

arranged head-to-tail and connected to each other *via* N-H---Br<sup>-</sup>---H-O(4) hydrogen bonds. The chains are parallel to the *y* axis and within each sheet they are cross-linked by N-H---Br<sup>-</sup>---O(2) hydrogen bonds. A view of the structure is shown in Fig. 5.

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## The Structure of a New Natural Amino Acid, 2,3-*cis*-3,4-*trans*-3,4-Dihydroxy-L-proline

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The formula of a new amino acid isolated from the cell walls of the diatom *Navicula pelliculosa* was confirmed by X-ray analysis to be 2,3-*cis*-3,4-*trans*-3,4-dihydroxyproline. The material crystallizes in space group  $P2_12_12_1$  with cell dimensions  $a = 8.38 \pm 0.01$ ,  $b = 8.43 \pm 0.01$  and  $c = 8.56 \pm 0.01$  Å,  $Z = 4$  and a calculated density of  $1.613 \text{ g.cm}^{-3}$ . Atoms C(4), C(5), N and C(2) of the five-membered ring lie in a plane to within  $\pm 0.009$  Å while C(3) is  $0.60$  Å above the plane. The carboxyl group is equatorial while each of the two hydroxyl groups is axial to the ring. Four different hydrogen bonds, two  $\text{NH} \cdots \text{O}$  bonds and two  $\text{OH} \cdots \text{O}$  bonds, bind the molecules into a tight network. The structure was determined with the use of the symbolic addition procedure for phase determination.

### Introduction

Proline, an imino acid rather than an amino acid, occurs in many proteins but is present in especially large quantities in collagen. 4-Hydroxyproline is found in scleroproteins and keratins. It was isolated from gelatin by Fischer in 1902. Recently, a dihydroxyproline was isolated from the protein material of the cell walls of the diatom *Navicula pelliculosa* (Nakajima & Volcani, 1969). The X-ray analysis was undertaken in order to confirm the structural formula of this new naturally occurring amino acid and to compare its

structure with that determined for proline (Kayushina & Vainshtein, 1966) and hydroxyproline (Donohue & Trueblood, 1952). A preliminary report on the structure and mass spectrum of dihydroxyproline has been published (Karle, Daly & Witkop, 1969).

### Experimental

Crystals in the form of colorless acicular prisms were provided by Dr B. E. Volcani of the Scripps Institute of Oceanography. The largest of these was selected for the X-ray analysis. Even though the cross-section of

the needle was only  $0.06 \times 0.06$  mm, the scattering extended to the edge of the Cu sphere. The space group was determined unambiguously from the extinctions to be  $P2_12_12_1$ . Cell parameters determined from precession photographs and other physical data are recorded in Table 1.

Table 1. *Experimental data for 2,3-cis-3,4-trans-3,4-dihydroxy-L-proline*

Molecular formula	$C_5H_9NO_4$
Molecular weight	147.13
Melting point	$262^\circ C$ (decomp.)
$[\alpha]_D$	$-61.2^\circ$ ( $\frac{1}{2}\%$ in $H_2O$ )
Habit	Acicular prism
Crystal size	$0.06 \times 0.5 \times 0.06$ mm
Radiation, $\lambda$	Cu, 1.5418 Å
Space group	$P2_12_12_1$
$a$	$8.384 \pm 0.01$ Å
$b$	$8.433 \pm 0.01$
$c$	$8.567 \pm 0.01$
$Z$	4
$F(000)$	312
Volume	$605.7$ Å <sup>3</sup>
Density (X-ray)	$1.613$ g.cm <sup>-3</sup>
No. of independent data	611
$\langle  E  \rangle$	0.881
$\langle   E ^2 - 1  \rangle$	0.797
$\langle  E  \rangle$	0.768
$\langle  E^2 - 1  \rangle$	0.916
$ E  > 3.0$	0.0%
$ E  > 2.0$	3.1%
$ E  > 1.0$	34.7%

Intensity data were collected with the multiple-film, equi-inclination Weissenberg technique only along one axis,  $h0l-h6l$ , since the needles were too tiny to mount along any other axis. The intensities were estimated visually by comparison with a calibrated film strip. Corrections were made for the Lorentz and polarization factors and spot size. Structure factor magnitudes  $|F|$  and normalized structure factor magnitudes  $|E|$  were derived with the use of a  $K$  curve (Karle & Hauptman, 1953). Averages for  $\langle |E| \rangle$  and  $\langle ||E|^2 - 1| \rangle$  were computed separately for the general reflections which have complex structure factors and for  $hk0$ ,  $0kl$  and  $h0l$  which have pure real or pure imaginary structure factors. The values for the two sets of reflections, Table 1, agree well with centrosymmetric and non-centrosymmetric distributions (Karle & Hauptman, 1956).

### Structure analysis

The application of the symbolic addition procedure for phase determination in noncentrosymmetric space groups (Karle & Karle, 1964, 1966) led to the structure readily. The origin and enantiomorph were specified by the phase assignments: 302 (0), 730 ( $+\pi/2$ ), 053 ( $+\pi/2$ ) and 707 ( $+\pi/2$ ). Phases for three additional reflections, 208 ( $a$ ), 137 ( $p$ ) and 543 ( $q$ ) were designated by symbols to facilitate the application of the relationship (Karle & Hauptman, 1950)

$$\varphi_{\mathbf{k}} \sim \langle \varphi_{\mathbf{h}} + \varphi_{\mathbf{h}-\mathbf{k}} \rangle_{\mathbf{k}_r} \quad (1)$$

where only those reflections with  $|E| > 1.7$  were used. It soon became apparent that  $a=0$ ,  $p=+\pi/2$  and probably  $q=-\pi/2$ .\* With this assignment, the reflections whose phases were determined by equation (1) were refined by the tangent formula (Karle & Hauptman, 1956) and phases for additional reflections with  $|E| > 1.1$  were obtained with the tangent formula. A total of 214 reflections were used for computing the initial  $E$  map, Fig. 1. The maxima for the ten peaks ranged in relative value from 151 for C(4) to 356 for O(4). There were no other peaks above the background ripple where the sharp oscillations were at most  $\pm 80$  and usually less than  $\pm 50$  on the same relative scale. Fig. 1

Coordinates as read from the  $E$  map were refined by means of a least-squares procedure (Busing, Martin & Levy, 1962). The function minimized was  $\sum w(|F_o| - |F_c|)$  where  $w=0.5$  for  $F_o=0$ ,  $w=1$  for  $|F_o| < 7.0$  and  $w=7.0/|F_o|$  for  $|F_o| > 7.0$ . With isotropic thermal parameters the  $R$  value was reduced to 9.5%. Scale factors for individual layers were refined during the isotropic refinement but were kept constant for the anisotropic refinement. They ranged in value between 1.1 and 1.2. Several cycles of anisotropic refinement lowered the  $R$  value to 7.3%. A difference map at this point revealed the positions of the nine hydrogen atoms. The maxima for these atoms ranged from 0.44 to 0.65 e.Å<sup>-2</sup> and there were no extraneous peaks of the same order of magnitude. Inclusion of the nine hydrogen atoms as constant parameters in the least-

\* The work sheets for this phase determination are being reproduced in the lecture notes entitled *General Procedure for Phase Determination* by I. L. Karle in *Proceedings of Crystallographic Computing*, Ed. F. R. Ahmed. Copenhagen: Munksgaard, 1969.

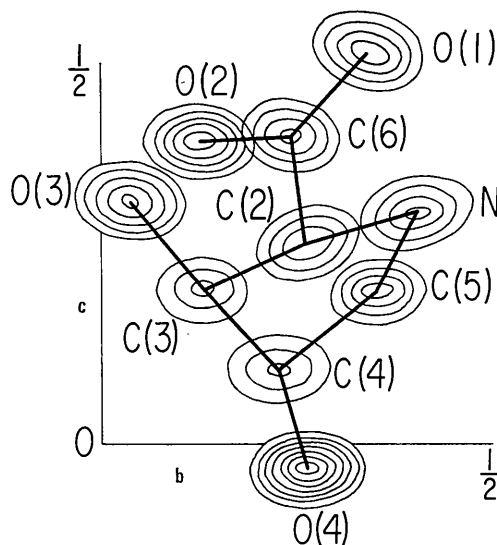


Fig. 1. Sections from a three-dimensional  $E$  map computed with 214 reflections with  $|E| > 1.1$  whose phases were determined directly from the structure factor magnitudes.

squares refinement resulted in a final *R* value of 5.8%. Observed and calculated structure factors are listed in Table 2.

The relatively low *R* value for visually estimated data can probably be correlated with the extensive hydrogen bonding and consequent low values for the thermal

Table 2. Observed and calculated structure factors  
The columns are the index *l*,  $|F_o|$ ,  $|F_c|$  and  $\phi$  (radians).

<i>l</i>	$ F_o $	$ F_c $	$\phi$ (radians)
0	0	0	0
1	15.8	15.8	1.57
2	31.7	31.7	3.14
3	47.5	47.5	4.71
4	63.3	63.3	6.28
5	79.1	79.1	7.85
6	94.9	94.9	9.42
7	110.7	110.7	10.99
8	126.5	126.5	12.56
9	142.3	142.3	14.13
10	158.1	158.1	15.70
11	173.9	173.9	17.27
12	189.7	189.7	18.84
13	205.5	205.5	20.41
14	221.3	221.3	21.98
15	237.1	237.1	23.55
16	252.9	252.9	25.12
17	268.7	268.7	26.69
18	284.5	284.5	28.26
19	300.3	300.3	29.83
20	316.1	316.1	31.40
21	331.9	331.9	32.97
22	347.7	347.7	34.54
23	363.5	363.5	36.11
24	379.3	379.3	37.68
25	395.1	395.1	39.25
26	410.9	410.9	40.82
27	426.7	426.7	42.39
28	442.5	442.5	43.96
29	458.3	458.3	45.53
30	474.1	474.1	47.10
31	489.9	489.9	48.67
32	505.7	505.7	50.24
33	521.5	521.5	51.81
34	537.3	537.3	53.38
35	553.1	553.1	54.95
36	568.9	568.9	56.52
37	584.7	584.7	58.09
38	600.5	600.5	59.66
39	616.3	616.3	61.23
40	632.1	632.1	62.80
41	647.9	647.9	64.37
42	663.7	663.7	65.94
43	679.5	679.5	67.51
44	695.3	695.3	69.08
45	711.1	711.1	70.65
46	726.9	726.9	72.22
47	742.7	742.7	73.79
48	758.5	758.5	75.36
49	774.3	774.3	76.93
50	790.1	790.1	78.50
51	805.9	805.9	80.07
52	821.7	821.7	81.64
53	837.5	837.5	83.21
54	853.3	853.3	84.78
55	869.1	869.1	86.35
56	884.9	884.9	87.92
57	900.7	900.7	89.49
58	916.5	916.5	91.06
59	932.3	932.3	92.63
60	948.1	948.1	94.20
61	963.9	963.9	95.77
62	979.7	979.7	97.34
63	995.5	995.5	98.91
64	1011.3	1011.3	100.48
65	1027.1	1027.1	102.05
66	1042.9	1042.9	103.62
67	1058.7	1058.7	105.19
68	1074.5	1074.5	106.76
69	1090.3	1090.3	108.33
70	1106.1	1106.1	109.90
71	1121.9	1121.9	111.47
72	1137.7	1137.7	113.04
73	1153.5	1153.5	114.61
74	1169.3	1169.3	116.18
75	1185.1	1185.1	117.75
76	1200.9	1200.9	119.32
77	1216.7	1216.7	120.89
78	1232.5	1232.5	122.46
79	1248.3	1248.3	124.03
80	1264.1	1264.1	125.60
81	1279.9	1279.9	127.17
82	1295.7	1295.7	128.74
83	1311.5	1311.5	130.31
84	1327.3	1327.3	131.88
85	1343.1	1343.1	133.45
86	1358.9	1358.9	135.02
87	1374.7	1374.7	136.59
88	1390.5	1390.5	138.16
89	1406.3	1406.3	139.73
90	1422.1	1422.1	141.30
91	1437.9	1437.9	142.87
92	1453.7	1453.7	144.44
93	1469.5	1469.5	146.01
94	1485.3	1485.3	147.58
95	1501.1	1501.1	149.15
96	1516.9	1516.9	150.72
97	1532.7	1532.7	152.29
98	1548.5	1548.5	153.86
99	1564.3	1564.3	155.43
100	1580.1	1580.1	157.00

Table 3. Fractional coordinates, and isotropic and anisotropic temperature factors for 2,3-cis-3,4-trans-3,4-dihydroxy-L-proline

The anisotropic thermal parameters ( $\times 10^4$ ) are of the form

$$T = \exp [ -(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl) ] .$$

	x	y	z	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$	B*
N(1)	0.7256 (5)	0.3953 (6)	0.3011 (4)	48	46	68	-12	5	-1	1.6
C(2)	0.6004 (5)	0.2737 (7)	0.2653 (5)	58	46	51	-11	2	3	1.5
C(3)	0.6964 (6)	0.1314 (8)	0.2044 (5)	59	44	45	-9	0	7	1.4
C(4)	0.8247 (6)	0.2108 (8)	0.1069 (5)	69	75	43	-12	4	4	1.8
C(5)	0.8702 (6)	0.3585 (8)	0.1977 (5)	50	86	50	-12	-2	14	1.6
C(6)	0.4890 (6)	0.2421 (7)	0.4035 (5)	58	77	44	-7	6	8	1.6
O(1)	0.5003 (5)	0.3371 (6)	0.5133 (4)	101	90	73	-34	36	-28	2.4
O(2)	0.3934 (5)	0.1299 (6)	0.3941 (4)	82	87	75	-38	26	-11	2.3
O(3)	0.7606 (5)	0.0388 (5)	0.3285 (4)	96	45	78	0	-11	28	2.2
O(4)	0.7620 (5)	0.2618 (5)	-0.0403 (4)	116	84	44	0	4	10	2.2

\* Values from the last cycle of isotropic refinement.

parameters. The X-ray diagrams were unusually sharp.

Coordinates and thermal factors for the ten heavy atoms are listed in Table 3 and the approximate coordinates for the nine hydrogen atoms are listed in Table 4.

Table 4. Approximate coordinates for hydrogen atoms as determined from a difference map

	x	y	z
NH(11)	0.758	0.378	0.400
NH(12)	0.675	0.520	0.278
CH(2)	0.538	0.310	0.182
CH(3)	0.605	0.058	0.160
CH(4)	0.938	0.142	0.057
CH(51)	0.878	0.445	0.112
CH(52)	0.950	0.358	0.265
OH(3)	0.838	0.108	0.388
OH(4)	0.750	0.150	-0.092

### Discussion

The X-ray diffraction analysis confirms the structural formula and stereochemistry and establishes the conformation of the molecule, Fig. 2. The two hydroxyl groups are both axial to the ring, while the carboxyl group is nearly equatorial. The five-membered ring has the four atoms N, C(2), C(4) and C(5) in the plane, whose equation is

$$3.08172x - 4.88650y + 6.23173z = 2.17168 ,$$

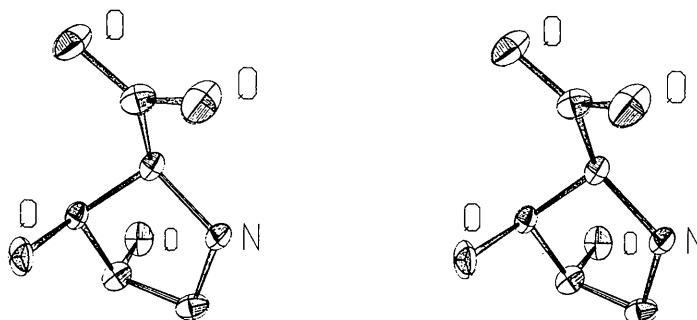


Fig. 2. Stereodiagrams of 2,3-cis-3,4-trans-dihydroxy-L-proline (drawn by a computer program written by C. K. Johnson, 1965).

with a maximum deviation of 0.009 Å. Atom C(3) is 0.60 Å out of the plane and is in the *cis* position with respect to the carboxyl group. It is interesting to note that in L-proline (Kayushina & Vainshtein, 1966), L-hydroxyproline (Donohue & Trueblood, 1952), copper proline (Mathieson & Welsh, 1952) and the prolyl residues in tosyl-prolyl-hydroxyproline (Fridrichsons & Mathieson, 1962) and in leucyl-prolyl-glycine (Leung & Marsh, 1958), it is atom C(4) rather than C(3) which is out of the plane in the five membered ring. It is not immediately apparent why the conformation of the pyrrolidine ring is changed by adding a hydroxyl group adjacent to the carboxyl group.

The bond distances and angles are shown in Fig. 3. Standard deviations based solely on the least-squares fit are  $\sim 0.008$  Å for the bond lengths and  $\sim 0.5^\circ$  for the bond angles. If other sources of error are considered, the standard deviations should be increased probably by a factor of two or three. For the moiety containing the N atom and the carboxyl ion, the parameters agree within 0.01 Å and  $1.0^\circ$  with the parameters derived from averaging the results of three-dimensional crystal structure analyses of various amino acids (Marsh & Donohue, 1967). The angle C(3)C(2)C(6) is  $3^\circ$  larger than the equivalent angle in L-hydroxyproline and  $5^\circ$  larger than in L-proline. Such an increase is probably caused by the presence of the OH group on C(3) in near proximity to the COO<sup>-</sup> group on C(2). The remaining bond lengths and angles have expected

values except perhaps for N-C(5). Carbon-nitrogen distances in saturated systems are usually about 0.03 Å shorter.

Both C-O distances in the carboxyl group have the same value within experimental error. This is expected for the  $\text{-COO}^-$  ion and, in fact, the extra proton has been found on the N atom to form a zwitterion as in other amino acids. The bonds around the N atom to C(2), C(5) and two H atoms are in an approximate tetrahedral arrangement. The two N-H bonds are directed approximately toward the carboxyl O(2) atom in two different molecules to form hydrogen bonds. Similarly the O(3)-H bond is directed toward O(1) of a carboxyl group and the O(4)-H bond is directed toward O(3). Table 5. lists the hydrogen bond lengths and the symmetry relation of the acceptor atom with respect to the donor.

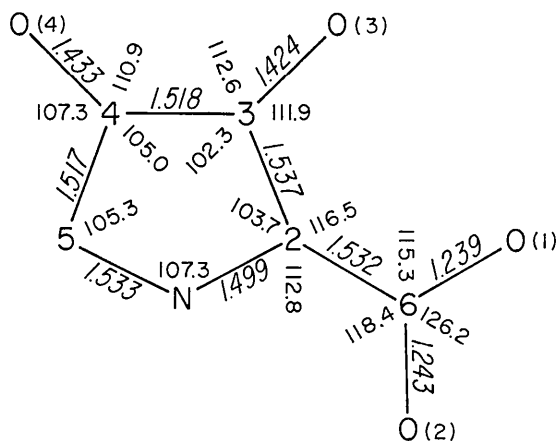


Fig. 3. Bond distances and angles.

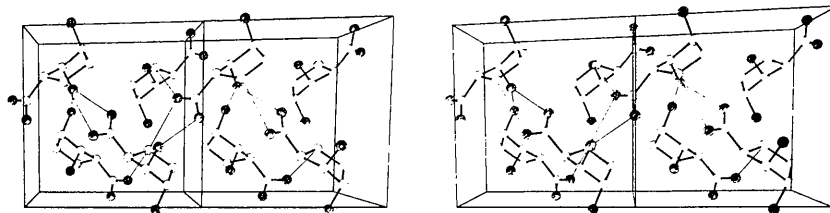


Fig. 4. Packing and hydrogen bonding in two unit cells. The directions of the axes are  $c \uparrow$ ,  $a \rightarrow$ , and  $b$  into the paper.

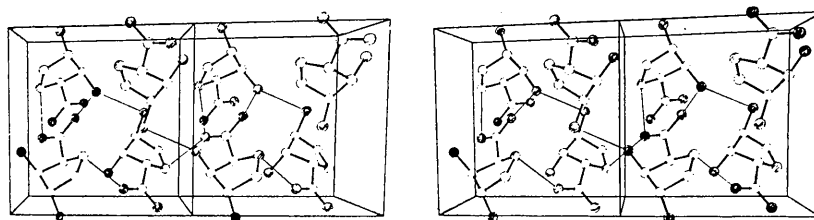


Fig. 5. A view with the axes rotated by  $90^\circ$  from the orientation in Fig. 4. The directions of the axes are  $c \uparrow$ ,  $b \rightarrow$ , and  $a$  out of the paper.

Table 5. *Hydrogen bonds*

Bonds	Symmetry operation to primed atom			Length
NH...O(2')	$\frac{1}{2}+x$	$\frac{1}{2}-y$	$\bar{z}$	2.97 Å
NH...O(2'')	$\bar{x}$	$\frac{1}{2}+y$	$\frac{1}{2}-z$	2.78
O(3)H...O(1')	$\frac{1}{2}+x$	$\frac{1}{2}-y$	$\bar{z}$	2.64
O(4)H...O(3')	$\frac{1}{2}-x$	$\bar{y}$	$\frac{1}{2}+z$	2.78

Figs. 4 and 5 show the packing and hydrogen bonding between the molecules. In the  $a$  direction, pairs of hydrogen bonds,  $\text{NH}\cdots\text{O}(2)$  and  $\text{O}(3)\text{H}\cdots\text{O}(1)$ , link the molecules into a saw-tooth chain. The chains are linked laterally in the  $b$  direction by  $\text{NH}\cdots\text{O}(2'')$  and  $\text{O}(4)\text{H}\cdots\text{O}(3')$ . The many hydrogen bonds and consequent close approaches between molecules account for the high density,  $1.61 \text{ g.cm}^{-3}$ , for an organic molecule. Aside from the atoms involved in hydrogen bonding, the nearest intermolecular approaches are  $3.17 \text{ \AA}$  between  $\text{C}(5)\cdots\text{O}(1')$  at  $\frac{1}{2}+x, \frac{1}{2}-y, \bar{z}$  and  $3.20 \text{ \AA}$  between  $\text{N}\cdots\text{O}(4')$  at  $\frac{1}{2}-x, \bar{y}, \frac{1}{2}+z$ .

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## The Structure of Dihydrothymidine\*

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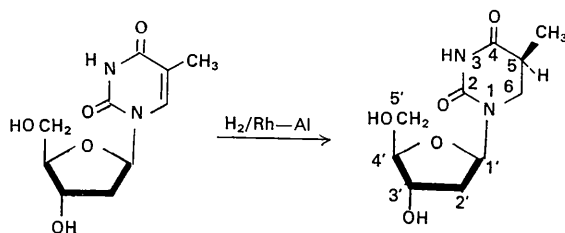
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Dihydrothymidine formed by the catalytic reduction of thymidine exists as only a single diastereoisomer. The six-membered ring in the dihydrothymine moiety has the half-chair conformation and the CH<sub>3</sub> group on C(5) is equatorial to the ring. In the furanose ring the four carbon atoms are coplanar while the O(1') atom is displaced by 0.42 Å from this plane. The O(5')H group in the sugar moiety is disordered with a 2:1 distribution. The material crystallizes in space group  $P2_12_12_1$  with  $a=9.554 \pm 0.001$ ,  $b=21.992 \pm 0.002$ ,  $c=5.475 \pm 0.001$  Å and  $Z=4$ . The structure was determined by application of the symbolic addition procedure for phase determination. The final  $R$  value was 5.1%.

### Introduction

The nucleoside thymidine is of particular interest since most radiation damage to deoxyribonucleic acid (DNA) involves the thymine moiety. Catalytic reduction of thymidine (Cohn & Doherty, 1956) yields dihydrothymidine:



From chemical and spectroscopic evidence, Kondo & Witkop (1968) have shown that in the above reaction only one diastereoisomer was produced and they have determined the stereoconfiguration about C(5). The purpose of this investigation was to confirm the configuration independently by means of a crystal struc-

ture analysis. The structure analysis has also shown that the OH group in the CH<sub>2</sub>OH chain of the sugar is disordered.

The irradiation by  $\gamma$ -rays of dihydropyrimidines in solution and in the solid state and the resulting conversion to unsaturated pyrimidines has been studied by Snipes & Bernhard (1968). A possibly similar effect of X-radiation on dihydrothymidine will be discussed.

### Experimental

Crystals of dihydrothymidine were supplied to us by Dr B. Witkop of the National Institutes of Health. From the first sample obtained, intensity data were collected along two axes with the multiple-film, equi-inclination Weissenberg technique. The intensities were estimated by visual comparison with a calibrated film strip. Corrections were made for Lorentz and polarization factors and spot size, the data from the two axes were cross-correlated, and normalized structure factors  $|E|$  were derived. These data were used for the phase determination from which the structure was derived. Least-squares refinement of the coordinates and thermal factors showed that the unit cell was a 1:1 mixture of dihydrothymidine and thymidine. Since a reaction caused by X-radiation was suspected, a crystal from a new sample of dihydrothymidine was used to collect the intensities of the  $hkl$  and  $\bar{h}kl$  reflec-

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