Anal. Calcd for $C_{14}H_{16}N_4O_7S \cdot 0.5H_2O$: C, 42.90; H, 4.10; N, 14.25. Found: C, 42.81; H, 4.04; N, 14.33.

4-Acetamido-6-carbethoxy-2-methylthio-5-oxo-8-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (29).—A 1.0-g sample of compound **18** (2.72 mmol) was mixed with 1.5 g of tetra-*O*-acetyl-β-D-ribofuranose. The mixture was fused at an oil bath temperature of 195–200° for 2.5 hr *in vacuo*. The black melt was dissolved in a minimum volume of chloroform, and the solution was filtered. The filtrate was concentrated to 5.0 ml and placed on a column packed with 50 g of silica gel in chloroform. The column was eluted with chloroform; the first 300 ml of eluent was discarded. The next 800 ml of eluent was evaporated *in vacuo* to dryness. The viscous residue was triturated with 50 ml of ether. On scratching the side wall of the beaker a white precipitate formed. The precipitate was filtered, washed with diethyl ether, and air-dried to give 0.95 g (61%), mp 106–107°. For analysis a sample was dried *in vacuo* over refluxing methanol in presence of phosphorus pentoxide.

Anal. Calcd for $C_{24}H_{28}N_4O_{11}S \cdot 0.5H_2O$: C, 49.20; H, 4.95; N, 9.55. Found: 49.09; H, 5.17; N, 9.26.

4-Amino-6-carboxamido-2-methylthio-5-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (30).—A 1.16-g sample of **29** (2.0 mmol) was dissolved in 80 ml of liquid ammonia in a glass-lined bomb. The bomb was sealed and left to stand at room temperature for 24 hr. The liquid ammonia was allowed to evaporate. The residue was dissolved in 200 ml of boiling methanol by the addition of water. The solution was filtered, and the filtrate was kept at 5° overnight. The white precipitate was filtered, washed with methanol, and air-dried to give 0.60 g (78%), mp 252–253°. For analysis a sample was dried *in vacuo* over refluxing toluene in the presence of phosphorus pentaoxide.

Anal. Calcd for $C_{14}H_{17}N_5O_8S \cdot H_2O$: C, 41.90; H, 4.73; N, 17.4. Found: C, 42.01; H, 5.03; N, 17.25.

4-Amino-6-carboxamido-5-oxo-8-(β-D-ribofuranosyl)pyrido-[2,3-*d*]pyrimidine (2).—A 0.58-g sample of **29** (1.0 mmol) was dissolved in 30 ml of ethanol; 2.0 g of Raney nickel (weighed wet and prewashed with distilled water followed by ethanol) was added. The mixture was refluxed for 24 hr, and 1 g more of Raney nickel (weighed wet and pretreated as above) was added. Refluxing was continued for another 4 hr. The mixture was filtered hot, and the Raney nickel was washed with 300 ml of boiling ethanol. The filtrate was evaporated to dryness. The residue was transfered to a glass-lined bomb and 80 ml of liquid ammonia was added; the bomb was sealed and left at room temperature for 24 hr. The liquid ammonia was allowed to evaporate. The residue was dissolved in a boiling mixture of 40 ml of methanol and 5 ml of water and kept at 5° overnight. The precipitate was filtered, washed with methanol, and air-dried to give 0.23 g, mp 253–254°, resolidifies (44.5% overall yield). For analysis a sample was dried *in vacuo* over refluxing toluene in the presence of phosphorus pentoxide.

Anal. Calcd for $C_{13}H_{15}N_5O_6$: C, 46.30; H, 4.46; N, 20.74. Found: C, 46.02; H, 4.35; N, 20.61.

Registry No.—**1**, 18417-89-5; **2**, 36707-00-3; **11**, 21025-64-9; **13**, 36707-40-1; **14**, 36707-41-2; **16**, 36707-42-3; **17**, 36707-43-4; **18**, 36707-44-5; **19**, 36707-45-6; **21**, 36707-46-7; **23**, 36707-47-8; **24**, 36707-48-9; **27**, 36707-01-4; **28**, 36707-02-5; **29**, 36707-03-6; **30**, 36707-04-7.

Directed Glycosylation of 8-Bromoadenine. Synthesis and Reactions of 8-Substituted 3-Glycosyladenine Derivatives

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The ratio of 3-glycosyl- *vs.* 9-glycosyladenine nucleosides using several glycosylation procedures was investigated. Treatment of the trimethylsilyl derivative of 8-bromoadenine with glycosyl halides leads to excellent yields of blocked 3-glycosyl-6-amino-8-bromopurine nucleosides. This method has been used to prepare 6-amino-8-bromo-3-β-D-ribofuranosylpurine (**6**), 3-β-D-ribofuranosyladenine (**7**), 6-amino-3-α-D-arabinofuranosyl-8-bromopurine (**10**), 3-α-D-arabinofuranosyladenine (**11**), and 3-β-D-arabinofuranosyladenine (**14**). Deamination of 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**5**) with NOCl–pyridine in DMF and removal of the blocking groups gave improved yields of 3-β-D-ribofuranosylhypoxanthine (**16**). Similar treatment of **11** gave 3-β-D-arabinofuranosylhypoxanthine (**17**). Deamination of 6-amino-3-(2,3,5-tri-*O*-benzoyl)-8-bromopurine (**4**), using NOCl in pyridine, and subsequent debenzoylation gave 3-β-D-ribofuranosyl-8-pyridiniumhypoxanthine betaine (**19**). The reactivity of **4** toward nucleophiles was investigated. Strongly basic nucleophiles such as methoxide, benzyloxide, and hydrazine caused decomposition. Displacement was accomplished with azide ion which gave, after hydrogenation and deblocking, 6,8-diamino-3-β-D-ribofuranosylpurine (**21**).

Interest in 3-substituted purine derivatives has been stimulated by the isolation of 3-β-D-ribofuranosyluric acid and 3-(3-methyl-2-butenyl)adenine from natural sources[1–3] and by the observation of interesting biological properties[4–7] of synthetic 3-β-D-ribofuranosyladenine (**7**). Adenine has been shown to undergo preferential alkylation at the 3 position;[3,8,9] however, direct alkylation of adenine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**1**) afforded 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**5**) in only 26% yield with 18% of the 9 isomer.[10] Glycosylation of 6-benzamidopurine with 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride gave some 3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (**13**) in addition to the expected 9 isomer.[11] Selective glycosylation at the 3 position has been achieved by utilizing 7-pivaloyloxymethyladenine

(1) H. S. Forrest, D. Hatfield, and J. M. Lagowski, *J. Chem. Soc.*, 963 (1961).
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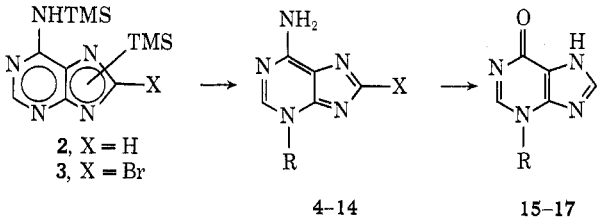
(10) N. J. Leonard and R. A. Laursen, *ibid.*, **4**, 354 (1965).
(11) K. R. Darnall and L. B. Townsend, *J. Heterocycl. Chem.*, **3**, 371 (1966).



4, X = Br; R = 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl
5, X = H; R = 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl
6, X = Br; R = β-D-ribofuranosyl
7, X = H; R = β-D-ribofuranosyl
8, X = Br; R = 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl
9, X = H; R = 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl
10, X = Br; R = α-D-arabinofuranosyl
11, X = H; R = α-D-arabinofuranosyl
12, X = Br; R = 2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl
13, X = H; R = 2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl
14, X = H; R = β-D-arabinofuranosyl
15, R = 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl
16, R = β-D-ribofuranosyl
17, R = β-D-arabinofuranosyl

followed by the sometimes difficult removal of the blocking groups.[12,13]

It was the purpose of this investigation to develop a synthetic procedure for preparing 3-glycosyladenines selectively and in good yields from readily accessible starting materials and to study their reactivity toward nucleophilic agents. Recent evidence for a 3 to 9 migration of alkyl or glycosyl substituents of purines has been presented by Shimizu and Miyaki[14-16] and the ratio of 3-substituted to 9-substituted products is thought to depend on the rate of this migration under the conditions used for alkylation.[16] The presence of a bulky substituent at the 8 position of adenine might be expected to offer steric hindrance to either direct alkylation or migration to the 9 position. Likewise an electron-withdrawing group at the 8 position might be expected to lower the electron density at the 9 position and thus slow the rate of alkylation or migration at that position. On this basis alkylation of 8-bromoadenine might be expected to give a preponderance of 3-substituted derivatives. With this in mind a study of the preparation of 3-glycosyladenines by various methods was undertaken.

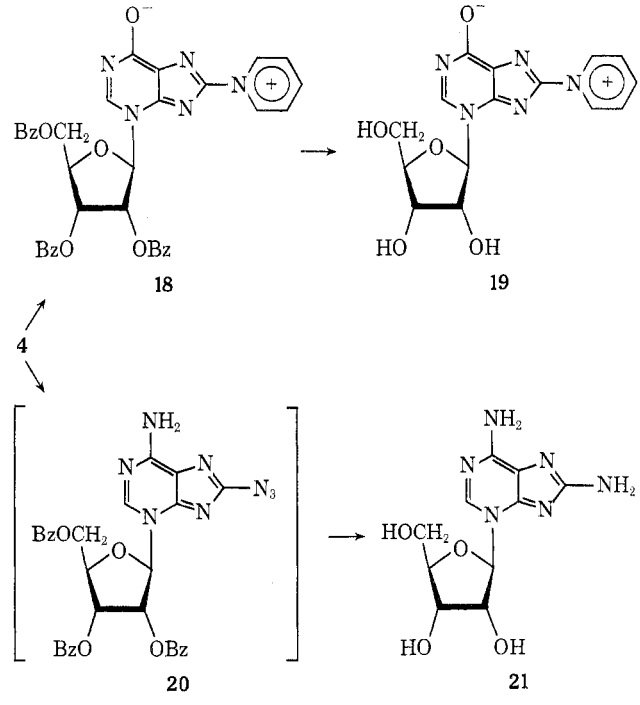
The low overall yields of nucleosides reported for direct alkylations of adenine led us at the outset to investigate the use of trimethylsilyl derivatives of adenine. Treatment of the crystalline trimethylsilyl adenine derivative (**2**) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**1**) in acetonitrile or dichloromethane gave a poor overall yield of nucleosides and represented no improvement over previous methods. However, treatment of the crystalline trimethylsilyl-8-bromoadenine derivative (**3**) with the same glycosyl halide (**1**) in dichloromethane gave an 80% yield of crystalline 6-amino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-8-bromopurine (**4**). This material was obtained by direct crystallization from the mixture of products. A yield of 7% of the 9 isomer could be obtained by chromatographic resolution of the crude reaction mixture. The structure of **4** was proved by hydrogenolysis to give 88% of the known[4] 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**5**).

(12) M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, **89**, 5439 (1967).
(13) N. J. Leonard and M. Rasmussen, *J. Org. Chem.*, **33**, 2488 (1968).
(14) B. Shimizu and M. Miyaki, *Chem. Pharm. Bull.*, **18**, 579 (1970).
(15) M. Miyaki and B. Shimizu, *ibid.*, **18**, 732 (1970).
(16) M. Miyaki and B. Shimizu, *ibid.*, **18**, 1446 (1970).

Other methods of condensation gave lower total yields and greater proportions of the 9 isomer (see Table I). Fusion of **1** and **3** under reduced pressure gave results which were not so satisfactory as those from the glycosylation in acetonitrile or dichloromethane at room temperature. Condensation of the silylated 8-bromoadenine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α-D-ribofuranose in the presence of stannic chloride also proved inferior for the preparation of **5**. The directive effect of the 8-bromo substituent in the mercury salt procedure was also investigated. For this study 6-benzamido-8-bromopurine was prepared in poor yield by bromination of 6-benzamidopurine. The chloromercury salt was condensed with **1** in refluxing toluene to give a low yield of 3 isomer and a much higher yield of the 9 isomer.

The 3 isomer (**4**) was debenzoylated and gave a 95% yield of 6-amino-8-bromo-3-β-D-ribofuranosylpurine (**6**). Hydrogenolysis of **4** (to give **5**) followed by debenzoylation afforded known[4] 3-β-D-ribofuranosyladenine (**7**) in 61% yield from **3**.

Condensation of **3** with 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromide in acetonitrile gave a 73% yield of 6-amino(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-8-bromopurine (**8**) which was debenzoylated to give 6-amino-3-α-D-arabinofuranosyl-8-bromopurine (**10**). Hydrogenolysis of **8** (to give **9**) followed by debenzoylation gave 3-α-D-arabinofuranosyladenine (**11**). Similar treatment of **3** with 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride gave a 37% yield of 6-amino-3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-8-bromopurine (**12**). Hydrogenolysis of **12** gave 3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (**13**) and under more strenuous conditions 3-β-D-arabinofuranosyladenine (**14**).[11]



The deamination of **5**, followed by debenzoylation to give 3-β-D-ribofuranosylhypoxanthine (**16**), has been reported[17] using nitrosyl chloride in a mixture of pyridine and chloroform. In our hands this method

(17) R. Wolfenden, T. K. Sharpless, I. S. Ragade, and N. J. Leonard, *J. Amer. Chem. Soc.*, **88**, 185 (1966).

TABLE I

Purine base	Glycosyl Reactant	Method	Anomeric Configuration	% 3 isomer	% 9 isomer	3:9
Adenine[a]	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	CH_3CN, reflux	β	26	18	1.4
Adenine (TMS) derivative	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	CH_3CN, room temp	β	27	10	2.7
6-Benzamido-8-bromopurine chloromercury salt	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	C_7H_8, reflux	β	4	39	0.1
8-Bromoadenine (TMS) derivative	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	CH_3CN, room temp	β	80	7	10.0
8-Bromoadenine (TMS) derivative	2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide	Fused, 125°	β	46	18	2.5
8-Bromoadenine (TMS) derivative	1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose	CH_3CN, $SnCl_4$[b]	β	39	20	2.0
8-Bromoadenine (TMS) derivative	2 3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl chloride	CH_3CN, room temp	β	37	4	9.2
8-Bromoadenine (TMS) derivative	2,3,5-Tri-*O*-benzoyl-D-arabinofuranosyl bromide	CH_3CN, room temp	α	73		

[a] Reference 4. [b] V. Niedballa and H. Vorbruggen, *Angew. Chem.*, **82**, 449 (1970).

proved too unreliable for the preparation of **14** in large quantities. However, 5 equiv of nitrosyl chloride in DMF with 5 equiv of pyridine caused rapid deamination of **5** and afforded high yields of the blocked hypoxanthine (**15**) which was deblocked to give the aforementioned 3-β-D-ribofuranosylhypoxanthine (**16**). Similar treatment of the blocked β-D-arabino nucleoside (**13**) gave a high yield of a syrupy blocked hypoxanthine derivative. Attempts to remove the benzyl groups by catalytic hydrogenolysis met with inconsistent and unreliable results, including cleavage to hypoxanthine in some instances and in others modification of the purine nucleus presumably by ring reduction of the imidazole ring since a shift in the neutral uv from 265 to 280 nm was observed. A sample of 3-β-D-arabinofuranosylhypoxanthine (**17**) was obtained in ~30% yield by hydrogenolysis for 3 days at 30° and 3 atm of hydrogen over 10% palladium-on-carbon. In light of the difficulties in removing benzyl groups from 3-substituted hypoxanthines as reported here and by others[18] deamination of the deblocked arabinoside (**14**) was undertaken. Treatment of **14** in DMF with pyridine and a large excess of nitrosyl chloride gave a smooth conversion into **17** which was purified by chromatography on silica gel and crystallization from water.

Attempts to prepare 8-bromo-3-β-D-ribofuranosylhypoxanthine by deamination of **4** with nitrosyl chloride and pyridine in chloroform or DMF gave high yields of 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)8-pyridinium hypoxanthine betaine (**18**) which was debenzoylated in methanolic ammonia to give 3-β-D-ribofuranosyl-8-pyridinium hypoxanthine betaine (**19**). The structure of **19** was apparent from its elemental analysis and its pmr spectrum which exhibited a two-proton doublet at δ 9.75 attributable to the α-pyridinium protons and three protons in addition to H-2 centered around δ 8.4. When the reaction was repeated using nitrosyl chloride and 2,6-lutidine in DMF or chloroform, neither deamination nor displacement at C-8 to form a betaine was observed. Attempts to displace the pyridinium group from the betaine with azide ion under various conditions resulted in no reaction and treatment of **19** with hydrazine or hydrazine hydrate in alcohol led to complex mixtures of products.

The utility of 8-bromo-3-glycosyladenines as intermediates in nucleophilic displacement reactions was investigated using **4** and **6** as models. Compound **4** could be debenzoylated cleanly with methanolic ammonia to give the 8-bromo derivative **6**. The base stability of **6** contrasts with the 3-glycosyladenines previously investigated (*i.e.*, **7**) which were reported to be labile to both acid and base.[4] Attempts to displace bromide from **6** using sodium methoxide in methanol, sodium benzyloxide in benzyl alcohol, sodium hydroxide in water, or hydrazine in alcohol all led to extensive degradation including cleavage to sugar and aromatic heterocyclic derivatives. The resistance of the 8-bromo substituent of **4** and **6** to nucleophilic displacement was shown by their failure to react under conditions utilized to replace the bromo moiety from 8-bromo-9-β-D-ribofuranosyladenine reflux at alcohol temperature 4–12 hr.[19] Attempts to displace bromide from **4** with sodium acetate in DMF, acetic anhydride, or acetic acid–acetic anhydride gave no displacement under mild conditions (80°) and under more rigorous conditions (100° or greater) gave only decomposition products (glycosidic bond cleavage). However, conversion of **4** to an unstable azido derivative was accomplished using sodium azide in hexamethylphosphoric triamide at 80° for 4 days. The azide (**20**) could not be easily purified, but was hydrogenated and debenzoylated to give a 35% yield of 6,8-diamino-3-β-D-ribofuranosylpurine (**21**).

Experimental Section

General Methods.—Solutions were evaporated below 50° under diminished pressure. Melting points were determined with a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer Model 247 spectrometer and KBr pellets. Uv spectra were recorded with a Cary Model 15 spectrometer. Optical rotations were measured in 1-dm tubes with a Perkin-Elmer Model 141 polarimeter. Nmr spectra were measured at 60 MHz with a Hitachi Perkin-Elmer R-20A nmr spectrometer (*ca.* 10% solutions measured at *ca.* 30°); tetramethylsilane (δ = 0) was used as the internal standard

(18) H. J. Thomas and J. A. Montgomery, *J. Org. Chem.*, **31**, 1413 (1966).

(19) R. E. Holmes and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1242 (1964).

for chloroform-*d* solutions. Sodium 4,4-dimethyl-4-silapentane-1-sulfonate ($\delta = 0$) was used as the internal standard for deuterium oxide and methyl sulfoxide-d_6 solutions. Microanalytical data were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn., and from M-H-W Laboratories, Garden City, Mich.

6-Amino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-8-bromopurine (4).—8-Bromoadenine (3.2 g, 15 mmol) was refluxed in hexamethyldisilazane (15 ml) with a few crystals of ammonium sulfate until complete solution was achieved (24 hr). The excess hexamethyldisilazane was removed by distillation under diminished pressure. To the crystalline residue, 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [from 7.0 g (14 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose] in acetonitrile (80 ml) was added, and the clear solution was kept in a sealed vessel for 20 hr. The solvent was evaporated, and the residual syrup was dissolved in chloroform–ethyl acetate (1:1, 30 ml). To the clear solution ethanol (100 ml) was added, and after a short time crystals precipitated. The mixture was kept at 0° for 12 hr and filtered to give 7.0 g (11.0 mmol, 71%) of **2a** as fine white needles. Concentration of the filtrate, storage at 4° several days, and filtration afforded an additional 1.2 g of needles. Recrystallization of the combined crops from ethanol gave pure **4** (7.6 g, 12 mmol, 80%): mp 221–222°; $[\alpha]^{25}D$ −72.1° (*c* 1, DMF).

Anal. Calcd for $C_{31}H_{24}BrN_5O_7$: C, 56.55; H, 3.68; N, 10.64. Found: C, 56.47; H, 3.69; N, 10.82.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (5).—Compound **4** (3.0 g, 4.5 mmol) was dissolved in 2-methoxyethanol (100 ml), and ethanol (100 ml) was added. Concentrated NH_4OH (1 ml) and 10% palladium-on-carbon (2 g) were added, and the suspension was shaken for 2 hr under 40 psi of hydrogen. Chloroform (250 ml) was added, and the suspension was filtered through a Celite pad. The filtrate was evaporated to give a white crystalline solid which was suspended in ethanol and filtered to give **5** (1.7 g). The mother liquors afforded an additional 0.7 g of product. Crystallization of the combined crops from ethanol gave white needles: yield 2.3 g (88%); mp 238–239°; $[\alpha]^{25}D$ −63.4° (*c* 1, DMF) [lit.[4] mp 246–247°; $[\alpha]^{26}D$ −69° (*c* 0.89, *DMF*)].

6-Amino-8-bromo-3-β-D-ribofuranosylpurine (6).—Compound **4** (5.0 g, 7.6 mmol) was dissolved in methanol (100 ml) which had been saturated with ammonia at 0°. The solution was sealed and kept at room temperature for 4 days. The solution was evaporated to a syrup which was triturated with chloroform to give a white crystalline solid. The suspension was filtered and washed with chloroform. The solid was dissolved in water (15 ml) and methanol (15 ml) was added. This solution was seeded and allowed to crystallize overnight to yield 2.5 g (7.2 mmol, 95%): mp 185° dec; $[\alpha]^{25}D$ −63.2° (*c* 1, DMF); $\lambda_{max}^{pH\ 1}$ 280 nm (ε 22,500); λ_{max}^{MeOH} 286 nm (ε 17,000); $\lambda_{max}^{pH\ 11}$ 284 nm (ε 17,000); nmr (DMSO-d_6) δ 5.95 (1-proton doublet, $J_{1',2'}$ = 5.5 Hz, H-1'), 8.39 (2-proton broad singlet, NH_2), 8.67 (1-proton singlet, H-2).

Anal. Calcd for $C_{10}H_{12}BrN_5O_4$ (0.5 H_2O): C, 33.84; H, 3.67; N, 19.71. Found: C, 33.76; H, 3.72; N, 19.57.

3-β-D-Ribofuranosyladenine (7).—Compound **5** (0.92 g, 1.7 mmol) was heated at reflux in a solution prepared from 30 mg of sodium in 15 ml of methanol. The starting material dissolved in 10 min, and after 15 min the product began to precipitate. After 30 min the reaction was placed in the refrigerator at 5° for 3 hr. The crystals were filtered, washed with methanol, and dried, yield 0.40 g (1.5 mmol, 87%), mp 185 (browns), 201° dec. Recrystallization from water (13 ml) gave 0.30 g of colorless needles: mp 210–211° dec; $[\alpha]^{29}D$ −98.5° (*c* 1, DMF); $[\alpha]^{25}D$ −29.4° (*c* 0.5, 0.05 *N* HCl); $\lambda_{max}^{pH\ 1}$ 274 nm (ε 17,000); λ_{max}^{MeOH} 280 nm (ε 12,000); $\lambda_{max}^{pH\ 11}$ 277 nm (ε 12,000); nmr (DMSO-d_6) δ 5.95 (1-proton doublet $J_{1',2'}$ = 7.0 Hz, H-1'), 7.86, 8.62 (1-proton singlets H-8, H-2), 8.30 (2-proton broad singlet NH_2) [lit.[4] mp 210–211°, $[\alpha]^{26}D$ −35° (*c* 0.6, 0.05 *N* HCl)].

General Procedure for Determining Percentage Yields of Isomers of β-D-Ribofuranosyladenine Derivatives.—Trimethylsilyl derivatives were prepared from 0.50 g of purine base and 1.0 equiv of glycosyl derivative was used. Solvents were removed by evaporation under reduced pressure, and the reaction mixtures were dissolved in chloroform and washed with saturated aqueous sodium bicarbonate and water. The resultant solutions were chromatographed [$CHCl_3$–acetone (4:1)] on thick layers of silica gel to give well-resolved bands from which the isomers could be eluted (chloroform). The chloromercury procedure was carried out on 100 mg of the chloromercury salt of 6-benzamido-8-bromopurine prepared by standard procedures.[20] After the usual work-up the chloroform soluble fraction was chromatographed on silica gel plates, and the products were eluted, weighed, and then identified by debenzoylation to the known 3 and 9 isomers (results are shown in Table I).

6-Amino-3-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-8-bromopurine (8).—Hydrogen bromide was bubbled through a solution of methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (7.0 g, 15 mmol) in dichloromethane (100 ml) at 0° for 0.5 hr. The solution was kept at 0° for 1 hr and allowed to warm to ambient temperature for 15 min. The solution was evaporated and toluene was evaporated from the resulting syrup. This syrup was dissolved in acetonitrile (120 ml) and added to the trimethylsilyl derivative prepared from 8-bromoadenine (3.2 g, 15 mmol). After 24 hr white crystals were observed in the flask. The mixture was refrigerated for 24 hr, filtered, and washed with methanol to furnish 7.5 g (11 mmol, 73%) of white needles, mp 139–141°. Recrystallization from methanol gave **8** (6.5 g), mp 139–141°, $[\alpha]^{25}D$ +16.0° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{31}H_{24}BrN_5O_7$: C, 56.54; H, 3.67; N, 10.63; Br, 12.13. Found: C, 56.56; H, 3.67; N, 10.64; Br, 12.28.

3-(2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl)adenine (9).—A solution of **8** (1.6 g, 2.3 mmol) in ethanol–ethyl acetate (1:1, 150 ml) was placed in a pressure bottle with concentrated NH_4OH (1 ml) and 10% palladium-on-carbon (0.4 g). The mixture was shaken under 40 psi of hydrogen for 2 hr. The suspension was filtered and the filtrate was evaporated to a syrup, which was dissolved in benzene (40 ml) and kept at room temperature overnight to precipitate white needles, yield 1.3 g (2.2 mmol, 93%), mp 164–165°, $[\alpha]^{25}D$ +17.8° (*c* 1, *MeOH*).

Anal. Calcd for $C_{31}H_{25}N_5O_7$: C, 64.24; H, 4.34; N, 12.08. Found: C, 64.07; H, 4.29; N, 12.08.

6-Amino-3-α-D-arabinofuranosyl-8-bromopurine (10).—A solution of **8** (2.5 g, 3.8 mmol) in saturated (at 0°) methanolic ammonia (100 ml) was kept in a sealed vessel for 3 days. The solvent was evaporated to give a white crystalline mass which was washed with chloroform and filtered to give **10** as white needles, yield 1.30 g (96%). Recrystallization from 100 ml of water gave pure compound: mp 220° dec; $[\alpha]^{25}D$ +53.2° (*c* 0.5, DMSO); $\lambda_{max}^{pH\ 1}$ 282 nm (ε 20,500); λ_{max}^{MeOH} 285 nm (ε 14,600); $\lambda_{max}^{pH\ 11}$ 285 nm (ε 14,600); nmr (DMSO-d_6) δ 5.98 (1-proton doublet, $J_{1',2'}$ = 3.0 Hz, H-1'), 8.25 (2-proton singlet, disappears on deuteration, NH_2), 8.43 (1-proton singlet, H-2).

Anal. Calcd for $C_{10}H_{12}BrN_5O_4$: C, 34.59; H, 3.20; N, 20.24. Found: C, 34.59; H, 3.36; N, 20.11.

3-α-D-Arabinofuranosyladenine (11).—To a solution of **8** (5.0 g, 7.6 mmol) in ethanol–ethyl acetate (1:1, 250 ml) was added concentrated NH_4OH (1 ml) and 10% palladium-on-carbon (2.5 g). The suspension was shaken for 2.5 hr under 40 psi of hydrogen, filtered, and evaporated to a syrup. The syrup was dissolved in methanol (125 ml), which had been saturated with ammonia at 0°, and kept in a sealed vessel for 3 days.

The solution was evaporated to a syrup and the syrup was dissolved in methanol (25 ml) from which it crystallized spontaneously. Recrystallization from aqueous methanol gave **11** as a monohydrate (1.7 g, 6.5 mmol, 85%): mp 195–196°; $[\alpha]^{25}D$ +40.8° (*c* 0.4, H_2O); $\lambda_{max}^{pH\ 1}$ 277 nm (ε 17,400); $\lambda_{max}^{H_2O}$ 280 nm (ε 12,500); $\lambda_{max}^{pH\ 11}$ 280 nm (ε 12,300); nmr (DMSO-d_6) δ 6.09 (after addition of D_2O, 1-proton doublet, $J_{1',2'}$ = 3.0 Hz), 7.87, 8.50 (1-proton singlets, H-2 and H-8), 8.25 (2-proton broad singlet, NH_2).

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.07; H, 5.15; N, 24.74.

6-Amino-3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-8-bromopurine (12).—To the crystalline trimethylsilyl derivative prepared from 8-bromoadenine (3.00 g, 13.8 mmol) was added 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride [prepared from 9.0 g (15.6 mmol) of 2,3,5-tri-*O*-benzyl-1-*p*-nitrobenzoyl-D-arabinofuranose] in dichloromethane (210 ml). The reaction was kept at ambient temperature for 1 week, methanol (20 ml) was added, and the mixture was evaporated to a syrup. The syrup was dissolved in chloroform, washed with saturated sodium bicarbonate solution, and evaporated to give a yellow solid. This material was chromatographed on 300 g of silica gel using chloroform–acetone (7:3) as eluent, to give a syrupy mixture of 3 and 9

(20) E.M. Acton and R. H. Iwamoto in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. I, W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N. Y., 1968, p 25.

isomers. The syrup was dissolved in ethanol, and the pure 3 isomer (**12**) crystallized slowly. The product was collected in five crops and recrystallized to yield 3.1 g (5.1 mmol, 37%): mp 152–154°; $[\alpha]^{25}D$ +124° (*c* 1.00, $CHCl_3$) {the 9 isomer could be isolated [silica gel, chloroform–acetone (4:1)] from the mother liquors by preparative layer chromatography in 4% yield}.

Anal. Calcd for $C_{31}H_{24}BrN_5O_7$: C, 60.39; H, 4.90; N, 11.35; Br, 12.96. Found: C, 60.56; H, 5.08; N, 11.25 Br, 13.01.

3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (13).—To a solution of **12** (4.0 g, 6.5 mmol) in 2-methoxyethanol (100 ml) was added 5% palladium-on-carbon (1 g) and concentrated NH_4OH (1 ml). This mixture was shaken at room temperature under 30 psi of hydrogen for 2 hr. The suspension was filtered, and the solution was evaporated to give a white solid. The solid was triturated with hot ethyl acetate (100 ml) and filtered to remove salts. The product **13** crystallized as fluffy white needles (3.2 g, 6.0 mmol, 92%): mp 163–164°; $[\alpha]^{25}D$ +74.8° (*c* 1, CH_2Cl_2) [lit.[11] mp 161–163°; $[\alpha]^{31}D$ +96.0° (*c* 1, CH_2Cl_2)].

3-β-D-Arabinofuranosyladenine (14).—To a solution of **12** (600 mg, 0.97 mmol) in 2-methoxyethanol (100 ml) was added concentrated NH_4OH (1 ml) and 10% palladium-on-carbon (300 mg), and the solution was shaken for 24 hr at 50° under hydrogen (50 psi). The solution was filtered and evaporated to give a white solid which was crystallized from 50% aqueous methanol (40 ml) to yield 204 mg (85%): mp 232–234° dec; $[\alpha]^{25}D$ +81° (*c* 0.4, H_2O); $\lambda_{max}^{pH\ 1}$ 277 nm (ε 15,500); λ_{max}^{MeOH} 277 nm (ε 11,600); $\lambda_{max}^{pH\ 11}$ 278 nm (ε 11,000). The nmr spectrum of **14** was identical with that reported in the literature.[11]

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)hypoxanthine (15).—To a solution of **5** (2.0 g, 3.4 mmol) in DMF (25 ml) and pyridine (1.5 ml) at −20° was added nitrosyl chloride (1.5 g, 23 mmol) in DMF (25 ml). The solution was kept at 0° for 30 min and then poured into saturated aqueous sodium bicarbonate (50 ml). The resultant mixture was extracted with chloroform (two 100-ml portions), and the extract was evaporated to a syrup which was dissolved in methanol–ethyl acetate, (1:1, 30 ml). White crystals formed slowly to give **15** (1.5 g, 75%), mp 118–119°, $[\alpha]^{25}D$ −64.2° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{31}H_{24}O_8N_4$: C, 64.13; H, 4.17; N, 9.65. Found: C, 63.99; H, 4.32; N, 9.44.

3-β-D-Ribofuranosylhypoxanthine (16).—A solution of **15** (1.5 g, 2.6 mmol) in methanol (100 ml) was saturated with ammonia at −10°. The solution was sealed and kept for 3 days at room temperature. The solvent was removed, and the residue was partitioned between water (50 ml) and chloroform (50 ml). The aqueous layer was washed with chloroform (two 50-ml portions) and evaporated to a syrup. The product (**16**) was crystallized from 50% aqueous ethanol (25 ml) to yield 0.68 g (91%): mp 183–185°; $[\alpha]^{25}D$ −35.2° (*c* 1, H_2O); $\lambda_{max}^{pH\ 1}$ 253 nm (ε 11,300); λ_{max}^{MeOH} 267 nm (ε 13,900); $\lambda_{max}^{pH\ 11}$ 269 nm (ε 11,000); nmr (DMSO-d_6) δ 5.98 (1-proton doublet, $J_{1',2'}$ = 6.0 Hz, H-1′), δ 8.32, 8.67 (1-proton singlets, H-2 and H-8) (lit.[17] mp 178°).

3-β-D-Arabinofuranosylhypoxanthine (17) from Deamination of 13.—A solution of **13** (1.0 g, 1.6 mmol) in DMF (5 ml) and pyridine (1.0 ml) was cooled to 5°, and a solution of nitrosyl chloride (0.8 g) in DMF (3 ml) was added. The solution was kept at 5° for 20 min and then poured into an excess of aqueous sodium bicarbonate. The mixture was extracted with chloroform and the extract was dried [$Mg(SO_4)_2$] and evaporated to give a dark syrup. Chromatography on silica gel using chloroform–acetone (4:1) as eluent gave a homogeneous syrup (700 mg) which was used in subsequent conversions.

A portion of the above syrup (300 mg, 0.49 mmol) was dissolved in 2-methoxyethanol and 5% palladium-on-carbon (300 mg), and sodium acetate (50 mg) was added. The mixture was shaken under 40 psi of hydrogen for 72 hr. The mixture was filtered and the solution was evaporated to a white solid which was chromatographed on silica gel (20 g) using the upper phase from ethyl acetate–1-propanol–water (4:1:2) as eluent, to give **17** as a white solid which was crystallized from water: yield 50 mg (38%); mp 194–196° dec; $[\alpha]^{25}D$ +41.0° (*c* 1.0, H_2O); $\lambda_{max}^{pH\ 1}$ 252 nm (ε 9800); λ_{max}^{MeOH} 264 nm (ε 12,600); $\lambda_{max}^{pH\ 11}$ 268 nm (ε 9400); nmr (DMSO-d_6) δ 6.45 (1-proton doublet, $J_{1',2'}$ = 4.0 Hz, H-1′), 8.20, 8.47 (1-proton singlets, H-2 and H-8).

Anal. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.78; H, 4.51; N, 20.89. Found: C, 44.63; H, 4.62; N, 20.69.

From Deamination of 14.—A suspension of **14** (1.0 g, 3.7 mmol) in DMF (10 ml) and pyridine (3 ml) was cooled to 0°, and a solution of nitrosyl chloride (2.5 g) in DMF (7 ml) was added. After 3 hr concentrated NH_4OH (10 ml) was added, and the solution was evaporated to dryness. The resultant syrup was triturated with methanol and filtered to remove salts. Silica gel (7 g) was added to the solution, and the mixture was dried under diminished pressure and applied to a column of dry silica gel (75 g). Elution with the same solvent as in the previous experiment afforded **17**, yield 320 mg (32%).

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-8-pyridiniumhypoxanthine Betaine (18).—A suspension of 6-amino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-8-bromopurine (**4**, 5.0 g, 7.6 mmol) in a mixture of chloroform (25 ml) and pyridine (25 ml) was stirred at 0°. Nitrosyl chloride (2 g, 40 mmol) in chloroform (25 ml) was added over 2 hr. The resulting solution was allowed to warm to room temperature, and the solution was evaporated to a dark yellow syrup. Toluene (three 25-ml portions) was evaporated from the syrup to remove pyridine, and the syrup was dissolved in ethanol. The major component, 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-8-pyridiniumhypoxanthine betaine, crystallized as yellow needles which were recrystallized from ethanol to give 4.2 g (84%) of bright yellow needles, mp 230° dec, $[\alpha]^{25}D$ −88.1° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{36}H_{27}N_5O_8$: C, 65.75; H, 4.14; N, 10.65. Found: C, 65.67; H, 4.34; N, 10.45.

3-(β-D-Ribofuranosyl)-8-pyridiniumhypoxanthine Betaine (19).—3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-8-pyridiniumhypoxanthine betaine (**8**, 1.9 g, 2.9 mmol) was suspended in 100 ml of anhydrous methanol saturated with ammonia at 0°. The mixture was stirred in a sealed vessel for 5 days. The solvent was evaporated under reduced pressure. The residue was triturated with chloroform, and the resulting insoluble yellow powder was dissolved in 35 ml of hot water. After 12 hr at room temperature crystals appeared and the suspension was cooled at 4° for 12 hr. The product (**19**) was collected by filtration: yield 0.85 g (85%); mp 225° dec; $[\alpha]^{25}D$ −13.9° (*c* 0.29, H_2O); $\lambda_{max}^{pH\ 1}$ 332 nm (ε 18,000); $\lambda_{max}^{H_2O}$ 390 nm (ε 3000); $\lambda_{max}^{pH\ 11}$ 263 nm (ε 18,500), 394 nm (17,500); nmr (DMSO-d_6) δ 5.94 (1-proton doublet, $J_{1',2'}$ = 5.7 Hz, H-1′), 8.1–8.9 (3-proton multiplet, β- and γ-pyridinium protons), 8.46 (1-proton singlet, H-2), 9.78 (2-proton doublet $J_{\alpha,\beta}$ = 5.2 Hz, α-pyridinium protons).

Anal. Calcd for $C_{15}H_{15}N_5O_5$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.96; H, 4.12; N, 20.02.

6,8-Diamino-3-β-D-ribofuranosylpurine (21).—A mixture of **4** (2.0 g, 3.0 mmol) and sodium azide (1.0 g) in hexamethylphosphoric triamide (7 ml) was stirred at 80° for 72 hr. The reaction was monitored by uv absorption change in methanol [285 (**4**) to 308 nm (**20**)]. The mixture was poured into rapidly stirred water (150 ml), and the resultant yellow precipitate was washed with water (150 ml) and partitioned between water (100 ml) and chloroform (100 ml). The chloroform layer was washed with water (3 × 50 ml) and evaporated to a powder which showed one major component on tlc and gave a strong absorption at 2061 cm^{-1} (azide). This material could not be obtained in a homogeneous form. The powder was dissolved in 2-methoxyethanol (100 ml) and shaken with 10% palladium-on-carbon (1.0 g) under 40 psi of hydrogen for 16 hr. The mixture was filtered and evaporated to a pale yellow solid which was dissolved in methanol saturated with ammonia at 0°. The solution was kept at room temperature in a sealed vessel for 3 days and then evaporated to dryness; the residue was partitioned between water (100 ml) and chloroform (100 ml). The aqueous phase was washed with chloroform (three 50-ml portions) and evaporated to give yellow solid. The solid was triturated with ethanol (two 25-ml portions) and crystallized from a small volume of water. Recrystallization from water gave **21** as colorless crystals: yield 300 mg (35%); mp 180° dec; $[\alpha]^{25}D$ −42.8° (*c* 0.34, H_2O); $\lambda_{max}^{pH\ 1}$ 232 nm (ε 18,900), 294 (17,700); λ_{max}^{MeOH} 232 nm (ε 15,900), 296 (15,300); $\lambda_{max}^{pH\ 11}$ 234 nm (ε 10,200), 304 (12,300); nmr (DMSO-d_6) δ 5.40 (5-proton multiplet, NH_2, OH's), 5.99 (1-proton doublet, $J_{1',2'}$ = 5.0 Hz, H-1′), 8.01 (2-proton broad singlet, NH_2), 8.69 (1-proton singlet, H-2).

Anal. Calcd for $C_{10}H_{14}O_4N_6$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.41; H, 5.08; N, 29.63.

Registry No.—**4**, 36258-93-2; **5**, 28837-63-0; **6**, 36258-95-4; **7**, 2273-78-1; **8**, 36208-01-2; **9**, 36258-97-6; **10**, 36258-98-7; **11**, 36258-99-8; **12**, 36259-00-4; **13**, 36259-01-5; **14**, 14365-78-7; **15**, 36259-03-7; **16**, 6835-54-7; **17**, 36259-05-9; **18**, 36259-06-0; **19**, 36259-07-1; **21**, 36259-08-2.