(34) For references see L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 2, W. W. Zorbach and R. S. Tipson, Ed., Wiley-Interscience, New York, N. Y., 1973, p 341.
(35) See, e.g., D. Horton and F. O. Swanson, *Carbohyd. Res.*, **14**, 159 (1970).
(36) For ease of comparison, we refer here to compounds derived from both **4** and **23** using the same numbering of the sugar protons and considering both as ribofuranosyl derivatives.
(37) S. Hanessian and A. G. Pernet, *Chem. Commun.*, 755 (1971).
(38) J. Bastide and J. LeMatre, *Bull. Soc. Chim. Fr.*, 1336 (1971).

Reactions of 2-Acyloxyisobutyryl Halides with Nucleosides. V. Reactions with Cytidine and Its Derivatives[1]

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The reaction of cytidine with 2-acetoxyisobutyryl chloride in acetonitrile at 80° leads to the isolation in good yield of 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**4a**). By conducting the reaction at room temperature an intermediate 5′-*O*-(trimethyldioxolanone) ether (**5**) is obtained and can be cleaved to **4a** in very high yield. Under different conditions of hydrolysis **5** can be efficiently converted into either 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrochloride or 1-(β-D-arabinofuranosyl)cytosine. A variety of base analogs of cytidine have also been treated with 2-acetoxyisobutyryl chloride to give related analogs of **4a**. The reaction can also be extended to other acyl derivatives, since cytidine and 2-butyryloxyisobutyryl chloride give 2,2′-anhydro-1-(3′-*O*-butyryl-β-D-arabinofuranosyl)cytosine hydrochloride in good yield.

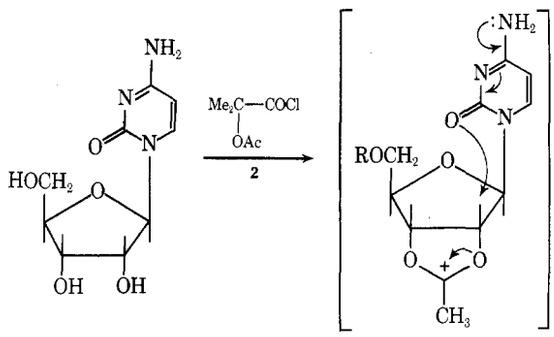
Previous papers in this series have outlined the anomalous reactions of 2-acetoxyisobutyryl halides with uridine,[1,4] adenosine,[5] and several adenosine analogs.[6] In all cases the observed products could be explained *via* the conversion of the 2′,3′-cis diol function to a reactive 2′,3′-acetoxonium ion.[4] In the case of the purine nucleosides[5-7] such acetoxonium ions are opened by attack of halide ion to form isomeric 2′,3′-trans chloro acetates with the 2′-*O*-acetyl-3′-deoxy-3′-halo-β-D-xylofuranosyl isomer predominating. In the uridine series, however, the acetoxonium ion undergoes preferential intramolecular attack by the C_2 carbonyl group of the pyrimidine ring to initially form 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil, which is then opened by halide ion giving a 3′-*O*-acetyl-2′-deoxy-2′-halouridine derivative with overall retention of configuration.

In the cytidine series one might expect a similar type of participation by the C_2 carbonyl of the cytosine ring, and in this paper we describe some of the reactions of cytidine and several cytidine derivatives and analogs with 2-acetoxyisobutyryl chloride.

The addition of an excess of 2-acetoxyisobutyryl chloride (**2**) to a suspension of cytidine (**1**) in acetonitrile at 80° led to the formation of a clear solution within about 5 min. On continued heating, a crystalline product began to separate and after a total of 30 min the remaining material was precipitated with ether. Crystallization of the residue from methanol–acetone then gave crystalline 2,2′-anhydro-(3′-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**4a**) in 68% yield. The structure of **4**, which undoubtedly arises *via* the 2′,3′-acetoxonium ion (**3**), was apparent from its analytical and spectroscopic properties. Thus the ultraviolet spectrum of **4a** showed double maxima at 231 and 263 nm typical of the 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine (**4b**) chromophore.[8] The presence of a single acetyl group was indicated by nmr spectroscopy and this function was located at $C_{3'}$ by the 0.9-ppm downfield shift of C_3 H relative to that in **4b**. Further confirmation of this structure *via* chemical degradation to **4b** will be presented later in this paper.

Our interest in **4a** became acute with the observation that this substance showed pronounced activity against several DNA viruses in tissue culture and against L-1210 leukemia in mice.[9] Subsequent to this aspect of our work several new methods for the synthesis of **4b** have been described[10] and this compound has been the subject of extensive examination as an antitumor agent of low toxicity.[11] In addition, there has been interest in the pharmacological properties of the related 3′-phosphate ester (**4c**).[12]

While the preparation of **4a** described above was quite efficient and simple on a modest scale, attempted scale up to a 100-mmol level led to reduced yields of crystalline material. This was largely due to the formation of by-products, the major ones being tentatively identified as cytosine nucleosides containing chlorinated sugars. It remains uncertain whether these products arise by direct opening of **3** with halide ion, or by further reactions of **4a**.



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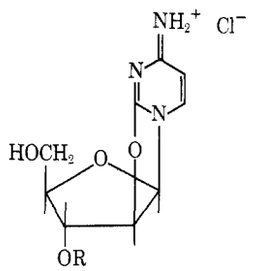
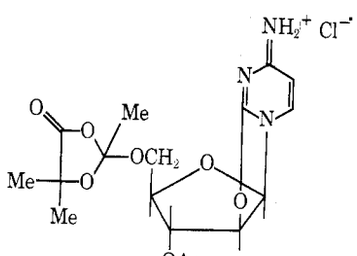


4a, R = $COCH_3$
b, R = H
c, R = PO_3H_2

In order to avoid this problem we have found that the reaction of cytidine with **2** at room temperature requires about 3 hr to give a homogeneous solution. Precipitation with ether at this point then gave a crude product that was predominantly the 5′-dioxolanone ether (**5**). The latter showed the usual spectral features of a dioxolanone ether (ν_{max} 1805 cm^{-1} and several nmr singlets at 1.3–1.9 ppm due to the chiral substituent)[4] and was a mixture of diastereoisomers due to the chiral dioxolanone function. Without any purification this substance was treated with 0.05 *M* methanolic hydrogen chloride at room temperature for 1.5 hr in order to cleave the dioxolanone ether. Crystallization of the resulting product then gave **4a** in an overall yield of 90% from cytidine and with a purity in excess of 95%. Trace amounts of cytidine and 1-(β-D-arabinofuranosyl)cytosine could be efficiently removed by a further crystallization if necessary. This procedure makes **4a** readily available in high yield and can be readily scaled up. It is presumed that **5** is also an intermediate in the reaction of cytidine with **2** at 80° and that the acid- and base-labile dioxolanone function is lost either during the reaction or during crystallization of **4a** from a polar solvent such as methanol.

Crude **5** can also be efficiently transformed into either 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine (**4b**) or 1-(β-D-arabinofuranosyl)cytosine, both compounds being of considerable current interest owing to their well-known biological activities.[11,13] Thus treatment of crude **5** with 0.3 *M* methanolic hydrogen chloride at room temperature for 3 days led to the direct crystallization of pure **4b** in overall yields of 73–80% from cytidine. A similar acidic treatment applied to crystalline **4a** gave **4b** in 89% yield. The above constitutes a facile and efficient route for the preparation of **4a** that has been successfully used on up to a multikilo scale. If, alternatively, crude **5** is treated with



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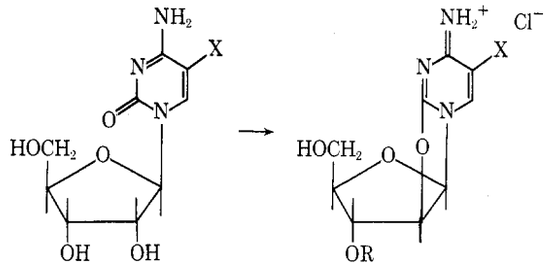
dilute ammonia, the protecting groups are removed and the anhydro bridge is cleaved, giving crystalline 1-(β-D-arabinofuranosyl)cytosine in an overall yield of 73% from cytidine. A similar cleavage of the unprotected anhydro nucleoside **4b** has previously been described by others.[10,14]

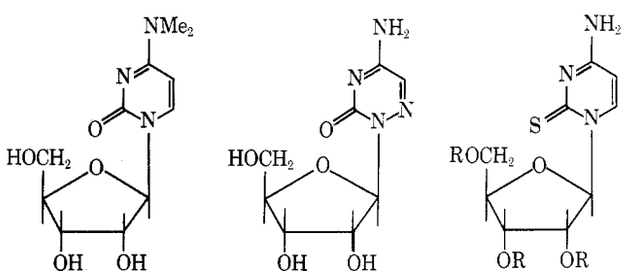
The facile preparations of **4a** and **4b** above encouraged us to examine the reactions of **2** with a variety of base analogs of cytidine. A variety of known 5-substituted cytidine derivatives were prepared as starting materials for the above reactions. Included were 5-methylcytidine (**6a**),[15] 5-fluorocytidine (**6b**),[16] 5-chlorocytidine (**6c**),[17] 5-bromocytidine (**6d**),[17] and 5-iodocytidine (**6e**),[18] all of which were prepared essentially according to known methods. It should be noted that the 5-chloro and 5-bromo derivatives (**6c, 6d**) were prepared by Fukuhara and Visser[17] by reaction of cytidine with chlorine or bromine in a mixture of acetic acid and pyridine using ultraviolet activation. The direct products of these reactions were the 2′,3′,5′-tri-*O*-acetyl derivatives of **6c** and **6d**, which were subsequently hydrolyzed. In our experience



6a, X = Me; **7a**, X = Me; R = H
b, X = F; **b**, X = F; R = Ac
c, X = Cl; **c**, X = Cl; R = H
d, X = Br; **d**, X = Br; R = H
e, X = I; **e**, X = I; R = H or OAc
f, X = NMe_2; **f**, X = NMe_2; R = H

the halogenation reactions proceeded readily under the above conditions[17] except that irradiation was unnecessary and the direct products were free **6c** and **6d**.

In addition, 5-bromocytidine (**6d**) was treated with anhydrous dimethylamine at 100°, conditions similar to those used by Ueda[19] for the preparation of 5-morpholinouridine, to give 5-dimethylaminocytidine (**6f**) in 59% yield. Other base analogs of cytidine that were prepared include N^4,N^4-dimethylcyctidine (**8**),[16] 6-azacytidine (**9**),[20] and 2-thiocytidine (**10b**). The latter compound was prepared by the condensation in nitromethane of 2-thiocytosine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in the presence of mercuric cyanide and a molecular sieve.

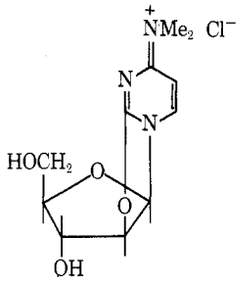


8 **9** **10a**, R = Bz; **b**, R = H

The tri-*O*-benzoyl derivative (**10a**) so obtained has previously been prepared by Niedballa and Vorbrüggen[21] *via* a different route and debenzoylation gave crystalline **10b**[22] in high yield.

The reactions of the cytidine base analogs (**6a, 6b, 8, 9,** and **10b**) with **2** were carried out in acetonitrile under conditions similar to those used with cytidine itself. Some of these reactions were done before the benefits of conducting the synthesis at room temperature were realized and hence it is quite likely that some of the yields could be improved. Nevertheless, in each case the corresponding 2,2′-anhydro nucleoside hydrochloride (**7a, 7b, 11, 12,** and **13**) was formed and isolated in crystalline form, generally in yields of 61–89%. In some cases there was partial loss of the 3′-*O*-acetyl function during the work-up and crystallization, and in those cases treatment with dilute methanolic hydrogen chloride was extended so as to complete the removal. Thus the compounds **7a, 7c–f, 11,** and **12** were obtained as the free 3′-hydroxy compounds.

Subsequent to the completion of this work the synthesis of **7d** and **7e** (R = H) has been described *via* reaction of the appropriate 5-halocytidine with partially hydrolyzed phosphorus oxychloride in ethyl acetate.[23] This method, however, requires a purification of the products by ion exchange chromatography. Using this same method the deacetylated derivative of **7b** has also been prepared as both



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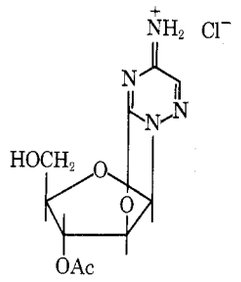

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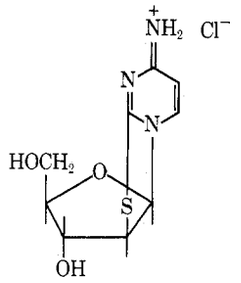

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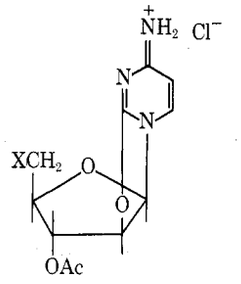

14a, X = Cl
b, X = I

the chloride[23] and formate[24] salts and shown to be an orally and parenterally active antileukemic agent in mice.

We have also treated 5′-chloro-5′-deoxycytidine[25] and 5′-deoxy-5′-iodocytidine, the latter being obtained in high yield by conventional treatment of N^4-acetyl-5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidenecytidine[26] with acetic acid and then ammonium hydroxide, with **2**, giving the crystalline anhydro nucleosides **14a** and **14b** in yields of 71 and 65%. Finally, we have shown that the basic reaction described in this paper is a general one that can be extended to the preparation of a wide range of other 3′-*O*-acyl derivatives of 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine. Thus through reaction of 2-hydroxyisobutyric acid with butyryl chloride and then with thionyl chloride, 2-butyryloxyisobutyryl chloride (**15**) was obtained as a distillable liquid. The reaction of cytidine with **15** at room temperature gave, by ether precipitation, the 5′-dioxolanone derivative **16a** which was identified only by its characteristic infrared and nmr spectra.[4] Without purification **16a** was briefly treated with dilute methanolic hydrogen chloride at room temperature to remove the dioxolanone function. The resulting product was readily crystallized, giving 2,2′-anhydro-1-(3′-*O*-butyryl-β-D-arabinofuranosyl)cytosine (**16b**) in 59% yield.

The formation of the latter compound constitutes the beginning of a quite extensive research program, since we have demonstrated that variations in the 3′-*O*-acyl function in compounds such as **4a** and **16b** can lead to wide differences in biological activities.[27] Details of both the

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EXPERIMENTAL

General Methods

The general methods used are as described previously[4]. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson for their continuing cooperation with nmr spectroscopy and to Mrs. J. Fajkos for excellent technical help.

2,2′-Anhydro-(3′-O-acetyl-β-D-arabinofuranosyl)-cytosine hydrochloride (4a)

(a) A suspension of cytidine (4.86 g, 20 mmol) and 2-acetoxyisobutyryl chloride (13.2 g, 80 mmol)[6] in acetonitrile (40 ml) was stirred at 80°. After 5 min a clear solution resulted and within a few minutes fine crystals began to separate. After a total of 30 min the mixture was cooled to room temperature and ether (100 ml) was gradually added to the stirred mixture. The solid was collected by filtration and washed with ether giving 6.37 g of crude product that was crystallized from methanol–acetone giving 4.11 g (68%) of pure **4a** with mp 254–255° (d): $\lambda_{max}^{H_2O}$ 231 nm (ε 9,500), 263 nm (ε 10,600); $[\alpha]_D^{23}$ −69.8° (c 0.13, H_2O); ORD (H_2O) $[\phi]_{285}^{pk}$ 4,800°, $[\phi]_{266}$ 0°, $[\phi]_{233}^{tr}$ −19,100°, $[\phi]_{216}$ 0°.

Anal. Calcd. for $C_{11}H_{14}N_3O_5Cl$ (303.7): C, 43.50; H, 4.65; N, 13.84
Found: C, 43.56; H, 4.78; N, 13.67

(b) A mixture of cytidine (24.3 g, 100 mmol) and **2** (58 ml, 400 mmol) in acetonitrile (400 ml) was stirred at room temperature until a clear solution resulted (~3 hr). The solvent was then largely evaporated *in vacuo* and the residue was triturated twice with ether (500 ml) giving a dry, white solid. The latter was washed with ether and dried *in vacuo* giving 4.85 g of crude **5**.

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This material was dissolved in 0.05 M methanolic hydrogen chloride (350 ml) and stored at room temperature for 1.5 hr. The solvent was evaporated *in vacuo* leaving a semicrystalline residue that was warmed for several minutes with chloroform–acetone (1:2, 250 ml), chilled and filtered giving 26.7 g (90%) of crystalline **4a** of at least 95% purity. Paper or silica thin layer chromatography (butanol–acetic acid–water, 5:2:3) and borate electrophoresis at pH 6 revealed the presence of trace amounts of cytidine and ara C. Recrystallization of a sample from aqueous acetone gave pure **4a** identical to that from (a) with better than 80% recovery.

2,2′-Anhydro-(β-D-arabinofuranosyl)-cytosine hydrochloride (4b)

(a) A solution of **4a** (1.52 g, 5 mmol) in methanol (99 ml) containing conc. hydrochloric acid (1 ml) was kept at room temperature for 7 days during which time needles (343 mg) of **4b** separated. The filtrate was evaporated to dryness and the residue was crystallized from methanol–acetone giving a further 824 mg (total yield 89%) of **4b** with mp 266–267° (d) (reported[8a] mp 248–250°, 262–264°[10a]): $\lambda_{max}^{H_2O}$ 231 nm (ε 9,900), 263 nm (ε 10,800); $[\alpha]_D^{23}$ −22.6° (c 0.2, H_2O); ORD (H_2O) $[\phi]_{279}^{pk}$ 5,400°, $[\phi]_{266}$ 0°, $[\phi]_{237}$ −17,800°.

Anal. Calcd. for $C_9H_{12}N_3O_4Cl$ (261.68): C, 41.31; H, 4.62; N, 16.06
Found: C, 41.20; H, 4.59; N, 15.83

(b) The crude ether precipitate of **5** obtained from cytidine (48.6 g, 230 mmol) as above was dissolved in 0.3 M methanolic hydrogen chloride (1.5 l.) and stored at room temperature for 3 days. The resulting crystalline product was removed, washed with methanol and dried *in vacuo* giving 29.7 g of pure **4b**. Concentration of the mother liquors gave a further 8.30 g (total yield 73%) of **4b** identical to that above.

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1-(β-D-arabinofuranosyl)-cytosine

A solution of the crude ether precipitate of **5** obtained from cytidine (2.43 g, 10 mmol) in 3 M ammonium hydroxide (25 ml) was stored for 16 hr at room temperature and then evaporated to dryness. The residue was coevaporated several times with methanol and then adjusted to pH 2 with methanolic hydrogen chloride. The resulting partially crystalline mixture was evaporated to dryness and crystallized from ethanol giving 2.02 g (73%) of ara C hydrochloride that was identical to an authentic sample. Adsorption on Dowex 50 (H^+) resin followed by elution with ammonium hydroxide and crystallization from methanol gave the free base with mp 210–212° (reported mp 212–213°[14], 210–212°[10a]): $\lambda_{max}^{H_2O}$ 227 nm (ε 7,900), 271 nm (ε 9,300); $[\alpha]_D^{23}$ 154.4° (c 0.2, H_2O); ORD (H_2O) $[\phi]_{285}^{pk}$ 23,500°, $[\phi]_{279}$ 0°, $[\phi]_{243}^{tr}$ −28,200°.

2,2′-Anhydro-(3′-O-acetyl-5-D-arabinofuranosyl)-6-azacytosine hydrochloride (12)

A mixture of 6-azacytidine (4.90 g, 20 mmol)[20] and **2** (13.2 g, 80 mmol) in acetonitrile (100 ml) was heated under reflux for 15 min. The solvent was then largely evaporated and the semi-crystalline residue was dissolved in methanol. Gradual addition of ether gave a crystalline product that was recrystallized from methanol–chloroform giving 4.75 g (78%) of **12** with mp 218–219° (d): λ_{max}^{MeOH} 233 nm (ε 9,400), 271 nm (ε 9,100); $[\alpha]_D^{23}$ −63.7° (c 0.17, H_2O); ORD (H_2O) $[\phi]_{303}$ 0°, $[\phi]_{288}^{pk}$ 1,100°, $[\phi]_{281}$ 0°, $[\phi]_{252}^{tr}$ −24,200°, $[\phi]_{223}$ 0°.

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Anal. Calcd. for $C_{10}H_{13}N_4O_5Cl$ (304.69): C, 39.42; H, 4.30; N, 18.39
Found: C, 39.18; H, 4.11; N, 18.12

2,2′-Anhydro-1-(6-D-arabinofuranosyl)-5-methylcytidine hydrochloride (7a)

A suspension of 5-methylcytidine (2.65 g, 10.3 mmol)[28] and **2** (6.5 ml, 45 mmol) in acetonitrile (50 ml) was stirred at room temperature for 1 hr giving a clear solution. The solvent was largely evaporated and the residue triturated twice with ether giving a crude 5′-dioxolanone derivative. The latter was dissolved in 0.2 M methanolic hydrogen chloride (350 ml) and stored at room temperature for 3 days before evaporation of the solvent. The residue was crystallized from methanol giving 1.96 g (69%) of **7a** with mp 257–258° (d): λ_{max}^{MeOH} 212 nm (ε 8,700), 230 nm (ε 8,400), 269 nm (ε 11,600); $[\alpha]_D$ −44.2° (c 1, H_2O); ORD (H_2O) $[\alpha]_{282}^{pk}$ 5,300°, $[\phi]_{271}$ 0°, $[\phi]_{238}^{tr}$ −18,200°.

Anal. Calcd. for $C_{10}H_{14}N_3O_4Cl$ (275.70): C, 43.56; H, 5.12; N, 15.24
Found: C, 43.67; H, 5.38; N, 15.09

2,2′-Anhydro-1-(3′-O-acetyl-β-D-arabinofuranosyl)-5-fluorocytosine hydrochloride (7b)

A suspension of 5-fluorocytidine (522 mg, 2 mmol)[16] in acetonitrile (10 ml) and **2** (1.32 g, 8 mmol) was stirred at 80° for 10 min during which time the starting material dissolved and a crystalline product separated. The mixture was cooled and **7b** (225 mg) was collected by filtration.

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Evaporation of the solvent and precipitation of a methanolic solution of the residue with ether gave a further 60 mg of crude product. Recrystallization of the combined crops from methanol–acetone gave 219 mg (68%) of **7b** which decomposed above 275°: $\lambda_{max}^{H_2O}$ 216 nm (sh, ε 9,100), 228 nm (ε 10,000), 268 nm (ε 10,300); $[\alpha]_D^{23}$ −66.2° (c 0.14, H_2O); ORD (H_2O) $[\phi]_{282}^{pk}$ 4,400°, $[\phi]_{268}$ 0°, $[\phi]_{236}^{tr}$ −15,600°, $[\phi]_{221}$ 0°.

Anal. Calcd. for $C_{11}H_{13}N_3O_5ClF$ (321.68): C, 40.82; H, 4.14; N, 12.94
Found: C, 41.07; H, 4.07; N, 13.06

5-Chlorocytidine (6c)

Cytidine (5 g, 20 mmol) was dissolved in glacial acetic acid (350 ml) and pyridine (250 ml) was added followed by a solution of chlorine (1.6 g) in carbon tetrachloride (6 ml). After storage overnight at room temperature paper electrophoresis using 1 M acetic acid showed the absence of cytidine. The solvents were evaporated *in vacuo* and co-evaporated with ethanol. The residue was precipitated from ethanol with acetone giving 4.4 g of crude product which was applied to a column containing 60 ml of Dowex 50 (H^+) resin and washed thoroughly with water. Elution with 1 M ammonium hydroxide followed by crystallization from ethanol gave 1.70 g (31%) of chromatographically homogeneous **6c** with mp 200–202°. An analytical sample from ethanol had mp 202–203° (reported[17] mp 202–202.5°): λ_{max}^{MeOH,H^+} 216 nm (ε 12,200), 302 nm (ε 12,600); ORD (MeOH) $[\phi]_{305}^{pc}$ 5,000°, $[\phi]_{288}$ 0°, $[\phi]_{235}^{tr}$ −12,000°, $[\phi]_{219}$ 0°.

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gave a precipitate which was washed with ether giving 469 mg of the quite pure 5′-dioxolanone derivative. This material was directly treated with 0.18 M methanolic hydrogen chloride (15 ml) for 3 days and then evaporated to dryness. The semi-crystalline residue was quickly washed with hot chloroform and then crystallized from a small volume of methanol giving 267 mg (84%) of **7c** with mp 244–247° (d): λ_{max}^{MeOH} 233 nm (ε 8,400), 277 nm (ε 9,600); ORD (MeOH) $[\phi]_{296}^{pk}$ 4,100°, $[\phi]_{281}$ 0°, $[\phi]_{244}^{tr}$ −11,900°, $[\phi]_{223}^{pk}$ −4,730°.

Anal. Calcd. for $C_9H_{11}N_3O_4Cl_2$ (296.11): C, 36.50; H, 3.75; N, 14.19
Found: C, 36.47; H, 3.77; N, 14.67

5-Bromocytidine (6d)

Bromine (9 ml, 175 mmol) in carbon tetrachloride (100 ml) was added to a solution of cytidine (40 g, 163 mmol) in glacial acetic acid (1680 ml) and pyridine (1200 ml). After storage overnight at room temperature the solvent was evaporated and the residue co-evaporated with ethanol. Crystallization from ethanol gave 47 g (90%) of chromatographically homogeneous **6d**. A repeatedly crystallized analytical sample had mp 170.5–171.5° (reported[17] mp 182–183°): λ_{max}^{MeOH,H^+} 214 nm (ε 11,000), 302 nm (ε 8,700).

2,2′-Anhydro-1-(3-D-arabinofuranosyl)-5-bromocytidine hydrochloride (7c)

A reaction between **6d** (967 mg, 3 mmol) and **2** (2.0 g, 12 mmol) in acetonitrile (5 ml) for 1 hr was worked up by ether precipitation as with **7c** above. The resulting crude dioxolanone (1.47 g) was treated with 0.18 M methanolic hydrogen chloride for 3 days at room temperature and then evaporated to dryness. The residue was washed with chloroform and then crystallized from methanol giving 634 mg (51%) of **7d** which decomposed above 230° (reported[23] mp 217°): λ_{max}^{MeOH} 234 nm (sh, ε 7,900), 280 nm (ε 8,900); ORD (MeOH) $[\phi]_{299}^{pk}$

2,2′-Anhydro-1-(3-D-arabinofuranosyl)-5-chlorocytosine hydrochloride (7c)

A mixture of **6c** (300 mg, 1.1 mmol) and **2** (0.5 g, 3 mmol) in acetonitrile (5 ml) was stirred at room temperature for 4.5 hr. Addition of ether (50 ml)

[28] Prepared by the method of Fox *et al.*[15], except that the crystalline intermediate 2′,3′,5′-tri-O-benzoyl-5-methyluridine was obtained in 83% yield via condensation of bis-(trimethylsilyl)-thymine with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in the presence of stannic chloride according to the general method of Niedballa and Vorbrüggen[21]

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3,200°, $[\phi]_{286}$ 0°, $[\phi]^{tr}_{250}$ -12,100°.

Anal. Calcd. for $C_9H_{11}N_3O_4BrCl$ (340.59): C, 31.74; H, 3.26; N, 12.34
Found: C, 31.55; H, 3.19; N, 12.37

2,2 -Anhydro-1-(6-O-arabinofuranosyl)-5-iodocytosine hydrochloride (7e)

5-Iodocytidine (3.69 g, 10 mmol)[18] and 2 (6.5 ml, 45 mmol) in acetonitrile (50 ml) was stirred at room temperature for 1.5 hr and then heated at 80° for 30 min. Methanol (200 ml) was then added and the solution was stored at room temperature for 30 min. The solvent was evaporated to dryness and the residue was triturated with ether giving a tan colored solid. The latter was precipitated twice by addition of its solution in the minimum amount of methanol to excess ether giving, after drying in vacuo, 1.99 g (48%) of the 3'-O-acetyl derivative of 7e as a cream colored solid. While this material gave a satisfactory nmr spectrum, it could not be crystallized and was somewhat hygroscopic. Accordingly a portion was treated with 0.2 N methanolic hydrogen chloride at room temperature for two days to effect deacetylation. Evaporation of the solvent and crystallization twice from methanol gave 686 mg of 7e as a tenacious methanol solvate with mp 175-176° (reported[23] mp 184-186°): λ^{MeOH}_{max} 236 nm (ε 8,900), 290 nm (ε 8,800); $[\alpha]^{23}_D$ -91.4° (c 1.0, MeOH); ORD (MeOH) $[\phi]^{pk}_{310}$ 630°, $[\phi]_{295}$ 0°, $[\phi]_{218}$ +18,600°.

Anal. Calcd. for $C_9H_{11}N_3O_4ClI\cdot CH_3OH$ (419.61): C, 28.62; H, 3.60; N, 10.01
Found: C, 29.13; H, 3.66; N, 10.01

5-Dimethylaminocytidine (6f)

5-Bromocytidine (1.0 g) was heated in a stainless steel bomb containing anhydrous dimethylamine (50 ml) at 100° for 18 hr. Evaporation of the solvent left a syrup that was applied to a column of Dowex 50 (H^+) resin and washed thoroughly with water. Elution with 1 M ammonium hydroxide and evaporation gave a syrup that crystallized slowly from ethanol giving 325 mg (37%) of 6f with mp 208-209°. An analytical sample had mp 209-210°. Preparative tlc of the mother liquors using ethyl acetate–methanol (7:3) gave a further 200 mg of chromatographically pure 6f suitable for use in the next step (total yield 59%): $\lambda^{MeOH,+}_{max}$ 219 nm (ε 9,600), 312 nm (ε 5,000); $\lambda^{MeOH,OH^-}_{max}$ 225 nm (ε 13,920), 296 nm (ε 5,700); ORD (MeOH) $[\phi]^{pk}_{312}$ 3,300°, $[\phi]_{295}$ 0°, $[\phi]^{tr}_{235}$ -13,800°.

Anal. Calcd. for $C_{11}H_{18}N_4O_5$ (286.26): C, 46.11; H, 6.33; N, 19.57
Found: C, 46.25; H, 6.66; N, 19.20

2,2'-Anhydro-1-(3'-O-acetyl-6-D-arabinofuranosyl)-5-dimethylamino-cytosine hydrochloride (7f)

A suspension of 6f (1.20 mg, 0.42 mmol) and 2 (0.4 g) in acetonitrile (2 ml) was stirred at room temperature for 90 min giving a clear solution. Addition of ether gave a precipitate (210 mg) of the essentially pure (nmr) 5 -dioxolanone of 7f. The latter (200 mg) was treated with 0.18 M methanolic hydrogen chloride (9 ml) at room temperature for 40 min and evaporated to dryness. The residue was dissolved in methanol and precipitated with chloroform and ether giving 140 mg (82%) of 7f which was homogeneous by paper electrophoresis: $\lambda^{pH\ 1}_{max}$ 218 nm (ε 12,100), 238 nm (sh, ε 8,100), 300 nm (ε 4,100).

Anal. Calcd. for $C_{13}H_{20}N_4O_5Cl_2$ (383.23): C, 40.74; H, 5.26; N, 14.62
Found: C, 40.90; H, 5.32; N, 14.67

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2',3',5'-tri-O-Benzoyl-2-thiocytidine (10a)

A suspension of 2-thiocytosine (3.17 g, 25 mmol) and mercuric cyanide (12.5 g, 50 mmol) in nitromethane (800 ml) was dried by distilling off about 200 ml of the solvent. A solution of 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide (from 50 mmol of the 1-O-acetyl derivative and gaseous hydrogen bromide in benzene) in nitromethane (200 ml) and Linde AW-500 molecular sieve (30 g) were added and the mixture was heated under reflux for 6.5 hr. The cooled mixture was filtered and the filtrate was evaporated, dissolved in chloroform and washed with 30% aqueous potassium iodide, aqueous sodium bicarbonate and water. The dried ($MgSO_4$) solution was dried ($MgSO_4$), evaporated, and chromatographed on a column of silicic acid (2 kg) using benzene–ethyl acetate and then ethyl acetate. The product eluted with ethyl acetate was crystallized from ethanol giving 6.47 g (45%) of 10a with mp 190-191.5° (reported mp 194-195°[21]): λ^{MeOH,H^+}_{max} 232 nm (ε 54,500), 277 nm (ε 19,500).

2-Thiocytidine (10b)

Sodium methoxide (3 mmol) was added to a solution of 10a (6.47 g, 11.3 mmol) in methanol (150 ml) and stored overnight at room temperature. The solution was then stirred with Amberlite IRC 50 (NH_4^+) resin (15 ml), filtered, and evaporated to dryness. The residue was co-evaporated with aqueous ethanol and then crystallized from aqueous ethanol giving 2.86 g (85%) of 10b as the dihydrate with mp 228-229° (reported[22] mp 208-209°, anhydrous): $\lambda^{H^+}_{max}$ 289 nm (ε 17,400), 275 nm (ε 18,200), 310 nm (sh, ε 5,800); $[\alpha]^{23}_D$ 62.2° (c 0.1, H_2O); ORD (H_2O,H^+) $[\phi]^{tr}_{360}$ -5,700°, $[\phi]_{350}$ 0°, $[\phi]^{pk}_{320}$ 26,700°, $[\phi]_{277}$ 0°, $[\phi]^{tr}_{260}$ -35,800°.

Anal. Calcd. for $C_9H_{13}N_3O_5S\cdot(H_2O)_2$ (298.32): C, 36.80; H, 5.80; N, 14.23
Found: C, 37.03; H, 5.74; N, 14.29

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2,2'-Anhydro-1-(3-O-arabinofuranosyl)-2-thiocytidine hydrochloride (13)

A solution of 10b (1.18 g, 4 mmol) was co-evaporated with dimethylformamide several times and then suspended in acetonitrile (14 ml) together with 2 (2.5 g, 16 mmol). After 1.5 hr at room temperature, ether (100 ml) was added and the resulting precipitate was washed with ether. It was then treated with 0.18 M methanolic hydrogen chloride (20 ml) at room temperature for 3.5 hr, evaporated to dryness and crystallized from methanol–chloroform giving 990 mg (89%) of 13 with mp 201-202.5°: λ^{MeOH}_{max} 242 nm (ε 29,100); $\lambda^{MeOH,OH^-}_{max}$ 244 nm (ε 27,200); $[\alpha]^{23}_D$ -110.6° (c 0.13, H_2O); ORD (.1 N HCl) $[\alpha]^{tr}_{240}$ -1,200°, $[\phi]_{226}$ 0°, $[\phi]^{pk}_{219}$ 620°.

Anal. Calcd. for $C_9H_{12}N_3O_3SCl$ (277.74): C, 38.92; H, 4.36; N, 15.13
Found: C, 38.95; H, 4.22; N, 15.29

2,2'-Anhydro-1-(6-O-arabinofuranosyl)-N^4,N^4-dimethylcytosine hydrochloride (11)

N^4,N^4-Dimethylcytidine (136 mg, 0.5 mmol)[29] and 2 (0.35 g, 2 mmol) were reacted for 3.5 hr at room temperature in acetonitrile (2.5 ml). Addition of ether (5 ml) precipitated a crude dioxolanone (199 mg) that was treated for 45 min at room temperature with 0.18 M methanolic hydrogen chloride (5 ml). Since the nmr spectrum of the product suggested partial loss of the 3'-O-acetyl group, the product was retreated with methanolic hydrogen chloride for 2 days and then crystallized from methanol–acetonitrile giving 103 mg (72%) of homogeneous 11 with mp 232-234°: λ^{MeOH}_{max} 226 nm (ε 10,000), 278 nm (ε 12,700); ORD (MeOH) $[\phi]^{pk}_{305}$ 5,100°, $[\phi]_{282}$ 0°, $[\phi]^{tr}_{260}$ -14,800°, $[\phi]_{233}$ 0°, $[\phi]^{pk}_{223}$ 4,900°.

[29] Prepared in 93% yield by the method of Kempen *et al.*[16]: mp 158.5-159.5°.

Anal. Calcd. for $C_{11}H_{16}N_3O_4Cl$ (289.72): C, 45.60; H, 5.57; N, 14.50
Found: C, 46.30; H, 5.40; N, 14.55

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2,2'-Anhydro-1-(3'-O-acetyl-5'-chloro-5'-deoxy-6-D-arabinofuranosyl)-cytosine hydrochloride (14a)

A mixture of 5'-chloro-5'-deoxycytidine (262 mg, 1 mmol)[25] and 2 (660 mg, 4 mmol) in acetonitrile (5 ml) was heated at 80° for 20 min during which time a clear solution was obtained and a crystalline product separated. The crystals (171 mg) were collected and the mother liquors were precipitated with ether giving a further 152 mg of crude 14a. Recrystallization of both crops from methanol–acetone gave 226 mg (71%) of 14a with mp 273-276°: λ^{MeOH}_{max} 235 nm (ε 10,500), 263 nm (ε 11,900); $[\alpha]^{23}_D$ -40.8° (c 0.1, H_2O).

Anal. Calcd. for $C_{11}H_{13}N_3O_4Cl_2$ (322.14): C, 41.01; H, 4.07; N, 13.04
Found: C, 41.18; H, 4.15; N, 12.91

5'-Deoxy-5'-iodocytidine

A solution of N^4-acetyl-5'-deoxy-5'-iodo-2',3'-O-isopropylidene-cytidine (3.02 g)[26] in 90% acetic acid (70 ml) was kept overnight at room temperature and then evaporated to dryness. The residue was co-evaporated several times with methanol and dried *in vacuo* leaving a white solid. The latter was stirred at room temperature in methanol (50 ml) and conc. ammonium hydroxide (50 ml) for 1 hr and the resulting clear solution was evaporated to dryness. The residue was triturated with acetone giving a dry solid that was dissolved in dimethylformamide (20 ml) and crystallized by slow addition of chloroform giving 2.08 g (85%) of 5'-deoxy-5'-iodocytidine with mp 176-178°. An analytical sample from methanol had mp 178.5-180°: λ^{MeOH,H^+}_{max} 282 nm (ε 13,000).

Anal. Calcd. for $C_9H_{12}N_3O_4I$ (353.12): C, 30.61; H, 3.43; N, 11.90
Found: C, 30.86; H, 3.21; N, 11.85

2,2'-Anhydro-1-(3'-O-acetyl-5'-deoxy-5'-iodo-6-D-arabinofuranosyl)-cytosine hydrochloride (12b)

A reaction between 5'-deoxy-5'-iodocytidine (353 mg, 1 mmol) and 2 (660 mg, 4 mmol) was carried out exactly as with 14a above. Recrystallization

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of the product from methanol–acetone gave 270 mg (65%) of 14b with mp 216-218°: $\lambda^{H_2O}_{max}$ 233 nm (ε 10,400), 262 nm (ε 11,600); $[\alpha]^{23}_D$ -24.3° (c 0.25, H_2O), ORD (H_2O) $[\phi]^{pk}_{278}$ 9,700°, $[\phi]_{265}$ 0°, $[\phi]^{tr}_{237}$ -6,000°.

Anal. Calcd. for $C_{11}H_{13}N_3O_4ClI$ (413.50): C, 31.94; H, 3.17; N, 10.16
Found: C, 32.19; H, 2.87; N, 10.05

2-Butyryloxyisobutyryl chloride (15)

A mixture of 2-hydroxyisobutyric acid (104 g, 1 mole) and butyryl chloride (185 g, 1.75 mole) was slowly heated at such a rate as to control the evolution of hydrogen chloride and finally held at 100° for 2 hr. Excess butyryl chloride was then removed by distillation at 50 mm pressure and the residue was carefully warmed with thionyl chloride (100 ml) and finally heated at 80° for 2 hr. Excess thionyl chloride was carefully removed by distillation at 50 mm pressure and a bath temperature of 60° and the final residue was distilled giving 81 g (42%) of 15 with bp 74-76°/6 mm: ν_{max} (film) 1745, 1805 cm^{-1}; nmr ($CDCl_3$) 0.98 (t, 3, CH_3), 1.61 (s, 6, CMe_2), 1.73 (m, 2, CH_2), 2.35 (t, 2, $COCH_2$). As obtained the material was completely satisfactory for use but it did not give an acceptable elemental analysis.

2,2'-Anhydro-1-(3'-O-butyryl-6-D-arabinofuranosyl)-cytosine hydrochloride (16b)

A suspension of cytidine (486 mg, 2 mmol) and 15 (1.3 ml, 8 mmol) in acetonitrile (5 ml) was stirred at room temperature for 2.5 hr. The resulting clear solution was evaporated to dryness and the residue was triturated with ether giving the crude 5'-dioxolanone (16a) as a dry solid. The latter was dissolved in 0.18 M methanolic hydrogen chloride and stored at room temperature for 40 min. After evaporation of the solvent the residue was triturated with ether and the resulting solid was crystallized from methanol giving 394 mg (59%) of 16b with mp 242-244°: λ^{MeOH}_{max} 230 nm (ε 10,800), 264 nm (ε 10,500); $[\alpha]^{23}_D$ -63.4° (c 0.2, H_2O).

Anal. Calcd. for $C_{13}H_{18}N_3O_5Cl$ (331.75): C, 47.06; H, 5.47; N, 12.67
Found: C, 47.22; H, 5.42; N, 12.64

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TABLE I N.M.R. Chemical Shifts (ppm)

Compound	Solvent[a]	C_1,H	C_2,H	C_3,H	C_4,H	$C_{5'a}$,H	$C_{5'b}$,H	C_5H	C_6H	Other
4a	D	6.52(d)	5.65(d)	5.38(br s)	4.45(br s)	3.31(dd)	3.53(dd)	6.73(d)	8.32(d)	2.10 (s,3,OAc), 9.29 and 9.87 (s,1,NH_2)
4b	D	6.57(d)	5.41(d)	4.47(br s)	4.21(m)	3.25(dd)[b]	3.43(dd)[b]	6.68(d)	8.23(d)	9.23 and 9.70 (s,1,NH_2)
6d	D	5.73(d)	4.0(m)	4.0(m)	4.0(m)	3.61(dd)	3.80(dd)	---	8.73(s)	
6f	P	6.83(d)	4.90(m)	4.90(m)	4.57(m)	4.35(m)		---	8.70(s)	2.45 (s,6,NMe_2)
7a	D	5.53(d)	5.42(d)	4.47(br s)	4.22(m)	3.21(dd)	3.39(dd)	---	8.24(s)	2.05 (s,3,C_6Ac), 8.85 and 9.38 (br s,1,NH_2)
7b	D	5.62(dd)	5.74(d)	5.39(br s)	4.51(m)	3.4(m)		---	8.87(d)	2.09 (s,3,OAc), 9.8 (br s,2,NH_2)
7c	D	6.56(d)	5.46(d)	4.48(br s)	4.25(br s)	3.30(dd)	3.45(dd)	---	8.91(s)	5.23 and 9.96 (br s,1,NH_2), 5.11 (t,1,C_5,OH), 6.29 (d,1,C_3,OH)
7d	D	6.53(d)	5.44(d)	4.47(br s)	4.25(m)	3.35(m)		---	8.93(s)	8.93 and 9.88 (br s,1,NH_2)
7e 3'-OAc	D	6.55(d)	5.66(d)	5.37(br s)	4.47(m)	3.4(m)		---	8.85(s)	2.09 (s,3,OAc), 8.60 and 9.86 (br s,1,NH_2)
7e	D	6.52(d)	5.43(d)	4.46(br s)	4.22(m)	3.36(~)		---	8.82(s)	8.53 and 9.80 (br s,1,NH_2)
7f	D	6.54(d)	5.64(d)	5.38(br s)	4.44(m)	3.29(dd)	3.49(dd)	---	8.12(s)	2.37 (s,6,NMe_2), 8.70 and 9.50 (br s,1,NH_2)
8	P D_2O	6.85(d)	4.87(m)	4.87(m)	4.71(m)	4.26(dd)	4.42(dd)	5.83(d)	8.64(d)	3.0 (br s,6,NMe_2) becoming 2.98 (s,6) at 80°
10a	P	8.02(d)[d]	6.56(dd)	6.23(dd)	5.1(m)	5.1(m)		6.05(d)	(c)	7.28-8.4 (~,15,Ar)
10b	P D_2O	7.52(s)[d]	4.82(s)	4.73(m)	4.73(m)	4.32(m)		6.31(d)	8.91(d)	
11	D	6.55(d)	5.42(d)	4.47(br d)	4.22(m)	3.25(dd)[b]	3.42(dd)[b]	6.86(d)	8.41(d)	3.21 and 3.25 (s,3,NMe_2), 5.05 (t,1,C_5,OH), 6.27 (d,1,C_3,OH)
12	D	6.54(d)	5.72(d)	5.37(br s)	4.45(br s)	3.29(dd)[b]	3.50(dd)[b]	8.49(s)	---	2.07 (s,3,OAc), 10.37 and 10.85
13	D	6.60(d)	4.48(dd)	4.4(m)	4.13(dt)	3.42(~)		6.71(d)	8.24(d)	
14a	D	6.65(d)	5.79(dd)	5.39(dd)	4.73(m)	3.79(~)		6.82(d)	8.42(d)	2.12 (s,3,OAc), 9.52 and 10.10 (br s,1,NH_2)
14b	D	6.68(d)	5.78(dd)	5.35(dd)	4.49(m)	3.19(dd)	3.43(dd)	6.85(d)	8.43(d)	2.12 (s,3,OAc), 9.53 and 10.12 (br s,1,NH_2)
16b	D	6.65(d)	5.67(dd)	5.39(br s)	4.43(br s)	3.78(dd)	3.51(dd)	6.75(d)	8.34(d)	0.90 (t,3,CH_3), 1.56 (m,2,CH_2), 2.36 (t,2,$COCH_2$)
5'-I Cy	P	6.72(d)	4.75(dd)[b]	4.45(m)	4.45(m)	3.78(m)		6.04(d)	7.97(d)	8.45 (br s,2,NH_2)

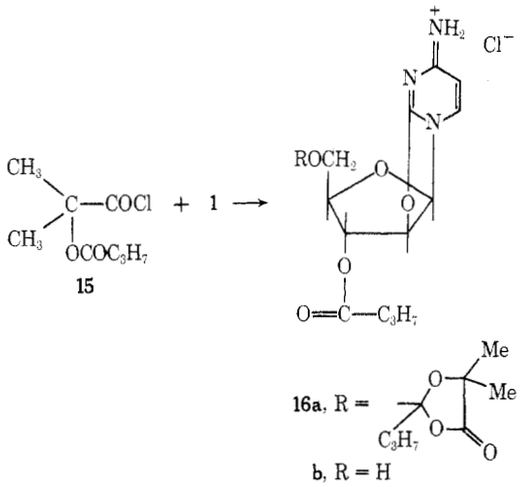
[a] The solvents used are designated as: D, d_6-DMSO; P, d_5-pyridine. [b] After addition of D_2O. [c] Hidden. [d] The very low yield signal is characteristic of 2-thiopyrimidine nucleosides. For references see E. H. Hamamura, K. Sato, and J. G. Moffatt, *J. Med. Chem.*, *15*, 1061 (1972).

TABLE II
Coupling Constants (Hertz)

JOC-25-14

Compound	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5,6}$	Other
4a	6	0	~1	3	2.5	12	8	
4b	6	0	~1	3.5	3	12	7.5	
6d	2	(a)	(a)	2	2	12	----	
6f	2	(a)	(a)	(a)	(a)	(a)	----	
7a	6	0	(a)	2.5	3	12	----	
7b	6	0	~1	(a)	(a)	(a)	----	$J_{1',F}$ = 1 Hz, $J_{6,F}$ = 5 Hz
7c	6	0	~1	2.5	2.5	12	----	
7d	6	0	~1	(a)	(a)	(a)	----	
7e 3'-OAc	5	0	~1	(a)	(a)	(a)	----	
7e	6	0	~1	(a)	(a)	(a)	----	
7f	6	0	~1	3	3	12	----	
8	2.5	(a)	(a)	3	2.5	12	8	
10a	3.5	5.5	5.5	(a)	(s)	(a)	7.5	
10b	~0.5	0	(a)	(a)	(a)	(a)	8	
11	5	0	~1	2	2	12	7.5	$J_{3',OH}$ = 4 Hz, $J_{5',OH}$ = 4.5 Hz
12	6	0	~1	2	2	12	----	
13	7	3	(a)	4	4	(a)	7.5	
14a	6	1	3	(a)	(a)	(a)	7.5	
14b	6	1	3.5	7	5	12	7.5	
16b	6	0	~1	3	2	12	7.5	
5'-I Cy	4	4	(a)	(a)	(a)	(a)	7.5	

(a) Unresolved.



chemical and biological extensions of this work will be described in detail shortly.

Registry No.—**1**, 65-46-3; **2**, 40635-66-3; **4a**, 50896-83-8; **4b**, 10212-25-6; **5**, 50721-05-6; **6a**, 2140-61-6; **6b**, 2341-22-2; **6c**, 25130-29-4; **6d**, 3066-86-2; **6e**, 1147-23-5; **6f**, 51391-95-8; **7a**, 51391-96-9; **7b**, 51391-97-0; **7c**, 51606-78-1; **7d**, 40502-95-2; **7e**, 40502-96-3; **7e** 3′-OAc, 51391-98-1; **7f** 3′-OAc, 51391-99-2; **8**, 13007-43-7; **10a**, 51392-00-8; **10b**, 13239-97-9; **11**, 51392-01-9; **12**, 51392-02-0; **13**, 51392-03-1; **14a**, 51392-04-2; **14b**, 51392-05-3; **15**, 51392-06-4; **16b**, 51392-07-5; 1-(β-D-arabinofuranosyl)cytosine, 147-94-4; 6-azacytidine, 3131-60-0; 2-thiocytosine, 333-49-3; 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide, 51392-08-6; 5′-chloro-5′-deoxycytidine, 31652-78-5; 5′-deoxy-5′-iodocytidine, 51392-09-7; N^4-acetyl-5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidenecytidine, 30685-49-5; 2-hydroxyisobutyric acid, 594-61-6; butyryl chloride, 141-75-3.

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