Studies on Biologically Active Nucleosides and Nucleotides. 7. Synthesis of Some N^4-Acyl and N^4-Acylaminomethyl 2,2'-Anhydronucleosides

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The synthesis of N^4-acyl-2,2'-anhydro-1-(3',5'-di-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrotetrafluoroborates (**2a–c**) has been achieved via direct N^4-acylation of the corresponding 2,2'-anhydronucleoside (**1a**). The reaction of 2,2'-anhydro-1-(3',5'-di-*O*-propionyl-β-D-arabinofuranosyl)cytosine hydrotetrafluoroborate (**1b**) with *N*-chloromethyl amides (**6a,b**) in the presence of boron trifluoride etherate gives the N^4-(acylamino)methyl derivatives (**8a,b**). Mild acidic treatment of **8a** and **8b** gives the depropionylated derivatives (**11a,b**) which, upon reaction with aqueous sodium bicarbonate, are converted into N^4-[(acylamino)methyl]-1-β-D-arabinofuranosylcytosines (**13a,b**).

2,2'-Anhydro-1-(β-D-arabinofuranosyl)cytosine (anhydro-ara-C) hydrochloride is a depot form of 1-β-D-arabinofuranosylcytosine (ara-C),[1] and its efficacy against several tumor systems has been confirmed.[2] The antitumor activity of anhydro-ara-C hydrochloride has prompted a number of synthetic investigations on modification of the base[3] and/or sugar portions.[4] Previously, the introduction of substituents at N^4 of anhydro-ara-C has been achieved via cyclization of N^4-substituted cytidines. By this method N^4-hydroxy, N^4-methoxy, N^4-methyl, N^4-phenyl,[3c] and N^4,N^4-dimethyl[3d] derivatives of anhydro-ara-C have been synthesized. However, attempts to prepare N^4-acyl derivatives of anhydro-ara-C by the cyclization of N^4-acylcytidines have not been successful[5] because of the high lability of the 2,2'-anhydro likage to alkaline hydrolysis;[6] the isolated products were N^4-acyl derivatives of ara-C. Recently the preparation of a N^4-benzoyl-2,4'-cyclonucleoside via an addition reaction on a N^4-benzoyl-4',5'-unsaturated nucleoside has been reported.[7]

Alkylation of the heterocyclic bases of pyrimidine nucleosides has been studied extensively and shown to proceed mainly at the N^3 position.[8] Shapiro and Shiuey[9] reported the relative yields of N^3- vs. N^4-substituted cytidine upon alkylation of cytidine. They concluded that the conditions which favor the N^4 substitution are those which favor the development of a positive charge on the alkylating agent.

In contrast to the many examples concerning alkylation of nucleosides, no work has been done on α-amidoalkylation[10] of nucleosides. The one related example involves the amidomethylation of 6-methyl-2-thiouracil which leads to the formation of the C_5-(acylamino)methyl derivatives.[11] Since α-amidoalkylating agents undergo acid catalysis to give resonance-stabilized carbonium immonium ions (**7**),[10] one might expect a selective N^4-α-amidoalkylation of suitably protected pyrimidine nucleosides under these conditions.

As a part of a study of modified anhydro-ara-C's as potential antitumor agents, we have undertaken the preparation of some N^4-substituted anhydro-ara-C's. This paper describes direct N^4-acylation and N^4-amidomethylation of 3',5'-di-*O*-acyl anhydro-ara-C hydrotetrafluoroborates (**1a,b**). The synthesis and antitumor activity of various 3',5'-di-*O*-acyl anhydro-ara-C hydrotetrafluoroborates have recently been reported by us.[4d,e]

The addition of an excess of acetic anhydride and triethylamine to a suspension of 3',5'-di-*O*-acetyl anhydro-ara-C hydrotetrafluoroborate (**1a**)[4d] in tetrahydrofuran at room temperature led to the formation of a clear solution within 16 h. Examination of the reaction mixture by TLC indicated disappearance of the starting material and formation of two new products. The major product was isolated in 45% yield by following a simple workup and determined to be the desired N^4,$O^{3'}$,$O^{5'}$-triacetyl-2,2'-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrotetrafluoroborate (**2a**). Acylation of the anhydro-ara-C chromophore was indicated by a bathochromic shift in the UV maxima of **2a** (λ_{max} 245 and 283 nm). In addition the ^{1}H NMR spectrum showed the presence of a three-proton singlet corresponding to the N^4-acetyl group, and both the C_5 and C_6 protons were deshielded relative to those in **1a** by the presence of the N^4-acetyl substituent. Further proof of the structure **2a** was obtained by conversion in 73% yield of **2a** to N^4,$O^{3'}$,$O^{5'}$-triacetyl-1-β-D-arabinofuranosylcytosine (**3a**)[5] upon treatment with aqueous sodium bicarbonate. The minor product from the above reaction was also isolated in 6% yield and shown to be **3a** resulting from the hydrolysis of **2a**.

The facile preparation of **2a** encouraged us to examine the reactions of **1a** with various acylating agents. The reaction of **1a** with picolinic anhydride in the presence of triethylamine gave the N^4-picolinoyl derivative (**2b**) in 46% yield and subsequent hydrolysis with aqueous sodium bicarbonate converted this to the corresponding ara-C

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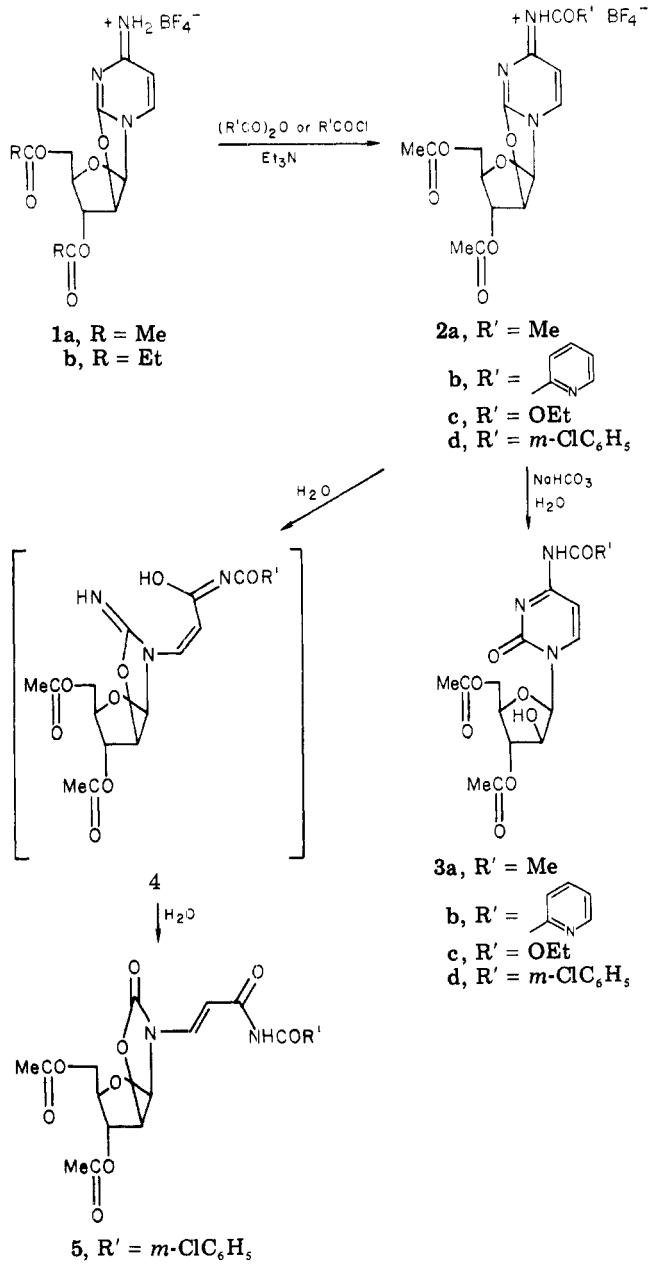

derivative (**3b**) in 67% yield. A similar reaction between **1a** and ethyl chloroformate gave the N^4-ethoxycarbonyl derivative (**2c**) in 40% yield. When an aqueous solution of the crude product obtained from **1a** and ethyl chloroformate was heated under reflux for 20 min, the ara-C derivative (**3c**) was obtained in 50% yield. Treatment of **1a** with *m*-chlorobenzoyl chloride and triethylamine in refluxing tetrahydrofuran for 1 h led to the formation of a mixture of two major products in a ratio of roughly 5:1 by TLC analysis. These were presumed to be the N^4-*m*-chlorobenzoyl derivative (**2d**) and the ara-C derivative (**3d**) from the fact that hydrolysis of the reaction mixture with aqueous sodium bicarbonate afforded **3d** in 36% yield. However, various attempts to isolate **2d** were unsuccessful owing to the lability of the 2,2′-anhydro linkage.

When the above hydrolysis was carried out in boiling aqueous methanol, the yield of **3d** fell to 20% and several byproducts were formed. One of these was isolated in 6% yield by chromatography on silicic acid and shown to be the oxazolidone **5**. The ^{1}H NMR spectrum in $CDCl_3$ revealed the vinyl group as two AB doublets (J = 14.5 Hz) at 7.13 and 8.05 ppm, and the large vicinal vinyl coupling allowed assignment of the E configuration.[12] In addition, the sugar proton was very similar to that of esters of β-D-arabinofurano[1′,2′:4,5]-2-oxazolidone.[13] The infrared spectrum showed the oxazolidone carbonyl absorption at 1793 cm^{-1} and the NH stretching band at 3290 cm^{-1}. The high carbonyl frequency of β-D-arabinofurano[1′,2′:4,5]-2-oxazolidone has been previously noted.[13a] Elemental analysis and the mass spectrum were also in accord with the assigned structure. The formation of the oxazolidone **5** can be rationalized by attack of water at C_4 of the pyrimidine ring to give the iminooxazolidine **4** with Z configuration. Subsequent hydrolysis of the imino group and an isomerization to the stable E configuration would give the observed product **5**. This degradation reaction was not anticipated, even though there is some precedent for the formation of 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline from 2,2′-anhydro pyrimidine nucleosides.[13a,14]

Our attention was next focused on the reactions of the dipropionyl ester (**1b**) with α-amidoalkylating agents. The reaction of **1b** with *N*-chloromethylbenzamide (**6a**) was carried out in the presence of boron trifluoride etherate without added solvent at room temperature for 16 h. After partition between ethyl acetate and aqueous sodium chloride, crystalline N^4-benzamidomethyl-2,2′-anhydro-1-(3′,5′-di-*O*-propionyl-β-D-arabinofuranosyl)cytosine hydrochloride (**8a**) was obtained in 64% yield. The structure of **8a** was obvious from its ^{1}H NMR spectrum, which showed the presence of a benzamidomethyl group. Location of this function at N^4 was shown by the coupling of methylene in the benzamidomethyl group to the N^4H. The assignments were confirmed by spin-decoupling studies (see Experimental Section). Two byproducts were also isolated from this reaction; these were identified as the imino ester (**9**, 4%) and *N*,*N*′-methylene bisbenzamide (**10**, 12%).[15] The structure of **9** was confirmed by ^{1}H NMR spectroscopy. The spectrum in Me_2SO-d_6 showed the presence of both the NCH_2N and NCH_2O groups. The ten aromatic protons appeared as two groups of multiplets at 7.2–7.7 and 7.8–8.1 ppm in a ratio of 4:1. This indicates the presence of magnetically equivalent phenyl protons of the benzimidate moiety in addition to the nonequivalent benzoyl protons. The equivalence of the phenyl protons of benzimidates has been noted.[16] Unlike the results from the acylaminomethylations of 6-methyl-2-thiouracil,[11] there was no indication of benzamidomethylation at C_5. The use of *N*-hydroxymethylbenzamide instead of **6a** resulted in a poor yield of **8a**, the major product being the bisamide **10**. The formation of methylene bisamides has been reported in acid-catalyzed α-amidoalkylation of relatively unreactive substrates.[11,17] A similar reaction using crude *N*-(chloromethyl)myristamide (**6b**), which was obtained from *N*-(hydroxymethyl)myristamide and thionyl chloride, gave the N^4-myristamidomethyl derivative **8b** in 58% yield.

In view of the interesting antitumor properties exhibited by N^4-substituted ara-C's,[3c,18] we have also decided to prepare N^4-benzamidomethyl and N^4-myristamidomethyl derivatives of ara-C (**13a** and **13b**, respectively). Treatment of **8a** with 0.3 M methanolic hydrogen chloride at

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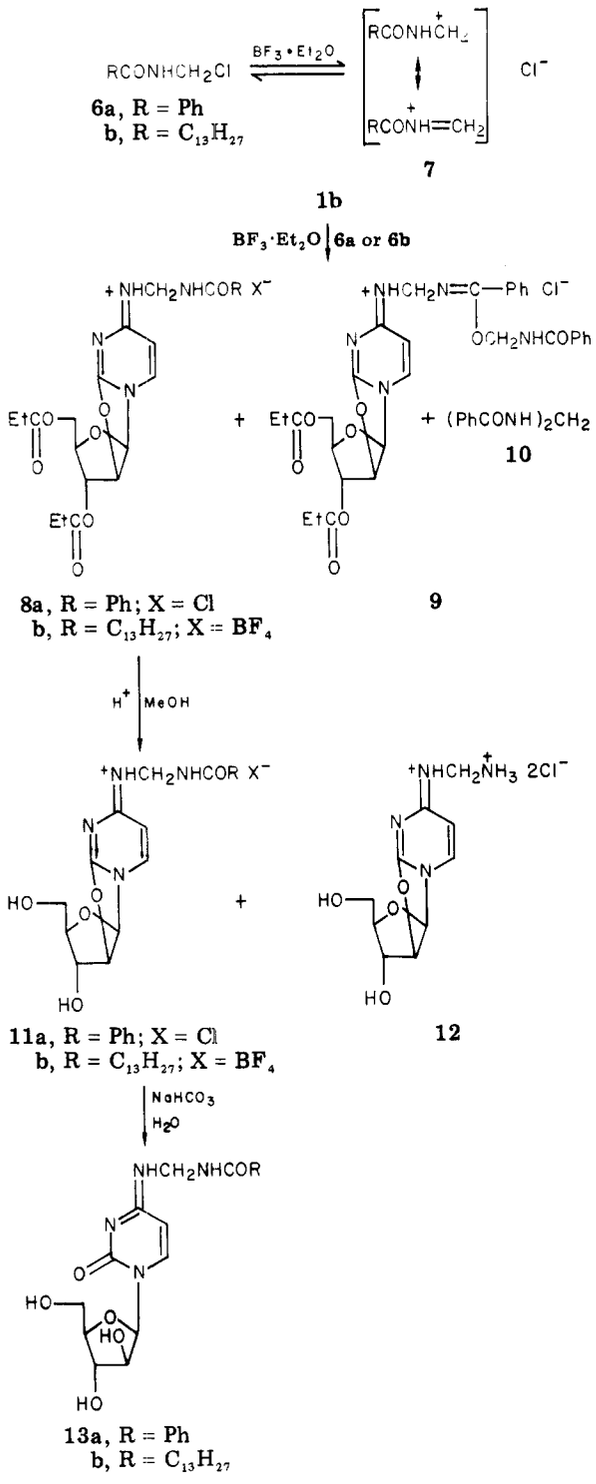

room temperature for 5 days gave N^4-(benzamidomethyl)anhydro-ara-C hydrochloride (**11a**) which was identified only by its ^{1}H NMR spectrum. Without purification, crude **11a** was treated with aqueous sodium bicarbonate at 80 °C for 20 min to cleave the 2,2′-anhydro linkage and give pure **13a** in an overall yield of 44% from **8a**. The structure of **13a** was apparent from its ^{1}H NMR spectrum, the sugar proton of which was very similar to that of ara-C. A similar acidic treatment of **8b** gave pure N^4-(myristamidomethyl)anhydro-ara-C hydrotetrafluoroborate (**11b**) in 42% yield. In this case a more polar byproduct was isolated in crystalline form in 12% yield. From analytical data and ^{1}H NMR spectroscopy, this compound was shown to be N^4-(aminomethyl)anhydro-ara-C dihydrochloride (**12**), the product of complete deblocking of **8b**. From the ^{1}H NMR spectrum, the presence of the N^4-aminomethyl group was apparent. Treatment of **11b** with aqueous sodium bicarbonate at room temperature for 4 days gave the desired **13b** in 65% yield.

Experimental Section

Infrared spectra were recorded on a Shimadzu IR-27G spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were measured with a Hitachi Perkin-Elmer R-20A spectrometer. Spectra are recorded in parts per million downfield from an internal standard of tetramethylsilane. Mass spectra were recorded with a Hitachi M-60 instrument at 30 eV and 120 °C by using an "in-beam" electron-impact technique.[19] UV spectra were measured on a Hitachi EPS-3T spectrometer. Column chromatography was done with Merck silica gel (0.05–0.20 mm particle size). Melting points are uncorrected.

2,2′-Anhydro-1-(3′,5′-di-*O*-propionyl-β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (1b). Cytidine (50 g, 0.21 mol) was treated with propionic anhydride (80 g, 0.62 mol) and boron trifluoride etherate (78 mL, 0.62 mol) in acetonitrile (1 L) as previously described.[4d] Crystallization from ethanol gave 60.6 g (68%) of **1b** as the hemihydrate: mp 157–159 °C; λ_{max} (MeOH) 235 nm (ε 11 800), 264 (13 300). Anal. Calcd for $C_{15}H_{20}N_3O_6BF_4 \cdot 0.5H_2O$ (mol wt, 434.18): C, 41.53; H, 4.70; N, 9.55; F, 17.07. Found: C, 41.50; H, 4.88; N, 9.68; F, 17.50.

Reaction of 2,2′-Anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (1a) with Acetic Anhydride. To a stirred suspension of **1a** hydrate[4d] (4.5 g, 11.2 mmol) in tetrahydrofuran (200 mL) were added acetic anhydride (1.7 g, 16.8 mmol) and triethylamine (1.2 g, 12.3 mmol). The mixture was stirred at room temperature for 16 h.

The resulting clear solution was evaporated to dryness, and the residue was triturated successively with ether, 2-propanol, and tetrahydrofuran. Crystallization from ethanol gave 2.4 g (45%) of N^4,$O^{3'}$,$O^{5'}$-triacetyl-2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrotetrafluoroborate (**2a**): mp 198–202 °C dec; λ_{max} (MeOH) 245 nm (ε 8100), 283 (13 500); ^{1}H NMR, see Table I.

Anal. Calcd for $C_{15}H_{18}N_3O_7BF_4 \cdot 1.5H_2O$ (mol wt, 466.18): C, 38.65; H, 4.54; N, 9.01; F, 16.30. Found: C, 38.90; H, 4.31; N, 8.93; F, 16.37.

Evaporation of the mother liquors from the crystallization of **2a** followed by fractional crystallization from ethanol gave 0.33 g (6%) of N^4,$O^{3'}$,$O^{5'}$-triacetyl-1-β-D-arabinofuranosylcytosine (**3a**): mp 225–228 °C dec (lit. mp 213–214,[5a] 217–220 °C[5b]); λ_{max} (MeOH) 248 nm (ε 15 400), 300 (7400).

Anal. Calcd for $C_{15}H_{19}N_3O_8$ (mol wt, 369.34): C, 48.78; H, 5.19; N, 11.38. Found: C, 48.85; H, 5.29; N, 10.99.

Hydrolysis of 2a. A suspension of **2a**·1.5H_2O (439 mg, 1 mmol) in water (7 mL) containing sodium bicarbonate (84 mg) was stirred at room temperature for 5 h. The crystalline product was collected by filtration and washed with water to give 0.27 g (73%) of **3a**, mp 225–228 °C dec, identical with that above.

N^4-Picolinoyl-2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (2b). The diester **1a** hydrate (4.0 g, 9.6 mmol) was treated with picolinic anhydride[20] (2.6 g, 9.6 mmol) and triethylamine (1.6 mL, 11.5 mmol) as in the above preparation of **2a** to the end of the first paragraph.

The resulting precipitate was collected by filtration and washed with methanol. Recrystallization from methanol gave 2.2 g (46%) of **2b**: mp 214–216 °C; λ_{max} (MeOH) 248 nm (ε 14 100), 294 (22 700); ^{1}H NMR, see Table I.

Anal. Calcd for $C_{19}H_{19}N_4O_7BF_4 \cdot 1.5H_2O$ (mol wt, 529.23): C, 43.12; H, 4.19; N, 10.59; F, 14.36. Found: C, 42.79; H, 3.82; N, 10.72; F, 14.14.

3′,5′-Di-*O*-acetyl-N^4-picolinoyl-1-β-D-arabinofuranosylcytosine (3b). A suspension of **2b** (1.5 g, 2.8 mmol) in water (50 mL) containing sodium bicarbonate (0.25 g) was heated in a water bath at 80 °C for 3 min, and the resulting clear solution was immediately cooled. The resulting crystals were collected and washed with methanol to give 0.86 g (67%) of **3b**: mp 223–225

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Table I. ^{1}H NMR Spectral Data[a]

compd	$C_1'H$	$C_2'H$	$C_3'H$	$C_4'H$	$C_5'H_2$	C_5H	C_6H	NCH_2N	other
2a	6.85 (d)[h]	5.90 (d)[j]	5.49 (d)[k]	4.6-4.9 (m)	3.7-4.4 (m)	8.12 (d)[m]	8.98 (d)		1.83, 2.13, 2.27 (3 s, 3 $COCH_3$), 12.30 (br s, NH)
2b[b]	7.00 (d)[h]	5.95 (d)	5.53 (br s)	4.6-4.9 (m)	4.0-4.6 (m)	8.53 (d)[m]	9.12 (d)		1.90, 2.21 (2 s, 2 $COCH_3$), 7.7-8.9 (m, 4, ArH)
2c	6.84 (d)[h]	5.90 (d)[j]	5.47 (d)[i]	4.6-4.9 (m)	3.9-4.4 (m)	7.94 (d)[m]	9.94 (d)		1.30 (t, CH_2CH_3), 1.84, 2.13 (2 s, 2 $COCH_3$), 4.29 (q, CH_2CH_3), 12.35 (br s, NH)
8a	6.68 (d)[h]	5.80 (d)[j]	5.41 (d)[k]	4.5-4.8 (m)	4.0-4.2 (m)	6.84 (d)[m]	8.38 (d)	4.98 (t)	0.7-1.3 (m, 2 CH_3), 1.9-2.7 (m, 2 $COCH_2$), 7.3-7.6, 7.8-8.1 (m, total 5, ArH), 9.60 (t, N^4H or CONH), 10.78 (t, N^4H or CONH)
8b[c]	6.61 (d)[h]	5.70 (d)	5.38 (br s)	4.4-4.7 (m)	3.8-4.3 (m)	6.61 (d)[m]	7.95 (d)	4.8-5.2 (m)	0.7-1.8 (m, 11 CH_2, 3 CH_3), 1.9-2.7 (m, 3 $COCH_2$), 7.20, 8.70 (2 br s, 2 NH)
9	6.65 (d)[h]	5.75 (d)	5.40 (br s)	4.5-4.8 (m)	3.8-4.3 (m)	6.89 (d)[m]	8.37 (d)	5.05 (s)[d]	0.7-1.3 (m, 2 CH_3), 1.8-2.6 (m, 2 $COCH_2$), 5.22 (s, OCH_2N),[d] 7.2-7.7 (m, 8, ArH), 7.8-8.1 (m, 2, ArH), 9.27, 11.25 (2 br s, 2 NH)
11b	6.55 (d)[h]	5.40 (d)	4.50 (br s)	4.1-4.3 (m)	3.2-3.3 (m)	6.55 (d)[f]	8.23 (d)[m]	4.6-4.9 (m)	0.6-1.8 (m, 11 CH_2, CH_3), 1.9-2.3 (m, 2 $COCH_2$), 4.4-4.9 (OH),[e] 5.85 (br s, OH), 8.64, 10.05 (2 t, NH)
12	6.69 (d)[h]	5.53 (d)	4.68 (br s)[d]	4.2-4.4 (m)	3.2-3.5 (m)	6.93 (d)[m]	8.47 (d)	4.65 (s)[d]	4.4-4.8 (2 OH),[e] 6.80 (br s, NH), 8.90 (br s, NH_3^+)
13a	6.08 (d)[i]	g	g	g	g	5.85 (d)[m]	7.52 (d)	4.7-5.2 (m)	3.4-4.2 (m, $C_2'H$, $C_3'H$, $C_4'H$, $C_5'H_2$), 4.7-5.2 (OH),[e] 5.3-5.5 (m, 2 OH), 7.4-8.4 (m, ArH, NH), 9.14 (t, NH)
13b	6.03 (d)[i]	g	g	g	g	5.73 (d)[m]	7.58 (d)	4.3-4.8 (m)	0.6-1.8 (m, 11 CH_2, CH_3), 1.9-2.3 (m, 2 $COCH_2$), 3.4-4.1 (m, $C_2'H$, $C_3'H$, $C_4'H$, $C_5'H_2$), 5.00 (br s, OH), 5.35 (d, 2 OH), 8.04 (br s, NH), 8.37 (t, NH)

[a] δ (ppm) from Me_4Si internal standard at 60 MHz. Me_2SO-d_6 was used as solvent unless otherwise indicated. [b] Solvent Me_2SO-d_6 + $CDCl_3$. [c] Solvent $CDCl_3$. [d] After addition of D_2O. [e] Under NCH_2N. [f] Under $C_1'H$. [g] See under other. [h] $J_{1',2'}$ = 6 Hz. [i] $J_{1',2'}$ = 3.5 Hz. [j] $J_{2',3'}$ = 0 Hz. [k] $J_{3',4'}$ = 2 Hz. [l] $J_{3',4'}$ = 2.5 Hz. [m] $J_{5,6}$ = 7.5 Hz.

°C; λ_{max} (MeOH) 264 nm (ε 15 800), 309 (9000).

Anal. Calcd for $C_{19}H_{20}N_4O_8$ (mol wt, 432.40): C, 52.78; H, 4.66; N, 12.96. Found: C, 52.71; H, 4.68; N, 13.02.

N^4-(Ethoxycarbonyl)-2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (2c). Ethyl chloroformate (0.99 g, 9.1 mmol) was added dropwise to a stirred refluxing suspension of **1a** hydrate (3 g, 7.6 mmol) and triethylamine (1.25 mL, 9.1 mmol) in tetrahydrofuran (90 mL) and the mixture was kept at the reflux temperature for 2 h. A further 0.99 g of ethyl chloroformate and 1.25 mL of triethylamine were added and the mixture was kept at the reflux temperature for an additional 2 h.

After the mixture was cooled, the resulting precipitate was collected by filtration and recrystallized from methanol to give 1.4 g (40%) of **2c**: mp 211–213 °C; λ_{max} (MeOH) 243 nm (ε 11 600), 280 (19 000); ^{1}H NMR, see Table I.

Anal. Calcd for $C_{16}H_{20}N_3O_8BF_4$ (mol wt, 469.18): C, 40.96; H, 4.30; N, 8.96; F, 16.20. Found: C, 40.69; H, 4.23; N, 8.84; F, 16.13.

3′,5′-Di-*O*-acetyl-N^4-ethoxycarbonyl-1-β-D-arabinofuranosylcytosine (3c). The diester **1a** hydrate (3 g) was treated with ethyl chloroformate as in the above preparation of **2c** to the end of the first paragraph.

The solvent was evaporated to dryness and the residue was dissolved in water (50 mL). The mixture was heated under reflux for 20 min and cooled. The resulting crystalline product was collected by filtration to give 1.5 g (50%) of **3c**: mp 228–231 °C; λ_{max} (MeOH) 242 nm (ε 16 000), 294 (8800).

Anal. Calcd for $C_{16}H_{21}N_3O_9$ (mol wt, 399.37): C, 48.12; H, 5.30; N, 10.52. Found: C, 48.07; H, 5.38; N, 10.42.

3′,5′-Di-*O*-acetyl-N^4-(*m*-chlorobenzoyl)-1-β-D-arabinofuranosylcytosine (3d). A. Using Aqueous Sodium Bicarbonate. The diester **1a** hydrate (8 g, 21.2 mmol) was treated with *m*-chlorobenzoyl chloride (5.6 g, 32 mmol) and triethylamine (4.4 mL, 32 mmol) as in the above preparation of **2c** to the end of the first paragraph.

The solvent was evaporated and the residue was triturated with ether. Examination of this mixture by TLC ($CHCl_3$–MeOH–AcOH, 85:15:3, silica gel) indicated it to be roughly a 5:1 mixture of two major products. The triturated residue was dissolved in tetrahydrofuran (40 mL), and saturated aqueous sodium bicarbonate (20 mL) was added. The mixture was stirred at room temperature overnight and most of the organic solvent was evaporated in vacuo. The resulting crystals were collected by filtration and washed with water to give 3.4 g (36%) of **3d**, mp 234–236 °C. An analytical sample from methanol had mp 237–238 °C; λ_{max} (MeOH) 259 nm (ε 23 600), 307 (11 000).

Anal. Calcd for $C_{20}H_{20}N_3O_8Cl$ (mol wt, 465.86): C, 51.56; H, 4.33; N, 9.02; Cl, 7.61. Found: C, 51.95; H, 4.45; N, 9.02; Cl, 7.59.

B. Using Aqueous Methanol. The diester **1a** hydrate (5 g) was treated with *m*-chlorobenzoyl chloride as in method A except that the triturated residue was dissolved in 70% methanol (100 mL). The mixture was heated under reflux for 30 min and the solvent was largely removed in vacuo. Crystallization of the residue from 2-propanol gave 0.12 g (2%) of **3d**, mp 237–238 °C, identical with that above.

The mother liquors from the crystallization of **3d** were evaporated, and the residue was chromatographed on a column of silicic acid (100 g) by using $CHCl_3$–MeOH (99:1). Evaporation of the pure product fractions followed by crystallization from benzene gave 0.3 g (6%) of (*E*)-N^3-[[(*m*-chlorobenzoyl)carbamoyl]-vinyl]-β-D-arabinofurano[1′,2′:4,5]-2-oxazolidone (**5**): mp 142–143 °C; λ_{max} (MeOH) 271 nm (ε 30 200); ^{1}H NMR ($CDCl_3$) δ 2.07 and 2.16 (s, 3, $COCH_3$), 3.9–4.4 (m, 2, $C_5'H_2$), 4.48 (m, 1, $C_4'H$), 5.18 (d, 1, $J_{1',2'}$ = 6 Hz, $C_2'H$), 5.47 (br s, 1, $C_3'H$), 6.17 (d, 1, $C_1'H$), 7.18 (d, 1, *J* = 14.5 Hz, NCH=), 7.2–8.3 (m, 4, Ar H), 8.09 (d, 1, COCH=), 9.08 (br s, 1, NH); mass spectrum, *m/e* 466, 468 (M^+), 406 (M–AcOH), 268 (M–ClC_6H_4CO); λ_{max} (Nujol) 3290, 1793, 1767, 1749, 1703, 1675 cm^{-1}.

Anal. Calcd for $C_{20}H_{19}N_2O_9Cl$ (mol wt, 466.85): C, 51.46; H, 4.10; N, 6.00; Cl, 7.60. Found: C, 51.27; H, 4.07; N, 5.92; Cl, 7.41.

***N*-(Chloromethyl)myristamide (6b).** A mixture of *N*-hydroxymyristamide[21] (1.0 g, 3.9 mmol) and thionyl chloride (2.8 g, 23.5 mmol) in ether (80 mL) was heated under reflux for 30 min. The resulting clear solution was evaporated and the residue was dried in vacuo over sodium hydroxide to give 1.1 g of crude **6b** as a white solid: ^{1}H NMR ($CDCl_3$) δ 5.20 (d, 2, NCH_2Cl). This material was used in the next step without further purification.

Reaction of 1b with *N*-(Chloromethyl)benzamide (6a). To a solution of **1b** hemihydrate (5.1 g, 11.8 mmol) in nitromethane (7 mL) were added boron trifluoride etherate (4.5 mL, 35.4 mmol) and chloroform (7 mL). The mixture was cooled to 5 °C and **6a**[22] (5 g, 29.4 mmol) was added. The solvents were immediately evaporated to dryness below ~5 °C in vacuo and the residue was then stored at room temperature for 16 h.

The resulting mixture was partitioned between ethyl acetate (200 mL) and saturated aqueous sodium chloride (100 mL) to give a white crystalline product. The crystals were collected by filtration and washed with ethyl acetate to give 3.3 g of N^4-(benzamidomethyl)-2,2'-anhydro-1-(3',5'-di-*O*-propionyl-β-D-arabinofuranosyl)cytosine hydrochloride (**8a**), mp 229–230 °C dec. An analytical sample from methanol had mp 231–232 °C dec: λ_{max} (MeOH) 238 nm (ϵ 14 000), 268 (14 900); ^{1}H NMR parameters are in Table I. Irradiation at δ 4.98 (NCH_2N) caused the triplets at both δ 9.60 (NH) and 10.78 (NH) to collapse to two singlets. Irradiation at either δ 9.60 (NH) or 10.78 (NH) caused the triplet at δ 4.98 (NCH_2N) to collapse to a doublet.

Anal. Calcd for $C_{24}H_{27}N_4O_7Cl$ (mol wt, 506.97): C, 54.49; H, 5.37; N, 11.05; Cl, 6.99. Found: C, 54.64; H, 5.37; N, 11.09; Cl, 6.87.

The ethyl acetate solution from the above partitioning was further washed with brine to give a white precipitate which was collected by filtration. Recrystallization from methanol gave 0.5 g (total yield 64%) of **8a**, identical with that above. The mother liquors from the recrystallization were concentrated to a small volume and the resulting precipitate was collected by filtration. Recrystallization from methanol gave 0.3 g (4%) of N^4-[[(α-(benzamidomethoxy)benzylidene)amino]methyl]-2,2'-anhydro-1-(3',5'-di-*O*-propionyl-β-D-arabinofuranosyl)cytosine hydrochloride (**9**): mp 238–239 °C; λ_{max} (MeOH) 232 nm (ϵ 14 800), 268 (11 100); ^{1}H NMR, see Table I.

Anal. Calcd for $C_{31}H_{34}N_5O_8Cl$ (mol wt, 640.11): C, 58.17; H, 5.35; N, 10.94; Cl, 5.54. Found: C, 58.17; H, 5.41; N, 11.06; Cl, 6.03.

The ethyl acetate solution from the final partitioning was evaporated and the residue was triturated with ethanol. Crystallization from water gave 0.5 g (12%) of *N,N'*-methylenebisbenzamide **10**: mp 215–217 °C (lit.[15] mp 219 °C); ^{1}H NMR (Me_2SO-d_6) δ 4.88 (t, 2, J = 5.5 Hz, CH_2), 7.2–7.7 and 7.7–8.1 (m, total 10, Ar H), 8.97 (t, 2, NHs).

***N*^{4}-(Myristamidomethyl)-2,2'-anhydro-1-(3',5'-di-*O*-propionyl-β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (8b).** The diester **1b** hemihydrate (2.4 g, 5.5 mmol) was treated with crude **6b** (3.8 g, ~16 mmol) and boron trifluoride etherate (2.1 mL, 16.4 mmol) as in the above preparation of **8a** to the end of the first paragraph.

The mixture was partitioned between ether (150 mL) and water (70 mL) to give a white precipitate which was removed by filtration. The ether layer was concentrated to a small volume and the resulting crystals were collected by filtration. Recrystallization from 2-propanol gave 2.1 g (58%) of **8b**: mp 116–118 °C; λ_{max} (MeOH) 239 nm (sh, ϵ 12 700), 268 (18 300); ^{1}H NMR, see Table I.

Anal. Calcd for $C_{30}H_{49}N_4O_7BF_4$ (mol wt, 664.57): C, 54.22; H, 7.43; N, 8.43; F, 11.44. Found: C, 54.43; H, 7.48; N, 8.42; F, 11.38.

***N*^{4}-(Benzamidomethyl)-1-β-D-arabinofuranosylcytosine (13a).** The diester **8a** (4.3 g, 8.5 mmol) was dissolved in 0.3 M methanolic hydrogen chloride (300 mL) and stored at room temperature for 5 days. The solvent was removed in vacuo and the residue was triturated with acetone. Methanol (50 mL) was added to the triturated residue and the resulting precipitate was removed by filtration. The methanol solution was evaporated in vacuo to give 2.0 g of N^4-(benzamidomethyl)-2,2'-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrochloride (**11a**) as a white foam which was essentially homogeneous by ^{1}H NMR analysis.

To a solution of crude **11a** (2 g, ~5 mmol) in water (2 mL) was added sodium bicarbonate (0.5 g, 6 mmol), and the mixture was heated at 80 °C for 20 min. After the solution was cooled, the resulting crystals were collected by filtration and recrystallized from water to give 1.4 g (44%) of **13a**: mp ~144 °C; λ_{max} (MeOH) 227 nm (ϵ 20 400), 275 (14 500); ^{1}H NMR, see Table I.

Anal. Calcd for $C_{17}H_{20}N_4O_6$·0.25H_2O (mol wt, 380.88): C, 53.61; H, 5.43; N, 14.71. Found: C, 53.83; H, 5.40; N, 14.91.

Methanolysis of 8b. The diester **8b** (8.6 g, 12.9 mmol) was treated with 0.3 M methanolic hydrogen chloride (110 mL) as in the preparation of **11a**, except that after evaporation of the methanol the residue was triturated with ether. The triturated residue was extracted with acetone (200 mL), and the insoluble material was collected by filtration. Recrystallization from methanol–ethanol gave 0.5 g (12%) of N^4-(aminomethyl)-2,2'-anhydro-1-(β-D-arabinofuranosyl)cytosine dihydrochloride (**12**): mp 170–173 °C dec; λ_{max} (MeOH) 237 nm (ϵ 5700), 268 (7500); ^{1}H NMR, see Table I.

Anal. Calcd for $C_{10}H_{16}N_4O_4Cl_2$ (mol wt, 327.18): C, 36.71; H, 4.93; N, 17.13; Cl, 21.67. Found: C, 36.71; H, 5.03; N, 17.06; Cl, 21.98.

The extracts were evaporated to dryness and the residue was partitioned between ethyl acetate and water. The organic layer was treated with activated charcoal, dried ($MgSO_4$), and concentrated to a small volume. Hexane was added and the resulting precipitate was collected by centrifugation to give 3.0 g (42%) of N^4-(myristamidomethyl)-2,2'-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrotetrafluoroborate (**11b**) as a homogeneous foam: λ_{max} (MeOH) 240 nm (ϵ 12 100), 269 (15 700); ^{1}H NMR, see Table I.

Anal. Calcd for $C_{24}H_{41}N_4O_5BF_4$ (mol wt, 552.44): C, 52.18; H, 7.48; N, 10.14; F, 13.76. Found: C, 52.24; H, 7.50; N, 10.17; F, 13.38.

***N*^{4}-(Myristamidomethyl)-1-β-D-arabinofuranosylcytosine (13b).** To a solution of **11b** (3.0 g, 5.4 mmol) in ethyl acetate (20 mL) was added saturated aqueous sodium bicarbonate (20 mL) and the mixture was stirred at room temperature for 4 days. The resulting crystals were collected by filtration and recrystallized from ethyl acetate to give 1.7 g (65%) of **13b**: mp ~170 °C; λ_{max} (MeOH) 238 nm (ϵ 11 000), 276 (12 900); ^{1}H NMR, see Table I.

Anal. Calcd for $C_{24}H_{42}N_4O_6$ (mol wt, 482.63): C, 59.73; H, 8.77; N, 11.61. Found: C, 59.64; H, 8.44; N, 11.64.

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Registry No. 1a, 62840-04-4; **1b**, 73088-61-6; **2a**, 73173-68-9; **2b**, 73049-01-1; **2c**, 73049-03-3; **3a**, 13241-19-5; **3b**, 73048-67-6; **3c**, 73048-68-7; **3d**, 73048-69-8; **5**, 73048-70-1; **6a**, 38792-42-6; **6b**, 73048-71-2; **8a**, 73048-72-3; **8b**, 73048-74-5; **9**, 73048-75-6; **10**, 1575-94-6; **11a**, 73048-76-7; **11b**, 73048-77-8; **12**, 73048-78-9; **13a**, 73048-79-0; **13b**, 73048-80-3; cytidine, 65-46-3; propionic anhydride, 123-62-6; acetic anhydride, 108-24-7; picolinic anhydride, 16837-39-1; ethyl chloroformate, 541-41-3; *m*-chlorobenzoyl chloride, 618-46-2; *N*-hydroxymyristamide, 17698-03-2.

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