13.47; S, 10.28; Cl. 11.37. Found for **18:** C, 36.91; H, 5.30; N, 13.32; S, 10.67; Cl, 11.37. Found for **19:** C, 36.96; H, 5.33; N, 13.43; S, 10.63, Cl, 11.58.

The ^{1}H NMR spectra (Me_2SO-d_6) of the analytical samples showed that both of them contained a small amount of methanol.

5-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)cytosine (20 and 21). A mixture of **9** (16.6 g, 0.033 mol) and urea (6.0 g, 0.1 mol) in ethanolic sodium ethoxide (200 ml, 0.7 N) was refluxed for 24 h. The mixture was concentrated to ~100 ml in vacuo and, after cooling, the concentrated solution was neutralized with 1 N HCl to give a white precipitate (7.2 g, 41%). One crystallization of the precipitate from methanol afforded crystals rich in **21**. Two more recrystallizations of the crystals gave the pure α isomer **21** (2.2 g, 12%) as colorless needles, mp 234–235 °C.

The mother liquors of crystallization were combined and evaporated to dryness. The residue was recrystallized from methanol. The pure β isomer **20** (1.8 g, 10%) was obtained as needles, mp 222–224 °C.

Anal. Calcd for $C_{31}H_{31}N_3O_5$: C, 70.86; H, 5.90; N, 8.00. Found for **20:** C, 70.67; H, 5.93; N, 7.95. Found for **21:** C, 71.03; H, 6.01; N, 8.17.

Registry No.—**5** β isomer, 56703-40-3; **5** α isomer, 56779-60-3; **8** β isomer, 61008-80-8; **8** α isomer, 61008-81-9; guanidine hydrochloride, 50-01-1; thiourea, 62-56-6; urea, 57-13-6.

References and Notes

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(8) Though no systematic studies have been done to assure the configurational assignment at glycosyl center of *C*-glycosyl derivatives, an extensive literature survey with more than a score of isomeric pairs of *C*-glycosyl derivatives including *C*-nucleosides showed that H-1′ signal always appears at lower field when it is cis than trans to H-2′.
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(11) Compound **5** has been prepared as previously described[6] but was not purified by chromatography. The by-product triphenylphosphine oxide was removed by precipitation three times from ether.

A General Method for the Synthesis of 2′-Azido-2′-deoxy- and 2′-Amino-2′-deoxyribofuranosyl Purines

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A new general method for the preparation of 2′-azido-2′-deoxy- and 2′-amino-2′-deoxyribofuranosyl purines is described. Treatment of 2′-azido-2′-deoxyuridine (**3**) with hydrazine hydrate and subsequent treatment of the products with benzaldehyde in boiling water affords 2-azido-2-deoxyribose (**4**), which is derivatized by standard methods to the 1,3,5-triacetate (**7**). Condensation of **7** with N^6-octanoyladenine and subsequent deacylation affords a mixture of α and β anomers of 2′-azido-2′-deoxyadenosine (**8a** and **8b**) which is separable on Dowex 1 × 2 (OH^-). Replacement of N^6-octanoyladenine by N^2-palmitoylguanine affords a mixture of products from which 7- and 9-(2-azido-2-deoxy-β-D-ribofuranosyl)guanine (**11b** and **10b**) are isolable by fractional crystallisation. The α anomers (**11a** and **10a**) also appear to be formed, but have not yet been isolated. Reduction of **8a, 8b, 10b,** and **11b** with triphenylphosphine and ammonia affords the corresponding 2′-amino-2′-deoxy nucleosides **9a, 9b, 2b,** and **13b** in good yield.

Analogues of the common ribonucleosides containing an azido or amino group at the 2′ position have valuable potential for investigation of chemical or biochemical problems in which the 2′ moiety is involved. Since the azido group is readily reducible to the amino group, the synthesis of 2′-azido-2′-deoxy nucleosides constitutes a primary aim.

2′-Azido-2′-deoxyuridine[1] and -cytidine[2] have already been described along with their nucleotides and polynucleotides derived by phosphorylation and enzymatic polymerization.[2-4] These compounds show promise for studying the control of synthesis of DNA,[5] among other properties.[6] Reduction of the azido group affords the corresponding 2′-amino-2′-deoxy compounds[1,2,38] in which further derivatization at the amino group allows a possible source of antibiotics[7] and affinity labels.[8]

The synthesis of the corresponding purine nucleosides has been fraught with difficulty. 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)adenine was recently obtained in low yield[9] by reaction of 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine with azide ion, and subsequent inversion of the configuration at C-3′. Since, however, the ring opening favors attack at the 3′ position over the 2′ position in a ratio of 10:1, this is not a promising synthetic method for the 2′-azido nucleosides. 9-(2-Amino-2-deoxy-β-D-ribofuranosyl)-6-dimethylaminopurine was obtained by Baker et al.,[10] following a 14-step synthesis from an aminated D-altrose derivative as "a noncrystalline substance of somewhat doubtful purity". The α and β anomers of 2′-amino-2′-deoxyadenosine have been obtained via a lengthy synthesis starting from 2-glucosamine.[11] The corresponding guanine nucleosides have not been reported, to our knowledge, although it has been suggested that a strain of Aerobacter produces a 2-amino-2-deoxypentofuranosyl guanine nucleoside which may be 2′-amino-2′-deoxyguanosine.[12]

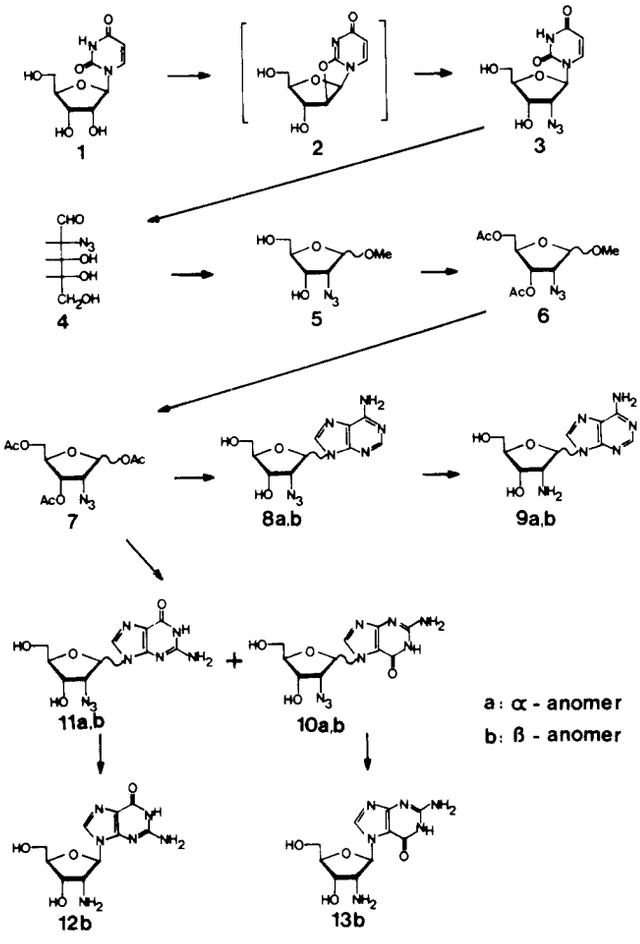
Although 2′-chloro-2′-deoxyuridine and -cytidine tend to form cyclonucleosides with loss of hydrogen chloride under hydrolytic conditions,[13] experience with the corresponding 2′-azido-2′-deoxy nucleosides indicates that these are comparatively stable.[14] Since 2′-azido-2′-deoxyuridine is relatively easily obtained from uridine,[1] we were led to investigate the possibility of detaching the sugar moiety from this nucleoside, and using it to form a derivative suitable for purine nucleoside

synthesis by one of the standard methods. We here describe the success of this approach in affording not only the adenosine nucleosides in better yield than previously obtainable, but also the guanosine nucleosides.

Results and Discussion

The synthetic method is indicated in Scheme I. The method of Verheyden et al.[1] was adapted to afford 2′-azido-2′-deoxyuridine in 50% yield in a "one-pot" reaction. Uridine (**1**) was treated with diphenyl carbonate in hexamethylphosphoramide at 140 °C with a little sodium bicarbonate as catalyst, and, on cessation of effervescence, lithium azide was added. The phenol liberated during O^2,2′-cyclouridine (**2**) formation serves as a proton source, aiding ring opening to give the desired product (**3**), and addition of benzoic acid as catalyst[1] was found unnecessary. The workup seemed cleaner than that experienced when benzoic acid was added, and **3** was obtained as a yellow gum which crystallized spontaneously at room temperature. A sample which had been decolorized by passage over Dowex 1 (OH^-) and allowed to crystallize melted over a range of 139–147 °C, with incipient decomposition. Since the preparation of the compound is also carried out in this temperature range, temperature and yield seem likely to be closely interdependent. It is probably significant that uracil was found to be a major by-product of this reaction.

Scheme I



Upon stirring **3** with 15% hydrazine hydrate at 65 °C for 1 h,[15] the ultraviolet absorption of the starting material disappeared. Evaporation of the solution in vacuo gave a pale orange gum, which was dissolved in water and heated with excess benzaldehyde at 100 °C. Upon cooling, benzaldehyde azine[16] and other insoluble condensation products crystallized out, leaving an aqueous solution containing 2-azido-2-deoxy-D-ribose (**4**), which was isolated as a pale yellow gum by chromatography on silica gel. The sugar was chromatographically homogeneous, as indicated by aniline phosphate spray,[17] and showed a strong azide stretching frequency in the infrared spectrum (all azido compounds reported here showed a strong infrared absorption in the range 2100–2140 cm^{-1}). A film of the gum showed no appreciable carbonyl stretch, however, indicating absence of the open-chain form.

The NMR spectrum of **4** in D_2O showed a strong resemblance to that reported for D-ribose by Lemieux and Stevens,[18] showing four doublets of total intensity one at δ 5.53, 5.28, 4.97, and 4.96, of relative intensity ca. 1:1:2:6, and with splittings of 4.0, 2.5, 7.5, and 2.0 Hz, respectively. We tentatively assign the signals at δ 4.97 and 4.96 to $H_1{}^{\beta}$ and $H_1{}^{\alpha}$ of the pyranose form and those at δ 5.28 and 5.53 to $H_1{}^{\beta}$ and $H_1{}^{\alpha}$ of the furanose form, respectively. Double-resonance studies support this assignment and are entirely consistent with the results of Lemieux and Stevens.[18] The total integral for these signals was one-fifth of that for the remaining protons in the molecule.

Conversion of **4** to its 1-*O*-methyl glycoside (**5**) took place rather slowly under standard conditions,[19] to afford a mixture of the α and β anomers in 67% yield after chromatography on silica gel, which also allowed unconsumed starting material to be reisolated. The anomers ran with the same R_f value on TLC, and were detected by spraying with aniline phosphate and incubating for an extended period at 100 °C. NMR in Me_2SO showed $H_1{}^{\alpha}$ at δ 4.97, $J^{\alpha}_{1,2}$ = 4.5 Hz, and $H_1{}^{\beta}$ as a singlet at δ 4.69, in a ratio 15:85, the total intensity corresponding to one proton. The methoxyl signal was also split giving sharp singlets at δ 3.31 and 3.24, total intensity three. These figures are similar to those given for methyl D-ribofuranoside in the same solvent.[20] The occurrence of a triplet at δ 4.68, strongly coupled to $H_{5a,b}$ at δ 3.48 and exchanging with deuteriomethanol, indicates that a primary hydroxyl group is present at C-5 and thus that the ribofuranose form is present.

Conversion of **5** to the diacetate **6** was performed using pyridine and acetic anhydride, to give a single product as indicated by TLC, consisting of the anomer mixture in the same proportions as **5**.

Treatment of **6** with concentrated sulfuric acid in acetic acid–acetic anhydride[19] afforded the triacetate **7** in high yield. It was found preferable to make the conversion **5** → **7** in two stages, as described, rather than in one direct stage,[19] since the direct method afforded a number of products as indicated by TLC, whereas the conversion as described gave only **7** as an anomeric mixture (α:β, 40:60) in which replacement of the methoxyl group in **6** by acetate was shown by NMR to have proceeded quantitatively.

No attempt was made to separate the α and β anomers of **5, 6,** and **7,** although the anomers of **5** should be separable by chromatography on Dowex-1 (OH^-).[21] The reason for this omission is that the anomer ratio changes during the conversion **6** → **7** rendering an earlier separation preparatively superfluous, and also indicating that the replacement of methoxyl by acetate in this system affords an equilibrium mixture of anomers as expected, rather than one generated by simple S_N2 displacement.

Decoupling experiments indicated differences in the chemical shifts of the H-2 in the α and β anomers of **5, 6,** and **7.** Some variation in the chemical shift of H-2 in α and β anomers in, for instance, the methyl *O*-methyl-D-xylofuranosides has been noted previously.[22]

7 was condensed with N^6-octanoyladenine in 1,2-dichloroethane using stannic chloride as catalyst, as described by Furukawa and Honjo.[23] Initially the quantities used were those described as optimum by these authors, namely sugar

derivative:acylated base:stannic chloride in the ratio 4:5:5, but it was subsequently found that a small further addition of stannic chloride (0.25 mol/mol **7**) was required to drive the reaction to completion. Following deacylation with sodium methoxide in methanol, the mixture obtained was separated on a Dowex 1 × 4 (OH^-) column according to the method of Dekker,[24] to give the α and β anomers of 2′-azido-2′-deoxyadenosine (**8a** and **8b**) in a ratio of 1:2, and a total yield of 60–65%. No other nucleoside products were obtained. **8b** was not affected by sodium methoxide under the conditions employed during deacylation. **8b** was found to be identical in all respects with an authentic sample[9] kindly supplied by Drs. H. Wiedner and R. Mengel, University of Konstanz, Germany.

Since no acylated group is present at the 2 position of the sugar derivative, Baker's rule[25] does not apply in this instance, and a mixture of the α and β anomers of the resultant nucleosides is to be expected. However, the proportions obtained were found to be critically dependent on the quantity of stannic chloride added to the reaction, and the time at reflux temperature. Thus, in another run in which no further stannic chloride was added to drive the reaction to completion, the overall yield was only 32%, but the ratio of **8a:8b** was 1:6.

When N^6-octanoyladenosine is replaced by N^2-palmitoylguanine[23,26] in the above condensation, a complex mixture is formed, condensation taking place rapidly compared with the adenine reaction. This is noteworthy, since Furukawa and Honjo,[23] using N^2-acetylguanine and tetraacetyl-β-D-ribofuranose, obtained no product under the same conditions, indicating that the solubility of the guanine derivative is the critical factor. Before deacylation, the mixture of crude products was passed over silica gel to separate unreacted N^2-palmitoylguanine, since this simplifies product separation. Deacylation was carried out with methoxide, and the products were applied to Dowex 1 × 4 (OH^-) as described above and eluted with 0.4 M triethylammonium bicarbonate solution. As anticipated, the products were a mixture of the 9 and 7 isomers of α- and β-2′-azido-2′-deoxyguanosine (**10a, 10b, 11a, 11b**). By knowing the ultraviolet characteristics of the 7 and 9 isomers of the β anomers (**10b** and **11b**), and assuming that those of the corresponding α anomers are identical, a total yield, based on **7**, of 56.5% was calculated. Fractional crystallization allowed the isolation of **10b** and **11b** (21 and 15%, respectively, based on **7**). Examination of the mother liquors by NMR showed the presence of four H-8 resonances and four H-1′ resonances, of which two are practically coincident. Two of the H-8 resonances and the H-1′ resonances could be assigned to **10b** and **11b** which had not crystallized out. The other resonances, tentatively assumed to be those of **10a** and **11a**, were "paired" by comparing their integrated intensities. The identification of **10b** and **11b** as the β anomers relies on (a) these having the two highest field resonances of the four H-1′ signals (as a general rule,[27] the proton at H-1′ trans to H-2′ appears at higher field); (b) analogy with the signals of the corresponding ribo compounds, reported by Imai et al.;[28] (c) CD data (see below).

Integration of the NMR signals allowed the distribution of products from this condensation to be determined as **10a:10b:11a:11b** = 7:51:12:30, giving a ratio of 58:42 for the distribution of 9-guanyl to 7-guanyl isomers, in good agreement with a value of 55:45 calculated from UV data and employing extinction coefficients determined for pure **10b** and **11b.**

Although very high yields of pyrimidine nucleosides have been obtained[29] on condensation of silylated pyrimidines with sugar acetates using Friedel–Crafts catalysts in 1,2-dichloroethane, the yields reported when silylated purines were employed are more modest,[30] and do not appear significantly better than those reported here. For this reason, we have not investigated the reaction using silylated bases. Reactions using aluminum chloride[15,26] in chlorobenzene or xylene afforded poor yields, with the α anomer predominating, and numerous side products.

8a, 8b, 10b, and **11b** were reduced on treatment with triphenylphosphine[31] in a mixture of equal volumes of dry pyridine and ammonia-saturated methanol, to afford the corresponding 2′-amino-2′-deoxy nucleosides **9a, 9b, 12b,** and **13b** in high yield. The data obtained for **9a** and **9b** concur with those previously published[11] for these compounds. Much difficulty was experienced in trying to obtain an analytical sample of **12b,** and despite apparent chromatographic and electrophoretic homogeneity in all systems tested and good purity as evidenced by the NMR spectrum, the elemental analysis repeatedly gave a high value for carbon, and the extinction coefficient was slightly low. Attempted recrystallization from aqueous solvents repeatedly gave rise to gels. Compound **13b** initially formed a gel, but crystallized satisfactorily from water, after long storage.

No formation of complexes in borate buffer at pH 10 could be detected in the 2′-azido nucleosides here reported, thus indicating that all contain the furanose, rather than the pyranose, form of the ribose. Small mobilities shown by the guanosine derivatives **10b** and **11b** are presumably due to the acidic pK_a of guanine, which lies at 9.6. All the 2′-amino nucleosides showed small mobilities in this buffer, which were, however, markedly less than those for the corresponding ribonucleosides. As expected, all the 2′-amino nucleosides had significantly higher mobilities at pH 3.5 than their ribofuranosyl counterparts, the differences observed between the adenine and guanine compounds again being consistent with the pK_a's of the bases.

In the circular dichroism spectra of the nucleosides, the β anomers of the adenosine compounds **8b** and **9b** have negative Cotton effects in the region of 260 nm, while those of the α anomers **8a** and **9a** have positive effects in agreement with the empirically determined rule.[32] The amplitudes of the spectra near 260 nm are higher for the α anomers than for the β anomers.

The 9-guanyl nucleosides **10b** and **12b** present marked contrasts in their CD spectra, and since the interpretation of the spectra of guanosine compounds is complicated, our conclusions are tentative. The spectrum of 2′-azido-2′-deoxyguanosine (**10b**) is markedly different from that of guanosine and resembles more that of 2′,3′,5′-triacetylguanosine or 2′,3′-*O*-isopropylideneguanosine, or certain 8-substituted guanosine derivatives.[33,34] However, the reduction product, 2′-amino-2′-deoxyguanosine (**12b**), possesses a CD spectrum almost superimposable with that of guanosine. The CD spectrum of **11b** strongly resembles that published for 7-β-D-ribofuranosylguanine,[33] and we take this similarity to indicate β configuration. However, the reduction product, **13b,** exhibits a similar spectrum above 250 nm, but sign inversion in the band at 220 nm.

The synthetic method described here affords products **8a, 8b, 9a,** and **9b** in yields of 3.2, 7.0, 2.6, and 6.8%, respectively, based on uridine as starting material, and represents a notable improvement, both in yield and synthetic length, over the syntheses previously described for **8b, 9a,** and **9b.** All chemicals required are either readily available or, in the case of the acylated bases, can be simply synthesized. The synthesis thus provides a general method for 2′-azido- and 2′-amino-2′-deoxyribosyl nucleosides, since any base which can be employed in standard nucleoside condensations could be used. Furthermore, it seems likely that such a synthetic method could be employed for other 2′ substituents where the uridine derivative is simply synthesized, provided that the 2′ substituent is reasonably stable to acid and base hydrolysis.

The azido nucleosides described here are convenient intermediates for the preparation of the corresponding nu-

cleotides. Thus, **8b** may be phosphorylated chemically in high yield,[14] and converted to the 5′-diphosphate or -triphosphate by standard methods.[35] Treatment with triphenylphosphine and ammonia then affords the 5′-diphosphate or -triphosphate of **9b** in high yield, thus circumventing any complications arising from reaction of a 2′-amino group with phosphorylating or condensing agents.

The 5′-triphosphate of **9b** has previously been obtained by enzymatic phosphorylation of the nucleoside,[36] a procedure in which great care must be taken to avoid ribonucleotides contaminating the products. The 5′-diphosphates of **8b** and **9b** are substrates for polynucleotide phosphorylase from *Micrococcus luteus* in the presence of Mn^{2+} thus forming poly(2′-azido-2′-deoxyadenylic acid) and poly(2′-amino-2′-deoxyadenylic acid). (Results not shown.) The corresponding homopolymers containing uracil and cytosine as base moieties have been described previously.[2,3]

2′-Azido and 2′-amino nucleosides and nucleotides have recently found useful application as enzyme inhibitors[37] and affinity labels.[8] Moreover, a 2′-amino group should afford a valuable attachment point for immobilizing nucleotides for use in affinity chromatography. We are currently investigating some of these applications.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 137 spectrometer, UV spectra on a Shimadzu Model UV 200 and Zeiss PMQ II spectrometer, NMR spectra on a Bruker Physik HFX 60 spectrometer, and CD spectra on a Cary 61 spectrometer. Chemical shifts are reported in δ units, parts per million downfield from internal tetramethylsilane.

Thin layer chromatography was performed on Merck Kieselgel 60 F 254 0.2 mm layer thickness, in solvent systems A [methanol–chloroform, 2:8 (v/v)] or B [ethanol–1 M ammonium acetate, 7:3 (v/v)] or as specified. Preparative layer chromatography was performed on 60 F 254 plates of 2 mm thickness from the same supplier. For column chromatography on silica gel, Merck Kieselgel 60 (0.063–0.2 mm) was used. Dowex 1 × 2 and 1 × 4 were obtained in their chloride forms from Serva Feinbiochemica, treated with a large excess of 2 N aqueous hydroxide, and washed to neutrality.

Electrophoresis was performed in the buffers as stated, using 30 V/cm for 90 min.

Paper chromatography was carried out using Schleicher and Schüll 2043 b (washed) paper, in solvent system B or as stated.

Elemental analyses were performed by Mikroanalytisches Labor Beller, Göttingen.

N^6-Octanoyladenine and **N^2-palmitoylguanine** were prepared essentially as described by Furukawa and Honjo.[23]

2′-Azido-2′-deoxyuridine (3) was prepared by a modification of the procedure given by Verheyden et al.[1] Uridine (10 g, 41 mmol) and diphenyl carbonate (12 g, 56 mmol) in hexamethylphosphoramide (80 ml) were heated on an oil bath at 140 °C with stirring, and sodium bicarbonate (0.24 g, 2.8 mmol) added. When effervescence had ceased (ca. 30 min), lithium azide (8 g, 163 mmol) was added to the solution which was heated for a further 2 h, after which TLC in system A showed that the intermediate O^2,2′-cyclouridine had almost disappeared, and the required compound was the major product. Workup was performed as described in ref 1. The product was obtained as a yellow gum, homogeneous on TLC in system A and acetone–ethyl acetate, 1:1 (v/v), yield 5.49 g (20.5 mmol, 50%). This material was used for further preparations without further purification. On standing at room temperature, the gum crystallized spontaneously. No solvent giving satisfactory recrystallization has yet been found.

A quantity of 2′-azido-2′-deoxyuridine was applied to Dowex 1 × 4 (OH^-),[24] and the column washed with water, 50% methanol, and finally with 0.1 M triethylammonium bicarbonate, which eluted the required material. Evaporation gave the product as a stiff, clear gum, crystallizing on scraping to give white needles, mp 139–147 °C with darkening and decomposition which became very rapid above 180 °C. Anal. Calcd for $C_9H_{11}N_5O_5$: C, 40.15; H, 4.12; N, 26.02. Found: C, 40.51; H, 3.80; N, 26.15. IR (film of gum) 2120 cm^{-1}. NMR (Me_2SO-d_6) identical with that reported in ref 1.

2-Azido-2-deoxyribose (4). 2′-Azido-2′-deoxyuridine (2.54 g, 9.5 mmol) was dissolved in 15% hydrazine hydrate solution (250 ml, 0.77 mol hydrazine) and heated with stirring on an oil bath at 65 °C for 1 h. At the end of this time TLC in system A indicated complete disappearance of starting material. The solution was evaporated in vacuo to give an orange gum, which was dissolved in water (100 ml). Benzaldehyde (10 ml, 100 mmol) was added, and the mixture heated for 8 min on a boiling water bath, with constant agitation. The solution was cooled rapidly to below room temperature and filtered to remove a sticky precipitate, mainly benzaldehyde azine. The filtrate was extracted with ether (3 × 100 ml) and the aqueous solution evaporated; the gum dissolved in the minimum quantity of methanol and applied to a silica gel column (2.3 × 32 cm) which had been prepared in chloroform. The column was eluted with 100-ml fractions of chloroform (200 ml), 5% methanol–chloroform (700 ml), and 10% methanol–chloroform (600 ml). The required product was eluted in fractions 9–13, and was detected by examining a sample of each fraction by TLC in system A, spraying the plates with aniline phosphate solution[17] (1-butanol, 17 ml; H_2O, 6 ml; aniline, 0.36 ml; 85% phosphoric acid, 0.28 ml) and heating in a drying oven at 110 °C for 10 min. 2-Azido-2-deoxyribose is revealed as a red-brown spot, R_f 0.5. The product-containing fractions were combined and evaporated to give a clear gum (1.05 g, 6 mmol, 64%) which did not crystallize. Anal. Calcd for $C_5H_9N_3O_4$: C, 34.29; H, 5.18; N, 23.99. Found: C, 34.45; H, 5.07; N, 23.60. IR (liquid film) 3270 (–OH), 2100 cm^{-1} ($-N_3$).

NMR (D_2O) δ 3.37–4.50 (5 H, complex pattern of H-2, H-3, H-4, and $H_{a,b}$-5 of furanose and pyranose forms (see discussion), 4.96 (0.2 H, $J_{1,2}$ = 2 Hz), 4.97 (0.6 H, $J_{1,2}$ = 7.5 Hz), 5.28 (0.1 H, $J_{1,2}$ = 2.5 Hz), 5.53 (0.1 H, $J_{1,2}$ = 4 Hz) (H-1 α and β anomers of pyranose and β and α anomers of furanose, respectively).

Methyl 2-Azido-2-deoxyriboside (5). 2-Azido-2-deoxyribose (1.02 g, 5.8 mmol) was dissolved in dry methanol (15 ml) and cooled to 0 °C. Concentrated sulfuric acid (0.075 ml) was added, and the reaction mixture stored in a refrigerator at 3–5 °C for 5 days. The course of reaction was followed by TLC in system A. Product is revealed as a gray-brown spot, R_f 0.7, by spraying with aniline phosphate solution (see above) and incubating at 110 °C for a prolonged period, the spot only reaching full intensity after incubation overnight. After 5 days pyridine (2 ml) was added, and the mixture evaporated to dryness, dissolved in the minimum quantity of methanol, and applied to a silica gel column (1.7 × 24 cm) made up in chloroform. The column was eluted with chloroform (300 ml) and 3% methanol–chloroform (700 ml), collecting 50-ml fractions. Fractions 10–17 contained material which gave a single spot on TLC as detailed above. The product-containing fractions were combined and evaporated to give a clear gum which did not crystallize (0.74 g, 3.9 mmol, 67%). Anal. Calcd for $C_6H_{11}N_3O_4$: C, 38.09; H, 5.86; N, 22.21. Found: C, 38.11; H, 6.01; N, 22.24. IR (liquid film) 3300 (–OH), 2910 ($-CH_3$), 2110 cm^{-1} ($-N_3$). NMR (Me_2SO-d_6) δ 3.24; 3.31 (3 H, two singlets, methoxy signals of β and α anomers, respectively), 3.33–4.0 (4 H, complex multiplet, $H_{a,b}$-5 centered at δ 3.48, H-4, H-2), 4.21 (1 H, q, H-3, $J_{2,3}$ = $J_{3,4}$ = 5.5 Hz), 4.68 (1 H, t, OH-5), 4.69 (0.85 H, s, H-1 of β anomer), 4.97 (0.15 H, d, $J_{1,2}$ = 4.5 Hz, H-1 of α anomer), 5.60 (1 H, d, OH-3).

Methyl 3,5-Di-*O*-acetyl-2-azido-2-deoxyriboside (6). Methyl 2-azido-2-deoxyriboside (0.666 g, 3.5 mmol) was dissolved in pyridine (10 ml) and acetic anhydride (4 ml, 42 mmol) added. After standing overnight at room temperature the solvents were evaporated, and the residue dissolved in chloroform (80 ml) and washed with water (3 × 20 ml). The chloroform phase was separated, dried with anhydrous magnesium sulfate, filtered, and evaporated to give the product as a clear gum (0.893 g, 3.3 mmol, 93%) giving a single spot, R_f 0.91, on TLC in ethyl acetate–diethyl ether (1:1 v/v) and development with aniline phosphate spray. Anal. Calcd for $C_{10}H_{15}N_3O_6$: C, 43.96; H, 5.53; N, 15.38. Found: C, 44.11; H, 5.38; N, 15.36. IR (liquid film) 2890 ($-CH_3$), 2100 ($-N_3$), 1740 cm^{-1} (carbonyl). NMR ($CDCl_3$) δ 2.06 (3 H, s), 2.15 (3 H, s), 3.35, 3.47 (3 H, two singlets, methoxy signals of β and α anomers respectively), 3.57–4.5 (4 H, complex pattern, H-4 centered at δ 4.25, H-2, $H_{a,b}$-5), 4.83 (0.85 H, s, H-1 of β anomer), 5.08 (0.15 H, d, $J_{1,2}$ = 4.5 Hz, H-1 of α anomer), 5.26 (1 H, t, H-3, $J_{2,3}$ = $J_{3,4}$ = 5.5 Hz).

1,3,5-Tri-*O*-acetyl-2-azido-2-deoxyribose (7). Methyl 3,5-di-*O*-acetyl-2-azido-2-deoxyriboside (0.87 g, 3.2 mmol) was dissolved in glacial acetic acid (4.5 ml) and acetic anhydride (1.2 ml, 12.7 mmol) and cooled to 0 °C. Concentrated sulfuric acid (0.23 ml) was added slowly with vigorous stirring. When addition was complete the solution was allowed to warm to room temperature, and left for 22 h, during which time a dark red color developed. Ice (6.25 g) was then added to the mixture, which was extracted with chloroform (4 × 13 ml). The combined chloroform phases were washed with saturated sodium bicarbonate solution (2 × 25 ml) and water (25 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to give the product as a clear gum (0.889 g, 2.95 mmol, 93%) having similar R_f (0.89) to the starting material on TLC in ethyl acetate–diethyl ether (1:1 v/v) but in which NMR revealed complete loss of the methoxy

signal. Anal. Calcd for $C_{11}H_{15}N_3O_7$: C, 43.86; H, 5.02; N, 13.95. Found: C, 44.17; H, 4.91; N, 13.82. IR (liquid film) 2920 ($-CH_3$), 2110 ($-N_3$), 1745 cm^{-1} (carbonyl). NMR ($CDCl_3$) δ 2.10 (4.1 H, s), 2.20 (4.9 H, s), 3.6–4.5 (4 H, complex pattern, H-4 centered at δ 4.30, H-2, $H_{a,b}$-5), 5.27 (1 H, m, H-3), 6.09 (0.6 H, s, H-1 of β anomer), 6.43 (0.4 H, d, $J_{1,2}$ = 4.5 Hz, H-1 of α-anomer).

9-(2-Azido-2-deoxyribofuranosyl)adenine (8a and 8b) (α and β Anomers). 1,3,5-Tri-*O*-acetyl-2-azido-2-deoxyribose (515 mg, 1.71 mmol) was dissolved in 1,2-dichloroethane (40 ml) and N^6-octanoyladenine (590 mg, 2.1 mmol) added. The mixture was heated to reflux temperature, and stannic chloride (588 mg, 2.1 mmol, 0.27 ml) added. After 6 h under reflux, a further 0.07 ml (0.5 mmol) of stannic chloride was added. After 9 h all solid material had dissolved, and the mixture had become dark in color. TLC in solvent system A showed a large spot running at the solvent front, and unconsumed octanoyladenine (R_f 0.74). The solution was evaporated, and the residue dissolved in 2 N sodium methoxide (8 ml) and methanol (28 ml). After 10 h at 37 °C, deacylation was complete, TLC in system A showing essentially only the α and β anomers of the product (R_f 0.42 and 0.55). The solvent was evaporated and the residue dissolved in 10% methanol/water and applied to a column (2.1 × 30 cm) of Dowex 1 × 4 (OH^-), which was washed with 30% methanol–water, and the products eluted with 50% methanol–water. The α anomer is eluted first. Separation was incomplete and further passage over Dowex 1 × 4 (OH^-) was necessary, affording finally the α anomer (4350 A_{260} units, 17%) and the β anomer (9700 A_{260} units, 38%) as well as a small unseparated fraction (1050 A_{260} units, 4%, mostly α anomer). Total yield, 15 100 A_{260} units, 59%. 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)adenine (**8b**) was obtained crystalline (190 mg, 0.65 mmol) on evaporation of the solution, but may be recrystallized from water: mp 217–220 °C dec, lit.[9] 205 °C; λ_{max} (H_2O) 259.5 nm (ϵ 14 900), λ_{max} (pH 1) 257 nm (ϵ 14 500); NMR (Me_2SO-d_6) identical with that in ref 9; CD λ_{max} (H_2O) 262 nm ([θ] −3530), $\lambda_{crossover}$ 240 nm.

9-(2-Azido-2-deoxy-α-D-ribofuranosyl)adenine (8a) was obtained as a clear gum which crystallized slowly from acetone (82 mg, 0.28 mmol), mp 171–173 °C dec. Anal. Calcd for $C_{10}H_{12}N_8O_3$ (292.3): C, 41.10; H, 4.14; N, 38.34. Found: C, 41.44; H, 4.31; N, 38.02. IR (KBr) 3300–3050 (OH, NH_2), 2120 (N_3) 1690, 1640, 1600 cm^{-1} (NH, purine); λ_{max} (H_2O) 259.5 nm (ϵ 14 900), λ_{max} (pH 1) 257.5 nm (ϵ 14 400); CD λ_{max} (H_2O) 259 nm ([θ] +1900), $\lambda_{crossover}$ 224 nm; NMR (Me_2SO-d_6) 3.59 (2 H, d, $H_{a,b}$-5′) 4.12 (1 H, m, H-4′), 4.56 (2 H, m, H-2′ and H-3′), 4.95 (1 H, t, OH-5′) 6.24 (1 H, d, OH-3′), 6.39 (1 H, d, $J_{1',2'}$ = 5 Hz, H-1′) 7.28 (2 H, s, $-NH_2$), 8.13, 8.24 (2 H, s, H-2 and H-8).

Electrophoretic mobilities in 0.1 M borate, pH 10: **8b,** 0.6 cm; **8a,** 0.5 cm; adenosine, 7.6 cm. R_f values on paper in solvent system B: **8b,** 0.73; **8a,** 0.76; adenosine, 0.66.

9-(2-Amino-2-deoxy-β-D-ribofuranosyl)adenine (9b). 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)adenine (37.9 mg, 0.13 mmol) was dissolved in dry pyridine (0.9 ml) and 50% saturated methanolic ammonia (0.9 ml) and triphenylphosphine (92 mg, 0.35 mmol) added. After standing overnight at room temperature, TLC in system B indicated almost quantitative conversion of the starting material (R_f 0.83) to a product, R_f 0.57. The solution was evaporated and the residue partitioned between benzene and water. The aqueous layer was separated, the benzene layer washed with water, and the combined aqueous solutions evaporated, redissolved in water, and applied to a column of Dowex 1 × 4 (OH^-) (1.2 × 16 cm). The required product (1800 A_{260}, 96%) was obtained on elution with water. The aqueous solution was evaporated and the residue crystallized from dry acetonitrile to give white crystals (27.3 mg, 0.11 mmol): mp 199–201 °C (lit.[11] 194–196 °C). CD λ_{max} (H_2O) 270 nm ([θ] −3460), 234 nm ([θ] +1590), $\lambda_{crossover}$ 248, 223 nm. The material was chromatographically and electrophoretically identical with an authentic sample.

9-(2-Amino-2-deoxy-α-D-ribofuranosyl)adenine (9a). 9-(2-Azido-2-deoxy-α-D-ribofuranosyl)adenine (81.4 mg, 0.28 mmol) was dissolved in dry pyridine (2 ml) and 50% saturated methanolic ammonia (2 ml) and triphenylphosphine (196 mg, 0.75 mmol) added. After standing overnight the starting material (R_f 0.75 on TLC in system B) had been converted almost quantitatively to a new spot (R_f 0.5). The solution was evaporated and the residue triturated with benzene–ether (1:1, 50 ml in three portions), and then taken up in water and passed over Dowex 1 × 2 (OH^-) (1.6 × 17 cm). Elution with water gave a homogeneous product (3540 A_{260}, 84%) which was crystallized from ethanol–water to give white crystals (60 mg, 0.22 mmol): mp 148–149 °C (lit.[11] 149–151 °C); CD λ_{max} (H_2O) 257 ([θ] +6650), 220 nm ([θ] +9900).

7-(2-Azido-2-deoxy-β-D-ribofuranosyl)guanine (10b), 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)guanine (11b), and Their α Anomers 10a and 11a. 1,3,5-Tri-*O*-acetyl-2-azido-2-deoxyribose (689 mg, 2.29 mmol) was dissolved in 1,2-dichloroethane (50 ml) and N^2-palmitoylguanine (1.11 g, 2.86 mmol) added. The mixture was heated to reflux temperature, and stannic chloride (0.34 ml, 2.8 mmol) added. After 90 min heating under reflux the solid material had all been consumed, and TLC in solvent system A showed two spots running almost at the solvent front (R_f 0.94 and 0.89) and palmitoylguanine (R_f 0.67, streaking). The solution was cooled to room temperature and evaporated, and the resulting dark gum dissolved in chloroform and applied to a silica gel column (2.2 × 36 cm) which had been prepared in chloroform. The column was washed with chloroform (400 ml) and eluted with 3% methanol–chloroform (600 ml). Fractions containing material which ran faster than palmitoylguanine in solvent system A were combined and evaporated to give a light brown gum (1.32 g), which was dissolved in 2 N sodium methoxide (10 ml) and methanol (40 ml) and maintained overnight at 37 °C, after which deacylation was found to be complete (TLC system A). The solution was evaporated and the residue suspended in water and applied to a column of Dowex 1 × 2 (OH^-) (2.2 × 36 cm), which was washed thoroughly with water, and then with 0.1 M triethylammonium bicarbonate solution (to remove strongly adsorbed inorganic salts), and the products then eluted as a single peak with 0.4 M triethylammonium bicarbonate. The peak contained 12 310 A_{253} units and 8620 $A_{285.5}$ units, indicating the formation of ca. 0.57 mmol of the 7-(2-azido-2-deoxyribofuranosyl)guanine isomers and ca. 0.71 mmol of the 9-(2-azido-2-deoxyribofuranosyl)guanine isomers (this necessarily assumes that the α and β anomers of each species possess the same λ_{max} (H_2O) and extinction coefficients). The total yield for the condensation was 1.29 mmol of nucleoside (56.5%). The solution was evaporated to dryness, traces of triethylamine being removed by addition and reevaporation of methanol, and the residue was dissolved in boiling water (ca. 250 ml). On cooling to room temperature, a crystalline precipitate formed. This was collected and recrystallized once from boiling water to give 7-(2-azido-2-deoxy-β-D-ribofuranosyl)guanine (**11b,** 102.3 mg, 0.33 mmol, 14.6% based on sugar triacetate) as white crystals, darkening above 238 °C, no melting point <300 °C. Anal. Calcd for $C_{10}H_{12}N_8O_4$ (308.3): C, 38.96; H, 3.92; N, 36.35. Found: C, 38.91; H, 3.92; N, 36.39. IR (KBr) 3350–3100 (OH, NH_2) 2850, 2650 (NH), 2120 (N_3), 1670, 1620, 1560, 1460 cm^{-1} (NH, CO, purine); λ_{max} (H_2O) 285.5 nm (ϵ 7600), 240 (sh) (6600), 216 (20 100); λ_{max} (pH 1) 250 nm (ϵ 9400), 270 (sh) (6700); λ_{max} (pH 13) 282 nm (ϵ 6400), 240 (sh) (7600). CD λ_{max} (H_2O) 287 nm ([θ] +2460), 249 ([θ] −720), 218 ([θ] +12 670), $\lambda_{crossover}$ 256, 240 nm. NMR (Me_2SO-d_6) δ 3.63 (2 H, m, $H_{a,b}$-5′), 3.92 (1 H, m, H-4′), 4.13–4.53 (2 H, m, H-2′ and H-3′), 5.07 (1 H, t, OH-5′), 5.90 (1 H, d, OH-3′), 6.15 (1 H, d, $J_{1',2'}$ = 5.0 Hz, H-1′), 6.22 (2 H, s, $-NH_2$), 8.32 (1 H, s, H-8).

On reduction of the volume of the mother liquor to about half and storage at room temperature, a further precipitate was formed and on investigation found to be virtually pure 9-(2-azido-2-deoxy-β-ribofuranosyl)guanine (**10b**) obtained as white crystals (149.3 mg, 0.48 mmol, 21% based on sugar triacetate), mp 206 °C dec. Anal. Calcd for $C_{10}H_{12}N_8O_4$ (308.3): C, 38.96; H, 3.92; N, 36.35. Found: C, 38.84; H, 4.18; N, 36.31. IR (KBr) 3400–3150 (OH, NH_2), 2900, 2700 (NH), 2120 (N_3), 1710, 1690, 1630, 1600, 1530, 1480 cm^{-1} (NH, CO, purine); λ_{max} (H_2O) 253 nm (ϵ 13 700), 270 (sh) (9800); λ_{max} (pH 1) 257.5 nm (ϵ 12 000), 280 (sh) (7900); λ_{max} (pH 13) 258–268 (ϵ 11 600). CD λ_{max} (H_2O) 267 nm ([θ] +1610), 215 ([θ] +10 020). NMR (Me_2SO-d_6) δ 3.58 (2 H, m, $H_{a,b}$-5′), 3.91 (1 H, m, H-4′), 4.32–4.58 (2 H, m, H-2′ and H-3′), 5.05 (1 H, t, OH-5′), 5.81 (1 H, d, $J_{1',2'}$ = 5.5 Hz, H-1′), 5.97 (1 H, d, OH-3′), 6.48 (2 H, s, $-NH_2$), 7.94 ([H, s, H-8).

Electrophoretic mobilities in 0.1 M borate, pH 10: **11b,** 4.2 cm; **10b,** 5.8 cm; guanosine, 11.6 cm. R_f values on paper in solvent system B: **11b,** 0.60; **10b,** 0.71; guanosine, 0.60.

Evaporation of the mother liquor and examination of the residue by NMR (Me_2SO-d_6) shows H-8 signals at δ 7.86, 7.94, 8.08, and 8.32 in ratio 25:45:40:16, a doublet at δ 5.81, $J_{1',2'}$ = 5.5 Hz, a broadened doublet, probably two almost coincident superimposed doublets, $J_{1',2'} \simeq 5$ Hz, at δ 6.17, and a further doublet at δ 6.56 ($J_{1',2'}$ = 4.5 Hz), the extra signals presumably being due to **11a** (at 8.08 and 6.56) and **10a** (at 7.86 and 6.17). The distribution of the products of condensation is thus **11a,** 12%; **11b,** 30%; **10a,** 7%; **10b,** 51%, and the ratio of 7 isomers:9 isomers is 42:58 (cf. result from UV estimation, 45:55).

9-(2-Amino-2-deoxy-β-D-ribofuranosyl)guanine (12b). 9-(2-Azido-2-deoxy-β-D-ribofuranosyl)guanine (30.0 mg, 0.097 mmol) was dissolved in dry pyridine (1 ml) and 50% saturated methanolic ammonia (1 ml) in a 10-ml flask and triphenylphosphine (91 mg, 0.35 mmol) added. The solution was stirred overnight at room temperature, transferred quantitatively to a larger flask with aqueous methanol, and evaporated. The residue was triturated with diethyl ether–benzene (1:1 v/v; three portions, totaling 25 ml) and the remaining solid product dissolved in 25 ml of H_2O and extracted with 2 × 10 ml of benzene. Evaporation of the aqueous solution afforded

a white, microcrystalline material (21.1 mg, 0.075 mmol, 77%) giving a single spot on TLC in system B, R_f 0.38 (starting material, R_f 0.76), mp 221–223 °C dec. Anal. Calcd for $C_{10}H_{14}N_6O_4$ (282.3): C, 42.55; H, 5.00; N, 29.78. Found: C, 43.26; H, 5.27; N, 29.44. IR (KBr) 3400–3050 (OH, NH_2) 2890, 2710 (NH), 1720, 1690, 1630, 1600, 1540, 1530, 1480 cm^{-1} (NH, CO, purine); λ_{max} (H_2O) 252 nm (ϵ 13 200), 270 (sh) (9400); λ_{max} (pH 1) 256 nm (ϵ 12 500), 280 (sh) (8200); λ_{max} (pH 13) 256–266 nm (ϵ 11 500). CD λ_{max} (H_2O) 253 nm ([θ] −1710), 217 ([θ] +8960), $\lambda_{crossover}$ 235 nm. NMR (Me_2SO-d_6) δ 3.28 (2 H, s, $-NH_2$-2′), 3.40–4.05 (5 H, m, H-2′, H-3′, H-4′, $H_{a,b}$-5), 5.00 (1 H, broad s, OH-5′), 5.46 (1 H, d, $J_{1',2'}$ = 8 Hz, H-1′), 6.40 (2 H, s, $-NH_2$), 7.84 (1 H, s, H-8).

Electrophoretic mobility in 0.1 M borate, pH 10: **12b,** 6.7 cm; guanosine, 11.7 cm. In 0.05 M ammonium formate, pH 3.5: **12b,** 14.6 cm; guanosine, 4.6 cm. R_f value on paper in solvent system B: **12b,** 0.54; guanosine, 0.60.

7-(2-Amino-2-deoxy-β-D-ribofuranosyl)guanosine (13b). 7-(2-Azido-2-deoxy-β-D-ribofuranosyl)guanine (50 mg, 0.16 mmol) was dissolved in dry pyridine (2 ml) and 50% saturated methanolic ammonia (2 ml) in a 10-ml flask, and triphenylphosphine (138 mg, 0.53 mmol) added. After stirring overnight at room temperature the solution was transferred to a larger flask with methanol–water and evaporated, and the residue shaken with 3 × 10 ml water; the filtered aqueous solutions were combined and extracted with 3 × 10 ml of benzene, and then evaporated to give 36.4 mg (0.13 mmol, 79.5%) of residue, which was pure by TLC. The residue was dissolved in hot water to form a stiff gel on cooling, which slowly decomposed depositing white microcrystals of product (25.6 mg, 0.091 mmol, 56%) which decomposed slowly above 250 °C and rapidly above 265 °C, but showed no melting point <300 °C. TLC in system B gave a single spot, R_f 0.35, streaking. Anal. Calcd for $C_{10}H_{14}N_6O_4$ (282.3): C, 42.55; H, 5.00; N, 29.78. Found: C, 42.54; H, 5.14; N, 29.77. IR (KBr) 3400–3100 (OH, NH_2), 2880, 2650 (NH), 1660, 1560, 1470 cm^{-1} (NH, CO, purine); λ_{max} (H_2O) 286.5 nm (ϵ 7700), 240 (sh) (6700), 215.5 (19 100); λ_{max} (pH 1) 250 nm (ϵ 8500), 270 (sh) (7200); λ_{max} (pH 13) 282.5 nm (ϵ 7900), 240 (sh) (7900). CD λ_{max} (H_2O) 283 nm ([θ] +1800), 220 ([θ] −8710), $\lambda_{crossover}$ 260 nm. NMR (Me_2SO-d_6) 3.30 (3 H, broad s, $-NH_2'$ + HO?) 3.42–4.07 (5 H, m, H-2′, H-3′, H-4′, $H_{a,b}$-5′), 4.94 (1 H, broad s, OH-5′?), 5.73 (1 H, d, $J_{1',2'}$ = 7.5 Hz, H-1′), 6.17 (2 H, s, $-NH_2$), 8.17 (1 H, s, H-8).

Electrophoretic mobility in 0.1 M borate, pH 10: **3b,** 6.1 cm; guanosine, 11.7 cm. In 0.05 M ammonium formate, pH 3.5: **13b,** 16.2 cm; guanosine, 4.6 cm. R_f values on paper in solvent system B: **13b,** 0.49; guanosine, 0.60.

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Registry No.—**1,** 58-96-8; **3,** 26929-65-7; **4a** pyranose form, 60921-16-6; **4a** furanose form, 60921-17-7; **4b** pyranose form, 60921-18-8; **4b** furanose form, 60921-19-9; **5a,** 60921-20-2; **5b,** 60921-21-3; **6a,** 60921-22-4; **6b,** 60921-23-5; **7a,** 60921-24-6; **7b,** 60921-25-7; **8a,** 60921-26-8; **8b,** 58699-61-9; **9a,** 10407-64-4; **9b,** 10414-81-0; **10a,** 60921-27-9; **10b,** 60921-28-0; **11a,** 60921-29-1; **11b,** 60921-30-4; **12b,** 60966-26-9; **13b,** 60921-31-5; N^6-octanoyladenine, 52854-12-3; N^2-palmitoylguanine, 21047-87-0.

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(38) After this manuscript was submitted for publication Lohrmann and Orgel [*Nature (London)*, **261,** 342 (1976)] published an alternative synthesis of 2′-azido- and 2′-amino-2′-deoxyadenosine. These compounds as well as the corresponding guanosine derivatives were also very recently reported by M. Ikehara, T. Maruyama, and H. Miki [*Tetrahedron Lett.*, 4485 (1976)].