The Crystal and Molecular Structure of the *p*-Bromobenzoate of Sterigmatocystin

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The crystals of the *p*-bromobenzoate of sterigmatocystin, $C_{25}H_{15}O_7Br$, are monoclinic, with the space group of $P2_1$, and with two molecules per unit cell with the dimensions of $a=13.062(7)$, $b=9.029(4)$, $c=8.942(4)$ Å, and $\beta=102.25(5)°$. The structure was refined by a least-squares method to $R=0.055$ for 1292 non-zero reflections. The absolute configuration of the molecule was determined by using the anomalous dispersion effect of the bromine atom. The absolute configuration of the bisdihydrofuran ring agrees with that in aflatoxin B_1.

Sterigmatocystin is one of the carcinogenic metabolites of the mold *Aspergillus versicolor* (Vuillemin) Tiraboschi. A preliminary report on the X-ray structural analysis of the *p*-bromobenzoate of sterigmatocystin has already been published.[1] In the series of studies of the structures of the metabolites of this mold,[1-3] the refinement of the structure and the determination of the absolute configuration of the *p*-bromobenzoate of sterigmatocystin have been undertaken.

Refinement of the Structure

The title compound, $C_{25}H_{15}O_7Br$, was prepared by the method described in the previous paper.[1] The unit-cell constants were remeasured on a Toshiba four-circle diffractometer with Ni-filtered Cu$K\alpha$ radiation ($\lambda=1.5418$ Å). The crystal data are: monoclinic, space group $P2_1$, $a=13.062$ (7), $b=9.029$ (4), $c=8.942$ (4) Å, $\beta=102.25$ (5)°, $V=1030.6$ Å^3, $Z=2$, $M=507.3$, $D_m=1.640$ g·cm^{-3}, $D_x=1.635$ g·cm^{-3}, $\mu=34.4$ cm^{-1}. The structure found in the previous paper[1] was refined by the block-diagonal least-squares procedure using the three-dimensional intensity data obtained by the Weissenberg method. Out of 1580 measured reflections,*** 1292 non-zero reflections were used for the refinement. After several cycles of refinement with individual anisotropic temperature factors, the discrepancy factor (R value) was reduced to 0.065. The difference electron density map at this stage revealed peaks corresponding to fifteen hydrogen atoms. Three cycles of refinement, including hydrogen atoms, brought the R value down to 0.057.

Determination of the Absolute Configuration

In the final stage of the analysis, the absolute configuration of the molecule was determined by using the anomalous scattering of Cu$K\alpha$ radiation by the bromine atom.[4] The structure factors were calculated for the two enantiomorphs with a scattering factor for bromine of the $f_{Br}=f^{\circ}_{Br}+\Delta f_{Br}'+i\Delta f_{Br}''$ form, where $\Delta f_{Br}'=-0.9$ and $\Delta f_{Br}''=1.5$. Sixteen Friedel pairs of reflections strongly affected by the anomalous dispersion effect were selected for accurate intensity measurements. The intensities were obtained by the $\omega-2\theta$ scan technique using Ni-filtered Cu$K\alpha$ radiation on the four-circle diffractometer with a specimen with dimensions of *ca.* $0.07\times0.04\times0.30$ mm^3. The absolute configuration was established by a comparison of the observed and calculated intensities shown in Table 1. Three further cycles of refinement including the anomalous dispersion effect reduced the R value to 0.055 for 1292 non-zero reflections. The unit weight was applied for all the non-zero reflections. The final atomic parameters are shown in Table 2. The absolute configuration is correctly represented by the atomic parameters of Table 2 if a right-handed coordinate system is adopted.

TABLE 1. FRIEDEL PAIRS OF REFLECTIONS USED IN DETERMINING THE ABSOLUTE CONFIGURATION
The right-handed coordinate system is adopted.

k	h	l	$F_c(hkl)$	$F_c(\bar{h}\bar{k}\bar{l})$	$I_o(hkl)$ $I_o(\bar{h}\bar{k}\bar{l})$
5	3	0	108	92	$>$
3	5	0	107	119	$<$
0	2	1	175	185	$\lesssim$
5	3	1	118	131	$<$
2	1	2	163	180	$<$
4	2	2	142	127	$>$
0	3	4	153	143	$>$
0	1	4	86	71	$>$
1	1	3	69	80	$<$
3	1	$\bar{4}$	109	98	$>$
1	3	$\bar{2}$	159	170	$\lesssim$
2	4	$\bar{2}$	161	174	$<$
3	4	$\bar{2}$	95	107	$\lesssim$
5	2	$\bar{2}$	125	115	$>$
2	1	$\bar{1}$	175	150	$>$
4	3	$\bar{1}$	63	73	$<$

The atomic scattering factors were taken from the International Tables for X-ray Crystallography.[5] A list of the observed and calculated structure factors is kept by the office of the Chemical Society of Japan, (Document No. 7511). The computations were performed on a TOSBAC 3400 computer at the Tottori University Computing Center and on a NEAC 2200—N700 computer at the Computation Center of Osaka University.

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*** The reflections in the blind regions of the Weissenberg method were measured on the diffractometer.

TABLE 2(a). FINAL ATOMIC PARAMETERS AND e.s.d.'s ($\times 10^4$) FOR NON-HYDROGEN ATOMS
The anisotropic temperature factors are of the form: $\exp(-\beta_{11}h^2-\beta_{22}k^2-\beta_{33}l^2-\beta_{12}hk-\beta_{13}hl-\beta_{23}kl)$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br	−616(1)	2484(3)	11595(2)	114(1)	265(3)	254(2)	−2(4)	178(3)	−5(6)
C(1)	1994(10)	−4562(14)	2848(12)	124(11)	104(24)	137(16)	−73(25)	83(22)	−5(30)
C(2)	1916(8)	−3363(13)	3790(11)	79(8)	112(21)	127(15)	18(21)	20(18)	26(28)
C(3)	2515(7)	−2058(12)	3841(10)	72(7)	93(23)	114(13)	−32(19)	35(15)	−21(25)
C(4)	2463(8)	−804(14)	4811(11)	66(7)	140(22)	141(16)	3(21)	43(17)	18(31)
C(5)	3119(7)	498(12)	4628(10)	62(7)	80(21)	114(13)	8(17)	23(15)	−9(24)
C(6)	3144(8)	1872(14)	5399(11)	87(8)	154(25)	119(15)	13(21)	62(18)	−60(28)
C(7)	3752(9)	3024(13)	5201(12)	111(10)	113(27)	155(17)	−79(24)	63(21)	−20(29)
C(8)	4402(9)	2872(17)	4144(12)	90(8)	206(31)	152(17)	−50(28)	23(19)	−42(36)
C(9)	4426(8)	1568(14)	3372(11)	82(8)	141(22)	112(14)	−44(22)	33(17)	−25(28)
C(10)	3789(8)	403(13)	3604(11)	64(7)	131(24)	122(15)	21(20)	14(16)	0(28)
C(11)	3218(7)	−2024(12)	2855(10)	59(6)	86(23)	118(13)	−5(17)	22(14)	−27(24)
C(12)	3320(9)	−3167(12)	1915(11)	97(9)	58(20)	119(15)	38(19)	36(18)	−19(24)
C(13)	2738(10)	−4409(13)	1936(12)	135(12)	37(22)	140(17)	67(23)	24(22)	22(27)
C(14)	3738(11)	−4999(16)	259(13)	138(13)	152(25)	158(19)	48(31)	91(25)	−15(36)
C(15)	3196(9)	−3528(15)	−1808(13)	86(9)	175(25)	173(18)	−33(25)	99(21)	−26(35)
C(16)	3581(7)	−2594(17)	−750(10)	74(7)	141(21)	153(15)	−10(27)	98(16)	−47(36)
C(17)	3992(9)	−3409(15)	720(12)	82(8)	164(24)	154(18)	4(24)	70(20)	−89(32)
C(18)	580(12)	−4680(19)	4699(15)	154(15)	259(36)	206(24)	−128(38)	151(31)	24(48)
C(19)	2689(8)	1515(13)	7796(11)	77(8)	87(20)	141(16)	10(21)	9(17)	−40(27)
C(20)	1867(8)	1768(13)	8657(10)	73(7)	114(21)	108(14)	22(18)	28(16)	−20(25)
C(21)	953(8)	2543(19)	8102(11)	102(9)	146(22)	164(17)	41(33)	46(19)	−29(41)
C(22)	234(9)	2840(17)	8987(13)	94(9)	168(30)	204(20)	90(27)	100(21)	86(40)
C(23)	385(8)	2183(16)	10391(11)	93(9)	161(28)	141(16)	−10(25)	81(19)	−35(33)
C(24)	1256(9)	1382(16)	10985(13)	91(9)	168(26)	171(19)	14(26)	67(21)	−7(36)
C(25)	2008(8)	1169(16)	10113(12)	78(8)	184(26)	133(16)	49(24)	14(18)	49(32)
O(1)	1221(6)	−3385(10)	4732(8)	100(6)	175(16)	136(11)	−100(16)	94(13)	−54(21)
O(2)	1933(6)	−794(10)	5829(9)	105(7)	172(11)	214(14)	−89(18)	169(16)	−110(25)
O(3)	2426(5)	2085(8)	6348(7)	77(5)	133(16)	121(9)	42(13)	53(11)	1(18)
O(4)	3849(5)	−840(9)	2760(7)	72(5)	117(13)	123(10)	−9(14)	54(11)	−65(19)
O(5)	2903(8)	−5521(10)	962(9)	172(9)	102(16)	171(13)	−23(19)	102(18)	−85(22)
O(6)	3345(8)	−5014(12)	−1352(9)	171(10)	210(19)	170(14)	−60(24)	129(19)	−206(26)
O(7)	3506(5)	950(10)	8261(8)	70(5)	203(17)	158(12)	11(16)	43(13)	49(24)

TABLE 2(b). FINAL POSITIONAL PARAMETERS ($\times 10^3$) AND ISOTROPIC TEMPERATURE FACTORS FOR HYDROGEN ATOMS

Attached to	x	y	z	B
H(1) C(24)	136(9)	103(15)	1218(13)	5.6(33)Å^2
H(2) C(25)	264(11)	48(18)	1046(16)	9.9(47)
H(3) C(21)	78(7)	296(13)	685(11)	4.1(28)
H(4) C(22)	−44(9)	351(15)	863(13)	6.3(36)
H(5) C(7)	375(10)	399(18)	567(15)	8.6(43)
H(6) C(8)	483(9)	375(15)	400(12)	5.3(32)
H(7) C(9)	490(8)	131(13)	249(11)	3.4(26)
H(8) C(17)	473(8)	−322(13)	119(12)	5.1(33)
H(9) C(16)	359(7)	−138(12)	−95(10)	1.7(22)
H(10) C(15)	281(10)	−327(17)	−302(15)	9.0(45)
H(11) C(14)	436(11)	−570(19)	47(16)	9.8(46)
H(12) C(1)	151(10)	−550(18)	269(15)	8.5(43)
H(13) C(18)	19(8)	−441(13)	560(11)	3.6(28)
H(14) C(18)	20(8)	−488(15)	371(12)	4.9(30)
H(15) C(18)	94(8)	−559(14)	521(12)	4.7(30)

Description of the Structure and Discussion

The present X-ray analysis has established the absolute configuration of the *p*-bromobenzoate of sterigmatocystin. Figure 1 shows a view of the packing of the molecules in the crystal and the numbering of atoms, while Fig. 2 shows the stereoscopic view of the molecule. Both figures are illustrated with the correct absolute configuration. As has been shown by Holker *et al.*,[7]

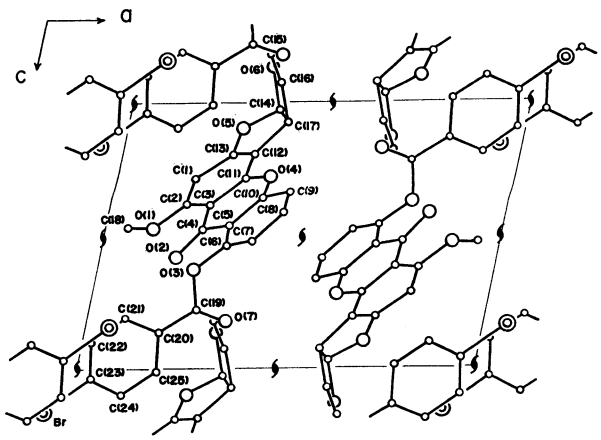

Fig. 1. The crystal structure viewed along the *b* axis and the numbering of atoms. Hydrogen atoms are omitted in the figure.

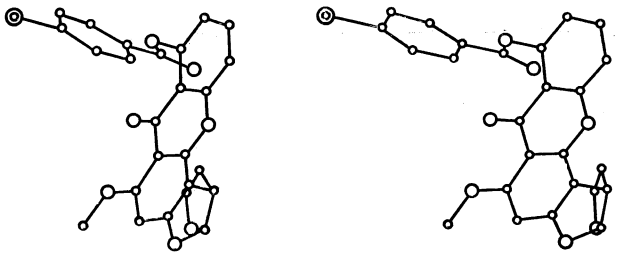

Fig. 2. Stereoscopic view of the molecule.

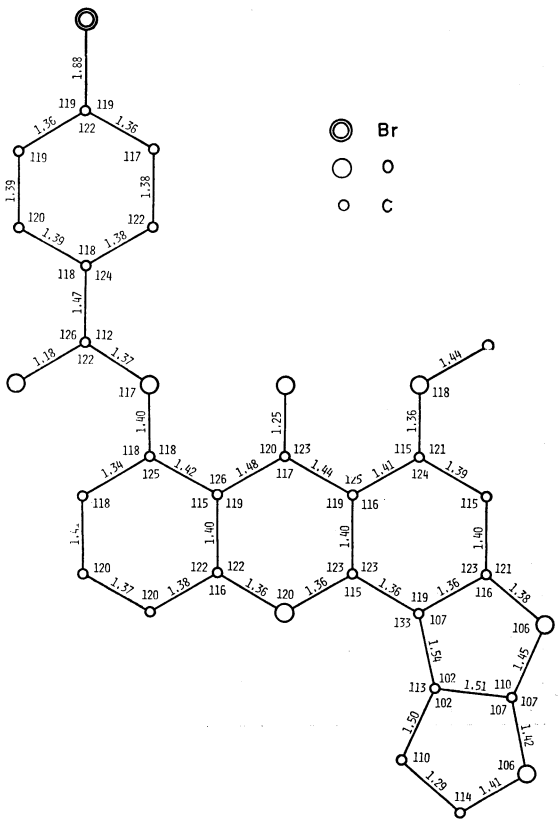

Fig. 3. The bond lengths (Å) and angles (°). The e.s.d.'s of the bond lengths and angles are about 0.02 Å and 1.2 °, respectively.

the absolute configuration of the bisdihydrofuran ring in this compound agrees with that found in aflatoxin B_1.[6] The bond lengths and angles for non-hydrogen atoms are illustrated in Fig. 3. The e.s.d.'s of the bond lengths and the angles for non-hydrogen atoms are about 0.02 Å and 1.2 ° respectively. The bond angles of C(3)–C(4)–C(5), C(9)–C(10)–O(4), and O(4)–C(11)–C(12) are 117 °, 116 °, and 115 ° respectively; these values are smaller than the trigonal sp^2 hybrid angle. On the other hand, the bond angles of C(2)–C(3)–C(4) and C(4)–C(5)–C(6) are larger than 120 °. This structural situation has also been found in the xanthone skeleton in sterigmatin.[3] The dimensions of the bisdihydrofuran ring are close to those in the compounds, such as aflatoxin B_1[6] and sterigmatin,[3] within the limit of experimental error.

The least-squares planes through the xanthone skeleton with O(1) and O(3) atoms, through the terminal five-membered ring, through the benzene ring, and through the C(19), C(20), O(3), and O(7) atoms are represented by the equations;

$$0.580X - 0.370Y + 0.726Z = 4.592 \quad \text{(I)}$$

$$0.973X - 0.055Y - 0.225Z = 4.956 \quad \text{(II)}$$

$$0.405X + 0.831Y + 0.383Z = 4.533 \quad \text{(III)}$$

and

$$0.345X + 0.880Y + 0.325Z = 4.135 \quad \text{(IV)}$$

respectively, where $X=ax+cz\cos\beta$, $Y=by$, and $Z=$

Table 3. Deviations of atoms from each least-squares plane and dihedral angles

(a) Deviations

(I) From xanthone-skeltone with O(1) and O(3) atoms					
C(1)	0.07 Å	C(2)	0.03 Å	C(3)	−0.01 Å
C(4)	−0.06	C(5)	−0.03	C(6)	0.01
C(7)	0.03	C(8)	0.04	C(9)	0.00
C(10)	−0.03	C(11)	−0.02	C(12)	0.02
C(13)	0.03	O(1)	0.06	O(2)	−0.19
O(3)	0.12	O(4)	−0.05	C(14)[a]	−0.04
C(17)[a]	0.05	O(5)[a]	0.04		
(II) From terminal five-membered ring					
C(14)	−0.05 Å	C(15)	−0.03 Å	C(16)	0.01 Å
C(17)	0.01	O(6)	0.06		
(III) From benzene ring					
C(20)	−0.01 Å	C(21)	0.04 Å	C(22)	−0.04 Å
C(23)	0.02	C(24)	0.00	C(25)	−0.01
Br[a]	0.01	C(19)[a]	−0.03		
(IV) From the plane through C(19), C(20), O(3), and O(7) atoms					
C(19)	0.01 Å	C(20)	0.00 Å	O(3)	0.00 Å
O(7)	−0.01				

(b) Dihedral angles

	I	II	III
II	65.1°		
III	78.2°	74.8°	
IV	83.7°	77.6°	5.5°

a) Not included in the least-squares calculation.

Table 4. Intermolecular contacts less than 3.6 Å

Br	C(15)[a]	3.54 Å	C(21)	C(18)[a]	3.49 Å
C(21)	O(1)[a]	3.48	C(22)	C(2)[a]	3.50
Br	O(2)[b]	3.52	C(19)	O(6)[c]	3.29
C(20)	O(5)[c]	3.30	C(20)	O(6)[c]	3.49
C(24)	O(5)[c]	3.53	C(25)	O(5)[c]	3.24
O(3)	O(6)[c]	3.39	C(25)	C(10)[d]	3.54
C(25)	O(4)[d]	3.50	O(1)	C(15)[d]	3.59
O(2)	C(15)[d]	3.43	O(7)	C(16)[d]	3.32
C(7)	C(1)[e]	3.52	C(8)	C(13)[e]	3.58
C(8)	O(5)[e]	3.42	C(7)	O(4)[f]	3.43
C(8)	C(10)[f]	3.58	C(8)	O(4)[f]	3.40
C(17)	O(7)[g]	3.25	C(18)	O(2)[h]	3.37
O(1)	C(21)[h]	3.48			

The superscripts refer to the following positions relative to the reference molecule at x,y,z; a) $-x,1/2+y,1-z$. b) $-x,1/2+y,2-z$. c) $x,1+y,1+z$. d) $x,y,1+z$. e) $x,1+y,z$. f) $1-x,1/2+y,1-z$. g) $1-x,-1/2+y,1-z$. h) $-x,-1/2+y,1-z$.

$cz \sin\beta$. Table 3 shows the deviations of the atoms from these planes and the dihedral angles between these planes. The dihedral angle between the I and II planes is 65.1 °; this value is close to the corresponding angle found in aflatoxin B_1.[6] The deviations of the atoms from the plane of the xanthone skeleton in this compound are large in comparison with those in sterigmatin;[3] the xanthone skeleton bends slightly about the O(2)–O(4) axis. The intermolecular distances for non-hydrogen atoms of less than 3.6 Å are listed in Table 4, which indicates that there is no abnormally short contact.

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