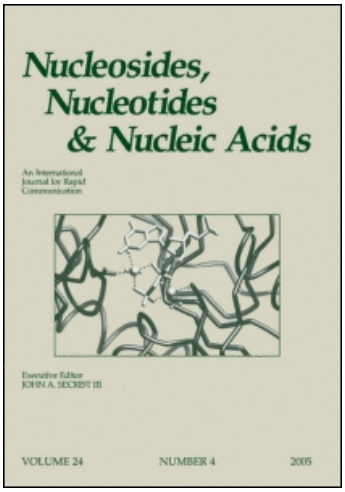

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Studies on the Chemistry of 5-Acetoxy-6-(Acetoxymethyl)-Uridines: Synthesis of a New type of 5'-Cyclonucleoside[1]

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STUDIES ON THE CHEMISTRY OF 5-ACETOXY-6-(ACETOXYMETHYL)-URIDINES: SYNTHESIS OF A NEW TYPE OF 5'-CYCLONUCLEOSIDE[1]

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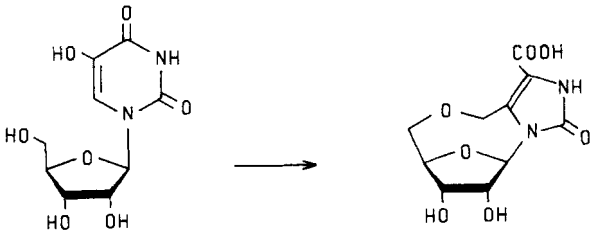
Abstract: The 5-acetoxy-6-(acetoxymethyl)-uridine derivative **18** is converted in aqueous sodium hydroxide solution into the imidazole cyclonucleoside **22**. Compound **22**, in which an oxygen bridge links the sugar and base methano groups, represents a new type of 5'-cyclonucleoside.

In addition to their traditional roles as synthetic intermediates,[2] cyclonucleosides provide useful tools for probing the conformational aspects of nucleoside-enzyme interactions.[3] The range of model conformations available has been increased in recent years by the introduction of several new types of cyclonucleosides[3,4] including compounds with multi-atom bridges. In continuation of this theme, we now report the conversion of 5-hydroxyuridine (**1**) into cyclonucleoside **2**, a compound in which O5' is linked to the base via a methano group. As far as we know, 5'-cyclonucleosides featuring this particular type of bridge have not been reported before.



1 **2**

We encountered cyclonucleoside **2** while extending some of our earlier findings[5] on the properties of 5-acetoxy-6-(acetoxymethyl)-uracils to the nucleoside area. Uracils of type **3** are convenient starting materials for

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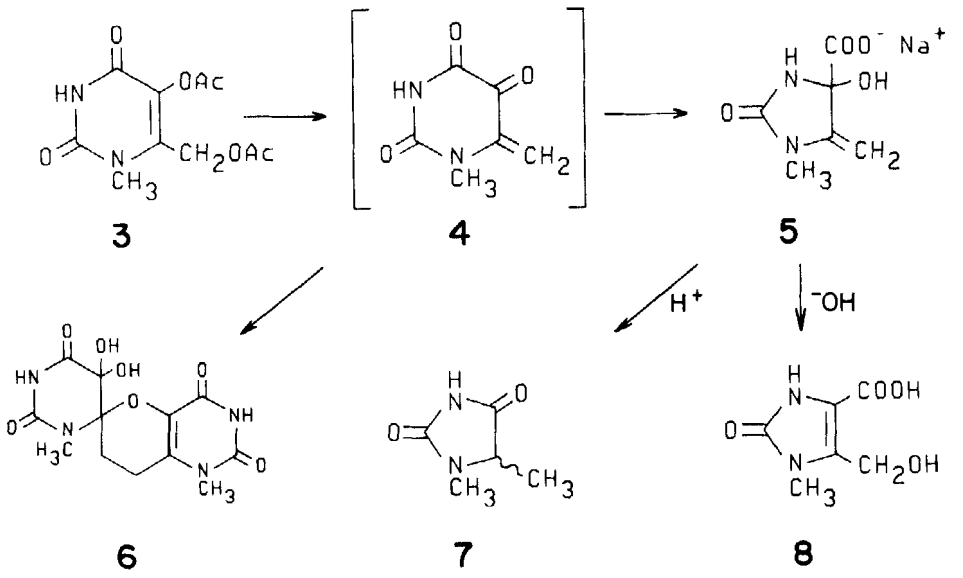
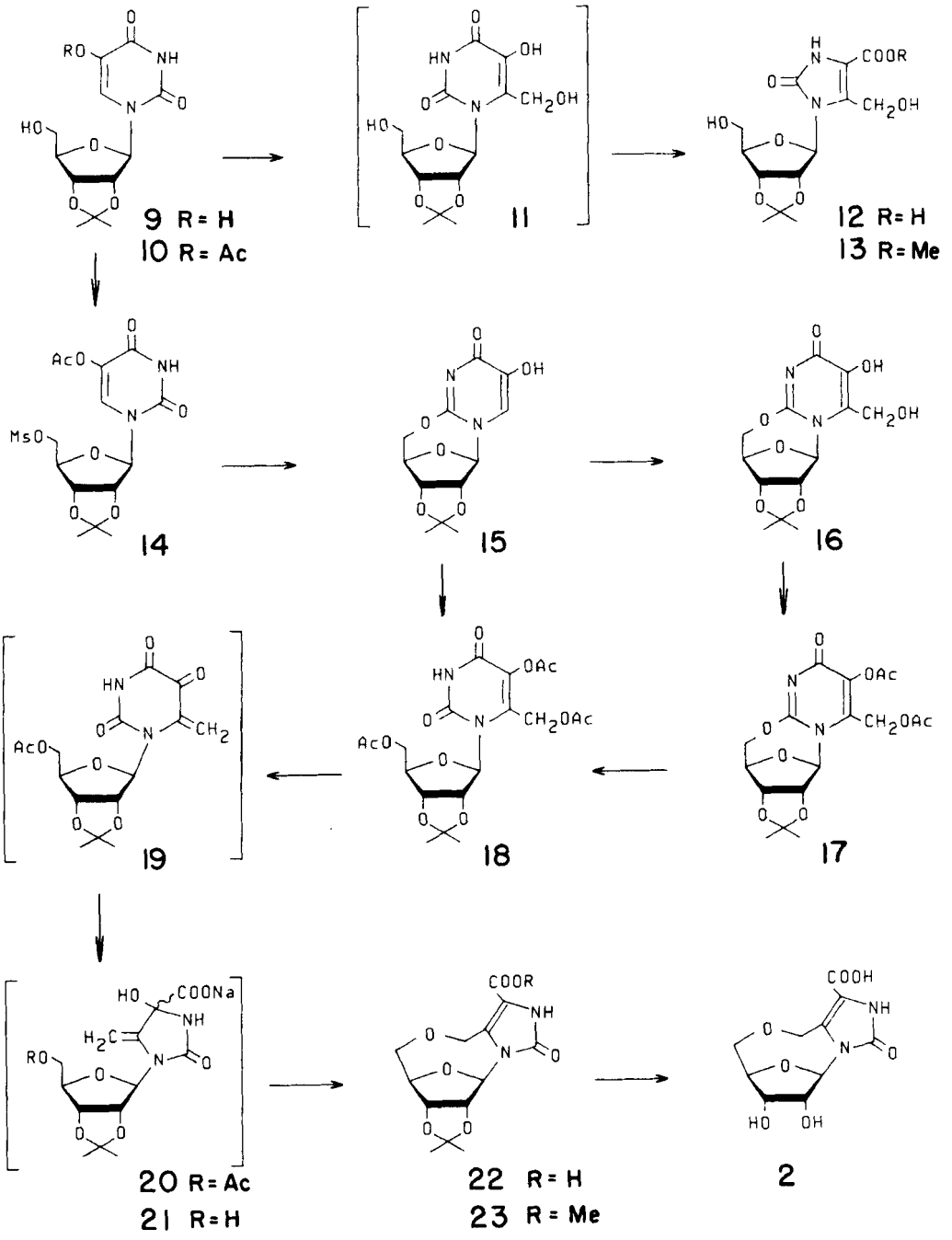


generating 5-oxo-6-methylenepyrimidines, for example, the 1-methyl derivative **4**. This substance is highly reactive and it either dimerizes[5a] to give **6** or undergoes ring-contraction [5b] to give **5**, depending on the reaction conditions. Imidazole **5** can then be converted into either the 5-methylhydantoin **7** or the 2,3-dihydro-5-(hydroxymethyl)-2-oxo-1H-imidazole-4-carboxylic acid **8** simply by altering the pH of the reaction mixture.[5b] Extension of these findings to the synthesis of the corresponding nucleosides requires the availability of a 5-hydroxy-6-(hydroxymethyl)-uridine, for example **11**, and we assumed initially that it would be possible to prepare such a compound by adding an excess of formaldehyde to the monosodium salt of the parent 5-hydroxypyrimidine (**9**). This procedure [5b] affords simple 5-hydroxy-6-(hydroxymethyl)- uracils in yields of about 70%, but the reaction with **9** proved to be more complex than expected. Although **11** is formed, it readily undergoes further reactions that lead to the formation of the ring-contracted product **12**, which was isolated as the methyl ester **13**.[6] However, a somewhat longer route to the required 6-substituted compounds became available when we found that application of the hydroxymethylation reaction to the 5-hydroxy-2,5'-anhydro nucleoside **15** affords **16** without difficulty. Cyclonucleoside **15** itself is available from 5-hydroxyuridine (**1**) *via* isopropylidenation and acetylation to give **10**, mesylation to give **14**, and



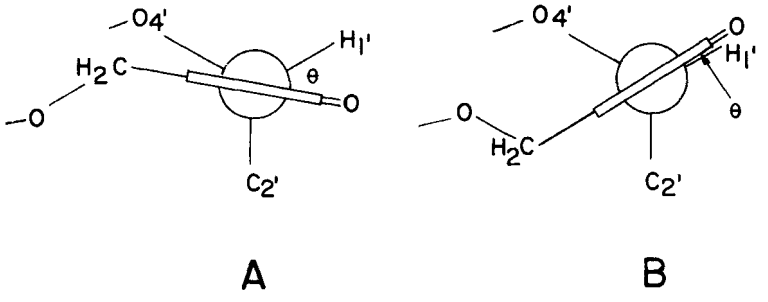
treatment with ethanolic sodium hydroxide to induce cyclization. With **16** on hand, the sequence was completed by acetylation to give **17** and cleavage of the 2,5'-anhydro linkage with silver acetate in pyridine. The spectroscopic properties of the resulting crystalline product are consistent with those expected for the triacetyl nucleoside **18**. In practice, the hydroxymethylation, acetylation and ring-opening reactions can be accomplished in one pot without purification of intermediates, thereby affording **18** from **15** in almost 60% yield.

The structure assigned to nucleoside **18** is also supported by its behaviour in base - that is, the uv-spectral changes that result from the addition of three equivalents of sodium hydroxide parallel those seen previously[5] with the simpler alkyl uracils such as **3**. In the case of **18**, the uv-absorption shifts rapidly from 268 nm to 228 nm, reflecting the formation of the ring-contracted product **20**. As with the earlier examples, the intermediate enone - **19** in this case - does not survive long enough to be observed directly under these reaction conditions. The addition of more sodium hydroxide to the solution containing **20** promotes uv-spectral changes that are diagnostic for the formation of a 2,3-dihydro-2-oxo-1H-imidazole-4-carboxylic acid, as might be expected by analogy with the behaviour of **5**. However, the product is not the 5-hydroxymethyl nucleoside **12**, but the novel cyclonucleoside **22**, which was obtained in crystalline form in about 60% yield. Compound **22** is clearly formed from **20** *via* rapid hydrolysis of the acetyl group to give **21** followed by attack of the resulting 5'-oxy anion on the exocyclic methylene group. Hydroxide ion itself apparently does not compete effectively with this intramolecular process.

The structure of **22** is convincingly demonstrated by its nmr spectral properties. In the ^{1}H-spectrum, for example, the non-equivalent H5' protons and the small values for the coupling constants J(1',2') and J(3',4') are typical of 5'-linked cyclonucleosides. The 5-methano protons are also non-equivalent, and their substantial chemical shift difference ($\Delta\delta$ = 1.25 ppm) suggests that one of them lies in the plane of the 4,5-double bond. Further evidence for the 5'-cyclo linkage of **22** is seen in the ^{13}C-nmr spectrum. Thus, the C5' and C5-methano carbons occupy β positions with respect to one another, and they are consequently deshielded (by 12.2 and 14.9 ppm, respectively) when compared with the corresponding carbons in the noncyclic nucleoside **12**. Smaller upfield

shifts (3.8 and 0.3 ppm) are seen for C5 and C4', respectively, in the cyclonucleoside **22** when compared with **12**, as expected for γ substitution effects. Similar β and γ effects are seen when the carbon shifts of ethers are compared with those of the corresponding alcohols.[7] The ester **23**, obtained by methylation of the sodium salt of **22** in methylformamide, and the deblocked acid **2**, obtained by simple acid hydrolysis of **22**, both exhibit nmr spectral properties consistent with their cyclic structures.

Examination of a Dreiding model of cyclonucleoside **22** suggests that the compound lacks the extreme rigidity of conventional 5'-cyclonucleosides such as **15**, and a number of conformational possibilities exist. The ^{1}H-nmr spectrum of **22** indicates that only the upfield H5' resonance is appreciably coupled to H4' (2.4 Hz), and this can be accommodated by the model when the torsion angle γ (O5'-C5'-C4'-C3') approaches 90°,[8] which also produces an approximately 90° value for the angle between C4' and the 5'-proton that projects towards the C2',C3' side of the furanose ring. This arrangement differs from that of 2,5'-cyclonucleosides,[9] and it is interesting to note that the main J(4',5') coupling in those compounds involves the downfield H-5' resonance rather than the upfield one as seen for **22**. With an approximately 90° value for angle γ , the O5' bridge of **22** can adopt conformations in which the 5-methano group is directed either towards (**A**) or away from (**B**) the furanose ring oxygen (O4'). These orientations produce glycosyl torsion angles χ(O4',C-1'-N1-C2), of approximately 200° and 240°, respectively, and torsion angles θ (C2-N1-C1'-H1') of 0° and -40°. Previous work by the groups of Lemieux[10a] and Danyluk[10b] have established that a Karplus-type relation-



A B

ship exists between the angle Θ and the value of the vicinal coupling constant J(C2,H1') in various cyclouridines. More recently, Davies[10c] and coworkers have determined that the magnitude of the one-bond coupling constant J(C1',H1') in pyrimidine cyclonucleosides is a function of the glycosyl bond conformation. Using the modified Karplus relationships developed by these authors[10b,c] and bearing in mind that **22** is a 2-oxo-imidazole rather than a 2-oxo-pyrimidine from which these equations were developed, it is seen that J(C2,H1') values of less than 1 Hz and J(C1',H1') values of 179 Hz are expected for conformation **A**, whereas values of 2.5 and 168 Hz, respectively, are expected for conformation **B**. The actual values measured for **22**, namely 1.8 ± 0.3 Hz and 167.8Hz agree reasonably well with conformation **B**, although the three bond coupling suggests a somewhat larger value for Θ (~25°) than does the one-bond coupling (0°). These data indicate that the 5-methano group of **22** projects towards the 2',3' edge of the furanose ring, an orientation similar to that noted previously for the methano group in 5',6-methanopyrimidine nucleosides.[4f] For the unblocked cyclonucleoside **2**, information on the conformation about the C4',C5' bond is lacking because of overlapping resonances in the ^{1}H-nmr spectrum. However, the vicinal coupling constant, J(C2,H1'), found for **2** is smaller than that observed for **22**, declining to a value of only 0.9 ± 0.2 Hz. This value indicates an angle Θ of about ± 40° for **2**, with the −40° value (as in **A**) being the more likely because of the restricted glycosyl rotation imposed by the 5'-bridge. The J(C1',H1') value of 170.0 Hz observed for **2** again corresponds to a smaller value of Θ (±15°) than that suggested by the vicinal coupling constant, but both measurements lead to the general conclusion that a different population of glycosyl conformers is favored after removal of the isopropylidene group. Further studies on the solution conformations of **22** and **2** are planned.

EXPERIMENTAL

General Procedures: Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra were measured on Gilford Response and Unicam SP-800 spectrophotometers. Preparative tlc separations were effected on 1000 μm (20 x 20 cm, Analtech, Inc.) GF254 silica gel plates. Nuclear magnetic resonance spectra

were determined with JEOL FX90Q and PFT-100 instruments. ^{1}H-chemical shifts were measured relative to internal tetramethylsilane (TMS) whereas ^{13}C-chemical shifts were measured relative to the solvent absorbance and then corrected to the TMS scale. Unless stated otherwise, all spectra were determined in DMSO-d_6 solution. Assignments of ribosyl carbons were confirmed by selective decoupling experiments. Proton-carbon coupling constants were observed under gated decoupling conditions using an increased number of data points and a decreased spectral width to improve the digital resolution: D_2O was also added to remove possible coupling between carbon and exchangeable protons. Microanalyses were performed by MHW Laboratories, Phoenix, Arizona. All evaporations were carried out in vacuo.

5-Acetoxy-2',3'-O-isopropylidene-5'-O-methanesulphonyluridine (14). Methanesulphonyl chloride (4 ml, 52.5 mmol) was added to a solution of 5-acetoxy-2',3'-O-isopropylideneuridine[11] **10** (15 g, 44 mmol) in pyridine (75 ml) and the reaction mixture was stirred at room temperature for 2 hr. A small amount of water (~3 ml) was added to hydrolyze the unreacted sulphonyl chloride and the solution was concentrated almost to dryness. Addition of cold water (150 ml) to the resulting thin syrup induced crystallization of **14**. After the mixture was stored overnight in the refrigerator, the solid was collected, washed generously with cold water and dried, affording 18.1 g (98%) of granular material. Recrystallization of this product from hot ethanol then afforded 14.8 g of pure **14**, mp 168-170°; uv (pH 1-7) λmax 267, λmin 234 nm; ^{1}H-nmr, δ 11.91 (1, s, NH), 7.91 (1, s, H6), 5.81 (1, d, H1'), 5.10 (1, dd, H-2'), 4.80 (1, dd, H-3'), ~4.37 (3, m, H4',H5',H5''), 3.20 (3, s, OMs), 2.24 (3, s, OAc), 1.50 and 1.30 (two s, 3H each, isopropylidene methyls). J(1',2') = 1.8 Hz, J(2',3') = 6.4 Hz, J(3',4') = 3.7 Hz.

Anal. Calcd. for $C_{15}H_{20}N_2O_{10}S$: C, 42.86; H, 4.80; N, 6.66. Found: C, 43.01; H, 4.75; N, 6.57.

5-Hydroxy-2',3'-O-isopropylidene-2,5'-anhydrouridine (15). Sodium hydroxide (80 ml of 1N solution, 2 eq) was added to a suspension of **14** (16.8 g, 40 mmol) in ethanol (700 ml), and the mixture was stirred at room temperature. The solid material dissolved within 15 min. The reaction is accompanied by a shift in the uv absorption maximum (pH 10) from 266

nm (anion of **11**) to 295 nm (isosbestic points at 219 and 262 nm), and is complete within 1.25 hrs. The reaction mixture was acidified with acetic acid to pH ~5 and most of the ethanol was removed by evaporation. Highly crystalline **15**, which appears during the evaporation, was obtained in several crops totalling 8.8 g (78%). An additional 0.5 g of **15** was obtained from the aqueous filtrate *via* ethyl acetate extraction, bringing the total yield to 82%.[12] Pure material showed the following properties: mp >250°; uv (pH 1-4) λmax 266.5, λmin 225.5; uv (pH 10) λmax 295 nm (sh at 277 nm), λmin 235 nm; ^{1}H-nmr δ 8.96 (1, s, 5-OH), 7.61 (1, s, H6), 5.75 (1, s, H1'), 4.99 (2, s, H2' and H3'), 4.68 (1, narrow, unresolved m, H4'), 4.53 (1, dd, H5'), 4.08 (1, dd, H5''), 1.43 and 1.30 (6, two s, isopropylidene methyls), J(4',5') = 1.5 Hz, J(4',5'') = 0.9 Hz, J(5',5'') = 12.8Hz.

Anal. Calcd. for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.92. Found: C, 50.92; H, 4.89; N, 9.80.

2',3'-O-Isopropylidene-5-hydroxy-6-(hydroxymethyl)-2,5'-anhydrouridine (16) Cyclonucleoside **15** (1.42 g, 5 mmol) was suspended in about 30 ml of water and converted into the soluble sodium salt by the addition of 5 ml of 1N sodium hydroxide solution. Aqueous formaldehyde (2 ml of 37% v/v solution) was added, the volume was adjusted to 50 ml with water and the reaction mixture was heated in a water bath at 50°. The hydroxymethylation reaction is accompanied by a shift in the uv absorption maximum (0.1 ml aliquots diluted to 50 ml, pH adjusted to 10) from 295 nm (anion of **15**) to 310 nm (anion of **16**), and the process is complete after 3 hr. After cooling, the reaction mixture was treated with an excess of Dowex 50 (H^+) and the filtrate and resin washings were evaporated to dryness. The product, which was obtained as a white powder after several portions of ethanol were evaporated from the residue, showed the following properties: uv (pH 1-7) λmax 274, λmin 232.5 nm; uv (pH 11) λmax 309.5 nm, sh at 275 nm, λmin 242 nm; ^{1}H-nmr (DMSO-d_6 + D_2O) δ 5.98 (1, s, H1'), 1.44 (3, s, CH_3), 1.30 (3, s, CH_3). The remaining resonances (7H) consist of a broad singlet at 4.64 (H4') and three overlapping AB quartets, namely H2',H3', at 4.97 and 4.87; H5',H5'' at 4.39 and 3.89; $-CH_2OD$ at 4.80 and 4.35; J(5',5'') = 12.6 Hz, J(CH_2) = 13.1 Hz, J2',3' = 5.5 Hz. Before exchange with deuterium, the 5-O<u>H</u> signal appears at δ 8.51 (1, s) and the $-CH_2O$<u>H</u> signal at δ 5.40 (1, bt).

5-Acetoxy-6-(acetoxymethyl)-1-(2,3-O-isopropylidene-5-O-acetyl-β-D-ribofuranosyl)uracil (18). Cyclonucleoside **15** was subjected to hydroxymethylation on four times the scale described above for the preparation of **16**. After the 3 hr heating period, the reaction mixture was neutralized with acetic acid and then evaporated to dryness. Two portions of ethanol (100 ml) were added to and evaporated from the syrupy residue in order to remove the remaining water and this procedure was repeated with two 100 ml portions of pyridine. The final residue was dissolved in fresh pyridine (140 ml) containing a large excess of acetic anhydride (60 ml) to ensure rapid and complete acetylation of the hydroxyl groups.[13] After removal of solvents (oil pump), the syrupy residue containing predominantly diacetate **17** was dissolved in pyridine (200 ml) and silver acetate (10 g) was added to the solution. The mixture was protected from light and stirred vigorously for 18 hrs at room temperature. Without filtration, the reaction mixture was carefully evaporated to dryness, using an oil pump for the later stages. The dark residue was suspended in ethyl acetate and silver ions were precipitated by bubbling hydrogen sulphide into the solution. After filtration through a celite pad, the ethyl acetate solution was evaporated to a syrup that crystallized from ethanol (80 ml) on standing at room temperature. The yellowish crystals of **18** (5.2 g in two crops, 57%) are sufficiently pure for the next step. The analytical sample of **18**, obtained as fine needle-like crystals after an ethanol solution of the initial product was decolorized with charcoal, showed the following properties: mp 174-175°; uv (pH 1-7) λmax 268 nm, λmin 234.5 nm; ^{1}H-nmr δ 12.07 (1, s, NH), 5.55 (1, d, H1'), 5.25 (1, dd, H2'), 5.12 (2, s, 6-CH_2), 4.80 (1, dd, H3'), 4.19 (3, m, H4',H5',H5''), 2.26 (3, s, 5-OAc), 2.01 and 2.05 (6, two s, 5'-OAc and 6-CH_2OAc), 1.46 and 1.30 (6, two s, isopropylidene methyls); J(1',2') = 1 Hz, J(2',3') = 6.5 Hz, J(3',4') = 2.2 Hz. In $CDCl_3$ solution, the 6-CH_2 resonances appear as an AB quartet at δ 5.24 and 4.98, with a geminal coupling constant of 13.4 Hz; ^{13}C-nmr δ 170.3 and 169.4 (5'-OAc and 6-CH_2OAc CO), 168.2 (5-OAc CO), 157.6 (C4), 149.2 (C2), 140.0 (C6), 126.6 (C5), 113.1 (MeCMe), 92.4 (C1'), 86.1 (C4'), 84.1 (C2'), 81.7 (C3'), 64.2 (C5'), 55.0 (6-CH_2), 26.9 and 25.2 (MeCMe), 20.6, 20.3 and 20.0 (acetyl methyls); J(C1',H1') = 165.0 Hz, J(C2,H1') = 6.8 Hz, (digital resolution 0.49 Hz).

Anal. Calcd. for $C_{19}H_{24}N_2O_{11}$: C, 50.00; H, 5.30; N, 6.14. Found: C, 50.05; H, 5.17; N, 6.09.

1-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-O5',5-methano-2,3-dihydro-2-oxo-1H-imidazole-4-carboxylic acid (22). Sodium hydroxide solution (1N, 6.75 ml, 3 equivalents) was added dropwise over a 15-20 min. period to a stirred suspension of triacetate **18** (1.02 g, 2.25 mmol) in 540 ml of water. Stirring was continued for 2 hr, during which time the shift in the uv absorption maximum from 268 nm to 228 nm (shoulder) was complete. Addition of 27 ml of 10N sodium hydroxide solution (thereby adjusting the reaction mixture to about 0.5 N in sodium hydroxide) causes the reappearance of uv absorption at 272 nm (dianion of **22**). After 4 hrs, washed Dowex 50(H^+) was added to neutralize the reaction mixture. The filtrate and resin washings were then evaporated to dryness, leaving a glassy residue that crystallized readily when dissolved in the minimum amount of water and acidified with about 1 ml of glacial acetic acid. Fine white needle-like crystals of **22** (415 mg, 60%) were obtained after thorough chilling, mp 245-247° (dec, with darkening above 230°), uv (pH 1) λmax 272, λmin 231; uv (pH 7) λmax 259, λmin 228.5 nm; uv (pH 12) λmax 272, λmin 235.5 nm; ^{1}H-nmr δ 10.76 (1, s, NH), 5.96 (1, d, H1'), 5.63 and 4.38 (two AB doublets, 1H each, 5-CH_2), 4.79 (1, d, H3'), 4.59 (1, dd, H2'), 4.48 (1, narrow, unresolved m, H4'), 4.01 (1, d) and 3.65 (1, dd, H5' and H5''), 1.47 and 1.27 (6, two s, isopropylidene methyls); J(1',2') = 1.4, J(2',3') = 5.8, J(3',4') = J(4',5') = 0, J(4',5'') = 2.4, J(5',5'') = 12.9, J(CH_2 gem) = 15.4 Hz; ^{13}C-nmr δ 160.8 (COOH), 151.1 (C2), 127.8 (C5), 111.7 (MeCMe), 110.1 (C4), 92.2 (C1'), 87.0 and 86.9 (C4' and C2'), 82.9 (C3'), 74.0 (C5'), 66.2 (5-CH_2), 26.6 and 24.7 (MeCMe); J(C1',H1') = 167.8 Hz, J(C2,H1') = 1.8 Hz (digital resolution = 0.37 Hz).

Prolonged storage of **22** in aqueous solution leads to hydrolysis of the isopropylidene group, and 150 mg of nucleoside **2** was recovered from the mother liquor in the present case.

Anal. Calcd. for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97. Found: C, 49.66; H, 5.38; N, 8.69.

1-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-O5',5-methano-2,3-dihydro-2-oxo-1H-imidazole-4-carboxylic acid, methyl ester (23). One equivalent of sodium hydroxide (0.5 ml of N solution) was added to 156 mg (0.5 mmol)

of **22** in 15-20 ml of water, and the solution was evaporated to dryness. The resulting powdery sodium salt of **22** was dissolved in 7 ml of methylformamide (dried over 4A molecular sieves) and 0.5 ml of methyl iodide was added to the solution. After stirring at room temperature for 4 hrs, the reaction mixture was evaporated to dryness and an aqueous solution of the residue was passed through an excess of Dowex 50 (H^+) in order to remove sodium ions. After removal of water, a solution of the residue in the minimum amount of methanol was applied to a preparative tlc plate, which was then developed with chloroform-methanol (9:1, v/v). Removal of the zone at Rf 0.6, extraction of the silica with methanol and evaporation then afforded crystalline **23** (150 mg, 92%), mp 100-105 ° (indistinct); uv (pH 1-7) λmax 273.5, λmin 234.5 nm; uv (pH 12) λmax 291, λmin 243 nm; ^{1}H-nmr δ 10.95 (1, s, NH), 5.96 (1, d, H1'), 5.57 and 4.37 (two AB doublets, 1H each, 5-CH_2), 4.79 (1, d, H3'), 4.59 (1, dd, H2'), 4.49 (1, narrow m, H-4'), 4.02 (1, d, H5'), ~3.67 (H5'', upfield d visible, downfield limb partially overlapped by OMe s at 3.72, total 4H), 1.46 and 1.27 (6, two s, isopropylidene methyls); J(1',2') = 1.1 Hz, J(2',3') = 6.1 Hz, J(5' gem) = 13.2 Hz, J(4',5'') est. 2.5 Hz, J(5-CH_2 gem) = 15.5 Hz).

Anal. Calcd. for $C_{14}H_{18}N_2O_7$: C, 51.53; H, 5.56; N, 8.59. Found: C, 51.46; H, 5.60; N, 8.46.

1-(β-D-Ribofuranosyl)-O5',5-methano-2,3-dihydro-2-oxo-1H-imidazole-4-carboxylic acid (2). A solution of **22** (70 mg) in 4 ml of 80% acetic acid was heated at reflux for 45 min. After cooling, the solvents were removed and the residue was crystallized from ethanol to afford colorless needles of **2** (50 mg, 83%), mp - darkens at 195°, forming a black mass that remains solid at 250°); uv (pH 1, neutral mol) λmax 271, λmin 233 nm; uv (pH 6.8, monoanion) λmax 258, λmin 231 nm; uv (pH 12, dianion) λmax 270.5, λmin 240 nm; ^{1}H-nmr δ 10.64 (1, s, NH), 5.56 (1, s, H1'), 5.60 and 4.32 (AB q, CH_2, J (gem) = 14.3 Hz), 4.01 (3, bs, H2',H3',H4') and 3.75 (2, bs, H5',H5''). The carboxyl proton resonance is too broad to be observed but the hydroxyl protons appear as broad signals (exchangeable) at ~4.9 and 4.5; ^{13}C-nmr δ 161.0 (COOH), 151.1 (C2), 128.5 (C5), 111.6 (C4), 90.9 (C1'), 85.8 (C4'), 76.2 (C2'), 70.6 (C3'), 70.8 (C5'), 64.4 (5-CH2); J(C1',H1') = 170.0 Hz, J(C2,H1') = 0.9 Hz, (digital resolution 0.2 Hz).

Anal. Calcd. for $C_{10}H_{12}N_2O_7.0.5H_2O$: C, 42.71; H, 4.66; N, 9.96. Found: C, 42.64; H, 4.87; N, 9.73.

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1. This investigation was supported by funds from the National Cancer Institute, U. S. Department of Health and Human Services, Grants CA-08748 and CA-36517.
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12. In addition to residual **15**, the aqueous filtrate contains four minor products. We considered it possible that **14**, after hydrolysis of the 5-O-acetyl group, might be converted into a 5'-deoxy-6,5'-cyclonucleoside by analogy with the previously studied[11] cyclization of the corresponding 5'-aldehydo nucleoside. However, the proton nmr spectra of material isolated by prep-tlc indicate that none of the minor components incorporates a 6,5'-linkage, showing in this case that the C6-carbanion form of the intermediate 5-hydroxypyrimidine does not compete successfully with O2 in displacing the 5'-mesyloxy group. These minor products have not been investigated further.

13. While the amount of acetic anhydride used might be overly generous, it is necessary to guard against partial acetylation, which could lead[5] to the formation of the corresponding 5-oxo-6-methylenepyrimidine under conditions that favor dimerization.

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