spectrophotometrically). Integration of the nmr spectrum of **18** indicated 18 protons including peaks at δ 10.6 (1, broad s, NH), 5.97 (1, d, H-1′), and 1.06 (3, t, CH_3 of ethanol). A broad peak at δ 4.6 (hydroxyl protons) disappeared on addition of D_2O to reveal peaks at 4.4 (1, q, H-2′) and 4.1 (1, t, H-3′). The remaining protons (H-4, H-5′, H-5, H-5, and CH_2CH_3) gave rise to a seven-proton multiplet at δ 3.3–3.9 which decreased in area to a five-proton multiplet after deuterium exchange of the geminal H-5 protons ($J_{1',2'} = 3.2$, $J_{2',3'} = J_{3',4'} \simeq 6.0$ Hz).

Anal. Calcd for $C_9H_{12}N_2O_7 \cdot C_2H_5OH$: C, 43.14; H, 5.88; N, 9.15. Found: C, 43.00; H, 5.64; N, 9.34.

1-(5-*O*-Benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)barbituric acid (19).—Sodium benzoate (3.02 g, 21 mmol) was added to a solution of **15** (5.64 g, 20 mmol) in 600 ml of DMF and the mixture was heated at 120° for 3 hr. The cooled solution was concentrated to dryness and the residue was dissolved in water (150 ml). The solution was acidified (~pH 2) with 1 *N* HCl and the resulting precipitate was filtered off and washed with water. Recrystallization from 50% ethanol, and then from ethanol, afforded pure material (3.0 g, 37%): mp 163–166°; nmr δ 11.8 (1, broad s, NH), ~8.2–7.3 (5, m, aromatic protons), 6.30 (1, d, H-1′), ~5.0 (2, m, H-2′, H-3′), ~4.50 (3, m, H-4′, H-5′, H-5′), 3.70 (2, broad s which exchanges in D_2O, H-5, H-5), 1.51, 1.31 (two singlets, six protons, isopropylidene methyls) ($J_{1',2'} = 1$ Hz); uv absorption at $\lambda_{max}^{H_2O}$ 232 and 260 mμ, $\lambda_{max}^{pH\ 1}$ 230 mμ.

Anal. Calcd for $C_{19}H_{20}N_2O_8$: C, 56.48; H, 4.95; N, 6.93. Found: C, 56.31; H, 4.91; N, 6.91.

Registry No.—**2,** 19556-57-1; **3c,** 19556-58-2; **9b,** 19556-59-3; **12,** 362-43-6; **14,** 19556-61-7; **15,** 19556-62-8; **18,** 19556-63-9; **19,** 19556-64-0; 5′-deoxy-5-bromouridine, 19556-65-1.

The Preparation of 6-Fluoropurines by the Modified Schiemann Reaction[1]

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The use of forcing conditions in the modified Schiemann reaction has now permitted the preparation of a number of 6-fluoro- and 2,6-difluoropurines. In the latter cases, the 2-aminoadenines are converted first into the 2-fluoroadenines which nitrosate more favorably than the corresponding adenines and are then converted into the 2,6-difluoropurines.

In a systematic study of the action of nitrous acid on a number of condensed 2,4-diaminopyrimidine ring systems, Trattner, *et al.*,[2] found that in all cases including 2-aminoadenine, nitrosation of the 2- but not the 4-amino group took place giving the corresponding 2-hydroxy-4-amino heterocycles.[3] They explained their results by assuming that protonation takes place at N-1 rather than at N-3.[4,5] These results and those of other investigators[6-10] have led to the conclusion[11] that the modified Schiemann reaction[12] is limited to the synthesis of 2-fluoropurines and this conclusion has been generally accepted. Despite the foregoing precedents, we now wish to report cases in which we have found that derivatives of adenine and 2-aminoadenine do undergo a modified Schiemann reaction to give 6-fluoropurines.[13]

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2,6-dichloropurine[14] (**1a**), prepared by the fusion procedure,[15] was converted through diazide **2a** into 2-amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**3a**) (Scheme I). Treatment of **3a** with sodium nitrite in 48% fluoroboric acid gave a mixture from which 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)isoguanine (**4a**, 24%), 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2-fluoroadenine (**5a**, 13%), and 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2,6-difluoropurine (**6a**, 16%) were isolated by means of column chromatography on silica gel. **4a** was identified by its chromatographic behavior and by its infrared and ultraviolet spectra. **6a** was identified by its elemental analysis; by its ultraviolet, infrared, and pmr spectra; and by its conversion into 2-fluoro-9-β-D-xylofuranosyladenine (**5b**) by treatment with alcoholic ammonia. **5a** was also converted into **5b** by treatment with alcoholic ammonia. **5b** was initially prepared by the diazotization of **3b** in 48% fluoroboric acid.

It is logical to assume that **3a** is initially converted into **5a**, which reacts further to give **6a**, and evidence in support of this pathway is found in our inability to identify any 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-amino-6-fluoropurine[16] in the diazotization of 2′,3′,5′-tri-O-acetyl-2-aminoadenosine in fluoroboric acid,[17] and also in the conversion of 2′,3′,5′-tri-O-acetyl-2-fluoroadenosine (**9**) into 9-(2,3,5-tri-O-acetyl-β D-ribofuranosyl)-2,6-difluoropurine (**12**) in 25% yield (*vide*

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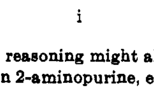
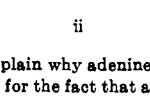
[1] This work was supported by funds from the Southern Research Institute, the C. F. Kettering Foundation, and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

[2] R. B. Trattner, G. B. Elion, G. H. Hitchings, and D. M. Sharefkin, *J. Org. Chem.*, **29**, 2674 (1964).

[3] In purine the numbering is not systematic so that 2-aminoadenine gives 2-hydroxy-6-aminopurine (isoguanine).

[4] Here again purine numbering causes confusion. Protonation in this case is at the ring nitrogen designated N-3 (i) not at N-1 (ii). In the other ring systems the designations are reversed.


i


ii

[5] This line of reasoning might also explain why adenine is more resistant to nitrosation than 2-aminopurine, except for the fact that adenine is thought to protonate at N-1, at least in the crystal, even though it undergoes nucleophilic attack primarily at N-3.

[6] A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Amer. Chem. Soc.*, **76**, 6073 (1954).

[7] A. G. Beaman, *ibid.*, **76**, 5634 (1954).

[8] A. Bendich, A. Giner-Sorolla, and J. J. Fox, *Ciba Found. Symp. Chem. Biol. Purines*, 3 (1957).

[9] A. Giner-Sorolla and A. Bendich, *J. Amer. Chem. Soc.*, **80**, 5744 (1958).

[10] A. G. Beaman and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 1067 (1962).

[11] A. G. Beaman and R. K. Robins, *J. Org. Chem.*, **28**, 2310 (1963).

[12] J. A. Montgomery and K. Hewson, *J. Amer. Chem. Soc.*, **79**, 4559 (1957); **82**, 463 (1960).

[13] A preliminary account of this work has appeared: J. A. Montgomery and K. Hewson, *J. Heterocycl. Chem.*, **4**, 463 (1967).

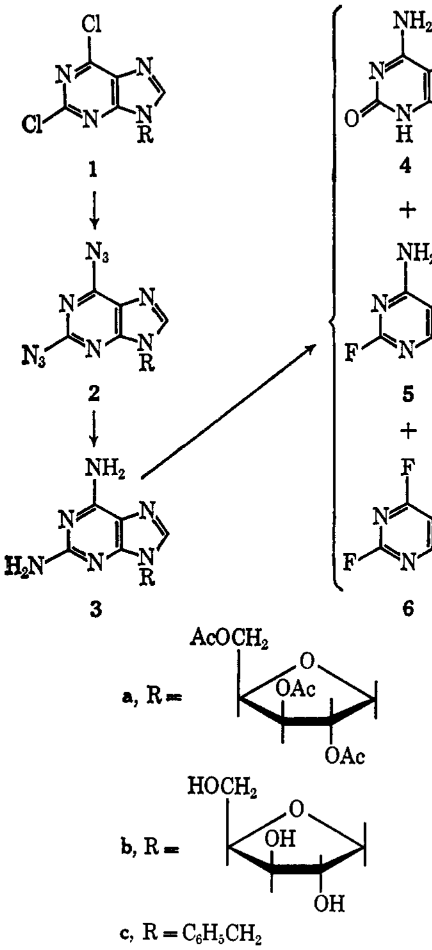
[14] E. J. Reist and L. Goodman, *Biochemistry*, **3**, 15 (1964).

[15] This fusion reaction gave predominantly the β anomer (<10% α).

[16] J. F. Gerster, A. G. Beaman, and R. K. Robins, *J. Med. Chem.*, **6**, 340 (1963).

[17] J. A. Montgomery and K. Hewson, *J. Org. Chem.*, **33**, 432 (1968).

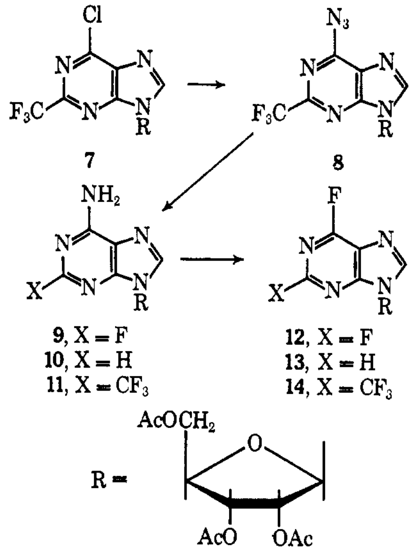
SCHEME I



infra). Furthermore, the yield of **12** from 2′,3′,5′-tri-O-acetyl-2-aminoadenosine can be greatly increased at the expense of the yield of **9** by using excess sodium nitrite.

In contrast to our results with **9**, the reaction of 2′,3′,5′-tri-O-acetyladenosine[18] was extremely sluggish, but, even though a high recovery of **10** was obtained, 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-6-fluoropurine (**13**) was formed and isolated in 3.3% yield (traces of other unidentified nucleosides were detected by thin layer chromatography).[18a] A much weaker base than **10**, 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-trifluoromethyladenine (**11**)—prepared from 6-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-trifluoromethylpurine (**7**)[19] *via* the azidopurine **8**—was nitrosated more readily giving a 30% yield of the 6-fluoropurine **14** (Scheme II). This result and the conversion of **9**, which is also a much weaker base than **10**, into **12** in 25% yield lend support to the idea that protonation in the strongly acid 48% fluoroboric acid may interfere with the nitrosation of 2′,3′,5′-tri-O-acetyladenosine (**10**) (adenosine is converted in high yield into inosine in aqueous acetic acid[20,21] in which it is not fully protonated).

SCHEME II



Not only does the amino group at C-2 of purines differ from the amino group at C-6 in the readiness with which it undergoes nitrosation in strongly acid media, but the diazonium salts, once formed, also react differently as evidenced by the fact that the 2-aminopurines give a higher yield of 2-oxopurines than 2-fluoropurines,[22] whereas the 6-aminopurines give only 6-fluoropurines. Aromatic diazonium salts are thought to react with nucleophiles *via* the aromatic carbonium ion, and presumably the 2-diazopurinium salts react in the same fashion. It would appear that the 6-diazopurinium salts react by a different mechanism, perhaps an S_Ni type mechanism.

The reaction of 2-amino-9-benzyladenine (**3c**) with sodium nitrite in fluoroboric acid[12] was reinvestigated and found to give a 9.6% yield of 9-benzyl-2,6-difluoropurine (**6c**) in addition to 9-benzyl-2-fluoroadenine (**5c**, 34%) and 9-benzylisoguanine (**4c**, 37%). In contrast, 2-aminoadenosine gave 2-fluoroadenosine and crotonoside,[12] but no evidence for the formation of 9-β-D-ribofuranosyl-2,6-difluoropurine (**15**).

Experimental Section

SilicAR-TLC-7 (Mallinckrodt) was used for column and thin layer (1 mm) chromatographic separations. Silica gel H (Brinkmann) was used for thin layer (0.25 mm) analyses. Spots were detected with either ultraviolet light after spraying the plates with Ultraphor WT highly concentrated (BASF Colors & Chemicals, Inc., Charlotte, N. C.) or heat charring after spraying with ammonium sulfate.[23] The ultraviolet absorption spectra were determined in 0.1 *N* HCl, 0.1 *N* NaOH, and pH 7 buffer with a Cary Model 14 spectrophotometer, the infrared absorption spectra were determined in pressed KBr disks with a Perkin-Elmer Model 521 spectrophotometer, and the pmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as an internal reference. The mass spectra were determined with an Hitachi-Perkin-Elmer RMU-7 mass spectrometer.

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2,6-dichloropurine (1a).—A mixture of 1,2,3,5-tetra-O-acetyl-β-D-xylofuranose[14] (7 g, 22 mmol) and 2,6-dichloropurine (4.2 g, 22 mmol) was heated with continuous stirring *in vacuo* (10 mm) at 130° until an opaque melt was obtained and vigorous gas evoluton had ceased (5–10 min). After the reaction flask had cooled but before the melt solidified, the vacuum was broken and *p*-toluenesulfonic acid (200 mg) was added. Vacuum and heat were reapplied and the reaction mixture was heated with continuous stirring at 130–135° for 20 min. A C_6H_6 (40 ml) solution of the resulting clear glass was washed with saturated aqueous $NaHCO_3$ (40 ml) and then

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[18] H. Bredereck and A. Martini, *Chem. Ber.*, **80**, 401 (1947).

[18a] NOTE ADDED IN PROOF.—A 30% yield of **13** was obtained by the action of Ag_2F_2 on 9-(2,3,5-tri-O-acetyl-D-β-ribofuranosyl)-6-chloropurine (unpublished observation of the authors).

[19] G. Gough and M. H. Maguire, *J. Med. Chem.*, **8**, 866 (1965).

[20] P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **111**, 313 (1935).

[21] J. M. Gulland and E. R. Holiday, *J. Chem. Soc.*, 765 (1936).

[22] An insignificant amount of 2′,3′,5′-tri-O-acetyl crotonoside is formed in the conversion of **9** into **12**, indicating that under the conditions of these reactions little hydrolysis of the 2-fluoro group occurs.

[23] T. Ziminski and E. Borowski, *J. Chromatogr.*, **23**, 480 (1966).

H_2O (20 ml). The washed C_6H_6 solution was dried ($MgSO_4$) before it was concentrated *in vacuo*. The resulting concentrate (10 ml) was absorbed on a silica gel column (2.6 × 35 cm), which had been packed and equilibrated (18 hr) with C_6H_6. The column was eluted with C_6H_6 (*ca.* 200 ml) to remove unreacted sugar before the solvent was changed to $CHCl_3$. Elution was continued until all the xyloside had been eluted (the column fractions were monitored by thin layer chromatography using 1:1 C_6H_6–EtOAc as the eluent). The combined column fractions containing the homogeneous product were evaporated to dryness *in vacuo* to give **1** as an oil: yield 6.86 g (78%); λ_{max} mμ ($\epsilon \times 10^{-3}$) (pH 1, 7) 273 (9.2), (pH 13) 265 (broad) (8.5); $\bar{\nu}_{max}$ cm^{-1} 3150, 3120, 3000–2930 (CH), 1745 (C=O), 1590, 1555 (C=C, C=N), 1240–1210 (C-O-C ester), 1050 (C-O-C sugar); δ ppm ($CDCl_3$) 2.07, 2.11, and 2.15 ($C-CH_3$), 4.36 m ($C_{4'}$-H and $C_{5'}$-H), 5.43 and 5.48 ($C_{2'}$-H and $C_{3'}$-H), 6.13 d ($J_{1'}J_{2'}$ = 1Hz) ($C_{1'}$-H), 8.3 (C_8-H). The presence of the α anomer (<10%) was detected by a small doublet at 5.56 ($J_{1'}J_{2'}$ = 2.5 Hz) and a small singlet at 8.1 ppm.

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)2,6-diazidopurine (2a).—A sodium azide solution (2.0 g, 30 mmol in 8 ml of H_2O) was added to a warm solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2,6-dichloropurine (**1a**, 6.8 g, 15 mmol) in EtOH (60 ml), and the resulting reaction mixture was refluxed for 1 hr. The inorganic salts that precipitated were removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in C_6H_6 (100 ml), and the resulting mixture concentrated *in vacuo* to remove residual EtOH and H_2O. The resulting dry C_6H_6 solution was filtered through dry Celite, and the filtrate was evaporated to dryness *in vacuo* to give **2a** as a glass, yield 6.6 g (93%). Thin layer chromatography using anhydrous Et_2O as the eluent indicated that the amorphous product contained only trace impurities and was suitable for use as an intermediate: $\bar{\nu}_{max}$ cm^{-1} 2160, 2130 (N≡N).

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2-aminoadenine (3a).—5% Pd-C (1.3 g) was added to a solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2,6-diazidopurine (**2a**, 6.6 g, 14 mmol) in absolute EtOH (500 ml), and the mixture was hydrogenated at atmospheric pressure for 6–18 hr. The hydrogen atmosphere was removed and replaced with fresh hydrogen after 30 min, 1 hr, and 2 hr. After hydrogenation was complete, the catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in EtOAc (10 ml), and the solution was filtered through dry Celite. The filtrate was evaporated to dryness *in vacuo* to give essentially pure **3a** as a glass, yield 4.6 g (78%). Thin layer chromatography using 95:5 $CHCl_3$–MeOH as the eluent indicated the product was sufficiently pure for use as an intermediate: λ_{max} mμ ($\epsilon \times 10^{-3}$) (pH 1) 253 (11.3), 291 (9.5), (pH 7) 255 (9.1), 278 (9.5), (pH) 13) 255 (8.7, 278 (9.7); δ ppm (DMSO-d_6) 4.04, 4.17, and 4.22 ($C-CH_3$), 4.30 m and 4.48 m ($C_{4'}$-H and $C_{5'}$-H), 5.48 m ($C_{3'}$-H), 5.67 ($C_{2'}$-H), 5.93 d ($J_{1'}J_{2'}$ = 1.8 Hz) ($C_{1'}$-H), 6.84 broad (NH), 7.90 (C_8H); δ ppm (DMSO-d_6) 4.04, 4.17, and 4.22 ($C-CH_3$), 4.30 m and 4.48 m ($C_{4'}$-H and $C_{5'}$-H), 5.48 m ($C_{3'}$-H), 5.67 ($C_{2'}$-H), 5.93 d ($J_{1'}J_{2'}$ = 1.8 Hz) ($C_{1'}$-H), 6.84 broad (NH), 7.90 (C_8-H).

2-Amino-9-β-D-xylofuranosyladenine (3b).—A solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2-aminoadenine (**3a**, 4.6 g, 11 mmol) in absolute MeOH (250 ml) was saturated at 5° with dry ammonia. After refrigeration for 3 days, the reaction solution was evaporated to dryness, and the residue was triturated with two 65-ml portions of Et_2O. The Et_2O insoluble residue solidified on trituration with hot EtOH (65 ml), and the solid that formed was collected by filtration and recrystallized from EtOH to give essentially pure **3b**, yield 1.9 g (56%). A second recrystallization from EtOH gave the analytically pure material as a crystalline solid containing 0.5 mol of EtOH: yield 1.2 g (35%); indefinite, mp,140–150°; $[\alpha]^{22}D$ −32.0 ± 0.4° (*c* 1.0, H_2O); λ_{max} mμ ($\epsilon \times 10^{-3}$) (pH 1) 252 (11.2), 290 (10.1), (pH 7) 255 (9.6), 278 (10.4), (pH) 13–255 (9.0), 278 (10.3); $\bar{\nu}_{max}$ cm^{-1} 3460, 3320, 3200, 3110 (OH, NH), 2920, 2900–2860 (CH), 1615, 1590, 1500 (C=C, C=N, NH), 1090, 1045 (COC).

Anal. Calcd for $C_{10}H_{14}N_6O_4 \cdot 0.5$ EtOH: C, 43.31; H, 5.62; N, 27.56. Found: C, 43.31; H, 5.70; N, 27.62.

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2-fluoroadenine (5a) and **9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2,6-difluoropurine (6a).**—A solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2-aminoadenine (**3a**, 816 mg, 2 mmol) in 48% fluoroboric acid (10 ml) was cooled to −20° and stirred continuously during the dropwise addition of a $NaNO_2$ solution (280 mg, 4 mmol, in 0.6 ml of H_2O). After completion of the nitrite addition (5 min), the reaction mixture was stirred for an additional 20 min at −10°. $CHCl_3$ (10 ml) was added to the reaction mixture, and the resulting emulsion was stirred vigorously while it was cooled to −20°. The emulsion was neutralized (pH 5–6) with 50% NaOH not allowing the temperature to exceed −10°. After the neutralization was complete, the $CHCl_3$ layer was separated from the aqueous salt solution, and the aqueous layer was extracted with three 10-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined and the resulting solution was washed with cold H_2O several times before it was dried ($MgSO_4$) and then evaporated to dryness *in vacuo*. The residue was triturated with C_6H_6 (60 ml), and the insoluble solid was collected by filtration and identified as 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)isoguanine (**4a**) by its spectral data: yield 197 mg (24%); λ_{max} mμ (pH 1) 235 (7.9), 280 (10.1), (pH 7) 248 (9.5), 292 (8.3), (pH 13) 253 (7.8), 283 (7.8); $\bar{\nu}_{max}$ cm^{-1} 3400 (broad, OH), 3120, 3140–2940, 2760 (NH, CH), 1750 (C=O), 1670, 1610–1590 (NH, C=C, C=N), 1220, 1050 (COC). The C_6H_6 filtrate was diluted with an equal volume of ligroin and the mixture was triturated until a filterable solid was obtained. The solid was collected by filtration and dried *in vacuo* to give crude **5a**. The filtrate was evaporated to dryness to give crude **6a**.

Each of the crude reaction products (**5a** and **6a**) was purified by thin layer chromatography. A $CHCl_3$ solution of the crude product was streaked on a 1 × 200 mm silica gel coated plate which had been activated for 1 hr at 120°. The plate was developed for a total ascending distance of 18 cm. The bands were eluted from the silica gel to give chromatographically homogeneous material.

Crude **5a** (175 mg) was chromatographed using 19:1 $CHCl_3$–MeOH as the eluent. The chromatographically homogeneous product was eluted from the silica gel with EtOH: yield 39 mg (4%); λ_{max} mμ (pH 1) 261 (11.5), 2.68 (sh), (pH 7, 13) 261 (12.2), 268 (sh); $\bar{\nu}_{max}$ cm^{-1} 3360–3330 (NH), 3180, 3020–2930 (CH), 1745 (C=O), 1640, 1610, 1585 (NH, C=C, C=N), 1220, 1050 (COC).

Crude **6a** (135 mg) was chromatographed using EtOAc as the eluent. Elution of the major product from the silica gel with EtOAc gave the chromatographically homogeneous material as an oil which was redissolved in $CHCl_3$. Evaporation of this $CHCl_3$ solution to dryness *in vacuo* gave the pure product as a hard glass containing 0.25 mol of $CHCl_3$: yield 76 mg (8.5%); λ_{max} mμ (pH 1) 254, (pH 13) 256; $\bar{\nu}_{max}$ cm^{-1} 3120, 3000, 2940 (CH), 1745 (C=O), 1630, 1590 (C=C, C=N), 1220, 1100, 1050, 1040, 1015 (COC); δ ppm ($CDCl_3$) 2.10, 2.13 and 2.18 (CCH_3), 4.34 m and 4.44 m ($C_{5'}$-H and $C_{4'}$-H), 5.49 and 5.54 ($C_{3'}$-H and $C_{2'}$-H), 6.17 d ($J_{1'}J_{2'}$ = 2.3 Hz) ($C_{1'}$-H), 7.28 ($CHCl_3$) 8.35 (C_8-H).

Anal. Calcd for $C_{16}H_{16}F_2N_4O_7 \cdot 0.25CHCl_3$: C, 43.95; H, 3.64; N, 12.62. Found: C, 44.29; H, 3.96; N, 12.24.

2-Fluoro-9-β-xylofuranosyladenine (5b). A.—A solution of $NaNO_2$ (660 mg, 9.5 mmol) in H_2O (1.3 ml) was added dropwise with stirring to a solution of 2-amino-9-β-D-xylofuranosyladenine (**3b**, 1.7 g, 5.5 mmol) in 48% fluoroboric acid (17 ml) maintained at −20 to −10°. After the nitrite addition was complete, the reaction mixture was stirred at −10° for 15 min before H_2O-saturated *n*-BuOH (35 ml) was added. The resulting slurry was neutralized (pH 5–6) with 25% NaOH keeping the temperature below −5°. The neutral mixture was extracted with five 90-ml portions of H_2O-saturated *n*-BuOH, and the combined extracts were washed with four 45-ml portions of *n*-BuOH-saturated H_2O. The *n*-BuOH solution was evaporated to dryness *in vacuo*, and the residue (850 mg) was mixed with silica gel (850 mg). The resulting mixture was packed on a previously prepared column (1.9 × 35 cm containing 40 g of silica gel wet packed $CHCl_3$). The column was eluted with 225 ml of 9:1 $CHCl_3$–MeOH to remove pigmented impurities before the eluent was changed to 4:1 $CHCl_3$–MeOH which eluted the chromatographically homogeneous product, yield 150 mg (9%). EtOH recrystallization gave an analytically pure sample of **5b**: mp 245–247° (Mel-Temp); $[\alpha]^{25}D$ −58.5 ± 0.4 (*c* 0.51, MeOH); λ_{max} mμ ($\epsilon \times 10^{-3}$) (pH 1) 262 (13.3), 267 (sh), (pH 7, 13) 262 (14.8), 267 (sh); $\bar{\nu}_{max}$ cm^{-1} 3350–3300, 3180–3110 (NH, OH, CH), 2920 (CH), 1670, 1615, 1570 (NH, C=C, C=N), 1090, 1085, 1060, 1050 (COC).

Anal. Calcd for $C_{10}H_{12}FN_5O_4$: C, 42.11; H, 4.24; N, 24.56. Found: C, 42.18; H, 4.20; N, 24.26.

B.—A solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2,6-difluoropurine (**6a**, 47 mg, 0.1 mmol) in anhydrous ethanolic ammonia (25 ml saturated at 5°) was sealed in a glass flask and allowed to stand at 5° for 3 days. The reaction solution was evaporated to dryness, and the residue was solidified by trituration with EtOH–Et_2O. The solid was collected by filtration, triturated with $CHCl_3$, and dried *in vacuo* to give 27 mg of impure **5b** as identified by its melting point (232°) and ultraviolet spectrum [λ_{max} ($\epsilon \times 10^{-3}$) (pH 1) 262 (11.5), 267 (sh), (pH 7, 13) 262 (12.8), 267 (sh)]. Thin layer chromatography on silica gel using 3:1 $CHCl_3$–MeOH as the eluent showed minor impurities.

C.—Treatment of 2-fluoro-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**5a**, 1.3 g, 3.16 mmol) as described in B gave 750 mg of crude **5b**. Recrystallization from EtOH with charcoal treatment gave 330 mg (37%) of pure **5b**: λ_{max} mμ ($\epsilon \times 10^{-3}$) (pH 1) 262 (13.7), 267 (sh), (pH 7, 13) 262 (15.0), 267 (sh).

9-Benzyl-2,6-difluoropurine (6c).—A suspension of 2-amino-9-benzyladenine (**3c**, 1.5 g, 6.2 mmol) in $CHCl_3$ (30 ml) was diluted with 48% fluoroboric acid (50 ml). The resulting mixture was cooled to −15° and stirred continuously during the dropwise addition of $NaNO_2$ (1.3 g, 18.8 mmol in 1.5 ml of H_2O). After completion of the nitrite addition (5 min), the reaction was stirred for an additional 30 min at −5° before $CHCl_3$ (25 ml) was added and the mixture was cooled to −20°. The resulting emulsion was neutralized (pH 5–6) with 50% NaOH not allowing the temperature to exceed −10°. After the neutralization was complete, the insoluble solid that formed was collected by filtration and washed with fresh $CHCl_3$. The resulting partially dried solid was triturated with excess Me_2CO, and the insoluble solid was dried *in vacuo* to give the crude 9-benzylisoguanine, (**5c**): yield 550 mg (37%); λ_{max} mμ (pH 1) 234 (sh), 242 (sh), 280; (pH 7) 250, 294; (pH 13) 255, 286.

Evaporation of the Me_2CO filtrate to dryness followed by trituration of the resulting residue with H_2O gave the crude 9-benzyl-2-fluoroadenine (**4c**): yield 460 mg (30%); λ_{max} mμ (pH 1) 264, (pH 7) 13-262.

The $CHCl_3$ layer was separated from the aqueous salt solution, combined with the $CHCl_3$ wash of the reaction mixture insoluble solid, and washed with H_2O. After drying ($MgSO_4$), the $CHCl_3$ filtrate was concentrated *in vacuo*, and the concentrate was streaked on a 1 × 200 mm silica gel coated plate. The chromatogram was developed with EtOAc and the major band was eluted with hot EtOAc. Evaporation of the EtOAc to dryness *in vacuo* gave the 9-benzyl-2,6-difluoropurine (**6c**) as an oil: yield 146 mg (9.6%); λ_{max} mμ ($\epsilon \times 10^{-3}$ (pH 1, 7) 256 (7.5), (pH 13) 256 (9.6); δ ppm 5.40 (CH_2 of benzyl), 7.35 (phenyl H), 8.06 d (C_8-H coupled to one or both fluorines). The mass spectrum of **6c** showed a strong peak at a mass to charge ratio of 246 (calcd mol wt, 246).

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-6-azido-2-trifluoromethylpurine (8).—A sodium azide solution (350 mg, 5.4 mmol in 1 ml of H_2O) was added to a hot solution of 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-6-chloro-2-trifluoromethylpurine[19] **7**, (2.5 g, 5.2 mmol) in EtOH (50 ml), and the resulting reaction mixture was refluxed for 1 hr. The inorganic salts that precipitated were removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in C_6H_6 (50 ml) and the resulting mixture concentrated *in vacuo* to remove residual EtOH and H_2O. The dry C_6H_6 solution was filtered through Celite and the filtrate was evaporated to dryness *in vacuo* to give **8** as a glass. Thin layer chromatography using 3:1 $CHCl_3$–EtOAc as the eluent indicated that the amorphous product contained only trace impurities and was suitable for use as an intermediate: $\tilde{\nu}_{max}$ cm^{-1} 2150, 2120 (N≡N), 1745 (C=O), 1620, 1595, 1575 (C=C, C=N), 1240–1220, 1140 (COC).

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2-trifluoromethyladenine (11).—5% Pd-C (400 mg) was added to a solution of 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl-6-azido-2-trifluoromethylpurine (**8**, 2.4 g, 4.9 mmol) in absolute EtOH (250 ml), and the mixture was hydrogenated at atmospheric pressure for 6 hr. The hydrogen atmosphere was removed and replaced with fresh hydrogen after 30 min, 1 hr, and 2 hr. After hydrogenation was complete, the catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$, and the resulting solution was absorbed on a previously packed silica gel column (2.6 × 35 cm). The column was eluted with 2:1 $CHCl_3$–EtOAc, and the fractions containing **11** were combined and evaporated to dryness *in vacuo* to give essentially pure material as an oil: yield 1.2 g (53%); λ_{max} mμ (pH 1, 7) 258, 275 (sh), (pH 13) 260, 274 (sh); $\tilde{\nu}_{max}$ cm^{-1} 3440–3420, 3340 (NH), 3220–3200, 3000–2980, 2940 (CH), 1740 (C=O), 1650, 1640, 1590 (NH, C=C, C=N), 1220, 1130, 1090, 1040 (COC); δ ppm ($CDCl_3$) 2.02, 2.13, 2.17 (CCH_3), 4.43 m ($C_{4'}$-H and $C_{5'}$-H), 5.68 m ($C_{3'}$-H), 5.85 m ($C_{2'}$-H), 6.15 d ($J_{1'}J_{2'}$ = 1.5 Hz), 6.38 (NH), 8.04 (C_8-H).

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine[17] (12).—$NaNO_2$ (69 mg, 1 mmol) suspended in H_2O (0.1 ml) was added (20 min) to a continuously stirred solution (−15°) of 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-fluoroadenine[17] (**9**, 205 mg, 0.5 mmol) in 48% fluoroboric acid (3 ml). The reaction mixture was stirred an additional 20 min at −10 to 0° before $CHCl_3$ (10 ml) was added. The resulting emulsion was stirred vigorously at −15° and neutralized (pH 5–6) with 50% NaOH. The $CHCl_3$ layer was separated from the aqueous salt solution and washed with two 10-ml portions of H_2O before it was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue (150 mg) was dissolved in $CHCl_3$, and the resulting solution of the crude product was purified by thin layer chromatography using EtOAc as the eluent. The two major products were eluted from the silica gel with warm EtOH. Evaporation of the EtOH solutions to dryness gave 37 mg (25%) of **12** and 95 mg (65%) of recovered starting compound (**9**). The identity of the isolated products was confirmed by tlc using EtOAc as the eluent.

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-6-fluoropurine (13).—To a solution of 2′,3′,5′-tri-O-acetyladenosine[18] (**10**, 2.9 g 7.35 mmol) in 48% fluoroboric acid (35 ml) at −20° was added dropwise with stirring a solution of $NaNO_2$ (0.86 g, 12.5 mmol) in H_2O (1.8 ml). An additional 1.2 g (17.4 mmol) of $NaNO_2$ in 25 ml of H_2O was added at 0° and 30 min later the solution was neutralized as described above (preparation of **12**). The semisolid residue resulting from evaporation of the $CHCl_3$ extracts of the reaction mixture was streaked on a 1 × 200 mm silica gel coated glass plate. After the plate was developed in 19:1 $CHCl_3$–MeOH, the fastest traveling band was eluted, and the eluate was evaporated to dryness *in vacuo* to give the pure product as a glass: yield 0.1 g (3.3%); $[\alpha]^{23}D$ −10.8 ± 0.9[6] (*c* 0.98, $CHCl_3$); λ_{max} mμ ($\epsilon \times 10^{-3}$) EtOH 243 (6.5), (pH 13) unstable; $\tilde{\nu}_{max}$ cm^{-1} 3100, 2940 (CH), 1745 (C=O), 1610, 1570 (C=C, C=N), 1220, 1090, 1045, 1010 (COC); δ ppm ($CDCl_3$) 2.11, 2.14, 2.17 (CCH_3), 4.44 m ($C_{5'}$-H and $C_{4'}$-H), 5.63 t ($C_{3'}$-H), 5.95 t ($C_{2'}$-H), 6.25 d ($C_{1'}$-H), 7.27 ($CHCl_3$), 8.28 (C_8-H), 8.65 (C_2-H). The integral of the spectrum shows nine CCH_3 protons, six sugar protons, and two purine protons. The mass spectrum of **13** showed a peak at a mass to charge ratio of 396 (calcd mol wt 396) and the expected fragmentation pattern. $CHCl_3$ was detected in the mass spectrometer before the spectrum of **13** appeared.

Anal. Calcd for $C_{16}H_{17}FN_4O_7 \cdot 0.2CHCl_3$: C, 46.31; H, 4.13; N, 13.33. Found: C, 46.38; H, 4.25; N, 13.27.

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-6-fluoro-2-trifluoromethylpurine (14).—9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2-trifluoromethyladenine (**11**, 1.1 g, 2.4 mmol) was diazotized as described above for the preparation of **12** from **9**. The glass (700 mg) resulting from evaporation of the $CHCl_3$ extracts of the neutalized reaction mixture was dissolved in C_6H_6, and the solution was absorbed on a previously packed silica gel column (2.6 × 35 cm). The column was eluted with 2:1 $CHCl_3$–EtOAc. The fractions containing **14** were combined and evaporated to dryness *in vacuo*. The resulting oil was dried *in vacuo* over P_2O_5 until it crystallized: yield 250 mg (25%); mp 131–133° (Heizbank); $[\alpha]^{25}D$ 0 (*c* 1.11, $CHCl_3$); λ_{max} mμ ($\epsilon \times 10^{-3}$) (pH 1) 248 (7.2), (pH 7, EtOH) 248 (7.5), (pH 13) 252.5 (11.3); $\tilde{\nu}_{max}$ cm^{-1} 3480–3400 (OH), 3110, 2955 (CH), 1740 (C=O), 1620, 1610, 1575 (C=C, C=N), 1240, 1220, 1145 (COC).

Anal. Calcd for $C_{17}H_{16}F_4N_4O_7$: C, 43.97; H, 3.47; N, 12.07. Found: C, 43.77; H, 3.36; N, 11.93.

Registry No.—**1a**, 19806-62-3; **2a**, 18354-12-6; **3a**, 18354-13-7; **3b**, 19768-89-9; **4a**, 18469-59-5; **5a**, 18354-14-8; **5b**, 19768-92-4; **6a**, 18354-15-9; **6c**, 19768-94-6; **8**, 19768-95-7; **11**, 19768-96-8; **13**, 18354-17-1; **14**, 19768-98-0.

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