The Synthesis of 3-Deazapyrimidine Nucleosides Related to Uridine and Cytidine and Their Derivatives (1a,b)

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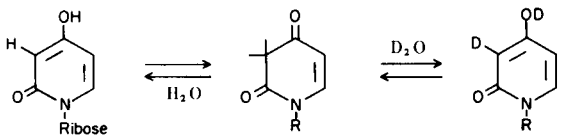
Condensation of 2,4-bis(trimethylsilyloxy)pyridine (**1**) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**2**) gave 4-hydroxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (**3**). Deblocking of **3** gave 4-hydroxy-1-β-D-ribofuranosyl-2-pyridone (3-deazauridine) (**4**). Treatment of **4** with acetone and acid gave 2′,3′-*O*-isopropylidene-3-deazauridine (**6**). Reaction of **4** with diphenylcarbonate gave 2-hydroxy-1-β-D-arabinofuranosyl-4-pyridone-O_2 → 2′-cyclonucleoside (**7**) which established the point of gylcosidation and configuration of **4**. Base-catalyzed hydrolysis of **7** gave 4-hydroxy-1-β-D-arabinofuranosyl-2-pyridone (3-deazauracil arabinoside) (**12**). Fusion of **1** with 3,5-di-*O*-*p*-toluyl-2-deoxy-D-*erythro*-pentofuranosyl chloride (**5**) gave the blocked anomeric deoxynucleosides **8** and **10** which were saponified to give 4-hydroxy-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (2′-deoxy-3-deazauridine) (**11**) and its α anomer (**9**). Condensation of 4-acetamido-2-methoxypridine (**13**) with **2** gave 4-acetamido-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (**14**) which was treated with alcoholic ammonia to yield 4-acetamido-1-β-D-ribofuranosyl-2-pyridone (**15**) or with methanolic sodium methoxide to yield 4-amino-1-β-D-ribofuranosyl-2-pyridone (3-deazacytidine) (**16**). Condensation of **13** and 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (**17**) gave the blocked nucleoside **22** which was treated with base and then hydrogenolyzed to give 4-amino-1-β-D-arabinofuranosyl-2-pyridone (3-deazacytosine arabinoside) (**23**). Fusion of **13** with **5** gave the blocked anomeric deoxynucleosides **18** and **20** which were deblocked with methanolic sodium methoxide to yield 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (2′-deoxy-3-deazacytidine) (**21**) and its α anomer **19**. The 2′-deoxy-*erythro*-pentofuranosides of both 3-deazauracil and 3-deazacytosine failed to obey Hudson's isorotation rule but did follow the "quartet"-"triplet" anomeric proton splitting pattern in the ^{1}H nmr spectra.

Considerable attention has been focused on aza analogs of pyrimidine (triazine) nucleosides. Šorm and coworkers (2) have reported the synthesis of 5-aza and 6-aza analogs of naturally occurring nucleosides. Certain of these derivatives, notably 5-azacytidine and 6-azauridine, show significant biological activity (3) and are in therapeutic use. We now wish to report the first systematic study of the synthesis of 3-deazapyrimidine nucleosides (4) (N_1-glycosides of pyridines substituted analogously to the nucleic acid bases) which represent a new class of nucleic acid component analogs for biological, biochemical, and physical studies.

Treatment of 2,4-dihydroxypyridine (5) with hexamethyldisilazane gave 2,4-bis(trimethylsilyloxy)pyridine (**1**). Condensation of **1** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (6) (**2**) gave a 68% yield of 2′,3′,5′-tri-*O*-benzoyl-3-deazauridine (**3**). Deblocking of **3** with alcoholic ammonia gave 4-hydroxy-1-β-D-ribofuranosyl-2-pyridone (3-deazauridine) (**4**) in 88% crude yield. It is interesting to note that the peak corresponding to the 3-proton in the ^{1}H nmr spectrum of **4** in DMSO-d_6 begins to disappear upon addition of deuterium oxide. This suggests a dynamic enol-keto (i-ii-iii) tautomerism in which the 4-position could participate in Watson-Crick hydrogen bond-



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ing either as in cytosine (i) or uracil (ii).

The method of Hampton (7) was used to convert **4** to its 2′,3′-*O*-isopropylidene derivative **6**. The ^{1}H nmr spectrum of **6** was consistent with the β configuration with $J_{1'-2'}$=1.3 Hz for the H_1' peak (8). The β configuration was firmly defined by the reaction of 3-deazauridine (**4**) with diphenyl carbonate (9) to give 2-hydroxy-1-β-D-arabinofuranosyl-4-pyridone-O_2 → 2′-cyclonucleoside (**7**).

Molecular models demonstrate that attack by O_2 on C_2' with displacement of a 2'-carbonyloxy function is possible only by the 1'-2'-*trans* arrangement of a β-riboside. This sequence also confirmed the position of glycosidation as N_1 as seen from inspection of the uv data of Table I.

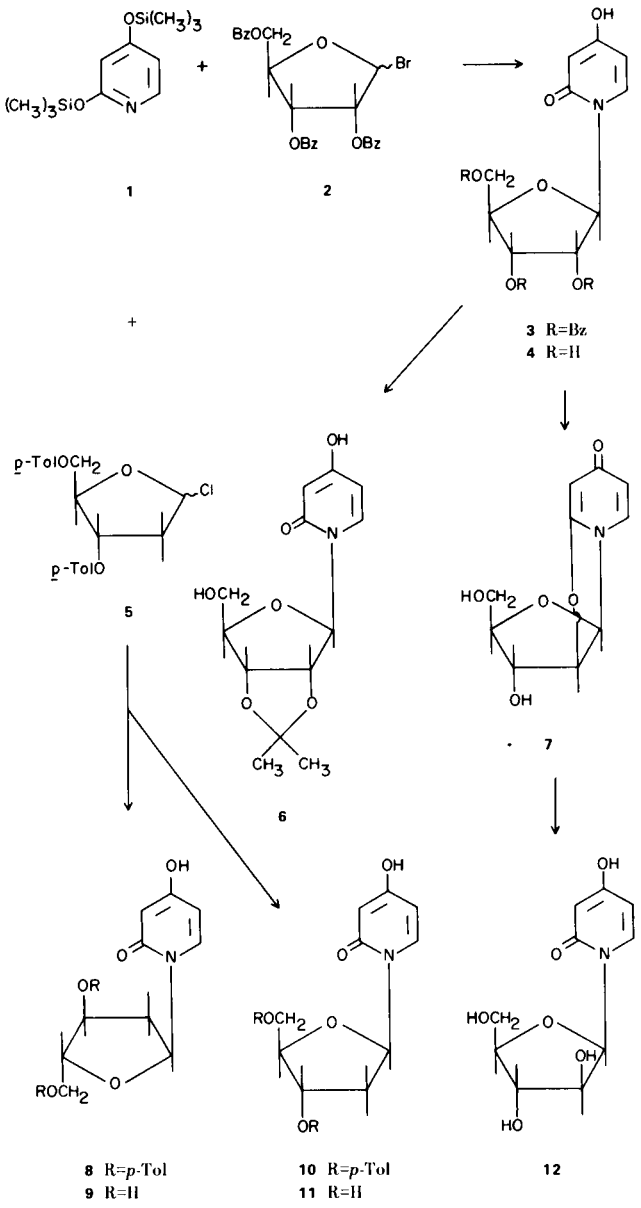
The ultra-violet absorption spectrum of 3-deazauridine (4) corresponds to that of 4-hydroxy-1-methyl-2-pyridone and not that of 2-methoxy-4-pyridone which eliminates the oxygen at position 2 as the site of ribose attachment. However, the uv maximum for 4-methoxy-2-pyridone is too close to that observed for **4** to eliminate the oxygen at position 4 as a possible glycosidation site. The uv data for 2-methoxy-1-methyl-4-pyridone and the cyclonucleoside **7** (a 1-ribosyl-2-alkoxy-4-pyridone) are in close agreement and it is impossible to construct a molecular model of a cyclonucleoside with a 4-ribofuranosyloxy structure. Therefore structure **7** must be correct for the cyclonucleoside and **4** for 3-deazauridine.

Treatment of **7** with dilute base provided a convenient systhesis of 4-hydroxy-1-β-D-arabinofuranosyl-2-pyridone (**12**).

Fusion of 2,4-bis(trimethylsilyloxy)pyridine (**1**) with 3,5-di-*O*-*p*-toluyl-2-deoxy-D-erythro-pentofuranosyl chloride (10) (**5**) gave a 62% yield of the anomeric blocked deoxynucleosides **8** and **10** which were resolved by column chromatography. Treatment of these pure anomers with alcoholic ammonia gave 4-hydroxy-1-(2-deoxy-β-D-erythro-pentofuranosyl)-2-pyridone (2'-deoxy-3-deazauridine) (**11**) and its α anomer (**9**). The uv spectra of **9** and **11** are essentially identical to those observed with 3-deazauridine (**4**) which indicates glycosidation at N_1.

For the synthesis of the cytidine analogs, a modified Hilbert-Johnson procedure was employed using 4-acetamido-2-methoxypridine (11) (**13**) as the base. Condensation of **13** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**2**) gave 4-acetamido-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (**14**) in 92% yield. Treatment of **14** with alcoholic ammonia gave 4-acetamido-1-β-D-ribofuranosyl-2-pyridone (**15**) in quantitative yield. Treatment of **15** with aqueous base (or the completely blocked nucleoside **14** with methanolic sodium methoxide) produced 4-amino-1-β-D-ribofuranosyl-2-pyridone (3-deazacytidine) (**16**).

The ^1H nmr spectra of **16** indicate the presence of a free amino group (2 identical N-H protons) and the uv spectrum of **16** is markedly different from that of 2-methoxy-4-aminopyridine (see Table I). Thus the position of glycosidation must be N_1. The splitting of the nmr peak corresponding to the anomeric proton ($J_{1'-2'}$=2.0 Hz) of **15** is similar to that obtained from 3-deazauridine (**4**) and suggested the β anomer. This configuration is further indicated by the similarity of the circular dichroism curves (12) of **16** and **4**, which parallels the CD behavior



of comparable cytidine and uridine analogs (13).

Condensation of 4-acetamido-2-methoxypyridine (**13**) with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (14) (**17**) according to the general procedure of Glaudemans and Fletcher (14) gave 4-acetamido-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-2-pyridone (**22**). Treatment of **22** with base followed by hydrogenolysis over palladium gave 4-amino-1-β-D-arabinofuranosyl-2-pyridone (3-deazacytosine arabinoside) (**23**).

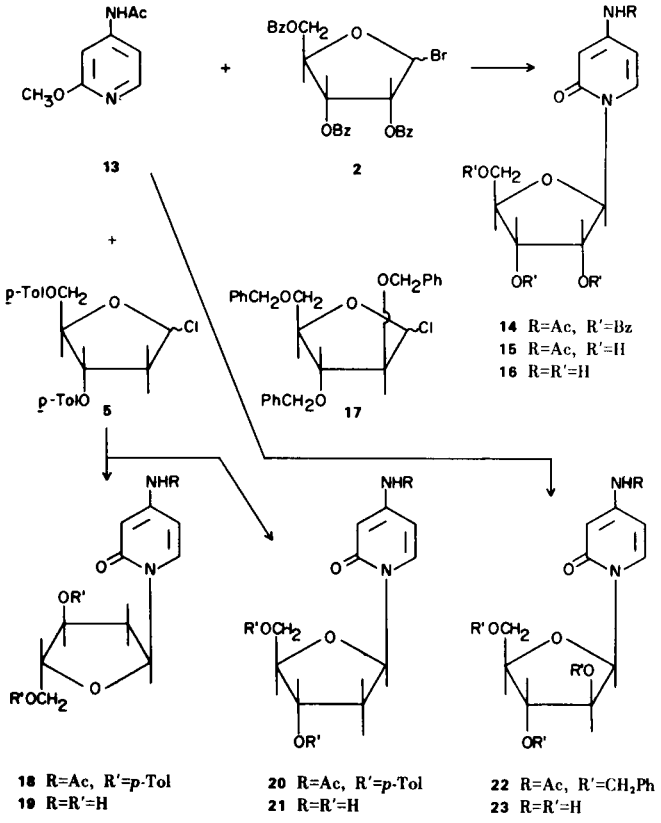
The uv and CD spectra of **23** and 3-deazacytidine (**16**) are very similar (12) and this coupled with the method of synthesis (14) and the large anomeric proton coupling constant ($J_{1'-2'}$=5 Hz) are strong support for the 1-β-structure **23**.

TABLE I (a)

Compound	λ max (mμ)	ε max x 10^{-3}	λ min (mμ)	ε min x 10^{-3}
2,4-Dimethoxypyridine (b)	260	2.24	242	0.89
2-Methoxy-4-pyridone (b)	248	11.2	225	2.82
4-Methoxy-2-pyridone (b)	276	4.47	243	1.12
4.Hydroxy-1-Methyl-2-pyridone (b)	280	3.98	247	1.00
3-Deazauridine (**4**)	281	4.74	249	2.06
2-Methoxy-1-methyl-4-pyridone (b)	251	11.2	227	2.51
3-Deazauridine-O_2 → 2′-cyclonucleoside (**7**)	252	16.9	227	2.75
2-Methoxy-4-amino-pyridine	241; 266 sh	9.77; 2.09	227	5.71
3-Deazacytidine (**16**)	260; 275 sh	8.51; 6.46	236	3.63

(a) All spectra determined in 50% aqueous ethanol. (b) Data taken from H. J. den Hertog and D. J. Buurman, *Rec. Trav. Chim. Pays-Bas*, 75, 257 (1956).

Fusion of 4-acetamido-2-methoxypyridine (**13**) and 3,5-di-*O*-*p*-toluyl-2-deoxy-D-*erythro*-pentofuranosyl chloride (5) gave the blocked anomeric nucleosides **18** and **20**. Treatment of a mixture of **18** and **20** with methanolic sodium methoxide gave 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (2′-deoxy-3-deazacytidine) (**21**) and its α anomer **19** which were separated on a column of Dowex 1-X2 (OH^-) according to the procedure of Dekker (15).



Again the anomers **19** and **21** had uv spectra similar to those observed for 3-deazacytidine (**16**) and the anomeric configurations of **19** and **21** as well as of the 2′-deoxy-3-deazauridines **9** and **11** were indicated by the "quartet"-"triplet" splitting patterns (16) for the peak corresponding to the anomeric proton in the ^1H nmr spectra of the α and β anomers, respectively. These deoxynucleosides failed to obey Hudson's isorotational rules (17) analogously to certain pyrimidine deoxynucleoside anomeric pairs (18).

The biological activity of these compounds will be reported separately (19).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns block and are uncorrected. Nmr spectra were determined on a Varian A-60 instrument with tetramethylsilane or sodium 5,5-dimethyl-5-silapentanesulfonate as internal standard. Uv spectra were determined on a Beckman DK-2 instrument. Hydrogenations were effected using a Parr hydrogenation apparatus at specified hydrogen gas pressure. Evaporations were accomplished using a Büchler rotating evaporater under reduced pressure (aspirator) unless specified otherwise. Optical rotations were determined on a Perkin-Elmer model 141 digital readout polarimeter. Thin layer chromatography (tlc) was run on glass plates coated with SilicAR-7GF (Mallinckrodt Chemical Works) using chloroform:acetone (8:2) unless otherwise specified.

2,4-Bis(trimethylsilyloxy)pyridine (**1**).

A suspension of 50 g. (0.45 mole) of powdered 2,4-dihydroxypyridine in 80 ml. of toluene was refluxed until no further water was collected in a Dean-Stark trap. The toluene was then removed by distillation and 75 ml. of hexamethyldisilazane was added. This suspension was refluxed with stirring while protected from moisture in an oil bath at 140-150° until complete solution was effected (about 3 hours). An additional 20 ml. of hexamethyldisilazane was added and the solution was heated for an additional 0.5 hour. A distillation head was attached and hexamethyldisilazane plus toluene was removed at b.p. 60-65°/22 mm Hg (bath temperature 110°). The 2,4-bis(trimethylsilyloxy)pyridine

(**1**) (98 g., 86%) distilled at b.p. 127-128°/20 mm Hg (bath temperature 155°); uv max (absolute *p*-dioxane) 262 mμ (ε 2190); uv min 241 mμ (ε 690) (see Table I for uv data on 2,4-dimethoxypyridine). A sample (0.255 g., 0.001 mole) of **1** was dissolved in absolute dioxane and hydrolyzed with 4 drops of water to give 0.104 g (93.7%) 2,4-dihydroxypyridine which established the presence of two trimethylsilyl substituents.

4-Hydroxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (**3**).

To a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (6) (**2**) [prepared from 10.1 g. (0.02 mole) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose] in 200 ml. of dry acetonitrile was added 5.1 g. (0.02 mole) of **1**. The solution was protected from moisture and allowed to stand for 8 days at room temperature and then was evaporated. The residue was treated with 70 ml. of 85% aqueous ethanol and boiled on a steam bath for 5 minutes. This solution was evaporated to dryness and the resulting dark solid foam was dissolved in 30 ml. of chloroform and applied to a column (2 in. diameter, 700 g.) of neutral alumina. The column was washed with 3000 ml. of chloroform followed by 3000 ml. of ethyl acetate and these washes containing sugar were discarded. Elution was begun with ethyl acetate:1-propanol:water (4:1:2) (upper phase) and the second 500 ml. portion was evaporated to yield 7.7 g. (68%) of **3**. Recrystallization of **3** from ethanol-water gave crystals, m.p. 140-141°.

Anal. Calcd for $C_{31}H_{25}NO_9 \cdot 0.75\ H_2O$: C, 65.43; H, 4.69; N, 2.46. Found: C, 65.50; H, 4.66; N, 2.48.

4-Hydroxy-1-β-D-ribofuranosyl-2-pyridone (3-Deazauridine) (**4**).

To 100 ml. of methanol presaturated with ammonia at -10° was added 1.0 g. (0.0018 mole) of **3**. The mixture was sealed and allowed to stand for 6 days at room temperature. The resulting solution was evaporated and the residue was triturated thoroughly with dry ether to give 0.41 g. (88%) of **4**. Recrystallization of this material from methanol-acetone gave 0.30 g. (64%) of pure **4**, m.p. 228-230°; $[\alpha]_D^{27}$ + 35.3° (*c* 1, water); uv max (*p*H 1) 278 mμ (ε 4260), (*p*H 11) 255 mμ (ε 8270) 268 mμ sh (ε 6440) (methanol) 282 mμ (ε 4620); nmr (DMSO-d_6) δ5.98 (d, 1, $J_{1'\text{-}2'}$=2.5 Hz, $H_{1'}$), 5.58 (d, 1, $J_{3\text{-}5}$=2.5 Hz, H_3), 5.95 ("q", 1, $J_{5\text{-}3}$=2.5 Hz, $J_{5\text{-}6}$=7.5 Hz, H_5), 7.77 (d, 1, $J_{6\text{-}5}$=7.5 Hz, H_6). Addition of deuterium oxide caused the peak at 5.58 (H_3) to disappear with corresponding collapse of the peak at δ5.95 (H_5) to a doublet with $J_{5\text{-}6}$=7.5 Hz.

Anal. Calcd for $C_{10}H_{13}NO_6$: C, 49.38; H, 5.39; N, 5.76 Found: C, 49.18; H, 5.34; N, 5.60.

4-Hydroxy-1-(2,3-*O*-isopropylidine-β-D-ribofuranosyl)-2-pyridone (**6**).

A suspension of 0.30 g. (0.0012 mole) of **4** in 10 ml. of absolute acetone and 10 ml. of 2,2-dimethoxypropane was stirred for 5 minutes at room temperature and 0.40 g. (0.0012 mole) of bis(*p*-nitrophenyl)phosphate was added. The mixture was stirred for 5 hours at room temperature (solution was complete in about 45 minutes) and 0.10 g. (0.0012 mole) of solid sodium bicarbonate was added. The mixture was stirred for 1 hour, filtered, and the filter cake was washed with acetone. The combined filtrate was evaporated and the residue dissolved in a minimum volume of chloroform and applied to a column (1 cm. diameter, 45 g.) of silica gel. The column was eluted with chloroform and then chloroform:acetone (8:2). The fractions containing product (followed by tlc) were combined and evaporated to give 0.098 g. (28%) of **6** which was recrystallized from chloroform:ether to give needles, m.p. 158-159°; nmr (DMSO-d_6-deuterium oxide) δ6.03 (d, 1, $J_{1'\text{-}2'}$=1.3 Hz, $H_{1'}$).

Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.95. Found: C, 55.03; H, 6.14; N, 4.82.

2-Hydroxy-1-β-D-arabinofuranosyl-4-pyridone-$O_2 \rightarrow 2'$-cyclonucleoside (**7**).

To a solution of 0.77 g. (0.0032 mole) of **4** in 3.1 ml. of dry DMF was added 0.88 g. (0.0041 mole) of diphenylcarbonate and 0.015 g. (0.00018 mole) of sodium bicarbonate. The mixture was heated with stirring for 22 minutes in an oil bath at 150°. The resulting brown solution was cooled to 60° and then poured into 60 ml. of ether with vigorous stirring. The tan solid which separated was triturated with three 25 ml. portions of ether and then recrystallized from methanol:acetone to yield 0.59 g. (82%) of white needles of **7**, m.p. 218-220°; $[\alpha]_D^{26}$ -70.2° (*c* 1.1, water); uv max (*p*H 1) 236 mμ (ε 9180) 253 mμ sh (ε 5190), (*p*H 11) 252 mμ (ε 16,900), (methanol) 252 mμ (ε 16,500); nmr (DMSO-d_6-deuterium oxide) δ6.42 (d, 1, $J_{1'\text{-}2'}$=5.5 Hz, $H_{1'}$), 5.30 (d, 1, $J_{2'\text{-}1'}$=5.5 Hz, $J_{2'\text{-}3'} \cong 0$ Hz, $H_{2'}$), 4.38 (broad s, 1, $H_{3'}$), 4.10 (broad t, 1, $J_{4'\text{-}5'}$=6.5 Hz, $H_{4'}$), 3.18 (broad d, 2, $J_{5'\text{-}4'}$=6.5 Hz, $H_{5'}$), 4.55 (d, 1, $J_{3\text{-}5}$=2.5 Hz, H_3), 6.00 ("q", 1, $J_{5\text{-}3}$=2.5 Hz, $J_{5\text{-}6}$=7.5 Hz, H_5), 7.71 (d, 1, $J_{6\text{-}5}$=7.5 Hz, H_6).

Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.31; H, 4.80; N, 6.21.

4-Hydroxy-1-β-D-arabinofuranosyl-2-pyridone (**12**).

A solution of 0.25 g. (0.0011 mole) of **7** in 25 ml. of 0.2 *N* sodium hydroxide was refluxed for 20 hours, cooled in an ice bath, neutralized to *p*H≅5 with 1 *N* hydrochloric acid (≅4.4 ml.), and evaporated to dryness. The residue was treated with 75 ml. of warm absolute ethanol, filtered, and the filtrate was evaporated to dryness. This second residue was extracted with 40 ml. of warm ethanol, filtered, and the filtrate evaporated to give a solid which was dissolved in 3 ml. of water and applied to a column (1 cm. diameter, 15 ml.) of Dowex-50W-X12 (H^+) (100-200 mesh) packed in water. The column was eluted with water and 4 ml. fractions were collected. Fractions 51 to 90 were pooled and evaporated to dryness and the solid was recrystallized from ethanol-acetone to give 0.12 g. (44%) of pure **12**, m.p. 168.5-170.5°; $[\alpha]_D^{29}$ + 164° (*c* 0.8, water); uv max (*p*H 1) 279 mμ (ε 3900), (*p*H 11) 255 mμ (ε 8300) 268 mμ sh (ε 6400), (water) 280 mμ (ε 5000); nmr (DMSO-d_6) δ6.22 (d, 1, $J_{1'\text{-}2'}$=4.0 Hz, $H_{1'}$).

Anal. Calcd for $C_{10}H_{13}NO_6$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.50; H, 5.44; N, 5.63.

4-Hydroxy-1-(3,5-di-*O*-*p*-toluyl-2-deoxy-α-D-*erythro*-pentofuranosyl)-2-pyridone (**8**) and 4-Hydroxy-1-(3,5-di-*O*-*p*-toluyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (**10**)

A well stirred mixture of 4.63 g. (0.012 mole) of crystalline 3,5-di-*O*-*p*-toluyl-2-deoxy-D-*erythro*-pentofuranosyl chloride (**10**) (**5**) and 3.05 g. (0.012 mole) of **1** was fused for 30 minutes at 110° *in vacuo* (aspirator). The light brown melt was treated with moist methylene chloride and unreacted 2,4-dihydroxypyridine (0.42 g.) was removed by filtration. The filtrate was evaporated to dryness and the residue dissolved in warm ethyl acetate. Three crops of crystals (2.37 g., 62% based on nonrecovered **1**) were obtained which all contained both anomers **8** and **10**. The total crystalline material was mixed with 10 g. of silica gel and 20 ml. of acetone and the mixture was evaporated to dryness and packed on top of a dry packed column (1 in. diameter, 140 g.) of silica gel. The column was washed with 1000 ml. of benzene, 1000 ml. of benzene:ethyl acetate (8:2), and then was eluted with benzene:ethyl acetate (6:4). The appropriate fractions (as determined by

tlc, R_{10}/R_8 = 1.3) were pooled and evaporated and the residue recrystallized from benzene:ethyl acetate. Early fractions contained pure β anomer **10** (0.20 g., 5.3% based on non-recovered **1**), m.p. 218.5-219°.

Anal. Calcd for $C_{26}H_{25}NO_7$: C, 67.38; H, 5.44; N, 3.02. Found: C, 67.54; H, 5.47; N, 3.01.

Middle fractions contained both anomers (0.51 g., 13.4% based on unrecovered **1**). Later fractions contained pure α anomer **8** (0.51., 13.4%), m.p. 185-189°.

Anal. Found: C, 67.21; H, 5.43; N, 3.08.

4-Hydroxy-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (2′-Dexoy-3-deazaurizine) (**11**).

To 100 ml. of methanol previously saturated with ammonia at -10° was added 0.19 g. (0.00041 mole) of **10** and the mixture was sealed and allowed to stand for 5 days at room temperature. The resulting solution was evaporated and the residue was triturated thoroughly in dry ether and then recrystallized from methanol-ether to yield 0.075 g. (80%) of pure **11**, m.p. 196-198°; $[\alpha]_D^{28}$ + 61.5° (*c* 1, water); uv max (*p*H 1) 278 mμ (ε 3820), (*p*H 11) 256 mμ (ε 7590) 268 mμ sh (ε 6120), (water) 276 mμ (ε 4920); nmr (deuterium oxide) δ6.33 ("t", 1, $J_{1'-2',2''}$=6.5 Hz, H_1').

Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.58; H, 5.56; N, 6.04.

4-Hydroxy-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-2-pyridone (**9**).

A 0.42 g. (0.00090 mole) sample of **8** was treated exactly as in the preparation of **11** above to yield 0.13 g. (64%) of **9**, m.p. 174-176°; $[\alpha]_D^{28}$ -41.7° (*c* 1.1, water); uv max (*p*H 1) 278 mμ (ε 3310), (*p*H 11) 254 mμ (ε 7360) 268 mμ sh (ε 5900), (water) 276 mμ (ε 4420); nmr (deuterium oxide) δ6.20 ("q", 1, $J_{1'-2',2''}$= 2.5 and 7.5 Hz, H_1').

Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.86; H, 5.72; N, 5.97.

4-Acetamido-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-pyridone (**14**).

To a solution of **2** [prepared from 5.66 g. (0.0112 mole) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose] in 55 ml. of dry acetonitrile was added 1.86 g. (0.0112 mole) of 4-acetamido-2-methoxypyridine (**11**) (**13**). The resulting solution was sealed, allowed to stand for 49 hours at room temperature, evaporated to dryness, and the residue was coevaporated with 100 ml. of chloroform. The resulting solid foam was dissolved in 30 ml. of chloroform and poured slowly into 270 ml. of ether with vigorous stirring. The mixture was refrigerated for 15 hours and 5.61 g. plus 0.54 g. second crop (6.15 g., 92%) of crystalline **14** was collected. Recrystallization of a small sample of this material from chloroform-ether gave crystals of **14**, m.p. 208-209°.

Anal. Calcd for $C_{33}H_{28}N_2O_9$: C, 66.43; H, 4.73; N, 4.70. Found: C, 66.30: H, 4.81; N, 4.47.

4-Acetamido-1-β-D-ribofuranosyl-2-pyridone (**15**).

To 200 ml. of methanol presaturated with ammonia at -10° was added 2.17 g. (0.00364 mole) of **14**. The mixture was sealed, allowed to stand for 5 days at room temperature, evaporated to dryness, and the residue was triturated thoroughly with dry ether to yield 1.03 g. (100%) of crystalline **15**. A small sample of this material was recrystallized from methanol-acetone to give crystals of **15**, m.p. 164-165°; uv max (*p*H 1) 297, 257 mμ (ε 4,100, 14,900), (*p*H 11) 297, 255 mμ (ε 4,600, 14,400), (methanol) 300, 255 mμ (ε 4,100, 13,200); nmr (DMSO-d_6) δ2.07 (s, 3,4-NHCOCH_3), 6.78 (d, 1, $J_{1'-2'}$=2.0 Hz, H_1').

Anal. Calcd for $C_{12}H_{16}N_2O_6 \cdot H_2O$: C, 47.68; H, 6.00; N, 9.27. Found: C, 47.84; H, 5.97; N, 9.60.

4-Amino-1-β-D-ribofuranosyl-2-pyridone (3-Deazacytidine) (**16**).

Method A.

A solution of 2.43 g. (0.00855 mole) of **15** in 150 ml. of 0.1 N sodium hydroxide was refluxed for 30 minutes, cooled in an ice bath, neutralized to *p*H ≅7 with 1*N* hydrochloric acid, evaporated to dryness, and coevaporated with two 50 ml. portions of methanol. The resulting solid was extracted with hot methanol and this mixture was filtered using a Celite bed to remove sodium chloride. The filtrate was evaporated and the residue was dissolved in 5 ml. of 30% aqueous methanol and applied to a column (1 in. diameter, 100 ml.) of Dowex 1-X2 (OH^-) (200-400 mesh) packed in the same solvent, which was also used for elution. Fractions (4 ml.) 161 to 280 were pooled and evaporated to yield 1.62 g. (78%) of a solid foam which was homogeneous [tlc, upper phase ethyl acetate:1-propanol:water (4:1:2)]. Recrystallization of this material from methanol-ether gave needles of **16**; m.p. 208.5-210°; $[\alpha]_D^{29}$ + 4.6° (*c*, 1, water); uv max (*p*H 1) 258.5 mμ (ε 15,500), (*p*H 11) 258.5 mμ (ε 8840) 275 mμ sh (ε 6780), (methanol) 260.5 mμ (ε 8230) 275 mμ sh (ε 6300); nmr (DMSO-d_6) δ 6.12 (s, 2, 4-NH_2), 5.95 (d, 1, $J_{1'-2'}$=3.5 Hz, H_1'), 5.25 (d, 1, J_{3-5}= 2.5 Hz, H_3), 5.76 ("q", 1, J_{5-3}=2.5 Hz, J_{5-6}=7.5 Hz, H_5), 7.52 (d, 1, J_{6-5}=7.5 Hz, H_6).

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.82; N, 11.57. Found: C, 49.39; H, 6.03; N, 11.33.

Method B.

A solution of 7.4 g. (0.137 mole) of sodium methoxide and 7.4 g. (0.0124 mole) of **14** in 1000 ml. of dry methanol was refluxed for 2.5 hours while protected from moisture. The solution was then cooled to -10°, neutralized to *p*H ≅7 with concentrated hydrochloric acid, and evaporated to dryness. The residue was treated with 200 ml. of water and extracted with four 150 ml. portions of ether. The aqueous layer was evaporated and the residue was extracted with 400 ml. absolute ethanol and filtered using a Celite bed. The filtrate was evaporated and the residue was dissolved in 20 ml. of 30% aqueous methanol and chromatographed on a column (1 in. diameter, 200 ml.) of Dowex 1-X2 (OH^-) as in Method A. giving 1.48 g. (49%) of crystalline **16**, m.p. 207-209° which was identical in all respects to the product from Method A.

4-Acetamido-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-2-pyridone (**22**).

To a solution of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (**14**) (**17**) [from 15.5 g. (0.0272 mole) of 1-*O*-*p*-nitrobenzoyl-2,3,5-tri-*O*-benzyl-D-arabinofuranose] in 150 ml. of methylene chloride was added 3.0 g. (0.018 mole) of **13** and 10 g. of 4 Å molecular sieves. This mixture was sealed, allowed to stand for 8 days at room temperature, filtered, and the sieves washed well with chloroform. The combined filtrate was evaporated and 50 ml. of ethanol was added to the residual sirup. This solution was heated for 5 minutes on the steam bath and evaporated. The resulting sirup was dissolved in 250 ml. of chloroform and this solution was washed with two 50 ml. portions of water, two 50 ml. portions of saturated aqueous sodium bicarbonate, two 50 ml. portions of water, dried (magnesium sulfate), and evaporated to dryness. The residue was dissolved in 25 ml. of chloroform and applied to a column (1 in. diameter, 220 g.) of silica gel packed in chloroform. The column was eluted with 2400 ml. of chloroform and then 2400 ml. of chloroform:acetone (8:2) and 200 ml.

fractions were collected. Fractions 14 to 24 were pooled and evaporated to yield 3.67 g. (37%) of **22** as a sirup which was crystallized from benzene-ligroin (b.p. 30-60°) to give needles of **22**, m.p. 112-113°; uv max (*p*H 1) 288, 258 mμ (ε 5550, ε 16,360), (*p*H 11) 292, 258 mμ (ε 5820, ε 16,100), (methanol) 300, 255 mμ (ε 5550, ε 16,800).

Anal. Calcd for $C_{33}H_{34}N_2O_6$: C, 71.46; H, 6.18; N, 5.05. Found: C, 71.16; H, 5.99; N, 4.97.

4-Amino-1-β-D-arabinofuranosyl-2-pyridone (3-Deazacytosine arabinoside) (**23**).

A solution of 1.0 g. (0.0018 mole) of **22** in 75 ml. of 0.035 *N* sodium hydroxide in 30% aqueous methanol was refluxed for 4.5 hours. Methanol was removed by evaporation and the resulting aqueous mixture was extracted with four 50 ml. portions of chloroform. The combined organic phase was washed with 50 ml. of water, dried (sodium sulfate), and evaporated to dryness to give 0.90 g. (97%) of a yellow solid foam, nmr (DMSO-d_6) δ 5.54 (s, 2, 4-NH_2). This material [1.12 g. (0.00218 mole)] was dissolved in 100 ml. of 50% aqueous ethanol and hydrogenated for 50 hours at 50 psi over 0.56 g. of 10% palladium-charcoal at room temperature.

The mixture was filtered using a Celite bed, the filter cake was washed with 25 ml. of hot ethanol, and the combined filtrate was evaporated to give 0.68 g. of a solid glass. This material was dissolved in 6.5 ml. of 50% aqueous methanol and applied to a column (1 cm. diameter, 20 ml.) of Dowex 1-X2 (OH^-) (200-400) mesh packed in the same solvent. Elution with 50% aqueous methanol was begun and 4 ml. fractions were collected. Fractions 46 to 110 were pooled and evaporated to give a residue which was crystallized from methanol-ether to yield 0.20 g. (38%) of needles of **23**, m.p. 217.5-219.5°; $[\alpha]_D^{28}$ + 128° (*c* 1, water); uv max (*p*H 1) 258.5 mμ (ε 16,700), (*p*H 11) 258.8 mμ (ε 9,570) 275 mμ/sh (ε 7140), (methanol) 260.5 mμ (ε 9,200) 275 mμ/sh (ε 6780), (water) 259.5 mμ (ε 9,100) 275 mμ/sh (ε 6780); nmr (deuterium oxide) δ 6.23 (d, 1, $J_{1'-2'}$=5.0 Hz, H_1').

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.82; N, 11.57. Found: C, 49.44; H, 5.88; N, 11.30.

4-Acetamido-1-(3,5-di-*O*-*p*-toluyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (**20**) and 4-acetamido-1-(3,5-di-*O*-*p*-toluyl-2-deoxy-α-D-*erythro*-pentofuranosyl)-2-pyridone (**18**).

A well stirred mixture of 2.0 g. (0.012 mole) of **13** and 4.6 g. (0.012 mole) of **5** was fused for 1 hour at 100° *in vacuo* (aspirator). The resulting light brown melt was treated with 50 ml. of ethyl acetate:ethanol (1:1) and the insoluble material was removed by filtration. The filtrate was evaporated and the residue was dissolved in 10 ml. of chloroform and applied to a dry packed column (1 x 23 in.) of silica gel. The column was washed with 1500 ml. of chloroform and elution was begun with chloroform: acetone (9:1). Fractions (100 ml.) 11 to 14 were pooled and evaporated to yield 0.15 g. of the β anomer **20** which was crystallized from ethyl acetate:benzene to give needles of **20**, m.p. 201.5-203.5°.

Anal. Calcd for $C_{28}H_{28}N_2O_7$: C, 66.66; H, 5.59; N, 5.55. Found: C, 66.57; H, 5.45; N, 5.49.

Fractions 15 to 35 were pooled and evaporated to yield 1.41 g. of an anomeric mixture of **20** and **18**. Fractions 36 to 41 were pooled and evaporated to yield 0.20 g. of **18** which was crystallized from ethyl acetate:benzene to give crystals of **18**, m.p. 192-194° [Total yield of **20** plus **18**, 1.76 g. (29%)].

Anal. Calcd for $C_{28}H_{28}N_2O_7 \cdot 1.5H_2O$: C, 63.30; H, 5.87; N, 5.27. Found: C, 63.52; H, 5.74; N, 4.96.

4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-pyridone (2'-deoxy-3-deazacytidine) (**21**).

A mixture of 1.27 g. (0.00252 mole) of an anomeric mixture (mainly **20** by tlc) of **20** and **18** in 250 ml. of methanol containing 1.27 g. of sodium methoxide was refluxed for 2.5 hours with stirring. The yellow solution was neutralized with 10 ml. of Dowex 50W-X12 (H^+) resin after cooling to room temperature. This mixture was filtered, the filtrate evaporated, the residue treated with 30 ml. of water and extracted with three 30 ml. portions of ether. The aqueous layer was evaporated and the residue dissolved in 3 ml. of water and applied to a column (2 cm. diameter, 90 ml.) of Dowex 1-X2 (OH^-). The column was eluted with water and 2 ml. fractions were collected. Fractions 148 to 200 were pooled and evaporated and the residue was crystallized from ethanol-acetone-chloroform to give 0.14 g. (25%) of crystalline **21**, m.p. 193-194°; $[\alpha]_D^{28}$ + 39.8° (*c* 1, water); uv max (*p*H 1) 258 mμ (ε 14,400), (*p*H 11) 259 mμ (ε 8670) 275 mμ/sh (ε 6700), (water) 260 mμ (ε 9000) 275 mμ/sh (ε 6800); nmr (deuterium oxide) δ 6.42 ("t", 1, $J_{1'-2',2''}$=6.7 Hz, H_1').

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.07; H, 6.02; N, 12.52.

4-Amino-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-2-pyridone (**19**).

A solution of 0.62 g. (0.0012 mole) of **18** in 150 ml. of methanol containing 0.62 g. of sodium methoxide was treated analogously to the preparation of **21** above. Fractions 99 to 130 were pooled and evaporated to give 0.12 g. (43%) of **19** as a white solid foam. This chromatographically homogeneous [tlc R_{21}/R_{19}=1.3 using upper phase ethyl acetate:1-propanol:water (4:1:2)] product was not obtained in crystalline form. $[\alpha]_D^{28}$ -16.1° (*c* 1.1, water); uv max (*p*H 1) 258 mμ (ε 14,000), (*p*H 11) 259 mμ (ε 7370) 275 mμ/sh (ε 5710), (water) 259 mμ (ε 7050) 275 mμ/sh (ε 5390); nmr (deuterium oxide) δ 6.28 ("q", 1, $J_{1'-2',2''}$=3.8 and 7.2 Hz, H_1').

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.90; H, 6.27; N, 12.11.

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