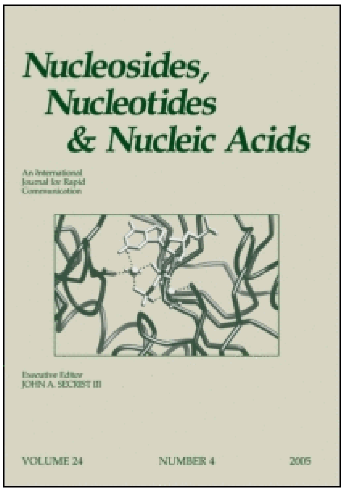

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CHEMICAL CONVERSION OF URIDINE TO 3'-BRANCHED SUGAR NUCLEOSIDES (NUCLEOSIDES AND NUCLEOTIDES. 42[1].)

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ABSTRACT

Deamination of 1-(3-amino-3-deoxy-β-D-glucopyranosyl)-uracil gave a ring contracted nucleoside, 3'-deoxy-3'-formyluridine as a hemiacetal form, and uracil. Similar treatment of the 2'-deoxyderivative, 1-(3-amino-2,3-dideoxy-β-D-glucopyranosyl)uracil, gave the corresponding 2',3'-dideoxy-3'-formyluridine in high yield. The 3'-epimerization of the 3'-formyluridine derivative was achieved and after reduction of the formyl groups, 2',3'-dideoxy-3'(R and S)-hydroxymethyluridine were obtained.

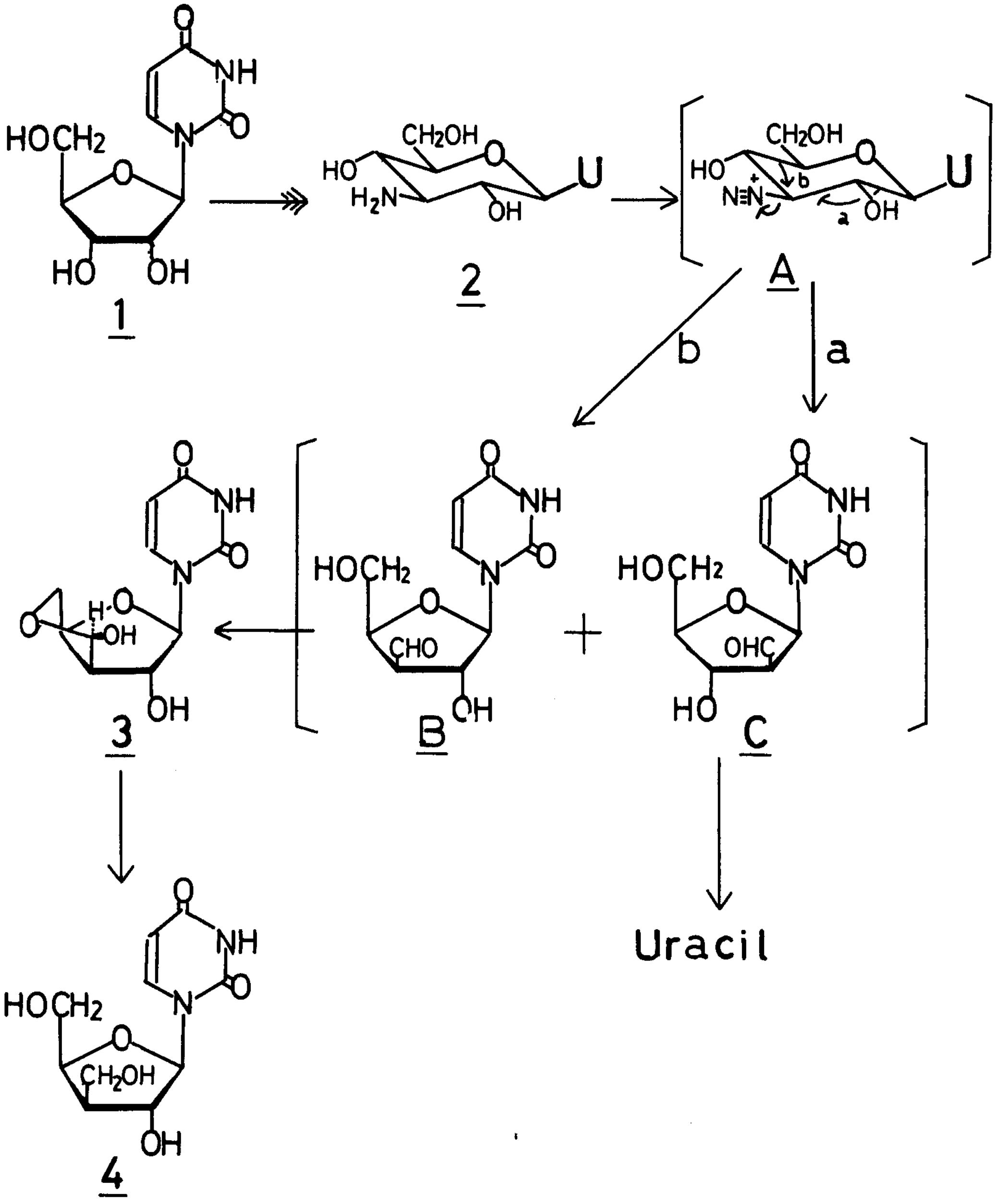
There has been much effort expended on the preparation of 3'-branched sugar nucleosides as potential antimetabolites. Most of these compounds have been synthesized by the prior preparation of branched sugars and successive condensation with nucleobases[2]. In the present paper we report the synthesis of 3'-hydroxymethyluridines from uridine (1) by reactions involving the ring expansion-recontraction of the ribosyl moiety.

It is known that the nitrite deamination of aminosugars such as methyl 3-amino-3-deoxy-β-D-glucopyranoside proceeds by regioselective ring contraction to give methyl 3-deoxy-3-formyl-β-D-xylofuranoside[3]. However, the O-acylated derivative of the same 3-aminoglucose[3b] or its uracil nucleoside[4] are reported to give the gluco or allo derivatives, respectively, without ring contraction during the deamination. It is of interest to examine whether the nitrite deamination of 3-amino-3-deoxyglucopyranosyluracil proceeds with regiospecific or stereospecific ring contraction or with a simple amino-hydroxy substitution.

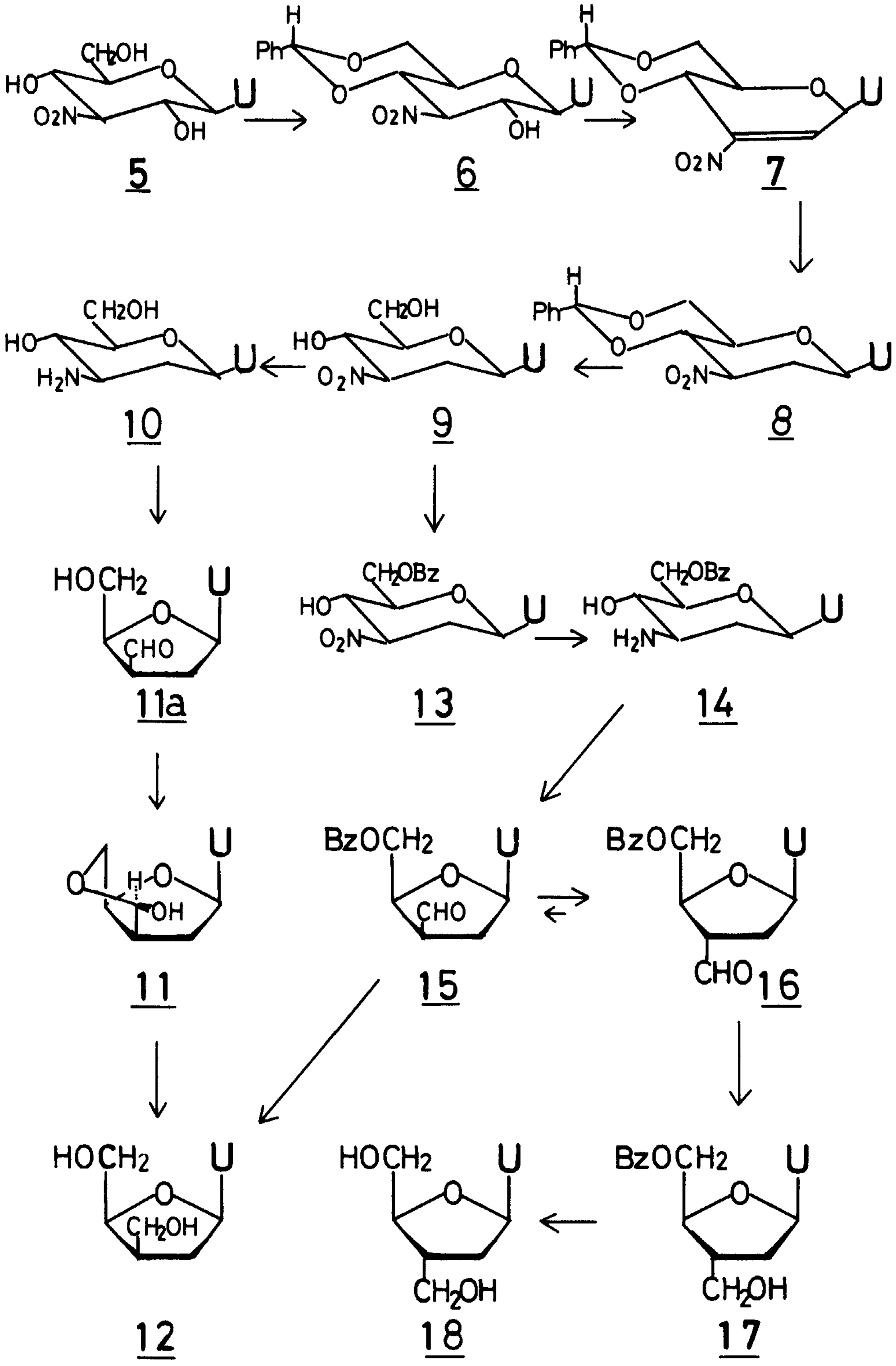
Treatment of 1-(3-amino-3-deoxy-β-D-glucopyranosyl)uracil (2, readily accessible from uridine via a periodate oxidation followed by condensation with nitromethane, and successive hydrogenation[5]) with sodium nitrite in 20% acetic acid at low temperature and separation of the products through a silica gel column afforded a crystalline material (3). The structure of 3 was determined on the basis of elemental analyses, mass and NMR spectra, as 3'-deoxy-3'-formyluridine in a form of cyclic hemiacetal (3). The (R)-configuration of the 3''-carbon of 3 was deduced as the coupling of the 3''-proton was observed only with that of the 3''-hydroxyl group in NMR measurement (Table 1). The structure of 3 was further confirmed by converting it to the 3'-hydroxymethyl derivative (4) by treatment of 3 with sodium borohydride (Scheme 1).

The yield of 3 was less than 50% from 2 and the reaction also gave a significant amount of uracil. This release of uracil may be best explained by assuming two pathways of ring contraction of the diazonium intermediate (A, Scheme 1), giving the 3'-formyl (B) and 2'-formyl (C) derivatives, respectively. The 3'-formyl derivative (B) is stabilized by a cyclic hemiacetal (3) formation while the 2'-formyl derivative is expected to undergo ready beta-elimination to release uracil.

Therefore it follows that for a similar ring contraction with the 2'-deoxy derivative of 2, the exclusive bond migration from the 4'-5' linkage would be expected giving the 3'-formyl-2'-deoxyuridine derivative as a sole product. Preparation of 3'-amino-2',3'-dideoxy-β-D-glucopyranosyluracil was achieved by the route shown in Scheme 2. 1-(3-Deoxy-3-nitro-β-D-glucopyranosyl)uracil[5] (5) was treated with benzaldehyde and zinc chloride to give the 4',6'-O-benzylidene derivative[6] (6). This was treated with methanesulfonyl chloride and triethylamine in


HOCH₂
HO
OH
1
2
CH₂OH
HO
H₂N
OH
U
A
N≡N
b
a
B
CHO
C
OHC
3
H
OH
4
CH₂OH
Uracil

Scheme 1



5
6
7
8
9
10
11a
11
12
13
14
15
16
17
18
CH2OH
HO
O2N
OH
U
Ph
H
H2N
CH2OBz
HOCH2
CHO
BzOCH2
CH2OH

Scheme 2

tetrahydrofuran to give the 2',3'-unsaturated derivative (7) which was hydrogenated with sodium borohydride to furnish the 2',3'-dideoxy-3'-nitro derivative (8) in a crystalline form. Deprotection of 8 with refluxing aqueous acetic acid gave crystalline 1-(2,3-dideoxy-3-nitro-β-D-glucopyranosyl)uracil (9). hydrogenation of 9 with Ni catalyst gave the 3'-amino compound (10).

Treatment of 10 with sodium nitrite in 25% acetic acid gave, after column chromatography with silica gel, a cyclic hemiacetal (11) of 2',3'-dideoxy-3'-formyluridine (11a) in a yield of 73%. In this case liberation of uracil was not observed. Reduction of 11 with sodium borohydride afforded cystalline 2',3'-dideoxy-3'(S)-hydroxymethyluridine (12).

As the analog of 2'-deoxyuridine the 3'-epimer of 12 would be more important. In order to obtain this compound the epimerization of the 3'-position at the step of 11a seemed promising and might be realized by the prior protection of the 5'-hydroxyl group of 11a to prevent the hemiacetal formation. Treatment of 9 with benzoyl chloride in a mixture of chloroform and pyridine at -20° to -5° gave the 6'-O-benzoyl derivative (13) in high yield. Hydrogenation of the 3'-nitro group of 13 to produce 14 followed by nitrite treatment gave the free 3'(R)-formyl derivative (15). When the product was applied to a silica gel column and kept for 24 hr in the column (solvent: chloroform-ethyl acetate) the epimerization at the C-3' took place to reach an equilibrium in which the 3'(S)-epimer (16) was predominant. The epimerization was readily checked by the NMR chemical shift of the aldehydic proton of 15 (9.93 ppm) to 16 (9.70 ppm). Reduction of the formyl group of 16 with sodium acetoxyborohydride gave 5'-O-benzoyl-2',3'-dideoxy-3'(R)-hydroxymethyluridine (17). Debenzoylation of 17 afforded the 3'-hydroxymethyluridine (18), a 3'-methylene homolog of 2'-deoxyuridine.

EXPERIMENTAL

General procedures-----NMR spectra were taken on a JEOL PS-100 spectrometer (100 MHz) or a JEOL PS-200 spectrometer

(200 MHz) with tetramethylsilane as internal standard, and were summarized in Table 1. Mass spectra were measured on a JEOL JMS-D300 spectrometer. Mass spectrum of all compounds gave a molecular ion, a sugar ion, and a base or base + 1 or base + 2 ion. UV spectra were measured on a Shimadzu UV-300 or UV-240 spectrophotometer. Melting points were measured on a Yanagimoto MP-3 micro melting point apparatus and were uncorrected.

3'-Deoxy-3'(R)-formyluridine-5',3''-hemiacetal (3)----Compound 2[5] (20 g) was dissolved in 400 mL of 25% AcOH and the solution was cooled in an ice-bath. Sodium nitrite (32 g) in 10 mL of H_2O was added dropwisely to the solution for 25 min. The mixture was stirred further for 30 min at room temperature and the solvent was removed *in vacuo*. The residue was dissolved in 50% MeOH (50 mL) and 100 g of silica gel was added to the solution. The mixture was dried *in vacuo* and the residue was applied on top of a silica gel column (500 g). The product was eluted with 30% iAmOH-$CHCl_3$ and crystallized from water to give 9.2 g (49%) of 3, mp 214-215°. *Anal*. Calcd for $C_{10}H_{12}N_2O_6$: C, 46.88; H, 4.72; N, 10.93. Found: C, 46.91; H, 4.71; N, 10.83.

3'-Deoxy-3'(R)-hydroxymethyluridine (4)----Compound 3 (135 mg) was dissolved in H_2O and 40 mg of $NaBH_4$ was added to the solution. After stirring overnight the solution was neutralized with 1 *N* HCl and the solvent was removed. The residue was mixed with 1.5 g of silica gel in MeOH and the mixture was dried *in vacuo*. The residue was applied on top of a silica gel column (20 g). The product was eluted with 10% MeOH-$CHCl_3$. Crystallization from MeOH gave 142 mg of 4, mp 161-163°. *Anal*. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.51; H, 5.44; N, 10.88.

1-(3-Deoxy-3-nitro-4,6-O-benzylidene-β-D-glucopyranosyl)-uracil (6)----Compound 5[5] (9.0 g) and $ZnCl_2$ (9.0 g, freshly fused) were taken in 150 ml of benzaldehyde and the mixture was

Table 1. ^{1}H-NMR Chemical Shifts of 3'-Branched Sugar Nucleosides and Related Compounds in DMSO-d_6.

Compound	H-N^3	H-6	H-5	H-1'	H-2'	H-3'	H-4'	H-5'	H-6'or3''	HO(position)	Ph-	PhCH-
6	11.41*	7.88 d (8.3)	5.71 d	5.82 d (8.7)	3.95 m	5.25 dd (10)	4.31 m	3.79 m	4.31 m	6.49(2') d (5.4)	7.38 s	5.67 s
8	11.46	7.86 d (8.0)	5.70 d	6.11 dd	2.5** m	4.8 m	3.87 m	3.87 m	4.31 m		7.83 s	5.73 s
9.	11.42	7.86 d (8.0)	5.64 d	5.82 dd (3.0,6.0)	2.5** m	5.05 m	4.0--------------3.5			5.88(4'),4.76(6') d t (6.7) (4.0)		
13	11.41	7.86 d (7.8)	5.64 d	5.98 dd (5.8,6.2)	2.5** m	5.15 m	4.1-----3.9		a 4.54d b 4.38dd (11.2,4.5,0)	6.20(4') d (6.3)	8.0-7.5 m	
3	11.36	7.44 d (8.2)	5.66 d	5.65 d (6.4)	3.92 m	2.56 dd (8.0,7.3)	4.84 br.d (7.3)	3.87 br.s	5.36 d (3.9)	5.76(2'),6.30(3'') d d (5.4) (3.9)		
4(+D$_2$O)		7.99 d (8.3)	5.68 d	5.71 d (6.6)	4.3- 3.9m	2.6-** 2.4m	4.3- 3.9m	3.68----- m	3.60 m			
11	11.31	7.51 d (7.8)	5.66 dd (1.9***)	5.94 dd (6.3,6.9)	2.8- 2.5m	1.78 m	4.71 dd (1.9,6.8)	a 3.94d b 3.90dd (11.0,2.0)	5.23 d (3.5)	6.20(3'') d (3.5)		
12	11.25	8.00 d (7.8)	5.63 d	5.96 dd (6.0,8.5)	a 2.5m** b 2.25m	1.80 m	4.04 dt (7.8,3.9)	3.5------ m	3.6 m	4.94, 4.74(3'',5') t t (4.2) (4.9)		
18	11.22	7.98 d (7.8)	5.60 d	5.96 dd (4.0,6.1)	2.40---- m	1.98 m	3.79 m	3.5 m	3.76 m	5.03, 4.77(3'',5') t t (4.0) (4.0)		
15(CDCl$_3$+D$_2$O)		7.94 d (7.8)	5.61 d	6.19 dd (6.0,6.2)	2.50** m	3.50 m	4.9-------- m	4.5 m	9.93 d (1.0)		8.0-7.4 m	
16	11.34	7.9 d	5.61 d (8.0)	6.05 dd (5.0,4.9)	a 2.7m b 2.3m	3.4 m	4.8--------4.4		9.70 d (1.5)		8.0-7.5 m	

*All signals of the N-3 protons are broad singlets. **Buried or partially buried in the signals of DMSO.
***Long-range coupling with the N-3 proton.

stirred for 2 days at room temperature. The mixture was poured into 1000 mL of n-hexane under vigorous stirring. The solvent was removed by decantation and the oily residue was taken up in EtOAc. The solution was washed with dil.HCl, $NaHCO_3$ solution, and H_2O and the organic layer was concentrated. The concentrate was applied to a column of silica gel. Elution with EtOAc-$CHCl_3$ (1:1) gave 7.9 g (67%) of 6 which was crystallized from MeOH, mp 255-260° (dec.). Anal. Calcd . for $C_{17}H_{17}N_3O_8$: C, 52.18; H, 4.38; N, 10.74. Found: C, 52.06; H, 4.29; N, 10.51.

From the later eluate 1-(3-deoxy-3-nitro-4,6-O-benzylidene-β-D-galactopyranosyl)uracil, 1.6 g(14%), was obtained as a crystal from MeOH, mp 254-256°. NMR (200 MHz, DMSO-d_6)δppm: 11.43 (broad s, 1, HN^3), 7.60 (d, 1, H-6, J= 7.60 Hz), 6.21 (d, 1, HO-2', J= 5.4 Hz), 5.76 (d, 1, H-5), 5.72 (d, 1, H-1', J= 8.8 Hz), 5.68 (s, 1, HCPh), 7.39 (s, 5, Ph), 5.35 (dd, 1, H-3', $J_{2',3'}$= 9.9 Hz, $J_{3',4'}$= 3.4 Hz), 4.82 (d, 1, H-4', $J_{4',5'}$= 0 Hz), 4.48 (m, 1, H-2'), 4.14 (broad s, 2, H-6'), 4.02 (s, 1, H-5'). Anal. Calcd for $C_{17}H_{17}N_3O_8$: C, 52.18; H, 4.38; N, 10.74. Found: C, 52.19; H, 4.31; N, 10.68.

1-(2,3-Dideoxy-3-nitro-4,6-O-benzylidene-β-D-glucopyranosyl)uracil (8)----Compound 6 (500 mg) was dissolved in 10 mL of THF and MsCl (0.2 mL) was added to the solution at room temperature. After stirring for 20 min the solution was cooled in an ice bath and Et_3N (0.5 mL) was added. The mixture was stirred for 45 min while the temperature was gradually raised to room temperature. After separation of precipitates by filtration, the filtrate was concentrated and the residue was taken up in EtOAc and washed with dil.$NaHCO_3$ solution. The solvent was evaporated to leave amorphous 7 which was dissolved in EtOH (10 mL) and treated with 150 mg of $NaBH_4$ for 5 hr. The mixture was neutralized with 1 N AcOH and the solvent was evaporated. The residue was taken up in EtOAc-H_2O, the organic layer was concentrated, and the residue was crystallized from MeOH to give 444 mg (81%) of 8, mp 245-247°.

1-(2,3-Dideoxy-3-nitro-β-D-glucopyranosyl)uracil (9)----Compound 8 (880 mg) in 10 mL of 75% AcOH was refluxed for 40 min and the solvent was removed in vacuo. The residue was taken up in a small volume of MeOH, which was adsorbed in silica gel. The dried gel was applied to a column of silica gel and was eluted with MeOH-$CHCl_3$ (1:10). After concentration of the eluate the residue was crystallized from MeOH to give 457 mg (67%) of 9, mp 244-247°. Anal. Calcd for $C_{10}H_{13}N_3O_7$: C, 41.81; H, 4.56; N, 14.63. Found: C, 41.62; H, 4.53; N, 14.47.

1-(2,3-Dideoxy-3-amino-β-D-glucopyranosyl)uracil (10)-----Compound 9 (457 mg) was dissolved in 30 mL of 60% MeOH and hydrogenated over Ni catalyst (wet weight 2 g) at 3 atm H_2 for 50 min. The mixture was filtered, the filtrate was concentrated, and the residue 10 (331 mg, 81%) was used for the next step without further purification.

2',3'-Dideoxy-3'(R)-formyluridine-3'',5'-O-hemiacetal (11)----Compound 10 (330 mg) was dissolved in 10 mL of 25% AcOH and a 5 mL solution of 600 mg of $NaNO_2$ in H_2O was added dropwise to the solution under ice-cooling. After stirring for 30 min at room temperature the mixture was concentrated and the residue was taken to 50% MeOH and mixed with silica gel. After drying the gel it was placed on a column of silica gel and developed with MeOH-$CHCl_3$ (1:19). From the eluate 226 mg of 11 (73%) was obtained which was crystallized from H_2O, mp 197-199°. Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.80; H, 5.20; N, 11.56.

2',3'-Dideoxy-3'(S)-hydroxymethyluridine (12)----Compound 11 (300 mg) in 12 mL of 80% MeOH was treated with 100 mg of $NaBH_4$ in 6 mL of MeOH. After stirring for 2 hr, the solvent was removed in vacuo and the residue was applied to a silica gel column and elution with MeOH-$CHCl_3$ (1:10) gave 280 mg (93%) of 12, which was crystallized from MeOH-EtOAc, mp 144-147°. Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.37; H, 5.78; N, 11.62.

1-(2,3-Dideoxy-3-nitro-6-O-benzoyl-β-D-glucopyranosyl) uracil (13)----Compound 9 (400 mg) was dissolved in 16 ml of $CHCl_3$-pyridine (1:1) and cooled to -20°. To the solution was added 0.26 mL (1.3 eq) of benzoyl chloride in 5 mL of $CHCl_3$

over 30 min. The solution was stirred overnight at -5°. The solvent was removed in vacuo and the residue was applied to a silica gel column. On elution with MeOH-$CHCl_3$ (1:19) 13 was obtained as a foam (504 mg, 82%) which was crystallized from iPrOH, mp 150-156°. Anal. Calcd for $C_{17}H_{17}N_3O_8$: C, 52.17; H, 4.38; N, 10.74. Found: C, 52.39; H, 4.41; N, 10.54.

2',3'-Dideoxy-3'(R)-formyl-5'-O-benzoyluridine (15)----Compound 13 (540 mg) was dissolved in 50 mL of 60% MeOH and was hydrogenated over Ni catalyst (3.0 g) under hydrogen at 3 atm. After separation of the catalyst the filtrate was concentrated and the residue (14) was taken in 15 mL of 40% AcOH. $NaNO_2$ (750 mg) in 5 mL of H_2O was added to the cold solution and the mixture was stirred for 30 min. After neutralization of the solution by adding $NaHCO_3$, it was extracted with EtOAc. The organic layer was dried and evaporated to leave 361 mg (76%) of 15 as a foam.

2',3'-Dideoxy-3'(S)-formyl-5'-O-benzoyluridine (16)----Compound 15 (100 mg) was dissolved in MeOH and silica gel was added to it. After evaporation and drying the silica gel it was placed on top of silica gel with $CHCl_3$-EtOAc and kept at room temperature overnight. Elution with the same solvent gave 84 mg of 16 as a foam.

2',3'-Dideoxy-3'(R)-hydroxymethyl-5'-O-benzoyluridine (17)----To a solution of compound 16 (60 mg) in 5 mL of THF was added $NaBH_3OAc$ (90 mg). After 2 hr the solvent was removed in vacuo and the residue was partitioned between EtOAc and H_2O. The organic layer was concentrated and the residue was crystallized from iPrOH to give 31 mg (51%) of 17, mp 165-166°. Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.09. Found: C, 59.07; H, 5.18; N, 8.14.

2',3'-Dideoxy-3'(R)-hydroxymethyluridine (18)----Compound 17 (30 mg) in 2 mL of EtOH was treated with 0.5 mL of 0.5 N NaOEt in EtOH at room temperature for 1 hr. The solution was neutralized by addition of Dowex 50 (H^+) resin, the resin was filtered off and the filtrate was concentrated. The residue was partitioned between $CHCl_3$ and H_2O and the organic layer was evaporated to leave 19 mg (90%) of 18. Crystallization of 18 from EtOAc-MeOH gave a pure sample, mp 140-141°.

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.31; H, 5.76; N, 11.65.

Reduction and Debenzoylation of 15 to 12----To a solution of 15 (360 mg) in 10 mL of THF was added 500 mg of $NaBH_3OAc$ and after stirring for 2 hr the solvent was evaporated and the residue was partitioned between EtOAc and H_2O. The organic layer was concentrated and the residue was applied to a column of silica gel. From the eluate of MeOH-$CHCl_3$ (1:19) 280 mg (77%) of 2',3'-dideoxy-3'(S)-hydroxymethyl-5'-O-benzoyluridine was obtained (mp 164.5-165.5° from EtOH. Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.09. Found: C, 58.71; H, 5.28; N, 8.08). Treatment of the product (35 mg) with 1 N NaOEt-EtOH (0.1 mL in 2 mL) at room temperature for 1 hr and, after neutralization, evaporation of the solvent gave 12 (21 mg, 86%) as amorphous form. The spectroscopic data of the compounds were identical with those of 12 from 11.

REFERENCES AND NOTES

1. Part 41: S. Watanabe and T. Ueda, This Journal, in press.
2. For example see: a. E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmermann and F. W. Holly, J. Am. Chem. Soc., 88, 4524 (1966). b. A. J. Brink, O. G. De Villiers, and A. Jordaan, Carbohyd. Res., 54, 285 (1977). c. A. Rosenthal and M. Sprinzl, Can. J. Chem., 47, 4477 (1966). d. E. M. Acton, R. N. Goerner, H. S. Uh, K. J. Ryan, D. W. Henry, C. E. Cass, and G. A. LePage, J. Medicin. Chem., 22, 518 (1977). e. J. M. J. Tronchet and J. F. Tronchet, Helv. Chim. Acta, 64, 425 (1981). f. H. P. Albracht and J. G. Moffatt, Tetrahedron Lett., 1064 (1970).
3. a. S. Inoue and H. Ogawa, Chem. Pharm. Bull. (Tokyo), 8, 79 (1960). b. For general discussions on the deamination of aminosugars see: J. M. Williams, Advan. Carbohyd. Chem. Biochem., 31, 9 (1975).
4. K. A. Watanabe, J. Beranek, H. A. Friedman, and J. J. Fox, J. Org. Chem., 30, 2735 (1965).
5. H. A. Friedman and J. J. Fox, in "Synthetic Procedures in Nucleic Acid Chemistry" vol 1, 362, W. W. Zorbach and R S. Tipson Eds, Interscience Publishers, New York (1968).
6. Compound 5 prepared by the method described in ref. 5 contained some galactopyranosyl derivative which can be separated at the step of 4',6'-O-benzylidenation (see experimental).

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