Synthesis of "Reversed" Nucleosides of Some Purine and Pyrimidine Bases

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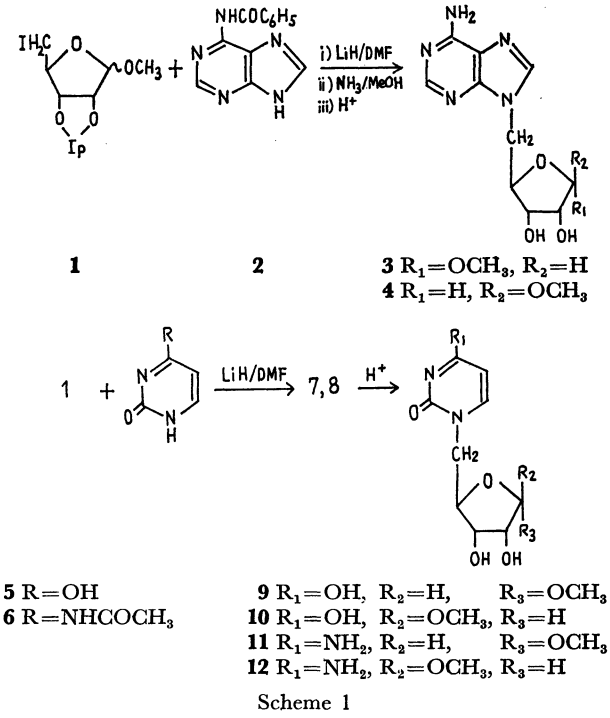
The title compounds have been synthesized by condensation of terminal iodo-sugars with purine bases and pyrimidine bases in dimethylformamide in the presence of sodium hydride or lithiu ı hydride.

As part of investigations of the synthesis of new nucleosides and analogues,[1-3] the synthesis of "reversed" nucleosides[4] (ribose derivatives of adenine bonded at C-5 of the sugar moiety) and their analogues seemed to be of interest, the compounds being useful as synthetic intermediates as in the synthesis[5] of eritadenine (lentynasine). Some reversed nucleosides were synthesized by Leonard *et al.*[4] and Hildesheim *et al.*[6] as compounds related to kinetin, a cell division factor.

The reversed nucleosides were synthesized by use of C-5 sulfonate derivatives of 2-deoxy-D-ribose and D-ribose.[4,5] Martinez and Lee[7] prepared 1-(2',2'-diethoxyethyl)uracil by the reaction of uracil with 2-bromo-1,1-diethoxyethane in dimethylformamide in the presence of sodium hydride. This was the first direct *N*-monoalkylation of uracil. We have extended the reaction to the preparation of reversed nucleosides by an alternative method using terminal iodo derivatives of sugars.

In the conventional synthesis of nucleosides using glycosyl halides, the mercuri-method[8] and fusion method[9] are known to be convenient, but attempts to apply these condensation methods to the present synthesis were unsuccessful.

Methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-D-ribofuranoside (**1**) was synthesized from the corresponding 5-*O*-methyl derivative by the procedure of Kissman and Baker.[10] The iodo compound (**1**) reacted smoothly with 6-benzamidopurine (**2**) in dimethylformamide in the presence of lithium hydride to afford, after removal of the protecting groups, methyl 5-(6-aminopurin-9-yl)-5-deoxy-α- and β-D-ribofuranoside (**3** and **4**) in a total yield of 24% (Scheme 1). The methyl riboside of this



1 **2** **3** R_1=OCH_3, R_2=H; **4** R_1=H, R_2=OCH_3

5 R=OH; **6** R=NHCOCH$_3$

9 R_1=OH, R_2=H, R_3=OCH_3; **10** R_1=OH, R_2=OCH_3, R_3=H; **11** R_1=NH_2, R_2=H, R_3=OCH_3; **12** R_1=NH_2, R_2=OCH_3, R_3=H

Scheme 1

β-compound was previously synthesized by Kawazu *et al.*[5] by an alternative procedure. An analogous reaction of **1** with uracil (**5**) or 4-*N*-acetylcytosine (**6**) gave a masked condensation product (**7** or **8**), which afforded, after removal of the protecting groups, methyl 5-deoxy-5-(uracil-1-yl)-α- and β-D-ribofuranoside (**9** and **10**) or methyl 5-(cytosin-1-yl)-5-deoxy-α- and β-D-ribofuranoside (**11** and **12**) (Table 1).

On the other hand, methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucoside (**13**) was prepared by treatment of methyl 2,3,4-tri-*O*-acetyl-6-tosyloxy-α-D-glucoside[11] with sodium iodide in acetic anhydride in a good yield. Condensation of **13** with **2** in dimethylformamide in the presence of sodium hydride afforded the masked condensation product (**15**), in a 35% yield, which gave, after removal of the protecting groups, methyl 6-(6-aminopurin-9-yl)-6-deoxy-α-D-glucoside (**17**) in a 60% yield. A similar condensation of 2,6-benzamidopurine (**14**), uracil (**5**) or 4-*N*-acetylcytosine (**6**) with **13** afforded the masked condensation products (**16**, **19**, or **20**), which gave, after removal of protecting groups, methyl 6-(2,6-diaminopurin-9-yl)-6-deoxy-α-D-glucoside (**18**), methyl 6-deoxy-6-(uracil-1-yl)-α-D-glucoside (**21**), and methyl 6-(cytosin-1-yl)-6-deoxy-α-D-glucoside (**22**) (Scheme 2).

9-Substitution on the purine bases and 1-substitution

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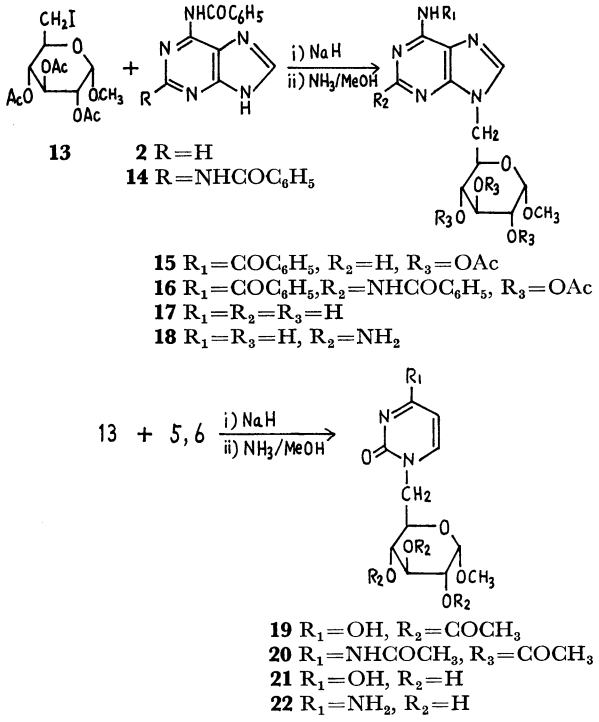
Table 1. Properties and elemental analyses

Compound	Mp, °C	Formula	Calcd, %			Found, %			Yield, %	$[\alpha]_D^{16}$(in water)
			C	H	N	C	H	N		
3	170 (dec)	$C_{11}H_{15}N_5O_4$	46.97	5.38	24.90	46.63	5.68	24.58	4	+34 (*c* 0.4)
4	197—198	$C_{11}H_{15}N_5O_4$	46.97	5.38	24.90	47.59	5.61	24.62	20	−12 (*c* 0.5)
9	81—85	$C_{10}H_{14}N_2O_6$	46.51	5.47	10.85	46.07	5.84	11.01	10	+62.8 (*c* 0.5)
10	84.5—85.5	$C_{10}H_{14}N_2O_6 \cdot H_2O$	43.48	5.84	10.14	43.98	6.00	10.55	20	+13.3 (*c* 0.5)
11	68—74	$C_{10}H_{15}N_3O_5$	47.62	5.84	16.34	47.48	6.26	15.91	4	+93 (*c* 0.5)
12	235—236.5	$C_{10}H_{15}N_3O_5$	47.62	5.84	16.34	47.90	6.02	16.73	11	+19.0 (*c* 0.5)
17	199—200(dec)	$C_{12}H_{17}N_5O_5$	46.30	5.50	22.51	45.98	5.58	22.13	20.7	+85 (*c* 0.5)
18	258—261(dec)	$C_{12}H_{18}N_6O_5$	44.17	5.52	24.54	44.60	5.98	24.83	16.7	+84.8 (*c* 0.35)
21	129—133	$C_{11}H_{16}N_2O_7 \cdot C_2H_5OH$	46.70	6.63	8.38	46.77	6.83	8.45	5.6	+122.4 (*c* 0.5)
22	170	$C_{11}H_{17}N_3O_6 \cdot C_2H_5OH$	46.85	6.91	12.61	46.57	6.93	12.51	27	+136 (*c* 1.0)



13 **2** R=H
14 R=$NHCOC_6H_5$

15 R_1=COC_6H_5, R_2=H, R_3=OAc
16 R_1=COC_6H_5, R_2=$NHCOC_6H_5$, R_3=OAc
17 R_1=R_2=R_3=H
18 R_1=R_3=H, R_2=NH_2

19 R_1=OH, R_2=$COCH_3$
20 R_1=$NHCOCH_3$, R_3=$COCH_3$
21 R_1=OH, R_2=H
22 R_1=NH_2, R_2=H

Scheme 2

on the pyrimidine bases have been established by determination of ultraviolet spectra (Table 2). The structures and stereochemistry of the above products have been confirmed by analyses of their NMR and IR spectra.

Table 2. Ultraviolet spectral data

Compound	λ_{max} mμ (ε × 10^3)		
	0.01N HCl	Water	0.01N NaOH
3	260(12.7)	262(12.4)	261(12.8)
4	260(15.4)	261(15.3)	261(15.1)
9	264(10.3)	265(11.2)	266(7.4)
10	266(13.1)	265(11.2)	265(9.8)
11	283(8.0)	273(5.0)	275(5.2)
12	285(11.4)	275(8.0)	275(8.6)
17	260(13.8)	260(13.9)	260(14.1)
18	253(10.0)	255(8.4)	256(8.8)
	291(10.0)	280(10.2)	281(10.4)
21	266(12.1)	266(12.1)	265(9.0)
22	282(12.0)	274(9.0)	277(6.6)

Since the aminopurines alkylated on the nitrogen atoms **7** or **9** have rarely been obtained by direct alkylation of the aminopurines,[12] the above-mentioned results are interesting.

Experimental

Methyl 5-(6-Aminopurin-9-yl)-5-deoxy-α- and β-D-Ribofuranoside (3 and 4). To a solution of 6-benzamidopurine (1.42 g, 6.0 mmol) in 60 ml of anhydrous dimethylformamide was added lithium hydride (48 mg, 6.0 mmol) with stirring. To this was added a solution of methyl 5-iodo-5-deoxy-2,3-*O*-isopropylidene-D-riboside (1.85 g, 6.0 mmol) in 10 ml of anhydrous dimethylformamide. The mixture was heated at 130—135 °C for 12 hr. After cooling to room temperature, the dimethylformamide solution was evaporated to dryness *in vacuo*. The residue was extracted with two 45 ml portions of chloroform, filtered and washed with two 30 ml portions of water. The chloroform solution was dried over anhydrous sodium sulfate, filtered and evaporated to dryness *in vacuo*. The residue (3.13 g) was dissolved in 30 ml of methanol and filtered. Alumina (8 g, Merck) was added, and the resulting suspension was evaporated to dryness. The residue was placed on the top of a column of 60 g (2×29 cm) of alumina packed with benzene and eluted successively with benzene, benzene–ethyl acetate (1: 1), ethyl acetate, and ethyl acetate–methanol (3: 1). Evaporation of the last eluate afforded 0.84 g of colorless solid, which was dissolved in 28 ml of anhydrous methanol. The solution was saturated with ammonia at 0 °C, sealed, and allowed to stand at 10 °C for 18 hr. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in 11 ml of methanol and the mixture was refluxed for 4 hr after addition of 5 ml of 0.4N sulfuric acid. The solution was cooled and barium carbonate was added until the pH was neutral. The precipitate was removed by filtration and washed with warm 50% methanol solution. The combined filtrate and washings were evaporated *in vacuo* to give a sirup. The residue was dissolved in water (10 ml) and chromatographed on a Dowex 1×2 (OH form) column (1×38 cm) and eluted with water. Fractions monitored by their ultraviolet absorption were separated into two portions. The first portion was evaporated to dryness to yield **3**, 0.07 g (0.25 mmol, 4%), α-anomer.

12) See, for example, G. A. Howard, "Purines and Related Ring Systems," Chapt. XX in "Chemistry of Carbon Compounds," Vol. IV, E. H. Rodd, Ed., Elsevier Publishing Co. (1960), p. 1691; J. H. Lister, "Physicochemical Aspects of Purines" in "Advances in Heterocyclic Chemistry," Vol. 6, A. R. Katritzky, Ed., Academic Press (1966), p. 40.

The solid was found homogenous by tlc, but could not be crystallized. The second portion was evaporated to dryness to yield **4**, 0.33 g (1.2 mmol, 20%) as colorless needles, β-anomer.

*Methyl 5-(Uracil-1-yl)-5-deoxy-α- and β-D-Ribofuranoside (**9** and **10**).* To a mixture of uracil (0.57 g, 5.2 mmol) and lithium hydride (41.5 mg, 5.2 mmol) in 10 ml of anhydrous dimethylformamide was added a solution of **1** (1.7 g, 5.2 mmol) in anhydrous dimethylformamide with stirring. The solution was heated at 130—132 °C for 12 hr. It was then evaporated *in vacuo* to give a sirup, which was dissolved in 16 ml of chloroform. The resulting solution was washed two 28 ml portions of water, dried over sodium sulfate and filtered. The filtrate was evaporated to dryness *in vacuo*. The residue (1.6 g) was recrystallized from ethanol to yield 0.54 g (1.6 mmol, 31%) of methyl 5-deoxy-2,3-*O*-isopropylidene-5-(uracil-1-yl)-D-riboside (**7**) as needles, mp 189—190 °C, $[\alpha]_D^{17}$ +78.7° (*c* 0.5, chloroform), λ_{max}^{MeOH} 266 mμ (ε 9940), ν_{max}^{KBr} (cm^{-1}), 3000 (NH, OH), 1715, 1680 (uracil), 1098 (C–O–C). Found: C, 52.63; H, 6.03; N, 9.01%. Calcd for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39%; mol wt, 298.

A sample of **7** (0.54 g, 1.6 mmol) was dissolved in a solution of methanol, the solution being refluxed for 2 hr after addition of 0.8N sulfuric acid (3 ml). It was then neutralized with barium carbonate and filtered. The filtrate was passed through a column of 20 ml (0.8×2.6 cm) of CG-400 (OH form), and eluted with 0.1% ammonia solution. Fractions monitored by their ultraviolet absorption were separated into two portions. The first portion was evaporated to dryness to yield **9**, α-anomer, 0.13 g (0.51 mmol), and the second to yield **10**, β-anomer, 0.26 g (1.02 mmol). The total yield including α- and β-anomers was 30%.

NMR (DMSO-d_6), α-anomer: δ 11.05 (1H, s, pyrimidine C_4–OH), 7.49 and 5.53 (1H, each d, J=8.0 Hz, pyrimidine H_5 and H_6), 4.64 (1H, s, $H_{1'}$), 3.25 (3H, s, CH_3O–); β-anomer: δ 4.82 (1H, d, J=3 Hz, $H_{1'}$).

*Methyl 5-(Cytosin-1-yl)-5-deoxy-α- and β-D-Ribofuranoside (**11** and **12**).* *N*-Acetylcytosine (1.54 g, 1.0 mmol) was made to react with lithium hydride (90 mg, 1.1 mmol) and **1** (3.4 g, 1.04 mmol) in 55 ml of anhydrous dimethylformamide. The solution was evaporated to give a sirup, which was dissolved in 120 ml of chloroform. The solution was washed with two 50 ml portions of water, dried over sodium sulfate, and filtered. The filtrate was evaporated *in vacuo* to give a gum, which was chromatographed on a column (2×36 cm) of alumina (100 g, acid washed, Merck), and eluted successively with benzene, benzene–ethyl acetate (1:1), ethyl acetate and ethyl acetate–methanol (1:1). Fractions as determined by their ultraviolet absorption were combined and evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to give methyl 5-(*N*-acetylcytosin-1-yl)-5-deoxy-2,3-*O*-isopropylidene-D-riboside (**8**) (1.37 g, 41%) as needles, mp 209—211 °C, $[\alpha]_D^{18}$ +75.4° (*c* 0.5, chloroform), λ_{max}^{MeOH} 248 mμ (ε 13200), 301 mμ (ε 6650), ν_{max}^{KBr} (cm^{-1}), 3290 (NH, OH), 1700 (*N*-acetyl), 1670, 1625 (pyrimidine), 1098 (C–O–C).

A 1.0 g portion of **8** was dissolved in 30 ml of methanolic ammonia (saturated at 0 °C) and kept at 0 °C for 16 hr. The solution was evaporated *in vacuo* to dryness. The residue was dissolved in a solution of 0.8N sulfuric acid (6.5 ml) and methanol (15 ml) and the solution was heated under reflux for 1 hr. The solution was neutralized to about pH 7 (test paper) with barium carbonate powder and filtered. The filtrate was passed through a column (1.5×30 cm) of CG-400 (OH form, 40 ml) and eluted with water. Fractions monitored by their ultraviolet absorption were separated into two portions, the first being evaporated to dryness to yield 0.1 g (4%) of **11**, α-anomer, and the second to yield 0.26 g (11%) of **12**, β-anomer.

*Methyl 2,3,4-Tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (**13**).* A solution of methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[10] (41.9 g, 0.088 mol) in 450 ml of acetic anhydride was refluxed with dry sodium iodide (25 g, 0.17 mol) for 1 hr. The mixture was cooled and poured with stirring into 1.2 l of ice water. The suspension was allowed to stand at about 10 °C in the refrigerator for 18 hr. The solid acetate was then filtered, washed with water, and dried *in vacuo* to yield 16.9 g (45%) of **13**, wihch was recrystallized from ethanol, mp 149—150 °C (lit,[10] mp 150—151 °C).

*Methyl 6-(6-Aminopurin-9-yl)-6-deoxy-α-D-glucoside (**17**).* 6-Benzamidopurine (**2**) (2.10 g, 8.8 mmol) was made to react with sodium hydride (250 mg, 10.4 mmol) and methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucoside (**13**) (3.50 g, 8.2 mmol) in 80 ml of dimethylformamide. The solution was evaporated *in vacuo* to give a sirup, which was extracted with two 75 ml portions of chloroform. The filtered chloroform extract was washed with two 75 ml portions of water, dried with sodium sulfate, filtered, and evaporated to dryness. The residue (4.96 g) was dissolved in 40 ml of methanol, the insoluble matter being removed by filtration. To the filtrate, was added alumina (10 g, acid washed, Merck) and the mixture was evaporated to dryness. The residue was placed on a column of alumina (80 g) and eluted with ethyl acetate–chloroform (6:4), ethyl acetate–methanol (1:1) and methanol, successively. Fractions monitored by their ultraviolet absorption (λ_{max}^{MeOH} 280 mμ) were combined and evaporated to dryness *in vacuo* to give a crude solid of **15**, 2.71 g, λ_{max}^{MeOH} 280 mμ.

A 1.7 g portion of the crude solid of **15** was dissolved in 600 ml of anhydrous methanol at room temperature, and the solution was saturated with dry ammonia at 0 °C. After storage in a refrigerator for 18 hr, the solution was evaporated to dryness *in vacuo*. The residue was dissolved in 30 ml of water, the solution was placed on a column of 120 ml of Dowex 1×2 (OH form, 200—400 Mesh) and the column was eluted with water. The fractions having ultraviolet absorption at 260 mμ were combined and evaporated to dryness *in vacuo*. The residue was crystallized from hot water to yield 0.57 g of **17**, colorless needles (20.7%, based on the iodo sugar), ν_{max}^{KBr} (cm^{-1}), 3380, 3340, 3210 (NH, OH), 1646, 1613, 1583 (purinyl), 1053, 1006 (C–O–C); NMR (DMSO-d_6), δ 8.12 and 8.22 (1H, each s, purine H_2 and H_8), 7.23 (2H, s, $-NH_2$), 4.55 (1H, d, J=3 Hz, $H_{1'}$), 3.90 (3H, s, CH_3O–).

*Methyl 6-(2,6-Diaminopurin-9-yl)-6-deoxy-α-D-glucoside (**18**).* 2,6-Benzamidopurine (**14**) was made to react with sodium hydride (50 mg, 2.0 mmol) and **13** (0.5 g, 1.2 mmol) in 16 ml of dimethylformamide and treated under the same conditions as for **15**. Chromatography of the residue (0.59 g) on a column of alumina (20 g) gave **16** as a colorless glass, 0.169 g (28.6%); λ_{max}^{MeOH} 248 mμ (ε 19150), 304 mμ (ε 8700), 345 mμ (ε 11600), ν_{max}^{KBr} (cm^{-1}), 1757 (ester), 1640, 1600, 1570 (purinyl). Found: N, 12.57%. Calcd for $C_{32}H_{32}N_6O_{10}$: N, 12.72%.

A 0.169 g portion of **16** was treated with methanolic ammonia followed by chromatography as the hydrolysis of **15** to **17** to give needles of **18**, 66 mg (16.7%).

*Methyl 6-Deoxy-6-(uracil-1-yl)-α-D-glucoside (**21**).* Uracil (6.0 g, 53.5 mmol) was made to react with sodium hydride (1.28 g, 53.5 mmol) and **13** (21.3 g, 49.5 mmol) to give a gum (25.1 g), which was chromatographed on a column of alumina (500 g, acid washed, Merck), being eluted succes-

sively with benzene, benzene–ethyl acetate (1:1), ethyl acetate, ethyl acetate–methanol (5:1) and methanol. Fractions containing the product of ultraviolet absorption (λ_{max}^{MeOH} 260 mμ) were combined and evaporated to dryness *in vacuo*. The residue was crystallized from ethanol to give needles of **19**, 2.46 g (12%), mp 195 °C $[\alpha]_D^{13}$ +133.6° (*c* 0.5, chloroform), λ_{max}^{MeOH} 260 mμ (ε 10300) NMR (DMSO-d_6) δ 5.53 and 7.52 (1H, each d, J=8 Hz, pyrimidine H_5 and H_6), 11.25 (1H, s, pyrimidine C_4–OH), 4.89 (2H, s, $-CH_2-$), 3.19 (3H, s, CH_3O-), 1.99 (6H, s, CH_3CO-), 1.93 (3H, s, CH_3CO-). Found: C, 49.46; H, 5.46; N, 6.65%. Calcd for $C_{17}H_{22}N_2O_{10}$: C, 49.28; H, 5.35; N, 6.76%; mol wt, 414.

A 0.53 g (1.3 mmol) portion of **19** was treated with methanolic ammonia as in the hydrolysis of **15** to **17** and then chromatographed on a column of Dowex 1×2 (OH form). Elution was effected with water and 0.3N ammonia, elution with 0.1N hydrochloric acid (40 ml). Fractions as determined by their ultraviolet absorption (266 mμ) were combined, and evaporated to dryness *in vacuo*. The residue was crystallized from ethanol–water to give needles of **21**, 0.2 g (46.5%). NMR (DMSO-d_6): δ 5.60 and 7.62 (1H, each d, pyrimidine H_5 and H_6), 4.60 (1H, d, J=3 Hz, $H_{1'}$), 3.16 (3H, s, CH_3O-).

Methyl 6-(Cytosin-1-yl)-6-deoxy-α-D-glucoside (22). *N*-Acetylcytosine (**6**) (2.8 g, 18.5 mmol) was made to react with sodium hydride (450 mg, 18.5 mmol) and **13** (7.4 g, 17.2 mmol) in 170 ml of anhydrous dimethylformamide to give a residue, which was dissolved in 253 ml of chloroform, washed with two 105 ml portions of water, dried with sodium sulfate, filtered, and evaporated to dryness. The residue was crystallized from ethanol to give needles, 2.73 g (35%) of methyl 6-(*N*-acetylcytosin-1-yl)-2,3,4,6-tetradeoxy-2,3,4-tri-*O*-acetyl-α-D-glucoside (**20**), mp 242—243 °C, $[\alpha]_D^{16}$ +260° (*c* 0.5, chloroform), λ_{max}^{EtOH} 243 mμ (ε 15600), 301 mμ (ε 7240), ν_{max}^{KBr} (cm^{-1}), 1760 (ester), NMR ($CDCl_3$), δ 7.68 and 7.37 (1H, each d, J=7.5 Hz, pyrimidine H_5 and H_6), 4.91 (2H, s, $-CH_2-$), 3.16 (3H, s, CH_3O-), 2.28 (3H, s, $-N-COCH_3$), 2.08, 2.04 and 1.99 (3H, each s, $-O-COCH_3$). Found: C, 49.73; H, 5.59; N, 8.96%. Calcd for $C_{19}H_{25}N_3O_{10}$: C, 50.22; H, 5.32; N, 9.25%; mol wt, 455.

A 2.0 g (4.4 mmol) portion of **20** was treated with methanolic ammonia followed by chromatography as in the hydrolysis of **15** to **17**. The fractions containing ultraviolet absorbing material were combined and evaporated to dryness. The residue was crystallized from ethanol–water (10:1) to give 1.13 g (27%) of needles of **22**.