2′-O-ZLeu isomer, 60967-52-3; XIa 3′-O-ZPhe isomer, 60967-53-5; XIa 2′-O-ZPhe isomer, 60967-54-6; XIb 3′-O-ZLeu isomer, 60967-55-7; XIb 2′-O-ZLeu isomer, 60967-56-8; XIIa 3′-O-Phe isomer, 60967-57-9; XIIa 2′-O-Phe isomer, 60967-58-0; XIIb 3′-O-Leu isomer, 60967-59-1; XIIb 2′-O-Leu isomer, 60967-60-4; XIII, 60687-64-1; 4-methoxytrityl chloride, 14470-28-1; dimethylformamide dimethyl acetal, 4637-24-5; ZPheOH, 1161-13-3; ZLeuOH, 2018-66-8.

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Nucleosides. 104. Synthesis of 4-Amino-5-(D-ribofuranosyl)pyrimidine *C*-Nucleosides from 2-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile[1]

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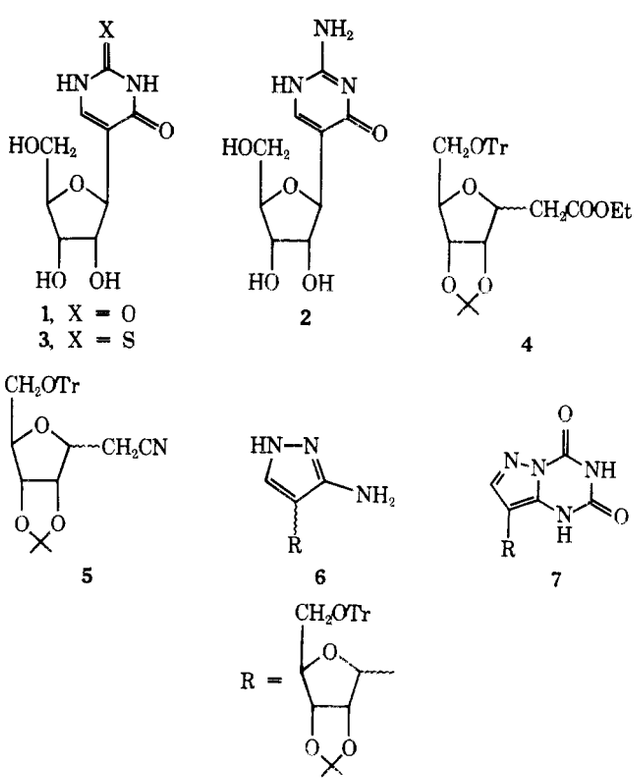
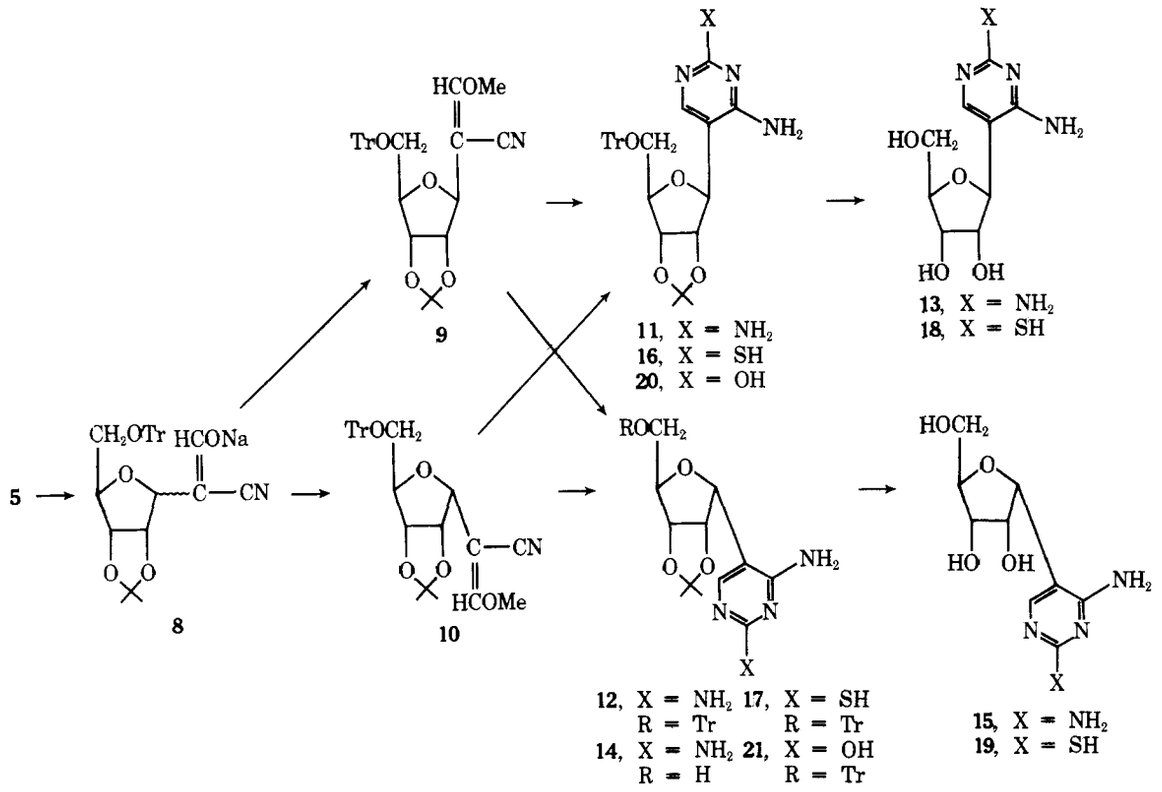
2,4-Diamino-5-(β-D-ribofuranosyl)pyrimidine and 5-(β-D-ribofuranosyl)-2-thiocytosine (2-thiopseudocytidine) were synthesized along with their α isomers in four steps from 2-(2,3-O-isopropylidene-5-O-trityl-D-ribofuranosyl)-acetonitrile.

As a part of our program in search of anticancer agents, we have recently developed[2] a novel method for general synthesis of pseudouridine (**1**) and its analogues, e.g., pseudoisocytidine (**2**) and 2-thiopseudouridine (**3**), from a common intermediate, ethyl 2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetate (**4**). Pseudoisocytidine (**2**) was found[3] to be as active chemotherapeutically as the naturally occurring antibiotic 5-azacytidine,[4] against various mouse leukemias, and more importantly, **2** was effective against arabinofuranosylcytosine (ara-C)-resistant mouse leukemia cell lines.[3] Further biochemical and preclinical toxicological studies are currently underway with **2** in our institute in preparation for clinical trials.

In our previous communication,[5] we have briefly described the use of 2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile (**5**) for the synthesis of 3-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)-4-thio-6-oxopyrazolo[1,5-*a*]-1,3,5-triazine (**7**) via the 3-aminopyrazole derivative (**6**).

In this report we describe the synthesis of pyrimidine C-5 nucleosides bearing a 4-amino function from the versatile intermediate **5** which was prepared previously by Ohrui et al.[6] Formylation of **5** with ethyl formate and sodium hydride in a mixture of ether and ethanol gave crude sodium enolate **8** which, without further purification, was treated with methyl iodide in dimethylformamide. Two products (**9** and **10**) in a ratio of ~4:1 were detected on a thin layer chromatogram and separated by silica gel column chromatography. ^1H NMR analyses showed that these products were the β (**9**) and α (**10**)





isomers[7,8] of 2-ribosyl-3-methoxyacrylonitrile. The compound with lower H-1 chemical shift was tentatively assigned to the α structure (**10**).[8] The separation and structural assignment, however, are not important from the practical viewpoint, since *either* isomer gave the same isomeric mixture of the protected 5-ribosyl-2,4-diaminopyrimidines (**11** and **12**) upon treatment with guanidine in the presence of sodium ethoxide. Both nucleosides **11** and **12** were isolated in pure form after separation on a silica gel column.

The assignment of the ribosyl configuration of **11** and **12** is based on ^{1}H NMR studies. The difference in chemical shifts of the two methyl signals of the isopropylidene group ($\Delta\delta$ 21 Hz) for **11** (which eluted from the column first) is larger than that for **12** ($\Delta\delta$ 19.5 Hz)[5] and H-1′ of **11** (δ 4.56) resonated in higher field than that of **12** (δ 5.19). These data indicate[2,5,8] that **11** and **12** are the β and α nucleoside, respectively.

When the protected β nucleoside **11** was treated with methanolic hydrogen chloride at room temperature, the free nucleoside **13** crystallized from the solution as its hydrochloride. Under the same conditions, however, the α isomer **12** did not give the corresponding free nucleoside **15,** but afforded the isopropylidene derivative **14.** In order to obtain **15,** more stringent conditions were required. The ^{1}H NMR spectra of **13** and **13** possessed quite common characteristics of those of the corresponding pairs of pseudouridine[9] and pseudoisocytidine.[2] The chemical shift for H-1′ of **13** (δ 4.63) is higher than that of **15** (δ 5.05), which establishes the configuration at C-1′ as β and α, respectively. The chemical shift of H-6 for the β isomer **13** (δ 7.77) is lower than that for the α isomer **15** (δ 7.75). This difference ($\Delta\delta$ 2 Hz), though small, is consistent with previous $\Delta\delta$ observations[2,9] for H-6 with other α,β pairs of related *C*-nucleosides. Isomerization (**13** $\rightleftarrows$ **15**) was not observed during the deblocking experiments. These data further confirm the assignment of configuration to protected nucleosides **11** and **12.**

The versatility of intermediates **9** and **10** was further demonstrated by the synthesis of 5-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)-2-thiocytosines (**16** and **17**). Cyclization of **9** with excess thiourea gave an isomeric mixture of **16** and **17** in good yield. Compound **10** also afforded the same mixture. Each isomer was separated by fractional crystallization from hot methanol. The β isomer **16** is more soluble in this solvent than the α nucleoside **17.** The assignment of the ribosyl configuration of these derivatives was based on ^{1}H NMR data of these and the corresponding unprotected nucleosides **18** and **19** as previously described for the diamino nucleosides **13** and **15.**

The protected 5-ribofuranosylcytosine derivatives (pseudocytidines **20** and **21**) were also prepared by cyclization of **9** with urea. Each isomer was isolated in pure state after fractional crystallization from methanol. ^{1}H NMR spectral as well as analytical data were consistent with the structure of protected pseudocytidines **20** and **21.** Treatment of **20** or **21** with methanolic hydrogen chloride at room temperature for 30 min, however, produced an intractable mixture which, according to its UV spectrum, was characteristic of a 5-substituted cytosine and showed at least four signals in the δ 4.8–5.1 region indicating that isomerization of the ribosyl configuration as well as of the ring size (furanosyl to pyranosyl) had occurred. Even at milder conditions (e.g., 10% methanolic hydrogen chloride at room temperature for 10 min) considerable coloration and some isomerization were observed. A yellow solid which could be obtained from the mixture was shown to contain ~20% impurities as judged by ^{1}H NMR.

Pseudocytidine (5-β-D-ribofuranosylcytosine) was obtained previously by David and Lubineau[10] in 4% overall yield and was purified by chromatography on Dowex 50 (H^+) using 0.1 M sulfuric acid as the eluent. Using similar conditions,[10] we were unable to elute pseudocytidine from the Dowex 50 column even using higher acid concentrations of eluent. The synthesis of pseudocytidine by alternate approaches is now being undertaken in our laboratory.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a JEOL PFT-100 spectrometer, and Me_4Si was the internal standard for organic solvents and $Me_3Si(CH_2)_3SO_3Na$ (external) for D_2O. TLC was performed on microscope slides coated with silica gel GF_{254} (Merck), and column chromatography on silica gel G or silica gel 60

Table I. ^{1}H NMR Parameters of 4-Amino-5-(D-ribofuranosyl)pyrimidines and Related Compounds

Registry no.	Compd	Chemical shifts, δ						Isopropyl CH_3		Solvent
		H-1′	H-2′	H-3′	H-4′	H-5′	H-6			
61008-78-4	9	4.81			4.05	3.28[a]		1.31	1.52	$CDCl_3$
61008-79-5	10	5.29	4.88	4.62	4.31	3.27[b]		1.31	1.60	$CDCl_3$
60949-51-1	11	4.56		4.98	4.14	3.49	7.85	1.37	1.58	$CDCl_3$
60949-52-2	12	5.19[c]	4.66	4.85	4.35[d]	3.2–3.3	7.77	1.29	1.50	$CDCl_3$
60949-53-3	13	4.63	4.12		4.32	3.82	7.77			D_2O
60949-54-4	14	4.92		5.12	4.42	3.72[e]	7.75			D_2O
60949-55-5	15	5.05[f]	4.31	4.49	4.10	3.82[g]	7.75	1.36	1.46	Me_2SO-d_6
60949-56-6	16	4.67	4.67	4.67	4.12	3.17[h]	7.50	1.28	1.51	Me_2SO-d_6
60949-57-7	17	4.79	4.79	4.61	4.25	3.08	7.35	1.20	1.31	Me_2SO-d_6
60978-37-2	18	4.15			4.80	3.81	7.88			D_2O
60949-58-8	19	5.10	4.26	4.45	4.08	3.75[i]	7.86			D_2O
60949-59-9	20	5.34	5.40	5.10	3.90	2.80	7.35	1.13	1.29	Me_2SO-d_6
60949-60-2	21	5.44	5.31	4.78	4.15	3.00	7.55	1.28	1.32	Me_2SO-d_6

[a] Octet, $J_{5',5''} \sim 10.4$, $J_{4',5'} \sim J_{4',5''} \sim 3.6$ Hz. [b] Doublet, $J_{4',5'} \sim 5.3$ Hz. [c] Doublet, $J_{1',2'} \sim 3.4$ Hz. [d] Triplet, $J_{3',4'} \sim J_{4',5'} \sim 4.3$ Hz. [e] Doublet, $J_{4',5'} \sim 5.8$ Hz. [f] Quartet, $J_{1',2'} \sim 3.3$, $J_{1',6} \sim 0.9$ Hz. [g] Octet, $J_{5',5''} \sim 13$, $J_{4',5'} \sim 5.0$, $J_{4',5''} \sim 3.8$ Hz. [h] Doublet, $J_{4',5'} \sim 5.8$ Hz. [i] Octet, $J_{5',5''} \sim 12.5$, $J_{4',5'} \sim 5.2$, $J_{4',5''} \sim 2.8$ Hz.

(70–230 mesh, ASTM, Merck). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

2-Formyl-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acetonitrile Sodium Enolate (8). To a suspension of sodium hydride (15 g, 50% in mineral oil) in absolute ether (150 ml, distilled over $LiAlH_4$) was added 4 ml of absolute ethanol followed immediately by dropwise addition of a mixture of compound **5**[11] (91 g, 0.2 mol), ethyl formate (70 ml, distilled over K_2CO_3), and absolute ethanol (4 ml) in dry ether (150 ml). The mixture was stirred overnight at room temperature, and the solvent was evaporated in vacuo below 30 °C. Crude **8** (105 g) was obtained as a brown syrup which was not purified but directly used in the next step.

3-Methoxy-2-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)acrylonitrile (9 and 10). The crude **8** (105 g) was dissolved in DMF (200 ml, dried over 4 Å molecular sieves). Methyl iodide (56 g, 0.4 mol) was added dropwise to the solution over a period of 1 h. The mixture was stirred for 5 h at room temperature and then poured into a mixture of ice and water (2 l.). The supernatant was removed by decantation and the residual syrup was dissolved in ether (1 l.), washed with water, dried over sodium sulfate, and evaporated to a brown syrup. TLC (benzene–ethyl acetate, 9:1) of the syrup showed that it contained three components [R_f 0.7 (starting material), 0.6 (major), and 0.55]. The lower two components were separated by silica gel 60 (1 kg) column chromatography using benzene–ethyl acetate (19:1) as the eluent. The less polar compound **9** (45 g, 43%) was obtained as a syrup (see Table I for ^{1}H NMR data).

The minor component **10** (5.0 g, 5%) was obtained as white crystals after crystallization from methanol, mp 164–165 °C.

Anal. Calcd for $C_{31}H_{31}NO_5$: C, 74.83; H, 6.27; N, 2.81. Found for **9:** C, 75.03; H, 6.23; N, 2.66. Found for **10:** C, 74.86; H, 6.50; N, 2.77.

2,4-Diamino-5-(2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl)pyrimidine (11 and 12). A mixture of **9** (21.5 g, 0.043 mol) and guanidine hydrochloride (7.5 g, 0.071 mol) in ethanolic sodium ethoxide (200 ml, 0.75 N) was refluxed for 15 h. The mixture was concentrated to ~100 ml in vacuo and neutralized with 1 N HCl. A brown precipitate was dissolved in ether (~200 ml), washed with water, dried over sodium sulfate, and evaporated to a brown semisolid. TLC (benzene–methanol, 4:1) showed that the brown solid contained two major components (R_f 0.65 and 0.60). The mixture was chromatographed over a column of silica gel G60 (1 kg) using chloroform–methanol (20:1) as the eluent. The first compound eluted (6.1 g, corresponding to R_f 0.65 on TLC) was obtained as a powder and assigned structure **11** by ^{1}H NMR analyses (see Table I).

Compound **12** was eluted as the second fraction (3.9 g) as a white powder.

Anal. Calcd for $C_{31}H_{32}N_4O_4$: C, 70.97; H, 6.15, N, 10.68. Found for **11:** C, 70.77, H, 6.19; N, 10.40. Found for **12:** C, 70.72; H, 6.35; N, 10.41.

2,4-Diamino-5-(β-D-ribofuranosyl)pyrimidine Hydrochloride (13). Compound **11** (1.26 g, 2.4 mmol) was dissolved in 10% methanolic hydrogen chloride (12 ml) and the solution was stirred for 1 h at room temperature. Compound **13** precipitated as colorless crystals which were filtered and washed with ether: 0.60 g (90%), mp 215–216 °C dec; UV λ_{max} (pH 1) 270 nm (ε 5080), λ_{max} (pH 7) 280 (5530), λ_{max} (pH 14) 286 (7090), 235 (13 050).

Anal. Calcd for $C_9H_{14}N_4O_4$·HCl: C, 38.78; H, 5.43; N, 20.10; Cl, 12.72. Found: C, 38.60; H, 5.38; N, 20.05; Cl, 12.85.

2,4-Diamino-5-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)pyrimidine Hydrochloride (14). A mixture of **12** (0.97 g, 18 mmol) and 12 ml of methanolic hydrogen chloride (10%) was stirred for 1 h, during which time colorless crystals precipitated. The mixture was evaporated to dryness below 30 °c in vacuo and the residue was coevaporated several times with ether. Recrystallization of the residue from acetone–methanol afforded 450 mg (80%) of **14:** mp 231–233 °C dec; UV λ_{max} (pH 1–7) 270 nm, λ_{max} (pH 13) 285, 235 nm (sh).

Anal. Calcd for $C_{12}H_{18}N_4O_4$·HCl: C, 45.21; H, 6.00; N, 17.57, Cl, 11.12. Found: C, 45.14; H, 5.97; N, 17.48; Cl, 11.39.

2,4-Diamino-5-(α-D-ribofuranosyl)pyrimidine Hydrochloride (15). Compound **12** (350 mg, 11 mmol) was dissolved in 8 ml of methanolic hydrogen chloride (saturated at 0 °C). The solution was left at room temperature for 15 h. The solvent was removed by evaporation and the residue was coevaporated several times with ether when a white solid was obtained. The residue was triturated with acetone and filtered. Compound **15** (300 mg, 98%) was obtained as white crystals: mp 185–188 °C dec; UV λ_{max} (pH 1) 270 nm (ε 4710), λ_{max} (pH 7) 280 (4910), λ_{max} (pH 14) 286 (6750), 234 (11 050).

Anal. Calcd for $C_9H_{14}N_4O_4$·HCl: C, 38.78; H, 5.43; N, 20.10; Cl, 12.72. Found: C, 38.55; H, 5.59; N, 20.04; Cl, 13.00.

5-(2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranosyl)-2-thiocytosine (16 and 17). A mixture of **9** (20.8 g, 0.042 mol) and thiourea (7.6 g, 0.1 mol) in ethanolic sodium ethoxide (200 ml, 1 N) was refluxed for 35 h. The mixture was concentrated under vacuum to ~100 ml, cooled to room temperature, and neutralized with 1 N HCl. The white precipitates were collected by filtration and recrystallized from methanol. The first crop (12.0 g, 53%) was rich in the α isomer **17.** After two recrystallizations of the first crop, pure **17** (3.5 g, 15%) was obtained as colorless needles, mp 214–215 °C.

The combined mother liquors were evaporated and the residue was recrystallized three times from methanol. The pure β isomer (6.1 g, 26%) was obtained as white crystals, mp 208–210 °C.

Anal. Calcd for $C_{31}H_{31}N_3SO_4$: C, 68.76; H, 5.73; N, 7.76; S, 5.92. Found for **16:** C, 68.81; H, 5.81; N, 7.80; S, 5.91. Found for **17:** C, 68.40; H, 5.73; N, 7.43; S, 5.76.

5-(D-Ribofuranosyl)-2-thiocytosine Hydrochloride (18 and 19). A mixture of **12** (1.0 g, 1.8 mmol) and 10% methanolic hydrogen chloride (10 ml) was stirred at room temperature for 1 h. The solvent was removed in vacuo at room temperature. The residue was triturated several times with ether. The β nucleoside **18** was obtained as a white powder, 0.47 g (98%): λ_{max} (pH 1) 280 nm (ε 20 700), 227 (9100), λ_{max} (pH 7) 274 (20 100), 245 (14 900), λ_{max} (pH 14) 269 (15 500), 287 (sh) (9000), 227 (15 900).

In the same manner 0.36 g (94%) after recrystallization from ethanol of the α isomer **19** was obtained from 0.8 g of **17:** mp 196–198 °C dec; UV λ_{max} (pH 1) 280 nm (ε 21 300), 227 nm (9600), λ_{max} (pH 7) 274 (22 100), 243 (16 200), λ_{max} (pH 14) 267 (15 360), 287 (sh) (8300), 224 (16 520).

Anal. Calcd for $C_9H_{13}N_3O_4S$·HCl·0.5CH_3OH: C, 36.60; H, 5.17; N,

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.

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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