The Crystal Structure of 1-Ethyl-5-bromouracil. II. The Crystal Structure of the Form II Crystal of 1-Ethyl-5-bromouracil

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Two crystalline forms of 1-ethyl-5-bromouracil were found. The crystal structure of the form II has been determined. The dimension of the tetragonal unit cell are $a=b=17.13$ Å, $c=5.36$ Å, and $Z=8$. The space group is $P4_2/n$. The final R is 0.064. The hydrogen bond scheme in this crystal, N(3)–H(3)···O(2), is the first finding in alkylated pyrimidine dimers. The carbon atom binding to the nitrogen atom of the pyrimidine ring deviates significantly from the pyrimidine ring plane.

Two crystalline forms of 1-ethyl-5-bromouracil were recently found. The study of these structures showed the presence of different modes of hydrogen bond.[2] The detail of the structure of the form I is presented in the preceeding paper.[3]

The present paper deals with details of the crystal structure of the form II, in which a new hydrogen-bonding type in the alkylated pyrimidine dimers has been found.

TABLE 1. CRYSTAL DATA

$C_6H_7BrN_2O_2$	M.W.=219.05
Tetragonal	$P4_2/n$
$a=b=17.13$ Å	$c=5.36$ Å
$D_{cal}=1.85$ g/cm^3	
$D_{obs}=1.84$ g/cm^3 (by flotation)	

Experimental

Two types of crystals were grown from a dimethyl sulfoxide solution at room temperature. From I crystal is a colorless plate-like crystal and the form II is a transparent needle. Preliminary Weissenberg and Precession photographs established that the form II was tetragonal with the c axis along the needle axis. The systematic extinction of ($00l$) for l odd and ($hk0$) for $h+k$ odd restricted the space group to $P4_2/n$. The crystal data are listed in Table 1.

A nickel filtered Cu-$K\alpha$ radiation was used to collect intensity data for all the reflections in the range $0<\sin\theta/\lambda<0.55$ Å^{-1} in octant (hkl) and ($\bar{h}k0$). All the intensities were measured on a Rigaku Denki computer-controlled four-circle diffractometer (AFC-II). A scintillation counter was used with a pulse-height discriminator. A crystal of approximate dimension, 0.02 mm×0.02 mm×0.10 mm ($0.14<\mu r<0.16$), was mounted with the c axis parallel to the ϕ-axis of the diffractometer. The ω-2θ scan technique was employed with a scan speed of 2°/min by ω, and backgrounds were measured for 6.00 sec at each start and end points of the scan range. A scan range of ω for each reflection was calculated by the formula;[4] scan range$=1.00°+0.15°\times\tan\theta$. Attenuators were automatically inserted when the maximum count rate exceeded 8000 cps. The intensities were corrected only for Lorentz and polarization factors.

Measurements of two reference reflections, (400) and (200), were repeated at every fifty reflections. For 35 time repetition of the measurements, $|F_o(400)|=149.50\pm0.57$ and $|F_o(002)|=93.14\pm0.56$. The standard deviation of $|F_o(hk0)|$ were assigned on the basis of the following equation

$$\sigma^2(|F_o|) = \langle((|F_o(hk0)| - |F_o(\bar{k}h0)|)/2)^2\rangle_{av} \quad (1)$$

where $\langle\ \rangle_{av}$ represents the average of 10 reflections of similar magnitude of F_o. The standard deviations of $|F_o(hkl)|$ were substituted for $\sigma(|F_o(hk0)|)$ of similar $|F_o|$. An index of experimental accuracy

$$\sum_{h.k}(|F_o(hk0)| - |F_o(\bar{k}h0)|)/\sum_{h.k}(|F_o(hk0)| + |F_o(\bar{k}h0)|) \quad (2)$$

is 0.0119, where the summation is over all reflections, of which $|F_o|$ are greater than 10.0. Figure 1 shows the distribution of $\sigma(|F_o(hk0)|)$ *versus* $|F_o|$.

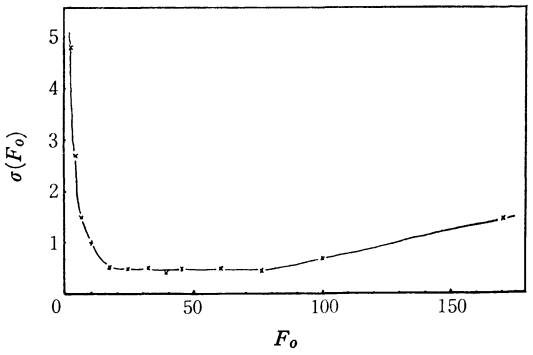

Fig. 1. The standard deviations of $|F_o(hk0)|$. Each symbol (x) represents the average of 10 reflections of similar $|F_o|$.

Structure Determination and Refinement

The position of the bromine atom was found from the three dimentional Patterson function. A Fourier synthesis was computed on the basis of the position of bromine atom. Eight extra atoms except ethyl group showed up on the first map. The definite location of the ethyl group could not be found on the electron density map. The peak which corresponds to the carbon atom C(7) binding to N(1) is too much elongated along the direction perpendicular to the pyrimidine ring plane.

Structure refinements were carried out by the block diagonal least-squares method. The function, $\sum w(|F_o|-|F_c|)^2$, was minimized for the least-squares refinements. The atomic scattering factors were taken from "Inter-

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Table 2. Final atomic coordinates and thermal parameters with their estimated standard deviations

	x	e.s.d. (x)	y	e.s.d. (y)	z	e.s.d. (z)
Br	0.3591	0.0007	0.6928	0.0006	1.3252	0.0007
C2	0.4139	0.0049	0.4906	0.0046	0.7649	0.0053
C4	0.4448	0.0045	0.6244	0.0047	0.9259	0.0047
C5	0.3841	0.0045	0.6125	0.0046	1.1045	0.0052
C6	0.3451	0.0049	0.5465	0.0052	1.1099	0.0057
N1	0.3587	0.0044	0.4860	0.0043	0.9462	0.0052
N3	0.4556	0.0036	0.5600	0.0036	0.7689	0.0039
O2	0.4279	0.0035	0.4397	0.0033	0.6139	0.0038
O4	0.4860	0.0034	0.6819	0.0031	0.9021	0.0035
H3	0.4962	0.0360	0.5649	0.0346	0.6603	0.0412
H6	0.2979	0.0393	0.5415	0.0388	1.2066	0.0444
C7	0.2884	0.0098	0.4258	0.0097	0.8958	0.0105
C8	0.3069	0.0121	0.3654	0.0120	1.0861	0.0118
C7′	0.3313	0.0109	0.3983	0.0107	1.0249	0.0116
C8′	0.2618	0.0126	0.3926	0.0126	0.8818	0.0134

	$B_{11}\times10^5$	$B_{22}\times10^5$	$B_{33}\times10^4$	$B_{12}\times10^5$	$B_{13}\times10^4$	$B_{23}\times10^4$
Br	663 (3)	459 (3)	485 (2)	174 (6)	6 (2)	−70 (2)
C2	383 (21)	342 (21)	436 (26)	−89 (37)	58 (12)	7 (13)
C4	317 (20)	321 (19)	349 (22)	109 (34)	−44 (12)	40 (12)
C5	308 (19)	323 (20)	358 (23)	−15 (33)	−8 (11)	−11 (12)
C6	338 (22)	532 (26)	470 (29)	20 (40)	92 (14)	−38 (15)
N1	515 (22)	416 (20)	708 (27)	−386 (35)	230 (14)	−79 (13)
N3	304 (15)	348 (16)	366 (19)	−22 (26)	55 (9)	16 (9)
O2	520 (17)	370 (15)	620 (21)	−233 (26)	163 (11)	−68 (10)
O4	481 (16)	320 (14)	501 (19)	−195 (25)	12 (10)	14 (9)

	B
H3	3.500 (0.897)
H6	3.500 (0.903)
C7	4.616 (0.233)
C8	6.747 (0.299)
C7′	5.445 (0.263)
C8′	7.499 (0.331)

Temperature factor
$=\exp(-(B_{11}\times h^2+B_{22}\times k^2+B_{33}\times l^2+B_{12}\times hk+B_{13}\times hl+B_{23}\times kl))$
or
$=\exp(-B(\sin\theta/\lambda)^2)$

national Table for X-ray Crystallography (1962)." To take into account of the anomalous scattering by bromine atom, $\Delta f'(-0.95)$ and $\Delta f''$ (1.40) were included in the calculations. The weighting scheme employed was

$w = 0.0$ ($|F_o|<10.0$ or attenuated reflection)
$w = \sigma^{-1}(|F_o|)$ (others).

Five cycles of least-squares refinement of positional parameters and anisotropic thermal parameters for the nine atoms except ethyl group resulted an a value of R of 0.1394. An (F_o—F_c) synthesis then revealed the two possible site of the ethyl group (Fig. 2).

After three cycles of least-squares refinements of the positional parameters, the anisotropic thermal parameters for the nine atoms except ethyl group and the isotropic thermal parameters for the four atoms of the two sites of the ethyl group, the R value decreased to 0.068. The ethyl group was supposed as equally distributed to the two sites, that is, the occupancies of the both sites are 0.5. In the course of the refinement,

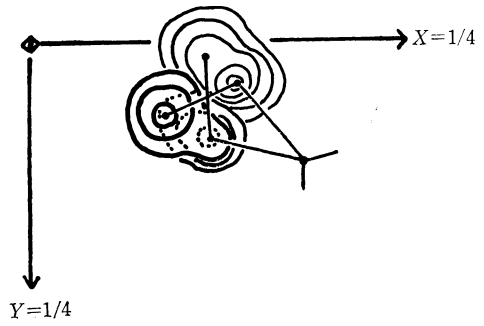

Fig. 2. The composite difference electron density map, for which the contribution of the hydrogen atoms and ethyl group carbon atoms were excluded from the calculated structure factors. Contours are drown at interval of 0.5 e/Å³, starting at 0.5 e/Å³.

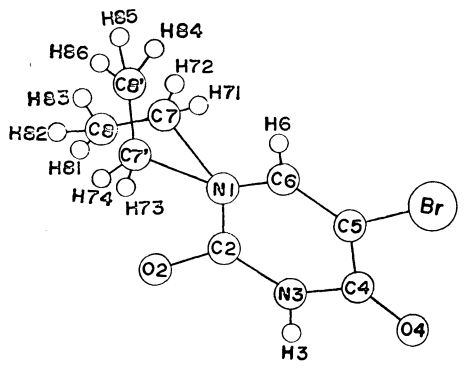

Fig. 3. Structural formula of 1-ethyl-5-bromouracil.

the temperature factor of an atom of the ethyl group compensated for particular choice of the occupancy of the same atom. Accurate occupancies of two ethyl group sites could not be determined, partly because only about 60% of reflections within the limiting sphere of Cu-$K\alpha$ radiation was used in the determination. For several sets of occupancies of two ethyl group sites, similar refinements were tried. These calculations suggested that two ethyl group sites should be multiplied by 0.60—0.45 and 0.45—0.60 respectively. The (F_o—F_c) synthesis at this stage revealed two hydrogen atoms bound to the pyrimidine ring.

The final refinement included all atoms except for the hydrogen atoms of the ethyl group. The final R is 0.064.*

Molecular Structure

Tables 4 and 5 give the bond distances in the pyrimidine ring of this crystal and some other crystals respectively. Comparison with these crystals shows that structure of the pyrimidine ring are in good agreement with each others. The molecule except ethyl group is nearly planar (Table 6), bromine atom being displaced from the plane by 0.04 Å. The carbon atom C(7) and C(7′) deviate significantly from the plane by 0.53 Å and 0.57 Å, respectively. This displacement suggests an increase of p-character in the bond orbitals of C(7)–N(1) and C(7′)–N(1). Triethylpyrazine[5] and bromodihydroacromycine[6] have a similar structure. In form I, the carbon atom C(7) does not displace from the pyrimidine ring plane. In form II, if the carbon atom C(7) is placed on the plane, the distance between the carbon atom C(8) and the oxygen atom O(2) or O(4) of the neighboring molecule is shorter than 3.2 Å.

Table 4. Bond lengths and angles with their estimated standard deviations

Bond	Length	e.s.d.	Angle	θ	e.s.d.
C6–N1	1.376 Å	0.008 Å	C6–N1–C2	121.8°	0.5°
N1–C2	1.360	0.007	C6–N1–C7	117.7	0.6
C2–N3	1.383	0.007	C7–N1–C2	116.1	0.6
N3–C4	1.399	0.006	C6–N1–C7′	118.8	0.6
C4–C5	1.429	0.007	C7′–N1–C2	116.1	0.6
C5–C6	1.313	0.008	N1–C2–N3	113.7	0.5
C2–O2	1.216	0.007	N1–C2–O2	124.7	0.5
C4–O4	1.218	0.006	O2–C2–N3	121.7	0.5
Br–C5	1.864	0.005	C2–N3–C4	128.7	0.4
N1–C7	1.599	0.012	C2–N3–H3	118.8	3.2
C7–C8	1.495	0.016	H3–N3–C4	113.2	3.2
N1–C7′	1.626	0.013	N3–C4–C5	112.7	0.4
C7′–C8′	1.425	0.018	N3–C4–O4	119.9	0.4
N3–H3	0.916	0.041	O4–C4–C5	127.4	0.5
C6–H6	0.963	0.045	C4–C5–C6	120.6	0.5
			C4–C5–Br	119.1	0.5
			Br–C5–C6	120.3	0.4
			C5–C6–N1	123.2	0.5
			C5–C6–H6	123.4	3.3
			H6–C6–N1	112.5	3.3
			N1–C7–C8	100.4	0.8
			N1–C7′–C8′	99.6	0.9

Table 5. Bond lengths and angles of uracil or thymine derivatives

Bond	T[7]	TD[8]	MT[9]	EBU (form I)[3],
C(6)–N(1)	1.382 Å	1.374 Å	1.383 Å	1.384 Å
N(1)–C(2)	1.355	1.385	1.379	1.361
C(2)–N(3)	1.361	1.381	1.379	1.400
N(3)–C(4)	1.391	1.378	1.375	1.381
C(4)–C(5)	1.447	1.453	1.432	1.432
C(5)–C(6)	1.349	1.343	1.346	1.339
C(2)–O(2)	1.234	1.206	1.214	1.212
C(4)–O(4)	1.231	1.230	1.237	1.226
σ	0.005	0.006	0.004	0.008

a) T, TD, MT and EBU represent thymine, thymidine, 1-methylthymine, and 1-ethyl-5-bromouracil respectively.

Table 6. The equation of the least-squares plane through atoms

Equation	Atom	Deviation
$-0.6617X+0.3866Y$ $-0.6425Z+4.0882=0$	Br	0.042 Å
	C2	0.016
	C4	−0.012
	C5	−0.010
	C6	−0.030
	N1	−0.014
	N3	−0.017
	O2	0.034
	O4	−0.010
	*H3	0.041
	*H6	0.092
	*C7	0.545
	*C8	−0.709
	*C7′	−0.563
	*C8′	0.660

where $X=ax$, $Y=by$, $Z=cz$

Atom not included in the least-squares calculation.

Molecular Packing

There are four intermolecular contact regions. Bromine atoms pack closely around a 4_2-axis. Hydrogen bonds, N–H···O, are formed around a center of symmetry. Disordered ethyl groups surround a $\bar{4}$-axis. The hydrogen atom H(6) and the oxygen atom O(4) contact closely with each other. One of the interesting

* Table 3 which gives a complete list of the observed and the calculated structure factors has been submitted to, and is kept as Document No. 7202 by, the office of the Bulletin of the Chemical Society of Japan, 1-5 Kanda-Surugadai, Chiyoda-ku, Tokyo. A copy may be secured by citing the Document number and by remitting, in advance, ¥400 for photo prints. Pay by check or money order payable to: Chemical Society of Japan.

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Table 7. Intermolecular contacts

Atom	Neighbor atom		Distance	Atom	Neighbor atom		Distance
Br	Br	g	4.012 Å	C(7)	C(8)	e	4.296 Å
Br	Br	h	4.012	C(7)	C(8)	f	4.360
Br	Br	j	4.012	C(7)	C(7′)	e	4.328
Br	Br	k	4.012	C(7)	C(8′)	c	3.999
Br	Br	i	4.223	C(8)	C(8)	b	4.435
				C(8)	C(8)	d	3.553
O(2)	N(3)	a	2.866	C(8)	C(7′)	d	4.288
O(2)	H(3)	a	1.958	C(8)	C(7′)	f	4.158
				C(8)	C(8′)	b	4.323
O(4)	C(6)	k	3.249	C(8)	C(8′)	c	3.680
O(4)	H(6)	k	2.268	C(8)	C(8′)	d	3.857
				C(7′)	C(8′)	c	3.711
				C(7′)	C(8′)	d	4.357
				C(8′)	C(8′)	e	3.781

Key for molecule position

a	$1.0-x$	$1.0-y$	$1.0-z$
b	x	y	$1.0+z$
c	y	$0.5-x$	$1.5-z$
d	y	$0.5-x$	$2.5-z$
e	$0.5-y$	x	$1.5-z$
f	$0.5-y$	x	$2.5-z$
g	$-0.5+y$	$1.0-x$	$0.5+z$
h	$-0.5+y$	$1.0-x$	$-0.5+z$
i	$0.5-x$	$1.5-y$	z
j	$1.0-y$	$0.5+x$	$0.5+z$
k	$1.0-y$	$0.5+x$	$-0.5+z$

aspects of this crystal structure is the packing of bromine atoms. Two non-equivalent distances between bromine atoms are 4.22 Å and 4.01 Å respectively (Table 7). This closest packing region elongates along the needle axis.

The hydrogen bond scheme in this crystal, N(3)–H(3)···O(2), is the first finding in the alkylated pyrimidine dimers. While the hydrogen bond scheme in form I, N(3)–H(3)···O(4), is usually found in the self-dimer of uracil and thymine derivatives, for example, uracil,[10,11] 1-methyluracil,[12] 5-ethyl-6-methyl uracil[13] and 1-methylthymine.[14] It seems that a change of electron distribution in pyrimidine ring by a substitution of a bromine atom or van der Waals interaction between closest packed bromine atoms perturbs the construction of the hydrogen bond scheme. Table 7 gives a list of all the intermolecular contacts between the disordered carbon atoms of the ethyl group. The distances of C(8)–C(8d)[15] and C(8)–C(8'c)[15] are shorter than usual, but a similar intermolecular contact between methyl groups in a crystal of octamethyltetraamidodiphosphono-2,3-butadiene-1,3.[16] The distance between H(6) and O(4), 2.27 Å, is fairly short, and the angle C(6)–H(6)–O(4) is 178.0°. In a thymine or uracil molecule, C(6) has a fairly positive charge.[17] Thus C(6)–H(6)···O(4) may be a hydrogen bond. Similar hydrogen bonds were reported in form I crystal and some other crystals, barium uridine-5′-phosphate,[18] β-adenosine-2′-β-uridine-5′-phosphoric acid[19] and calcium thymine phosphate.[20]

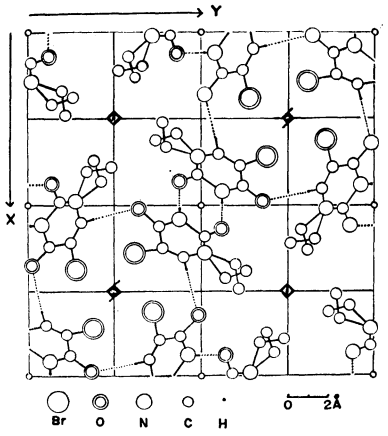

Fig. 4. The crystal structure viewed along the *c* axis. Hydrogen bonds are indicated by broken lines.

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