Studies on the Ionophorous Antibiotics. Part IV.[1] Crystal and Molecular Structure of the Thallium Salt of Lonomycin

By **Noboru Ōtake** * and **Mitsuo Koenuma**, Institute of Applied Microbiology, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan
Hiroshi Miyamae, Shoichi Sato, and **Yoshihiko Saito**, Institute for Solid State Physics, University of Tokyo, Roppongi-7, Minato-ku, Tokyo 106, Japan

Lonomycin (I) is an antibiotic produced by *Streptomyces ribosidicus*. The crystal and molecular structure of its thallium salt has been established by a three-dimensional *X*-ray analysis by the heavy-atom method from diffractometer data. Crystals are orthorhombic, space group $P2_12_12_1$, $a = 16.257(2)$, $b = 25.731(4)$, $c = 12.502(2)$ Å, $Z = 4$. The structure was refined by block-diagonal least-squares to R 0.075 for 3 225 reflections. The lonomycin molecule contains six ring systems: three five-membered rings have an envelope conformation, while the other three are six-membered and adopt a chair conformation. The molecule as a whole takes a circular conformation and the thallium ion is located in a cavity.

LONOMYCIN,[2] $C_{44}H_{76}O_{14}$, is a new antibiotic elaborated by *Streptomyces ribosidicus* and exhibits antimicrobial activity against gram-positive bacteria, including mycobacteria, as well as some kinds of filamentous fungi. In addition, it is effective in the treatment of coccidial infections in poultry.

In the light of its biological activity and physicochemical properties, lonomycin was thought to be a new member of the polyether monocarboxylic acid antibiotics, which includes monensin,[3] nigericin,[4] grisorixin,[5] A 204A,[6] X-206,[7] X-537,[8] dianemycin,[9] salinomycin,[10] septamycin,[11] lysocellin,[12] and alborixin,[13] which are well known to act as ionophores to effect the transport of essential cations across cell membranes.

As part of a series of investigations on the ionophorous antibiotics,[9,11] the crystal structure of lonomycin has been determined by use of its thallium complex. A preliminary report has been published.[1]

EXPERIMENTAL

Instruments.—M.p.s were measured with a Yanagimoto m.p. apparatus. ^1H N.m.r. spectra were taken with a JNM 4H 100 spectrometer, and mass spectra measured with a RMU 6A spectrometer. *X*-Ray diffraction intensities were measured on a Rigaku four-circle *X*-ray diffractometer and calculations were carried out on our HITAC 8700/8800.

Preparation of Thallium Salt of Lonomycin.—To a solution of the sodium salt of lonomycin (50 mg) in methanol (10 ml) was added dropwise an aqueous solution of thallium acetate (20 mg) in redistilled water (5 ml) and the whole mixture was placed in the dark for a week. Crystals (m.p. 150.2—150.3 °C), grown by allowing the methanol to evaporate, were plates, elongated along the *b* axis.

The molecular formula, $C_{44}H_{75}O_{14}Tl$, was confirmed by elementary analyses as well as by comparison of the formulae of the methyl ester, $C_{45}H_{78}O_{14}$ ($M^+ - H_2O$, m/e 824), and the sodium salt, $C_{44}H_{75}O_{14}Na$ (M^+, m/e 850).

In addition, the ^1H n.m.r. (deuteriochloroform) and i.r. (Nujol) spectra of (I) were almost superposable with those of the sodium and the silver salt.

From the ^1H n.m.r. data for the thallium salt it was revealed that the molecule contains four methoxy-groups at *ca.* δ 3.3—3.5 p.p.m. and a number of methyl groups attached to secondary or tertiary carbons which overlap each other in the range δ 0.80 to δ 1.80.

Crystal Data.—$C_{44}H_{75}O_{14}Tl$, $M = 1\,032.43$. Orthorhombic, $a = 16.257(2)$, $b = 25.731(4)$, $c = 12.502(2)$ Å, $U = 5\,229.7$ Å^3, $D_m = 1.36$, $Z = 4$, $D_c = 1.33$ g cm^{-3}. Mo-K_α radiation, $\lambda = 0.710\,7$ Å; μ(Mo-K_α) = 5.26 cm^{-1}. Space group $P2_12_12_1$.

Crystals *ca.* 0.3 × 0.3 × 0.4 mm were used for data collection. Since the salt deteriorated during exposure to *X*-rays, four crystals were used for intensity measurement. Intensity data were collected on an automated four-circle diffractometer up to 2θ 53° with graphite-monochromated Mo-K_α radiation ($\lambda = 0.710\,7$ Å) using the θ—2θ scan technique at 2° min^{-1} in θ.

Backgrounds were counted at the beginning and the end of each scan for 10 s. In this way 3 225 independent reflections with $|F| > 3\sigma$ were recorded and used for the structure determination. No absorption correction was made.

The structure was solved by the heavy-atom method. The position of the thallium atom was easily deduced from a three-dimensional Patterson map. Subsequent calculations of the structure factors and the electron-density distribution fixed the co-ordinates of all the non-hydrogen atoms. Refinement was carried out by a block-diagonal least-squares program with anisotropic thermal parameters.

Convergence was attained at R 0.075 for the 3 225 observed reflections. At the final stage of the refinement all the shifts of the atomic co-ordinates were < one ninth of their standard deviations. Final atom parameters are presented in Table 1. Atom thermal parameters, final

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observed and calculated structure factors, and i.r. and n.m.r. spectra of the thallium, silver, and sodium salts are listed in Supplementary Publication No. SUP 21842 (26 pp., 1 microfiche).*

TABLE 1

Atom parameters

	x	y	z
Tl	346(0.1)	835(0.0)	−182(0.3)
C(1)	390(3)	1 666(2)	−2 094(3)
C(2)	707(2)	2 065(2)	−2 882(5)
C(3)	1 700(6)	1 993(2)	−2 996(1)
C(4)	2 022(3)	2 354(0)	−3 868(3)
C(5)	2 998(0)	2 331(1)	−3 690(4)
C(6)	3 236(1)	2 440(1)	−2 592(2)
C(7)	2 872(4)	2 044(1)	−1 857(0)
C(8)	3 073(3)	2 115(4)	−652(9)
C(9)	2 555(4)	1 766(0)	71(3)
C(10)	2 329(1)	2 017(1)	1 152(7)
C(11)	1 836(1)	1 624(1)	1 841(4)
C(12)	2 250(1)	1 084(4)	1 894(17)
C(13)	2 637(0)	860(0)	815(10)
C(14)	3 280(5)	475(1)	981(5)
C(15)	3 261(0)	179(4)	−53(3)
C(16)	2 367(2)	248(3)	−426(11)
C(17)	1 875(1)	−260(3)	−319(8)
C(18)	1 745(4)	−446(2)	824(1)
C(19)	959(3)	−802(0)	729(4)
C(20)	605(1)	−642(1)	−427(1)
C(21)	−320(1)	−462(0)	−445(6)
C(22)	−962(1)	−905(2)	−303(1)
C(23)	−1 732(0)	−528(1)	−138(1)
C(24)	−1 345(2)	−101(2)	623(10)
C(25)	−1 688(1)	453(1)	380(4)
C(26)	−2 600(4)	453(3)	649(1)
C(27)	−2 985(8)	949(3)	149(4)
C(28)	−2 781(2)	997(3)	−982(13)
C(29)	−1 825(1)	1 002(6)	−1 148(3)
C(30)	−1 563(2)	1 032(6)	−2 298(11)
C(31)	440(6)	2 610(1)	−2 640(2)
C(32)	1 779(7)	2 233(4)	−5 027(6)
C(33)	4 141(5)	2 624(4)	−4 760(22)
C(34)	3 122(6)	3 012(1)	−2 237(1)
C(35)	3 973(3)	2 071(4)	−442(3)
C(36)	3 069(7)	2 196(1)	1 833(11)
C(37)	440(5)	1 962(2)	1 428(19)
C(38)	2 372(0)	435(0)	−1 642(2)
C(39)	665(1)	−1 062(1)	−1 266(10)
C(40)	−819(7)	−1 299(4)	694(5)
C(41)	−2 895(3)	−1 083(3)	−174(5)
C(42)	−2 732(3)	451(3)	1 858(8)
C(43)	−4 254(18)	1 290(4)	925(34)
C(44)	−3 177(3)	1 485(3)	−1 456(0)
O(1)	585(2)	1 209(3)	−2 184(1)
O(2)	−71(2)	1 825(0)	−1 342(3)
O(3)	1 964(1)	2 107(0)	−1 973(2)
O(4)	1 857(2)	1 478(1)	−3 301(2)
O(5)	3 311(1)	2 687(2)	−4 458(3)
O(6)	3 021(0)	1 278(2)	234(1)
O(7)	1 008(1)	1 543(1)	1 315(3)
O(8)	2 010(0)	645(1)	256(11)
O(9)	1 042(0)	−185(1)	−775(0)
O(10)	−448(2)	−116(0)	435(5)
O(11)	−2 367(1)	−77(2)	494(0)
O(12)	−1 529(3)	550(1)	−712(2)
O(13)	−3 891(5)	928(5)	282(9)
O(14)	−1 521(1)	1 439(0)	−531(1)

The absolute configuration was determined by the use of the anomalous scattering effect of the Tl atom for Cu-K_α radiation. An equi-inclination Weissenberg photograph was taken of the first layer around the a axis with Cu-K_α radiation. Differences between intensities of some reflections and those of their counter-reflections were clearly discernible (Table 2).

All differences were confirmed by measuring the intensities of the same reflections on a diffractometer using Mo-K_α radiation. The set of atomic co-ordinates given in Table 1 correctly represents the absolute configuration of the molecule shown in (I) when referred to the right-handed set of axes.

TABLE 2

Determination of absolute configuration of lonomycin

h	k	l	$F_o(hkl)$	$F_c(hkl)$	$F_o(h\bar{k}l)$	$F_c(h\bar{k}l)$
1	4	1	52	45	66	61
1	1	2	23	31	40	47
1	2	2	109	104	165	163
1	9	2	57	50	44	43
1	10	3	46	37	36	27
1	17	5	66	72	54	57
1	4	6	76	87	90	105
1	1	7	57	57	47	43
1	11	7	83	80	70	70
1	14	7	56	55	38	44
1	3	10	54	45	74	52

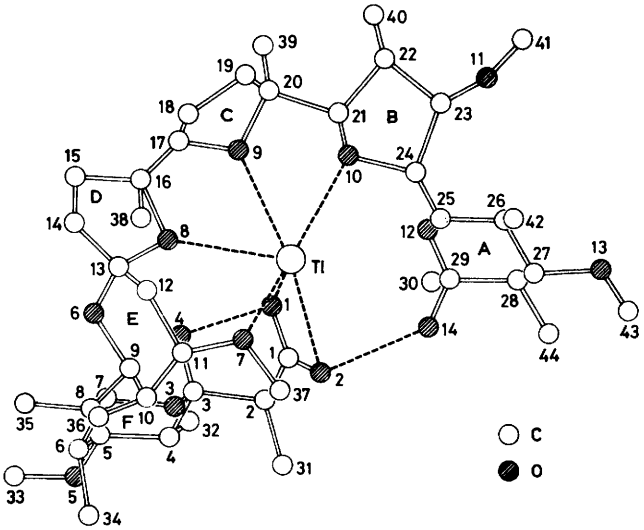

FIGURE 1 Projection of the structure of lonomycin viewed along c axis

RESULTS AND DISCUSSION

On the basis of the foregoing results, the chemical structure and the absolute configuration of lonomycin is established as depicted in (I) and in a projection of the structure along the c axis in Figure 1.

The bond lengths and angles in the molecule are given in Figures 2 and 3, respectively, and are all as expected.

It was thus revealed that lonomycin is a new member of the monocarboxylic polycyclic ether antibiotics closely related to nigericin [4] and grisorixin.[5]

The whole molecule takes a circular conformation and the thallium(I) ion is located in the cavity. A thallium atom co-ordinates to six oxygen atoms, with $\text{Tl}\cdots\text{O}$ distances ranging from 2.56(2) to 3.01(2) Å.

Most of the oxygen atoms are located in the interior of the molecule, rendering the exterior surface hydrophobic.

Lonomycin contains six ring systems, three of them

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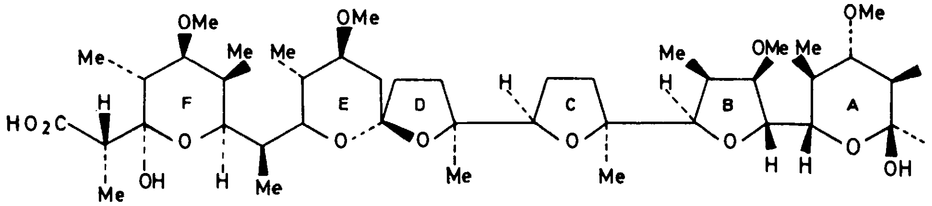
* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue.

(B, C, and D) are five-membered and have an envelope conformation, while the remaining three six-membered rings (A, E, and F) adopt a chair conformation.

For ring A, the C(30), C(42), and C(44) methyl groups and the O(13) methoxy-group are equatorial, while the O(14) hydroxy-group is axial. For ring E, both the C(36) methyl and the O(7) methoxy-groups are axial.

For ring F, however, the C(32) methyl and the O(5) methoxy-groups are equatorial, while the C(34) methyl and the O(4) hydroxy-groups are axial.

It is of particular interest that lonomycin contains two hemiacetal groups, in rings A and F, which take a rather unstable axial conformation and that the spiroacetal ring system formed by rings D and E occurs also in monensin.



(1)

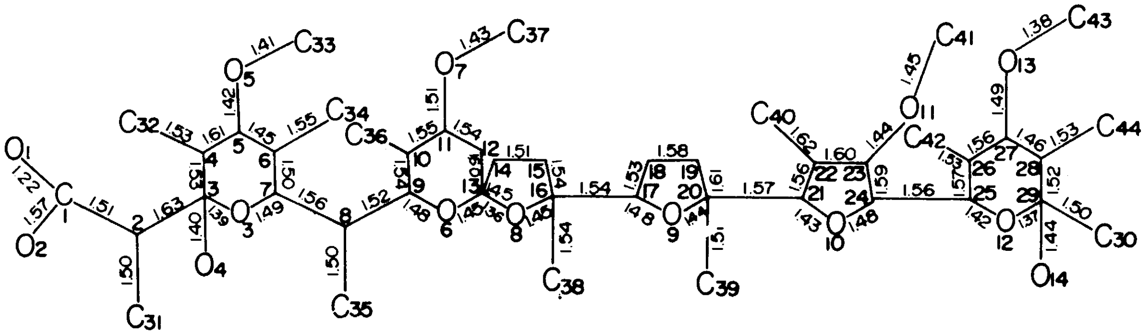


FIGURE 2 Bond lengths (Å) of lonomycin; mean standard deviation 0.0 Å

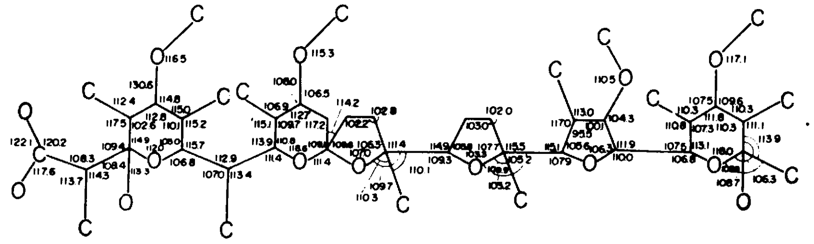


FIGURE 3 Bond angles (°) of lonomycin; mean standard deviation 2°

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