The Synthesis and Reactions of Some 8-Substituted Purine Nucleosides[1]

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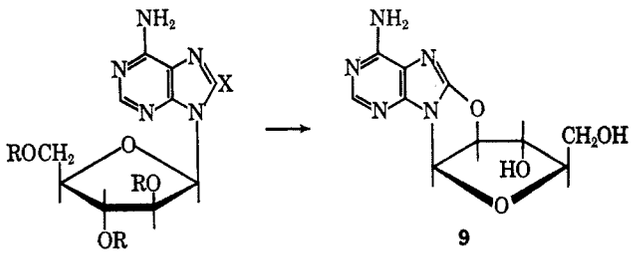
The preparation of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) was accomplished by the bromination of 9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**2**). The reaction of **3** with basic nucleophiles such as sodium methoxide and ammonia effected an intramolecular displacement of bromide to give 8,2′-anhydro-8-hydroxy-9-(β-D-arabinofuranosyl)adenine (**9**). Displacement of the bromine of **3** by the nonbasic nucleophiles, thiourea and sodium azide, gave the 8-thiol and 8-azide. A similar set of reactions was carried out starting from 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**12**). The displacement of bromide from 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) by both neutral and basic nucleophiles proceeded normally to give the appropriate 8-substituted purine xylofuranoside. There was no evidence for an intramolecular displacement of bromide to give 8,3′-anhydro nucleosides.

Enzymic hydroxylation of 6-methylthiopurine by hepatic aldehyde oxidase to give 6-methylthio-8-hydroxypurine was described in a recent paper.[2] It was suggested that such a mechanism may contribute significantly to the rapid biological inactivation of 6-methylthiopurine in the intact animal. On the basis of such a rationale, it might be expected that properly chosen 8-substituted derivatives of biologically active nucleosides can not be inactivated in this fashion, and hence may prove to be more satisfactory than the parent compound. 8-Aminoadenosine has been reported to be an effective inhibitor of *Streptococcus faecalis* (8043) and sarcoma S-180 ascites cells although it caused only slight inhibition of leukemia L-1210.[3] In view of the observed biological activity of 9-(β-D-arabinofuranosyl)adenine[4] (**1**) and 9-(β-D-xylofuranosyl)adenine[5] (**11**), it was of interest to prepare a series of 8-substituted derivatives of these compounds.

A number of papers have appeared recently which describe the facile preparation of 8-substituted purines and the corresponding nucleosides and nucleotides[6,7] by way of bromination of the 8 position of the adenine or guanine derivative. Displacement of the 8-bromo group by the appropriate nucleophile gave a variety of 8-substituted nucleosides. Such a general procedure appeared to offer a useful route for the preparation of the desired xylose and arabinose nucleosides.[2]

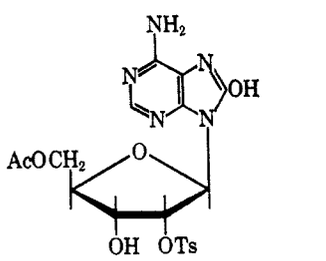
Acetylation of 9-(β-D-arabinofuranosyl)adenine[8] (**1**) at 0° gave crystalline 9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**2**). Bromination of **2** using N-bromoacetamide[6c] produced crystalline 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) after purification *via* silica gel chromatography. Treatment of **3** with thiourea in ethanol[6c] displaced the bromine function to give 6-amino-9-(2,3,5-tri-O-acetyl-β-D-arabinosuranosyl)-9H-purine-8-thiol (**4**) as a crystalline solid which could be deacetylated easily to give 6-amino-9-(β-D-arabinofuranosyl)-9H-purine-8-thiol (**5**).

When the blocked bromo nucleoside (**3**) was treated with methanolic ammonia at room temperature as described by Holmes and Robins[6c] for the preparation of 8-bromoadenosine, the product isolated contained no bromine and had physical properties which were similar to those reported by Ikehara, *et al.*,[6a] for 8,2′-anhydro-8-hydroxy-9-(β-D-arabinofuranosyl)adenine (**9**) prepared from 6-amino-8-hydroxy-9-(5-O-acetyl-2-O-*p*-tolylsulfonyl-β-D-ribofuranosyl)-9H-purine (**10**).



1, R = H; X = H
2, R = Ac; X = H
3, R = Ac; X = Br
4, R = Ac; X = SH
5, R = H; X = SH
6, R = Ac; X = N_3
7, R = Ac; X = NH_2
8, R = H; X = NH_2

9



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The anhydro nucleoside (**9**) was hydrolyzed using dilute aqueous sulfuric acid. The sugar obtained from this acid hydrolysis was identified as arabinose by paper chromatography. Thus, the anhydro nucleoside must have the 8,2′ structure (**9**).[9] This same anhydro nucleoside (**9**) was formed when the blocked bromo nucleoside (**3**) was treated with methanolic sodium methoxide in an attempt to prepare the 8-methoxyadenine arabinoside. Apparently basic nucleophiles such as sodium methoxide remove the O-acetates before any significant displacement of the bromine on C-8 occurs. The SN2 displacement is completely

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(2) T. L. Loo, C. Lim, and D. G. Johns, *Biochim. Biophys. Acta*, **134**, 467 (1967).

(3) A. Bloch, E. Mihich, C. A. Nichol, R. K. Robins, and R. H. Whistler, *Proc. Amer. Assoc. Cancer Res.*, **7**, 7 (1966).

(4) (a) J. J. Brink and G. A. LePage, *Cancer Res.*, **24**, 312 (1964); (b) G. A. LePage and I. G. Junga, *ibid.*, **23**, 739 (1963).

(5) (a) G. A. LePage and I. G. Junga, *ibid.*, **25**, 46 (1965); (b) D. B. Ellis and G. A. LePage, *Can. J. Biochem.*, **43**, 617 (1965); (c) J. G. Cory and R. J. Suhadolnik, *Biochemistry*, **4**, 1729 (1965).

(6) (a) M. Ikehara, H. Tada, K. Muneyama, and M. Kaneko, *J. Amer. Chem. Soc.*, **88**, 3165 (1966); (b) R. E. Holmes and R. K. Robins, *ibid.*, **87**, 1772 (1965); (c) R. E. Holmes and R. K. Robins, *ibid.*, **86**, 1242 (1964).

(7) M. Ikehara and H. Tada, *Chem. Pharm. Bull.* (Tokyo), **15**, 94 (1967).

(8) (a) E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3274 (1962); (b) E. J. Reist, V. J. Bartuska, and L. Goodman, *ibid.*, **29**, 3725 (1964).

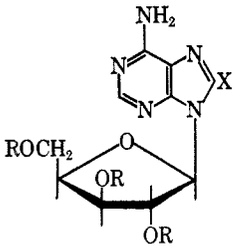
(9) Compound **9** was identical chromatographically and had an infrared spectrum similar to that of a sample of 8,2′-anhydro-8-hydroxy-9-(β-D-arabinofuranosyl)adenine which was kindly given to us by Dr. H. Tada.

overshadowed by the resulting intramolecular cyclization and anhydro nucleoside (**9**) is the sole product.

Neutral SN2 reactions which do not remove the O-acetate proceed in a straightforward fashion. Thus, treatment of the bromotriacetate (**3**) with sodium azide in N,N-dimethylformamide (DMF) took place normally to give 8-azido-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**6**). Deacetylation of the blocked azide (**6**) to give the 8-azido-9-(β-D-arabinofuranosyl)-adenine failed. The product isolated was again the anhydro nucleoside (**9**). Although the blocked azide (**6**) was noncrystalline, spectral data, halogen analysis, and tlc data provided convincing proof that the anhydro nucleoside formed in this reaction did not come from unreacted 8-bromide (**3**) but must have come by the intramolecular displacement of the 8-azide by the sugar alkoxide, a somewhat surprising result for such mild conditions.

The preparation of 8-amino-9-(β-D-arabinofuranosyl)-adenine (**8**) was accomplished by hydrogenation of the blocked azide (**6**) to the blocked 8-amine (**7**) prior to deacetylation. Thus, the crystalline 8-amine (**8**) could be prepared in good yield.

By the same general procedure, 9-β-D-xylofuranosyladenine[10] (**11**) was acetylated, then brominated to give 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) again purified by chromatography. The re-



11, R = X = H
12, R = Ac; X = H
13, R = Ac; X = Br
14, R = H; X = Br
15, R = Ac; X = SH
16, R = H; X = SH
17, R = H; X = OCH_3
18, R = H; X = N_3
19, R = H; X = NH_2

action of **13** with thiourea gave the syrupy 6-amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-9H-purine-8-thiol (**15**), which could be deacetylated to give crystalline 6-amino-9-(β-D-xylofuranosyl)-9H-purine-8-thiol (**16**). Treatment of the blocked 8-bromoxyloside (**13**) with either methanolic ammonia or methanolic sodium methoxide at room temperature gave a good yield of 8-bromo-9-(β-D-xylofuranosyl)adenine (**14**). There was no detectable evidence for any 8,3′-anhydro nucleoside formation. Treatment of either the 8-bromoxyloside (**14**) or its triacetate (**13**) with refluxing methanolic sodium methoxide gave 8-methoxy-9-(β-D-xylofuranosyl)adenine (**17**) again with no evidence for any 8,3′-anhydro nucleoside. The preparation of 8-azido-9-(β-D-xylofuranosyl)adenine (**18**) was accomplished by the displacement of 8-bromo-9-(β-D-xylofuranosyl)-adenine (**14**) by sodium azide in DMF. Hydrogenation of the azide gave 8-amino-9-(β-D-xylofuranosyl)-adenine (**19**).

(10) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

The failure to obtain any 8-3′-anhydro-8-hydroxy-9-(β-D-xylofuranosyl)adenine from the 8-bromoxyloside (**14**) is somewhat surprising in view of the exceptional ease with which the 8-bromoarabinoside (**3**) and 8-azidoarabinoside (**6**) were converted into the 8,2′-anhydro nucleoside. The ease of formation of 8,2′-anhydroarabinoside using alkaline conditions compared with the failure to form an 8,3′-anhydroxyloside from the 8-bromoxyloside (**14**) was also indicated during the measurement of the ultraviolet spectra of **3** and **14**. Thus, the 8-bromoxyloside (**14**) has a band at $\lambda_{max}^{pH\ 13}$ 265 mμ (ε 16,700). Holmes and Robins[6b] report a band at $\lambda_{max}^{pH\ 11}$ 264 mμ (ε 17,600) for 8-bromoadenosine. The 8-bromoarabinoside (**3**) on the other hand had an absorption at $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 13,380), a value which indicated a significant conversion into the 8,2′-anhydroarabinoside (**9**).

Examination of molecular models gives no indication of any steric problem to account for the failure to form the 8,3′-anhydro bond. The chemistry of anhydro nucleosides in the pyrimidine series showed similar results. Thus 2,2′-anhydro nucleosides were formed inevitably in preference to 2,3′-anhydro nucleosides,[11] although 2,3′-anhydro nucleosides have been prepared.[12a] The "up" 2′-hydroxyl of arabinopyrimidine nucleosides is reported to attack the pyrimidine C-6, whereas the up 3′-hydroxyl of 2′-deoxyxylopyrimidine nucleosides does not.[12b]

Experimental Section[13]

9-(2,3,5-Tri-O-acetyl-β-D-arabinofuranosyl)adenine (2).—A suspension of 2.5 g (9.36 mmol) of 9-(β-D-arabinofuranosyl)-adenine (**1**) and 4.6 ml (48.8 mmol) of acetic anhydride in 35 ml of dry pyridine was stirred at 0° under a nitrogen atmosphere for 19 hr, then the excess acetic anhydride was decomposed by the addition of 2 ml of ethanol. The decomposed mixture was stirred for 1 hr at 0°, then was evaporated to dryness *in vacuo*. The residue was dissolved in 40 ml of chloroform and washed with 15 ml each of water, saturated aqueous sodium bicarbonate, and water; then it was dried and evaporated to dryness *in vacuo* to give 3.26 g of product as an orange gum. Two recrystallizations from ethanol gave 1.26 g (34%) of white crystals: mp 128.5–129.0°; $[\alpha]^{22}D$ −13° (*c* 0.74, chloroform); $\lambda_{max}^{ethanol}$ 259 mμ (ε 14,200).

Anal. Calcd for $C_{16}H_{19}N_5O_7$: C, 48.9; H, 4.87; N, 17.8. Found: C, 48.7; H, 4.61; N, 17.5.

8-Bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (3).—A mixture of 3.15 g (8.0 mmol) of 9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**2**) and 3.5 g (22.4 mmol) of N-bromoacetamide in 50 ml of chloroform, which had been dried over sulfuric acid, was heated at reflux with stirring while protected from moisture for 15 hr, then was evaporated to dryness *in vacuo*. The residue was partitioned between 50 ml each of ethyl acetate and 10% aqueous sodium hydrosulfite. The organic layer was washed with 10 ml of water, then was dried and evaporated to dryness *in vacuo*. The residue was dissolved in chloroform, then was applied to a column of silica gel (450 g, 4.9 × 47 cm). Elution with chloroform (500 ml) then ethyl

(11) (a) D. M. Brown, D. B. Parihar, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958); (b) N. C. Yung and J. J. Fox, *J. Amer. Chem. Soc.*, **83**, 3060 (1961); (c) T. Naito, M. Hirata, Y. Nakai, T. Kobayashi, and M. Kanao, *Chem. Pharm. Bull.* (Tokyo), **13**, 1258 (1965).

(12) (a) J. F. Codington, R. Fecher, and J. J. Fox, *J. Amer. Chem. Soc.*, **82**, 2794 (1960); (b) J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Lett.*, 4927 (1966).

(13) Melting points are corrected. Thin layer chromatograms were run on silica gel HF (E. Merck A-G Darmstadt). Paper chromatograms were run on Whatman No. 1 paper by the descending technique. Spots were detected by visual examination under an ultraviolet lamp for the nucleosides. Reducing sugars were detected by aniline citrate. The solvent systems used were solvent A, chloroform–methanol (9:1); solvent B, absolute ethanol; solvent C, 65% aqueous 2-propanol–ethyl acetate (35:65).

acetate–chloroform (500 ml of 1:3 then 1 l. of 3:1) removed some impurities. Elution with an additional 1 l. of ethyl acetate–chloroform (3:1) and finally 4 l. of ethyl acetate gave a total of 1.01 g (36%) of **3** as pale orange needles: mp 178.5–179.0°; $[\alpha]^{22}D$ −73° (*c* 0.4, chloroform); $\lambda_{max}^{pH\ 1}$ 262 mμ (ε 17,250); $\lambda_{max}^{pH\ 7}$ 263 mμ (ε 15,400); $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 13,380).

Anal. Calcd for $C_{16}H_{18}BrN_5O_7$: C, 40.7; H, 3.82; Br, 16.9; N, 14.9. Found: C, 40.7; H, 3.98; Br, 16.6; N, 14.5.

6-Amino-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)-9H-purine-8-thiol (4).—A solution of 614 mg (1.3 mmol) of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) and 135 mg (1.77 mmol) of thiourea in 30 ml of ethanol was stirred at reflux under nitrogen for 18 hr, then was evaporated to dryness *in vacuo*. The residue was partitioned between 30 ml of chloroform and 10 ml of water. The organic phase was dried, then evaporated to dryness *in vacuo* to give crude product as a yellow foam. This material was dissolved in chloroform and applied to a column of silica gel (55 g, 1.4 × 36 cm). After elution of some by-products using chloroform (425 ml) and 10% ethyl acetate in chloroform (500 ml), product was eluted using ethyl acetate–chloroform (1:1, 800 ml) and 100% ethyl acetate. The residue from these last fractions was a white foam weighing 365 mg (86%). Crystallization was effected by dissolving the foam in ethanol then allowing the solvent to evaporate to give material with mp 176.5–179.5°; $[\alpha]^{21}D$ −39° (*c* 0.40, chloroform); $\lambda_{max}^{pH\ 1}$ 308 mμ (ε 23,200), 243 (9360), 222 (12,600); $\lambda_{max}^{pH\ 7}$ 297 mμ (ε 21,900), 227 (18,300); $\lambda_{max}^{pH\ 13}$ 297 mμ (ε 21,000).

Anal. Calcd for $C_{16}H_{19}N_5O_7S \cdot C_2H_5OH$: C, 45.9; H, 5.35; N, 14.9; S, 6.80. Found: C, 45.8; H, 5.13; N, 14.7; S, 6.97.

The nmr spectrum contained a triplet at τ 8.75 and a quartet at 6.24, thus demonstrating the presence of ethanol.

6-Amino-9-(β-D-arabinofuranosyl)-9H-purine-8-thiol (5).—A solution of 234 mg (0.55 mmol) of 6-amino-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)-9H-purine-8-thiol (**4**) and 33 mg (0.61 mmol) of sodium methoxide in 15 ml of methanol was stirred at room temperature under a nitrogen atmosphere for 15 hr. The solution was neutalized with 2 drops of glacial acetic acid, then evaporated to dryness *in vacuo*. The residue was purified by means of the lead salt[14] to give 96 mg (60%) of product as a white solid. Recrystallization from methanol gave 74 mg (45%) of white needles: mp 199.5–202.5°; $[\alpha]^{22}D$ 9° (*c* 0.40, methanol); $\lambda_{max}^{pH\ 1}$ 308 mμ (ε 22,600), 242 (10,500), 222 (11,700); $\lambda_{max}^{pH\ 7}$ 302 mμ (sh, ε 21,500), 297 (22,000), 228 (17,500); $\lambda_{max}^{pH\ 13}$ 296 mμ (ε 21,200).

Anal. Calcd for $C_{10}H_{13}N_5O_4S \cdot 0.6H_2O$: C, 38.7; H, 4.62; N, 22.6; S, 10.3. Found: C, 39.0; H, 4.92; N, 22.2; S, 10.4.

A thiol titration consumed 93% (based on 0.6 H_2O) of the theoretical uptake of iodine.

8,2′-Anhydro-8-hydroxy-9-(β-D-arabinofuranosyl)adenine (9).—A solution of 0.5 g of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) in 15 ml of methanol which had been saturated previously with anhydrous ammonia at 0° was kept at room temperature in a Parr bomb for 32 hr. The reaction was cooled to 0° then filtered to give 158 mg of pink crystals. Recrystallization from water gave 117 mg (42%) of product: mp 212.0–212.5° dec; $[\alpha]^{23}D$ −108° (*c* 0.30, pyridine); $\lambda_{max}^{pH\ 1}$ 259 mμ (ε 12,900); $\lambda_{max}^{pH\ 7}$ 255 mμ (ε 13,100); $\lambda_{max}^{pH\ 13}$ 259 mμ (ε 12,700).

The nmr spectrum had a band at δ 6.42 (J = 5 cps) assigned to H′-1.

Anal. Calcd for $C_{10}H_{11}N_5O_4 \cdot 0.2H_2O$: C, 44.7; H, 4.27; N, 26.0. Found: C, 44.4; H, 4.14; N, 26.2.

Ikehara, *et al.*,[8a] report mp >190° dec; $[\alpha]^{19}D$ −122° (*c* 0.75, pyridine); $\lambda_{max}^{pH\ 1}$ 260 mμ (ε 10,800); $\lambda_{max}^{H_2O}$ 260 mμ (ε 11,000); $\lambda_{max}^{pH\ 14}$ 260 mμ (ε 10,700). The nmr spectrum had a band at δ 6.50 (J = 5.4 cps) which he assigned to H′-1.

A 50-mg sample of the cyclonucleoside **9** was heated at reflux for 8 hr with 8 ml of 0.1 *N* sulfuric acid. The reaction was cooled to room temperature and neutralized with Amberlite IR-45 (OH^-) to pH 7. Paper chromatography of the product, using solvent C as the developing solvent, showed one spot at R_{ribose} 0.69 that gave a positive test for reducing sugar with aniline citrate. D-Arabinose had a spot at R_{ribose} 0.69; D-xylose had a spot at R_{ribose} 0.84.

8-Amino-9-(β-D-arabinofuranosyl)adenine (8).—To a solution of 3.0 g (6.34 mmol) of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) in 28 ml of dry DMF was added 1.32 g (20 mmol) of sodium azide. The resulting solution was stirred at 75° for 10 hr, then was evaporated to dryness *in vacuo*. The residue was partitioned between 20 ml each of dichloromethane and water. The organic layer was dried then evaporated to dryness *in vacuo* to give 2.9 g of crude 8-azido-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**6**) as a syrup: λ_{max}^{film} 4.6 μ (N_3); $\lambda_{max}^{pH\ 1}$ 279 mμ (ε 15,600); $\lambda_{max}^{pH\ 13}$ 264 mμ (ε 11,400).

Thin layer chromatography using solvents A and B showed one main spot with R_f 0.61 and 0.53, respectively. There were two trace components with slower R_f values. Bomine analysis showed 1.44% Br indicating a maximum of 8.5% starting material.

A solution of 1.98 g (4.56 mmol) of crude 8-azido-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**6**) in 250 ml of 95% ethanol was hydrogenated at room temperature for 15 hr using 1 g of 5% palladium on charcoal. The mixture was filtered through a Celite pad and the filtrate was evaporated to dryness *in vacuo* to give 1.76 g of 8-amino-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**7**) as a yellow foam. There was no azide absorption at 4.6 μ. Tlc using solvents A and B showed one spot with R_f values of 0.26 and 0.32, respectively.

Treatment of 1.49 g of 8-amino-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**7**) with methanolic sodium methoxide at 0° for 3 days caused the precipitation of 0.66 g of 8-amino-9-(β-D-arabinofuranosyl)adenine (**8**). The mother liquors after the removal of crystalline **8** were neutralized and worked up in the usual fashion to give an additional 0.2 g of crystalline product. The fractions were combined and recrystallized from 80% aqueous ethanol to give 0.71 g (54% over-all yield from **3**) of crystals, mp 142–145°, which resolidified and remelted at 237.5–240° dec.

The analytical sample [dried at 100° (1 mm) for 16 hr] had mp 142.5–146°, resolidifing and remelting at 238–240° dec. It was redried at 152° (1 mm) for 2 hr and had mp 239–241° dec; $[\alpha]^{22}D$ +10° (*c* 1.0, 2-methoxyethanol); $\lambda_{max}^{pH\ 1}$ 269 mμ (ε 13,500); $\lambda_{max}^{pH\ 7}$ 273 mμ (ε 16,600); $\lambda_{max}^{pH\ 13}$ 275 mμ (ε 16,800).

Anal. Calcd for $C_{10}H_{14}N_6O_4$: C, 42.6; H, 5.00; N, 29.8. Found: C, 42.7; H, 5.21; N, 29.6.

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)adenine (12).—Acetylation of 12.0 g (45 mmol) of 9-(β-D-xylofuranosyl)adenine (**11**)[9] in 285 ml of pyridine using 13.1 ml (128 mmol) of acetic anhydride was carried out as described for the preparation of 9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**2**) to give 15.5 g (88%) of **12** as a white foam: $[\alpha]^{24}D$ −14° (*c* 0.56, chloroform); $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 14,750); $\lambda_{max}^{pH\ 7}$ 258 mμ (ε 14,750); $\lambda_{max}^{pH\ 13}$ 256 mμ (ε 18,200).

Anal. Calcd for $C_{16}H_{19}N_5O_7 \cdot {}^1/_2H_2O$: C, 47.8; H, 5.01; N, 17.4. Found: C, 47.6; H, 5.05; N, 17.4.

8-Bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (13).—A solution of 2.0 g of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-adenine (**12**) in 20 ml of dichloromethane was dried by the azeotropic distillation of 10 ml of the solvent. The dry solution was added to a stirred suspension of 2.5 g (17.4 mmol) of N-bromoacetamide in 350 ml of dry carbon tetrachloride. The reaction was stirred under reflux for 16 hr while protected from moisture, then it was evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml of chloroform–ethyl acetate (1:1) and was extracted with 25 ml each of 10% aqueous sodium bisulfite, saturated aqueous sodium bicarbonate, and water; then it was dried and evaporated to dryness *in vacuo* to give 2.53 g of an orange gum. The crude product was dissolved in 10 ml of chloroform and applied to a column of silica gel (300 g, 1.5 × 30 cm). The column was eluted with ethyl acetate–chloroform (3:1) until all uv-absorbing by-products were eluted (*ca.* 3 l.). Finally elution with ethyl acetate gave 2.0 g (83%) of **13** as a yellow foam. Further elution with ethyl acetate–methanol gave varying amounts of starting material (**12**).

The analytical sample of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) from the column was homogeneous on tlc using ethanol as the developing agent and had a spot at R_f 0.6; $[\alpha]^{25}D$ −8° (*c* 0.4, methanol); $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 17,400); $\lambda_{max}^{pH\ 7}$ 265 mμ (ε 15,700); $\lambda_{max}^{pH\ 13}$ 265 mμ (ε 16,000).

Anal. Calcd for $C_{16}H_{18}BrN_5O_7$: C, 40.7; H, 3.82; Br, 16.9; N, 14.9. Found: C, 40.8; H, 3.88; Br, 16.9; N, 14.5.

8-Bromo-9-(β-D-xylofuranosyl)adenine (14).—A solution of 250 mg of purified 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) in 20 ml of methanol in a Parr bomb was cooled to 0° and saturated with gaseous ammonia. The reaction was kept at room temperature for 16 hr, then it was evaporated to

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

dryness *in vacuo*. The solid residue was recrystallized from water to give 135 mg (74%) of crystalline product, mp 197.5–198.0°.

The analytical sample had mp 194.5–195.5°; $[\alpha]^{25}D$ −46° (*c* 0.5, methanol); $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 17,700); $\lambda_{max}^{pH\ 7,\ 13}$ 265 mμ (ε 16,700).

Anal. Calcd for $C_{10}H_{12}BrN_5O_4 \cdot {}^1/_4H_2O$: C, 34.3; H, 3.59; Br, 22.8; N, 20.0. Found: C, 34.3; H, 4.05; Br, 22.8; N, 20.0.

6-Amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-9H-purine-8-thiol (15).—A solution of 5.47 g (11.6 mmol) of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) and 1.2 g (15.8 mmol) of thiourea in 200 ml of absolute ethanol was heated at reflux under a nitrogen atmosphere for 5 hr. The yellow solution was evaporated to dryness *in vacuo* and the residue was partitioned between 15 ml of water and 50 ml of chloroform. The chloroform layer was dried and evaporated to dryness *in vacuo* to give 5.2 g of crude blocked thiol (**15**) as a yellow foam. A solution of crude **15** in chloroform was chromatographed on 150 g of silica gel. After elution with dichloromethane to remove by-products, elution with ethyl acetate gave 2.96 g (66%) of **15** as a yellow gum: $[\alpha]^{23}D$ −6° (*c* 0.5, chloroform); $\lambda_{max}^{pH\ 1}$ 307.5 mμ (ε 24,800), 242 (10,000); $\lambda_{max}^{pH\ 7,\ 13}$ 297 mμ (ε 22,500).

Anal. Calcd for $C_{16}H_{19}N_5O_7S$: C, 45.2; H, 4.50; N, 16.5; S, 7.54. Found: C, 44.6; H, 4.38; N, 15.9; S, 7.33.

6-Amino-9-(β-D-xylofuranosyl)-9H-purine-8-thiol (16). A.—Deacetylation of 1.38 g (3.24 mmol) of 6-amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-9H-purine-8-thiol (**15**) was carried out using 193 mg (3.56 mmol) of sodium methoxide in 45 ml of methanol in the manner described for the deacetylation of the arabinoside (**5**). After purification by means of the lead salt, 540 mg of crude product was obtained as a yellow gum. Crystallization was accomplished by dissolving the gum in 8 ml of methanol and diluting with 20 ml of acetonitrile. On cooling 333 mg (34%) of product was obtained: mp 238–239° dec; $[\alpha]^{21}D$ −69° (*c* 0.4, methanol); $\lambda_{max}^{pH\ 1}$ 308 mμ (ε 24,500), 245 (11,150); $\lambda_{max}^{pH\ 7,\ 13}$ 297 mμ (ε 23,200).

Anal. Calcd for $C_{10}H_{13}N_5O_4S$: C, 40.1; H, 4.35; N, 23.4; S, 10.7. Found: C, 40.4; H, 4.44; N, 23.5; S, 10.4.

B.—A solution of 2.87 g (8.28 mmol) of 8-bromo-9-(β-D-xylofuranosyl)adenine (**14**) and 0.86 g (11.3 mmol) of thiourea in 150 ml of absolute ethanol was heated at reflux for 18 hr, then evaporated to dryness *in vacuo*. Purification, by means of the lead salt, then crystallization from methanol–acetonitrile (25 ml: 200 ml) gave 1.13 g (46%) of product, mp 230–232° dec, which was identical with material obtained in method A.

8-Methoxy-9-(β-D-xylofuranosyl)adenine (17).—A solution of 2.2 g (6.35 mmol) of crystalline 8-bromo-9-(β-D-xylofuranosyl)-adenine (**14**) and 1.21 g (22.3 mmol) of sodium methoxide in 100 ml of methanol was heated at reflux under a nitrogen atmosphere for 17 hr. The reaction was cooled to room temperature, neutralized with acetic acid, and evaporated to dryness *in vacuo*. Trituration of the residue with 10 ml of ice-cold water gave 1.43 g of crude product as a tan powder. Recrystallization from 40 ml of water gave 1.2 g (63%) of crystals: mp 197.5–199.0°; $[\alpha]^{23}D$ −63° (*c* 0.4, methanol); $\lambda_{max}^{pH\ 1}$ 261 mμ (ε 12,850); $\lambda_{max}^{pH\ 7,\ 13}$ 260 mμ (ε 13,650).

Anal. Calcd for $C_{11}H_{15}N_5O_5 \cdot {}^1/_5H_2O$: C, 43.9; H, 5.16; N, 23.3. Found: C, 44.2; H, 5.01; N, 22.9.

8-Azido-9-(β-D-xylofuranosyl)adenine (18).—To a solution of 2.76 g (7.98 mmol) of 8-bromo-9-(β-D-xylofuranosyl)adenine (**14**) in 35 ml of dry N,N-dimethylformamide was added 1.66 g of sodium azide. The resulting solution was stirred for 10 hr at 75°, then was evaporated to dryness *in vacuo*. The residue was triturated first with 30 ml of dichloromethane, then with 40 ml of water. The resulting residue was recrystallized from 60 ml of 95% aqueous ethanol to give 1.66 g (67%) of product: mp *ca.* 270° dec; $[\alpha]^{24}D$ −74° (*c* 0.5, 2-methoxyethanol); $\lambda_{max}^{pH\ 1}$ 281 mμ (ε 18,400); $\lambda_{max}^{pH\ 7}$ 281 mμ (ε 14,900); $\lambda_{max}^{pH\ 13}$ 280 mμ (ε 16,200).

Anal. Calcd for $C_{10}H_{12}N_8O_4$: C, 39.0; H, 3.92; N, 36.4. Found: C, 38.8; H, 4.22; N, 36.1.

8-Amino-9-(β-D-xylofuranosyl)adenine (19).—A suspension of 1.48 g (4.8 mmol) of 8-azido-9-(β-D-xylofuranosyl)adenine (**18**) and 1.0 g of 5% palladium on charcoal in 325 ml of water was stirred at room temperature under a hydrogen atmosphere for 15 hr. The mixture was filtered through a Celite pad, then the filtrate was evaporated to dryness *in vacuo* to give 0.7 g (52%) of product as a white solid, mp 150–153°. There was no absorption attributable to azide at 4.7 μ in the infrared.

Recrystallization from 98% aqueous ethanol gave the analytical sample: mp 155–160° dec; $[\alpha]^{22}D$ −51° (*c* 1.0, 2-methoxyethanol); $\lambda_{max}^{pH\ 1}$ 270 mμ (ε 13,400); $\lambda_{max}^{pH\ 7}$ 273 mμ (ε 16,430); $\lambda_{max}^{pH\ 13}$ 275 mμ (ε 16,400).

Anal. Calcd for $C_{10}H_{14}N_6O_4 \cdot 0.75H_2O$: C, 40.6; H, 5.28; N, 28.4. Found: C, 40.7; H, 5.37; N, 28.4.

Registry No.—**2**, 15830-52-1; **3**, 15830-53-2; **4**, 15830-54-3; **5**, 15830-55-4; **6**, 15830-56-5; **8**, 15830-57-6; **9**, 13089-44-6; **12**, 15830-77-0; **13**, 15830-59-8; **14**, 15830-78-1; **15**, 15830-60-1; **16**, 15830-61-2; **17**, 15830-79-2; **18**, 15830-80-5; **19**, 15830-62-3.

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