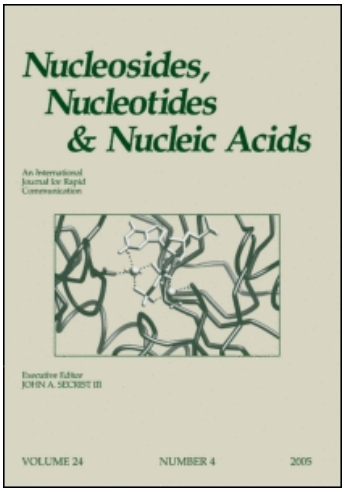

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NUCLEOSIDES. 131. THE SYNTHESIS OF 5-(2-CHLORO-2-DEOXY-β-D-ARABINO-FURANOSYL)URACIL. REINTERPRETATION OF REACTION OF ψ-URIDINE WITH α-ACETOXYISOBUTYRYL CHLORIDE. STUDIES DIRECTED TOWARD THE SYNTHESIS OF 2'-DEOXY-2'-SUBSTITUTED ARABINO-NUCLEOSIDES. 2.

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Abstract: Treatment of ψ-uridine (3) with α-acetoxyisobutyryl chloride in acetonitrile gave, after deprotection, a mixture of four products: 5-(2-chloro-2-deoxy-β-D-arabinofuranosyl)uracil (10a), its 3'-chloro xylo isomer (11a), 2'-chloro-2'-deoxy-ψ-uridine (9a) and 4,2'-anhydro-ψ-uridine (8a). Each component was isolated by column chromatography. Compound 9 was converted to the known 1,3-dimethyl derivative 2 by treatment with DMF-dimethylacetal. Treatment of 10 and 11 with NaOMe/MeOH afforded the same 4,2'-anhydro-C-nucleoside 8. The 1,3-dimethyl analogues of 10 and 11, however, were converted to 2',3'-anhydro-1,3-dimethyl-ψ-uridine (13) upon base treatment. The epoxide 13 was also prepared in good yield by treatment of 10 and 11 with DMF-dimethylacetal.

In the previous paper of this series,[2] we reported that treatment of 2'-O-mesyl-1,3-dimethyl-ψ-uridine (1) (Chart 1) with LiCl in N,N-dimethylformamide (DMF) afforded 2'-chloro-2'-deoxy-1,3-dimethyl-ψ-uridine (2a) in high yield. The results indicate the transitional formation of the 4,2'-anhydro linkage which was subsequently attacked by the chlorine nucleophile from the α-side of the nucleoside to give the "down" chloro (ribo) product. This report describes the results obtained from 2'-O-mesyl-ψ-uridine (6) by the similar LiCl treatment which does not afford 2'-chloro-2'-deoxy-ψ-uridine (9a) but, instead, results in the exclusive formation of 4,2'-anhydro-5-(β-D-arabinofuranosyl)-uracil (8a). Also reported herein is the quite intriguing outcome of our detailed study of the reaction of ψ-uridine (3) with α-acetoxyisobutyryl chloride.

The synthesis of 2'-O-mesyl-ψ-uridine (6) was achieved in two steps in high overall yield from the known[3] 3',5'-O-(1,1,3,3-tetraisopropyldisiloxan-1,3-di-yl)-ψ-uridine (4) (Chart 1). Treatment of 4 with MsCl in pyridine afforded the crystalline mesylate 5 which was desilylated to 6 by $Et_3N \cdot HF$ treatment.[4] When 6 was treated with LiCl in DMF at reflux,

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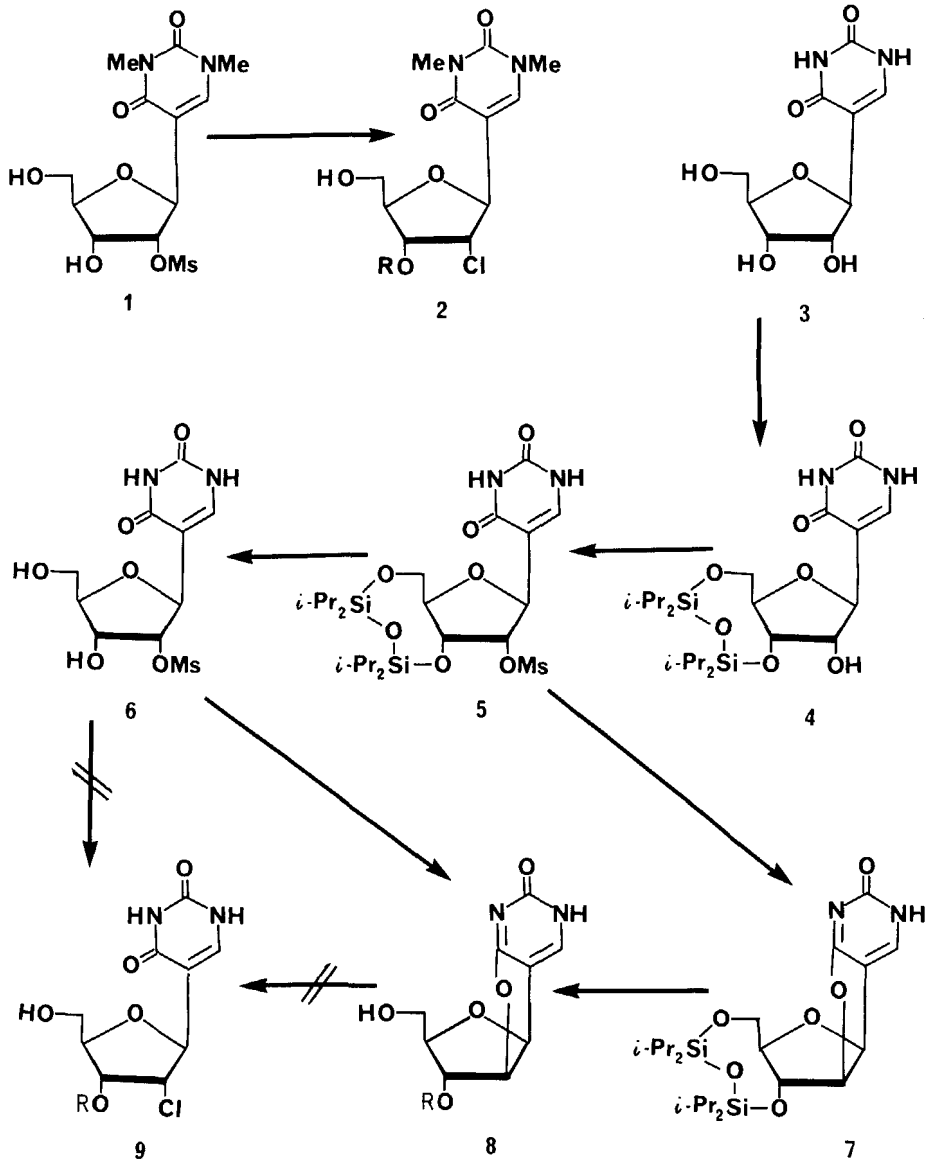


a Series R = H

b Series R = Ac

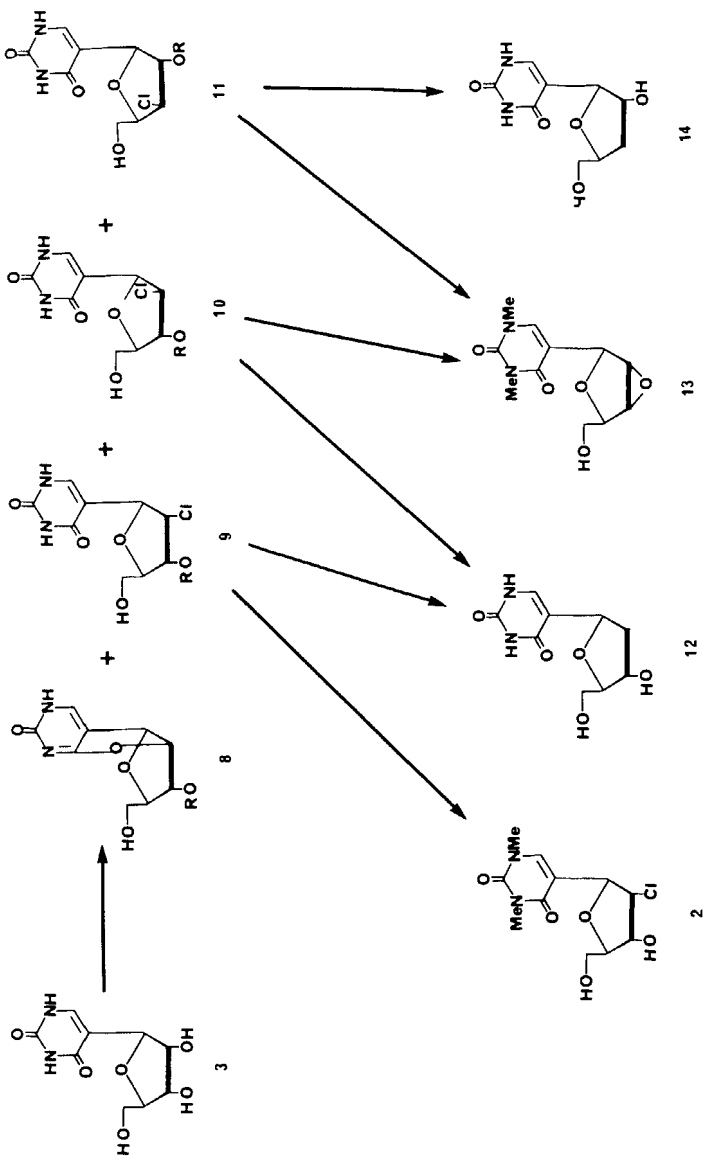
Chart 1

the 4,2'-anhydro-C-nucleoside 8a was the sole product detectable on TLC and was obtained in 71% yield after purification by recrystallization. Compound 8a was also prepared in lower yield by treatment of 5 with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) to give 7 (Chart 1) followed by desilylation. The overall yield of 8 prepared via 7 was only about 20%.

The chemical synthesis of 2'-deoxy-ψ-uridine (12) (Chart 2) was first achieved in our laboratory[5] by treatment of 3 with α-acetoxyisobutyryl chloride[6] or o-acetoxybenzoyl chloride[7] followed by reductive dechlorination of the product under Barton's conditions.[8] We assigned the 2'-chloro-2'-deoxy-ψ-uridine (ribo) structure (9) to the chloro intermediate (which was converted to 12 upon reduction) on the assumption that it was derived from the initially formed 4,2'-anhydro nucleoside (8) by further nucleophilic reaction with chloride, as in the case of uridine.[6] Later, Robins and Muhs[9] repeated the reaction of 3 with α-acetoxyisobutyryl chloride in the presence of solvent, and obtained 3'-deoxy-ψ-uridine (14) as well as 12 after reduction of the chlorinated products. However, they did not separate or identify the chlorinated intermediates.

To our surprise, the anhydro nucleoside 8a was not converted into 2'-chloro-2'-deoxy-ψ-uridine (9a) by treatment with HCl in MeCN under the conditions employed for conversion of 2,2'-anhydrouridine to 2'-chloro-2'-deoxyuridine.[6,10] Consequently, the conversion of 8 into 9 may not occur readily, and our original assignment of the ribo configuration 9 to the 2'-chloro intermediate[5] is unfounded. We therefore studied the reaction of ψ-uridine (3) with α-acetoxyisobutyryl chloride again in order to identify the structure of the 2'-chloro product.

The reaction was carried out in dry acetonitrile as reported previously.[11] After removal of the 2,2,5-trimethyldioxolan-2-yl protecting group from the 5'-position, the crude products were separated on a silica gel column. Two major (10b and 11b) and two minor (8b and 9b) products were isolated from the mixture. Each product was deacetylated to the respective unprotected C-nucleoside. The position of the chlorine substituent in 9 - 11 was unambiguously established by Barton reduction of these compounds. Nucleosides 9a and 10a were both converted into 2'-deoxy-ψ-uridine (12),[5,9,12,13] whereas 11 afforded the known 3'-deoxy C-nucleoside (14). The xylo structure for the 3'-chloro-C-nucleoside was established by ^{1}H NMR analysis of the monoacetate. The small magnitude of $J_{1',2'}$ and $J_{2',3'}$ along with the relatively large $J_{3',4'}$ value (3.0, 1.5 and 5.4 Hz, respectively) are consistent only with the β-xylo configuration 11b.[14,15] The ribo configuration 9 for the minor nucleoside was



a Series R = H
b Series R = Ac

Chart 2

established by conversion to the known 2'-chloro-2'-deoxy-1,3-dimethyl-ψ-uridine (2a) by methylation of 9a with dimethoxymethyldimethylamine (DMF-dimethylacetal).[16] The conversion of 9 to 2 also established the arabino structure 10 for the major 2'-chloro product. It is interesting to note that the reaction of 1,3-dimethyl-ψ-uridine with α-acetoxyisobutyryl chloride afforded the 2'-chloro ribo nucleoside as the major product and 3'-chloro xylo and the 2'-chloro arabino nucleosides as minor products.[2]

It should also be noted that the corresponding N-nucleoside uridine gave exclusively 2'-chloro-2'-deoxyuridine via the 2,2'-anhydrointermediate.[6] Thus, our results indicate that under Moffatt's reaction conditions, mainly the chloride ion attacks the ψ-uridine-2',3'-acetoxonium ion at the C-2' and C-3' positions. On the other hand, intramolecular participation of the C-4 and C-2 carbonyl groups prevail in the case of 1,3-dimethyl-ψ-uridine and uridine, respectively, and 2'-chloro ribo derivative is formed as a major or exclusive (uridine) product.

Differences in the mode of the Moffatt reaction of ψ-uridine, 1,3-dimethyl-ψ-uridine and uridine might be attributed to the differences in nucleophilicity of the aglycon carbonyl group, to the length of the glycosyl bond and/or the differences in an energy barrier to rotation about the glycosyl bond. Our assignment of molecular structures of the chlorinated products derived from ψ-uridine is made by the following studies.

Treatment of 10 and 11 with DMF-dimethylacetal did not afford the corresponding 1,3-dimethyl derivatives but gave the same crystalline product which did not contain chlorine. This product was analyzed correctly as an anhydride. The ^{1}H NMR spectrum (DMSO-d_6), which is very similar to that of 3-methyl-2',3'-anhydrouridine,[17] showed that there is only one dissociable proton, which appeared as a triplet at δ 4.96 indicating the presence of a primary OH group in the molecule. These data established a 2',3'-anhydro structure for the product. Since the chlorine substituent in 10 and 11 is in the "up" configuration, the epoxide formed has to be in the "down" ribo configuration. Consequently, the ribo structure 13 was assigned to the product. Compound 13 was also obtained when 1 was treated with KF in ethyleneglycol at 140°C. When 10 and 11 were treated with NaOMe/MeOH, they were converted to the same 4,2'-anhydro-C-nucleoside 8a. However, 9a was recovered unchanged from the reaction mixture after the same NaOMe treatment. Reaction of the 1,3-dimethyl analogs[2] of 10 and 11 with NaOMe, on the other hand, afforded 13 in good yield. These results are in agreement with the recent report[17] by Kuszmann et al.,

who found that 2,2'-anhydrouridine is in equilibrium with the corresponding 2',3'-epoxide in base. Though the epoxide was never isolated, it was trapped by N-3 methylation.[17]

Thus, the reaction of ψ-uridine (3) with α-acetoxyisobutyryl chloride gives rise to the formation of 2'-chloro-2'-deoxy-β-D-arabino (10) and 3'-chloro-3'-deoxy-β-D-xylo (11) nucleosides as the major products, and 4,2'-anhydro- (8) and 2'-chloro-2'-deoxy-ψ-uridine (9) as the minor products. Unambiguous structural assignments for all the products 8-11 for the first time require the reinterpretation of earlier reports.[18]

EXPERIMENTAL

General Methods: Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL-PFT-100 spectrometer and Me_4Si was the internal standard for organic solvents and DDS for deuterium oxide; chemical shifts are reported in parts per million (δ). Apparent shapes of signals are described as s (singlet), d (doublet), t (triplet), q (quarted), dd (double doublet), m (multiplet), brs (broad singlet). Values given for coupling constants are first order. TLC was performed on Uniplates (Analtech Co., Newark, DE) and column chromatography on Woelm silica gel (70-230 mesh). Microanalyses were performed by Galbraith Laboratories, Inc., or by M.H.W. Laboratories.

3',5'-O-(1,1,3,3-Tetraisopropyldisiloxan-1,3-di-yl)-2',-O-mesyl-ψ-uridine (5).

A mixture of 4 (972 mg, 2 mmol), MsCl (180 μL) in pyridine (20 mL) was stirred overnight at room temperature and then concentrated in vacuo. The residue was dissolved in $CHCl_3$ (100 mL), washed with water, dried (Na_2SO_4), and chromatographed on a silica gel column (42 x 3 cm) using $CHCl_3$-EtOH (19:1 v/v) as the eluent. The nucleoside-containing fractions were collected, evaporated, and the residue was recrystallized from MeOH to give 5, 960 mg (85%), mp 178-180°C. ^{1}H NMR (DMSO-d_6) δ 1.02 (28H, m, i-Pr), 3.31 (3H, s, Ms), 3.72-5.01 (3H, m, H-4',5',5"), 4.40 (1H, dd, H-3', $J_{2',3'}$ = 4.7, $J_{3',4'}$ = 9.1 Hz), 4.81 (1H, s, H-1'), 5.00 (1H, d, H-2', $J_{2',3'}$ = 4.7 Hz), 7.33 (1H, s, H-6), 11.04 (1H, s, NH), 11.30 (1H, s, NH).

Anal. Calcd. for $C_{22}H_{40}N_2O_2SSi_2$: C, 46.78; H, 7.14; N, 4.96; S, 5.67. Found: C, 46.61; H, 7.21; N, 4.52; S, 5.42.

2'-O-Mesyl-ψ-uridine (6).

To a solution of 5 (1.0 g, 1.77 mmol) in THF (10 mL) was added 1M Et_3NHF/THF (4.4 mL, 2.5 equiv.) The mixture was left standing overnight at room temperature and the resulting crystals were collected by filtration and washed with Et_2O and MeOH to give 6 (530 mg, 93%), mp 170°C. ^1H NMR (DMSO-d_6) δ 3.28 (3H, s, Ms), 3.52-3.73 (3H, m, H-4',5',5"), 4.15 (1H, dd, H-3', $J_{2',3'}$ = 2.5, $J_{3',4'}$ = 4.9 Hz), 4.79-4.94 (3H, m, H-1',2', OH), 5.47 (1H, d, OH), 7.67 (1H, s, H-6), 11.19 (2H, brs, 2 NH).

Anal. Calcd. for $C_{10}H_{14}N_2O_8S$: C, 37.27; H, 4.38; N, 8.69; S, 9.95. Found: C, 37.09; H, 4.55; N, 8.49; S, 9.75.

4,2'-Anhydro-5-(3 ,5 -O-tetraisopropyldisiloxan-1,3-di-yl-β-D-arabinofuranosyl)uracil (7).

A mixture of 5 (2.7 g, 4.8 mmol) and DBU (937 μL) in MeCN (80 mL) was heated at reflux for 2 h and then concentrated in vacuo. The residue was chromatographed on a silica gel column using $CHCl_3$-Me_2CO (3:1 v/v as the eluent to give crystalline 7 (700 mg, 31%), mp 235-237°C. ^1H NMR (DMSO-d_6), δ 1.02 (28H, m, i-Pr), 3.67-3.90 (3H, m, H-4',5',5"), 4.28 (1H, dd, H-3', $J_{2',3'}$ = 3.5, $J_{3',4'}$ = 8.6 Hz), 5.29 (2H, m, H-1',2'), 8.04 (1H, s, H-6), 11.48 (1H, brs, NH).

Anal. Calcd. for $C_{21}H_{36}N_2O_6Si$: C, 53.81; H, 7.74; N, 5.97. Found: C, 53.54; H, 7.79; N, 6.13.

4,2'-Anhydro-5-(β-D-arabinofuranosyl)uracil (8a, 4,2'-Anhydro-ψ-uridine).

A. From 7.

To a solution of 7 (234 mg, 0.5 mmol) in THF (5 mL) was added 1M Et_3NHF/THF (1.5 mL). The mixture was kept at room temperature for 30 min. A syrupy product separated and was crystallized from MeOH to give 8a (100 mg, 88%), mp 225°C. The ^1H NMR spectrum of this sample was indistinguishable from that of an authentic sample.[11]

B. From 6.

A mixture of 6 (200 mg, 0.62 mmol) and LiCl (50 mg, 1.2 mmol) in DMF (2 mL) was heated at 100°C for 6 h and then concentrated in vacuo. The residue was crystallized from MeOH to give 8a (100 mg, 71%), mp 225°C. The ^1H NMR spectrum was identical with that of an authentic sample.[11]

Reaction of ψ-Uridine (3) with α-Acetoxyisobutyryl Chloride.

A mixture of 3 (6.0 g, 24.6 mmol) and α-acetoxyisobutyryl chloride (10.0 g, 60.6 mmol) in dry MeCN (300 mL) was heated at reflux until a clear solution was obtained. The solvent was removed in vacuo and the residue was dissolved in $CHCl_3$ (500 mL) containing MeOH (5 mL, saturated

with HCl at 0°C). The solution was kept at room temperature overnight and then concentrated in vacuo. The residue was placed on a silica gel column (42 x 3 cm) which was successively eluted with 2.5% EtOH/$CHCl_3$ (1 L), 5% EtOH/$CHCl_3$ (2 L), 10% EtOH/$CHCl_3$ (2 L) and 20% EtOH/$CHCl_3$ (1 L) and the fractions monitored by TLC (MeOH/$CHCl_3$ 1:9 v/v). Compound 9b was eluted from the column first, followed by 10b, 11b and 8b.

Compound 9b was obtained in 4% yield (400 mg) after crystallization from MeOH-Et_2O, mp 225°C. ^{1}H NMR (DMSO-d_6), δ 2.11 (3H, s, OAc), 3.56 (2H, m, H-5',5"), 3.99 (1H, apparent 1, H-4', $J_{3',4'} = J_{4',5'} = J_{4',5'} =$ 4.3 Hz), 4.71 (2H, m, H-1',2'), 5.23 (1H, pseudo t, H-3', $J_{2',3'} = J_{3',4'} =$ 4.3 Hz), 7.72 (1H, s, H-6), 11.16 (1H, s, NH), 11.28 (1H, brs, NH).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_6$: C, 43.36; H, 4.30; Cl, 11.63; N, 9.19. Found: C, 43.53; H, 4.52; Cl, 11.54; N, 8.96.

Compound 10b was obtained as colorless micro-flakes (1.05 g, 10.5%) after crystallization from MeOH-Et_2O, mp 263°C. ^{1}H NMR (DMSO-d_6) δ 2.10 (3H, s, OAc), 3.61 (2H, m, H-5',5"), 3.90 (1H, six peaks, H-4'), 4.57 (1H, d, H-2', $J_{1',2'} = 3.4$; $J_{2',3'} = 0$ Hz), 4.92 (1H, dd, H-1', $J_{1',2'} =$ 3.4, $J_{1',6'} = 0.2$ Hz), 5.03 (1H, t, 5'-OH), 5.11 (1H, d, H-3', $J_{2',3'} =$ 0, $J_{3',4'} = 3.0$ Hz), 7.30 (1H, d, H-6, $J_{1',6'} = 0.2$ Hz), 11.03 (1H, brs, NH), 11.27 (1H, s, NH).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_4$: C, 43.36; H, 4.30; Cl, 11.63; N, 9.19. Found: C, 43.34; H, 4.33; Cl, 11.47; N, 9.18.

Compound 11b was crystallized from MeOH-Et_2O, (1.5 g, 15%), mp 239°C. ^{1}H NMR (DMSO-d_6) δ 2.08 (3H, s, OAc), 3.67 (2H, t, H-5',5", $J_{4',5'} =$ $J_{4',5"} = 5.4$ Hz), 4.17 (1H, q, H-4', $J_{3',4'} = J_{4',5'} = J_{4',5"} = 5.4$ Hz), 4.54 (1H, dd, H-3', $J_{2',3'} = 1.5$, $J_{3',4'} = 5.4$ Hz), 4.67 (1H, dd, H-1', $J_{1',2'} = 3.0$, $J_{1',6'} = 0.2$ Hz), 4.99 (1H, t, 5'-OH), 5.15 (1H, dd, H-2', $J_{1',2'} = 3.0$, $J_{2',3'} = 1.5$ Hz), 7.31 (1H, d, H-6, $J_{1',6} = 0.2$ Hz), 10.92 (1H, s, NH), 11.24 (1H, s, NH).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_6$: C, 44.36; H, 4.30; Cl, 11.63; N, 9.19. Found: C, 43.27; H, 4.42; Cl, 11.78; N, 9.06.

The 4,2'-anydro-C-nucleoside 8b was eluted last from the column, 660 mg (6.6%), mp 220-225°C. ^{1}H NMR (DMSO-d_6) δ 2.10 (3H, s, OAc), 3.34 (2H, d. H-5',5"), 4.01 (1H, q, H-4', $J_{3',4'} = J_{4',5'} = J_{4',5'} = 5.1$ Hz), 5.20 (1H, dd, H-3', $J_{2',3'} = 0.2$, $J_{3',4'} = 5.1$ Hz), 5.32 (1H, dd, H-2', $J_{1',2'} = 6.1$, $J_{2',3'} = 0.2$ Hz), 5.48 (1H, d, H-1', $J_{1',2'} = 6.1$ Hz), 8.02 (1H, s, H-6), 11.32 (1H, brs, NH). This product gave the known[11] 4,2-anhydro-ψ-uridine (8a) upon deacetylation.

The low yields of pure isomers 9-11 were the result of considerable losses experienced due to the difficulty of chromatographic separation

of these compounds. Semi-quantitative TLC analyses of the reaction mixture showed that 10 and 11 were the major and 8 and 9 the minor products.

5-(2 -Chloro-2 -deoxy-β-D-ribofuranosyl)uracil. (9a, 2'-Chloro-2'-deoxy-ψ-uridine). Compound 9b (200 mg, 0.66 mmol) was dissolved in NH_3/MeOH (10 mL, saturated at 0°C). After 30 min at room temperature, the solution was concentrated in vacuo. The residue was triturated well with $CHCL_3$ and the precipitates were dried in vacuo. Compound 9a was obtained as a foam, 171 mg (90%). ^1H NMR (D_2O) δ 3.57 (2H, m, H-5',5"), 3.78 (1H, m, H-4'), 4.13 (1H, t, H-3', $J_{2',3'} = J_{2',3'} = J_{3',4'} = 5.3$ Hz), 4.44 (1H, t, H-2', $J_{1',2'} = J_{2',3'} = 5.3$ Hz), 4.75 (1H, d, H-1', $J_{1',2'} = 5.3$ Hz), 7.67 (1H, s, H-6).

Anal. Calcd. for $C_9H_{11}ClN_2O_5$: C, 41.15; H, 4.22; Cl, 13.50; N, 10.66. Found: C, 41.35; H, 4.49; Cl, 13.26; N, 10.85.

In a similar manner, 10b, 11b and 8b were converted to the corresponding deacetylated products. Compound 10a; mp 248°C, ^1H NMR (DMSO-d_6) δ 3.48-3.70 (3H, m, H-4',5',5"), 4.16 (1H, m, H-3', collapsed to a doublet upon addition of D_2O, $J_{2',3'} = 0$, $J_{3',4'} = 2.1$ Hz), 4.40 (1H, d, H-2', $J_{1',2'} = 3.6$, $J_{2',3'} = 0$ Hz), 4.91 (1H, t, 5'-OH, 4.96 (1H, d, H-1', $J_{1',2'} = 3.6$ Hz), 5.87 (1H, d, 3'-OH), 7.30 (1H, d, H-6, $J_{6,NH}$ - 5.6 Hz, became a singlet upon exchange), 10.49 (1H, d, NH), 11.22 (1H, s, NH).

Anal. Calcd. for $C_9H_{11}ClN_2O_5$: C, 41.15; H, 4.22; Cl, 13.50; N, 10.66. Found: C, 41.01; H, 4.45; Cl, 13.70; N, 10.51.

Compound 11a; mp 195-197°C, ^1H NMR (DMSO-d_6) δ 3.65 (2H, m, H-5',5"), 4.19-4.24 (3H, m, H-2',3',4'); 4.50 (1H, dd, H-1', $J_{1',2'} = 2.7$, $J_{1',6'} = 0.2$ Hz), 4.92 (1H, t, 5'-OH), 5.91 (1H, d, 2'-OH), 7.26 (1H, d, H-6, $J_{1',6'} = 0.2$ Hz), 11.06 (2H, brs, 2 NH).

Anal. Calcd. for $C_9H_{11}ClN_2O_5$: C, 41.15; H, 4.22; Cl, 13.50; N, 10.66. Found: C, 40.92; H, 4.29; Cl, 13.18; N, 10.36.

Compound 8a; mp 225°C, was obtained as colorless crystals. The ^1H NMR spectrum of this sample was identical with that of 4,2'-anhydro-ψ-uridine.[11]

4,2'-Anhydro-ψ-uridine (8a) from 10b.

Compound 10b (100 mg, 0.35 mmol) was dissolved in 1M NaOMe (5 mL), and the solution was heated at reflux for 1 h. After cooling to room temperature, the mixture was neutralized with Dowex 50 (H^+). The resin was filtered, the filtrate concentrated, and the residue triturated with EtOH to give 8a (63 mg, 80%).

Compound 8a was also obtained in a similar manner from 11b. However, similar treatment of 9a did not afford 8a but, instead, 9a was recovered unchanged.

1,3-Dimethyl-5-(3 -O-acetyl-2 -chloro-2 -deoxy-β-D-ribofuranosyl)uracil (2b).

A mixture of 9b (200 mg, 0.69 mmol) and DMF-dimethylacetal (400 mg, 3.3 mmol) in DMF (4 mL) was heated at 100°C for 1 h, and then concentrated in vacuo. The residue was chromatographed on a silica gel column using $CLCl_3$-EtOH (19:1 v/v) as the eluent. Pure 2b was obtained as a foam (185 mg). ^{1}H NMR (DMSO-d_6) δ 2.11 (3H, s, OAc), 3.18 (3H, s, NMe), 3.33 (3H, s, NMe), 3.62 (2H, m, H-5',5"), 4.03 (1H, m, H-4'), 4.63-4.85 (2H, m, H-1',2'), 5.03 (1H, t, 5'-OH), 5.23 (1H, t, H-3', $J_{2',3'} = J_{3',4'} =$ 4.6 Hz), 7.96 (1H, s, H-6).

Anal. Calcd. for $C_{13}H_{17}ClN_2O_6$: C, 46.92; H, 5.15; Cl, 10.65; N, 8.42. Found: C, 47.05; H, 5.20; Cl, 10.55; N, 8.50.

Upon brief treatment of 2b with NH_3/MeOH, the known[2] crystalline 1,3-dimethyl-2'-chloro-2'-deoxy-ψ-uridine (2a) was obtained.

1,3-Dimethyl-5-(2 ,3 -anhydro-β-D-ribofuranosyl)uracil (13).

Similar treatment of 10b and 11b with DMF-dimethylacetal resulted in the formation of 13 (150 mg, 85%), 210°C; ^{1}H NMR (DMSO-d_6) δ 3.18 (3H, s, NMe), 3.32 (3H, s, NMe), 3.52 (2H, t, H-5',5"), 3.87 (1H, d, H-3', $J_{2',3'}$ = 3.0, $J_{3',4'}$ = 0 Hz), 3.91 (1H, d, H-2', $J_{1',2'}$ = 0, $J_{2',3'}$ = 3.0 Hz), 4.03 (1H, t, H-4', $J_{4',5'} = J_{4',5"}$ = 5.5 Hz), 4.78 (1H, s, H-1'), 4.96 (1H, t, 5'-OH), 7.66 (1H, s, H-6).

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5-55; N, 11.02. Found: C, 51.61; H, 5.64; N, 10.99.

This epoxide 13 was also obtained (80 mg) from 1[2] (200 mg) by treatment with KF (500 mg) in dry $(CH_2OH)_2$ (5 mL) at 140°C for 15 min followed by evaporation of the solvent in vacuo, and chromatographic purification of the residue.

Reduction of 9a with n-Bu_3SnH.

A suspension of 9a (200 mg, 0.76 mmol) and ammonium sulfate (20 mg) in hexamethyldisilazane (10 mL) was heated under reflux for 1 h and then concentrated in vacuo. The residue was dissolved in toluene (10 mL) and treated with a mixture of n-Bu_3SnH (200 mg, 0.7 mmol) and 2,2'-azobis(2-methylpropionitrile) (50 mg) for 2 h at reflux. The mixture was concentrated in vacuo and the residue chromatographed on a silica gel column using CCL_4-EtOAc (5:3 v/v) as the eluent. The fractions containing the nucleoside product were collected, concentrated and the residue treated with 1M Et_3 NHF/THF (3 mL). The precipitates were collected by filtration and crystallized from MeOH to give 113 mg (65%) of 2'-deoxy-ψ-uridine (12), mp 220-221°C. The ^{1}H NMR spectrum of this sample was

superimposable with that of 2'-deoxy-ψ-uridine.[3] (Lit.[12] mp 221-223°C, lit.[14] mp 216-217°C).

Similar treatment of 10a also afforded 12, whereas 11 was converted into 3'-deoxy-ψ-uridine (14),[10,14] mp 216-217°C (lit.[13] mp 216-217°C) upon reduction with n-Bu_3SnH.

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REFERENCES AND NOTES

1. This investigation was supported in part by funds from the National Cancer Institute, D.H.H.S., Grants CA-08748 and CA-33907.
2. Pankiewicz, K. W.; Watanabe, K. A.; Takayanagi, H.; Itoh, T.; Ogura, H. J. Heterocyclic Chem., 1985, 22, 0000.
3. Pankiewicz, K.; Matsuda, A.; Watanabe, K. A. J. Org. Chem., 1982, 47, 475.
4. Markiewicz, W. T.; Biala, F.; Adamiak, R. W.; Grzeskowiak, K.; Kierzek, R.; Kraszewski, A.; Stawinski, J.; Wiewiorwski, M. Nucleic Acid Res. Symp. Ser. 1980, 7, 115.
5. Chu, C. K.; Reichman, U.; Watanabe, K. A.; Fox, J. J. J. Heterocyclic Chem., 1977, 14, 1119.
6. Greenberg, S.; Moffatt, J. G. J. Am. Chem. Soc., 1973, 95, 4016.
7. Reichman, U.; Chu, C. K.; Hollenberg, D. H.; Watanabe, K. A.; Fox, J. J. Synthesis, 1976, 533. Hanamura, E. K.; Prystas, M.; Verheyden, J. P. H.; Moffatt, J. G.; Yamaguchi, K.; Uehida, N.; Seto, K.; Nomura, A.; Shiratori, O.; Takase, S.; Katagiri, K. J. Med. Chem.,1976,19,654. Akhren, A. A.; Zaitseva, G. V.; Mikhailopulo, I. A. Bioorg. Khim., 1976, 13, 1325.
8. Barton, D. J. R.; Subramanian, R. J. Chem. Soc., Chem. Commun., 1976, 863. J. Chem. Soc., Perkin Trans. 1., 1977, 1718.
9. Robins, M. J.; Muhs,W. H. J. Chem. Soc.,Chem. Commun., 1978, 677.
10. Codington, J. F.; Doerr, I. L.; Fox, J. J. J. Org. Chem., 1964, 29, 558.
11. Reichman, U.; Chu, C. K.; Wempen, I.; Watanabe, K. A.; Fox, J. J. J. Heterocyclic Chem., 1976, 13, 933. Chu, C. K.; Reichman, U.; Watanabe, K. A.; Fox, J. J. J. Med. Chem., 1978, 21, 96.

12. Bridges, S. D.; Brown, D. K.; Ogden, R. C. J. Chem. Soc., Chem. Commun., 1977, 460. Brown, D. M.; Bridges, S. D.; Ogden, R. C.; Conrad, R. P. L. Nucleic Acid Res., 1978, 4, s/121.
13. Matsuda, A.; Chu, C. K.; Reichman, U.; Pankiewicz, K.; Watanabe, K. A.; Fox, J. J. J. Org. Chem., 1981, 46, 3603.
14. Stevens, J. D.; Fletcher, H. G. J. Org. Chem., 1968, 33, 1799.
15. Alfold, J.; Pecier, C.; Palovcik, R.; Kovak, P. Carbohyd. Res., 1972, 25, 249.
16. Hirota, K.; Watanabe, K. A.; Fox, J. J. J. Org. Chem., 1978, 43, 1193.
17. Marton-Meresz, M.; Kuszmann, J.; Percger, I. Tetrahedron, 1983, 39, 275.
18. In the reported syntheses[5,9,13] of 2'-deoxy-ψ-uridine (12), the 2'-chlorinated intermediates, which upon reduction yielded 12, consisted of both the ribo (9, minor) and arabino (10, major) isomers, and not just the ribo compound 9 as previously indicated.[5,13] The structural assignments arrived at in the present study also require that the isomer that was crystallized from the mixture of chlorinated compounds obtained by reaction of 3 and α-acetoxyisobutyryl chloride, and assigned the 2'-chloro-ribo configuration 9, was in fact the 3'-chloro-xylo nucleoside 11.

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