Stereochemically Controlled Photoreactions between Two Thymine Rings[1-3]

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Abstract: Polymethylene bridges have been employed as synthetic spacers to study interactions between pyrimidine bases. The acetone-sensitized photolysis at 300 nm of bisthymine analogs linked by polymethylene bridges between the 3,3′, 1,5′, and 1,3′ positions has yielded, by stereochemical control of intramolecular dimerization, cis–syn (**4**), trans–anti (**8**), and cis–anti (**14**) cyclobutane products, respectively. The internal dimeric photoproducts were correlated with respect to positions of linkage and relative orientations of the 5,6 double bonds, relative rates of formation within a series, and relative stabilities of the cyclobutane products with respect to acid, base, and response to 254-nm irradiation. Synthetic schemes were devised for the 3,3′-polymethylenebisthymines (**3**), 1-(uracil-5-yl)alkylthymines (**7**), and 3-(thymin-1-yl)alkylthymines (**12**). The intramolecular interactions of the two thymine units in each of these series of compounds were examined by the hypochromism (per cent) of the first ultraviolet transition with respect to the constituent half-molecules.

Polymethylene bridges, and in particular the trimethylene bridge, $-(CH_2)_3-$, have been used as synthetic spacers to study intramolecular interactions between nucleic acid bases.[4] Such bridges also provide the possibility of controlling the inter-ring interactions by attachment of the chain to different positions on the heterocyclic termini.[3] When these termini are both thymine or thymine like, the photoproducts formed on irradiation at 300 nm should depend upon the relative orientations of the pairs of C5,C6 double bonds with respect to each other. To test this thesis, series of 1,1′-,[5-7] 1,3′-, 3,3′-, and 1,5′-polymethylenebisthymines have been synthesized and their photoreactions in dilute aqueous solution at 300 nm have been examined. We have sought to correlate (a) the stereochemistry of the photoproducts with the geometry permitted or favored by the positions of linkage; (b) the relative rates of internal photodimerization as a function of chain length; (c) sensitized *vs.* unsensitized reactions as a function of both factors; and (d) relative stabilities of the photoproducts possessing different stereochemistry with respect to base and acid treatment and to irradiation with short wavelength ultraviolet light (254 nm).

Other examples involving polymethylene spacers for the investigation of internal photodimerization include α,α'-trimethylenebisnaphthalenes and related bisaromatics,[8,9] N,N'-polymethylenebismaleimides,[10,11] and 7,7′-polymethylenebisoxycoumarins.[12,13] In the solid state, the photochemical reaction of crystalline 1,1′-trimethylenebisthymine leads to a trans–syn cyclobutane polymer,[7] and an X-ray crystallographic study has shown that the process is subject to topochemical control involving the orientation of the participating orbitals, or "orbital lattice control,"[14] an important new concept. By contrast, 1,1′-trimethylenebisthymine, when irradiated at 300 nm in aqueous solution, either with or without acetone sensitization, forms the cis–syn intramolecular dimer.[7] Photochemical synthesis of a mixture of cis–syn and trans–syn internal cytobutane dimers was possible when the two thymines were maintained in close but flexible proximity by their location on the 1′ and 5′ positions of a deoxyribofuranose spacer.[15]

Within the limitation of cisoid fusions between cyclobutane and dihydropyrimidine rings, the isomeric possibilities for the thymine photodimers are cis–syn, trans–syn, cis–anti, and trans–anti, where cis and trans relate to the geometry of the cyclobutane ring and syn and anti relate to the orientation (head-to-head and head-to-tail, respectively).[16-21] All of these geo-

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(2) The present paper is No. XIII in the series on Synthetic Spectroscopic Models Related to Coenzymes and Base Pairs.

(3) For the preceding paper (XII) in the series, see N. J. Leonard and K. Ito, *J. Amer. Chem. Soc.*, **95**, 4010 (1973).

(4) D. T. Browne, J. Eisinger, and N. J. Leonard, *J. Amer. Chem. Soc.*, **90**, 7302 (1968).

(5) N. J. Leonard, K. Golankiewicz, R. S. McCredie, S. M. Johnson, and I. C. Paul, *J. Amer. Chem. Soc.*, **91**, 5855 (1969).

(6) K. Golankiewicz and L. Strekowski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **18**, 499 (1970); *Rocz. Chem.*, **45**, 3, 11 (1971).

(7) N. J. Leonard, R. S. McCredie, M. W. Logue, and R. L. Cundall, *J. Amer. Chem. Soc.*, **95**, 2320 (1973).

(8) (a) E. A. Chandross and C. J. Dempster, *J. Amer. Chem. Soc.*, **92**, 703, 3586 (1970); (b) E. A. Chandross and A. H. Schiebel, *ibid.*, **95**, 611 (1973); (c) M. Itoh, T. Mimura, and T. Okamoto, *ibid.*, **95**, 4388 (1973).

(9) See also F. Hirayama, *J. Chem. Phys.*, **42**, 3163 (1965).

(10) F. C. De Schryver, I. Bhardwaj, and J. Put., *Angew. Chem., Int. Ed. Engl.*, 8, 213 (1969).

(11) F. C. De Schryver, W. J. Feast, and G. Smets, *J. Polym. Sci., Part A-1*, 8, 1939 (1970).

(12) L. H. Leenders and F. C. De Schryver, *Angew. Chem., Int. Ed. Engl.*, **10**, 338 (1971).

(13) L. H. Leenders, E. Schouteden, and F. C. De Schryver, *J. Org. Chem.*, **38**, 957 (1973).

(14) J. K. Frank and I. C. Paul, *J. Amer. Chem. Soc.*, **95**, 2324 (1973).

(15) M. W. Logue and N. J. Leonard, *J. Amer. Chem. Soc.*, **94**, 2842 (1972).

(16) D. L. Wulff and G. Fraenkel, *Biochim. Biophys. Acta*, **51**, 332 (1961).

(17) D. Weinblum and H. E. Johns, *Biochim. Biophys. Acta*, **114**, 450 (1966).

(18) G. M. Blackburn and R. J. H. Davies, *J. Chem. Soc. C*, 2239 (1966).

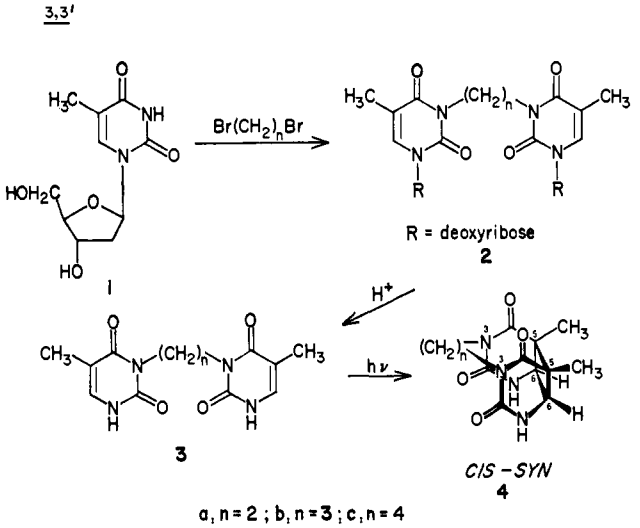
(19) Review: E. Fahr, *Angew. Chem., Int. Ed. Engl.*, 8, 578 (1969).

(20) Review: J. G. Burr, *Advan. Photochem.*, **6**, 193 (1968).

(21) In keeping with the symbolism of pyrimidine photoproducts suggested by Dr. W. E. Cohn, Director of the NAS-NRC Office of Biochemical Nomenclature, and proposed formally in an article by W. E. Cohn, N. J. Leonard, and S. Y. Wang, *Photochem. Photobiol.*, **19**, 89 (1974), using the IUPAC-IUB symbols (*Biochemistry*, **9**, 4022 (1970)), the following shortened forms can be used to designate the four cyclobutane homodimers: Thy[]Thy(c,s), Thy[]Thy(t,s), Thy[]Thy(c,a), Thy[]Thy(t,a). Thy(3(CH$_2$)$_3$3)Thy or Thy^3-C$_3$-Thy^3 is the symbol for 3,3′-trimethylenebisthymine (**3b**) and Thy[3(CH$_2$)$_3$3]Thy(c,s) the symbol for its photoproduct (**4b**). The other trimethylene-bridged precursors and photoproducts discussed in the present paper are respectively Thy(1(CH$_2$)$_3$5)Ura (**7b**) and Thy[1(CH$_2$)$_3$5]Ura(t,a) (**8b**) and Thy(1(CH$_2$)$_3$3)-Thy (**12b**) and Thy[1(CH$_2$)$_3$3]Thy(c,a) (**14b**).

metric isomers have been prepared by ultraviolet radiation of one precursor or another: DNA, TpT, frozen solutions of thymidine and thymine, and crystalline derivatives of thymine, in some cases with acetone sensitization, followed by hydrolysis and chromatographic separation of mixtures as necessary.[19,20] Linkage of the thymines by polymethylene bridges between selected positions on the nuclei afforded the possibility of obtaining *single* isomeric photoproducts of each type. Cis–syn and trans–syn photoproducts obtainable by 1,1′ linkage have already been described.[5–7,14,15]

3,3′ Linkage. If the polymethylene chain attached to two thymines at N3 is short enough, scale molecular models suggest that the photoproduct to be expected from 3,3′-polymethylenebisthymine (**3**) will have cis–syn geometry (**4**). For the synthesis of the 3,3′-poly-



methylenebisthymines with bridges consisting of n = 2, 3, and 4 methylene groups, N1 protection was used to ensure N3 alkylation.[22–28] The deoxyribosyl group offered the advantages of commercial availability (as thymidine, **1**) and of conferring water solubility which facilitated separation and purification. The reaction of 1,ω-dibromoalkanes with thymidine in dimethyl sulfoxide at room temperature gave the corresponding 3,3′-polymethylenebisthymidines (**2**) from which the protecting groups were removed by acid hydrolysis. The photoreaction of **3b** in dilute aqueous solution at 300 nm proceeded very slowly in contrast to the 1,1′-trimethylenebisthymines,[7] since the 3,3′ series exhibited practically no absorption above 300 nm. However, the acetone-sensitized (10% in water) photoreaction proceeded at a rapid, zero-order rate as measured by loss in the uv absorption maximum to less than 5% of the original value. The ethylene compound **3a** required about seven times the irradiation time of the trimethylene homolog **3b** to form a cyclobutane photoproduct, reflecting the lower probability of approach of the two C5,C6 double bonds in the molecule constrained by the shorter bridge.

The photoproducts from **3** were shown to be of the cyclobutane type by their lack of absorption maximum above 220 nm and by their photoreversion to **3** by irradiation at 254 nm, reaching apparent photostationary states containing >95, 86, and 80% of undimerized **3a**, **3b**, and **3c**, respectively. The same length bridge from 3 to 3′ in the internal photodimers, *e.g.*, Thy[3(CH$_2$)$_2$3]Thy (**4a**), introduces greater strain than from 1 to 1′ in Thy[1(CH$_2$)$_2$1]Thy.[7] The nmr spectra for the internal dimers of the 3,3′ series exhibit close parallels to the cis–syn 1,1′ series and, together with model considerations, permit the assignment of cis–syn rather than cis–anti stereochemistry (Table I).

Table I. Chemical Shift Data for Thy[3(CH$_2$)$_n$3]Thy(c,s) (**4**) Internal Dimers[a]

Assignment	n = 2	3	4
N1 H			
Singlet, 2	7.33	7.28	7.34
N3 methylene			
Two multiplets, 2 each	4.35 (sym) (ABA′B′)	4.33, 4.11 (ABXYA′B′)	4.08 Overlapping
C methylene C			
Multiplet		2.5 (br, 1) 1.8 (br, 1)	1.98
C6 H			
Singlet	4.37	4.22	4.21
C methyl			
Singlet	1.70	1.64	1.68

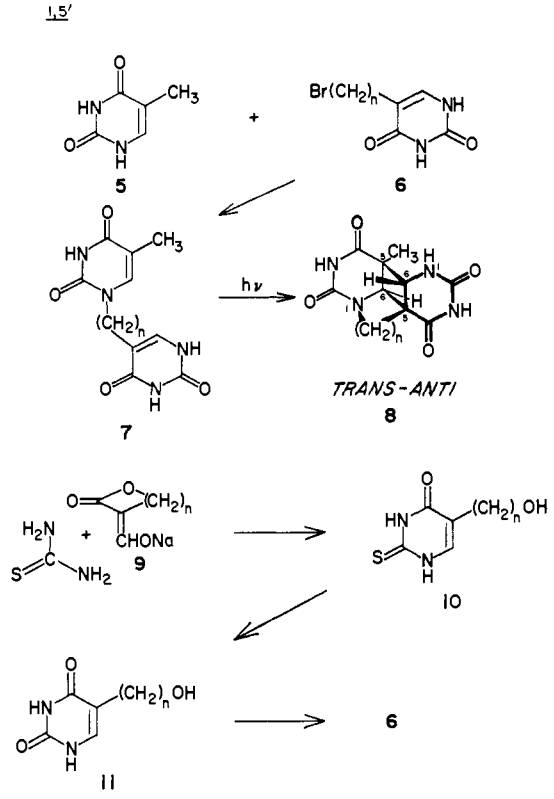
[a] 220 MHz; δ, ppm from Me$_4$Si in CF$_3$COOH.

For example, the signals for the N3-methylene protons of **4a** indicate a symmetrical ethylene bridge, ABA′B′, rather than an unsymmetrical bridge. Moreover, the nmr spectra of the internal photodimers in the 3,3′ series show that the polymethylene homologs have the same cyclobutane geometry. All of the N-methylene protons are in the deshielding region of the carbonyl groups, and one of the central methylene protons (~0.7 ppm separation between the geminal proton signals) is clearly in the deshielding region of the flanking carbonyl groups.

1,5′ Linkage. A 1,5′-polymethylene bridge between thymine and uracil (**7**) would constrain any internal photodimerization to anti (head-to-tail) orientation. Further, scale molecular models show that it would be unfavorable for a short chain (n = 2, 3, 4) to be stretched from the nitrogen so as to end up cis to the methyl. Thus, cyclobutane photoproducts of trans–anti geometry (**8**) are to be expected from Thy(1(CH$_2$)$_n$5)Ura precursors (**7**). Synthetic approaches to 5-alkyl-substituted uracils commonly involve reaction with protected 5-lithiouracils,[29] reduction of protected 6-chlorouracils,[30] or direct synthesis from α-formyl esters.[31]

(22) H. Seliger and F. Cramer, *Angew. Chem., Int. Ed. Engl.*, 8, 609 (1969).
(23) Y. Mizuno, W. Limn, K. Tsuchida, and K. Ikeda, *J. Org. Chem.*, 37, 39 (1972).
(24) A. L. Pogolotti, Jr., D. Failla, and D. V. Santi, *J. Heterocycl. Chem.*, 9, 1423 (1972).
(25) R. T. Markiw and E. S. Canellakis, *J. Org. Chem.*, **34**, 3707 (1969).
(26) R. T. Markiw, *J. Org. Chem.*, 37, 2165 (1972).
(27) A. Holý, R. W. Bald, and Ng. D. Hung, *Collect. Czech. Chem. Commun.*, 36, 2658 (1971).
(28) C. C. Price, G. M. Gaucher, P. Koneru, R. Shibahawa, J. R. Sowa, and M. Yamaguchi, *Biochim. Biophys. Acta*, **166**, 327 (1968).
(29) (a) W. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 2215 (1966); (b) D. M. Brown, M. G. Burdon, and R. P. Slatcher, *J. Chem. Soc., London*, 1051 (1968); (c) D. M. Molvey, R. D. Babson, S. Zawoiski, and M. A. Ryder, *J. Heterocycl. Chem.*, **10**, 79 (1973); (d) H. Hayashi and K. Nakanishi, *J. Amer. Chem. Soc.*, **95**, 4081 (1973).
(30) (a) A. von Merkats, *Ber.*, 52, 4489 (1907); (b) J. Shapira, *J. Org. Chem.*, 27, 1918 (1962); (c) T. D. Kilikowski and D. Shugar, *Acta Biochim. Pol.*, 18, 209 (1971).
(31) (a) T. B. Johnson and G. A. Menge, *J. Biol. Chem.*, **2**, 105 (1906); (b) J. H. Burckhalter and H. C. Scarborough, *J. Amer. Pharm. Ass.*, **44**, 545 (1955).

The 5-ω-bromoalkyluracil intermediates (**6**) were synthesized by elaboration of the preparations that have been described for 5-hydroxyethyluracil derivatives.[3,2] The condensation route involved formylation of the appropriate lactone, reaction of the sodium salt of the α-hydroxymethylene intermediate (**9**) with thiourea to give the ω-hydroxymethylene-2-thiouracil (**10**), removal of the 2-thio function by means of chloroacetic acid (→**11**), and substitution of the 5-ω-alkyl OH by the use



of hydrobromic acid. The 1-[ω-(uracil-5-yl)alkyl]thymine compounds (**7**) were formed by reaction of the 5-(ω-bromoalkyl)uracils (**6**) with excess thymine (**5**) in dimethyl sulfoxide with potassium carbonate at room temperature.[4] These compounds of the Thy(1(CH$_2$)$_n$5)Ura type (**7**) show much lower uv absorption near 300 nm than the Thy(1(CH$_2$)$_n$1)Thy series;[7] hence, the standard photoreaction at 300 nm in dilute aqueous solution was very slow. Expressed in relative terms (to compound **7a** as 1.0), the averaged times required for first-order *half-reaction* leading to internal dimers were 1:4:14 for the series n = 2, 3, and 4 (compounds **7a**, **7b**, and **7c**, respectively). Since in this series the N1 of the thymine portion, in concert with the polymethylene chain, takes part in five-, six-, and seven-membered ring formation as n = 2, 3, and 4, respectively, the relative order of the internal photodimerizations is consistent at least with the general order of rates of closure for rings of different size. In the acetone-sensitized (10% in water) irradiation of the compounds **7a–c** at 300 nm, there was a rapid zero-order decrease in the uv maximum to less than 5% of the original value. The ethylene compound **7a** reacted about 1.4 times faster than the tri- (**7b**) and tetramethylene (**7c**) homologs.

(32) (a) J. D. Fissekis, A. Myles, and G. B. Brown, *J. Org. Chem.*, **29**, 2670 (1964); (b) J. D. Fissekis and F. Sweet, *ibid.*, **38**, 264 (1973); (c) K. A. Chkhikvadze and O. Yu. Magidson, *Zh. Obshch. Khim.*, **34**, 2577 (1964); *J. Gen. Chem. USSR*, **34**, 2599 (1966).

The change in uv spectra indicates that the individual photoproducts are all of the cyclobutane type. The nmr spectra of the internal photodimers in this 1,5′ series show that the homologs have the same cyclobutane geometry. Model studies indicate that this is limited to the trans–anti possibility at least in the case of the ethylene product, Thy[1(CH$_2$)$_2$5]Ura (**8a**), and therefore that **8b** and **8c** also have the trans–anti structures indicated. For the cyclobutane product from **7a** to be cis–anti rather than trans–anti would have required a transoid configuration at the central bond of a bicyclo[3.2.0]heptane system with further restrictions imposed by the two additional nearly planar six-membered rings. The lowest-field nmr signals, 9.62 and 9.55 for **8a**, accounting for two protons exchangeable in CF$_3$COOD, were assignable to the imide (N3) protons (Table II). The next lowest field signal, 7.54 for

Table II. Chemical Shift Data for Thy[1(CH$_2$)$_n$5]Ura(t,a) (**8**) Internal Dimers[a]

Assignment	n = 2[b]	3[b]	4[c]
N3 H	9.62	9.55	9.53 (br)
Singlet, 2[d]	9.55	9.49	
N1 H			
Doublet, 1, J = 4.5 Hz[d]	7.54	7.44	7.44
C6 H, Ura			
Doublet, 1, J = 4.5 Hz[e]	4.81	4.86	4.49
C6 H, Thy			
Singlet, 1	4.36	4.36	4.20
N1 CH*H*			
Multiplet, 1	4.70	4.50	4.64
N1 C*H*H			
Multiplet, 1	3.76 (sym)	3.14	3.09
C5 CH$_2$ and CCH$_2$C	2.68 (2) (d of d)	2.7 (4) (m, br)	2.6–1.4 (6) (m's, br)
C5 CH$_3$			
Singlet, 3	1.68	1.66	1.65

[a] δ, ppm from Me$_4$Si in CF$_3$COOH. [b] 100 MHz. [c] 220 MHz. [d] Exchangeable in CF$_3$COOD. [e] Singlet in CF$_3$COOD.

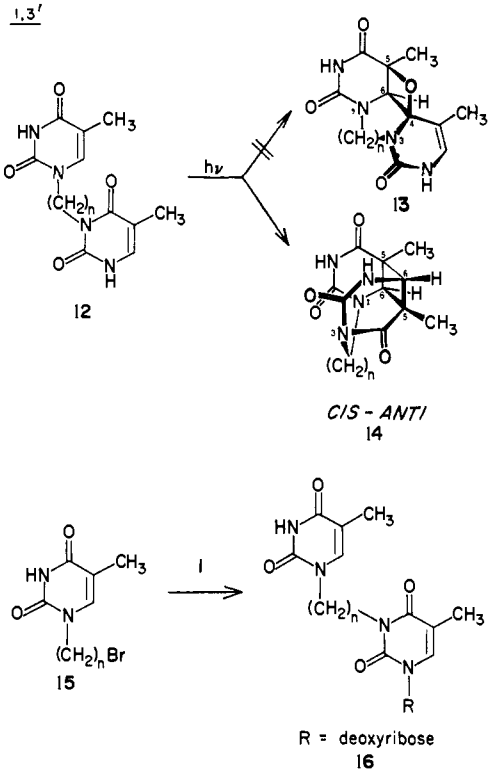
8a, corresponding to a one-proton doublet exchangeable in CF$_3$COOD, could be assigned to the N1 hydrogen of uracil, and the doublet at 4.81, to the C6 hydrogen of the uracil portion since the coupling constants were identical, J = 4.5 Hz, and the δ 4.81 signal collapsed to a singlet in CF$_3$COOD. The C6 protons (thymine portion) and the C5-methyl protons gave singlet signals which were also consistent throughout the series (Table II). The resonances of the two N1-methylene protons are well separated since one of the protons is strongly deshielded by the adjacent carbonyl. For **8a**, the upfield N1-methylene proton appears as a symmetrical multiplet, and the C5-methylene protons appear as an apparent doublet of doublets with vicinal coupling constants of 5 and 9 Hz.

Reirradiation of the reaction solutions leading to the Thy[1(CH$_2$)$_n$5]Ura(t,a) compounds (**8**) with 254-nm light did not yield photostationary states for these analogs.[33] Rather rapid changes in absorption to apparent cyclobutane photoequilibrium were followed by a slow decrease in absorbance. A probable explanation is provided by the finding of Shugar and his coworkers

(33) H. E. Johns, S. A. Rapaport, and M. Delbrück, *J. Mol. Biol.*, **4**, 104 (1962).

who observed that intramolecular electrocyclic photoaddition and subsequent cleavage of the alkyl substituent occur at short wavelengths with 5-alkyluracils.[34]

1,3′ Linkage. The 1,3′-polymethylene-linked thymines (**12**) were constructed to favor the formation of either oxetane type (**13**)[35] or cis–anti cyclobutane (**14**) photoproducts. The synthesis originated with the reaction of the 1-(ω-bromoalkyl)thymines (**15**)[4,7] with thymidine (**1**) in dimethyl sulfoxide in the presence of anhydrous potassium carbonate in a nitrogen atmosphere to yield the corresponding Thy(1(CH$_2$)$_n$3)Thd intermediate (**16**), followed by acid hydrolysis to give



the 1,3′-polymethylenebisthymines, Thy(1(CH$_2$)$_n$3)Thy (**12**). The photoreactions in this series are exemplified by the photosensitized irradiation of **12b** at 300 nm in 10% acetone in water, which proceeded rapidly in a zero-order process in which the uv absorption maximum fell to less than 5% of the original for **12b**, while a new absorption maximum developed near 236 nm. The 254-nm photoequilibrium (**12b** ⇄ **14b**) concentration of **12b** was about 94%. The product of the 300-nm photosensitized irradiation was thus shown to be a cyclobutane internal dimer by its altered ultraviolet absorption and by its photoreversibility to an open bisthymine derivative. We found no increase in absorbance at 300–320 nm upon irradiation of **12b**,[17,36] indicating that oxetane-derived photoproducts of the type identified by Wang and his coworkers[35,37] were not formed. Thus, under the conditions presently employed, an oxetane type initial photoproduct (**13b**), although sterically favored, was not produced. The cyclobutane structure shown, *e.g.*, Thy[1(CH$_2$)$_3$3]Thy(c,a) (**14b**), was favored by model studies and its cis–anti geometry was consistent with the nmr data. The methyl-protons singlet resonance was at lower field (δ 1.95) than those of **4b** (adjacent methyls) and **8b** (some carbonyl shielding), and the multiplet resonance of one of the N1-methylene protons was in the same region, shielded by the opposite carbonyl, according to the model, and at much higher field than the signals for N1-methylene protons in Thy[1(CH$_2$)$_3$1]Thy(c,s)[7] and in Thy[1(CH$_2$)$_3$5]Ura(t,a) (**8b**).

The 254-nm equilibria (**12** ⇄ **14**) for **14a** and **14c** were both at greater than 97% on the undimerized (**12**) side. Relative rates for photosensitized dimerization of the 1,3′-polymethylene-linked thymines were 3 : 4 : 4.8 for the tri-, tetra-, and dimethylene homologs **12b**, **12c**, and **12a**, respectively. The cis–anti geometry was confirmed by our ability to synthesize a cyclobutane photodimer from **12a**.

We can conclude from the samples cited that all of the internal cyclobutane dimers produced (**4**, **8**, **14**) are restricted to defined cyclobutane geometries by the positions of attachment of the linking polymethylene chains and that the C5,C6 double bonds themselves are able to undergo photocyclization in any orientation.

Photoproduct Stability. The stabilities of the photoproducts are presented in Table III. Within the series, stability under the stated conditions follows the order predicted from relative strain energies, with the shortest bridged compound (C$_2$) being the least stable. It is of special interest to compare the stabilities of our photoproducts as a function of their stereochemical structures with the stabilities of the corresponding photodimeric thymines of similar cyclobutane geometry. For example, the trans–anti photodimer of thymine, Thy[]Thy(t,a),[21,38] and both anti dimers of uracil[39] yield monomeric pyrimidines in boiling water. In our series, only the anti compounds (**8**, **14**) undergo cyclobutane cleavage on refluxing in water; the cis–syn compounds (Thy[1(CH$_2$)$_n$1]Thy(c,s)[7] and **4** are stable. The anti dimers of thymine are reported to undergo cyclobutane ring opening to monomer molecules under alkaline conditions,[38] although there is some controversy as to the stability to base of the cis–anti *vs.* the trans–anti dimer.[40] The anti dimers of uracil[39]

Table III. Photoproduct Stability

Conditions	N1 to N1[a] cis–syn[7]	**8** N1 to C5 trans–anti	**14** N1 to N3 cis–anti	**4** N3 to N3 cis–syn
H_2O reflux	+	−	−	+
0.1 *N* NaOH, room temp	+	−	−	+
HCl 6 *N* 24 hr, room temp	+	+	−	+
HCl 6 *N*, 100°, 2 hr	+	−	−	+

[a] The positions of attachment of the polymethylene bridges are indicated.

(34) (a) I. Pietrzykavska and D. Shugar, *Acta Biochem. Pol.*, **17**, 361 (1970); (b) E. Krajewska and D. Shugar, *Science*, **173**, 435 (1971).
(35) M. N. Khattak and S. Y. Wang, *Science*, **163**, 1341 (1969).
(36) M. L. Pearson, P. Ottensmeyer, and H. E. Johns, *Photochem. Photobiol.*, **4**, 739 (1965).
(37) A. J. Varghese and S. Y. Wang, *Science*, **160**, 186 (1968); *ibid.*, **156**, 955 (1967).
(38) M. A. Herbert, J. C. LeBlanc, D. Weinblum, and H. E. Johns, *Photochem. Photobiol.*, **9**, 33 (1969).
(39) B. H. Jennings, S. Pastra-Landis, and J. W. Lerman, *Photochem. Photobiol.*, **15**, 479 (1972).
(40) T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, **93**, 3493 (1971).

and 6-methyluracil[41] are opened to their monomers in concentrated NH_4OH and in 2 *N* NaOH, respectively. In our series, the anti compounds (**8**, **11**) were found to be unstable to 0.1 *N* NaOH at room temperature, with regeneration of the original precursors of the photoproducts. The anti dimers of 6-methyluracil[41] and of thymine[38,42,43] are also unstable to strong acid. Again, the anti compounds **8** and **14** also showed susceptibility to acid to the degree shown in Table III. Khattak and Wang[41] have proposed satisfactory generalized mechanisms to account for the instability of the anti compounds and the stability of the syn compounds with respect to acid and base. The internal photodimers here described can fit these differentiating patterns; moreover, their behavior is diagnostic[41] of the assigned anti and syn structures.

Hypochromism. The ultraviolet absorption spectra of the polymethylenebisthymines and the corresponding "half" molecules, the 1-, 3-, and 5-propylthymines, were determined in aqueous solution at concentrations low enough (*ca.* 5×10^{-5} *M*) to avoid intermolecular association so that perturbations resulting from the 1:1 interaction between a pair of thymines within the same molecule alone would be detected. From the ultraviolet spectra, the per cent hypochromism, *H*, was calculated for the long wavelength band as for previous models,[3,4] with the results shown in Table IV. The

Table IV. Computed Per Cent Hypochromism, *H*, of Polymethylenebisthymines[a]

1,1′ Series[7]	*H*, %	1,3′ Series (**12**)	*H*, %
n = 2	6.6	*n* = 2	4.8
3	10.5[b]	3	8.9
4	4.6	4	6.7
5	7.2		
6	3.9		
3,3′ Series (3)	***H*, %**	**1,5′ Series (7)**	***H*, %**
n = 2	3.9	*n* = 2	7.8
3	4.5	3	6.8
		4	5.2

[a] Aqueous solution, pH 7, 0.05 *N* phosphate buffer. These values are considered reproducible to ±0.4. [b] This value is refined over that previously reported[4] by taking a different cut-off point for this compound and the others in the series.

uniqueness of water as a solvent for favoring intramolecular interaction between the thymine rings may again be stressed, since the hypochromism vanishes in ethanol solution.[4]

In general, for the 1,1′, 3,3′, and 1,3′ series, the trimethylene-bridged members show the largest hypochromism, consistent with the greater probability in these compounds of the planar rings assuming near parallelism in interacting conformations. Also in general, for *n* = 2 and 3, the 1,1′ series shows larger hypochromism values than the other series. If we consider the 1,1′ type, *e.g.*, with *n* = 3, to be near ideal for interaction or stacking and for parallel arrangement of the transition moments, the 1,3′ and 1,5′ series with *n* = 3 in similar conformations would have the moments rotated 120° (≈60°) from parallel. Thus, even for the same theoretical degree of interaction, the *H* values might be expected to be lower than that for *n* = 3 in the 1,1′ series, as is actually observed (Table IV). The lower *H* values for the 3,3′ series can be attributed to interactions which permit widest variation in the relative positions of the transition moments. The small differences in *H* reported throughout, although real in the sense of the measurements, are not sufficient to provide definitive information with respect to the interacting conformations. In this connection, the alternation of *H* values for *n* = 3, 4, 5, 6 in the 1,1′ series appears to be real, and the higher value for *n* = 5 (than for *n* = 4, 6) cannot be accommodated as a function of distance alone. As with *n* = 3, the polymethylene chain of odd-carbon length permits stacked plane-parallel structures with all chain hydrogens in gauche conformation. For the even-numbered chains several hydrogen atoms are in close contact in equivalent stacked conformers. Finally, the per cent hypochromism, as a partial means of assessing interaction, is supplementary to the relative ease of internal photodimerization within these series.

Experimental Section[44]

3,3′-Trimethylenebisthymine, Thy(3(CH_2)3)Thy (3b). A solution of 4.8 g (20 mmol) of thymidine (**1**) and 2.5 g (12.4 mmol) of 1,3-dibromopropane in 100 ml of dry $(CH_3)_2SO$ and 6.9 g of anhydrous K_2CO_3 was stirred for 12 hr under nitrogen. The suspension was filtered, the solids were washed with $(CH_3)_2SO$, and the combined filtrates were concentrated to dryness *in vacuo*. The concentrate was dissolved in 25 ml of water, applied to a 100 × 5 cm Sephadex G-10 column, and eluted with water. The concentrate from the column was treated with 210 ml of acetic acid–hydrochloric acid (2:1, v/v) on a steam bath for 1 hr. The solution was concentrated *in vacuo* to a yellow oil. Two precipitation–recrystallization steps by acidification of a basic solution of the product yielded 0.79 g (27%) of colorless microcrystals: mp >300°; nmr (CF_3COOH) δ 9.97 (br s, 2, N1 H's); 7.42 (br s, 2, C6 H's), 4.28 (t, 4, *J* = 7 Hz, N3 CH_2's), 2.23 (m, *J* = 7 Hz, CCH_2C), overlapped by 2.07 (d, *J* = 1 Hz, C5 CH_3's) (8); tlc (Eastman 6060 silica gel sheets, $CHCl_3$–CH_3OH, 4:1) R_f 0.57; (EtOAc–EtOH, 4:1) R_f 0.30; mass spectrum (10 eV) *m/e* (%1/sum) 293 (5.8), 292 (45.8), 167 (3.9) 166 (13.9), 154 (1.4), 153 (17.1), 151 (2.5), 140 (4.9), 127 (1.3).

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.27; H, 5.39; N, 19.19.

3,3′-Ethylenebisthymine, Thy(3(CH_2)$_2$3)Thy (3a). The compound was prepared from thymidine (**1**) and 1,2-dibromoethane as for **3b**. Four recrystallizations were required to give analytically pure, colorless microcrystals (15% yield): mp >300°; nmr (CF_3COOH) δ 9.83 (br s, 2, N1 H's), 7.40 (br s, 2, C6 H's), 4.60 (s, 4, N3 CH_2's), 2.02 (d, *J* = 1 Hz, 6, C5 CH_3's); mass spectrum (10 eV) *m/e* (%1/sum) 279 (4.4), 278 (21.4), 153 (8.9), 152 (32.5), 151 (4.2), 139 (1.4), 128 (1.1), 127 (16.1), 126 (1.5), 110 (2.6).

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.71, H, 5.04; N, 20.41.

3,3′-Tetramethylenebisthymine, (Thy(3(CH_2)$_4$3)Thy (3c), was isolated in 72% yield after two precipitation–recrystallization steps from the reaction of 1,4-dibromobutane with thymidine followed by hydrolysis as for **3b**: mp >300°; nmr (CF_3COOH) δ 10.0 (m, 2, N1 H's), 7.45 (m, 2, C6 H's), 4.24 (m, 4, N3 CH_2's), and 2.07 (s) and 1.9 (m, C5 CH_3's and C–CH_2CH_2–C) (10).

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(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. J. Nemeth and his staff at the University of Illinois, who weighed samples for quantitative ultraviolet spectra. We sought advice from *Chemical Abstracts* on the naming of the photoproducts, but the systematic names are very complicated and not very revealing. We have elected to use the approved abbreviations[21] and formulas for illustration.

Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.65; H, 6.08; N, 18.27.

5-(3-Hydroxypropyl)-2-thiouracil (10b). A 14-g portion of 50% sodium hydride in oil was washed well with pentane and suspended by stirring in 300 ml of anhydrous ethyl ether cooled on an ice bath. A mixture of 20.0 g (0.20 mol) of δ-valerolactone (**9b**) and 22.4 g (0.3 mol) of ethyl formate was added dropwise to the cooled suspension in 3 hr under nitrogen. Stirring was continued at room temperature for 4 hr and at gentle reflux for 12 hr. The volatile components were removed *in vacuo*, and the residue (**10b**) was charged with 13 g (0.17 mol) of thiourea and 300 ml of absolute ethanol. The new solution was heated at reflux for 8 hr and concentrated to a tan solid under reduced pressure. This residue was treated with 300 ml of water, the basic solution was filtered, and neutralization with hydrochloric acid yielded a light tan precipitate. Recrystallization from water afforded 18.1 g (49% based on lactone) of transparent needles: mp 181–183°; tlc (Eastman 6060 silica gel sheets, $CHCl_3$–CH_3OH, 4:1) R_f 0.57, thiourea 0.52, (EtOAc–EtOH, 4:1) R_f 0.49, thiourea 0.48; nmr (CF_3COOH) δ 7.40 (s, 1, C6 H), 4.46 (t, 2, J = 5.5 Hz, CH_2OH), 2.63 (m, 2, C5 CH_2), 2.15 (m, 2, CCH_2C); mass spectrum (14 eV) *m/e* (%I/sum) 188 (1.9), 187 (2.6), 186 (33.2), 168 (13.8), 156 (2.0), 155 (3.3), 142 (16.0), 141 (2.5), 129 (2.3), 110 (2.7), 109 (3.0), 96 (2.5), 84 (2.7), and 82 (5.2).

Anal. Calcd for $C_7H_{10}N_2O_2S$: C, 45.15; H, 5.41; N, 14.76. Found: C, 45.12; H, 5.40; N, 14.76.

5-(4-Hydroxybutyl)-2-thiouracil (10c) was prepared as for **10b** with a yield of 45% (based on ε-caprolactone) of tan needles from a bright yellow intermediate: mp 162°; tlc (Eastman 6065 cellulose sheets, *n*-PrOH·H_2O, 7:3) R_f 0.87, thiourea 0.69; nmr (CF_3COOH) δ 7.3 (s, 1, C6 H), 4.45 (t, 2, J = 5.5 Hz, CH_2OH), 2.53 (t, 2, J = 6.5 Hz, C5 CH_2), and 1.8 (m, 4, CCH_2CH_2C); mass spectrum (14 eV) *m/e* (%I/sum) 202 (1.9), 201 (4.0), 200 (31.6), 183 (1.2), 182 (7.4), 170 (4.3), 169 (1.7), 156 (2.7), 155 (8.1), 154 (9.4), 142 (3.0), 141 (7.8), 129 (3.3), 96 (1.6), and 82 (3.6).

Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 47.93; H, 6.04; N, 13.99.

5-(3-Bromopropyl)uracil (16b). A solution of 24.2 g (0.13 mol) of 5-(3-hydroxypropyl)-2-thiouracil (**10b**) in 750 ml of 10% chloroacetic acid was heated at reflux for 10 hr and cooled to give a colorless precipitate which was collected, washed with water, and recrystallized from water: yield, 17.0 g (77%) of **11b** as colorless microcrystals. A stirred suspension of 16.6 g of the crude product in 90 ml of 48% hydrobromic acid was treated with hydrogen bromide until solution was complete. The clear solution was heated at 85–90° for 3 hr. Precipitation was noted within 1.5 hr. The suspension was cooled and filtered, and the precipitate was washed well with cold water to yield 16.8 g (74%) of colorless plates: mp 258–259°; nmr (CF_3COOH) δ 7.48 (s, 1, C6 H), 3.43 (t, 2, J = 6 Hz, CH_2Br), 2.69 (t, 2, J = 7 Hz, C5 CH_2), and 2.17 (m, 2, CCH_2C); mass spectrum (14 eV) *m/e* (%I/sum) 234 (3.3), 232 (3.3), 154 (3.7), 153 (39.0), 139 (4.2), 126 (21.6), 125 (13.6), 110 (2.5), and 82 (6.3).

Anal. Calcd for $C_7H_9BrN_2O_2$: C, 36.07; H, 3.89; N, 12.02. Found: C, 36.23; H, 3.89; N, 12.07.

5-(4-Bromobutyl)uracil (16c) was prepared as for **16b** from 5-(4-hydroxybutyl)-2-thiouracil (**10c**) through **11c** in an overall yield of 61% as tan microcrystals: mp 242–243° dec; nmr (CF_3COOH) δ 7.38 (s, 1, C6 H), 3.40 (t, 2, J = 6 Hz, CH_2Br), 2.49 (t, 2, J = 6 Hz, C5 CH_2), and 1.85 (m, 4, CCH_2–CH_2C); mass spectrum (14 eV) *m/e* (%I/sum) 248 (0.71), 246 (0.74), 168 (4.4), 167 (36.5), 153 (2.0), 140 (1.5), 139 (7.1), 126 (2.5), 125 (27.0), 94 (1.3), and 82 (13.8).

Anal. Calcd for $C_8H_{11}BrN_2O_2$: C, 38.89; H, 4.49; N, 11.34. Found: C, 39.01; H, 4.64; N, 11.33.

1-[4-(Uracil-5-yl)butyl]thymine, Thy(1(CH_2)$_4$5)Ura (7c). A solution of 2.47 g (10 mmol) of 5-(4-bromobutyl)uracil (**6c**) and 6 g (50 mmol) of thymine (**5**) in 75 ml of dry dimethyl sulfoxide and 2.8 g of anhydrous potassium carbonate was stirred for 9 hr in a dry nitrogen atmosphere. The suspension was filtered and washed well with $(CH_3)_2SO$, and the filtrate was evaporated to dryness *in vacuo*. The residue was suspended in 75 ml of warm dimethylformamide, the suspension was filtered, and the cooled filtrate was applied to a 110 × 5.0 cm Sephadex LH-20 column packed in DMF and eluted with the same solvent. The first (product) fraction was concentrated under reduced pressure and crystallized from water to yield 2.14 g (73%) of colorless microcrystals: mp 261–262°; nmr (CF_3COOH, 100 MHz) δ 8.64 and 8.57 (ss, 2, C6 H's), 4.08 (t, 2, J = 6.5 Hz, N1 CH_2), 2.63 (t, 2, J = 6.5 Hz, C5 CH_2), and 2.13 (s) and 1.9 (br m, 7, C5 CH_3 and CCH_2CH_2C); mass spectrum (10 eV) *m/e* (%I/sum) 293 (1.5), 292 (7.3), 167 (7.2), 166 (18.8), 154 (7.4), 153 (2.9), 140 (2.7), 139 (1.4), 127 (3.5), 126 (26.7), 83 (3.8), and 55 (6.7).

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.44; H, 5.39; N, 19.31.

1-[2-(Uracil-5-yl)ethyl]thymine, Thy(1(CH_2)$_2$5)Ura (7a), was prepared from 5-(2-bromoethyl)uracil (**6a**)[3,2c] as for **7c** in 39% yield as colorless microcrystals: mp >310°; tlc (Eastman 6065 cellulose sheets, *n*-PrOH·H_2O, 7:3) R_f 0.66, thymine 0.78, (Eastman silica gel sheets, EtOAc–EtOH, 4:1) R_f 0.21, thymine 0.39; nmr (CF_3COOH) δ 7.46 (s) and 7.36 (d, 2, J = 1 Hz, C6 H's), 4.07 (t, 2, J = 6.5 Hz, N1 CH_2), 2.87 (t, 2, J = 6.5 Hz, C5 CH_2), and 2.01 (s, 3, C5 CH_3); mass spectrum (10 eV) *m/e* (%I/sum) 264 (5.3), 140 (2.3), 139 (12.0), 138 (43.2), 127 (10.2), 126 (6.6), 125 (1.1), and 96 (5.3).

Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.84; H, 4.85; N, 21.17.

1-[3-(Uracil-5-yl)propyl]thymine, Thy(1(CH_2)$_3$5)Ura (7b), was prepared as for **7c** from 5-(3-bromopropyl)uracil (**6b**) to yield (28%) colorless microcrystals: mp >310°; nmr (CF_3COOH, 100 MHz) δ 7.66 (m) and 7.57 (s, 2, C6 H's), 4.10 (t, 2, J = 6.5 Hz, N1 CH_2), 2.63 (m, 2, C5 CH_2) and 2.2–2.1 (m) with 2.13 (s, 5, CCH_2C and C5 CH_3); mass spectrum (10 eV) *m/e* (%I/sum) 279 (2.6), 278 (14.4), 263 (1.5), 166 (1.1), 154 (1.8), 153 (11.6), 152 (7.8), 141 (2.4), 140 (24.2), 139 (9.2), 127 (1.9), 126 (12.6), 110 (2.0), 83 (2.0), and 55 (2.5).

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.81; H, 5.23; N, 20.16.

1-[3-(Thymin-3-yl)propyl]thymine, Thy(1(CH_2)$_3$3)Thy (12b). A solution of 2.47 g (10 mmol) of 1-(3-bromopropyl)thymine (**15b**)[4] and 4.84 g (20 mmol) of thymidine (**1**) in 100 ml of dry dimethyl sulfoxide and 4.1 g of anhydrous K_2CO_3 was stirred overnight in a nitrogen atmosphere. The reaction mixture was filtered, the filter cake was washed well with dimethyl sulfoxide, and the combined filtrates were concentrated to dryness *in vacuo*. The residue was dissolved in 25 ml of water, applied to a 100 × 5 cm Sephadex G-10 column, and eluted with water. The concentrated eluate containing **16b** was heated with 210 ml of acetic acid–hydrochloric acid (2:1, v/v) on a steam bath for 1 hr. The solution was concentrated *in vacuo* to a yellow gum. This was dissolved in 2 ml of formic acid, applied to a 100-g silica gel column packed in chloroform–methanol (4:1, v/v), and eluted with the same solvent. Recrystallization of the middle fraction from water yielded 1.46 g (50%) of cream colored microcrystals: mp >300°; nmr (CF_3COOH) δ 7.67 and 7.45 (br ss, 2, C5 H's), 4.17 (m, 4, N1 and N3 CH's), 2.2 and 2.08 (m and s, 8, CCH_2C and C5 CH_3's); mass spectrum (10 eV) *m/e* (%I/sum) 293 (4.6), 292 (26.4), 167 (7.0), 166 (16.6), 154 (1.6), 153 (12.8), 140 (6.6), and 127 (2.8).

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.42; H, 5.74; N, 19.19.

3-[2-(Thymin-1-yl)ethyl]thymidine, Thy(1(CH_2)$_2$3)Thd (16a). A solution of 2.00 g (8.6 mmol) of 1-(2-bromoethyl)thymine (**15a**)[7] and 4.18 g (20 mmol) of thymidine (**1**) in 100 ml of dry dimethyl sulfoxide and 4.2 g of anhydrous K_2CO_3 was stirred for 12 hr. The suspension was filtered and washed well with dimethyl sulfoxide and the combined filtrates were concentrated *in vacuo* to a colorless semisolid. The residue was dissolved in 40 ml of warm water, applied to a 100 × 5 cm Sephadex G-10 column, and eluted with water. The early (product) fraction was concentrated *in vacuo* to a colorless semisolid which was twice recrystallized from *n*-propyl alcohol: yield 0.85 g (25% based on **15a**); mp 201–202°; nmr (CF_3COOH, 100 MHz) δ 7.63 and 7.54 (ss, 2, C6 H's), 6.35 (m, 1, C1′ H), 4.85 and 4.3 (mm's, 8, $-CH_2CH_2-$, C3′ H, C4′H, and C5′ H's), 2.65 (m, 2, C2′ H's), and 2.03 (s, 6, C5 CH_3's); mass spectrum (70 eV) *m/e* (off-scale spectrum) 395 (1.8) $(M + 1)^+$, 292 (2.9), 281 (1.1), 280 (8.6), 279 (46.2), and 278 (100, off scale).

Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.62; N, 14.71. Found: C, 51.73; H, 5.70; N, 14.43.

1-[2-(Thymin-3-yl)ethyl]thymine, Thy(1(CH_2)$_2$3)Thy (12a), was prepared by hydrolysis of **16a** with hydrochloric acid–acetic acid (2:1, v/v) as for **12b** and the product was recrystallized twice from water as colorless microcrystals: yield 55%; mp >300°; nmr (CF_3COOH, 100 MHz) δ 7.48 and 7.42 (mm, 2, C6 H's), 4.42 (sym m, A_2B_2, 4, CH_2CH_2), and 2.02 (s, 6, CH_3's).

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.11; N, 20.13. Found: C, 51.73; H, 5.10; N, 19.99.

1-[4-(Thymin-3-yl)butyl]thymine, Thy(1(CH_2)$_4$3)Thy, (12c) was prepared from 1-(4-bromobutyl)thymine[7] as for **12a** in 50% yield after two recrystallizations from water: mp >300°; nmr (CF_3COOH) 7.53 and 7.46 (ss, 2, C6 H's), 4.12 (mm, 4, N1 and N3 C_2H's), and 2.08 (s) with 1.9 (m, 10, C5 CH_3's and CCH_2CH_2C); mass spectrum (10 eV) *m/e* (%I/sum) 307 (5.9), 306 (35.1), 291

(3.0), 181 (4.8), 180 (21.4), 167 (9.8), 165 (1.0), 154 (2.3), 153 (2.5), 140 (2.8), 139 (1.1), 127 (3.8), and 126 (2.8).

Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.83; H, 6.03; N, 18.04.

Photosensitized irradiations were performed in deoxygenated distilled water containing 10% acetone within a Rayonet RPR-208 reactor equipped with 300-nm lamps. Solutions were made by dissolving the bisthymine type compound in boiling water, cooling the solution in a Pyrex reaction vessel equipped with an inlet tube for sparging with deoxygenated nitrogen, and adding redistilled acetone to bring the solution to 1 m*M* analog concentration. Reaction progress and acetone concentration were monitored by uv absorption, and acetone was added periodically to maintain an approximately steady concentration of photosensitizer. Substrate aliquots were concentrated to dryness *in vacuo* and diluted to volume. In each photosensitized reaction the final aliquot exhibited no uv absorption peak near 270 nm for starting material, and absorption near 270 nm was less than 5% of the original and was part of a smooth tailing curve from a low-wavelength peak. No absorption was noted above 290 nm in any experiment, and in each case disappearance of the bisthymine absorbance was linear with respect to time.

Cis-syn photoproduct Thy[3(CH$_2$)$_3$3]Thy(c,s) (4b) was prepared from 292 mg (1 mmol) of 3,3′-trimethylenebisthymine, Thy(3-(CH$_2$)$_3$3)Thy (**3b**). The reaction was complete within 35 min in our system. Concentration under reduced pressure to 100 ml and cooling yielded 269 mg (89%) of cream colored microcrystals. Recrystallization from water removed a slight impurity of acetone polymer to yield colorless microcrystals: mp >300°; uv (pH 7) shoulder at 218; 270 nm (ϵ 330), $\lambda_{max}^{pH\ 1}$ 215 (8070); nmr (Table I); mass spectrum (10 eV) *m/e* (%1/sum) 292 (2.7), 167 (6.3), 166 (16.6), 154 (2.4), 153 (27.6), 152 (1.1), 151 (9.4), 141 (1.1), 140 (10.8), 127 (5.7), 126 (1.3), 110 (1.7), 84 (1.9), and 83 (2.0).

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.27; H, 5.39; N, 19.19.

Thy[3(CH$_2$)$_2$3]Thy(c,s), 4a, was prepared by the same method using acetone as the photosensitizer: colorless microcrystals; mp >300°; nmr (Table I).

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.71; H, 5.04; N, 20.14.

Thy[3(CH$_2$)$_4$3]Thy(c,s) (4c). The cis–syn photoproduct of **3c** was isolated in 75% yield as colorless microcrystals: mp >300°.

Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 55.05; H, 6.04; N, 18.45.

Trans-anti photoproduct Thy[1(CH$_2$)$_3$5]Ura(t,a) (8b) was prepared from 278 mg (1 mmol) of 1-[3-(uracil-5-yl)propyl]thymine, Thy(1(CH$_2$)$_3$5)Ura (**7b**). Concentration of the photolysis reaction mixture at reduced pressure to about 100 ml followed by cooling yielded 211 mg (76%) of colorless microcrystals: mp >300°; uv (pH 1 and 7) shoulder at 220 nm; 270 (ϵ 100); (Table II), mass spectrum (10 eV) *m/e* (%1/sum) 279 (1.1), 278 (8.1), 263 (2.7), 206 (1.0), 154 (1.6), 153 (17.5), 152 (7.6), 149 (1.6), 141 (1.8), 140 (28.8), 139 (12.8), 127 (1.1), 126 (3.4), 110 (4.7), 96 (1.2).

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.93; H, 5.03; N, 19.84.

Thy[1(CH$_2$)$_2$5]Ura(t,a) (8a) was obtained in 75% yield from 1-[2-(uracil-5-yl)ethyl]thymine (**7a**) as colorless microcrystals: mp >300°.

Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.42; H, 4.96; N, 20.70.

Thy[1(CH$_2$)$_4$5]Ura(t,a) (8c) was obtained from 1-[4-(uracil-5-yl)-butyl]thymine (**7c**) in 76% yield: mp 253–254° dec.

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.67; H, 5.74; N, 19.03.

Cis–anti photoproduct Thy[1(CH$_2$)$_3$3]Thy(c,a) (14b) was isolated in 78% yield from the irradiation of 1-[3-(thymin-3-yl)propyl]-thymine, Thy(1(CH$_2$)$_3$3)Thy (**12b**), as colorless microcrystals: mp >300°; uv $\lambda_{max}^{pH\ 7}$ 236 (ϵ 5520), $\lambda_{min}^{pH\ 7}$ 221 (4880), $\lambda_{max}^{pH\ 1}$ 236 (5540), $\lambda_{min}^{pH\ 1}$ 221 (4900), 270 (pH 1 and 7) (ϵ 910), opening in 0.1 *N* NaOH gives two isobestic points, 255 and 237 nm; nmr (CF_3COOH, 100 or 220 MHz) δ 9.64 (s, 1, N3 H), 7.64 (s, 1, N1 H), 4.45, 4.40, 4.15, 4.0 (overlapping m's, 5, N3 CH_2, N1 C*H*H, C6 H's), 2.8 (m, 2, CCH_2C), 1.95 (s and overlapping m, 7, CH_3's and N1 CH*H*); mass spectrum (10 eV) *m/e* (%1/sum) 293 (1.1), 292 (6.1), 167 (9.8), 166 (19.7), 165 (1.0), 154 (2.0), 153 (20.5), 151 (2.1), 141 (1.2), 140 (13.3), 127 (4.4), 110 (2.5), and 83 (1.6).

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.42; H, 5.66; N, 18.96.

Thy[1(CH$_2$)$_4$3]Thy(c,a) (14c) was prepared in 75% yield by the irradiation of 1-[4-(thymin-3-yl)butyl]thymine (**12c**): colorless microcrystals; mp >300°; nmr (CF_3COOH, 100 MHz) δ 9.64 (s, 1, N3 H), 7.55 (s, 1, N1 H), 4.3–3.8 (overlapping m's, 5, N3 CH_2, N1 CH*H*, C6 H's), and 2.5 (m, N1 C*H*H), 1.92 (s, CH_3's) with 1.9–1.5 (m, $CH_2CH_2CH_2CH_2$, 11 total).

Anal. Calcd for $C_{14}H_{18}N_4O_4 \cdot {}^1/_2(H_2O)$: C, 53.33; H, 6.07; N, 17.77. Found: C, 53.16; H, 5.92; N, 17.84.

Thy[1(CH$_2$)$_2$3]Thy(c,a) (14a) was isolated by the same techniques with precipitation by ethanol as colorless hygroscopic microcrystals (65%) transparent at 270 nm. Reirradiation with 254-nm light readily regenerated the noncyclobutane starting material 1-[2-(thymin-3-yl)ethyl]thymine (**12a**). The cyclobutane product **14a** was very soluble in water: mp >300°; nmr (CF_3COOH, 100 MHz) 9.4 (br m, 1, N3 H), 7.6 (br m, 1, N1 H), 4.1, 3.4, 2.2 (overlapping m's, N3 CH_2 and N1 C*H*H), and 2.2 (m) with 1.64 (br s, N1 CH*H* and CH_3's).

Anal. Calcd for $C_{12}H_{14}N_4O_4 \cdot H_2O$: C, 48.65; H, 5.44. Found: C, 48.63; H, 5.49.

Electronic Absorption Studies. For quantitative measurements, a specified amount of material weighed to the nearest 0.002 mg was placed inside a 100-ml volumetric flask and dissolved in the appropriate amount of water. The water employed was double distilled, the second distillation being carried out in an all-glass system under a carbon dioxide free atmosphere. Three equal aliquots were withdrawn and placed in 100-ml volumetric flasks. These were diluted to give three solutions of equal volume, two in 0.05 *N* aqueous phosphate buffer adjusted to pH 7 and one in 0.1 *N* aqueous HCl or 0.1 *N* aqueous NaOH. All final solutions had peak absorbance of approximately 0.7–0.9, corresponding to a concentration of *ca.* 4–10 × 10^{-5} *M*. All spectra were determined against the appropriate blank using a matched set of cells.

Spectra of the polymethylenebisthymines and the corresponding propyl bases at pH 7 were determined a minimum of eight times, and average values of ϵ max and oscillator strength are reported (Table V). All values reported are to 0.3% standard deviations with only four above 0.2%. The electronic absorption spectra were digitized at intervals of 2.5 nm using a Benson-Lehner Corp. decimal converter Model F. Oscillator strengths were calculated from these data by an IBM 1500 computer using a program based on Simpson's rule. Hypochromism values (Table IV) were calculated as previously described.[3,4]

Table V. Ultraviolet Absorption Spectra at pH 7[a]

Compd	λ_{max}	ϵ_{max}	λ_{min}	ϵ_{min}	f[b]
Thy^1-C$_3$	272.8	9,800	236.5	1700	0.21456
Thy^1-C$_2$-Thy^1	269.0	17,080	236.0	3990	0.40079
Thy^1-C$_3$-Thy^1	270.1	16,910	236.3	3770	0.38424
Thy^1-C$_4$-Thy^1	272.2	18,540	236.9	3280	0.40959
Thy^1-C$_5$-Thy^1	272.3	18,090	237.2	3180	0.39819
Thy^1-C$_6$-Thy^1	272.5	18,770	237.5	3260	0.41229
Thy^3-C$_3$	264.8	7,090	235.7	2110	0.15222
Thy^3-C$_2$-Thy^3	264.5	13,400	236.0	4230	0.29241
Thy^3-C$_3$-Thy^3	264.8	13,420	235.8	4130	0.29064
Ura^5-C$_3$	265.2	7,880	235.4	2030	0.17130
Thy^1-C$_2$-Ura^5	268.2	14,750	235.5	3860	0.35391
Thy^1-C$_3$-Ura^5	269.2	15,580	236.0	3990	0.35959
Thy^1-C$_4$-Ura^5	269.2	16,160	235.7	3450	0.36597
Thy^1-C$_2$-Thy^3	268.8	15,500	236.0	3840	0.34927
Thy^1-C$_3$-Thy^3	269.8	14,770	237.0	3670	0.33423
Thy^1-C$_4$-Thy^3	269.2	15,250	237.0	3540	0.34218

[a] 0.05 *N* phosphate buffer, 23°. [b] Oscillator strength.

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