intermediate, a direct displacement reaction might also be possible with the relative amounts of bond breaking and bond formation with the nucleophile varying as the pK_a of the attacking amine varies. However, in the case of imidazole catalysis this would require direct expulsion of a much more basic species. Also, it would then be expected that *N*-methylimidazole would catalyze hydrolysis of the ionized species as well as imidazole which is not the case. Therefore, it is most likely that a tetrahedral intermediate is being formed.

Acknowledgment. This work was supported by a research grant from the National Institutes of Health.

"Abbreviated" Dinucleosides of Thymidine and Deoxyuridine and Their Photoproducts[1]

Marshall W. Logue and Nelson J. Leonard*

Contribution from the School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801. *Received September 20, 1971*

Abstract: The photodimerization of two thymines and of thymine and uracil held in close proximity by a ribofuranose backbone has been examined. "Abbreviated" dinucleosides 5′-deoxy-5′-(1-thyminyl)thymidine (**3a**) and 2′,5′-dideoxy-5′-(1-thyminyl)uridine (**3b**) have been synthesized *via* ring closure of the appropriate 5′-*N*-(β-methoxy-α-methylacryloyl)ureidodeoxynucleosides **2a** and **2b**. Intermediates **2a** and **2b** were prepared by the treatment of 5′-amino-5′-deoxythymidine (**1a**) and 5′-amino-2′,5′-dideoxyuridine (**1b**), respectively, with β-methoxy-α-methylacryloyl isocyanate. Direct irradiation of **3a** at 300 nm in dilute aqueous solution leads exclusively to an internal cis–syn photodimer (*cis*-**4a**, where the additional cis refers to the relation of the furanose oxygen to the 2- and 2′′-carbonyls). Acetone-sensitized photolysis of **3b** leads to an internal cis-syn photodimer (*cis*-**4b**) and an internal trans-syn photodimer (**7** with the furanose oxygen in cis relation to the 2-carbonyl and in trans relation to the 2′′-carbonyl) in approximately a 1:1 ratio. The results are informative with regard to base stacking and favored conformations.

The isolation of an internal cis-syn dimer from direct photolysis of 1,1′-trimethylenebisthymine (Thy-C_3-Thy) at 300 nm in dilute aqueous solution[2a] prompted us to devise a model system more closely related to DNA[3] and to examine its photochemistry. In "abbreviated" dinucleosides,[4] ribonucleosides, or deoxyribonucleosides containing an extra base on the 5′-carbon, the two bases have the possibility of existing in a stacked conformation approximately 3.4 Å apart, which is in the range generally observed for the interplanar distances between bases in nucleic acids.[5] We now describe the syntheses of "abbreviated" dinucleosides 5′-deoxy-5′-(1-thyminyl)thymidine (**3a**) and 2′,5′-dideoxy-5′-(1-thyminyl)uridine (**3b**) and their photochemistry. Ureidodeoxynucleosides **2a** and **2b** were prepared by the reaction of β-methoxy-α-methylacryloyl isocyanate with 5′-amino-5′-deoxythymidine (**1a**) and 5′-amino-2′,5′-dideoxyuridine (**1b**), respectively. Ring closure of intermediates **2a** and **2b** in the presence of ammonium hydroxide[6,7] gave the corresponding "abbreviated" dinucleosides **3a** and **3b**.

When compound **3a** was irradiated at 300 nm in dilute aqueous solution (1.1×10^{-3} *M*) while sparging with deoxygenated nitrogen, the ultraviolet absorption at 262 nm decreased to 7% of its original value after 20 hr. Thin layer chromatography on cellulose indicated only one product in addition to a small amount of recovered **3a**. Fractional crystallization from water served to separate **3a** (2%) from internal photodimer **4a** (88%). The structure of **4a** was established by chemical and spectroscopic means.

The anti-type dimers can be ruled out due to the geometrical restraint caused by the attachment of both thymine rings to the single carbohydrate moiety. A single-crystal X-ray analysis was not possible due to dissociation of **4a** under the influence of X-rays.[8] The

(1) (a) For part VIII, the preceding paper in the series on Synthetic Spectroscopic Models Related to Coenzymes and Base Pairs, see J. A. Secrist III and N. J. Leonard, *J. Amer. Chem. Soc.*, **94**, 1702 (1972); (b) the present paper may be regarded as part IX in this series.

(2) (a) N. J. Leonard, K. Golankiewicz, R. S. McCredie, S. M. Johnson, and I. C. Paul, *J. Amer. Chem. Soc.*, **91**, 5855 (1969); (b) internal photodimerization of 5-EtUra-C_3-Ura and Thy-C_3-Ura has also been reported: K. Golankiewicz and L. Strekowski, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, **19**, 97 (1971).

(3) For reviews of the products of ultraviolet radiation of nucleic acids and their components, see: E. Fahr, *Angew. Chem., Int. Ed. Engl.*, **8**, 578 (1969); J. G. Burr, *Advan. Photochem.*, **6**, 193 (1968).

(4) "Doubled-headed" deoxyribonucleosides have been made in the Merck Sharp and Dohme Research Laboratories bearing adenine and/or thymine moieties at the 1′ and 5′ positions: R. Fecher, K. H. Boswell, J. J. Wittick, and T. Y. Shen, *J. Amer. Chem. Soc.*, **92**, 1400 (1970); *Carbohyd. Res.*, **13**, 105 (1970). The authors are grateful to Dr. Shen for providing a preprint of their communication while our work was in progress. For a review, see T. Y. Shen, *Angew. Chem., Int. Ed. Engl.*, **9**, 678 (1970). The present authors prefer the designation "abbreviated" in referring to coenzyme or dinucleoside models of this type. In keeping with the symbolism of pyrimidine photoproducts suggested by Dr. Waldo Cohn, Director of the Office of Biochemical Nomenclature, National Research Council, the following shortened forms may be applied: for **3a**, Thy(1dRib5)Thy; **3b**, Ura(1dRib5)Thy; *cis*- and *trans*-**4a**, Thy[1dRib5]Thy(*c*) (the brackets indicate cyclobutane dimer formation and (*c*) indicates its cis geometry; the relationship of the furanose oxygen to the 2- and 2′′-carbonyls is not specified in this terminology); *cis*- and *trans*-**4b**, Ura[1Rib5]Thy(*c*); **6** and **7**, Ura[1dRib5]Thy(*t*).

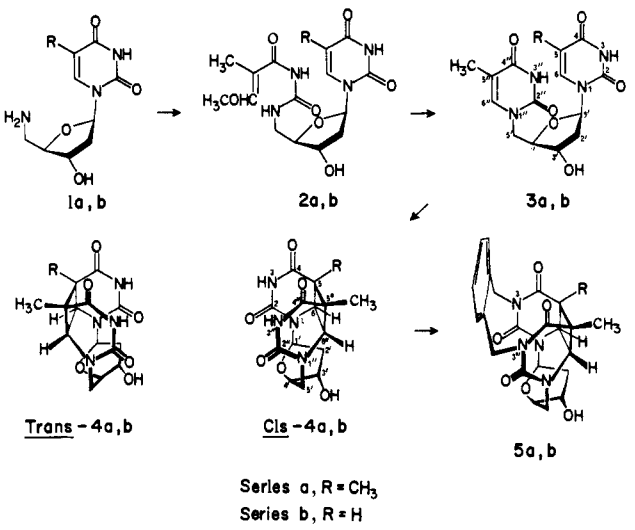
(5) M. Sundaralingam, *Biopolymers*, **7**, 821 (1969).

(6) G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 157 (1958).

(7) T. Ukita, A. Hamada, and M. Yoshida, *Chem. Pharm. Bull.*, **12**, 454 (1964).

(8) We are grateful to Professor I. C. Paul, University of Illinois, for carrying out and monitoring the X-irradiation. Crystals of **4a** which had been exposed to X-irradiation for 1 week had dissociated to an

sodium salt of the cis-syn dimer of thymine[9] and the cis-syn dimers of 1,3-dimethylthymine[10] and Thy-C_3-Thy[2a] have been observed to dissociate upon X-irradiation. The trans-syn dimers of 1-methylthymine and 1,3-dimethylthymine also undergo monomerization,[10b] although not as rapidly as the cis-syn dimers. In contrast, the cis-syn dimers of uracil[11] and 6-methyluracil,[12] the cis-syn dimer portion of thymine trimer,[13] and the cis-anti and trans-anti dimers of both 1-methylthymine[10b] and 1,3-dimethylthymine[10b] are reported to be stable to X-irradiation. That **4a** is a cis-syn dimer



of the two thymine rings was indicated by this collection of data and was proved conclusively by the formation of an *o*-xylylene derivative[2a] **5a** of **4a** in which the *o*-xylylene group bridges N-3 and N-3''. Derivative **5a** was prepared in 90% yield by the reaction of *o*-xylylene dibromide with the dipotassium salt of **4a** in dimethylformamide.[2a]

Although **4a** has thus been shown to be an internal cis-syn dimer, an added complication exists because there are two possible cis-syn configurations, *cis*-**4a** and *trans*-**4a**, where the additional cis or trans refers to the relation of the furanose oxygen to the two carbonyls. We were able to assign the former to **4a** on the basis of nmr spectroscopy. Comparisons[14] of the nmr spectra of 5- and 6-methylcytidine and of 5- and 6-methyluridine have revealed downfield shifts of 0.5–0.6 ppm for H-2' and 0.15–0.2 ppm for H-3', and upfield shifts of 0.16–0.25 ppm for H-1', 0.17 ppm for H-4', and 0.04–0.10 ppm for H-5'a,5'b in the 6-methyl derivatives. Similar shifts have also been observed[15] for orotidine and ribosyl-β-cyanuric acid with respect to uridine. These observations were interpreted to mean that 6-methyluridine and 6-methylcytidine exist in a syn conformation as opposed to the usual anti conformation for pyrimidine nucleosides.[5,16–25] The changes in the chemical shifts of the ribose protons were ascribed to the anisotropic effect of the 2-keto group. Inspection of the chemical shifts for H-1', H-2'a,2'b, and H-3' of 5'-amino-5'-deoxythymidine (**1a**), thymidine, and **3a** (see Table I)

Table I. Chemical-Shift Data[a] for **3a**

Compd	Chemical shifts, ppm from TMS H-1'	H-2'a,2'b	H-3'
1a	6.18	2.15	4.25
Thymidine	6.22	2.13	4.28
3a	6.17	2.19	4.25

[a] Spectra recorded on a Varian A-60 spectrometer in $(CD_3)_2SO$.

indicates that the thymine ring attached to C-1' exists predominately in the anti conformation in **1a** and **3a**. A comparison of H-4' and H-5'a,5'b chemical shifts for the same series was not considered diagnostic due to the differences in the functionalities attached to C-5'. Since the thymine ring on C-1' in **3a** resides mainly in an anti conformation, a stacking interaction with the other thymine ring on C-5' to produce a conformation necessary for cis-syn photodimerization in aqueous solution would lead to *cis*-**4a** and not to *trans*-**4a**.

It is interesting to note that in orotidine, uridine, ribosyl-β-cyanuric acid, α-pseudouridine, and β-pseudouridine the chemical shifts for H-5'a *vs.* H-5'b differ by no more than 0.18 ppm,[24,26] whereas in *cis*-**4a** H-5'a and H-5'b are separated by 1.34 ppm. The H-3', H-4', H-5, and H-5'' resonances all fall between the H-5'a and H-5'b resonances.

The mass spectra of *cis*-**4a** and **3a** are practically identical except for individual peak intensities. As in the case of the cis-syn internal dimer of 1,1'-trimethylenebisthymine (Thy-C_3-Thy), there are no indications in the spectrum of *cis*-**4a** of ions having the cyclobutane ring intact, or having resulted in cleavage of the cyclobutane ring, other than the molecular ion at *m/e* 350. The fragmentation patterns are those normally observed[2a,27–29] for pyrimidine nucleosides and 2,4-dioxypyrimidines.

extent of at least 4% as indicated by the change in absorbance in the 260-nm region of the ultraviolet.

(9) C. H. Wei and J. R. Einstein, Abstracts, American Crystallographers Association, Buffalo, N. Y., July 1968, paper L9, p 102.
(10) (a) N. Camerman and A. Camerman, *Science*, **160**, 1451 (1968); (b) N. Camerman and A. Camerman, *J. Amer. Chem. Soc.*, **92**, 2523 (1970).
(11) (a) E. Adman, M. P. Gordon, and L. H. Jensen, *Chem. Commun.*, 1019 (1968); (b) E. Adman and L. H. Jensen, *Acta Crystallogr., Sect. B*, **26**, 1326 (1970).
(12) J. W. Gibson and I. L. Karle, *J. Crystal. Mol. Struct.*, 1, 115 (1971).
(13) J. L. Flippen and I. L. Karle, *J. Amer. Chem. Soc.*, **93**, 2762 (1971).
(14) M. P. Schweizer, J. T. Witkowski, and R. K. Robins, *ibid.*, **93**, 277 (1971).
(15) (a) F. E. Hruska, *ibid.*, **93**, 1795 (1971); (b) H. Dugas, B. J. Blackburn, R. K. Robins, R. Deslauriers, and I. C. P. Smith, *ibid.*, **93**, 3468 (1971).
(16) J. Donohue and K. N. Trueblood, *J. Mol. Biol.*, **2**, 363 (1960).
(17) A. E. V. Haschemeyer and A. Rich, *ibid.*, **27**, 369 (1967).
(18) T. R. Emerson, R. J. Swan, and T. L V. Ulbricht, *Biochemistry*, **6**, 843 (1967).
(19) D. W. Miles, W. H. Inskeep, M. J. Robins, M. W. Winkley, R. K. Robins, and H. E. Eyring, *J. Amer. Chem. Soc.*, **92**, 3872 (1970).
(20) S. S. Danyluk and F. E. Hruska, *Biochemistry*, **7**, 1038 (1968).
(21) M. P. Schweizer, A. D. Brown, P. O. P. Ts'o, and D. P. Hollis, *J. Amer. Chem. Soc.*, **90**, 1042 (1968).
(22) F. E. Hruska, A. A. Grey, and I. C. P. Smith, *ibid.*, **92**, 214, 4088 (1970).
(23) B. J. Blackburn, A. A. Grey, I. C. P. Smith, and F. E. Hruska, *Can. J. Chem.*, **48**, 2866 (1970).
(24) A. A. Grey, I. C. P. Smith, and F. E. Hruska, *J. Amer. Chem. Soc.*, **93**, 1765 (1971).
(25) J. H. Prestegard and S. I. Chan, *ibid.*, **91**, 2843 (1969).
(26) F. E. Hruska, *ibid.*, **93**, 1795 (1971).
(27) J. M. Rice, G. O. Dudek, M. and M. Barber, *ibid.*, **87**, 4569 (1965).

In order to obtain a rough estimate of the rate of photodimerization of **3a**, simultaneous irradiations[30] of **3a** and Thy-C_3-Thy in aqueous solution were run since the latter is known[31] to undergo photodimerization about 3.5 times faster than thymidylyl-(3′ → 5′)-thymidine. Aliquots taken at 10, 20, and 30 min showed (uv) essentially equivalent extents of dimerization, reflecting approximately equivalent time-averaged separation of the thymine rings in **3a** and in Thy-C_3-Thy.

Mixed cyclobutane dimers of thymine and uracil have been produced by uv irradiation of DNA,[32-35] thymine–uracil mixtures,[36-39] and cytidine– and deoxycytidine–thymidine mixtures.[35] Although the mixed thymine–uracil dimers have been detected, no structure elucidation has been done. However, a cis-syn configuration has been proposed[33] on the basis of similar elution on ion-exchange chromatography to cis-syn thymine dimer.

When "abbreviated" dinucleoside **3b** was irradiated at 300 nm in dilute aqueous solution (1.0×10^{-3} *M*) containing 1% acetone,[40] while sparging with deoxygenated nitrogen, the uv absorption at 260 nm decreased to 3% of its original value after 4 hr. The 260-nm absorption did not increase upon heating for 1 hr on a steam plate, reflecting the absence of any photohydrate. Thin layer chromatography on cellulose indicated two products and no starting material. Upon concentration of the irradiated solution crystals of photodimer **4b** were deposited in 42% yield, and subsequent passage of the filtrate down a Sephadex G-15 column[41] gave the other photodimer in 44% yield.

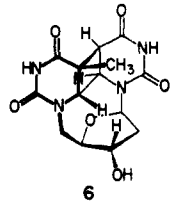
Internal photodimer **4b**, like **4a**, formed an *o*-xylylene derivative **5b** when its dipotassium salt was treated with *o*-xylylene dibromide in dimethylformamide.[2a] Thus, **4b** is aldo a cis-syn internal dimer. Again there are two possible configurations, *cis*-**4b** and *trans*-**4b**. The chemical-shift data in Table II indicate that the uracil ring in **1b** and **3b** exists predominately in the anti conformation. Therefore, a stacking interaction between the uracil and thymine rings to produce the necessary conformation for cis-syn dimerization would lead to *cis*-**4b**. Accordingly, we have assigned the structure of *cis*-**4b** to the first internal photodimer isolated from the photolysis of **3b**. Crystals of *cis*-**4b** suitable for single-crystal X-ray analysis have been obtained, and the X-ray structure determination is presently being undertaken because of the absence of structural data on the interesting mixed dimer types.

Table II. Chemical-Shift Data[a] for **3b**

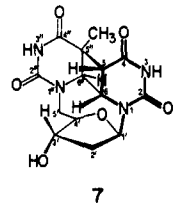
Compd	Chemical shifts, ppm from TMS H-1′	H-2′a,2′b	H-3′
1b	6.10	2.12	4.18
2′-Deoxyuridine	6.18	2.13	4.27
3b	6.22	2.20	4.25

[a] Spectra recorded on a Varian A-60 spectrometer in $(CD_3)_2SO$.

The second photodimer isolated from the photolysis of **3b** appeared to be a trans-syn internal dimer. There are two possible trans-syn dimers, **6** and **7**, and both



6



7

can be produced from **3b** with the uracil ring in an anti conformation. A comparison (Table III) of the

Table III. Chemical-Shift Data[a] of **7** *vs.* *cis*-**4b**

Compd	Chemical shifts, ppm from TMS H-3′	H-5	H-6	H-6″
cis-**4b**	4.36	3.42	4.27	3.81
7	4.31	3.30	4.15	3.99

[a] Spectra recorded on Varian HR-220 spectrometer in $(CD_3)_2SO$.

H-3′, H-5, H-6, and H-6″ chemical shifts for *cis*-**4b** and for the trans-syn internal dimer reveals that H-5 and H-6 are shielded by 0.12 ppm, H-3′ is shielded by 0.05 ppm, and H-6″ is deshielded by 0.18 ppm in the trans-syn dimer. These observations can be rationalized in terms of structure **7** but not with structure **6**. Molecular models of **7** show that (1) H-6″ lies directly over O-1′ and should be deshielded,[42] (2) H-5 and H-6 lie over the 4″- and 2″-carbonyl groups, respectively, and should be shielded,[43] and (3) H-3′ lies somewhat over the 2″-carbonyl group and should be shielded, but to a lesser extent than H-5 or H-6. By contrast, models of **6** show that (1) H-6 lies over O-1′, (2) H-5 and H-6″ lie over the 4″- and 2″-carbonyl groups, respectively, and (3) H-3′ has essentially the same environment as in *cis*-**4b** and should not be shifted. Accordingly, we have assigned structure **7** to the second internal photodimer isolated from the photolysis of **3b**.

As in the case of *cis*-**4a**, the H-5′a and H-5′b resonances are widely separated in *cis*-**4b** and **7**, 1.32 and 1.63 ppm, respectively, with the H-3′, H-4′, H-5, H-6, and H-6″ resonances falling in between. The proton assignments were made on the basis of coupling constants and spin decoupling experiments (see Experimental Section).

(28) T. Nishiwaki, *Tetrahedron*, **22**, 3117 (1966).
(29) S. M. Hecht, A. S. Gupta, and N. J. Leonard, *Biochim. Biophys. Acta*, **182**, 444 (1969).
(30) Equimolar aqueous solutions of **3a** and Thy-C_3-Thy in quartz vessels were irradiated at 300 nm in a Rayonet RPR 208 reactor.
(31) D. T. Browne, J. Eisinger, and N. J. Leonard, *J. Amer. Chem. Soc.*, **90**, 7302 (1968).
(32) R. B. Setlow and W. L. Carrier, *J. Mol. Biol.*, **17**, 237 (1966).
(33) D. Weinblum, *Biochem. Biophys. Res. Commun.*, **27**, 384 (1967).
(34) R. Ben-Ishai, E. Ben-Hur, and Y. Hornfeld, *Israel J. Chem.*, **6**, 769 (1968).
(35) A. J. Varghese, *Biochemistry*, **10**, 2194 (1971).
(36) R. Beukers and W. Berends, *Biochim. Biophys. Acta*, **41**, 550 (1960).
(37) A. Wacker, D. Weinblum, L. Träger, and Z. H. Moustafa, *J. Mol. Biol.*, **3**, 790 (1961).
(38) K. C. Smith, *Photochem. Photobiol.*, **2**, 503 (1963).
(39) D. F. Rhoades and S. Y. Wang, *Biochemistry*, **9**, 4416 (1970).
(40) Acetone sensitization was used in order to suppress the uracil photohydration process: see, C. L. Greenstock and H. E. Johns, *Biochem. Biophys. Res. Commun.*, **30**, 21 (1968).
(41) The Sephadex G-15 column was used to remove a small amount of an oily yellow material which arose from the photochemical reaction of acetone itself.
(42) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 183–190.
(43) B. H. Jennings, S.-C. Pastra, and J. L. Wellington, *Photochem. Photobiol.*, 11, 215 (1970), have observed 0.12-ppm shielding of the methine protons of the trans-syn dimer of thymine *vs.* the cis-syn dimer of thymine.

The mass spectra of **3b**, *cis*-**4b**, and **7** are practically identical as were **3a** and *cis*-**4a**, differing only in individual peak intensities. As before, there is no evidence of ions having the cylcobutane ring intact or having resulted in cleavage of the cyclobutane ring other than the molecular ion at *m/e* 336.

Our data on the irradiation of "abbreviated" dinucleoside **3a** at 300 nm suggest that stacking interactions favor combination of the two thymine rings predominately, if not exclusively, in a cis-syn manner. Any significant amount of a trans-syn internal photodimer, produced from a trans-syn-stacked conformation of **3a**, would have been detectable by thin layer chromatography in the systems employed. In the case of the photoreaction of the "abbreviated" dinucleoside **3b** at 300 nm with photosensitization, two of the possible four photoproducts differing in configuration were obtained. The fact that a single cis-syn and a single trans-syn internal photodimer resulted was indicative of partial discrimination in stacked conformations leading to photoproducts.

Experimental Section[44]

5′-*O*-Tosylthymidine was prepared essentially as described[45] in 68% yield: mp 168–170° dec (lit.[45] mp 168–169°); nmr ($(CD_3)_2SO$) δ 1.83 (d, 3, J = 1 Hz, C-5 CH_3), 2.12 (m, 2, H-2′a,2′b), 2.44 (s, 3, Ar CH_3), 3.85–4.48 (c, m, 4, H-3′, H-4′, and H-5′a,5′b), 4.83 (br s, 1, C-3′ OH), 6.22 (t, 1, J = 7 Hz, H-1′), 7.33–8.00 (m, 5, Ar H and H-6), 11.23 (s, 1, H-3).

5′-Azido-5′-deoxythymidine was prepared essentially as described[46] in 73% yield: mp 163–164° (lit.[46] mp 165–166°); nmr ($(CD_3)_2SO$) δ 1.82 (d, 3, J = 1 Hz, C-5 CH_3), 2.22 (m, 2, H-2′a,2′b), 3.57 (d, 2, J = 4.5 Hz, H-5′a,5′b), 3.87 (m, 1, H-4′), 4.23 (m, 1, H-3′), 5.37 (d, 1, J = 4.0 Hz, C-3′ OH), 6.22 (t, 1, J = 7 Hz, H-1′), 7.48 (d, 1, J = 1 Hz, H-6), 11.20 (s, 1, H-3).

5′-Amino-5′-deoxythymidine (1a). 5′-Azido-5′-deoxythymidine was hydrogenolyzed at 2–3 atm over 5% palladium/carbon in ethanol to give **1a** quantitatively. Crystallization from ethanol gave colorless needles: mp 173.5–175° [lit.[46] mp 173.5–174.5°]; nmr ($(CD_3)_2SO$) δ 1.83 (s, 3, C-5 CH_3), 2.15 (t, 2, J = 6 Hz, H-2′a,2′b), 2.80 (m, 2, H-5′a,5′b), 3.72 (m, 1, H-4′), 4.25 (m, 1, H-3′), 4.85 (br s, 4, C-3′ OH, C-5′ NH_2, and H-3), 6.18 (t, 1, J = 7 Hz, H-1′), 7.63 (br s, 1, H-6).

5′-Deoxy-5′-*N*-(β-methoxy-α-methylacryloyl)ureidothymidine (2a). To a solution of 313 mg (1.3 mmol) of **1a** in 5 ml of dry DMF was added a benzene solution of β-methoxy-α-methylacryloyl isocyanate[47] which had been prepared by treating 202 mg (1.5 mmol) of β-methoxy-α-methylacryloyl chloride[47] with 298 mg (2.0 mmol) of silver cyanate in benzene. The reaction mixture was stirred for 1 hr at room temperature and for 1 hr under reflux, and then evaporated to dryness under reduced pressure. The residue was stirred with hot ethanol and filtered to give 383 mg (77%) of **2a**: mp 252–253°; nmr ($(CD_3)_2SO$) δ 1.63 and 1.81 (2 d, 6, J = 1 Hz, C-5 CH_3 and C-5′′ CH_3), 2.11 (t, 2, J = 6 Hz, H-2′a,2′b), 3.53 (m, 2, H-5′a,5′b), 3.81 (m overlapping s, 4, OCH_3 and H-4′), 4.15 (m, 1, H-3′), 5.31 (d, 1, J = 5 Hz, C-3′ OH), 6.17 (t, 1, J = 7 Hz, H-1′), 7.45 (m, 2, H-6 and H-6′′), 8.75 (t, 1, J = 5 Hz, H-1′′), 9.68 (s, 1, H-3′′), 11.22 (s, 1, H-3).

Anal. Calcd for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.76; N, 14.66. Found: C, 49.98; H, 5.81; N, 14.46.

5′-Deoxy-5′-(1-thyminyl)thymidine (3a). To a suspension of 1.05 g (2.75 mmol) of **2a** in 10 ml of ethanol under reflux was added 10 ml of concentrated ammonium hydroxide over 1 hr. The mixture was heated under reflux for 24 hr with intermittent addition of another 10 ml of concentrated ammonium hydroxide. After the removal of solvent under reduced pressure, the residue was recrystallized from aqueous ethanol to give 759 mg (79%) of 3a as colorless rods: mp 306–307° dec; $\lambda_{max}^{H_2O}$ 262.5 nm (ϵ 16,630), $\lambda_{min}^{H_2O}$ 234.5 (4300); $\lambda_{max}^{0.1\ N\ HCl}$ 262.5 (16,600), $\lambda_{min}^{0.1\ N\ HCl}$ 234.5 (4300); $\lambda_{max}^{0.1\ N\ NaOH}$ 266 (12,550), $\lambda_{min}^{0.1\ N\ NaOH}$ 245.5 (7800); nmr ($(CD_3)_2SO$) δ 1.73 and 1.82 (2 d, 6, J = 1 Hz, C-5 CH_3 and C-5′′ CH_3), 2.19 (m, 2, H-2′a,2′b), 3.92 (m, 3, H-4′ and H-5′a,5′b), 4.20 (m, 1, H-3′), 5.24 (br s, 1, C-3′ OH), 6.17 (t, 1, J = 7 Hz, H-1′), 7.42 and 7.48 (2 d, 2, J = 1 Hz, H-6 and H-6′′), 11.17 (br s, 2, H-3 and H-3′′); mass spectrum (70 eV) *m/e* (rel intensity) 350 (0.5), 225 (4), 207 (4), 206 (12), 139 (3), 127 (8), 126 (27), 96 (6), 82 (10), 81 (100), 55 (25), 54 (11), 53 (17), 43 (2), 39 (7), 28 (15), 27 (14).

Anal. Calcd for $C_{15}H_{18}N_4O_6$: C, 51.43; H, 5.18; N, 16.00. Found: C, 51.16; H, 5.23; N, 15.76.

Cis-Syn Photodimer *cis*-4a. A solution of 350 mg (1.0 mmol) of **3a** dissolved in 900 ml of distilled water in a Pyrex vessel was irradiated at 300 nm in a Rayonet RPR-100 reactor while sparging with a slow stream of deoxygenated nitrogen. The reaction was monitored by the change in uv absorption at 262 nm. After 20 hr, the 262-nm absorption had dropped to 7% of the initial value. The water was removed under reduced pressure and the residue was crystallized from distilled water to give 8.0 mg (2.3%) of **3a**. Concentration of the filtrate yielded 306 mg (88%) of *cis*-**4a** as colorless needles: mp >350°; tlc (Eastman 6065 cellulose sheets) *n*-BuOH–AcOH–H_2O (80:12:30), R_f 0.55, *n*-BuOH–H_2O (84:16), R_f 0.39, *i*-PrOH–NH_4OH–H_2O (70:20:10), R_f 0.57; $\lambda_{max}^{H_2O}$ sh 214 nm (ϵ 7930), $\lambda_{max}^{0.1\ N\ HCl}$ sh 214 (7880), $\lambda_{max}^{0.1\ N\ NaOH}$ 239 (15,850), $\lambda_{min}^{0.1\ N\ NaOH}$ 230 (13,810); nmr ($(CD_3)_2SO$) δ 1.30 and 1.34 (2 s, 6, C-5 CH_3 and C-5′′ CH_3), 2.39 (br t, 2, J = 7.5 Hz, H-2′a,2′b), 3.74 (AB q, 2, $J_{6,6''}$ = 7.5 Hz, H-6 and H-6′′), 3.06 and 4.40 (2 d, 2, $J_{5'a5'b}$ = −15 Hz, H-5′a and H-5′b), 3.91 (br d, 1, $J_{3'4'}$ = 4 Hz, H-4′), 4.33 (m, 1, H-3′), 5.28 (d, 1, J = 5 Hz, C-3′ OH), 6.33 (dd, 1, J = 7 and 2 Hz, H-1′), 10.38 and 10.46 (2 s, 2, H-3 and H-3′′); mass spectrum (70 eV) *m/e* (relative intensity) 350 (0.6), 225 (20), 207 (19), 206 (2), 139 (12), 127 (14), 126 (10), 96 (20), 82 (9), 81 (100), 55 (16), 54 (6), 53 (4), 43 (4), 39 (3).

Anal. Calcd for $C_{15}H_{18}N_4O_6$: C, 51.43; H, 5.18; N, 16.00. Found: C, 51.49; H, 5.26; N, 16.00.

Dipotassium Salt of *cis*-4a. To a suspension of 221 mg (0.631 mmol) of *cis*-**4a** in 5 ml of distilled water was added 1.26 ml of 1 *N* potassium hydroxide. The solution was stirred for 15 min, then filtered and evaporated to dryness under reduced pressure to give a pale pink solid. The pink solid was washed with ethanol, collected, and dried *in vacuo* at 80° to give 264 mg (95% based on a monohydrate) of colorless powder: mp >350°.

Anal. Calcd for $C_{15}H_{16}N_4O_6K_2 \cdot H_2O$: C, 40.53; H, 4.08; N, 12.60. Found: C, 40.86; H, 4.20; N, 12.43.

***o*-Xylylene Derivative 5a of *cis*-4a.** To a suspension of 226 mg (0.51 mmol) of the dipotassium salt (monohydrate) of *cis*-**4a** in 50 ml of DMF was added 135 mg (0.51 mmol) of *o*-xylylene dibromide. The mixture was stirred at room temperature for 71 hr, then evaporated to dryness under reduced pressure. The residue was collected, washed with water and ethanol, and dried *in vacuo* at 80° to give 217 mg (90% as monohydrate) of colorless microcrystalline **5a**: mp 257° dec; mass spectrum (70 eV) *m/e* (relative intensity) 434 (10), 354 (24), 308 (11), 229 (26), 228 (100), 227 (29), 206 (3) 200 (6), 199 (29), 186 (52), 185 (52), 184 (6), 183 (9), 162 (8), 157 (10), 146 (33), 139 (2), 132 (10), 128 (4), 127 (15), 126 (12), 118 (40), 117 (97), 110 (55), 104 (27), 103 (11), 91 (22), 90 (19), 84 (11), 82 (18), 81 (91), 77 (11), 55 (32), 54 (26), 53 (21), 43 (9), 39 (9), 28 (26), 27 (14).

Anal. Calcd for $C_{23}H_{24}N_4O_6 \cdot H_2O$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.99; H, 5.43; N, 11.82.

2′-Deoxy-5′-*O*-tosyluridine was prepared essentially as for 5′-*O*-tosylthymidine in 56% yield as prisms which retained a beige color: mp 156–157° dec; nmr ($(CD_3)_2SO$) δ 2.17 (t, 2, J = 6 Hz, H-2′a,2′b), 2.45 (s, 3, Ar CH_3), 3.78–4.43 (m, 4, H-3′, H-4′, and H-5′a,5′b), 5.25 (br s, 1, C-3′ OH), 5.60 (dd, 1, $J_{5,3}$ = 2 Hz, $J_{5,6}$ = 8 Hz, H-5), 6.15 (t, 1, J = 7 Hz, H-1′), 7.20–7.97 (overlapping q and d, 5, 4 Ar H and H-6), 11.22 (s, 1, H-3). Exchange with D_2O causes the H-5 doublet of doublets to collapse to a doublet.[48]

(44) All melting points were determined using a Thomas-Hoover capillary melting point apparatus and are corrected. The ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60, HA-100, or HR-220 spectrometer. Mass spectra were run on a Varian-MAT CH-5 spectrometer. Microanalyses were performed by Mr. Josef Nemeth and staff, who weighed samples for quantitative ultraviolet spectra.

(45) E. J. Reist, A. Benitz, and L. Goodman, *J. Org. Chem.*, **29**, 554 (1964).

(46) J. P. Horwitz, A. J. Tomson, J. A. Urbanski, and J. Chua, *ibid.*, 27, 3045 (1962).

(47) G. Shaw and R. M. Warrener, *J. Chem. Soc.*, 153 (1958).

(48) A. J. H. Nollet, G. H. Koomen, W. F. A. Grose, and U. K. Pandit, *Tetrahedron Lett.*, 4607 (1969).

Anal. Calcd for $C_{16}H_{18}N_2O_7S$: C, 50.26; H, 4.74; N, 7.33. Found: C, 50.11; H, 4.77; N, 7.20.

5′-Azido-2′,5′-dideoxyuridine was prepared as for 5′-azido-5′-deoxythymidine in 86% yield as colorless needles: mp 139.5–140.5°; nmr ($(CD_3)_2SO$) δ 2.22 (t, 1, J = 6.5 Hz, H-2′a,2′b), 3.54 (d, 2, J = 5 Hz, H-5′a,5′b), 3.67–4.00 (two overlapping triplets, 1, $J_{3',4'}$ = 5 Hz, $J_{4',5'}$ = 4 Hz, H-4′), 4.03–4.36 (q, 1, J = 5 Hz, H-3′), 5.35 (br s, 1, C-3′ OH), 5.64 (d, 1, J = 8 Hz, H-5), 6.17 (t, 1, J = 6.5 Hz, H-1′), 7.62 (d, 1, J = 8 Hz, H-6), 11.16 (br s, 1, H-3).

Anal. Calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.66. Found: C, 42.89; H, 4.47; N, 27.39.

5′-Amino-2′,5′-dideoxyuridine (1b) was prepared as for **1a** in 93% yield as a colorless solid: mp 230° dec; nmr ($(CD_3)_2SO$) δ 2.12 (q, 2, J = 7 and 5 Hz, H-2′a,2′b), 2.77 (br m, 2, H-5′a,5′b), 3.68 (m, 1, H-4′), 4.18 (m, 1, H-3′), 4.85 (br s, 4, C-3′ OH, C-5′ NH_2, and H-3), 5.60 (d, 1, J = 8 Hz, H-5), 6.10 (t, 1, J = 7 Hz, H-1′), 7.75 (d, 1, J = 8 Hz, H-6).

Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.52; H, 5.75; N, 18.21.

2′,5′-Dideoxy-5′-*N*-(β-methoxy-α-methylacryloyl)ureidouridine (2b) was prepared as for **2a** in 54% yield. Due to difficulty in handling, only a very small amount of **2b** was obtained in analytical purity: mp 222.5–223.5°. The remainder was used directly in the next step.

Anal. Calcd for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 48.69; H, 5.58; N, 15.29.

2′,5′-Dideoxy-5′-(1-thyminyl)uridine (3b) was prepared as for **3a** in 56% yield as a colorless powder: mp 277° dec; $\lambda_{max}^{H_2O}$ 260.5 nm (ε 16,990), $\lambda_{min}^{H_2O}$ 232 (4580); $\lambda_{max}^{0.1\ N\ HCl}$ 260.5 (17,010), $\lambda_{min}^{0.1\ N\ HCl}$ 232 (4580); $\lambda_{max}^{0.1\ N\ NaOH}$ 263 (12,650), $\lambda_{min}^{0.1\ N\ NaOH}$ 243.5 (8680); nmr ($(CD_3)_2SO$) δ 1.78 (s, 3, C-5′′ CH_3), 2.25 (m, 2, H-2′a,2′b), 3.98 (br s, 3, H-4′ and H-5′a,5′b), 4.25 (m, 1, H-3′), 5.53 (br s, 1, C-3′ OH), 5.70 (d, 1, J = 8 Hz, H-5), 6.22 (t, 1, J = 7 Hz, H-1′), 7.50 (d, 1, J = 1 Hz, H-6′′), 7.80 (d, 1, J = 8 Hz, H-6), 11.33 (br s, 2, H-3 and H-3′′); mass spectrum (70 eV) *m/e* (relative intensity) 336 (0.5), 225 (11), 224 (15), 207 (13), 206 (9), 140 (7), 139 (19), 127 (20), 126 (18), 125 (2), 113 (13), 112 (14), 99 (9), 97 (7), 96 (42), 82 (12), 81 (100), 70 (6), 69 (15), 68 (8), 55 (18), 54 (9), 53 (8), 43 (6), 42 (11), 41 (18), 40 (6), 39 (8), 28 (12), 27 (7).

Anal. Calcd for $C_{14}H_{16}N_4O_6$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.04; H, 4.67; N, 16.92.

Cis-Syn Photodimer *cis*-4b and Trans-Syn Photodimer 7 from 3b. A solution of 268 mg (0.8 mmol) of **3b** dissolved in 800 ml of distilled water containing 1% acetone was irradiated at 300 nm (Pyrex vessel) in a Rayonet RPR-208 reactor while sparging with a slow stream of deoxygenated nitrogen. The reaction was monitored by the change in the 260-nm absorption. After 4 hr, the absorption had dropped to 3% of its original value. The irradiated solution was heated on a steam plate for 1 hr without a resultant increase in absorbance at 260 nm, indicating the absence of any photohydrate. The solution was then concentrated under reduced pressure, resulting in the deposition of 113 mg (42%) of ***cis*-4b**: mp >350°; tlc (Eastman 6065 cellulose sheets) *n*-BuOH–AcOH–H_2O (80:12:30), R_f 0.33, *i*-PrOH–NH_4OH–H_2O (70:20:10), R_f 0.38; $\lambda_{max}^{H_2O}$ 214 nm sh (6950), $\lambda_{max}^{0.1\ N\ HCl}$ 214 sh (6980), $\lambda_{max}^{0.1\ N\ NaOH}$ 238 (11,590), $\lambda_{min}^{0.1\ N\ NaOH}$ 230 (10,510); nmr ($(CD_3)_2SO$) δ 1.32 (s, 3, C-5′′ CH), 2.41 (m, 2, H-2′a,2′b), 3.11 and 4.43 (2 d, 2, J = −15 Hz, H-5′a,5′b), 3.42 (d, 1, J = 10.5 Hz, H-5), 3.81 (d, 1, J = 7.5 Hz, H-6′′), 4.03 (br d, 1, J = 5 Hz, H-4′), 4.27 (dd, 1, $J_{5,6}$ = 10.5 Hz, $J_{6,6''}$ = 7.5 Hz, H-6), 4.36 (m, 1, H-3′), 5.38 (d, 1, J = 5 Hz, C-3′ OH), 6.33 (dd, 1, J = 7 and 3 Hz, H-1′), 10.47 (br s, 2, H-3 and H-3′′). Irradiation at δ 3.11 collapsed the δ 4.43 doublet to a singlet and irradiation at δ 4.27 collapsed the doublets at δ 3.41 and 3.81 to singlets. Upon D_2O exchange, the δ 5.38 doublet disappeared and the δ 4.36 multiplet sharpened. The mass spectrum (70 eV) exhibited *m/e* (relative intensity) 336 (1), 225 (17), 224 (21), 207 (19), 206 (8), 140 (5), 139 (18), 127 (2), 126 (11), 125 (3), 113 (14), 112 (3), 99 (5), 97 (4), 96 (30), 82 (11), 81 (100), 70 (5), 69 (6), 68 (7), 55 (17), 54 (6), 53 (5), 43 (8), 42 (7), 41 (14), 40 (3), 39 (5), 28 (39), 27 (6).

Anal. Calcd for $C_{14}H_{16}N_4O_6 \cdot 0.5H_2O$: C, 48.69; H, 4.96; N, 16.23. Found: C, 48.63; H, 5.14; N, 16.23.

The filtrate was passed down a Sephadex G-15 column (2.5 × 37 cm) to give a small amount of an oily yellow material which arose from the photochemical reaction of acetone itself and 117 mg (44%) of **7**: mp >350°; tlc (Eastman 6065 cellulose sheets) *n*-BuOH–AcOH–H_2O (80:12:30), R_f 0.16, *i*-PrOH–NH_4OH–H_2O (70:20:10), R_f 0.32; $\lambda_{max}^{H_2O}$ 214 nm sh (ε 7080), $\lambda_{max}^{0.1\ N\ NaOH}$ 214 sh (7080), $\lambda_{max}^{0.1\ N\ NaOH}$ 239 (10,510), $\lambda_{min}^{0.1\ N\ NaOH}$ 230 (9310); nmr ($(CD_3)_2SO$) δ 1.53 (s, 3, C-5′′ CH_3), 2.16 (m, 2, H-2′a,2′b), 2.81 (d, 1, $J_{5'a,5'b}$ = −15 Hz, H-5′a or H-5′b), 3.30 (d, 1, J = 9 Hz, H-5), 3.96 (m, 1, H-4′), 3.99 (d, 1, J = 5 Hz, H-6′′), 4.15 (dd, 1, $J_{5,6}$ = 9 Hz, $J_{6,6''}$ = 5 Hz, H-6), 4.31 (m, 1, H-3′), 4. 44 (dd, 1, $J_{5'a,5'b}$ = −15 Hz, J = 7.5 Hz, H-5′a or 5′b), 5.36 (d, 1, J = 5 Hz, C-3′ OH), 6.30 (d, 1, J = 7.5 Hz, H-1′), 10.24 and 10.32 (2 s, 2, H-3 and H-3′′). Irradiation at δ 2.81 collapsed the δ 4.44 doublet of doublets to a doublet and irradiation at δ 3.30 collapsed the δ 4.15 doublet of doublets to a doublet. Exchange with D_2O caused the δ 5.36 doublet to disappear and sharpened the multiplet at δ 4.31. The mass spectrum (70 eV) exhibited *m/e* (relat iveintensity) including: 336 (0.7), 225 (7), 224 (14), 207 (17), 206 (12), 140 (5), 139 (13), 127 (11), 126 (11), 125 (3), 113 (10), 112 (6), 99 (3), 97 (4), 96 (25), 82 (10), 81 (100), 70 (3), 69 (6), 68 (6), 55 (10), 54 (11), 53 (9), 43 (21), 42 (11), 41 (10), 40 (3), 39 (6), 28 (13).

Anal. Calcd for $C_{14}H_{16}N_4O_6 \cdot 0.5H_2O$: C, 48.69; H, 4.96; N, 16.23. Found: C, 48.34; H, 4.95; N, 16.16.

***o*-Xylylene Derivative 5b of *cis*-4b.** To a suspension of 105 mg (0.312 mmol) of ***cis*-4b** in 5 ml of distilled water was added 0.62 ml (0.624 mmol) of 1 *N* potassium hydroxide. After stirring for 15 min, the solution was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was dried *in vacuo* at 80° to give 137 mg of a pale yellow dipotassium salt. The salt was suspended in 25 ml of DMF and 80 mg (0.312 mmol) of *o*-xylylene dibromide was added. After stirring for 71 hr, the solution was evaporated to dryness under reduced pressure. The residue was washed with water and ethanol and dried *in vacuo* to give 138 mg (97% based on a monohydrate) of **5b** as a colorless powder: mp 279° dec; mass spectrum (70 eV) *m/e* (relative intensity) 207 (2), 206 (14), 162 (1), 132 (2), 127 (1), 126 (2), 119 (1), 118 (1), 117 (1), 113 (2), 112 (1), 110 (1), 109 (2), 104 (1), 96 (5), 95 (1), 91 (2), 82 (9), 81 (100), 80 (9), 55 (3), 54 (1), 53 (14), 44 (13), 45 (5), 39 (3), 28 (7), 27 (5). An M − 18 peak at *m/e* 420 appears in the 18-eV spectrum of **5b**.

Anal. Calcd for $C_{22}H_{22}N_4O_6 \cdot H_2O$: C, 57.89; H, 5.30; N, 12.27. Found: C, 57.78; H, 5.49; N, 11.79.

Acknowledgment. The authors are pleased to acknowledge the support of this work by a research grant (USPHS-GM-05829) from the National Institutes of Health, U.S. Public Health Service.