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The Crystal and Molecular Structures of Tetronolide

Noriaki Hirayama,* Masaji Kasai, Kunikatsu Shirahata,
Yuji Ohashi,† and Yoshio Sasada†
*Tokyo Research Laboratory, Kyowa Hakko Kogyo Co., Ltd., 3-6-6
Asahimachi, Machida-shi, Tokyo 194*
† *Laboratory of Chemistry for Natural Products, Tokyo Institute of Technology,
Nagatsuta, Midori-ku, Yokohama 227*

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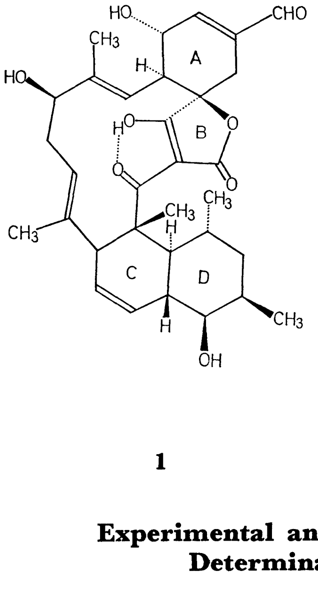
Tetronolide is an aglycone moiety of novel antitumor antibiotics tetrocarcins. The space group of the crystal is $P2_12_12_1$ with $a=20.138(3)$, $b=22.680(3)$, $c=7.848(1)$ Å and $Z=4$. The structure was solved by direct methods and refined by the block-diagonal least-squares using 3577 independent reflexions. The final R value was 0.085. It is established that tetronolide is [1R-(1R*,3R*,4R*,4aR*,6aR*,7E,10R*,11E,12aS*,13R*,16aR*,20aR*,20bS*)]-1,2,3,4,4a,6a,9,10,12a,13,16,20,20a,20b-tetradecahydro-4,10,13,21-tetrahydroxy-1,3,7,11,20a-pentamethyl-18,20-dioxo-18*H*-16a,19-metheno-16a*H*-benzo[*b*]naphth[2,1-*j*]oxacyclotetradecin-15-carbaldehyde or its enantiomer.

Tetronolide (**1**) is an aglycone moiety of novel antitumor antibiotics tetrocarcins,[1,2] which are produced by *Micromonospora chalcea KY11091*. The structure of tetronolide could not be determined by the ordinary spectroscopic and chemical methods.[3] Therefore X-ray analysis of tetronolide was undertaken. It has been revealed that the molecule contains a peculiar skeleton; chlorothricolide (**2**)[4] is the only compound which possesses the similar molecular skeleton.[5] The preliminary results have already been published.[6]



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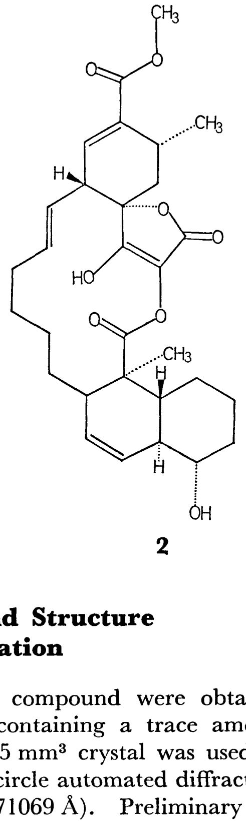

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Experimental and Structure Determination

Prismatic crystals of the title compound were obtained from an ethyl acetate solution containing a trace amount of methanol. A 0.22×0.22×0.65 mm³ crystal was used for data collection on a Rigaku four-circle automated diffractometer with Mo $K\alpha$ radiation ($\lambda=0.71069$ Å). Preliminary unit cell dimensions and space group were obtained from photographs. The space group was assigned to be $P2_12_12_1$ from systematic absences ($h00$ for odd h, $0k0$ for odd k, $00l$ for odd l). Accurate cell dimensions were determined by the least-squares calculation with 2θ values of 16 high-angle reflexions measured on the diffractometer. Crystal data are as follows: $C_{32}H_{40}O_8$; M. W.=552.664; $P2_12_12_1$; Z=4; $a=20.138(3)$, $b=22.680(3)$, $c=7.848(1)$ Å; $D_x=1.19$ g cm^{-3}; $\mu(\text{Mo } K\alpha)=3.65$ cm^{-1}. All independent reflexions within the range $2\theta\leqq55°$ were collected by use of the ω-2θ scan mode with a scanning rate 4°(2θ) min^{-1}. Stationary background counts were accumulated for 10 s before and after each scan. Periodic checks of the intensity values of three standard reflexions showed no significant X-ray damage or crystal decay. Any corrections for absorption or extinction were not applied. A total of 3655 independent reflexions were obtained, of which 3577 ($|F_o|>3.0\sigma(|F_o|)$) were used for the structure determination.

The phases of 260 reflexions with $|E_o|\geqq1.67$ were assigned with MULTAN 78.[7] The best set of phases was employed to calculate an E map, which gave the appropriate peaks for all non-hydrogen atoms. The structural parameters were refined by the block-diagonal least-squares methods with the modified HBLS program. All of the hydrogen atoms were located from difference syntheses. In addition to the hydrogen atoms many peaks with height of about 0.3 eÅ^{-3} appeared on the difference map. Most of them were located between the molecules, of which six were regarded to correspond to solvent molecules of ethyl acetate, and their atomic parameters were successfully refined isotropically with the occupancy of 0.2. The weighting system applied was $w=1/(\sigma^2(F_o)+(0.015F_o)^2)$. The final R value is 0.085. Atomic scattering factors were taken from "International Tables for X-Ray Crystallography."[8] The final positional and thermal parameters are given in Table 1.**

Results and Discussion

Bond Lengths and Angles. The atomic numbering and ring names are shown in Fig. 1. The stereoscopic drawing of the tetronolide molecule is given in Fig. 2. Absolute configuration was not determined. Bond lengths and angles are tabulated in Table 2. The C–C bonds around the ring B are short, *i.e.*, C(30)–C(32)=1.48(1), C(2)–C(32)=1.42(1), C(1)–C(2)=1.49(1), and C(2)–C(3)=1.41(1) Å. This indicates that the π electrons are delocalized extensively through-

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** The tables of the observed and calculated structure factors, the anisotropic thermal parameters of non-hydrogen atoms, the atomic parameters of hydrogen atoms and the solvent molecule, and torsional angles in the molecule are kept as Document No. 8241 at the Chemical Society of Japan.

Table 1. Final atomic parameters with their estimated standard deviations, multiplied by 10^4 for C and O atoms

Atom	x	y	z	$B_{eq}/\text{Å}^2$	Atom	x	y	z	$B_{eq}/\text{Å}^2$
O(1)	8837 (2)	1182 (2)	8546 (6)	3.01	C(13)	10607 (5)	1765 (5)	4594 (12)	5.54
O(2)	7990 (2)	1783 (2)	7979 (7)	3.62	C(14)	10105 (4)	2732 (4)	5519 (11)	4.05
O(3)	9437 (2)	686 (2)	4576 (7)	3.45	C(15)	9604 (4)	2831 (4)	4050 (12)	4.46
O(4)	9527 (3)	837 (2)	10050 (9)	6.24	C(16)	8925 (4)	2611 (3)	4457 (10)	3.45
O(5)	10816 (2)	1449 (2)	10138 (7)	3.90	C(17)	8453 (4)	2465 (3)	3362 (10)	3.03
O(6)	9908 (3)	3032 (3)	7023 (9)	4.66	C(18)	8553 (4)	2489 (4)	1486 (11)	4.38
O(7)	5785 (2)	2288 (2)	−178 (7)	3.38	C(19)	7775 (3)	2282 (3)	4026 (10)	2.84
O(8)	8520 (2)	1128 (2)	2783 (6)	3.40	C(20)	7266 (4)	2702 (3)	3376 (11)	3.22
C(1)	8374 (3)	1428 (3)	7441 (9)	2.65	C(21)	6771 (4)	2541 (3)	2355 (11)	3.44
C(2)	8513 (3)	1212 (3)	5685 (10)	2.49	C(22)	6640 (3)	1920 (3)	1788 (9)	2.38
C(3)	9122 (3)	911 (3)	5785 (10)	2.50	C(23)	6362 (3)	1901 (3)	−39 (10)	2.80
C(4)	9356 (3)	879 (3)	7631 (10)	2.84	C(24)	6190 (4)	1275 (3)	−647 (9)	2.70
C(5)	9397 (4)	244 (3)	8248 (11)	4.08	C(25)	5527 (4)	1052 (3)	−233 (10)	3.40
C(6)	9783 (4)	176 (3)	9850 (10)	3.40	C(26)	6754 (3)	858 (3)	−233 (10)	2.87
C(7)	10131 (4)	617 (3)	10549 (10)	3.59	C(27)	6997 (3)	874 (3)	1639 (10)	3.36
C(8)	10163 (4)	1230 (3)	9829 (7)	2.82	C(28)	7456 (4)	359 (3)	1980 (13)	4.02
C(9)	10000 (4)	1231 (3)	7923 (9)	2.76	C(29)	7250 (3)	1506 (3)	2021 (9)	2.15
C(10)	9786 (5)	−413 (4)	10641 (13)	5.25	C(30)	7564 (3)	1607 (3)	3799 (9)	2.31
C(11)	9940 (3)	1859 (3)	7293 (10)	2.56	C(31)	7056 (3)	1448 (4)	5209 (10)	3.62
C(12)	10199 (4)	2086 (3)	5894 (10)	3.21	C(32)	8202 (3)	1303 (3)	4082 (9)	2.36

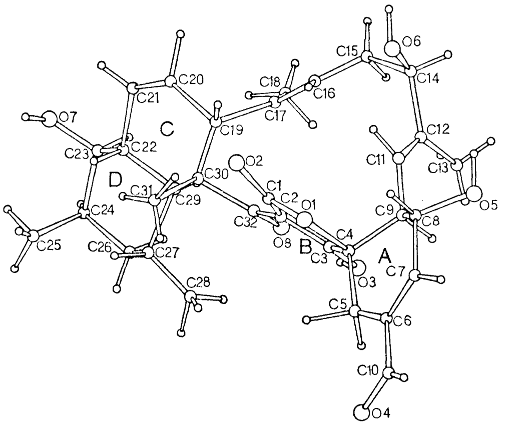

Fig. 1. The numbering system of tetronolide.

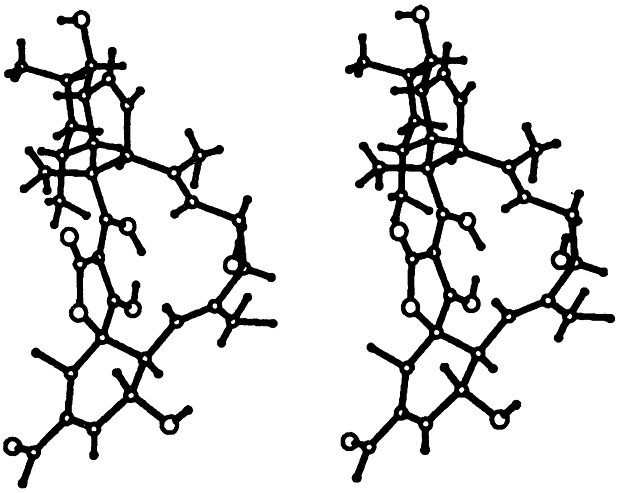

Fig. 2. Stereoscopic drawing of tetronolide.
The figure and Fig. 4 were drawn by TSD:XTAL, which is a computer-graphics interactive modeling program for a NOVA 3 computer.[9]

out this part. There is an intramolecular hydrogen bond between the O(3) and O(8) atoms. The bond lengths of C(3)–O(3) and C(32)–O(8) (1.250 and 1.267 Å, respectively) show that both of these bonds are intermediate of carbonyl and hydroxyl C–O bonds. Moreover the elctron density which corresponds to the two hydrogen atoms bonded to O(3) and O(8) atoms appeared on the difference map. These facts indicate that there are two tautomeric fomrs as $\begin{array}{c}\text{O}\cdots\text{HO}\\ \|\qquad\;\; |\\ -\text{C}-\text{C}=\text{C}-\end{array}$ and $\begin{array}{c}\text{OH}\cdots\text{O}\\ |\qquad\;\; \|\\ -\text{C}=\text{C}-\text{C}-\end{array}$. The geometry of the hydrogen bond is as follows: O(3)···O(8) = 2.528(7), H(O(3))···O(8) = 1.81(3), H(O(8))···O(3) = 1.81(3) Å, ∠O(3)–H···O(8) = 139(3), and ∠O(3)···H–O(8) = 138(3)°.

In chlorothricolide (**2**) containing a closely related skeleton,[4] there is a similar but much weaker intramolecular C=O···H–O hydrogen bond; the O···O distance averaged over the two independent molecules of **2** in asymmetric unit is 2.95 Å.

The C(19)–C(30) distance is remarkably long (1.60 Å) and the corresponding C–C distance in **2** is also long (the average distance is 1.58 Å).

Of the two intramolecular short contacts, the contact between the C(28) atom and the O(8) atom is of perticular interest; the C(28)···O(8), HAC(28)···O(8) and HBC(28)···O(8) distances are 2.83(1), 2.35(7), and 2.56(9) Å, respectively. These values indicate that the C(28) methyl group is so sterically hindered by the O(8) atom that the rotation of the methyl group may be considerably restricted. On the other hand, the C(31) methyl group also contacts with the O(2) carbonyl oxygen atom. The geometry, the C-

TABLE 2. BOND LENGTHS AND ANGLES

Bond length	l/Å	C(19)-C(30)	1.60(1)	C(15)-C(14)-O(6)	111.5(7)
C(1)-C(2)	1.49(1)	C(27)-C(29)	1.55(1)	C(12)-C(14)-C(15)	111.6(7)
C(1)-O(1)	1.390(9)	C(29)-C(30)	1.55(1)	C(14)-C(15)-C(16)	112.9(8)
C(1)-O(2)	1.194(9)	C(30)-C(31)	1.55(1)	C(15)-C(16)-C(17)	127.1(8)
C(2)-C(3)	1.41(1)	C(30)-C(32)	1.48(1)	C(16)-C(17)-C(18)	122.5(8)
C(2)-C(32)	1.42(1)	C(32)-O(8)	1.267(9)	C(16)-C(17)-C(19)	119.4(7)
C(3)-C(4)	1.53(1)	C(10)-O(4)	1.19(1)	C(18)-C(17)-C(19)	118.1(7)
C(3)-O(3)	1.250(9)	Bond angle	ϕ/°	C(17)-C(19)-C(20)	109.0(6)
C(3)-C(4)	1.53(1)	C(2)-C(1)-O(1)	108.6(6)	C(17)-C(19)-C(30)	117.6(6)
C(4)-C(5)	1.52(1)	C(3)-C(2)-C(1)	105.7(6)	C(20)-C(19)-C(30)	112.9(6)
C(4)-C(9)	1.54(1)	O(1)-C(1)-O(2)	119.0(7)	C(19)-C(20)-C(21)	123.1(8)
C(4)-O(1)	1.442(9)	C(2)-C(1)-O(2)	132.1(7)	C(20)-C(21)-C(22)	124.6(8)
C(5)-C(6)	1.49(1)	C(1)-C(2)-C(32)	133.7(7)	C(21)-C(22)-C(29)	113.1(6)
C(6)-C(10)	1.47(1)	C(3)-C(2)-C(32)	120.3(7)	C(22)-C(29)-C(30)	109.8(6)
C(6)-C(7)	1.34(1)	C(2)-C(3)-O(3)	126.7(7)	C(29)-C(30)-C(19)	110.7(6)
C(7)-C(8)	1.50(1)	C(2)-C(3)-C(4)	110.3(6)	C(21)-C(22)-C(23)	111.5(6)
C(8)-C(9)	1.53(1)	C(4)-C(3)-O(3)	123.0(7)	C(29)-C(22)-C(23)	112.4(6)
C(8)-O(5)	1.427(9)	C(1)-O(1)-C(4)	111.5(5)	C(22)-C(23)-C(24)	113.4(6)
C(9)-C(10)	1.51(1)	C(3)-C(4)-O(1)	103.1(6)	C(22)-C(23)-O(7)	110.1(6)
C(11)-C(12)	1.32(1)	C(3)-C(4)-C(9)	112.1(6)	C(24)-C(23)-O(7)	110.7(6)
C(12)-C(13)	1·50(1)	O(1)-C(4)-C(5)	109.4(6)	C(23)-C(24)-C(26)	110.0(6)
C(12)-C(14)	1.51(1)	C(9)-C(4)-C(5)	113.5(6)	C(23)-C(24)-C(25)	113.0(6)
C(14)-O(6)	1.42(1)	C(4)-C(5)-C(6)	113.3(7)	C(26)-C(24)-C(25)	111.8(6)
C(14)-C(15)	1.55(1)	C(5)-C(6)-C(7)	122.9(8)	C(24)-C(26)-C(27)	115.2(6)
C(15)-C(16)	1.49(1)	C(5)-C(6)-C(10)	117.0(8)	C(26)-C(27)-C(28)	110.0(7)
C(16)-C(17)	1.32(1)	C(7)-C(6)-C(10)	120.2(8)	C(29)-C(27)-C(28)	118.6(7)
C(17)-C(18)	1.49(1)	C(6)-C(10)-O(4)	124.5(9)	C(26)-C(27)-C(29)	108.0(6)
C(17)-C(19)	1.52(1)	C(6)-C(7)-C(8)	124.0(7)	C(22)-C(29)-C(27)	106.0(6)
C(19)-C(20)	1.49(1)	C(7)-C(8)-C(9)	111.1(6)	C(19)-C(30)-C(32)	101.4(6)
C(20)-C(21)	1.33(1)	C(7)-C(8)-O(5)	107.3(6)	C(29)-C(30)-C(31)	109.9(6)
C(21)-C(22)	1.50(1)	C(9)-C(8)-O(5)	111.3(6)	C(31)-C(30)-C(32)	110.9(6)
C(22)-C(29)	1.56(1)	C(8)-C(9)-C(4)	108.9(6)	C(3)-C(4)-C(5)	111.3(6)
C(22)-C(23)	1.54(1)	C(8)-C(9)-C(11)	109.8(6)	C(9)-C(4)-O(1)	106.8(6)
C(23)-C(24)	1.54(1)	C(4)-C(9)-C(11)	111.9(6)	C(29)-C(30)-C(32)	115.0(6)
C(23)-O(7)	1.460(9)	C(9)-C(11)-C(12)	127.5(7)	C(19)-C(30)-C(31)	108.5(6)
C(24)-C(25)	1.53(1)	C(11)-C(12)-C(13)	126.4(8)	C(30)-C(32)-C(2)	125.9(7)
C(24)-C(26)	1.51(1)	C(11)-C(12)-C(14)	119.5(7)	C(30)-C(32)-O(8)	117.7(6)
C(26)-C(27)	1.55(1)	C(13)-C(12)-C(14)	114.1(7)	C(2)-C(32)-O(8)	116.4(7)
C(27)-C(28)	1.51(1)	C(12)-C(14)-O(6)	109.9(7)		

(31)···O(2) distance of 2.793 Å and the C(31)-H···O(2) angle of 145°, indicates that this contact is a hydrogen bond. Since a similar methyl group in **2** is trans to the carbonyl oxygen atom, there is no possibility for such an intramolecular hydrogen bond.

Some exo- and endocyclic bond angles of the γ-lactone ring are distorted. The C(1)-C(2)-C(32), O(2)-C(1)-C(2), and C(2)-C(3)-O(3) angles are 133.7, 132.1, and 126.7°, respectively. The corresponding bond angles in chlorothricolide are also large (the average values are 135.9, 126.8, and 133.0°). Such distortion of the bond angles may be explained by the planar geometry of ring B with O(3), C(32), and O(8) atoms caused by the extensive delocalization of the π electrons.

The O(1)-C(4)-C(3) angle of 101.1(6)° at the spiro group in tetronolide is small (the corresponding averaged value of 102.8° in **2** is also small).

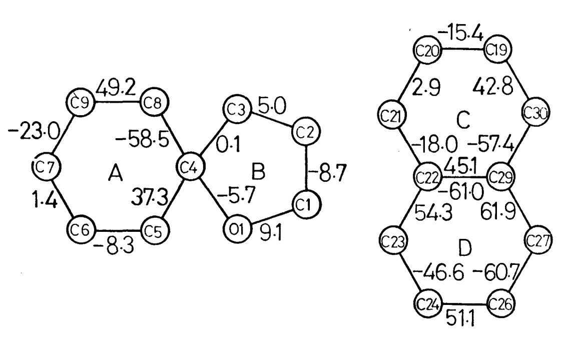

Fig. 3. Torsional angles in the rings, τ/°.

Although the C(19)-C(30)-C(32) angle of 101.4(6)° is remarkably small in tetronolide, but the corresponding value 107.3° in **2** is within the expected region. Other bond lengths and angles are normal.

Conformation. The thirteen-membered ring, two cyclohexene rings, and the cyclohexane ring take the crown, the half-chair, and the chair conformation, respectively. The γ-lactone ring is in the envelope con-

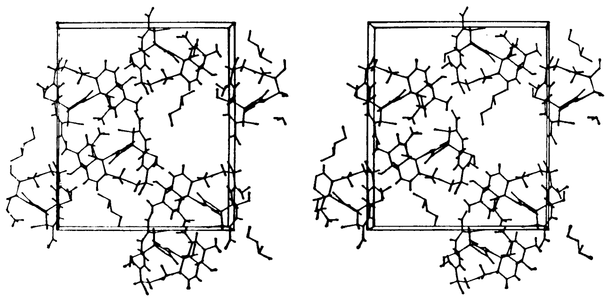

Fig. 4. Crystal structure viewed along the c axis. The vertical and holizontal axes denote b and a axes.

formation. The ring torsional angles in each ring are shown in Fig. 3. The conformational characteristics as a whole is similar to that of **2**. Ring A is more flattened than C. In the cyclohexane ring C(27) and C(29) are puckered, and C(23) and C(24) are flattened. Rings C and D are fused in the *trans*-decalin type.

Crystal Structure. The crystal structure viewed along the c axis is shown in Fig. 4. The molecules are connected by the two intermolecular hydrogen bonds and form the helical chain along the a axis. The geometry of the hydrogen bonds are $O(5)^{I}\cdots O(7)^{II}=2.865(8)$ Å, $\angle O(5)\text{-}H^{I}\cdots O(7)^{II}=172(3)°$; $O(7)^{II}\cdots O(6)^{I}=3.127(8)$ Å, $\angle O(7)\text{-}H^{II}\cdots O(6)^{I}=166(3)°$. Symmetry codes I and II denote (x,y,z) and $(0.5+x,\ 0.5-y,\ 1.0-z)$, respectively. The helical chains are stacked mainly by van der Waals interactions. There are large cavities between the helical chains, and the ethyl acetate molecule is located in the cavity. As mentioned in the experimental section many fragments corresponding to the low but significant electron density still remained at the final stage of the refinement. The fact indicates that much more solvent molecules must exist in the crystal.

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