2-*O*-isopropylidene-α-D-glucofuranose. The melting point of **5a** that we observed was several degrees higher than has been previously reported.[11a,13] Chromatography of the mother liquors from this reaction also led to the isolation, in 12% yield, of a crystalline, isomeric triol which we have identified as 4-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (**5b**). This product has not previously been reported as arising from the reaction of **4a** with formaldehyde, but has been described as the *minor* product from a comparable reaction with 1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdofuranose (**4b**).[13]

In order to further investigate steric control of this reaction, we have also prepared **4b** by periodate oxidation of 1,2-*O*-isopropylidene-α-D-allofuranose.[17] The resulting crude aldehyde **4b** in this case showed only a single 2,4-dinitrophenylhydrazine positive spot upon TLC examination and was converted into the crystalline 1,3-diphenylimidazolidine derivative, **3b**, in an overall yield of 77%. A similar oxidation of 1,2-*O*-isopropylidene-α-D-allofuranose has been described using lead tetraacetate, but the resulting **4b** was not characterized other than by reduction to 1,2-*O*-isopropylidene-α-D-ribofuranose.[18] The reaction of crude **4b** with formaldehyde was conducted essentially as with **4a** and gave the identical products **5a** and **5b** in overall yields of 18 and 23%, respectively. The combined yields of purified **5a** and **5b** were not as high as those starting with **4a**, and some difficulty was experienced in separation of the isomers from some impurities. Hence, samples of both **5a** and **5b** were converted into their tri-*O*-toluoyl derivatives, which were obtained only as syrups that were not more readily separated by chromatography. Clearly, the reaction starting with **4b** offers no advantage over that with the more readily available **4a** since almost equal amounts of the erythro and threo isomers **5b** and **5a** were obtained. The mechanism of this isomerization has been addressed in our concurrent work on the reactions of nucleoside

Table I. 100 MHz ^{1}H NMR Chemical Shifts (ppm)

compd	sol-vent[a]	sugar protons[b] H-1	H-2	H-3	H-4	H-5a	H-5b	H-5′a	H-5′b	base protons C_5 H	C_6 H	C_2 H, C_8 H	other
3a	D	5.81 (d)	4.45 (d)	3.90 (d)	4.05 (dd)	5.67 (d)							1.20, 1.35 (s, 3, CMe_2), 3.5 (m, 4, NCH_2)
3b	D	5.59 (d)	4.37 (dd)	3.66 (dd)	4.25 (d)	5.52 (br s)							1.20, 1.23 (s, 3, CMe_2), 3.6 (m, 4, NCH_2)
5a	D	5.86 (d)	4.50 (dd)	4.11 (d)		3.39 (d)	3.54 (d)	3.47 (s)					1.25, 1.44 (s, 3, CMe_2)
5b	D	5.68 (d)	4.53 (dd)	4.22 (d)		3.30 (d)	3.53 (d)	3.55 (d)	3.72 (d)				1.25, 1.49 (s, 3, CMe_2)
tritoluoyl **5a**	D	6.12 (d)	4.93 (d)	5.65 (s)		4.51 (d)	4.68 (d)	4.66 (s)					1.30, 1.54 (s, 3, CMe_2), 2.34 (s, 9, ArMe)
tritoluoyl **5b**	D	5.96 (d)	5.05 (dd)	5.55 (d)		4.59 (s)		4.82 (s)					1.29, 1.54 (s, 3, CMe_2), 2.33 (s, 9, ArMe)
6	D	5.80 (d)	4.34 (d)	4.03 (d)		3.13 (d)	3.68 (d)	3.29 (d)	3.45 (d)				0.94, 1.11 (s, 3, CMe_2), ..38 (d, 1, OH)
7	D	6.26 (d)	4.77 (d)			2.99 (d)	3.42 (d)	3.14 (d)	3.16 (d)				1.13, 1.31 (s, 3, CMe_2)
8a	D	5.79 (d)	4.54 (dd)	4.36 (d)		3.00 (d)	3.56 (d)	3.09 (d)	3.51 (d)				1.00, 1.20 (s, 3, CMe_2), 4.92 (d, 1, OH)
9	D	6.07 (br s, β), 6.29 (d, α)	5.29 (d)	5.46 (d)		4.05–4.35 (m)							1.95–2.1 (m, 15, OAc)
10	D	5.99 (s)	4.87 (d)	4.78 (d)		4.07 (d)	4.24 (d)	4.11 (s)					1.29, 1.42 (s, 3, CMe_2), 2.01, 2.03 (s, total 9, OAc)
12a	D	5.83 (d)	4.79 (dd)	4.04 (dd)	4.30 (dd)	9.54 (d)							1.29 (s, 6, CMe_2), 4.36, 4.67 (d, 1, $ArCH_2$)
12b	D	5.68 (d)	4.73 (dd)	3.71 (dd)	4.38 (br d)	5.59 (br s)							1.24 (s, 6, CMe_2), 4.36, 4.62 (d, 1, $ArCH_2$)
13	D	5.68 (d)	4.70 (dd)	4.14 (d)		3.32 (d)	3.58 (d)	3.49 (d)	3.80 (d)				1.24, 1.48 (s, 3, CMe_2), 4.49, 4.67 (d, 1, $ArCH_2$)
14	D	5.81 (d)	4.81 (dd)	5.14 (d)		4.00 (d)	4.16 (d)	4.20 (d)	4.39 (d)				1.25, 1.47 (s, 3, CMe_2), 1.99, 2.00, 2.05 (s, 3, OAc)
15	D	6.45 (d)	6.16 (dd)	5.87 (dd)		4.23 (d)	4.27 (d)	4.42 (d)	4.44 (d)			8.85, 8.90	1.99, 2.02, 2.06, 2.10 (s, 3, OAc)
16	P	6.64 (d)	5.72 (dd)	5.17 (d)		4.37 (d)	4.52 (d)	4.41 (s)				8.56 (s, 2)	8.27 (br s, 2, NH_2)
17	P	6.77 (d)	5.61 (dd)	5.18 (d)			4.2–4.6 (m, 4)					8.63, 8.92	4.08 (s, 3, OMe)
18a	D	6.29 (d)	6.02 (dd)	5.78 (d)		4.21 (d)	4.41 (d)	4.26 (d)	4.41 (d)			8.21, 8.48	2.01 (s, 6, OAc), 2.04, 2.10 (s, 3, OAc)
18b	D	5.94 (d)	4.70 (dd)	4.26 (d)			3.5–3.8 (m, 4)					8.21, 8.54	
19	D	6.04 (d)	4.87 (dd)	4.27 (d)			3.5–3.8 (m, 4)					8.70, 8.75	2.67 (s, 3, SMe), 5.21, 5.96 (d, 1, OH), 4.62, 5.10 (t, 1, OH)
20a	C	6.10 (dd)	5.58 (dd)	5.46 (d)		4.21 (d)	4.47 (d)	4.25 (d)	4.42 (d)		7.55 (d)		2.09 (s, 6, OAc), 2.14, 2.18 (s, 3, OAc)
20b	D	5.82 (dd)	4.15 (dd)	4.04 (d)			3.3–3.7 (m, 4)				8.03 (d)		
21a	C	7.17 (d)	5.16 (d)	5.62 (d)			4.1–4.6 (m, 4)			7.68 (s)			2.05, 2.07 (s, 3, OAc), 2.10 (s, 6, OAc)
21b	P	7.86 (d)	4.93 (dd)	5.06 (d)			4.19 (s)[c]		4.49 (s)[c]	7.65 (s)			
22	D	5.81 (d)	4.55 (dd)	4.24 (d)			3.50 (s)[c]		3.58 (s)[c]	8.85 (s)			7.58, 7.78 (br s, 1, $CONH_2$)

[a] Solvents are designated as D (Me_2SO-d_6), P (pyridine-d_5), and C ($CDCl_3$). [b] Unless otherwise indicated, carbinol protons are reported after addition of D_2O. [c] While these signals appeared as clean singlets, it is not unlikely that they are in fact doublets with very tiny outer lines that cannot be resolved from the baseline.

5′-aldehydes with formaldehyde.[8b,c] From these studies it has been suggested that epimerization at C_3 is a consequence of a base-catalyzed reverse aldol cleavage of the C_3–C_4 bond of either the starting hydroxy aldehyde (**4**) or the initial mixed aldol product followed by subsequent aldol cyclization.[8b] Details of these studies are considered separately.[8c,19]

In view of the ease with which the above epimerizations occur, it was of some importance to verify the configurations at C_3 in **5a** and **5b.** Some reasonable confirmation of the assigned structures was available from an examination of the 100-MHz ^{1}H NMR spectra. Thus, typical of the spectra of many 1,2-*O*-isopropylideneglycofuranoses,[20] the values of $J_{1,2}$ for **5a** and **5b** are very similar (3.5–4 Hz). However, the erythro isomer (**5b**), having an all-cis arrangement of the hydrogens on C_1, C_2, and C_3, shows a value of $J_{2,3}$ = 5.5 Hz while the threo isomer, **5a,** shows a typically small $J_{2,3}$ of 1.5 Hz. Further confirmation comes from a consideration of the ^{13}C NMR spectra of **5a** and **5b,** which were readily interpretable by heteronuclear decoupling. As might be expected, the only striking differences in chemical shifts were observed for the C_2 and C_3 signals, which in **5b** appeared 7.90 and 5.25 ppm upfield of those in **5a.** This is entirely to be expected in view of the well-known upfield shift that accompanies a cis orientation of vicinal substituents on five-membered rings.[21]

The ^{1}H NMR spectra of **5a** and **5b** are also rather interesting when one considers the signals due to the two hydroxymethyl groups in Me_2SO-d_6 after addition of D_2O to eliminate H,OH coupling. Thus, in the erythro isomer **5b,** all four protons are magnetically nonequivalent and appear as four well-resolved doublets showing geminal couplings of 11 and 12 Hz. In the threo isomer **5a,** however, the protons of one of the hydroxymethyl groups are nonequivalent and appear as doublets (J = 11 Hz) at 3.39 and 3.54 ppm while the other hydroxymethyl protons appear to be equivalent and appear as a singlet at 3.47 ppm. At this point we are unable to make specific assignments for these four protons and hence cannot tell which group appears to be the magnetically nonequivalent one. From a consideration of molecular models it is certainly not easy to see why **5a** and **5b** should behave so differently. The system is, however, quite sensitive to structural changes since the di-*O*-toluoyl derivative of **5b** shows both hydroxymethyl groups as two-proton singlets. The spectrum of the di-*O*-toluoyl derivative of **5a,** on the other hand, is similar in form to that of **5a,** showing two doublets and one singlet (see Tables I and II).

Since the extent of epimerization of C_3 accompanying the aldol condensation of the ribo aldehyde, **4b,** was considerably greater than that with **4a** and the overall yield was at the same time lower, it seemed advantageous to pursue the more readily available xylo series. Selective protection of the two primary hydroxyl groups in **5a** was achieved in almost quantitative yield via formation of the di-*O*-trityl ether (**6**) which was then oxidized by treatment with dimethyl sulfoxide and acetic anhydride.[22] The latter method is convenient with a highly water-insoluble compound such as **6** and, by a very simple workup, gave crystalline 1,2-*O*-isopropylidene-5-*O*-trityl-4-(trityloxymethyl)-D-*glycero*-pentofuranos-3-ulose (**7**) in 64% yield. As would be expected from the well-known directive influence of the 1,2-*O*-isopropylidene function on the reduction of other 3-ketofuranoses,[23] treatment of **7** with sodium borohydride led to the isolation of the crystalline D-*erythro*-pentofuranose (**8a**) in 72% yield. This compound was dis-

Table II. Coupling Constants (hertz) for Compounds in Table I

compd	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{5a,5b}$	$J_{5'a,5'b}$	other
3a	4	0	2.5			$J_{4,5} = 8.5$
3b	3.5	4	9			$J_{4,5} \sim 1$
5a	4	1.5		11	0	
5b	3.5	5.5		12	11	
tritoluoyl **5a**	4	0		12	0	
tritoluoyl **5b**	3.5	5.5		0	0	
6	4	<0.5		8	11	$J_{3,OH} = 5$
7	4			9	10	
8a	3.5	5		8.5	10	$J_{3,OH} = 5$
9	<1 (β), 4 (α)	5		*a*	*a*	
10	0	5		11	0	
12a	3.5	4	9			$J_{4,5} = 2$
12b	3.5	4	8.5			$J_{4,5} \sim 1$
13	4	5		12	11	$J_{gem}(ArCH_2) = 12.5$, $J_{H,OH} = 3, 4, 4, 5$
14	3.5	5.5		12	11	
15	5	6		12	12	
16	7	5		11	0	
17	6.5	5.5		*a*	*a*	
18a	5.5	6		12	12	
18b	6.5	5.5		*a*	*a*	
19	6.5	5		*a*	*a*	
20a	5.5	5.5		12	12	$J_{1',F} = 1.5$, $J_{6,F} = 6$
20b	6	6		*a*	*a*	$J_{1',F} = 1.5$, $J_{6,F} = 7.5$
21a	3.5	6.5		*a*	*a*	
21b	2.5	5.5		0[b]	0[b]	
22	5.5	5.5		0[b]	0[b]	

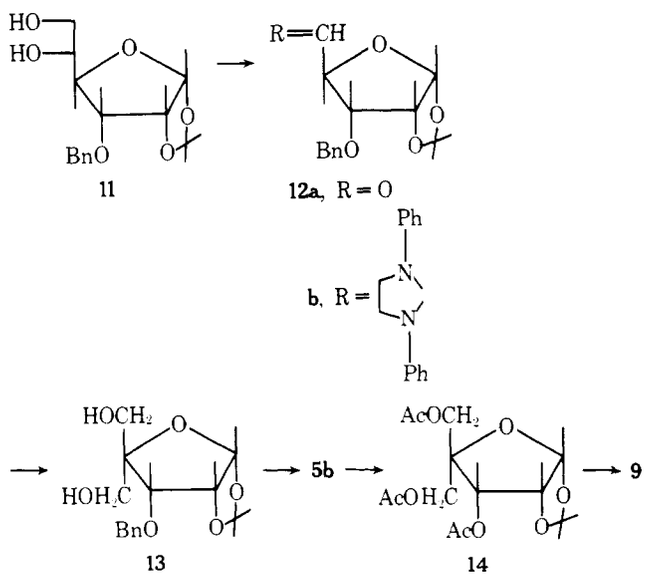
[a] Unresolved. [b] See Table I, footnote *c*.

tinctly less polar than **6**, and its configuration was confirmed by the typical value of $J_{2,3} = 5$ Hz (cf. $J_{2,3} = <0.5$ Hz) as previously discussed. Acetolysis of both the trityl and isopropylidene functions was accomplished by treatment with acetic anhydride and acetic acid containing sulfuric acid. This reaction, however, led to several byproducts, and the desired pentaacetate (**9**) was isolated as a syrupy 7:3 mixture of β and α anomers (β $J_{1,2} < 1$ Hz, α $J_{1,2} = 4$ Hz) in only 37% yield by chromatography on silicic acid. The major byproduct was isolated in 33% yield and proved, by NMR analysis, to be the 2,3-*O*-isopropylidene triacetate (**10**) as the pure β anomer ($J_{1,2} = 0$ Hz). Since this product arises by acetal migration during the acetolysis, its formation could perhaps be avoided by conducting this reaction starting with the crystalline 3-*O*-acetyl derivative (**8b**). This possibility has not been explored in view of our success with an alternate synthetic path.

In view of the known occurrence of partial epimerization at C_2 during acetolysis of certain 2,3-cis oriented sugars,[24] it is important to confirm that the key intermediate **9** has, indeed, the desired erythro configuration. While the major β isomer could clearly be seen to have the expected value of $J_{2,3} = 5$ Hz typical of an acylated ribofuranose derivative,[25] unfortunately the signals for the minor α anomer were superimposed upon those of the major component and a value of $J_{2,3}$ could not be assigned. Convincing proof of the desired erythro configuration was achieved by the identity of the 4'-(hydroxymethyl)adenosine (**16**) prepared by condensation of **9** with adenine as described later to that prepared by condensation of N^6-benzoyl-2',3'-*O*-isopropylideneadenosine-5'-aldehyde with formaldehyde.[8c] The latter reaction could not be expected to lead to epimerization at $C_{2'}$ and hence must have the desired erythro configuration.

The realization that the epimerization at C_3 which accompanies the condensation of **4** with formaldehyde is initiated by a reverse aldol cleavage[8,19] suggests that this problem could be avoided if the 3-hydroxyl group in **4b** is blocked. Accordingly, an alternative approach (Scheme II) for the synthesis of **9** was pursued. Thus, the readily available 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose (**11**)[26] was oxidized with sodium periodate to give an essentially quantitative yield of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdofuranose (**12a**), which gave a single spot upon TLC analysis. For characterization, an aliquot of **12a** was converted into its crystalline 1,3-diphenylimidazolidine derivative **12b** in an overall yield of 82% from **11**. It is interesting to note that, unlike the other compounds in this paper, the isopropylidene protons of **12a** and **12b** appeared as six-proton singlets rather than as the usual well-separated three-proton singlets. Crude **12a** was then condensed with formaldehyde and aqueous sodium hydroxide essentially as described for **4a,b** to give, after preparative TLC, crystalline 3-*O*-benzyl-4-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (**13**), which was isolated in 67% yield from **11**. Repetition of the above reaction on a 0.2-mol scale was advantageously carried out in aqueous tetrahydrofuran. Following chroma-

Scheme II

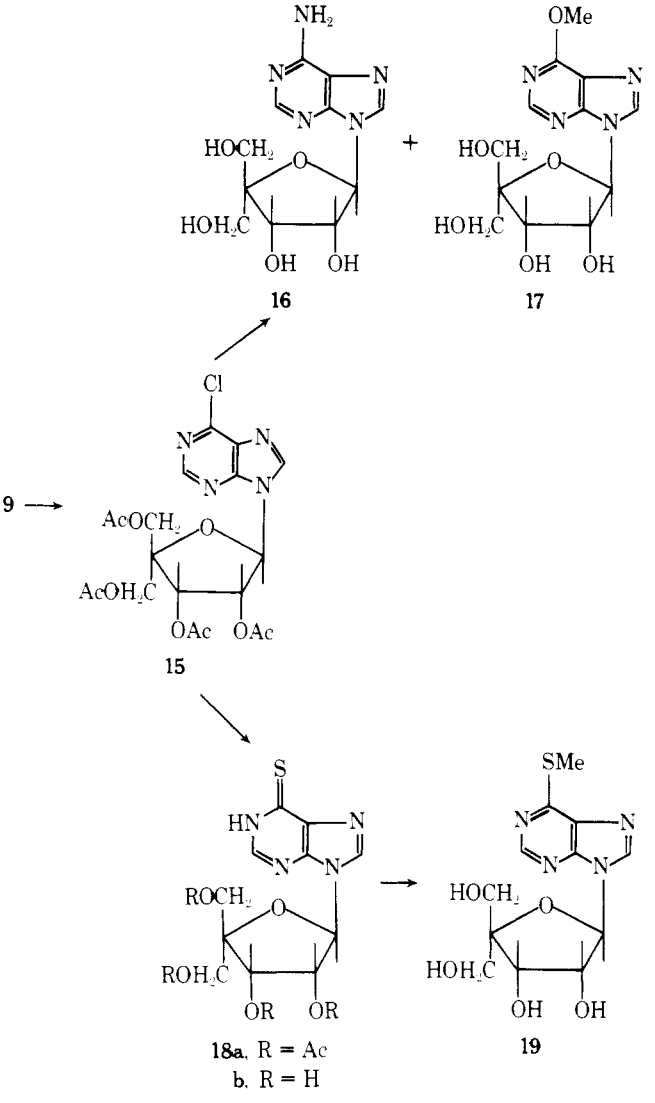


tography of the product on a column of silicic acid, pure **13**, identical with that above by NMR and TLC analysis, was obtained in 77% yield. Catalytic hydrogenolysis of the benzyl ether was readily accomplished and gave crystalline **5b**, identical with that obtained via Scheme I, in 84% yield. In the absence of a free 3-hydroxyl group there was, as expected, no indication of epimerization at that center.

In order to both avoid isopropylidene migration (as was found with **8a**) and ensure the furanose structure, **5b** was acetylated, giving the triacetate **14** as a TLC and NMR homogeneous syrup in 92% yield. Subsequent acetolysis of the isopropylidene group then gave an 87% yield of **9** that was identical with that obtained via Scheme I. In our hands, the overall yield of **9** from 1,3:5,6-di-*O*-isopropylidene-α-D-glucofuranose via Scheme II and using conventional literature procedures for the steps leading to **11** was 31%. By contrast, the use of Scheme I led to **9** in an overall yield of only 10% from 1,2-*O*-isopropylidene-α-D-glucofuranose. The latter process could be somewhat simplified if the mixed isomers **5a** and **5b** were tritylated and oxidized together, but still Scheme II provides a much more efficacious procedure. It should be noted that a synthesis of **9** has recently been described via a totally different reaction sequence.[27] Condensation of the glycosyl bromide derived from **9** with an appropriate adenine derivative was reported to give both the α and β anomers of **16** in modest yields. Some discussion of the physical characteristics of these compounds can be found in our companion paper.[8c]

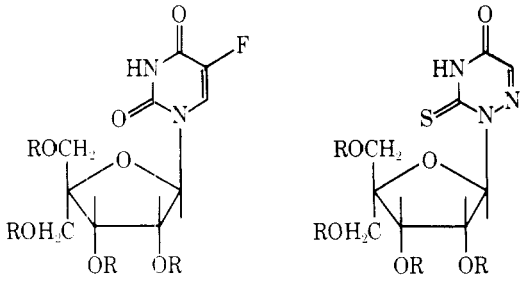
The availability of a ready source of **9** led us to investigate its condensation with a variety of purine and pyrimidine bases and their analogues in order to prepare 4′-hydroxymethyl nucleosides. To this end, the condensation of **9** with 6-chloropurine proceeded readily in acetonitrile in the presence of stannic chloride and mercuric cyanide, giving crystalline 9-[4-(acetoxymethyl)-2,3,5-tri-*O*-acetyl-β-D-*erythro*-pentofuranosyl]-6-chloropurine (**15**) in 84% yield. The position of glycosidation and the anomeric configuration were confirmed by a comparison of the ultraviolet spectrum of **15** with those of 7- and 9-methyl-6-chloropurine[28] and by its conversion to the adenosine derivative **16** (see below). While stannic chloride catalyzed condensations of acetylated sugars with silylated pyrimidines[29] and purines[30] are well known, we have found the combination of stannic chloride and mercuric cyanide with free purines to frequently provide excellent results.[31]

The 6-chloro function in **15** provides convenient access to a variety of other 6-substituted analogues via conventional routes. Thus, reaction of **15** with liquid ammonia at room temperature for 18 h gave 4′-(hydroxymethyl)adenosine (**16**) in a yield of 76%. As mentioned above, this crystalline substance was identical with that prepared starting with N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine-5′-aldehyde.[8c] If, on the other hand, **15** was treated with saturated methanolic ammonia at room temperature for 18 h, a mixture of **16** and the corresponding 6-methoxypurine analogue, **17**, was formed. These compounds were readily separated by preparative TLC, and the latter was isolated in 33% yield. The identity of **17** was confirmed by comparison of its UV spectrum with that of 6-methoxy-9-β-D-ribofuranosylpurine[32] and by the presence of a three-proton singlet (OMe) at 4.08 ppm in its NMR spectrum. The reaction of **15** with thiourea in hot 1-propanol readily gave the crystalline 6-thione derivative, **18a**, in 84% yield, and deacetylation with methanolic ammonia converted this into 4-(hydroxymethyl)-6-thioinosine (**18b**) in high yield. The UV spectra of **18a** and **18b** were in agreement with that of 6-thioinosine itself.[33] Treatment of **18b** with methyl iodide in methanolic sodium hydroxide led to the expected formation of 9-[4-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]-6-methylthiopurine (**19**) in 84% yield. Once again, **19** was characterized by the similarity of its UV spectrum to that of the



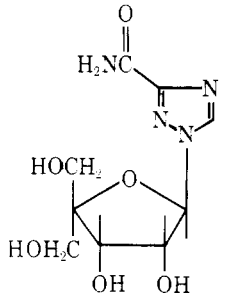
related riboside[33] and by the presence of a three-proton singlet at 2.67 ppm in its NMR spectrum.

The pentaacetate **9** was also condensed with several monocyclic nitrogen heterocycles related to nucleosides of known biological activity. Thus, **9** was condensed with bis(trimethylsilyl)-5-fluorouracil[34] in the presence of stannic chloride according to the general method of Niedballa and Vorbrüggen.[29] Following removal of a trace of unreacted 5-fluorouracil by preparative TLC, 4′-(acetoxymethyl)-2′,3′,5′-tri-*O*-acetyl-5-fluorouridine (**20a**) was obtained in 84% yield. Subsequent deprotection with methanolic ammonia gave crystalline 4′-(hydroxymethyl)-5-fluorouridine (**20b**) in 62% yield. The anomeric configuration of **20b** was confirmed by its ORD spectrum, which showed a positive Cotton effect typical of pyrimidine β-nucleosides,[35] and the site of glycosidation was confirmed by its UV spectrum and by the typical homoallylic fluorine coupling ($J_{1',F}$ = 1.5 Hz) exhibited by the anomeric proton in the NMR spectrum.[36] Similarly, the stannic chloride catalyzed condensation of **9** with the bis(trimethylsilyl) derivative of 6-aza-2-thiouracil[37] gave the blocked nucleoside **21a** as a low melting solid in 80% yield. Crystalline 2-[4-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]-*as*-triazin-5(4*H*)-one-3(2*H*)-thione (**21b**) was then obtained by deacetylation using methanolic ammonia. The closely related 2-thio-6-azauridine has been reported to possess antiviral and antipsoriatic activities.[38] The site of glycosidation in **21** was expected to be N^2 by analogy with condensations involving 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride.[37] This was supported by the UV spectrum of **21b** and by the strongly deshielded position of the anomeric proton



20a, R = Ac
b, R = H

21a, R = Ac
b, R = H



22

(7.86 ppm in pyridine-d_5) typical of 2-thiopyrimidine-N^1-ribosides.[39] While the anomeric configuration of **21** is expected to be β by consideration of the "trans rule", confirmation of this point by use of ORD spectra is not as simple as in other cases. It is known that 6-azapyrimidine nucleosides exhibit anomalous ORD spectra, 6-azauridine giving a negative Cotton effect rather than the positive one usually shown by pyrimidine β-nucleosides.[35] The ORD spectrum of **21b**, however, is very similar to that shown by a sample of 2-thio-6-azauridine kindly supplied by Dr. H. Vorbrüggen of Schering A. G., Berlin, and strongly suggests that both compounds have the identical β configuration.

Finally, **9** was condensed with 3-(methoxycarbonyl)-1,2,4-triazole[40] in the presence of stannic chloride and mercuric cyanide, and the resulting crude nucleoside was directly treated with methanolic ammonia in order to effect deacetylation and conversion of the methoxycarbonyl group to an amide. The resulting 1-[4-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]-1,2,4-triazole-3-carboxamide (**22**), the 4′-hydroxymethyl derivative of the antiviral agent Ribavirin,[40] was isolated by chromatography in an overall yield of 50%. The absence of any UV maximum above 210 nm precludes the use of this technique to confirm the site of ribosidation. It is, however, well established that condensation of the triazole methyl ester with a variety of sugars leads predominantly to the desired 1-glycosyl-1,2,4-triazole-3-carboxylic acid derivatives.[40] This orientation is confirmed by the NMR spectrum of **22**, which shows the triazole ring proton as a singlet at 8.85 ppm. It has been shown that this proton in a variety of 1-glycosyl-1,2,4-triazole-3-carboxamides appears at 8.7–8.9 ppm while that in the isomeric 1-glycosyl-1,2,4-triazole-5-carboxamides appears at 8.15 ppm. No precedent appears to exist for the formation of N^4-glycosyl derivatives in this series.

Clearly, the quite readily available pentaacetate **9** provides a versatile starting material for synthesis of a wide range of 4′-hydroxymethyl nucleosides. It is interesting to note, however, that **15–22** have been examined in a number of biological test systems and found to be essentially inactive. These tests, conducted through the cooperation of the Shionogi Research Laboratories, Osaka, Japan, showed the above compounds to possess no significant in vitro antibacterial or antifungal activity, no antiviral (vaccinia and influenza A_o/WSN) activity or cytotoxicity in tissue culture systems, and no in vivo antineoplastic activity against L-1210 leukemia or Ehrlich ascites carcinoma in mice. The only exception to the above was a very slight cytotoxicity of **22** (ED_{50} = 38 μg/mL) against HeLa cells and a marginal activity of the same compound against *Streptococcus pyogenes* (MIC. 50 μg/mL). Thus, the introduction of the 4′-hydroxymethyl function leads to a dramatic reduction in the biological activities of a variety of nucleoside antimetabolites. At this point we have no information concerning the transport properties of these compounds or their metabolic fate. It would, however, appear that enzymatic cleavage of the *N*-glycosidic bonds does not occur since certain of the heterocyclic bases themselves (e.g., 5-fluorouracil from **20b**) would be expected to elicit observable biological responses.

It should be noted that very recently Secrist and Winter[41] have described the synthesis of several $C_{4'}$-alkylated derivatives of uridine using the corresponding enamine as the intermediate. In a separate paper we will consider the synthesis of certain other 4′-hydroxymethyl nucleosides starting from the parent nucleoside 5′-aldehydes. Such studies have cast considerable light on the mechanism of these reactions and have enabled some further synthetic transformations of intermediates in the mixed aldol condensations.[8b,c]

Experimental Section

General Methods. The general experimental techniques used were essentially those described previously.[1]

1,2-*O*-Isopropylidene-α-D-*xylo*-pentodialdofuranose (4a) and Its 1,3-Diphenylimidazolidine Derivative (3a). 1,2-*O*-Isopropylidene-α-D-glucofuranose (3.0 g, 13.6 mmol) was added over 30 min to a stirred solution of sodium periodate (3.0 g, 14 mmol) in water (25 mL) at 0 °C. After a further 30 min, ethylene glycol (0.4 mL) was added and the solution was lyophilized. The residue was extracted three times with ethyl acetate (50 mL), and the dried extracts were evaporated to leave crude **4a** and its dimers (3.0 g),[12] which upon TLC (chloroform–methanol, 9:1) showed three spots, all positive to acidic 2,4-dinitrophenylhydrazine spray.[14]

A solution of this product (300 mg, 1.38 mmol) and *N,N′*-diphenylethylenediamine (340 mg, 1.60 mmol) in methanol (5 mL) containing acetic acid (0.3 mL) was heated at 60 °C for 10 min. After a further 20 min at room temperature, the solution was evaporated to dryness and the residue was extracted with methylene chloride. The dried ($MgSO_4$) extracts were evaporated and the residue was crystallized from ether–pentane, giving 384 mg (74% from 1,2-*O*-isopropylidene-α-D-glucofuranose) of **3a** with mp 156–157 °C.

Anal. Calcd for $C_{22}H_{26}N_2O_4$ (382.45): C, 69.09; H, 6.85; N, 7.33. Found: C, 68.92; H, 6.57; N, 7.36.

1,2-*O*-Isopropylidene-α-D-*ribo*-pentodialdofuranose (4b) and Its 1,3-Diphenylimidazolidine Derivative (3b). 1,2-*O*-Isopropylidene-α-D-allofuranose (3.0 g, 13.6 mmol)[17] was oxidized with sodium periodate as described above for the preparation of **4a**. The resulting crude **4b** (2.84 g) showed a single 2,4-dinitrophenylhydrazine positive spot upon TLC using chloroform–methanol (9:1).

A portion (300 mg) of crude **4b** was reacted with *N,N′*-diphenylethylenediamine as described above, giving 426 mg (77% overall) of **3b** with mp 140–141 °C when recrystallized from ether–pentane.

Anal. Calcd for $C_{22}H_{26}N_2O_4$ (382.45): C, 69.09; H, 6.85; N, 7.33. Found: C, 68.87; H, 6.84; N, 7.25.

4-(Hydroxymethyl)-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (5a) and 4-(Hydroxymethyl)-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (5b). (a) From Crude 4a. Aqueous sodium hydroxide (27 mL of 1.0 N) was added at 0 °C to a stirred solution of crude **4a** (2.7 g) in a mixture of water (20 mL) and 37% aqueous formaldehyde (2.7 mL), and the mixture was then stirred overnight at room temperature. The mixture was neutralized with formic acid and evaporated to dryness, leaving a residue that was extracted three times with ethyl acetate (50 mL). The dried ($MgSO_4$) extracts were evaporated, and the residue (2.53 g) was crystallized from chloroform–ether, giving 180 mg (7% from 1,2-*O*-isopropylidene-α-D-glucofuranose) of **5a** with mp 103–104 °C (reported mp 97–99[11a] and 98–100 °C[13]): ^{13}C NMR (acetone-d_6) 105.78 (C_1), 89.50 (C_2), 78.09 (C_3), 90.86 (C_4), 63.85 and 63.29 (C_5 and $C_{5'}$), 27.40, 26.75 and 112.81 (Ip) ppm.

The mother liquors were chromatographed on a column of silica gel G (800 g) using benzene–acetone (1:1) to give some 1,2-*O*-isopropylidene-α-D-xylofuranose followed by two isomeric products. The less polar of these gave 1.44 g (total yield 60%) of **5a**, identical with

that above, and was followed by 310 mg (12%) of **5b** with mp 113–114 °C when recrystallized from chloroform–ether (reported[13] mp 114–115 °C): $[\alpha]^{23}_D$ 17.2° (*c* 0.32, EtOH); ^{13}C NMR (acetone-d_6) 105.43 (C_1), 81.60 (C_2), 72.85 (C_3), 88.65 (C_4), 64.85 and 63.52 (C_5 and $C_{5'}$), 26.98, 26.49, and 113.46 (Ip) ppm.

Anal. Calcd for $C_9H_{16}O_6$ (220.22): C, 49.08; H, 7.32. Found: C, 49.16; H, 7.70.

(b) From Crude 4b. Crude **4b** (1.46 g) was reacted with 37% formaldehyde (1.4 mL) and sodium hydroxide (14 mL of 1.0 N)[42] in water (14 mL) as in a. The ethyl acetate extracts were directly chromatographed on a column of silica gel G (260 g) using chloroform–methanol (9:1) to give 273 mg (18% from 1,2-*O*-isopropylidene-α-D-allofuranose) of **5a** with mp 103–104 °C and 348 mg (23%) of **5b** with mp 113–114 °C, both compounds being identical with those from a by NMR analysis.

(c) From 13. A solution of **13** (1.81 g, 5.84 mmol) in ethanol (100 mL) was stirred under 3 atm of hydrogen in the presence of 10% palladium on charcoal catalyst (600 mg) for 48 h. The catalyst was removed by filtration, and the filtrates were evaporated and crystallized from chloroform–ether, giving 1.09 g (84%) of **5b** that was identical with that above. Repetition on a 17-g scale gave an identical product in 82% yield.

1,2-*O*-Isopropylidene-3,5-di-*O*-*p*-toluoyl-4-(*p*-toluoyloxymethyl)-α-D-*erythro*-pentofuranose. A solution of **5b** (22 mg, 0.1 mmol) and *p*-toluoyl chloride (77 mg, 0.5 mmol) in pyridine (0.3 mL) was stored overnight at room temperature. After addition of methanol, the mixture was evaporated and a chloroform solution of the residue was washed with water, dried, and evaporated. An analytical sample of the resulting residue (38 mg) was prepared by preparative TLC using hexane–ether (4:1) to give the tri-*O*-*p*-toluoyl derivative of **5b** as a clear syrup.

Anal. Calcd for $C_{33}H_{34}O_9$ (574.60): C, 68.97; H, 5.96. Found: C, 68.76; H, 6.35.

Similar treatment of **5a** gave the tri-*O*-*p*-toluoyl derivative as a syrup. Toluoylation of a crude mixture of **5a** and **5b** gave a mixture of the above esters, but their chromatographic separation was not easier than that of the parent triols.

1,2-*O*-Isopropylidene-5-*O*-trityl-4-(trityloxymethyl)-β-L-*threo*-pentofuranose (6). A solution of **5a** (2.0 g, 9.1 mmol) and trityl chloride (5.2 g, 18.7 mmol) in pyridine (20 mL) was stored for 18 h at room temperature and then evaporated to dryness. A solution of the residue in dichloromethane was washed with water, dried ($MgSO_4$), and evaporated, leaving a crystalline residue of essentially pure **6** (6.12 g, 95%). An analytical sample recrystallized from ether had mp 220–222 °C.

Anal. Calcd for $C_{47}H_{44}O_6$ (704.82): C, 80.09; H, 6.29. Found: C, 80.30; H, 6.14.

1,2-*O*-Isopropylidene-5-*O*-trityl-4-(trityloxymethyl)-D-*glycero*-pentofuranos-3-ulose (7). A solution of **6** (1.5 g, 2.13 mmol) in a mixture of dimethyl sulfoxide (10 mL) and acetic anhydride (2 mL) was stored overnight at room temperature and then poured into water. The resulting mixture was extracted with ether, and the extracts were washed with water, dried, and evaporated. Crystallization of the residue from aqueous ethanol gave 960 mg (64%) of **7** with mp 96–98 °C.

Anal. Calcd for $C_{47}H_{42}O_6$ (702.81): C, 80.32; H, 6.02. Found: C, 80.52; H, 6.23.

1,2-*O*-Isopropylidene-5-*O*-trityl-4-(trityloxymethyl)-α-D-*erythro*-pentofuranose (8a) and Its 3-*O*-Acetyl Derivative (8b). Sodium borohydride (580 mg, 10 mmol) was added to a solution of **7** (800 mg, 1.14 mmol) in 80% ethanol (15 mL), and after 5 min at room temperature the mixture was evaporated to dryness. The residue was extracted with dichloromethane, and the extracts were washed with water, dried ($MgSO_4$), and evaporated. Crystallization of the residue from methanol gave 580 mg (72%) of homogeneous **8a** with mp 152–157 °C. An analytical sample recrystallized from ether–hexane had mp 155–157 °C.

Anal. Calcd for $C_{47}H_{44}O_6$ (704.82): C, 80.09; H, 6.29. Found: C, 80.35; H, 6.49.

Acetylation of **8a** (200 mg, 0.28 mmol) with acetic anhydride (0.4 mL) in pyridine (2 mL) followed by the usual workup gave the 3-*O*-acetyl derivative (**8b**) with mp 178–180 °C.

Anal. Calcd for $C_{49}H_{46}O_7$ (746.86): C, 78.33; H, 6.20. Found: C, 79.34; H, 6.17.

4-(Acetoxymethyl)-1,2,3,5-tetra-*O*-acetyl-D-*erythro*-pentofuranose (9). (a) From 8a. Concentrated sulfuric acid (2 drops) was added to a solution of **8a** (1.41 g, 2 mmol) in a mixture of acetic acid (5 mL) and acetic anhydride (3 mL). After storage overnight at room temperature, the mixture was added to water and extracted with ethyl acetate. The dried ($MgSO_4$) extracts were evaporated, leaving a residue (1.68 g) that was separated into two major carbohydrate components by preparative TLC using ether–hexane (7:3). Elution of the less polar band gave 233 mg (33%) of the 2,3-*O*-isopropylidene derivative **10** that was identified by NMR but not further studied. The more polar band gave 290 mg (37%) of **9** as a clear syrup after careful drying in vacuo for 3 days. By NMR **9** was 70% β and 30% α. Repetition of this reaction on a 16-g scale gave similar results.

Anal. Calcd for $C_{16}H_{22}O_{11}$ (390.34): C, 49.23; H, 5.68. Found: C, 49.11; H, 5.71.

(b) From 14. Concentrated sulfuric acid (0.5 mL) was added to a solution of **14** (17.3 g, 50 mmol) in a mixture of acetic acid (100 mL) and acetic anhydride (30 mL). After 16 h at room temperature, the mixture was added to water and extracted with dichloromethane. The extracts were washed with aqueous sodium bicarbonate and water, dried ($MgSO_4$), and evaporated, leaving 17 g (87%) of **9** that was identical with the product from a by TLC and NMR and was used directly in subsequent steps.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdofuranose (12a) and Its 1,3-Diphenylimidazolidine Derivative (12b). An aqueous solution of **11** (1.85 g, 6 mmol)[26] was slowly added with stirring to a solution of sodium periodate (1.5 g, 7 mmol) in water (5 mL) at 0 °C. After a further 30 min, ethylene glycol (0.2 mL) was added and the mixture was extracted three times with ethyl acetate. The dried extracts were evaporated, leaving 1.66 g (quantitative) of **12a** as a syrup that showed essentially a single spot by TLC using ether. A pure sample for NMR analysis was obtained by preparative TLC of a portion of this material. A separate portion of crude **12a** (230 mg, 0.8 mmol) was reacted with *N,N'*-diphenylethylenediamine (180 mg, 0.85 mmol) in methanol (5 mL) containing acetic acid (0.2 mL) at 60 °C for 5 min. On cooling, the crystalline imidazolidine derivative (**12b**; 320 mg, 82% from **11**) separated and showed mp 144–145 °C after recrystallization from methanol, $[\alpha]^{23}_D$ 10.6° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{29}H_{32}N_2O_4$ (472.56): C, 73.70; H, 6.83; N, 5.93. Found: C, 73.40; H, 6.92; N, 5.81.

On a larger scale, the reaction of 74 g (0.24 mol) of **11** with sodium periodate (55 g, 0.26 mol) essentially as above gave 58 g (87%) of essentially TLC homogeneous **12a** that was used directly in the next step.

3-*O*-Benzyl-4-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (13). (a) Aqueous 37% formaldehyde (2 mL) and then 1 N sodium hydroxide (10 mL) were added at 0 °C to a stirred solution of crude **12a** (1.0 g, ~3.5 mmol) in water (9 mL). The mixture was then stored at room temperature for 4 days and evaporated to dryness. The residue was extracted with dichloromethane, and the dried extracts were purified by preparative TLC using ether. Elution of the major UV-absorbing band followed by crystallization from ethyl acetate–methanol and then from ether–pentane gave 747 mg (67%) of **13** with mp 101–102 °C, $[\alpha]^{25}_D$ 82.9° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{22}O_6$ (310.34): C, 61.92; H, 7.15. Found: C, 61.87; H, 7.18.

(b) On a large scale, **12a** (55 g, 0.2 mol), 37% formaldehyde (75 mL), and 1 N sodium hydroxide (300 mL) were reacted for 16 h at room temperature in a mixture of water (200 mL) and tetrahydrofuran (200 mL). The crude product obtained as above was chromatographed on a column of silicic acid (1 kg) using benzene–ether (4:1) to give 47.2 g (77%) of **13** as a syrup that was identical with the crystalline product by TLC and NMR and was used directly in the next step.

4-(Acetoxymethyl)-3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (14). A solution of **5b** (11.0 g, 50 mmol) and acetic anhydride (18 mL) in pyridine (100 mL) was stored at room temperature for 16 h and then poured into ice water. The mixture was extracted with dichloromethane, and the extracts were washed three times with water, dried, and evaporated, leaving 15.2 g (92%) of **14** as a TLC homogeneous (ether) syrup after careful drying under high vacuum. Thus obtained, **14** was pure by NMR analysis and was used directly in the next step.

9-[4-(Acetoxymethyl)-2,3,5-tri-*O*-acetyl-β-D-*erythro*-pentofuranosyl]-6-chloropurine (15). Stannic chloride (2.8 mL, 23.9 mmol) was added to a solution of **9** (5.0 g, 12.8 mmol) and 6-chloropurine (1.98 g, 12.8 mmol) in acetonitrile (300 mL) containing 6.5 g (25.7 mmol) of mercuric cyanide. The mixture was stirred at 55 °C for 2 h and then added to saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, and the extracts washed with 30% aqueous potassium iodide and water, dried, and evaporated. Crystallization of the residue from ether gave 5.22 g (84%) of **15** with mp 166–167 °C: $[\alpha]^{25}_D$ −13.6° (*c* 1.0, $CHCl_3$); λ_{max} (EtOH) 250 nm sh (ε 6500), 264 (8400).

Anal. Calcd for $C_{19}H_{21}ClN_4O_9$ (484.85): C, 47.06; H, 4.37; N, 11.55. Found: C, 47.09; H, 4.55; N, 11.48.

4'-(Hydroxymethyl)adenosine (16). A solution of **15** (122 mg, 0.25

mmol) in liquid ammonia (5 mL) was stored in a steel bomb at room temperature for 18 h and then evaporated to dryness. The residue was purified by preparative TLC (chloroform–methanol, 7:3), giving 57 mg (76%) of pure **16**. By crystallization from methanol–chloroform an analytical sample with mp 218–219 °C was obtained: λ_{max} (0.1 N NaOH) 260 nm (ϵ 11 000).

Anal. Calcd for $C_{11}H_{15}N_5O_5$ (297.27): C, 44.44; H, 5.09; N, 23.56. Found: C, 44.49; H, 5.01; N, 23.62.

Crystallization from water gave needles of a hemihydrate that underwent a phase change at 132–135 °C but did not distinctly melt below 230 °C: λ_{max} (0.01 N HCl) 256 nm (ϵ 14 400).

Anal. Calcd for $C_{11}H_{15}N_5O_5 \cdot 0.5\ H_2O$ (306.28): C, 43.13; H, 5.92; N, 22.87. Found: C, 42.77; H, 5.91; N, 22.60.

9-[4-(Hydroxymethyl)-β-D-*erythro*-pentofuranosyl]-6-methoxypurine (17). A solution of **15** (1.0 g, 2.07 mmol) in saturated methanolic ammonia (10 mL) was stored at room temperature for 18 h and then evaporated to dryness. The residue was separated into two major products by preparative TLC using chloroform–methanol (4:1). Elution of the less polar product gave 215 mg (33%) of **17** which had mp 179–180 °C after crystallization from methanol–chloroform: $[\alpha]^{25}_D$ −55.0° (*c* 1.0, pyridine); λ_{max} (H_2O) 250 nm (ϵ 10 000); λ_{max} (0.1 N NaOH) 250 nm (ϵ 10 300).

Anal. Calcd for $C_{12}H_{16}N_4O_6$ (312.28); C, 46.15; H, 5.16; N, 17.94. Found: C, 45.91; H, 5.08; N, 18.33.

Elution of the more polar band gave 310 mg (48%) of slightly impure **16**. Chromatography on silica gel G using chloroform–methanol (7:3) followed by crystallization from methanol–tetrahydrofuran gave pure **16** with mp 218–219 °C and in all ways identical with that above.

4′-(Acetoxymethyl)-2′,3′,5′-tri-*O*-acetyl-6-thioinosine (18a). A solution of **15** (2.30 g, 4.7 mmol) and thiourea (400 mg, 5.5 mmol) in 1-propanol (100 mL) was heated under reflux for 3 h and then concentrated to ~25 mL, giving 1.92 g (84%) of crystalline **18a**. An analytical sample recrystallized from methanol had mp 232–233 °C: λ_{max} (0.1 N NaOH) 311 nm (ϵ 22 000), 232 (14 400).

Anal. Calcd for $C_{19}H_{22}N_4O_9S$ (482.47): C, 47.35; H, 4.56; N, 11.62. Found: C, 47.18; H, 4.49; N, 11.71.

4′-(Hydroxymethyl)-6-thioinosine (18b). A solution of **18a** (1.0 g, 2.08 mmol) in saturated methanolic ammonia (20 mL) was stored at room temperature for 4 h and then evaporated to dryness. The residue was washed with ether, leaving 590 mg (91%) of TLC homogeneous **18b**. Crystallization from methanol gave mp 222–224 °C: $[\alpha]^{25}_D$ −66.9° (*c* 1.0, pyridine); λ_{max} (0.1 N NaOH) 232 nm (ϵ 14 100), 310 (23 300).

Anal. Calcd for $C_{11}H_{14}N_4O_5S$ (314.32): C, 42.03; H, 4.49; N, 17.84. Found: C, 41.87; H, 4.63; N, 17.75.

9-[4-(Hydroxymethyl)-β-D-*erythro*-pentofuranosyl]-6-methylthiopurine (19). A solution of **18b** (0.50 g, 1.6 mmol) and methyl iodide (0.3 mL, 4.8 mmol) in a mixture of methanol (3 mL) and 0.3 N sodium hydroxide (10 mL) was stirred at 40 °C for 2 h. It was then neutralized with acetic acid and evaporated to dryness, leaving a residue that was extracted into ethyl acetate. The extracts were washed with a small volume of cold water, dried, and evaporated, leaving a TLC homogeneous (chloroform–methanol, 9:1) residue (0.44 g, 84%) that was crystallized from methanol–ether with mp 132–134 °C: $[\alpha]^{25}_D$ −55.3° (*c* 1.0, pyridine); λ_{max} (0.1 N NaOH) 223 nm (ϵ 11 700), 287 (18 600), 292 (18 700).

Anal. Calcd for $C_{12}H_{16}N_4O_5S$ (328.35): C, 43.89; H, 4.88; N, 17.06. Found: C, 43.72; H, 5.19; N, 16.40.

4′-(Acetoxymethyl)-2′,3′,5′-tri-*O*-acetyl-5-fluorouridine (20a). A solution of **9** (1.30 g, 3.3 mmol), bis(*O*-trimethylsilyl)-5-fluorouracil (1.22 g, 4.45 mmol),[34] and stannic chloride (1.3 g, 5 mmol) in 1,2-dichloroethane (100 mL) was heated at 60 °C for 1 h and then stored overnight at room temperature. The mixture was then neutralized by addition of cold, saturated aqueous sodium bicarbonate, and some solid material was removed by filtration. The organic phase was washed with water, dried ($MgSO_4$), and evaporated, leaving a residue that was contaminated with a trace of 5-fluorouracil. Purification by preparative TLC (chloroform–methanol, 19:1) gave 1.3 g (84%) of pure **20a** with mp 68–71 °C from 1,2-dichloroethane–ether: λ_{max} (MeOH) 263 nm (ϵ 8800).

Anal. Calcd for $C_{18}H_{21}FN_2O_{11}$ (460.37): C, 46.96; H, 4.60; N, 6.08. Found: C, 46.70; H, 4.58; N, 5.88.

4′-(Hydroxymethyl)-5-fluorouridine (20b). A solution of **20a** (1.0 g, 2.2 mmol) in saturated methanolic ammonia (15 mL) was maintained at room temperature for 3 h and then evaporated to dryness. The residue was washed with ether and then crystallized from methanol–chloroform to give 0.46 g (62%) of **20b** with mp 197–199 °C: $[\alpha]^{25}_D$ −31.9° (*c* 1.0, pyridine); λ_{max} (0.1 N HCl) 269 nm (ϵ 10 000); ORD (MeOH) $[\Phi]_{293}^{pk}$ 4800°, $[\Phi]_{281}$ 0°, $[\Phi]_{265}^{tr}$ −10 000°, $[\Phi]_{240}$ 0°.

Anal. Calcd for $C_{10}H_{13}FN_2O_7$ (292.22): C, 41.10; H, 4.48; N, 9.58. Found: C, 40.97; H, 4.58; N, 9.44.

2-[4-(Acetoxymethyl)-2,3,5-tri-*O*-acetyl-β-D-*erythro*-pentofuranosyl]-*as*-triazin-5(4*H*)-one-3(2*H*)-thione (21a). Stannic chloride (1.0 g, 3.9 mmol) was added to a solution of 5-(trimethylsilyloxy)-3-(trimethylsilylthio)-*as*-triazine (1.12 g, 4 mmol)[37] and **9** (1.45 g, 3.7 mmol) in acetonitrile. The solution was heated at 55 °C for 1 h and then stored overnight at room temperature before being neutralized with ice-cold, saturated, aqueous sodium bicarbonate. The mixture was evaporated to dryness, the residue was partitioned between dichloromethane and water, and the organic phase was washed with water, dried, and evaporated, leaving 1.53 g of an oil. Crystallization from dichloromethane–ether at a low temperature gave 1.36 g (80%) of **21a** as a low melting solid that was carefully dried in vacuo: λ_{max} (MeOH) 217 nm (ϵ 12 900), 272 (16 600).

Anal. Calcd for $C_{17}H_{21}N_3O_{10}S$ (459.43): C, 44.44; H, 4.61; N, 9.15. Found: C, 44.17; H, 4.69; N, 8.66.

2-[4-(Hydroxymethyl)-β-D-*erythro*-pentofuranosyl]-*as*-triazin-5(4*H*)-one-3(2*H*)-thione (21b). A solution of **21a** (800 mg, 1.74 mmol) in saturated methanolic ammonia was stored at room temperature for 2 h and then evaporated to dryness. The residue was chromatographed on a column of silica gel G (80 g) using chloroform–methanol (7:3) to give 220 mg (43%) of **21b** with mp 173–175 °C after crystallization from ethanol–tetrahydrofuran: $[\alpha]^{23}_D$ −152.6° (*c* 1.0, pyridine); λ_{max} (0.1 N HCl) 218 nm (ϵ 14 300), 270 (16 600); ORD (MeOH) $[\Phi]_{285}^{tr}$ −6900°, $[\Phi]_{266}$ 0°, $[\Phi]^{pk}$ 21 600°. Compare with ORD (0.01 N HCl) of 2-thio-6-azauridine: $[\Phi]_{285}^{tr}$ −7800°, $[\Phi]_{260}$ 0°, $[\Phi]^{pk}$ 15 500°.

Anal. Calcd for $C_9H_{13}N_3O_6S$ (291.28): C, 37.11; H, 4.50; N, 14.43. Found: C, 36.90; H, 4.52; N, 14.32.

1-[4-(Hydroxymethyl)-β-D-*erythro*-pentofuranosyl]-1,2,-4-triazole-3-carboxamide (22). A mixture of **9** (1.95 g, 5 mmol), 3-(methoxycarbonyl)-1,2,4-triazole (560 mg, 5 mmol), mercuric cyanide (2.52 g, 10 mmol), and stannic chloride (2.60 g, 10 mmol) in acetonitrile (100 mL) was stirred at 50 °C for 2 h. The mixture was neutralized by the addition of saturated aqueous sodium bicarbonate, and the organic phase was evaporated, dissolved in ethyl acetate, washed with 30% potassium iodide and water, dried, and evaporated. The residue was dissolved in saturated methanolic ammonia and stored at room temperature for 18 h. Evaporation of the solvent left a residue that was triturated with ether and then precipitated with ether from methanol, giving 685 mg (50%) of **22** as a hygroscopic powder: $[\alpha]^{23}_D$ −36.2° (*c* 1.0, pyridine); no UV max above 210 nm.

Anal. Calcd for $C_9H_{14}N_4O_6$ (274.23): C, 39.42; H, 5.15; N, 20.43. Found: C, 39.24; H, 5.20; N, 20.21.

Registry No.—**3a,** 68069-45-4; **3b,** 63846-99-1; **4a,** 53167-11-6; **4b,** 63846-98-0; **5a,** 55797-64-3; tritoluoyl **5a,** 68024-01-1; **5b,** 55797-65-4; tritoluoyl **5b,** 68024-02-2; **6,** 68024-03-3; **7,** 68024-04-4; **8a,** 68024-05-5; **8b,** 68024-10-2; **9** β isomer, 63640-32-4; **9** α isomer, 68024-11-3; **10,** 68024-06-6; **11,** 57099-04-4; **12a,** 63593,02-2; **12b,** 63592-95-0; **13,** 63593-03-3; **14,** 63070-04-2; **15,** 63593-04-4; **16,** 63070-09-7; **17,** 68024-07-7; **18a,** 68024-08-8; **18b,** 63592-97-2; **19,** 63592-98-3; **20a,** 68024-09-9; **20b,** 63592-99-4; **21a,** 63593-06-6; **21b,** 63619-00-1; **22,** 63593-00-0; 1,2-*O*-isopropylidene-α-D-glucofuranose, 18549-40-1; 1,2-*O*-isopropylidene-α-D-allofuranose, 4495-04-9; trityl chloride, 76-83-5; *N,N′*-diphenylethylenediamine, 150-61-8; 6-chloropurine, 87-42-3; bis(*O*-trimethylsilyl)-5-fluorouracil, 17242-85-2; 5-(trimethylsilyloxy)-3-(trimethylsilylthio)-*as*-triazine, 33088-44-7; 3-(methoxycarbonyl)-1,2,4-triazole, 4928-88-5.

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companion paper, this issue.
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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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