at 2135 cm^{-1} disappeared (after ca. 6 h). Upon cooling and partial evaporation of the solvent, **4a** crystallized out in almost quantitative yield.

Compound **2a** was obtained as a colorless oil in 26% yield: IR (neat) 2960, 1240, 1100–1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (d, 6 H, J = 7 Hz), 3.20 (sept, 1 H), 7.3–7.6 (m, 5 H). Anal. Calcd for $M^{+\cdot}$: 188.1061. Found: 188.1072. This compound was identical in all respects with the product obtained from the corresponding imidoyl chloride and sodium azide.[17]

Compound **2b** was similarly obtained in 57% yield: mp 78–79 °C (*n*-hexane–chloroform); IR (KBr) 2960, 2920, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (d, 6 H, J = 7 Hz), 2.48 (s, 3 H), 3.2 (sept, 1 H), 7.3–7.4 (2d, 4 H). Anal. Calcd for $M^{+\cdot}$: 202.1217. Found: 202.1205. This compound was identical in all respects with the product obtained from the corresponding imidoyl chloride and sodium azide.[17]

Compound **3a** was obtained in 13% yield: mp 165 °C dec ($CHCl_3$); IR (KBr) 3200 cm^{-1} (OH); ^1H NMR (Me_2SO-d_6; HMDS as reference) δ 1.44 (s, 6 H, $2CH_3$), 7.52 (s, 5 H), 11.64 (s, 1 H, OH). Anal. Calcd for $C_{10}H_{12}N_4O_2$ (220): C, 54.51; H, 5.49. Found: C, 54.45; H, 5.44.

Compound **3b** was similarly obtained in 26% yield: mp 128–129 °C dec (ether); IR (KBr) 3180 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.60 (s, 6 H), 2.45 (s, 3 H), 9.30 (s, OH), 7.27–7.45 (m, 4 H). Anal. Calcd for $C_{11}H_{14}N_4O_2$ (234): C, 56.37; H, 6.03; N, 23.93. Found: C, 56.24; H, 5.95; N, 23.91.

Compound **4a** was obtained in 24–35% yield: mp 84–84.5 °C; IR (KBr) 3360–3380, 1590, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 6 H), 1.96 (s, 2 H), 7.4–7.6 (m, 5 H). Anal. Calcd for $C_{10}H_{13}N_5$ (203): C, 59.09; H, 6.45; N, 34.45. Found: C, 58.93; H, 6.37; N, 34.39.

Compound **4b** was similarly obtained as the HN_3 salt in 16% yield. The free base **4b** exhibited the following characteristics: mp 102–103 °C ($CHCl_3$); IR (KBr) 3380, 3320, 2980, 1580, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 6 H), 1.80 (s, 2 H, NH_2), 2.48 (s, 3 H), 7.36 (s, 4 H). Anal. Calcd for $C_{11}H_{15}N_5$ (217): C, 60.81; H, 6.96; N, 32.23. Found: C, 60.83; H, 6.99; N, 32.08.

Crystal Structure Determination of 3b and 4b. Compound 3b. Crystal data: $C_{11}H_{14}N_4O_2$ (234); monoclinic; a = 7.421 Å, b = 12.588 Å, c = 13.635 Å, β = 100.70°; space group $P2_1/c$, Z = 4. Intensity data were collected on a Syntex tape-controlled diffractometer using Mo Kα radiation, 2θ max = 45°. A total of 1630 independent reflections were measured, of which 1181 were considered as observed. The structure has been solved with the MULTAN 77 program[18] and refined with the X-RAY 72 system[19] to an R factor of 3.9%.

Compound 4b. Crystal data: $C_{11}H_5N_5$ (217); monoclinic; a = 13.565 Å, b = 10.937 Å, c = 8.223 Å, β = 102.48°; space group $P2_1/n$, Z = 4. Intensity data were collected on a Picker card-controlled diffractometer using filtered Mo Kα radiation, 2θ max = 45°. A total of 1550 independent reflections were measured, of which 1103 were considered as observed. The structure has been solved with the MULTAN 77 program[18] and refined with the X-RAY 72 system[19] to an R factor of 9.2%.

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Registry No.—**1a,** 14016-34-3; **1b,** 18779-86-7; **2a,** 66418-07-3; **2b,** 66418-08-4; **3a,** 66418-09-5; **3b,** 66418-10-8; **4a,** 66418-11-9; **4a** NH_3 salt, 66418-12-0; **4b,** 66418-13-1; **4b** NH_3 salt, 66523-90-8; hydrazoic acid, 7782-79-8; dimethyl acetylenedicarboxylate, 762-42-5.

Supplementary Material Available: Tables with ^{13}C NMR data and atomic coordinates of **3b** and **4b,** as well as the Experimental Section for the preparation of compounds **7–12** (4 pages). Ordering information is given on any current masthead page.

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Synthesis of 3′-Azido-2′,3′-dideoxyribofuranosylpurines

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The transglycosylation reaction of 3′-azido-3′-deoxy-5′-*O*-acetylthymidine (**4b**), which is readily available from thymidine, with silylated N^6-octanoyladenine using trimethylsilyl trifluoromethanesulfonate as a catalyst affords a mixture of α and β anomers of 3′-azido-2′,3′-dideoxyadenosine (**5a** and **5b**), which is separable on a silica gel column. Replacement of silylated N^6-octanoyladenine by silylated N^2-palmitoylguanine affords a mixture of product from which α and β anomers of 9-(3-azido-2,3-dideoxy-D-ribofuranosyl)guanine (**7a** and **7b**) can be isolated. The N^7 isomers (**8a** and **8b**) are also obtained, but could not be separated from each other. Treatment of **5b** and **7b** with triphenylphosphine and subsequent hydrolysis afford the corresponding 3′-amino-2′,3′-dideoxy nucleosides **6** and **9** in good yield. A further simplification of this transglycosylation reaction and its applicability to syntheses of ribonucleoside derivatives are demonstrated.

It has recently been observed that the 5′-diphosphates of 2′-azido-2′-deoxyribofuranosylpurines and -pyrimidines inhibit the ribonucleotide reductases of various organisms by interaction with the active sites of these enzymes.[1] This has led to the discovery that 2′-azido-2′-deoxycytidine in particular is an inhibitor of DNA replication in mammalian cells, presumably interfering with DNA initiation.[2] The details of the mechanism of action of this compound are as yet not un-

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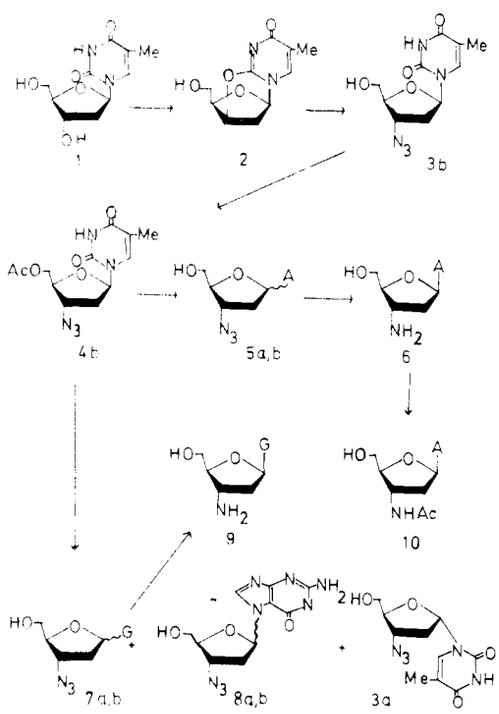
derstood and it is therefore of interest to test other azido derivatives of nucleosides and nucleotides in various in vivo as well as in vitro systems to assess the specificity of this inhibition. We have therefore undertaken the synthesis of 3′-azido-2′,3′-dideoxyribofuranosyl purines which are also convenient intermediates for the amino derivatives. 3′-Amino-2′,3′-dideoxyadenosine has been reported by Lee et al.,[3] but this required a 12-step synthesis from xylose.

A general synthesis of 2′-azido-2′-deoxypurine nucleosides from 2′-azido-2′-deoxyuridine was recently demonstrated in our laboratory[4] utilizing the sugar moiety derived from the pyrimidine nucleoside for condensation with adenine and guanine. We have, therefore, chosen the readily available 3′-azido-3′-deoxythymidine (**3b**)[5] as the precursor for the synthesis of 3′-azido-2′,3′-dideoxyribofuranosylpurines. In order to simplify the synthesis we adopted a direct transglycosylation reaction with purine base derivatives instead of isolating and condensing the sugar moiety separately.

The synthesis of purine nucleosides from pyrimidine nucleosides through such a transglycosylation reaction of ribonucleosides has been reported by Miyaki et al.[6] However, their procedure requires conditions which seemed too drastic for application to azido-sugar nucleosides. Milder reaction conditions have been described for the counterpart reaction, the transpurination, but were not applicable to the conversion of a pyrimidine to a purine nucleoside.[7] Azuma et al.[8-10] reported recently transglycosylation reactions of octosyl acid A and uracil polyoxin C derivatives to adenine nucleosides using trimethylsilyl perchlorate or trimethylsilyl trifluoromethanesulfonate[11] as Friedel–Crafts catalyst under mild conditions. We thought that this reaction would also be suitable for the 2′-deoxyribonucleoside series and describe here the use of this approach for the synthesis of 3′-azido-2′,3′-dideoxyadenosines and -guanosines.

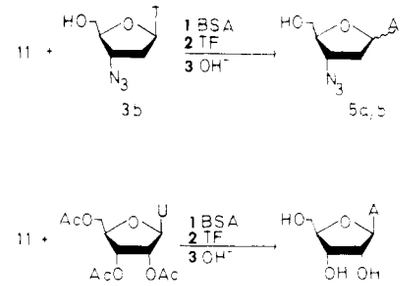
The synthetic method is indicated in Scheme I. The method of Kowollik et al.[12] was adopted for the synthesis of O^2-3′-cyclothymidine (**2**) directly from thymidine in 53% yield using 2-chloro-1,1,2-trifluoroethyldiethylamine. Treatment of **2**

Scheme I[a]



[a] A = adenin-9-yl, G = guanin-9-yl, a = α anomer, b = β anomer.

Scheme II[a]



[a] T = thymin-1-yl, A = adenin-9-yl, U = uracil-1-yl, a = α anomer, b = β anomer, BSA = bis(trimethylsilyl)acetamide, TF = trimethylsilyl trifluoromethanesulfonate.

with lithium azide as reported by Roesler[13] gave crystalline 3′-azido-3′-deoxythymidine (**3b**) in 66% yield. Conversion of **3b** to the 5′-acetate **4b** was performed with acetic anhydride without organic base. It was obtained as a gum in quantitative yield. **4b** was directly utilized for the transglycosylation reaction without benzoylation at N-3. Though the pyrimidine nucleoside has in previous reports[6,8-10] been usually acylated at the basic moiety in order to undergo facile cleavage of the glycosyl linkage, it was found to be unnecessary for our reaction.

Thus N^6-octanoyladenine (**11**)[14] was silylated with hexamethyldisilazane and chlorotrimethylsilane and reacted with **4b** in acetonitrile using 1.3 equiv of trimethylsilyl trifluoromethanesulfonate as a catalyst. Following deacylation with aqueous ammonia the mixture obtained was treated with Dowex 1 × 4 (OH^-) to remove all bases and nucleosides other than adenine nucleosides. The mixture of α and β anomers of adenine nucleosides (**5a** and **5b**) was separated on a silica gel column to give **5a** and **5b** in a yield of 35 and 27%, respectively.

Since no acylated group is present at the 2′ position of the sugar, a mixture of α and β anomers of the resultant nucleoside is to be expected. The relative proportions obtained were found by thin-layer chromatography to be essentially independent of the reaction time. The slightly higher yield of the α anomer was also experienced in the condensation reactions[15,16] of adenine and 2′-deoxyribose derivatives. Both **5a** and **5b** show triplets for the anomeric proton in the NMR so that the NMR data cannot be used for the assignment of the anomeric configuration. This is based, in this case, on the CD data and the reduction of **5b** to the known amino derivative **6** (see below).

When silylated N^6-octanoyladenine (**11**) is replaced by silylated N^2-palmitoylguanine (**12**)[14] in the above reaction, a complex mixture is formed. The mixture of crude products was chromatographed over silica gel before deacylation because of the poor solubility of the free guanosine derivatives. As anticipated, besides the 9 and 7 isomers of fully acylated α- and β-3′-azido-2′,3′-dideoxyguanosine, the α anomer (**4a**) of the starting azido nucleoside (**4b**) was obtained (10%), which was deacylated to give 1-(3-azido-2,3-dideoxy-α-D-ribofuranosyl)thymine (**3a**). Each separated fraction of guanine nucleoside was treated with saturated methanolic ammonia to give the 9 isomers **7a** and **7b** as crystals (14 and 28%). The 7 isomers (**8a** and **8b**) were not separable and were obtained as an amorphous powder (total yield 13%). The assignment of the N-glycosidic linkage of these compounds as the N^7 derivatives is based on the characteristic UV spectra of such derivatives.

5b and **7b** were reduced by treatment with triphenylphosphine[17] followed by hydrolysis to afford the corresponding 3′-amino-2′,3′-dideoxy nucleosides **6** and **9** in high yield. The data obtained for **6** agree with those previously published[3] for

this compound. Treatment of **6** with acetic anhydride in methanol yielded the $N^{3'}$-acetyl derivative **10.**

For the guanosine derivatives the identification of **7b** and **9** as the β anomers relies on (a) CD data (see below) and (b) the splitting of the H-1′ protons of these compounds in the NMR. The signals for these compounds are triplets, while that of **7a** is a doublet of a doublet. As an empirical rule,[18] a "pseudotriplet" is observed for the anomeric proton of the β anomer and the corresponding peak for the α anomer appears as a doublet of a doublet. Although there are exceptions to this rule as, e.g., **5a** and **6,** it may be used judiciously particularly if the NMR spectra of both anomers are available for comparison[19] as in the case of **7a** and **7b.**

In the circular dichroism spectra of the nucleosides, the β anomers of the adenosine compounds, **5b, 6,** and **10,** have negative Cotton effects in the region of 260 nm, while that of the α anomer **5a** has a positive effect in agreement with the empirically determined rule.[20] The amplitude of the spectra near 260 nm are higher for the α anomer than for the β anomers. The spectrum of 3′-azido-2′,3′-dideoxyguanosine (**7b**) is markedly different from that of 2′-deoxyguanosine[21] and shows no Cotton effect in the region of 240–280 nm. However, the reduction product **9** possesses a CD spectrum almost superimposable with that of 2′-deoxyguanosine. In contrast, the CD spectrum of the α anomer of the 9-guanyl azidonucleoside (**7a**) has a positive Cotton effect in the region of 260 nm and resembles that published for 9-(2-deoxy-α-D-ribofuranosyl)-guanine.[21] The CD spectrum obtained for the β anomer of the thymine nucleoside derivative **3b** has a positive Cotton effect in the region of 270 nm in good agreement with that for thymidine,[22] while the α anomer (**3a**) has a negative Cotton effect in this region.

Further studies on this transglycosylation reaction were performed in an attempt to simplify it even more. In order to exclude the silylation reaction 3′-azido-3′-deoxy-5′-*O*-acetylthymidine (**4b**) and N^6-octanoyladenine (**11**) were treated with stannic chloride in acetonitrile. However, no adenine nucleoside was found even after 7 h. We then used bis(trimethylsilyl)acetamide (BSA) as silylating reagent which is converted during the reaction into acetamide whereas the other silylating reagents afford acids or bases which have to be carefully removed to obtain a good yield in the condensation reaction. Thus, 3′-azido-3′-deoxythymidine (**3b**) and 1.8 equiv of **11** were treated with a slight excess of BSA in acetonitrile. This solution was used without workup for the transglycosylation reaction catalyzed by trimethylsilyl trifluoromethanesulfonate to give **5a** (30%) and **5b** (28%) after hydrolysis. When stannic chloride was used as a catalyst in the reaction, adenine nucleosides were obtained in lower yield.

This improved method also made possible the use of the unprotected nucleoside as starting material because of protection of the hydroxyl group by the silylating reagent. The success of this reaction also indicated that BSA is generally useful to prepare silylated bases for condensation reactions in nucleoside syntheses using Friedel–Crafts catalysts. We could also demonstrate that purine ribonucleosides were obtainable from pyrimidine ribonucleoside derivatives under similar reaction conditions. When 3′-azido-3′-deoxythymidine (**3b**) was replaced by 2′,3′,5′-tri-*O*-acetyluridine (**13**) in the above reaction without benzoylation at the N^3 position,[23] the appearance of an adenosine derivative was observed. Following deacylation the mixture was separated on a Dowex 1 × 4 (OH^-) column according to the method of Dekker[24] to give adenosine in a yield of 56%. As expected from Baker's rule,[25] no α anomer was isolated in this case.

All the findings described in this section suggest that initial silylation at the pyrimidine base caused the lability of the glycosyl linkage and made the transglycosylation possible under mild conditions. It is noteworthy that the catalytic Lewis acid trimethylsilyl trifluoromethanesulfonate is itself a strong trimethylsilylating agent. It therefore seems likely that this synthetic method could be widely employed for the preparation of base analogues of a variety of nucleosides.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 137 spectrometer, UV spectra were recorded on a Shimadzu Model UV 200 spectrometer and Zeiss PMQ III spectrometer, NMR spectra were recorded on a Bruker HFX 60 spectrometer, and CD spectra were recorded on a Cary 61 spectrometer. $[\alpha]_D$ was measured with a Schmidt + Haensch Polartronic II polarimeter. Chemical shifts are reported in δ units, part per million downfield from internal tetramethylsilane or sodium 3-(trimethylsilyl)propionate-d_4.

Thin-layer chromatography was performed on Merck Kieselgel 60 F 254, 0.2 mm layer thickness, in solvent systems A [ethanol–chloroform, 8:92 (v/v)], B [methanol–chloroform, 2:8 (v/v)], C [ethyl acetate], or D [ethanol–1 M ammonium acetate, 3:1 (v/v)]. For column chromatography on silica gel Merck Kieselgel 60 (0.2–0.5 mm) was used.

Elemental analyses were performed by Mikroanalytisches Labor Beller, Göttingen.

3′-Azido-3′-deoxythymidine (3b). This compound was prepared from **2** essentially as described by Roesler[13] and Glinski et al.[5] Crystallization from acetone–benzene afforded needles (yield 66%): mp 106–108 °C (lit. 105–106 °C from diethyl ether, 118–120 °C from 2-propanol,[5] 118–120 °C from aqueous ethanol[13]); CD λ_{max} 271 ($[\theta]$ +5900), 240 ($[\theta]$ −2000), 216 nm ($[\theta]$ −700).

3′-Azido-3′-deoxy-5′-*O*-acetylthymidine (4b). 3′-Azido-3′-deoxythymidine (**3b**) (1.90 g, 7.1 mmol) in acetic anhydride (10 mL) was heated with stirring in an oil bath at 80 °C for 6 h. The solution was evaporated in vacuo and the residual acetic anhydride and acetic acid were removed by several additions and reevaporations with benzene–toluene [1:1 (v/v)]. The clear gum (2.23 g, 102%) gave a single spot, R_f 0.67 on TLC in system A. This material was used for further preparations without purification.

For analytical purposes a quantity of **4b** was applied to a silica gel column made up in chloroform and eluted with 2% ethanol–chloroform. The required fractions were evaporated to give the product as a clear gum which did not crystallize: UV λ_{max} (EtOH) 264.5 nm (ϵ 9600); IR (Nujol) 2110 cm^{-1} (N_3); NMR ($CDCl_3$) δ 1.94 (s, 3 H, CH_3-5), 2.15 (s, 3 H, MeCOO), 2.35–2.77 (m, 2 H, H-2′a,b), 3.93–4.28 (m, 2 H, H-3′ and H-4′), 4.34 (d, 2 H, $J_{4'5'}$ = 3.5 Hz, H-5′a,b), 6.11 (t, 1 H, $J_{1',2a} = J_{1',2b}$ = 6 Hz, H-1′), 7.23 (s, 1 H, H-6), 9.99 (bs, 1 H, NH).

Anal. Calcd for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.89; N, 22.64. Found: C, 46.75; H, 5.18; N, 22.40.

9-(3-Azido-2,3-dideoxy-α-D-ribofuranosyl)adenine and 9-(3-Azido-2,3-dideoxy-β-D-ribofuranosyl)adenine (5a and 5b). A. N^6-Octanoyladenine (**11**) (2.90 g, 11.1 mmol) was suspended in hexamethyldisilazane (18.0 mL) and chlorotrimethylsilane (0.6 mL). The mixture was heated to reflux temperature. Ammonium chloride deposited in the reflux condenser and after 2 h all solid material had dissolved. The solution was evaporated, traces of hexamethyldisilazane being removed by addition and reevaporation with toluene. To the remaining gum of silylated N^6-octanoyladenine was added 3′-azido-3′-deoxy-5′-*O*-acetylthymidine (**4b**) (1.90 g, 6.1 mmol) in acetonitrile (25 mL), followed by trimethylsilyl trifluoromethanesulfonate (1.4 mL, 8.2 mmol) with stirring. The mixture was heated to reflux temperature. After 2 h, TLC in system C indicated four spots (R_f 0.64, 0.61,[26] 0.47, and 0.34) which were UV active and were positive against 10% H_2SO_4 solution and two spots (R_f 0.18 and 0.13) which were only UV active and were due to thymine (R_f 0.18) and N^6-octanoyladenine (R_f 0.13). The fastest running spot was starting material **4b** and the third and fourth were the β and α anomers of 9-(3-azido-2,3-dideoxy-5-*O*-acetylribofuranosyl)-N^6-octanoyladenine, respectively.[27] The brown colored solution was poured into 250 mL of ethanol–concentrated NH_4OH (4:1) with stirring. After 1 day at room temperature deacylation was complete (TLC in system B). The solution was evaporated and the residue was dissolved in 90 mL of ethanol–1 M aqueous ammonia solution (1:2) and applied to a column of Dowex 1 × 4 (OH^-) (130 mL), which was washed with 600 mL of ethanol–water (1:2). The eluate which contained essentially the α and β anomers of the product (R_f 0.54 and 0.66 on TLC in system B) was evaporated, traces of water being removed by addition and reevaporation of 2-propanol. The residue was dissolved in 10 mL of 2% methanol–chloroform and applied to a silica gel (35 g) column made up in chloroform. The column was eluted with 250 mL each of 2, 4, 6, and 9% methanol–chloroform, collecting 20.8-mL fractions. Frac-

tions 12–25 contained material which gave a single spot (R_f 0.66 in system B). These fractions were combined and evaporated to dryness. 9-(3-Azido-2,3-dideoxy-β-D-ribofuranosyl)adenine (**5b**) was crystallized as plates from ethanol (460 mg, 27%): mp 189–191 °C; UV λ_{max} (H_2O) 259.5 (ε 15300) and (pH 1) 257 nm (ε 14900); CD λ_{max} (H_2O) 259 ([θ] −1900) and 212.5 nm ([θ] +4600); IR (KBr) 2120 cm^{-1} (N_3); NMR (Me_2SO-d_6) δ 2.48 (m, 1 H, $J_{1',2'b}$ = 6.5 Hz, $J_{2'a,2'b}$ = 13.5 Hz, $J_{2'b,3'}$ = 4.5 Hz, H-2′b), 3.01 (m, 1 H, $J_{1',2a}$ = $J_{2'a,3'}$ = 6.5 Hz, H-2′a), 3.62 (m, 2 H, H-5′a,b), 3.97 (q, 1 H, $J_{3',4'}$ = $J_{4',5'}$ = 4.5 Hz, H-4′), 4.64 (m, 1 H, H-3′), 5.35 (t, 1 H, OH), 6.32 (t, 1 H, H-1′), 7.32 (bs, 2 H, NH_2), 8.16, 8.35 (s, 2 H, H-2 and H-8).

Anal. Calcd for $C_{10}H_{12}N_8O_2$: C, 43.48; H, 4.38; N, 40.56. Found: C, 43.77; H, 4.48; N, 40.23.

Fractions 29–48 contained material which gave a single spot (R_f 0.54 on TLC in system B). These fractions were combined and evaporated to give 9-(3-azido-2,3-dideoxy-α-D-ribofuranosyl)adenine (**5a**) as fine needles (601 mg, 35%) from 2-propanol–*n*-heptane: mp 140–141 °C; UV λ_{max} (H_2O) 260 (ε 15600) and (pH 1) and 257.5 nm (ε 15200); CD λ_{max} (H_2O) 261 ([θ] +8200) and 219 nm ([θ] −2900); IR (KBr) 2100, 2130 cm^{-1} (N_3); NMR (Me_2SO-d_6) δ 2.67–2.96 (m, 2 H, H-2′a,b), 3.57 (m, 2 H, H-5′a,b), 4.18–4.46 (m, 2 H, H-3′ and H-4′), 5.08 (t, 1 H, OH), 6.36 (t, 1 H, $J_{1',2a}$ = $J_{1',2b}$ = 5.5 Hz, H-1′), 7.30 (bs, 2 H, NH_2), 8.17, 8.29 (s, 2 H, H-2 and H-8).

Anal. Calcd for $C_{10}H_{12}N_8O_2$: C, 43.48; H, 4.38; N, 40.56. Found: C, 43.68; H, 4.41; N, 40.69.

B. N^6-Octanoyladenine (**11**) (238 mg, 0.92 mmol) and 3′-azido-3′-deoxythymidine (**3b**) (134 mg, 0.50 mmol) were suspended in acetonitrile (3 mL) and BSA (0.75 mL, 3.0 mmol) was added. The mixture was heated at reflux temperature for 15 min. To the clear solution, trimethylsilyl trifluorometanesulfonate (0.11 mL, 0.65 mmol) was added. After heating at reflux temperature for 2 h, the reaction mixture was worked up as described in A to give **5a** (41 mg, 30%, mp 140–141 °C) and **5b** (39 mg, 28%, mp 189–191 °C) as crystals.

9-(3-Azido-2,3-dideoxy-α-D-ribofuranosyl)guanine (7a), 9-(3-Azido-2,3-dideoxy-β-D-ribofuranosyl)guanine (7b), and Their 7-α, 7-β Isomers 8a and 8b. N^2-Palmitoylguanine (**12**) (3.90 g, 10.0 mmol) was suspended in hexamethyldisilazane (27 mL) and chlorotrimethylsilane (1.5 mL). The mixture was heated to reflux temperature. After 1 and 4 h a 1.0-mL portion of chlorotrimethylsilane was added. After a further 5 h all solid material had dissolved. The reagents were removed from the mixture by a workup similar to that described in the silylation of octanoyladenine (**11**). To the gum of silylated N^2-palmitoylguanine was added 3′-azido-3′-deoxy-5′-*O*-acetylthymidine (**4b**) (1.82 g, 5.9 mmol) in acetonitrile (28 mL), followed by addition of trimethylsilyl trifluoromethanesulfonate (1.3 mL, 7.6 mmol) with stirring. The mixture was heated to reflux temperature. After 3 h the reaction mixture was cooled to room temperature and poured under stirring into a 1:1 (v/v) mixture of 300 mL of 10% aqueous $KHCO_3$–ethyl acetate. Two phases were separated and the water phase was extracted with ethyl acetate (2 × 100 mL). The combined ethyl acetate phase was filtered to remove turbidity and evaporated in vacuo. The residue was dissolved in chloroform and applied to a column of silica gel (300 g) made up in chloroform. The column was eluted with 800 mL of 1% ethanol–chloroform and 1000 mL each of 2, 3, 4, 5.5, and 7% ethanol–chloroform, collecting 27.5-mL fractions. Fractions 108–114 contained starting material **4b** (R_f 0.64 on TLC system C) and gave 144 mg (8%) of oil after evaporation. Fractions 151–171 contained a material which gave a single spot on TLC in system A (R_f 0.53). These fractions were evaporated and the residue was dissolved in saturated methanolic ammonia and left at room temperature for 1 day. The solution was evaporated and the residue was crystallized from ethanol–concentrated NH_4OH (10:1) to give 482 mg (28%) of 9-(3-azido-2,3-dideoxy-β-D-ribofuranosyl)-guanine (**7b**) as fine plates: darkening above 235 °C, no melting <310 °C; UV λ_{max} (H_2O) 253 (ε 13700), 270 (sh) (9700); (pH 1) 255.5 (ε 12300) and 275 (sh) (8500); and (pH 13) 265 nm (ε 11500); CD λ_{max} (H_2O) 212.5 nm ([θ] +13600); IR (KBr) 2120 cm^{-1} (N_3); NMR (Me_2SO-d_6) δ 2.40 (m, 1 H, $J_{1',2'b}$ = 6.5 Hz, $J_{2'b,3'}$ = 5 Hz, $J_{2'a,2'b}$ = 13 Hz, H-2′b), 2.83 (m, 1 H, $J_{1',2'a}$ = $J_{2'a,3'}$ = 6.5 Hz, H-2′a), 3.60 (m, 2 H, H-5′a,b), 3.90 (q, 1 H, $J_{3',4'}$ = $J_{4',5'}$ = 4.5 Hz, H-4′), 4.57 (m, 1 H, H-3′), 5.12 (t, 1 H, OH-5′), 6.08 (t, 1 H, H-1′), 6.49 (bs, 2 H, NH_2), 7.93 (s, 1 H, H-8), 10.63 (bs, 1 H, NH-1).

Anal. Cacld for $C_{10}H_{12}N_8O_3$: C, 41.10; H, 4.14; N, 38.34. Found: C, 41.23; H, 4.26; N, 38.12.

9-(3-Azido-2,3-dideoxy-α-D-ribofuranosyl)guanine (7a) was obtained after methanolic ammonia treatment of fractions 173–206, which contained a material giving a single spot in system A (R_f 0.47) and crystallized as fine plates from ethanol–concentrated NH_4OH (10:1) (243 mg, 14.3%): darkening above 233 °C, no melting <310 °C; UV λ_{max} (H_2O) 253 (ε 13700) and 271 (sh) (9700); (pH 1) 255 (ε 12200) and 275 (sh) (8300); and (pH 13) 266 nm (ε 11600); CD λ_{max} (H_2O) 275 ([θ] +3300), 259 nm (sh) ([θ] +2400), and 212 nm ([θ] −5900); IR (KBr) 2110 cm^{-1} (N_3); NMR (Me_2SO-d_6) δ 2.37–3.11 (m, 2 H, H-2′a,b), 3.54 (m, 2 H, H-5′a,b), 4.10–4.53 (m, 2 H, H-3′, H-4′), 5.06 (bs, 1 H, OH-5′), 6.13 (dd, 1 H, $J_{1',2'a}$ = 5 Hz, $J_{1',2'b}$ = 6.5 Hz, H-1′), 6.48 (bs, 2 H, NH_2), 7.86 (s, 1 H, H-8), 10.68 (bs, 1 H, NH-1).

Anal. Calcd for $C_{10}H_{12}N_8O_3$: C, 41.10; H, 4.14; N, 38.34. Found: C, 41.24; H, 4.16; N, 38.17.

Fractions 115–140 contained material which gave two spots (R_f 0.61 and 0.56) on TLC in system C. These compounds were separated by further silica gel (110 g) chromatography. The chloroform solution of the mixture was applied to a column made up in chloroform and was eluted with 600 mL each of 33, 50, and 67% ethyl acetate–chloroform, collecting 24.5 mL. Fractions 35–39 contained 1-(3-azido-2,3-dideoxy-5-*O*-acetyl-α-D-ribofuranosyl)thymine (**4a**) (R_f 0.61) and afforded after evaporation 179 mg (10%) of a clear gum: NMR ($DCDl_3$) δ 1.97 (s, 3 H, CH_3-5), 2.14 (s, 3 H, MeCOO). The structure of this compound was fully confirmed by deacylation. Fractions 55–73 contained the product which gave a R_f value of 0.56 on TLC in system C. The fractions were combined and evaporated and the residue was treated with saturated methanolic ammonia. Noncrystalline **8a** and **8b**[28] were obtained as a mixture from ethanol–concentrated NH_4OH (10:1) (226 mg, 13%): UV λ_{max} (H_2O) 285 (ε 7400), 241 (sh) (6400), and 215 (22000); (pH 1) 269 (sh) (ε 6600) and 249 (10000); and (pH 13) 281.5 nm (ε 6600); IR (KBr) 2100 cm^{-1} (N_3); NMR (Me_2SO-d_6) δ 8.13 (s, 0.55 H, H-8 of **8a**), 8.31 (s, 0.45 H, H-8 of **8b**).

Anal. Calcd for $C_{10}H_{12}N_8O_3$: C, 41.10; H, 4.14; N, 38.34. Found: C, 41.24; H, 4.28; N, 38.43.

1-(3-Azido-2,3-dideoxy-α-D-ribofuranosyl)thymine (3a). 1-(3-Azido-2,3-dideoxy-5-*O*-acetyl-α-D-ribofuranosyl)thymine (**4a**) (150 mg, 0.48 mmol) was dissolved in saturated methanolic ammonia (5 mL) and left at room temperature overnight. The solution was evaporated and the residue was treated with acetone–benzene (1:4) to give a hygroscopic powder (108 mg, 83%): UV λ_{max} (H_2O) 268 (ε 10200) and (pH 13) 267 nm (ε 7900); CD λ_{max} (H_2O) 271 ([θ] −9400), 240 ([θ] +2100), 221 nm ([θ] −4500); IR (KBr) 2110 cm^{-1} (N_3); NMR (CD_3OD) δ 1.90 (s, 3 H, CH_3-5), 2.17 (m, 1 H, $J_{1',2'b}$ = $J_{2'b,3'}$ = 4 Hz, $J_{2'a,2'b}$ = 14 Hz, H-2′b), 2.80 (m, 1 H, $J_{1',2'a}$ = 6.5 Hz, $J_{2'a,3'}$ = 7 Hz, H-2′a), 3.64 (d, 2 H, $J_{4',5'}$ = 3.5 Hz, H-5′a,b), 4.31 (m, 2 H, H-3′ and H-4′), 6.12 (dd, 1 H, H-1′), 7.53 (bs, 1 H, H-6).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.91; H, 4.90; N, 26.20. Found: C, 45.16; H, 5.13; N, 25.79.

9-(3-Amino-2,3-dideoxy-β-D-ribofuranosyl)adenine (6). 9-(3-Azido-2,3-dideoxy-β-D-ribofuranosyl)adenine (**5b**) (55 mg, 0.20 mmol) was dissolved in dioxane (6 mL) and triphenylphosphine (130 mg, 0.50 mmol) was added. The solution was stirred for 3 h at room temperature and water (3 mL) was added. After incubation for 1 day at 50 °C, the solution was evaporated and the residue was partitioned between benzene and water. The aqueous layer was separated, the benzene layer was washed with water, and the combined aqueous solutions were evaporated. The crude **6** was absorbed on Dowex 50 W × 8 (NH_4^+) (12 mL), washed with water, and eluted with 1 M aqueous ammonia. The eluates were concentrated, passed through Dowex 1 × 4 (OH^-) (12 mL), and evaporated to dryness. The residue was treated with boiling acetonitrile to afford colorless crystals of **6** (38 mg, 76% giving a single spot on TLC in system D, R_f 0.50, starting material, R_f 0.75): mp 188–190 °C (lit.[3] 184.5–6 °C); UV λ_{max} (H_2O) 259 (ε 14900) and (pH 1) 257 nm (ε 14700); $[\alpha]^{25}_D$ −25° (*c* 0.41 in H_2O) (lit.[3] $[\alpha]^{26}_D$ −22° (*c* 0.77 in H_2O); CD λ_{max} (H_2O) 265 ([θ] −800) and 225 nm ([θ] +1100); NMR (D_2O) δ 2.51–2.83 (m, 2 H, H-2′a,b), 3.7–4.1 (m, 4 H, H-3′, H-4′, H-5′a,b), 6.33 (dd, $J_{1',2'a}$ = 5 Hz, $J_{1',2'b}$ = 6.5 Hz, H-1′), 7.99, 8.22 (s, 2 H, H-2 and H-8).

Anal. Calcd for $C_{10}H_{14}N_6O_2$: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.15; H, 5.84; N, 33.65.

9-(3-Amino-2,3-dideoxy-β-D-ribofuranosyl)guanine (9). 9-(3-Azido-2,3-dideoxy-β-D-ribofuranosyl)guanine (**7b**) (117 mg, 0.40 mmol) was dissolved in dioxane (12 mL) and DMF (6 mL) and triphenylphosphine (262 mg, 1.0 mmol) was added. The solution was stirred 3 h at room temperature and H_2O (7 mL) was added. After incubation for 1 day at 50 °C, the solution was evaporated and the residue was partitioned between benzene and water. The aqueous layer was separated, the benzene layer was washed with water, and the combined aqueous solutions were evaporated to dryness. Recrystallization from water gave a microcrystalline material (76 mg, 71%) giving a single but streaking spot on TLC in system D, R_f 0.32 (starting material, R_f 0.48): darkening and sintering above 210 °C, no definite melting <300 °C; UV λ_{max} (H_2O) 270 (sh) (ε 9400) and 252.5 (13200); (pH 1) 275 (sh) (ε 8500) and 255.5 (12100); and (pH 13) 265 nm (ε 11300); CD λ_{max} (H_2O) 249 ([θ] −2200) and 212.5 nm ([θ] +7400); NMR (NaOD) δ 2.5 (m, 2 H, H-2′a,b), 3.77 (m, 4 H, H-3′, H-4′,

and H-5'a,b), 6.20 (t, $J_{1',2'a} = J_{1',2'b} = 6.5$ Hz, 1 H, H-1'), 7.88 (s, 1 H, H-8).

Anal. Calcd for $C_{10}H_{14}N_6O_3$: C, 45.11; H, 5.30; N, 31.56. Found: C, 45.24; H, 5.42; N, 31.19.

9-(3-Acetylamino-2,3-dideoxy-β-D-ribofuranosyl)adenine (10). 9-(3-Amino-2,3-dideoxy-β-D-ribofuranosyl)adenine (**6**) (35 mg, 0.14 mmol) was dissolved in methanol (10 mL) and treated with acetic anhydride (0.03 mL, 0.3 mmol) and triethylamine (0.05 mL). The solution was stirred over night at room temperature and evaporated. The residue was dissolved in a minimal amount of 9% methanol–chloroform and applied to a column of silica gel (15 g) made up in chloroform and was eluted with 200 mL each of 9 and 15% methanol–chloroform, collecting 17.4-mL fractions. Fractions 17–21 contained a material which gave a single spot (R_f 0.41 in system B). These fractions were combined and evaporated to dryness. 9-(3-Acetylamino-2,3-dideoxy-β-D-ribofuranosyl)adenine (**10**) was crystallized as fine plates from methanol (33 mg, 81%): mp 235–237 °C; UV λ_{max} (H_2O) 259.5 (ε 15300) and (pH 1) 257 nm (ε 14800); CD λ_{max} 265 ([θ] −900), 226 ([θ] +1100), and 217 nm ([θ] −600); NMR (Me_2SO-d_6) δ 1.89 (s, 3 H, MeCO), 2.2–2.9 (m, 2 H, H-2'a,b), 3.64 (m, 2 H, H-5'a,b), 3.93 (m, 1 H, H-4'), 4.50 (m, 1 H, H-3'), 5.17 (brs, 1 H, OH-5'), 6.39 (t, 1 H, $J_{1',2'a} = J_{1',2'b} = 6.5$ Hz, H-1'), 7.31 (brs, 2 H, NH_2), 8.16, 8.38 (s, 2 H, H-2 and H-8), 8.41 (d, 1 H, $J_{3',NH} = 7$ Hz, NH-3').

Anal. Calcd for $C_{12}H_{16}N_6O_3$: C, 49.31; H, 5.52; N, 28.75. Found: C, 49.15; H, 5.56; N, 28.66.

Synthesis of Adenosine from 2',3',5'-Tri-*O*-acetyluridine (13). N^6-Octanoyladenine (**11**) (238 mg, 0.91 mmol) and 2',3',5'-tri-*O*-acetyluridine (**13**) (185 mg, 0.50 mmol) were suspended in acetonitrile (3 mL) and BSA (0.5 mL, 2.0 mmol) was added. The mixture was heated at reflux temperature for 15 min. Trimethylsilyl trifluoromethanesulfonate (0.11 mL, 0.65 mmol) was added to the clear solution. After heating at reflux temperature for 4 h, the reaction mixture was poured in 25 mL of ethanol–concentrated NH_4OH (4:1) with stirring. After 1 day at room temperature, the solution was evaporated and the residue was dissolved in 40 mL of 60% methanol–water and applied to a column of Dowex 1 × 4 (OH^-) (20 mL) which was eluted with 60% methanol–water (300 mL) and 75% methanol–water (150 mL). The main fractions containing adenosine were combined and evaporated to dryness. The residue was recrystallized from water (75 mg, 56%), mp 236–238 °C. This compound was found to be identical in all respects with an authentic sample.

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Registry No.—**2,** 15981-92-7; **3a,** 66323-40-8; **3b,** 30516-87-1; **4a,** 66323-41-9; **4b,** 66323-42-0; **5a,** 66323-43-1; **5b,** 66323-44-2; **6,** 7403-25-0; **7a,** 66323-45-3; **7b,** 66323-46-4; **8a,** 66323-47-5; **8b,** 66323-48-6; **9,** 66323-49-7; **10,** 66323-50-0; **11,** 52854-12-3; **12,** 21047-87-0; **13,** 4105-38-8; adenosine, 58-61-7.

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(26) This spot was probably the α anomer (**4a**) of the starting material (**4b**) which was isolated in the synthesis of the guanine derivatives.
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(28) All attempts to separate **8a** and **8b** were unsuccessful.

Aminoglycoside Antibiotics. 3.[1] Synthesis of a Furanosyl Isomer of Kanamycin B from a Protected 3-Amino-3-deoxyglucofuranosyl Chloride

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A new crystalline glycosylating agent, comprised of a mixture of α- and β-3-acetamido-2,5,6-tri-*O*-benzyl-3-deoxy-D-glucofuranosyl chlorides (**7a,b**), was synthesized. It was used to prepare, via a Koenigs–Knorr type condensation, the 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-6-*O*-(3-amino-3-deoxy-α- and β-D-glucofuranosyl)-D-streptamines, **1** and **2,** isomers of the antibiotic kanamycin B. The structure of α-glycoside **1** was confirmed by its ^{13}C NMR spectrum.

The aminoglycoside antibiotics have provided a versatile backbone for the organic chemist to construct analogues with improved antimicrobial properties.[2] While studies have concentrated on modifications of the 2-deoxystreptamine or on the aminosugar appended to its O-4 position, fewer analogues have appeared with modified sugars on the O-5 or O-6 positions. Usually in nature, there is a furanoside at the O-5 position or a pyranoside at the O-6 position, with the only reported O-6 furanosides being the relatively inactive 6-*O*-(β-D-ribofuranosyl)paromamine, synthesized by Hanessian et al.[3a] and the corresponding neamine derivative synthesized by Suami et al.[3b] As part of our program aimed at evaluating the antibacterial properties of pseudodisaccharides and pseudotrisaccharides derived from neamine, the α- and β-(*cis*

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