Photo- and Stereochemistry of 5,6-Methylenepyrimidine Nucleosides, Bicyclic Isomers of Thymidine, and 5-Methyluridine

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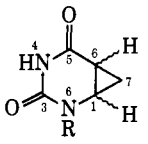
Abstract: Excess dimethyloxosulfonium methylide converted 1,3-dimethyl- or 1,3-dibenzyluracil, 1,3-dibenzylthymine, and 3-methyl- or 3-pivaloyloxymethyl(Pom)-2′,3′-*O*-isopropylidene-5′-*O*-trityluridine into the novel 2,4-disubstituted 2,4-diazabicyclo[4.1.0]heptane-3,5-diones which, as ribosides, were separable into diastereoisomers with the 1,6-hydrogens above (β) and below (α) the plane of the ring in a ratio of 7:3 (3-methyl substituent) or 5:4 (3-Pom substituent). The 3-Pom-5,6-methyleneuridines in aqueous alkaline dioxane solution opened up to the corresponding *cis*-2-ureidocyclopropane-1-carboxylic acids and as such became separable from the fully protected 3-Pom-uridine starting material. Recyclization with *N*-carbethoxy-2-ethoxy-1,3-dihydroquinoline, removal of all blocking groups by acid, and chromatography on silica gel gave 1-β-D-ribofuranosyl-5,6-cyclothymine, which on the basis of the positive Cotton effect of the ORD curve was assigned the 1*R*,6*S* configuration. Uv irradiation opened these bicyclic thymines and 5-cyclomethyluridines to 1(3)-(di)substituted seven-membered 1,5-dihydro-2*H*-1,3-diazepine-2,4(3*H*)-diones, easily convertible to the tetrahydro derivatives by catalytic hydrogenation. The cyclothymines and their nucleosides, in analogy to dihydropyrimidine nucleosides, opened up with alkali to *cis*-2-ureidocyclopropane-1-carboxylic acids, and underwent hydrogenolysis with sodium borohydride to *cis*-2-ureidocyclopropyl-1-carbinols. While these bicyclic isomers, hybrids between dihydrouridine and 5-(hydroxy)methyluridines (thymidines), show no direct effect *in vitro* in a number of virus and cancerous tissue cultures, they act as substrates or inhibitors for some enzymes involved in the biosynthesis or breakdown of nucleic acids.

Pyrimidine nucleosides and nucleotides modified at the 5,6-double bond play an increasingly important role as antivirus and anticancer agents. Template activity, photolesions and -dimerizations, ability to be incorporated into sRNA and DNA, and therefore potential cytotoxic activity, are intimately associated with the 5,6 unsaturation and substitution of pyrimidine nucleosides and nucleotides.[2,3]

In this regard 5,6-methylenepyrimidine nucleosides, bicyclic isomers of thymidine or 5-methyluridine, would be the missing intermediates between the 5,6-unsaturated and 5,6-dihydropyrimidine nucleosides.

In this paper, we describe the synthesis, resolution, and photorearrangements of the bicyclic isomers of thymines and 5-methyluridenes, whose skeletal name and numbering are as 2,4-diazabicyclo[4.1.0]-heptane-3,5-diones.

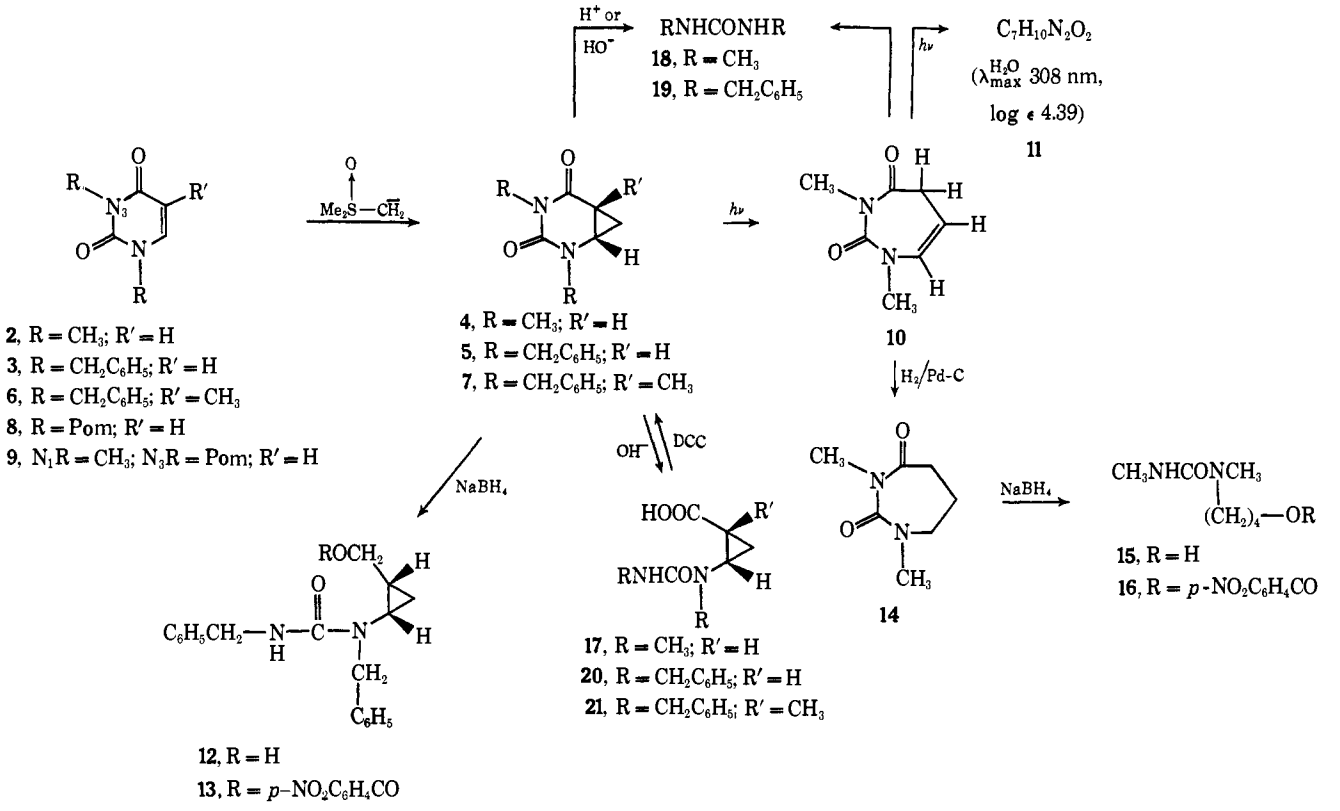


Dimethyloxosulfonium methylide (**1**),[4] in contrast to iodomethylzinc iodide,[5] reacted with the conjugated 5,-6-double bond of 1,3-dialkyluracils and -uridines and converted them into novel cyclopropane derivatives. In this way, 1,3-dimethyl- (**2**) and 1,3-dibenzyluracil (**3**), mp 76.5°, with excess ylide in tetrahydrofuran, gave 1,3-dimethylcyclothymine (**4**), mp 46°, *m/e* 154 (M^+), bp 120° (0.5 mm), and 1,3-dibenzylcyclothymine (**5**), mp 103°, *m/e* 306 (M^+), in 65 and 60% yields, respectively. Side products are 1,3-dimethylurea (**18**), mp 104°, and 1,3-dibenzylurea (**19**), mp 172°, which arise by alkaline hydrolysis of **4** and **5**, respectively. Excess sodium hydride in this reaction gave the substituted ureas in high yield. This provides an easy method for the direct conversion of pyrimidine nucleosides to urea derivatives, a reaction reminiscent of their hydrazinolysis.[6] The uv spectra of **4** and **5** (Figure 1A) showed no absorption maxima at 260 nm, and only slight shoulders at 250 and 225 nm, which straddled the absorptions of 1,3-dimethyluracil [$\lambda_{max}^{H_2O}$ 267 nm (log ϵ 3.93)][7] and of 5,-6-dihydrouracil [$\lambda_{max}^{H_2O}$ 222 nm (log ϵ 3.70)].[8] The nmr spectra of cyclothymines **4** and **5** displayed high-field peaks[9] characteristic of three-membered ring protons, in addition to methyl and benzyl protons (Table I). The signals of **4** appeared as multiplets at τ 9.23 ($H_{7\,endo}$), 8.64 ($H_{7\,exo}$), 7.88 (H_5), and 7.03 (H_6), in addition to the singlet at τ 6.86 (6 H) of the methyl protons with the coupling constants shown in Table I. The nmr spectral data of other cyclothymine derivatives are summarized in Table I.

The peaks due to the 1-benzylic methylene protons of **5** form an AB pattern (Figure 2) indicative of interaction with the three-membered ring. By contrast, 1,3-dibenzyl-5-methylcyclothymine (**7**) has a sharp singlet, probably because the 5-methyl group interferes with such an interaction. The steric hindrance of the 5-methyl group became evident when 1,3-dibenzylthymine (**6**), mp 93°, was converted to 1,3-dibenzyl-5-methylcyclothymine (**7**) in a reaction which was much less facile than the conversion of **3** → **5**.

The reaction of 1,3-bis(pivaloyloxymethyl)uracil (**8**), mp 86°, with the ylide, led to loss of one protective

(1) Fellow in the Visiting Program of the USPHS, 1966–1970.
(2) *Cf.* B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," Wiley, New York, N. Y., 1967.
(3) A. Goldin, H. B. Wood, Jr., and R. E. Engle, *Cancer Chemother. Rep.*, 1 (2), 1 (1968).
(4) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 87, 1353 (1965).
(5) H. E. Simmons and R. D. Smith, *ibid.*, 81, 4256 (1959).
(6) P. A. Levene and L. W. Bass, *J. Biol. Chem.*, 71, 167 (1926).
(7) S. Y. Wang, M. Apicella, and B. R. Stone, *J. Amer. Chem. Soc.*, 78, 4180 (1956).
(8) C. Janion and D. Shugar, *Acta Biochem. Polon.*, 7, 309 (1960).
(9) K. B. Wiberg and B. J. Nist, *J Amer. Chem. Soc.*, 85, 2788 (1963); *cf.* U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, 7, 588 (1968).



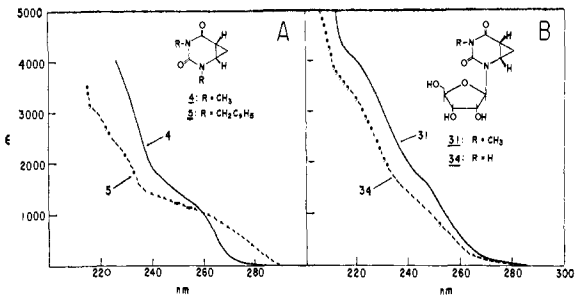


Figure 1. Ultraviolet spectra (ethanol) of 1,3-dimethyl- (**4**) and 1,3-dibenzylcyclothymine (**5**) (A) and of 1-β-D-ribofuranosylcyclothymine (**34**) and its 3-methyl homolog **31** (B) (water).

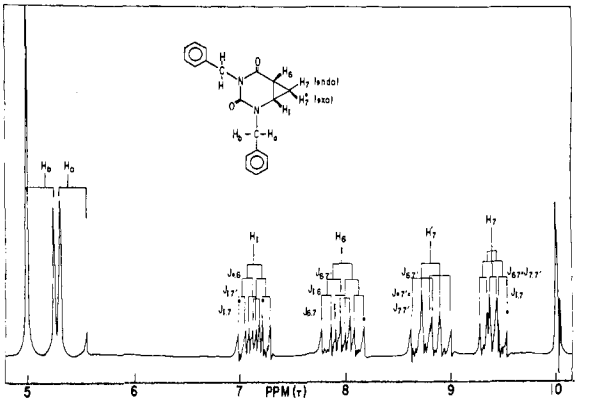


Figure 2. Nmr spectrum of 1,3-dibenzylcyclothymine (**5**) in $CDCl_3$.

group and gave 1-methyl-3-Pom[10]-uracil (**9**), mp 91°, as the major product (50% yield),[11] identical with the compound, mp 91°, prepared from 1-methyluracil and chloromethyl pivalate.

When an aqueous solution (4×10^2 *M*) of dimethylcyclothymine (**4**) was irradiated with a 450-W Hanovia high-pressure mercury lamp for 6 hr, instead of rearranging to a 6-methyluracil in analogy to the photorearrangement of bicyclo[4.1.0]heptan-2-one,[12] it underwent expansion to the seven-membered ring compound **10**, mp 63°, 45% yield,[13] *m/e* 154 (M^+), $\lambda_{max}^{H_2O}$ 225 nm (sh) (log ε 3.75), identified as 1,3-dimethyl-1,5-dihydro-2*H*-1,3-diazepine-2,4(3*H*)-dione on the basis of spectral data. In addition an unidentified isomer **11**, $C_7H_{10}N_2O_2$, mp 186°, $\lambda_{max}^{H_2O}$ 308 nm (log ε 4.39), was obtained in 12% yield. The latter was also obtained on separate uv irradiation of the former, indicative of the possibility of **10** as a precursor. The structure of the unconjugated diazepinedione **10** was supported by the nmr spectrum which showed methylene protons at τ 6.93 (2 H, doublet, J = 7.0 Hz) and olefinic protons at τ 4.52 (1 H, quartet, J = 7.0 Hz) and 3.93 (1 H, doublet, J = 7.0 Hz) in addition to methyl protons. This selective photorearrangement **4** → **10** indicates that the distorted conformation of **4** permits an easier overlap of the C_5–C_6 bond with the carbonyl π orbital than for the C_6–C_7 bond. The preferred position for photolytic cleavage becomes then the six- and not the three-membered ring, in contrast to bicyclo[4.1.0]ketones.[14]

(10) M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, **89**, 5439 (1967).

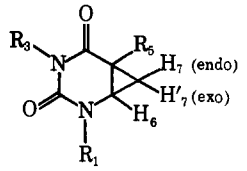
(11) *Cf.* H. Metzger, H. König, and K. Seelert, *Tetrahedron Lett.*, 867 (1964). N-Methylation of heterocyclic compounds with **1** is the subject of a separate report (T. Kunieda and B. Witkop, *J. Org. Chem.*, **35**, 3981 (1970).

(12) W. G. Dauben and G. W. Shaffer, *ibid.*, **32**, 4415 (1967).

(13) The corrected yields of **10** and **11** based on unrecovered starting material were 70 and 18%, respectively.

(14) O. L. Chapman, J. B. Sieja, and W. J. Welstead, Jr., *J. Amer. Chem. Soc.*, **88**, 161 (1965); L. D. Hess and J. N. Pitts, Jr., *ibid.*, **89**, 1973 (1967). There is no metastable photoproduct at 72°K observable on irradiation; we are indebted to Professor O. L. Chapman for arranging for this experiment.

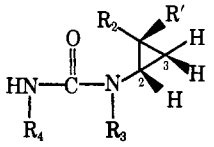
Table I. Nmr Spectra of Cyclothymine Derivatives[a]



Structures	H_7 (endo)	$H_{7'}$ (exo)	R_5	H_6	R_1, R_3
$R_1 = R_3 = CH_3$	9.23 sxt	8.64 sxt	7.88 oct	7.03 oct	6.86 s (6 H, s)
$R_5 = H$	$J_{7,6} = 4.0$	$J_{7,6} = J_{7,7} = 5.8$	$J_{5,7} = 5.8$	$J_{6,7} = 4.0$	6.83 (3 H, s) and
4[b]	$J_{7,5} = J_{7,7'} = 5.8$	$J_{7',5} = 10.5$	$J_{5,6} = 8.0$	$J_{6,7} = 5.8$	6.92 (3 H, s) in D_2O
			$J_{5,7'} = 10.5$	$J_{6,5} = 8.0$	
$R_1 = R_3 = CH_2C_6H_5$	9.40 sxt	8.81 sxt	7.98 oct	7.15 oct	5.38 (1 H, d, J = 15)
$R_5 = H$	$J_{7,5} = J_{7,7'} = 6.0$,	$J_{7',7} = J_{7',6} = 6.0$,	$J_{5,6} = 8.0$	$J_{6,5} = 8.0$	5.19 (1 H, d, J = 15)
5[b]	$J_{7,6} = 4.0$	$J_{7',5} = 10.5$	$J_{5,7} = 6.0$	$J_{6,7} = 4.0$	5.01 (2 H, s)
			$J_{5,7'} = 10.5$	$J_{6,7'} = 6.0$	2.69 (10 H, s)
$R_1 = R_3 = CH_2C_6H_5$	9.29 qu	9.00 t	8.73 s	7.31 qu	5.29 (2 H, s)
$R_5 = CH_3$	$J_{7,7'} = 6.0$	$J_{7',7} = J_{7',6} = 6.0$		$J_{6,7'} = 6.0$	4.99 (2 H, s)
7[b]	$J_{7,6} = 4.5$			$J_{6,7'} = 4.5$	2.67 (10 H, s)
R_1 = ribofuranosyl	8.99 sxt	8.45 sxt	7.75 oct	6.56 oct	
$R_3 = CH_3$	$J_{7,6} = 4.5$	$J_{7',6} = J_{7,7'} = 6.0$	$J_{5,7} = 6.0$	$J_{6,7} = 4.5$	4.05 (H_1', d, J = 6.0)
$R_5 = H$	$J_{7,5} = J_{7,7'} = 6.0$	$J_{7',5} = 10.5$	$J_{5,6} = 8.0$	$J_{6,7'} = 6.0$	6.90 (NCH_3, s)
31[c]			$J_{5,7'} = 10.5$	$J_{6,5} = 8.0$	

[a] Values are given in τ, J values in hertz. [b] $CDCl_3$ with TMS as internal standard. [c] D_2O with TMS as external standard.

Table II. Nmr Data for Cyclopropane Derivatives



Compounds	R'	H_2	H_3	R_3	R_4	R_2
$R' = H$; $R_2 = CH_2OH$	8.70 m	7.43 m	9.63 (endo) m	5.72 d	5.63 s	6.73 d,d
$R_3 = R_4 = CH_2C_6H_5$			9.20 (exo) m	J = 15.5		J = 9.0, J' = 11.5
12[a]				5.28 d		6.23 d,d
				J = 15.5		J = 4.5, J' = 11.5
$R' = H$; $R_2 = COOH$	8.20 m	7.00 m	8.66 m	7.38 s	7.25 s	
$R_3 = R_4 = CH_3$						
17[b]						
$R' = H$; $R_2 = COOH$	8.05 m	7.10 m	8.70 m	5.83 d	5.64 d	3.10 t
$R_3 = R_4 = CH_2C_6H_5$				J = 16.0	J = 6.0	J = 6.0 (NH)
20[c]				5.10 d		
				J = 16.0		
$R' = CH_3$; $R_2 = COOH$	8.77 s	7.04 d, d	9.03 t	5.68 d	5.53 d	4.73 t
$R_3 = R_4 = CH_2C_6H_5$		J = 5.5	J = 5.5	J = 15.5	J = 5.0	J = 5.0 (NH)
21[a]		J' = 8.0	8.42 d, d	5.17 d		
			J = 5.5	J = 15.5		
			J' = 8.0			

[a] In $CDCl_3$. [b] D_2O. [c] DMSO-d_6.

Reaction of cyclothymine **5** with aqueous sodium borohydride reductively and quantitatively cleaved the pyrimidine ring to the cis 1,2-disubstituted cyclopropane derivative **12**, *m/e* 310 (M^+), which was crystallized as the *p*-nitrobenzoate **13**, mp 108°. The nmr spectrum of **12** (Table II) showed double doublets at τ 6.73 (1 H, J = 9.0, J' = 11.5 Hz) and 6.23 (1 H, J = 4.5, J' = 11.5 Hz) due to *O*-methylene protons. The product of catalytic hydrogenation of **10** on Pd/C, *viz.*, 1,3-dimethyltetrahydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (**14**), with sodium borohydride underwent the same type of ring-opening reaction to afford 1-(4-hydroxybutyl)-1,3-dimethylurea (**15**), *m/e* 160 (M^+), characterized as the *p*-nitrobenzoate (monohydrate) **16**, mp 66°. The diazepinone **10** itself, with sodium borohydride, cleaved to dimethylurea **18** in addition to oily unstable products. These reductive cleavages have been observed with 5,6-dihydropyrimidine nucleosides[15] and thymine photodimers.[16]

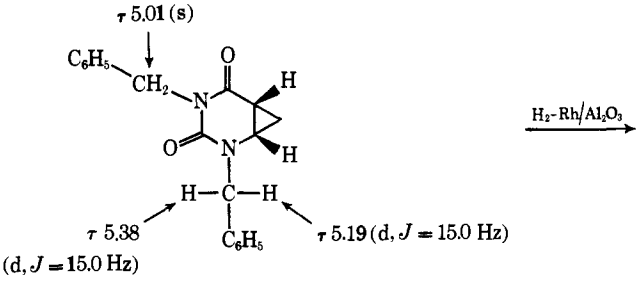
Dimethylcyclothymine **4** opened up with dilute alkali at room temperature to *cis*-ureidocyclopropanecarboxylic acid (**17**) (mp 145°, 85% yield, ν_{max}^{Nuj} 1705 cm^{-1} (–COOH)), which reclosed to cyclothymine **4** with dicyclohexylcarbodiimide in acetonitrile. Hydrolysis of **4** and **5** by hot base or acid gave 1,3-dialkylureas **18** and **19** as major products. Similarly, mild base hydrolysis of dibenzylcyclothymines **5** and **7** gave the corresponding cyclopropanecarboxylic acids **20** (mp 194°, ν_{max}^{Nuj} 1710 cm^{-1}) and **21** (mp 131°, ν_{max}^{Nuj} 1700 cm^{-1}).

The nmr spectral data of these cyclopropane derivatives are summarized in Table II.

(15) P. Cerutti, Y. Kondo, W. R. Landis, and B. Witkop, *J. Amer. Chem. Soc.*, **90**, 771 (1968).
(16) T. Kunieda and B. Witkop, *ibid.*, **89**, 4243 (1967).

These reactions relate cyclothymine much more to 5,6-dihydropyrimidines[8,15] than to uracil and thymine.

Dibenzylcyclothymine (**5**) was surprisingly stable to attempted catalytic hydrogenation (Pd/C) at atmospheric pressure. Unchanged starting material was recovered. On the other hand, hydrogenation over 5% Rh/Al_2O_3 at 30 lb of hydrogen gave a product which is tentatively formulated as the selectively hydrogenated 1-(cyclohexylmethyl)-3-benzylcyclothymine on the basis of the survival of the peaks for the cyclopropyl protons and the absence of an AB pattern due to the methylene protons of the 1-benzyl group in the nmr spectrum.



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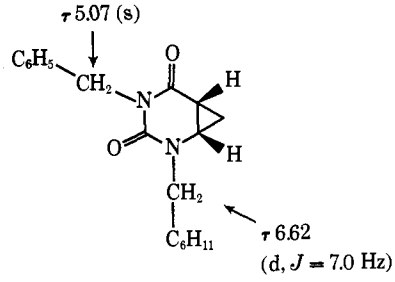
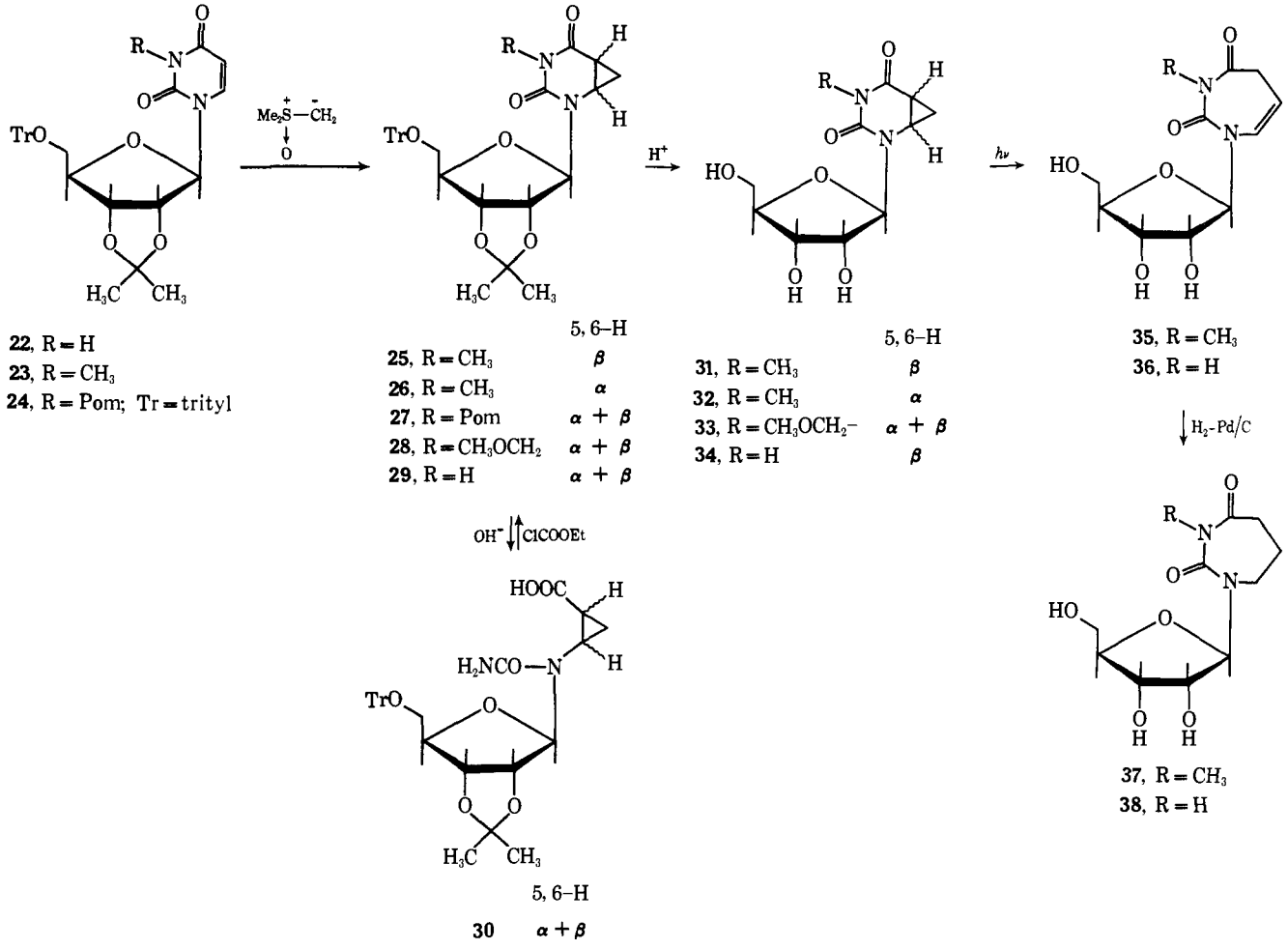


The difficulties of preparing 3-unsubstituted cyclothymine nucleosides became apparent when 2′,3′-*O*-isopropylidene-5′-*O*-trityluridine[17] (**22**) was treated with a threefold excess of the methylide to yield the two diastereoisomeric 3-methylcyclothymine nucleosides **25**, $[\alpha]^{25}D$ +3.0° (MeOH, 25% yield), and **26**, $[\alpha]^{25}D$ −46° (MeOH, 10% yield), in addition to the methylation product **23**, mp 195°, $[\alpha]^{25}D$ −5.5° ($CHCl_3$, 20% yield), which could all be separated by careful chromatography on silica gel (benzene–acetone). Product **23** was identified as the 3-methyluridine derivative by direct comparison with an authentic specimen prepared by direct methylation of **22** with diazomethane.[18] The nmr spectra ($CDCl_3$) of the diastereomers **25** and **26** differed by the doublet peaks due to the C_1' protons, τ 3.99 (J = 3.5 Hz) and 4.17 (J = 2.5 Hz), respectively.

The protected 3-methyluridine **23** gave the diastereoisomers **25** and **26** in 80% yield in a ratio of 7:3. This ratio was calculated from the nmr spectra by integration of the characteristic peaks at τ 4.0 due to the C_1' proton of the ribofuranosyl moiety.



22, R = H
23, R = CH_3
24, R = Pom; Tr = trityl

	5,6-H
25, R = CH_3	β
26, R = CH_3	α
27, R = Pom	α + β
28, R = CH_3OCH_2	α + β
29, R = H	α + β

	5,6-H
31, R = CH_3	β
32, R = CH_3	α
33, R = CH_3OCH_2–	α + β
34, R = H	β

35, R = CH_3
36, R = H

37, R = CH_3
38, R = H

30 5,6-H α + β

Acidic cation exchange resin was found to be the reagent of choice to remove simultaneously the trityl and isopropylidene groups of the acid-labile nucleosides

(17) E. Kuechler and J. Derkosch, *Z. Naturforsch.*, **21**, 209 (1966).
(18) W. Szer and D. Shugar, *Acta Biochim. Polon.*, **8**, 235 (1960).

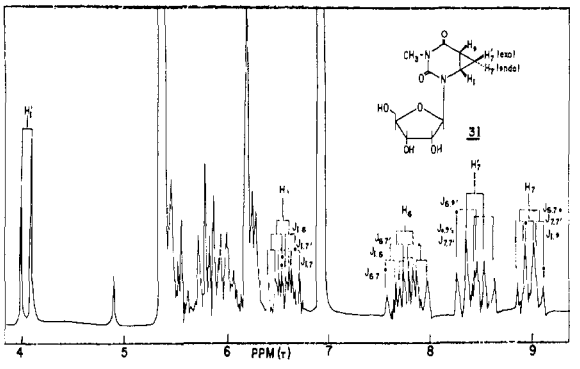


Figure 3. Nmr spectrum of one diastereoisomer of 3-methyl-1-β-D-ribofuranosylcyclothymine (**31**) in D_2O.

25 and **26**. This method was much superior to formic, acetic, and hydrochloric acids.[19] When **25** was treated with HCl another isomer, presumably the α anomer, was obtained (doublet peak due to the C_1' proton at τ 4.33, J = 9.5 Hz), in addition to the unprotected nucleoside **31**.

Treatment of **25** and **26** with cation exchange resin (Bio-Rad AG-50W-X8 (H^+)) in aqueous methanol at room temperature quantitatively removed the protecting groups of the sugar moiety to yield 1-β-D-ribofuranosyl-3-methylcyclothymines **31**, $[\alpha]^{25}D$ +20° (H_2O), and **32**, mp 146°, $[\alpha]^{25}D$ −108° (H_2O), which had only uv end absorption (Figure 1B). The nmr spectra of **31** (Figure 3) and **32** differed by the peaks due to the C_1' protons, τ 4.05 (doublet, J = 6.0 Hz) and 4.08 (doublet, J = 5.5 Hz), respectively.

The ORD curves (Figure 4) of the nucleosides **31** and **32** displayed strongly positive and negative Cotton effects with amplitudes of a = +832 and −1220,[20] respectively, at 245 nm, presumably due to n–π* transition of the ureidocarbonyl group.[21] The signs of the Cotton effects of cyclothymine nucleosides would not be affected by the configurations of their sugar moieties.

On the basis of the *abnormal contribution of the three-membered ring*[22] to the Cotton effect and the *positive Cotton effect of (S)-(−)-dihydrothymidine*,[21] the absolute configuration of **31** is assumed to be 5*R*,6*S* and that of **32**, 5*S*,6*R*.

Analogously, a mixture of diastereomeric 3-Pom-cyclothymine nucleosides (**27**) was obtained from 3-Pom-2′,3′-*O*-isopropylidene-5′-*O*-trityluridine (**24**) (20% yield), in addition to *N*-methylnucleosides, **23** (31% yield), **25**, and **26**, as a result of the lability of the Pom group to nucleophilic reagents. The diastereomers contained in **27** were not separable by chromatography on silica gel (benzene–acetone) in contrast to the 3-methyl compounds **25** and **26**. The nmr spectrum of the diastereomeric mixture **27** showed doublet peaks at τ 4.12 (J = 3.0 Hz) and 3.99 (J = 2.0 Hz) in a ratio of 4:5.

(19) A. Hampton, J. C. Fratantoni, P. M. Carroll, and S. Wang, *J. Amer. Chem. Soc.*, 87, 5481 (1965).

(20) Amplitudes a are defined as $\{[\phi]_P - [\phi]_T\}/100$. The large amplitude approaches that of thymine photodimer C (a = ±1260 [*cf.* B. Witkop, *Photochem. Photobiol.*, 7, 813 (1968)], indicative of the same type of perturbation: T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, 93, 3487 (1971).

(21) Y. Kondo and B. Witkop, *ibid.*, 90, 764 (1968).

(22) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, 21, 163 (1965).

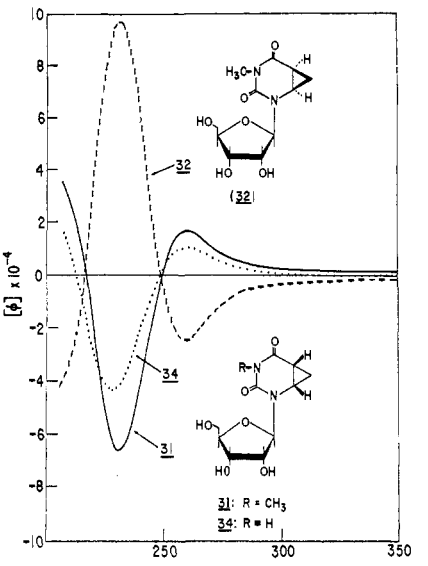


Figure 4. ORD curves of 1-β-D-ribofuranosyl-3-methyl-5,6α-(A) and 5,6-β-cyclothymine (B) and of 1-β-D-ribofuranosyl-5,6β-cyclothymine (C) in H_2O.

The cyclothymine nucleosides **27** were difficult to separate from starting material **24** by chromatography on silica gel. Therefore, **27** was opened by potassium hydroxide in aqueous dioxane to the cyclopropane nucleoside **30** which was easily purified by chromatography. Pure **30** was reclosed to the desired cyclothymine nucleoside **29** by the action of ethyl chloroformate in the presence of triethylamine (56% yield) or by *N*-carbethoxy-2-ethoxy-1,2-dihydroquinoline in tetrahydrofuran (63% yield).[23] The mixture contained the α and β diastereomers in a ratio of 4:1, as calculated from the doublet peaks at τ 3.95 (J = 3.3 Hz) and 4.07 (J = 2.3 Hz). Dicyclohexylcarbodiimide failed to reclose **30** to **29**.

The residual blocking groups of **29** were removed by treatment with cation exchange resin in analogy to **25** and **26**. Purification by chromatography on silica gel (MeOH–$CHCl_3$) gave 1-β-D-ribofuranosylcyclothymine (**34**), $[\alpha]^{25}D$ +15° (H_2O), as a colorless solid in an overall yield of 35% from **27**. The uv spectrum showed only end absorption with slight shoulders at 245 (log ε 3.09) and 225 nm (log ε 3.53) (Figure 1B). The nmr spectrum had a doublet peak at τ 4.11 (J = 6.0 Hz) due to the C_1' proton of the sugar moiety, indicative of the absence of the α isomer. The α isomer has so far not been isolated.

The ORD curve of **34** showed a positive Cotton effect (a = +550) closely resembling that of the β-5,6-diastereoisomer **31**, indicative of the absolute configuration of the three-membered ring as 5*R*,6*S*.

Dowex 1-X8 (OH^-) in MeOH at room temperature converted **27** to the 3-(methoxymethyl)nucleoside (**28**) (76% yield), whose nmr spectrum showed singlet peaks at τ 6.65 and 4.86 due to the *O*-methyl and *O*-methylene protons, respectively. This compound closely resembled the 3-methylcyclothymine nucleosides **25** and **26** in the uv spectrum and was quantitatively hydrolyzed to 1-β-D-ribofuranosyl-3-(methoxymethyl)cyclothymine (**33**) as described above. The nmr spectrum of **33** showed a doublet peak for the C_1' proton at τ 4.03

(23) B. Belleau and G. Malek, *J. Amer. Chem. Soc.*, 90, 1651 (1968).

(J = 6.0 Hz) and singlet peaks of methoxymethyl protons at τ 6.67 (3 H) and 4.85 (2 H).

In analogy to the model compound **4**, the cyclothymine nucleosides **31**, **32**, and **34**, on irradiation in aqueous solution with a low-pressure mercury lamp, gave seven-membered nucleosides, such as 3-methyl-1-β-D-ribofuranosyl-1,5-dihydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (**35**) and 1-β-D-ribofuranosyl-1,5-dihydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (**36**) (70% yield).

The nmr spectra of **35** and **36** showed peaks of olefinic protons at τ 3.57 (1 H, doublet, J = 7.0 Hz) and 4.10 (1 H, quartet, J = 7.0 Hz) and 3.58 (1 H, doublet, J = 7.5 Hz) and 4.19 (1 H, quartet, J = 7.5 Hz), respectively. These data support the unconjugated seven-membered ring structure. Further uv irradiation converted **35** and **36** to compounds with $\lambda_{max}^{H_2O}$ 296 and 293 nm (mp 225–230°), respectively, presumably analogs of the unidentified photoproduct **11**.

Photoproducts **35** and **36** were catalytically hydrogenated (10% Pd/C at 25 lb of hydrogen) to 3-methyl-1-β-D-ribofuranosyltetrahydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (**37**), mp 177°, $[\alpha]^{25}D$ −78.3° (H_2O), and 1-β-D-ribofuranosyl-2*H*-1,3-diazepine-2,4(3H)-dione (**38**), mp 161°, $[\alpha]^{25}D$ −57.5° (H_2O), which showed negative plain ORD curves in the uv region in contrast to 5,6-dihydrouridine.[21]

Both nucleosides **37** and **38** have no absorption maxima in the uv region (at pH 7), while **36** had a maximum at 230 nm at pH 11, which completely disappeared in a few hours at room temperature indicative of pyrimidine ring opening in analogy to dihydrouridine.[8]

Preliminary Cytoactivity and Antiviral Assays. Neither cyclothymine ribosides, 2′-deoxyribosides (to be described elsewhere), nor the isomeric seven-membered ring enlarged photoproducts showed any direct effects at 10^{-4} M in preventing the growth of Hela and L5178 cells. For these preliminary tests, we are indebted to Professor Charles Heidelberger, University of Wisconsin. In addition, through the good offices of Dr. Koert Gerzon, The Lilly Research Laboratories, the nucleosides 34 and 36 failed to show activity in the *in vitro* virus systems against Vaccinia, polio III, Herpes, Coe, Adeno, Rhino (two strains), Semlik forest, and an A-type influenza virus at concentrations of 125–2000 μg/ml as applied to the pad resting on the agar virus culture plate. However, these novel bicyclic nucleosides are capable of acting as substrates or inhibitors for some of the enzymes involved in the biosynthesis of nucleic acids (P. Torrence, this laboratory).

Experimental Section

The melting points which were determined on a Büchi capillary melting point apparatus are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer with TMS as an internal ($CDCl_3$) or external (D_2O) standard. Chemical shifts are given as parts per million (ppm) on the τ scale and as coupling constants, J values, in hertz (Hz). Infrared spectra and ORD curves were taken on Perkin-Elmer Model 237B and Cary-60 instruments. Mass spectral data were obtained on a Hitachi RMU-6D mass spectrometer.

1,3-Dimethylcyclothymine 4 (2,4-Dimethyl-2,4-diazabicyclo[4.1.0]-heptane-3,5-dione). Dimethyloxosulfonium methylide was prepared by refluxing a mixture of NaH (*ca.* 50%, 6.4 g) and trimethyloxosulfonium chloride (17.1 g) in THF (200 ml) under nitrogen for 2 hr.[4] To the above ylide was added 1,3-dimethyluracil (14.4 g) and the mixture was gently refluxed under N_2 for 4 hr. The precipitate was removed by filtration and washed with THF. The combined filtrate and washings were evaporated *in vacuo* to leave a yellow liquid. Distillation under reduced pressure gave a slightly yellow liquid, bp 110–120° (0.5 mm), which solidified on cooling, yield 10.5 g (66%).

The product was purified twice by chromatography on silica gel with benzene–acetone (20:1) and chloroform–acetone (20:1) as eluting solvents. This purification gave cyclothymine as colorless plates: mp 43–46°; homogeneous by tlc (silica gel) and vpc (3% Carbowax at 195°); ir (cap) 1700 and 1660 cm^{-1} (CONCON); uv end absorption with slight shoulders at 250 (log ε ~3.09) and 223 nm (log ε 3.43); nmr ($CDCl_3$) 9.23 (1 H, multiplet, H_7 endo), 8.64 (1 H, multiplet, H_7 exo), 7.88 (1 H, multiplet, H_5), 7.03 (1 H, multiplet, H_6), 6.86 (6 H, singlet, N–CH_3), which in D_2O showed two peaks at 6.98 (3 H, singlet) and 6.92 (3 H, singlet); mass (80 eV) main peaks at m/e 154 (M^+), 97, 69, 68, and 42.

Anal. Calcd for $C_7H_{10}N_2O_2$: m/e 154.07422. Found: m/e 154.07418.

***cis*-2-(1,3-Dimethylureido)cyclopropanecarboxylic Acid (17).** Dimethylcyclothymine **4** (750 mg) was treated with 0.5 *N* NaOH (40 ml) at room temperature overnight. The solution was neutralized with Bio-Rad AG-50 W (H^+) and the filtrate was evaporated *in vacuo*. The oily residue was crystallized from acetone–benzene, or MeOH–ether, to give colorless prisms; mp 123–125°; yield 650 mg (83%). Recrystallization from MeOH–ether gave the cyclopropylcarboxylic acid **17** as colorless small needles, mp 144–145°, which, with the modified Ehrlich reagent (*p*-dimethylaminocinnamaldehyde), gave a pink color on paper: ir (Nujol) 3380 (NH), 1705 (COOH), 1615 cm^{-1} (NCON); nmr (D_2O) 8.66 (2 H, multiplet, cyclopropyl methylene), 8.20 (1 H, multiplet, cyclopropyl methine proton adjacent to carboxyl group), 7.38 (3 H, singlet, N–CH_3), 7.25 (3 H, singlet, N–CH_3), 7.00 (1 H, multiplet, cyclopropyl methine adjacent to nitrogen).

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 49.12; H, 7.25; N, 16.51.

Recyclization of 17 to 1,3-Dimethylcyclothymine 4. The cyclopropylcarboxylic acid **17** (30 mg) was treated with DCC (200 mg) in acetonitrile (10 ml) at room temperature overnight. The solvent was removed *in vacuo* and the residue was treated with Bio-Rad AG-50 W-X8 (H^+) in H_2O at room temperature overnight. The insoluble material was collected and the filtrate was evaporated *in vacuo* to give a colorless oil (20 mg), which showed a spot identical with 1,3-dimethylcyclothymine on tlc (silica gel) in benzene–acetone (8:2) and $CHCl_3$–MeOH (9:1) as solvent systems.

1,3-Dimethylurea (18). A solution of dimethylcyclothymine **4** (350 mg) in 6.0 *N* HCl was refluxed for 2 hr and evaporated *in vacuo*. Chromatography on silica gel ($CHCl_3$–MeOH, 3:1) gave 1,3-dimethylurea (**18**), mp 100–104°, yield 130 mg (65%), as the only crystalline product, identical with an authentic sample (ir and nmr).

1,3-Dimethyl-5,6-dihydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (10). A solution of 1,3-dimethylcyclothymine **4** (3.0 g) in H_2O (500 ml) was irradiated for 6 hr with a Hanovia high-pressure mercury lamp (450 W). After the water was removed *in vacuo*, the residue was dissolved in a small amount of MeOH and chromatographed on silica gel with benzene–acetone (7:3) as an eluting solvent.

The major photoproduct was eluted first in pure form followed by some unchanged starting material (1.05 g, 35%). Recrystallization of the photoproduct from benzene–ligroin gave 1,3-dimethyl-5,6-dihydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (**10**) as colorless prisms: mp 62–63°; yield 1.35 g (45%); ir (Nujol) 1700 (amido C=O), 1650 cm^{-1} (broad, ureido C=O and C=C); uv $\lambda_{max}^{H_2O}$ 225 nm (shoulder) (log ε 3.75); nmr ($CDCl_3$) 6.93 (2 H, doublet, J = 7.0 Hz, CH_2), 6.82 (3 H, singlet, NCH_3), 6.78 (3 H, singlet, NCH_3), 4.52 (1 H, quartet, J = 7.0 Hz, olefinic proton adjacent to methylene), 3.93 (1 H, doublet, J = 7.0 Hz, olefinic proton adjacent to nitrogen); mass (80 eV) parent peak at m/e 154.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.66; H, 6.65; N, 18.28.

The photoproduct **11**, to be eluted in third place, was also obtained on direct irradiation of diazepinedione **10** and was recrystallized from benzene–acetone to give colorless needles: mp 185–186°; yield 350 mg (12%); uv $\lambda_{max}^{H_2O}$ 308, 241, and 210 nm (log ε 4.39, 3.54, 4.06).

Anal. Calcd for $C_7H_{10}N_2O_2$: m/e 154.0742. Found: m/e 154.0733.

1,3-Dimethyltetrahydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (14). The diazepinedione **10** (250 mg) was catalytically hydrogenated on 10% PdC (200 mg) in aqueous EtOH at 30 lb of hydrogen pressure. After 3 hr, tlc showed quantitative hydrogenation to the saturated compound. The catalyst was collected and the filtrate evaporated *in vacuo* to leave a colorless homogeneous oil (240 mg): ir (cap)

1695 and 1650 cm^{-1} (CONCON); nmr (D_2O) 7.3–8.1 (4 H, multiplet, $-C(=O)CH_2CH_2-$), 7.03 (3 H, singlet, NCH_3), 6.95 (3 H, singlet, NCH_3), 6.57 (2 H, triplet, J = 7.0, NCH_2-).

1,3-Dimethyl-1-(4-hydroxybutyl)urea (15). An aqueous solution (30 ml) of tetrahydrodiazepinedione **14** (200 mg) and $NaBH_4$ (200 mg) was stirred at room temperature overnight. After neutralization with Amberlite CG-50 (H^+), the solution was evaporated *in vacuo* to dryness. The residue was flash evaporated with MeOH several times to remove boric acid, and purified by chromatography on silica gel with $CHCl_3$–MeOH (10:1) as an eluting solvent. The hydrogenolysis product **15** was obtained in 50% yield (100 mg) as a hygroscopic liquid: ir (cap) 3340 (OH, NH), 1630 cm^{-1} (ureido C=O); nmr ($CDCl_3$) 8.43 (4 H, multiplet, CCH_2CH_2C), 7.23 (3 H, broad singlet, $NHCH_3$, sharp singlet on addition of D_2O), 7.12 (3 H, singlet, NCH_3), 6.72 (2 H, triplet, J = 7.0 Hz, $-CH_2O$), 6.35 (2 H, triplet, J = 6.0 Hz, NCH_2-), 5.72 (1 H, broad singlet, OH), 4.55 (1 H, broad singlet, NH); mass (80 eV) parent peak at m/e 160 and other peaks at 130, 102, 101, and 87.

***p*-Nitrobenzoate 16.** A solution of the above alcohol **15** (100 mg) and *p*-nitrobenzoyl chloride (100 mg) in pyridine (5 ml) was allowed to stand at room temperature overnight. Ice–water was added and the oil which separated was extracted with $CHCl_3$. The extract was washed with dilute $NaHCO_3$ and hydrochloric acid and dried (Na_2SO_4). The chloroform was removed *in vacuo* and the residue was chromatographed on silica gel with acetone as an eluting solvent to give the benzoate as a pale yellow liquid. This was crystallized from aqueous EtOH as the *p*-nitrobenzoate monohydrate, mp 64–66°. When it was further dried on P_2O_5, it became an oil at room temperature: ir (Nujol) 3400 (NH), 3300 (H_2O), 1725 cm^{-1} (ester C=O); nmr ($CDCl_3$) 8.22 (4 H, multiplet, CCH_2CH_2C), 7.17 (3 H, doublet, J = 4.5 Hz, $NHCH_3$), singlet at 7.18 (on addition of D_2O), 7.05 (3 H, singlet, NCH_3), 6.57 (2 H, triplet, J = 6.5 Hz, NCH_2), 5.55 (2 H, triplet, J = 6.0 Hz, $-CH_2O$), 5.02 (1 H, broad multiplet, NH), 1.72 (4 H, singlet, aromatic protons).

Anal. Calcd for $C_{14}H_{19}N_3O_5 \cdot H_2O$: C, 51.37; H, 6.47; N, 12.84. Found: C, 51.43; H, 6.44; N, 12.78.

1,3-Dibenzyluracil (3). A mixture of uracil (5.6 g), benzyl bromide (22 g), and anhydrous K_2CO_3 (20 g) was refluxed in acetone (150 ml) for 30 hr. The precipitate was collected and the combined filtrate and washings were evaporated *in vacuo*. The oily residue was dissolved in benzene and washed with dilute NaOH and H_2O. After drying (Na_2SO_4), removal of the solvent gave a colorless viscous oil which was crystallized from ligroin.

Recrystallization from benzene–ligroin gave dibenzyluracil as colorless prisms: mp 75–76.5°; yield 12 g (82%); nmr ($CDCl_3$) 5.10 (2 H, singlet, $-CH_2C_6H_5$), 4.85 (2 H, singlet, $-CH_2C_6H_5$), 4.29 (1 H, doublet, J = 8.0, H_5), 2.93 (1 H, doublet, J = 8.0 Hz, H_6), 2.67 (10 H, singlet, aromatic protons).

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.74; H, 5.62; N, 9.43.

1,3-Dibenzylcyclothymine 5 (2,4-Dibenzyl-2,4-diazabicyclo[4.1.0]-heptane-3,5-dione). Dimethyloxosulfonium methylide was prepared from NaH (*ca.* 50%, 2.5 g) and trimethyloxosulfonium chloride (6.5 g) in dry THF (100 ml). To this ylide was added dropwise a solution of 1,3-dibenzyluracil **3** (10 g) in THF (40 ml) and the mixture was refluxed for 4 hr under N_2. The precipitate was collected and the filtrate was evaporated *in vacuo*. The residue was dissolved in benzene and washed with H_2O. After drying, removal of the solvent left a reddish oil, which was chromatographed on silica gel with benzene–acetone (20:1) as an eluting solvent.

The first eluted solid (yield 5.6 g, 60%) was recrystallized repeatedly from benzene–ligroin to give dibenzylcyclothymine **5** as colorless prisms: mp 101–103°; uv end absorption with shoulders at 267 nm (ϵ 400), 263 (650), 257 (1100), 250 (1400); ir (Nujol) 1700 and 1655 cm^{-1} (NCONCO); nmr ($CDCl_3$) 9.40 (1 H, multiplet, $H_{7(endo)}$), 8.81 (1 H, multiplet, $H_{7(exo)}$), 7.98 (1 H, multiplet, H_5), 7.15 (1 H, multiplet, H_6), 5.38 and 5.19 (2 H, AB pattern, doublets, J = 15 Hz, $C_6H_5CH_2-$), 5.01 (2 H, singlet, $C_6H_5CH_2-$), 2.69 (10 H, singlet, aromatic protons); mass parent peak at m/e 306.

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.68; H, 6.02; N, 9.13.

1,3-Dibenzyl-1-[2-(hydroxymethyl)cyclopropyl]urea (12). A mixture of 1,3-dibenzylcyclothymine **5** (120 mg) and $NaBH_4$ (100 mg) in 90% EtOH (15 ml) was stirred at room temperature overnight. The solution was concentrated *in vacuo* and acidified with dilute HCl. The oil which separated was extracted with benzene and dried (Na_2SO_4). Benzene was removed *in vacuo* to leave a colorless oil. The product was purified by chromatography on silica gel with benzene–acetone (9:1) as eluting system. A colorless oil was obtained in 91% yield (110 mg); ir (cap) ~3350 (NH, OH), 1640 (ureido C=O), 1030 cm^{-1} (OH); nmr ($CDCl_3$) 9.63 (1 H, multiplet, endo proton of cyclopropylmethylene), 9.20 (1 H, multiplet, exo proton of cyclopropylmethylene), ~8.70 (1 H, multiplet, cyclopropylmethylene proton adjacent to carbon), 7.43 (1 H, multiplet, cyclopropylmethylene proton adjacent to nitrogen), 6.73 (1 H, doublets of AB doublet, J = 9.0, J_{AB} = 11.5 Hz, $OCHH-$), 6.23 (1 H, doublet of doublets, J = 4.5, J_{AB} = 11.5 Hz, $OCHH-$), 5.72 and 5.28 (2 H, AB pattern, J = 15.0 Hz, $C_6H_5CH_2-$), 5.72 (2 H, singlet, $C_6H_5CH_2-$); mass (80 eV) parent peak at m/e 310 and main peaks at 292, 279, 251, 239, 219, and 177.

***p*-Nitrobenzoate 13.** A solution of the above cyclopropylmethanol **12** (100 mg) and *p*-nitrobenzoyl chloride (150 mg) in pyridine (5 ml) was kept at room temperature overnight and then poured into ice–water. The oil was extracted with $CHCl_3$. The extract was washed with $NaHCO_3$, HCl, and H_2O and the chloroform solution was evaporated *in vacuo*. Chromatography on silica gel (benzene–acetone, 10:1) gave the benzoate as a colorless oil, which crystallized on trituration with benzene. Recrystallization from benzene–*n*-hexane gave the monobenzoate **13** as colorless needles: mp 107–108°; ir (Nujol) 3380 (NH), 1720 (ester C=O), 1640 cm^{-1} (ureido C=O).

Anal. Calcd for $C_{26}H_{23}N_3O_5$: C, 67.96; H, 5.48; N, 9.15. Found: C, 68.31; H, 5.61; N, 9.23.

***cis*-2-(1,3-Dibenzylureido)cyclopropanecarboxylic Acid (20).** A suspension of 1,3-dibenzylcyclothymine **5** (300 mg) in 0.5 *N* NaOH (30 ml) was stirred at room temperature overnight. The clear solution which resulted was acidified with dilute HCl to deposit a colorless solid which was washed with water and dried (yield 310 mg, 98%). Recrystallization from EtOH gave the cyclopropanecarboxylic acid **20** as colorless plates: mp 192–194°; mass m/e 324 (M^+); ir (Nujol) 3450 (NH), 1710 (COOH), 1620 cm^{-1} (NCON); nmr (DMSO-d_6) 8.70 (multiplet, 2 H, cyclopropyl methylene), 8.05 (1 H, multiplet, H_1), 7.10 (1 H, multiplet, H_2), 5.64 (2 H, doublet, J = 6.0 Hz, benzylic methylene), 5.83 and 5.10 (2 H, doublet, AB pattern, J = 16.0 Hz, benzylic methylene), 3.10 (1 H, doublet, J = 6.0 Hz, NH), 2.68 (10 H, singlet, aromatic protons).

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.63; H, 6.23; N, 8.39.

1,3-Dibenzylurea 19. A solution of cyclothymine **5** in 1 *N* KOH (50% aqueous EtOH) was refluxed for 4 hr and then cooled. The urea deposited as long colorless needles, mp 170–172° (lit.[24] 171.5°), identical with an authentic sample[25] (ir spectra, Nujol).

Catalytic Hydrogenation of 5 to 1-Cyclohexylmethyl-3-benzyl-5,6-cyclothymine. A mixture of cyclothymine **5** (200 mg) and 5% $RhAl_2O_3$ (200 mg) in MeOH (30 ml) was shaken at 30 lb of H_2 gas for 7.5 hr. The catalyst was collected and the filtrate evaporated *in vacuo*. The oily residue was chromatographed on silica gel to give a slight yellow oil (200 mg): nmr ($CDCl_3$) 7.10 (1 H, multiplet, H_6), 6.62 (2 H, doublet, J = 7.0 Hz, cyclohexyl CH_2-), 5.07 (2 H, singlet, $C_6H_5CH_2-$), 2.73 (5 H, multiplet, aromatic protons), in addition to 7.8–9.2 (14 H, multiplet).

1,3-Dibenzylthymine 6. This homolog was prepared like dibenzyluracil and recrystallized from benzene–ligroin to give colorless prisms; mp 90–91°; uv λ_{max}^{MeOH} 273 nm (log ϵ 3.96); λ_{min}^{MeOH} 241 (log ϵ 3.36); nmr ($CDCl_3$) 8.13 (3 H, doublet, J = 1.3 Hz, CH_3), 5.13 (2 H, singlet, $C_6H_5CH_2$), 4.85 (2 H, singlet, $C_6H_5CH_2$), 3.07 (1 H, quartet, J = 1.3 Hz, H_6), 2.72 (10 H, singlet, aromatic protons).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.54; H, 5.69; N, 8.97.

1,3-Dibenzyl-5-methylcyclothymine 7. A mixture of dibenzylthymine **6** (1.5 g) and the ylide prepared from NaH (ca. 50%, 1.0 g) and trimethyloxosulfonium chloride (3.0 g), was refluxed under N_2 overnight. The precipitate was collected and the filtrate evaporated *in vacuo*. The residue was dissolved in benzene and washed with H_2O. The solution was dried and evaporated *in vacuo* to leave a yellow oil, whose nmr spectrum showed the presence (~50%) of unchanged starting material. This oil was treated again with dimethyloxosulfonium methylide under the same conditions.

(24) P. A. Arzabright and B. L. Phillips, *J. Org. Chem.*, 32, 3261 (1967).

(25) J. Derkosch, K. Schlögl, and H. Waidich, *Monatsh. Chem.*, 88, 35 (1957).

Purification by chromatography on silica gel (benzene–acetone, 10:1) gave 1,3-dibenzyl-5-methylcyclothymine **7** as a viscous liquid; yield 0.9 g (58%); ir (Nujol) 1700 and 1660 cm^{-1} (–CON-CON–); nmr ($CDCl_3$) 9.29 (1 H, doublet of doublets, J = 4.5, J' = 6.0 Hz, $H_{7\,endo}$), 9.00 (1 H, triplet, J = 6.0 Hz, $H_{7\,exo}$), 8.73 (3 H, singlet, CH_3), 7.31 (1 H, doublets of doublet, J = 4.5, 6.0 Hz, H_6), 5.29 (2 H, singlet, $C_6H_5CH_2$), 4.99 (2 H, singlet, $C_6H_5CH_2$), 2.67 (10 H, singlet, aromatic protons).

Anal. Calcd for $C_{20}H_{20}N_2O_2$: *m/e* 320.152469. Found: *m/e* 320.152599.

***cis*-2-(1,3-Dibenzylureido)-1-methylcyclopropanecarboxylic Acid (21).** In analogy to dimethylcyclothymine, dibenzylcyclohomothymine **7** was hydrolyzed in 0.5 *N* NaOH at room temperature. After neutralization with Dowex-50W X8 (H^+), the filtrate was evaporated *in vacuo*. The residue was crystallized from benzene–ligroin to yield colorless prisms: mp 131–132°; ir (Nujol) 3400 (NH), 1700 (COOH), 1605 cm^{-1} (CON); nmr ($CDCl_3$) 9.03 (1 H, triplet, J = 5.5 Hz, endo proton of cyclopropyl methylene), 8.77 (3 H, singlet, CH_3), 8.42 (1 H, doublet of doublets, J = 5.5, J' = 8.0 Hz, exo proton of cyclopropyl methylene), 7.04 (1 H, doublet of doublets, J = 5.5, J' = 8.0 Hz, cyclopropyl methine), 5.68 and 5.17 (2 H, AB pattern, doublets, J = 15.5 Hz, $C_6H_5CH_2$), 5.53 (2 H, doublet, J = 5.0 Hz, CH_2NH), 4.73 (1 H, triplet, J = 5.0 Hz, NH).

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.28; H, 6.81; N, 7.96.

1,3-Bis(pivaloyloxymethyl)uracil (8). A mixture of uracil (11 g), chloromethyl pivalate (40 g), and anhydrous K_2CO_3 (30 g) was refluxed in acetone (280 ml) overnight. The crude product (30 g) was purified by chromatography on silica gel (benzene–acetone, 20:3) to afford a colorless solid, which was recrystallized from benzene–ligroin as colorless plates: mp 85–86°; yield 19 g (56%); nmr ($CDCl_3$) 8.82 (9 H, singlet, *tert*-butyl), 8.79 (9 H, singlet, *tert*-butyl), 4.32 (2 H, singlet, CH_2), 4.05 (2 H, singlet, CH_2), 4.23 (1 H, doublet, J = 8.0 Hz, H_5), 2.51 (1 H, doublet, J = 8.0 Hz, H_6); uv λ_{max}^{MeOH} 258 nm (log ϵ 3.95); λ_{min}^{MeOH} 229 nm (log ϵ 3.16); mass peaks at *m/e* 341 ($M^+ + 1$) and 340 (M^+).

Anal. Calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.50; H, 6.94; N, 8.30.

Reaction of Di-Pom-uracil 8 with Excess Ylide. Di-Pom-uracil **8** (4.0 g) was added to the dimethyloxosulfonium methylide prepared from NaH (50%, 3.0 g) and trimethyloxosulfonium chloride (9.0 g) in THF. The mixture was refluxed for 18 hr under N_2. The precipitate was removed by filtration and the filtrate evaporated *in vacuo*. The oily residue was taken up in benzene and washed with H_2O. After removal of the benzene, the residue was chromatographed on silica gel (200 g) with benzene–acetone (9:1) as an eluting solvent.

Unchanged starting material (2.0 g, 50%) was first eluted. The subsequent eluted fraction, a solid, was recrystallized from benzene–*n*-hexane to give 1-methyl-3-Pom-uracil **9** as colorless prisms: mp 90–91°; yield 0.8 g (30%). The ir and nmr spectra were identical with those of an authentic sample of **9** prepared from 1-methyluracil, as described below.

1-Methyl-3-(pivaloyloxymethyl)uracil (9). A mixture of 1-methyluracil (300 mg) and chloromethyl pivalate (600 mg) in acetone (10 ml) was refluxed in the presence of K_2CO_3 (1 g) for 18 hr. The precipitate was removed by filtration and the filtrate evaporated *in vacuo*. The product was purified by chromatography on silica gel with benzene–acetone (9:1) as an eluting solvent. Recrystallization from benzene–ligroin gave colorless prisms: mp 90–91°; nmr ($CDCl_3$) 8.80 (18 H, singlet, *tert*-butyl), 6.57 (3 H, singlet, CH_3), 4.27 (1 H, doublet, J = 8.0 Hz, H_5), 4.05 (2 H, singlet, OCH_2N), 2.75 (1 H, doublet, J = 8.0 Hz, H_6); uv λ_{max}^{MeOH} 269 nm (log ϵ 3.94); λ_{min}^{MeOH} 233 nm (log ϵ 3.04).

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.13; H, 6.62; N, 11.92.

2′,3′-*O*-Isopropylidene-5′-*O*-trityluridine (22).[17] A mixture of 2′,3′-*O*-isopropylideneuridine (15 g) and trityl chloride (15 g) in dry pyridine (150 ml) was first stirred at room temperature overnight and then heated for 1 hr and poured into ice water. The precipitate was extracted with $CHCl_3$ and washed with dilute HCl and $NaHCO_3$. After removal of the solvent, the product was purified by chromatography on silica gel with $CHCl_3$ as an eluting solvent. 5′-*O*-Trityluridine was obtained as a colorless amorphous powder: $[\alpha]^{25}D$ −4.4° (MeOH, *c* 0.64); yield 18 g (65%); nmr ($CDCl_3$) 8.69 (3 H, singlet, CH_3), 8.43 (3 H, singlet, CH_3), 6.57 (2 H, doublet, J = 4.0 Hz, H_5'), 5.67 (1 H, multiplet, H_4'), 5.17 (2 H, multiplet, H_2' and H_3'), 4.57 (1 H, doublet, J = 8.0 Hz, H_5), 4.10 (1 H, broad, H_1'), 2.50 (1 H, doublet, J = 8.0 Hz, H_6), 2.30 (aromatic protons); ir (Nujol) 3200 (NH), 1690 (broad, C=O); uv λ_{max}^{MeOH} 260 nm (log ϵ 3.98); λ_{min}^{MeOH} 243 nm (log ϵ 3.78).

Anal. Calcd for $C_{31}H_{30}N_2O_6$: N, 5.32. Found: N, 5.37.

Reaction of 2′,3′-*O*-Isopropylidene-5′-*O*-trityluridine (22) with the Ylide. 2′,3′-*O*-Isopropylidene-5′-*O*-trityluridine (4.4 g, 8.3 mmol) was added to a solution of dimethyloxosulfonium methylide (51 mmol) which had been prepared from sodium hydride (50% suspension in mineral oil, 2.4 g, 51 mmol) and trimethyloxosulfonium chloride (6.5 g, 51 mmol). After the mixture was refluxed overnight under a stream of dry nitrogen, it was filtered to remove precipitate and the filtrate was evaporated *in vacuo*. The residue was dissolved in benzene and the benzene solution was washed with water and dried (anhydrous sodium sulfate). After evaporation of the benzene *in vacuo*, the viscous residue was applied to a silica gel column and elution was carried out with benzene–acetone (9:1).

1-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-3-methylcyclothymines 25 and 26 were the first eluted products which were obtained as a colorless, amorphous powder: yield, 1.86 g (40%); nmr ($CDCl_3$) 7:3 ratio of diastereomers; λ_{max}^{MeOH} 250 nm (sh); *m/e* (80 eV), 554 (M^+).

2′,3′-*O*-Isopropylidene-3-methyl-5′-*O*-trityluridine (23) was eluted subsequently with the same solvent system to give, after recrystallization from methanol, colorless prisms: mp 185–186°; $[\alpha]^{25}D$ −5.1° (*c* 1.0, $CHCl_3$); yield 0.9 g (20%); nmr ($CDCl_3$) 8.65 (3 H, singlet, CH_3), 8.43 (3 H, singlet, CH_3), 6.75 (3 H, singlet, NCH_3), 6.57 (2 H, doublet, J = 3.5 Hz, H_5'), 4.48 (1 H, doublet, J = 7.5 Hz, H_5), 4.10 (1 H, doublet, J = 1.0 Hz, H_1'), 2.70 (aromatic protons), 2.50 (1 H, doublet, J = 7.5 Hz, H_6); uv λ_{max}^{MeOH} 259 nm (log ϵ 3.86); λ_{min}^{MeOH} 2.44 nm (log ϵ 3.73). This was identified by the direct comparison with the authentic compound prepared from the methylation of **22** with diazomethane.

Anal. Calcd for $C_{32}H_{32}N_2O_6$: C, 71.09; H, 5.97; N, 5.18. Found: C, 71.32; H, 5.78; N, 5.19.

1-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-3-methylcyclothymines 25 and 26 were prepared by treating 2′,3′-*O*-isopropylidene-3-methyl-5′-*O*-trityluridine (2.0 g, 3.7 mmol, identical with that prepared by the action of diazomethane on **22**) with dimethyloxosulfonium methylide (11.1 mmol, prepared from sodium hydride and trimethyloxosulfonium chloride). The mixture was gently refluxed under dry nitrogen for 4 hr after which time the ultraviolet absorption maximum (260 nm) had disappeared. After removal of the precipitate by filtration and evaporation of the filtrate *in vacuo*, the residue was taken up in benzene which was then washed with water, separated, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give a viscous yellow oil. Chromatography of the oil on silica gel (benzene–acetone, 9:1) gave the cyclothymine ribosides (yield 1.66 g, 80%) as a diastereomeric mixture in a ratio of 7:3. Careful rechromatography on silica gel with benzene–acetone (40:3) gave three fractions; the first (650 mg) and the third (50 mg) were the homogeneous isomers **25** and **26**, respectively, while the second fraction (110 mg) was a mixture of diastereomers.

Isomer 25 was a colorless amorphous solid: $[\alpha]^{25}D$ +3.0° (*c* 0.4, MeOH); uv end absorption with fine shoulders around 255 nm; ir (Nujol) 1705 and 1660 cm^{-1} (CONCON); nmr ($CDCl_3$) 9.19 (1 H, multiplet, $H_{7\,endo}$), 8.85 (1 H, multiplet, $H_{7\,exo}$), 8.63 (3 H, singlet, CCH_3), 8.43 (3 H, singlet, CCH_3), 8.18 (1 H, multiplet, H_5), 6.90 (3 H, singlet, NCH_3), 6.70 (1 H, multiplet, H_6), 6.60 (2 H, doublet, J = 3.5 Hz, H_5'), 5.76 (1 H, quartet, J = 3.5 Hz, H_4'), 5.20 (1 H, doublet of doublets, J = 6.5, J' = 3.5 Hz, H_3'), 4.98 (1 H, doublet of doublets, J = 6.5, J' = 3.5 Hz, H_2'), 3.99 (1 H, doublet, J = 3.5 Hz, H_1'), 2.67 (aromatic protons).

Anal. Calcd for $C_{33}H_{34}N_2O_6$: C, 71.46; H, 6.18; N, 5.05. Found: C, 71.17; H, 6.25; N, 5.04.

Isomer 26 was a colorless solid: mp 105°; $[\alpha]^{25}D$ −46° (*c* 0.2, MeOH); nmr ($CDCl_3$) 9.20 (1 H, multiplet, $H_{7\,endo}$), 8.80 (1 H, multiplet, $H_{7\,exo}$), 8.65 (3 H, singlet, CCH_3), 8.42 (3 H, singlet, CCH_3), 8.0 (1 H, multiplet, H_5), 6.92 (3 H, singlet, NCH_3), 6.90 (1 H, multiplet, H_6), 6.62 (2 H, doublet, J = 4.5 Hz, H_5'), 5.72 (1 H, triplet of doublets, J = 4.5, J' = 3.5 Hz, H_4'), 5.26 (1 H, doublet of doublets, J = 6.5, J' = 3.5 Hz, H_3'), 5.08 (1 H, doublet of doublets, J = 6.5, J' = 2.5 Hz, H_2'), 4.17 (1 H, doublet, J = 2.5 Hz, H_1'), 2.70 (aromatic protons).

Anal. Calcd for $C_{33}H_{34}N_2O_6$: C, 71.46; H, 6.18; N, 5.05. Found: C, 71.22; H, 6.07; N, 5.16.

3-Methyl-1-β-D-ribofuranosylcyclothymine (31). A solution of 1-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-3-methylcyclothymime (**25**) (0.5 g, 0.93 mmol) in methanol–water (9:1, 60 ml) was stirred at room temperature for 18 hr with Bio-Rad

AG-50W (H^+) (5 ml). At this point tlc showed complete conversion to the free sugar nucleoside. The resin was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in water and centrifuged to remove insolubles. The clear supernate was evaporated to dryness at room temperature *in vacuo* to give a colorless solid which was further purified by silica gel chromatography (methanol–chloroform, 1:4). The isomer **31** was obtained as a hygroscopic colorless powder: $[\alpha]^{25}D$ +20° (*c* 0.11, H_2O); uv $\lambda_{max}^{H_2O}$ 245 (sh), 225 (sh) nm (log ϵ 3.23, 3.56); ORD (*c* 0.11, H_2O at 25°) $[\phi]_{300}$ +2480, $[\phi]_{260}$ +16,050 (peak), $[\phi]_{249}$ 0, $[\phi]_{236}$ −67,200 (trough), $[\phi]_{217}$ 0, $[\phi]_{210}$ +27,200; nmr (D_2O) 8.99 (1 H, multiplet, $H_{7\,endo}$), 8.45 (1 H, multiplet, $H_{7\,exo}$), 7.75 (1 H, multiplet, H_5), 6.90 (3 H, singlet, NCH_3), 6.56 (1 H, multiplet, H_6), 6.22 (2 H, uneven triplet, H_5'), 4.05 (1 H, doublet, J = 6.0 Hz, H_1').

3-Methyl-1-β-D-ribofuranosylcyclothymine (**32**) was obtained as an oil (yield, 60 mg, 100%) after the protected nucleoside **26** was treated with Bio-Rad AG-50W (H^+). Crystallization from ethanol–ether gave colorless needles which had the same ultraviolet spectrum as that of the isomer **31**. The compound had: mp 145–146°; $[\alpha]^{25}D$ −108° (*c* 0.1, H_2O); ORD (*c* 0.1, H_2O at 25°) $[\phi]_{300}$ −3260, $[\phi]_{260}$ −24,600 (trough), $[\phi]_{248.5}$ 0, $[\phi]_{230}$ +97,400 (peak), $[\phi]_{216}$ 0, $[\phi]_{210}$ −32,500; nmr (D_2O) 9.0 (1 H, multiplet, $H_{7\,endo}$), 8.43 (1 H, multiplet, $H_{7\,oxo}$), 7.80 (1 H, multiplet, H_5), 6.92 (3 H, singlet, NCH_3), 6.70 (1 H, multiplet, H_6), 6.24 (2 H, uneven triplet, H_5'), 4.08 (1 H, doublet, J = 5.5 Hz, H_1').

Anal. Calcd for $C_{11}H_{16}N_2O_6$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.89; H, 5.69; N, 10.13.

3-Methyl-1-β-D-ribofuranosyl-1,5-dihydro-2*H*-1,3-diazepine-2,4-(3*H*)-dione (**35**). A solution of 3-methyl-1-β-D-ribofuranosylcyclothymine (**31**, 2.5 g, 9.3 mmol) in water (250 ml) was irradiated with a Hanovia low-pressure mercury lamp for 7 hr. Solvent was removed *in vacuo* and the residue was chromatographed on silica gel using chloroform–methanol (10:1) as eluting agent. As the first major eluted product, a homogeneous colorless oil (1.07 g, 43%) was obtained. Further elution produced approximately 0.9 g (36%) of product, **35**, contaminated with unchanged starting material **31**. All attempts at recrystallization of the photoproduct **35** failed. The product's nmr (D_2O) gave: 6.90 (3 H, singlet, NCH_3), 6.77 (2 H, doublet, J = 7.0 Hz, $-CH_2-$), 6.40 (2 H, uneven triplet, H_5'), 5.75 (3 H, multiplet, $H_2'H_3'H_4'$), 4.10 (1 H, quartet, J = 7.0 Hz, olefinic proton adjacent to methylene), 4.08 (1 H, doublet, J = 5.0 Hz, H_1'), 3.57 (1 H, doublet, J = 7.0 Hz, olefinic proton adjacent to nitrogen); ir 3400 (broad, OH), 1695 (C=O), 1645 cm^{-1} (CONC=C); uv (H_2O) end absorption only.

3-Methyl-1-β-D-ribofuranosyltetrahydro-2*H*-1,3-diazepine-2,4-(3*H*)-dione (**37**). The above dihydro-1,3-diazepine **35** (0.2 g, 0.74 mmol) was dissolved in water (20 ml) and hydrogenated over a 10% palladium/charcoal catalyst (0.15 g) at 25 lb of H_2 pressure and ambient temperature overnight. Removal of the catalyst by filtration and *in vacuo* evaporation of the filtrate gave a colorless oil which solidified on standing. Recrystallization from methanol–ether gave **37** as colorless prisms: mp 176–177°, $[\alpha]^{25}D$ −78.3° (*c* 0.68 H_2O); uv (H_2O) end absorption only; ORD (*c* 0.1, H_2O) negative plain, $[\phi]_{300}$ −3200, $[\phi]_{210}$ −11,900; ir (Nujol) 3440 (OH), 1690, and 1655 (CONCON); nmr (D_2O) 7.87 (2 H, multiplet, $-CCH_2C$), 7.60 (2 H, multiplet, $COCH_2$), 6.93 (3 H, singlet, NCH_3), 6.50 (2 H, multiplet, NCH_2), 6.26 (2 H, doublet, J = 4.0 Hz, H_5'), 4.23 (1 H, doublet, J = 6.0 Hz, H_1').

Anal. Calcd for $C_{11}H_{18}N_2O_6$: C, 48.17; H, 6.62; N, 10.21. Found: C, 48.13; H, 6.35; N, 10.09.

2′,3′-*O*-Isopropylidene-3-(pivaloyloxymethyl)-5′-*O*-trityluridine (**24**). A solution of 2′,3′-*O*-isopropylidene-5′-*O*-trityluridine (2.65 g, 5 mmol) and chloromethyl pivalate (1.5 g, 10 mmol) in acetone (40 ml) was refluxed for 20 hr in the presence of anhydrous potassium carbonate (2.0 g, 14.5 mmol). The insoluble material was removed by filtration and the filtrate evaporated *in vacuo* to leave a pale brown liquid which was further purified by chromatography on silica gel with benzene–acetone (9:1). A colorless solid (2.45 g, 76%) was obtained which had $[\alpha]^{25}D$ +3.4° (*c* 2.0, methanol); ir (Nujol) 1725 (ester C=O), 1675 cm^{-1} (ureido C=O); nmr ($CDCl_3$) 8.82 (9 H, singlet, *tert*-butyl), 8.63 (3 H, singlet, CH_3), 8.42 (3 H, singlet, CH_3), 6.55 (2 H, doublet, J = 4.0 Hz, H_5'), 5.63 (1 H, multiplet, H_4'), 5.20 (2 H, multiplet, H_2', H_3'), 4.55 (1 H, doublet, J = 8.5 Hz, H_5), 4.12 (2 H, singlet, OCH_2N), 4.08 (1 H, broad peak, H_1'), 2.67 (aromatic protons), 2.45 (1 H, doublet, J = 8.5 Hz, H_6); uv λ_{max}^{MeOH} 262 nm (log ϵ 3.95); λ_{min}^{MeOH} 243 nm (log ϵ 3.63).

Anal. Calcd for $C_{37}H_{40}N_2O_8$: C, 69.36; H, 6.29; N, 4.37. Found: C, 68.76; H, 6.19; N, 4.20.

1-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-3-(pivaloyloxymethyl)cyclothymine (**27**) was prepared by gently refluxing under nitrogen a solution of **24** (7.0 g, 11 mmol) and dimethyloxosulfonium methylide (31 mmol) in dry tetrahydrofuran for 10 hr. The precipitate was filtered off, the filtrate was evaporated *in vacuo*, and the residue was dissolved in benzene. The benzene solution was washed with water and then dried over anhydrous sodium sulfate. After removal of the benzene *in vacuo*, the oily residue was chromatographed on silica gel using benzene–acetone (20:1) as eluting agent. The first fraction eluted consisted of trityl alcohol. The second fraction gave **27** as a colorless solid; yield 1.35 g (19%).[26] This was demonstrated to be a mixture of diastereomers in a ratio of 5:4 by nmr. The compound had: λ_{max} 260 (sh), 254 nm (sh); ir (Nujol) 1725 (ester C=O), 1680 cm^{-1} (ureido C=O); nmr ($CDCl_3$) 9.15 (1 H, multiplet, $H_{7\,endo}$), 8.83 (9 H, singlet, *tert*-butyl), 8.67 (3 H, singlet, CCH_3), 8.47 (3 H, singlet, CCH_3), 8.15 (1 H, multiplet, H_5), 6.85 (1 H, multiplet, H_6), 6.60 (2 H, H_5'), 4.26 (2 H, singlet, OCH_2N), 4.12 (3/8 H, doublet, J = 2.0 Hz, H_1'), and 3.99 (5/8 H, doublet, J = 3.0 Hz, H_1').

Anal. Calcd for $C_{38}H_{42}N_2O_8$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.89; H, 6.66; N, 4.14.

Further elution of the column with benzene–acetone (20:1) gave 2′,3′-*O*-isopropylidene-3-methyl-5′-*O*-trityluridine (2.2 g, 31%) and its cyclothymine derivatives **25** and **26**, in 1% yield.

***cis*-2-[1-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)ureido]cyclopropanecarboxylic acid** (**30**) was prepared by treating **27** (2.8 g, 4.4 mmol) with 1.0 *N* KOH (50 ml) and 250 ml of dioxane for 5 hr at room temperature. After neutralization with Bio-Rad AG-50 (H^+), the resin was filtered off and the filtrate was lyophilized to give a colorless solid. Chromatography on silica gel (chloroform–methanol, 9:1) gave 1.5 g (66%) of pure **30** as a colorless solid. This compound gave a positive Ehrlich reaction and had no *tert*-butyl protons as determined by nmr.

1-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)cyclothymine (**29**). To a cooled (−15°) solution of **30** (1.3 g, 2.34 mmol) and triethylamine (0.55 g, 5.4 mmol) in chloroform (50 ml), ethyl chloroformate (0.5 g, 4.6 mmol) was added. The solution was stirred at −10° for 1 hr and then allowed to stand at room temperature overnight. After concentration of the solution to a few milliliters *in vacuo* at <30°, the solution was chromatographed on silica gel (benzene–acetone, 8:2) to give, in the first fraction, a colorless solid which was chromatographically identical with **22**. The yield of this product was 56% as a diastereomeric mixture which was shown to be **29**: λ_{max}^{MeOH} 270 (sh), 260 (sh), 255 (sh), and 248 nm (sh); nmr ($CDCl_3$) 8.63 (3 H, singlet, CCH_3), 8.43 (3 H, singlet, CCH_3), 6.57 (2 H, H_5'), 4.07 (0.2 H, doublet, J = 2.3 Hz, H_1'), and 3.95 (0.8 H, doublet, J = 3.3 Hz, H_1').

Anal. Calcd for $C_{32}H_{32}N_2O_6$: N, 5.28. Found: N, 5.02.

Unreacted **30** was recovered by further column elution with chloroform–methanol (7:3). This was resubjected to the cyclizing reaction to give an additional 400 mg of product **29**.

1-β-D-Ribofuranosylcyclothymine (**34**). Treatment of **29** (0.35 g, 0.65 mmol) with Bio-Rad AG-50W (H^+) in 80% methanol at room temperature overnight gave, after removal of resin, concentration of the filtrate to a few milliliters, and filtration to remove trityl alcohol, a glassy solid (145 mg, 90%), which was practically pure and was chromatographically identical with uridine. Further purification by silica gel chromatography (methanol–chloroform, 2:8) gave a colorless solid: $[\alpha]^{25}D$ +15° (*c* 0.2, H_2O); uv $\lambda_{max}^{H_2O}$ 245 (sh), 217 (sh) nm (log ϵ 3.09, 3.53); ORD (*c* 0.1, H_2O at 25°) $[\phi]_{300}$ +490, $[\phi]_{257.5}$ +9800 (peak), $[\phi]_{247}$ 0, $[\phi]_{225}$ −43,300 (trough), $[\phi]_{212}$ 0, $[\phi]_{210}$ +6860; nmr (D_2O) 8.93 (1 H, multiplet, $H_{7\,endo}$), 8.45 (1 H, multiplet, $H_{7\,exo}$), 7.97 (1 H, multiplet, H_5), 6.62 (1 H, multiplet, H_6), 6.28 (2 H, uneven triplet, H_5'), ~5.92 (2 H, multiplet, H_3', H_4'), ~5.52 (1 H, multiplet, H_2'), 4.11 (1 H, doublet, J = 6.0 Hz, H_1').

Anal. Calcd for $C_{10}H_{14}N_2O_6 \cdot CH_3OH$: C, 45.51; H, 6.25; N, 9.65. Found: C, 45.97; H, 6.01; N, 9.55. After further drying over P_2O_5, Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.34; H, 5.16; N, 10.47.

1-β-D-Ribofuranosyl-1,5-dihydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (**36**). **34** (0.3 g, 1.15 mmol) was dissolved in water (250 ml) and irradiated with a Hanovia low-pressure mercury lamp for 2 hr. Solvent was removed *in vacuo* and the residue was chromato-

(26) Usually separation of this product from starting material was difficult and incomplete. Routinely the mixture was used for the next step.

graphed on silica gel using methanol–chloroform (1:4) as the eluting agent. The first product to be eluted was a small amount of solid (mp 225–230°, $\lambda_{max}^{H_2O}$ 292 nm). The diazepine nucleoside (100 mg, 33%) was then eluted and was recrystallized from methanol–ether to give a colorless crystalline solid: mp 140–145°; $\lambda_{max}^{H_2O}$ 212 nm; nmr (D_2O) 6.68 [1 H, doublets (J = 7.5 Hz) of AB pattern doublet (J = 14.5 Hz), COC*H*H–], 6.66 [1 H, doublets (J = 1.0 Hz) of doublets (J = 6.5 Hz) of AB pattern doublet (J = 14.5 Hz), COCH*H*–], 6.20 (2 H, H_5'), 4.19 [1 H, doublets (J = 6.5 Hz) of doublets (J = 7.5 Hz) of AB pattern doublet (J = 14.5 Hz), C=C*H*C], 4.14 (1 H, doublet, J = 5.3 Hz, H_1'), 3.57 [1 H, doublets (J = 1.0) of doublet (J = 7.5 Hz), NCH=C].

1-β-D-Ribofuranosyltetrahydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (38) was obtained by hydrogenation of **36** on 10% palladium/carbon in a manner analogous to the preparation of **37**. The product was recrystallized from methanol–ether to give colorless prisms: mp 160–161°; $[\alpha]^{25}D$ −57.5° (c 0.4, H_2O); ir (Nujol) 3450 (NH), 3280 (OH), 1695 and 1660 cm^{-1} (CONCON); uv (H_2O) end absorption only (at pH 7); $\lambda_{max}^{pH\ 11}$ 230 nm; ORD (c 0.1, H_2O) negative plain, $[\phi]_{300}$ −3700, $[\phi]_{250}$ −6400, $[\phi]_{210}$ −18,100.

Anal. Calcd for $C_{10}H_{16}N_2O_6$: C, 46.15; H, 6.20; N, 10.77. Found: C, 45.89; H, 6.28; N, 10.49.

1-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-3-(methoxymethyl)cyclothymine (28). **27** (2.2 g, 3.4 mmol) was stirred with Dowex 1-X8 (30 ml) in methanol at room temperature for 5 hr. The resin was filtered off and the filtrate was evaporated *in vacuo*. Chromatography of the residue on silica gel (benzene–acetone, 10:1) gave **26** as a colorless solid (1.5 g, 76%): ir (Nujol) 1710 and 1670 cm^{-1} (CONCON); uv (MeOH) end absorption; nmr ($CDCl_3$) 8.75–9.25 (2 H, multiplet, H_7), 8.65 (3 H, singlet, CCH_3), 8.42 (3 H, singlet, CCH_3), 8.10 (1 H, multiplet, H_5), 6.65 (3 H, singlet, OCH_3), 6.65 (1 H, multiplet, H_6), 4.86 (2 H, singlet, OCH_2N), 3.99 (1 H, doublet, J = 3.0 Hz, H_1').

Anal. Calcd for $C_{34}H_{36}N_2O_7 \cdot 0.5H_2O$: C, 68.80; H, 6.24; N, 4.72. Found: C, 69.20; H, 6.68; N, 4.78.

1-β-D-Ribofuranosyl-3-(methoxymethyl)cyclothymine (33) was obtained in 100% yield (170 mg) by treating **28** (330 mg, 0.56 mmol) with Bio-Rad AG-50 (H^+) in methanol in a manner analogous to that used in the preparation of **25**. A colorless glassy solid was obtained: ir (Nujol) 1710, 1670 cm^{-1} (CONCON); nmr (D_2O) 8.92 (1 H, multiplet, $H_{7\ endo}$), 8.40 (1 H, multiplet, $H_{7\ exo}$), 7.75 (1 H, multiplet, H_5), 6.67 (3 H, singlet, OCH_3), 6.60 (1 H, multiplet, H_6), 6.32 (2 H, H_5'), 4.85 (2 H, singlet, OCH_2N), 4.03 (1 H, doublet, J = 6.0 Hz, H_1'); uv (H_2O) end absorption.

Preparation and Photochemistry of Pyrimidine Nucleoside Sulfonium Ylides

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Abstract: Protected anhydropyrimidine nucleosides, such as 2′,3′-*O*-isopropylidene-2,5′-*O*-cyclouridine, 2,2′-anhydro-1-(5-*O*-trityl- or benzoylarabinofuranosyl)uracil, or 2,3′-anhydro-1-(5-*O*-trityl-2-deoxyxylofuranosyl)-thymine, are easily opened by dimethyloxosulfonium methylide to the corresponding stable dimethyloxosulfonium pyrimidine methylides. Further O-methylation of 2′- or 3′-pentose hydroxy groups was observed in the opening of 2,2′-anhydro-1-(5-*O*-trityl-β-D-arabinofuranosyl)uracil with excess dimethyloxosulfonium methylide. Ground-state reactions of the new class of compounds include desulfurization with Raney nickel to 2-methylpyrimidine nucleosides or, after hydrolysis, 2-methyl-4-hydroxypyrimidines, analogs of toxopyrimidine, and hydrolysis to dimethyloxosulfonium 4-hydroxy-2-pyrimidinemethylide, which smoothly reacts with amines, such as dimethylamine, to give 2-(dimethylaminomethyl)-4-hydroxypyrimidine, a reaction which is not possible on the level of the comparable nucleoside. Photolysis of such pyrimidinemethylide nucleosides leads to intramolecular participation, mostly of the C-2′ position, with the formation of 2,2′-methylenecyclopyrimidine nucleosides, such as 3a(α),4(β)-dihydro-4-(hydroxymethyl)-2,2-dimethyl-5a*H*(β)-[1,3]dioxolo[3′,4′]furo[3′,2′:4,5]pyrrolo[1,2-*a*]pyrimidin-9(11*H*)-one, presumably *via* carbene intermediates. Photolysis of dimethyloxosulfonium 4-hydroxy-2-pyrimidinemethylides, in which intramolecular interaction with the sugar moiety is not possible, leads to participation of solvent, water, or methanol, with the formation of 2-hydroxy- or 2-methoxymethyl-4-hydroxypyrimidine, or in the presence of sodium borohydride of 4-hydroxy-2-methylpyrimidine.

Pyrimidine nucleosides have been transformed by inversion of configurations, introduction of functional groups, and rearrangement of the pyrimidine ring *via* anhydronucleosides[2] ever since they have been first synthesized by Todd and coworkers.[3] Anhydronucleosides containing sulfur[4,5] and nitrogen[6] as the bridging heteroatoms are but variations on the general theme of modifications of nucleosides by this approach. In this paper we describe exploratory synthetic routes to 2-substituted and 2,2′-carbocyclic pyrimidine nucleosides starting from anhydronucleosides *via* oxosulfonium methylides of pyrimidine nucleosides. Several dimethyloxosulfonium ylides stabilized by carbonyl,[7,8] sulfonyl,[9] or other electronegative groups[10–12] have been

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