Hz, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.93 (m, 1, $C_{4'}H$), 5.00 (d, 1, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 6.53 (s, 1, $C_{1'}H$), 8.10 (s, 1, C_8H).

Iodination of 2',3'-O-Isopropylideneinosine.—2',3'-O-Isopropylideneinosine (616 mg, 2 mmol) and **1** (1.7 g) were allowed to react overnight in DMF (10 ml) containing pyridine (0.8 ml). After addition of methanol and evaporation of the solvent, the residue was partitioned between water and chloroform. Pyridine (0.5 ml) was added to the aqueous phase and the solvent was evaporated leaving a crystalline residue that was recrystallized from ethanol giving 470 mg (76%) of 2',3'-O-isopropylidene-N^3,5'-cycloinosine (**25**) with mp 265–268° (lit.[33b] mp 266–269°); $\lambda_{max}^{H_2O}$ 252 mμ (ε 6500); $\lambda_{max}^{pH\ 2}$ 253 mμ (ε 7300); $\lambda_{max}^{pH\ 12}$ 253 mμ (ε 6700) and changing to λ_{max} 269 mμ (ε 11,300) within 2 hr; nmr (d_5-pyridine) 1.23 and 1.46 ppm (s, 3, CMe_2), 3.04 (q, 1, J_{gem} = 14 Hz, $J_{4',5'a}$ = 1.5 Hz, $C_{5'a}H$), 4.83 (m, 1, $C_{4'}H$), 4.93 (s, 1, $J_{2',3'}$ = $J_{3',4'}$ = 0 Hz, $C_{3'}H$ or $C_{2'}H$), 4.95 (s, 1, $C_{3'}H$ or $C_{2'}H$), 5.10 (q, 1, J_{gem} = 14 Hz, $J_{4',5'}$ = 2.5 Hz, $C_{5'a}H$), 6.39 (s, 1, $C_{1'}H$), 8.02 (s, 1, C_2H or C_8H), 8.91 (s, 1, C_2H or C_8H).

Anal. Calcd for $C_{13}H_{14}N_4O_4 \cdot H_2O$: C, 50.64; H, 5.23; N, 18.18. Found: C, 50.61; H, 5.40; N, 18.34.

Evaporation of the chloroform phase left a syrup (1.04 g) that was crystallized from ethanol giving 65 mg of 5'-deoxy-5'-iodo-2',3'-O-isopropylideneinosine (**26**) as needles of mp 195–197° dec (lit.[34] mp 203–204° dec). Chromatography of the mother liquors on a column of silicic acid using a gradient (0–30%) of methanol in chloroform gave a further 70 mg (total yield 15%) of **26**: λ_{max}^{MeOH,H^+} 249 mμ (ε 11,600); $\lambda_{max}^{MeOH/OH^-}$ 254 mμ (ε 12,200); nmr (d_6-DMSO) 1.52 and 1.32 ppm (s, 3, CMe_2), 3.41 (m, 2, $C_{5'}H_2$), 4.35 (h, 1, $J_{3',4'}$ = 3 Hz, $J_{4',5'}$ = 6.5 Hz, $C_{4'}H$), 4.99 (q, 1, $J_{3',4'}$ = 3 Hz, $J_{2',3'}$ = 6 Hz, $C_{3'}H$), 5.45 (q, 1, $J_{2',3'}$ = 6 Hz, $J_{1',2'}$ = 2.5 Hz, $C_{2'}H$), 6.24 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{1'}H$), 8.16 (s, 1, C_2H or C_8H), 8.36 (s, 1, C_2H or C_8H); ORD (H_2O) negative Cotton effect with a trough at 285 mμ (Φ −3300°) and a peak at 255 mμ (Φ −580°).

Anal. Calcd for $C_{13}H_{15}N_4O_4I$: C, 37.33; H, 3.62; N, 13.40. Found: C, 37.55; H, 3.82; N, 13.71.

Registry No.—**1**, 17579-99-6; **5a**, 362-43-6; **8b**, 14842-09-2; **10b**, 24498-13-3; **15b**, 24453-27-8; **19**, 24453-28-9; **22**, 24453-29-0; **29**, 24453-30-3; **14a**, 50-89-5.

Nucleosides. LXV. Synthesis and Reactions of Some Pyrimidine 2',6-Anhydronucleosides[1]

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The synthesis of a series of 4-substituted 2-oxo-6-hydroxypyrimidine 2',6-anhydronucleosides (4-oxo, 4-thio, 4-methylthio, 4-hydroxylamino, and 4-amino) is described, and their chemical properties are compared with certain 5',6-anhydronucleosides. These 2',6-anhydro compounds undergo facile ring opening in aqueous base to give the corresponding 6-oxo-1-β-D-arabinofuranosylpyrimidines, but unlike the 5',6-anhydronucleosides they are exceedingly stable in dilute aqueous acid. Treatment of either 4-amino- or 4-methylthio-1-β-D-arabinofuranosylpyrimidine-2,6-dione with aqueous acid gives 2',6-anhydro-1-(β-D-arabinofuranosyl)barbituric acid as the major product. In anhydrous base the 4-amino- and 4-methylthio-2',6-anhydro compounds undergo rearrangement to their 2',2-anhydro isomers. A plausible mechanism for this rearrangement is given.

Although pyrimidine nucleosides containing a 5',6-anhydro linkage (for example **1**) are now well known,[2-4] only one example (**2**) of the corresponding 2',6-anhydro system has been reported.[5,6] This study deals with the synthesis of a series of 2',6-anhydronucleosides and demonstrates that their chemical properties differ in several important respects from those of the 5',6-anhydro compounds.

The 2',6-anhydronucleoside **2**, which is readily prepared by treatment of arabinosyl-5-bromouracil with sodium methoxide in methanol,[5,7] was converted into a series of 4-substituted derivatives as outlined in Scheme I. These transformations involve the 4-thione **7**, a key intermediate that was prepared in 78% yield by thiation of the dibenzoate **4** with P_2S_5 in refluxing 1,4-dioxane.[8] Attempts to prepare the 4-amino nucleoside **9** by treatment of the 4-thione **7** with alcoholic ammonia under a variety of conditions resulted in either no reaction or in considerable degradation with very low yields (<10%) of the desired product **9**. Similarly, treatment of the 4-methylthio nucleoside **8** with either liquid or alcoholic ammonia failed to give acceptable yields of **9**. As will be shown later, the low yields of **9** obtained in these amination reactions are due in part to unexpected rearrangements of the 4-methylthio nucleoside **8** and of **9** itself.

A satisfactory synthesis of the 4-amino nucleoside **9** was achieved *via* the 4-hydroxylamino nucleoside **12**. The 4-methylthio derivative **8** (obtained *via* **10**) reacted with an excess of hydroxylamine in methanol to give **12** directly. Under the same conditions, however, the 4-thione **10** afforded an intermediate bishydroxylamino compound[9] **11** which underwent acid-catalyzed elimination of hydroxylamine to give **12** in 66% yield. Reduction of **12** using palladium–charcoal catalyst gave the 4-amino nucleoside **9**. Attempts to deaminate **9** with nitrous acid, as part of the structural proof, failed

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748).

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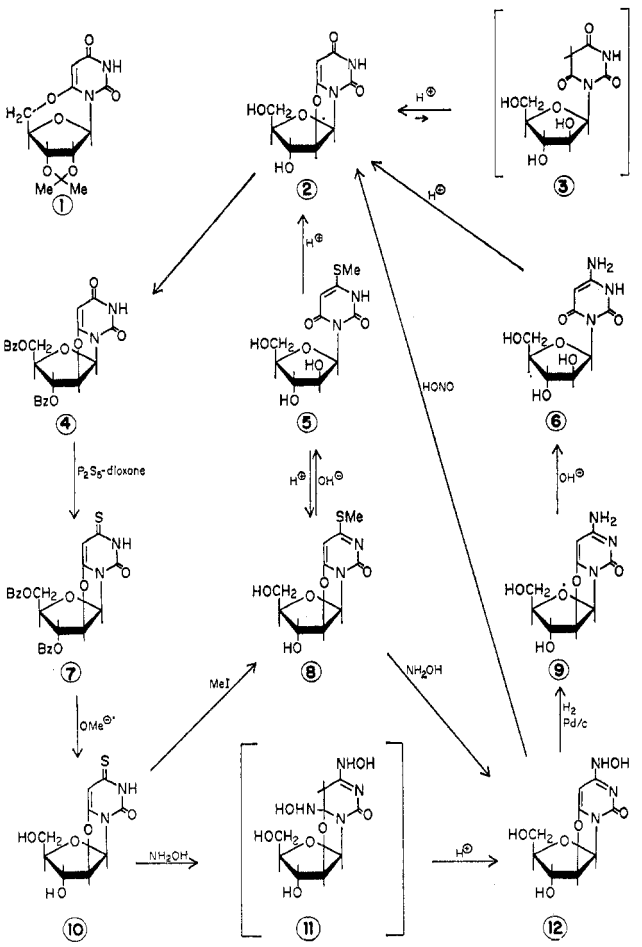
(7) Compound **2** has also been prepared[6] by reductive dehalogenation of the corresponding 5-iodo nucleoside. The latter compound was isolated (yield unstated) from a mixture of products obtained by iodination of 1-β-D-arabinofuranosylcytosine.

(8) This reagent combination (P_2S_5–dioxane) affords higher yields of 4-thiones in a shorter reaction time than the conventional P_2S_5–pyridine system (R. S. Klein, *et al.*, manuscript in preparation) for the thiation of nucleosides. With the conventional system **7** was obtained in only ~50% yield after a 24-hr reaction period. The authors are indebted to Dr. M. P. Kotick of this institute for suggesting the applicability of the P_2S_5–dioxane reagent to nucleosides.

(9) An intermediate bishydroxylamino compound has also been observed in the hydroxylamination of 4-thiouridine; see I. Wempen, N. Miller, E. A. Falco, and J. J. Fox, *J. Med. Chem.*, **11**, 144 (1968), and references therein.

SCHEME I



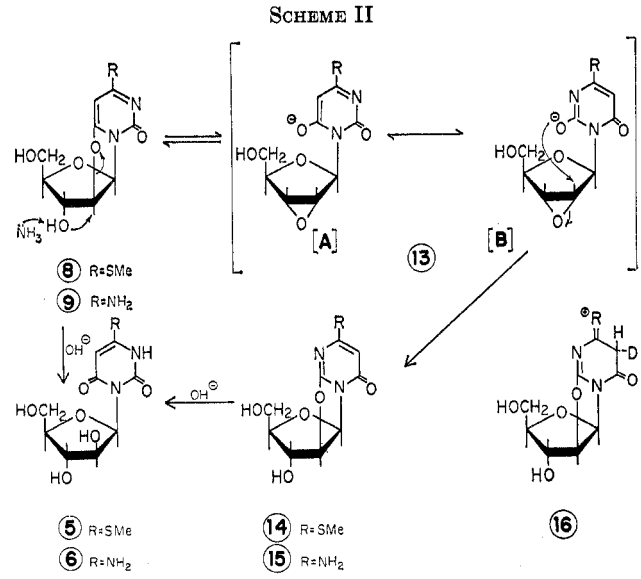
to give any 2 and 9 was recovered unchanged. However, the 4-hydroxylamino compound 12, the immediate precursor of 9, could be converted into 2 by treatment with nitrous acid, thereby confirming the 2',6-anhydro structure.

Acid–Base Stability of the 2',6-Anhydro Linkage.—The 2',6-anhydronucleosides are in general unstable in aqueous alkali and in this regard they resemble their 5',6-anhydro counterparts.[2,3] Thus treatment of 9 with 1 *N* sodium hydroxide at room temperature afforded 4-amino-1-(β-D-arabinofuranosyl)pyrimidine-2,6-dione (6) in excellent yield. The structure of 6 was demonstrated by the similarity of the ultraviolet spectral and acidic (pK_a = 8.52) data to that of 4-aminopyrimidine-2,6-dione (pK_a = 8.25) and its 1-β-D-ribofuranosyl derivative.[10] Similarly, the 4-methylthio nucleoside 8 underwent rapid anhydro ring opening in 1 *N* sodium hydroxide to give the 4-methylthiopyrimidine-2,6-dione nucleoside 5, which was identified by comparison of its ultraviolet spectrum with that of the corresponding ribonucleoside.[10,11] As expected, the 4-oxo nucleoside 2 is relatively stable in 1 *N* sodium hydroxide at 25°, presumably because it can exist as a monoanion which is not readily attacked by hydroxide ion. However some ring opening does occur as shown by a 25% decrease in concentration of 2 over a 1-week period under the above conditions. 1-β-D-Arabinofuranosylbarbituric acid (3) was not detected in the reaction mixture probably because this compound, like the corresponding ribonucleoside,[2] would be unstable in aqueous base.

Unlike the seven-membered 5',6-anhydro ring of 1, the five-membered 2',6-anhydro ring of 2 is remarkably stable in acidic media. Thus 2 was recovered unchanged after refluxing in 1 *N* hydrochloric acid over a 24-hr period; in 12 *N* hydrochloric acid at room temperature, 2 is stable for at least 4 days. This behavior contrasts to that of 1 which is completely hydrolyzed within 8 hr by 0.1 *N* hydrochloric acid at 50° to give 1-β-D-ribofuranosylbarbituric acid.[2] That any equilibrium between 2 and 3 is almost exclusively in favor of the ring-closed form 2 is shown by the following data. Treatment of the 4-amine 6 with 1 *N* hydrochloric acid at 48° resulted in the quantitative formation of 2. This reaction *must* proceed *via* the barbituric acid nucleoside 3 rather than the 2',6-anhydro-4-amino compound 9, because compound 9 is itself stable under these reaction conditions. Ring closure of 3 would then involve addition of the 2'-hydroxy group across the 6-carbonyl function followed by acid-catalyzed elimination of water from the resulting dihydro intermediate. In a similar manner, acid treatment of the 4-methylthio nucleoside 5 afforded predominately 2 together with a small amount of the 2',6-anhydro 4-methylthio nucleoside 8. Since compound 8 is stable under the reaction conditions, the major product 2 is again formed *via* 3.

Rearrangement of 2',6-Anhydronucleosides.—It was pointed out earlier that treatment of the 4-methylthio nucleoside 8 with ethanolic ammonia (105°, 5 hr) afforded only small amounts of the 4-amino derivative 9. Instead, 8 undergoes rearrangement to the isomeric 2',2-anhydro-1-(β-D-arabinofuranosyl)-2-hydroxy-4-methylthiopyrimidin-6-one (14, Scheme II), a crystalline compound which was isolated in 27% yield. The structure assigned to 14 rests on the following data: base-catalyzed hydrolysis of 14 afforded the same product (5) as was formed by hydrolysis of 8, thus establishing that 14 is an *arabino* nucleoside containing an anhydro bridge at either the 5' or 2' position. That the 5' position is not involved in the anhydro linkage

SCHEME II



(10) M. W. Winkley and R. K. Robins, *J. Chem. Soc. C*, 791 (1969).

(11) Attempts to displace the 4-methylthio group of 5 with liquid ammonia (50°), ethanolic hydroxylamine (108°), or anhydrous hydrazine (25°) were unsuccessful and in each case 5 was recovered unchanged.

of **14** follows from the nmr spectrum which showed the H-5′ signals as a narrow multiplet at δ 3.30. In a 5′-anhydro structure the H-5′ signals would appear at lower field (for example[2] δ 4.08, 4.73 for compound **1**) as a widely spaced quartet with $J_{5',5'} \cong 13$ Hz.[2] In fact, except for the H-5 signal at δ 5.81, the nmr spectrum of **14** is almost identical with that of starting material **8** (H-5, δ 6.07). The similarity of the nmr spectra of **8** and **14** means that both compounds have the same conformation and, therefore, contain anhydro rings of the same size. This requirement is met only by a 2′,2-anhydro structure for **14**. Further support for this assignment is that H-5 of **14** undergoes slow exchange for deuterium in DMSO-d_6–DCl. This exchange is consistent with a 4-methylthio-6-oxo system where the cation **16** can be formed by deuteration at C-5. This type of ion clearly cannot be formed in a 4-methylthio-2-oxo system such as **8**, and, in fact, no measurable incorporation of deuterium at C-5 was observed when **8** was treated with DMSO-d_6–DCl over a 24-hr period.

A mechanism that accounts for the formation of **14** from **8** involves displacement of the 2′-anhydro linkage by the 3′-hydroxyl group to form the *ribo*-epoxide **13**. Attack of the initially formed C-6 oxygen anion (structure A) on C-2′ would regenerate **8** but attack by the C-2 oxygen anion (structure B) would lead to **14**. Ammonia functions only as a base in this mechanism and this is supported by the observed formation of **14** when **8** is treated with hot ethanolic triethylamine. The mechanism is also consistent with the observation that the 4-oxo nucleoside **2** is stable in ethanolic ammonia (105°, 24 hr). In this case dissociation of the N-3 hydrogen occurs and the monoanionic form predominates, a fact which we have determined spectrophotometrically.[12] Displacement of the anhydro linkage of **2** by attack of the C-3′ substituent (to form a *ribo*-epoxide) would be less favored because the negatively charged aglycon would be a poor leaving group.

As with compound **8**, treatment of **9** with ethanolic ammonia (108°, 24 hr) afforded a crystalline product (**15**) with analytical and spectroscopic data consistent with the 2,2′-anhydro structure. The basic pK_a of **9** (4.22) and **15** (<1) are in the expected order and may be compared with those of 1-methylcytosine (pK_a = 4.57)[13] and 1-methyl-4-aminopyrimidin-6-one (pK_a = 0.98),[14] respectively. Compound **15** underwent rapid exchange of H-5 for deuterium when treated with DMSO-d_6–DCl, probably *via* the cation **16**, and formed a blue, crystalline nitroso compound when treated with nitrous acid. In contrast, the 4-amino 2′,6-anhydronucleoside **9** did not undergo deuterium exchange and failed to react with nitrous acid.

General Considerations.—The phenomenon of anhydro bond migration has been observed previously. It has been shown that 2,3′-anhydro-1-(2,5-di-*O*-benzoyl-β-D-xylofuranosyl)uracil undergoes thermal rearrangement to the 2,2′-anhydro isomer *via* a 2′,3′-benzoxonium ion intermediate.[15] The isomerization of a 2,5′-anhydro-*arabino*-nucleoside to the 2,2′ isomer[16] and of a 2,5′-anhydro-*xylo*-nucleoside to a 2,3′ isomer[17] have also been recorded. In these cases, however, anhydro migration resulted from attack by an "up" sugar hydroxyl on the C-2 position of the anhydro linkage.

That a 2′,3′-*ribo*-epoxide **13** is involved in the conversion of a 2′,6-anhydronucleoside into its 2,2′ isomer is supported by several studies[18] which attest to the extreme susceptibility of such epoxides to attack by nucleophiles including the 2-carbonyl of the aglycon. It is reasonable to expect that suitable derivatives of the as yet unknown 3′,6-anhydronucleosides will also undergo rearrangement to the 2,2′ isomers *via* the same epoxide intermediate **13**.

Experimental Section

General Procedures.—Melting points were determined with a Thomas–Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer and nuclear magnetic resonance spectra were measured with a Varian A-60 spectrometer using DMSO-d_6 as a solvent and tetramethylsilane as an internal standard. Values given for coupling constants (hertz) and chemical shifts (δ) are first order. Preparative chromatographic separations were carried out on 20 × 20 cm plates coated with thin layers (0.25 mm) of silica gel GF_{254} or thick layers (2 mm) of silica gel PF_{254}. In each case separated materials were detected with uv light and recovered by extraction of the silica with hot ethanol. Apparent pK_a values were determined spectrophotometrically and are accurate to ± 0.05 pH unit unless otherwise specified. Evaporations were carried out under reduced pressure with bath temperatures kept below 45°. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

2′,6-Anhydro-1-(3,5-di-*O*-benzoyl-β-D-arabinosyl)-6-hydroxypyrimidine-2,4-dione (4).—Benzoyl chloride (8.1 g, 58 mmol) was added dropwise to a stirred solution of **2** (7.0 g, 29 mmol) in 200 ml of dry pyridine. The solution was kept at room temperature overnight, concentrated to ~100 ml, and then poured into ice water. The resulting solid (11.3 g, 87%) was washed well with water, and a portion was crystallized from methanol to give an analytical sample: mp 158–160°; nmr, 10.9 (1, broad s, NH), 8.2–7.3 (10, m, benzoyl protons), 6.45 (1, d, H-1′, $J_{1',2'}$ = 5.0 Hz), 5.73 (2, m, H-2′, H-3′), 5.11 (1, s, H-5), 4.82 (1, m, H-4′), 4.45 (2, m, H-5′, H-5′), 3.32 (1, s, 0.5 H_2O).

Anal. Calcd for $C_{23}H_{18}N_2O_8 \cdot {}^1/_2H_2O$: C, 60.15; H, 4.13; N, 6.10. Found: C, 59.80; H, 4.15; N, 5.97.

2′,6-Anhydro-1-(3,5-di-*O*-benzoyl-β-D-arabinosyl)-6-hydroxy-2-oxopyrimidine-4-thione (7).—Phosphorus pentasulfide (6.44 g, 29 mmol) was dissolved in a hot solution of **4** (13.2 g, 29 mmol) in dioxane (200 ml) and the solution was refluxed for 35 min. A further charge of P_2S_5 (6.44 g) was added and refluxing was continued for a further 40 min. The cooled solution was concentrated to ~50 ml and poured into ice water. The aqueous mixture was extracted with chloroform (700 ml), sodium chloride was added to facilitate dispersal of the resulting emulsion, and the chloroform layer was washed with aqueous sodium chloride. The chloroform solution was dried (Na_2SO_4) and then concentrated to dryness. The residue was dissolved in ethyl acetate (50 ml), and the solution was diluted with methanol (200 ml) and set aside to crystallize. The yield of pure **7** was 7.6 g (56%). A second crop, obtained by concentration, was recrystallized to give a further 3.0 g (total yield 78%): mp 114–115°; nmr, 12.3 (1, broad s, NH); 8.2–7.4 (10, m, benzoyl protons), 6.50 (1, d, H-1′, $J_{1',2'}$ = 5.5 Hz), 6.00 (1, s, H-5), 5.75 (2, m, H-2′,

(12) Compound **2** exhibits spectral shifts in aqueous solution between pH 7 and 12.[5,6] Similar spectral shifts are observed in ethanol *vs.* ethanolic ammonia.

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H-3'), 4.85 (1, m, H-4'), 4.47 (2, m, H-5', H-5'), 3.31 (1, s, 0.5 H_2O).

Anal. Calcd for $C_{28}H_{18}N_2O_7S \cdot {}^1/_2H_2O$: C, 58.11; H, 4.00; N, 5.89; S, 6.73. Found: C, 58.12; H, 4.28; N, 5.76; S, 6.57.

2',6-Anhydro-1-(β-D-arabinofuranosyl)-6-hydroxy-2-oxopyrimidine-4-thione (10).—Compound **7** (5 g, 10.5 mmol) was dissolved in methanol (200 ml) containing sodium (200 mg), and the solution was kept at room temperature for 4 hr. Water (20 ml) was added and the solution neutalized with ~2 g of Dowex 50 (H^+). The filtrate was concentrated to dryness, and the residue (2.09, 87%) was crystallized from 95% ethanol to give needles: mp 223–224° dec; $\lambda_{max}^{pH\ 1}$ 320 mμ (ε 36,700) and 250 (3600), $\lambda_{min}^{pH\ 1}$ 273 (520), $\lambda_{max}^{pH\ 14}$ 306.5 mμ (ε 31,250) and 274 (9600), $\lambda_{min}^{pH\ 14}$ 281 (8800); nmr, 12.1 (1, broad s, NH), 6.24 (1, d, H-1', $J_{1',2'}$ = 5.5 Hz), ~5.80 (2, H-5, s at 5.85 overlapped by 3'-OH), 5.24 (1, d, H-2'), 4.95 (1, t, 5'-OH), 4.33 (1, narrow m, H-3'), 4.05 (1, sextet, H-4', $J_{3',4'}$ = 2 Hz, $J_{4',5'}$ = 5 Hz), 3.3 (2, m, H-5', H-5').

Anal. Calcd for $C_9H_{10}N_2O_5S$: C, 41.86; H, 3.88; N, 10.85; S, 12.40. Found: C, 41.88; H, 3.88; N, 10.77; S, 12.40.

2',6-Anhydro-1-(β-D-arabinofuranosyl)-6-hydroxy-4-methylthiopyrimidin-2-one (8).—Methyl iodide (1 ml) was added to a stirred solution of **10** (516 mg, 2 mmol) in 40 ml of methanol, and 1 *N* sodium hydroxide was added dropwise to keep the solution at pH ~9. After 2 hr of stirring at room temperature the reaction mixture was neutralized with 1 *N* HCl, and the solution was concentrated to remove the methanol. Water (10 ml) was added and the solution was passed through a column (2.5 × 12 cm) of Dowex 50 (H^+). The column was washed with 250 ml of water, and then the product was eluted with 0.7 *N* aqueous ammonia. The eluate was concentrated to dryness and the residue (440 mg, 81%) crystallized from 35 ml of ethanol to give colorless needles: mp 200–203° (sinters 193°); $\lambda_{max}^{pH\ 1}$ 304 mμ (ε 29,400) and 256 (5700), $\lambda_{min}^{pH\ 1}$ 270 (4350), $\lambda_{max}^{pH\ 10}$ 294 (ε 19,000) and 263 (11,960), $\lambda_{min}^{pH\ 10}$ 272 (11,150) basic pK_a ~2; nmr, 6.30 (1, d, H-1', $J_{1',2'}$ = 5.5), 6.07 (1, s, H-5), 5.87 (1, d, 3'-OH, $J_{3',OH}$ = 4.5), 5.27 (1, d, H-2'), 4.91 (1, t, 5'-OH, $J_{5',OH}$ = 5.0), 4.37 (1, m, H-3'), 4.04 (1, m, H-4'), 3.25 (2, m, H-5', H-5'), 2.45 (s, overlapped by solvent signal, SCH_3).

Anal. Calcd for $C_{10}H_{12}N_2O_5S$: C, 44.12; H, 4.41; N, 10.29; S, 11.76. Found: C, 44.02; H, 4.44; N, 10.25; S, 11.82.

2',6-Anhydro-1-(β-D-arabinofuranosyl)-4-hydroxylamino-6-hydroxypyrimidin-2-one (12).—A solution of hydroxylamine (58 mmol) in methanol [freshly prepared by adding sodium (1.3 g) in methanol (200 ml) to a solution of hydroxylamine hydrochloride (4.05 g) in methanol and then removing the precipitated sodium chloride] was added to 1.5 g (5.8 mmol) of compound **10**. The solution was kept at 48° for 19 hr, at which time an aliquot showed loss of uv absorption at 320 mμ. The reaction mixture was concentrated to 50 ml and water (100 ml) was added. The solution was adjusted to pH 1 with 12 *N* HCl, and the appearance of absorption at 269 mμ (at pH 1) was monitored. After 1 hr the reaction mixture was passed through a column (2.5 × 15 cm) of Dowex 50 (H^+), and the resin was washed with 250 ml of water. Elution with 0.7 *N* aqueous ammonia then afforded 1 g (66%) of **12** which crystallized from 95% ethanol as colorless rods: mp 211–212° dec; $\lambda_{max}^{pH\ 1}$ 269 mμ (ε 21,450), $\lambda_{min}^{pH\ 1}$ 235 (2700); nmr, 9.6 (2, broad peak, NHOH), 6.08 (1, d, H-1', $J_{1',2'}$ = 5.0 Hz), ~5.7 (1, broad peak, 3'-OH), ~5.0 (3, m, H-5, H-2', 5'-OH), 4.24 (1, m, H-3'), 3.95 (1, m, H-4'), 3.30 (2, m, H-5', H-5').

Anal. Calcd for $C_9H_{11}N_3O_6$: C, 42.02; H, 4.28; N, 16.34. Found: C. 42.00; H, 4.36; N, 16.34.

4-Amino-2',6-anhydro-1-(β-D-arabinofuranosyl)-6-hydroxypyrimidin-2-one (9).—A solution of **12** (538 mg, 2.1 mmol) in water (25 ml containing 3 drops of 12 *N* HCl) was hydrogenated at atmospherric pressure over 10% palladium–charcoal catalyst (150 mg). When the theoretical amount of hydrogen had been taken up, the catalyst was removed and the filtrate was passed through a column (2.5 × 10 cm) of Dowex 50 (H^+). The resin was washed with water until the eluate was neutral, and then the product was eluted with 0.7 *N* aqueous ammonia. Concentration of the eluate afforded 320 mg (63%) of **9** which crystallized from 95% ethanol as micaceous plates, mp 278–279° eff; $\lambda_{max}^{pH\ 7}$ 261 mμ (ε 14,260), $\lambda_{min}^{pH\ 7}$ 240 (5260), $\lambda_{max}^{pH\ 0}$ 265 (ε 22,320), $\lambda_{min}^{pH\ 0}$ 233 mμ (2340); basic pK_a = 4.22; nmr, 7.06 (2, broad s, NH_2), 6.14 (1, d, H-1', $J_{1',2'}$ = 5.2 Hz), 5.77 (1, d, 3'-OH, $J_{3',OH}$ = 4.5 Hz), ~5.1 (2, H-5 s at 5.11 overlapped by H-2' d at 5.14), 4.89 (1, t, 5'-OH, $J_{5',OH}$ = 5.5 Hz), 4.28 (1, m, H-3'), 3.95 (1, m, H-4'), 3.27 (2, m, H-5', H-5').

Anal. Calcd for $C_9H_{11}N_3O_5$: C, 44.81; H, 4.56; N, 17.42. Found: C, 44.75; H, 4.58; N, 17.41.

4-Methylthio-1-(β-D-arabinofuranosyl)pyrimidine-2,6-dione (5).—A solution of **8** (1 g) in 5 ml of 1 *N* sodium hydroxide was kept at room temperature for 1 hr. The solution was then neutralized with an excess of Dowex 50 (H^+) and the filtrate was concentrated to dryness. The residue (1.02 g, 98%) crystallized from methanol as a monomethanolate which melted indistinctly (foams ~110–120°). Drying *in vacuo* at 100° for 24 hr failed to remove the methanol: uv $\lambda_{max}^{pH\ 0}$ 225 mμ (ε 9800), (shoulder at 236), and 283 (15,600), $\lambda_{min}^{pH\ 0}$ 250 (2900); $\lambda_{max}^{pH\ 14}$ 231 (ε 11,400), 248 (12,800) and 295 (12,800), $\lambda_{min}^{pH\ 14}$ 238 (11,300), and 268 (3700); nmr, 11.3 (1, broad s, NH), 6.41 (1, d, H-1', $J_{1',2'}$ = 7.5 Hz), 5.41 (1, s, H-5), ~5.16 (2, broad peak, 2'-OH, 3'-OH), ~4.2 (4, m, H-2', H-3', 5'-OH and methanol OH), ~3.6 (3, m, H-4', H-5', H-5'), 3.18 (3, s, CH_3OH), 2.45 (s, overlapped by solvent signal, SCH_3).

Anal. Calcd for $C_{10}H_{14}N_2O_6S \cdot CH_3OH$: C, 40.99; H, 5.59; N, 8.70; S, 9.94. Found: C, 40.93; H, 5.59; N, 8.73; S, 9.91.

4-Amino-1-(β-D-arabinofuranosyl)pyrimidine-2,6-dione (6).—A solution of **9** (482 mg) in 10 ml of 1 *N* NaOH was kept at room temperature until the change in uv absorption from 262.5 to 272 mμ (as determined with aliquots at pH 11) was complete (~72 hr). The solution was neutralized with excess Dowex 50 (H^+) and the filtrate was concentrated to dryness. The residue (320 mg, 62%) was recrystallized from a small volume of water to give colorless crystals: mp 231–232° dec; $\lambda_{max}^{pH\ 2-7}$ 266 mμ (ε 22,970), $\lambda_{min}^{pH\ 2-7}$ 237 (2600), $\lambda_{max}^{pH\ 12}$ 272 (ε 16,100), $\lambda_{min}^{pH\ 12}$ 245 (1570); acidic pK_a = 8.52; nmr, 10.2 (1, broad s, NH), 6.25 (3, broad peak, NH_2 and H-1'), 5.0 (2, broad, 2'-OH, 3'-OH), ~4.1 (4, H-5 s at 4.50 overlapped by H-2', H-3' and 5'-OH), ~3.5 (3, m, H-4', H-5', H-5').

Anal. Calcd for $C_9H_{13}N_3O_6$: C, 41.72; H, 5.01; N, 16.21. Found: C, 41.76; H, 4.89; N, 16.22.

2,2'-Anhydro-1-(β-D-arabinofuranosyl)-2-hydroxy-4-methylthiopyrimidin-6-one (14).—A solution of **8** (252 mg) in 50 ml of anhydrous ethanolic ammonia (saturated at 0°) was heated in a sealed tube at 105° for 5 hr. The cooled solution was concentrated to dryness, and the residue was separated into three components (R_f ~0, 0.5, and 0.6) by thick layer chromatography in methanol–chloroform (1:10). The material with R_f 0.5 (20 mg) was identical (uv, ir, melting point) with starting material **8**. The material with R_f 0.6 was recrystallized from ethyl acetate to give pure **14** (63 mg, 27%): mp 194–196°; $\lambda_{max}^{pH\ 1-10}$ 285 mμ (ε 13,000), 248 (11,300), and 232 (11,310); $\lambda_{min}^{pH\ 1-10}$ 239.5 mμ (ε 10,150) and 261 (6100); basic pK_a <0; nmr, 6.34 (1, d, H-1', $J_{1',2'}$ = 5.8 Hz), ~5.8 (s, H-5 s at 5.81 overlapped by 3'-OH d at 5.84), 5.18 (1, d, H-2'), 4.92 (1, t, 5'-OH, $J_{5',OH}$ = 5.2 Hz), 4.39 (1, m, H-3'), 4.05 (1, m, H-4'), 3.30 (2, m, H-5', H-5'), 2.45 (s, overlapped by solvent signal, SCH_3).

Anal. Calcd for $C_{10}H_{12}N_2O_5S$: C, 44.12; H, 4.41; N, 10.29; S, 11.76. Found: C, 44.16; H, 4.28; N, 10.18; S, 11.64.

The material with R_f ~0 was separated into two fractions on thin layer chromatography in chloroform–methanol (4:1). These trace components were identified from their uv spectra as compounds **9** and **15**.

4-Amino-2,2'-anhydro-1-(β-D-arabinofuranosyl)-2-hydroxypyrimidin-6-one (15).—Treatment of **9** (30 mg) with alcoholic ammonia for 24 hr, as described above in the preparation of **14**, and fractionation of the crude residue by thin layer chromatography [triple development in chloroform–methanol (4:1)] gave unchanged starting material (9 mg) and 16.7 mg (80%) of **15** recrystallized from methanol: mp 217–218° (sinters at 193°); $\lambda_{max}^{pH\ 1}$ 264 mμ (ε 11,330) and 209 (23,000); $\lambda_{min}^{pH\ 1}$ 232 (2200); $\lambda_{max}^{pH\ 7}$ 264.5 mμ (ε 11,800) and 210 (24,100); $\lambda_{min}^{pH\ 7}$ 232 (1320); basic pK_a <1; nmr 6.60 (2, broad s, NH_2), 6.25 (1, d, H-1, $J_{1',2'}$ = 5.7 Hz), 5.78 (1, d, 3'-OH, $J_{3',OH}$ = 4.5 Hz), 5.15 (1, d, H-2'), 4.92 (1, t, 5'-OH, $J_{5',OH}$ = 5.5 Hz), 4.72 (1, s, H-5), 4.33 (1, m, H-3'), 3.97 (1, m, H-4'), 3.28 (2, m, H-5', H-5').

Anal. Calcd for $C_9H_{11}N_3O_5$: C, 44.81; H, 4.56; N, 17.42. Found: C, 44.33; H, 4.77; N, 17.09.

Acid-Catalyzed Conversion of 4-Substituted 1-(β-D-Arabinofuranosyl)-pyrimidine-2,6-diones into 2. From 5.—A solution of **5** (100 mg) in 50 ml of 1 *N* hydrochloric acid was heated at 48° for 19 hr. Periodic examination of aliquots (diluted to 1 × 10^{-4} with water and adjusted to pH 1) showed a gradual loss of absorption at 283 mμ together with appearance of peaks at 252 mμ (corresponding to ~80% yield of **2**) and 306 mμ (corresponding to ~7% yield of **8**). The reaction mixture was passed through a column containing excess Amberlite IR-45, and the effluent

and washings were concentrated to dryness. A portion of the residue was fractionated by thin layer chromatography (chloroform–methanol, 5:1) to give crystalline material identical (uv, ir, melting point) with authentic **2**. A faster moving component was identified as **8** from its uv spectrum and chromatographic properties.

From 6.—A solution of **6** (10 mg) in 10 ml of 1 *N* hydrochloric acid at 48° was monitored (at pH 12) in the ultraviolet. The initial absorption at 272 mμ shifted over a 50-min period to give a peak at 252 mμ having a final ε value corresponding to a quantitative yield of **2**. Concentration of the reaction mixture and isolation of the product by thin layer chromatography (chloroform–methanol, 5:1) afforded a single component which gave uv and ir spectra identical with those of authentic **2**.

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Nucleosides. LXVII. The Chemistry of 4-Methyl-2-pyrimidinone Ribonucleosides[1]

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The synthesis of 4-methyl-2-pyrimidinone and 4,5-dimethyl-2-pyrimidinone ribonucleosides **3a** and **3b** is described. The site of glycosylation is determined by two independent routes. Nitrosation of the 4-methyl group converts **3a** and **3b** into their corresponding oxime derivatives (**7a** and **7b**) which, by treatment with acetic anhydride, afford the corresponding nitriles (**8a** and **8b**). The nitrile groups are easily displaced by a variety of nucleophiles. Reduction of oxime **7a** followed by acetylation gives the N-acetylated aminomethyl derivative (**10**) which undergoes facile air oxidation to the 4-carboxymethyl derivative (**11**). In model studies, the structure of **11** is established by an unambiguous synthesis of 1-methyl-2-oxo-4-pyrimidinecarboxylic acid methyl ester (**16**) from 3-methylorotic acid. 1-Methyl-2-oxo-4-pyrimidinecarboxaldehyde oxime (**14**) is also shown to undergo reduction, acetylation, and autoxidation to **16**.

As part of a program directed toward the syntheses of nucleosides of potential biological interest, we have investigated the chemistry of the hitherto unknown ribofuranosyl derivatives of 4-methyl-2-pyrimidinones. Such nucleosides containing a basic aglycon may be viewed as isosteres of cytidine and, since they also contain a potential enamine system, may undergo reactions at the allylic position with electrophilic reagents leading to new types of nucleoside analogs.

Condensation of 4-methyl-2-pyrimidinone (**1a**) or its 5-methyl derivative (**1b**) with tri-*O*-benzoyl-D-ribofuranosyl chloride by the mercuric cyanide–nitromethane procedure[2] gave the blocked nucleosides **2** which were isolated as their hydrochloride salts in good yields (Scheme I). After debenzoylation of **2**, the unblocked nucleosides **3a** and **3b** were obtained as the crystalline hydrochloride salts.

The site of ribosylation (N-1) was established for nucleosides **3** as follows. Condensation of 6-methyluracil (**4**) with the halogenose by the generalized mercuric cyanide–nitromethane procedure[2b] afforded crystalline 3-(tri-*O*-benzoyl-β-D-ribofuranosyl)-6-methyluracil (**5**) in 70% yield, which exhibited an nmr spectrum with values identical with those reported for this product (as a syrup) by Winkley and Robins,[3] and by Prystaš and Šorm.[4] Debenzoylation of **5** followed by acetylation afforded the known[3] crystalline tri-*O*-acetate. Treatment of tri-*O*-benzoate **5** with phosphorus pentasulfide in pyridine, a widely used method for thiation of nucleosides,[5] was accompanied by extensive decomposition. When dioxane instead of pyridine was used as solvent in this reaction, a facile conversion of **5** to 4-thione **6** in above 70% yield occurred.[6] Assignment of the thioxo group to the 4 position of **6** rests on analogy with the thiation of 3-methyluracil (which gave the 4-thione exclusively)[7] and from subsequent reactions of **6**. Reductive desulfurization of **6** with various preparations of Raney nickel under a variety of conditions was complicated by excessive ring reduction. Partial reduction of **6** under mild conditions with activated Raney nickel prepared according to Brown[8] allowed at least the isolation by column chromatography of **2a** from the reaction mixture. Compound **2a**, thus obtained, was identical with that prepared by direct condensation from **1** and afforded the same crystalline picrate. These results establish unambiguously both the site of glycosylation in **2a** at N-1 and the 4-thioxo structure for **6**. Since nucleosides **3** derived from **2** exhibited very similar ultraviolet absorption spectral properties, both **3a** and **3b** are 1-substituted ribosyl derivatives.

Compound **1a** has been shown[9] to undergo nitrosa-

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