total integral three protons, present in similar proportion, were assigned to the NAc group of **3** and **4**, respectively. Multiplets, total integral six protons, in the range τ 5.42–6.63, were assigned to H-2, -3, -4, -5, -6, and -6′.

D. 2-Amino-2-deoxy-D-glucose Hydrochloride.—Crystalline 2-amino-2-deoxy-α-D-glucopyranose hydrochloride[29] was dissolved in deuterium oxide to give a 30% solution. The nmr spectrum, measured 2 min after dissolution, showed a one-proton doublet at τ 4.54, $J_{1,2}$ = 3.5 cps (equatorial H-1 of **5**) (lit.[7] τ 4.54, $J_{1,2}$ = 3.8 cps). After 10 min a doublet was detectable at τ 5.03, $J_{1,2}$ = 8.3 cps (axial H-1 of **6**) (lit.[7] τ 5.04, $J_{1,2}$ = 8.5 cps); it increased in intensity with time at the expense of the lower field signal, and at equilibrium the integrated peak intensities (measured at 70°) indicated that **5** and **6** were present in 63:37 proportion. The spectrum showed the HOD signal at τ 5.25 (τ 5.46 at 70°), and a six-proton multiplet, τ 5.9–7.2 (H-2, -3, -4, -5, -6, and -6′).

E. 2-Amino-2-deoxy-D-galactose Hydrochloride.—The crystalline substance[29] had mp 176–190°, λ_{max}^{Nujol} 11.45 with no absorption 11.6–12.6 μ (axial H at C-1), X-ray powder diffraction data 6.78 s (2), 5.45 vw, 4.93 m, 4.71 m, 4.26 m, 3.97 vs (1), 3.64 m, 3.56 m, 3.41 m, 3.21 m, 3.10 w, 2.97 w, 2.93 w, 2.79 vw, 2.72 vw, 2.60 w, 2.52 vw, 2.45 w, 2.36 w, 2.32 vw, 2.21 w, 2.15 w, 2.07 w. The nmr spectrum of a 34% solution in deuterium oxide, measured 5 min after dissolution, showed a one-proton doublet, τ 5.11 ($J_{1,2}$ = 8.3 cps, axial H-1 of **8**) (lit.[7] τ 5.12, $J_{1,2}$ = 8.3 cps) and a one-proton multiplet, 6.82 (width 22 cps, H-5 of **8**). A very weak doublet, observed at τ 4.52 ($J_{1,2}$ = 3.4 cps, equatorial H-1 of **7**) (lit.[7] τ 4.53, $J_{1,2}$ = 3.8 cps), increased in intensity with time at the expense of the signal at τ 5.11, and simultaneously a multiplet at 6.42 (H-5 of **7**) appeared at the expense of the signal at 6.82. At equilibrium, the H-1 signals for **7** and **8** were in the relative proportions 47:53; the spectrum was measured at 70° for integration so that the HOD signal did not interfere with the signal for the axial H-1. Signals for H-2, -3, -4, -6, and -6′ were observed in the region τ 5.7–6.35.

F. D-Galactose, D-Glucose, and D-Mannose.—Solutions (25–30%) of the aldoses in deuterium oxide were allowed to reach mutarotational equilibrium, and spectra were measured at 80–100°. The chemical shifts observed for the H-1 signals are listed in Table I, together with shifts reported[5] relative to an external standard of tetramethylsilane. Anomeric compositions determined by integration were in good agreement with the reported[5] values given in Table II.

Pyrrolidine Sugars. Synthesis of 4′-Acetamidoadenosine and Other Derivatives of 4-Amino-4-deoxy-D-ribose[1]

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Derivatives of 4-amino-4-deoxy-D-ribose have been prepared starting from methyl 2-*O*-benzoyl-3,4-di-*O*-(*p*-tolylsulfonyl)-β-L-arabinopyranoside (**1**). Thus, selective displacement of the 4-tosylate of **1** by azide gave methyl 4-azido-2-*O*-benzoyl-4-deoxy-3-*O*-(*p*-tolylsulfonyl)-α-D-xylopyranoside (**2**). Conversion of **2** to the 4-acetamide followed by intramolecular displacement of the 3-tosylate gave after deacylation methyl 4-acetamido-4-deoxy-α-D-ribopyranoside (**7**). Acetolysis of **7** effected a ring contraction to 4-acetamido-1,2,3,5-tetra-*O*-acetyl-4-deoxy-D-ribofuranose (**10**). An alternative synthesis of **10** from methyl 2,3-*O*-isopropylidene-4-*O*-(*p*-tolylsulfonyl)-α-L-lyxopyranoside was also described. Conversion of **10** to methyl 4-acetamido-4-deoxy-D-ribofuranoside (**16**) and its tri(*p*-nitrobenzoate) (**17**) was described. Compound **16** exhibited hindered internal rotation about the C–N bond in the nmr spectrum. Benzoylation of **7** gave methyl 4-acetamido-2,3-di-*O*-benzoyl-4-deoxy-α-D-ribopyranoside (**20**) as well as methyl 4-acetamido-2,3-di-*O*-benzoyl-4-*N*-benzoyl-4-deoxy-α-D-ribopyranoside (**21**). Acetolysis of **20** again gave ring contraction to give 4-acetamido-1,5-di-*O*-acetyl-2,3-di-*O*-benzoyl-4-deoxy-D-ribofuranose (**22**) which was converted to 4′-acetamidoadenosine (**23**). The nucleoside **23**, also exhibited hindered internal rotation in the nmr, a phenomenon which is observed in the nmr of amido sugars with nitrogen in the ring when the spectrum is run in D_2O.

Nucleoside analogs of the natural nucleic acid components frequently show striking differences, both qualitative and quantitative, as compared to the natural nucleosides, as substrates for important enzymes such as adenosine deaminase or nucleoside phosphorylase. The adenosine analogs, 9-(β-D-arabinofuranosyl)-adenine and 9-(β-D-xylofuranosyl)adenine, for example are not cleaved by nucleoside phosphorylase.[2]

Substitution of the sugar ring oxygen of a nucleoside by another atom represents another type of structural change which could have effects of biological significance. The synthesis of 4′-thioadenosine[3] represents one example of this type of alteration; this manuscript describes the synthesis of an adenosine analog in which the sugar heteroatom is nitrogen.

Azide displacement of a C-4 sulfonate ester was the most attractive entrée to a 4-amino sugar. Methyl 2-*O*-benzoyl-3,4-di-*O*-(*p*-tolylsulfonyl)-β-L-arabinopyranoside (**1**)[4] could be expected to yield selectively the 4-azido derivative (**2**) on the basis of several considerations. First, there is considerable documentation that C-4 sulfonates of hexopyranosides are readily displaced by sodium benzoate in N,N-dimethylformamide (DMF)[5] even if the sulfonate has the equatorial configuration. Secondly, Dick and Jones[6] have described the reaction of a number of methyl 2,3,4-tri-*O*-methylsulfonylpentopyranosides with sodium azide in DMF in which the C-4 sulfonate was more readily displaced than either the C-2 or C-3 sulfonate, *e.g*, reaction of methyl 2,3,4-tri-*O*-methylsulfonyl-β-L-arabinopyranoside yielded methyl 4-azido-4-deoxy-2,3-di-*O*-methylsulfonyl-α-D-xylopyranoside.

Treatment of the di-*p*-toluenesulfonate (**1**) with sodium azide in DMF afforded a crystalline monoazide that could be converted to methyl 2,3-anhydro-4-azido-4-deoxy-α-D-ribopyranoside (**5**) by treatment with

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. Certain portions of this work have been reported previously. See E. J. Reist, D. E. Gueffroy, and L. Goodman, *J. Am. Chem. Soc.*, **87**, 677 (1965).

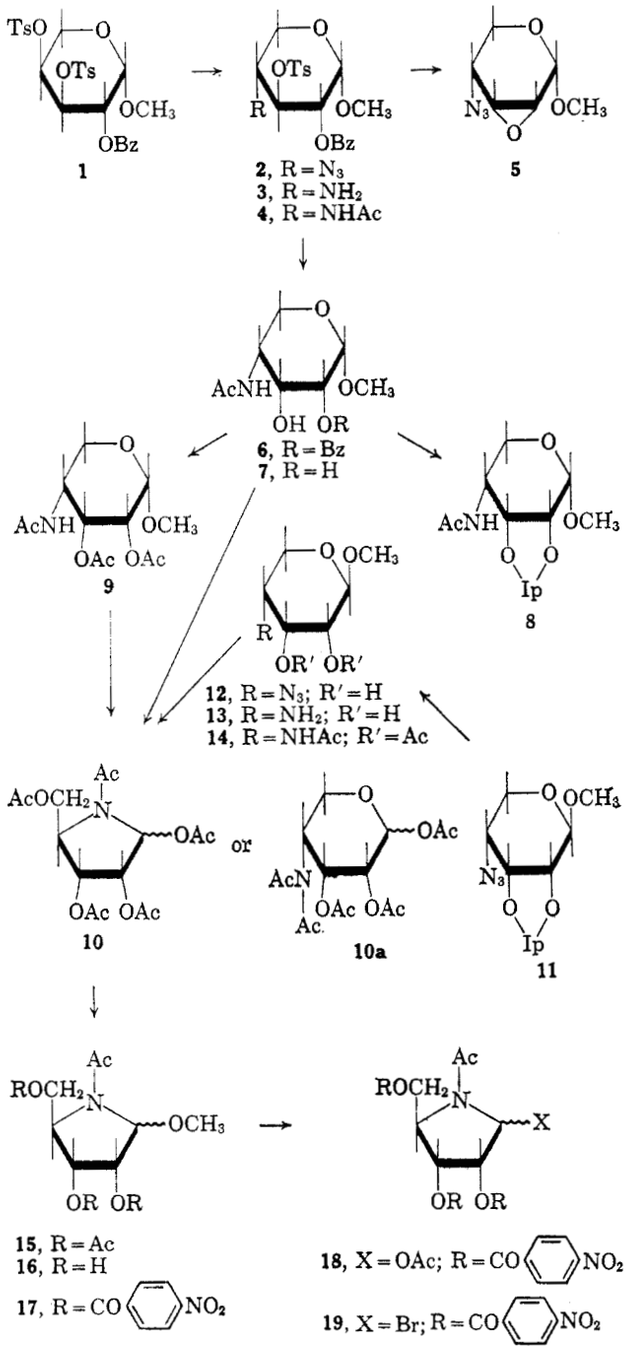
(2) G. A. LePage and I. G. Junga, *Cancer Res.*, **25**, 46 (1965).

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

(4) E. J. Reist, L. V. Fisher, and D. E. Gueffroy, *J. Org. Chem.*, **31**, 226 (1966).

(5) (a) E. J. Reist, R. R. Spencer, and B. R. Baker, *ibid.*, **24**, 1618 (1959); (b) J. Hill, L. Hough, and A. C. Richardson, *Proc. Chem. Soc.*, 346 (1963); (c) C. L. Stevens, P. Blumbergs, D. H. Otterbach, J. L. Strominger, M. Matsuhashi, and D. N. Dietzler, *J. Am. Chem. Soc.*, **86**, 2937 (1964).

(6) A. J. Dick and J. K. N. Jones, *Can. J. Chem.*, **44**, 79 (1966).



sodium methoxide. Thus, the azide displacement product is methyl 4-azido-2-*O*-benzoyl-4-deoxy-3-*O*-(*p*-tolylsulfonyl)-α-D-xylopyranoside (**2**); if the azide group had been at C-3, epoxide formation would not have been possible.

Hydrogenation of the tosyl azide (**2**) with sponge nickel gave the crystalline methyl 4-amino-2-*O*-benzoyl-deoxy-3-*O*-(*p*-tolylsulfonyl)-α-D-xylopyranoside (**3**) which was then acetylated to the N-acetate (**4**).

Treatment of the tosylamide (**4**) with sodium acetate in aqueous DMF effected the elimination of the 3-*O*-tosylate by participation of the amide to yield methyl 4-acetamido-2-*O*-benzoyl-4-deoxy-α-D-ribopyranoside (**6**). Debenzoylation with sodium methoxide gave crystalline methyl 4-acetamido-4-deoxy-α-D-ribopyranoside (**7**). Reaction of **7** with 2,2-dimethoxypropane and hydrogen chloride afforded the crystalline methyl 4-acetamido-4-deoxy-2,3-*O*-isopropylidene-α-D-ribopyranoside (**8**), thus both proving the *cis* relationship of the two hydroxyls and further indicating that the nitrogen function was indeed on C-4.

Acetylation of crystalline **7** gave methyl 4-acetamido-2,3-di-*O*-acetyl-4-deoxy-α-D-ribopyranoside (**9**) as an analytically pure syrup. Acetolysis of either the crystalline **7** or syrupy **9** yielded a syrup that was homogeneous on thin layer chromatography and that showed no infrared NH absorption at 2.9 or 6.5 μ. The analytical data and nmr spectrum were compatible with the furanose structure of the desired 4-acetamido-1,2,3,5-tetra-*O*-acetyl-4-deoxy-D-ribofuranose (**10**) or the isomeric N,N-diacetylpyranose **10a**. The furanose structure (**10**) was regarded as the more likely choice from the nmr spectrum since all of the acetate protons were located in the range between τ 7.88 and 8.02. The isomeric N,N-diacetate (**10a**) might be expected to have N-acetate absorption at *ca.* τ 7.6.[7] In addition, acetolysis experiments on methyl 4-acetamido-4-deoxy-α-D-glucopyranoside using similar reaction conditions gave 4-acetamido-1,2,3,5,6-penta-*O*-acetyl-4-deoxy-D-glucopyranose[8] in which the nitrogen did not become the ring heteroatom. In this case, there was no evidence for any N,N-diacetate, and the infrared spectrum contained bands at 3.0 and 6.5 μ which clearly indicated the presence of NH absorption of a secondary amide. These two pieces of evidence, while circumstantial, were indicative that the acetolysis product from **7** and **9** was in the desired furanose configuration (**10**). That this assignment was correct, was proved subsequently.

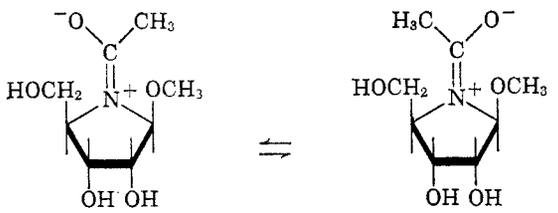
A second route to the pentaacetate (**10**) which was not dependent on either a selective sulfonate displacement or on a participation reaction to give the desired ribose configuration started with the reaction of methyl 2,3-*O*-isopropylidene-4-*O*-(*p*-tolylsulfonyl)-α-L-lyxopyranoside[2] with sodium azide in DMF that gave methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (**11**) as the product. Removal of the isopropylidene group of **11** with 66% aqueous acetic acid afforded methyl 4-azido-4-deoxy-β-D-ribopyranoside (XII) as an analytically pure oil. Hydrogenation of **12** yielded the crystalline methyl 4-amino-4-deoxy-β-D-ribopyranoside (**13**) which was then acetylated to the triacetate (**14**) and acetolyzed directly to the pentaacetate (**10**). The product was identical spectroscopically in all respects with **10** prepared from the di-*p*-toluenesulfonate (**1**). Furthermore, **10** prepared by either route could be converted to the same crystalline tris(*p*-nitrobenzoate) (**17**) in the following fashion.

Methanolysis of the pentaacetate (**10**) with 0.5% methanolic hydrogen chloride followed by reacetylation gave methyl 4-acetamido-2,3,5-tri-*O*-acetyl-4-deoxy-D-ribofuranoside (**15**) as a colorless oil. The infrared spectrum of **15** was free of NH absorption at 3.0 and 6.5 μ. The nmr spectrum (in deuteriochloroform) showed the presence of four acetate bands at τ 7.87–7.98. The single methoxyl band at τ 6.62 together with the small coupling constant (J = 1.5 cps) at 5.10 for H-1 suggested that **15** was essentially the β anomer with little if any α anomer.

Deacetylation of **15** with methanolic sodium methoxide gave methyl 4-acetamido-4-deoxy-D-ribofuranoside (**16**) as an oil. The infrared spectrum of **16** was

(7) F. A. L. Anet, R. A. B. Bannard, and L. D. Hall, *Can. J. Chem.*, *ibid.*, **41**, 2331 (1963).
(8) E. J. Reist, D. F. Calkins, and L. Goodman, unpublished data.

compatible with the assigned furanose structure. It contained the amide carbonyl band at 5.95, but no NH absorption at 6.5 μ. An interesting feature was illustrated in the nmr spectrum (in D_2O) of **16**. There was the necessary acetate band present as a singlet at τ 7.67. The methoxyl band, rather than occurring as a clean singlet, appeared as two singlets at τ 6.45 and 6.51 with relative intensities of 5:1, respectively. Additionally the nmr absorption which was assigned to H-1 also occurred as two doublets (J = 1.5 cps) at τ 4.88 and 4.69 again with relative intensities of 5:1. When the nmr spectrum was run at 70°, the spectrum resolved itself to one singlet in the methoxyl region and a one doublet for H-1. A similar phenomenon was reported by Szarek, Wolfe, and Jones[9] when they described the nmr spectra of various acetamido sugars in which the acetamido nitrogen was the ring heteroatom, *e.g.*, methyl 5-acetamido-5-deoxy-D-xylopyranoside and methyl 4-acetamido-4-deoxy-D-erythrofuranoside. This unusual behavior in such molecules was attributed to hindered internal rotation about the N-acetate bond so that the rate of interconversion between two rotational conformers is sufficiently slow to allow a chemical-shift difference from signals arising from the two conformers (*e.g.*, **16a** and **16b**). At elevated temperatures this hindrance vanishes and the spectrum assumes the expected characteristics.



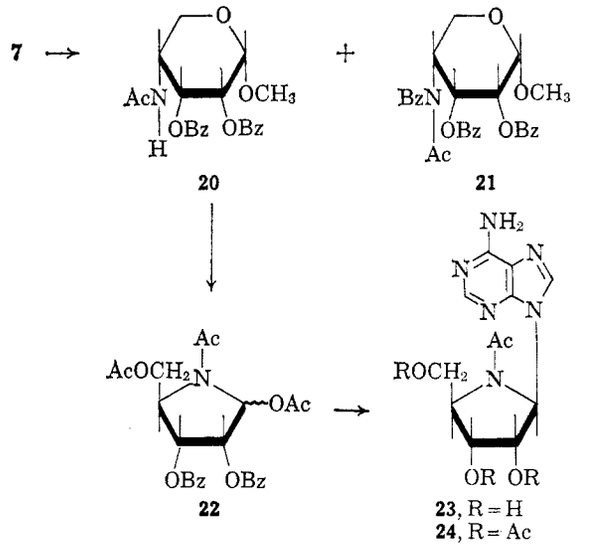
16a **16b**

Treatment of **16** with *p*-nitrobenzoyl chloride gave crystalline methyl 4-acetamido-4-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-D-ribofuranoside (**17**). The infrared spectrum of **17** was compatible with the assigned structure **17**, including the absence of NH absorption at 6.5 μ. The nmr spectrum (in deuteriochloroform) showed none of the characteristics attributed to hindered internal rotation in **16**. Probably the hindered internal rotation is dependent on the solvent, since the spectra run in deuteriochloroform (**15** and **17**) appeared normal while those run in D_2O (**16** and subsequent compounds) showed this phenomenon. Deacylation of **17** with methanolic ammonia regenerated **16** complete with its unusual nmr spectrum.

Acetolysis of the *p*-nitrobenzoate (**17**) gave 4-acetamido-1-*O*-acetyl-4-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-D-ribofuranose (**18**) from which one anomer could be crystallized. The crude acetolysis product appeared to be a mixture of α and β anomers in the ratio 2:1 as determined by the nmr spectrum. The nmr spectrum of the crystalline anomer had a $J_{1,2}$ of 1 cps. Thus, it might be reasoned that the crystalline anomer was in the β configuration. However, the optical rotation of the crystals was +52° (chloroform) while the mother liquors had an optical rotation of −130°. If the crystalline anomer is indeed β, compound **18** represents another example of the failure of Hudson's isorotation rules.

Treatment of **18** with hydrogen bromide in acetic acid gave the 1-bromide (**19**) as an amorphous solid that was highly unstable and could not be condensed with chloromercuri-6-benzamidopurine to give a nucleoside. For this reason an alternative approach, which started with methyl 4-acetamido-4-deoxy-α-D-ribopyranoside (**7**) was used to prepare the nucleoside (**23**).

Benzoylation of **7** with benzoyl chloride in pyridine gave a syrupy product which contained two components on thin-layer chromatography and which were resolved by silica gel chromatography. The first component analyzed for a tribenzoate and showed no NH absorption at 6.5 μ and proved to be methyl 4-acetamido-2,3-di-*O*-benzoyl-4-*N*-benzoyl-4-deoxy-α-D-ribopyranoside (**21**), formed in 16% yield. The remaining component, in 69% yield showed NH absorption at 6.5



20 **21**

22

23, R = H
24, R = Ac

μ in the infrared and was the desired methyl 4-acetamido-2,3-di-*O*-benzoyl-4-deoxy-α-D-ribopyranoside (**20**). The *N*-benzoylation of the amide of **7** was unexpected; however, a similar observation has been reported by Inch and Fletcher[10] who obtained benzyl 2-(*N*-acetylbenzamido)-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside from benzyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside and benzoyl chloride in pyridine.

Acetolysis of the dibenzoate (**20**) gave 4-acetamido-1,5-di-*O*-acetyl-2,3-di-*O*-benzoyl-D-ribofuranose (**22**) as a syrup which consisted of approximately equal amounts of each anomer according to its nmr. The conversion of the 1-*O*-acetate (**22**) to the nucleoside (**23**) was accomplished by either the standard condensation of the chloro sugar with chloromercuri-6-benzamidopurine or by the titanium tetrachloride catalyzed reaction of the 1-*O*-acetate with chloromercuri-6-benzamidopurine. After deacylation with methanolic sodium methoxide, 9-(4-acetamido-4-deoxy-β-D-ribofuranosyl)adenine (**23**) was obtained in 30–40% yields as an amorphous form. The infrared spectrum was compatible with the furanose structure since there was no NH absorption at 6.5 μ. The nmr spectrum (in D_2O) again showed the phenomenon of hindered internal rotation about the NC=O

(9) W. A. Szarek, S. Wolfe, and J. K. N. Jones, *Tetrahedron Letters*, **No. 38**, 2743 (1964).

(10) T. D. Inch and H. G. Fletcher, Jr., Abstracts of the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, p 27D.

bond. Thus, there were two acetate singlets at τ 7.93 and 8.38. H′-1 was a complex multiplet at τ 4.0 and there were two sets of aromatic proton peaks at τ 1.7–2.1. When the nmr of **23** was repeated at 70°, the expected collapse was observed and the aromatic peaks became two singlets at τ 1.52 and 1.65. The *N*-acetate was a broad singlet at τ 7.90 and H′-1 became a doublet at 3.88 (J = 6 cps). This coupling constant is in good agreement with that observed for H′-1 of adenosine (τ 3.95, $J_{1,2}$ = 6 cps) and supports the assignment of the β configuration to **23**. Acetylation of **23** gave a crystalline, sharp-melting tetracetate (**24**) with spectral properties which were compatible with the furanose ring structure. The nmr spectrum (in DMSO-d_6) did not indicate any hindered internal rotation as shown for the unblocked nucleoside (**23**) and was qualitatively quite similar to the nmr spectrum of 2′,3′,5′-tri-*O*-acetyladenosine in the same solvent.

Deacetylation of the crystalline acetylated nucleoside (**24**) gave back the 4′-acetamidoadenosine (**23**) which was identical in all respects with the material obtained by the nucleoside condensation, a further indication that **23** was pure and that the double peaks in the nmr were due to hindered rotation rather than contamination.

One of the major problems in the chemistry of amino sugars in which the possibility exists for nitrogen to become the heteroatom of the ring, is to determine whether ring closure has occurred on nitrogen or oxygen. The use of nmr spectroscopy of the *N*-acylate should be quite useful in making this determination, since the spectral anomalies due to hindered internal rotation apparently occur only when nitrogen is the ring heterocycle.

Experimental Section[11]

Methyl 4-Azido-2-*O*-benzoyl-4-deoxy-3-*O*-(*p*-tolylsulfonyl)-α-D-xylopyranoside (2).—A solution of 1.0 g (1.75 mmoles) of methyl 2-*O*-benzoyl-3,4-di-*O*-(*p*-tolylsulfonyl)-β-L-arabinopyranoside[4] (**1**) and 0.42 g (6.5 mmoles) of sodium azide in 20 ml of DMF was heated with stirring at 120° for 6 hr, then was evaporated to dryness *in vacuo*. The residue was partitioned between 25 ml each of water and ether. The aqueous layer was extracted with two additional 25-ml portions of ether. The combined ether layers were washed with 25 ml each of saturated aqueous sodium bicarbonate and water, then were dried and evaporated to dryness *in vacuo* to yield 745 mg of crude product. The residue was crystallized from ethanol to give 550 mg (74%) of product, mp 89–94°, which was satisfactory for the next step.

The analytical sample was recrystallized from 2-propanol: mp 100.5–101.0°, $[\alpha]^{24}D$ +230° (*c* 1, chloroform).

Anal. Calcd for $C_{20}H_{21}N_3O_7S$: C, 53.7; H, 4.73; N, 9.39; S, 7.16. Found: C, 53.4; H, 4.93; N, 9.42; S, 7.16.

On a larger scale, 10.0 g of **1** gave 5.9 g (77%) of **2**, mp 100–101°.

Methyl 4-Amino-2-*O*-benzoyl-4-deoxy-3-*O*-(*p*-tolylsulfonyl)-α-D-xylopyranoside (3).—To a suspension of *ca.* 3 g of sponge nickel catalyst[12] in 200 ml of 2-methoxyethanol was added 2.0 g of the azide (**2**). The mixture was stirred at room temperature under an atmosphere of hydrogen, for 18 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo* to give a quantitative yield of a colorless oil which crystallized on standing, mp 105–109°.

The analytical sample, obtained by recrystallization from absolute ethanol, had mp 111–112°, $[\alpha]^{23}D$ +202° (*c* 1, chloroform).

Anal. Calcd for $C_{20}H_{23}NO_7S$: C, 57.0; H, 5.50; N, 3.33; S, 7.61. Found: C, 57.5; H, 5.57; N, 3.00; S, 7.74.

Methyl 4-Acetamido-2-*O*-benzoyl-4-deoxy-3-*O*-(*p*-tolylsulfonyl)-α-D-xylopyranoside (4).—Acetylation of 1.6 g of **3** with acetic anhydride in pyridine gave a colorless oil which was crystallized from absolute ethanol to yield 1.17 g (67%) of white crystals, mp 140–141°, resolidifying and remelting at 149–151°.

The analytical sample, obtained from absolute ethanol had a double melting point, mp 140–141°, then 149–150°, $[\alpha]^{23}D$ +217° (*c* 1, chloroform).

Anal. Calcd for $C_{22}H_{25}NO_8S$: C, 57.0; H, 5.42; N, 3.02; S, 6.92. Found: C, 56.9; H, 5.51; N, 2.94; S, 7.09.

Methyl 2,3-Anhydro-4-azido-4-deoxy-α-D-ribopyranoside (5).—A solution of 2.0 g (4.5 mmoles) of azide **2** in 75 ml of methanol that contained 0.55 g (10 mmoles) of sodium methoxide was stored at room temperature for 6 hr then was neutralized to pH 7 with IRC 50 (H) resin.[13] The neutralized solution was evaporated to dryness *in vacuo* and the residue was partitioned between 50 ml each of water and petroleum ether (bp 62–70°) to remove methyl benzoate. The aqueous layer was extracted with three 25-ml portions of chloroform. The combined chloroform fractions were dried and evaporated to dryness *in vacuo* to yield 540 mg (78%) of product **5** as a colorless oil.

The analytical sample was obtained, by sublimation at 45° (0.01 mm), as white crystals: mp 44.5–45.5°, λ_{max}^{Nujol} 4.73 (N_3), 8.02, and 11.45 μ (epoxide). There was no carbonyl absorption at 5.8 or sulfonate absorption at 8.5 μ.

Anal. Calcd for $C_6H_9N_3O_3$: C, 42.0; H, 5.3; N, 24.5. Found: C, 41.9; H, 5.30; N, 24.4.

Methyl 4-Acetamido-4-deoxy-α-D-ribopyranoside (7).—A solution of 10.3 g (24.5 mmoles) of amide **4** and 8.9 g of sodium acetate in 500 ml of 95% aqueous DMF was heated at 140° under nitrogen for 8 hr then was evaporated to dryness *in vacuo*. The residue was partitioned between 250 ml each of chloroform and water. The aqueous phase was extracted with three additional 75-ml portions of chloroform. The combined chloroform fractions were dried and evaporated to dryness *in vacuo* to yield 5.68 g (75%) of crude methyl 4-acetamido-2-*O*-benzoyl-4-deoxy-α-D-ribopyranoside (**6**) as a yellow oil. The aqueous layer was evaporated to dryness *in vacuo* and the white residue was triturated with several portions of hot chloroform. The chloroform solution was evaporated to dryness. The residue was crystallized from ethyl acetate to give 1.23 g of methyl 4-acetamido-4-deoxy-α-D-ribopyranoside (**7**), mp 153–155°. The infrared spectrum was identical with that of the analytical sample.

A solution of 5.68 g of crude **6** in 75 ml of methanol that contained 1.0 g of sodium methoxide was stirred at room temperature for 15 hr. After neutralization to pH 7 with Amberlite IRC 50 (H) the solution was evaporated to dryness. The residue was partitioned between 50 ml each of water and chloroform. The aqueous phase was evaporated to dryness *in vacuo*, and the residue was crystallized from ethyl acetate to give 1.94 g of product **7**, mp 156–157° for a total yield of 3.17 g (84%).

The analytical sample from a previous reaction was recrystallized from 2-propanol and had mp 157–158°, $[\alpha]D$ +120° (*c* 1, water).

Anal. Calcd for $C_8H_{15}NO_5$: C, 46.8; H, 7.37; N, 6.83. Found: C, 46.6; H, 7.29; N, 6.62.

Methyl 4-Acetamido-4-deoxy-2,3-*O*-isopropylidene-α-D-ribopyranoside (8).—A solution of 500 mg of methyl 4-acetamido-4-deoxy-α-D-ribopyranoside (**7**) in 12 ml of 2,2-dimethoxypropane containing 0.5 ml of 4 *N* hydrogen chloride in dioxane was stirred at 30° for 18 hr. The reaction was evaporated to dryness *in vacuo*

(11) Melting points were determined with the Fisher-Johns apparatus or Thomas–Hoover apparatus and are corrected. Optical rotations were determined with the Rudolph photoelectric polarimeter. Thin layer chromatograms were run on silica gel HF (E. Merck A.-G., Darmstadt). Spots were detected by spraying with sulfuric acid, then developing at *ca.* 100° for a few minutes. Paper chromatograms were run by the descending method on Whatman No. 1 paper with adenine used for a standard. Spots were located by visual examination under ultraviolet light and were reported as R_{Ad} values with adenine arbitrarily given the value 1.0. Solvent systems used were water–saturated butanol (solvent A); 5% aqueous disodium hydrogen phosphate (solvent B); butanol–acetic acid–water (5:2:3) (solvent C). Organic solutions were dried over magnesium sulfate. Nmr spectra were run as solutions in deuteriochloroform using tetramethylsilane as an internal standard, or D_2O using 5% tetramethylsilane in tetrachloroethane as an internal standard, or dimethyl sulfoxide-d_6 using the same external standard. The nmr spectrometer used was the Varian A-60 or HA-100.

(12) Sponge nickel catalyst, Davison Chemical Co., Cincinnati, Ohio.

(13) A weak acid cation-exchange resin manufactured by the Rohm and Haas Co., Philadelphia, Pa. When used for the neutralization of methanolic solutions of sodium methoxide, it was washed initially with methanol until the methanol washes were colorless.

and partitioned between 50 ml each of chloroform and water. The chloroform layer was washed with 25 ml each of saturated aqueous sodium bicarbonate and water, and then was dried and evaporated to dryness *in vacuo*. The solid residue was recrystallized from benzene–cyclohexane (1:2) to give 400 mg (62%) of product (**8**)

The analytical sample had mp 114–115°, $[\alpha]_D$ +119° (*c* 1, chloroform).

Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.9; H, 7.81; N, 5.71. Found: C, 54.0; H, 7.51; N, 5.78.

Methyl 4-Acetamido-2,3-di-*O*-acetyl-4-deoxy-α-D-ribopyranoside (**9**).—Methyl 4-acetamido-4-deoxy-α-D-ribopyranoside (1.0 g) was acetylated using 5 ml of acetic anhydride in 20 ml of pyridine in the usual manner to yield 1.1 g (80%) of product **9** as a colorless syrup which was homogeneous on thin layer chromatography using methanol–ethyl acetate (2:3) with R_f 0.70.

Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.8; H, 6.60; N, 4.80. Found: C, 49.9; H, 6.70; N, 4.60.

Methyl 4-Azido-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (**11**).—A mixture of 24.0 g (67 mmoles) of methyl 2,3-*O*-isopropylidene-4-*O*-(*p*-tolylsulfonyl)-α-L-lyxopyranoside[3] and 16.2 g (250 mmoles) of sodium azide in 800 ml of DMF was heated at 115° for 48 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was partitioned between 250 ml each of water and chloroform. The chloroform layer was washed with 200 ml of saturated aqueous sodium bicarbonate and 100 ml of water, then dried and evaporated to dryness *in vacuo*. The resulting oil was distilled to give 6.0 g (39%) of product as a colorless oil: bp 76–78° (0.3 mm), $[\alpha]^{23}_D$ −60° (*c* 1, chloroform).

Anal. Calcd for $C_9H_{15}N_3O_4$: C, 47.1; H, 6.60; N, 18.3. Found: C, 47.8; H, 6.72; N, 18.8.

A similar reaction using methyl 2,3-*O*-isopropylidene-4-*O*-(*p*-tolylsulfonyl)-α-D-lyxopyranoside[14] gave a 46% yield of methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-β-L-ribopyranoside: bp 64–65° (0.02 mm), $[\alpha]_D$ +51° (*c* 1, chloroform).

Anal. Calcd for $C_9H_{15}N_3O_4$: C, 47.1; H, 6.60; N, 18.3. Found: C, 47.1; H, 6.53; N, 18.4.

Methyl 4-Azido-4-deoxy-β-D-ribopyranoside (**12**).—A solution of 5.9 g of methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (**11**) in 120 ml of 66% aqueous acetic acid was heated at 50° for 3 hr, then was evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml of ethanol, treated with Norit, then evaporated to dryness *in vacuo*. The residue was codistilled with tetrachloromethane to remove last traces of acetic acid.

The analytical sample was evaporatively distilled and had $[\alpha]^{24}_D$ −120° (*c* 2, water).

Anal. Calcd for $C_6H_{11}N_3O_4$: C, 38.1; H, 5.86; N, 22.2. Found: C, 38.2; H, 5.90; N, 22.4.

Methyl 4-Amino-4-deoxy-β-D-ribopyranoside (**13**).—A solution of 4.7 g (25 mmoles) of methyl 4-azido-4-deoxy-β-D-ribopyranoside (**12**) in 75 ml of water was hydrogenated at room temperature for 4 hr using 780 mg of 5% palladium-on-carbon catalyst. The mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was crystallized from ethyl acetate to give 1.1 g of product, mp 109–111°.

The analytical sample was recrystallized from ethyl acetate and had mp 109.5–111.0°, $[\alpha]^{24}_D$ −83° (*c* 1, water).

Anal. Calcd for $C_6H_{13}NO_4$: C, 44.2; H, 8.03; N, 8.59. Found: C, 44.0; H, 8.00; N, 8.37.

4-Acetamido-1,2,3,5-tetra-*O*-acetyl-4-deoxy-D-ribofuranose (**10**).

A. From Methyl 4-Acetamido-4-deoxy-α-D-ribopyranoside (**7**).—To a cold solution of 2.0 g of methyl 4-acetamido-4-deoxy-α-D-ribopyranoside (**7**) in 60 ml each of acetic acid and acetic anhydride was added 3.6 ml of concentrated sulfuric acid dropwise with stirring. The reaction was kept at 0° for 2 days, was decomposed by the addition of 14 g of sodium acetate, and then was evaporated to dryness *in vacuo* at room temperature. The residue was dissolved in 50 ml of methanol and evaporated *in vacuo* to remove acetic anhydride. This methanol treatment was repeated, then the residue was partitioned between 100 ml each of chloroform and saturated aqueous sodium bicarbonate. The chloroform layer was washed with water, then dried and evaporated to dryness *in vacuo* to yield 3.4 g (97%) of product (**10**) as a yellow syrup, λ_{max}^{film} 5.70, (OAc), 5.95 (N-acetate), and 8.15 μ (acetate COC). There was no NH absorption at 2.9 or 6.5 μ.

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.1; H, 5.89; N, 3.90. Found: C, 49.9; H, 6.00; N, 3.82.

B. From Methyl 4-Amino-4-deoxy-β-D-ribopyranoside (**13**).—Acetylation of 1.7 g of methyl 4-amino-4-deoxy-β-D-ribopyranoside (**13**) using acetic anhydride in pyridine gave 1.8 g (60%) of methyl 4-acetamido-2,3-di-*O*-acetyl-4-deoxy-β-D-ribopyranoside (**14**) as a yellow oil.

Acetolysis of crude **14** in the manner described for the acetolysis of methyl 4-acetamido-4-deoxy-α-D-ribopyranoside (**7**, method A) gave 1.87 g (85%) of **10** as a colorless oil, $[\alpha]^{25}_D$ −22° (*c* 1, chloroform).

Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.1; H, 5.89; N, 3.90. Found: C, 50.4; H, 5.82; N, 3.81.

The infrared and nmr spectra of **10** prepared by methods A and B were identical in all respects.

Methyl 4-Acetamido-4-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-D-ribofuranoside (**17**).—A solution of 1.0 g of 4-acetamido-1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (**10**) in 25 ml of 0.5% methanolic hydrogen chloride was heated at reflux for 0.5 hr, then the dark solution was neutralized with IR 45 (OH). The neutralized solution was treated with Norit then filtered through Celite, and the filtrate was evaporated to dryness *in vacuo* to give a pale yellow oil. Acetylation of the oil with acetic anhydride in pyridine gave 500 mg (54%) of methyl 4-acetamido-2,3,5-tri-*O*-acetyl-4-deoxy-β-D-ribofuranoside (**15**) as a colorless oil which was essentially homogeneous on thin layer chromatography using ethyl acetate with the main spot at R_f 0.33. The infrared spectrum showed no absorption at 2.9 and 6.5 μ assignable to NH. The nmr spectrum showed the presence of 12 acetate protons at τ 7.87–7.98.

Deacetylation of **15** was accomplished by refluxing in 5 ml of 0.1% methanolic sodium methoxide for 1 hr. The cooled solution was neutralized with IRC-50 (H) then filtered through Celite, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 2-propanol, and the remaining inorganic salts were removed by filtration. The filtrate was evaporated to dryness *in vacuo* to give 270 mg (87%) of methyl 4-acetamido-4-deoxy-D-ribofuranoside **16** as a pale yellow oil which had no infrared absorption at 5.7 or 6.5 μ assignable to *O*-acetate and amide NH, respectively. The nmr spectrum showed the presence of 1 acetate at τ 7.75.

Acylation of 150 mg (0.73 mmole) of **16** with 1.0 g (5.4 mmoles) of *p*-nitrobenzoyl chloride in 3 ml of pyridine at 0° for 15 hr gave 210 mg of white crystals, mp 175–177° after two crystallizations from benzene.

An analytical sample was obtained from absolute ethanol and had mp 175.5–177.0°, $[\alpha]^{23}_D$ +115° (*c* 1, chloroform), λ_{max}^{Nujol} 5.75 (O-carbonyl) and 6.05 μ (N-acetate). There was no amide NH absorption at 3.0 and 6.5 μ. The nmr spectrum contained absorption at τ 7.80 equivalent to one acetate methyl.

Anal. Calcd for $C_{29}H_{24}N_4O_{14}$: C, 53.4; H, 3.71; N, 8.59. Found: C, 53.5; H, 3.74; N, 8.45.

4-Acetamido-1-*O*-acetyl-4-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-D-ribofuranose (**18**).—Acetolysis of 2.3 g of methyl 4-acetamido-4-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-D-ribofuranose (**17**) by the procedure used to prepare 4-acetamido-1,2,3,5-tetra-*O*-acetyl-4-deoxy-D-ribofuranose (**10**) gave a white foam which was crystallized from 2-propanol–ethyl acetate to yield 1.45 g (61%) of white crystals, mp 163.0–164.5°.

The analytical sample was recrystallized from benzene and had mp 164.5–165.0°; $[\alpha]^{23}_D$ +52° (*c* 1, chloroform).

Anal. Calcd for $C_{30}H_{24}N_4O_{15}$: C, 52.9; H, 3.56; N, 8.23. Found: C, 52.7; H, 3.63; N, 8.17.

The mother liquors from the 2-propanol–ethyl acetate crystallization were evaporated to give a white foam which could not be crystallized, and which had $[\alpha]^{24}_D$ −13° (*c* 1, chloroform).

Anal. Found: C, 52.7; H, 3.74.

4-Acetamido-1-bromo-4-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-D-ribofuranose (**19**).—A solution of 100 mg of the 1-*O*-acetate (**17**) in 3 ml of 30% hydrogen bromide in acetic acid was stored at room temperature for 18 hr, then was evaporated to dryness *in vacuo* to give 105 mg of an amorphous, pink powder that decomposed on heating.

Anal. Calcd for $C_{28}H_{21}BrN_4O_{13}$: Br, 11.4. Found: Br, 12.1.

Methyl 4-Acetmido-2,3-di-*O*-benzoyl-4-deoxy-α-D-ribopyranoside (**20**) **and Methyl 4-Acetamido-2,3-di-*O*-benzoyl-4-*N*-benzoyl-4-deoxy-α-D-ribopyranoside** (**21**).—A solution of 12.0 g (58.5 mmoles) of methyl 4-acetamido-4-deoxy-α-D-ribopyranoside (**7**) in 360 ml of dry pyridine was cooled to 0°, then 24 ml (265 mmoles) of benzoyl chloride was added dropwise with stirring, and cooling

(14) P. W. Kent and P. F. V. Ward, *J. Chem. Soc.*, 416 (1953).

was continued. The reaction mixture was kept at 0° for 3 days, then excess benzoyl chloride was decomposed by the addition of 20 ml of water. After 1 hr at room temperature, the mixture was evaporated to dryness *in vacuo* and the residue was partitioned between 300 ml each of chloroform and water. The chloroform layer was washed with three 100-ml portions of saturated aqueous sodium bicarbonate. The chloroform layer was dried and evaporated to dryness. The residue was codistilled with toluene to remove the last traces of pyridine. Thin layer chromatography using ethyl acetate–chloroform (1:1) as the developing agent showed the major component at R_f 0.46 with a minor one at R_f 0.78.

The residue was dissolved in a minimum quantity of benzene then applied to the top of a silica gel column (4.5 × 60 cm). The column was eluted with dichloromethane, then 10% ethyl acetate in dichloromethane to obtain 3.85 g (16%) of crystalline tribenzoate (**21**) with R_f 0.78, followed by 1.2 g of a mixture of **20** and **21**, then 16.5 g (69%) of syrupy dibenzoate (**20**) with R_f 0.46.

Methyl 4-acetamido-2,3-di-*O*-benzoyl-4-deoxy-α-D-ribopyranoside (**20**) had $[\alpha]^{22}D$ +123° (*c* 1, chloroform); λ_{max}^{film} 3.0, 6.5 (NH), 5.75, 7.85 (benzoate), and 6.0 μ (amide CO).

The nmr spectrum had a doublet at τ 3.42 which is assignable to NH.

Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.9; H, 5.61; N, 3.39. Found: C, 64.0; H, 5.80; N, 3.28.

Methyl 4-acetamido-2,3-di-*O*-benzoyl-4-*N*-benzoyl-4-deoxy-α-D-ribopyranoside (**21**) was recrystallized from methanol and had mp 122–123°; $[\alpha]^{20}D$ +182° (*c* 1, chloroform); λ_{max}^{Nujol} 5.75, 7.85 (O-benzoate), 5.85, and 5.90 μ (imide carbonyls). There was no NH absorption at 3.0 and 6.5 μ.

Anal. Calcd for $C_{29}H_{27}NO_8$: C, 67.3; H, 5.26; N, 2.71. Found: C, 67.6; H, 5.17; N, 2.73.

4-Acetamido-1,5-di-*O*-acetyl-2,3-di-*O*-benzoyl-4-deoxy-D-ribofuranose (22).—A solution of 6.0 g (14.5 mmoles) of methyl 4-acetamido-2,3-di-*O*-benzoyl-4-deoxy-α-D-ribopyranoside (**20**) in a mixture of 192 ml each of acetic anhydride and acetic acid which contained 5.7 ml of concentrated sulfuric acid was kept at 0° for 4 days, then was neutralized with 25 g of anhydrous sodium acetate. The mixture was evaporated to dryness *in vacuo* and the residue was partitioned between 200 ml of chloroform and 500 ml of water. The chloroform layer was stirred for several hours with 500 ml of saturated aqueous sodium bicarbonate solution, then the layers were separated and the chloroform layer was dried and evaporated to dryness *in vacuo* to yield 6.5 g (92%) of product **22** as a pale brown oil: $[\alpha]^{25}D$ −22° (*c* 1, chloroform), λ_{max}^{film} 5.70–5.75 (O-carbonyl) and 5.90 μ (N-carbonyl). There was no NH absorption at 3.0 and 6.5 μ.

Anal. Calcd for $C_{25}H_{25}NO_9$: C, 62.1; H, 5.22; N, 2.90. Found: C, 62.3; H, 5.47; N, 2.75

9-(4-Acetamido-4-deoxy-β-D-ribofuranosyl)adenine (23). A. Chloro Sugar Method.—A solution of 1.85 g (3.87 mmoles) of 4-acetamido-1,5-di-*O*-acetyl-2,3-di-*O*-benzoyl-4-deoxy-D-ribofuranose (**22**) in 100 ml of dry ether that contained 2 ml of acetyl chloride was cooled to 0°, then saturated with hydrogen chloride gas. The ether solution was kept at 0° for 4 days then evaporated to dryness *in vacuo*. The resulting chloro sugar was heated at reflux with 3.0 g (4.0 mmoles) of chloromercuri-6-benzamidopurine in 100 ml of dry benzene for 4 hr. The hot solution was filtered through Celite and the filtrate was diluted with 500 ml of petroleum ether (bp 62–70°). The white precipitate was collected and dissolved in 200 ml of dichloromethane. The dichloromethane solution was washed with 100 ml of 30% aqueous potassium iodide and 100 ml of water, then was dried and evaporated to dryness *in vacuo* to give 1.75 g of crude blocked nucleoside as a yellow foam.

Deacylation was accomplished by heating at reflux for 1 hr with 200 mg of sodium methoxide in 20 ml of methanol. After neutralization with acetic acid, the solution was evaporated to dryness and the residue was partitioned between 40 ml each of water and chloroform. The aqueous fraction was evaporated to dryness *in vacuo*, then the residue was dissolved in a minimum volume of water and applied to a chromatography column (1.5 cm in diameter) which contained 50 ml of Dowex 1 (OH) resin.[15] Elution with water gave 321 mg (32%) of product (**23**) as an amorphous foam: $[\alpha]^{21}D$ −128° (*c* 1, water), $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 13,780), $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 14,380), $\lambda_{max}^{pH\ 13}$ 259 mμ (ε 14,220).

The product was homogeneous in three solvent systems[11] and had R_{Ad} values of 0.55, 1.71, and 0.87 in solvent systems A, B, and C, respectively.

Anal. Calcd for $C_{12}H_{16}N_6O_4$: C, 46.8; H, 5.23; N, 27.3. Found: C, 46.6; H, 5.36; N, 27.1.

The infrared spectrum showed no absorption at 6.5 μ which could be assigned to amide NH.

B. Titanium Tetrachloride Method.[16]—A mixture of 2.0 g (4.24 mmoles) of 4-acetamido-1,5-di-*O*-acetyl-2,3-di-*O*-benzoyl-4-deoxy-D-ribofuranose (**22**), and 5.0 g (6.7 mmoles) of chloromercuri-6-benzamido purine (64% on Celite) in 450 ml of 1,2-dichloroethane was dried by distillation of 100 ml of dichloroethane from the mixture. The mixture was cooled to 0° and 0.74 ml (6.7 mmoles) of titanium tetrachloride was added with stirring. The reaction was stirred at room temperature for 39 hr, then it was poured into 400 ml of saturated aqueous sodium bicarbonate and stirred for 2 hr. The organic layer was separated and filtered through Celite, then was evaporated to dryness *in vacuo*. The residue was dissolved in 100 ml of chloroform. The chloroform was washed with 100 ml of 30% aqueous potassium iodide and 100 ml of water, then was dried and evaporated to dryness *in vacuo*.

Deacylation with methanolic sodium methoxide and ion-exchange chromatography with Dowex 1 (OH) as described in procedure A, gave 545 mg (42%) of product as a yellow foam which was identical with product obtained by method A according to infrared, nmr and paper chromatography, and optical rotation.

9-(4-Acetamido-2,3,5-tri-*O*-acetyl-4-deoxy-β-D-ribofuranosyl)-adenine (24).—To a solution of 297 mg (0.96 mmole) of 9-(4-acetamido-4-deoxy-β-D-ribofuranosyl)adenine (**23**) in 20 ml of pyridine was added 0.25 ml (2.6 mmoles) of acetic anhydride. The reaction was stirred at room temperature under a nitrogen atmosphere for 4 hr, then was evaporated to dryness *in vacuo*. The residue was triturated with absolute ethanol to give 227 mg (60%) of white product, mp 240.0–240.5°.

Anal. Calcd for $C_{18}H_{22}N_6O_7$: C, 49.7; H, 5.11; N, 19.4. Found: C, 49.4; H, 5.19; N, 19.3.

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