4'-Substituted Nucleosides. 3. Synthesis of Some 4'-Fluorouridine Derivatives[1]

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The reaction of 1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**1**) with iodine fluoride in methylene chloride leads to the stereospecific formation of 5'-deoxy-4'-fluoro-5'-iodo-2',3'-*O*-isopropylideneuridine (**4a**) in almost quantitative yield. The 5'-iodo function of **4a** can be converted into the analogous 5'-azido derivative (**5a**) by vigorous treatment with lithium azide in dimethylformamide. Treatment of **5a** with nitrosyl tetrafluoroborate leads to the isolation of 2,5'-anhydro-4'-fluoro-2',3'-*O*-isopropylideneuridine (**6a**) which can be readily hydrolyzed to 4'-fluoro-2',3'-*O*-isopropylideneuridine (**7a**). The latter compound has been converted into 4'-fluoro-5'-*O*-sulfamoyluridine (**8b**), the uracil analogue of nucleocidin, by treatment with sulfamoyl chloride followed by mild acidic hydrolysis. The synthesis of 4'-fluorouridine 5'-phosphate (**8d**] has also been achieved via conversion of **7a** to its bis(2,2,2-trichloroethyl)phosphate ester followed by careful removal of protecting groups. The unusual stabilities of 4'-fluorouridine derivatives are discussed. In addition, it has been shown that treatment of 2',3'-methoxymethylene- and 2',3'-methoxyethylideneuridine derivatives with nitrosyl tetrafluoroborate leads to the formation of 2,2'-anhydro-1-β-D-arabinofuranosyluracils, presumably via 2',3'-acyloxonium ions.

Recent work from this laboratory has explored methods for the introduction of substituents at $C_{4'}$ of the furanose ring in both purine and pyrimidine nucleosides.[3] While other types of substituents have subsequently been introduced via different routes,[4] addition reactions to 4',5'-unsaturated nucleosides have proved to provide a facile route to 4'-fluoro[1] and 4'-methoxynucleosides.[5] Thus the reactions of various 2',3' derivatives of 1-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil with iodine in methanol have been shown to lead to 5'-iodo-4'-methoxynucleosides with both the β-D-ribo and α-L-lyxo configurations.[5] The nature of the substituents on the 2'- and 3'-hydroxyl groups exerted striking steric control upon the addition reaction, the isopropylidene derivative leading to the β-D-ribo and α-L-lyxo derivatives in a ratio of 3:2 while the 2',3'-carbonate gave only the former. In a related study it was shown that the addition of iodine fluoride (from iodine and silver fluoride) to a suitably protected 4',5'-unsaturated adenosine derivative led to the formation of the epimeric 4'-fluoro-5'-iodonucleosides. The β-D-ribo isomer from the above reaction constituted the key intermediate in the total synthesis of the nucleoside antibiotic nucleocidin.[1,6] In the present paper we extend the above work to a study of the preparation of 4'-fluorouridine derivatives including the uracil analogue of nucleocidin.

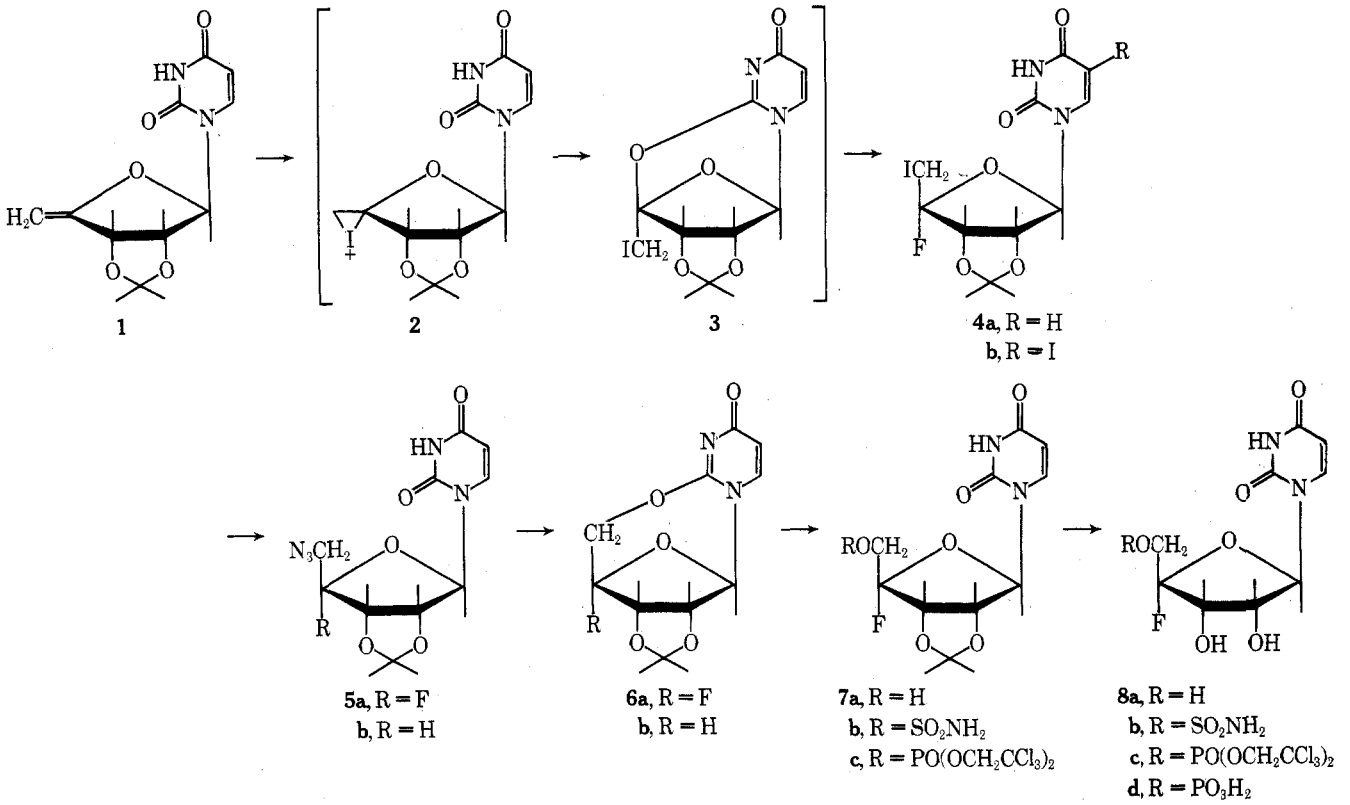
Our previous experience with the reactions of 4',5'-unsaturated uridine derivatives with iodine and methanol suggested that the use of a 2',3'-cyclic carbonate protecting group would probably be necessary in order to stereospecifically direct the addition of iodine fluoride so as to give the desired 4'-fluoro-β-D-ribofuranosyl configuration. As a prelude to this, however, we decided to examine the addition of iodine fluoride to 1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**1**).[7] Accordingly, a solution of iodine was gradually added to a solution of pure **1** in methylene chloride in the presence of an excess of finely divided silver fluoride. A rapid reaction ensued and was terminated once an iodine color persisted and the formation of a single new spot with an R_f just greater than that of **1** was shown by TLC.

By a simple workup this substance was isolated in quantitative yield and ^1H NMR analysis clearly showed that only a single isomer was present. This spectrum also strongly indicated that the product was only the desired 5'-deoxy-4'-fluoro-5'-iodo-2',3'-*O*-isopropylideneuridine (**4a**) since our previous work in the adenosine series had allowed the development of several empirical rules distinguishing between 4'-fluoronucleosides in the β-D-ribofuranosyl and α-L-lyxofuranosyl series.[1] Thus the values of $J_{3',F}$ and $J_{1',F}$ were found to be 11.5 and 0 Hz, respectively, while the α-L-lyxofuranosyl epimer of **4a** would be expected to show values of roughly 5–6 and 2–2.5 Hz, respectively. In addition, the chemical shift difference between the isopropylidene methyl signals of **4a** was found to be 32 Hz, a figure similar to those observed for the 4'-fluoro-β-D-ribofuranosyl series (24–30 Hz) but quite unlike the α-L-lyxofuranosyl counterparts (16–19 Hz).[1] It is to be emphasized, however, that the chemical shift difference for isopropylidene groups is strongly solvent dependent, $\Delta\delta$ for **4a** being 32, 24, 21, and 16 Hz in deuterated benzene–acetone (3:1), pyridine, chloroform, and acetone, respectively. The rule appears to be reliable in chloroform and pyridine, but caution must be used in extrapolations to other solvents. The surprising stereoselectivity of this addition reaction suggests the participation of the uracil ring in its mechanism. Thus, opening of the presumed initial iodonium ion (**2**), or its oxonium counterpart, by the C_2 carbonyl of the uracil ring would form the O^2,4'-cyclonucleoside (**3**) which could be opened by fluoride ion to give exclusively the β-D-ribo compound **4a**. The 5'-bromo analogue of **3** has recently been isolated by Sasaki et al.[8] and opened with methanol, although the latter reaction appears to involve a subsequent epimerization.[5] The absence of comparable steric control during reaction of **1** with iodine in methanol[5] suggests that when methanol is the reaction solvent it can favorably compete with the uracil ring for direct attack at $C_{4'}$ of **2**.

It should be noted that if larger excesses of iodine (e.g., 8 equiv) and longer reaction times (e.g., 2 h) are used, a less polar by-product is also formed. This material has been separated in slightly impure form in 10–20% yields and on the basis of its uv, NMR, and mass spectra has been identified as the 5-iodouracil analogue **4b**. Formation of this substance has not been detected using the reaction conditions described in the Experimental Section.

As might be expected for a fluoro acetal, **4a** was quite labile toward both acid and base treatment. Thus, treatment of **4a** with 90% formic acid at room temperature for 1–2 h or with 1 M sodium hydroxide at 80° for 16 h led to uracil as the principal product. Further comments on the stabilities of 4'-fluoronucleosides have been noted[1] and others will appear later in this paper.

Previously, **1** has been prepared by treatment of the 5'-*O*-*p*-toluenesulfonyl[7a] or 5'-iodo[7b] derivatives of 2'3'-*O*-isopropylideneuridine in *tert*-butyl alcohol or dimethyl sulfoxide. While the yields of **1** are quite high, our experience has shown that the removal of several by-products requires careful chromatography and is hence awkward on a large scale. The



reaction of the readily available 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine[9] with potassium *tert*-butoxide in dioxane, however, leads to the rapid formation of **1** contaminated only with a little (5–10%) unreacted iodo compound. The latter creates no problem in the subsequent addition of iodine fluoride to crude **1** since it is quantitatively converted into O^2,5′-anhydro-2′,3′-*O*-isopropylideneuridine (**6b**)[9,10] which is removed during aqueous extraction. Using this approach it was possible to prepare essentially pure **1** (contaminated with only a trace of **6b**) in an overall yield of 91% from the iodonucleoside.

As was the case in the 4′-fluoro-5′-iodoadenosine series,[1] the iodo function of **4a** proved to be very resistant to nucleophilic displacement. Displacement by azide ion was possible under forcing conditions, but monitoring of this reaction has proved to be very difficult since we have been unable to find a TLC solvent system that separates **4a** from the resulting 5′-azido-4′-fluoronucleoside **5a.** It was, however, possible to follow the course of the reaction by NMR spectroscopy of worked-up aliquots since the chemical shifts of the $C_{5'}$ protons in **4a** and **5a** were found to be different (doublets at 3.47 and 3.54 ppm, respectively, in $CDCl_3$). By this technique a rough half-time of 1.5 h in dimethylformamide at 105 °C was observed. This is to be contrasted with a half-time of approximately 30 min for the conversion of 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine to its 5′-azido analogue with lithium azide in dimethylformamide at 21 °C. This indicates that the introduction of the 4′-fluoro substituent leads to about a 1000-fold decrease in the ease of displacement of the 5′-iodide. Based upon these guidelines the preparative conversion of **4a** to **5a** was conducted in dimethylformamide at 105 °C for 17 h. The reaction mixture rapidly became very dark colored, even under nitrogen, but most of the decomposition products appear to be water soluble and crystalline **5a** could be easily isolated in yields of 38–48%. All attempts to increase the yield of crystalline product have been unsuccessful. The ^1H (see Tables I and II) and ^{19}F NMR spectra of **5a** exhibit the same general characteristics shown by **4a** and further support the β-D-ribo configuration for these substances. It may be noted that the overall sequence from 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine to crystalline **5a** can be carried out in an overall yield of 37% without purification of any intermediates.

In the adenosine series the conversion of a 5′-azido-4′-fluoronucleoside analogous to **5a** to the desired 4′-fluoro-5′-hydroxyl counterpart was achieved via photolysis to the 5′-aldehyde followed by borohydride reduction.[1] An alternative route, based upon the work of Doyle and Wierenga,[11] involving reaction of the 5′-azido compound with nitrosyl tetrafluoroborate, led only to a complex mixture. It was our feeling, however, that this failure was predominantly due to side reactions with the adenine ring and, hence, it was of interest to see if the uracil counterpart would behave differently. As a model, 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**5b**) was reacted with 2 equiv of nitrosyl tetrafluoroborate in acetonitrile at 0 °C leading to a transient green color and gas evolution. Direct crystallization of the crude, extracted product gave not the expected 2′,3′-*O*-isopropylideneuridine, but rather O^2,5′-anhydro-2′,3′-*O*-isopropylideneuridine (**6b**)[9,10] in 75% yield. The suggested mechanism for this reaction[11] involves nitrosation of the azide and loss of nitrous oxide and nitrogen leading to a 5′-carbonium species. The latter must clearly undergo preferential intramolecular reaction with the C_2 oxygen of the uracil ring giving the cyclonucleoside **6b** rather than the 5′-alcohol. Since O^2,5′-cyclonucleosides such as **6b** are known to be readily hydrolyzed by both acid and base,[10] this approach seemed well suited to our purposes. Accordingly, **5a** was similarly treated with nitrosyl tetrafluoroborate and, while the reaction was somewhat slower than that with **5b,** it proceeded readily at room temperature giving amorphous O^2,5′-anhydro-4′-fluoro-2′,3′-*O*-isopropylideneuridine (**6a**) in 67% yield. The latter substance was pure by TLC and NMR analysis, and its unique uv spectrum (λ_{max} 237 nm) left no doubt as to its cyclonucleoside structure. While **6a** could be obtained in crystalline form, we prefer, because of its lability, to use the amorphous product directly in the next step.

The ^1H NMR spectrum of **6a** is quite unusual since the $C_{5'}$ protons appear as a sharp doublet (J_{gem} = 11.5 Hz), neither showing any coupling to the 4′-fluorine. Coupling of $C_{3'}$ H to

Table I. 100-MHz Proton Chemical Shifts (ppm)

Compd	Solvent[d]	$C_{1'}$ H	$C_{2'}$ H	$C_{3'}$ H	$C_{4'}$ H	$C_{5'}$ H_a	$C_{5'}$ H_b	C_5 H	C_6 H	Other
4a	B–A 3:1	5.51 (s)	4.85 (d)	5.08 (dd)		3.38 (d)		5.29 (d)	6.67 (d)	1.21 and 1.53 (s, 3, CMe_2)
4b	C	5.67 (s)	5.1 (m)	5.1 (m)		3.48 (ABX)			7.66 (s)	1.36 and 1.57 (s, 3, CMe_2)
5a	B–A 3:1	5.57 (br s)	4.85 (d)	5.08 (dd)		3.33 (d)		5.33 (d)	6.73 (d)	1.22 and 1.53 (s, 3, CMe_2)
6a	P	6.18 (s)	4.91 (d)[b]	5.02 (dd)[b]		4.41 (d)	4.72 (d)	6.10 (d)	7.90 (d)	1.30 and 1.47 (s, 3, CMe_2)
6b	P	5.94 (s)	5.02 (d)	4.94 (d)	4.76 (m)	4.24 (dd)	4.51 (dd)	6.10 (d)	7.83 (d)	1.31 and 1.48 (s, 3, CMe_2)
7a	D	6.15 (br s)	5.01 (d)	4.99 (dd)		3.44 (dd)	3.56 (dd)	5.61 (d)	7.66 (d)	1.29 and 1.46 (s, 3, CMe_2)
7b	P	6.38 (d)	5.30 (dd)	5.57 (dd)		4.82 (ABX)[a]	4.85 (ABX)[a]	5.77 (d)	7.69 (d)	1.37 and 1.63 (s, 3, CMe_2)
7c	C	5.69 (d)	5.07 (dd)	5.23 (dd)		4.9 (m)		5.74 (d)	7.22 (d)	1.37 and 1.58 (s, 3, CMe_2), 4.69 (d, 4, $POCH_2$)
8b	P	6.82 (d)	4.91 (dd)	5.15 (dd)		4.99 (d)		5.75 (d)	7.79 (d)	
8c	P	6.62 (d)	4.92 (dd)	5.20 (dd)		4.9 (m)		5.80 (d)	7.74 (d)	5.03 (d, 4, $POCH_2$)
9a	C	5.69 (s)	5.0 (m)	5.0 (m)		3.0 (m)		5.72 (d)	7.23 (d)	1.37 and 1.58 (s, 3, CMe_2)
9b	P	6.25 (br s)	5.29 (dd)	5.54 (dd)		3.91 (ddd)	4.17 (ddd)	5.75 (d)	7.62 (d)	1.33 and 1.63 (s, 3, CMe_2), 2.07 (s, 3, NAc)
11	C	5.81 (d)	5.25 (dd)	4.98 (dd)		3.5 (ABX)		5.74 (d)	7.19 (d)	3.41 (s, 3, OMe), 5.95 (d, 1, HCOMe), 9.5 (br s, NH)
13b	D	6.45 (d)	5.37 (dd)	4.47 (dd)		3.60 (dd)[c]	3.82 (dd)	5.90 (d)	7.92 (d)	
16a	D	6.28 (d)	5.17 (d)	4.35 (d)	4.06 (dt)	3.25 (m)		5.81 (d)	7.82 (d)	
16c	P	6.69 (d)	5.71 (d)	5.84 (d)	4.65 (dt)	3.81 (dd)	3.98 (dd)	6.11 (d)	7.82 (d)	1.98 (s, 3, OAc)

[a] Via computer analysis of the ABX pattern by Dr. M. L. Maddox. [b] After addition of D_2O. In pyridine-d_5 alone, $C_{2'}$ H and $C_{3'}$ H are not resolved. [c] Partially obscured by HDO. [d] B = benzene-d_5; A = acetone-d_6; P = pyridine-d_5; C = $CDCl_3$; D = dimethyl sulfoxide-d_6.

Table II. First-Order Coupling Constants (Hz)

Compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5,6}$	Other
4a	0	6	11.5	16	16	0	7.5	
4b	0	*a*	*a*	*a*	*a*	*a*		
5a	~0.5	6	12	13.5	13.5	0	8	
6a	0	6	1.5	0	0	11.5	7.5	
6b	0	5.5	0	1	2	12.5	7	
7a	~0.5	6	11	7	1.5	13	7.5	
7b	1	6	12	10.3[b]	16.2[b]	11[b]	8	
7c	1	6	11.5	*a*	*a*	*a*	8	J_{POCH} = 6.5
8b	2	6.5	18	7	7	0	8	
8c	2	6	18	7.5	7.5	0	8	J_{POCH} = 6.5
9a	0	*a*	*a*	*a*	*a*	*a*	8	
9b	~0.5	0	13	14	8	14	8	$J_{5'a,NH}$ = 6, $J_{5'b,NH}$ = 6.5
11	2	7.5	7.5	*a*	*a*	*a*	8	$J_{HCOMe,F}$ = 1.5
13b	6.5	4	18	11	5	9	7.5	
16a	5.5	0	1.5	5	5	*a*	7.5	
16c	6	0	1.5	4	4	12	7	

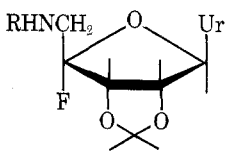
[a] Unresolved. [b] Via computer analysis of the ABX pattern by Dr. M. L. Maddox.

fluorine was also very small (1.5 Hz), and the surprisingly small magnitude of H–F couplings was confirmed by the ^{19}F NMR spectrum of **6a**, which showed only a slightly broadened singlet. These results are not readily predicted from a consideration of the known angular dependence of H–F couplings.[12] They are less surprising, however, when compared with the ^1H NMR spectrum of **6b**, which shows $J_{3',4'} = 0$ and only very small (1 and 2 Hz) 4',5' couplings. This suggests that cyclonucleosides such as **6a** and **6b** can adopt a conformation in solution that is not readily predicted from molecular models.

As expected, the 4'-fluorocyclonucleoside **6a** was rapidly hydrolyzed under acidic conditions and some care had to be taken to avoid partial spontaneous hydrolysis during reaction workup or chromatography. The course of the acidic hydrolysis could be readily followed by ultraviolet spectroscopy of aliquots in methanol, the initial spectrum of **6a** (λ_{max} 237 nm) rapidly changing to that of a uridine derivative (λ_{max} 256 nm).

In water adjusted to pH 2.0 with hydrochloric acid the half-times for hydrolysis of **6a** and **6b** were roughly 3.5 and 6 min, respectively. The similarities of these rates strongly suggest that it is the uracil C_2–oxygen bond that is undergoing cleavage rather than the $C_{5'}$–oxygen bond since the presence of the 4′-fluorine might be expected to exert a greater influence on the latter. In support of this, it was shown that treatment of **6a** with 1% trifluoroacetic acid in methanol at room temperature for 30 min led to the accumulation of a relatively stable component with λ_{max} 228 and 248 nm, very similar to the spectrum of O^2-methyluridine derivatives.[10] For preparative purposes the hydrolysis of **6a** could be readily accomplished using either very dilute (0.01–0.05 N) hydrochloric or trifluoroacetic acids in aqueous tetrahydrofuran or dioxane. Using, e.g., 0.05 N trifluoroacetic acid in tetrahydrofuran–water (9:1), the hydrolysis was shown to be essentially complete within 15 min at room temperature and 4′-fluoro-2′,3′-*O*-isopropylideneuridine (**7a**) could be isolated by preparative TLC in 75% yield. While we have been unable to obtain **7a** in crystalline form, it is an analytically and spectrally pure substance that can be purified and stored without undue difficulty. For preparative purposes it is advantageous to directly hydrolyze crude **6a,** and in this way pure **7a** can be obtained in 58% overall yield from **5a.**

It may be noted that in one larger scale preparation of **7a** as above a minor crystalline by-product with a TLC mobility just slower than that of **6a** was isolated in 5% yield. This substance was readily characterized as 5′-acetamido-5′-deoxy-4′-fluoro-2′,3′-*O*-isopropylideneuridine (**9b**) by the presence of a three-proton singlet at 2.07 ppm in its ^{1}H NMR spectrum in addition to the other usual features of a 4′-fluoronucleoside. The spectrum in pyridine-d_5 showed the 5′ protons as a very complex multiplet due to coupling with the $C_{5'}$ NH as well as the normal H_1 F and geminal couplings. Upon addition of D_2O this pattern collapsed to a pair of readily analyzed ABX signals. The same compound could also be obtained by palladium-catalyzed reduction of **5a** to give the 5′-amino-4′-fluoronucleoside **9a,** which was then acetylated with acetic anhydride. The formation of acetamide by-products has previously been observed during reactions of azides with nitrosyl tetrafluoroborate[11] and has been explained via trapping of the generated carbonium ion by the solvent acetonitrile. In smaller scale reactions, particularly when temperature control is stringent, the formation of **9b** seems negligible.

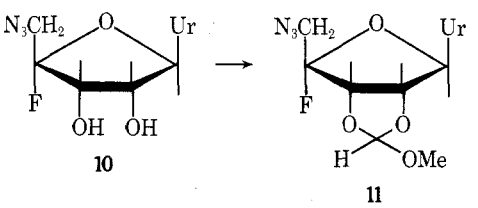


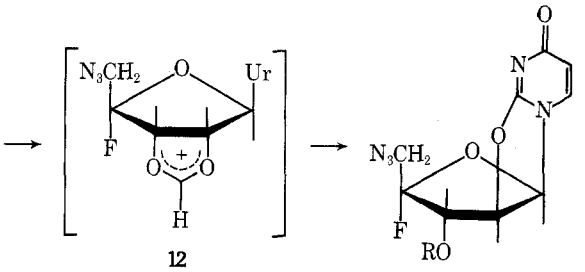
9a, R = H
b, R = $COCH_3$

The availability of **7a** made it attractive to undertake the synthesis of the 5′-*O*-sulfamoyl derivative, the uracil analogue of the antibiotic nucleocidin. In previous work, sulfamoylation of the adenine analogue of **7a** could only be readily accomplished via intermediate formation of an intermediate 5′-*O*-tributylstannyl derivative.[1] In the present case it was found that treatment of **7a** with an excess of sulfamoyl chloride in dioxane in the presence of a mixture of Linde 4A and AW-500 molecular sieves led to the isolation of the 5′-*O*-sulfamoyl derivative (**7b**) in 69% yield by chromatography on silicic acid. A similar method was used previously for the sulfamoylation of 2′,3′-di-*O*-acetyluridine by Shuman et al.[13] Hydrolysis of the isopropylidene function from **7b** could be accomplished by treatment with 90% formic acid at room temperature but was accompanied by considerable concomitant glycosidic cleavage giving uracil. By preparative TLC, however, chromatographically homogeneous 4′-fluoro-5′-*O*-sulfamoyluridine (**8b**) could be isolated in 45% yield. While the latter compound was homogeneous by ^{1}H NMR analysis, it could not be obtained in crystalline form and we have been unable to remove some contaminating silicic acid that was simultaneously eluted from the preparative TLC plate. Elemental analysis showed that there was a fortuitous 1 molar equiv of silica contaminating the product. We have, as yet, found no way of removing this impurity largely due to the alkaline and, to a lesser degree, acidic lability of **8b,** which precludes a number of possible methods. The impetus to achieve this goal was diminished by the finding that **8b** showed much reduced antibacterial and cytotoxic properties in comparison with those of nucleocidin itself.[14]

As was the case in the adenosine series, the stability of 4′-fluorouridine derivatives is strongly dependent upon the presence and nature of substituents on the 2′-, 3′- and 5′-hydroxyl groups. Thus, fully blocked compounds such as **4, 5a, 7b,** and **9** are reasonably stable compounds that can readily be chromatographed and stored without decomposition. In the presence of a suitable 5′ substituent the 2′,3′-diol derivatives (e.g., **8b**) are still reasonably stable, but the fully deblocked nucleoside **8a** is quite unstable. Thus **7a** was treated under a variety of acidic conditions in an effort to remove the isopropylidene group but inevitably uracil was the major product. For example, treatment of **7a** with 90% formic acid for 10 min at room temperature gave roughly 40% unreacted **7a,** 35% uracil, and only 25% of the desired **8a** as judged by TLC. Clearly, the rate of glycosidic cleavage is greater than that for acetal hydrolysis, and as yet we have not been successful in isolating a pure sample of **8a.**

The 5′-azido function does, however, provide a stabilizing influence on the glycosidic bond, and treatment of **5a** with 90% formic acid at room temperature for 105 min led to satisfactory formation of 5′-azido-5′-deoxy-4′-fluorouridine (**10**). The crude lyophilized product was not, however, completely pure by TLC and NMR analysis although no uracil was present as a contaminant. Attempted purification by chromatography on silicic acid led to partial decomposition giving uracil and hence crude **10** was used directly in subsequent steps. Attempted reaction of **10** with nitrosyl tetrafluoroborate did not look at all promising and was complicated by formation of uracil and the difficulty of separating the desired labile, water-soluble **8a** from inorganic salts. Hence it seemed necessary to use a 2′,3′-protecting group that is more acid labile than the isopropylidene function. Crude **10** was accordingly treated with methyl orthoformate in the presence of *p*-toluenesulfonic acid[15] giving the crystalline 2′,3′-*O*-methoxy-



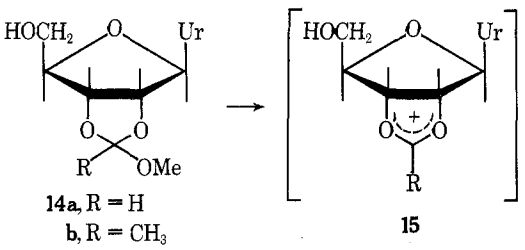


13a, R = CHO
b, R = H

methylene derivative (11) in an overall yield of 52% from **5a**. As obtained, crystalline 11 appeared to be a single diastereomer as judged by its ^{1}H NMR spectrum.

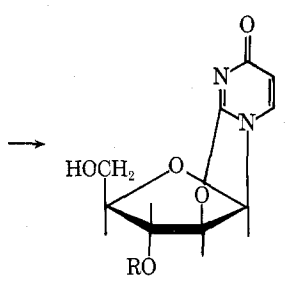
The reaction between 11 and a small excess of nitrosyl tetrafluoroborate proceeded rapidly at 0 °C giving a rather complex mixture of products. The major component could be separated from the others by virtue of its remaining in the aqueous phase during partitioning with chloroform. Subsequent desalting and preparative TLC led to the isolation of this substance in roughly 35% yield. While it still contained traces of silicic acid or other inorganic impurities that precluded obtaining an acceptable elemental analysis, this compound was clearly shown by spectral methods to be 2,2′-anhydro-1-(5′-azido-5′-deoxy-4′-fluoro-β-D-arabinofuranosyl)uracil (**13b**) rather than the expected 2′,3′-*O*-methoxymethylene analogue of **6a**. Thus **13b** was shown to have the typical ultraviolet spectrum of *O*^{2},2′-cyclouridine derivatives (λ_{max} 223 and 247 nm).[16] In addition, its ^{1}H NMR spectrum was very similar to that of *O*^{2},2′-cyclouridine except that both the $C_{3'}$ and $C_{5'}$ protons showed clear-cut H,F couplings and the $C_{5'}$ protons were somewhat deshielded by the presence of the azido substituent. The continued presence of the azido group was apparent from the ir spectrum (2110 cm^{-1}), and the mass spectrum of **13b** showed a molecular ion at *m/e* 269. The formation of **13b** suggests that nitrosyl tetrafluoroborate must react preferentially with the methoxymethylene group rather than with the azide. Collapse of an intermediate species, for which several possibilities exist, would then give the oxonium ion **12**, which in turn would be opened by intramolecular attack by the C_2 carbonyl oxygen of the uracil ring giving **13a**. The formate ester was presumably hydrolyzed during workup giving the observed **13b**. Ample precedent for the formation of *O*^{2},2′-cyclonucleosides via collapse of 2′,3′-acyloxonium ions has been developed in this laboratory,[17] and the generation of oxonium ions from orthoesters in the presence of Lewis acids and related species has been documented.[18]

In order to cast further light on the generality of this unexpected reaction, we have also reacted 2′,3′-*O*-methoxymethyleneuridine (**14a**) with nitrosyl tetrafluoroborate in



14a, R = H
b, R = CH_3

15

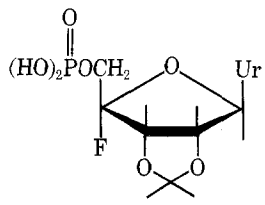


16a, R = H
b, R = CHO
c, R = $COCH_3$

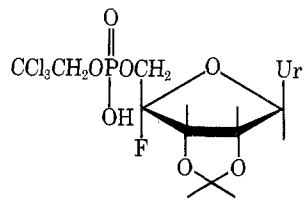
acetonitrile at 0–20 °C and obtained crystalline 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (**16a**) in 84% yield. The latter compound was in all ways identical with an authentic sample prepared by an independent route.[19] Once again, an intermediate 3′-*O*-formate (**16b**) was presumably lost by spontaneous hydrolysis during workup. A similar, but somewhat less efficient, conversion of **14a** to **16a** was also achieved using boron trifluoride etherate rather than nitrosyl tetrafluoroborate in acetonitrile at room temperature. In a closely related study, 2′,3′-*O*-methoxyethylideneuridine (**14b**)[20] was reacted with nitrosyl tetrafluoroborate at 0 °C and, following preparative TLC, crystalline 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil (**16c**) was isolated in 82% yield. The latter compound was identical by NMR, uv, and infrared analysis to a previously prepared sample of this compound.[17a] The presence of the 3′-*O*-acetyl group strongly supports the formation of **16** via the suggested 2′,3′-oxonium ion (**15**). Once again, the conversion of **14b** to **16c** could also be achieved using boron trifluoride etherate, the yield in this case being 68%.

Since the 5′-*O*-sulfamoyl group was found to exert a favorable influence on the stability of **8b**, it was of interest to see whether a phosphate ester would have a similar effect. Since 4′-fluorouridine 5′-phosphate (**8d**) was still expected to be fairly labile, the choice of phosphorylating agents was limited to those leading to products from which protecting groups could be removed under mildly acidic conditions. Accordingly, **7a** was reacted with commercially available bis(2,2,2-trichloroethyl) phosphorochloridate[21] in pyridine at room temperature for 1.5 h giving 4′-fluoro-2′,3′-*O*-isopropylideneuridine 5′-*O*-bis(2,2,2-trichloroethyl)phosphate (**7c**). Following removal of some unreacted **7a** and by-products by preparative TLC, **7c** was isolated as a foam in 50–80% yields. A somewhat better yield (90%) of **7c** was obtained by condensation of **7a** and bis(2,2,2-trichloroethyl)phosphoric acid,[22] prepared by hydrolysis of the phosphorochloridate, in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride. The latter reagent has previously been used with success for the condensation of nucleosides with mono(2,2,2-trichloroethyl)phosphoric acid.[23]

In small-scale experiments it was clear that the trichloroethyl groups could be largely removed from **7c** by treatment with zinc dust and acetic acid in dimethylformamide for 30 min at room temperature.[21,24] Analysis of the reaction product showed it to consist of 90% of the desired dianion (**17**) and 10%



17



18

of a monoanion, presumably the mono(trichloroethyl) ester (**18**). Similar accumulation of minor amounts of stubbornly resistant monoanions has previously been encountered in related reactions.[21,24c] Attempted hydrolysis of the isopropylidene group from crude **17** by treatment with 90% formic acid at room temperature was accompanied by extensive glycosidic cleavage giving uracil.

On the other hand, treatment of the phosphotriester **7c** with 90% formic acid led to removal of the isopropylidene group accompanied by relatively little glycosidic cleavage. The reaction had to be monitored rather carefully by TLC, and, since uracil formation became significant during the later stages, it was worked up before all **7c** had disappeared. By this technique it was possible to isolate the pure diol (**8c**) in 54–65% yields by preparative TLC. Treatment of **8c** with zinc dust and acetic acid in aqueous dimethylformamide was investigated under a number of conditions and the addition of a catalytic amount of silver acetate seemed to be advantageous.[25] Under all conditions the reaction appeared to stop while 5–15% of a monoanion species (presumably the diol related to **18**) still remained but formation of uracil was not significant. Pre-

liminary attempts to purify the major product (**8d**) by ion exchange chromatography were not promising. An effective separation of **8d** from the contaminating monoanion was achieved on columns of DEAE Sephadex (HCO_3^-) but some degradation to uracil accompanied evaporation of the aqueous triethylammonium bicarbonate eluents.

Fortunately, a separation of **8d** from the contaminating monoanion was readily accomplished as its barium salt. Following removal of zinc ions from the reaction mixture using Dowex 50 (NH_4^+) resin, an excess of barium acetate was added, followed by three volumes of ethanol. The resulting precipitated barium salts still contained some monoanion but reprecipitation using only two volumes of ethanol gave pure **8d** in a yield of 44% from **8c**. Once isolated in this way the barium salt seems reasonably stable and does not undergo decomposition upon storage at room temperature for several months.

The availability of pure **8d** allowed us to briefly examine its chemical stability. Its rate of alkaline hydrolysis was readily followed by uv spectroscopy since the hydrolysis product, uracil, has λ_{max} 284 nm in alkali while **8d** has very low absorption at that wavelength. Using this simple technique it was found that in 0.01 N sodium hydroxide at room temperature **8d** underwent roughly 20% hydrolysis to uracil in 45 min. In 0.05 N sodium hydroxide there was approximately 37% hydrolysis to uracil in 30 min. Under acidic conditions **8d** was considerably more stable as judged by the decrease in absorption at 260 nm in proceeding from a typical uridine spectrum (ϵ_{260} 10 000) to that of uracil (ϵ_{260} 7800). Thus, **8d** underwent no significant hydrolysis in 1 N hydrochloric acid at room temperature for 15 min, but was roughly 58% hydrolyzed in that acid after 30 min at 60 °C. It should be pointed out that these studies were done using the barium salt of **8d** and do not take into account any catalytic effects of the divalent metal ion. By way of comparison, 4′-fluoro-2′,3′-*O*-isopropylideneuridine (**7a**) is considerably more stable toward alkali, treatment with 0.6 N sodium hydroxide at room temperature giving roughly 50% uracil only after 2 h. It may be noted that the hydrolysis of **7a** cannot be followed by changes in the uv spectrum since there is generation of unknown uv absorbing by-products, probably via base-catalyzed eliminations on the initially formed 4-keto sugar. Clearly, the stabilizing effects of substituents on the different hydroxyl groups of 4′-fluorouridine vary widely and must be taken into consideration if **8d** is to be incorporated into other more complex molecules. Certainly syntheses of nucleoside polyphosphate and nucleotide coenzyme analogues derived from 4′-fluorouridine would be of interest for enzymological study. The present paper provides a sound foundation upon which to design such syntheses.

Experimental Section

General Methods. Thin layer chromatography (TLC) was done using 250-μ layers of silica gel GF obtained from Analtech, Inc., Newark, Del., and preparative TLC on 20 × 100 cm glass plates coated with a 1.3 mm layer of Merck silica gel HF. Column chromatography was done using the short column technique[26] with Merck silica gel GF. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian HA-100 instrument and are recorded in parts per million downfield of an internal standard of tetramethylsilane. Mass spectra were obtained on an Atlas CH-4 instrument fitted with a direct inlet system. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson and to Dr. L. Tökés for their continuous help with NMR and mass spectrometry. Most other analytical data were obtained by the staff of the Analytical Laboratories of Syntex Research, to whom we extend our thanks. Melting points were determined using a hot-stage microscope and are corrected.

5′-Deoxy-4′-fluoro-5′-iodo-2′,3′-*O*-isopropylideneuridine (4a). A. A saturated solution of iodine (2.72 g, 10.7 mmol) in methylene chloride (~50 ml) was added dropwise over 10 min to a stirred solution of purified 1 (1.33 g, 5 mmol)[7] in methylene chloride (100 ml) in the presence of finely divided silver fluoride (3.175 g, 25 mmol) until a permanent iodine color persisted. An aqueous solution (100 ml) containing 5% sodium bicarbonate and 5% sodium thiosulfate was then added and the mixture was filtered through a bed of Celite and washed with chloroform. The aqueous phase was extracted with chloroform and the combined organic phases were washed with the bicarbonate–thiosulfate solution and with water, dried ($MgSO_4$), and evaporated, leaving 2.04 g (99%) of **4a** as a dry foam that could not be crystallized. Analytical TLC separation of **4a** from **1** could be achieved using two developments with toluene–ethyl acetate–acetone (3:1:1) and ^1H NMR showed the presence of a single isomer.[27] An analytical sample prepared by preparative TLC (chloroform–methanol, 9:1) had λ_{max} (MeOH) 257 nm (ϵ 9400); mass spectrum (70 eV) *m/e* 412 (M^+), 397 ($M^+ - CH_3$), 354 (M^+ − acetone), 301 (M^+ − base), 243 (*m/e* 301 − acetone); ^{19}F NMR ($CDCl_3$) 101.8 ppm upfield of $CFCl_3$.

Anal. Calcd for $C_{12}H_{14}FIN_2O_5$ (412.16): C, 34.97; H, 3.42; N, 6.80. Found: C, 34.87; H, 3.53; N, 6.70.

B. A solution of potassium *tert*-butoxide (38 g, 340 mmol) in dioxane (1 l.) was added over 20 min to a stirred solution of 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine (66 g, 168 mmol)[9] in dioxane (1 l.). After a further 20 min a solution of sodium dihydrogen phosphate (138 g, 1 mol) in water (250 ml) was added with vigorous stirring and the resulting solution was partitioned between methylene chloride (1 l.) and water (1 l.). The organic phase was washed twice with water (1 l.), dried ($MgSO_4$), and evaporated, leaving crude 1 (~50 g) contaminated with ~10% unreacted iodo compound. A portion purified by preparative TLC (chloroform–methanol, 19:1) was identical with an authentic sample of 1.[7b] Without purification crude 1 was dissolved in methylene chloride (3 l.) in the presence of finely divided silver fluoride (128 g, 1 mol) and solid iodine (89 g, 350 mmol) was added portionwise over 20 min. The reaction mixture was worked up as in A giving 63.2 g (91% from the iodo compound) of **4a** that was contaminated with only a faint trace of **6b**. The aqueous phase was shown by TLC to contain some cyclonucleoside (**6b**) that could be partially recovered by repeated extraction with chloroform. Following crystallization from ethanol it was shown to be identical with an authentic sample of **6b** (see later).

5′-Azido-5′-deoxy-4′-fluoro-2′,3′-*O*-isopropylideneuridine (5a). A. A solution of **4a** (13.6 g, 33 mmol) and lithium azide (8.3 g, 170 mmol) in dimethylformamide (300 ml) was stirred at 105 °C for 17 h. The mixture was then cooled and partitioned between chloroform (1.5 l.) and aqueous sodium bicarbonate (1 l.). The organic phase was then washed three times with water, dried ($MgSO_4$), and evaporated. The oily residue was crystallized from chloroform–hexane giving 3.82 g of pure **5a** with mp 153–153.5 °C. Chromatography of the mother liquors on a column of silicic acid using chloroform–methanol (99:1) gave a further 540 mg (total yield 40%) of crystalline **5a**: λ_{max} (MeOH) 256 nm (ϵ 9900); ^{19}F NMR ($CDCl_3$) 109.5 ppm upfield of $CFCl_3$; mass spectrum (70 eV) *m/e* 312 ($M^+ - CH_3$); ir (KBr) 2110 cm^{-1} (N_3).

Anal. Calcd for $C_{12}H_{14}FN_5O_5$ (327.27): C, 44.04; H, 4.31; N, 21.40. Found: C, 44.03; H, 4.32; N, 21.14.

B. The sequence 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine → **1** → **4a** → **5a** was carried out essentially as above starting with 66.45 g (168.6 mmol) of the 5′-iodonucleoside and without purification of any of the intermediates. In this way the overall yield of crystalline **5a** was 20.5 g (37%).

5′-Acetamido-5′-deoxy-4′-fluoro-2′,3′-*O*-isopropylideneuridine (9b). A solution of **5a** (654 mg, 2 mmol) in methanol (60 ml) was vigorously stirred for 2 h in an atmosphere of hydrogen in the presence of 10% palladium on carbon catalyst (500 mg). The mixture was filtered through Celite and the filtrate was evaporated leaving 586 mg (97%) of **9a** as a dry glass that failed to crystallize: ir (KBr) 3390 (NH_2), no N_3, 1680 cm^{-1}; mass spectrum (70 eV) *m/e* 300 (M^+ − H), 286 ($M^+ - CH_3$), 281 (M^+ − HF), 243 (M^+ − acetone). A portion of this material (301 mg, 1 mmol) was treated overnight with acetic anhydride (1 ml) in pyridine (10 ml). Following evaporation of the solvents the residue was purified by preparative TLC using chloroform–methanol (9:1). Crystallization from chloroform–hexane gave 247 mg (72%) of pure **9b**. An anlytical sample from chloroform–hexane and then ethyl acetate had mp 150.5–153.5 °C: λ_{max} (MeOH) 256 nm (ϵ 9400); mass spectrum (70 eV) *m/e* 328 ($M^+ - CH_3$), 323 (M^+ − HF), 285 (M^+ − acetone), 265 (M^+ − HF and acetone).

Anal. Calcd for $C_{14}H_{18}FN_3O_6$ (343.31): C, 48.98; H, 5.28. Found: C, 49.20; H, 5.40.

2,5′-Anhydro-2′,3′-*O*-isopropylideneuridine (6b). Solid nitrosyl tetrafluoroborate (300 mg, 2.6 mmol) was added to a solution of **5b** (309 mg, 1 mmol) in dry acetonitrile (5 ml) at 0 °C. Gas evolution took place as the nitrosyl salt dissolved leaving a pale yellow solution. After 15 min aqueous disodium hydrogen phosphate (5 ml of 1 M) was

added and the solution was extracted three times with chloroform. The extracts were dried ($MgSO_4$) and evaporated leaving 251 mg of a crystalline residue that was shown by TLC (chloroform–methanol, 9:1) to be **6b** contaminated with roughly 5% of 2′,3′-*O*-isopropylideneuridine. Crystallization from ethanol gave 175 mg of **6b** which sintered at 190 °C and slowly decomposed without melting until above 270 °C. Preparative TLC of the mother liquors followed by crystallization gave a further 25 mg (total yield 75%) of **6b**: λ_{max} (MeOH) 236 nm (ϵ 13 900) and NMR identical with that of an authentic sample.[9,10]

2,5′-Anhydro-4′-fluoro-2′,3′-*O*-isopropylideneuridine (6a). Solid nitrosyl tetrafluoroborate (700 mg, 6 mmol) was added to a stirred solution of **5a** (654 mg, 2 mmol) in anhydrous acetonitrile (10 ml). After 20 min at 0 °C the mixture was allowed to warm to room temperature and stirred for an additional 50 min with addition of a further 50 mg of nitrosyl salt after 45 min. At this point TLC (chloroform–methanol, 9:1) showed the starting material to have disappeared and a saturated aqueous solution of sodium chloride and disodium hydrogen phosphate (25 ml) was added. The aqueous phase was extracted three times with methylene chloride and the combined organic phases were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated, leaving 380 mg (67%) of **6a** as a foam that was homogeneous by TLC and NMR analysis. An analytical sample was crystallized from ethanol to give **6a** which slowly sintered and turned brown above 180 °C and melted with decomposition at 240–245 °C: λ_{max} (MeOH) 237 nm (ϵ 13 400); ^{19}F NMR (pyridine-d_5) 141.76 ppm upfield of $CFCl_3$.

Anal. Calcd for $C_{12}H_{13}FN_2O_5$ (284.24): C, 50.71; H, 4.61; N, 9.85. Found: C, 50.56; H, 4.68; N, 9.74.

4′-Fluoro-2′,3′-*O*-isopropylideneuridine (7a). A. Trifluoroacetic acid (0.015 ml) was added to a solution of **6a** (50 mg) in a mixture of tetrahydrofuran (2.7 ml) and water (0.3 ml). The reaction was monitored by examination of the uv spectra of 2-μl aliquots, the initial λ_{max} of 236 nm changing to λ_{max} 256 nm within 15 min. After 20 min the solvent was evaporated in vacuo at room temperature and the residue was coevaporated four times with methanol. The final residue was purified by preparative TLC using benzene–acetone (2:1), elution of the major band giving 40 mg (75%) of **7a** as a dry foam that could not be crystallized: λ_{max} (MeOH) 256 nm (ϵ 9300); mass spectrum (70 eV) *m/e* 287 ($M^+ - CH_3$).

Anal Calcd for $C_{12}H_{15}FN_2O_6$ (302.26): C, 47.67; H, 5.00; N, 9.27. Found: C, 47.45; H, 5.01; N, 9.06.

B. A solution of **5a** (3.27 g, 10 mmol) and nitrosyl tetrafluoroborate (2.40 g, 20 mmol) in acetonitrile (100 ml) was stored at 0 °C for 30 min and then at room temperature for 30 min. The reaction mixture was worked up as in A and the crude product was directly dissolved in dioxane–water (9:1) and made 0.01 N in hydrochloric acid. After 2 h at room temperature the solution was neutralized with ammonium hydroxide and evaporated to dryness. The residue was dissolved in chloroform–methanol (98:2), filtered, and applied to a column of silicic acid (120 g). Elution with 3% methanol in chloroform gave 1.74 g (58% from **5a**) of pure **7a** identical with that from A by TLC and NMR analysis.

In one experiment similar to B on an 8-mmol scale, a by-product with a TLC mobility just lower than that of **6a** was isolated in 5% yield by chromatography as above. This material was crystallized from chloroform and found to be identical with **9b**.

4′-Fluoro-2′,3′-*O*-isopropylidene-5′-*O*-sulfamoyluridine (7b). A solution of **7a** (1.6 g, 5.3 mmol) and sulfamoyl chloride (1.85 g, 16 mmol) in anhydrous dioxane (120 ml) was stirred at room temperature for 18 h in the presence of a 1:1 mixture (60 g) of Linde 4A and AW-500 molecular sieves. At this point TLC (chloroform–methanol, 9:1) showed the reaction to be essentially complete and ammonium hydroxide (1 M, 20 ml) was added. The mixture was filtered and the filtrate was evaporated leaving a syrup that was triturated with methanol and filtered to remove ammonium chloride. The evaporated filtrate was chromatographed on a column of silicic acid (80 g) using chloroform–methanol (19:1) giving 1.39 g (69%) of **7b** that was homogeneous by TLC and NMR analysis. An analytical sample was crystallized from acetone–hexane with mp 163.5–166.5 °C dec. In a separate experiment crystalline **7b** was isolated in 45% yield: λ_{max} (MeOH) 255 nm (ϵ 9700).

Anal. Calcd for $C_{12}H_{16}FN_3O_8S$ (381.34): C, 37.79; H, 4.23; N, 11.02. Found: C, 38.25; H, 4.50; N, 10.79.

4′-Fluoro-5′-*O*-sulfamoyluridine (8b). A solution of **7b** (1.25 g, 3.2 mmol) in 90% formic acid (10 ml) was stored at room temperature for 2 h and then evaporated to dryness. Following several coevaporations with ethanol the residue was purified by preparative TLC using chloroform–methanol (3:1). Elution of the major band with chloroform–methanol (1:2) gave 579 mg (45%) of **8b** as a colorless glass that contained a small amount of silicic acid that could not be removed. All attempts at crystallization were unsuccessful and analytical data were obtained on a sample lyophilized from water: λ_{max} (MeOH) 259 nm (ϵ 9600).

Anal. Calcd for $C_9H_{12}FN_3O_8S \cdot SiO_2$ (401.36): C, 26.93; H, 3.01; N, 10.47; residue, 14.97. Found: C, 26.68; H, 3.19; N, 10.37; residue, 16.17.

Bis(2,2,2-trichloroethyl) Phosphate. Water (0.80 ml, 44.5 mmol) was added with stirring to bis(2,2,2-trichloroethyl) phosphorochloridate (15.17 g, 40 mmol) that had been melted and maintained at 80–85 °C. After 30 min the mixture was thoroughly evacuated leaving a crystalline mass. Crystallization from hexane gave 12.58 g (87%) of bis(2,2,2-trichloroethyl) phosphate with mp 81–84 °C: NMR ($CDCl_3$) 4.61 ppm (d, 4, $J_{H,P}$ = 6.5 Hz, OCH_2), 11.5 (s, 1, POH).

Anal. Calcd for $C_4H_5Cl_6O_4P$ (360.77): C, 13.32; H, 1.40. Found: C, 13.22; H, 1.41.

4′-Fluoro-2′,3′-*O*-isopropylideneuridine 5′-*O*-Bis(2,2,2-trichloroethyl)phosphate (7c). A solution of **7a** (1.64 g, 5.4 mmol), bis(2,2,2-trichloroethyl) phosphate (2.35 g, 6.5 mmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (5.15 g, 17 mmol) in pyridine (40 ml) was stored at room temperature for 3 h and then quenched by addition of water (2 ml). After 30 min the solvent was evaporated and the residue was partitioned between chloroform and 10% aqueous sodium bicarbonate. The organic phase was washed with water, dried ($MgSO_4$), and evaporated, leaving a residue that was chromatographed on a column of silicic acid using chloroform–methanol (9:1). Evaporation of the major product left 3.12 g (90%) of **7c** as a TLC homogeneous foam: λ_{max} (MeOH) 255 nm (ϵ 9700).

Anal. Calcd for $C_{16}H_{18}Cl_6FN_2O_9P$ (645.02): C, 29.79; H, 2.81; N, 4.34. Found: C, 30.14; H, 3.13; N, 4.14.

4′-Fluorouridine 5′-*O*-Bis(2,2,2-trichloroethyl)phosphate (8c). A solution of **7c** (1.29 g, 2 mmol) in 90% formic acid (2 ml) was stored at room temperature, the hydrolysis being monitored by TLC using benzene–acetone (1:1). After 20 h the solvent was evaporated in vacuo and the residue was coevaporated several times with toluene–methanol. The residue was purified by preparative TLC using benzene–acetone (1:1) to separate unreacted **7c** (185 mg, 14%) and uracil (~10%) from the major product. Elution of the main band gave 655 mg (54%) of **8c** as a TLC homogeneous foam: λ_{max} (MeOH) 257 nm (ϵ 9600).

Anal. Calcd for $C_{13}H_{14}Cl_6FN_2O_9P$ (604.98): C, 25.81; H, 2.33; N, 4.63. Found: C, 25.87; H, 2.46; N, 4.20.

4′-Fluorouridine 5′-*O*-Phosphate (8d). Acetic acid (0.5 ml of 8.5 M) was added dropwise at room temperature over 2–3 min to a stirred solution of **8c** (121 mg, 0.2 mmol) in dimethylformamide (3 ml) and water (2 ml) in the presence of zinc powder (260 mg, 4 mmol)[28] and silver acetate (9 mg, 40 μmol). After 30 min paper electrophoresis at pH 7.5 showed the presence of a dianion and monoanion in a ratio of roughly 85:15 and this did not subsequently change. After 1.5 h Dowex 50 (NH_4^+) resin (2 ml) was added and the mixture was stirred and filtered. The filtrate was passed through a column of Dowex 50 (NH_4^+) resin (15 ml) and the eluates and water washings (1850 OD units at 259 nm) were carefully evaporated to dryness at 30 °C. The residue was dissolved in water (2 ml) and aqueous 1 M barium acetate (0.6 ml) was added followed by ethanol (8 ml). The resulting precipitate was reprecipitated twice using three volumes of ethanol to give 64 mg of **8d** that was shown by paper electrophoresis to still contain a small amount of a monoanion. Reprecipitation of this material from water (2 ml) by addition of two volumes of ethanol gave 45 mg (44%) of homogeneous **8d** as a dihydrate after careful drying in vacuo: λ_{max} (H_2O) 260 nm (ϵ 9600); P:uridine[29] = 1.03. An analytical sample was further reprecipitated to ensure the absence of inorganic salts.

Anal. Calcd for $C_9H_{10}FN_2O_9PBa \cdot 2H_2O$ (513.54): C, 21.04; H, 2.75; N, 5.45. Found: C, 21.00; H, 2.78; N, 4.92.

5′-Azido-5′-deoxy-4′-fluoro-2′,3′-*O*-methoxymethyleneuridine (11). A solution of **5a** (654 mg, 2 mmol) in 90% formic acid (5 ml) was stored at room temperature, the reaction being monitored by TLC using chloroform–methanol (9:1). After 105 min the solution was evaporated to dryness in vacuo and the residue was lyophilized from water giving 640 mg of **10** as a dry glass that was essentially pure by TLC analysis. The product is not stable and attempted purification led to partial hydrolysis to uracil. The crude product was dissolved in a mixture of dioxane (8 ml) and methyl orthoformate (2 ml) together with *p*-toluenesulfonic acid (18 mg) and stored at room temperature. After 1 h the solution was neutralized by dropwise addition of methanolic sodium methoxide and then evaporated to dryness. A chloroform solution of the residue was washed with aqueous sodium bicarbonate and water, dried, and evaporated, leaving a crystalline solid. Crystallization from chloroform–hexane gave 344 mg (52% from **5a**) of a single diastereoisomer (^1H NMR) of **11** with mp 157–162 °C:

λ_{max} (MeOH) 256 nm (ϵ 9800); ν_{max} (KBr) 2110 (N_3), 1700 cm^{-1} (CO); mass spectrum (70 eV) *m/e* 329 (M^+), 298 ($M^+ - OCH_3$), 273 ($M^+ - CH_2N_3$), 218 (M^+ − uracil), 113 (uracil + 2 H).

Anal. Calcd for $C_{11}H_{12}FN_5O_6$ (329.24): C, 40.13; H, 3.67; N, 21.27. Found: C, 40.00; H, 3.72; N, 21.12.

Reaction of 11 with Nitrosyl Tetrafluoroborate. Nitrosyl tetrafluoroborate (82 mg, 0.7 mmol) was added to a stirred solution of **11** (165 mg, 0.5 mmol) in acetonitrile (10 ml) at 0 °C. After 30 min TLC analysis (chloroform–methanol, 9:1) showed **11** to be absent and saturated aqueous disodium hydrogen phosphate (15 ml) was added. The precipitated salts were removed by filtration and the aqueous phase was extracted repeatedly with chloroform. The major ultraviolet absorbing product remained in the aqueous phase, which was diluted with methanol and filtered to remove inorganic salts. The filtrate was evaporated and purified by preparative TLC using chloroform–methanol (9:1). The major uv absorbing band (R_f 0.17) was eluted with methanol and evaporated giving 50 mg of a glass with the typical uv spectrum of O^2,2′-cyclouridine: λ_{max} (MeOH) 223, 247 nm; λ_{min} 235 nm; ν_{max} (KBr) 2110 (N_3), 1660, 1630 cm^{-1}; mass spectrum (70 eV) *m/e* 269 (M^+), 213 ($M^+ - CH_2N_3$), 112 (uracil + H). See Tables I and II for ^1H NMR. The sample still contained traces of silica gel or inorganic salts and an acceptable elemental analysis was not obtained.

Reaction of 2′,3′-*O*-Methoxymethyleneuridine (14a) with Nitrosyl Tetrafluoroborate. Nitrosyl tetrafluoroborate (400 mg, 3.4 mmol) was added to a stirred solution of **14a** (572 mg, 2 mmol)[15] in acetonitrile (20 ml) at 0 °C and the mixture was allowed to warm to room temperature. After 20 min the mixture was concentrated to roughly 5 ml and directly purified by preparative TLC using chloroform–methanol (4:1). The major, broad, slow moving band was eluted with methanol–chloroform (1:1) giving 542 mg of a glass which was crystallized from methanol giving only 86 mg of **16a.** Rechromatography of the mother liquors using chloroform–methanol (3:1) followed by crystallization from methanol gave a further 291 mg (total yield 377 mg, 84%) of pure **16a** with mp 238–240 °C that was identical with an authentic sample by TLC, uv, and NMR.

2,2′-Anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil (16c). A. Nitrosyl tetrafluoroborate (400 mg, 3.4 mmol) was added to a solution of **14b** (600 mg, 2 mmol)[20] in acetonitrile (20 ml) at 0 °C. After 20 min a saturated solution of disodium hydrogen phosphate was added leading to separation of two phases. The upper phase was evaporated to dryness and purified by preparative TLC using chloroform–methanol (85:15) giving 611 mg of crude, crystalline **16c.** Recrystallization from ethanol gave 440 mg (82%) of **16b** with mp 200–202 °C and identical with an authentic sample[17a] by TLC, NMR, uv, and infrared analysis: λ_{max} (MeOH) 225 nm (ϵ 9300), 250 (7900).

B. Boron trifluoride etherate (0.28 ml, 2.2 mmol) was added to a solution of **14b** (300 mg, 1 mmol) in acetonitrile (10 ml) at 0 °C. After 15 min the mixture was worked up as in A giving 181 mg (68%) of **16c** identical with that above.

Registry No.—**1,** 17331-67-8; **4a,** 59462-99-6; **4b,** 59463-00-2; **5a,** 40764-48-5; **5b,** 15083-05-3; **6a,** 59463-01-3; **6b,** 3868-21-1; **7a,** 40654-03-3; **7b,** 59463-02-4; **7c,** 59463-03-5; **8b,** 59463-04-6; **8c,** 59463-05-7; **8d,** 59463-06-8; **9a,** 59463-07-9; **9b,** 59463-08-0; **11,** 59463-09-1; **13b,** 59463-10-4; **14a,** 16628-81-2; **14b,** 16667-57-5; **16a,** 3736-77-4; **16b,** 59463-11-5; **16c,** 38642-32-9; iodine, 7553-56-2; 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidenenuridine, 14671-65-9; lithium azide, 19597-69-4; acetic anhydride, 108-24-7; sulfamoyl chloride, 7778-42-9; bis(2,2,2-trichloroethyl) phosphate, 59463-12-6; bis(2,2-trichloroethyl) phosphorochloridate, 17672-53-6; nitrosyl tetrafluoroborate, 14635-75-7.

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