Discussion

Now we can conclude that, when any suitable value of S is given to the aglycon moiety, the $M^{20}D - S$ (or RD for halogen) plot can, although it is generally zigzag, be straight under the following special conditions: (1) when an atom (such as H, F, Cl, Br, or I) attaches (whether in the axial or equatorial position) to the 1 position of the pyranose ring (whether acetylated or benzoylated);[1,2] (2) when an axial OCH_3 attaches to the 1 position of the pyranose ring (whether acetylated or unacetylated); (3) when an axial radical (such as OH or OC_6H_5 attaches to the 1 position of the pyranose ring (unacetylated only).

These three conditions are tabulated as Table V.

TABLE V

CONDITIONS FOR THE STRAIGHT LINE OF $M^{20}D - S$ (OR RD FOR HALOGEN) PLOT

Condition	1 Position	Other position
1	Atom, axial or equatorial	OAc or OBz
2	Axial, OCH_3	OH or OAc
3	Axial, OH or OC_6H_5	OH

The details of the physical meanings of these conditions (especially of the first condition) are left for the future. The second and third conditions can, however, be explained qualitatively as follows.

As was already shown in the equatorial radical at the 1 position, the slopes of $M^{20}D - S$ (or RD for halogen) lines can be explained by using the estimation methods of optical rotatory power.[17-19] These methods may be available also in the axial radical at the 1 position. From the standpoint of the stereochemistry, the most stable position of O-1–W bond in the axial OW radical is *trans* to the C-1–C-2 bond (Figure 2), and the partial molecular rotation of the O*–C-1–O-1–W moiety should, owing to the estimation methods of optical rotation,[17-19] be positive in sign. Moreover, the O_1–W bond in this situation is relatively far from the pyranose ring plane and, as O* is the nearest atom to the W atom, the greater part of the partial molecular rotation of W (or O-1–W bond) in OW radical may be the one contributed by this $O^*–C_1–O_1–W$ moiety and accordingly it may be almost indifferent to the configurations at the other positions in the ring. This may be the principal reason for the fact that $M^{20}D - S$ (or RD for halogen) plot of the compounds which have an axial radical at the 1 position are nearly parallel and their slopes are positive in sign (*i.e.*, upward). When there are bulky acetoxy radicals at the other position in the ring, however, these acetoxy radicals may be able to interact with OH or OC_6H_5 at the 1 position to cause the zigzag shape of the $M^{20}D - S$ plots.

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Thio Sugars. Synthesis of the Adenine Nucleosides of 4-Thio-D-xylose and 4-Thio-D-arabinose[1]

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The preparation of methyl 2,3-di-*O*-benzoyl-4-*S*-benzoyl-4-thio-α-D-xylopyranoside (**2**) has been accomplished starting from methyl β-L-arabinopyranoside. Acetolysis of **2** effected a ring contraction to give 1,5-di-*O*-acetyl-2,3-di-*O*-benzoyl-4-thio-D-xylofuranose (**4**). A nucleoside condensation of **4** with chloromercuri-6-benzamidopurine gave a mixture of α and β anomers of 9-(4-thio-D-xylofuranosyl)adenine (**5**) which could be separated as their 3,5-*O*-isopropylidene derivatives (**6**). Methylsulfonation of **6**, followed by deacetonation of the resulting mesylate (**7**) and then treatment with sodium methoxide, gave 9-(2,3-anhydro-4-thio-β-D-lyxofuranosyl)adenine (**9**). Reaction of **9** with sodium acetate in *N*,*N*-dimethylformamide (DMF) gave a mixture of 9-(4-thio-β-D-arabinofuranosyl)adenine (**10**) and the isomeric xyloside (**5b**), in the ratio 8:1.

In recent years, a number of monosaccharides have been prepared in our laboratories in which the C-4 hydroxyl has been replaced by a sulfur or nitrogen function in order to prepare ultimately, nucleosides in which the furanose ring oxygen has been substituted by sulfur or nitrogen. We have reported previously on the preparation of 4′-thioadenosine[2] and 4′-acetamidoadenosine[3] as well as 9-(4-acetamido-4-deoxy-β-D-xylofuranosyl)adenine.[4] A report by Bloch[5] described a reduction by 50% in the growth of *Streptococcus faecalis* by a 4.5×10^{-7} *M* solution of 4′-thioadenosine. Evidence was presented that the action was due to interference by thioadenosine with the formation of deoxyadenylates. This activity of a nucleoside of 4-thioribose together with the known biological activity of 9-(β-D-xylofuranosyl)adenine[6] and 9-(β-D-arabinofuranosyl)adenine[7] made it desirable to prepare the sulfur analogs, 9-(4-thio-β-D-xylofuranosyl)adenine (**5b**) and 9-(4-thio-β-D-arabinofuranosyl)adenine (**10**), for biological evaluation. The synthesis of these nucleosides is the subject of this paper.

The sulfonate displacement of methyl 2,3-*O*-benzoyl-4-*O*-(*p*-tolylsulfonyl)-β-L-arabinopyranoside (**1**) by so-

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(2) E. J. Reist, D. E. Gueffroy, and L. Goodman, *J. Am. Chem. Soc.*, **86**, 5658 (1964).

(3) E. J. Reist, D. E. Gueffroy, R. W. Blackford, and L. Goodman, *J. Org. Chem.*, **31**, 4025 (1966).

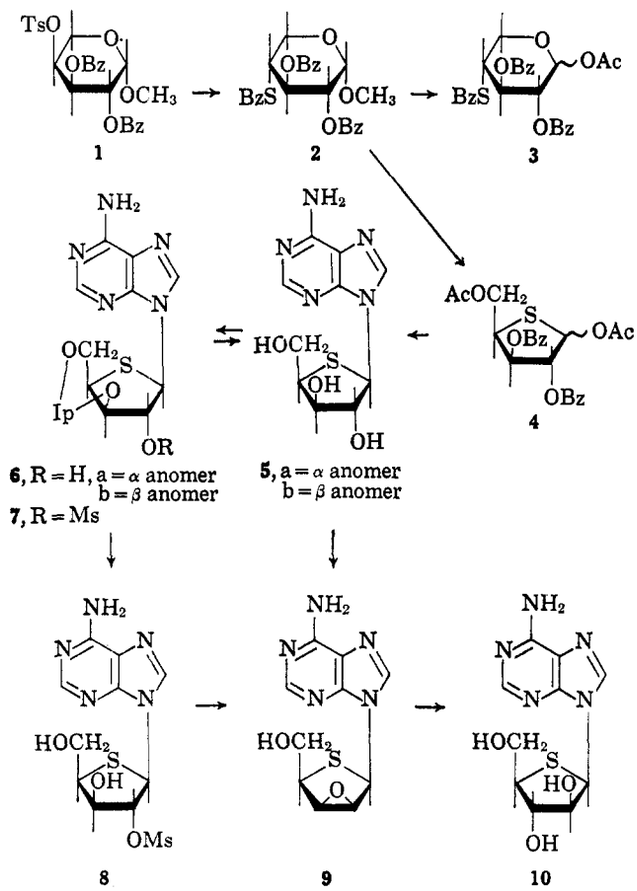
(4) E. J. Reist, L. V. Fisher, and L. Goodman, *ibid.*, **32**, 2541 (1967).

(5) A. Bloch, *Proc. Am. Assoc. Cancer Res.*, **6**, 6 (1965).

(6) (a) G. A. LePage and I. G. Junga, *Cancer Res.*, **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).

(7) (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).

dium azide in *N,N*-dimethylformamide (DMF) proved to be a practical entree to the 4-amino-4-deoxy-D-xylose series.[4] This same starting material proved to be equally useful for the preparation of 4-thio-D-xylose derivatives. Thus, treatment of methyl 2,3-di-*O*-benzoyl-4-*O*-*p*-tolylsulfonyl-β-L-arabinopyranoside (**1**)



with potassium thiolbenzoate in DMF gave a 75% yield of crystalline methyl 2,3-di-*O*-benzoyl-4-*S*-benzoyl-4-thio-α-D-xylopyranoside (**2**). Acetolysis of **2** with acetic anhydride, acetic acid, and sulfuric acid gave a 1-*O*-acetate as a syrup. The infrared spectrum of this product showed that there was little if any thiolbenzoate. Thus, ring contraction to the furanose **4** must have occurred in a manner similar to that observed in the 4-thioribose series.[2] Thin layer chromatograms of the crude acetolysis product gave an indication that small amounts of a by-product which could be the pyranose **3** were present. Preparative thin layer chromatography of this material on silica gel did give a second component which had an infrared spectrum which was compatible with the pyranose structure **3** while the main fraction had the spectral properties expected for the thiofuranose **4**. The maximum ratio of pyranose to furanose in the acetolysis of **2** was 1:16. It might be noted that the acetolysis of the ribose analog of **2** gave no evidence of pyranose.[2] The conversion of the 1-*O*-acetate **4** to an adenine nucleoside was accomplished by either of two methods, the classical chloro sugar condensation with chloromercuri 6-benzamido purine or by the Prokop and Murray modification using titanium tetrachloride.[8] Both gave an approximately 20% yield of adenine nucleoside (**5**) when isolated by means of ion-exchange chromatography.[9] Although the nucleoside **5** had a relatively sharp melting point, was homogeneous on paper chromatography, and was homogeneous on ion exchange chromatography, the nmr spectrum and thin layer chromatograms indicated that this nucleoside was a mixture of α and β anomers in the ratio 2:3. On the basis of numerous examples reported by Dekker and Gin,[10] ion-exchange chromatography of the α,β-nucleoside mixture **5** should have been resolved with the α-nucleoside being eluted first. Hence, the failure of the column to effect a resolution, even on an analytical scale is surprising. All efforts to separate **5a** and **5b** by fractional crystallization or by chromatography were unsuccessful. Acetonation of the anomeric mixture (**5**) using 2,2-dimethoxypropane and hydrogen chloride[11] gave an anomeric mixture of 9-(3,5-*O*-isopropylidene-4-thio-α- (and β-) D-xylofuranosyl)adenine (**6a** and **6b**) which could be resolved, both by fractional crystallization and by ion-exchange chromatography. The resolved nucleosides (**5a** and **5b**) could then be prepared by deacetonation of the separated **6a** and **6b**.

Treatment of 9-(3,5-*O*-isopropylidene-4-thio-β-D-xylofuranosyl)adenine (**6b**) with methanesulfonyl chloride in pyridine gave crystalline 9-(3,5-*O*-isopropylidene-2-*O*-methylsulfonyl-4-thio-β-D-xylofuranosyl)adenine (**7**) which was then deacetonated using 80% aqueous acetic acid to 9-(2-*O*-methylsulfonyl-4-thio-β-D-xylofuranosyl)adenine (**8**). Anhydride formation occurred easily when **8** was treated with methanolic sodium methoxide to give 9-(2,3-anhydro-4-thio-β-D-lyxofuranosyl)adenine (**9**).

The nucleophilic cleavage of the epoxide (**9**) was accomplished using sodium acetate in aqueous DMF to give a mixture of 9-(4-thio-β-D-xylofuranosyl)adenine (**5b**) and 9-(4-thio-β-D-arabinofuranosyl)adenine (**10**). Resolution of **5b** and **10** was carried out by ion-exchange chromatography to give arabinoside **10** and xyloside **5b** in the ratio 8:1. Thus, substitution of the ring oxygen by sulfur does not alter significantly the predominance of nucleophilic attack at C-3 over C-2 to give the arabinose configuration.[12]

Experimental Section[13]

Methyl 2,3-Di-*O*-benzoyl-4-*S*-benzoyl-4-thio-α-D-xylopyranoside (2).—A solution of 4.0 g (7.6 mmoles) of methyl 2,3-di-*O*-benzoyl-4-*O*-(*p*-tolylsulfonyl)-β-L-arabinopyranoside (**1**)[4] and 4.0 g (22.8 mmoles) of potassium thiolbenzoate in 90 ml of dry DMF was heated at 100° for 16 hr under a nitrogen atmosphere. The reaction mixture was evaporated to dryness *in vacuo* and the residue was partitioned between 100 ml each of ether and water. The ether layer was washed with water, then dried and evaporated to dryness *in vacuo* to a yellow syrup which was crystallized and recrystallized from methanol to give 2.8 g (75%) of product:

(8) J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).

(9) C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).

(10) C. A. Dekker and J. Gin, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p 37C.

(11) S. Chládek and J. Smrt, *Collection Czech. Chem. Commun.*, **28**, 1301 (1963).

(12) E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3274 (1962).

(13) Melting points were determined with a Fisher-Johns apparatus and are corrected. Thin layer chromatograms were run on silica gel HF (E. Merck A-G Darmstadt). Spots were detected by visual examination under an ultraviolet lamp or by spraying with sulfuric acid, then developing at *ca* 100° for a few minutes. Nmr spectra were run on the Varian A-60 or HA-100 spectrometers. The solvent used for the nmr spectra was dimethyl sulfoxide-d_6 using a solution of 25% tetramethylsilane in tetrachloromethane as an external standard. Organic solutions were dried over magnesium sulfate.

mp 125–127°; $[\alpha]^{22}D$ +149° (*c* 1, chloroform); λ_{max}^{Nujol} 5.72 (*O*-benzoate C=O), 5.91 μ (*S*-benzoate C=O).

Anal. Calcd for $C_{27}H_{24}O_7S$: C, 65.8; H, 4.91; S, 6.51. Found: C, 65.7; H, 5.07; S, 6.29.

A 20.0 g preparation gave 10.4 g (55%) of product, mp 121–123.5°.

1,5-Di-*O*-acetyl-2,3-di-*O*-benzoyl-4-thio-D-xylofuranose (4).—To a stirred solution of 295 ml each of acetic acid and acetic anhydride was added 17 ml of concentrated sulfuric acid and the solution was cooled to 0°. To this cold solution was added 12.9 g (26 mmoles) of methyl 2,3-di-*O*-benzoyl-4-*S*-benzoyl-4-thio-α-D-xylopyranoside (2) with continued stirring, then the reaction was stored at 4° for 75 hr. The acid reagent was destroyed by the addition of 65 g of anhydrous sodium acetate and the resultant slurry was evaporated to dryness *in vacuo* at room temperature. The residue was partitioned between 200 ml each of ether and water. The ether extract was washed with 100 ml of saturated aqueous sodium bicarbonate and 100 ml of water then was dried and evaporated to dryness *in vacuo* to give 14.9 g of product as a yellow syrup. The infrared spectrum showed strong acetate absorption at 5.70 and 8.15 μ and an almost complete loss of *S*-benzoate absorption at 5.9 μ.

Thin layer chromatography using 2% absolute ethanol in benzene as developing solvent showed three spots with R_f values 0.43, 0.48, and 0.59, attributed to the α and β anomers of the pyranose (3) and furanose (4)-1-acetates.

Thick layer chromatography of 100 mg of this material, developing three times with 2% absolute ethanol in benzene, gave 80 mg of 1,5-di-*O*-acetyl-2,3-di-*O*-benzoyl-4-thio-D-xylofuranose (4) as an anomeric mixture which was free of *S*-benzoyl absorption at 5.9 μ in the infrared and which showed two spots on tlc (2% ethanol in benzene) with R_f 0.43 and 0.48.

Anal. Calcd for $C_{28}H_{22}O_8S$: C, 60.2; H, 4.84; S, 6.99. Found: C, 60.1; H, 5.05; S, 7.18.

The faster moving component from the preparative thick-layer chromatogram weighed 5 mg and had $\lambda_{max}^{CHCl_3}$ 5.65 (acetate C=O), 5.70 (*O*-benzoate C=O), 5.90 μ (*S*-benzoate C=O).

The acetolysis of 20.7 g of 4 gave 19.4 g (101%) of syrupy product which was of satisfactory purity for the nucleoside condensation.

9-(4-Thio-β- (and α-) D-xylofuranosyl)adenine (5).—A mixture of 19.4 g (42 mmoles)of crude 1,5-di-*O*-acetyl-2,3-di-*O*-benzoyl-4-thio-D-xylofuranose (4) and 39.2 g of chloromercuri-6-benzamido purine (53 mmoles containing 14.1 g Celite) in 1100 ml of 1,2-dichloroethane was dried by the azeotropic distillation of 250 ml of solvent. To the dried mixture was added dropwise with stirring 5.8 ml (53 mmoles) of titanium tetrachloride in 85 ml of dry 1,2-dichloroethane and the reaction was heated at reflux under nitrogen atmosphere for 24 hr. The reaction was cooled to room temperature, then was stirred with 810 ml of saturated aqueous sodium bicarbonate for 2 hr and was filtered through a Celite pad. The organic phase was washed with 410 ml of 30% aqueous potassium iodide then with 410 ml of water. The chloroform layer was dried, then was evaporated to dryness *in vacuo* to give 19.3 g of crude blocked nucleoside as a tan foam.

Deacylation of the blocked nucleoside was accomplished by refluxing it for 3 hr in a solution of 555 ml of methanol which contained 3.1 g of sodium methoxide.

The reaction was cooled, neutralized with 55.5 g of IRC-50 (H) resin, and then evaporated to dryness *in vacuo* to a dark red syrup. The syrup was partitioned between 400 ml each of chloroform and water. The aqueous extract was filtered, then evaporated to dryness *in vacuo* to give 7.0 g of crude nucleoside (5) as a dark foam.

The nucleoside was purified by applying 7.0 g to a column of Dowex 1 (OH) (4.2 cm × 36 cm) prepared from 300 g of Dowex 1 (Cl). The column was eluted with 900 ml of water, 1 l. of methanol–water (3:7), and finally with 4 l. of methanol–water) (7:3). The main component, weighing 2.41 g (20%) was eluted with the methanol–water (7:3).

The analytical sample from a previous reaction was recrystallized from methanol: mp 215–218°; $[\alpha]^{21}D$ −12° (*c* 0.43, methanol); $\lambda_{max}^{pH\ 1}$ 259 mμ (ε 14,840); $\lambda_{max}^{pH\ 7,\ 13}$ 261 mμ (ε 15,310).

Anal. Calcd for $C_{10}H_{13}N_5O_3S$: C, 42.4; H, 4.63; N, 24.7; S, 11.3. Found: C, 42.2; H, 4.72; N, 24.4; S, 11.2.

Thin layer chromatography, using chloroform–methanol (4:1) as the developing solvent, showed two components with R_f values 0.18 and 0.25.

The nmr spectrum had bands at τ 1.60, 1.83 (H_2 and H_8 of **5b**), 1.70 and 1.79 (H_2 and H_8 of **5a**), 3.65 (d, J = 4 cps, H′-1 of **5a**), 4.20 (d, J = 3 cps, H_1' of **5b**), 5.5–6.4 (H'_2–H'_5, unresolved). The ratio of **5a**:**5b** was *ca* 2:3.

9-(3,5-*O*-Isopropylidene-4-thio-α- (and β-) D-xylofuranosyl)-adenine(6a and 6b).—To a stirred solution of 1.4 g (5 mmoles) of 9-(4-thio-D-xylofuranosyl)adenine (5) (purified by means of ion-exchange chromatography) in 15 ml of dry DMF and 30 ml of 2,2-dimethoxypropane was added dropwise 2.5 ml of 4 *N* hydrogen chloride in dioxane. The reaction was stirred for 72 hr, then was neutralized to pH 7 with IR-45 (OH) resin, and was evaporated to dryness *in vacuo*. Tlc using chloroform–methanol (9:1) as developing solvent showed two spots at R_f values 0.36 and 0.59, assignable to the α and β anomers, respectively.

The solid residue was stirred with 5 ml of water for 3 hr, then was filtered. The water-insoluble material was pure β anomer (**6b**) and weighed 0.74 g (46%), mp 253–260°. The aqueous filtrate was evaporated to dryness *in vacuo* to give a gummy yellow solid which was crystallized from absolute ethanol to give 0.43 g (27%) of the α anomer.

Recrystallization from absolute ethanol gave the analytical sample of α anomer **6a**: mp 267–270°; $[\alpha]^{21}D$ +19° (*c* 0.91, 2-methoxyethanol); $\lambda_{max}^{ethanol}$ 259 mμ (ε 14,950).

Anal. Calcd for $C_{13}H_{17}N_5O_3S$: C, 48.3; H, 5.30; N, 21.7; S, 9.91. Found: C, 48.5; H, 5.38; N, 21.5; S, 10.1.

The nmr spectrum showed H_2 and H_8 as two singlets at τ 1.80 and 1.93. H_1' occurred as a doublet (J = 4 cps) at τ 3.62.

Recrystallization of the β anomer from absolute ethanol gave the analytical sample of **6b**: mp 269–279° dec; $[\alpha]^{22}D$ −0.6° (*c* 0.99, 2-methoxyethanol); $\lambda_{max}^{ethanol}$ 260 mμ (ε 14,700).

Anal. Found: C, 48.5; H, 5.40; N, 21.5; S, 10.1.

The nmr spectrum showed H-2 and H-8 as two singlets at τ 1.52 and 1.87. H′-1 occurred as a singlet at τ 4.16.

In one experiment, the residue remaining (0.23 g) after removal of the β-nucleoside by water trituration was applied to the top of an ion-exchange column of Dowex 1 (OH) (2 cm × 29 cm). After prior elution with water and 50% aqueous methanol, elution with 500 ml of methanol–water (7:3) gave two fractions. The first fraction (74 mg) was pure α-nucleoside **6a**. The second fraction (42 mg) was pure β-nucleoside **6b**.

9-(4-Thio-α-D-xylofuranosyl)adenine (5a).—A solution of 0.35 g of 9-(3,5-*O*-isopropylidene-4-thio-α-D-xylofuranosyl)adenine (**6a**) in 12 ml of 80% aqueous acetic acid was heated on a steam bath for 1 hr then was evaporated to dryness *in vacuo* to a gum which was crystallized by trituration with 2-propanol to give 0.25 g of product (81%), which was essentially homogeneous on tlc using chloroform–methanol (4:1) with R_f 0.23.

Recrystallization from 98% aqueous ethanol gave the analytical sample: mp 248–251°; $[\alpha]^{23}D$ +15° (*c* 0.45, 2-methoxyethanol); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 15,030); $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 15,480); $\lambda_{max}^{pH\ 13}$ 261 mμ (ε 15,620).

Anal. Calcd for $C_{10}H_{13}N_5O_3S$: C, 42.4; H, 4.63; N, 24.7; S, 11.3. Found: C, 42.6; H, 4.62; N, 24.8; S, 10.9.

The nmr spectrum had bands at τ 1.72 and 1.86 (H_2 and H_8) and τ 3.67 (d, J = 3.5 cps, H_1').

9-(4-Thio-β-D-xylofuranosyl)adenine (5b).—A solution of 0.18 g of 9-(3,5-*O*-isopropylidene-4-thio-β-D-xylofuranosyl)adenine (**6b**) in 10 ml of 80% aqueous acetic acid was heated for 1 hr on a steam bath then was evaporated to dryness *in vacuo* to give 0.11 g of crude product as a white foam. Crystallization from absolute ethanol gave 74 mg of product (47%), mp 217–220°.

The analytical sample was crystallized from absolute ethanol and had mp 217–220° and $[\alpha]^{24}D$ −29° (*c* 0.5, 2-methoxyethanol); ultraviolet bands were at $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 14,400) and $\lambda_{max}^{pH\ 7,\ 13}$ 260 mμ (ε 14,900).

Anal. Calcd for $C_{10}H_{13}N_5O_3S$: C, 42.4; H, 4.63; N, 24.7; S, 11.3. Found: C, 42.3; H, 4.81; N, 24.6; S, 11.3.

9-(3,5-*O*-Isopropylidene-2-*O*-methylsulfonyl-4-thio-β-D-xylofuranosyl)adenine (7).—A solution of 0.2 g (0.61 mmole) of **6b** in 4 ml of dry pyridine was cooled to 0° and 0.12 ml (1.53 mmoles) of methanesulfonyl chloride was added dropwise with stirring. The mixture was stirred at room temperature for three days, then the excess reagent was decomposed by the addition of water. The reaction was partitioned between chloroform and water. The chloroform layer was washed with saturated aqueous sodium bicarbonate and water, then was dried and evaporated to dryness *in vacuo*. The residue was crystallized and recrystallized from methanol to give 70 mg (28%) of product, mp 203–205°.

The analytical sample had mp 204–206°, $[\alpha]^{22}D$ −20° (*c* 0.88, chloroform).

Anal. Calcd for $C_{14}H_{19}N_5O_5S_2$: C, 41.9; H, 4.77; N, 17.4; S, 16.0. Found: C, 41.8; H, 5.05; N, 17.1; S, 15.8.

Thin layer chromatography using *n*-propanol–ethyl acetate–water (12:8:1) as the developing solvent showed one spot with R_f 0.72.

Subsequent methylsulfonations on **6b** gave yields of 62% of product, mp 196–204°.

9-(2-*O*-Methylsulfonyl-4-thio-β-D-xylofuranosyl)adenine (8).—A solution of 0.45 g (1.12 mmoles) of **7** in 18 ml of 80% aqueous acetic acid was heated on a steam bath for 1 hr then was evaporated to dryness *in vacuo*. The residue was dissolved in hot absolute ethanol and evaporated to dryness to give 0.44 g of yellow foam.

Crystallization from absolute ethanol gave 0.22 g (54%) of white crystals: mp 168–172°; $[\alpha]^{21}D$ −17° (*c* 0.98, methanol).

Anal. Calcd for $C_{11}H_{15}N_5O_5S_2$: C, 36.6; H, 4.18; N, 19.4; S, 17.7. Found: C, 36.4; H, 4.23; N, 19.6; S, 17.8.

9-(2,3-Anhydro-4-thio-β-D-lyxofuranosyl)adenine (9).—A solution of 380 mg (1.05 mmoles) of crude **8** in 8 ml of methanol and 75 mg (1.4 mmoles) of sodium methoxide was heated at reflux for 12 min. The solution was cooled to room temperature and neutralized with IRC-50 (H) then was evaporated to dryness *in vacuo* to give 470 mg of crude product. Trituration of the residue with water gave 170 mg (62%) of white solid which was homogeneous on thin layer chromatography using chloroform–methanol (4:1). The analytical sample was obtained by two recrystallizations from 80% aqueous acetone and had mp 220–229° dec, $[\alpha]^{21}D$ +7° (*c* 0.96, 2-methoxyethanol).

Anal. Calcd for $C_{10}H_{11}N_5O_2S$: C, 45.3; H, 4.18; N, 26.4; S, 12.1. Found: C, 45.4; H, 4.19; N, 26.4; S, 12.4.

9-(4-Thio-β-D-arabinofuranosyl)adenine (10).—A mixture of 0.17 g (0.65 mmole) of 9-(2,3-anhydro-4-thio-β-D-lyxofuranosyl)-adenine (**9**) and 0.16 mg (1.97 mmoles) of anhydrous sodium acetate in 10 ml of 95% aqueous DMF was heated at reflux with stirring for 8 hr, then was evaporated to dryness *in vacuo*. The residue was triturated with several portions of DMF to remove the relatively insoluble sodium acetate. The DMF solution was evaporated to dryness *in vacuo* to give 0.22 g of crude residue which contained two major components with R_f values 0.21 and 0.30 on thin layer chromatography using chloroform–methanol (4:1). The two components were resolved by ion exchange chromatography using 40 g of Dowex 1 (OH). Washing the column with water, then with methanol–water (1:1) eluted small quantities of by-products. Elution with methanol–water (3:2) gave two uv absorbing fractions. The first, which contained 22 mg was 9-(4-thio-β-D-xylofuranosyl)adenine (**5b**) contaminated with a small amount of material which had an R_f value (0.57) identical with that of starting epoxide **9** on tlc using chloroform–methanol (4:1).

The arabinoside **10** was contained in the second fraction, which weighed 97 mg (53% yield) and was homogeneous on tlc (R_f 0.23) using chloroform–methanol (4:1). It crystallized upon trituration with water. The analytical sample was obtained by recrystallization from water and had mp 135–142° and $[\alpha]^{21}D$ −8° (*c* 0.5, water); ultraviolet bands were at $\lambda_{max}^{pH\ 1}$ 259 mμ (ε 14,800) and $\lambda_{max}^{pH\ 7,\ 13}$ 260 mμ (ε 15,400).

Anal. Calcd for $C_{10}H_{13}N_5O_3S \cdot H_2O$: C, 39.9; H, 5.02; N, 23.3; S, 10.6. Found: C, 40.2; H, 5.06; N, 23.3; S, 10.9.

Registry No.—**2**, 15076-96-7; **4**, 15076-97-8; **5a**, 15023-72-0; **5b**, 15023-73-1; **6a**, 15023-74-2; **6b**, 7687-51-6; **7**, 15023-78-6; **8**, 15023-76-4; **9**, 15026-14-9; **10**, 15023-77-5.

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Indole and 4-Aminoindole Nucleosides

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The synthesis of 1-(β-D-ribopyranosyl) and 1-(β-D-ribofuranosyl)indole is described. Reaction of indoline with 1,2,3,4-tetra-*O*-acetyl-β-D-ribopyranose and with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose produced the related 1-(β-D-ribosyl)indolines which were oxidized to the corresponding indoles with 2,3-dichloro-5,6-dicyanobenzoquinone. Removal of the acyl blocking groups with methanolic sodium methoxide led to the desired 1-(β-D-ribosyl)indoles. Application of essentially the same reaction scheme to 4-benzamidoindoline and 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose led to 4-amino-1-(β-D-ribofuranosyl)indole, the 1,3,7-trideaza analog of adenosine. A method for the synthesis of the required 4-benzamidoindoline from 4-aminoindole is described. Some attempts to treat sugar derivatives directly with indoles are described as well as some trials toward alternative syntheses of 4-aminoindole. Through a combination of nmrs measurements, periodate oxidations, and ORD determinations, the assignment of the β anomeric configuration to all of the glycosyl indoles was substantiated.

During the past ten years a veritable flood of adenosine analogs, showing a variety of biological activities, has been obtained by synthesis or from natural sources.[1] It is striking that what might, in one sense, be described as the simplest adenosine analog, 4-amino-1-(β-D-ribofuranosyl)indole (**12**, 1,3,7-trideazaadenosine), has not been reported. The lack of a requirement for a full complement of purine ring nitrogen heteroatoms for biological activity as exemplified by the antibiotic tubercidin, as well as the variety of biological effects shown by variously substituted indoles, encouraged us to undertake the synthesis of **12**.

Examination of the literature revealed that the synthesis of 1-glucopyranosylindole (**3**) reported by Suranov and Preobrazhenskaya[2] was the only prior example of a 1-glycosyl indole. The synthetic approach used by these workers involved reaction of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose with 2 moles of indoline. The intermediate 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)indoline (**1**) was separated from 1-acetylindoline and oxidized with tetrachloro-*p*-benzoquinone to produce the glucosyl indole **2** which was deblocked to give **3**.

In order to have on hand a supply of 1-(β-D-glucopyranosyl)indole (**3**) for confirmation of the β configurational assignment,[2] as well as for configurational comparisons with the ribofuranosyl derivative **12** which we planned to prepare, the synthesis of **3** was repeated following the published directions. As the yield of the indole from the oxidation of the intermediate indo-

(1) Many of these are to be found in reviews by (a) J. A. Montgomery and H. J. Thomas, *Advan. Carbohydrate Chem.*, **17**, 301 (1962); (b) J. J. Fox, K. A. Watanabe, and A. Block, in "Progress in Nucleic Acid Research and Molecular Biology," J. N. Davidson and W. E. Cohn, Ed., Academic Press Inc., New York, N. Y., 1966, p 251.

(2) N. N. Suranov and M. N. Preobrazhenskaya, *Zh. Obshch. Khim.*, **31**, 2839 (1961).