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STUDIES ON THE IONOPHOROUS ANTIBIOTICS. PART III.
THE STRUCTURE OF LONOMYCIN, A POLYETHER ANTIBIOTIC

Noboru Ōtake and Mitsuo Koenuma

Institute of Applied Microbiology, The University of Tokyo

Hiroshi Miyamae, Shoichi Sato and Yoshihiko Saito

Institute for Solid State Physics, The University of Tokyo

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Lonomycin[1] is an antibiotic elaborated by *Streptomyces ribosidificus* and shows an antimicrobial activity against gram-positive bacteria including mycobacteria as well as some kind of filamentous fungi. Lonomycin is also effective in the treatment of coccidial infections in poultry and shows some chemical and biological characteristics common in the family of polyether antibiotics.

In the course of our serial studies[2,3] on the ionophores, we have elucidated the entire structure of lonomycin as depicted in Fig. 1 using the thallium salt by a three dimensional X-ray analysis.

The thallium salt of lonomycin crystallizes from methanol-water in plates, m.p. 150.2-150.3°C The molecular formula, $C_{44}H_{75}O_{14}Tl$ is confirmed by comparison with 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). Crystal data: orthorhombic, space group $P_{2_12_12_1}$, a=16.257(2), b=25.731(4) and c=12.502(2)Å, Dm=1.36 (flotation in aqueous KI), Dc=1.33 g/cm^3 for Z=4.

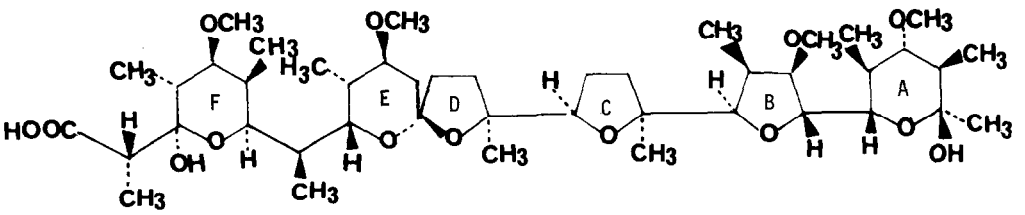

Fig. 1 The structure of lonomycin

The intensity data were collected on an automated four-circle diffractometer using Mo Kα radiation (λ=0.7107Å). The maximum value of 2θ was 53° in the ω-2θ scan technique. Since the thallium salt of lonomycin decomposed gradually in the X-ray beam, four crystals were used and the intensities were corrected by comparison with the standard reflexions.

The structure was solved by the heavy-atom method. The positional and thermal parameters for the non-hydrogen atoms were refined by the block-diagonal least-squared method using anisotropic temperature factors. The final R-value for the 3225 reflexions used in the refinement was 0.078. The final coordinates and their standard deviations are given in Table 1.

Table 1. Positional parameters for the non-hydrogen atoms ($\times 10^3$), with their e.s.d.'s in parentheses

	X	Y	Z		X	Y	Z
Tl	35(0)	83(0)	-18(0)	C(30)	-156(2)	103(1)	-229(2)
C(1)	39(2)	167(1)	-209(2)	C(31)	44(2)	261(1)	-264(3)
C(2)	71(1)	206(1)	-288(2)	C(32)	178(2)	223(1)	-502(2)
C(3)	170(2)	199(1)	-300(2)	C(33)	312(2)	301(1)	-224(3)
C(4)	202(2)	235(1)	-387(2)	C(34)	414(2)	263(1)	-475(4)
C(5)	300(2)	233(1)	-369(2)	C(35)	397(2)	207(1)	-44(3)
C(6)	324(2)	244(1)	-259(2)	C(36)	307(2)	220(1)	184(3)
C(7)	287(1)	204(1)	-186(2)	C(37)	44(2)	196(2)	144(4)
C(8)	307(2)	211(1)	-65(3)	C(38)	237(2)	44(1)	-164(2)
C(9)	255(1)	177(1)	7(3)	C(39)	67(2)	-106(1)	-127(3)
C(10)	233(2)	202(1)	116(2)	C(40)	-82(2)	-130(1)	69(3)
C(11)	184(2)	162(1)	184(2)	C(41)	-290(2)	-108(1)	-17(4)
C(12)	225(2)	109(1)	190(3)	C(42)	-273(2)	45(1)	186(3)
C(13)	264(1)	86(1)	82(2)	C(43)	-318(2)	149(1)	-146(3)
C(14)	328(2)	48(1)	98(2)	C(44)	-426(3)	129(2)	91(4)
C(15)	326(1)	18(1)	-5(3)	O(1)	58(1)	121(1)	-218(2)
C(16)	237(1)	25(1)	-43(3)	O(2)	-7(1)	183(1)	-134(2)
C(17)	188(2)	-26(1)	-32(2)	O(3)	196(1)	211(1)	-197(1)
C(18)	174(2)	-45(1)	82(3)	O(4)	186(1)	148(1)	-330(2)
C(19)	96(2)	-80(1)	73(3)	O(5)	331(1)	269(1)	-446(2)
C(20)	60(1)	-64(1)	-43(2)	O(6)	302(1)	128(1)	23(1)
C(21)	-32(2)	-46(1)	-45(2)	O(7)	101(1)	154(1)	132(2)
C(22)	-96(2)	-90(1)	-30(2)	O(8)	201(1)	64(1)	25(2)
C(23)	-173(2)	-53(1)	-14(3)	O(9)	104(1)	-19(1)	-78(1)
C(24)	-135(1)	-10(1)	63(2)	O(10)	-45(1)	-12(1)	44(1)
C(25)	-169(1)	45(1)	38(2)	O(11)	-237(1)	-77(1)	49(1)
C(26)	-260(2)	45(1)	65(2)	O(12)	-153(1)	55(1)	-71(1)
C(27)	-298(1)	95(1)	15(3)	O(13)	-389(1)	92(1)	28(2)
C(28)	-278(1)	100(1)	-99(2)	O(14)	-152(1)	144(1)	-53(2)
C(29)	-183(2)	100(1)	-115(2)				

The absolute configuration was determined by use of the anomalous dispersion effect of the thallium atom for Mo Kα radiation. Differences between intensities of some reflexions and those of their counter-reflexions were clearly discernible as shown in Table 2.

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

The resulting molecular structure of lonomycin thallium salt viewed along the c axis is illustrated in Fig. 2 which correctly represents the absolute configuration of the antibiotic. The whole molecule takes a circular conformation and the thallium (I) ion is located in a cavity The thallium atom co-ordinates to six oxygen atoms in the distance ranging from 2.6 to 3.0Å.

The structure of lonomycin is similar to those found for nigericin[4] and grisorixin[5], however, it differs in the conformation of ring F and the side chain bearing the carboxylic function.

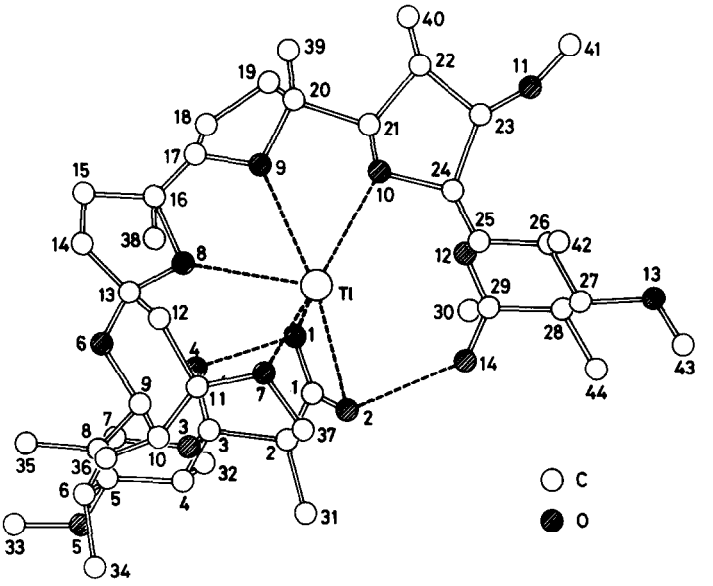

Fig. 2 The molecular structure of lonomycin viewed along the c-axis

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