The Crystal and Molecular Structure of γ-Metasantonin

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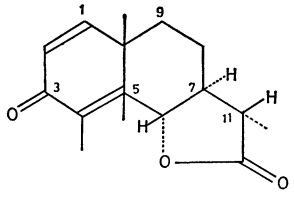
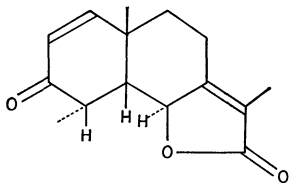
The crystal and molecular structure of γ-metasantonin has been determined by the X-ray method. The crystal is orthorhombic, $P2_12_12_1$, with lattice parameters $a=10.371(1)$, $b=7.904(1)$, $c=15.975(1)$ Å. The molecule has two independent α,β-unsaturated ketone chromophores which take a chiral configuration. The chromophores show good planarity. A/B ring fusion is *cis*.

Many investigations concerning the stereochemistry of santonin(I) and its related compounds have been made by the chemical methods,[1,2] NMR,[3,4] CD,[5,6] and X-ray analysis.[7-9] γ-Metasantonin, 6β-hydroxy-3-oxo-5β-eudesma-1,7(11)-dien-12-oic acid γ-lactone, is obtained by the reaction of concentrated sulfuric acid on santonic acid or metasantonic acid. Woodward and Yates[1] assigned the gross structure (II) to γ-metasantonin.



I



II

Hortman, Daniel, and Schaefer[3] and McMurry and Rane[4] confirmed the structure (II) by NMR. The conformation of this molecule, containing two separated α,β-unsaturated ketones, is interesting from the viewpoint of CD analysis. We determined the structure by X-ray analysis.

Experimental

The crystals are of transparent prismatic forms. The space group was determined as $P2_12_12_1$ from the oscillation and Weissenberg photographs. The density was measured by the flotation method with aqueous KI solution. The unit-cell parameters were determined by the least-squares methods, using twelve reflections measured on a Hilger & Watts four circle diffractometer with Zr-filtered Mo $K\alpha$ radiation ($\lambda=0.71069$ Å). The intensity data were collected on the diffractometer with the 2θ-ω scanning mode ($2\theta \leqq 54°$). The size of the crystal used was $0.2\times0.3\times0.1$ mm. The crystal used for X-ray measurement was mounted in a glass capillary. The intensities of three standard reflections were monitored after every 50 reflections. They were stable to 1% from their mean values. Neither absorption nor extinction correction was made. The crystal data are given in Table 1.

Table 1. Crystal data

$C_{15}H_{18}O_3$
M.W.: 246.31
Space group: $P2_12_12_1$; $Z=4$
$a=10.371(1)$, $b=7.904(1)$, $c=15.975(1)$ Å
$D_m=1.244$, $D_c=1.249$ g cm^{-3}
$\mu=0.92$ cm^{-1} (for Mo $K\alpha$ radiation)

Determination and Refinement of the Structure

The structure was determined by the direct method with the program MULTAN[10] using 201 reflections

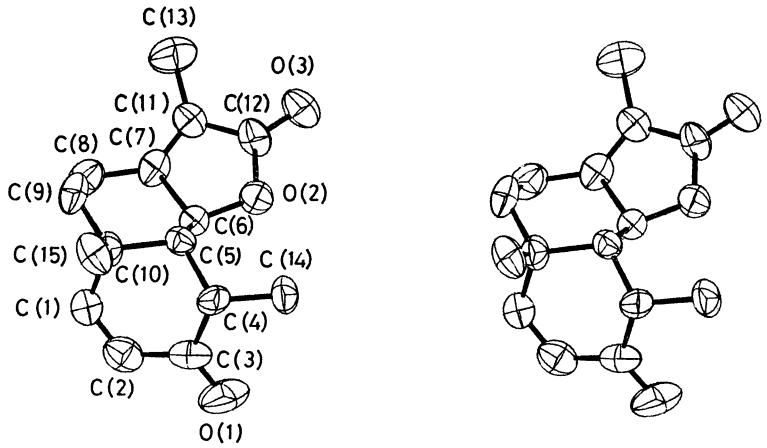


Fig. 1. The atomic labelings and a stereoscopic view of γ-metasantonin. Carbon and oxygen atoms are represented as thermal ellipsoids of a size such that the vibrating atoms have a 50% probability of being found within them. The absolute configuration of the molecule was drawn to be in conformity with the established configuration by a chemical correlation method.

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with $|E| \geqq 1.30$. An E map computed from the phase set with the highest figure of merit ($FOM = 1.12$) revealed a partial structure containing a lactone ring. Other atoms were found by the succesive Fourier synthesis. Refinement of the structure was performed by the block-diagonal least-squares method with 752 independent reflections of $|F_o| \geqq 3\sigma$. R-index converged to 0.065 with an equal weight for each reflection. The atomic scattering factors were taken from "International Tables for X-Ray Crystallography."[11] The program HBLS-IV coded by Ashida in UNICS was utilized for the refinement. The program ORTEP[12] was used for drawing Figs. 1 and 2. A part of computation was performed at the Nagoya University Computation Center. The observed and calculated structure factors are given in Table 2.[13]

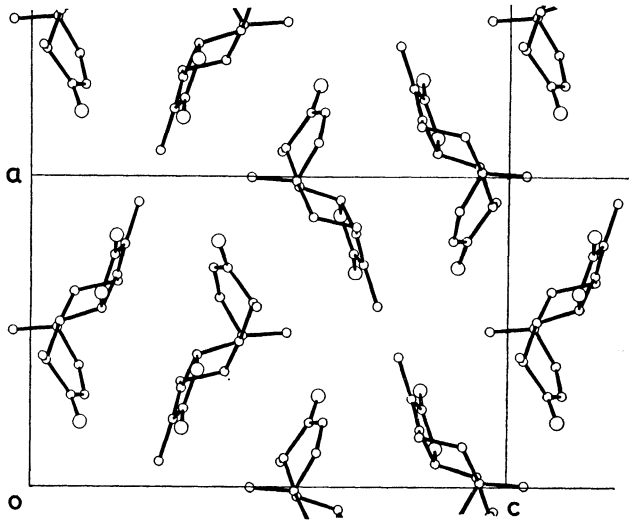

Fig. 2. The projection of the crystal structure along the b-axis. Carbon atoms are depicted as small circles and oxygen atoms as large circles. The configuration is the same as in Fig. 1.

Results and Discussion

The molecular structure, atomic labelings, and thermal ellipsoids are shown in Fig. 1. The positional and thermal parameters of non-hydrogen atoms with their standard deviations are given in Tables 3 and 4, respectively. The coordinates and isotropic thermal parameters of hydrogen atoms are given in Table 5.

Molecular Structure. The bond lengths and angles

Table 3. Atomic coordinates and their standard deviations[a]

	x	y	z
O(1)	0.2078 (6)	0.2162 (11)	0.1052 (5)
O(2)	0.6235 (6)	0.3066 (7)	0.1489 (4)
O(3)	0.8099 (6)	0.4320 (8)	0.1809 (4)
C(1)	0.3909 (9)	−0.1630 (11)	0.1018 (6)
C(2)	0.2935 (9)	−0.0586 (12)	0.1150 (6)
C(3)	0.2937 (8)	0.1204 (12)	0.0860 (5)
C(4)	0.4074 (8)	0.1723 (11)	0.0330 (5)
C(5)	0.5319 (8)	0.0844 (11)	0.0616 (5)
C(6)	0.7544 (8)	0.1362 (10)	0.1488 (5)
C(7)	0.6825 (8)	0.0318 (10)	0.1820 (4)
C(8)	0.6612 (9)	−0.1557 (13)	0.1830 (6)
C(9)	0.6294 (10)	−0.2056 (11)	0.0920 (6)
C(10)	0.5131 (9)	−0.1129 (10)	0.0557 (5)
C(11)	0.7831 (8)	0.1310 (11)	0.1990 (5)
C(12)	0.7483 (8)	0.3051 (11)	0.1775 (5)
C(13)	0.9181 (10)	0.0868 (16)	0.2276 (7)
C(14)	0.4196 (10)	0.3659 (11)	0.0260 (7)
C(15)	0.5029 (10)	−0.1681 (12)	−0.0369 (5)

a) The estimated standard deviations are given in parentheses and refer to the last decimal position of respective values.

Table 4. Anisotropic thermal factors[a] ($\times 10^4$) and their standard deviations of heavy-atoms

	B_{11}	B_{22}	B_{33}	B_{12}	B_{23}	B_{31}
O(1)	105 (8)	405 (21)	85 (4)	136 (25)	13 (19)	55 (11)
O(2)	101 (7)	171 (11)	53 (3)	−1 (17)	−27 (11)	−46 (8)
O(3)	132 (8)	221 (13)	58 (3)	−114 (21)	−33 (13)	−29 (9)
C(1)	111 (11)	156 (18)	61 (5)	−14 (25)	1 (17)	0 (13)
C(2)	114 (11)	254 (22)	45 (4)	−59 (30)	10 (19)	−24 (12)
C(3)	70 (9)	290 (24)	41 (4)	−4 (28)	−47 (18)	2 (11)
C(4)	78 (9)	172 (18)	45 (4)	32 (24)	3 (15)	−50 (10)
C(5)	75 (8)	143 (16)	35 (3)	−23 (21)	−11 (13)	−6 (10)
C(6)	80 (9)	138 (15)	41 (4)	5 (22)	−6 (14)	3 (10)
C(7)	119 (10)	168 (16)	19 (3)	45 (24)	47 (13)	−7 (10)
C(8)	114 (12)	231 (22)	74 (6)	76 (30)	53 (21)	−15 (15)
C(9)	155 (13)	131 (16)	56 (5)	82 (29)	−21 (16)	14 (14)
C(10)	113 (11)	118 (15)	48 (4)	−14 (23)	17 (14)	16 (12)
C(11)	108 (10)	182 (17)	35 (4)	−41 (25)	6 (15)	3 (11)
C(12)	131 (11)	166 (17)	34 (4)	−78 (26)	−41 (16)	−40 (11)
C(13)	118 (13)	361 (30)	69 (6)	70 (36)	24 (25)	−39 (15)
C(14)	129 (13)	122 (16)	88 (7)	−37 (27)	61 (18)	−55 (15)
C(15)	169 (14)	197 (21)	36 (4)	−119 (32)	−66 (15)	2 (13)

a) The anisotropic thermal factors are of the form $\exp\{-(h^2B_{11}+k^2B_{22}+l^2B_{33}+hkB_{12}+hlB_{31}+klB_{23})\}$.

are given in Tables 6 and 7, respectively. The various types of bond have lengths in good agreement with those reported for santonins.[7-9] The bond angles are all normal. The torsion angle O(1)–C(3)–C(2)–C(1) is −174°, and the maximum deviation from the least-squares plane containing these atoms is 0.031 Å at O(1), showing the good planarity of the α,β-unsaturated ketone group in the six-membered ring. The cyclohexenone ring A is puckered, C(5) being displaced by *ca.* 0.7 Å from the plane. The methyl group attached to C(4) is equatorial.

The molecule has a *cis* A/B ring fusion, and the ring B has a chair conformation. The mean endocyclic torsion angle for B is 54°, which is between santonins and *epi*-santonins,[9] and the value is similar to those for steroids.[14,18] The torsion angle C(6)–C(5)–C(10)–C(9) is −49° and the rotation around the bond C(5)–C(10) is in the opposite direction compared with the *epi*-santonins, the mean value being 47°.

Table 5. Hydrogen atoms and their standard deviations

	x	*y*	*z*	*B*/Å²
H(C1)	0.379(8)	−0.290(11)	0.116(5)	4.2(2.4)
H(C2)	0.206(9)	−0.119(11)	0.158(5)	4.6(2.4)
H(C4)	0.387(7)	0.117(9)	−0.028(4)	1.4(1.8)
H(C5)	0.601(7)	0.106(9)	0.022(4)	1.9(1.9)
H(C6)	0.496(6)	0.119(9)	0.192(4)	0.7(1.6)
H(C8a)	0.731(7)	−0.201(11)	0.196(4)	2.7(2.0)
H(C8b)	0.583(7)	−0.183(10)	0.232(4)	2.3(2.0)
H(C9a)	0.710(9)	−0.194(12)	0.047(5)	4.7(2.5)
H(C9b)	0.627(8)	−0.328(10)	0.093(4)	2.6(2.0)
H(C13a)	0.924(8)	−0.037(12)	0.246(6)	5.3(2.6)
H(C13b)	0.969(9)	0.079(12)	0.190(5)	6.2(2.7)
H(C13c)	0.936(8)	0.144(12)	0.282(5)	4.7(2.5)
H(C14a)	0.490(8)	0.403(11)	0.001(5)	3.6(2.2)
H(C14b)	0.341(8)	0.422(10)	−0.011(5)	3.6(2.3)
H(C14c)	0.443(9)	0.417(12)	0.077(5)	4.9(2.6)
H(C15a)	0.477(2)	−0.283(10)	−0.051(4)	3.0(2.1)
H(C15b)	0.598(7)	−0.163(10)	−0.071(4)	2.2(1.9)
H(C15c)	0.423(10)	−0.096(13)	−0.072(6)	6.7(2.9)

Table 6. Bond lengths and their standard deviations

O(1)–C(3)	1.210(14) Å	O(2)–C(6)	1.439(10) Å
O(2)–C(12)	1.373(11)	O(3)–C(12)	1.190(11)
C(1)–C(2)	1.322(14)	C(1)–C(10)	1.519(13)
C(2)–C(3)	1.488(15)	C(3)–C(4)	1.508(13)
C(4)–C(5)	1.537(12)	C(4)–C(14)	1.539(14)
C(5)–C(6)	1.516(12)	C(5)–C(10)	1.575(13)
C(6)–C(7)	1.489(12)	C(7)–C(8)	1.498(13)
C(7)–C(11)	1.333(13)	C(8)–C(9)	1.539(14)
C(9)–C(10)	1.523(14)	C(10)–C(15)	1.545(14)
C(11)–C(12)	1.463(13)	C(11)–C(13)	1.514(16)
C(*i*)–H(*i*)			
average	1.02(9)		
range	0.83—1.24		

The α,β-unsaturated lactone of γ-metasantonin is perfectly planar. The torsion angle O(3)–C(12)–C(11)–C(7) is −178°, the largest endocyclic torsion angle being 1.4°, and the maximum deviation from a least-squares plane of the conjugated double bond is 0.034 Å at O(2).

Some empirical rules[15,16] related to the sign of Cotton effect and the chirality of α,β-unsaturated lactones were reported. McMurry and his coworkers[17] investigated that the sign of $n\rightarrow\pi^*$ transition of the photolysis products of 4-hydroxysantonene, which had the same conformation as the lactone ring of γ-metasantonin, agreed with the rules. The CD spectrum of this molecule shows no peak due to $n\rightarrow\pi^*$ transition, presumably because of the planarity of the unsaturated ketone chromophore.[4] The CD spectrum shows a negative band around 230 nm and a positive one at 205 nm due to the coupled $\pi\rightarrow\pi^*$ transition.[19] Two independent chromophores, of which dihedral angle is 48°, take a chiral configuration, and the CD bands might appear owing to this configuration

Crystal Structure. Figure 2 shows the arran-

Table 7. Bond angles and their standard deviations

C(6)–O(2)–C(12)	109.1(6)°	C(2)–C(1)–C(10)	123.5(9)°
C(1)–C(2)–C(3)	122.9(10)	C(2)–C(3)–C(4)	115.8(9)
O(1)–C(3)–C(2)	121.0(10)	O(1)–C(3)–C(4)	123.3(9)
C(3)–C(4)–C(5)	111.5(7)	C(3)–C(4)–C(14)	112.1(8)
C(5)–C(4)–C(14)	113.7(7)	C(4)–C(5)–C(6)	113.3(7)
C(4)–C(5)–C(10)	109.0(7)	C(6)–C(5)–C(10)	111.1(7)
C(5)–C(6)–C(7)	113.3(7)	O(2)–C(6)–C(5)	110.9(7)
O(2)–C(6)–C(7)	104.4(7)	C(6)–C(7)–C(11)	109.6(8)
C(6)–C(7)–C(8)	116.2(8)	C(8)–C(7)–C(11)	134.0(9)
C(7)–C(8)–C(9)	105.7(8)	C(8)–C(9)–C(10)	114.2(8)
C(1)–C(10)–C(5)	109.4(7)	C(1)–C(10)–C(9)	110.6(8)
C(1)–C(10)–C(15)	109.5(8)	C(5)–C(10)–C(9)	110.5(8)
C(5)–C(10)–C(15)	110.2(8)	C(9)–C(10)–C(15)	106.6(8)
C(7)–C(11)–C(12)	108.2(8)	C(7)–C(11)–C(13)	130.5(9)
C(12)–C(11)–C(13)	121.0(9)	O(2)–C(12)–O(3)	120.9(8)
O(2)–C(12)–C(11)	108.5(7)	O(3)–C(12)–C(11)	130.5(9)

Table 8. Short van der Waals contacts

The Roman numerals represent the symmetry operators relevant to the atoms listed second.

C(10)-O(3)^{i}	3.605(12) Å	O(3)-C(14)^{ii}	3.575(13) Å
C(11)-O(3)^{ii}	3.594(11)	O(3)-C(2)^{iii}	3.454(13)
C(9)-C(2)^{iii}	3.513(14)	O(3)-C(15)^{iv}	3.404(14)

Symmetry code

Superscript	Symmetry operator		
i)	x	$-1+y$	z
ii)	$1/2+x$	$1/2-y$	$-z$
iii)	$1-x$	$1/2+y$	$1/2-z$
iv)	$2-x$	$1/2+y$	$1/2-z$

gement of molecules in the crystal, viewed along the b-axis. The intermolecular contacts shown in Table 8 are all greater than 3.4 Å and correspond to normal van der Waals interactions; the shortest separations involve the oxygen atom O(3).

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