Carbocyclic Analogs of Anhydrothymidines

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The carbocyclic analog of thymidine (C-Thymidine, **2**) was converted to the analog of 3'-(*O*-methanesulfonyl)-5'-*O*-tritylthymidine, which was cyclized in alkaline solution or with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) to the carbocyclic analog of 5'-*O*-trityl-2,3'-anhydrothymidine (**6**). Hydrolysis of the latter compound produced the carbocyclic analog of all-*cis*-thymidine. C-Thymidine was also converted to the carbocyclic analog of 3'-*O*-acetyl-2,5'-anhydrothymidine (**12**) by treating the 5'-*O*-methanesulfonyl analog with DBU. Hydrolysis of the anhydro derivative gave back C-thymidine. The carbocyclic analog (**3**) of 3'-deoxy-2'-hydroxythymidine was converted similarly to the corresponding 2,2'-anhydrothymidine (**15**) and 2,5'-anhydrothymidine (**21**) analogs. As expected, C-5'-*O*-trityl-2,2'-anhydrothymidine formed more readily than did the 2,3'-anhydrothymidine analog. Hydrolysis of these 2,2'- and 2,5'-anhydrothymidine analogs gave, respectively, the carbocyclic analog of all-*cis*-3'-deoxy-2'-hydroxythymidine and **3**.

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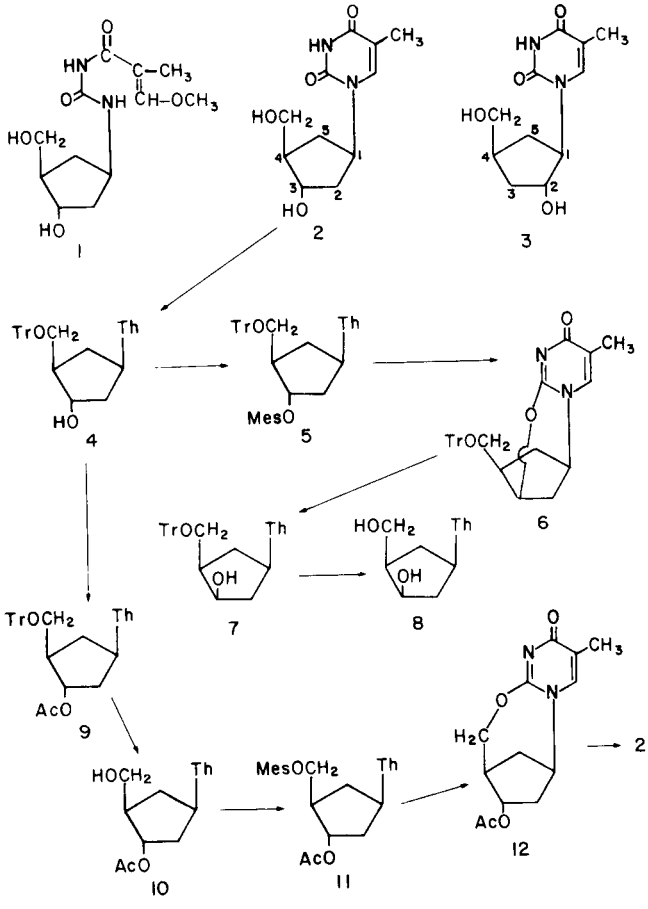
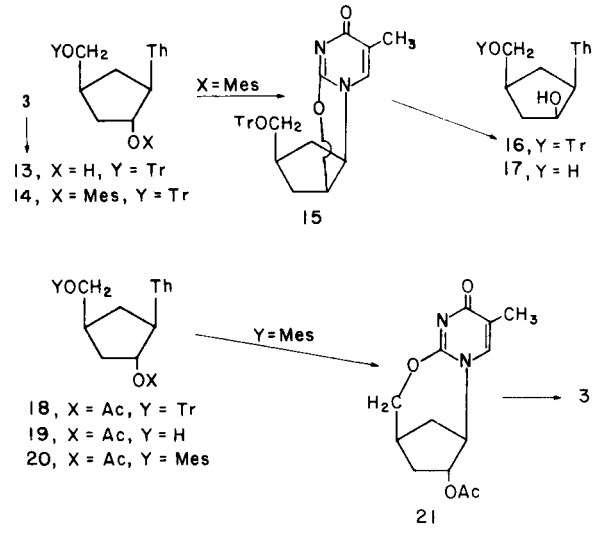
The carbocyclic analog (**2**, C-thymidine) (1) of thymidine was synthesized by cyclization of the 3-methoxy-2-methylacryloylurea (**1**) formed from 3-methoxy-2-methylacryloyl isocyanate and (±)-(1α,2β,4α)-4-amino-2-hydroxycyclopentanemethanol (2,3). Several related 1-substituted thymines were synthesized similarly (3). The method of synthesis was one of the routes to uracil nucleosides and other 1-substituted 2,4(1*H*,3*H*)-pyrimidinediones devised by G. Shaw and co-workers (4,5). The required aminocyclopentane was synthesized by stereospecific routes from *exo*-norbornenol (6,7). Earlier, a synthesis of C-thymidine by a Prins reaction of 1-(3-cyclopentenyl)thymine had been reported (8). The assignment of the structure was based on the formation of anhydro derivatives from methanesulfonyl derivatives of the hydroxymethyl and the hydroxy groups. These anhydro derivatives were believed to be the carbocyclic analogs (**6,12**) of 2,3'-anhydrothymidine and 2,5'-anhydrothymidine derivatives (1). Since this body of chemical evidence was analogous to that used in the original structure elucidation of thymidine (9) and to the formation of 5'-*O*-trityl-2,3'-anhydrothymidine (10-12), it appeared to be very good evidence that the Prins reaction product was, indeed, C-thymidine. Consequently, we subjected C-thymidine (**2**) obtained (2,3) *via* the Shaw route (**1**) to the same sequences of reactions. During the course of this study, it became evident that the Prins reaction and the Shaw route had produced two different 1-[hydroxy(hydroxymethyl)cyclopentyl]thymines, and this fact was confirmed by direct comparison of the two compounds (3). We describe here our studies of the conversions of C-thymidine (**2**, synthesized by the Shaw route) and C-3'-deoxy-2'-hydroxythymidine (**3**) to anhydronucleoside analogs (**6, 12, 15, 21**), together with hydrolyses of the anhydro derivatives to the all-*cis* isomers (**8, 17**) or to the original carbocyclic analogs (**2, 3**).

The trityl (**4**) and mesyl-trityl (**5**) derivatives of C-thymidine (**2**) were prepared by conventional procedures. Treatment of the mesyl-trityl derivative (**5**) with 1.1 equivalents of sodium hydroxide in 90% ethanol and isolation of the product by preparative thin-layer chromatography afforded C-5'-*O*-trityl-2,3'-anhydrothymidine (**6**) in 62% yield, whereas treatment of **5** with an excess of alkali under similar conditions furnished, after preparative tlc, both **6** (41% yield) and **7** (37% yield). Longer treatment of **6** with more concentrated ethanolic sodium hydroxide produced **7**, and deblocking of the latter compound furnished the carbocyclic analog (**8**) of all-*cis*-thymidine. Cyclization of **5** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in acetonitrile, a method known to form 2,3'- and 2,5'-anhydrothymidine derivatives from mesylates (12,13), readily produced the anhydrothymidine analog **6**. The conversion of C-thymidine (**2**) to a 2,5'-anhydrothymidine analog proceeded through the trityl (**4**), trityl-acetyl (**9**), acetyl (**10**), and mesyl-acetyl (**11**) derivatives. Attempts to cyclize the mesyl-acetyl derivative (**11**) by the procedure [methyldiisopropylamine in dimethylformamide at 100° for 4 hours (8)] used to form an anhydro derivative from the Prins reaction product met with little, or no, success. Mass spectral analysis of the material obtained after these conditions had been applied showed that it was the starting materal

(**11**) containing a small amount of acetyl derivative **10**. A weak peak (m/e 264) corresponding to the molecular ion of **12** was present, but the spectrum of untreated **11** includes this peak, which corresponds to the loss of methanesulfonic acid. Prolonging the reaction time did not significantly alter the results. (The acetyl derivative (**10**) might have been formed by hydrolysis of **12** *in situ* if small amounts of water were present.) In contrast, treatment of **11** with DBU readily formed the anhydro derivative **12**; alkaline hydrolysis of **12** gave **2**, completing and confirming the cycle *via* **4** and **9-12**.





Tr (trityl) = triphenylmethyl
Mes (mesyl) = methanesulfonyl

Analogous sequences of steps were carried out beginning with C-3'-deoxy-2'-hydroxythymidine (**3**). However, in the route (**13-17**) to the all-*cis* isomer (**17**), cyclization of the C-2'-*O*-mesyl derivative (**14**) to the C-2,2'-anhydro derivative (**15**) was especially facile, as expected. In fact, a pure specimen of **14** was not obtained. The material isolated after treatment of trityl derivative **13** with methanesulfonyl chloride in pyridine by the usual procedure was **14** containing some of the anhydro derivative (**15**). Attempts to purify **14** were not successful because of the cyclization reaction. Treatment of a mixture of **14** and **15** with 1.2 equivalents (based on pure **14**) of 0.1 *N* sodium hydroxide in aqueous ethanol furnished a product containing the desired anhydro derivative and a considerable amount of the trityl all-*cis* isomer (**16**). (Since the material treated with 0.1 *N* sodium hydroxide already contained **15**, the amount of base was actually greater than the

Table I

^{1}H-NMR Spectra of Carbocyclic Analogs of Thymidine (a)

Assignments Positions of Protons (b)	**2**	**8**	**3**	**17**
5 (*cis* to Th)	1.1-1.7 (1, m)	1.2-1.7 (1, m)		1.1-1.5 (1, m)
5 + 3 + 4			1.1-2.4 (5, m)	
5 (*trans* to Th) + 2 + 4	1.7-2.3 (4, m)	1.7-2.5 (4, m)		
5 (*trans* to Th) + 3 + 4				1.5-2.3 (4, m)
CH_3	1.78 (3, s)	1.78 (3, s)	1.80 (3, s)	1.79 (3, s)
CH_2OH	3.45 (2, m)	3.52 (2, m)	3.34 (2, m)	3.42 (2, m)
3 (*CH*OH)	3.98 (1, m)	4.13 (1, m)		
2 (*CH*OH)			4.17 (1, m)	4.05 (1, m)
Primary OH	4.55 (1, t)	4.33 (1, t)	4.57 (1, t)	
Secondary OH	4.67 (1, d)	4.92 (1, d)	4.99 (1, d)	
Primary + Secondary OH				4.86 (2, br)
1	4.96 (1, m)	5.00 (1, m)	4.48 (1, m)	4.48 (1, m)
Pyrimidine CH	7.52 (1, s)	7.73 (1, s)	7.54 (1, s)	7.49 (1, s)
NH	11.13 (1, s)	11.16 (1, s)	11.14 (1, s)	11.1 (1, s)

(a) Chemical shifts are in parts per million downfield from internal tetramethylsilane. The number of protons and the multiplicity are given in parentheses. Spectra were determined at 100.1 MHz from DMSO-d_6 solutions. (b) The numbers represent the numbered positions on the cyclopentane ring of structures **2** and **3**.

nominal 1.2 equivalents.) Treatment of the mixture of **14** and **15** with stronger base afforded pure **16**; the overall yield of crude **16** from **13** was 86%. A pure specimen of anhydro derivative **15** was isolated after treatment of a mixture of **14** and **15** with DBU. The all-*cis* isomer (**17**) of **3** was obtained by the usual removal of the trityl group with aqueous acetic acid.

Reactions in the sequence **13→18→19→20→21** proceeded as expected. The 2,5'-anhydro derivative (**21**) was formed by treating **20** with DBU; and, again, the cycle beginning with **3** and proceeding through **18**, **19**, **20**, and **21** was completed by hydrolyzing **21** back to **3**.

Data from nmr spectra of thymine derivatives **2**, **3**, **8**, and **17** are summarized in Tables I (^{1}H-nmr) and II (^{13}C-nmr). Comparison of the chemical shifts of CH protons at position 1 and at position 2 or 3 (C*H*OH) with the chemical shifts of the corresponding protons in model compounds were made previously (3). In the ^{13}C-nmr spectra of **2** and **8**, the chemical shifts of C1 (position 1), which has two adjacent methylene groups, are upfield from the chemical shifts of C1 of **3** and **17**, which has an adjacent CHOH group. The CH at position 4 (C4) of **3** and **17** has two adjacent methylene groups, and appears upfield from C4 of **2** and **8**, which has an adjacent CHOH. Also, C3 of **3** and **17** has only one adjacent deshielding substituent and appears upfield relative to C2 of **2** and **8**, which has two deshielding substituents on the adjacent carbons. These upfield locations are consistent with the expectation that carbon atoms with adjacent -CH_2- or -CH-CH_2- groups will have chemical shifts upfield relative to those in an environment with deshielding groups at adjacent positions.

Table II

^{13}C-NMR Spectra of Carbocyclic Analogs of Thymidine (a)

Carbon Atom	**2**	**8**	**3**	**17**
CH_3	11.97	12.28	11.92	12.07
CH_2, position 5 (b)	32.30	32.94	31.02	29.70
CH_2, position 2 (b)	38.64	41.78		
CH_2, position 3 (b)			34.54	35.93
CH, position 4	48.93	47.02	35.44	36.60
CH, position 1	53.25	52.52	62.98	58.08
CH_2OH	62.69	60.09	65.06	65.46
CHOH, position 3	71.38	70.06		
CHOH, position 2			72.15	69.17
Pyrimidine C5	109.03	109.26	108.74	106.67
Pyrimidine C6	137.62	138.13	138.07	139.52
Pyrimidine C2	150.94	150.97	151.20	151.33
Pyrimidine C4	163.64	163.61	163.70	163.85

(a) Chemical shifts are in parts per million downfield from internal tetramethylsilane. Spectra were determined at 25.2 MHz from DMSO-d_6 solutions. The positions of the carbon atoms in the cyclopentane ring are shown in structures **2** and **3**. (b) These assignments of chemical shifts to position 5 and position 2 or 3 might be interchanged. If this interchange is made, the chemical shifts of the CH_2 groups at position 3 of **3** and **17** are still upfield, as mentioned in the text, from those of the CH_2 groups at position 2 of **2** and **8**.

The chemical shift of the CH_2OH carbon of **8** shows the expected upfield shift from that of **2**; this difference is attributable to the well-known shielding effect of an hydroxyl group in the γ position on the same side of the cyclopentane ring. No such difference is observed in **3** and **17** where neither compound has a *cis* hydroxyl γ to the CH_2OH carbon.

The four sequences represented by **2-12** and by **3** and **13-21** served a three-fold purpose: they confirmed with chemical evidence the structural assignments of **2** and **3** based on the synthesis routes and nmr data (2,3), they provided the all-*cis* isomers (**8** and **17**) for biological evaluation, and they furnished intermediates (**5**, **6**, **12**, **15**, and **21**) for syntheses of additional carbocyclic analogs of pyrimidine nucleosides.

We postulated (3) that the Prins reaction product (**8**) might have one of the structures that could be formed if the double bond of the precursor cyclopentenylthymine shifted from position 3 to position 2 during the Prins reaction. Recently, Murdock and coworkers (14) have obtained X-ray crystallographic evidence that the Prins reaction product is (±)-(1α,3β,4β)-1-[3-hydroxy-4-(hydroxymethyl)-cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione; *i.e.*, **2** with the hydroxymethyl group on the opposite side of the plane of the cyclopentane ring from the thyminyl group.

EXPERIMENTAL

General.

Unless otherwise stated, decomposition and melting temperatures were determined in capillary tubes heated in a Mel-Temp apparatus. Ultraviolet spectra (uv) were recorded with a Cary Model 17 spectrophotometer, and maxima are reported in nanometers; sh = shoulder. Aqueous solutions for ultraviolet determinations were prepared by diluting a 5-ml aliquot portion of an ethanol solution to 50 ml with 0.1 *N* hydrochloric acid, phosphate buffer (*p*H 7), or 0.1 *N* sodium hydroxide; absorption maxima of these solutions are reported as being determined in 0.1 *N* hydrochloric acid, at *p*H 7, or in 0.1 *N* sodium hydroxide, respectively. Infrared spectra (ir) were recorded with Perkin-Elmer Model 621 or Nicolet MX-1E spectrometers from samples in potassium bromide disks; s = strong, w = weak, sh = shoulder. Mass spectral data (ms) were taken from low resolution spectra determined at 70 eV with a Varian/MAT Model 311A spectrometer equipped with a combination electron-impact, field-ionization, and field-desorption ion source. The peaks listed are those due to the molecular ion (M), those attributable to the loss of certain fragments from the molecular ion (M - fragment), and some other prominent peaks; Th = thyminyl ($C_5H_5N_2O_2$). Nuclear magnetic resonance spectra were determined with a Varian Model XL-100-15 spectrometer operating at 100.1 MHz for proton (^{1}H-nmr) and at 25.2 MHz for carbon-13 (^{13}C-nmr) spectra. The positions of the cyclopentyl protons and carbon atoms are shown on structures **2** and **3**. The internal standard was TMS; s = singlet, d = doublet, m = multiplet. Thin-layer chromatography (tlc) was performed on plates of silica gel (15), and developed plates were examined by uv light (254 nm). Other pertinent information (amount applied, developing solvent, other methods of detection) are given parenthetically at the appropriate places in the experimental procedures.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-[(triphenylmethoxy)methyl]cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**4**).

A mixture of 1.50 g of the carbocyclic analog of thymidine (**2**), 1.79 g of triphenylmethyl chloride, and 44 ml of anhydrous pyridine was stirred at room temperature for 13 days. The reaction mixture was poured into a water-ice mixture (300 ml), the mixture (including a gummy precipitate) was stored in a refrigerator, and the supernatant solution was decanted from the gummy precipitate. The precipitate was washed with water, dried, and dissolved in hot methanol (45 ml), and the hot solution was filtered. White crystals were collected from the cool solution, washed with cold methanol, and dried at 78° *in vacuo*: yield, 2.63 g (87%); mp 230-233°; uv (methanol): λ max 271 (ε 9800); ir: (1800-1200 cm^{-1} region) 1680 s, 1595 w, 1510 w, 1490, 1480, 1470 sh, 1445, 1440, 1425, 1410, 1395, 1385, 1370, 1325, 1315 sh, 1295, 1280, 1265 sh, 1255 sh, 1225; ms: (direct-probe temperature, 210°) m/e 482 (M), 481 (M − 1), 465 (M − OH), 405 (M − C_6H_5), 367, 259 (triphenylmethoxy), 243 (triphenylmethyl), 239 (M − triphenylmethyl), 228, 223 (M − triphenylmethoxy), 221 (M − H_2O − triphenylmethyl), 215, 165, 153 (Th + C_2H_4), 127 (Th + 2H), 126 (Th + H); ^{1}H-nmr (DMSO-d_6): δ 1.3-2.4 (m, CH_2 and CH at positions 2, 4, 5), 1.75 (s, pyrimidine CH_3), 2.8-3.4 (m, CH_2O), 4.03 (m, CH at position 3), 4.83 (m, OH), 4.95 (m, CH at position 1), 7.1-7.6 (m, trityl and pyrimidine CH), 11.2 (NH).

Anal. Calcd. for $C_{30}H_{30}N_2O_4 \cdot H_2O$: C, 71.98 H, 6.04; N, 5.60. Found: C, 71.94; H, 6.44; N, 5.35.

After this material had been dried at 135° for 2 hours, analytical data indicated less hydration.

Anal. Calcd. for $C_{30}H_{30}N_2O_4 \cdot \frac{1}{4}H_2O$: C, 73.97; H, 6.31; N, 5.75. Found: C, 73.28; H, 6.66; N, 5.66.

(±)-5-Methyl-1-[(1α,3β,4α)-3-(methanesulfonyloxy)-4-[(triphenylmethoxy)-methyl]cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (**5**).

Methanesulfonyl chloride (0.1 ml) was added to a cold (0°) solution of 200 mg of the trityl-thymidine analog (**4**) in 3 ml of dry pyridine. The reaction mixture was kept at 0° overnight, a small amount of water (0.1 ml) was then added, and the solution was stirred for 1 hour at 0° and poured into a water-ice mixture (25 ml). A white precipitate was collected by filtration, washed thoroughly with water; and dried *in vacuo*; weight, 218 mg (94%). A mixture of ethyl acetate and cyclohexane was added to and evaporated from the crude product. A solution of the glassy residue in ethyl acetate (2 ml) was diluted with an equal volume of cyclohexane and stored in a refrigerator. The white crystalline product was separated by filtration, washed with cyclohexane, and dried *in vacuo* at 56°: yield, 180 mg (78%); mp 168-172°; tlc 1 spot (40 mcg, 99:1 chloroform:-methanol); field desorption ms: (14 mA; solvent, DMSO) m/e 560 (M), 465 (M − OSO_2CH_3). The ir spectrum included strong pyrimidine carbonyl bands at 1700 and 1660 cm^{-1} and a medium band at 1735 cm^{-1} due to the presence of ethyl acetate.

Anal. Calcd. for $C_{31}H_{32}N_2O_6S \cdot 1/10C_2H_5OCOCH_3$: C, 64.79; H, 6.21; N, 4.32. Found: C, 64.90; H, 6.36; N, 4.26.

Carbocyclic Analog (**6**) of 2,3′-Anhydro-5′-*O*-tritylthymidine.

Procedure A.

A solution of 150 mg of methanesulfonate **5**, 30 ml of ethanol, and 3 ml of 0.1 *N* sodium hydroxide (1.1 equivalents) was boiled under reflux for 0.5 hour and then concentrated to dryness *in vacuo*. An ethanol solution of the residual gum was applied to a preparative tlc plate of silica gel, the plate was developed in 9:1 chloroform:methanol, and the product band was removed and extracted in a Soxhlet extractor with ethanol. The extract was concentrated to dryness, the residual white solid (122 mg) was dissolved in ethanol (4 ml), the mixture was filtered to remove a slight turbidity, and the filtrate was heated and diluted with cyclohexane. A white crystalline precipitate was separated by filtration, washed with cyclohexane, and dried *in vacuo*: weight, 77 mg (62%); mp 261-263°; tlc, 1 spot (40 mcg, 95:5 chloroform:methanol); ms: (direct-probe temperature, 120°) m/e 464 (M), 387 (M − C_6H_5), 243 (trityl), 239, 228, 221 (M − trityl), 165, 127 (Th + 2H), 126 (Th + H); ir: (1800-1300 cm^{-1} region) 1660 s, 1630 sh, 1620, 1565 w, 1520 s, 1485 s, 1475, 1450, 1425, 1390, 1380, 1350 w, 1320, 1310; ^{1}H-nmr (DMSO-d_6): δ 1.3-2.8 (m, CH_2 and CH at positions 2, 5, 4), 1.74 (s, pyrimidine CH_3), 2.8-3.4 (m), 4.37 (m), 5.14 (m), 7.1-7.6 (m, trityl and pyrimidine CH); ^{13}C-nmr (DMSO-d_6): δ 13.06, 32.88, 35.17, 43.17, 60.12, 62.11, 80.27, 86.16, 116.43, 126.85, 127.77, 128.20, 137.40, 143.62, 153.46, 170.79.

Anal. Calcd. for $C_{30}H_{28}N_2O_3 \cdot \frac{1}{4}C_2H_5OH$: C, 75.80; H, 6.56; N, 5.61. Found: C, 75.99; H, 6.33; N, 5.79.

Procedure B.

To a suspension of 215 mg (0.383 mmole) of **5** in 20 ml of dry acetonitrile was added 64 mg (0.422 mmole) of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (12,13). The mixture became homogeneous when DBU was added, and the tlc of an aliquot portion indicated that most of **5** was converted to **6** within 15 minutes. The solution was boiled under reflux for 17 hours and concentrated to dryness *in vacuo*, the residue was triturated with acetone (4 ml), and the mixture was refrigerated. White crystals were separated by filtration, washed with cold acetone, and dried *in vacuo* at 56°: yield, 137 mg (77%); tlc, moved with the specimen obtained by Procedure A; uv (ethanol): λ max 257 (ε 7300); ms: (direct-probe temperature, 250°) m/e 464 (M), 387 (M − phenyl), 243 (trityl), 241, 239, 228, 221 (M − trityl), 165, 152, 151, 127 (Th + 2H). This specimen was a polymorphic form (mp 235-237°) of the specimen that crystallized from ethanol-cyclohexane (Procedure A). The solid-state ir spectra of the two specimens showed the same bands or clusters of bands, but there were differences in fine structure consistent with the differences in crystal form. The ^{1}H-nmr spectrum was identical with that of the specimen obtained by Procedure A.

Treatment of **5** With Excess Base. **6** + **7**.

A solution of 456 mg of **5**, 90 ml of ethanol, and 9 ml of 1 *N* sodium hydroxide (11.1 equivalents) was boiled under reflux for 0.5 hour, and **6** was isolated by preparative tlc as described above (Procedure A): yield, 156 mg (41%). Crude **7** (226 mg) was isolated similarly from a diffuse band on the preparative tlc plate between the band containing **6** and the solvent front. Recrystallization of the crude product twice from ethanol gave 103 mg of **7**, mp 213-215°, identified by its ir and mass spectra (below). Additional **7** (40 mg) was isolated by preparative tlc of the filtrate from the first recrystallization (total yield, 37%).

(±)-1-(1α,3α,4α)-3-Hydroxy-4-[(triphenylmethoxy)methyl]cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**7**).

To a boiling solution of 148 mg of **6** in 9 ml of ethanol was added 6 ml of 1 *N* sodium hydroxide. The solution was boiled under reflux for 2 hours, diluted with water (5 ml), concentrated *in vacuo* to remove ethanol, and neutralized (*p*H 6) with acetic acid. The white precipitate was separated by filtration, washed thoroughly with water, and dried *in vacuo*: yield 108 mg (70%); mp 208-216°. Recrystallization of a specimen of **7** from ethanol afforded white crystals: recovery, 79%; mp 213-215°, tlc, 1 spot (20 mcg, 95:5 chloroform-methanol); ms: (direct-probe temperature, 220°) m/e 483 (M + 1), 481 (M − 1), 405 (M − C_6H_5), 367, 328 (M − $2C_6H_5$), 259 (triphenylmethoxy), 243 (trityl), 239 (M − trityl), 228, 223 (M − triphenylmethoxy), 221 (M − H_2O − trityl), 215, 183, 165, 153 (Th + C_2H_4), 127 (Th + 2H), 126 (Th + H); ir: (1800-1200 cm^{-1} region) 1695 s, 1655 s, 1630 s, 1595 sh, 1480 (broad), 1445, 1425, 1410, 1395, 1385, 1365, 1350 sh, 1310, 1295, 1275, 1235, 1210 (broad).

Anal. Calcd. for $C_{30}H_{30}N_2O_4 \cdot \frac{1}{4}C_2H_5OH$: C, 74.14; H, 6.42; N, 5.67. Found: C, 74.10; H, 6.32; N, 5.61.

(±)-1-[(1α,3α,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**8**).

A solution of 105 mg of the trityl all-*cis*-thymidine analog (**7**) in 6 ml of 80% acetic acid was heated at 100° for 15 minutes and then concentrated to dryness *in vacuo*. An ethanol solution of the residue was applied to a preparative tlc plate of silica gel, the plate was developed in 9:1 chloroform:methanol, the product band was removed and extracted in a Soxhlet extractor with ethanol, and the filtered extract was concentrated to a gummy solid. An ethanol-ether (1:2) solution of the residue was filtered to remove a small amount of silica gel and evaporated to dryness. Careful

addition of hot cyclohexane (2 ml) to a hot ethanol (2 ml) solution of the residue caused precipitation of white crystals, which were filtered from the chilled mixture, washed with cyclohexane, and dried *in vacuo* at 78°: yield, 24 mg (46%); mp 177-180°; tlc, 1 spot (80 mcg, 9:1 chloroform:methanol); ms: (direct-probe temperature, 20°) m/e 240 (M), 222 (M − H_2O), 204 (M − $2H_2O$), 203, 196, 181, 153 (Th + C_2H_4), 138, 127 (Th + 2H), 126 (Th + H); ir: (1800-1200 cm^{-1} region) 1680 s, 1650, 1515 w, 1475, 1460 sh, 1450 sh, 1440 w, 1425, 1395, 1380 sh, 1365 w, 1345, 1320, 1280, 1245 w, 1235; nmr, see Tables I and II.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.69; H, 6.96; N, 11.28.

(±)-1-[(1α,3β,4α)-3-(Acetyloxy)-4-[(triphenylmethoxy)methyl]cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**9**).

A solution (protected from atmospheric moisture) of 275 mg of **4**, 0.66 ml of acetic anhydride, and 2.75 ml of anhydrous pyridine was stirred at room temperature for 22 hours. The reaction solution was poured slowly into a water-ice mixture (50 ml), and the white precipitate was collected by filtration, washed thoroughly with water, and dried *in vacuo* at 56° for 4 hours; weighted, 292 mg. Since mass spectral analysis showed that this material, probably a hydrate, was **9** and since tlc indicated that it was homogeneous, it was used to prepare **10**. Another specimen prepared in the same way was recrystallized from methanol. It liquified at 98-102°, resolidified, and remelted at 186-188°; ir: (1800-1200 cm^{-1} region) 1785 w, 1730, 1680 s, 1595 w, 1490, 1470, 1450, 1365, 1310, 1240 s; ms: (direct-probe temperature, 150°) m/e 524 (M), 523 (M − 1), 464 (M − HOAc), 447 (M − phenyl), 387 (M − phenyl − HOAc), 281 (M − triphenylmethyl), 265 (M − triphenylmethoxy), 259, 243 (base peak, triphenylmethyl), 221, 165.

Anal. Calcd. for $C_{32}H_{32}N_2O_5 \cdot \frac{1}{4}H_2O$: C, 72.64; H, 6.19; N, 5.29. Found: C, 72.65; H, 6.28; N, 5.28.

(±)-(1α,3β,4α)-1-[3-(Acetyloxy)-4-(hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**10**).

A solution of 1.30 g of **9** in 5.25 ml of 80% acetic acid was boiled under reflux for 10 minutes, cooled to room temperature, and diluted with cold water (100 ml). Triphenylmethanol was removed by filtration, and the filtrate was concentrated to dryness *in vacuo*. Hot ethyl acetate was added to the residual syrup, the turbid mixture was filtered, the hot filtrate was diluted with cyclohexane, and the resulting solution was seeded with previously obtained **10** and refrigerated. The crystalline precipitate was collected by filtration, washed with cyclohexane, and dried *in vacuo* at 56°: yield, 568 mg (81%); mp 142-146°; uv: λ max 272 (ε 10,300) at *p*H 1 and *p*H 7; ms: (direct-probe temperature, 20°) m/e 283 (M + 1), 282 (M), 264 (M − H_2O), 251 (M − CH_2OH), 222 (M − HOAc), 203, 191 (M − HOAc − CH_2OH); ^{1}H-nmr (DMSO-d_6): δ 1.4-2.34 (m, CH_2 at positions 2 and 5, CH at position 4), 1.78 (s, pyrimidine CH_3), 2.02 (s, acetyl CH_3), 3.5 (center of m, CH_2OH), *ca.* 4.5-4.85 (m, OH), 4.75-5.12 (m, CH at positions 1 and 3 read from DMSO-d_6 + deuterium oxide spectrum), 7.58 (approximate s, pyrimidine CH), 11.18 (NH of pyrimidine ring).

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.93. Found: C, 55.38; H, 6.47; N, 9.76.

(±)-1-[(1α,3β,4α)-3-(Acetyloxy)-4-[(methanesulfonyloxy)methyl]cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (**11**).

Methanesulfonyl chloride (1.47 ml) was added to a solution, cooled to 0°, of 500 mg of **10** in 8.7 ml of dry pyridine. The reaction solution was stirred at 0° overnight, diluted cautiously with a small amount of water, stirred 1.5 hours, and poured into a water-ice mixture (60 ml). The aqueous mixture was extracted with chloroform (3 × 75 ml), and the chloroform extract was dried (magnesium sulfate) and concentrated *in vacuo* to a viscous residue (510 mg). A chloroform (10 ml) solution of the residue was diluted with ethyl acetate (20 ml), the precipitate (220 mg, mp 154-157°) was separated, the filtrate residue was triturated with ethyl acetate, and a buff-colored solid (196 mg, mp 145-155°) was collected by filtration. Additional crude **11** (120 mg) was obtained by preparative tlc of the residue from the ethyl acetate filtrate as described for the purification of **9** except that methanol was both the application and the extraction solvent. The three portions were combined and chromatographed in 95:5 chloroform:methanol (application and elution solvent) on a column of silica gel. The product-containing eluate fractions, identified by tlc, were combined and concentrated *in vacuo* to a colorless gum; weight, 510 mg (80%); tlc 1 spot (40 or 80 mcg, 95:5 chloroform:methanol). Crystallization of amorphous **11** from chloroform:cyclohexane (1:2) afforded white crystals: mp 158-160°; ms: (direct-probe temperature, 20°) m/e 360 (M), 318 (M − acetyl + H), 300 (M − HOAc), 264 (M − CH_3SO_3H), 235 (M − Th), 223, 221, 203 (base peak), 191, 161, 153 (Th + C_2H_4), 148, 127 (Th + 2H), 126 (Th + H).

Anal. Calcd. for $C_{14}H_{20}N_2O_7S \cdot \frac{1}{4}H_2O$: C, 46.08; H, 5.66; N, 7.68. Found: C, 45.97; H, 5.58; N, 7.34.

Carbocyclic Analog (**12**) of 3′-(Acetyloxy)-2,5′-anhydrothymidine.

A solution of 510 mg (1.42 mmoles) of **11**, 238 mg (1.56 mmoles) of DBU, and 70 ml of dry acetonitrile was boiled under reflux for 17 hours, cooled, filtered, and concentrated *in vacuo* to a gummy solid. The residue was triturated with cold acetone, and a white solid was separated by filtration, washed with acetone, and dried *in vacuo* at 56°: yield, 247 mg (66%); mp 247-250° (inserted at 100°, 3°/minute), tlc, 1 spot (40 mcg, 95:5 chloroform:methanol) detected with uv and iodine vapor); uv: λ max 238 (ε 8400) and 250-255 (sh) in 0.1 *N* hydrochloric acid, 247 (ε 10,700) at *p*H 7, 243 (ε 12,100) in ethanol; ms: (direct-probe temperature, 150°) m/e 264 (M), 222, 221 (M − acetyl), 204 (M − HOAc), 126 (Th + H); ^{1}H-nmr (DMSO-d_6): δ 1.6-2.5 (m, CH_2 and CH at positions 2, 5, 4), 1.78 (s, pyrimidine CH_3), 2.01 (s, CH_3CO), 3.27 (H_2O), 3.8-4.6 (m, CH_2O), 4.56 (m, CH at position 1), 5.25 (m, CH at position 3), 7.65 (approximate s, pyrimidine CH).

Anal. Calcd. for $C_{13}H_{16}N_2O_4 \cdot \frac{1}{4}H_2O$: C, 58.09; H, 6.19; N, 10.42. Found: C, 58.41; H, 6.24; N, 10.81.

Hydrolysis of Anhydro Derivative **12** to C-Thymidine (**2**).

A solution of 6 mg of anhydro derivative **12** in 3 ml of 1 *N* sodium hydroxide was boiled under reflux for 2 hours, cooled and diluted to about 10 ml with water. The *p*H was lowered to 5 by adding a cation resin (Rexyn 101, H^+ form) to the stirring solution. The mixture was filtered and concentrated to dryness, the gummy residue was triturated with acetone to induce crystallization, and the mixture was concentrated to dryness: yield, 5 mg (94%); mp 222-224° (undepressed by **2**); tlc, moved with **2**. The ir spectrum was identical with that of previously synthesized **2** (2,3): 1680 s, 1640, 1530 w, 1515 w, 1480, 1430, 1405, 1375, 1340, 1310, 1290, 1270, 1250 w, 1240 w, 1220 w.

(±)-1-[(1α,2β,4α)-2-Hydroxy-4-[(triphenylmethoxy)methyl]cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**13**).

The trityl derivative of **3** was prepared by the procedure described for the preparation of **4**. The crude product (the gummy precipitate) was purified by preparative tlc as described for the purification of compound **6** (Procedure A): application solvent, methanol; developing solvent, 97:3 chloroform:methanol; extraction solvent, methanol. A methanol solution of the Soxhlet-extracted product was filtered to remove a small amount of silica gel and then concentrated to dryness. Trituration of the residue with ethyl acetate:cyclohexane (1:1) furnished **13**: yield, 72%; mp 217-223°; tlc, 1 spot (60 mcg, 98:2 chloroform:methanol); ms: (direct-probe temperature, 20°) m/e 483 (M + 1), 482 (M), 481 (M − 1), 464 (M − H_2O), 405 (M − phenyl), 387, 367, 354, 259 (triphenylmethoxy), 243 (triphenylmethyl), 239 (M − triphenylmethyl), 228, 223 (M − triphenylmethoxy), 221 (M − H_2O − triphenylmethyl), 215, 205, 165, 127 (Th + 2H); ir: (1800-1200 cm^{-1} region) 1700 s, 1680 s, 1665 sh, 1630, 1590, 1560 sh, 1515 w, 1485, 1480 sh, 1475, 1465 sh, 1445, 1425, 1410, 1380, 1370 sh, 1360, 1350 sh, 1335 w, 1315, 1295, 1285 w, 1260, 1215. From a larger run, **13** was isolated by chromatography in 98:2 chloroform:methanol on a column of silcia gel.

Anal. Calcd. for $C_{30}H_{30}N_2O_4$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.13; H, 6.43; N, 5.83.

(±)-5-Methyl-1-[(1α,2β,4α)-2-(methanesulfonyloxy)-4-[(triphenylmethoxy)-methyl]cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (**14**).

Methanesulfonate **14** was prepared from **13** (545 mg), methanesulfonyl chloride (0.28 ml), and dry pyridine (5.5 ml) by the procedure described for the preparation of **5**. The crude product (mp 128-133° dec) was dried *in vacuo* at 56° for 2 hours and at room temperature overnight; weight, 625 mg (98.7% yield calculated as **14**). Since the tlc indicated that this material was **14** containing a small amount of **15**, it was used without further purification for cyclization to **15** in alkaline solution (below). A field desorption mass spectrum (14 mA; DMSO as solvent) of the crude product showed only **15**, m/e 464 (M). It provided, therefore, additional evidence of the facility of the cyclization of **14** to **15** since the cyclization must have occurred during the determination.

(±)-1-[(1α,2α,4α)-2-Hydroxy-4-[(triphenylmethoxy)methyl]cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**16**) *via* **15**.

The specimen of crude **14** (620 mg) described above (containing a small amount of **15**) was dissolved in 50 ml of ethanol and 13.3 ml of 0.1 *N* sodium hydroxide (1.2 equivalents), and the solution was boiled under reflux for 45 minutes. The tlc of an aliquot removed after 15 minutes showed that **14** had disappeared and that **15** and a small amount of **16** had formed, and tlc after 45 minutes indicated that additional **16** had formed from **15**. The reaction mixture was concentrated under low pressure (oil pump) to a glassy residue. A field desorption mass spectrum showed the presence of both **15** and **16**, but indicated that **15** was present in greater amount: m/e 464 (M of **15**), 487 (464 + Na, very strong), 504 (Na salt of **16**); relative intensity 487 > 464 > 504. Because both tlc and the mass spectrum showed that some **16** had already formed, this material was used without purification for the preparation of **16**.

A solution of the glassy residue described above, 31 ml of ethanol, and 22 ml of 1 *N* sodium hydroxide was boiled under reflux for 2 hours, concentrated to remove methanol, neutralized (*p*H 5) with acetic acid, and refrigerated. A white precipitate was separated by filtration: washed thoroughly with water, and dried *in vacuo* at 56°; weight, 465 mg (86% yield from **13**); field desorption mass spectrum (16 mA, DMSO as solvent) m/e 505 (M + Na), 483 (M + H), 482 (M). This material, which was **16** containing a trace amount of **13** according to tlc, was recrystallized from methanol; weight, 236 mg (44% from **13**); mp 225-227°; tlc, 1 spot (40 mcg, 97:3 chloroform:methanol); ms: (direct-probe temperature, 180°) m/e 483 (M + H), 482 (M), 481 (M − H), 464 (M − H_2O), 405 (M − phenyl), 387, 367, 356, 259 (triphenylmethoxy), 243 (trityl), 239 (M − trityl), 228, 223 (M − triphenylmethoxy), 221 (M − H_2O − trityl), 215, 183, 178, 165, 127 (Th + 2H), 126 (Th + H); ir: (1800-1200 cm^{-1} region) 1685 s (broad), 1595, 1515 w, 1490, 1470, 1445, 1420, 1405 w, 1390, 1370, 1330, 1310, 1305 w, 1290, 1275, 1265, 1220.

Anal. Calcd. for $C_{30}H_{30}N_2O_4 \cdot \frac{1}{2}H_2O$: C, 73.30; H, 6.36; N, 5.70. Found: C, 73.16; H, 6.66; N, 5.68.

After a specimen had been dried at 110° for 3 hours, microanalytical data were in good agreement with unhydrated **16**.

Carbocyclic Analog (**15**) of 2,2'-Anhydro-3'-deoxy-5-methyl-5'-*O*-tritylthymidine.

A specimen of crude methanesulfonate (**14**), prepared as described above and again containing some **15** (according to tlc) was dissolved in 98:2 chloroform:methanol, and a solution was passed through a column of silica gel. The tlc of the eluted material indicated that it had been converted mainly to **15**. This mixture of **14** and **15** was treated with DBU as described for the preparation of **6** (Procedure B). The reaction residue was stirred with ether, the ether was decanted, and the solid residue was triturated with acetone. The solid was collected by filtration, washed sparingly with acetone, and dried *in vacuo* at 56°: mp 206-209°; tlc, 1 spot (40 mcg, 95:5 chloroform:methanol); ms: (direct-probe temperature, 20°) m/e 464 (M), 387 (M − phenyl), 243 (triphenylmethyl), 239, 228, 221 (M − trityl), 205, 165, 149.

Anal. Calcd. for $C_{30}H_{28}N_2O_3$: C, 74.98; H, 5.87; N, 5.83. Found: C, 74.68; H, 6.06; N, 5.64.

(±)-1-[(1α,2α,4α)-2-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**17**).

Compound **17** was prepared from **16** (385 mg) and purified by the procedure described for preparation of **8**. The following solvents were employed for the purification by preparative tlc (2 plates): application solvent, methanol; developing solvent, 5:1 chloroform:methanol; extraction solvent, ethanol. The ethanol extract was concentrated to dryness *in vacuo*, and the residual solid was redissolved in a small quantity of ethanol. The solution was filtered to remove a small amount of silica gel, concentrated to a low volume, diluted with ethyl acetate, and concentrated further. The white crystalline precipitate was collected by filtration: washed with ethyl acetate, and dried *in vacuo* at 56°; weight, 130 mg (68% yield); mp 208-210°. Recrystallization from ethanol afforded white crystals: recovery, 75%; mp 219-221°, tlc, 1 spot (80 mcg, 4:1 chloroform:methanol); uv: λ max 272 (ε 10,600) and 211 (ε 8400) at *p*H 1, 273 (ε 10,700) and 211 (ε 8400) at *p*H 7, and 271 (ε 8000) at *p*H 13; ms: (direct-probe temperature, 110°) m/e 240 (M), 222 (M − H_2O), 212 (M − CO), 191 (M − H_2O − CH_2OH), 153 (Th + C_2H_4), 127 (Th + 2H), 126 (Th + H); ir: (1800-1200 cm^{-1} region) 1680 s (broad), 1510 w, 1475, 1460, 1455 sh, 1425, 1390, 1375, 1345, 1320, 1315, 1300, 1280, 1265, 1235, 1225 sh; nmr, see Tables I and II.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.91; H, 6.71; N, 11.66. Found: C, 54.53; H, 6.94; N, 11.36.

(±)-1-[(1α,2β,4α)-2-(Acetyloxy)-4-[(triphenylmethoxy)methyl]cyclopentyl]-5-methyl-2,4-(1*H*,3*H*)-pyrimidinedione (**18**).

Acetyl derivative **18** was prepared by the procedure described for the preparation of **9**. The crude product (mp 221-224°) was used without purification for the preparation of **19**; ms: (direct-probe temperature, 240°), m/e 524 (M), 464 (M − HOAc), 447 (M − phenyl), 387 (M − phenyl − HOAc), 380 (M − 2 phenyl), 323, 281 (M − triphenylmethyl), 265 (M − triphenylmethoxy), 243 (triphenylmethyl), 221, 165; ir (1800-1200 cm^{-1} region) 1790 w, 1730 s, 1700 s, 1685 s, 1660, 1595 w, 1570 w, 1490, 1470 sh, 1460, 1450, 1440, 1420 w, 1385, 1370, 1320, 1295 w, 1265, 1250 s, 1230, 1215 sh.

(±)-1-[(1α,2β,4α)-2-(Acetyloxy)-4-hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**19**).

Compound **19** was prepared by the procedure described for the preparation of **10**. After removal of triphenylmethanol by filtration, the filtrate was concentrated to dryness *in vacuo*, and the colorless syrup was chromatographed in 95:5 chloroform:methanol on a column of silica gel. Fractions of the eluate containing **19** (determined by tlc) were combined and concentrated to dryness *in vacuo*. Trituration of the residue with ethyl acetate furnished white crystals: yield, 76%; mp 183-185°; tlc, 1 spot (40 mcg, 95:5 chloroform:methanol); ms: (direct-probe temperature, 20°) m/e 282 (M), 22 (M − HOAc), 191 (M − CH_2OH − HOAc), 153 (Th + C_2H_4), 127 (Th + 2H), 126 (Th + H); ir: (1800-1200 cm^{-1} region) 1725 s, 1695 s, 1650, 1515 w, 1475, 1435, 1400, 1390, 1375, 1360, 1340, 1320, 1300, 1275 s, 1255 s, 1205.

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.26; H, 6.69; N, 9.95.

(±)-1-[(1α,2β,4α)-3-(Acetyloxy)-4-[(methanesulfonyloxy)methyl]cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (**20**).

Methanesulfonate **20** was prepared by the procedure described for the preparation of **11**. The crude product was chromatographed in 95:5 chloroform:methanol (application and elution solvent) on a column of silica gel: yield, 86%; mp 195-198°; tlc, 1 spot (60 mcg, 95:5 chloroform:methanol); ms: (direct-probe temperature, 220°) m/e 360 (M), 300 (M − HOAc), 264 (M − CH_3SO_3H), 221, 204 (M − HOAc − CH_3SO_3H), 203, 191, 161, 153 (Th + C_2H_4), 148, 127 (Th + 2H), 126 (Th + H); ir: (strong bands only, cm^{-1}) 1725, 1710, 1675, 1660, 1350, 1250, 1175, 955, 835.

Anal. Calcd. for $C_{14}H_{20}N_2O_7S$: C, 46.65; H, 5.59; N, 7.77. Found: C, 46.59; H, 5.75; N, 7.95.

Carbocyclic Analog (**21**) of 2'-(Acetyloxy)-2,5'-anhydro-3'-deoxythymidine.

Anhydro derivative **21** was obtained by treating **20** with DBU as described for the formation of **12**: yield, 55%; mp 228-230°; tlc, 1 spot (60 mcg, 9:1 chloroform:methanol); uv: λ max 239 (ε 8300) and 250-255 (sh) in 0.1 *N* hydrochloric acid 248 (ε 11,000) at *p*H 7, 245 (ε 12,200) in ethanol; ms: (direct-probe temperature, 20°) m/e 264 (M), 222, 204 (M − HOAc), 149; ir: (1800-1200 cm^{-1} region) 1745 s, 1695 w, 1655 s, 1635 s, 1620, 1565 w, 1530 sh, 1525 s, 1475 s, 1450, 1395, 1390, 1375, 1360, 1330, 1310, 1290, 1280 w, 1260, 1240 sh, 1230 s, 1205.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.12; H, 6.23; N, 10.48.

Hydrolysis of **21** to **3**.

Anhydro derivative **21** was hydrolyzed to **3** by the procedure described for the alkaline hydrolysis of **12**. Ethyl acetate was added to and evaporated *in vacuo* from the residual product. The resulting white solid was dried *in vacuo* at 56°: yield, 66%; mp 202-204° (undepressed on admixture with a specimen of **3** (3)); tlc (40 mcg, 5:1 chloroform:methanol), 1 spot that moved identically with that of a specimen of **3**. The ir spectrum was identical to that of a specimen prepared by the Shaw method (3); 1695 sh, 1685 s, 1515 w, 1480, 1465, 1440, 1395, 1385, 1375, 1345, 1335, 1315, 1295 sh, 1285, 1265, 1240 w, 1225 w.

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REFERENCES AND NOTES

(1) The prefix C- means "carbocyclic analog of". For simplicity, the 3'-deoxynucleoside analog **3** is named C-3'-deoxy-2'-hydroxythymidine, and anhydro derivatives of this compound and of C-thymidine are named as anhydrothymidine derivatives although **6** and **15** are actually analogs of other deoxypentofuranosylthymines.

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(15) Silica Gel GF precoated thin-layer chromatography plates (fluorescent), 250 microns in thickness, were purchased from Analtech. Preparative tlc was performed with precoated plates of silica gel (Whatman PLK5F), 20 × 20 cm, 1 mm in thickness, purchased from Whatman, Inc., Clifton, NJ 07014.