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Structure of (+)-Epigriseofulvin

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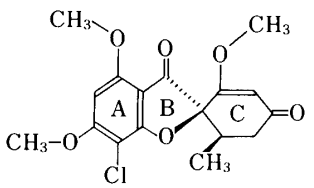
The crystal and molecular structure of (+)-epigriseofulvin were elucidated by X-ray structure analysis. The crystal belongs to a triclinic space group $P\bar{1}$, with the unit cell parameters of $a=11.718$ (4), $b=9.800$ (3), $c=9.870$ (3) Å, $\alpha=103.49$ (3), $\beta=102.38$ (3), $\gamma=96.26$ (3)°, $V=1061(1)$ Å^3. The unit cell contains two crystallographically independent (+)-epigriseofulvin molecules and two chloroform molecules. The structure was solved by the direct method and refined to an R-value of 0.093 for 3971 non-zero reflections. No significant conformational differences between the two molecules were observed. The cyclohexenone rings take half-chair conformations with planar conjugated enone systems.

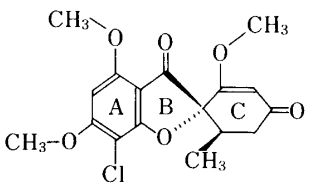
Keywords—(+)-epigriseofulvin; (+)-griseofulvin; conformation; X-ray analysis; crystal structure

Epigriseofulvin (**1**) is an isomer of griseofulvin (**2**) obtained in the course of the structural study of **2**.[1] The structure of **1** was determined as (2*R*,6′*R*)-7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione.[2] The name epigriseofulvin was first proposed by Brossi *et al.*[3] for the stereoisomer of **2**, which was synthesized as an intermediate in the total synthesis of **2**. (+)-Griseofulvin and related compounds have been investigated by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy,[4] and the results suggested that an equatorial methyl on a half-chair C-ring is predominant in both **1** and **2**; this was based on an analysis of the –CH–CH_2–patterns, which are strikingly dissimilar in breadth, and an examination of Dreiding models. On the other hand, the preferred conformation of griseofulvin in solution has been investigated by Levin and Hicks,[5] who used an NMR "shift reagent" with a partially deuterated sample of griseofulvin, and suggested a half-chair ring C conformation with *trans*, diaxial hydrogen substituents at 5′β-H and 6′α-H.

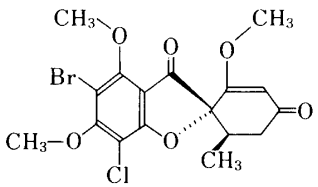
In connection with our studies on both the microbial transformation of dehydrogriseofulvin analogs[6,7] and the structure–activity relation[8] of griseofulvin derivatives in their action on microtubules, it was necessary to determine the crystal structure of **1**, since the structures of the C rings of **1** and **2** were used as the standard conformations in the elucidation



(+)-epigriseofulvin (**1**)



(+)-griseofulvin (**2**)



5-bromogriseofulvin

Chart 1

of the structures of many related derivatives. Shefter *et al.*[9] have reported the crystal structure analysis of (+)-griseofulvin (**2**), demonstrating substantial differences in the packing arrangements of the chloroform solvate and a non-solvated form of **2**. Recently, Sakegowda and his associates[10] described the crystal and molecular structure of (+)-griseofulvin.

This paper describes the structure of (+)-epigriseofulvin.

Experimental

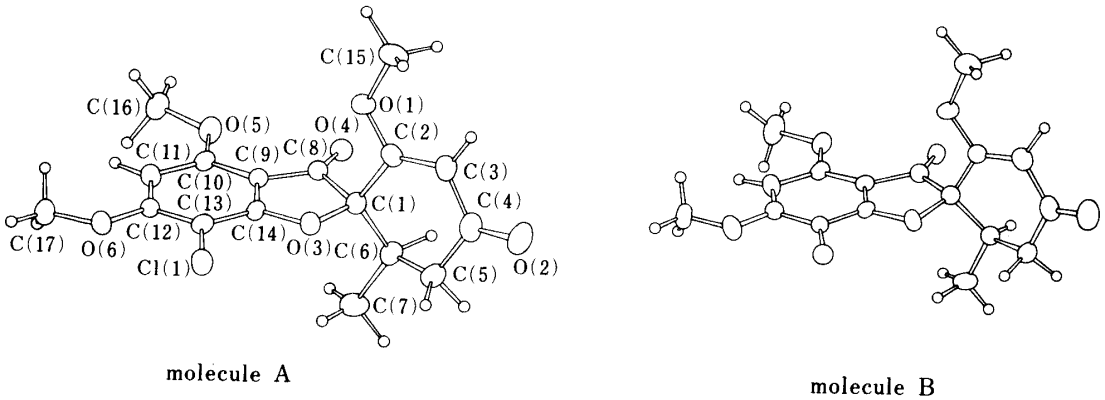
Material——The synthesis and physicochemical data of (+)-epigriseofulvin (**1**) were reported in a previous paper.[11]

X-Ray Analysis——Crystals of **1** were obtained from $CHCl_3$ solution as colorless prisms. The crystals belong to a triclinic space group $P\bar{1}$. The unit cell contains two epigriseofulvin molecules along with two chloroform molecules. Crystal data are shown in Table I. Intensity data were collected on a Philips PW1100 automated four-circle diffractometer using CuK_α radiation monochromated by a graphite plate.

A total of 3971 non-zero independent reflections out of 4027 reflections within the range of $3 \leq \theta \leq 78°$ were measured and used for structure determination and refinement. Corrections were applied for Lorentz and polarization factors, but not for absorption and extinction. The structure was solved by the direct method using the MULTAN program.[12] An E-map generated using 432 reflections with $E \geq 1.52$ gave 41 atomic positions out of 56 non-hydrogen atoms. Several cycles of isotropic least-squares calculation and subsequent difference Fourier synthesis

TABLE I. Crystal Data

Molecular formula	$C_{17}H_{17}O_6Cl \cdot CHCl_3$
Formula weight	472.15
Crystal dimensions	$0.3 \times 0.3 \times 0.25$ mm
Crystal system	Triclinic
Space group	$P\bar{1}$
$a = 11.718(4)$ Å	
$b = 9.800(3)$	
$c = 9.870(3)$	
$\alpha = 103.49(3)°$	
$\beta = 102.38(3)$	
$\gamma = 92.26(3)$	
$V = 1061(1)$ Å^3	
$Z = 2$	
$\lambda = 1.5418$ Å	
$\mu(\mathrm{Cu}K_\alpha) = 5.46\,\mathrm{mm}^{-1}$	
$Dx = 1.482\,\mathrm{g \cdot cm}^{-3}$	



molecule A molecule B

Fig. 1. ORTEP Drawings of the (+)-Epigriseofulvin Molecules A and B, along with the Atomic Numbering Used in This Structure Analysis

Non-H atoms are represented by 30% probability thermal ellipsoids and H atoms are on an arbitrary scale.

TABLE II. Atomic Coordinates ($\times 10^4$) and Isotropic Thermal Parameters ($Å^2$) for Non-hydrogen Atoms with the Estimated Standard Deviations in Parentheses

$$B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} (a_i \cdot a_j)$$

1	C1A	4057	2588	8332	2.78
2	C2A	5060 (9)	3125 (11)	9685 (11)	3.25
3	C3A	5023 (11)	4253 (12)	10729 (12)	3.64
4	C4A	4101 (11)	5073 (12)	10589 (13)	4.21
5	C5A	3128 (11)	4681 (13)	9214 (14)	4.33
6	C6A	2906 (9)	3073 (12)	8497 (12)	3.51
7	C7A	1931 (11)	2681 (15)	7090 (15)	4.80
8	C8A	3911 (8)	915 (11)	7794 (11)	2.99
9	C9A	4175 (9)	593 (10)	6437 (10)	2.61
10	C10A	4203 (8)	−679 (10)	5468 (11)	2.68
11	C11A	4513 (9)	−644 (11)	4191 (11)	3.05
12	C12A	4808 (8)	645 (11)	3891 (10)	2.70
13	C13A	4822 (9)	1950 (11)	4881 (11)	2.88
14	C14A	4504 (8)	1895 (10)	6148 (10)	2.49
15	C15A	6894 (11)	2678 (15)	10879 (15)	4.73
16	C16A	3995 (13)	−3229 (12)	4947 (15)	4.56
17	C17A	5039 (12)	−519 (14)	1555 (13)	4.61
18	C18A	1049 (14)	2170 (18)	1890 (18)	7.70
19	O1A	5910 (6)	2339 (8)	9635 (8)	3.73
20	O2A	4102 (10)	6147 (11)	11557 (12)	6.37
21	O3A	4464 (6)	3035 (7)	7174 (7)	2.70
22	O4A	3518 (7)	136 (8)	8470 (8)	3.95
23	O5A	3907 (7)	−1884 (7)	5844 (8)	3.77
24	O6A	5102 (7)	767 (9)	2695 (8)	3.77
25	CL1A	5208 (3)	3550 (3)	4511 (3)	4.02
26	CL2A	2215 (6)	1215 (9)	1287 (10)	12.51
27	CL3A	429 (7)	2628 (9)	197 (10)	5.93
28	CL4A	1508 (10)	3700 (9)	3054 (12)	17.20
29	CL5A	1544 (11)	1219 (16)	3541 (12)	9.79
30	C1B	8344 (9)	7346 (11)	495 (10)	2.98
31	C2B	9486 (9)	6851 (12)	435 (11)	3.33
32	C3B	9623 (11)	5667 (13)	−508 (14)	4.10
33	C4B	8595 (12)	4756 (14)	−1561 (14)	4.70
34	C5B	7368 (11)	5193 (12)	−1601 (13)	3.99
35	C6B	7442 (9)	6832 (11)	−966 (12)	3.10
36	C7B	6212 (11)	7177 (16)	−939 (15)	4.91
37	C8B	8553 (9)	8953 (11)	1029 (11)	2.94
38	C9B	8262 (8)	9279 (10)	2464 (10)	2.69
39	C10B	8309 (9)	10502 (10)	3471 (11)	2.92
40	C11B	8002 (10)	10463 (12)	4775 (11)	3.37
41	C12B	7664 (9)	9149 (11)	4978 (10)	2.91
42	C13B	7600 (8)	7860 (10)	3950 (10)	2.55
43	C14B	7908 (8)	7939 (9)	2684 (10)	2.54
44	C15B	11560 (12)	7446 (19)	1527 (18)	5.91
45	C16B	8757 (14)	13043 (12)	4255 (14)	4.89
46	C17B	7346 (13)	10207 (14)	7255 (13)	4.53
47	C18B	1184 (10)	8057 (15)	6669 (14)	4.34
48	O1B	10377 (7)	7736 (9)	1459 (9)	4.03
49	O2B	8678 (11)	3667 (11)	−2411 (11)	6.61
50	O3B	7882 (7)	6804 (7)	1574 (7)	3.24
51	O4B	8806 (7)	9782 (8)	346 (8)	3.84
52	O5B	8690 (7)	11747 (7)	3187 (8)	3.65
53	O6B	7334 (7)	8968 (8)	6179 (8)	3.68
54	CL1B	7249 (3)	6214 (3)	4228 (3)	3.79
55	CL2B	818 (4)	8261 (8)	4914 (6)	9.02
56	CL3B	1106 (6)	6174 (5)	6547 (7)	9.56
57	CL4B	298 (5)	8722 (6)	7681 (6)	8.33

The positions of the atoms in the disordered chloroform molecule are set at: C18A (1.0), CL2A (1.0), CL3A (0.5), CL4A (1.0) and CL5A (0.5). Multiplicity factors in parentheses.

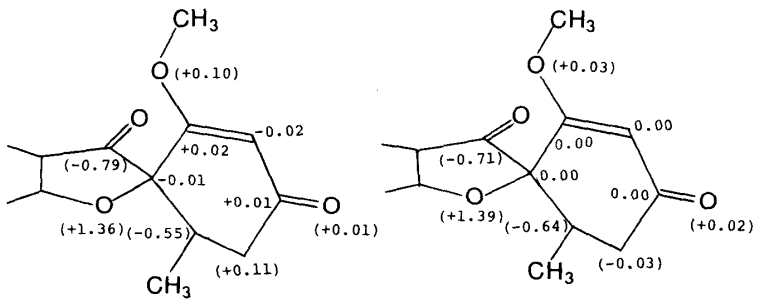
showed the remaining non-hydrogen atoms as well as an extra chlorine site due to the disordered arrangement of a chloroform molecule. Some hydrogen atoms were located on a difference map calculated from non-hydrogen atoms, but the others were generated computationally on the basis of stereochemical and geometrical considerations. The structure was refined by the block-diagonal least-squares method[13] assuming anisotropic temperature factors for the non-hydrogen atoms and isotropic ones for the hydrogen atoms. The final R-value was 0.093 using the following weighting scheme: $\sqrt{w}=0.8$ when $F_0<2.0$, $\sqrt{w}=1.0$ when $2.0\leq F_0\leq 20.0$ and $\sqrt{w}=20.0/F_0$ when $F_0>20.0$. The scattering factors for non-H atoms were taken from International Tables for X-ray Crystallography Vol. IV[14] and those for H atoms were taken from Stewart, Davidson and Simpson.[15] Figure 1 shows the molecular structure of (+)-epigriseofulvin as an ORTEP drawing[16] along with the atomic numbering used in this structure analysis. The final atomic coordinates and isotropic thermal parameters are given in Table II.

Discussion

Bond lengths (Å), bond angles (°) and selected torsion angles (°) are listed in Table III. There was no significant differences in bond lengths and angles between the two crystallographically independent molecules, A and B. The torsion angles about the C(1)–C(2) and C(4)–C(5) bonds in the cyclohexenone ring show that there are small conformational differences in torsion angles, C(3)–C(2)–C(1)–O(3) (8.7°), C(6)–C(1)–C(2)–O(3) (6.3°) and C(3)–C(4)–C(5)–C(6) (5.8°). As can be seen from Figure 2, which shows the atomic deviations (Å) from the least-squares planes through the four atoms C(1), C(2), C(3) and C(4), both cyclohexenone rings seem to adopt a half-chair conformation in which atom C(6) is on the same side of the plane as C(8).

Comparing this structure with three X-ray results on griseofulvin,[9,10,17] no serious distortion was found in the (+)-epigriseofulvin structure, though the griseofulvin structures showed a significant distortion in enone conjugation. The torsion angles of C(2)=C(3)–C(4)=O(2) and C(2)=C(3)–C(4)=C(5) are −177.8° (A), 178.7° (B) and −0.6° (A), 1.6° (B) in (+)-epigriseofulvin, respectively, while in griseofulvin,[10] the corresponding values are −166.1° and 13.1°, and in 5-bromogriseofulvin[17] the values are 170.7° and −15.8°, respectively. In another X-ray analysis of griseofulvin and $CHCl_3$-solvated griseofulvin,[9] distorted torsion angles of C(2)=C(3)–C(4)=C(5) were also observed (11.2° and −8.2°, respectively).

The two methyl carbons C(16), C(17) in the methoxyl groups are coplanar with the benzene ring just as in the griseofulvin structures. In 5-bromogriseofulvin, these are nearly perpendicular to the benzene ring, which can be attributed mainly to the steric hindrance due to the bromine atom. One of the chloroform molecules could not be located at one discrete position, but seem to have approximately two disordered positions, resulting in four chlorine



molecule A molecule B

Fig. 2. Deviations (Å) from the Least-Squares Plane through Four Atoms, C(1), C(2), C(3) and C(4)

Those of atoms which were not included in the least-squares calculation are shown in parentheses.

TABLE III. Bond Lengths (Å), Bond Angles (°) and Selected Torsion Angles (°) for Non-hydrogen Atoms with the Estimated Standard Deviations in Parentheses

	Molecule A	Molecule B
a. Bond lengths (Å)		
C(1)–C(2)	1.52 (1)	1.48 (2)
C(1)–C(6)	1.51 (1)	1.53 (1)
C(1)–C(8)	1.58 (1)	1.51 (1)
C(1)–O(3)	1.47 (1)	1.47 (1)
C(2)–C(3)	1.34 (2)	1.36 (2)
C(2)–O(1)	1.33 (1)	1.34 (1)
C(3)–C(4)	1.42 (2)	1.46 (2)
C(4)–C(5)	1.51 (2)	1.54 (2)
C(4)–O(2)	1.25 (2)	1.22 (2)
C(5)–C(6)	1.54 (2)	1.57 (2)
C(6)–C(7)	1.54 (2)	1.52 (2)
C(8)–C(9)	1.41 (2)	1.50 (2)
C(8)–O(4)	1.24 (2)	1.22 (2)
C(9)–C(10)	1.39 (1)	1.35 (1)
C(9)–C(14)	1.40 (2)	1.41 (1)
C(10)–C(11)	1.39 (2)	1.42 (2)
C(10)–O(5)	1.35 (1)	1.36 (1)
C(11)–C(12)	1.39 (2)	1.38 (2)
C(12)–C(13)	1.41 (1)	1.41 (1)
C(12)–O(6)	1.33 (1)	1.37 (1)
C(13)–C(14)	1.39 (2)	1.39 (2)
C(13)–Cl(1)	1.73 (1)	1.72 (1)
C(14)–O(3)	1.35 (1)	1.36 (1)
C(15)–O(1)	1.44 (1)	1.44 (2)
C(16)–O(5)	1.43 (1)	1.43 (1)
C(17)–O(6)	1.46 (1)	1.41 (1)
b. Bond angles (°)		
C(2)–C(1)–C(6)	113.8 (6)	111.7 (9)
C(2)–C(1)–C(8)	109.4 (6)	109.6 (9)
C(2)–C(1)–O(3)	107.2 (5)	108.2 (9)
C(6)–C(1)–C(8)	112.1 (6)	111.0 (9)
C(6)–C(1)–O(3)	111.3 (5)	109.9 (8)
C(8)–C(1)–O(3)	102.4 (5)	106.2 (8)
C(3)–C(2)–C(1)	121.2 (9)	125.2 (11)
C(3)–C(2)–O(1)	128.0 (10)	124.3 (11)
C(1)–C(2)–O(1)	110.8 (8)	110.4 (9)
C(4)–C(3)–C(2)	122.1 (11)	120.1 (12)
C(5)–C(4)–C(3)	119.6 (11)	118.6 (11)
C(5)–C(4)–O(2)	119.2 (12)	119.3 (12)
C(3)–C(4)–O(2)	121.1 (12)	122.1 (13)
C(6)–C(5)–C(4)	111.3 (10)	112.7 (10)
C(7)–C(6)–C(1)	114.0 (9)	114.1 (10)
C(7)–C(6)–C(5)	111.2 (10)	110.1 (10)
C(1)–C(6)–C(5)	109.9 (9)	110.3 (9)
C(9)–C(8)–C(1)	107.2 (8)	105.9 (8)
C(9)–C(8)–O(4)	131.2 (10)	128.3 (10)
C(1)–C(8)–O(4)	121.2 (8)	125.5 (10)
C(10)–C(9)–C(8)	133.1 (10)	133.6 (9)
C(10)–C(9)–C(14)	119.9 (9)	121.2 (9)
C(8)–C(9)–C(14)	106.9 (9)	105.2 (8)
C(11)–C(10)–C(9)	119.4 (9)	120.4 (10)

TABLE III. (continued)

	Molecule A	Molecule B
C(11)–C(10)–O(5)	124.3 (9)	122.2 (9)
C(9)–C(10)–O(5)	116.3 (9)	117.3 (9)
C(12)–C(11)–C(10)	120.5 (10)	117.8 (10)
C(13)–C(12)–C(11)	121.1 (9)	123.1 (10)
C(13)–C(12)–O(6)	114.8 (9)	113.4 (9)
C(11)–C(12)–O(6)	124.2 (9)	123.5 (10)
C(14)–C(13)–C(12)	117.6 (9)	117.5 (9)
C(14)–C(13)–Cl(1)	121.5 (8)	118.9 (7)
C(12)–C(13)–Cl(1)	120.8 (8)	123.4 (8)
O(3)–C(14)–C(9)	114.7 (8)	114.8 (8)
O(3)–C(14)–C(13)	123.9 (9)	125.2 (9)
C(9)–C(14)–C(13)	121.4 (9)	120.0 (9)
C(1)–O(3)–C(14)	108.7 (6)	107.6 (8)
C(2)–O(1)–C(15)	117.1 (9)	118.0 (10)
C(10)–O(5)–C(16)	119.4 (9)	117.6 (9)
C(12)–O(6)–C(17)	119.2 (9)	117.3 (9)
c. Selected torsion angles		
C(1)–C(2)–C(3)–C(4)	−5.0 (15)	−0.8 (17)
C(2)–C(3)–C(4)–C(5)	−0.6 (15)	1.6 (16)
C(3)–C(4)–C(5)–C(6)	29.8 (13)	24.0 (13)
C(4)–C(5)–C(6)–C(1)	−51.9 (10)	−49.1 (10)
C(5)–C(6)–C(1)–C(2)	47.6 (8)	49.5 (10)
C(6)–C(1)–C(2)–C(3)	−19.9 (12)	−26.2 (15)
C(2)–C(3)–C(4)–O(2)	−177.8 (7)	−178.7 (8)
C(3)–C(2)–C(1)–O(3)	103.6 (10)	94.9 (12)
C(4)–C(3)–C(2)–O(1)	174.5 (3)	178.6 (5)
C(4)–C(5)–C(6)–C(7)	−179.1 (7)	−176.0 (7)

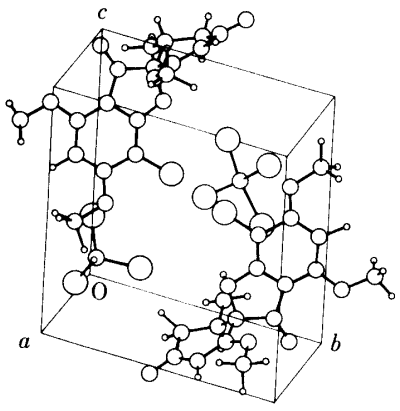


Fig. 3. Molecular Packing Diagram Drawn by Means of the PLUTO Program

sites. This caused considerable difficulties in the structure refinement. Figure 3 shows a packing diagram drawn by use of the PLUTO program.[18] The molecules are associated head-to-head by van der Waals and dipole interactions between the dimethoxy-chlorobenzene moieties. At the other end of the molecule, the cyclohexenone ring moiety associates with that of the neighboring molecule by similar interactions, forming a chain of molecules running along [111]. The solvent chloroform molecule fills the spaces between the chains. There are no intermolecular contacts that are significantly shorter than the sum of the corresponding van der Waals radii.

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