Synthetic Spectroscopic Models Related to Coenzymes and Base Pairs. III. A 1,1'-Trimethylene-Linked Thymine Photodimer of *cis-syn* Structure[1]

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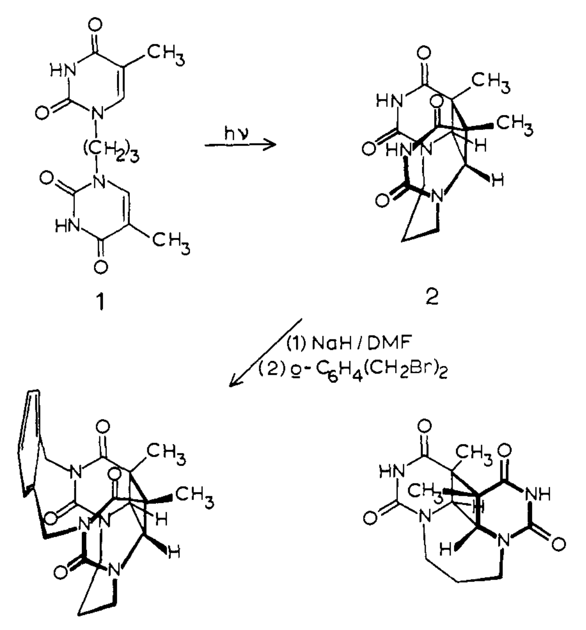
Abstract: 1,1'-Trimethylenebisthymine (**1**), Th–C_3–Th, rapidly undergoes photoreaction when irradiated at 300 nm in dilute aqueous solution to form an intramolecular dimer. The shortness of the trimethylene bridge connecting the 1- and 1'-nitrogens of the thymine moieties precludes an *anti* structure and permits only *cis-syn* (**2**) or *trans-syn* (**3**) geometry. The conversion of the internal photodimer to a product having an additional *o*-xylylene bridge between the 3- and 3'-nitrogens (**4**) excluded the *trans-syn* possibility. X-Ray study reveals that the crystals of the internal photodimer of 1,1'-trimethylenebisthymine are monoclinic, space group $P2_1/c$, with $a = 9.04$ Å, $b = 17.70$ Å, $c = 12.48$ Å, and $\beta = 138°30'$, and there are four molecules in the cell. The structure has been refined to an R factor of 0.046 on 1823 structure amplitudes collected on a diffractometer. The *cis-syn* stereochemistry (**2**) has been established for the photodimer. The virtual planarity of the cyclobutane ring results in almost complete overlap of the projections of the thymine rings in the dimer. About 10% of the molecules exist in the monomeric form after prolonged X irradiation. The complete structural analysis of crystalline Th$\widehat{C_3}$Th is of special interest because of its relationship, in *cis-syn* stereochemistry, with the major thymine photoproduct from native DNA.

We have recently reported[3] that 1,1'-trimethylenebisthymine (**1**), Th–C_3–Th,[4] in dilute aqueous solution undergoes photoreaction about 3.5 times faster than thymidylyl-(3'–5')-thymidine, TpT, reflecting a smaller time-average separation of the thymine rings in the analog **1** than in the dinucleoside phosphate. Since thymine itself in aqueous solution is almost completely insensitive to small doses of uv,[5] the rapid photoreaction of Th–C_3–Th suggested ground-state conformations of **1** favorable for internal dimerizations. Examination of models indicates that Th–C_3–Th can form products (**2, 3**) analogous to the *cis-syn-* and *trans-syn*-thymine dimers[6–13] but that the shortness of the trimethylene bridge prevents the formation of *anti*-type[10,14–16] intramolecular dimers.



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(4) The following abbreviations are used: Th, thym-1-yl; Th–C_3–Th, two thymidine moieties connected between the 1 and 1' positions by a trimethylene bridge; Th$\widehat{C_3}$Th, the intramolecular photodimer of Th–C_3–Th; TpT, thymidylyl-(3'–5')-thymidine; $\widehat{TpT}$, the photodimer of TpT; DNA, deoxyribonucleic acid; TFA, trifluoroacetic acid.

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Experimental Section

Intramolecular Photodimer (2) of 1,1'-Trimethylenebisthymine (1). A solution of 700 mg (2.4 mmol) of 1,1'-trimethylenebisthymine (**1**) in redistilled deionized water (1.4 l.) at 90° was allowed to cool to ambient temperature in a 1.5-l. quartz vessel with a stream of deoxygenated nitrogen bubbling through it. The solution was irradiated at 300 nm in a Rayonet RPR 208 reactor, and the reaction was monitored by the uv absorption at 270 nm of a 50:1 diluted aliquot of test solution after 0.5, 1, 2, and 3 hr. The absorption dropped to a minimum of 12% of its initial value after 2 hr, and after 3 hr the irradiation was discontinued. The solution was buffered at pH 9 with aqueous sodium bicarbonate to facilitate the

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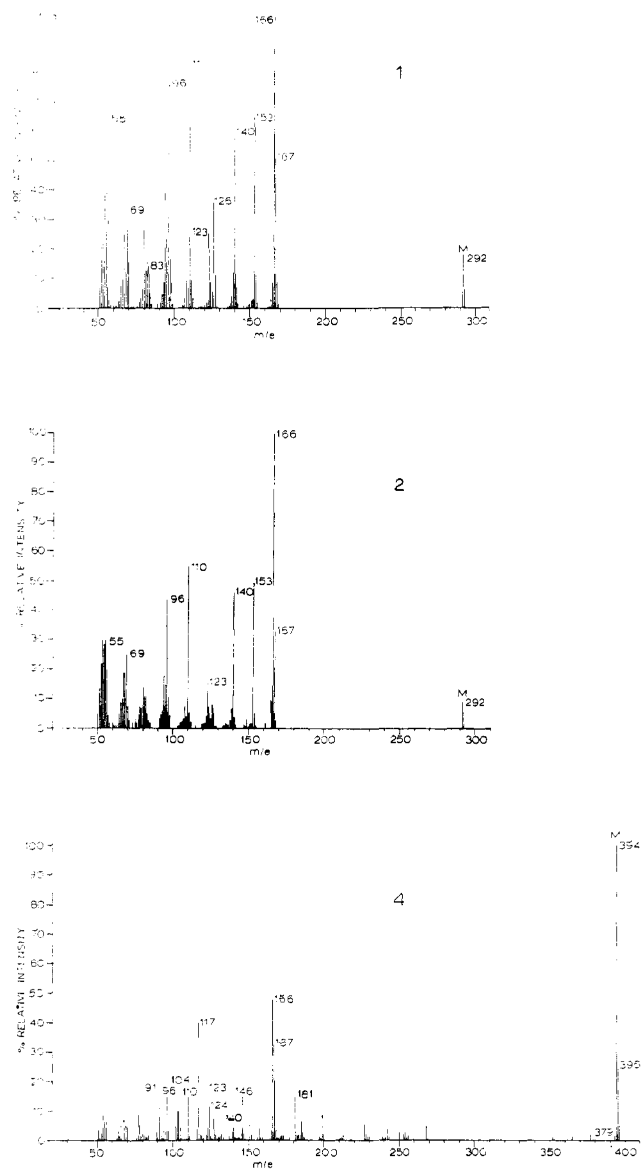


Figure 1. Mass spectra of compounds **1**, **2**, and **4** at 70 eV.

subsequent degradation of the remaining Th-C_3-Th (84 mg, 0.29 mmol estimated from uv) to water-soluble fragments by potassium permanganate (118 mg, 0.75 mmol, 1.3 equiv).[17] After several hours at about 35°, addition of a few drops of saturated aqueous sodium hydrosulfite to the solution precipitated manganese dioxide, which was removed by filtration. The carbonates in the filtrate were decomposed by careful addition of formic acid since the greater solubility of its salts precluded the coprecipitation of inorganic material with the product. Concentration of the solution under reduced pressure to about 100 ml furnished the crude photodimer which, after recrystallization from water, was obtained in a final yield of 425 mg (60%); mp >350°, uv transparent above 260 nm; nmr (TFA) τ 8.24 (s, CH_3's), 5.86 (s, CH's).

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.17; H, 5.57; N, 19.32.

Irradiation of $\widehat{\text{Th-C}_3\text{-Th}}$ with short-wavelength ultraviolet light caused regeneration of the maximum at 269 nm, corresponding to Th-C_3-Th.

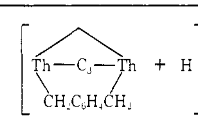
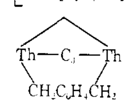
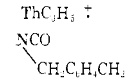
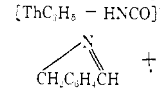
Dipotassium Salt of Intramolecular Dimer 2. A suspension of 386 mg (1.3 mmol) of the intramolecular photodimer of 1,1′-trimethylenebisthymine (**2**), $\widehat{\text{Th-C}_3\text{-Th}}$, in 2 ml of redistilled deionized water became clear during treatment with 2.65 ml of 1 *M* aqueous potassium hydroxide, and the resulting solution was concentrated under reduced pressure to about 1 ml. The dipotassium salt was precipitated by the addition of an equal volume of absolute ethanol, washed with three 1-ml portions of ethanol, and dried at 100° *in vacuo*; mp >350°; yield 270 mg (55%); uv shoulder near 220 nm (ε 5700) in water;[7c] no ir maximum corresponding to NH stretching; nmr (D_2O) τ 8.58 (s, CH_3's), 6.17 (s, CH's).

Anal. Calcd for $C_{13}H_{14}K_2N_4O_4$: C, 42.37; H, 3.83; N, 15.20. Found: C, 42.60; H, 3.91; N, 15.29.

The residual material was recovered as photodimer from the combined mother liquor and washings by acidification with concentrated hydrochloric acid.

***o*-Xylylene Derivative (4) of Th-C_3-Th Intramolecular Photodimer.** To a stirred solution prepared from 146 mg (0.5 mmol) of Th-C_3-Th photodimer in 20 ml of anhydrous redistilled dimethylformamide was added 36 mg (1.5 mmol) of sodium hydride (60 mg of a 60% dispersion in mineral oil). Within 20 min the gray hydride dissolved and a white suspension, presumed to be the disodium salt of the bisimide, separated. To this was added a solution of 198 mg (0.75 mmol) of *o*-xylylene dibromide in 10 ml of dimethylformamide. After 20 min most of the suspended material had gone into solution. Filtration was followed by concentration under reduced pressure to a volume of about 5 ml. To this was added an equal volume of 20% aqueous ethanol, and the solution was refrigerated. The crystals which deposited were collected, washed with water and ethanol, and dried, mp 330–331°; ir showed no maxima correspondint to NH or C=N stretching, but had a complex broad band centered at 1675 cm^{-1}. The mass spectrum and the fragmentation pattern are given in Figure 1 and Table I.

Table I. Comparative Fiagments of Compounds **1**, **2**, and **4** Determined by Mass Spectrometry at 70 eV

m/e	Formula	Assignment	% total abundance[a] 1	2	4
395	$C_{21}H_{22}N_4O_4$				3.6[b]
394	$C_{21}H_{22}N_4O_4$				14.5
292	$C_{13}H_{16}N_4O_4$	$ThC_3Th^{+\cdot}$	1.5	1.0	
181	$C_9H_{13}N_2O_2$	$CH_2ThC_3H_6^+$			2.2
167	$C_8H_{11}N_2O_2$	$ThC_3H_6^+$	4.2	3.8	4.8
166	$C_8H_{10}N_2O_2$	$ThC_3H_5^{+\cdot}$	8.1	11.4	7.0
146	C_9H_8NO				2.2
140	$C_6H_8N_2O_2$	$ThCH_2^{+\cdot}$	4.9	5.3	0.8
126	$C_5H_6N_2O_2$	$ThH^{+\cdot}$	3.0		
124	$C_7H_{10}NO$	$[ThC_3H_6 - HNCO]^+$			1.7
123	C_7H_9NO	$[ThC_3H_5 - HNCO]^{+\cdot}$	2.1	1.9	2.6
117	C_8H_7N				5.8
110	C_6H_8NO	$[ThC_2H_4 - HNCO]^+$	6.8	6.3	2.2
104	C_8H_8	$C_8H_8^{+\cdot}$			2.6
96	C_5H_6NO	$[ThCH_2 - HNCO]^+$	6.3	5.0	2.2
91	C_7H_7	$C_7H_7^+$			2.6
83	C_4H_5NO	$[ThH - HNCO]^{+\cdot}$	1.2		
69	C_4H_5O	$[ThCH_2 - HNCO - HCN]^+$	2.8	2.6	
55	C_3H_5N	$[ThH - HNCO - CO]^{+\cdot}$	5.3	3.4	

[a] Of all peaks above *m/e* 50. [b] Percentages less than 0.5% have been omitted from consideration.

The compound was also obtained from the dipotassium salt, starting with 200 mg (0.54 mmol) dissolved in 1 ml of redistilled deionized water, diluted with 100 ml of redistilled dimethylformamide, and then clarified with a further 2 ml of water. To this solution was added 143 mg (0.54 mmol) of *o*-xylylene dibromide in 10 ml of dimethylformamide with vigorous stirring. The solution was stirred for 16 hr at 25°, concentrated under reduced pressure to about 1 ml, and diluted with 3 ml of absolute ethanol. The precipitated material was collected and washed successively with

(17) M. H. Benn, B. Chatamra, and A. S. Jones, *J. Chem. Soc.*, 1014 (1960).

two 2-ml portions of 1 *M* potassium hydroxide, three 2-ml portions of water, and three 2-ml portions of absolute ethanol, then dried at 100° *in vacuo*, mp 329–331°, yield 20 mg (9%).

Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.94; H, 5.62; N, 14.21. Found: C, 63.68; H, 5.58; N, 14.28.

The high-resolution mass spectrum showed a molecular ion peak at 394.1670 (calcd 394.1641).

Mass Spectrometric Determinations. The mass spectra were obtained at 70 eV using an Atlas CH4 mass spectrometer with the assistance of Mr. J. Wrona. The spectra of compounds **1**, **2**, and **4** are given in Figure 1. The fragmentation patterns for these three compounds, outlined in Table I, are described in the section on Results and Discussion. The CEC 21-110 double-focusing mass spectrometer was used at high resolution, and the sample was introduced directly into the ion source. The compositions of all the fragments were confirmed by mass matching at high resolution.

Crystallographic Examination. The internal photodimer of 1,1′-trimethylenebisthymine crystallizes as well-formed, small, transparent prisms.

Crystal Data for $C_{13}H_{16}N_4O_4$ are as follows: M = 292.3, monoclinic, a = 9.04 (2), b = 17.70 (4), c = 12.48 (2) Å, β = 138° 30′ (20′), V = 1323.2 × 10^{-24} cm^3, ρ_{meas} = 1.44 g cm^{-3}, Z = 4, ρ_{calcd} = 1.47 g cm^{-3}. $F(000)$ = 616. Systematic absences, $h0l$, when $l = 2n + 1$, and $0k0$, when $k = 2n + 1$, established the space group as $P2_1/c$ (C^5_{2h}).

The crystals are generally elongated along the minor *ac* diagonal, and the initial examination and alignment was carried out by assuming the $P2_1/n$ description. A crystal, 0.21 × 0.20 × 0.49 mm, was mounted along the *ac* diagonal (0.49 mm length) on a Picker FACS-1 four-angle diffractometer. The cell dimensions were determined by a least-squares fit to the settings for the four angles for nine reflections. The take-off angle was 4°; pulse height analysis and a Ni filter were used to give approximately monochromatic Cu Kα radiation (λ 1.5418 Å). The reflections were measured on a scintillation counter, with attenuators being inserted when necessary. All the symmetry nonequivalent reflections in the 2θ range 0–130° were measured using a moving crystal–moving counter technique, with a 2θ scan rate of 1°/min. A standard reflection was monitored after every 100 measurements. Out of 2435 possible reflections, 1823 were considered to be significantly above background. No absorption or extinction corrections were applied. The crystal remained transparent during the course of the irradiation. The intensity of the standard reflection did not vary by more than 1% while the data used in the subsequent analysis were being collected.[18]

Structure Determination. The structure was solved by the symbolic addition procedure,[19,20] using the reflections shown in Table II (see below). An E map using 274 reflections ($E > 1.5$), with signs obtained from the six reflections given in Table II, revealed the positions of the 21 nonhydrogen atoms. Incorporation of these atoms in six cycles of full-matrix least-squares refinement, varying positional and isotropic temperature factors, gave a conventional R factor of 0.14. All nonzero reflections were given unit weight, and the quantity minimized was $\Sigma w(|F_{obsd}| - |F_{calcd}|)^2$. Introduction of anisotropic temperature factors required that the atoms be divided into two groups [N(1), C(2), N(3), C(4), O(9), O(10), C(11) and N(1′), C(2′), N(3′), C(4′), O(9′), O(10′), C(11′), with the atoms of the cyclobutane ring and the three methylene carbon atoms being common to both groups]. Two cycles of such refinement reduced R to 0.089. All 16 hydrogen atoms were located from a difference map, and their inclusion in a structure factor calculation gave an R of 0.067. Two cycles of refinement, again dividing the atoms as described above and including the hydrogen atoms with the heavy atom to which they are bonded, reduced R to 0.052 and R_2, defined as $[\Sigma w(|F_{obsd}| - |F_{calcd}|)^2/\Sigma w|F_{obsd}|^2]^{1/2}$, to 0.056. The C(5)–C(5′) and C(6)–C(6′) bonds calculated at this point were surprisingly long, 1.614 (9) and 1.581 (8) Å, respectively. A difference map computed at this stage in the analysis revealed two positive peaks in the plane of the cyclobutane ring but displaced by about 1 Å from the positions of C(5) and C(5′) by linear extension of the C(5)–C(5′) bond. There were also two peaks similarly located with respect to atoms C(6) and C(6′). These peaks are considered to represent sites for the atoms C(5), C(5′), C(6), and C(6′) in the Th–C_3–Th molecule (**1**), formed by dissociation of the dimer (**2**) in the crystal upon X irradiation. As the heights of these four peaks were slightly less than those considered earlier to represent hydrogen atoms, about 10% of the molecules must have existed as **1** during data collection. We were unable to locate minor sites for C(11) and C(11′), probably because these sites are very close to the positions of C(11) and C(11′) in the internal photodimer. We carried out further refinement assigning 90% occu-

Table II. Sign-Determining Reflections Used in Symbolic Addition Procedure

h	k	l	E	Sign
$\bar{3}$	14	4	2.47	–
$\overline{10}$	15	8	2.84	+ to determine origin
$\bar{2}$	14	3	3.05	–
$\bar{6}$	1	1	3.11	+ to determine origin
$\bar{3}$	16	3	3.20	–
3	13	2	2.87	+ to determine origin

Table III. Final Atomic Coordinates in Fractions of the Unit Cell Edge. Estimated Standard Deviations in Parentheses

	x	y	z
N(1)	0.9035 (4)	0.1254 (1)	0.1118 (3)
C(2)	0.6936 (5)	0.1031 (2)	−0.0217 (4)
N(3)	0.5270 (4)	0.1354 (1)	−0.0488 (3)
C(4)	0.5495 (5)	0.1874 (2)	0.0434 (4)
C(5)	0.7833 (6)	0.2122 (2)	0.1996 (5)
C(6)	0.9724 (7)	0.1750 (2)	0.2350 (6)
C(7)	1.0868 (5)	0.0862 (2)	0.1545 (4)
C(8)	1.1459 (5)	0.0113 (2)	0.2395 (4)
O(9)	0.6438 (3)	0.0572 (1)	−0.1180 (3)
O(10)	0.3863 (4)	0.2116 (2)	0.0011 (3)
C(11)	0.7858 (6)	0.2989 (2)	0.2007 (5)
N(1′)	1.0610 (4)	0.0527 (1)	0.3795 (3)
C(2′)	0.8907 (4)	0.0099 (2)	0.3210 (3)
N(3′)	0.7236 (4)	0.0451 (1)	0.2891 (3)
C(4′)	0.7215 (5)	0.1183 (2)	0.3244 (4)
C(5′)	0.8807 (5)	0.1726 (2)	0.3573 (4)
C(6′)	1.0618 (5)	0.1348 (2)	0.3852 (4)
C(7′)	1.2287 (5)	0.0184 (2)	0.3986 (4)
O(9′)	0.8811 (3)	−0.0585 (1)	0.3003 (3)
O(10′)	0.5921 (4)	0.1382 (1)	0.3233 (3)
C(11′)	0.9787 (7)	0.2256 (2)	0.4947 (5)
H(12)	0.397 (6)	0.120 (2)	−0.137 (4)
H(13)	1.087 (6)	0.215 (2)	0.274 (4)
H(14)	1.032 (6)	0.080 (2)	0.043 (4)
H(15)	1.224 (6)	0.119 (2)	0.230 (4)
H(16)	1.010 (6)	−0.024 (2)	0.163 (4)
H(17)	1.271 (6)	−0.011 (2)	0.266 (4)
H(18)	0.929 (6)	0.319 (2)	0.286 (4)
H(19)	0.685 (6)	0.318 (2)	0.208 (4)
H(20)	0.730 (6)	0.319 (2)	0.106 (4)
H(12′)	0.611 (6)	0.015 (2)	0.251 (4)
H(13′)	1.222 (7)	0.152 (2)	0.487 (5)
H(14′)	1.267 (6)	−0.034 (2)	0.448 (4)
H(15′)	1.374 (6)	0.051 (2)	0.491 (4)
H(18′)	1.076 (5)	0.198 (2)	0.607 (4)
H(19′)	1.108 (5)	0.264 (2)	0.534 (4)
H(20′)	0.864 (5)	0.253 (2)	0.465 (4)

Minor Sites for Four Atoms

	x	y	z	B (Å^2)
M(5)	0.737 (9)	0.225 (3)	0.133 (6)	5 (1)
M(6)	0.902 (8)	0.191 (3)	0.179 (6)	4 (1)
M(5′)	0.997 (7)	0.145 (2)	0.470 (5)	7 (1)
M(6′)	1.150 (9)	0.125 (3)	0.470 (7)	7 (1)

(18) Four or five days after the crystal was put on the diffractometer there were some instrumental difficulties which caused an interruption in collection of data for several days. During the first 4–5 days of irradiation, the intensity of the standard reflection fell gradually to about 95% of its initial value. While the data finally used in the analysis were being collected (after the instrumental problems had been solved), the intensity of the standard did not vary more than ±1% from the starting value after repair of the instrument.

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Table IV. Final Thermal Parameters[a]

	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23} ($\times 10^4$)
N(1)	180 (7)	22 (1)	122 (4)	−5 (4)	243 (10)	−10 (3)
C(2)	207 (9)	23 (1)	147 (5)	−10 (5)	286 (12)	2 (4)
N(3)	175 (7)	29 (1)	142 (5)	−8 (4)	228 (10)	−19 (3)
C(4)	213 (9)	26 (1)	151 (6)	26 (5)	264 (13)	6 (4)
C(5)	192 (11)	16 (1)	126 (7)	13 (5)	246 (16)	3 (5)
C(6)	158 (11)	16 (1)	120 (7)	−4 (6)	217 (16)	−4 (5)
C(7)	205 (9)	32 (1)	159 (6)	−8 (5)	309 (13)	−10 (4)
C(8)	220 (9)	27 (1)	168 (6)	19 (5)	318 (14)	−7 (4)
O(9)	259 (7)	39 (1)	166 (4)	−62 (4)	334 (10)	−69 (3)
O(10)	219 (7)	52 (1)	211 (5)	55 (5)	298 (11)	−28 (4)
C(11)	402 (14)	17 (1)	216 (7)	18 (6)	460 (18)	11 (4)
N(1′)	175 (7)	18 (1)	134 (4)	9 (4)	250 (10)	4 (3)
C(2′)	179 (8)	22 (1)	108 (5)	−1 (4)	204 (11)	−1 (3)
N(3′)	204 (7)	22 (1)	156 (4)	−8 (4)	291 (10)	−5 (3)
C(4′)	261 (10)	26 (1)	184 (6)	9 (5)	373 (15)	6 (4)
C(5′)	180 (9)	17 (1)	117 (5)	8 (5)	234 (13)	−6 (4)
C(6′)	141 (9)	17 (1)	105 (6)	−7 (5)	186 (13)	−8 (4)
C(7′)	180 (8)	26 (1)	150 (5)	35 (5)	254 (13)	9 (4)
O(9′)	236 (6)	19 (1)	191 (4)	−9 (3)	302 (9)	−16 (3)
O(10′)	415 (9)	37 (1)	338 (6)	19 (5)	686 (14)	−1 (4)
C(11′)	397 (13)	30 (1)	191 (7)	15 (7)	442 (18)	−24 (5)

[a] Anisotropic temperature factors are expressed in the form, exp $[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)]$. Estimated standard deviations are given in parentheses.

pancy to the major sites for C(5), C(5′), C(6), and C(6′) and 10% occupancy to the minor sites. This gave R = 0.046 and R_2 = 0.050. While the lengths of the bonds joining the two thymine molecules in the dimer decreased by 0.02–0.03 Å, the rest of the molecule was little affected by the change of model. The final values of the atomic coordinates and thermal parameters are given in Tables III and IV. The temperature factors of the hydrogen atoms were held constant at 3.0 Å^2. Calculation of the amplitudes for the "unobserved" reflections did not indicate any anomalies. The atomic scattering curves used in the analysis were taken from the compilation by Ibers.[21]

The crystal, which had received a probable total of 3 weeks of X irradiation during a 6-week period, was preserved for a 7-month period thereafter, and the ultraviolet spectrum was determined. This exhibited an absorption at 270 nm of intensity such as to indicate that a reversion in the order of 10% of photodimer to open Th–C_3–Th had occurred during the X irradiation. The nearly complete disappearance of this absorption following treatment of the test solution by the permanganate–bisulfite procedure was taken to confirm the identity of this chromophore as that of 1,1′-trimethylenebisthymine (**1**). A crystal of **2** which had been similarly treated except that it had not received X irradiation did not show any reversion to **1**.

Table V. Bond Lengths (Ångströms) with Estimated Standard Deviations

N(1)–C(2)	1.341 (6)	N(1′)–C(2′)	1.339 (5)
N(1)–C(6)	1.444 (8)	N(1′)–C(6′)	1.455 (4)
N(1)–C(7)	1.480 (5)	N(1′)–C(7′)	1.477 (5)
C(2)–N(3)	1.395 (5)	C(2′)–N(3′)	1.388 (5)
C(2)–O(9)	1.223 (5)	C(2′)–O(9′)	1.228 (3)
N(3)–C(4)	1.365 (6)	N(3′)–C(4′)	1.374 (4)
C(4)–C(5)	1.513 (8)	C(4′)–C(5′)	1.508 (6)
C(4)–O(10)	1.214 (6)	C(4′)–O(10′)	1.213 (6)
C(5)–C(6)	1.555 (8)	C(5′)–C(6′)	1.548 (6)
C(5)–C(11)	1.534 (5)	C(5′)–C(11′)	1.526 (7)
C(7)–C(8)	1.522 (5)	C(7′)–C(8)	1.514 (7)
C(5)–C(5′)	1.596 (8)		
C(6)–C(6′)	1.551 (9)		
N(3)–H(12)	0.86 (10)	N(3′)–H(12′)	0.91 (7)
C(6)–H(13)	1.02 (6)	C(6′)–H(13′)	1.02 (11)
C(7)–H(14)	1.07 (7)	C(7′)–H(14′)	1.01 (5)
C(7)–H(15)	1.00 (8)	C(7′)–H(15′)	1.06 (8)
C(11)–H(18)	0.93 (9)	C(11′)–H(18′)	1.06 (7)
C(11)–H19)	1.05 (5)	C(11′)–H(19′)	1.10 (6)
C(11)–H(20)	0.94 (7)	C(11′)–H(20′)	0.93 (6)
C(8)–H(16)	1.03 (8)		
C(8)–H(17)	1.00 (6)		
Lengths Involving Minor Sites			
M(5)–M(6)	1.28 (10)	M(5)–C(11)	1.44 (7)
M(5′)–M(6′)	1.42 (10)	C(4′)–M(5′)	1.72 (12)
C(4)–M(5)	1.31 (12)	N(1′)–M(6′)	1.49 (9)
N(1)–M(6)	1.44 (6)	M(5′)–C(11′)	1.50 (5)

Results and Discussion

When Th–C_3–Th (**1**) was irradiated at 300 nm in dilute aqueous solution (1.7×10^{-3} *M*), with degassing, photoequilibrium was reached within 3 hr. Separation of the photoproduct from starting material (12% estimated by uv) proved difficult, but removal of the latter by partial chemical degradation using potassium permanganate[17] permitted the isolation of the internal photodimer, $\widehat{\text{Th–C}_3\text{–Th}}$, mp >350°, in 60% yield. The structure of this product was indicated by chemical means and was firmly established by concomitant single crystal X-ray analysis.

The proximity of the 3- and 3′-nitrogens in the *cis-syn* possibility **2** suggested that construction of a short bridge between these positions would support this structure and exclude the *trans-syn* possibility **3**, in which the same positions cannot be connected by a short bridge. According to molecular models, the *o*-xylylene group should be ideal for bridging between N(3) and N(3′) of **2**. Direct alkylation of **2** with *o*-xylylene dibromide failed, but treatment of the bisimide with sodium hydride in dimethylformamide followed by *o*-xylylene dibromide, or reaction between the dipotassium salt of **2** with *o*-xylylene dibromide, produced a new product, $C_{21}H_{22}N_4O_4$. The structure was indicated as **4** by the molecular ion peak and the fragmentation pattern in the mass spectrum, and by comparison with the mass spectra of **1** and **2**.

The mass spectra of 1,1′-trimethylenebisthymine and its internal photodimer are very similar (Figure 1). The initial reaction of the photodimer in the heated inlet system or under electron bombardment may be the reversion to Th–C_3–Th since none of the ions in its spectrum can reasonably be accounted for by species in which the cyclobutane ring has remained intact or has undergone the alternative cleavage. The mass spectra of Th–C_3–Th (**1**) and $\widehat{\text{Th–C}_3\text{–Th}}$ (**2**) differ only in the absence from the spectrum of the internal dimer of fragment ions indicative of the presence of thymine itself, specifically at *m/e* 126 and 83 (Table I). The common fragmentation process appears to involve loss from the molecular ion of a thymine fragment to form $ThC_3H_5^+$, *m/e* 166, as the base peak and further loss of C_1, C_2, and C_3 units from the side chain.[3] An alternate pathway consists in the loss of HNCO from the thymine ring of $ThC_3H_5^+$ in a manner characteristic of 2,4-dioxypyrimidines,[22–24] followed by a similar side-chain fragmentation process.

(21) J. A. Ibers in "International Tables for X-Ray Crystallography," Vol. III, The Kynoch Press, Birmingham, England, 1962, pp 201–209. The final values of *h*, *k*, *l*, $|F_{obsd}|$, and F_{calcd} are available (order document no. NAPS-00527) from ASIS National Auxiliary Publications Service, c/o CCM Information Sciences, Inc., 22 West 34th St., New York, N. Y. 10001; remit $1.00 for microfilm, or $3.00 for photocopy.

(22) J. M. Rice, G. O. Dudek, and M. Barber, *J. Amer. Chem. Soc.*, **87**, 4569 (1965).

(23) T. Nishiwaki, *Tetrahedron*, **22**, 3117 (1966).

(24) S. M. Hecht, A. S. Gupta, and N. J. Leonard, *Biochim. Biophys. Acta*, **182**, 444 (1969).

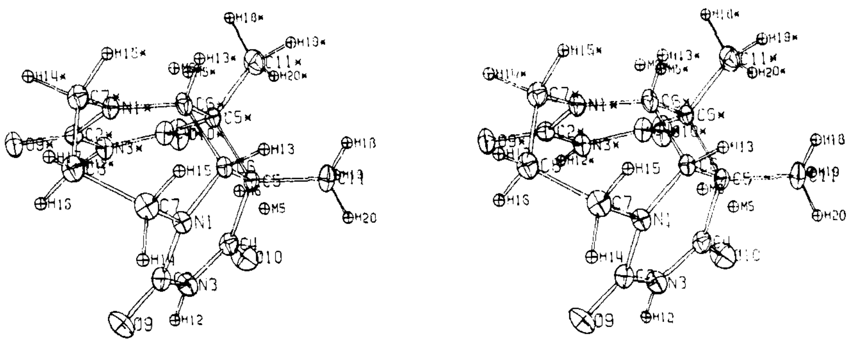

Figure 2. Stereoscopic view of a molecule of the internal dimer also showing the positions of the four sites [M(5), M(5′), M(6), and M(6′)] due to monomer. Atoms designated by primes in the paper are marked by asterisks.

In contrast to compounds **1** and **2**, the *o*-xylylene derivative (**3**) of $\widehat{\text{Th–C}_3\text{–Th}}$ shows the molecular ion as the base peak in its mass spectrum (Figure 1), in which three types of fragments are recognizable. The significant ions from the fragmentation of a $\widehat{\text{Th–C}_3\text{–Th}}$ moiety which are found in this spectrum are taken to arise from the decomposition of the residue left from the loss of the xylylene group or a portion thereof from the molecular ion. Second, as would be expected, there are several ions arising from the xylylene group itself. Finally, another fragmentation pathway is represented by species that have the xylylene group together with portions of a thymine ring (Table I).

The complete structural analysis of crystalline $\widehat{\text{Th–C}_3\text{–Th}}$ was of special interest because of its potential relationship, in *cis-syn* stereochemistry, with the major thymine photoproduct from native DNA. The structure of the *cis-syn* intramolecular dimer (**2**) is shown in Figure 2. The molecule approximates C_s symmetry with respect to a plane perpendicular to the cyclobutane ring and passing through the central carbon atom of the trimethylene bridge. Bond lengths and angles, uncorrected for any effects of thermal vibration, are listed in Tables V and VI.

Unlike the cyclobutane ring in the *cis-syn* dimer of uracil (dihedral angle 155°),[25] that in the *cis-syn* dimer of dimethylthymine ("markedly puckered"),[13] and that in the *cis-anti* dimer of dimethylthymine (dihedral angle 154°),[26] the four-membered ring in the present dimer is close to being planar (dihedral angle 178°). The planar cyclobutane rings in the *trans-anti* dimers of thymine[27] and of 1-methylthymine[28] occupy centers of symmetry in the crystal. In fact, all reported planar cyclobutane rings occupy crystallographic centers of symmetry,[29] the present structure being apparently the first exception to this rule. While the bonds C(5)–C(6) and C(5′)–C(6′) are only slightly longer than the C(5)–C(6) bond in dihydrothymine (1.52 Å)[30] and in dihydrouracil (1.51 Å),[31] the C(5)–C(5′) bond (1.596 Å), which has two attached methyl groups in an effectively eclipsed configuration (angle of twist 2.6°) consequent upon the near-planarity of the cyclobutane ring, is considerably longer than the bonds linking the two monomer molecules in the *cis-syn* dimer of uracil (1.572 and 1.563 Å)[25] and those in the *cis-anti* dimer of dimethylthymine (1.571 and 1.577 Å).[26] In cyclobutane rings,

Table VI. Bond Angles (Degrees) with Standard Deviations in Parentheses

C(2)N(1)C(6)	125.6 (3)	C(2′)N(1′)C(6′)	123.6 (3)
C(2)N(1)C(7)	118.0 (3)	C(2′)N(1′)C(7′)	118.5 (2)
C(6)N(1)C(7)	115.3 (4)	C(6′)N(1′)C(7′)	115.8 (3)
N(1)C(2)N(3)	116.5 (4)	N(1′)C(2′)N(3′)	117.6 (3)
N(1)C(2)O(9)	123.6 (3)	N(1′)C(2′)O(9′)	122.9 (4)
N(3)C(2)O(9)	119.8 (2)	N(3′)C(2′)O(9′)	119.5 (2)
C(2)N(3)C(4)	128.3 (4)	C(2′)N(3′)C(4′)	127.2 (3)
C(2)N(3)H(12)	112 (3)	C(2′)N(3′)H(12′)	116 (3)
C(4)N(3)H(12)	120 (3)	C(4′)N(3′)H(12′)	116 (3)
N(3)C(4)C(5)	117.7 (4)	N(3′)C(4′)C(5′)	116.7 (4)
N(3)C(4)O(10)	120.4 (3)	N(3′)C(4′)O(10′)	121.0 (3)
C(5)C(4)O(10)	121.9 (4)	C(5′)C(4′)O(10′)	122.3 (4)
C(4)C(5)C(6)	114.9 (4)	C(4′)C(5′)C(6′)	114.7 (3)
C(4)C(5)C(5′)	114.2 (3)	C(4′)C(5′)C(5)	114.3 (3)
C(4)C(5)C(11)	107.4 (3)	C(4′)C(5′)C(11′)	109.3 (4)
C(6)C(5)C(5′)	89.4 (4)	C(6′)C(5′)C(5)	88.9 (3)
C(6)C(5)C(11)	114.6 (4)	C(6′)C(5′)C(11′)	112.8 (3)
C(5′)C(5)C(11)	115.9 (4)	C(5)C(5′)C(11′)	115.8 (4)
N(1)C(6)C(5)	116.7 (5)	N(1′)C(6′)C(5′)	117.1 (4)
N(1)C(6)C(6′)	115.3 (4)	N(1′)C(6′)C(6)	114.8 (4)
N(1)C(6)H(13)	113 (3)	N(1′)C(6′)H(13′)	108 (3)
C(5)C(6)C(6′)	90.3 (5)	C(5′)C(6′)C(6)	91.4 (4)
C(5)C(6)H(13)	111 (3)	C(5′)C(6′)H(13′)	115 (3)
C(6′)C(6)H(13)	108 (3)	C(6)C(6′)H(13′)	110 (3)
N(1)C(7)C(8)	111.9 (3)	N(1′)C(7′)C(8)	112.5 (2)
N(1)C(7)H(14)	106 (2)	N(1′)C(7′)H14′)	108 (3)
N(1)C(7)H(15)	109 (3)	N(1′)C(7′)H(15′)	103 (3)
C(8)C(7)H(14)	113 (2)	C(8)C(7′)H(14′)	109 (3)
C(8)C(7)H(15)	108 (3)	C(8)C(7′)H(15′)	118 (2)
H(14)C(7)H(15)	109 (4)	H(14′)C(7′)H(15′)	105 (4)
C(5)C(11)H(18)	113 (3)	C(5′)C(11′)H(18′)	114 (2)
C(5)C(11)H(19)	109 (2)	C(5′)C(11′)H(19′)	114 (2)
C(5)C(11)H(20)	113 (3)	C(5′)C(11′)H(20′)	110 (3)
H(18)C(11)H(19)	109 (4)	H(18′)C(11′)H(19′)	98 (3)
H(18)C(11)H(20)	106 (4)	H(18′)C(11′)H(20′)	110 (4)
H(19)C(11)H(20)	108 (4)	H(19′)C(11′)H(20′)	111 (4)
C(7)C(8)C(7′)	114.4 (3)		
C(7)C(8)H(16)	109 (3)		
C(7)C(8)H(17)	107 (3)		
C(7′)C(8)H(16)	110 (3)		
C(7′)C(8)H(17)	106 (3)		
H(16)C(8)H(17)	110 (4)		

(25) E. Adman, M. P. Gordon, and L. H. Jensen, *Chem. Commun.*, 1019 (1968).

(26) N. Camerman, D. Weinblum, and S. C. Nyburg, *J. Amer. Chem. Soc.*, 91, 982 (1969). These authors depart from convention (see, *e.g.*, ref 7c), and call this dimer a *syn* head-to-tail dimer; we prefer the designation *cis-anti*.

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(28) J. R. Einstein, J. L. Hosszu, J. W. Longworth, R. O. Rahn, and C. H. Wei, *Chem. Commun.*, 1063 (1967).

(29) A list of such structures is given by E. Adman and T. N. Margulis, *J. Amer. Chem. Soc.*, 90, 4517 (1968).

(30) S. Furberg and L. H. Jensen, *ibid.* 90, 470 (1968).

(31) D. Rohrer and M. Sundaralingam, *Chem. Commun.*, 746 (1968).

Table VII. Details of Various Best Planes in the Molecule[a]

N(1)		**0.020**			**0.000**			0.090	**0.000**	**0.004**
C(2)		**−0.013**			**0.001**			0.041	**−0.002**	
N(3)		**−0.012**			**−0.001**			**−0.001**	**0.000**	
C(4)		**0.023**			**0.001**			**0.006**	0.009	
C(5)	**0.011**	**−0.003**			−0.065			**−0.003**	−0.052	
C(6)	**−0.015**	**−0.051**			−0.110			−0.002	−0.102	−1.118
C(7)		−0.137			−0.155			−0.020	−0.158	**−0.009**
C(8)										0.669
O(9)		−0.037			0.009			0.037	**0.000**	
O(10)		0.053			0.033			**−0.001**	0.043	
N(1′)			**−0.065**	**0.009**		−0.563	**−0.003**			**−0.004**
C(2′)			**0.029**	**−0.026**		−0.321	**0.014**			
N(3′)			**0.053**	**0.022**		**0.002**	**−0.003**			
C(4′)			**−0.132**	**−0.020**		**−0.013**	−0.159			
C(5′)	**−0.007**		**0.040**	0.301		**0.004**	0.100			
C(6′)	**0.009**		**0.085**	0.321		−0.287	0.190			−1.134
C(7′)			0.049	0.100		−0.770	0.155			**0.008**
O(9′)			0.049	−0.144		−0.417	**−0.003**			
O(10′)			−0.378	−0.262		**0.003**	−0.446			
χ^2	30	212	3059	186	0.2	19	25	3.1	0.25	16.9
P	<0.01	<0.01	<0.01	<0.01	>0.5	<0.01	<0.01	~ 0.05	~ 0.5	<0.01

[a] The distances from the plane of atoms included in the plane calculations are given in bold type. In the calculations of the best planes, the atoms were weighted as the reciprocal of the square of the estimated standard deviation as obtained from the least-squares refinement. The results of a χ^2 significance test are also shown with the probability (P) of a planar set of atoms having such a χ^2 value.

the bond lengths between atoms with large, eclipsed substituents are greater than those between atoms with *trans* substituents.[32] While the disorder, caused by approximately 10% reversion to monomer in the crystal, reduces the accuracy of the analysis in this region of the unit cell, the relative differences in the C(5)–C(5′) and C(6)–C(6′) lengths are probably significant and do indicate a very long bond between C(5) and C(5′). Another consequence of the near-planarity of the cyclobutane ring is the almost complete overlap of the projection of the two thymine rings as compared to angles of rotation of 24–29° in other *cis* dimers.[13,25,26]

The two constituent dihydrothymine rings in **2** are strikingly different. While the unprimed dihydrothymine ring is significantly nonplanar (Table VII), the distances of the constituent atoms from the best plane range only from −0.051 to +0.023 Å. The four atoms N(1), C(2), N(3), and C(4) are exactly planar, with C(5), C(6), C(7), O(9), and O(10) all lying within 0.16 Å of that plane. In contrast, the distances of the constituent atoms from the best plane through the six atoms of the primed dihydrothymine ring range from −0.132 to +0.085 Å; the four atoms N(1′), C(2′), N(3′), and C(4′) are significantly nonplanar, while C(5′), C(6′), C(7′), O(9′), and O(10′) lie +0.301, +0.321, +0.100, −0.144, and −0.262 Å, respectively, from the best plane through these four atoms. Even the sets of four atoms, comprising a carbonyl group and its two immediate neighbors, are closer to an exact plane in the primed ring than in the unprimed ring.

The effects resulting from the hydrogenation of the C(5)–C(6) bond noted by Furberg and Jensen in dihydrothymine[30] are confirmed in the present structure. When compared to the structures of thymine monohydrate[33] and 1-methylthymine,[34] the C(2)–N(3) bond is longer, while the N(1)–C(2) and N(3)–C(4) bonds are shorter (see Table VIII).

The conformation of the diazacycloheptane ring is close to a chair.[35] The torsion angles around the ring are compared to those calculated theoretically by Hendrickson[36] for the chair conformation in a carbocyclic seven-membered ring (Table IX). While the

Table VIII. Comparison of Some Bond Lengths in Present Structures with Corresponding Lengths in Related Molecules

	N(1)–C(2)	C(2)–N(3)	N(3)–C(4)
Present work[a]	1.340	1.392	1.370
cis-syn-Uracil dimer[a,b]	1.334	1.394	1.362
Dihydrouracil[c]	1.34	1.39	1.38
Dihydrothymine[d]	1.326	1.383	1.358
1-Methylthymine[e]	1.379	1.379	1.375
Thymine monohydrate[f]	1.355	1.361	1.391

[a] Distances averaged in these two molecules. [b] See ref 25. [c] See ref 31. [d] See ref 30. [e] See ref 34. [f] See ref 33.

Table IX. Torsion and Bond Angles in the Diaza Seven-Membered Ring Compared to Those Calculated by Hendrickson[a,b]

A–B–C–D	Present work[c]	Hendrickson
N(1)C(6)C(6′)N(1′)	−0.7	0
C(6)C(6′)N(1′)C(7′)	71.6	66.1
C(6′)N(1′)C(7′)C(8)	−87.2	−83.5
N(1′)C(7′)C(8)C(7)	60.8	63.8
C(7′)C(8)C(7)N(1)	−61.7	−63.8
C(8)C(7)N(1)C(6)	88.7	83.5
C(7)N(1)C(6)C(6′)	−71.2	−66.1
	Bond Angles	
N(1)C(7)C(8)	111.9	114
C(7)C(8)C(7′)	114.4	115
C(6′)C(6)N(1)	115.3	118
C(6)N(1)C(7)	115.3	115

[a] See ref 36. [b] The torsion angle A–B–C–D is considered to be positive if, when looking along the B–C bond, atom A has to be rotated clockwise to eclipse atom D. [c] Using the formulae given by Huber [P. J. Huber, Appendix to E. Huber-Buser and J. D. Dunitz, *Helv. Chim. Acta*, **44**, 2027 (1961)], the errors in torsion angles are of the order of twice those for the valency angles (*i.e.*, from 0.6 to 1.0°).

(32) B. Greenberg and B. Post, *Acta Cryst.*, **B24**, 918 (1968).
(33) R. Gerdil, *ibid.*, **14**, 333 (1961).
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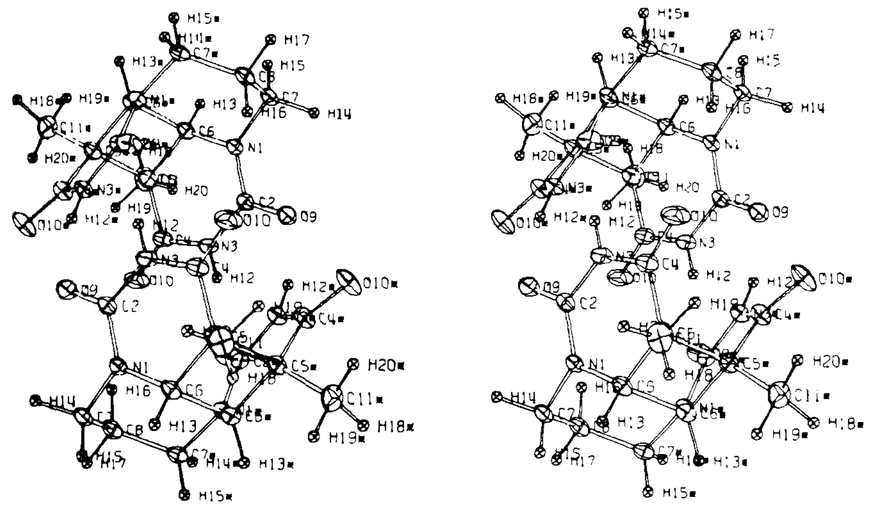

Figure 3. Stereoscopic view of two molecules of **2** forming the hydrogen-bonded centrosymmetric dimer.

agreement is fair, it should be noted that the bond angles in the seven-membered ring also differ slightly from those calculated by Hendrickson for the chair conformation in the carbocyclic series.

The principal feature of the crystal packing is the association of the molecules in pairs to form hydrogen-bonded centrosymmetric dimers (Figure 3). The N(3) hydrogen atom bonds to O(9′) and the N(3′) hydrogen atom bonds to O(9); the respective N---O distances are 2.82 and 2.87 Å, and the corresponding H---O distances are both 1.99 Å (Table X). The N–H---O angles are both

Table X. Intermolecular Contacts (<3.60 Å)[a,b]

C(11′)---N(1)^{I}	3.32	C(2)---O(9′)^{IV}	3.56
C(11′)---C(6)^{I}	3.51	N(3)---O(9′)^{IV}	2.82
N(1′)---N(3′)^{II}	3.44	O(9)---C(2′)^{IV}	3.58
C(2′)---C(2′)^{II}	3.28	O(9)---N(3′)^{IV}	2.87
C(2′)---N(3′)^{II}	3.37	O(9)---O(9′)^{IV}	3.39
C(2′)---O(9′)^{II}	3.57	H(12)---O(9′)^{IV}	1.99
N(3′)---O(9′)^{II}	3.41	O(9)--H(12′)^{IV}	1.99
C(4′)---O(9′)^{II}	3.28		
O(9′)---C(11′)^{II}	3.47		
C(8)---O(9)^{III}	3.42		

[a] Superscripted Roman numerals refer to atom transformations. [b] I refers to translation x, $\frac{1}{2} - y$, $\frac{1}{2} + z$. II refers to translation $2 - x$, $-y$, $1 - z$. III refers to translation $2 - x$, $-y$, $-z$. IV refers to translation $1 - x$, $-y$, $-z$.

163°. The angle made by the best plane through N(1), C(2), N(3), and O(9) and the best plane through the four atoms related by symmetry ($1 - x$, $-y$, $-z$) to N(1′), C(2′), N(3′), and O(9′) is 42°. While N(3) and O(9) form chains by hydrogen bonding in the crystal of the *trans-anti* dimer of 1-methylthymine,[28] N(3) and O(10) are the atoms in thymine which form the base pairs in DNA by hydrogen bonding to adenine.[37] The two C=O bond lengths involved in the hydrogen bonding [C(2)–O(9) and C(2′)–O(9′)] are somewhat longer than the two carbonyl bonds which do not act as hydrogen acceptors [*i.e.*, C(4)–O(10) and C(4′)–O(10′)]. Several atoms of the primed dihydrothymine ring have quite close contacts with atoms of another primed dihydrothymine ring (related by symmetry $2 - x$, $-y$, $1 - z$) (Figure 4). The shortest individual atom contacts are

(37) J. D. Watson and F. H. C. Crick, *Nature*, **171**, 964 (1953).

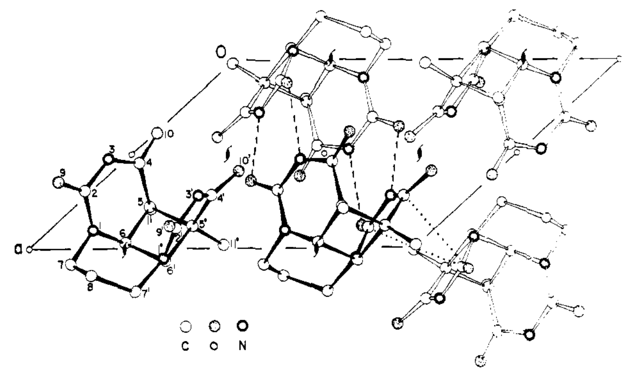

Figure 4. Packing diagram viewed along the *b* axis. In the center of the cell, two molecules form hydrogen-bonded dimers about the center of inversion at $\frac{1}{2}$, $\frac{1}{2}$, $\frac{1}{2}$, while the ring–ring contacts between C(2′) and C(2′) and between C(4′) and O(9′) are shown for the two molecules at the lower right-hand portion of the cell.

C(2′)---C(2′)^{II} and C(4′)---O(9′)^{II} which are both 3.28 Å (Table X).

The present study reveals the third example of a thymine-type dimer having *cis-syn* stereochemistry and being dissociated by X radiation into monomer in the crystalline state; the others are the sodium salt of the *cis-syn* dimer of thymine,[38] and the *cis-syn* dimer of dimethylthymine.[13] The dissociation of thymine dimer to monomer under the influence of X-rays has also been observed in solution.[39] The *cis-syn* dimer of uracil appears to be stable to X-rays.[25] The temperature parameters of the atoms included in the minor sites suggest that the 10% occupancy may be a slight overestimate.

In conclusion, the structure of the major product of 300-nm irradiation of the simplified dinucleoside phosphate model, 1,1′-trimethylenebisthymine (**1**), has been shown to be that of the *cis-syn* intramolecular dimer **2**. Since the trimethylene-bridged structure represents one extreme among possible conformational constraints placed upon a thymine dimer moiety, its geometry and intermolecular hydrogen-bonding properties in the crystal may proyide useful guidelines in relation to the *cis-syn* product formed in the photodimerization of the

(38) C. H. Wei and J. R. Einstein, Abstracts of the American Crystallographic Association, Buffalo, N. Y., July, 1968, paper L9, p 102.

(39) E.-R. Lochmann, *Naturwissenschaften*, **50**, 474 (1963).

TpT segment of DNA. The use of *o*-xylylene dibromide to link conjoined bases having proximate nitrogens may find further application in structure establishment and modification.

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The Structural and Stereochemical Course of *in Vitro* Epoxy Olefin Cyclization. Diterpenoid Intermediates[1]

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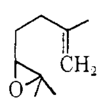
Abstract: Thc cyclization of unsaturated epoxides to tricyclic systems is shown to be a stereospecific process. Boron fluoride etherate treatment of an epoxy olefin with a central *trans*-substituted double bond, *trans*-**7**, leads to two tricyclic alcohols, **12** and **14**, both of which have *trans*-fused A/B rings. The corresponding *cis* compound, *cis*-**7**, produces an A/B *cis*-fused alcohol, **20**. These reactions also yield monocyclized products of specific geometry depending on the stereochemistry of the original double bond and the conformational folding of the epoxy olefin chain. The stereochemistry of these products suggests that cyclization occurs *via* intermediate cations of fixed geometry rather than as a "nonstop" process.

The first cyclization of an acyclic epoxy olefin, geraniolene monoepoxide, **1**, was reported[3] by us as a model system for the biosynthesis of cholesterol. Subsequent biochemical experimentation[4] has shown this type of cyclization to be the actual pathway used by cholesterol synthesizing enzymatic systems. A number of *in vitro* cyclizations of unsaturated oxiranes have also been reported[5] including one leading to the synthesis of the naturally occurring farnesiferol series of sesquiterpenoids. These studies have been patterned on the "biogenetic" process producing, as exemplified by our cyclization of **1** → **2** + **3**, 3-hydroxy-4,4-dimethylcyclohexyl systems. In this paper we wish to report the application of epoxide cyclization to "nonbiogenetic" systems with the object of preparing intermediates for diterpene acid synthesis, and the obtaining of the first definitive evidence for the stereospecificity of epoxy olefin cyclization.[1]



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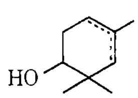

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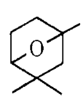

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(1) (a) This work was submitted but not published as a Communication to the Editor of *J. Am. Chem. Soc.* in June 1968. It constituted at that time the first demonstration of *stereospecific in vitro* epoxy olefin cyclization. The results and conclusions incorporated in that communication and this paper have been subsequently supported by a recently published communication: E. E. van Tamelen and J. P. McCormick, *J. Am. Chem. Soc.*, **91**, 1847 (1969). (b) This work was supported in part by a grant (GM-11729) from the Public Health Service. (c) Steroid numbering is used throughout the text of this paper.

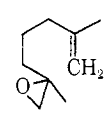
(2) Trainee, 1967–1969, NIH Training Grant GM-01394.

(3) D. J. Goldsmith, *J. Am. Chem. Soc.*, **84**, 3913 (1962).

(4) (a) E. J. Corey, W. E. Russey, and P. R. Ortiz de Montellano, *ibid.*, **88**, 4750 (1966); (b) E. E. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, *ibid.*, **88**, 4752 (1966).

(5) For a review of this work, see E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 11 (1968).

In order to produce useful intermediates for diterpene acid synthesis it was necessary to employ an unsaturated epoxide which would lead to a product having a potential C_4-carboxyl group. We chose, therefore, to investigate the reactivity of terminal epoxides. In one of our initial model studies[6] we found that treatment of terminal epoxide **4** with boron fluoride etherate in benzene gave two monocyclic products, **5** and **6**, with the desired structural features: a cyclohexane ring system with an oxygenated carbon substituent at the potential C_4 position of a diterpene acid.



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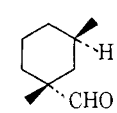

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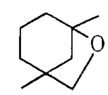

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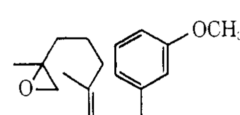
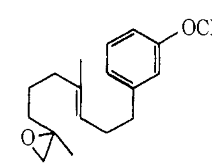
As a result of this successful monocyclic case, we turned our attention to the preparation of potential tricyclic substances. The epoxy olefins we chose for study are the *cis* and *trans* isomers of **7**. As discussed in the sequel, we expected the cyclizations of both *cis*- and *trans*-double bond isomers to yield information on the stereochemical course of epoxide cyclization as well as to lead to synthetically useful intermediates.



cis-7



trans-7

(6) D. J. Goldsmith and B. C. Clark, Jr., *Tetrahedron Letters*, 1215 (1967).