the derivations mentioned in the text (6 pages). Ordering information is given on any current masthead page.

Registry No.—Cytidine, 65-46-3; bisulfite, 15181-46-1.

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(10) Assuming that the catalytic properties of general bases are similar for the well-characterized deamination of 1-methyl-5,6-dihydrocytosine,[7] and the rate-determining step of cytidine deamination (See Reaction Mechanism), then $k_{SO_3} = 2k_{HSO_3}$; $k_{HPO_4^{2-}} = 5k_{H_2PO_4^-}$. Under the experimental conditions, the relative concentrations of the basic species present can be calculated to be: $[SO_3^{2-}]/[HSO_3^-]$ = 1.50 (pH 6.55), 9.00 (pH 7.30); $[HPO_4^{2-}]/[H_2PO_4^-]$ = 1.86 (pH 6.55), 10.8 (pH 7.30). The relative catalytic contribution of each species becomes $(k_{SO_3^{2-}}[SO_3^{2-}])/(k_{HSO_3^-}[HSO_3^-])$ = 3.0 (pH 6.55), 18 (pH 7.30); $(k_{HPO_4^{2-}}[HPO_4^{2-}])/(k_{H_2PO_4^-}[H_2PO_4])$ = 9.3 (pH 6.55), 54 (pH 7.30). Should the rate constant ratio $(k_{SO_3^{2-}}/k_{HSO_3^-})$ equal one (a lower limit), the relative catalytic contribution would become $(k_{SO_3^{2-}}[SO_3^{2-}])/(k_{HSO_3^-}[HSO_3^-])$ = 1.50 (pH 6.55), 9.0 (pH 7.30). The possible error introduced into the calculations by this estimate is not significant enough to modify the final conclusions.
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Fluorinated Pyrimidine Nucleosides. 2.[1] Reaction of 2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine Hydrochloride with Nitrogen and Sulfur Nucleophiles

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Reaction of 2,2′-anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine hydrochloride (**1**, anhydro-ara-FC) with ammonia gave 1-β-D-arabinofuranosyl-2,4-diamino-5-fluoropyrimidinium chloride (**2**) by attack at C_2 of the pyrimidine ring. Reaction of **1** with methylamine gave the corresponding 2-methylamino derivative **3**, which was rapidly converted into the 2,4-bis(methylamino)arabinoside **4** by amine exchange at C_4. Treatment of **1** with ethylamine or *n*-propylamine similarly produced the corresponding 2,4-bis(alkylamino) derivatives **14** and **15**. Reaction of **1**, **2**, or **4** with methylamine for a prolonged reaction period resulted in rearrangement with loss of the sugar moiety to produce 2-amino-5-fluoro-1-methyl-4-methyliminopyrimidine hydrohalide (**9**), the structure of which was confirmed by X-ray crystallography. The reaction of **1** with ^{15}N-enriched ammonia was examined; in addition to C_2 attack and amine exchange at C_4, evidence was found for incorporation of ^{15}N into the pyrimidine ring. Reaction of **1** with sodium hydrosulfide or hydrogen sulfide induced defluorination without cleavage of the anhydro bond to give 2,2′-anhydro-1-β-D-arabinofuranosylcytosine (**21**); the oxazolidinethione **22** was also isolated as a byproduct. Treatment of the corresponding sulfur- and nitrogen-bridged analogues **23** and **26** with sodium hydrosulfide also produced the corresponding defluorinated anhydro nucleosides **25** and **27**.

2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine hydrochloride (**1**, anhydro-ara-FC; Scheme I), a compound first synthesized by Fox et al.,[2] has been shown by Burchenal et al.[3] to be a promising new agent for the treatment of acute myeloblastic leukemia. As part of a synthetic program in the area of fluorinated pyrimidine nucleosides, we have employed anhydro-ara-FC as starting material for the preparation of some 5-fluoropyrimidine nucleosides with potential antitumor activity. The reactions of nitrogen and sulfur nucleophiles form the basis for this report.

Reaction of anhydro-ara-FC (**1**) with methanolic ammonia yielded the highly crystalline 2,4-diamino-5-fluoropyrimidine arabinoside **2** by reaction at C_2 of the pyrimidine ring.[4] This reaction is to be expected since Doerr and Fox have previously shown that the corresponding unfluorinated analogue 1-β-D-arabinofuranosyl-2,4-diaminopyrimidinium chloride was produced by the reaction of 2,2′-anhydro-1-β-D-arabinofuranosylcytosine with ammonia.[5] Although difficulty was experienced by Doerr and Fox in the isolation of the unfluorinated analogue due to the hygroscopic nature of the salt, together with its propensity for recrystallization to the 2,2′-anhydro compound, the hydrochloride salt of **2**, in contrast, was found to be stable indefinitely at room temperature. In aqueous solution, **2** was found to be much less stable; storage of a solution for 4 days at room temperature resulted in almost complete conversion to arabinosyl-5-fluorocytosine. A small amount of a byproduct was isolated from the reaction of **1** with ammonia; this was identified as 2-amino-β-D-arabinofu-

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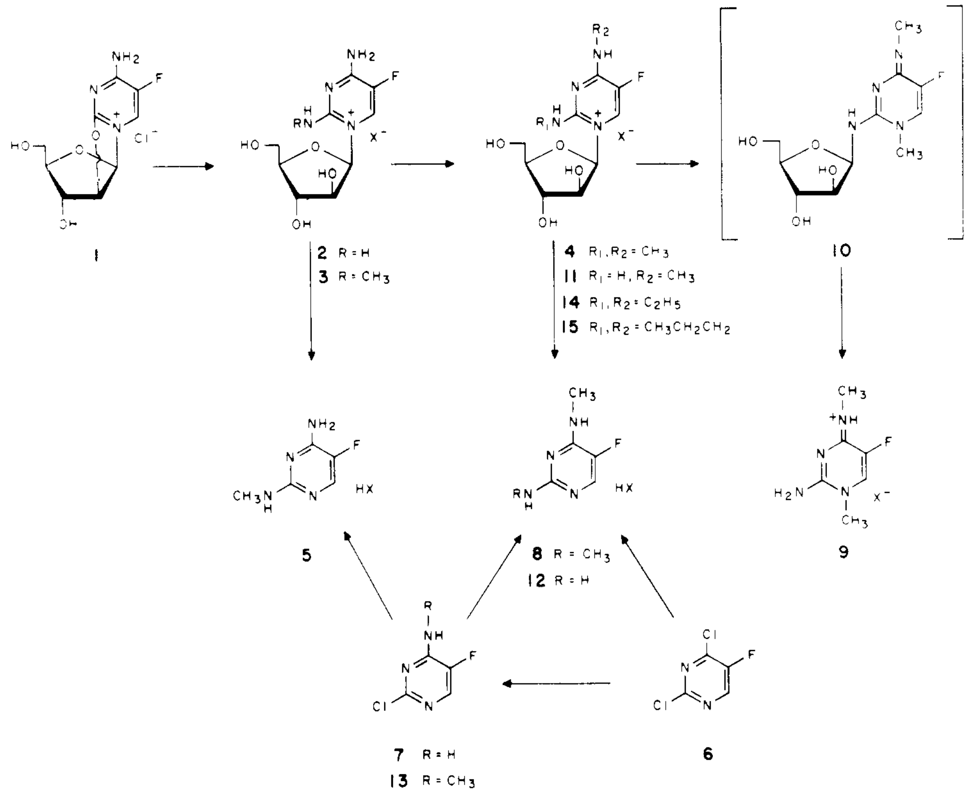
Scheme I



rano[1′,2′:4,5]-2-oxazoline and was found to be identical with a sample prepared from D-arabinose and cyanamide by the method of Shannahoff and Sanchez.[6] This oxazoline was previously isolated by Fox and Otter[7] from the reaction of 1 with sodium hydroxide and presumably arose from degradation of the pyrimidine ring of 1 while preserving the 2,2′-anhydro linkage intact.

Our attention was next focused on the reaction of 1 with methylamine. Reaction with 3 equiv in methanol at room temperature gave initially the arabinosyl-2-methylaminopyrimidine 3 as expected. This compound, however, was rapidly converted by excess methylamine into the 2,4-bis(methylamino)pyrimidine nucleoside **4**; after only 15 min at room temperature, the latter was found to be the major product. Thus, an extremely facile amine exchange reaction had apparently taken place at C_4 in addition to the expected attack of methylamine at C_2. The presence of two methylamino functions in 4 was particularly evident from an examination of its NMR spectrum; two three-proton doublets at δ 2.91 and 3.00 due to two CH_3NH– functions both collapsed to singlets on addition of D_2O.

Further experiments were carried out to examine this amine exchange reaction at C_4 in more detail; reaction of 1 with only 1 equiv of methylamine gave, after 10 min, a complex mixture of starting material, monomethyl compound **3,** and dimethyl compound 4 in a ratio of approximately 3:3:1. After 40 min, the monomethyl derivative **3** was found to be the main product, with substantial amounts of 1 and 4 present; 3 could be isolated with difficulty by conversion into its picrate salt and characterized by its NMR spectrum, which revealed only one doublet (δ 2.87) due to one CH_3NH functionality. Reaction of a sample of 3 with methylamine also produced the dimethyl compound **4,** thus implicating **3** as the probable intermediate in the conversion of 1 to **4.**

The reactivity of the C_4 position in this series of compounds is in distinct contrast to the results obtained by the reaction of 5-fluorocytidine with methylamine in methanol; even after 96 h at room temperature in the presence of 9 equiv of methylamine, no reaction was detected.

A pyrimidine byproduct was obtained from the reaction of 1 with methylamine and was isolated as the hydrochloride. An analysis of its NMR spectrum revealed one three-proton doublet at δ 2.88 due to a CH_3NH group and a broad exchangeable two-proton singlet at δ 8.55 due to a primary amino group in addition to signals due to the CH=CF and NH protons. This material was designated as 4-amino-5-fluoro-2-methylaminopyrimidine hydrochloride (**5**), the formation of which could be accounted for by attack of methylamine on 1 followed by aminolysis of the nucleoside 3 or by acidic hydrolysis of 3 during the preparation of the picrate. Since physicochemical methods were unable to determine the exact location of the methyl group, confirmation of the structural assignment of 5 was obtained by an alternate synthesis. Reaction of 2,4-dichloro-5-fluoropyrimidine **6** with ammonia as previously reported[8] gave 4-amino-2-chloro-5-fluoropyrimidine **7;** treatment of 7 with methylamine for 75 h at room temperature in a stainless steel bomb induced nucleophilic displacement of the relatively unreactive 2-chloro substituent, and **5** was obtained in 21% yield. This material proved to be identical with the sample obtained from the reaction of 1 with methylamine.

Compound 1 was also treated with methylamine for a prolonged reaction period (2–3 days), and thin-layer chromatographic analysis of the reaction mixture indicated the complete absence of 1 and 4 with the formation of a new product which was subsequently isolated in crystalline form as the picrate and as the hydrochloride. The latter gave a correct elemental analysis for a dimethylpyrimidine of empirical formula $C_6H_{10}ClFN_4$. The most likely structure to be expected from such a reaction would be 2,4-bis(methylamino)-5-fluoropyrimidine hydrochloride **8,** the formation of which could be explained by aminolysis of the dimethylated nucleoside **4.** Compound **4** therefore was synthesized by an unambiguous route by reaction of **6** with anhydrous methylamine at room temperature in a stainless steel bomb. This material, however, proved to be different from the dimethyl derivative obtained from the reaction of 1 with methylamine. Moreover, a comparison of the NMR data of these two compounds indicated that **8,** when isolated as the picrate, revealed the presence of two three-proton doublets at ca. δ 2.9 due to two CH_3NH

groups, which on addition of D_2O collapsed to two singlets. The picrate of the dimethylpyrimidine obtained from the reaction of 1 with methylamine, on the other hand, revealed the presence of only one doublet at δ 2.93 due to one CH_3NH function, but a three-proton singlet at lower field suggested the presence of an uncoupled *N*-methyl group, presumably located directly on the pyrimidine ring. Since NMR and UV studies were unable to determine the exact location of the two methyl groups, an X-ray crystallographic analysis of the hydrobromide was carried out. The structure was thus revealed to be 2-amino-5-fluoro-1-methyl-4-methyliminopyrimidine hydrohalide (**9**).

The formation of this compound can be rationalized as follows: (a) formation of the bis(methylamino)pyrimidine arabinoside **4** by attack at C_2 and C_4 as previously discussed, (b) Dimroth rearrangement of **4** to the glycosylamine **10** during which the sugar is transferred to the exocyclic nitrogen, and (c) attack of methylamine at C_1 of the sugar moiety to give the 1-methylpyrimidine **9**. Dimroth rearrangement of 1-alkyl-2-alkyliminopyrimidines has been well documented,[9] and the rearrangement of **4** can be considered as a nucleoside example of this class of reactions. Since the normal driving force for the Dimroth rearrangement, i.e., the production of a formally aromatic ring, is absent in this example, **4** would be expected to undergo rearrangement to produce a mixture of isomers in a ratio controlled by steric and/or electronic factors; in cases where the two alkyl groups are electronically similar, the equilibrium favors the isomer bearing the bulky substituent on the exocyclic nitrogen. Thus, the equilibrium for the Dimroth rearrangement of **4** would be expected to favor the formation of **10** in which the bulky sugar substituent is in the exocyclic N_2 position. The glycosylamine **10** would then be expected to undergo attack by methylamine at the C_1' atom with the formation of the 1-methylpyrimidine **9**. The overall yield of **9** from **1** was found to be 44% by direct cyrstallization of the picrate.

In order to demonstrate the intermediacy of the 2,4-bis(methylamino)arabinosyl nucleoside (**4**) in this scheme, **4** was directly treated with methylamine under essentially the same reaction conditions as for **1**. A thin-layer chromatographic examination of the reaction mixture revealed the presence of two products; the major product proved to be chromatographically identical with the 1-methyl-4-methyliminopyrimidine **9**, and the minor component corresponded to the 2,4-bis(methylamino)pyrimidine **8**. The mixture was resolved by column chromatography on silica, and **9** and **8** were isolated as their picrate salts in yields of 54 and 2.5%, respectively. This latter material could have been produced either by Dimroth rearrangement of the 1-methylpyrimidine **9** in the presence of methylamine or by direct aminolysis of the nucleoside **4**. Since direct treatment of **9** with methylamine failed to produce **8**, the latter was presumably produced by aminolysis of the bis(methylamino) nucleoside **4**. Exposure of **8** to methylamine similarly failed to produce any trace of **9**, providing further evidence that the Dimroth rearrangement to produce **9** occurred at the nucleoside level rather than the pyrimidine level. In contrast, acidic hydrolysis of **4** produced **8** as the only UV-absorbing product; the physicochemical characteristics of the picrate of **8** proved to be identical with the material previously obtained by the reaction of 2,4-dichloro-5-fluoropyrimidine (**6**) with methylamine.

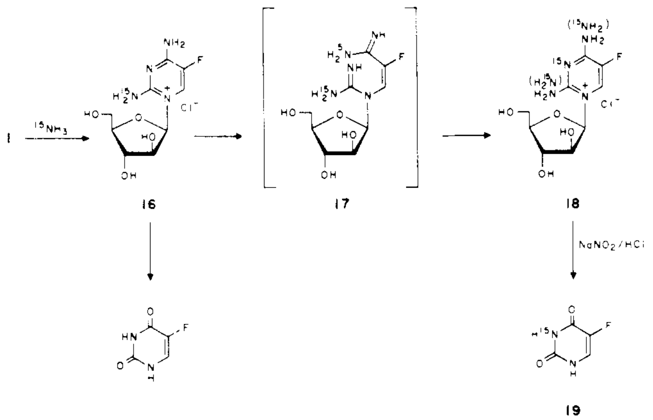
Reaction of 1-β-D-arabinofuranosyl-2,4-diamino-5-fluoropyrimidine (**2**) with methylamine for 1 h produced a new compound which was not isolated in pure form, but which was tentatively assigned to be the 4-methylamino nucleoside **11**, obtained by amine exchange at C_4. The reaction mixture was hydrolyzed with hot aqueous picric acid to give a new monomethyl pyrimidine which was isomeric with but different from the 2-methylaminopyrimidine **5**; its structure was therefore deduced to be 2-amino-5-fluoro-4-methylaminopyrimidine (**12**). The NMR signal for the methyl group in the free base or the hydrochloride appeared as a three-proton doublet in the δ 2.8 region, thus confirming the presence of the CH_3NH function rather than a methyl group located on the pyrimidine ring. The structure of **12** was confirmed by synthesis from **6**; reaction with methylamine in methanol overnight at 5 °C gave 2-chloro-5-fluoro-4-methylaminopyrimidine (**13**), from which **12** was obtained by reaction with ammonia at elevated temperature and pressure. Prolonged reaction of the diamino nucleoside **2** with methylamine (for 2 days) introduced two methyl groups into the pyrimidine ring, and 1-methyl-4-methyliminopyrimidine **9** was produced as the major product, isolated as the picrate in 31% yield. The formation of **9** from **2** can be explained on the basis of (a) amine exchange at both C_2 and C_4 to give the bis(methylamino)pyrimidine **4**, and (b) Dimroth rearrangement of **4** via the intermediate **10** as previously discussed. The bis(methylamino) nucleoside **4** was in fact isolated in small quantities from the reaction mixture, thus providing support for the intermediacy of this compound in the conversion of **2** to **9**. The isolation of the dimethylamino nucleoside **4** demonstrates that amine exchange at C_2 is experimentally possible; amine exchange at C_4 has previously been discussed.

Reactions of anhydro-ara-FC with other amines were also briefly studied. Reaction with excess ethylamine gave the 2,4-bis(ethylamino) compound **14**, and, similarly, reaction with *n*-propylamine gave the di-*n*-propyl derivative **15**; with the conditions employed (5 equiv of amine in methanol, 25 °C, 15 min), starting material was completely consumed and no degradation of the nucleoside linkage was detected. Reaction of **1** with dimethylamine was less successful; after treatment with 6 equiv for 40 min, a complex mixture was obtained, from which no crystalline products could be isolated.

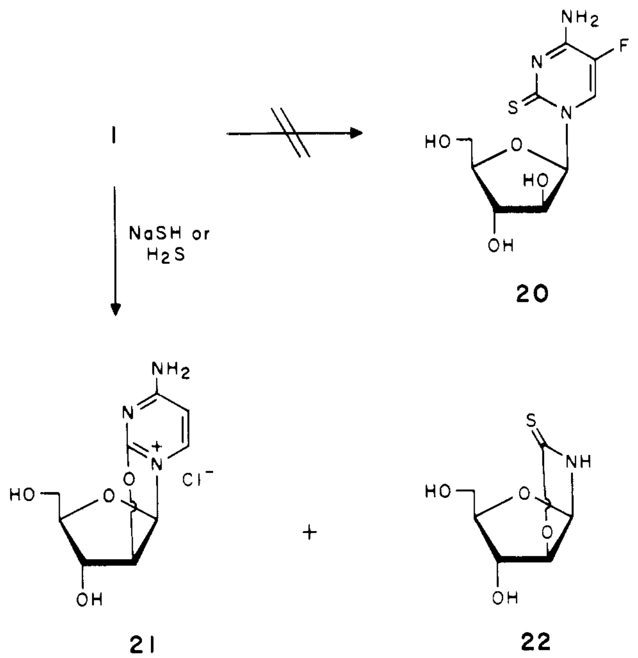
The reactivity of C_4 in this series of compounds prompted us to examine the reaction of anhydro-ara-FC with ^{15}N-enriched ammonia. Using 6 equiv of 99% ^{15}N-enriched ammonia, a reaction with **1** was carried out for 3 h at 25 °C; under these conditions, only the diamino nucleoside could be detected by TLC. The extent of reaction of $^{15}NH_3$ at C_4, in addition to attack at C_2, was calculated by mass spectrometry;[10] although the molecular ion for the nucleoside was not detected, the peaks derived from the 2,4-diamino-5-fluoropyrimidine fragment were observed. A comparison of the relative proportions of these peaks at *m/e* 129 and 130 as compared with those obtained from unenriched material gave an indication of the extent of incorporation of a second molecule of $^{15}NH_3$ in addition to incorporation at C_2. These experiments indicated that incorporation of a second molecule of $^{15}NH_3$ had occurred to the extent of 22%. In addition, a small peak at *m/e* 131 indicated that a small percentage (1%) of incorporation of a third atom of ^{15}N had taken place.

In order to determine the extent of ^{15}N incorporation into the pyrimidine ring, in addition to the exocyclic amino groups, a sample of the diamino nucleoside obtained by treatment of anhydro-ara-FC with ^{15}N-enriched ammonia was hydrolyzed and deaminated using sodium nitrite in aqueous hydrochloric acid to produce 5-fluorouracil. This sample was analyzed by mass spectrometry and again compared with a sample of unenriched material. By this method it was determined that ^{15}N had been incorporated into the pyrimidine ring to the extent of about 6%, in addition to incorporation at the exocyclic amino groups. One suggested mechanism for ring incorporation of ^{15}N is illustrated in Scheme II. Initial attack by $^{15}NH_3$ would produce the singly labeled species **16**, and attack of a second molecule of $^{15}NH_3$ on C_4 followed by ring opening would produce an amidine such as **17**. This molecule is capable of recyclization so that an ^{15}N atom is incorporated into the N_3 position of the pyrimidine ring to give **18**. The exocyclic

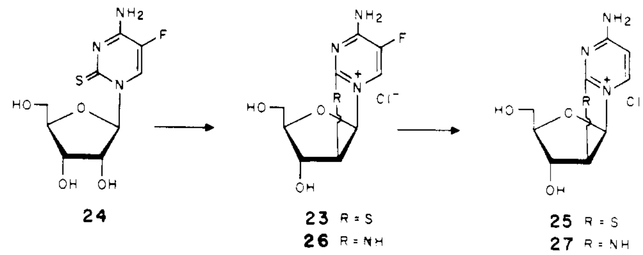
Scheme II



Scheme III



Scheme IV



amino groups of **18** would contain either ^{14}N or ^{15}N atoms, depending upon the direction of ring closure and whether subsequent exchange reactions had taken place. This reaction can be considered as another nucleoside example of the Dimroth rearrangement. Subsequent degradation of **18** with sodium nitrite/hydrochloric acid would lead to the production of [^{15}N]-5-fluorouracil (**19**).

A second series of reactions was carried out by reaction of anhydro-ara-FC (**1**) and analogues with sodium hydrosulfide or hydrogen sulfide. It was anticipated at the outset that reaction of the sulfur nucleophile would take place at C_2 to yield 2-thio-ara-FC (**20**; Scheme III). Reaction of **1** with 1.4 equiv of sodium hydrosulfide did not lead to the expected 2-thioarabinoside, but instead yielded the defluorinated anhydro nucleoside **21** in a yield of 49%. Reaction of **1** with hydrogen sulfide was carried out in DMF as solvent in the presence of triethylamine. After 9 h at room temperature, a considerable amount of starting material was still present, but a small amount (5%) of defluorinated anhydro nucleoside **21** was again isolated; in addition, a new product was obtained. This latter material, which was formulated as the oxazolidinethione **22**, was presumably produced by reaction of hydrogen sulfide at C_2 followed by degradation of the pyrimidine ring in preference to the 2,2′-anhydro linkage. The preparation of **22** from D-arabinose has previously been described by Ranganathan,[11] although no analytical data were given. Thus, the 2,2′-anhydro bond, which has previously been shown to be quite labile under alkaline conditions,[7] is remarkably stable toward sodium hydrosulfide or hydrogen sulfide. The inability of these sulfur nucleophiles to form **20** may be a reflection of the fact that although the SH^- ion is strongly nucleophilic, the sulfur atom forms the C═S bond with reluctance as compared with C═O.

The formation of the defluorinated anhydro nucleoside was not anticipated, even though there is some precedent for debromination of bromouracil derivatives under similar conditions. Szabo, Kalman, and Bardos, for example, have reported that reaction of 1-methyl-5-bromouracil with sodium hydrosulfide gave 1-methyluracil.[12] Deuterium exchange studies led these workers to propose a mechanism of addition, followed by displacement of the bromo substituent by hydrosulfide ion and subsequent elimination; such a mechanism would seem to be applicable to the defluorination reaction, although we have not studied the mechanistic aspects of this reaction. Other workers have described the debromination of 5-bromouracil with either cysteine[13] or sodium bisulfite,[14] and the enzyme thymidylate synthetase has also been reported to catalyze debromination of 5-bromo-2′-deoxyuridylate, although the corresponding 5-chloro and 5-fluoro nucleotides were not dehalogenated under the same conditions.[15] Defluorination has also been observed as a side reaction in the aminolysis of 5-fluoro-4-thiopyrimidine nucleosides.[16]

We have also studied this defluorination reaction using analogues of anhydro-ara-FC in which the oxygen of the 2,2′-anhydro bridge was replaced by sulfur or nitrogen. The sulfur analogue **23** (Scheme IV) was synthesized in a conventional manner[17] by reaction of acetoxyisobutyryl chloride with 2-thio-5-fluorocytidine (**24**). The latter compound was in turn prepared by reaction of the silyl derivative of 2-thio-5-fluorocytosine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose using the silyl procedure of Vorbrüggen and Strehlke.[18] Reaction of **23** with sodium hydrosulfide (2.6 equiv) for 3 h at room temperature did produce the defluorinated anhydro nucleoside **25**, a compound which has been previously synthesized by Russell et al.[17]

The first paper in this series dealt with the synthesis of the nitrogen-bridged analogue **26**. Treatment of a small sample of this compound with sodium hydrosulfide gave as the major product a compound with the same chromatographic properties as the defluorinated analogue **27**;[19] insufficient material was available for a rigorous characterization. The facility with which these anhydro nucleosides undergo defluorination prompted an examination of a reaction of 5-fluorocytidine with sodium hydrosulfide; even after a prolonged reaction time (3 days at room temperature), no evidence for defluorination could be detected. The lability of the 5-fluoro substituent therefore seems to be particularly enhanced in the anhydro series.

Experimental Section

General. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. NMR spectra were obtained using either a Varian XL-100 or HA-100 spectrometer and IR spectra with either a Perkin-Elmer 621 or a Beckman IR-9 instrument. UV spectra were obtained using a Cary Model 14 recording spectrometer.

1-β-D-Arabinofuranosyl-2,4-diamino-5-fluoropyrimidinium Chloride (2). A suspension of anhydro-ara-FC (1; 20 g) in methanolic ammonia (25 mL, saturated) was stirred at room temperature for 20 min. During this time the starting material dissolved and a crystalline precipitate was formed. At this point 2-propanol (400 mL) was added and the suspension was stored at 0 °C for 1 h. The crystals were collected by filtration, washed with 2-propanol, and dried in vacuo to give **2**: 16.2 g (76%); mp 175–176 °C dec; UV (H_2O) λ_{max} 205–206 nm (ϵ 18 000), 235–237 (11 000), 274–276 (7450); NMR (D_2O) δ 4.6 (m, 4, C_3' H, C_4' H, CH_2), 5.13 (d, 1, C_2' H), 6.55 (q, 1, C_1' H), 8.85 (d, 1, CHCF). Anal. Calcd for $C_9H_{14}ClFN_4O_4$: C, 36.43; H, 4.76; N, 18.88; F, 6.40. Found: C, 36.70; H, 4.87; N, 19.24; F, 6.78.

The liquors were evaporated to ca. 100 mL, and on storage crystals of 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline were deposited, 2.6 g (21%). Recrystallization from methanol gave pure material, mp 177–178 °C (lit.[6] mp 175–176 °C).

1-β-D-Arabinofuranosyl-4-amino-5-fluoro-2-methylaminopyrimidinium Picrate (3). A suspension of 1 (629 mg) in methanolic methylamine (4.5 M, 0.5 mL) was stirred at room temperature for 5 h. The residual solid was removed by filtration, and the filtrate was evaporated to dryness and treated with aqueous picric acid (30 mL, saturated). After storage at room temperature overnight, the crystals were collected and recrystallized from water (10 mL) to give **3**, 352 mg (31%), as the hemihydrate: mp 95–103 °C (indefinite); NMR (Me_2SO-d_6) δ 2.87 (d, 3, CH_3NH). Anal. Calcd for $C_{16}H_{18}FN_7O_{11}\cdot 0.5H_2O$: C, 37.51; H, 3.74; F, 3.71; N, 19.14. Found: C, 37.32; H, 3.66; F, 3.68; N, 18.91.

1-β-D-Arabinofuranosyl-5-fluoro-2,4-bis(methylamino)pyrimidinium Chloride (4). A suspension of anhydro-ara-FC (1; 3 g) in methanol (50 mL) containing methylamine (1 g) was stirred at room temperature for 15 min. The solution was evaporated to dryness and dried in vacuo for 2 h, and aqueous picric acid (saturated, 190 mL) was added. After 1 h at 0 °C, the crystals were collected by filtration and the liquors were concentrated to ca. 40 mL and cooled to 0 °C. This procedure yielded a second batch of picrate (total 3.27 g, 59%). A sample was recrystallized from water: mp 78 °C (indefinite); UV (MeOH) λ_{max} 213 nm (ϵ 34 400), 284 (9400), 355 (14 900); NMR (Me_2SO-d_6) δ 2.89 (d, 3, CH_3NH), 2.97 (d, 3, CH_3NH), 5.91 (d, 1, C_1' H), 8.12 (m, 1, NH), 8.50 (d, 1, CHCF), 8.59 (s, 2, picrate), 9.18 (m, 1, NH). Anal. Calcd for $C_{17}H_{20}FN_7O_{11}$: C, 39.46; H, 3.90; F, 3.67; N, 18.95. Found: C, 39.09; H, 3.87; F, 3.43; N, 18.55.

A sample of the picrate (1.07 g) was dissolved in methanol/water (110 mL, 1:10) and stirred with an excess of AG 1-X8 resin (chloride form, Bio-Rad Labs) until a colorless solution was obtained. The resin was filtered off, and the filtrate was evaporated to dryness and dried by repeated coevaporation of ethanol over the residue. The dried material was dissolved in ethanol (4 mL) and added dropwise with stirring to ether (50 mL). The precipitate was collected by centrifugation, washed with ether twice, and dried in vacuo to give the hydrochloride salt of 4 as an amorphous powder: 257 mg; mp 120 °C (indefinite); UV (H_2O) λ_{max} 213 nm (ϵ 15 380), 247–248 (14 620), 280 sh (7630); NMR (Me_2SO-d_6) δ 2.91 (d, 3, CH_3NH), 3.00 (d, 3, CH_3NH), 8.55 (m, 1, NH), 9.29 (m, 1, NH). Anal. Calcd for $C_{11}H_{18}ClFN_4O_4\cdot 1.5H_2O$: C, 37.55; H, 6.01; N, 15.92. Found: C, 37.90; H, 6.27; N, 16.26.

The combined liquors from the picrate of 4 were concentrated to a small volume, and a third batch of crystals was deposited. Recrystallization from methanol/water yielded the picrate of **5**, 487 mg (12%). Treatment with AG 1-X8 resin (chloride form) in the usual manner and recrystallization from ethanol/ether gave **5** as the hydrochloride: 150 mg (8%); mp 214–215 °C; UV (0.1 N HCl) λ_{max} 210 sh nm (ϵ 15 720), 222–223 (18 320), 279–281 (3400); NMR (Me_2SO-d_6) δ 2.88 (d, 3, CH_3NH), 8.09 (d, 1, CHCF), 8.23 (m, 1, NH), 8.55 (brd s, 2, NH_2). Anal. Calcd for $C_5H_8ClFN_4$: C, 33.62; H, 4.51; Cl, 19.85; N, 31.37. Found: C, 33.79; H, 4.62; Cl, 19.85; N, 31.05.

4-Amino-5-fluoro-2-methylaminopyrimidinium Chloride (5) from 4-Amino-2-chloro-5-fluoropyrimidine (7). 4-Amino-2-chloro-5-fluoropyrimidine (7; 1 g)[8] was treated with methylamine (40 mL) in a stainless steel bomb at room temperature for 75 h. The product was evaporated to dryness, dissolved in methanol, and impregnated onto silica gel (15 g, Merck). This material was applied to the top of a silica column (250 g) which had been packed in chloroform/ethyl acetate (1:1), and the column was eluted with the same solvent (1.5 L) followed by ethyl acetate (2 L). Fractions 125–170 (20-mL size) were evaporated to dryness, dissolved in ethanol (50 mL), and treated with aqueous hydrochloric acid (1 N, 9.2 mL). This solution was evaporated to dryness, coevaporated with ethanol, and recrystallized from the same solvent to give **5**, 256 mg (21%). This material proved to be identical with the sample of 5 previously isolated.

5-Fluoro-2,4-bis(methylamino)pyrimidinium Chloride (8). (a) Via 2,4-Dichloro-5-fluoropyrimidine (6). Liquid methylamine (20 mL) was added to 2,4-dichloro-5-fluoropyrimidine[8] (**6**; 1 g) in a stainless steel bomb which had been cooled in a dry ice–acetone bath. The vessel was sealed and stored at room temperature for 5 days. After this time, the bomb was cooled, opened, and allowed to warm to room temperature to allow methylamine to evaporate. The residue was dissolved in methanol (100 mL) and filtered through Celite, and the filtrate was evaporated to dryness and pumped in vacuo. The residue was dissolved in water (120 mL) and filtered through Celite, and the filtrate was treated with saturated aqueous picric acid (200 mL). Crystals were deposited on storage overnight, and recrystallization gave pure **8** as the picrate: 0.9 g (39%); mp 240–242.5 °C dec; UV (CH_3OH) λ_{max} 209 nm (ϵ 40 200), 300 (7200), 354 (15 100); NMR (Me_2SO-d_6) δ 9.00 (m, 1, NH), 8.60 (s, 2, picrate), 7.92 (d, 1, CHCF), 7.90 (m, 1, NH), 2.96 (d, 3, CH_3NH), 2.88 (d, 3, CH_3NH). Anal. Calcd for $C_{12}H_{12}FN_7O_7$: C, 37.41; H, 3.14; F, 4.93. Found: C, 37.32; H, 3.34; F, 4.80.

A sample (0.4 g) in methanol/water (500 mL, 1:1) was warmed to dissolve it and was stirred with an excess of AG 1-X8 resin (chloride form). The mixture was applied to the top of a column (20 mL) of the same resin, which was eluted with methanol/water (1:1). The eluate (560 mL) was collected, evaporated to dryness, and crystallized from methanol/ethyl acetate to give **8** as the hydrochloride: 157 mg (79% from the hydrochloride); mp 243–244 °C; UV (H_2O) λ_{max} 215 nm (ϵ 20 220), 280 sh (5200); NMR (Me_2SO-d_6) δ 9.10 (m, 1, NH), 8.31 (m, 1, NH), 8.01 (d, 1, CHCF), 2.93 and 2.97 (overlapping d, 6, $2CH_3NH$). Anal. Calcd for $C_6H_{10}ClFN_4$: C, 37.41; H, 5.23; F, 9.86; N, 29.09. Found: C, 37.40; H, 5.22; F, 9.69; N, 29.20.

(b) Via Hydrolysis of 4. A solution of the picrate of 4 (0.5 g) in aqueous hydrochloric acid (1 N, 20 mL) was heated at 100 °C for 1 h and then stored at 0 °C for 2 h. The crystals were collected and recrystallized from water to give the picrate of **8**, 90 mg (24%).

2-Amino-5-fluoro-1-methyl-4-methyliminopyrimidinium Chloride (9). (a) Reaction of 1 with Methylamine. A suspension of 1 (15 g) in methanol (80 mL) containing methylamine (15 g) was stirred at room temperature until the solid dissolved. The solution was then stored at room temperature for 36 h, evaporated to dryness, and evacuated for 1 h. The residue was treated with aqueous picric acid (960 mL) with stirring for 1 h, and the crystals were filtered off and recrystallized from water to give **9** as the picrate: 10.4 g (50%); mp 224–226 °C; UV (CH_3OH) λ_{max} 207 nm (ϵ 46 500), 353 (15 700); NMR (Me_2SO-d_6) δ 8.88 (m, 1, NH), 8.54 (s, 1, picrate), 8.17 (d, 1, CHCF), 8.02 (brd s, 2, NH_2), 3.47 (s, 3, CH_3N), 2.93 (d, 3, CH_3NH). Anal. Calcd for $C_{12}H_{12}FN_7O_7$: C, 37.41; H, 3.14; F, 4.93; N, 25.45. Found: C, 37.64; H, 2.87; F, 4.81; N, 25.75.

The picrate was dissolved in methanol/water (1 L, 4:1), and the solution was treated with an excess of AG 1-X8 resin (chloride form) with stirring for 1 h. The resin was removed by filtration, and the filtrate was treated with carbon and filtered through Celite. The filtrate was evaporated to a solid which was dried and recrystallized from ethanol/ethyl acetate to give **9** as the chloride: 4.5 g (44%); mp 295 °C dec; UV (0.1 N HCl) λ_{max} 239–240 nm (ϵ 11 550), 275–276 (8400); NMR (Me_2SO-d_6) δ 2.93 (s, 3, CH_3), 3.58 (s, 3, CH_3), 8.42 (d, 1, CHCF), 8.5 (m, 3, 3NH). Anal. Calcd for $C_6H_{10}ClFN_4$: C, 37.41; H, 5.23; N, 29.09; Cl, 18.40; F, 9.86. Found: C, 37.38; H, 5.35; N, 28.93; Cl, 18.50; F, 9.87.

(b) Reaction of 4 with Methylamine. The picrate of 4 (2 g) was converted into the chloride by passage through an AG 1-X8 column (chloride form), and the eluate was evaporated to dryness. The residue was coevaporated with ethanol twice, pumped in vacuo overnight, and then treated with a solution of methylamine in methanol (0.11 g/mL, 15 mL) for 66 h at room temperature. This solution was evaporated to dryness, dissolved in 1-butanol/acetic acid/water (12:3:5, 10 mL), and applied to a silica column (3.5 × 60 cm) which was packed and eluted with the same solvent mixture. Fractions of 20 mL were collected and tubes 35–43 were combined and evaporated to dryness. Treatment of the residue with saturated aqueous picric acid (10.8 mL) gave a crystalline precipitate. After storage overnight, the crystals were collected and dried in vacuo to give **8**, 37 mg (2.5%).

Fractions 46–70 were combined and evaporated, and the residue was dissolved in a minimum amount of water and treated with aqueous picric acid (54 mL). The crystals were collected and dried in vacuo to give **9** as the picrate, 0.81 g (54%).

Crystals of the hydrobromide of 9 are monoclinic, space group $P2_1/a$, with $a = 7.137$ (1) Å, $b = 20.590$ (4) Å, $c = 6.254$ (1) Å, $\beta = 95.39$ (1)°, and $d_{calcd} = 1.720$ g cm^{-3} for $Z = 4$. X-ray crystallographic intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans). The approximate size of the crystal used for data collection was 0.07 × 0.10 × 0.4 mm; the data were corrected for absorption. There were 1237 accessible reflections with $\theta < 57°$, of which 1094 were considered to be observed. The structure was solved by a multiple solution procedure and was refined by full matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The final discrepancy indices are $R = 0.055$ and $R_w = 0.065$ for the 1094 observed reflections.[20]

The relatively short C_2–N_3 and C_4–N_4 bond distances (1.317 and 1.320 Å, respectively) as compared with the C_2–N_2 and N_3–C_4 distances (1.349 and 1.342 Å) imply the existence of a 2-amino-4-methylimino tautomer rather than a 2-imino-4-methylamino structure.

2-Amino-5-fluoro-4-methylaminopyrimidinium Chloride (12). (a) From 2. Compound **2** (1 g) was stirred with methylamine in methanol (0.72 M, 30 mL) for 1 h at room temperature and evaporated to dryness. The residue was treated with aqueous picric acid (100 mL) at 100 °C for 6 h, and on cooling crystals were deposited. These crystals were collected and recrystallized from methanol/water to give the picrate of **12**, 332 mg (27%). A second crop of 557 mg (45%) was obtained by evaporation of the liquors. A sample was converted into the chloride form by stirring a methanolic solution of the picrate with AG 1-X8 resin (chloride form). Recrystallization from ethanol/ether gave pure **12** as the hydrochloride: mp 209–210 °C; UV (0.1 N HCl) λ_{max} 206 nm (ϵ 20 500), 235 sh (12 650), 267 (7500); NMR (Me_2SO-d_6) δ 2.92 (d, 3, CH_3NH), 7.90 (s, 2, NH_2), 8.06 (d, 1, CHCF), 8.99 (m, 1, NH). Anal. Calcd for $C_5H_8ClFN_4$: C, 33.62; H, 4.51; Cl, 19.85; N, 31.37. Found: C, 33.84; H, 4.64; Cl, 20.14; N, 31.02.

(b) From 6. A 0 °C solution of **6** (0.95 g) in methanol (10 mL) was treated with methylamine in methanol (3.55 N, 9.6 mL), stored overnight at 5 °C, and evaporated to a white solid which was triturated with water (10 mL). The solid was collected by filtration and dried in vacuo to give crude **13**, 629 mg (68%). For analytical purposes, a sample was recrystallized from water: mp 131.5–132.5 °C; UV (CH_3OH) λ_{max} 240 nm (ϵ 10 800), 280 (5350); NMR (Me_2SO-d_6) δ 2.84 (d, 3, CH_3NH), 8.02 (d, 1, CHCF), 8.08 (brd s, 1, NH). Anal. Calcd for $C_5H_5ClFN_3$: C, 37.17; H, 3.12; Cl, 21.95; N, 26.01. Found: C, 37.05; H, 3.25; Cl, 22.06; N, 26.01.

A sample (249 mg) of crude **13** in liquid ammonia (6 mL) was stored in a steel bomb for 64 h at 100 °C. The bomb was cooled in a dry ice–acetone bath, and methanol (30 mL) was added. The solution was filtered through Celite to remove some insoluble brown material, and the filtrate was evaporated to dryness and dissolved in chloroform/methanol (10:1, 10 mL). This solution was applied to a silica column (100 g) and the column eluted with the same solvent. Fractions of 20 mL were collected, and tubes 42–58 were combined and evaporated to give crude **12** as the free base, 0.1 g (46%). Recrystallization from water gave analytically pure material, mp 158–160 °C. A sample of the picrate was prepared by the usual procedure and found to be identical with the sample obtained from the reaction of **1** with methylamine (melting point, IR, and NMR).

Prolonged Reaction of 2 with Methylamine. A suspension of **2** (3 g) in methanol (25 mL) containing methylamine (2.75 g) was stirred until completely dissolved, and the solution was stored at room temperature for 45 h and then evaporated to dryness. The residual gum was dissolved in methanol (20 mL) and applied to a silica column (700 g) which had been packed in the same solvent. The column was eluted with methanol (2 L) followed by methanol/acetic acid (100:1, 2 L), and fractions of 20 mL were collected. Fractions 158–300 were combined, evaporated to dryness, dissolved in water (10 mL), and treated with saturated aqueous picric acid (116 mL). After storage at 0 °C for 2 h, the yellow precipitate was collected and recrystallized from methanol/water to give the picrate of **9**, 1.2 g (31%).

Fractions 130–150 were combined and evaporated to dryness (1.29 g). A portion (0.89 g) of this material was triturated with ethanol (10 mL), and after storage at 5 °C overnight, a white solid was removed by filtration and discarded. The filtrate was evaporated to a brown gum (450 mg), which was dissolved in a minimum amount of water and treated with picric acid (22 mL). After storage at 5 °C overnight, crystals (33 mg) were deposited. Recrystallization from water gave pure **4**, 21 mg.

1-β-D-Arabinofuranosyl-2,4-bis(ethylamino)-5-fluoropyrimidinium Chloride (14). A suspension of **1** (5 g) in methanol (40 mL) containing ethylamine (3 g) was stirred for 15 min at room temperature. The solution was evaporated to dryness, pumped in vacuo for 1 h, and treated with aqueous picric acid (325 mL). After 1 h at 0 °C, the solid was collected, washed briefly with ice water, and dissolved in methanol/water (1:1, 100 mL). The solution was stirred with an excess of AG 1-X8 (chloride) resin until colorless, and the resin was removed by filtration. The filtrate was evaporated to dryness and triturated with ethyl acetate (50 mL) and methanol (0.1 mL). Crystallization commenced on standing. The solid was recrystallized from methanol (5 mL)/ethyl acetate (50 mL) to give **14**, 2.9 g (46%): mp 147–148 °C; UV (H_2O) λ_{max} 217 nm (ϵ 17 500), 251 (16 200), 285 sh (8300); NMR (Me_2SO-d_6) δ 1.28 (t, 6, $2CH_3CH_2$), 3.55 (m, 4, $2CH_3CH_2$). Anal. Calcd for $C_{13}H_{22}ClFN_4O_4$: C, 44.26; H, 6.29; Cl^-, 10.05; N, 15.88. Found: C, 44.28; H, 6.36; Cl^-, 10.05; N, 15.96.

Table I

m/e	no. of ^{15}N atoms	% incorporation
128	0	6
129	1	71
130	2	22
131	3	1

1-β-D-Arabinofuranosyl-5-fluoro-2,4-bis(n-propylamino)-pyrimidinium Chloride (15). Anhydro-ara-FC (**1**; 5 g) was treated with n-propylamine (7.35 mL) in methanol (50 mL) for 15 min at room temperature and isolated as described for **14**: 4.0 g (59%); mp 147–149 °C, then resolidified and mp 181 °C dec; UV (0.1 N HCl) λ_{max} 219–220 nm (ϵ 17 500), 253 (16 500), 285 sh (8600); NMR (Me_2SO-d_6) δ 0.90 (t, 6, $2CH_3$), 1.63 (m, 4, $2CH_3CH_2$), 3.35 (m, 4, $2CH_2N$). Anal. Calcd for $C_{15}H_{26}ClFN_4O_4$: C, 47.31; H, 6.88; Cl^-, 9.31; N, 14.71. Found: C, 47.20; H, 6.97; Cl^-, 9.51; N, 14.58.

Reaction of 1 with $^{15}NH_3$. A suspension of **1** (207 mg, 0.74 mmol) in methanol (1 mL) containing ammonia (99% ^{15}N-enriched, 4.46 mmol) was stirred at room temperature for 3 h and then treated with 2-propanol (3 mL). After storage at 0 °C overnight, the solid was collected, washed with 2-propanol, and dried in vacuo. Recrystallization from methanol/ethyl acetate gave the diamino nucleoside (132 mg, 60%), mp 172–173 °C. Mass spectrometric examination of the peaks assigned to the 2,4-diamino-5-fluoropyrimidinium ion (m/e 128, 129, 130, and 131), as compared with those obtained from an unenriched sample, gave the results in Table I.

Degradation of ^{15}N-Enriched Diamino Nucleoside to 5-Fluorouracil. A sample of ^{15}N-enriched diamino nucleoside (45 mg) in aqueous hydrochloric acid (1 N, 2 mL) was heated with sodium nitrite (400 mg) at 60 °C for 24 h and then evaporated to dryness. The residue was extracted with methanol, and the extract was applied to a silica gel plate (3 mm thickness) which was developed in tetrahydrofuran/methanol (10:1). The band corresponding to 5-fluorouracil was cut out and extracted with methanol, and the extract was evaporated to dryness and redissolved in methanol. Solids were removed by centrifugation, and the supernatant was evaporated to dryness for examination by mass spectrometry. The relative intensities of the peaks at m/e 130 and 131 in the synthetic sample (corresponding to the molecular ion peaks for [^{14}N]- and [^{15}N]fluorouracil, respectively) were compared with those obtained from authentic material. By this method it was determined (after correction for the natural abundance of ^{15}N) that (m/e 130)/(m/e 131) = 94/6; i.e., 6% of the synthetic sample of 5-fluorouracil contained one ^{15}N atom per molecule.

Reaction of 1 with Sodium Hydrosulfide. A suspension of **1** (580 mg) and sodium hydrosulfide (255 mg) in methanol (50 mL) was stirred at room temperature for 3 h and concentrated to 10 mL. Silica gel (13 g) was added, and the slurry was applied to the top of a silica gel column (125 g) which had been packed in methanol/acetic acid (100:1). After a preliminary wash with methanol (150 mL), the column was eluted with methanol/acetic acid (100:1) and fractions of 20 mL were collected. Tubes 24–60 were combined, evaporated to dryness, and dissolved in water. Some insoluble material was removed by filtration, and the filtrate was evaporated to dryness, dried by evaporation of ethanol over the residue, and crystallized from methanol to give the acetate of **21** (278 mg, 49%), mp 179–180 °C dec (lit.[5] mp 190–192 °C). A sample was converted into the hydrochloride salt by passage through an AG 1-X8 (chloride) column and recrystallized from methanol: mp 249 °C dec (lit.[17] 266–267 °C); UV (H_2O) λ_{max} 231 nm (ϵ 9350), 262 (10 380); NMR (Me_2SO-d_6) δ 6.70 (d, 1, C_5 H), 8.28 (d, 1, C_6 H), 9.21 (s, 1, NH), 9.69 (s, 1, NH). Anal. Calcd for $C_9H_{12}ClN_3O_4$: C, 41.31; H, 4.62; N, 16.06. Found: C, 41.38; H, 4.70; N, 16.02.

Reaction of 1 with Hydrogen Sulfide. Hydrogen sulfide was bubbled into a suspension of **1** (2.8 g) in DMF (100 mL, dry) and triethylamine (3 mL). After 9 h, a stream of nitrogen was bubbled into the solution for 30 min to remove hydrogen sulfide, and the solution was filtered to remove unreacted starting material (1.35 g). Silica gel (25 g) was added to the filtrate, and the slurry was evaporated to dryness and applied to the top of a silica gel column (250 g) which had been packed in chloroform. The column was initially developed with chloroform, and fractions were evaporated and crystallized from ethanol to give 238 mg (12%) of the oxazolidinethione **22**: mp 132–133.5 °C; UV (CH_3OH) λ_{max} 243 nm (ϵ 18 950), 285 sh (1010); NMR (Me_2SO-d_6) δ 3.27 (m, 2, CH_2), 3.87 (m, 1, CH), 4.23 (m, 1, CH), 4.88 (t, 1, CH_2OH), 5.05 (d, 1, OH), 5.66 (d, 1, OH), 5.79 (d, 1, C_1' H), 10.76 (s, 1, NH). Anal. Calcd for $C_6H_9NO_4S$: C, 37.69; H, 4.74; N, 7.33; S, 16.77. Found: C, 37.55; H, 4.69; N, 7.31; S, 16.85.

The column was subsequently eluted with chloroform/methanol (10:1, 5 L) to remove a number of minor impurities which were discarded. Elution with methanol/acetic acid (1 L, 50:1) gave a fraction which was evaporated to dryness and converted into the chloride form in the usual way. Recrystallization from methanol yielded **21**, 125 mg (5%).

5-Fluoro-2-thiocytidine (24). A solution of 4-amino-2-chloro-5-fluoropyrimidine[8] (25.2 g) and sodium hydrosulfide (51 g) in ethylene glycol (75 mL) was heated with stirring to 103 °C. At this point, heating was discontinued since the solution began to foam. After 15 min, the solution was heated to 140 °C and maintained at that temperature for 15 min. The product was cooled, treated with water (250 mL), adjusted to pH 6.5 with aqueous hydrochloric acid (6 N, 50 mL), and cooled to 0 °C for 1 h. The precipitate was filtered, washed with water (3 × 60 mL), and dried in vacuo. Recrystallization from water (2.6 L) yielded 5-fluoro-2-thiocytosine (14.8 g, 60%), mp 265 °C (indefinite) dec. Anal. Calcd for $C_4H_4FN_3S$: C, 33.10; H, 2.78; F, 13.10; N, 28.95; S, 22.09. Found: C, 32.99; H, 2.77; F, 13.00; N, 28.73; S, 22.37.

This material (4.5 g) was suspended in dry dioxane (120 mL) and treated with 1,1,1,3,3,3-hexamethyldisilazane (22.5 mL) and chlorotrimethylsilane (3 mL) under reflux for 5.5 h. The solid was removed by filtration, and the filtrate was concentrated to a yellow paste. This material was dissolved in 1,2-dichloroethane (100 mL, distilled over P_2O_5) and treated with a solution of tri-*O*-benzoyl-1-*O*-acetyl-D-ribofuranose (14 g) in dry acetonitrile (125 mL). This solution was treated with freshly distilled stannic chloride (3 mL) in dichloroethane (25 mL) for 3 h at room temperature. The reaction mixture was cooled to 0 °C and treated with aqueous sodium bicarbonate (1 M, 450 mL) with vigorous stirring at room temperature for 18 h. The emulsion was filtered through Celite, and the organic layer was washed with water (2 × 400 mL), dried over anhydrous sodium sulfate, and concentrated to a foam. This material was dissolved in chloroform (50 mL), applied to a silica gel column (1.6 kg), and eluted with chloroform/acetone (85:15). Fractions of 20 mL were collected, and tubes 400–660 were combined and evaporated to yield 8.2 g (45%) of 2′,3′,5′-tri-*O*-benzoyl-5-fluoro-2-thiocytidine as a white solid. A sample was crystallized with difficulty from ethanol at 0 °C: mp 165–168 °C dec; NMR (Me_2SO-d_6) δ 7.4–8.0 (m, 15, $3C_6H_5$); UV (CH_3OH) λ_{max} 232 nm (ϵ 46 000), 262 (26 200), 315 sh (3000). Anal. Calcd for $C_{30}H_{24}FN_3O_7S$: C, 61.11; H, 4.10; F, 3.22; N, 7.13; S, 5.44. Found: C, 61.00; H, 4.21; F, 3.22; N, 7.06; S, 5.51.

The crude tribenzoyl derivative (7.05 g) was treated with saturated methanolic ammonia (200 mL) for 18 h at room temperature. After evaporation to dryness, the residue was dissolved in water (200 mL) and extracted with ether (3 × 200 mL). The aqueous layer was evaporated to dryness, and the residue was coevaporated with ethanol. The residue was dissolved in hot methanol (15 mL), treated with activated carbon, and filtered through Celite. On cooling to 0 °C, crystalline **24** (3.02 g, 91%) was deposited: mp 127 °C; UV (H_2O) λ_{max} 217 nm (ϵ 5900), 260 (21 550); NMR (Me_2SO-d_6) δ 3.17 (d, 3, CH_3OH), 3.70 (m, 2, CH_2), 3.95 (m, 4, C_2', C_3', and C_4' H, OH), 4.88 (d, 1, OH) 5.33 (d, 2, OH), 6.44 (brd s, 1, C_1' H), 7.8 (brd s, 1, NH), 8.2 (brd s, 1, NH), 8.72 (d, 1, CHCF). Anal. Calcd for $C_9H_{12}FN_3O_4S \cdot CH_3OH$: C, 38.83; H, 5.21; N, 13.58; S, 10.36. Found: C, 38.38; H, 5.05; N, 13.36; S, 10.55.

2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluoro-2-thiocytosine Hydrochloride (23). A suspension of **24** (2.0 g) in dry acetonitrile (24 mL) was treated with acetoxyisobutyryl chloride (4 mL) for 3.5 h. The solution was added dropwise to anhydrous ether (400 mL), and the precipitate was collected, washed with ether, and treated with methanolic hydrogen chloride (0.15 N, 52 mL) for 72 h. The solution was evaporated, and on trituration with boiling isopropyl alcohol (30 mL) **23** was obtained, 1.4 g (72%). An analytically pure sample was obtained by crystallization from methanol/isopropyl alcohol: mp 211–212 °C; UV (CH_3OH) λ_{max} 247 nm (ϵ 23 500), 285 sh (5100); NMR (Me_2SO-d_6) δ 3.44 (d, 2, CH_2), 4.15 (q, 1, C_4' H), 4.41 (t, 1, C_3' H), 4.55 (q, 1, C_2' H), 6.64 (d, 1, C_1' H), 8.78 (d, 1, CHCF), 9.59 (s, 1, NH), 9.84 (s, 1, NH). Anal. Calcd for $C_9H_{11}ClFN_3O_3S$: C, 36.55; H, 3.75; F, 6.42; N, 14.21; S, 10.84. Found: C, 36.63; H, 3.79; F, 6.25; N, 13.96; S, 10.85.

Reaction of 23 with Sodium Hydrosulfide. A solution of **23** (1 g) in methanol (100 mL, dry) was treated with sodium hydrosulfide (0.81 g) with stirring at room temperature for 3 h. A small amount of insoluble material was removed by filtration, and the filtrate was applied directly to a silica gel column (silica gel 60, size C; E. Merck, Darmstadt). The column was eluted with methanol (600 mL) followed by methanol/acetic acid (50:1, 1 L), and fractions of 20 mL were collected. Fractions 77–100 were combined, evaporated to dryness, dissolved in water (10 mL), and applied to an AG 50-X8 column (1 × 10 cm, chloride form) which was washed with water. The fractions containing UV-absorbing material were pooled and evaporated to dryness, and the residue was triturated with hot 2-propanol (13 mL) to yield **25** as an amorphous solid, 198 mg (21%). An analytically pure sample was obtained by recrystallization from methanol/chloroform, mp 195–197 °C (lit.[17] mp 201–202.5 °C).

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Registry No.—**1**, 40505-45-1; **2**, 67316-25-0; **3**, 67316-27-2; **4** picrate, 67316-29-4; **4** HCl, 67316-30-7; **5** picrate, 67316-32-9; **5** HCl, 67316-33-0; **6**, 2927-71-1; **7**, 155-10-2; **8** picrate, 67316-35-2; **8** HCl, 67316-36-3; **9** picrate, 67316-38-5; **9** HCl, 67316-39-6; **9** HBr, 67360-74-1; **12**, 67316-40-9; **12** picrate, 67316-41-0; **12** HCl, 67316-42-1; **13**, 67316-43-2; **14** HCl, 67316-44-3; **15** HCl, 67316-45-4; **21** HCl, 10212-25-6; **21** acetate, 10212-28-9; **22**, 56270-92-9; **23**, 67316-46-5; **24**, 67316-47-6; **25**, 51392-03-1; methylamine, 74-89-5; 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline, 67316-48-7; ethylamine, 75-04-7; propylamine, 107-10-8; 5-fluoro-2-thiocytosine, 67316-49-8; tri-*O*-benzoyl-1-*O*-acetyl-D-ribofuranose, 6974-32-9; 2′,3′,5′-tri-*O*-benzoyl-5-fluoro-2-thiocytidine, 67316-50-1.

References and Notes

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