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Nucleosides. 107. Synthesis of 5-(β-D-Arabinofuranosyl)isocytosine and Related *C*-Nucleosides[1]

C. K. Chu, U. Reichman, K. A. Watanabe,* and J. J. Fox

Laboratory of Organic Chemistry, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Division of Graduate School of Medical Scienes, Cornell University, New York, New York 10021. *Received July 6, 1977*

The synthesis of 5-(β-D-arabinofuranosyl)isocytosine (ψ-*ara*-isoC) (**7**), an isostere of the antileukemic agent, *ara*-C, was achieved. 5-(β-D-Ribofuranosyl)isocytosine (**4**, ψ-isocytidine, also an antileukemic agent) was converted into 4,2′-anhydro-5-(β-D-arabinofuranosyl)isocytosine (anhydro-ψ-*ara*-isoC) (**14**) by treatment with α-acetoxyisobutyryl chloride or *o*-acetoxybenzoyl chloride, followed by removal of the protecting groups. The anhydro nucleoside was hydrolyzed with 10% NaOH to give ψ-*ara*-isoC (**7**). Treatment of anhydro-ψ-*ara*-isoC with NH_3MeOH gave both α and β isomers of 2,4-diaminopyrimidine *C*-nucleosides (**18a,b**). A total synthesis of ψ-*ara*-isoC from 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**8**) was attempted. The benzyl sugar **8** was converted by Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane to ethyl 2-(tri-*O*-benzyl-D-arabinofuranosyl)acetate (**9**) which was formylated and then methylated to give 3-methoxy-2-arabinosylacrylate **10b**. Cyclization of the latter with guanidine followed by debenzylation with BCl_3–CH_2Cl_2 gave, however, the α isomer of ψ-*ara*-isoC as the sole isolable product. Treatment of ψ-uridine (**18**) with α-acetoxyisobutyryl chloride gave 4,2′-anhydro-5-(β-D-arabinofuranosyl)uracil (**19**, anhydro-ψ-*ara*-U) or 2′-chloro-2′-deoxy-ψ-uridine (**20**) depending upon the reaction conditions. 5-(β-D-Arabinofuranosyl)uracil (ψ-*ara*-U, **23**) and 5-(β-D-arabinofuranosyl)cytosine (ψ-*ara*-C, **24**) were also prepared from anhydro-ψ-*ara*-U (**22**). All the new *C*-nucleosides showed no significant inhibitory activity against leukemic cells in culture even though they are closely related structurally to the antileukemic agents, *ara*-C and ψ-isocytidine.

1-(β-D-Arabinofuranosyl)cytosine (**1**, *ara*-C) is a potent drug against acute myeloblastic leukemia.[2] This drug is converted in vivo into the 5′-triphosphate (*ara*-CTP) which is a strong inhibitor of mammalian DNA polymerase.[3] However, *ara*-C undergoes rapid deamination in vivo by cytidine deaminase to give an inactive metabolite, *ara*-U[4] (**2**). Leukemic cells develop resistance to *ara*-C by decreasing the activities of kinases[5] (which catalyze the phosphorylation of *ara*-C) or by increasing the deaminase activity.[6] Recently, it was found that 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine (**3a**, AAC)[7] or its 5-fluoro analogue (**3b**, AAFC)[8] are not substrates of deaminase but are slowly hydrolyzed under the physiological conditions giving rise to their respective arabino nucleosides (see Chart I).

5-(β-D-Ribofuranosyl)isocytosine (**4**, ψ-isocytidine),[9,10] an isostere of both cytidine (**5**) and 5-azacytidine (**6**), is active in vitro and in vivo against various *ara*-C resistant lines of mouse leukemia[11] and is currently undergoing phase I clinical trials. ψ-Isocytidine is not deaminated by cytidine deaminase from mouse kidney.[12] This report deals with the synthesis of *C*-nucleoside analogues and/or isosteres of *ara*-C and of ψ-isocytidine. A preliminary report of a portion of this work has appeared.[13]

Our first approach to the synthesis of 5-(β-D-arabinofuranosyl)isocytosine (**7**, ψ-*ara*-isoC) utilized 2,3,5-tri-*O*-benzyl-D-arabinose (**8**) which, on treatment with (ethoxycarbonylmethylene)triphenylphosphorane in acetonitrile, gave ethyl 2-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)acetate (**9**) in good yield as a mixture of glycosyl isomers. The major isomer was isolated as an analytically pure liquid after chromatography on a silica gel column. The purified isomer **9** was formylated with ethyl formate in the presence of sodium hydride to afford the crude

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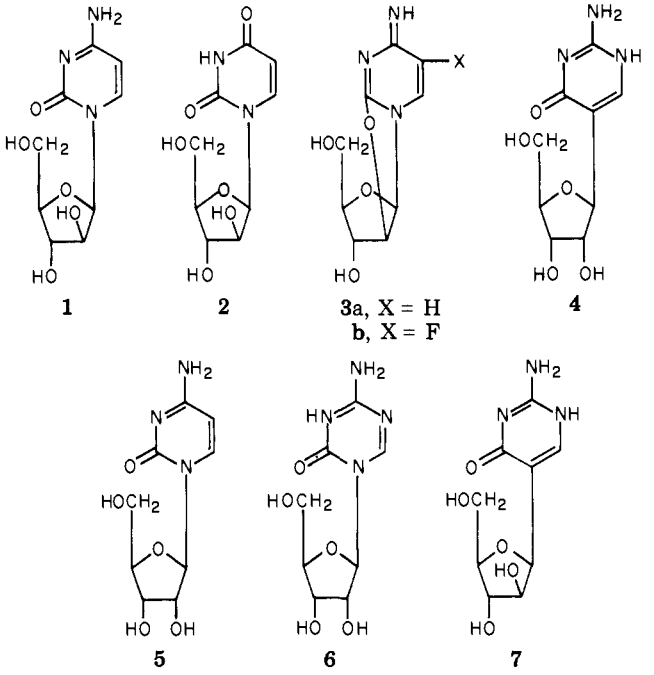
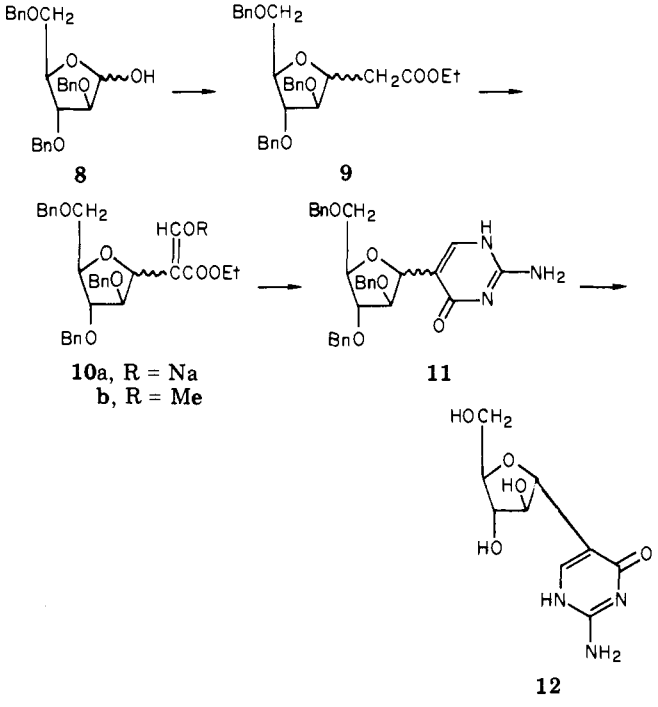
Chart I



1 2 3a, X = H b, X = F 4

5 6 7

Scheme I



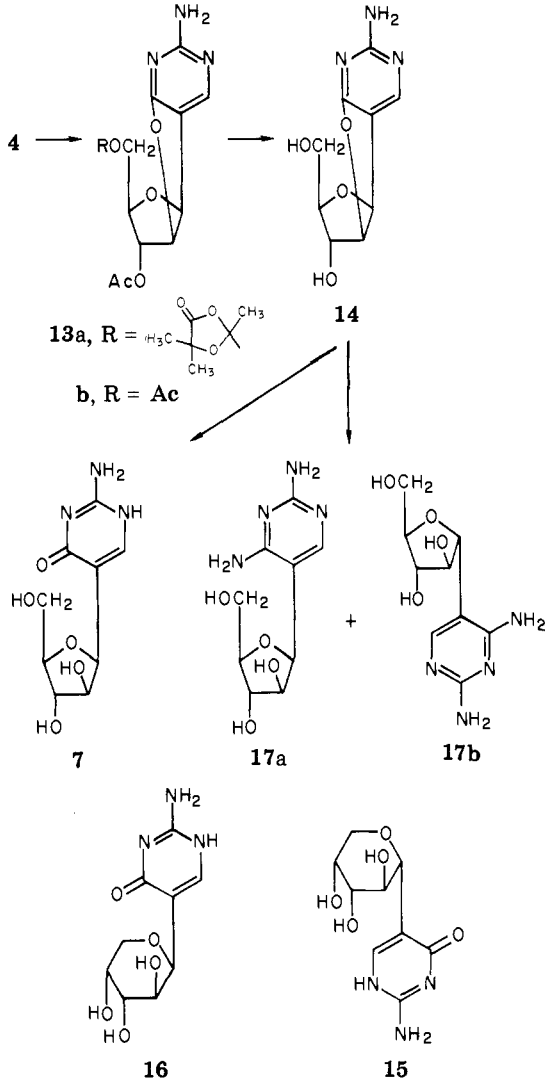
8 9

10a, R = Na b, R = Me 11

12

sodium enolate **10a** which, without purification, was methylated with methyl iodide in DMF. A mixture of 3-methoxyacrylate derivatives **10b** was obtained (see Scheme I). After chromatographic purification of the product, a sample with correct elemental analyses was obtained. The ^{1}H NMR showed, however, that the analytical sample was a mixture of the α and β isomers even though a single isomer of **9** was employed. Ring closure of **10b** with guanidine afforded the protected nucleoside **11** which was isolated in crystalline form. Debenzylation of **11** with BCl_3 in methylene chloride[14] gave a pure isomer of the free nucleoside **12**. Compound **12** was stable in dilute acid and dilute base at room temperature for several days. The ^{1}H NMR spectrum of **12** in D_2O showed signals for H-6 and H-1′ at δ 7.70 (singlet) and 4.66 (doublet, $J_{1',2'}$ = 6.1 Hz), respectively. Though these data, per se, do not permit assignment of glycosyl configuration,

Scheme II



13a, R = 13b, R = Ac 14

7 17a 17b

16 15

subsequent studies (vide infra) established the α configuration for **12**. Nucleoside **12** showed no significant inhibitory activity against L1210 cells in vitro.[15] We were not able to isolate the other isomer even though the starting material **10b** was an α,β mixture, due probably to isomerization of one isomer to the other in the process.

The other isomer of the above nucleoside was obtained from ψ-isocytidine (**4**). Treatment of **4** with α-acetoxyisobutyryl chloride[16] in acetonitrile under reflux afforded the protected 4,2′-anhydro nucleoside **13a** in good yield. Similarly, treatment of **4** with *o*-acetoxybenzoyl chloride (acetylsalicyloyl chloride)[17] gave the diacetate **13b** in crystalline form in equally good yield (see Scheme II). Deprotection of **13** with methanolic hydrogen chloride afforded the crystalline anhydro nucleoside **14** as the HCl salt. The 4,2′-anhydro linkage of **14** was found to be much more stable to base than the 2,2′-anhydro linkage of AAC (**3a**),[18] and stringent conditions (10% NaOH at reflux for 30 min) were required to cleave the 4,2′-anhydro linkage with exclusive formation of one isomer of 5-(D-arabinofuranosyl)isocytosine (**7**, ψ-*ara*-isoC). Compound **7** was different from **12** obtained by the total synthesis from tri-*O*-benzyl-D-arabinofuranose. Since compound **7** was derived from the β-anhydro nucleoside **14**, it was assigned the β-arabino configuration. Unlike **12**, the β-nucleoside **7** underwent isomerization slowly at room temperature in dilute acid to give the α isomer **12**. The isomerization was monitored by ^{1}H NMR which showed the appearance of

a doublet at δ 4.66 indicative of the α isomer. When the solution was heated to 75 °C, the isomerization (**7** → **12**) occurred much faster and the α isomer **12** was further converted into the pyranosyl derivatives **15** and **16**. At equilibrium, as expected, the major component (~80%) was the α-pyranosyl derivative **15**. The β-pyranosyl isomer **16**, which is expected to be less favored due to the Δ^2 effect,[19] was present in the equilibrium mixture to the extent of ~10%. Small amounts of the furanosyl derivatives, **12** and **7** (total ~10%), were also found in the reaction mixture.

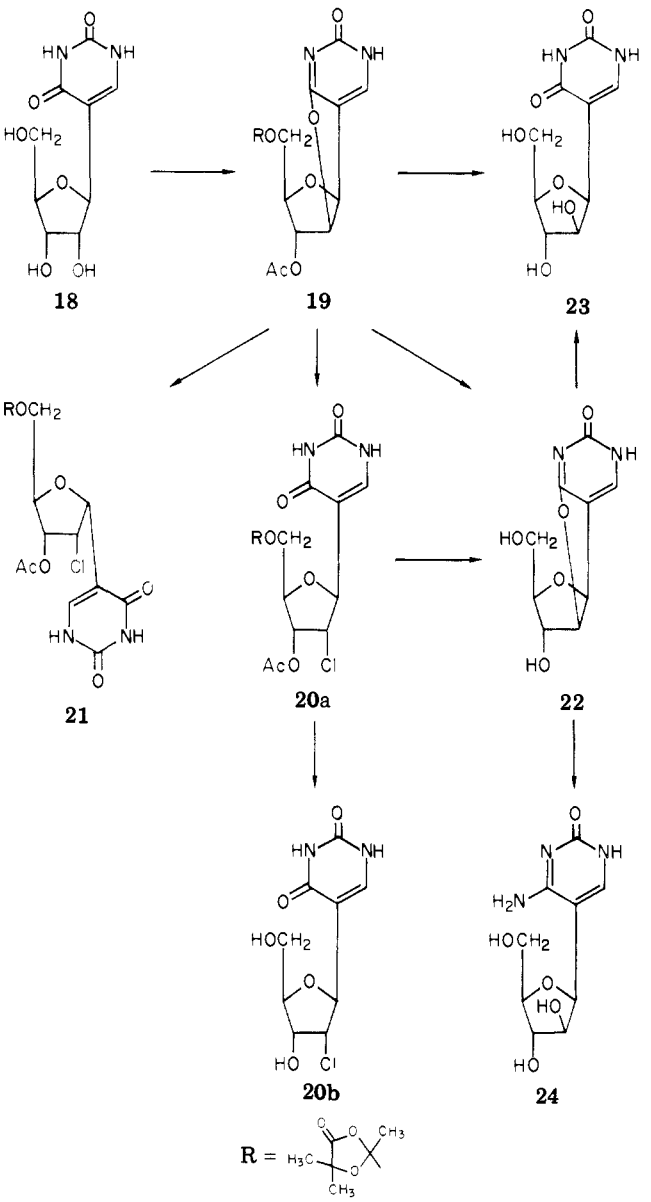
The ^{1}H NMR spectrum of **7** is distinctly different from that of **12**. The H-1′ signal of **7** (in which H-1′ and H-2′ are in cis disposition) appeared at lower field (δ 5.02) than that of **12** (trans nucleoside δ 4.66). This observation is consistent with the report of Acton et al.,[20] who assigned the glycosyl configuration of arabinosyl analogues of the *C*-nucleoside oxoformycin B on the basis that the H-1′ of the cis nucleosides (β-arabino) resonates at lower field than that of the trans nucleoside (α-arabino). Their assignments[20] are in agreement with the observation[21] that H-1 in furanose rings resonates further downfield when it is cis to H-2 (α-ribo or β-arabino) than when it is trans. This method may be generally applicable to the assignment of glycosyl configuration of *C*-nucleosides.[10,20,22]

The stability of the 4,2′-anhydro linkage of **14** was further demonstrated by NH_3–MeOH treatment. Unlike 2,2′-anhydro-*ara*-C (**3**), which undergoes conversion with alcoholic ammonia to a 2,4-diaminopyrimidine nucleoside very rapidly,[18] compound **14** was recovered unchanged after several days at room temperature. Treatment of **14** with NH_3–MeOH at 140 °C for 6 days in a steel container, however, afforded a mixture of 2,4-diaminopyrimidine nucleosides **17** from which the α isomer was obtained in crystalline form. The pure β isomer was isolated from the mother liquor as a syrup.

Reaction of ψ-uridine (**18**) with α-acetoxyisobutyryl chloride proceeded rather differently than that of ψ-isocytidine (**4**). Even under carefully controlled conditions, a mixture of several variously protected anhydro nucleosides **19** and 2′-chloro-2′-deoxy-ψ-uridine (**20a**) was obtained. In large-scale reactions, formation of the α isomer (**21**) of the 2′-chloro derivative **20a** was also observed. Apparently, **21** arose from the acid-catalyzed epimerization of **20a**. A shorter reaction time favored formation of the anhydro nucleoside **19** as the major product. Treatment of **19** with 0.5 M sodium methoxide gave the unblocked anhydro nucleoside **22**. The same compound was also obtained by treatment of the chloro derivative **20a** with sodium methoxide. For a practical synthesis of crystalline **22**, isolation of intermediates was not necessary. The crude product from the reaction of ψ-uridine (**18**) with α-acetoxyisobutyryl chloride was treated with methoxide whereupon all the components (except **21**) were converted into **22**. The 4,2′-anhydro linkage of **22** was labile to acid. Thus, treatment of **22** with Dowex 50 (H^+) in water for 10 min at 55 °C afforded crystalline 5-(β-D-arabinofuranosyl)uracil (**23**, ψ-*ara*-U) in high yield. Prolonged Dowex 50 (H^+) treatment slowly isomerized the β isomer into its α counterpart. 5-(β-D-Arabinofuranosyl)cytosine (**24**, ψ-*ara*-C) was obtained in crystalline form by treatment of the 4,2′-anhydro derivative **22** with NH_3–MeOH at 85 °C for 40 h (see Scheme III).

Although ψ-*ara*-isoC (**7**) is an isostere of a powerful antileukemic agent, *ara*-C (**1**), and the structure of **7** is closely related to those of the antileukemic agents, 5-azacytidine (**6**) and ψ-isocytidine (**4**), it did not show any significant inhibitory activity against L1210 cells in vitro

Scheme III



(ID_{50} > 10 μg/mL). Other new *C*-nucleosides described herein also did not inhibit the growth of leukemic cells in culture.[15]

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are corrected. ^{1}H NMR spectra were obtained on a JEOL JIM-PET-100 spectrometer, and Me_4Si was the internal standard for organic solvents and $Me_3Si(CH_2)_3SO_3Na$ for D_2O; chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet); δ and J values are first order. TLC was performed on microscope slides coated with silica gel GF_{254} (Merck), and spots were detected with UV light and by spraying with 20% v/v H_2SO_4 in EtOH, followed by charring. Evaporations were carried out in vacuo with bath temperatures kept below 40 °C. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Ethyl 2-(2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl)acetate (9). 2,3,5-Tri-*O*-benzyl-D-arabinofuranose (4.2 g, 0.01 mol) and (ethoxycarbonylmethylene)triphenylphosphorane (3.83 g, 0.011 mol) were dissolved in dry MeCN (70 mL, dried over 4Å molecular sieves), and the solution was heated under reflux for 24 h. The solvent was removed by evaporation and the syrupy residue was dissolved in Et_2O (50 mL). The Ph_3PO which precipitated upon

cooling was removed by filtration and the filtrate was evaporated to dryness. This procedure was repeated three times to remove most of the Ph_3PO. TLC of the crude product (C_6H_6–AcOEt, 10:1) showed two spots (R_f 0.5 major, 0.1 minor). The syrup was chromatographed on a column of silica gel G60 (30 × 5.5 cm diameter) using C_6H_6–Et_2O (11:1) as the eluent. Fractions were checked by TLC and the major component (3.5 g, 71%) was obtained as a colorless syrup after evaporation of the appropriate fractions: ^1H NMR ($CDCl_3$) δ 1.20 (3 H, t, $-CO_2CH_2CH_3$, spacing 7.0 Hz), 2.65 (2 H, d, $-CH_2CO_2Et$, 7.0 Hz), 3.56 (2 H, d, H-5′,5″, 6.2 Hz), 4.10 (2 H, q, $-CO_2CH_2CH_3$, 7.0 Hz), 4.51 (6 H, d, CH_2Ph), 7.27 (15 H, s, CH_2Ph). Contamination of another isomer was indicated by the presence of a small doublet at δ 2.75 ($-CH_2CO_2Et$, 7.0 Hz). Anal. ($C_{30}H_{34}O_6$) C, H.

Ethyl 3-Methoxy-2-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)acrylate (10b). To a suspension of NaH (2.0 g, 50% in mineral oil) in absolute Et_2O (30 mL) was added absolute EtOH (1 mL), followed immediately by dropwise addition of a mixture of **9** (5.9 g, 0.033 mol) and HCO_2Et (15 mL, distilled over K_2CO_3) in anhydrous Et_2O. The mixture was stirred overnight at room temperature, and then the solvent was removed by evaporation in vacuo at room temperature. The residual brown syrup was dissolved in DMF (50 mL) and MeI (14.2 g, 0.1 mol) was added dropwise over a period of 20 min. The mixture was stirred for 4 h at room temperature and then poured into a mixture of ice and water (500 mL). The mixture was extracted with $CHCl_3$ (100 mL × 3) and the organic extracts were dried (Na_2SO_4) and evaporated in vacuo to a syrup. TLC (C_6H_6–AcOEt, 9:1) of this syrup showed that it contained at least five components (R_f 0.34, 0.35 major, 0.36, 0.70, 0.71). The major component was obtained as a syrup (3.0 g, 46%) after column chromatography on silica gel G60 (60 × 5.5 cm) using C_6H_6–AcOEt (19:1) as the eluent. The ^1H NMR spectrum showed that the major component is an α,β mixture (~5:1) of **10b**: ^1H NMR ($CDCl_3$) major signals at δ 1.25 (t, $-CO_2CH_2CH_3$, spacing 7.0 Hz), 3.59 (d, H-5′,5″, 3.4 Hz), 3.81 (s, OCH_3), 4.56 (s, CH_2Ph), 7.29 (d, CH_2Ph). The presence of another isomer is indicated by the presence of a small singlet of OCH_3 at δ 3.78. No signal corresponding to $-CH_2CO_2Et$ was detected. Anal. ($C_{32}H_{36}O$) C, H.

5-(2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl)isocytosine (11). Guanidine hydrochloride (0.64 g, 6.6 mmol) was added to EtONa in EtOH solution (prepared by dissolving 0.16 g of Na in 25 mL of absolute EtOH), and the mixture was stirred for 10 min at room temperature and then filtered through Celite. The filtrate was added to compound **10b** (1.73 g, 3.3 mmol) and the mixture was refluxed for 45 h, concentrated to ~5 mL, and then neutralized with 1 N HCl to pH ~7. Water was added to complete precipitation. The supernatant was decanted, and the residual syrup was dissolved in C_6H_6, dried (Na_2SO_4), and chromatographed on a column of silica gel 60 (30 × 5.5 cm) using C_6H_6–MeOH (15:1) as the eluent. After evaporation of the solvent of the UV-absorbing fractions, the residue was crystallized from EtOH to give **11** (600 mg, 35%): mp 160–162 °C; ^1H NMR (Me_2SO-d_6) δ 3.55 (2 H, d, H-5′,5″, spacing 5.5 Hz), 4.02 (1 H, t, H-4′), 4.28 (2 H, m, H-2′,3′), 4.49 (2 H, s, CH_2Ph), 4.52 (2 H, s, CH_2Ph), 4.56 (2 H, s, CH_2Ph), 4.83 (1, H, d, H-1′, spacing 3.7 Hz), 6.69 (3 H, br s, exchangeable), 7.2–7.4 (16 H, s, H-6 and CH_2Ph). Anal. ($C_{30}H_{31}N_3O_5$) C, H, N.

5-(α-D-Arabinofuranosyl)isocytosine (12). Compound **11** (600 mg) was dissolved in 1 M BCl_3 in CH_2Cl_2 solution (5 mL) at ca. −70 °C with stirring. After 15 h at −70 °C the cooling bath was removed and EtOH (2 mL) was added dropwise. The mixture was neutralized with Dowex 1 (OH^-) resin. The resin was filtered and washed with a small amount of EtOH. The combined filtrate and washings were evaporated in vacuo, and the residue was triturated with a small amount of EtOH. A colorless powder was collected by filtration and crystallized from EtOH to give 175 mg (63%) of **12** which did not show a definite melting point but slowly colorlized above 150 °C: ^1H NMR data have been reported;[13] UV λ_{max} (pH 1) 262 nm (ε 6000), λ_{max} (pH 7) 290 (4800), λ_{max} (pH 10) 279 (5000). Anal. ($C_9H_{13}N_3O_5$) C, H, N.

4,2′-Anhydro-5-[3-*O*-acetyl-5-(2,5,5-trimethyldioxolanon-2-yl)-β-D-arabinofuranosyl]isocytosine Hydrochloride (13a). ψ-Isocytidine hydrochloride (2.8 g, 10 mmol) and α-acetoxyisobutyryl chloride (6.5 g) in MeCN (250 mL) were refluxed for 3 h and then evaporated to dryness in vacuo. The residue was triturated with a small amount of Me_2CO and filtered to give crystalline **13a** (3.3 g, ~75%), mp 195–197 °C. Anal. ($C_{17}H_{21}N_3O_8$·HCl) C, H, N, Cl.

4,2′-Anhydro-5-(3,5-di-*O*-acetyl-β-D-arabinofuranosyl)isocytosine Hydrochloride (13b). ψ-Isocytidine hydrochloride (1.4 g, 5 mmol) and *o*-acetoxybenzoyl chloride (3.9 g) in MeCN (100 mL) were refluxed for 14 h and then evaporated to dryness in vacuo. The residue was triturated with Me_2CO and crystalline **13b** (1.3 g, 75%) was collected by filtration: mp 195–200 °C dec; ^1H NMR (D_2O) δ 2.03 (3 H, s, OAc), 2.19 (3 H, s, OAc), 4.22 (2 H, d, H-5′,5″, spacing 4.6 Hz), 4.52 (1 H, m, H-4′), 5.42 (1 H, q, H-3′), 5.70 (1 H, q, H-2′, $J_{1',2'}$ = 6.1, $J_{2',3'}$ = 1.5 Hz), 5.83 (1 H, d, H-1′), 8.30 (1 H, s, H-6); UV λ_{max} (pH 1) 277 nm (ε 3800), λ_{max} (pH 7) 285 (5800), λ_{max} (pH 10) 285 (5500). Anal. ($C_{13}H_{15}N_3O_6$·HCl) C, H, N, Cl.

4,2′-Anhydro-5-(β-D-arabinofuranosyl)isocytosine (14). Compound **13b** (170 mg, 0.5 mmol) was dissolved in 20 mL of saturated HCl–MeOH and the solution was kept at room temperature for 40 h. The HCl salt of **14** which separated was collected by filtration (100 mg, 80%): mp >275 °C; ^1H NMR data have been reported.[13] Anal. ($C_9H_{11}N_3O_4$·HCl) C, H, N, Cl.

The HCl salt (260 mg, 1 mmol) was dissolved in H_2O (50 mL) and the solution was stirred with Amberlite IR-45 (OH^-, 10 mL). After 2 h the resin was filtered and washed with H_2O (50 mL). The combined filtrate and washings were evaporated to dryness and coevaporated three times with C_6H_6. The solid residue was triturated with Me_2CO and filtered to give **14** (160 mg, 70%): mp 195–199 °C; UV λ_{max} (pH 1) 278 nm (ε 3500), λ_{max} (pH 7) 286 (5800), λ_{max} (pH 10) 285 (6000). Anal. ($C_9H_{11}N_3O_4$) C, H, N.

5-(β-D-Arabinofuranosyl)isocytosine (7). Compound **13b** (3.4 g, 10 mmol) was dissolved in 10% NaOH (40 mL) and the solution was refluxed gently for 30 min, cooled to room temperature, and neutralized with Dowex 50 (H^+). The neutral solution was evaporated in vacuo and the residue was crystallized from H_2O to give **7** (2.1 g, 85%): mp >270 °C; ^1H NMR data have been reported;[13] UV λ_{max} (pH 1) 262 nm (ε 7600), λ_{max} (pH 7) 290 and 266 (sh, 4100 and 3800), λ_{max} (pH 10) 277 (6400). Anal. ($C_9H_{13}N_3O_5$) C, H, N.

5-(D-Arabinofuranosyl)-2,4-diaminopyrimidines (17a and 17b). A suspension of **14** (200 mg) in 20 mL of saturated NH_3–MeOH was heated in a steel container at 140 °C for 6 days. The solution was evaporated to dryness and the residual syrup was dissolved in EtOH and left overnight at room temperature. The α isomer **17b** crystallized as colorless needles, mp 218–223 °C dec, which were collected by filtration: ^1H NMR (D_2O) δ 3.69 (2 H, d, H-5′,5″, spacing 3.4 Hz), 4.10 (2 H, m, H-3′,4′), 4.26 (1 H, d, H-2′, $J_{1',2'}$ = 7.6 Hz), 4.54 (1 H, d, H-1′), 7.71 (1 H, s, H-6); UV λ_{max} (pH 1) 270 nm (ε 4600), λ_{max} (pH 7) 282 (5300), λ_{max} (pH 10) 285 (6100). Anal. ($C_9H_{14}N_4O_4$) C, H, N.

The mother liquor was evaporated to dryness and the residual syrup was dissolved in saturated HCl–MeOH. After 2 h at room temperature, the solvent was removed by evaporation in vacuo. The HCl salt of the β-nucleoside **17a** was obtained as a syrup: ^1H NMR (D_2O) δ 3.86 (2 H, m, H-5′,5″), 3.96 (1 H, m, H-4′), 4.15 (1 H, m, H-3′), 4.36 (1 H, q, H-2′, $J_{1',2'}$ = 4.0 $J_{2',3'}$ = 1.8 Hz), 5.04 (1 H, q, H-1′, $J_{1',6}$ = 0.9 Hz), 7.79 (1 H, d, H-6). Anal. Calcd for $C_9H_{14}N_4O_4$·1.5HCl·0.5MeOH: C, 36.52; H, 5.50; N, 17.93; Cl, 17.02. Found: C, 36.24; H, 5.30; N, 17.61; Cl, 17.40. The presence of 0.5 mol of MeOH in the analytical sample was detected by ^1H NMR.

4,2′-Anhydro-5-[3-*O*-acetyl-5-(2,5,5-trimethyldioxolanon-2-yl)-β-D-arabinofuranosyl]uracil (19). A mixture of ψ-uridine (0.5 g, 2 mmol) and α-acetoxyisobutyryl chloride (1.3 g, 8 mmol) in MeCN (60 mL) was refluxed gently until a clear solution was obtained (~1 h). The solvent was removed in vacuo and the residue was triturated with Et_2O until the crude product solidified. Crystallization of the solid from Me_2CO–Et_2O gave **19** (400 mg, 50%): mp 137–139 °C (collapsed), 170–200 °C dec; ^1H NMR (Me_2SO-d_6) δ 1.42 (6 H, s, Me), 1.62 (3 H, s, Me), 2.11 (3 H, s, OAc), 3.57 (2 H, m, H-5′,5″), 4.20 (1 H, m, H-4′), 5.18 (1 H, narrow m, H-3′), 5.36 (1 H, d, H-2′, $J_{1',2'}$ = 6.1 Hz), 5.54 (1 H, d, H-1′), 9.00 (1 H, s, H-6). Anal. ($C_{17}H_{20}N_2O_9$·0.5HCl) C, H, N, Cl.

This compound is unstable and decomposes into a dark syrup after several weeks at room temperature.

2′-Chloro-2′-deoxy-ψ-uridine (20b). A mixture of ψ-uridine (10.0 g) and α-acetoxyisobutyryl chloride (15 g) in dry MeCN (500

mL, over 4Å molecular sieves) was refluxed gently for 2 h and the solvent evaporated in vacuo. The residual syrup was dissolved in MeOH (30 mL) and the solution was diluted with Et_2O (500 mL). Crude 3′-*O*-acetyl-2′-chloro-2′-deoxy-5′-*O*-(2,5,5-trimethyldioxolanon-2-yl)-ψ-uridine (**20a**, 11.0 g) separated as a syrup. After decantation of the supernatant, the residue was stirred with concentrated NH_4OH (60 ml) for 3 h and evaporated, and the residue was triturated with EtOH to give crude **20b** as a solid. Three recrystallizations of the solid from MeOH afforded the pure β isomer **20b** (4.0 g): mp 201–203 °C dec; ^1H NMR data have been reported;[13] UV λ_{max} (pH 1) 262 nm (ε 8400), λ_{max} (pH 7) 262 (8800), λ_{max} (pH 10) 285 (6500). Anal. ($C_9H_{11}N_2ClO_5$) C, H, N, Cl.

The mother liquors of crystallization were combined and evaporated to dryness in vacuo. TLC and ^1H NMR showed that the residue was a mixture of several compounds including the α isomer **21**.

4,2′-Anhydro-5-(β-D-arabinofuranosyl)uracil (22, Anhydro-ψ-*ara*-U). (a) From 19. Compound **19** (100 mg) was dissolved in 0.5 M NaOMe–MeOH (25 mL). After 12 h, the solution was neutralized with Dowex 50 (H^+). The resin was removed by filtration and the filtrate was evaporated to dryness in vacuo. Crystallization of the residue from EtOH gave 40 mg (80%) of **22**: mp 225–227 °C; UV λ_{max} (pH 1) 277 nm (ε 4200), λ_{max} (pH 7) 277 (3900), λ_{max} (pH 10) 283 (5800); ^1H NMR data have been reported.[13] Anal. ($C_9H_{10}N_2O_5$) C, H, N.

(b) From 20a. Crude **20a** (2 g) was dissolved in 1 N NaOMe–MeOH (50 mL), and the solution was heated to 60 °C for 30 min. The solution was cooled to room temperature, neutralized with Dowex 50 (H^+), and evaporated to dryness. Crystallization of the residue from EtOH gave 600 mg (60%) of the 4,2′-anhydro nucleoside **22**, mp 225–227 °C.

5-(β-D-Arabinofuranosyl)uracil (23, ψ-*ara*-U). (a) From 22. Compound **22** (150 mg) was dissolved in 50% EtOH (30 mL). Dowex 50 (H^+) (2 mL) was added and the mixture was stirred and heated to 55 °C for 10 min. The resin was removed by filtration and the filtrate was evaporated to dryness. Upon trituration of the residue with EtOH, **23** was obtained as colorless crystals: 150 mg; mp 232–234 °C; UV λ_{max} (pH 1) 262 nm (ε 7500), λ_{max} (pH 7) 263 (7200), λ_{max} (pH 10) 267.5 and 290 (sh, 4900 and 3800); ^1H NMR data have been reported.[13] Anal. ($C_9H_{12}N_2O_6$) C, H, N.

(b) Directly from ψ-Uridine (18). A mixture of **18** (10 g) and α-acetoxyisobutyryl chloride (15.0 g) in dry MeCN (200 mL) was refluxed for 2 h and evaporated in vacuo. The residue was triturated with Et_2O and the Et_2O was removed by decantation. The residual syrup was dissolved in 0.5 M NaOMe–MeOH (200 mL). After 12 h, the mixture was neutralized with Dowex 50 (H^+) (70 mL) with heating and stirring at 55 °C for 10 min. The resin was removed by filtration and the filtrate was evaporated in vacuo to dryness. The residue was crystallized from EtOH to give **23** (3.9 g) as colorless crystals, mp 232–234 °C.

5-(β-D-Arabinofuranosyl)cytosine (24, ψ-*ara*-C). A mixture of **22** (100 mg) and saturated NH_3–MeOH (15 mL) in a steel container was heated at 85 °C for 40 h. The solution was filtered from a small amount of insoluble material and evaporated to dryness. The residue was triturated with Me_2CO to give **25** (70 mg) as colorless crystals: mp 212–213 °C dec; ^1H NMR (D_2O) δ 3.85 (2 H, m, H-5′,5″), 3.92 (1 H, m, H-4′), 4.14 (1 H, d, H-3′, $J_{3',4'}$ = 3.6 Hz), 4.31 (1 H, d, H-2′, $J_{1',2'}$ = 4.2 Hz), 4.97 (1 H, d, H-1′), 7.65 (1 H, s, H-6); UV λ_{max} (pH 1) 283 nm (ε 9100), λ_{max} (pH 7) 272 (5500), λ_{max} (pH 10) 272 (5000). Anal. ($C_9H_{13}N_3O_5$) C, H, N.

References and Notes

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