Anal. Calcd for $C_{51}H_{74}O_{13}$: C, 68.43; H, 8.33. Found: C, 68.58; H, 8.16.

Further processing of the mother liquor from **35** gave the cyclic carbonate **31** in a total yield of 30 mg (33%), mp 235–238°. Continued development of the column with ethyl acetate–isooctane (4:1) provided 11 mg of starting material (**29**) mp 212–214°.

17,21-Cyclocarbonyldioxypregn-5-ene-3,11,20-trione 3,20-Bis(ethylene Ketal) (32) from 30.—Phosgenation of 17,21-dihydroxypregn-5-ene-3,11,20-trione 3,20-bis(ethylene ketal)[14] (448 mg, 1 mmol) was effected using condition B. Crystallization of the product from methanol gave platelets (385 mg, mp 286–288°; 70 mg, mp 278–281°) in a yield of 96%: $[\alpha]_{365}$ −23.2°; $[\alpha]_D$ −31.3°; ν_{max} 1755 and 1110 cm^{-1} (17,21-cyclic carbonate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.99; H, 7.27.

17,21-Cyclocarbonyldioxypregn-4-ene-3,11,20-trione 20-Ethylene Ketal (34) from 32.—Treatment of 17,21-cyclocarbonyldioxypregn-5-ene-3,11,20-trione 3,20-bis(ethylene ketal) (50 mg) with *p*-TSA in methylene chloride–acetone was carried out as in the preparation of **33** from **31**. The product crystallized from methanol as needles (37 mg, mp 259–261°) in a yield of 82%: $[\alpha]_{365}$ 553°; $[\alpha]_D$ 131°; λ_{max} 238 mμ (ε 15,300); ν_{max} 1755 and 1115 cm^{-1} (17,21-cyclic carbonate).

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 67.05; H, 7.11.

Bis(17-hydroxy-3,20-bisethylenedioxy-11-oxopregn-5-en-21-yl) Carbonate (36) and 32 from 30.—The reaction mixture from phosgenation under condition A of 17,21-dihydroxypregn-5-ene-3,11,20-trione 3,20-bis(ethylene ketal) (90 mg) was chromatographed on a 20 × 730 mm silica gel column in ethyl acetate–isooctane (3:2). After emergence of fraction 300 the system was changed to ethyl acetate–isooctane (4:1). Fractions (5 ml) were collected every 10 min. Fractions 171–280 contained the 17,21-cyclic carbonate **32**. Crystallization from methanol gave 38 mg (40%) of platelets, mp 285–286°. Crystallization of the residue from fractions 311–400 gave the bisteroidal carbonate **26** as needles (34 mg, 37%): mp 254–257°; $[\alpha]_{365}$ 91.8°, $[\alpha]_D$ −0.94°; ν_{max} 1760, 1265, and 787 cm^{-1} (bisteroidal carbonate).

Anal. Calcd for $C_{51}H_{70}O_{15}$: C, 66.36; H, 7.64. Found: C, 66.47; H, 7.48.

Registry No.—**1**, 36674-99-4; **2**, 36623-73-1; **3**, 36623-74-2; **4**, 36623-75-3; **5**, 36623-76-4; **6**, 36675-00-0; **7**, 36623-11-7; **8**, 36623-12-8; **9**, 36675-01-1; **10**, 36623-13-9; **11**, 36623-14-0; **12**, 36623-15-1; **13**, 36623-16-2; **14**, 36623-17-3; **15**, 36623-18-4; **17a**, 36623-19-5; **17b**, 36623-20-8; **19**, 36623-21-9; **21**, 36623-22-0; **22**, 36623-23-1; **23**, 36623-24-2; **24**, 36623-25-3; **25**, 36623-26-4; **27**, 36623-27-5; **28**, 36623-28-6; **31**, 36675-02-2; **32**, 36623-29-7; **33**, 36623-30-0; **34**, 36623-31-1; **35**, 36675-03-3; **36**, 36623-32-2; phosgene, 75-44-5.

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Nucleosides. LXXVI. A Synthesis of a Carbon–Carbon Bridged Pyrimidine Cyclonucleoside[1]

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The synthesis of a pyrimidine cyclonucleoside containing a carbon to carbon linkage between C-6 and C-5′ has been achieved. Oxidation of 5-acetoxy-2′,3′-*O*-isopropylideneuridine (**2**) with DMSO–DCC gave the corresponding 5′ aldehyde isolated as its 1,3-diphenylimidazolidine derivative **3**. Hydrolysis of the ester **3** gave the 5-hydroxy derivative **4**, which upon treatment with Dowex-50 (H^+) in aqueous THF afforded the 5′ aldehyde of 2′,3′-*O*-isopropylidene-5-hydroxyuridine (**5**). Base-catalyzed intramolecular hydroxyalkylation of **5** proceeded stereoselectively to give cyclonucleoside **6**, which on treatment with acid yielded the free cyclonucleoside **6a**. Formation of **6** from **5**, facilitated by the presence of the isopropylidene group, is thought to proceed by addition of the C-6 anion to the 5′ aldehyde group. Experimental evidence supporting this mechanism is discussed.

Cyclonucleosides containing a bond from a ribose carbon to a purine or pyrimidine carbon were first reported by Hogenkamp[2] and by Johnson and coworkers.[3] Thus aerobic photolytic cleavage of coenzyme B_{12} gave, among other products, the so-called Nucleoside A. The latter nucleoside was identical with the product obtained by anaerobic photolysis of coenzyme B_{12} and it was tentatively identified as 8,5′-cycloadenosine.[2] Likewise, photolysis of 5′-deoxyinosylcobalamin gave the cyclic nucleoside of hypoxanthine.[3a] In contrast to these results, the anaerobic photolysis of 5′-deoxy-2′,3′-*O*-isopropylideneuridinylcobalamin gave hydroxycobalamin and a crystalline nucleoside which was tentatively identified as 2′,3′-*O*-isopropylidene-6,5′-cyclo-5,6-dihydrouridine.[3b] On the other hand, Keck and Hagen[4] reported the formation of 8,5′-cycloadenylic acid by irradiation of adenylic acid. Presumably all of these reactions involve free-radical mechanisms. Of related interest is the reported synthesis[5] of 2,2′-methylene cyclonucleosides by the photolysis of pyrimidine nucleoside oxosulfonium ylides. More recently Harper and Hampton[6] reported that treatment of 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid with methyllithium in tetrahydrofuran gave a complex mixture of products from which 2′,3′-*O*-isopropylidene-5′-keto-8,5′-cycloadenosine was isolated in ~5% yield. This latter nucleoside was reduced with sodium borohydride to 2′,3′-*O*-isopropylidene-8,5′-cycloadenosine.[6]

Since hydroxymethylation of 5-hydroxy-1-methyluracil had been shown to proceed readily to yield 5-

(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), and a Postdoctoral Fellowship (J. A. R.) from the Gimbel Foundation.

(2) H. P. C. Hogenkamp, *J. Biol. Chem.*, **238**, 477 (1963).

(3) (a) A. W. Johnson, L. Mervyn, N. Shaw, and E. L. Smith, *J. Chem. Soc.* 4146 (1963); (b) A. W. Johnson, D. Oldfield, R. Rodrigo, and N. Shaw, *ibid.* 4080 (1964).

(4) K. Keck and U. Hagen, *Naturwissenschaften*, **53**, 304 (1966); E. Fahr, *Angew. Chem., Int. Ed. Engl.*, **8**, 578 (1969).

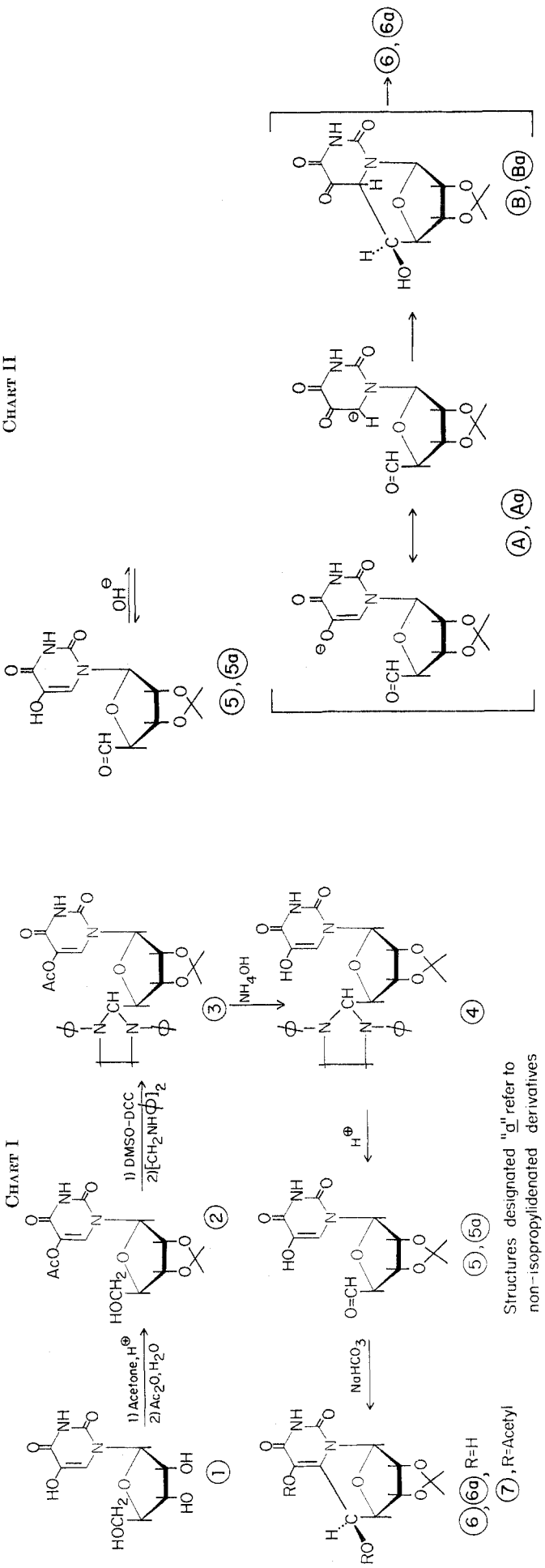
(5) T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, **91**, 7752 (1969).

(6) P. J. Harper and A. Hampton, *J. Org. Chem.*, **37**, 795 (1972).

hydroxy-6-hydroxymethyl-1-methyluracil,[7] we envisioned that the synthesis of a 6,5′ cyclonucleoside could be achieved by intramolecular hydroxyalkylation of the 5′ aldehyde of 5-hydroxyuridine (**5a**). (5-Hydroxyuridine is a naturally occurring component of certain yeast RNAs.)[8] This paper describes the synthesis of **5a** and its ketal **5** and their conversion into their corresponding 6,5′ cyclonucleosides **6a** and **6** as part of our program to prepare 6-substituted pyrimidine nucleosides of potential biochemical interest.

Isopropylidination of 5-hydroxyuridine (**1**, Chart I) in acetone containing 2,2-dimethoxypropane[9] followed by acetylation in aqueous medium gave 5-acetoxy-2′,3′-*O*-isopropylideneuridine (**2**). Oxidation of **2** with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) in the presence of pyridinium trifluoroacetate[10] gave the 5′ aldehyde of **2**, which was isolated as its crystalline 1,3-diphenylimidazolidine derivative **3** upon reaction with *N*,*N*′-diphenylethylenediamine.[11] Treatment of **3** with ethanolic ammonia gave the free 5-hydroxy derivative **4**, which on treatment with Dowex 50 (H^+) in 70% tetrahydrofuran–water[12] gave the free aldehyde **5**. A facile conversion to the cyclonucleoside **6** (or **6a**) was observed when **5** (or **5a**) was treated with 1 equiv of sodium bicarbonate in aqueous medium. The structure of **6** was demonstrated on the basis of the following evidence: elemental analysis was consistent with the empirical formula; the ultraviolet absorption characteristics were very similar to those reported for 5-hydroxy-6-alkylpyrimidines;[7] the pmr spectrum of **6a** in dimethyl sulfoxide-d_6 showed the lack of H-6 absorption and the anomeric proton signal was a singlet, a good indication of cyclo- (or anhydro-) nucleoside linkage involving C-5′.[3b,6,13] Three exchangeable protons were detected upon addition of deuterium oxide. Furthermore, nucleoside **6** showed *well-resolved* signals for H-4′ and H-5′ as a pair of doublets at δ 4.47 and δ 4.97, respectively, with a coupling constant of $J_{4',5'}$ = 7.5 Hz. These results are in contrast to the pmr data reported by Harper and Hampton[6] for 2′,3′-*O*-isopropylidene-8,5′-cycloadenosine, which showed poorly resolved signals for H-4′ and H-5′ attributable to a mixture of diastereoisomers in their product. Acetylation of **6** with excess acetic anhydride in pyridine gave the diacetate **7**. In the latter compound H-5′ appeared at δ 6.03 and was coupled to H-4′, which appeared as a doublet at δ 4.65 ($J_{4',5'}$ = 7.5 Hz), thus confirming the previous assignments.

Theoretically, the intramolecular hydroxyalkylation of **5** could lead to two diastereoisomers. However, inspection of Dreiding models of the two possible isomers shows that the large coupling constant ($J_{4',5'}$ = 7.5 Hz) could be rationalized *only* in terms of the isomer having the *S* configuration at C-5′ as depicted in structure **6**. (The $J_{4',5'}$ value for the *R* isomer should be much smaller since the dihedral angle in that case is almost 90°.) The pmr spectrum of a reaction mix-



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(13) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 1390 (1969).

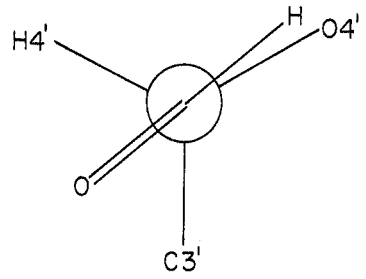

Figure 1.—Newman projection of a portion of **5** or **5a** showing C-4′–C-5′ viewed from C-5′.

ture containing nucleoside **6** was almost identical with that of isolated **6**, indicating that isomer **6** is the main—if not the exclusive—product. This remarkable stereoselectivity in the formation of **6** from **5** may be explained by consideration of the factors which determine the rotamer population around C-4′ and C-5′. The most favorable conformation would be that in which the carbonyl oxygen is farthest removed from the pyrimidine ring and sugar ring oxygen, as shown in Figure 1. In such a conformation, the 5′ carbonyl is flanked by H-4′ and C-3′. Attack by the C-6 anion[14] (*vide infra*) on the 5′ aldehyde would then be expected to give mainly—or solely—**6**.

At the outset of this work we expected that the intramolecular hydroxyalkylation at C-6 by the 5′-aldehyde group would be promoted by the presence of the isopropylidene group.[15] The following results give support to this expectation. An aqueous solution of **5** ($\sim 2 \times 10^{-4}$ *M*) lost ~75% of its selective absorption at 280 nm over a period of ~10 min, after which time a new peak at 286 nm slowly emerged and reached a maximum value in ~1.5 hr. The absorption of this latter peak is that of **6**. This sequence of events was not observed when the pH of the solution containing **5** was kept below 3.5. However, the appearance of the maximum at 286 nm could not be prevented by acidifying the solution of **5**, which had lost 75% of its selective absorption at 280 nm. In sharp contrast to these observations, it was found that an aqueous solution of **5a** did not undergo any appreciable change for as long as 1 hr. Instead its absorption maximum slowly shifted from ~280 nm toward ~285 nm, indicating that **6a** was being formed. This latter transformation took place however in ~6 days at room temperature. In contrast, formation of **6a** was immediately observed when a solution of **5a** was treated with dilute sodium hydroxide (pH ~10–11). That **6a** was the product formed was proved by synthesis from **5a**. It could then be shown that **6a** was identical with the product obtained by treating **6** with acid.

Formation of **6** (or **6a**) from **5** (or **5a**) probably proceeds through the formation of the mesomeric anion A[14,16] (or Aa) (Chart II). Nucleophilic attack of C-6 anion on the 5′-carbonyl group would yield intermediate B (or Ba) which could tautomerize to yield cyclonucleoside **6** (or **6a**). Clearly, this mechanism is supported by the observations made in the transformation of **5** to **6** in dilute aqueous solution: first, when the ionization of the 5-OH group in **5** was prevented by addition of acid no change was noticed, indicating that anion A could not be formed; secondly, the loss of uv absorption is a good indication that intermediate B is formed. In the case of **5**, formation of B is facilitated by the presence of the isopropylidene group.[15] Formation of B from **5** is fast compared with the rate of formation of **6** from B; therefore accumulation (loss of uv) of B is noticed. In contrast, **5a** does not lose uv absorption (Ba is not accumulated) but slowly yields **6a**. In this latter case the rate of formation of **6a** from Ba is faster than the formation of Ba from **5a**.

(14) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **34**, 2636 (1969).

(15) For a discussion of this effect see ref 13 and references therein. More recent references to this effect: Y. Kondo, J. L. Fourrey, and B. Witkop, *J. Amer. Chem. Soc.*, **93**, 3527 (1971); K. Isono and T. Azuma, *Chem. Pharm. Bull.*, **20**, 193 (1972).

(16) K. Ikeda and Y. Mizuno, *ibid.*, **19**, 564 (1971).

Experimental Section

General Procedures.—Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The proton magnetic resonance spectra (pmr) were recorded on a Varian A-60 spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in parts per million (δ). Values for coupling constants (hertz) are first order. Pmr signals are s = singlet, d = doublet, m = multiplet, b = broad. Thin layer chromatography was performed on silica gel GF_{254}. Detection of various compounds on the plates was done under ultraviolet light, and by spraying with 10% v/v sulfuric acid in ethanol followed by heating at 110°. Free 5-hydroxy derivatives were detected with a $FeCl_3$ spray and aldehydes with a phenylhydrazine spray. Evaporations were carried out *in vacuo* with bath temperature below 40°. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. Uv spectra were recorded on a Unicam SP 500 spectrometer.

5-Acetoxy-2′,3′-*O*-isopropylideneuridine (2).—5-Hydroxyuridine[17] (10.4 g, 40 mmol) was suspended in a solution of *p*-toluenesulfonic acid (2.85 g, 15 mmol) in 300 ml of dry acetone containing 12 ml of 2,2-dimethoxypropane. After 1 hr, the rapidly stirred reaction mixture still contained some unreacted starting material as shown by tlc ($CHCl_3$–MeOH, 10:1). An additional 5 ml of 2,2-dimethoxypropane was added and the reaction was continued for an additional 1.5 hr. Tlc of the reaction mixture showed that most of the starting material had disappeared to give mainly the desired ketal (R_f 0.50) and a small amount of a faster moving, unidentified product. The reaction mixture was then concentrated and the gummy residue was taken up in a solution of 1.4 g of $NaHCO_3$ in 200 ml of water. The resulting solution was stirred at room temperature and 5 ml of acetic anhydride was added at once. After a few minutes precipitation of the product started. The reaction mixture was then cooled and filtered. The product was washed with several portions of cold water and dried *in vacuo* at 70°, giving 10.3 g (76%) of **2**, mp 155–156°. The mother liquors were extracted with two 100-ml portions of ethyl acetate. The organic layer was dried over $MgSO_4$ and then evaporated. The white residue was recrystallized from water to yield 2 g of **2** (total yield 90%). Tlc examination of these two crops showed only one spot. A small amount of **2** was recrystallized from water to yield an analytical sample: mp 170–171°; pmr δ 7.97 (s, 1, H-6), 5.84 (d, 1, $J_{1',2'}$ = 2.3 Hz, H-1′), 4.83 (m, 2, H-2′ and H-3′), 4.11 (m, 1, H-4′), 3.58 (m, 2, H-5′s), 2.23 (s, 3, acetyl), 1.49 and 1.29 (s, 3 each, isopropylidene methyls); two exchangeable protons were detected by addition of D_2O (NH and 5′-OH).

Anal. Calcd for $C_{14}H_{18}N_2O_8$: C, 49.12; H, 5.30; N, 8.18. Found: C, 48.99; H, 5.01; N, 8.03.

1-[4(*R*)-(1′,3′-Diphenyl-2′-imidazolidinyl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]-5-acetoxyuracil (3).—Compound **2** (6.84 g, 20 mmol) and 16 g of DCC were dissolved in 200 ml of DMSO. Pyridine (2 ml) and trifluoroacetic acid (1 ml) were than added and the resulting mixture was rapidly stirred at room temperature for 15 hr. Water (20 ml) was then added and the resulting mixture was stirred for an additional 30 min. Dicyclo-

(17) D. W. Visser in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N. Y., 1968, p 428.

hexylurea was removed by filtration and the clear yellowish solution was evaporated until most of the DMSO was eliminated. The product was dissolved in 200 ml of CH_2Cl_2 and filtered to eliminate some dicyclohexylurea still present. 1,2-Diphenylethylenediamine (4.24 g, 20 mmol) dissolved in 10 ml of ether was then added and the resulting mixture was refluxed for 45 min. An additional 2 mmol of the diamine was added and the reaction was continued for a total of 2 hr. The reaction mixture was cooled and extracted with water (3 × 30 ml). The organic layer was dried over magnesium sulfate and evaporated to a syrup, which was taken up in 150 ml of diethyl ether and refluxed for 15 min with continuous stirring. This partially dissolved the syrup and gave some finely divided precipitate. The mixture was allowed to cool and then stored overnight in the cold. The product was triturated and filtered to yield 7.0 g of compound **3**. A second crop was obtained (total yield 7.6 g, 71%). This material was recrystallized from absolute ethanol, filtered, washed with ether, and dried to give 6 g of pure **3**: mp 217–218°; pmr δ 7.52 (s, 1, H-6), 6.95 (m, 10, phenyls), 5.85 (m, 2, H-1′ and H-5′), 4.97 (bm, 2, H-2′ and H-3′), 4.33 (bm, 1, H-4′), 3.63 (b, 4, $-CH_2CH_2-$), 2.22 (s, 3, acetyl), 1.37 and 1.23 (2 s, 3 each, isopropylidene methyls). Upon addition of D_2O, one exchangeable proton could be detected.

Anal. Calcd for $C_{28}H_{30}N_4O_7$: C, 62.91; H, 5.66; N, 10.48. Found: C, 63.52; H, 5.68; N, 10.44.

1-[4(*R*)-(1′,3′-Diphenyl-2′-imidazolidinyl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]-5-hydroxyuracil (4).—Compound **3** (2.136 g, 4 mmol) was dissolved in 120 ml of boiling ethanol, and 8 ml of concentrated aqueous ammonia was added. The mixture was kept under reflux and after 10 min the product started to separate. After 30 min the condenser was removed and the heating was continued until all ammonia was eliminated. The reaction mixture was allowed to cool and then it was left at 4° for 16 hr. The product was removed by filtration and washed with cold ethanol and then with ether to afford 1.87 g (95%) of compound **4**. This product showed only one spot on tlc ($CHCl_3$–MeOH, 10:1): mp 232–233° dec; pmr δ 7.12 (s, 1, H-6), 6.97 (m, 10, phenyls), 5.83 (m, 2, H-1′ and H-5′), 4.98 (m, 2, H-2′ and H-3′), 4.28 (m, 1, H-4′), 3.63 (b, 4, $-CH_2CH_2-$), 1.40 and 1.23 (2 s, 3 each, isopropylidene methyls). Two exchangeable protons were detected on addition of D_2O (5-OH and NH).

Anal. Calcd for $C_{26}H_{28}N_4O_6$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.69; H, 5.77; N, 11.33.

1-(2,3-*O*-Isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanosyl)-5-hydroxyuracil (5).—Compound **4** (0.493 g, 1 mmol) was dissolved in 20 ml of tetrahydrofuran and 10 ml of water. Dowex 50 (H^+), 5 g, was then added in one portion and the reaction mixture was rapidly stirred at room temperature. After 40 min all the starting material (R_f 0.58) had disappeared as shown by tlc ($CHCl_3$–MeOH, 10:1) and **5** was the only uv-absorbing product. However, if the plate was first sprayed with 10% H_2SO_4 and then heated, two new spots could be detected. These have not yet been identified but presumably are formed in solution by intramolecular interactions between the sugar and the aglycon moiety. The resin was filtered off and the filtrate was concentrated *in vacuo* to a white residue. The residue was suspended in chloroform and then it was filtered and dried *in vacuo* to give 0.273 g (91.5%) of the aldehyde **5**: mp 160–162° dec; uv max (0.1 *N* HCl) 280 nm; pmr δ 9.30 (s, 1, –CHO). On addition of D_2O the absorption at δ 9.30 rapidly disappeared to give the hydrate: pmr (DMSO-d_6–D_2O) δ 7.38 (s, 1, H-6), 5.88 (d, 1, $J_{1',2'}$ = 2.8 Hz, H-1′), 4.93 (d, 1, $J_{4',5'}$ = 4.4 Hz, H-5′), 4.83 (m, 2, H-2′ and H-3′), 3.88 (dd, $J_{4',5'}$ = 4.4, $J_{3',4'}$ = 1.5 Hz, H-4′), 1.49 and 1.30 (pair of singlets, 3 each, isopropylidene methyls). Addition of D_2O to the solution of **5** in DMSO-d_6 also allowed the detection of 1.5 mol of water.

Anal. Calcd for $C_{12}H_{14}N_2O_7 \cdot 1.5\ H_2O$: C, 44.31; H, 5.23; N, 8.62. Found: C, 44.41; H, 4.90; N, 8.82.

1-(β-D-*ribo*-Pentodialdo-1,4-furanosyl)-5-hydroxyuracil (5a).—The product obtained from the treatment of 1 mmol of **4** with Dowex 50 (H^+) was dissolved in a mixture of 2 ml of trifluoroacetic acid and 0.5 ml of water.[18] As the reaction proceeded, **5a** started to separate and after 10 min the solvents were removed *in vacuo*. The residue was dissolved in water and the solution was concentrated again. The residue was suspended in acetone and filtered to give 0.2 g (77%) of aldehyde **5a**, uv max (0.1 *N* HCl) 280 nm. A 35-mg portion of this product was dissolved in D_2O and then concentrated *in vacuo*. This operation was repeated twice. The residue was dissolved in D_2O and the pmr was obtained (TMS as external standard): δ 7.50 (s, 1, H-6), 5.97 (m, 1, H-1′), 5.20 (d, 1, $J_{4',5'}$ = 3.8 Hz, H-5′), 4.78 (s, DOH), 4.33 (m, 2, H-2′ and H-3′), 4.02 (dd, 1, $J_{4',5'}$ = 3.8 Hz, H-4′).

2′,3′-*O*-Isopropylidene-6,5′(*S*)-cyclo-5-hydroxyuridine (6).—Compound **4** (1.97 g, 4 mmol) was dissolved in 100 ml of 70% aqueous tetrahydrofuran. To the well-stirred solution 20 g of Dowex 50 (H^+) were added at once and the reaction was kept at room temperature for 1.5 hr. During this step some deisopropylidenation was observed as detected by tlc. The resin was filtered off and the filtrate was treated with 0.335 g of $NaHCO_3$. After 15 min the solution ($\lambda_{max}^{pH\ 1}$ 286) was neutralized with Dowex 50 (H^+) and evaporated to dryness, yield 1.02 g. Pmr of this material showed it to be a mixture of **6** (82%) and **6a** (18%). The combined yield was 87%. This material was twice recrystallized from ethanol to yield pure **6**: mp 242–244° dec; uv max (0.1 *N* HCl) 286 nm (ϵ 9540), uv min (0.1 *N* HCl) 248 nm (ϵ 1870), shoulder ~225 nm, uv max (pH 10) 313, 243 nm (ϵ 8040, 6100), uv min (pH 10) 273.5 nm (ϵ 2900); uv max (0.1 *N* NaOH) 309 nm, shoulder at 245 nm, uv min (0.1 *N* NaOH) 271.5 nm (ϵ 2605); pmr δ 5.83 (s, 1, H-1′), 5.12 (d, 1, $J_{2',3'}$ = 5.5 Hz, H-2′), 4.97 (d, 1, $J_{4',5'}$ = 7.5 Hz, H-5′), 4.68 (d, 1, $J_{2',3'}$ = 5.5 Hz, H-3′), 4.47 (d, 1, $J_{4',5'}$ = 7.5 Hz, H-4′), 1.40 and 1.27 (2 s, 3 each, isopropylidene methyls). On addition of D_2O, three protons were exchanged (NH, 5-OH, and 5′-OH).

Anal. Calcd for $C_{12}H_{14}N_2O_7$: C, 48.33; H, 4.73; N, 9.39. Found: C, 48.52; H, 4.94; N, 9.32.

6,5′(*S*)-Cyclo-5-hydroxyuridine (6a).—A portion of the above mixture containing **6** (0.45 g) was dissolved in 10 ml of 80% acetic acid. The reaction mixture was then heated under reflux and the progress of the hydrolysis was followed by tlc using CH_2Cl_2–MeOH (5:1) as solvent. After 3 hr, most of **6** (R_f 0.71) disappeared. The solvent was removed *in vacuo* and the residue was taken up in 25 ml of hot ethanol. Enough water was added to dissolve the solid and the solution was filtered and allowed to cool. After standing for 15 hr at 4° the crystalline product was filtered, washed with ethanol and ether, and dried to give 0.31 g (78%) of cyclonucleoside **6a**. Recrystallization from water gave an analytical sample: mp 215–217° dec; pmr δ 11.48 (b, 1, NH), 8.67 (b, 1, 5-OH), 5.72 (s, 1, H-1′), 5.21 (b, d, 1, $J_{5',5'\text{-OH}} \cong 5$ Hz, 5′-OH), 4.92 (b d, 1, $J_{5',5'\text{-OH}} \simeq 5$, $J_{4',5'}$ = 7 Hz, H-5′), 4.53 (b d, 1, $J_{2',3'}$ = 6 Hz, H-2′), 4.28 (d, 1, $J_{4',5'}$ = 7 Hz, H-4′), 4.02 (b d, 1, $J_{2',3'}$ = 6 Hz, H-3′), 3.42 (b, 2, 2′-OH and 3′-OH). Addition of D_2O exchanged the signals at δ 11.48, 8.67, 5.21, and 3.42 and the broad doublets became sharper.

Anal. Calcd for $C_9H_{10}N_2O_7$: C, 41.87; H, 3.90; N, 10.85. Found: C, 41.73; H, 3.91; N, 10.77.

6,5′(*S*)-Cyclo-5-hydroxyuridine (6a) from 5a.—Compound **5a** (0.1 g, 0.38 mmol) was dissolved in 10 ml of water, and 40 mg of $NaHCO_3$ was added. After ~2 hr, the uv maximum shifted from 280 nm to ~285 nm and remained constant thereafter. The mixture was adjusted to pH 5 with Dowex 50 (H^+) and the resulting mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in ~2 ml of hot water. On cooling, 40 mg of **6a** crystallized, mp 215–217°. Its pmr spectrum was identical with that of **6a** obtained from **6** by acid hydrolysis.

5-Acetoxy-5′-acetyl-2′,3′-*O*-isopropylidene-6,5′(*S*)-cyclouridine (7).—Compound **6** (0.149 g, 0.5 mmol) was dissolved in 10 ml of pyridine, and 2 ml of acetic anhydride was added. The resulting mixture was allowed to stand at room temperature for 36 hr. The solvent was evaporated and the residue was dissolved in ethanol and evaporated again. This last procedure was repeated twice. Finally the glassy residue was dissolved in ~0.5 ml of ethanol, and water was added to precipitate the product. The mixture was left at 4° overnight and the precipitate was collected, washed with water, and dried to give 0.145 g (76%) of the diacetate **7**: mp 228.5–229.5°; pmr δ 6.03 (d, 1, $J_{4',5'}$ = 7.5 Hz, H-5′), 5.96 (s, 1, H-1′), 4.96 (m, 2, H-2′ and H-3′), 4.65 (d, 1, $J_{4',5'}$ = 7.5 Hz, H-4′), 2.15 (s, 6, 5-acetoxy and 5′-acetyl), 1.42 and 1.30 (pair of singlets, 3 each, isopropylidene methyls). One exchangeable proton (NH) could be detected by addition of D_2O.

Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 50.27; H, 4.75; N, 7.33. Found: C, 50.44; H, 4.71; N, 7.36.

Registry No.—**2**, 36507-00-3; **3**, 36507-01-4; **4**, 36507-02-5; **5**, 36507-03-6; **5a**, 36507-04-7; **6**, 36507-05-8; **6a**, 36507-06-9; **7**, 36507-07-0.

(18) J. E. Christensen and L. Goodman, *Carbohyd. Res.*, **7**, 510 (1968).