The Chemistry of 5-Hydroxy-6-(hydroxyalkyl)uracils. Synthesis of Spiro[pyrimidine-4,2′-pyrano[3,2-*d*]pyrimidines] (1)

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Both 5-acetoxy-6-(acetoxymethyl)-1-methyluracil **1** and its parent diol **11** are converted into the spiro[pyrimidine-4,2′-pyrano[3,2-*d*]pyrimidine] **6** when treated, respectively, with hot methanolic pyridine and with one equivalent of acetic anhydride. The formation of **6** can be explained in terms of the generation and dimerization of the reactive 5-oxo-6-methylene pyrimidine **2**. The structure of **6** was determined by ^{13}C nmr spectroscopy and by chemical transformations that lead to the pyrimidinylethylhydantoin **9** and the 6,6′-[1,2-ethanediyl]bispyrimidine **10**. The more complex 5-hydroxy-6-(hydroxyalkyl)uracils represented by the 6,5′-cyclouridines **17** undergo an analogous dimerization when treated with acetic anhydride to give structures **22a** and **22b**. Dimer **22a** was also prepared *via* the 5-phosphate ester **18**. The stereochemistry of dimers **22a** and **22b**, which is apparent from their ^1H nmr spectra, indicates that two molecules of the enones **21a** or **21b** dimerize in a highly stereoselective manner.

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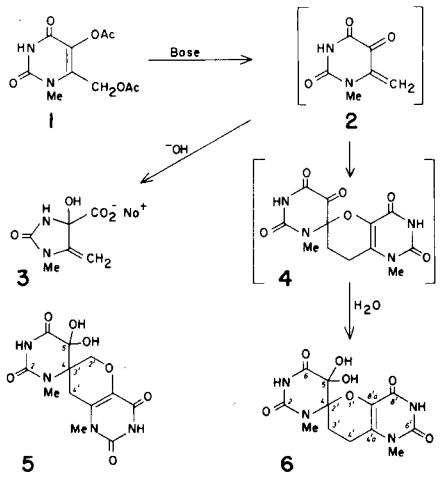
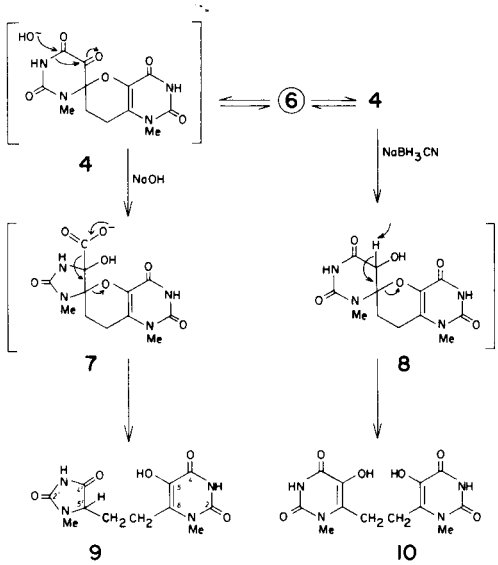
In previous studies (2) we have shown that the conversion of 5-acetoxy-6-(acetoxymethyl)uracils into a variety of imidazole derivatives involves the intermediacy of highly reactive 5-oxo-6-methylenepyrimidines. For example, the 1-methylpyrimidine **1** (Scheme 1) is converted rapidly in the presence of hydroxide ions into the relatively stable 5-methyleneimidazole **3**, apparently *via* ring contraction of the initially formed enone **2**. In order to gain additional information on the properties of 5-oxo-6-methylenepyrimidines, we have now examined the generation and reactions of **2** in the absence of hydroxide ions. In this paper, we report that such compounds dimerize spontaneously in a manner reminiscent of the chemistry of *o*-quinone methides (3) and other α,β-unsaturated carbonyl compounds (4).

When the diacetate **1** was heated in 50% methanolic pyridine for 7 hours, the product obtained after an aqueous work-up was identified as the novel spiro[pyrimidine-4,2′-pyrano[3,2-*d*]pyrimidine] **6**, which was isolated as the crystalline methanolate in 80% yield. Clearly, **1** undergoes deacetylation-elimination (2) under these conditions to give **2**, which immediately dimerizes *via* a type of Diels-Alder reaction where the enone system of one molecule adds across the exocyclic double bond of another. Hydration of the 5-oxo group of the resulting **4**, by analogy with the hydration of alloxan (5), then leads to the observed product **6**. In principle, Diels-Alder dimerization of **2** could afford two types of product — **5** and/or **6** — and precedents for both of these orientations are known for spirodimers obtained from *o*-quinone methides (6). However, structures **5** and **6** differ rather substantially in the heteroatom substitution patterns of the 2′ and 3′ carbons of the pyran rings, and a distinction between them can readily be made on the basis of ^{13}C nmr spectroscopy (Table I). Thus, the observed chemical shifts of the two methylene carbons (δ 20.7 and 21.7, both triplets under proton-coupled condi-

SCHEME 1



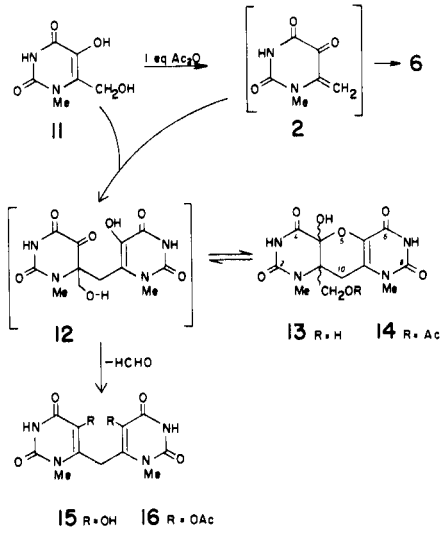
SCHEME 2



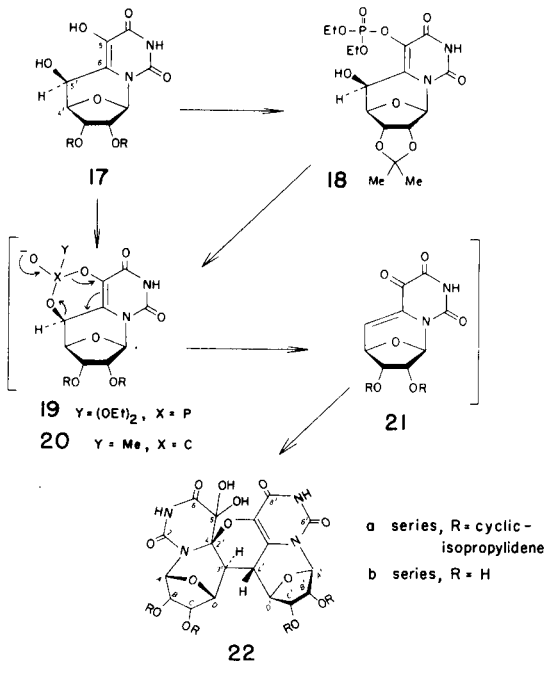
tions) indicate that neither of them are bonded directly to a heteroatom, which is compatible only with structure **6**. If the structure was **5**, the oxygen-bearing C—2′ would resonate approximately 40 ppm downfield from C—4′ (7). Similarly, the observed chemical shift of the spiro-carbon (δ 88.5) is appropriate for the heteroatom substitution pattern of **6** but not **5**. Structure **6** is also supported by the ^{1}H nmr spectrum which, in addition to the *N*-methyl and exchangeable protons, shows methylene signals at δ 2.85 (H—4′a, b) and 2.48 (H—3′a, b). These resonances are too close together for clear-cut decoupling, but their complex multiplicity indicates that the methylene groups are vicinal as in **6**, rather than isolated as in **5**.

Although dimer **6** exists in solution as the 5-hydrate (hydroxyls, 2H exchangeable singlet at δ 7.47), the 5-oxo group can be regenerated as shown in the following examples. These reactions provide additional proof of the structure of **6**, but they also afford products that otherwise would be accessible only by much longer routes. Thus, treatment of **6** with aqueous sodium hydroxide affords the 5-substituted hydantoin **9** (Scheme 2) in 70% yield. Apparently, this product is formed *via* ring contraction of **4** (8) followed by decarboxylation-elimination of the resulting hydroxy acid **7**. The structure of **9** is demonstrated convincingly by the ^{13}C nmr spectrum, which confirms the loss of one carbon atom relative to **6**; by the ^{1}H nmr spectrum which shows H—5′ as a triplet at δ 4.14; and by the uv spectrum, which consists essentially of the spectrum of a 1,6-dialkyl-5-hydroxyuracil superimposed on that of a 1,5-dialkylhydantoin. A second reaction involving the 5-position of **6** concerns its reduction with sodium cyanoborohydride in aqueous acetic acid. This reaction affords an unstable intermediate (**8**) that is converted in either acid or alkaline solution into the symmetrical 6,6′-[1,2-ethanediyl]bispyrimidine **10** in high yield. The structure of **10** follows from integration of the ^{1}H nmr spectrum, which shows NH, OH, *N*-methyl and methylene resonances in a ratio of 1:1:3:2.

SCHEME 3



SCHEME 4



Since the conversion of the diacetate **1** into the enone **2** must proceed *via* a transient monoacetate intermediate (2), it is reasonable to suppose that **2** (and hence **6**) could also be generated from the diol **11** (Scheme 3) by partial acetylation. This proved to be the case (9), although the reaction is more complicated than anticipated. Thus, treatment of **11** with an equivalent amount of acetic anhydride in pyridine at room temperature affords a mixture containing five products, among which the dimer **6** (58% yield) and the diacetate **1** (11% yield) predominate. Much smaller amounts of three crystalline minor products were isolated by chromatography and identified as the pyrano-[3,2-*d*:5,6-*d*′]dipyrimidines **13** and **14**, and the 6,6′-methylenebispyrimidine **16**. These compounds are related in the sense that they probably arise from the common intermediate **12**, namely the product formed if some of the enone **2** is captured by C—6 alkylation of the starting diol **11**. To a very small extent, **12** must undergo a pyridine-catalyzed retro-aldol loss of formaldehyde to form **15**, which subsequently acetylates to give **16**. The 6,6′-methylenebispyrimidine **15** is a known compound (10), and it affords a diacetate identical with **16** isolated in the present study. The major portion of **12**, however, undergoes cyclization to the hemiacetal **13**, most of which is converted into the primary acetate **14**. The ^{1}H nmr spectrum of **14**, which is entirely consistent with the assigned structure, indicates a 6:1 mixture of isomers. As would be expected for this structure,

treatment of **14** with sodium hydroxide affords **15** in good yield, clearly *via* the intermediate **12**. The uv spectral data indicate that **13** is also converted into **15** in base, the transformation being accompanied by an approximate doubling of the extinction coefficient as required by the double chromophore of **15**, relative to **13**.

The finding that 5-hydroxy-6-(hydroxymethyl)-1-methyluracil (**11**) and its diacetate **1** are readily converted *via* the 5-oxo-6-methylenepyrimidine **2** into the spiro-dimer **6** can now be used to explain some observations we have made with the more complex 5-hydroxy-6-(hydroxyalkyl)uracil system represented by the 6,5′-cyclouridines **17** (Scheme 4). When we were investigating methods for the removal of the phenolic 5-hydroxyl groups from these cyclonucleosides, we prepared the 5-phosphate ester **18** by selective esterification of the sodium salt of **17a** with diethyl chlorophosphate (11). This procedure affords **18** in better than 60% yield, but it also leads to smaller amounts of a second product (8% yield) which we now recognize is the complex dimer (**22a**) analogous to **6**. Treatment of isolated **18** with ethanolic triethylamine also leads to **22a**, and a probable mechanism for the generation of the obligatory enone **21a** is the formation and collapse of the cyclic ion **19a**. Dimer **22a** and its tetrahydroxy counterpart **22b** are also formed when the cyclouridines **17a,b** are treated with limited amounts of acetic anhydride. For example, **17a** is converted into **22a** (70% yield) when treated with one equivalent of acetic anhydride in pyridine; **22b** is obtained in 48% yield when acetic anhydride is added to an aqueous solution of the monosodium salt of **17b**. Since it is likely in both of these cases that acetylation occurs selectively at the pyrimidine 5-hydroxyl groups, the formation of the enones **21a,b** probably occurs *via* the cyclic ions **20a,b**.

The structures assigned to **22a** and **22b** follow from the nmr data. The ^{13}C nmr values (Table I), where comparable, are closely similar to those found for the spiro-dimer **6**, except that the increased substitution of C—3′ and C—4′ produces the expected increase in the chemical shifts of these carbons. In spite of the apparent complexity of dimers **22a** and **22b**, their ^{1}H nmr spectra are remarkably simple, primarily because the coupling constants $J_{A,B}$, $J_{C,D}$, $J_{A',B'}$ and $J_{C',D'}$ are essentially zero. These zero couplings are characteristic of ribosyl-6,5′-cyclopyrimidine nucleosides (12). The spectra of **22a,b** are further simplified because the coupling constants $J_{4',D'}$ and $J_{3',D}$ are also zero, a finding which establishes the illustrated C—3′ and C—4′ stereochemistry (13). The 3′ and 4′ protons are consequently held in a *trans* arrangement, and this is confirmed by the $J_{3',4'}$ values of 10.7 and 10.4 Hz, respectively, observed for **22a** and **22b**. The inversion of the C—3′ and C—4′ configurations of **22a,b**, relative to the C—5′ configurations of the starting materials **17a,b** and **18**, indicates a dimerization mechanism in which two molecules of **21a** or **21b** approach each other from their less hindered, rear sides. This orientation is not unexpected in view of our earlier findings that nucleophiles attack C—5′ of 6,5′-cyclopyrimidine nucleosides stereoselectively from the rear side (12c,d).

Table I

^{13}C-NMR Chemical Shifts of Spiro[pyrimidine-4,2′-pyrano[3,2-*d*]pyrimidine] Derivatives (a)

	6 (b)	**22a** (c)	**22b** (d)
C—6	169.3	167.7	168.2
C—8′	157.8	157.2	157.7
C—2	152.5	150.2	150.6
C—6′	149.8	148.1	148.6
C—4′a	134.6	134.5	135.3
C—8′a	129.2	128.9	129.3
C—5	90.3	89.9	90.2
C—4,2′	88.5	89.6	90.2
C—3′	21.7	40.9	43.7
C—4′	20.7	35.5	37.4

(a) δ Values in DMSO-d_6 relative to internal TMS. Values for C—2 and C—6′ can be interchanged. C—3′ and C—4′ have not been assigned unambigously because the proximity of H—3′ and H—4′ does not allow selective decoupling of the ^{13}C spectrum. (b) N—CH_3 at 29.9 and 29.6, methanol (solvate) at 48.6. For comparison, the values found for alloxan hydrate are 169.8 (C—6/C—4), 149.8 (C—2) and 85.0 (C—5). (c) Isopropylidene carbons at 112.7 and 112.3; 26.21 and 25.87; 25.04 and 24.80; ethanol (solvate) at 56.2 and 18.5; sugar carbons at 86.1 and 84.8 (A,A′); 83.4 (four carbons), 81.2 and 80.1 (B,B′,C,C′,D,D′). (d) Sugar carbons at 89.0 and 88.1 (A,A′); 85.3 and 83.9 (D,D′); 74.8, 74.3 (two carbons) and 71.5 (B,B′,C,C′).

EXPERIMENTAL

General Procedures.

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra were measured on a Varian Superscan 3 spectrophotometer. Thin-layer chromatography (tlc) was performed on 250 μm silica gel GF_{254} plates (2.8 × 8 cm; Analtech, Inc), and separated materials were detected with ultraviolet light and/or by spraying with sulfuric acid in ethanol (10% v/v) followed by charring. Preparative separations were effected on 500 μm (20 × 20 cm) plates. Nuclear magnetic resonance spectra were obtained with a JEOL PFT-100 instrument operating at 100 MHz for ^{1}H nmr and 25.15 MHz for ^{13}C nmr spectra. Tetramethylsilane was used as an internal standard. Microanalyses were performed by MHW Laboratories, Phoenix, Arizona, and by Galbraith Laboratories, Inc, Knoxville, Tennessee. All evaporations were carried out *in vacuo*.

3′,4′-Dihydro-5,5-dihydroxy-3,5′-dimethylspiro[pyrimidine-4(5*H*),2′[2*H*]-pyrano[3,2-*d*]pyrimidine]-2,6,6′,8′(1*H*,3*H*,5′*H*,7′*H*)-tetrone **6**.

A solution of 5-acetoxy-6-(acetoxymethyl)-1-methyluracil (**1**, 160 mg) (2) in 2 ml of a 1:1 (v/v) mixture of methanol and pyridine was heated under reflux for 7 hours. The reaction mixture was evaporated to dryness and residual pyridine was removed by evaporating several batches of aqueous ethanol from the residue. Preparative tlc (chloroform-methanol, 9:1, v/v) afforded 20 mg of starting material **1** and 78 mg of dimer **6** (80%, corrected for recovered **1**), which crystallized as the methanolate from aqueous methanol, mp 195° (dec, turns yellow above 140°); uv (water): λ max 285.5 nm (ε 7,500), λ min 250 (ε 2,050); ^{1}H nmr (DMSO-d_6): δ 11.33 (1H, s, NH), 10.92 (1H, s, NH), 7.47 (2H, s, 5-hydroxyls), 4.10 (1H, q, MeO*H*), 3.20 (3H, s, N—5′ Me), 3.17 (3H, d, *Me*OH), 2.96 (3H, s, N—3 Me), 2.85 (2H, m, H—4′), 2.48 (2H, m, H—3′, solvent peak removed by using T_1 pulse se-

quence).

Anal. Calcd. for $C_{12}H_{14}N_4O_7 \cdot MeOH$: C, 43.58; H, 5.06; N, 15.64. Found: C, 44.00; H, 5.41; N, 15.38.

Reaction of 5-Hydroxy-6-(hydroxymethyl)-1-methyluracil (**11**) With Acetic Anhydride.

Acetic anhydride (400 μl, 4.24 mmoles) was added over a twenty minute period, *via* a precision syringe, to a solution of **11** (729 mg, 4.24 mmoles) (10) in dry pyridine (10 ml). After the addition was complete, the reaction mixture was stored at room temperature for 1 hour and then evaporated to dryness. The resulting semisolid mass was dissolved in boiling 90% methanol (11 ml) and the solution was cooled to room temperature to afford (after 2 hours) 340 mg (45%) of pure **6** identical (tlc, nmr, uv) with the material obtained from **1**. The mother liquor was evaporated to dryness and the residue was dissolved in the minimum amount of pyridine. Silica was added, the slurry was dried by rotary evaporation, and the dry powder was added to a column (2.6 × 27 cm) of Silica gel 60 (230-400 mesh, E. M. Reagents) packed in chloroform. The column was washed sequentially with 200 ml each of chloroform and chloroform-methanol (20:1, v/v) to remove pyridine. Elution with 10:1 v/v chloroform-methanol then afforded the following materials, where Rf values refer to tlc using chloroform-methanol, 9:1 v/v:

i) 5-Acetoxy-6-(acetoxymethyl)-1-methyluracil (**1**), Rf 0.54, 116 mg (11%), which was identical with authentic material (2).

ii) 6,6'-Methylenebis[5-acetoxy-1-methyl-2,4[1*H*,3*H*)-pyrimidinedione] (**16**) had Rf 0.30, 2 mg (0.25%), identical (tlc, nmr, uv) with **16** described later.

iii) The spiro-dimer **6** had Rf 0.25, 102 mg (13%, total isolated yield 58%).

iv) 10a-Acetoxymethyl-10,10a-dihydro-1,9-dimethyl-4a*H*-pyrano-[3,2-*d*:5,6-*d'*]dipyrimidin-4a-ol-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone **14** had Rf 0.21, 15 mg (2%). This compound partially overlaps **6** and the actual yield is slightly higher. Material recrystallized from water showed the following properties: mp 265-268° (dec, shrinks and darkens above 200°); uv (water): λ max 284 nm (ε 7,100), λ min 250 (ε 2,150); ^{1}H nmr (DMSO-d_6): δ 11.52 (1H, s, NH), 11.41 (1H, s, NH), 8.64 (1H, s, OH), 4.53 and 4.04 (two 1H, doublets, J_{gem} = 11.9 Hz, CH_2OAc), 3.27 (3H, s, N—9 Me), 2.83 (5H, H—10 (m) overlapping N—1 Me), 1.97 (3H, s, OAc). Signals from the minor isomer (ratio ~6:1) are observed at δ 10.64 (NH), 8.58 (OH), 4.37 and 3.76 (ABq, CH_2OAc, J_{gem} = 11.9 Hz) and 1.95 (OAc).

Anal. Calcd. for $C_{14}H_{16}N_4O_8$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.55; H, 4.45; N, 15.24.

The non-acetylated version of **14**, namely **13**, was obtained admixed with the starting diol **11** when the column was eluted with chloroform-methanol (5:1 v/v). A sample of pure **13** (3.5 mg) was obtained from the final fractions, Rf 0.035, mp >300° (darkens above 200°); uv (water): λ max 284 nm, λ min 252; ^{1}H nmr (DMSO-d_6 + deuterium oxide): δ 3.27 (s, N—9 Me) and 2.85 (s, N—1 Me), each overlapping multiplets from the allylic (H—10) and exocyclic methylene groups.

6-[2-(1-Methyl-2,4-imidazolidinedione-5-yl)ethyl]-5-hydroxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione **9**.

Sodium hydroxide solution (0.33 ml of 1*N*) was added to a stirred suspension of the spiro-dimer **6** (107.4 mg, 0.30 mmole) in water (3 ml). Additional portions (0.33 ml) of 1*N* sodium hydroxide were added to the now clear solution at 30 and 45 minutes and a final addition of 0.33 ml of 10*N* sodium hydroxide was made at 60 minutes. After a further 15 minutes when the shift of the original uv absorption (285 nm) to 310 nm was complete, the reaction mixture was acidified to *p*H 6 with acetic acid. Colorless crystals of **9** appeared overnight (60 mg, 71%), mp ~285° (indistinct, dec, darkens above 200°); ^{13}C nmr (DMSO-d_6): δ 173.8 (C—4'), 159.6 (C—4), 156.5 (C—2'), 149.7 (C—2), 135.8 (C—6), 129.3 (C—5), 6.0 (C—5'), 30.1 (N—1 Me), 27.0 (N—1' Me), 25.1 (allylic CH_2), 19.9 (CH_2); ^{1}H nmr (DMSO-d_6): δ 11.41 (1H, bs, NH), 10.86 (1H, bs, NH), 8.40 (1H, s, 5—OH), 4.14 (1H, t, 5'—H, J = 4.6 Hz), 3.21 (3H, s, N—1 Me), 2.81 (3H, s, N—1' Me), 2.48 (2H, m, allylic CH_2, solvent peak removed by T_1 pulse sequence), 1.95 (2H, m, CH_2); uv (*p*H 4): λ max 287.5 nm (ε 8,400), λ min 250 (ε 2,050); uv (*p*H 14): λ max 310 nm (ε ~ 8,100 unstable), λ min 271 (ε ~3,000). At *p*H 10 and above, the contribution of the ionized hydantoin moiety to the uv spectrum is apparent in a peak at 232 nm (ε 9,250).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.58; H, 4.90; N, 19.99.

6,6'-(1,2-Ethanediyl)bis-[5-hydroxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione] **10**.

Sodium cyanoborohydride (63 mg, 1 mmole) was added to a suspension of **6** (119.4 mg, 0.33 mmole) in 50% acetic acid (3 ml) and the mixture was stirred at room temperature for 1 hour. The resulting dark yellow solution was deionized with Dowex 50 (H^+), the column effluent and washings were evaporated to dryness, and several portions of methanol were added to, and evaporated from, the residue. At this point, the uv spectrum indicated that the conversion of intermediate **8** into **10** was in complete. However, heating a suspension of the residue in 1*N* hydrochloric acid (50 ml) on a steam bath for 30 minutes afforded a suspension of crystalline material (90 mg, 87%) containing only **10**, mp >300°; uv (*p*H 2): λ max 288 nm (ε 15,300), λ min 250 (ε 4,350); uv (*p*H 14): λ max 320 nm (ε ~14,800, unstable), 245 sh (ε ~10,500), λ min 272.5 (ε ~5,250), ^{1}H nmr (DMSO-d_6): δ 11.38 (1H, s, NH), 8.43 (1H, s, OH), 3.31 (3H, s, NMe), 2.81 (2H, s, CH_2).

Anal. Calcd. for $C_{12}H_{14}N_4O_6$: C, 46.45; H, 4.55; N, 18.06. Found: C, 46.43; H, 4.66; N, 18.20.

6,6'-Methylenebis[5-hydroxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione] **15**.

A solution of **14** (24 mg, 0.065 mmole) in 1*N* sodium hyrdroxide (1 ml) was stored at room temperature for 10 minutes, during which time the uv maximum shifted from 284 nm to 322 nm, with an approximate doubling of the absorption. Acidification of the solution with hydrochloric acid afforded 15 mg (76%) of **15**, identical (uv, nmr) with an authentic sample (10). The uv spectral changes resulting from the addition of sodium hydroxide to **13** also indicate the formation of **15**.

6,6'-Methylenebis[5-acetoxy-1-methyl-2,4(1*H*,3*H*)-pyrimidinedione] **16**.

The diol **15** (148 mg, 0.5 mmole), suspended in water (4 ml), was converted into the soluble bis-sodium salt by the addition of 1 ml of 1*N* sodium hydroxide. Addition of acetic anhydride (0.2 ml) to the stirred solution resulted in the almost immediate appearance of a white crystalline precipitate. Recrystallization of the collected solid from aqueous ethanol afforded 150 mg (79%) of pure **16**, mp >300° (shrinks and discolors above 250°); uv (water): 275 nm, λ min 238; ^{1}H nmr (DMSO-d_6): δ 11.83 (1H, s, NH), 4.10 (1H, s, CH_2), 3.29 (3H, s, NMe), 2.11 (3H, s, OAc). Addition of deuterium oxide in exchange of the NH protons and, at a much slower rate, the doubly allylic methylene protons.

Anal. Calcd. for $C_{15}H_{16}N_4O_8$: C, 47.37; H, 4.24; N, 14.73. Found: C, 47.15; H, 4.41; N, 14.58.

2',3'-*O*-Isopropylidene-6,5'(*S*)-cyclouridinyl-5-diethylphosphate **18**, and Dimer **22a**.

The diol **17a** (12a,b) (1.49 g, 5 mmoles) was dissolved in 75 ml of a 1:1 (v/v) mixture of acetonitrile-ethanol and the solution was cooled to 0-5°. Two equivalents of sodium hydroxide (1 ml of 10*N* solution) were added with stirring, followed by 5.76 ml (50 mmoles) of diethylchlorophosphate. Stirring was continued for 10 minutes, at which time tlc (dichloromethane-methanol, 5:1 v/v) showed the absence of **17a** (Rf 0.39). The reaction mixture was evaporated to dryness and the residue was partitioned between water and ethyl acetate. Concentration of the dried ethyl acetate layer and addition of ether afforded 891 mg (41%) of pure **18** in two crops, mp 179-180°; uv (10% ethanol): λ max 274.5 nm (ε 9,200), λ min 237 (ε 1,550) (14); ^{1}H nmr (DMSO-d_6): exchangeable protons at δ 11.88 (1H, s, NH) and 6.12 (1H, d, 5'—OH, $J_{5',5'OH}$ = 6.7 Hz); ^{1}H nmr (deuteriochloroform-deuterium oxide): δ 6.06 (1H, s, H—1'), 5.30 (1H, d, H—2'), 4.71 (1H, d, H—3'), 4.68 (1H, d, H—4'), 5.19 (1H, dd, H—5'), 4.35 and 4.33 (4H, two overlapping eight-line systems, 13 lines visible POCH_2CH_3), 1.39 and 1.37 (two overlapping double triplets POCH_2CH_3) overlapping 1.51 and 1.34 (two singlets, isopropylidene methyls, total

methyls = 12H); $J_{1',2'} = J_{3',4'} = 0$, $J_{4',5'} = 7.6$ $J_{2',3'} = 5.7$ $^4J_{P,CH_3} = 1.3$, $^5J_{P,5'} = 1.8$, $^3J_{P,CH_2} = 8.4$, $J_{CH_2,CH_3} = 7.0$.

Anal. Calcd. for $C_{16}H_{23}N_2O_{10}P$: C, 44.24; H, 5.33; N, 6.45. Found: C, 44.61; H, 5.52; N, 6.32.

Concentration of the filtrate obtained after removal of **18** afforded 1.26 g of material that contained additional **18**, dimer **22a** and unidentified components. This mixture was separated on a prep-500 Waters Associates hplc apparatus [using prep-pak 500 silica cartridges and dichloromethane-methanol (20:1 v/v) at a flow rate of 200 ml/minute] to afford 496 mg of **18** (23%, total yield = 64%) and 122 mg (8%) of dimer **22a** which crystallized from 95% ethanol as the ethanolate, mp >300° (decomposes over a wide range, yellow at 145°, giving eventually a black powder); uv (water): λ max 285.5 nm (ε 7,700), λ min 250.5 (ε 2,500); ^{1}H nmr (DMSO-d_6): exchangeable protons at δ 11.32 (1H, s, NH), 10.91 (1H, s, NH), 7.54 (1H, s, OH), 7.14 (1H, s, OH), 4.35 (1H, t, EtO*H*, CH_2 dq at 3.44, CH_3 t at 1.06); ^{1}H nmr (pyridine-d_5): 6.78 and 6.54 (two 1H s, H—A, H—A'), 5.33 and 5.19 (two 1H, s, H—D, H—D'); 5.02 (2H, s), 5.55 and 5.26 (two 1H d, J = 5.5 Hz, H—B, H—C, H—B', H—C'), 3.75 and 3.33 (two 1H, d, J = 10.7 Hz, H—4', H—3', CH_2 of ethanol removed by T_1 pulse sequence), 1.64, 1.39 and 1.57, 1.35 (12H, four s, isopropylidene methyls).

Anal. Calcd. for $C_{24}H_{26}N_4O_{13}\cdot C_2H_5OH$: C, 50.00; H, 5.16; N, 8.97. Found: C, 49.85; H, 5.00; N, 9.09.

Reactions of the 5-Hydroxy-6,5'*(S)*-cyclouridines **17a** and **17b** With Acetic Anhydride. Dimers **22a** and **22b**.

1) Acetic anhydride (200 μl) was added all at once to a stirred solution of **17a** (613 mg, 2.05 mmoles) in pyridine (7 ml) and the mixture was stirred at room temperature for 30 minutes. Removal of solvents and crystallization of the residue from 95% ethanol (11 ml) afforded **22a** (450 mg, 70%) as the ethanolate, identical (uv, nmr, tlc) with that obtained *via* **18**.

2) 5-Hydroxy-6,5'*(S)*-cyclouridine (12a) (516 mg, 2 mmoles) was dissolved with stirring in 10 ml of 0.2*N* sodium hydroxide. Addition of acetic anhydride (0.2 ml) to the stirred solution produced a bright yellow coloration gradually faded as crystalline material appeared. The mixture was stored at room temperature for 1 hour before the solid was collected and recrystallized from hot water to afford 239 mg (48%) of the colorless dimer **22b** as the monohydrate, mp >300° (decomposes over a wide range, yellow at 120°, giving eventually a black powder); uv (water): λ max 283.5 nm (ε 7,800), λ min 248.5 (ε 2,500); ^{1}H nmr (DMSO-d_6): exchangeable protons at δ 11.24 (1H, s, NH), 10.83 (1H, s, NH), 7.52 (1H, s, OH), 7.07 (1H, s, OH); sugar hydroxyls at 5.48 (1H, d, J = 4.3), 5.30 (1H, d, J = 6.1), 5.22 (1H, d, J = 5.8), 5.09 (1H, d, J = 5.2); ^{1}H nmr (pyridine-d_5): δ 6.73 and 6.55 (two 1H s, H—A and H—A'), 5.27 and 5.15 (two 1H s, H—D and H—D'), 4.84 (2H, s), 5.02 and 4.95 (two 1H, d, J = 5.8, H—B, H—C, H—B' and H—C'), 3.84 and 3.45 (two 1H d, J = 10.4, H—4' and H—3').

Anal. Calcd. for $C_{18}H_{16}N_4O_{13}\cdot H_2O$: C, 41.87; H, 3.90; N, 10.85. Found: C, 41.67; H, 3.91; N, 10.93.

REFERENCES AND NOTES

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(8) It is conceivable that the ring-contraction could be a true benzilic-acid type of rearrangement in which abstraction of one of the 5-hydroxyl protons of **6** and migration of the 4,5-bond would also lead to **7**. However, we prefer the mechanism shown in Scheme 2 because the related ring contraction of alloxan to alloxanic acid proceeds with C—N bond migration. See G. M. Badger and J. W. Clarke-Lewis, "Molecular Rearrangements", P. de Mayo, ed, Wiley Interscience, New York, NY, 1963, Part 1, chapter 10.

(9) Although hardly of preparative importance, the dimer **6** is also formed in substantial amounts when the diol **11** is simply melted (195°) and heated to 200° for five minutes.

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(11) In practice, reduction of the phosphate ester **18** (unlike the corresponding mesyl ester, reference 12b) does not result in 5-deoxygenation.

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(13) If either C—3' or C—4' of **22a,b** had the opposite configuration, then the appropriate coupling constant ($J_{3',D}$ or $J_{4',D'}$) would have a substantial value. In fact, the analogous $J_{4',5'}$ value in **18**, which has the opposite configuration, is 7.6 Hz; see references 12b-12d for similar examples.

(14) On addition of 5 μl of 1*N* sodium hydroxide to 4 ml of a 5.2×10^{-5} *M* solution of **18**, the uv absorption shifts immediately to λ max 237 nm (ε 8,600), λ min 214 (ε 4,200). The reaction is analogous to the conversion of **1** into **3** (see reference 2).