Studies on Biologically Active Nucleosides and Nucleotides. 1. Reactions of Tetraacetoxysilane with Pyrimidine Ribonucleosides

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Tetraacetoxysilane was found to react with 5′-*O*-acetyluridine to give 3′,5′-di-*O*-acetyluridine as a major product. When the reaction was carried out in the presence of $ZnCl_2$, 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)uracil (**6a**) was obtained in good yield. A similar treatment of uridine also afforded **6a**. The reaction of tetrachlorosilane with uridine in acetic acid gave, after hydrolysis, 2′-chloro-2′-deoxyuridine. In the case of 5-bromouridine followed by hydrolysis, 2′-chloro-2′-deoxy-5-bromouridine and 1-(3′-chloro-3′-deoxy-β-D-xylofuranosyl)-5-bromouracil were obtained in 34 and 2% yields, respectively. The structure of the latter was confirmed by its chemical conversion to 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil. An alternative method for the syntheses of 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine and the 5-bromo analogue was also achieved by using these reagents.

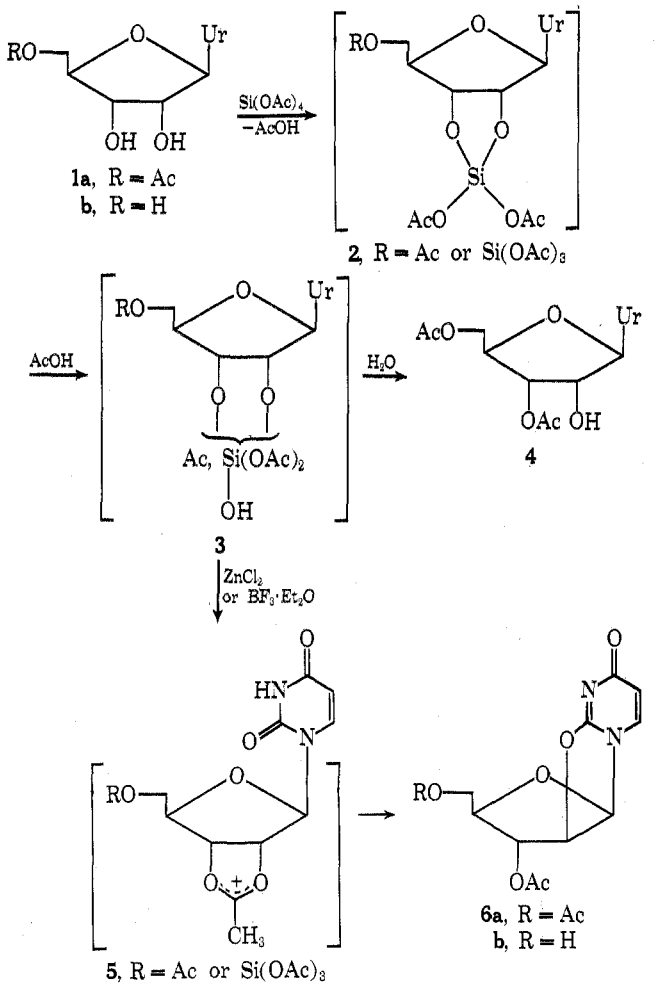
Introduction of a silyl group has been widely exploited in the nucleoside and nucleotide chemistry as a valuable synthetic tool. However, its use is limited mainly to the protection[1] of the hydroxyl group and the activation[2] of the heterocyclic base. Little attention has been devoted to the chemical alterations of nucleosides by using silyl compounds such as tetrachlorosilane and tetraacetoxysilane.

Tetraacetoxysilane[3] was first prepared in 1868 by Friedel and Landenburg[4] from tetrachlorosilane and acetic anhydride, and has been demonstrated to function as an acetylating agent.[5] Dorgov and co-workers[6] reported that aliphatic alcohols react with tetraacetoxysilane to give tetraalkoxy- or alkoxyacetoxysilanes and acetic acid depending on the reaction conditions. They also stated that when the reactions were carried out at the elevated temperatures, the products were the corresponding alkyl acetates and a silicopolymer gel. Mehrotra and Pant[7] isolated spiro alkoxysilanes by treating simple 1,2-glycols with tetraacetoxysilane. In view of the reactivities of tetraacetoxysilane toward hydroxy compounds, especially 1,2-glycols, it was of interest to investigate its reactions with ribonucleosides, since one could expect a selective acylation of the glycosyl hydroxyl groups. In this paper we describe the application of the reagents to the selective transformations of pyrimidine ribonucleosides, and discuss the reaction mechanisms.

Results and Discussion

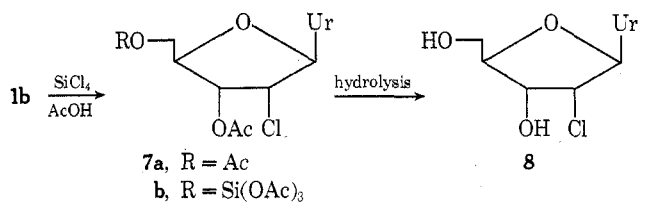
Reactions with Uridine Derivatives. It has been shown that the treatment of 5′-*O*-acetyluridine[8,9] (**1a**) with 1 equiv of acetic anhydride afforded a roughly equimolar mixture of 3′,5′-di-*O*-acetyluridine, 2′,3′,5′-tri-*O*-acetyluridine, and the unchanged starting material.[8,9] In order to study the reactivity of tetraacetoxysilane with nucleoside cis glycol, **1a** was first chosen as a model compound which could avoid the complexity in the analysis of the result. Treatment of **1a** with 2 equiv of tetraacetoxysilane at 90–95 °C in acetic acid for 2 h followed by mild hydrolysis of the product afforded two products, which were separated by silica gel column chromatography. The major product, isolated in 57% yield, proved to be 3′,5′-di-*O*-acetyluridine (**4**);[8,9] the minor component, isolated only in 8% yield, was determined to be 2,2′-anhydro-1-(3′-5′-di-*O*-acetyl-β-D-arabinofuranosyl)uracil (**6a**).[10] A mechanistic explanation of the monoacetylation would involve initial formation of a 1,3-dioxa-2-silacyclopentane derivative (**2**)[11] which could give rise to a mixture of 2′ (and 3′),5′-di-*O*-acetyluridines probably via a silylated intermediate **3**. Crystallization of the crude mixture from a polar solvent led to equilibration of the acetyl function and isolation of pure **4**.[9,12] As a result, in contrast to acetic anhydride, the monoacetylation took place even in the presence of the excess reagent. An effective method for the monoacetylation of a ribonucleoside via 2′,3′-*O*-stannylene intermediate has been reported by Moffatt et al.[13] In fact, the intermediate was isolated and characterized by spectral analyses. However, our effort to isolate a corresponding intermediate (**2**) was unsuccessful. It is interesting to note the concomitant formation of **6a**, though in low yield, under the relatively mild acidic condition. This product could be derived from **2** through an acetoxonium ion **5** which has been proposed as an intermediate under more acidic conditions in the preparation of 2,2′-anhydro-1-β-D-arabinofuranosylpyrimidines.[14] The formation of a similar acetoxonium ion from the 1,3-dioxa-2-silacyclopentane derivative of pinacol has been demonstrated by Magnuson et al.[15] In an attempt to determine the effect of an acidic catalyst, the above reaction mixture was further heated with 2 equiv of zinc chloride. Examination of the reaction by thin layer chromatography (TLC) and ultraviolet (uv) spectral analysis showed the exclusive formation of **6a**. In practice, the treatment of **1a** with 2 equiv of tetraacetoxysilane in the presence of 2 equiv of zinc chloride in acetic acid[16] afforded **6a** in 78% yield as the sole product. As was shown by Holý,[17] anhydro linkage of a 2,2′-anhydro-3′,5′-di-*O*-acyluridine is cleaved by Lewis acid (boron trifluoride etherate) catalysis. It is noteworthy that such a cleavage could not be observed in our zinc chloride catalyzed cyclization. To obtain more information concerning the unusual stability of the anhydro linkage of **6a** under our reaction conditions, **6a** was treated with 2 equiv of zinc chloride in acetic acid at 80 °C for 30 min. The uv absorption maxima at 224 and 251 nm shifted to 260 nm indicating the occurrence of the cleavage. In contrast, the treatment of **6a** with 2 equiv of zinc chloride in the presence of 2 equiv of tetraacetoxysilane under the same conditions showed no change of the uv spectrum. These results strongly suggest that the unexpected stability of **6a** is due to the interaction between zinc chloride and tetraacetoxysilane, which prevented the activation[17] of the C-2′. Similar result was obtained from the reaction of uridine (**1b**) with tetraacetoxysilane. The reaction of **1b** with 2 equiv of tetraacetoxysilane in the presence of 2 equiv of zinc chloride was performed in acetic acid at 75–80 °C for 15 h. The NMR spectrum of the crude product indicated it to be a roughly equal mixture of **6a** and 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil (**6b**).[14a] By a combination of fractional crystallization and preparative TLC, **6a** and **6b** were isolated in yields of 21 and 30%, respectively. The latter would result from the hydrolysis of a C-5′ silyloxy derivative [**6**, R = $Si(OAc)_3$], indicating that the acetylation of the cis glycol group proceeded faster than that of the C-5′ hydroxyl group. Prolongation of the reaction to 48 h led to a completion of the acetylation at the C-5′ hydroxyl group, and only **6a** was obtained in 54% yield. When boron trifluoride etherate, which is a stronger Lewis acid than zinc chloride,[18] was employed as the catalyst, the reaction was

Scheme I



completed at a lower temperature (50–55 °C) within 7 h; **6a** was obtained together with 2′,3′,5′-tri-*O*-acetyluridine[8a] in yields of 65 and 11%, respectively. The overall scheme for the above reactions is shown in Scheme I. It has previously been shown by several authors[19] that 2,2′-anhydropyrimidine nucleosides react with hydrogen halides to give 2′-halogeno-2′-deoxy nucleosides. Therefore, the use of tetrachlorosilane, which generates tetraacetoxysilane and hydrogen chloride in situ in the reaction with acetic acid,[4,20] was expected to give 8 as a final product. Thus, the treatment of **1b** with 2 equiv of tetrachlorosilane in boiling acetic acid for 3 h led to the formation of a mixture of two major products on TLC. These were presumed to be 3′,5′-di-*O*-acetyl-2′-chloro-2′-deoxyuridine (**7a**)[21] and 3′-*O*-acetyl-5′-*O*-triacetoxysilyl-2′-chloro-2′-deoxyuridine (**7b**)[22] from the mechanistic considerations and the following experimental result. Mild alkaline hydrolysis of the mixture afforded 2′-chloro-2′-deoxyuridine (**8**)[19] in 58% yield, and no other halogenated nucleoside was detected in the reaction (Scheme II). A plausible mechanism would involve the formation of the protonated anhydro nucleoside via the corresponding acetoxonium intermediate, followed by the anhydro bond cleavage by the attack of chloride ion on C-2′[19] to produce **7a** and **7b**.

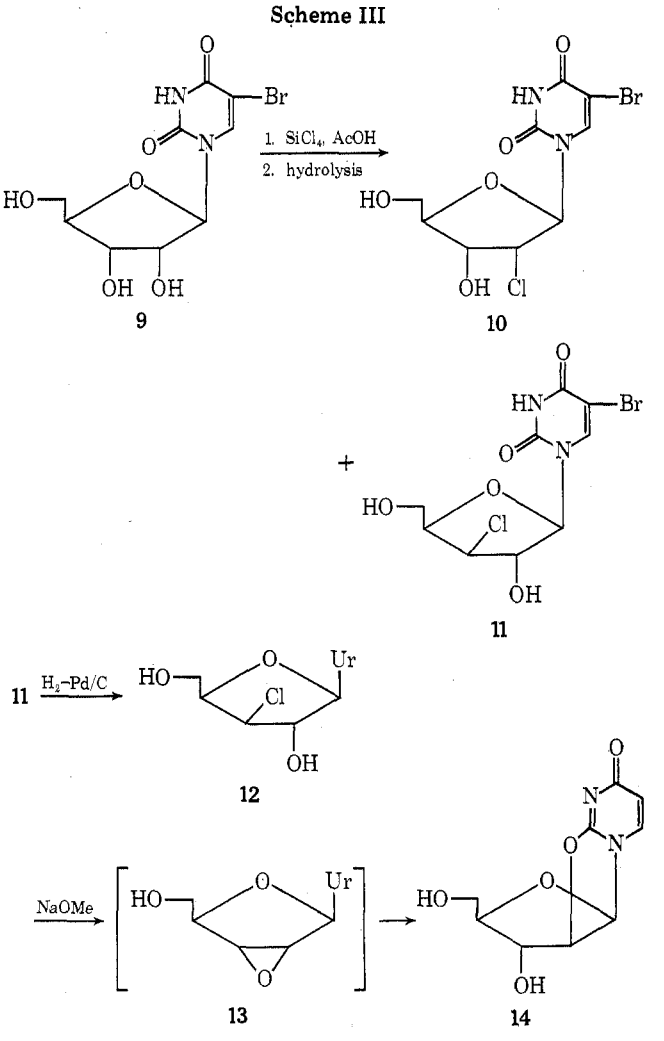
Scheme II



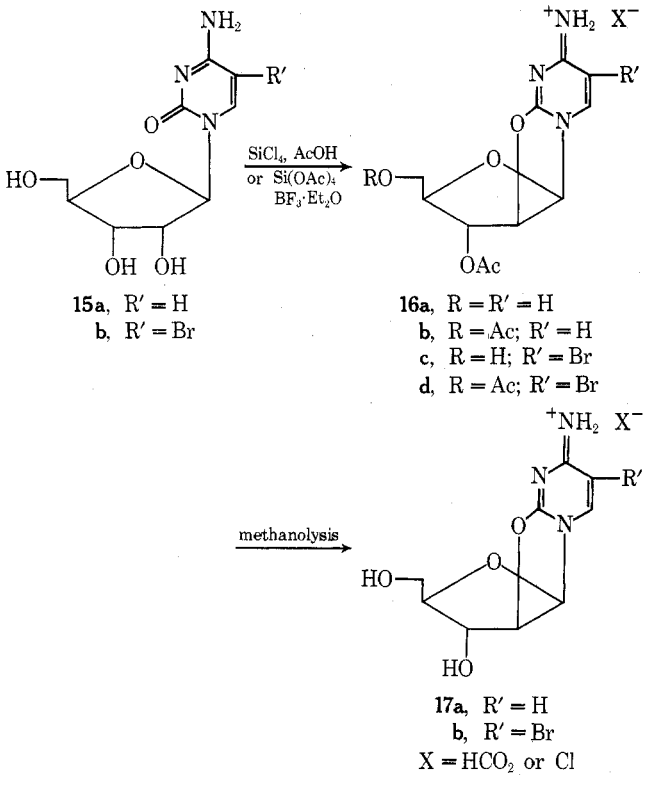
Treatment of 5-bromouridine (**9**)[23] with tetrachlorosilane under the same condition followed by the mild acid hydrolysis led to the formation of a roughly 4:1 (NMR) mixture of two products. By fractional crystallization of the mixture, the major component, 2′-chloro-2′-deoxy-5-bromouridine (**10**), was obtained in 34% yield. The minor product, isolated only in 2% yield, proved to be 1-(3′-chloro-3′-deoxy-β-D-xylofuranosyl)-5-bromouracil (**11**) (Scheme III). The NMR spectrum of **11** in Me_2SO-d_6 showed the signals assignable to the C-3′ and C-4′ protons which were shifted downfield, while the C-2′ proton was shifted upfield relative to **10**. These data support the location of the chloro function at the C-3′.

Recently Zemlicka and Horwitz[24] demonstrated that the C-5′ oxygen atom is one of the factors influencing the C-6 proton chemical shift in pyrimidine nucleosides. They suggested that a gauche–gauche (g,g) conformation at the C-4′–C-5′ bond brought the C-5′ oxygen in close proximity to the C-6 proton and resulted in enhancement of deshielding effect, compared with other conformers. The signal for the C-6 proton in **11** was observed roughly 0.4 ppm upfield compared to that in **10**. This suggests the up configuration of the C-3′ chloro function, because the decrease or the lack of the deshielding may be explained by an inability to attain the g,g conformation due to the bulkiness of the C-3′ substituent in the up configuration. The xylo configuration of **11** was further established on the basis of the chemical conversion of **11** into 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (**14**).[25] Thus, selective catalytic hydrogenation of **11** in the presence of 5% Pd/C gave 1-(3′-chloro-3′-deoxy-β-D-xylofuranosyl)uracil (**12**) in 74% yield. Treatment of **12** with 2 equiv of methanolic sodium methoxide at room temperature led to the formation of

Scheme III



Scheme IV



15a, R′ = H
b, R′ = Br

16a, R = R′ = H
b, R = Ac; R′ = H
c, R = H; R′ = Br
d, R = Ac; R′ = Br

17a, R′ = H
b, R′ = Br
X = HCO_2 or Cl

14 in 64% yield. The formation of 14 would be explained by the base-catalyzed rearrangement of a transient intermediate, 1-(2′,3′-anhydro-β-D-ribofuranosyl)uracil (**13**),[26,27] providing strong support for the xylo configuration of **11** and **12**. The formation of **11** would be due to the competitive attack of chloride ion from the β face on the C-3′ of the acetoxonium ion intermediate, while in the case of **1b** preferential attack of the C-2 carbonyl occurred and the corresponding 3′-chloro-3′-deoxy isomer could not be obtained. Accordingly, this differences would be attributed to the decreased nucleophilicity of the C-2 carbonyl caused by the inductive effect of the bromo group.

Reactions with Cytidine Derivatives. From a viewpoint of medicinal chemistry, the application of this reaction to cytidine derivatives was of great interest, since 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine derivatives have been known to have marked antileukemic activity.[28] Treatment of cytidine (**15a**) with 2 equiv of tetrachlorosilane in acetic acid, followed by column chromatographic separation of the reaction products, afforded 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**16a**, X = Cl)[14c] and 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)-cytosine hydrochloride (**16b**, X = Cl)[14b] in yields of 32 and 14%, respectively. When the mixture of the crude products was treated with hot methanol on a cation exchange resin, the acetyl groups were easily removed, and 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine formate (**17a**, X = HCO_2)[29] was obtained in 72% yield by the elution of the resin with pyridinium formate buffer (Scheme IV). Addition of boron trifluoride etherate to the reaction effected again the acetylation of the C-5′ hydroxyl group, giving **16b** in 48% yield as a sole product. Treatment of **15a** with 2 equiv of tetraacetoxysilane and boron trifluoride etherate in acetic acid at reflux temperature for 30 min followed by the methanolysis of the crude product afforded **17a** (X = HCO_2) in 61% yield. Similarly, the reaction of 5-bromocytidine (**15b**)[14c,30] with tetrachlorosilane in acetic acid followed by solvolysis in methanol yielded 2,2′-anhydro-1-(β-D-arabinofuranosyl)-5-bromocytosine formate (**17b**, X = HCO_2)[14c] in 43% yield.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R20A spectrometer and are reported in parts per million downfield from an internal standard of tetramethylsilane. Me_2SO-d_6 was used as the solvent in every case. Uv spectra were measured on a Hitachi EPS-3T spectrometer. Thin layer chromatography (TLC) was performed on Merck silica gel $60F_{254}$ and preparative TLC on Merck silica gel GF_{254}. Spots were detected by uv examination. Column chromatography was done using Merck silica gel 60.

Reaction of 5′-*O*-Acetyluridine (1a) with Tetraacetoxysilane. A. Without Lewis Acid. To a solution of **1a**[9] (1.0 g, 3.5 mmol) in dry AcOH (20 ml) was added $Si(OAc)_4$[32] (1.86 g, 7.0 mmol). The mixture was heated with stirring at 65–70 °C for 1 h, and then at 90–95 °C for 2 h. The reaction mixture was concentrated to dryness in vacuo and the residue was triturated with ice–water. The resulting mixture was evaporated in vacuo below 45 °C and the residue was coevaporated with H_2O twice. The final residue was slurried with $CHCl_3$ and the slurry was added to the top of a column of silica gel (100 g). Elution with $CHCl_3$–MeOH (95:5) gave 1.0 g of a mixture of 2′(3′),5′-di-*O*-acetyluridines (2′:3′ roughly 1:3 by NMR)[33] as a syrup in the first fraction. Crystallization of the syrup from *i*-PrOH gave 0.65 g (57%) of 3′,5′-di-*O*-acetyluridine (**4**) with mp 143–145 °C. An analytical sample from *i*-PrOH had mp 145–146 °C (reported mp 138–140,[6a] 152–154 °C[9]); λ_{max} (EtOH) 260 nm (ε 8900); NMR 2.09 (s, 3, OAc), 2.11 (s, 3, OAc), 4.6–3.9 (m, 4, $C_{2'}$ H, $C_{4'}$ H, $C_{5'}$ H_2), 4.9–5.2 (m, 1, $C_{3'}$ H), 5.5–6.0 (br s, 1, $C_{2'}$ OH), 5.73 (d, J = 8 Hz, 1, C_5 H), 5.77 (d, J = 5.5 Hz, 1, $C_{1'}$ H), 7.70 ppm (d, J = 8 Hz, 1, C_6 H). Anal. Calcd for $C_{13}H_{16}N_2O_8$ (328.31): C, 47.56; H, 4.91; N, 8.53. Found: C, 47.32; H, 5.05; N, 8.52. Evaporation of the second fraction followed by crystallization of the residue from *i*-PrOH gave 90 mg (8%) of 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)uracil (**6a**): mp 185–186 °C (reported mp 186–187,[10a] 178–179 °C[10b]); λ_{max} (pH 6.8) 224 nm (ε 8400), 251 (8200); NMR 1.91 (s, 3, OAc), 2.12 (s, 3, OAc), 3.9–4.2 (m, 2, $C_{5'}$ H_2), 4.5–4.7 (m, 1, $C_{4'}$ H), 5.32 (d, J = 1.5 Hz, 1, $C_{3'}$ H), 5.54 (d, J = 6 Hz, 1, $C_{2'}$ H), 5.90 (d, J = 8 Hz, 1, C_5 H), 6.43 (d, J = 6 Hz, 1, $C_{1'}$ H), 7.88 ppm (d, J = 8 Hz, 1, C_6 H). Anal. Calcd for $C_{13}H_{14}N_2O_7$ (310.26): C, 50.32; H, 4.55; N, 9.03. Found: C, 50.14; H, 4.42; N. 9.05. The third fraction contained 30 mg (3%) of the starting material **1a** with mp 162–164 °C.

B. With Lewis Acid. To a solution of **1a** (2.0 g, 7.0 mmol) in dry AcOH (80 ml) were added $Si(OAc)_4$ (3.7 g, 14.0 mmol) and $ZnCl_2$ (1.9 g, 14.0 mmol). This mixture was heated at 75–80 °C for 6 h with stirring and then evaporated to dryness in vacuo. The residue was dissolved in cold H_2O (100 ml) and the solution was adjusted to pH 6.2 with $NaHCO_3$ (7 g). The resulting precipitate was removed by filtration (Celite) and the filtrate was applied to a column of activated charcoal (20 g). The column was washed with H_2O (1.5 l.) and eluted with EtOH–pyridine (4:1). The eluate (165 g) was evaporated to dryness in vacuo and the residue was crystallized from EtOH, giving 1.7 g (78%) of **6a** with mp 182–184 °C. This product was identical with the authentic sample prepared as above.

Reactions of Uridine (1b) with Tetraacetoxysilane in the Presence of Zinc Chloride. A. For 15 h. To a solution of uridine (2.0 g, 8.2 mmol) in dry AcOH (80 ml) were added $Si(OAc)_4$ (4.3 g, 16.4 mmol) and $ZnCl_2$ (2.2 g, 16.4 mmol). This mixture was heated at 75–80 °C for 15 h with stirring and evaporated to dryness in vacuo. The residue was worked up as described above to give a crystalline solid (**6a**:**6b** roughly 1:1 by NMR). This material was recrystallized from EtOH (50 ml) to give 0.52 g of pure 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)uracil (**6b**). The mother liquor from the recrystallization was concentrated to dryness, and crystallization from H_2O (8 ml) gave 0.24 g of **6a** identical with the authentic sample obtained above. The combined mother liquors were separated into two major bands on preparative TLC by five developments with $CHCl_3$–MeOH (9:1). Elution of the faster moving band gave a further 0.29 g of **6a** (total yield 0.53 g, 21%). Elution of the slower moving band afforded a further 0.14 g of **6b** (total yield 0.66 g, 30%): mp 189–192 °C (reported[14a] mp 202–204 °C); λ_{max} (MeOH) 224 nm (ε 9700), 251 (7900); NMR δ 2.13 (s, 1, OAc), 2.4–2.6 (m, 2, $C_{5'}$ H_2), 4.2–4.5 (m, 1, $C_{4'}$ H), 5.12 (t, J = 4.5 Hz, $C_{5'}$ OH), 5.36 (br s, 1, $C_{3'}$ H), 5.46 (d, J = 6 Hz, 1, $C_{2'}$ H), 5.86 (d, J = 7.5 Hz, C_5 H), 6.40 (d, J = 6 Hz, 1, $C_{1'}$ H), 7.84 (d, J = 7.5 Hz, C_6 H). Anal. Calcd for $C_{11}H_{12}N_2O_6$ (268.22): C, 49.25; H, 4.51; N, 10.45. Found: C, 49.23; H, 4.63; N, 10.41.

B. For 48 h. To a solution of uridine (5.0 g, 0.021 mol) in dry AcOH (200 ml) were added $Si(OAc)_4$ (10.8 g, 0.041 mol) and $ZnCl_2$ (5.6 g, 0.041 mol). This mixture was heated at 75–80 °C for 48 h with stirring and evaporated to dryness in vacuo. The residue was processed in the usual way to give a syrup. Crystallization from EtOH gave 3.7 g (54%) of **6a**, mp 183–185 °C, identical with that above.

Reaction of Uridine with Tetraacetoxysilane in the Presence of Boron Trifluoride Etherate. To a stirred mixture of uridine (1.0 g, 4.1 mmol) and $Si(OAc)_4$ (2.2 g, 8.2 mmol) in dry AcOH (20 ml) was added BF_3·Et_2O (0.52 ml, 4.1 mmol). This mixture was heated at 50–55 °C for 7 h and then the solvent was evaporated to dryness in vacuo. The residue was dissolved in cold H_2O (30 ml) and the solution was adjusted to pH 6.0 with $NaHCO_3$. The mixture was evaporated to dryness in vacuo below 45 °C and the residue was triturated with hot MeOH (2 × 15 ml). The combined MeOH extract were filtered and concentrated in vacuo. The residual syrup was purified by preparative TLC using two developments with *n*-BuOH–H_2O (84:16) giving two major bands. Elution of the slower moving band with EtOH gave 0.83 g (65%) of **6a** with mp 179–182 °C and identical with that above. Elution of the faster moving band with the same solvent, followed by crystallization from *i*-PrOH, gave 0.17 g (11%) of 2′,3′,5′-*tri*-*O*-acetyluridine with mp 126–127 °C (*reported*[8] *mp* 128–130 °C). This material was identical with an authentic sample prepared by an alternate route.[8]

2′-Chloro-2′-deoxyuridine (8). To a solution of uridine (500 mg, 2.1 mmol) in dry AcOH (20 ml) was added $SiCl_4$ (0.47 ml, 4.1 mmol). The mixture was heated at 60–70 °C for 20 min with stirring and then refluxed for 3 h. The resulting clear solution was concentrated to dryness in vacuo and the residue was dissolved in 2 N NaOH (10 ml). After standing at room temperature for 1 h, the solution was neutralized with 2 N AcOH and the resulting mixture was filtered (Celite). The filtrate was passed through a column of Diaion SK-1B (H^+, 20 ml) and the column was washed with H_2O (300 ml). The combined eluate and washings were evaporated in vacuo to give a crystalline solid, which was recrystallized from MeOH to give 308 mg (58%) of **8**: mp 204–205 °C (reported mp 207–212,[19] 206–207 °C[14a]); λ_{max} (H_2O) 260 nm (ε 9800); NMR 3.5–3.8 (m, 2, $C_{5'}$ H_2), 3.8–4.1 (m, 1, $C_{4'}$ H), 4.1–4.4 (m, 1, $C_{3'}$ H), 4.4–4.7 (m, 1, $C_{2'}$ H), 5.22 (t, *J* = 5 Hz, 1, $C_{5'}$ OH), 5.70 (d, *J* = 8 Hz, 1, C_5 H), 5.85 (d, *J* = 5 Hz, 1, $C_{3'}$ OH), 6.04 ppm (d, *J* = 5 Hz, 1, $C_{1'}$ H). Anal. Calcd for $C_9H_{11}N_2O_5Cl$ (262.66): C, 41.15; H, 4.22; N, 10.66; Cl, 13.49. Found: C, 41.53; H, 4.35; N, 10.85; Cl, 13.45.

Reaction of 5-Bromouridine (9) with Tetrachlorosilane in Acetic Acid. To a suspension of **9**[23] (10 g, 0.031 mol) in dry AcOH (200 ml) was added $SiCl_4$ (7.1 ml, 0.062 mol). This mixture was refluxed for 6 h and then evaporated to dryness in vacuo. The residue was dissolved in 1 N HCl (200 ml) and the solution was heated at 90–95 °C for 30 min. The solvent was evaporated in vacuo and the residue was coevaporated several times with EtOH. The final residue was extracted with hot MeOH and the extract was filtered. Evaporation of the filtrate gave a syrup which was found to be a mixture of 2′-deoxy-2′-chloro-5-bromouridine (**10**) and 1-(3′-chloro-3′-deoxy-β-D-xylofuranosyl)-5-bromouracil (**11**) in a ratio of roughly 4:1 by NMR. Crystallization from H_2O followed by recrystallization from MeOH gave 3.17 g of pure **10**: mp 210–211 °C; λ_{max} (pH 6.9) 279 nm (ε 9700); NMR δ 3.70 (br s, 2, $C_{5'}$ H_2), 3.8–4.1 (m, 1, $C_{4'}$ H), 4.1–4.5 (m, 1, $C_{3'}$ H), 4.5–4.7 (m, 1, $C_{2'}$ H), 5.40 (t, *J* = 4 Hz, 1, $C_{5'}$ OH), 5.83 (d, *J* = 5 Hz, 1, $C_{3'}$ OH), 5.99 (d, *J* = 4 Hz, 1, $C_{1'}$ H), 8.55 (s, 1, C_6 H), 11.88 (br s, 1, NH). Anal. Calcd for $C_9H_{10}N_2O_5BrCl$ (341.58): C, 31.65; H, 2.95; N, 8.20. Found: C, 31.80; H, 3.11; H, 8.27. Storage of the original H_2O washings in a refrigerator gave 0.08 g of **11**, mp 207–208 °C. Recrystallization from MeOH gave analytically pure **11**: mp 208–209 °C; λ_{max} (pH 6.9) 280 nm (ε 9200); NMR 3.74 (br s, 2, $C_{5'}$ H_2), 4.2–4.6 (m, 3, $C_{2'}$ H, $C_{3'}$ H, and $C_{4'}$ H), 5.2 (br s, 1, OH), 5.70 (d, *J* = 3 Hz, 1, $C_{1'}$ H), 6.3 (br s, 1, OH), 8.18 (s, 1, C_6 H), 11.9 (br s, 1, NH). Anal. Calcd for $C_9H_{10}N_2O_5BrCl$: C, 31.65; H, 2.95; N, 8.20. Found: C, 31.67; H, 3.09; N, 8.28. The repeated fractional crystallization of the crystals recovered from the combined mother liquors gave a further 0.42 g of **10** (total yield 3.59 g, 34%) and 0.11 g of **11** (*total yield* 0.19 g, 2%).

1-(3′-Chloro-3′-deoxy-β-D-xylofuranosyl)uracil (12). To a solution of **11** (510 mg, 1.49 mmol) in MeOH (100 ml) were added $BaCO_3$ (440 mg) and 5% palladium on charcoal (180 mg). This mixture was hydrogenated under atmospheric pressure at 25 °C for 1 h. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was dissolved in H_2O and the solution was applied to a column of activated charcoal (4 g). The column was washed with H_2O (300 ml) and eluted with EtOH–pyridine (4:1). The eluate (100 g) was concentrated to dryness in vacuo and the residue was dissolved in $CHCl_3$. The solution was applied to a column of silica gel (5 g) and the desired product was eluted with $CHCl_3$–MeOH (9:1) giving 290 mg (74%) of **12**. An analytical sample from methyl *n*-propyl ketone had mp 171–172 °C; λ_{max} (MeOH) nm 262 (ε 10 600); NMR 3.77 (br s, 2, $C_{5'}$ H_2), 4.2–4.6 (m, 3, $C_{2'}$ H, $C_{3'}$ H, and $C_{4'}$ H), 5.07 (t, *J* = 5 Hz, $C_{5'}$ OH), 5.63 (d, *J* = 4 Hz, 1, $C_{1'}$ H), 5.68 (d, *J* = 8.5 Hz, 1, C_5 H), 6.27 (d, *J* = 5 Hz, 1, $C_{2'}$ OH), 7.74 (d, *J* = 8.5 Hz, C_6 H), 11.38 (br s, 1, NH). Anal. Calcd for $C_9H_{11}N_2O_5Cl$ (262.67): C, 41.15; H, 4.22; N, 10.66; Cl, 13.50. Found: C, 41.42; H, 4.34; N, 10.52; Cl, 13.86.

Reaction of 12 with Sodium Methoxide. To a suspension of **12** (100 mg, 0.39 mmol) in MeOH (0.5 ml) was added 2 N methanolic MeONa (0.38 ml, 0.76 mmol). The resulting clear solution was stirred at room temperature for 48 h, acidified with AcOH, and evaporated in vacuo. The residue was crystallized from H_2O to give 55 mg (64%) of **14**, mp 238–239 °C dec. This material was identical with an authentic sample of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil prepared by a different route[9] in the criteria of infrared and ultraviolet spectra.

Reactions of Cytidine with Tetrachlorosilane. A. Without Lewis Acid. To a solution of cytidine (3 g, 0.012 mol) in dry AcOH (30 ml) was added with stirring $SiCl_4$ (2.84 ml, 0.025 mol). The mixture was heated at 60–70 °C for 30 min and then refluxed for 3 h. The solvent was evaporated to dryness in vacuo and the residue was applied to a column of silica gel (90 g). The column was eluted with *n*-BuOH–H_2O–AcOH (5:2:1, 700 ml). The eluate was evaporated in vacuo below 40 °C and the residue was repeatedly coevaporated with H_2O. Crystallization of the residue from EtOH gave 1.2 g (32%) of 2,2′-anhydro-1-(3′-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**16a**, X = Cl): mp 243–244 °C dec (reported mp 254–255 °C dec[12c]); λ_{max} (EtOH) 234 nm (ε 10 000), 265 (10 900); NMR δ 3.3–3.6 (m, 2, $C_{5'}$ H_2), 4.48 (br s, 1, $C_{4'}$ H), 5.40 (br s, 1, $C_{3'}$ H), 5.68 (d, *J* = 6 Hz, 1, $C_{2'}$ H), 6.64 (d, *J* = 6 Hz, 1, $C_{1'}$ H), 6.75 (d, *J* = 7.5 Hz, 1, C_5 H), 8.32 (d, *J* = 7.5 Hz, C_6 H). Anal. Calcd for $C_{11}H_{14}N_3O_5Cl$ (303.7): C, 43.50; H, 4.65; N, 13.84; Cl, 11.68. Found: C, 43.34; H, 4.82; N, 13.62; Cl, 11.18. The mother liquors from the crystallization were evaporated and the residue was chromatographed on a column of silica gel (80 g). The required fraction was eluted with $CHCl_3$–MeOH (3:1, 600 ml). The eluate was evaporated and the residue was crystallized from EtOH, giving 0.41 g (14%) of 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)cytosine hydrochloride (**16b**) with mp 217–219 °C dec. Recrystallization from EtOH gave analytically pure **16b**: mp 220–222 °C dec; λ_{max} (EtOH) 236 nm (ε 10 300), 264 (11 500); NMR δ 1.88 (s, 1, OAc), 2.12 (s, 1, OAc), 4.07 (br s, 1, $C_{5'}$ H_2), 4.5–4.8 (br s, 1, $C_{4'}$ OH), 5.40 (br s, 1, $C_{3'}$ H), 5.77 (d, *J* = 6 Hz, 1, $C_{2'}$ H), 6.67 (d, *J* = 6 Hz, 1, $C_{1'}$ H), 6.82 (d, *J* = 7.5 Hz, 1, C_5 H), 8.39 (d, *J* = 5 Hz, 1, C_6 H). Anal. Calcd for $C_{13}H_{16}N_3O_6Cl$ (345.75): C, 45.16; H, 4.67; N, 12.15; Cl, 10.26. Found: C, 45.14; H, 4.89; N, 12.00; Cl, 10.25. In a separate experiment, the crude product from the reaction of cytidine with $SiCl_4$ in AcOH was dissolved in H_2O (50 ml). The solution was applied to a column of Diaion SK-1B (H^+, 200 ml). The column was washed with H_2O (4 l.) and then with MeOH (1 l.). The resin was suspended in MeOH (250 ml). The mixture was refluxed with vigorous stirring for 30 min and cooled, and the resin was packed again in a column. The column was eluted with 0.5 M pyridinium formate (pH 4.8, 3 l.), and evaporation of the eluate gave a solid foam which was crystallized from EtOH to give 8.1 g (72%) of 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine formate (**17a**, X = HCO_2): mp 173–176 °C dec (reported mp 173–174 °C dec[26]); uv λ_{max} (MeOH) 233 nm (ε 12 300), 264 (13 000); NMR δ 3.37 (br s, 2, $C_{5'}$ H_2), 4.24 (br s, 1, $C_{4'}$ H), 4.52 (br s, 1, $C_{3'}$ H), 5.45 (d, *J* = 6 Hz, 1, $C_{2'}$ H), 6.55 (d, *J* = 6 Hz, 1, $C_{1'}$ H), 6.68 (d, *J* = 7 Hz, 1, C_5 H), 7.1–8.7 (br s, 2, OH), 8.27 (d, *J* = 7 Hz, 1, C_6 H), 8.52 (s, 1, HCO_2). Anal. Calcd for $C_{10}H_{13}O_6N_3$ (271.23): C, 44.28; H, 4.83; N, 15.49. Found: C, 44.28; H, 5.02; N, 15.37.

B. With Lewis Acid. To a solution of cytidine (2 g, 8.2 mmol) in dry AcOH (120 ml) was added with stirring $SiCl_4$ (1.89 ml, 16.5 mmol). The mixture was refluxed for 1 h and then BF_3·Et_2O (1.04 ml, 8.23 mmol) was added. Refluxing was continued for 1 h and the solvent was evaporated in vacuo. The residue was applied to a column of silica gel (60 g). Elution with $CHCl_3$–MeOH (7:3, 400 ml) gave an oily material, which was dissolved in H_2O (15 ml). The solution was passed through a column of Diaion SA-11B (Cl^-, 50 ml) and the column was washed with H_2O (150 ml). The combined eluate and washings were evaporated to dryness in vacuo and crystallization of the residue from EtOH gave 1.36 g (48%) of **16b** with mp 217–218 °C. This compound was identical with the sample prepared as above.

Reaction of Cytidine with Tetraacetoxysilane. To a solution of cytidine (10 g, 0.0412 mol) in dry AcOH (400 ml) was added with stirring $Si(OAc)_4$ (21.8 g, 0.0824 mol) and BF_3·Et_2O (7.8 ml, 0.0618 mol). The mixture was heated at 60–70 °C for 30 min and then refluxed for 30 min. The solvent was evaporated to dryness in vacuo and the residue was dissolved in ice–water (200 ml). The solution was filtered (Celite) and the filtrate was worked up as above to give 5.5 g of **17a** (X = HCO_2) with mp 173–174 °C dec which was identical with a sample prepared as above. Evaporation of the mother liquors from the crystallization of **17a** (X = HCO_2) followed by fractional crystallization from EtOH gave a further 1.2 g of **17a** (X = HCO_2) (total yield 6.7 g, 61%).

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(17b). To a solution of **15b**[30] (5.0 g, 15.5 mmol) in dry AcOH (50 ml) was added with stirring $SiCl_4$ (3.6 ml, 31 mmol). The mixture was heated at 60–70 °C for 20 min and then refluxed for 2.5 h. The mixture was proccessed as described for the preparation of **17a** (X = HCO_2) to give 3.0 g of crude **17b** (X = HCO_2). The formate was dissolved in H_2O (15 ml) and passed through a column of Amberlite IRA-400 (Cl^-, 100 ml), and the column was washed with H_2O (150 ml). The combined eluate and washings were evaporated, and the residue was recrystallized from 80% EtOH to give 2.3 g (43%) of **17b** (X = Cl): mp 218–220 °C dec (reported mp 217 °C dec,[31a] 230 °C dec[14c]); λ_{max} (pH 7.2) 235 nm (sh, ϵ 8500), 280 (9600); NMR 3.3–3.5 (m, 2, $C_{5'}$ H_2), 4.1–4.4 (m, 1, $C_{4'}$ H), 4.4–4.6 (m, 1, $C_{3'}$ H), 5.12 (t, J = 5 Hz, 1, $C_{5'}$ OH), 5.49 (d, J = 6 Hz, 1, $C_{2'}$ H), 6.29 (d, J = 4.5 Hz, 1, $C_{3'}$ OH), 6.58 (d, J = 6 Hz, 1, $C_{1'}$ H), 8.00 (s, 1, C_6H). Anal. Calcd for $C_9H_{11}N_3O_4BrCl$ (340.59): C, 31.73; H, 3.25; N, 12.33. Found: C, 31.90; H, 3.33; N, 12.26.

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Registry No. —**1a,** 6773-44-0; **1b,** 58-96-8; **4,** 6773-48-4; **6a,** 28309-53-7; **6b,** 38642-32-9; **8,** 4753-04-2; **9,** 957-75-5; **10,** 55612-19-6; **11,** 59588-21-5; **12,** 59588-22-6; **14,** 3736-77-4; **15a,** 65-46-3; **15b,** 3066-86-2; **16a** (X = Cl), 50896-83-8; **16b** (X = Cl), 50896-84-9; **17a** (X = HCO_2), 26790-12-5; **17b** (X = Cl), 40502-95-2; **17b** (X = HCO_2), 59653-50-8; $Si(OAc)_4$, 562-90-3; 2′,3′,5′-tri-*O*-acetyluridine, 4105-38-8; $SiCl_4$, 10026-04-7.

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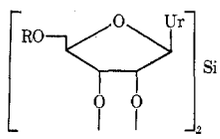

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