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Nucleosides. CXLIII. Synthesis of 5′-Deoxy-5′-substituted-2,2′-anhydro-1-(β-D-arabinofuranosyl)uracils. A New 2,5′- to 2,2′-Anhydronucleoside Transformation. Studies Directed toward the Synthesis of 2′-Deoxy-2′-substituted *arabino* Nucleosides. (4)[1]

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Treatment of 2,5′-anhydro-3′-*O*-acetyl-2′-*O*-triflyluridine with a nucleophile such as NaOAc, NaN_3, LiCl or LiBr, did not afford the 2′-substituted 2,5′-anhydro-arabinosyluracil, but gave 2,2′-anhydro-1-(5-substituted-β-D-arabinofuranosyl)uracil instead.

Keywords——nucleoside; anhydronucleoside; 2,5′-anhydrouracilnucleoside; 2,2′-anhydrouracilnucleoside; 2,5′-anhydro-3′-*O*-acetyl-2′-*O*-triflyluridine; 5′-substituted-2,2′-anhydroabinosyluracil; new transformation

The two pyrimidine nucleosides, 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine and -thymine (2′-F-5-iodo-ara-C or FIAC and 2′-F-5-methyl-ara-U or FMAU), developed in our laboratory[2] have shown potent *in vitro* and *in vivo* activity against herpes simplex viruses types 1 and 2 (HSV-1 and -2) and varicella zoster virus (VZV).[3-5] Both compounds inhibited human cytomegalovirus (HCMV)[6-8] *in vitro* as well as Epstein-Barr virus (EBV).[9] FIAC has demonstrated clinical efficacy against VZV in both phase I[10] and phase II[11] clinical trials. More recently, the triphosphates of FIAC and FMAU have been shown[12] to be the most potent inhibitors of deoxyribonucleic acid (DNA) polymerases from woodchuck hepatitis virus (WHV) and human hepatitis B virus *in vitro*. *In vivo*, both were active against chronic active hepatitis in the woodchuck, with FMAU giving immediate and long-lasting inhibition of WHV replication.

These nucleosides were synthesized by condensation of 3,5-di-*O*-acyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide and pyrimidine base.[2,12] Introduction of a substituent to the 2′-"up" position of a preformed pyrimidine *N*-nucleoside by nucleophilic reaction has not been achieved due to close proximity of the 2-carbonyl group to the 2′-position. Thus, treatment of a uridine derivative bearing a leaving group at the 2′-position with a nucleophile results in the formation of the *arabino* nucleoside or 2′-substituted *ribo* nucleoside *via* the anhydronucleoside intermediate, depending upon the nature of the nucleophile and reaction conditions.

In this report, we describe our attempts to convert uridine into a 2′-substituted-2′-deoxy-arabinosyluracil, and our discovery of anhydronucleoside interconversion. In this investigation, we chose 2,5′-anhydrouridine (**1**)[13] as the starting material. Treatment of **1** with *n*-Bu_2SnO in MeOH afforded the 2′,3′-*O*-stannylene derivative which was, without purification, directly acetylated[14] with Ac_2O in dimethylformamide (DMF) to give the 3′-acetate **2** in 84% yield after crystallization from EtOH. Triflylation of **2** with triflyl chloride in methylene chloride containing 4-dimethylaminopyridine (DMAP) and triethylamine afforded

3′-*O*-acetyl-2,5′-anhydro-1-*O*-triflyluridine (**3**) in high yield as colorless crystals. In this nucleoside **3**, we hoped that intramolecular nucleophilic reaction by O2 could be prevented during the displacement that would occur at C2′, since O2 is tied up with C5′.

Reaction of **3** with sodium acetate in DMF at 50—60 °C afforded two products in approximately equal amounts. The less polar compound was identical with 2,2′-anhydro-(3,5-di-*O*-acetyl-β-D-arabinofuranosyl)uracil (**4a**).[15] The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the more polar product was very similar to that of **4a** except that one acetyl signal at δ 1.90 was absent, but a signal characteristic of a formyl proton was present at δ 7.99. This product is assigned to the 5′-*O*-formyl derivative **4b**. Deformylation of **4b** according to Smrt[16] gave 2,2′-anhydro-1-(3-*O*-acetyl-β-D-arabinofuranosyl)uracil (**4c**). These results show that the intermolecular nucleophilic reaction occurred first on the C5′ position, liberating 2-oxide, which then attacked C2′, resulting in the formation of the 2,2′-anhydro nucleoside linkage. The formation of **4a** from **3** indicates that the 2,5′-anhydro linkage in **3** is less stable than the 4,5′-anhydro bond of the C-nucleoside 4,5′-anhydro-pseudouridine, and the 2′-triflate group in **3** is less reactive than that in the C-nucleoside, since it had already been demonstrated[17] that 4,5′-anhydro-3′-*O*-acetyl-2′-*O*-triflyl-1-methyl-pseudouridine (a C-nucleoside structurally very similar to **3**) could be directly converted into various 2′-substituted 2′-arabinosyl C-nucleosides by nucleophilic reactions.

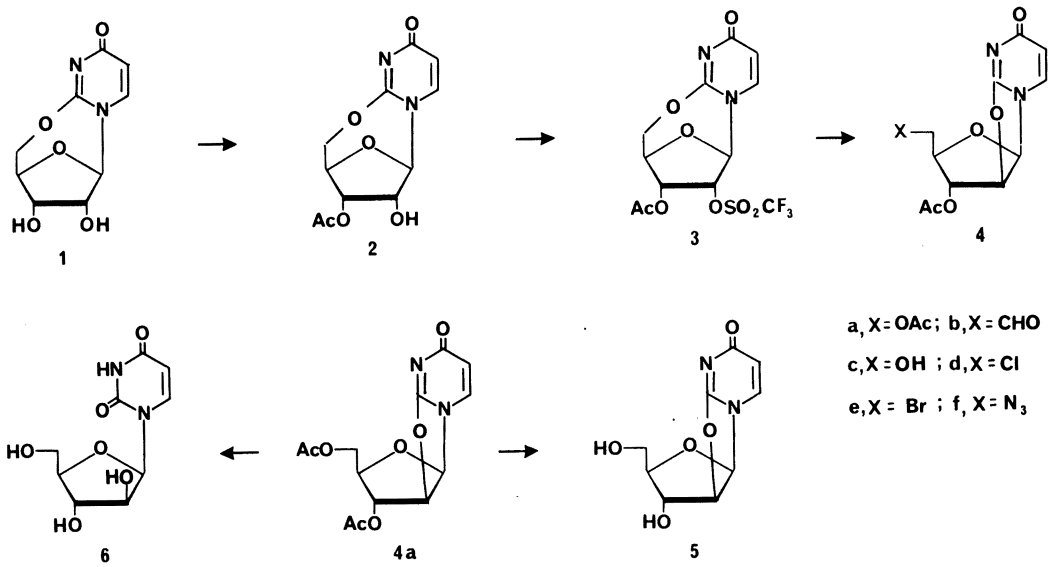

Chart 1

When **3** was treated with NaOAc in hexamethylphosphoric triamide (HMPA) at room temperature, the diacetate **4a** was the exclusive product. We also treated **3** with better nucleophilic reagents than NaOAc, *i.e.*, sodium azide, lithium bromide, sodium chloride, in HMPA at room temperature. In all cases, we obtained the 5′-substituted 5′-deoxy-3′-*O*-acetyl derivatives (**4d**—**f**) of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil in high yield.

Experimental

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Column chromatography was performed on Silica gel G60 (70—230 mesh, ASTM, Merck). Thin-layer chromatography was performed on Analtech Uniplates with short-wavelength UV light for visualization. Elemental analyses were performed by M.H.W. Laboratories, Phoenix, AZ, or Spang Microanalytical Laboratory, Eagle Harbor, MI. ^{1}H-

NMR spectra were recorded on a JEOL FX90Q spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ) and signals are described as a (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), dt (double triplet), br s (broad singlet). Values given for coupling constants are first order.

3'-*O*-Acetyl-2,5'-anhydrouridine (2)——A suspension of 2,5'-anhydrouridine[13] (6.5 g, 28.8 mmol) and *n*-Bu_2SnO (7.2 g, 28.8 mmol) in MeOH (500 ml) was heated under reflux until a clear solution was obtained (~30 min). The solution was concentrated *in vacuo*, and residue was dissolved in DMF (300 ml). Ac_2O (29 ml) was added to the solution, and the mixture was kept overnight at ~4 °C, and then concentrated *in vacuo*. The residue was triturated with EtOH to give a solid which was crystallized from EtOH to afford 6.5 g (84%) of **2**, mp 210—211 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.09 (s, 3H, Ac), 4.15 (d, 1H, H-5', $J_{5',5''}$=12.8 Hz), 4.23—4.63 (m, 3H, H-2',4',5'), 5.40 (d, 1H, H-3', $J_{2',3'}$=6.4 Hz), 5.61 (s, 1H, H-1'), 5.99 (m, 2H, H-5, 2'-OH, $J_{5,6}$=7.6 Hz), 7.98 (d, 1H, H-6). *Anal.* Calcd for $C_{11}H_{12}N_2O_6$: C, 49.25; H, 4.51; N, 10.44. Found: C, 49.49; H, 4.79; N, 10.15.

3'-*O*-Acetyl-2,5'-anhydro-2'-*O*-triflyluridine (3)——To a suspension of **2** (6.1 g, 22.8 mmol), DMAP (2.8 g, 22.8 mmol) and Et_3N (6.4 ml, 45.5 mmol) in CH_2Cl_2 (700 ml) was added dropwise a solution of triflyl chloride (4.8 ml, 45.5 mmol) in CH_2Cl_2 (20 ml) while stirring. The mixture became clear and then precipitation occurred. Stirring was continued and then crystals were collected by filtration and washed with CH_2Cl_2 (50 ml) to give **3** (7.8 g, 85%), mp 155—157 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.13 (s, 3H, Ac), 4.25 (d, 1H, H-5', $J_{5',5''}$=13.0 Hz), 4.62 (d, 1H, H-5''), 4.92 (s, 1H, H-4'), 5.70 (d, 1H, H-3', $J_{2',3'}$=6.4 Hz), 6.00 (d, 1H, H-5, $J_{5,6}$=7.3 Hz), 6.19 (d, 1H, H-2'), 6.44 (s, 1H, H-1'), 7.95 (d, 1H, H-6). *Anal.* Calcd for $C_{12}H_{11}F_3N_2O_8S$: C, 36.00; H, 2.77; N, 7.00; S, 8.01. Found: C, 35.85; H, 2.89; N, 6.88; S, 8.03.

Reaction of 3 with NaOAc in DMF——To a solution of **3** (400 mg, 1 mmol) in DMF (10 ml) was added NaOAc (410 mg, 5 mmol), and the mixture was stirred overnight at 50—60 °C. After concentration of the mixture *in vacuo*, the residue was chromatographed on a silica gel column using $CHCl_3$–EtOH (9 : 1, v/v) followed by $CHCl_3$–EtOH (5 : 1, v/v).

Two nucleosidic fractions were obtained. From the less polar fraction, 2,2'-anhydro-1-(3-*O*-acetyl-5-*O*-formyl-β-D-arabinofuranosyl)uracil (**4b**) (100 mg, 33.8%) was obtained after concentration, mp 187—189 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.11 (s, 3H, Ac), 4.13 (d, 2H, H-5',5''), 4.60 (m, 1H, H-4'), 5.34 (d, 1H, H-3', $J_{3',4'}$=1.5 Hz), 5.52 (d, 1H, H-2', $J_{1',2'}$=5.8 Hz), 5.88 (d, 1H, H-5, $J_{5,6}$=7.6 Hz), 6.40 (d, 1H, H-1'), 7.87 (d, 1H, H-6), 7.99 (s, 1H, CHO). *Anal.* Calcd for $C_{12}H_{12}N_2O_6$: C, 48.65; H, 4.08; N, 9.45. Found: C, 48.45; H, 4.22; N, 9.19.

From the second fraction, 120 mg of 2,2'-anhydro-1-(3,5-di-*O*-acetyl-β-D-arabinofuranosyl)uracil (**4a**) was obtained (38.7%), mp 178—180 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.90 (s, 3H, Ac), 2.11 (s, 3H, Ac), 3.95 (dd, 1H, H-5', $J_{5',5''}$=12.5, $J_{4',5'}$=4.9 Hz), 4.13 (dd, 1H, H-5'', $J_{5',5''}$=12.5, $J_{4',5''}$=4.0 Hz), 4.58 (m, 1H, H-4'), 5.31 (d, 1H, H-3', $J_{3',4'}$=2.1 Hz), 5.52 (d, 1H, H-2', $J_{1',2'}$=5.8 Hz), 5.88 (d, 1H, H-5, $J_{5,6}$=7.6 Hz), 6.39 (d, 1H, H-1'), 7.88 (d, 1H, H-6). *Anal.* Calcd for $C_{13}H_{14}N_2O_7$: C, 50.32; H, 4.55; N, 9.03. Found: C, 50.14; H, 4.55; N, 8.83.

2,2'-Anhydro-1-(3-*O*-acetyl-β-D-arabinofuranosyl)uracil (4c)——A mixture of **4b** (100 mg, 0.34 mmol), MeOH (2 ml), tetrahydrofuran (THF) (1 ml) and Et_3N (303 mg, 3 mmol) was stirred at room temperature for 30 min, and then concentrated *in vacuo*. The residue was chromatographed on a silica gel column using $CHCl_3$–EtOH (5 : 1, v/v) to give **4c** (69 mg, 78%), mp 190—195 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.11 (s, 3H, Ac), 3.28 (dd, 1H, H-5', $J_{5',5''}$=12.0, $J_{4',5'}$=5.5 Hz), 3.39 (dd, 1H, H-5'', $J_{5',5''}$=12.0, $J_{4',5''}$=4.2 Hz), 4.34 (m, 1H, H-4'), 5.11 (t, 1H, OH), 5.34 (s, 1H, H-3'), 5.46 (d, 1H, H-2', $J_{2',2'}$=5.8 Hz), 5.84 (d, 1H, H-5, $J_{5,6}$=7.6 Hz), 6.34 (d, 1H, H-1'), 7.82 (d, 1H, H-6). *Anal.* Calcd for $C_{11}H_{12}N_2O_6$: C, 49.25; H, 4.51; N, 10.44. Found: C, 49.12; H, 4.62; N, 10.27.

2,2'-Anhydro-1-(β-D-arabinofuranosyl)uracil (5)——A mixture of **4a** (100 mg, 0.32 mmol), Et_3N (10 ml) and MeOH (20 ml) was stirred for 4 h at room temperature, and was then concentrated *in vacuo*. Upon trituration of the residue with EtOH, crystalline **5** (50 mg, 68%) was obtained, mp 239—240 °C, unchanged upon admixture of an authentic sample.[18]

1-(β-D-Arabinofuranosyl)uracil (6)——Compound **4a** (310 mg, 1 mmol) was dissolved in 2 N NaOH (20 ml). After being kept at room temperature for 4 h, the mixture was neutralized with 1 N HCl, and concentrated *in vacuo*. The residue was taken up in pyridine and the suspension filtered from inorganic salt. The filtrate was concentrated *in vacuo*, and the residue crystallized from EtOH to give **6** (166 mg, 68%), mp 209—211 °C. The mixture's melting point with an authentic sample[19] was undepressed.

Acetylation of 5——A mixture of **5** (226 mg, 1 mmol), Ac_2O (1 ml) in pyridine (5 ml) was stirred at room temperature for 2 h, and then diluted with EtOH (5 ml). After concentration of the mixture *in vacuo*, the residue was crystallized from EtOH to give **4a** (300 mg, 97%), mp 178—180 °C, undepressed upon admixture with an authentic sample.[15]

2,2'-Anhydro-1-(3-*O*-acetyl-5-substituted-β-D-arabinofuranosyl)uracils (4a, d—f)——A mixture of **3** (400 mg, 1 mmol) and NaOAc, LiCl, LiBr, or NaN_3 (5—10 mmol) in HMPA (10 ml) was stirred at room temperature for 2—3 d. After concentration of the mixture *in vacuo*, the residue was now chromatographed on a silica gel column using $CHCl_3$–EtOH (5 : 1, v/v) or Me_2CO–$CHCl_3$ (3 : 1, v/v) as the eluent to give: **4a** (263 mg, 85%), mp 178—180 °C. **4d** (264 mg, 92%), mp 222—225 °C, ^{1}H-NMR (DMSO-d_6) δ: 2.11 (s, 3H, Ac), 3.59 (dd, 1H, H-5', $J_{5',5''}$=12.2, $J_{4',5'}$=4.9 Hz), 3.72 (dd, 1H, H-5'', $J_{5',5''}$=12.2, $J_{4',5''}$=5.2 Hz), 4.55 (m, 1H, H-4'), 5.31 (d, 1H, H-3', $J_{3',4'}$=3.0 Hz), 5.53 (d, 1H, H-2', $J_{1',2'}$=5.8 Hz), 5.90 (d, 1H, H-5, $J_{5,6}$=7.3 Hz), 6.40 (d, 1H, H-1'), 7.9 (d, 1H, H-6). *Anal.* Calcd for

$C_{11}H_{11}ClN_2O_5$: C, 46.09; H, 3.87; Cl, 12.36; N, 9.77. Found: C, 45.83; H, 4.00; Cl, 12.21; N, 9.68. **4e** (172 mg, 52%), glass. ^{1}H-NMR (DMSO-d_6) δ: 2.11 (s, 3H, Ac), 3.40 (dd, 1H, H-5′, $J_{5',5''}=11.3$, $J_{4',5'}=5.2$ Hz), 3.58 (dd, 1H, H-5″, $J_{5',5''}=11.3$, $J_{4',5''}=6.7$ Hz), 4.52 (m, 1H, H-4′), 5.32 (d, 1H, H-3′, $J_{3',4'}=2.5$ Hz), 5.53 (d, 1H, H-2′, $J_{1',2'}=5.8$ Hz), 5.90 (d, 1H, H-5, $J_{5,6}=7.3$ Hz), 6.40 (d, 1H, H-1′), 7.93 (d, 1H, H-6). *Anal.* Calcd for $C_{11}H_{11}BrN_2O_5$: C, 39.90; H, 3.35; Br, 24.13; N, 8.46. Found: C, 39.72; H, 3.40; Br, 24.11; N, 8.28. **4f** (200 mg, 69%), mp 160—163 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.11 (s, 3H, Ac), 3.34 (dd, 1H, H-5′, $J_{5',5''}=13.5$, $J_{4',5'}=4.3$ Hz), 3.55 (dd, 1H, H-5″, $J_{5',5''}=13.5$, $J_{4',5''}=6.0$ Hz), 4.50 (m, 1H, H-4′), 5.26 (d, 1H, H-3′, $J_{3',4'}=2.4$ Hz), 5.52 (d, 1H, H-2′, $J_{1',2'}=5.8$ Hz), 5.94 (d, 1H, H-5, $J_{5,6}=7.6$ Hz), 6.41 (d, 1H, H-1′), 7.90 (d, 1H, H-6). *Anal.* Calcd for $C_{11}H_{11}N_5O_5 \cdot 1/3H_2O$: C, 43.28; H, 3.83; N, 22.95. Found: C, 42.94; H, 3.73; N, 22.77.

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