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The Crystal and Molecular Structure of Versicolorin C, A Metabolite of *Aspergillus versicolor*

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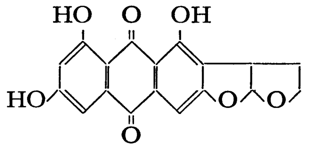
The crystal structure of versicolorin C, $C_{18}H_{12}O_7$, has been determined by the X-ray diffraction method. The crystals are monoclinic, with the space group $P2_1/a$, and with four molecules in a unit cell with dimensions of $a=24.918(7)$, $b=7.922(3)$, $c=7.003(3)$ Å, and $\beta=92.85(4)°$. The structure was refined by the least-squares method to $R=0.053$ for 1693 non-zero reflections. There are two intramolecular hydrogen bonds. A pair of molecules related by a center of symmetry forms a dimer by means of intermolecular hydrogen bonds.

Aspergillus versicolor (Vuillemin) Tiraboschi and *Aspergillus flavus* Link ex Fries produce a variety of compounds which contain a tetrahydrofuranofuran or a dihydrofuranofuran moiety. Versicolorin C, containing a tetrahydrofuranofuran moiety, was isolated as a metabolite of *Aspergillus versicolor*.[1] The crystal structures of several compounds containing a dihydrofuranofuran moiety have been determined in our laboratory. The structural investigation of the title compound is of interest in connection with the metabolites containing a dihydrofuranofuran moiety; these metabolites are believed to be toxic to animals.[2] The crystal and molecular structure of aflatoxin B_2, which has a tetrahydrofuranofuran moiety, was described in detail by van Soest *et al.*[3] As few X-ray analysis have, however, been done on the compounds involving a tetrahydrofuranofuran moiety, it seems worth carrying out the X-ray analysis of versicolorin C in order to obtain additional information about the dimensions of this moiety. Another point of interest in this analysis is to confirm the structural formula (shown below) proposed on the basis of the chemical



and spectroscopic methods.[1] This investigation has been undertaken as part of a series of systematic studies of the structures of the metabolites of the genus *Aspergillus*.[4–6]

Experimental

Versicolorin C, crystallized from an acetone solution in the form of orange red plates elongated along the b-axis. The crystal data and experimental conditions are summarized in Table 1. The intensities were collected on a Rigaku Denki computer-controlled four-circle diffractometer with a scintillation counter equipped with a pulse-height analyser. Attenuators were inserted when the maximum counting rate exceeded 8000 cps. The background was measured for 8 sec at both the start and end points of the scan range. Out of 2024 independent reflections measured up to $\sin\theta/\lambda=0.562$, 1696 reflections had a non-zero intensity. No significant variation in the intensities of the three reference reflections were observed during the data-collection process. The intensities were corrected for the Lorentz and polarization factors, but not for the absorption.

Table 1. Crystal data and experimental conditions of versicolorin C

Molecular formula	$C_{18}H_{12}O_7$
Molecular weight	340.3
Crystal system	monoclinic
Space group	$P2_1/a$
$a=24.918(7)$, $b=7.922(3)$, $c=7.003(3)$ Å	
$\beta=92.85(4)°$	
$V=1381$ Å^3	
$D_c=1.637$ g cm^{-3} (for $Z=4$)	
$\mu(\mathrm{Cu}K\alpha)=11.0$ cm^{-1}	
Crystal size	*ca.* $0.05\times0.10\times0.15$ mm
Radiation	Ni-filtered Cu$K\alpha$
Scan technique	ω-2θ
Scan speed (ω)	2° min^{-1}
Scan range (ω)	$1.0°+0.15°\tan\theta$

Structure Determination and Refinement

The orientation and location of the anthraquinone skeleton was determined by an interpretation of a three-dimensional Patterson map. A three-dimensional Fourier synthesis computed with the signs due to the skeleton revealed all the remaining non-hydrogen atoms. The atomic coordinates and isotropic temperature factors were refined by a block-diagonal least-squares method. By introducing anisotropic temperature factors for the non-hydrogen atoms in the refinement, the R value was reduced to 0.081. Three intense reflections, 220, 221, and 321, were rejected from the subsequent calculations. The positions of the hydrogen atoms were determined by a difference Fourier synthesis computed at this stage. The final refinement was made by including the positional parameters and isotropic temperature factors of the hydrogen atoms, using the following weighting scheme: $w=0.0$ for $F_o=0$, $w=1.0$ for $0<F_o\leqq40$, and $w=1.0/(1.0+0.467(F_o-40))$ for $40<F_o$. The final R value was 0.053 for 1693 non-zero reflections. The final atomic parameters are listed in Table 2. A list of observed and calculated structure factors is preserved by the Chemical Society of Japan (Document No. 7517).

The atomic scattering factors were taken from the International Tables for X-ray Crystallography.[7] The computations were performed on a TOSBAC 3400

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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}
C (1)	1476(1)	5043(4)	6822(4)	12(1)	155(6)	158(7)	3(3)	3(3)	−21(11)
C (2)	969(1)	4567(4)	7381(4)	13(1)	122(6)	150(6)	6(3)	12(3)	−8(10)
C (3)	622(1)	3679(4)	6106(4)	11(1)	128(6)	149(6)	12(3)	7(3)	15(10)
C (4)	83(1)	3210(4)	6633(4)	12(1)	127(6)	154(6)	11(3)	10(3)	11(10)
C (5)	−268(1)	2285(4)	5316(4)	11(1)	119(5)	147(6)	10(3)	0(3)	34(10)
C (6)	−789(1)	1758(4)	5780(4)	12(1)	148(6)	161(7)	12(3)	15(3)	16(11)
C (7)	−1115(1)	849(4)	4501(4)	11(1)	149(6)	195(7)	10(3)	4(3)	37(11)
C (8)	−935(1)	436(4)	2721(4)	12(1)	145(6)	186(7)	8(3)	−11(3)	19(11)
C (9)	−422(1)	928(4)	2204(4)	13(1)	145(6)	172(7)	7(3)	−1(3)	7(11)
C (10)	−96(1)	1812(4)	3488(4)	12(1)	119(6)	160(7)	10(3)	8(3)	34(10)
C (11)	460(1)	2233(4)	2948(4)	14(1)	122(6)	143(6)	10(3)	5(3)	30(10)
C (12)	802(1)	3251(4)	4274(4)	12(1)	122(6)	143(6)	7(3)	14(3)	10(10)
C (13)	1302(1)	3756(4)	3695(4)	13(1)	166(6)	163(7)	−4(3)	14(3)	−7(11)
C (14)	1617(1)	4673(4)	4985(4)	12(1)	172(7)	180(7)	−2(3)	19(3)	17(12)
C (15)	2326(1)	6214(5)	6294(5)	15(1)	187(7)	209(8)	−13(3)	3(3)	31(13)
C (16)	2693(1)	4169(6)	8244(5)	18(1)	262(9)	209(8)	23(4)	7(4)	81(14)
C (17)	2238(1)	4865(5)	9352(5)	15(1)	241(8)	191(8)	0(4)	−2(3)	−10(14)
C (18)	1920(1)	5959(5)	7875(5)	13(1)	174(7)	200(7)	−1(3)	6(3)	−48(12)
O (1)	842(1)	5003(3)	9166(3)	15(1)	203(5)	148(5)	−2(2)	14(2)	−76(8)
O (2)	−79(1)	3660(3)	8240(3)	14(1)	225(5)	144(5)	4(2)	23(2)	−75(8)
O (3)	−988(1)	2138(3)	7496(3)	14(1)	221(5)	184(5)	−7(2)	29(2)	−52(8)
O (4)	−1271(1)	−442(3)	1508(3)	14(1)	232(5)	204(5)	−11(2)	−6(2)	−73(9)
O (5)	624(1)	1713(3)	1428(3)	16(1)	200(5)	155(5)	−9(2)	25(2)	−76(8)
O (6)	2111(1)	5310(3)	4601(3)	14(1)	222(5)	200(5)	−25(2)	20(2)	−20(9)
O (7)	2806(1)	5503(4)	6921(3)	12(1)	320(6)	235(6)	−5(3)	8(2)	78(10)

Table 2(b). Final positional parameters ($\times 10^3$) and isotropic temperature factors (Å^2)

	x	y	z	B
H(1)	52(2)	447(6)	939(6)	6.4(12)
H(2)	−74(2)	270(5)	820(5)	4.6(16)
H(3)	−148(1)	47(4)	490(4)	1.7(7)
H(4)	−110(2)	−83(5)	48(5)	4.6(10)
H(5)	−30(1)	66(5)	88(5)	3.4(9)
H(6)	139(1)	343(5)	231(5)	3.1(8)
H(7)	238(1)	748(5)	585(5)	3.2(8)
H(8)	257(1)	303(5)	748(5)	4.0(9)
H(9)	306(2)	402(5)	914(5)	4.5(10)
H(10)	240(2)	552(6)	1044(6)	5.1(11)
H(11)	201(1)	386(4)	977(4)	2.2(7)
H(12)	181(1)	707(5)	846(5)	3.0(8)

computer at the Tottori University Computing Center and on a NEAC 2200-N700 computer at the Computation Center of Osaka University.

Results and Discussion

The structural formula of versicolorin C has been confirmed by this X-ray analysis. The difference-electron-density map and the numbering of atoms are shown in Fig. 1, which indicates the presence of two intramolecular hydrogen bonds, O(1)–H(1)⋯O(2) and O(3)–H(2)⋯O(2). The bond lengths and angles are shown in Fig. 2 and Table 3. In the quinonoid group, the lengths of the C(3)–C(4) and C(4)–C(5) bonds are shorter than those of the C(10)–C(11) and C(11)–C(12) bonds, and the length of the C(4)–O(2) bond is longer than that of the C(11)–O(5) bond. Such a lack of equivalence of bond lengths in the quinonoid group implies that the double-bond character at the C(11)–O(5) bond in the $\substack{\mathrm{C(10)}\\ \mathrm{C(12)}}\!>\!\mathrm{C(11)=O(5)}$ system is greater than that at the C(4)–O(2) bond in the $\substack{\mathrm{C(3)}\\ \mathrm{C(5)}}\!>\!\mathrm{C(4)=O(2)}$ system. These features are also found in averufin5) and N,N'-diphenyl-1,8-diaminoanthraquinone.8) As is shown in Table 4,

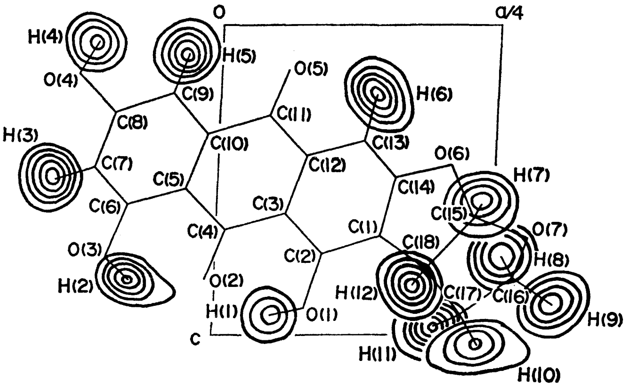

Fig. 1. The difference electron density map of versicolorin C. The contours are at equally spaced intervals on an arbitrary scale.

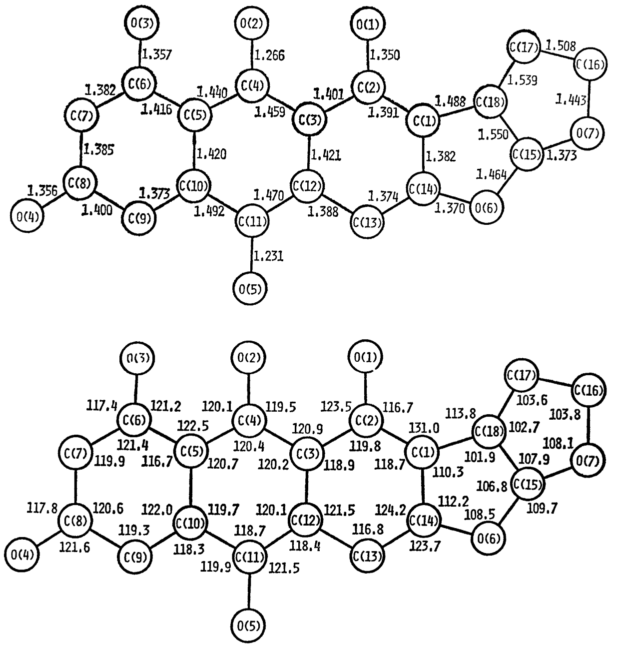

Fig. 2. The bond lengths (Å) and angles (°). The mean estimated standard deviations for the bond lengths and angles are about 0.004 Å and 0.3°, respectively.

Table 3. Bond lengths and angles involving hydrogen atoms
The mean estimated standard deviations of the bond lengths and angles are 0.04 Å and 2°, respectively. Broken lines indicate hydrogen bonds.

(a) Bond lengths (Å)			
O (1)-H (1)	0.93	O (2)···H (1)	1.78
O (3)-H (2)	0.89	O (2)···H (2)	1.81
C (7)-H (3)	1.01	O (4)-H (4)	0.91
O (5)[a)]···H (4)	1.96	C (9)-H (5)	1.02
C (13)-H (6)	1.04	C (15)-H (7)	1.06
C (16)-H (8)	1.08	C (16)-H (9)	1.09
C (17)-H (10)	0.99	C (17)-H (11)	1.03
C (18)-H (12)	1.02		
(b) Bond angles (°)			
C (2)-O (1)-H (1)	107	O (1)-H (1)···O (2)	143
C (4)-O (2)···H (1)	102	O (6)-O (3)-H (2)	109
O (3)-H (2)···O (2)	146	C (4)-O (2)···H (2)	101
H (2)···O (2)···H (1)	154	C (6)-C (7)-H (3)	119
C (8)-C (7)-H (3)	121	C (8)-O (4)-H (4)	111
O (4)-H (4)···O (5)[a)]	171	C(11)[a)]-O (5)[a)]···H (4)	162
C (8)-C (9)-H (5)	120	C (10)-C (9)-H (5)	121
C (12)-C (13)-H (6)	115	C (14)-C (13)-H (6)	128
C (18)-C (15)-H (7)	116	O (6)-C (15)-H (7)	106
O (7)-C (15)-H (7)	111	C (17)-C (16)-H (8)	111
O (7)-C (16)-H (8)	110	C (17)-C (16)-H (9)	112
O (7)-C (16)-H (9)	105	H (8)-C (16)-H (9)	113
C (16)-C (17)-H (10)	107	C (18)-C (17)-H (10)	114
C (16)-C (17)-H (11)	108	C (18)-C (17)-H (11)	110
H (11)-C (17)-H (10)	113	C (1)-C (18)-H (12)	114
C (15)-C (18)-H (12)	112	C (17)-C (18)-H (12)	111

a) $-x$, $-y$, $-z$

the dimensions of the tetrahydrofuranofuran moiety in versicolorin C are in good agreement with those of the moiety in aflatoxin B_2.[3)] Among the three C(sp^3)–O bonds in the tetrahydrofuranofuran moiety, the length of the C(15)–O(7) bond (1.373 Å) is significantly shorter than the others (1.464 and 1.443 Å), and

Table 4. Comparison of the bond lengths and angles in the tetrahydrofuranofuran moiety of versicolorin C and those of aflatoxin B_2
Standard deviations are given in parentheses.

(a) Bond lengths (Å)		
	versicolorin C	aflatoxin B_2
C (1)-C (14)	1.382 (5)	1.382 (3)
C (1)-C (18)	1.488 (5)	1.504 (3)
C (14)-O (6)	1.370 (4)	1.359 (3)
C (15)-C (18)	1.550 (5)	1.553 (4)
C (15)-O (6)	1.464 (5)	1.465 (3)
C (15)-O (7)	1.373 (5)	1.385 (5)
C (16)-C (17)	1.508 (6)	1.513 (6)
C (16)-O (7)	1.443 (5)	1.434 (5)
C (17)-C (18)	1.539 (5)	1.523 (5)
(b) Bond angles (°)		
	versicolorin C	aflatoxin B_2
C (2)-C (1)-C (18)	131.0 (3)	132.2 (3)
C (14)-C (1)-C (18)	110.3 (3)	110.5 (2)
C (1)-C (14)-O (6)	112.2 (3)	112.5 (2)
C (13)-C (14)-O (6)	123.7 (3)	122.4 (3)
C (18)-C (15)-O (6)	106.8 (3)	107.3 (2)
C (18)-C (15)-O (7)	107.9 (3)	107.7 (5)
O (6)-C (15)-O (7)	109.7 (3)	110.0 (5)
C (17)-C (16)-O (7)	103.8 (3)	103.9 (6)
C (16)-C (17)-C (18)	103.6 (3)	103.1 (5)
C (1)-C (18)-C (15)	101.9 (3)	101.0 (3)
C (1)-C (18)-C (17)	113.8 (3)	115.4 (3)
C (15)-C (18)-C (17)	102.7 (3)	102.9 (4)
C (14)-O (6)-C (15)	108.5 (3)	107.3 (3)
C (15)-O (7)-C (16)	108.1 (3)	108.6 (4)

Table 5. Deviations of atoms from each plane (Å)

(a) Plane through anthraquinone-skeleton with O(1), O(3), and O(4) atoms			
C (1)	0.003	C (2)	0.025
C (3)	0.007	C (4)	−0.013
C (5)	−0.020	C (6)	0.001
C (7)	0.014	C (8)	0.006
C (9)	−0.011	C (10)	−0.006
C (11)	0.058	C (12)	−0.004
C (13)	−0.056	C (14)	−0.082
O (1)	0.065	O (2)	−0.058
O (3)	−0.002	O (4)	0.006
O (5)	0.174	C (15)[a)]	−0.182
C (18)[a)]	0.032	O (6)[a)]	−0.180
(b) Plane through the terminal five-membered ring			
C (15)	0.030	C (17)	0.017
C (18)	−0.027	O (7)	−0.021
C (16)[a)]	0.525		

a) Not included in the least-squares calculation.

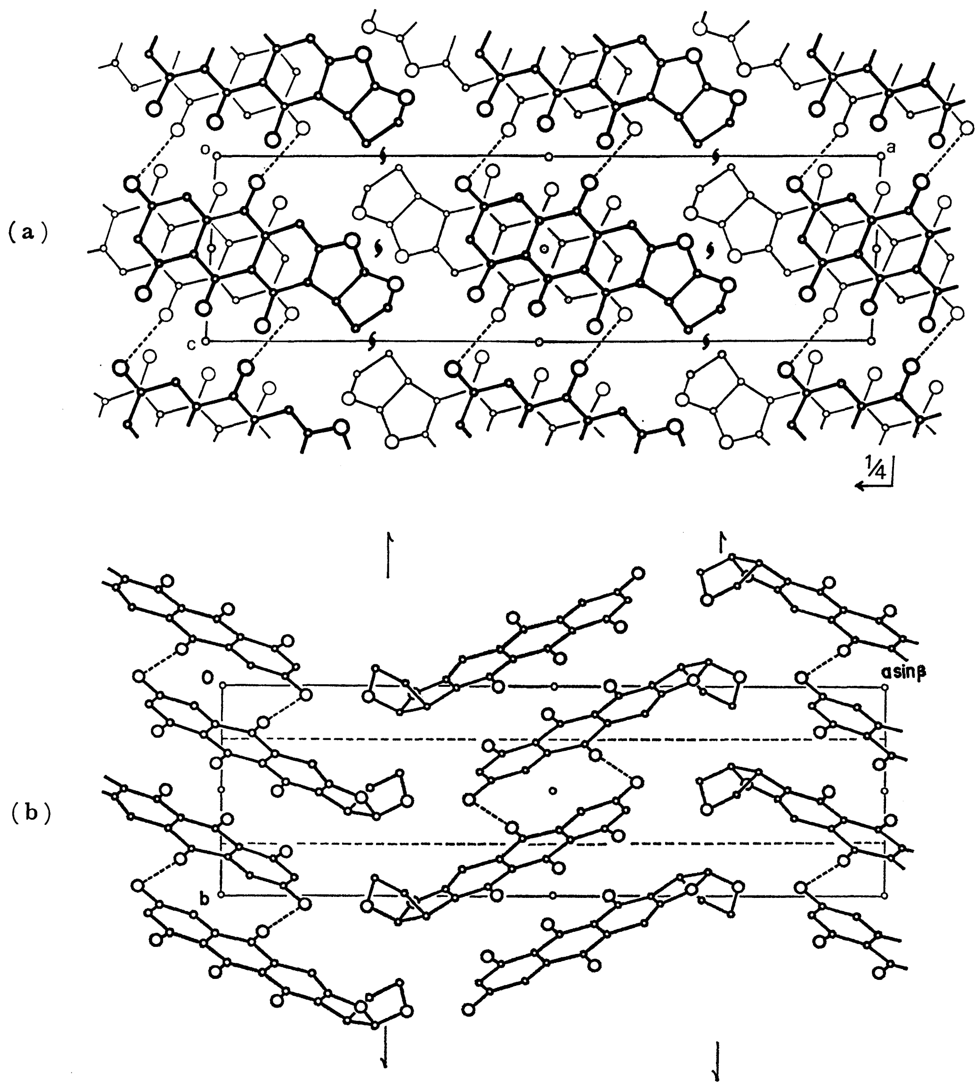

Fig. 3. The crystal structure of versicolorin C; (a) viewed along the b-axis, (b) viewed along the c-axis. Broken lines indicate intermolecular hydrogen bonds.

among the three C(sp^3)–C(sp^3) bonds in the moiety, the length of the C(16)–C(17) bond (1.508 Å) is slightly shorter than the others (1.539 and 1.550 Å).

The least-squares planes through the anthraquinone skeleton with the O(1), O(3), and O(4) atoms and through the terminal five-membered ring except the C(16) atom are represented by these equations:

$$0.3501X - 0.8582Y + 0.3754Z = -0.4366,$$

and

$$0.2722X + 0.8409Y + 0.4678Z = 7.7470$$

respectively, where $X = ax + cz\cos\beta$, $Y = by$, and $Z = cz\sin\beta$. The dihedral angle between the above planes is 63.2°, compared with that of 62.8° in aflatoxin B_2.[3)] The deviations of the atoms from these planes are listed in Table 5, which indicates that the anthraquinone skeleton is slightly twisted along the longitudinal axis of the molecule and that the terminal five-membered ring is puckered at the C(16) atom.

The crystal structure is shown in Fig. 3. A pair of molecules related by a center of symmetry are linked together by intermolecular hydrogen bonds, O(4)–H(4)···O(5) (2.857 Å), to form a dimer. The parallel dimers are held together by van der Waals

Table 6. Intermolecular distances (Å) less than 3.5 Å

C (8)···O (5)$^{\mathrm{i}}$	3.488	C (9)···O (5)$^{\mathrm{i}}$	3.313
O (5)···O (4)$^{\mathrm{i}}$	2.857$^{\mathrm{a)}}$	C (13)···O (1)$^{\mathrm{ii}}$	3.462
O (5)···O (1)$^{\mathrm{ii}}$	3.112	O (5)···O (2)$^{\mathrm{ii}}$	3.169
C (2)···O (4)$^{\mathrm{iii}}$	3.434	C (3)···C (8)$^{\mathrm{iii}}$	3.441
C (3)···O (4)$^{\mathrm{iii}}$	3.422	C (4)···C (9)$^{\mathrm{iii}}$	3.472
C (5)···C (9)$^{\mathrm{iii}}$	3.486	C (5)···C (10)$^{\mathrm{iii}}$	3.462
C (6)···O (5)$^{\mathrm{iii}}$	3.387	C (6)···C (11)$^{\mathrm{iii}}$	3.374
C (11)···C (7)$^{\mathrm{iii}}$	3.395	C (12)···C (7)$^{\mathrm{iii}}$	3.439
O (3)···O (5)$^{\mathrm{iii}}$	3.260	C (1)···C (7)$^{\mathrm{iv}}$	3.489
C (5)···C (3)$^{\mathrm{iv}}$	3.451	C (11)···O (2)$^{\mathrm{iv}}$	3.478
C (12)···O (2)$^{\mathrm{iv}}$	3.467	C (13)···O (3)$^{\mathrm{iv}}$	3.439
C (14)···O (3)$^{\mathrm{iv}}$	3.403	C (13)···O (7)$^{\mathrm{v}}$	3.444
O (7)···C (7)$^{\mathrm{vi}}$	3.420		

Symmetry code: i) $-x, -y, -z$ ii) $x, y, -1+z$ iii) $-x, -y, 1-z$ iv) $-x, 1-y, 1-z$ v) $1/2-x, -1/2+y, 1-z$ vi) $1/2+x, 1/2-y, z$

a) Hydrogen bond

forces to stack in the direction of the b-axis; the interplanar distances are 3.39 and 3.40 Å. The intermolecular distances for the non-hydrogen atoms shorter than 3.5 Å are listed in Table 6, which indicates the absence of any abnormally short contact.

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