3,3-Dimethyl-1-nitrobutane (13).—3,3-Dimethyl-1-nitrobut-1-ene (2.83 g) was dissolved in 50 ml of methanol and 1.00 g of sodium borohydride was added. This mixture was stirred for 24 hr at room temperature, poured into water, made acidic with dilute hydrochloric acid, and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to give 0.483 g (17%) of 3,3-dimethyl-1-nitrobutane: nmr peaks at τ 5.54 (t, 2), 8.04 (t, 2).

A. Reaction of *trans*-Stilbene with Silver Nitrite and Iodine.—The general procedure was used incorporating 5.85 g (32.5 mmol) of *trans*-stilbene, 2.50 g (16.3 mmol) of silver nitrite, and 8.25 g (32.5 mmol) of iodine in 75 ml of ether. After reaction the mixture was filtered and the solids were washed free of iodine color with ether. The solids were heated on a steam bath with 150 ml of benzene and filtered while hot. The combined filtrates were worked up as usual. Recrystallization from benzene gave 4.232 g of product **14**: mp 167–169°; infrared absorption at 1540, 1352, and 723 cm^{-1}; nmr peaks at τ 3.43 (d, 1, J = 12 Hz), 3.74 (d, $W_{1/2}$ = 12 Hz), and 3.86 (d, $W_{1/2}$ = 12 Hz). The analytical sample melted at 172–173°.

Anal. Calcd for $C_{14}H_{12}NO_2I$: C, 47.61; H, 3.43; I, 35.94. Found: C, 47.81; H, 3.67; I, 36.24.

The mother liquor gave 4.087 g of unreacted olefin which was found to be only *trans*-stilbene by nmr with a signal at τ 2.9.

B. Reaction of *cis*-Stilbene with Silver Nitrite and Iodine.—The previous reaction was repeated incorporating 2.56 g of silver nitrite, 16.5 g of iodine, and 3.0 g of *cis*-stilbene. After work-up 2.40 g of crude **14**, mp 167–169°, was obtained. The infrared and nmr spectra were identical with those of the analyzed sample. The nmr of the mother liquor indicated that the recovered olefin consisted solely of *cis*-stilbene with a signal at τ 3.45.

***cis*-α-Nitrostilbene (15).**—A solution of 1.50 g of 1,2-diphenyl-1-iodo-2-nitroethane (**14**) was dissolved in 10 ml of ether and 10 ml of pyridine and allowed to stand at room temperature for 2 hr. This mixture was extracted with pentane–water and the pentane was repeatedly washed with water. After drying ($MgSO_4$) and evaporation 1.132 g of a dark brown solid was obtained. Chromatography on silica gel gave 0.812 g of **15** as a bright yellow solid, mp 72–73° (89%) (lit.[7] mp 74–75°).

Registry No.—Nitryl iodide, 15465-40-4; **1**, 20429-43-0; **3**, 13643-70-4; **8**, 20429-45-2; **9**, 20429-46-3; **12**, 20429-42-9; **14**, 20429-47-4.

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Nucleosides. LX.[1a] Fluorocarbohydrates. XXII.[1b] Synthesis of 2-Deoxy-2-fluoro-D-arabinose and 9-(2-Deoxy-2-fluoro-α- and -β-D-arabinofuranosyl)adenines[2]

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Nucleophilic attack of KHF_2 on methyl 2,3-anhydro-5-*O*-benzyl-α-D-riboside is shown to occur largely at the 2 position (in contrast to the β-D anomer) and leads to methyl 5-*O*-benzyl-2-deoxy-2-fluoro-α-D-arabinoside (**4b**), thus achieving the first *direct* synthesis of a 2-fluoropentose derivative. From **4b**, 2-deoxy-2-fluoro-D-arabinose (**6**) is obtained. Fusion of 1,3-di-*O*-acetyl-5-*O*-benzyl-2-deoxy-2-fluoro-D-arabinose with 2,6-dichloropurine affords a readily resolved α-β mixture of 9-glycosylpurine nucleosides, which are converted into 9-(2-deoxy-2-fluoro-α- and -β-D-arabinofuranosyl)adenines (**14** and **15**). Confirmation of the anomeric configuration of these nucleosides is obtained by conversion into their 5′-tosylates (**16** and **17**) and by cyclization of the β anomer to its 3,5′-cyclo nucleoside (**18**).

9-β-D-Arabinofuranosyladenine[3] (Ara-A) is an effective inhibitor of the growth of several mouse tumors.[4,5] However, the efficacy of this drug is reduced by the conversion of Ara-A *in vivo* into the inactive inosine analog by adenosine deaminase.[5] These results suggest that an analog of Ara-A which would maintain its chemotherapeutic effect without undergoing enzymatic degradation would be desirable. Toward this end, the synthesis of the 2′-fluoro analog of Ara-A was undertaken. Such a nucleoside may also be regarded as a 2′-fluoro analog of 2′-deoxyadenosine occurring in DNA.

In previous studies we reported the synthesis of 2′-deoxy-2′-fluoro analogs of uridine,[6a] 5-fluorouridine,[6a] ribothymidine,[6a] and cytidine[6b] by treatment of 2,2′-anhydro nucleosides with hydrogen fluoride. By glycosyl cleavage of the 5,6-dihydro derivative of 2′-deoxy-2′-fluorouridine, 2-deoxy-2-fluoro-D-ribose[6c] was obtained. We now report the first synthesis of a 2-fluoropentose from a pentoside precursor and its conversion into 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (**10b**).

It was demonstrated[7] that treatment of the β-epoxide (**1**) with KHF_2 in ethylene glycol gave the 3-fluoro xyloside (**2**) as the only isolable product (Scheme I). That the 3-fluoro isomer was the predominant product from this reaction may be due to steric factors related to the methoxy group in the β configuration. It may be expected, particularly in view of previous results with

(1) For previous papers in these series see (a) Nucleosides. LIX: K. A. Watanabe, M. P. Kotick and J. J. Fox, *Chem. Pharm. Bull.*, **17**, 416 (1969). (b) Fluorocarbohydrates. XXI: R. C. Young, R. A. Dwek, and P. W. Kent, *Carbohyd. Res.*, in press.

(2) This work was supported in part by funds from British Scientific Research Council (J. A. W.), the British Medical Research Council (N. F. T.) and the National Cancer Institute, National Institutes of Health, U. S. Public Health Service Grant 08748 (J. J. F. and J. A. W.).

(3) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 2648 (1960); E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3247 (1962); C. P. J. Glaudemans and H. G. Fletcher, Jr., *ibid.*, **28**, 3004 (1963); E. J. Reist, V. J. Bartuska, and L. Goodman, *ibid.*, **29**, 3725 (1964).

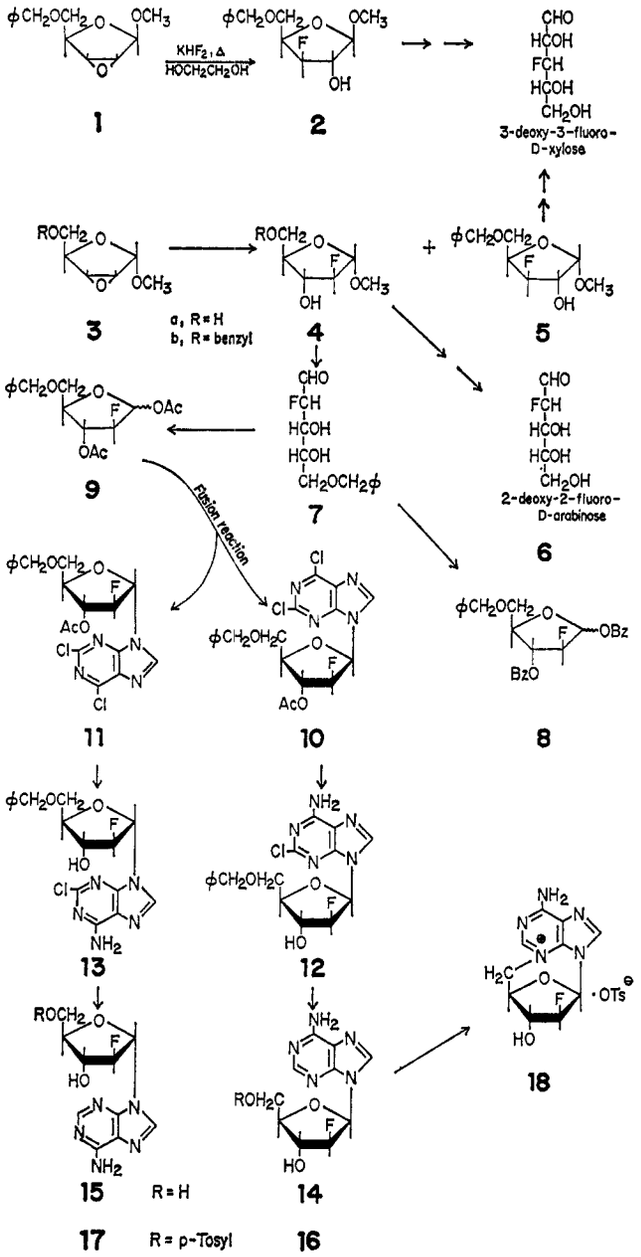
(4) R. Koshiura and G. A. LePage, *Cancer Res.*, **28**, 1014 (1968) and leading references therein.

(5) For a review of the biochemistry of arabinosyl nucleosides see S. S. Cohen, *Progr. Nucleic Acid Res. Mol. Biol.*, **5**, 1 (1966).

(6) (a) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964); (b) I. L. Doerr and J. J. Fox, *ibid.*, **32**, 1462 (1967); (c) J. F. Codington, I. L. Doerr, and J. J. Fox, *Carbohyd. Res.*, **1**, 455 (1966).

(7) J. A. Wright and N. F. Taylor, *ibid.*, **6**, 347 (1968).

SCHEME I



other nucleophiles,[8] that the α-epoxide (**3**)—where this steric inhibition to attack on C2 is not present—would react with KHF_2 to give a significant proportion of the 2-fluoro isomer. Accordingly, the known[9] methyl 2,3-anhydro-α-D-ribofuranoside (**3a**) was converted into the 5-*O*-benzyl ether (**3b**) and treated with KHF_2 in refluxing ethylene glycol to give a mixture of fluoro sugars **4b** and **5b**. The former (**4b**) was obtained in 40% yield, whereas the *xylo* isomer (**5b**) was present in only small amounts. Separation of the isomers was achieved by short column chromatography on silica gel. The identity of the 3-fluoro *xylo* isomer was established by debenzylation (hydrogenolysis) followed by acid hydrolysis to give 3-deoxy-3-fluoro-D-xylose, identical with that previously reported.[7]

Compound **4b** was isolated as a pure syrup which gave satisfactory elemental analyses (C, H, F) and showed the presence of the methoxyl and benzyl groups in its nmr spectrum. Assuming a normal *trans* opening of epoxide **3b**, it is clear that **4b** must be the 2-deoxy-2-fluoroarabinofuranoside. Final confirmation of the position of the fluoro atom in **4b** is given later in the proof of the structure of nucleoside **10**.

Catalytic hydrogenolysis of **4b** using 5% Pd/C proceeded readily, giving rise to glycoside **4a** as a colorless syrup, whose nmr and ir spectra showed the absence of the benzyl substituent. Acid hydrolysis of **4a**, using conditions similar to those employed for hydrolysis of the methyl 3-deoxy-3-fluoro-D-*xylo*- and -*arabino*-furanosides previously reported,[7,10] was much slower. Thus, while methyl 3-deoxy-3-fluoro-α-D-arabinofuranoside was completely hydrolyzed in 1 hr in refluxing 0.05 *M* H_2SO_4, compound **4a** required 5 hr under similar conditions. This finding is in agreement with others attesting to the influence of electronegative substituents[11] at C-2 upon the rate of hydrolysis of glycosides.

The hydrolysis product **6** was isolated as a viscous, colorless, analytically pure syrup which reduced Fehling's solution and which differed chromatographically from 3-deoxy-3-fluoro-D-xylose and -arabinose and from 2-deoxy-2-fluoro-D-ribose. These data allow the structural assignment of 2-deoxy-2-fluoro-D-arabinose to **6**. The 60-MHz nmr spectrum of **6** was very complex, and no first-order analysis was attempted.

Acid hydrolysis of methyl 5-*O*-benzyl-2-deoxy-2-fluoroarabinoside (**4b**) using conditions similar to those employed with 3-deoxy-3-fluoro analogs[7,10] was also slow, requiring 4 hr for completion. From this reaction 5-*O*-benzyl-2-deoxy-2-fluoro-D-arabinose (**7**) was obtained as a chromatographically pure syrup which reduced Fehling's solution. Periodate oxidation of **7** proceeded slowly, and in 100 hr the consumption of 3.2 mol of oxidant per mol was observed with the liberation of 1.5 mol of formic acid and 0.5 mol of fluoride ion. These results contrast with those obtained from the isomeric 3-deoxy-3-fluoro analogs[7,10] and are in keeping with the behavior of methyl 2-deoxy-2-fluoro-D-ribopyranoside[6c] and of malondialdehydes[12] toward this oxidant. Compound **7**[13] was characterized as the crystalline 1,3-di-*O*-benzoyl derivative (**8**).

Acetylation of **7** gave the 1,3-di-*O*-acetyl derivative **9** which was chromatographically homogeneous on tlc and gave satisfactory elemental analyses. Condensation of **9** with 2,6-dichloropurine at 160° using *p*-toluenesulfonic acid as catalyst (fusion procedure)[14] gave an anomeric mixture[15] which was readily resolved by short column chromatography[16] on silica gel G into the β nucleoside **10** (30%), the α nucleoside **11** (29%), and unreacted sugar **9** (15%). The β anomer **10** crystallized

(8) G. Casini and L. Goodman, *J. Amer. Chem. Soc.*, **85**, 235 (1963); L. Goodman, *ibid.*, **86**, 4167 (1964); P. W. Austin, J. G. Buchanan, and E. M. Oakes, *Chem. Commun.*, 374 (1965).

(9) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 5247 (1958).

(10) J. A. Wright and N. F. Taylor, *Carbohyd. Res.*, **3**, 333 (1967).

(11) J. N. BeMiller, *Advan. Carbohy. Chem.*, **22**, 25 (1967).

(12) C. F. Huebner, S. R. Ames, and E. C. Bubl, *J. Amer. Chem. Soc.*, **68**, 1621 (1946).

(13) Compounds **7** and **6** are depicted in the aldehydo form for convenience only.

(14) B. Helferich and E. S. Hillebrecht, *Chem. Ber.*, **66**, 378 (1933); T. Sato, T. Shimadate, and Y. Ishodo, *Nippon Kagaku Zasshi*, **81**, 1440 (1960); M. J. Robins, W. A. Bowles, and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1251 (1964).

(15) This result was expected in view of the absence of a substituent at C-2 capable of neighboring-group participation.

(16) B. J. Hunt and W. Rigby, *Chem. Ind.* (London), 1868 (1967).

readily, but the α anomer was isolated only as a glass, although chromatographically pure. The site of glycosylation in both anomers was shown to be on position 9 by comparison of their ultraviolet spectra with those of the 7- and 9-methyl-2,6-dichlorpurines.[17] The benzyl substituent in **10** and **11** is an isolated chromophore absorbing only weakly in the 250–300-mμ region and thus does not interfere significantly with λ_{max} values. Thus, compounds **10**, **11**, and 2,6-dichloro-9-methylpurine exhibit λ_{max} at 274 mμ, whereas the λ_{max} of 2,6-dichloro-7-methylpurine is at 278–284 mμ.

The nmr spectra of **10** and **11** furnished clear proof that the fluorine atom is at carbon 2 of the sugar. Thus, the anomeric proton in each isomer appeared as a quartet at about δ 6.5 ppm, displaying the characteristically large vicinal H–F coupling; H-1′ of **11** possessed $J_{1'\text{-F}}$ of 14.5 Hz, and $J_{1',2'}$ of 2.0 Hz, while for **10** the comparable values were 17.3 Hz and 4.0 Hz, respectively, measured in acetone-d_6. It was also noted that in the spectrum of **10** the signal at δ 8.55 assigned to H-8 was split into a doublet with a coupling constant of 2.6 Hz. This splitting, also observed in compounds **12** and **14** (see below), is believed to be long-range (^5J) coupling to the 2′-fluoro substituent, since spin-decoupling experiments ruled out H-8–H-1′ coupling. In addition, a fine-splitting of about 1 Hz in the signals assigned to the 5′ protons in **10**, **11**, and some of the other compounds described herein was attributed to long-range coupling with the fluorine atom, since the ring proton signals showed no such splitting. Fluorine nmr spectra should provide confirmation of these extra couplings. The rest of the signals in the spectra of **10** and **11** were well-resolved, including those assigned to H-2′, which showed geminal H–F couplings of 50.5 Hz in agreement with the assigned structures.

Treatment of **10** and **11** with alcoholic ammonia at room temperature resulted in hydrolysis of the 3′-*O*-acetyl esters and replacement of the 6-chloro substituent by amino groups, to give **12** and **13** in 85–90% yields. Conversion into the fully deblocked nucleosides was effected by hydrogenolysis in the presence of Pd/C catalyst. Tlc showed this reaction to proceed stepwise, with rapid removal of the 5′-*O*-benzyl group followed by slow replacement of the 2-chloro substituent by hydrogen, to give 80–85% yields of **14**, mp 232–234°, and **15**, mp 209–210°. The uv spectra of **14** and **15** closely resembled that of adenosine in water and at pH 1, providing further confirmation of the 9-substituted adenine structure. In the nmr spectra, signals at δ ~8.2 (sharp singlet) and ~7,3 ppm (broad singlet) were assigned to H-2 and NH_2 respectively.

Chemical confirmation of the configurational assignments at the anomeric center of **14** and **15** was obtained from their 5′-*O*-tosyl esters **16** and **17** using the method originated by Todd, *et al.*[18] The position of the tosyl substituents in **16** and **17** was indicated in their nmr spectra by a downfield shift of ~0.7 ppm in the signals assigned to the 5′ protons. Compound **17** remained unchanged after 5-hr reflux in dioxane, whereas **16** underwent complete conversion into the 3,5′-cyclo nucleoside **18**. The conversion of **16** into **18** was accompanied by a bathochromic shift in the uv spectrum from 262 to 274 mμ, by the appearance of new absorption bands at 685, 1010, and 1210 cm^{-1} in the ir spectrum characteristic of the tosylate anion, by loss of solubility in nonaqueous solvents, and by a large reduction in chromatographic mobility.

(17) A. G. Beaman and R. K. Robins, *J. Org. Chem.*, **28**, 2310 (1963).
(18) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

Experimental Section

General Procedures.—Melting points were determined using a Hoover–Thomas capillary apparatus, and are corrected. Thin layer chromatography (tlc) was performed on microscope slides coated with silica gel GF 254 (Merck), using ethyl acetate–benzene (1:3) (solvent A) and methanol–chloroform (1:5) (solvent B) as eluting solvents. Compounds were detected by viewing under uv light and by spraying with 20% (v/v) H_2SO_4 in ethanol followed by heating to 130°. Reducing sugars were detected using aniline hydrogen phthalate reagent. All evaporations were carried out *in vacuo*.

Nmr spectra were measured on a Varian A-60 instrument, using TMS as internal standard. Chemical shifts are reported in ppm (δ), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (complex multiplet). Coupling constants are first order. Uv spectra were measured using a Unicam Model SP 800, and ir spectra on a Perkin-Elmer Model 221 spectrophotometer. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Methyl 2,3-Anhydro-5-*O*-benzyl-α-D-ribofuranoside (3b).—To a solution of **3a**[9] (10 g, 0.068 mol) in anhydrous DMF (50 ml), silver oxide (14 g) and benzyl bromide (12 ml, 0.10 mol) were added. The mixture was shaken 24 hr at room temperature, then diluted with chloroform (500 ml) and water (500 ml). The chloroform layer was separated and filtered, pyridine (50 ml) was added, and the solution was washed successively with water (six times, 200 ml), 2 *N* HCl (thrice, 200 ml), and saturated $NaHCO_3$ (200 ml), then dried ($MgSO_4$) and evaporated. The resulting oil was distilled *in vacuo* to give colorless **3b** (13.4 g): bp 110–115° (0.02 Torr); $[\alpha]^{22}D$ −18.1° (*c* 1.3, ethanol); nmr (acetone-d_6) signals at δ 7.34 (s 5, aromatic), 5.17 (s 1, H-1), 4.55 (s 2, benzyl CH_2), 4.25 (t 1, H-4, $J_{4,5}$ 3.9 Hz), 3.71 (s 2, H-2, H-3), 3.60 (d 2, H-5), and 3.38 (s 3, OCH_3).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.18; H, 6.68.

Methyl 5-*O*-Benzyl-2-deoxy-2-fluoro-α-D-arabinofuranoside (4b).—A solution of **3b** (7 g) and KHF_2 (10 g) in ethylene glycol (140 ml) was refluxed gently for 1 hr. A further charge of KHF_2 (5 g) was added, and reflux continued another 0.5 hr. The cooled mixture was poured into saturated $NaHCO_3$ (500 ml) and extracted with chloroform (thrice, 200 ml). The dried ($MgSO_4$) chloroform layers were evaporated and the syrupy residue was chromatographed on a large diameter column of silica gel G (200 g), eluting with ethyl acetate–petroleum ether (bp 30–60°) (1:3). Fractions were collected containing **4b** (3.2 g), unreacted **3b** (1.1 g), and methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-xylofuranoside (**5**) (1.0 g), identified by hydrogenolysis and acid hydrolysis to 3-deoxy-3-fluoro-D-xylose, identical (ir and nmr spectra and chromatography) with an authentic sample.

4b had $[\alpha]^{22}D$ 94.3 (*c* 0.5, ethanol); nmr ($CDCl_3$) signals at δ 7.36 (s 5, aromatic), 5.06 (d 1, H-1, $J_{1,F}$ 10.3 Hz), 4.82 (q 1, H-2, $J_{2,F}$ 51, $J_{2,3}$ 1.6 Hz), 4.62 (s 2, benzyl CH_2), 4.1 (m 2, H-3, H-4), 3.92 (s 1, OH-3), 3.64 (d 2, H-5, $J_{4,5}$ 5.5 Hz), and 3.40 ppm (s 3, OCH_3).

Anal. Calcd for $C_{13}H_{17}O_4F$: C, 60.92; H, 6.69; F, 7.41. Found: C, 61.06; H, 6.88; F, 7.37.

Methyl 2-Deoxy-2-fluoro-α-D-arabinofuranoside (4a).—A solution of **4b** (510 mg) in ethanol (50 ml) containing 5% Pd/C (100 mg) was shaken in an atmosphere of hydrogen until uptake ceased (3 hr, 1 mol). The filtered solution was evaporated, leaving the product **4a** as a viscous syrup with a characteristic sweet odor, $[\alpha]^{21}D$ 141° (*c* 0.7, ethanol). The nmr spectrum in acetone-d_6 was rather complex, but signals could be observed at δ 4.96 (d 1, H-1, $J_{1,F}$ 12.0 Hz), 4.85 (octet 1, H-2, $J_{2,F}$ 52.0, $J_{2,3}$ 2.6, $J_{2,1}$ 1.0 Hz), and 3.7–4.5 (m 6, H-3, H-4, H-5, OH-3 and OH-5).

Anal. Calcd for $C_5H_{11}O_4F$: C, 43.37; H, 6.67; F, 11.44. Found: C, 43.47; H, 6.64; F, 11.46.

2-Deoxy-2-fluoro-D-arabinose (6).—A solution of **4a** (218 mg) in 0.1 *N* aqueous sulfuric acid (20 ml) was refluxed until tlc monitoring (solvent B) showed the hydrolysis to be complete (5 hr). The solution was cooled to room temperature and neutralized with barium carbonate. After filtration, the aqueous solution

was evaporated to dryness, and the residue extracted with absolute ethanol (twice, 5 ml). Evaporation to dryness gave **6** as a pale yellow syrup, which reduced Fehling's solution, $[\alpha]^{21}D$ −72.4° (*c* 1.0, water).

Anal. Calcd for $C_5H_9O_4F$: C, 39.48; H, 5.96; F, 12.49. Found: C, 39.80; H, 6.10; F, 12.08.

5-*O*-Benzyl-2-deoxy-2-fluoro-D-arabinose (7).—A solution of **4b** (5.0 g) in dioxane (250 ml) and 2 *N* H_2SO_4 (250 ml) was refluxed 5 hr, cooled to 0–5°, and neutralized by careful addition of concentrated ammonia. The solution was evaporated, and the residue extracted with chloroform (twice, 100 ml). The dried ($MgSO_4$) chloroform solution was evaporated, leaving **7** as a syrup (4.5 g) which reduced Fehling's solution and on tlc (solvent B) showed slight contamination with slower moving components. An analytical sample was obtained by preparative tlc on silica gel PF_{254} (Merck), eluting twice with solvent A, $[\alpha]^{23}D$ (after 1.5 hr equilibration) 37.2° (*c* 0.6, ethanol). The nmr spectrum ($CDCl_3$) contained signals at δ 7.37 (s 5, aromatic), 5.42 (d 1, H-1, $J_{1,F}$ 9.7 Hz), 4.87 (q 1, H-2, $J_{2,F}$ 50, $J_{2,3}$ 1.6 Hz), 4.54 (s 2, benzyl CH_2), 4.23 (m 1, H-3), 3.86 (m 1, H-4), 3.81 (s 2, OH) and 3.56 (d 2, H-5, $J_{4,5}$ 6 Hz).

Anal. Calcd for $C_{12}H_{15}O_4F$: C, 59.49; H, 6.24; F, 7.84. Found: C, 59.34; H, 6.25; F, 7.52.

Benzoylation of **7** using a two fold excess of benzoyl chloride in pyridine gave a 70% yield of the 1,3-di-*O*-benzoyl ester **8**, mp 53–56° after two recrystallizations from methanol. Nmr had signals ($CDCl_3$) at δ 7.0–8.3 (m 15, aromatic), 6.75 (d 1, H-1, $J_{1,F}$ 9 Hz), 5.60 (q 1, H-3, $J_{3,F}$ 19.5, $J_{3,4}$ 3.4 Hz), 5.50 (d 1, H-2, $J_{2,F}$ 49 Hz), 4.67 (m 3, H-4 + benzyl CH_2), and 3.86 ppm (d 2, H-5, $J_{4,5}$ 5.0 Hz).

Anal. Calcd for $C_{26}H_{23}O_6F$: C, 69.32; H, 5.15; F, 4.21. Found: C, 69.49; H, 5.29; F, 3.27.

1,3-Di-*O*-acetyl-5-*O*-benzyl-2-deoxy-2-fluoro-D-arabinose (9).—Acetylation of **7** (1.43 g, 0.0059 mol) using acetic anhydride (1.74 ml, 0.0185 mol) in pyridine (15 ml) at room temperature for 18 hr gave a syrup **9** (1.85 g), which failed to reduce Fehling's solution and showed no hydroxyl absorption in the ir spectrum. **9** had $[\alpha]^{22}D$ 53.1° (*c* 0.6, ethanol). The nmr spectrum (acetone-d_6) contained signals centered at δ 7.33 (s 5, aromatic), 6.26 (q 1, H-1, $J_{1,F}$ 10.5, $J_{1,2}$ 0.7 Hz), 5.25 (q 1, H-3, $J_{3,F}$ 22.8, $J_{3,4}$ 4.5 Hz), 5.10 (q 1, H-2, $J_{2,F}$ 49.0), 4.60 (s 2, benzyl CH_2), 4.47 (q, 1, H-4, $J_{4,5}$ 4.5), 3.74 (d 2, H-5), 2.09 and 2.06 ppm (each s, 3, acetyls).

Anal. Calcd for $C_{16}H_{19}O_6F$: C, 58.89; H, 5.87; F, 5.82. Found: C, 59.03; H, 5.99; F, 5.87.

2,6-Dichloro-9-(3-*O*-acetyl-5-*O*-benzyl-2-deoxy-2-fluoro-α-and -β-D-arabinofuranosyl)purines (10 and 11).—A mixture of **9** (950 mg, 2.92 mmol) and 2,6-dichloropurine (500 mg, 2.64 mmol) in a round-bottomed flask was placed in an oil bath preheated to 160°, and stirred. Within 1 min the mixture became homogeneous. Toluene-*p*-sulfonic acid (10 mg) was added, and heating and stirring maintained under reduced pressure for a further 20 min. After cooling, the gummy residue was dissolved in ethyl acetate (10 ml) and chromatographed on a large-diameter column of silica gel G (100 g), eluting with solvent A. Fractions containing unreacted **9** (129 mg), **11** (344 mg), and **10** (357 mg) were collected.

11 was obtained as a colorless gum, $[\alpha]^{22}D$ 8.6° (*c* 1.3, ethanol). Nmr signals (in acetone-d_6) were assigned as follows: δ 8.31 (s 1, H-8), 7.42 (s 5, benzyl aromatic), 6.70 (q 1, H-1′, $J_{1,F}$ 14.5, $J_{1,2}$ 2.0 Hz), 5.96 (sextet 1, H-2′, $J_{2,F}$ 50.5, $J_{2,3}$ 2.0 Hz), 5.69 (octet 1, H-3′, $J_{3,F}$ 13.5, $J_{3,4}$ 4.0 Hz), 4.92 (quartet 1, H-4′ $J_{4,5}$ 5.0 Hz), 4.25 (s 2, benzyl CH_2), 3.93 (q 2, H-5′, $J_{5,F}$ 1.0 Hz), and 2.12 ppm (s 3, acetyl). The uv spectrum showed λ_{max} (ethanol) 274.5, 254 (shoulder) mμ (ε 7780, 4780).

Anal. Calcd for $C_{19}H_{17}N_4O_4Cl_2F$: C, 50.12; H, 3.76; N, 12.30; Cl, 15.58; F, 4.17. Found: C, 50.28; H, 3.84; N, 12.19; Cl, 15.67; F, 4.16.

10 crystallized on evaporation of the appropriate fraction. Recrystallization from ether–petroleum ether afforded colorless needles, mp 115–117°, $[\alpha]^{22}D$ 23.5° (*c* 0.9, ethanol). Nmr signals (in acetone-d_6) were centered at δ 8.35 (d 1, H-8, $J_{8,F}$ 2.6 Hz), 7.35 (s 5, benzyl aromatic), 6.54 (q 1, H-1′, $J_{1,F}$ 17.3, $J_{1,2}$ 4.0 Hz), 5.62 (octet 1, H-3′, $J_{3,F}$ 17.5, $J_{3,2}$ 2.0, $J_{3,4}$ 3.9 Hz), 5.5 (octet 1, H-2′, $J_{2,F}$ 50.5 Hz), 4.67 (s 2, benzyl CH_2), 4.42 (q 1, H-4′, $J_{4,5}$ 4.8 Hz), 3.93 (q 2, H-5′, $J_{5,F}$ 0.8 Hz), and 2.15 ppm (s 3, acetyl). The uv spectrum showed λ_{max} (ethanol) 273.5, 253 (shoulder) mμ (ε 8930, 5300).

Anal. Found: C, 49.88; H, 3.76; N, 12.18; Cl, 15.68; F, 4.15.

6-Amino-2-chloro-9-(5-*O*-benzyl-2-deoxy 2-fluoro-α- and -β-D-arabinofuranosyl)purines (12 and 13).—The same procedure was used for both anomers. A solution of **10** (623.3 mg) in ethanol (50 ml) previously saturated with ammonia at −5° was kept in a bomb at room temperature for 1 week. Evaporation produced a pale yellow amorphous residue which could be crystallized from aqueous ethanol to give clusters of needles, **12** (468.3 mg), mp 163–166°. Recrystallization from ethanol afforded pure material, mp 169–171, $[\alpha]^{22}D$ 29.8° (*c* 0.7 ethanol). The uv spectrum showed λ_{max}^{EtOH} 264 mμ (ε 15,200).

Anal. Calcd for $C_{17}H_{17}N_5O_3ClF$: C, 51.84; H, 4.35; N, 17.78; Cl, 9.00; F, 4.82. Found: C, 51.77; H, 4.39; N, 17.65; Cl, 9.10; F, 4.84.

Similar treatment of **11** gave a similar yield of **13**, mp 149–155°. Recrystallization from ethanol gave colorless needles: mp 158–160°; $[\alpha]^{22}D$ 34.4° (*c* 0.4, ethanol); nmr spectrum (acetone-d_6) δ 8.32 (s 1, H-8), 7.37 (s 5, benzyl aromatic), 7.42 (broad 2, NH_2), 6.36 (q 1, H-1′, $J_{1',F}$ 17.0, $J_{1,2}$ 2.1 Hz), 5.76 (sextet 1, H-2′, $J_{2',F}$ 51, $J_{2',3'}$ 2.1 Hz), 5.54 (d 1, OH-3′), J 6.3 Hz), 4.64 (s 2, benzyl CH_2), 4.2–4.9 (m 2, H-3′, H-4′), 3.77 (q 2, H-5′, $J_{4',5'}$ 5.0, $J_{F,5'}$ 1.0 Hz); uv spectrum λ_{max}^{EtOH} 265 mμ (ε 14,400).

Anal. Found: C, 51.72; H, 4.19; N, 17.30; Cl, 8.79; F, 4.77.

9-(2-Deoxy-2-fluoro-α- and -β-D-arabinofuranosyl)adenines (14 and 15).—The same procedure was used for both anomers. To a previously hydrogenated suspension of 5% Pd/C (1.5 g) in 50% aqueous ethanol (100 ml), a solution of **12** (827.7 mg, 2.10 mmol) in ethanol (50 ml) containing NaOH (2.1 ml, 1.0 *N*) was added, and the mixture hydrogenated in a Parr apparatus. When uptake ceased (30 hr), the mixture was filtered (Whatman No. 42) and the catalyst was thoroughly washed with boiling aqueous ethanol. Filtrate and washings were evaporated to small volume, whereupon the product **14** crystallized as clusters of needles (475.4 mg). Recrystallization from ethanol gave a product of mp 232–234°, $[\alpha]^{24}D$ 22.6° (*c* 0.7, water). The nmr spectrum (DMSO-d_6) contained signals at δ 8.35 (d 1, H-8, $J_{8,F}$ 2.0 Hz), 8.19 (s 1, H-2), 7.32 (1 broad, NH_2), 6.33 (q 1, H-1′, $J_{1',F}$ 14.7, $J_{1',2'}$ 4.2 Hz), 5.95 (broad 1, OH-3′), 5.70 (sextet 1, H-2′, $J_{2,F}$ 53 Hz, $J_{2',3'}$ 4.2 Hz), 5.08 (1 broad, OH-5′), 3.6–4.8 (m 4, H-3′, H-4′, H-5′). The uv spectrum showed $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,970); $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 14,800).

Anal. Calcd for $C_{10}H_{12}N_5O_3F$: C, 44.61; H, 4.49; N, 26.01; F, 7.05. Found: C, 44.42; H, 4.46; N, 25.77; F, 7.00.

15 had mp 209–210°, $[\alpha]D$ 62.0° (*c* 0.5, water). The nmr spectrum (DMSO-d_6) contained signals at δ 8.35 (s 1, H-8), 8.22 (s 1, H-2), 7.36 (broad s 2, NH_2), 6.33 (q 1, H-1′, $J_{1',F}$ 16.3, $J_{1',2'}$ 3.4 Hz), 5.76 (sextet 1, H-2′, $J_{2',F}$ 52.0, $J_{2',3'}$ 3.4 Hz), 5.0 (broad 1, OH-3′), 4.2–4.8 (m 2, H-3′, H-4′), 3.62 (q 2, H-5′, $J_{4',5'}$ 4.1, $J_{F,5'}$ 1.0 Hz), and 3.36 ppm (s 1, OH-5′); uv spectrum $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,400); $\lambda_{max}^{pH\ 1}$ 257.5 mμ (ε 14,300).

Anal. Found: C, 44.79; H, 4.48; N, 25.96; F, 7.05.

9-(2-Deoxy-2-fluoro-5-*O*-tosyl-α- and -β-D-arabinofuranosyl)-adenines (16 and 17).—Toluene-*p*-sulfonylation of **14** (78.1 mg, 0.29 mmol) was carried out in anhydrous pyridine (4 ml) using toluene-*p*-sulfonyl chloride (130 mg, 0.67 mmol). Tlc (solvent B) showed complete disappearance of **14** (R_f 0.22) after 24 hr, with a major new spot of R_f 0.55 and a trace component of R_f 0.75. The mixture was poured into water (40 ml) and extracted with chloroform (six times, 15 ml). After two washings with saturated $NaHCO_3$ (20 ml), the dried ($MgSO_4$) chloroform extract was evaporated, leaving a gummy residue. Reevaporation from aqueous ethanol gave a colorless foam (50.0 mg) which on tlc (solvent B) was seen to contain one major component, R_f 0.55, and trace spots, R_f 0.04 and 0.75. No further purification was carried out. The compound possessed uv spectrum with λ_{max}^{EtOH} 262 mμ (ε 13,700). In the ir spectrum, strong absorption bands at 1170 and 1350 cm^{-1} indicated the presence of the sulfonoxy substituent. Similarly, **15** gave the 5′-tosyl derivative **17**, λ_{max}^{EtOH} 259 mμ (ε 14,600); in the ir spectrum new bands at 1175 and 1360 cm^{-1} indicated the presence of the sulfonoxy substituent.

Anal. Calcd for $C_{17}H_{18}N_5O_5FS$: C, 48.22; H, 4.28; N, 16.54; F, 4.49; S, 7.57. Found: C, 48.05; H, 4.38; N, 16.45; F, 4.25; S, 7.50.

3,5′-Cyclo-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine toluene-*p*-sulfonate (18).—A solution of **16** (11.6 mg) in anhydrous dioxane (1 ml) was refluxed until the uv spectrum became constant (80 min) with λ_{max} 274 mμ. Tlc of the mixture at this point showed complete disappearance of the spot R_f 0.55 (sol-

vent B), leaving only the spot R_f 0.04, which was the cyclic tosylate. Evaporation to dryness gave a colorless foam. This had, in the uv spectrum, $\lambda_{max}^{H_2O}$ 274 mμ (ε 12,300). In the ir spectrum, new bands at 685, 1010, and 1210 cm^{-1} indicated the presence of the tosylate anion.

Anal. Calcd for $C_{17}H_{18}N_5O_5FS$: C, 48.22; H, 4.28; N, 16.54; F, 4.49; S, 7.57. Found: C, 48.20; H, 4.51; N, 16.38; F, 4.35; S, 7.55.

Registry No.—**3b**, 20187-72-8; **4a**, 20187-73-9; **4b**, 20187-74-0; **6**, 20187-75-1; **7**, 20187-76-2; **8**, 20187-77-3; **9**, 20187-78-4; **10**, 20187-79-5; **11**, 20187-80-8; **12**, 20227-40-1; **13**, 20187-81-9; **14**, 20227-41-2; **15**, 20187-82-0; **16**, 20187-83-1; **17**, 20187-84-2; **18**, 20187-85-3.

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Nucleosides. LXI. Transformations of Pyrimidine Nucleosides in Alkaline Media. IV. The Conversion of 5-Hydroxyuridines into Imidazoline Nucleosides[1,2]

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Isopropylidene-5-hydroxyuridine (**2**) and 1-methyl-5-hydroxyuracil (**8**) undergo a benzilic acid type of rearrangement and dehydration in 0.1 *N* NaOH at 100° to give the corresponding 1-substituted 2-oxo-4-imidazoline-4-carboxylic acids **5** and **9**. 1,3-Dimethyl-5-hydroxyuracil (**10a**) and 1-methyl-3-benzyl-5-hydroxyuracil (**10b**) are converted under these conditions into the corresponding 1,3-disubstituted 4-hydroxy-2-oxoimidazolidine-4-carboxylic acids **11a** and **b**. Compound **11b** was converted into the crystalline methyl ester **14** by treatment with diazomethane. The 4-hydroxyimidazolidines **11a** and **b** undergo acid-catalyzed dehydration to give the 1,3-disubstituted 2-oxo-4-imidazoline-4-carboxylic acids **12a** and **b**. Evidence for the existence of the tautomeric 5-keto forms of the 5-hydroxyuracil derivatives necessary for benzilic acid rearrangement is presented. The 5-hydroxyuracil derivatives are prepared by treatment of the corresponding 5-bromouracils with CO_2-buffered sodium bicarbonate solution at 100°. In unbuffered sodium bicarbonate solution, isopropylidene-5-bromouridine (**1**) and 2′-deoxy-5-bromouridine are converted *via* their 5-hydroxy derivatives into the 2-oxo-4-imidazoline-4-carboxylic acid nucleosides. The potential application of this rearrangement to DNAs containing 2′-deoxy-5-bromouridine instead of thymidine is discussed. An *in situ* method for the conversion of uridine into the imidazoline nucleoside **6** is described. Ultraviolet spectral and pK_a data for the 5-hydroxyuracil derivatives are given.

We have previously reported[3] that 5-halogeno derivatives of isopropylideneuridine (**1**, X = F, Br, I) undergo rearrangement in 1 *N* sodium hydroxide to give the 2-oxo-4-imidazoline-4-carboxylic acid nucleoside **5** in varying yield. This rearrangement involves participation of the 5′-hydroxyl group, and it was suggested that the reaction proceeds *via* the 5′,6-anhydro acyclic ureide **4** (X = F, Br, I). We now wish to report that certain derivatives of 5-hydroxyuracil (isobarbituric acid) also undergo base-catalyzed rearrangement to 2-oxo-4-imidazoline-4-carboxylic acids. This new rearrangement does not involve participation of a sugar hydroxyl group and proceeds by a mechanism different from that of the rearrangement **1** → **4** → **5** in 1 *N* sodium hydroxide (Scheme I).

Our interest in the alkaline stability of 5-hydroxyuracil derivatives resulted from experiments which indicate that isopropylidene-5-hydroxyuridine (**2**) is stable in 1 *N* sodium hydroxide but unstable in 0.1 *N* sodium hydroxide. First, compound **2** was formed along with the imidazoline nucleoside **5** (20% yield) when a 0.1 *M* solution of the 5-bromo nucleoside **1** in 1 *N* sodium hydroxide was heated at 55° for 20 hr.[3] Moreover, compound **2** appeared to be stable under these reaction conditions, as shown by a gradual increase in the intensity of the uv absorption maximum of **2** at ~305 mμ. Secondly, isopropylidene-5-hydroxyuridine (**2**) was also formed when a 0.02 *M* solution of **1** (X = Br) in 0.1 *N* sodium hydroxide was heated at 100°. In this case, however, the concentration of **2** as monitored spectrally first increased and then gradually decreased with the concomitant formation of the imidazoline nucleoside **5**. After acidic hydrolysis of the isopropylidene group, the known[3] 1-(β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid (**6**) was obtained in 45% yield. This finding suggests the possibility that isopropylidene-5-hydroxyuridine (**2**) is an intermediate in the formation of **5** from **1** (X = Br) in 0.1 *N* sodium hydroxide. Evidence supporting the intermediacy of **2** was obtained when an attempt was made to synthesize this compound by using the procedure of Wang.[4] Accordingly, when **1** (X = Br) was heated under nitrogen in dilute sodium bicarbonate solution, the formation of **2** was indicated by the appearance of an absorption peak at 305 mμ. During the 22-hr reaction period, however, the pH of the reaction mixture increased from ~8.3 to ~10 and the slow disappearance of **2** and concomitant formation of **5** was again noted. The unblocked nucleoside **6** was isolated in 54% yield. Formation of **5** was considerably reduced when the reaction mixture of **1** (X = Br) with sodium bicarbonate was buffered (~ pH 8.3) with carbon dioxide gas. After a reaction period of 5 hr, crystalline **2** was isolated in 46% yield and characterized by conversion into the known 5-hydroxy-

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