available through Biomedical Support Grant No. RR-07055 from the General Research Branch, Division of Research Resources, Bureau of Health Professions Education and Manpower Training, National Institutes of Health, and through a multidisciplinary research grant from the National Aeronautics and Space Administration to Washington University.

We are most grateful to R. Self and J. Eagles of the Food Reseach Institute (Norwich, England) Mass Spectrometry Group for obtaining all the high resolution, and a good part of the low resolution, mass spectral data; to M. W. Johnson of the John Innes Institute (Norwich, England) for the high resolution computer program; and to B. J. Gordon, F. R. I. Mass Spectrometry Group, for the low resolution computer program used in this work.[37]

(37) Some preliminary precise mass determinations on a few ions were made by R. Graham Cooks of the Purdue University Mass Spectrometry Center; this Center was supported by U. S. Public Health Service Grant No. FR-00354.

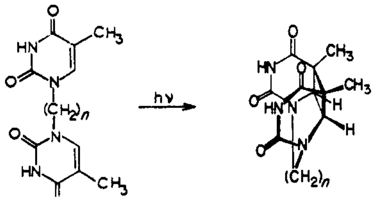
Solid State Ultraviolet Irradiation of 1,1′-Trimethylenebisthymine and Photosensitized Irradiation of 1,1′-Polymethylenebisthymines[1,2]

Nelson J. Leonard,* Robert S. McCredie, Marshall W. Logue, and Robert L. Cundall

Contribution from the Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801. *Received July 20, 1972*

Abstract: Solid state ultraviolet irradiation of 1,1′-trimethylenebisthymine (**1**) at 300 nm yielded, by topochemical control, a polymer made up of trans–syn thymine cyclobutane dimer units, each joined to the next by a trimethylene chain. Photosensitized irradiation of **1** in acetone (10%)–water solution and also of the di- and tetramethylene homologs yielded practically exclusively the cis–syn internal cyclobutane dimers. The relative rate of internal photodimerization was dependent upon the chain length ($C_3 > C_4 > C_2 > C_6$) and was maximal for the trimethylene chain. As a group, the rates were faster than those for the unsensitized internal photodimerizations in aqueous solution, reflecting the longer lifetime of the triplet state. Only in the case of **1** was the unsensitized photoreaction practical. The photosensitized irradiation of 1,1′-trimethylenebisuracil also gave a cis–syn internal dimer, the structure of which was established by spectroscopic and chemical means.

We have utilized a ribofuranose backbone[3] and a trimethylene bridge[4,5] as spacers for examining the interactions and photoreactions between two thymine rings held in close proximity. For example, 1,1′-trimethylenebisthymine (**1**), Thy-C_3-Thy or Thy-$(1(CH_2)_31)$Thy,[6] rapidly undergoes photoreaction when irradiated at 300 nm in dilute aqueous solution to form the intramolecular cis–syn photodimer **2**, Thy$[1(CH_2)_3$-$1]$Thy(c,s).[4,6] This finding has led to further questions as to the influence of chain length on the intramolecular reaction, the effect of photosensitization for both the thymine and the uracil series, and possible topochemical control[7] of the photoreaction in the solid state. To all of these questions we are now able to provide reasonable answers.



1, $n = 3$ **4**, $n = 2$
6, $n = 4$ **8**, $n = 6$

2, $n = 3$ **5**, $n = 2$
7, $n = 4$ **9**, $n = 6$

Solid State Irradiation of Thy-C_3-Thy. From the time we first utilized the trimethylene-bridged heterocycles, B–$(CH_2)_3$–B,[5] to serve as spectroscopic models of stacked base pairs in aqueous solution, we assumed that the chain length was particularly advantageous in permitting nearly plane-parallel stacking of the rings. We were somewhat gratified, therefore, that the X-ray structure analysis of crystals of Thy-C_3-Thy(**1**) as obtained from aqueous solution showed the thymine rings to be lying over each other with the exact geometry indicated in the accompanying paper by

---

(1) The present paper is no. XI in the series on Synthetic Spectroscopic Models Related to Coenzymes and Base Pairs.

(2) For the preceding paper (X) in this series, see J. H. Craig, P. C. Huang, T. G. Scott, and N. J. Leonard, *J. Amer. Chem. Soc.*, **94**, 5872 (1972), and references therein.

(3) M. W. Logue and N. J. Leonard, *ibid.*, **94**, 2842 (1972).

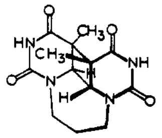
(4) N. J. Leonard, K. Golankiewicz, R. S. McCredie, S. M. Johnson, and I. C. Paul, *ibid.*, **91**, 5855 (1969).

(5) D. T. Browne, J. Eisinger, and N. J. Leonard, *ibid.*, **90**, 7302 (1968), and references therein.

(6) In keeping with the symbolism of pyrimidine photoproducts suggested by Dr. Waldo E. Cohn, Director of the NAS-NRC Office of Biochemical Nomenclature, using the IUPAC–IUB symbols (*Biochemistry*, **9**, 4072 (1970)), the following shortened forms are employed: for 1, Thy-C_3-Thy (the three-letter abbreviation is preferred over Th[5]) or, more explicitly, Thy$(1(CH_2)_31)$Thy, which indicates the position of attachment to each thymine ring and the nature and length of the chain between these; for 2, Thy$[1(CH_2)_31]$Thy(c,s), where the *brackets* indicate cyclobutane dimer formation and (c,s) indicates its cis–syn geometry; for the simple cyclobutane photodimers of thymine: Thy[ ]Thy(c,s), Thy[ ]Thy(t,s), Thy[ ]Thy(c,a), and Thy[ ]Thy(t,a), where t = trans and a = anti. Instead of brackets, the symbols ⟨ ⟩ may also be used, *e.g.*, Thy$\langle 1(CH_2)_31 \rangle$Thy(c,s) for 2.

(7) (a) M. D. Cohen and G. M. J. Schmidt, *J. Chem. Soc.*, 1996 (1964); (b) G. M. J. Schmidt, *ibid.*, 2014 (1964).

Frank and Paul.[8,9] The arrangement of the thymine rings is such that an intramolecular photodimer resulting from irradiation of the crystalline solid would be expected to attain trans–syn geometry **3**. Stewart[10] had demonstrated lattice control in the ultraviolet irradiation of a single crystal of 1-methylthymine to produce the trans–syn photodimer (Thy[ ]Thy(t,s)). We therefore irradiated a sample of crystalline 1,1′-trimethylenebisthymine (**1**), spread out in a thin layer, at 300 nm. The conversion was incomplete, but a trans–syn photoproduct was indeed formed.



3

The geometry was suggested by the nmr spectrum,[11] since both the methyl and cyclobutane protons were observed to resonate at higher field than those of the cis–syn internal dimer **2**: δ 1.29 and 3.39 compared with δ 1.42 and 3.80, in NaOD–D_2O. In contrast to the relative ease with which the cis–syn compound **2** could be isolated, either by permanganate destruction of remaining starting material or, in sensitized reactions (see below), by direct crystallization from the photoreaction solution, the trans–syn material proved difficult to handle. The material was insoluble in a wide variety of solvents except for aqueous alkali in which it underwent partial degradation. The insolubility was turned to good advantage in that all of the Thy-C_3-Thy could be leached from the solid state reaction mixture with trifluoroacetic acid to leave an analytically pure amorphous solid, $(C_{13}H_{16}N_4O_4)_x$. On the basis of its insolubility in comparison with other products,[11,12] we were forced to conclude that the solid state photoproduct is polymeric. It would not be expected to be homogeneous, but we provide no confirmatory data for this property. The photochemical reaction of crystalline Thy-C_3-Thy (**1**) thus leads to a trans–syn cyclobutane polymer, (–1-Thy[ ]Thy-1-$(CH_2)_3$)–$)_x$,[6] reflecting lattice control due to the position of the thymine of one molecule relative to the thymine of the next molecule. The structural features that help decide whether intramolecular or intermolecular photoreaction takes place are discussed in detail by Frank and Paul[8] and lead to a greater appreciation of the orbital interactions involved in the process. The mass spectrum recorded from a sample of the trans–syn polymer resembled that of the cis–syn internal dimer, mp > 350°, and that of the open-chain compound, mp 330–332°,[4] with exceptions of some new peaks, or peaks of different intensity, at *m/e* values especially ±1 with respect to those for **1** and **2**.

Photosensitized Irradiation of Thy-C_3-Thy. In carrying out the photoreaction of Thy-C_3-Thy in aqueous solution at 300 nm, we were careful to employ very low concentration so as to avoid the formation of intermolecular products.[4,13] We followed this precaution in carrying out the same reaction photosensitized by acetone. Photosensitized triplet reactions have been well studied with DNA, dT-dT, thymidine, and thymine and its derivatives.[11,14–20] Acetone-sensitized irradiation of a 1 mM solution of Thy-C_3-Thy (**1**) in 1:9 acetone–water (v/v) proceeded more rapidly than the unsensitized reaction and yielded the same cis–syn product. No internal dimer other than **2**, Thy-[1$(CH_2)_3$]1]Thy(c,s), could be detected by nmr. Since the product is constrained by the trimethylene bridge to be syn, the stereochemical result is consistent with earlier findings on thymine derivatives, which showed the cis isomer to predominate among syn possibilities.

Influence of Length of Polymethylene Chain. In view of the detailed crystal structures of the trimethylene-bridged products **1** and **2**,[4,8] we felt that it would be instructive to determine the effect of changing the length of the polymethylene chain from what we considered ideal for the intramolecular dimerization. Accordingly, we prepared 1,1′-ethylenebisthymine (**4**) (Thy-C_2-Thy or Thy(1$(CH_2)_2$1)Thy), 1,1′-tetramethylenebisthymine (**6**), and 1,1′-hexamethylenebisthymine (**8**)[21] and followed their internal photodimerizations in aqueous solution, both unsensitized and sensitized with acetone. The photoreaction for the Thy(1$(CH_2)_n$1)-Thy series at 300 nm in dilute aqueous (1 mM) solution showed a marked dependence on the chain length. Irradiation led to first-order decreases in absorbance at λ_{max} to *ca.* zero absorbance at 270 nm. Reirradiation with a 254-nm source gave increases in absorbance to photoequilibrium states, for which absorbance at λ_{max} was unchanged on continued 254-nm irradiation.[22] Expressed in relative terms (to compound **1** as 1.0), the averaged times required for first-order *half-reaction* leading to internal dimers were 26, 1, and 7.5 for the series $n = 2$, 3, and 4 (compounds **4**, **1**, and **6**, respectively. For $n = 6$ (compound **8**), the reaction was much slower, and we detected no photoreaction under equivalent conditions when *n* became very large, *e.g.*, with 1-propylthymine. The percentages of undimerized Thy-C_n-Thy after 254-nm reirradiation of the photoproducts to apparent equilibrium at this wave-

---

[8] J. K. Frank and I. C. Paul, *J. Amer. Chem. Soc.*, **94**, 2324 (1973).

[9] For similar stacking of rings in another trimethylene-bridged compound, 8,8′-trimethylenebistheophylline, as determined by X-ray structure analysis, see L. S. Rosen and A. Hybl, *Acta Crystallogr., Sect. B*, 27, 952 (1971).

[10] R. F. Stewart, *Biochim. Biophys. Acta*, **75**, 129 (1963).

[11] B. H. Jennings, S.-C. Pastra, and J. L. Wellington, *Photochem. Photobiol.*, **11**, 215 (1970).

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

[13] R. Kleopfer and H. Morrison, *J. Amer. Chem. Soc.*, **94**, 255 (1972).

[14] (a) A. A. Lamola, *Photochem. Photobiol.*, **9**, 291 (1969); (b) J. Eisinger and A. A. Lamola, *Biochem. Biophys. Res. Commun.*, **28**, 558 (1967).

[15] (a) E. Ben-Hur, D. Elad, and R. Ben-Ishai, *Biochim. Biophys. Acta*, **149**, 355 (1967); (b) H. E. Johns, M. L. Pearson, J. C. LeBlanc, and C. W. Helleiner, *J. Mol. Biol.*, **9**, 503 (1964).

[16] P. L. Wagner and D. J. Bucheck, *J. Amer. Chem. Soc.*, **92**, 181 (1970).

[17] I. von Wilucki, H. Matthäus, and C. H. Krauch, *Photochem. Photobiol.*, **6**, 497 (1967).

[18] D. Elad, C. Krüger, and G. M. J. Schmidt, *ibid.*, **6**, 495 (1967).

[19] A. A. Lamola and J. Eisinger, *Proc. Nat. Acad. Sci. U. S.*, **59**, 46 (1968).

[20] A. Kornhauser, J. N. Herak, and N. Trinajstić, *Chem. Commun.*, 1108 (1968).

[21] (a) K. Golankiewiccz and L. Strekowski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **18**, 499 (1970); *Rocz. Chem.*, **45**, 3, 11 (1971), have made 1,1′-pentamethylenebisthymine and studied its spectroscopic properties. (b) See K. Golankiewicz and L. Strekowski, *Bull. Acad. Pol. Sci., Ser. Sci. Chem.*, **20**, 291 (1972), for the nmr spectrum of 5-EtUra[1$(CH_2)_3$1]5-EtUra.

[22] R. Beukers and W. Berends, *Biochim. Biophys. Acta*, **41**, 550 (1960); **49**, 181 (1961).

length for $n = 2$, 3, and 4 were observed to be 90, 60, and 85%, respectively. Solvents other than water were not investigated since we were primarily interested in the behavior of these compounds as models of dinucleotides in inter-ring interactions and photoreactions in aqueous media. The chain-length dependence is much more pronounced in this series of homologs than for the intramolecular photocycloadditions of *N*,*N*′-polymethylenebismaleimides of chain length 3–7 in acetonitrile or methylene chloride[23] or of 7,7′-polymethylenebisoxycoumarins of chain length 3–5 in methylene chloride.[24]

Acetone-photosensitized (10% in water) irradiation of the Thy-C$_n$-Thy series led to rapid, pseudo-zero-order decreases in absorbance at λ_{max}. Expressed in relative terms (to compound **1** as 1.0), the averaged times required for *complete reaction* for the series $n = 2$, 3, 4, and 6 were 5, 1, 2.5, and 20. For the photosensitized dimerization of 1-propylthymine ($n \approx$ very large), the corresponding value was 40. Complete internal photodimerization of Thy-C$_3$-Thy (**1**) in the photosensitized experiments was about five times faster than in the unsensitized experiments. Both the greater relative rates of reaction and the lower relative dependence upon chain length for the acetone-sensitized series reflect the longer lifetime of the triplet excited state. The 254-nm photoequilibrium states corresponded to those obtained in the unsensitized experiment for $n = 2$, 3, and 4, suggesting the formation of the same photoproducts. All of the internal photodimers were stable to 0.1 *N* acid and base. The structures of the internal photodimers, Thy[1(CH$_2$)$_n$1]Thy,[6] for $n = 2$ and 4 were shown to be cis–syn (**5** and **7**) by comparison of their nmr spectra with that of the known $n = 3$ dimer **2** (Table I). The strikingly similar chemical shifts of the separate N-1 methylene and the cyclobutane ring-substituent proton resonances constitute sufficient structure proof. There were no shifts of methine resonances which might indicate the formation of a trans–syn dimer.[11] The methylene protons of the $n = 2$ internal dimer resonate as a pair of AA′XX′ multiplets and for the $n = 4$ dimer the N-1 methylene protons appear as a pair of broadened doublets with a coupling constant of 14 Hz for the geminal protons. In the spectrum of the $n = 3$ dimer the N-1 methylene proton resonances are relatively more complex, the downfield signal appearing as a doublet with a coupling constant of 15 Hz, with additional superimposed structure, which is triplet-like, 3.3 Hz on each side of the doublet peaks. The higher field N-1 methylene signal appears like a broadened triplet, with separations of 12.5 Hz, which simplified to a multiplet with two major peaks separated by 10 Hz when the sample was irradiated at the lower field signal. Irradiation of the higher field signal caused the lower field signal to collapse to a singlet-like peak.

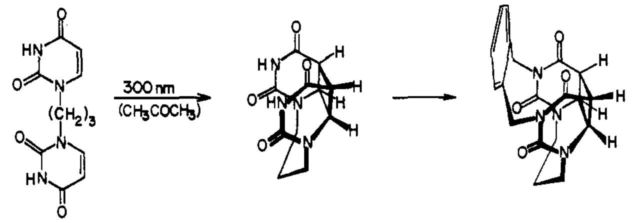
Table I. Chemical Shift Data for Thy[1(CH$_2$)$_n$1]Thy Dimers[a]

	n		
	2	3	4
Multiplet, 2 N-1 methylene, endo	4.68	4.65	4.51
Singlet, 2 6-H	4.19	4.26	4.22
Multiplet, 2 N-1 methylene, exo	3.19	3.04	3.01
Multiplet, methylene		2.3	2.0
Singlet, 6 5-CH$_3$	1.82	1.80	1.76

[a] 100 MHz; δ, ppm from Me$_4$Si in CF$_3$COOH.

Examination of models shows one proton of the N-1 methylene pair to be held in the deshielding region of the C-2 carbonyl in each of the Thy[1(CH$_2$)$_n$1]Thy dimers. Geminal coupling for the N-1 methylene protons was about 14–15 Hz. A coupling of ~10 Hz between the nondeshielded, axial-like, exo N-1 methylene proton and the central methylene proton in a trans periaxial position was sorted out for the $n = 3$ dimer, assuming predominate pseudo-chair form.[4] The side broadening on the deshielded endo proton signal can then be seen to arise from couplings with the central methylene protons of about 3–4 Hz. The chemical shifts, spin–spin coupling patterns, and our analysis of these for Thy[1(CH$_2$)$_3$1]Thy agree with the more detailed treatment of the nmr spectrum of 5-EtUra[1(CH$_2$)$_3$1]5-EtUra reported independently by Golankiewicz and Strekowski.[21b] The mass spectra of the Thy[1(CH$_2$)$_n$1]Thy internal dimers differed only in peak intensities from the spectra of the corresponding Thy(1(CH$_2$)$_n$1)Thy precursors.

The direct irradiation of the related 1,1′-trimethylenebisuracil (**10**),[5] Ura(1(CH$_2$)$_3$1)Ura or Ura-C$_3$-Ura, in dilute aqueous solution at 300 nm gave thermally reversible product(s) assumed to be photohydrate(s). Acetone photosensitization suppressed the photohydration process,[25] and a single internal photodimer product was obtained. The trimethylene bridge, as observed earlier, constrains the geometry of the product to syn,[26] and the stereochemistry is further defined as cis (therefore, cis–syn as in **11**, Ura[1(CH$_2$)$_3$]Ura)[6] by the nmr chemical shift of the cyclobutane ring protons, the difference in shielding of two of the trimethylene bridge protons adjacent to the N's and the formation of an *o*-xylylene derivative **12**. The last observation requires the two N-3's to be in proximity,[4] which would not be the case for the trans isomer. In **11**, the cyclobutane ring protons appear as an A$_2$B$_2$ system at δ 4.52 (CF$_3$COOH) while in the cis–syn uracil photodimer, Ura[]Ura(c,s), they appear as the same pattern at δ 4.4.[27] The geminal protons of the methylenes attached to N-1 and N-1′ are nonequivalent multiplets, δ 3.0 and 4.7, similar to **2**, in which they appear at δ 3.04



10 **11** **12**

---

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

[24] L. Leenders and F. C. De Schryver, *ibid.*, 10, 338 (1971).

(25) C. L. Greenstock and H. E. Johns, *Biochem. Biophys. Res. Commun.*, 30, 21 (1968).

(26) For uracil and its derivatives, for example, *cf.* ref 16 and 18 and D. Elad, I. Rosenthal, and S. Sasson, *J. Chem. Soc. C*, 2053 (1971); *Tetrahedron Lett.*, 4513 (1970); E. Adman and L. H. Jensen, *Acta Crystallogr., Sect. B*, 26, 1326 (1970); E. Adman, M. P. Gordon, and L. H. Jensen, *Chem. Commun.*, 1019 (1968).

(27) G. M. Blackburn and R. J. H. Davies, *Tetrahedron Lett.*, 4471 (1966).

and 4.65. The nmr data are consistent throughout, but of course the formation of **12** by treatment of the dipotassium salt of the Ura-C_3-Ura acetone-sensitized photoproduct is compelling for cis–syn stereochemistry (**11**, **12**).

In conclusion, we have demonstrated, with our colleagues Frank and Paul,[8] topochemical control in the solid state irradiation of 1,1′-trimethylenebisthymine. We have demonstrated the dependence upon chain length of the unsensitized and acetone-sensitized irradiation in dilute aqueous solution of a series of 1,1′-polymethylenebisthymines to form the corresponding internal photodimers of the cyclobutane variety. In addition, we have shown that 1,1′-trimethylenebisuracil undergoes acetone-sensitized photoreaction to give the corresponding cis–syn internal dimer. In all but the solid state irradiation case, the stereochemistry of the cyclobutane photoproducts is cis, and in all cases, the arrangement of the heterocyclic rings on the cyclobutane is forced syn by the 1,1′-polyalkylene bridge.

Experimental Section[28]

Photosensitized Irradiation of 1,1′-Trimethylenebisthymine, Thy($1(CH_2)_31$)Thy (1). A solution of 292 mg (1 mmol) of 1,1′-trimethylenebisthymine (**1**)[6] in 900 ml of boiling water was cooled, with nitrogen sparging, in a Pyrex reaction vessel, charged with 100 ml of acetone, and irradiated at 300 nm in a Rayonet RPR 208 reactor. Reaction progress and acetone concentration were determined at 15-min intervals, and acetone was added to maintain an approximately steady concentration. Ultraviolet absorption characteristic of the undimerized starting material disappeared in pseudo-zero-order manner, and reaction was complete at 105 min. The solution was concentrated *in vacuo* at low temperature to about 20 ml and cooled, to deposit 231 mg of white microcrystals. Recrystallization from water yielded 182 mg (62%) of pure colorless prisms identical with the previously reported cis–syn photoproduct (**2**): mp > 360°, confirmed by microanalysis; $\lambda_{max}^{H_2O}$ 221 nm (ϵ 4990); $\lambda_{max}^{0.1N\ HCl}$ 221 (5430); $\lambda_{max}^{0.1N\ NaOH}$ 242 (9570); λ_{min} 229 (8050). Concentration of the mother liquors and wash solutions to dryness *in vacuo* and complete dissolution in 1 *N* NaOD–D_2O showed no signals in the nmr spectrum due to unreacted starting material or to internal dimer other than Thy[$1(CH_2)_31$]Thy(c,s).[4,6]

Solid State Irradiation of 1,1′-Trimethylenebisthymine (1). A 1.0-g (3.43 mmol) sample of ground crystalline 1,1′-trimethylenebisthymine from the same source as used in the X-ray study[8] was spread in a thin layer in a 6-in. Pyrex Petri dish and irradiated at 300 nm in a Rayonet RPR 208 reactor. The irradiation was stopped after 6 days, when about a third of the starting material was estimated by nmr to have reacted. The residue was dispersed in 20 ml of trifluoroacetic acid and filtered. The insoluble material was washed sequentially with 10 ml of trifluoroacetic acid, 10 ml of water, and 10 ml of ethanol and dried *in vacuo*, yielding 100 mg (10%) of an amorphous solid: mp >360°; uv transparent above 260 nm; nmr (NaOD, D_2O) δ 1.29 (s, 6, 5-CH_3 and 5′-CH_3), 2.8 (m, 2, CCH_2C), 3.39 (s, 2, 6-H and 6′-H), 3.8 (m, 4, NCH_2C); ν_{max}^{KBr} 1690 cm^{-1} (br).

Anal. Calcd for $(C_{13}H_{16}N_4O_4)_x$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.20; H, 5.52; N, 18.83.

1-(2-Bromoethyl)thymine. A solution of bis(trimethylsilyl)thymine[29] in dry 1,2-dibromoethane maintained at 50° under dry nitrogen for 7 days gave 1-(2-bromoethyl)thymine in 55% yield under these mild conditions,[6] mp 197–198°.

Anal. Calcd for $C_7H_9BrN_2O_2$: C, 36.07; H, 3.89; N, 12.02. Found: C, 36.19; H, 3.87; N, 11.95.

1-(4-Bromobutyl)thymine. This compound was prepared in the same way from bis(trimethylsilyl)thymine and 1,4-dibromobutane in 91% yield, mp 134–135°.

Anal. Calcd for $C_9H_{13}BrN_2O_2$: C, 41.40; H, 5.02; N, 10.73. Found: C, 41.71; H, 5.05; N, 10.89.

1,1′-Ethylenebisthymine, Thy($1(CH_2)_21$)Thy (4), was prepared from 1-(2-bromoethyl)thymine and thymine by the same method employed for the trimethylene compound,[6] yield 77%, mp >310°.

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.65; H, 5.03; N, 20.18.

1,1′-Tetramethylenebisthymine, Thy($1(CH_2)_41$)Thy (6), was prepared from 1-(4-bromobutyl)thymine and thymine by the same procedure, yield 51%, mp >320°.

Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.75; H, 5.93; N, 18.36.

1,1′-Hexamethylenebisthymine, Thy($1(CH_2)_61$)Thy (8), was prepared similarly in this laboratory, first by Dr. K. Golankiewicz, from 1-(6-bromohexyl)thymine[6] and thymine, yield 38%, mp 236–237°.

Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.48; H, 6.70; N, 16.50.

Photosensitized irradiation of 1,1′-ethylenebisthymine, Thy($1(CH_2)_21$)Thy (4), was carried out as in the case of 1,1′-trimethylenebisthymine (see above). After 8 hr the isolated yield of pure product **5** was 77%: mp >310°; mass spectrum (10 eV) *m/e* (% I/sum) 278 (1.1), 154 (1.4), 153 (17.3), 152 (53.8), 139 (1.8), 127 (4.0), 126 (3.3), 110 (1.8), 109 (6.8), and 96 (2.2).

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.37; H, 4.95; N, 20.38.

The combined filtrates were concentrated *in vacuo* to a light tan powder, for which the nmr spectrum was determined in trifluoroacetic acid. No signals other than those of Thy[$1(CH_2)_21$]Thy(c,s) (**5**) were noted.

Photosensitized irradiation of 1,1′-tetramethylenebisthymine, Thy($1(CH_2)_41$)Thy (6), was carried out for 5 hr under the same conditions; isolated yield of **7**, 72%; mp >310°; mass spectrum (10 eV) *m/e*(% I/sum) 181 (7.5), 180 (48.4), 167(4.3), 154 (7.6), 153 (4.4), 140 (1.4), 139 (2.8), 127 (2.1), 126 (8.3), and 110 (1.4).

Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 55.01; H, 5.92; N, 18.34.

Concentration of the mother liquors and wash solutions to dryness *in vacuo* and complete dissolution in trifluoroacetic acid gave a solution which showed no nmr signals due to starting material or to dimer other than Thy($1(CH_2)_41$]Thy(c,s) (**7**).

Photosensitized Irradiation of 1,1′-Trimethylenebisuracil, Ura($1(CH_2)_31$)Ura (10). A stirred solution of 64 mg (0.25 mmol) of 1,1′-trimethylenebisuracil (**10**) in 225 ml of boiling water was cooled, with nitrogen sparging, in a Pyrex vesssl. The cooled solution was charged with 25 ml of acetone and irradiated at 300 nm in a Rayonet RPR-208 reactor. Additional 10-ml portions of acetone were added after 1 and 2 hr irradiation time. After 3 hr an acetone-free aliquot exhibited no absorbance at 260 nm due to unreacted starting material, and another acetone-free aliquot was refluxed for 1 hr with no accompanying absorbance change. Concentration of the reaction mixture at low temperature *in vacuo* to 10 ml and cooling yielded 41 mg (64%) of colorless microcrystals which were recrystallized from water to yield Ura[$1(CH_2)_31$]Ura(c,s)[6] (**11**): mp >300°; $\lambda_{max}^{H_2O}$ sh 220 nm (ϵ 5350); $\lambda_{max}^{0.1N\ HCl}$ sh 219 (5420); $\lambda_{max}^{0.1N\ NaOH}$ 241 (9800), λ_{min} 228 (7500); nmr (CF_3COOH) δ 4.7 (m, 2 H, NCH*H*), 4.52 (m, 4 H, C_5H's and C_6H's), 3.02 (m, 2 H, NC*H*H), 2.0 (m, 2 H, CCH_2C); ν_{max}^{KBr} 1690 cm^{-1} (br).

Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.85; H, 4.74; N, 20.95.

Concentration of the combined filtrates to dryness gave a tan residue which was dissolved in trifluoroacetic acid and examined by nmr. No signals attributable to species other than Ura[$1(CH_2)_31$]-Ura (**11**) were observed.

***o*-Xylylene Derivative (12) of 11.** To a suspension of 100 mg (0.39 mmol) of **11** was added 0.76 ml (0.758 mmol) of 1 *N* KOH. After 15 min the solution was filtered, evaporated to dryness under reduced pressure, and dried *in vacuo* at 80°. The resulting powdery dipotassium salt of **11** was suspended in 25 ml of $HCONMe_2$ and 98.5 mg (0.37 mmol) of *o*-xylylene dibromide was added. After 12 days the reaction mixture was evaporated to dryness under reduced pressure; the residue was washed with water and ethanol and dried *in vacuo* at 139° to give 81 mg (56%) of **12**, mp 325° dec. The mass spectrum included a molecular ion at *m/e* 366. Difficulty was experienced with the nitrogen determination, although repeated checks were obtained for carbon and hydrogen.

---

[28] 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 or HA-100 spectrometer. Mass spectra were run on a Varian-MAT CH-5 spectrometer. Microanalyses were performed by Mr. Josef Nemeth and his staff at the University of Illinois, who weighed samples for quantitative ultraviolet spectra.

[29] T. Nishimura and I. Iwai, *Chem. Pharm. Bull.*, **12**, 352 (1964).

Anal. Calcd for $C_{19}H_{18}N_4O_4 \cdot H_2O$: C, 59.37; H, 5.24; N, 14.58. Found: C, 59.29; H, 5.37; N, 13.42.

Direct comparative irradiations of 1, 4, 6, and 8 and of 1-propylthymine were carried out under nitrogen in separate Pyrex test tubes on a circularly rotating reaction table which ensured constancy of the absorbed light intensity. The monomer concentrations were identical with those used in the photosensitized reactions (1 mM for **1**, **4**, **6**, and **8** and 2 mM for 1-propylthymine). Ultraviolet absorption characteristic of the undimerized starting materials diminished in a well-mannered first-order fashion. Using our apparatus, the irradiation of **4**, **6**, and **8** could not be practically carried to completion. Relative first-order half-reaction times reported in the Discussion, *i.e.*, 26, 1, and 7.5 for compounds **4**, **1**, and **6**, respectively, are averaged values from three or more independent runs on these compounds measured simultaneously.

Acknowledgment. The authors gratefully acknowledge the support of this work by Research Grant GP-8407X from the National Science Foundation. One of us (R. L. C.) has been supported by a traineeship under USPHS Trainining Grant No. GM-722. Throughout the investigation we benefitted from discussion with our colleagues Dr. JoAnn K. Frank and Professor Iain C. Paul.

Crystal and Molecular Structure of 1,1'-Trimethylenebisthymine (Thy-C_3-Thy). A Study of the Environment of a Solid State Photochemical Reaction[1]

JoAnn K. Frank and Iain C. Paul*[2]

Contribution from the W. A. Noyes Chemical Laboratory,
School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801.
Received July 20, 1972

Abstract: The crystal structure of 1,1'-trimethylenebisthymine (**1**), Thy-C_3-Thy, has been determined to provide information on the base–base interaction and to establish the lattice environment of the reactant in a solid state photochemical process. The crystals of **1** are monoclinic with a = 7.144 (1), b = 16.734 (3), c = 12.067 (2) Å, and β = 112° 39' (1'); the space group is $C2/c$. The structure was solved by the symbolic addition method and has been refined to an R factor of 0.034 on 895 nonzero reflections measured on a diffractometer. Disorder in the position of the atoms of the trimethylene bridge permits the molecule to have C_2 crystallographic symmetry and substantial intramolecular overlap of the two thymine rings. The dimensions, conformation, and crystal packing of the thymine moieties are described and compared with those found in other thymine derivatives. The thymine rings in the crystal of **1** are arranged such that both intramolecular and intermolecular photoreaction could occur, although in each case trans–syn geometry for the product would be anticipated. Chemical studies indicate a polymeric product which would arise from intermolecular reaction. A comparison of the intra- and intermolecular ring–ring interactions is given in the light of this finding.

A series of dinucleotide analogs, base-C_3-base or base(1-$(CH_2)_3$-1) base, were synthesized by Leonard and coworkers to investigate various interactions between nucleic acid bases under the constraints imposed by the trimethylene bridge.[3] One of these analogs, Thy-C_3-Thy (**1**), undergoes photoreaction in dilute aqueous solution to an intramolecular dimer (**2**) with cis–syn geometry.[4] During the X-ray study of the structure of **2**, it was observed that, in the crystal, **2** reverted to **1** to the extent of about 10%. An X-ray study of **1** was undertaken to determine the conformation of **1** in the crystal in order to assess the forces influencing conformation in this analog of thymidylyl(3'–5')thymidine (TpT). The structural results so obtained served to initiate an investigation of the solid state photoreaction as topochemical considerations would predict a product having trans–syn (as in **3**) rather than cis–syn geometry. The chemical aspects of this study are reported in the preceding paper.[5]

Experimental Section

The crystals of **1** (mp 330–332°[3]) obtained from aqueous solution are colorless, transparent, almost hexagonal-shaped plates with rounded edges. The developed face of the plate is (100). Crystal data: $C_{13}H_{16}N_4O_4$, M = 292.3; monoclinic, a = 7.144 (1), b = 16.734 (3), c = 12.067 (2) Å; β = 112° 39' (1'); V = 1331.2 × 10^{-24} cm^3, ρ_{measd} (flotation in a hexane–carbon tetrachloride mixture) = 1.45 g cm^{-3}; Z = 4; ρ_{calcd} = 1.46 g cm^{-3}; $F(000)$ = 616, μ (Cu Kα) = 9.4 cm^{-1}. With systematic absences for hkl when $h + k = 2n + 1$ and for $h0l$ when $l = 2n + 1$, the space group is either $C2/c$ or Cc.

A platelet crystal, 0.04 × 0.20 × 0.45 mm, was mounted about the elongated c axis on a Picker FACS-1 diffractometer. The cell dimensions were determined by a least-squares fit to the angular settings for ten reflections. Approximately monochromatic Cu Kα (λ 1.5418 Å) radiation was obtained by use of a nickel filter and pulse height analysis, and the diffracted intensities were measured on a scintillation counter with attenuators being inserted when necessary. The octants of data, $hk\bar{l}$ and $\bar{h}\bar{k}l$, to 2θ = 130° were measured at ambient room temperature by means of a moving crystal–moving counter technique, with a 2θ scan rate of 1°/min and 10-sec background counts at each end of the scan. The monitoring of a standard reflection after every 30 measurements indicated that no crystal decomposition occurred during data collection. Of 1113 possible unique reflections, 895 were considered to be significantly above background, *i.e.*, 200 net counts or 10%

---

(1) This work was supported in part by USPH GM 12470 and GM 19336 and by the award of an NIH biophysical predoctoral traineeship to J. K. F. (GM-722).

(2) Alfred P. Sloan Foundation Fellow, 1968–1970.

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

(4) N. J. Leonard, K. Golankiewicz, R. S. McCredie, S. M. Johnson, and I. C. Paul, *ibid.*, **91**, 5855 (1969).

(5) N. J. Leonard, R. S. McCredie, M. W. Logue, and R. L. Cundall, *ibid.*, **95**, 2320 (1973). See ref 6 of this paper for an explanation of notation for dinucleotide analogs.