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Studies on the Ionophorous Antibiotics.
I. The Crystal and Molecular Structure of Salinomycin *p*-Iodophenacyl Ester

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The crystal structure and absolute configuration of the *p*-iodophenacyl ester of salinomycin, $C_{50}H_{75}O_{12}I$, an antibiotic produced by *Streptomyces albus*, has been determined by three-dimensional X-ray analysis. The crystals are orthorhombic, space group $P2_12_12_1$ with four molecules in the unit cell of dimensions $a=20{\cdot}981$ (2), $b=22{\cdot}761$ (2), $c=10{\cdot}493$ (1) Å. The structure was solved by the heavy-atom method and refined by the block-diagonal least-squares method with anisotropic thermal factors for the non-hydrogen atoms. The final R is 0·066 for 3288 observed reflexions collected by diffractometry. The absolute configuration was determined by the use of the anomalous dispersion effect of the iodine atom for Cu $K\alpha$ radiation. This work reveals that salinomycin is a new member of the polyether antibiotics containing a unique tricyclic spiroketal ring system and an unsaturated six-membered ring in the molecule.

Introduction

Salinomycin, $C_{42}H_{70}O_{11}$, is a new antibiotic isolated from the cultured broth of *Streptomyces albus* and has an antimicrobial activity against gram-positive bacteria, mycobacteria and fungi. Furthermore salinomycin is effective in controlling coccidiosis in chickens (Miyazaki, Shibuya, Sugawara, Kawaguchi, Hirose, Nagatsu & Esumi, 1974). In the light of its biological activity coupled with physicochemical properties, the antibiotic is assumed to belong to a new member of the polyether antibiotics including monensin (Agtarap, Chamberlin, Pinkerton & Steinrauf, 1967), nigericin (Steinrauf, Pinkerton & Chamberlin, 1968; Kubota, Matsutani, Shiro & Koyama, 1968) and lysocellin (Ōtake, Koenuma, Kinashi, Sato & Saito, 1975). The polyether antibiotics are the ionophores which form the alkaline ion complexes and effect the transport of the alkaline ions across the cell membranes (Pressman, 1968).

Unlike other polyether antibiotics, metal salts of salinomycin could not form crystals suitable for X-ray analysis. Therefore the *p*-iodophenacyl ester of salinomycin was subjected to X-ray analysis in order to establish the entire molecular structure and the absolute configuration of the antibiotic. A preliminary report of this work has been published (Kinashi, Ōtake, Yonehara, Sato & Saito, 1973).

Experimental

The *p*-iodophenacyl ester of salinomycin was prepared by the reaction of salinomycin with *p*-iodo-α-diazoacetophenone in dioxane in the presence of cupric chloride as a catalyst (Erickson, Dechary & Kesling, 1951), and purified by thin-layer chromatography on silica gel using a mixture of chloroform and methanol (40:1). The crystals were grown by allowing the ethanol solution to evaporate in the dark. The crystals are colourless prisms elongated along the *c* axis. The unit-cell dimensions and space group were determined from Weissenberg photographs. The former were refined on a diffractometer.

Crystal data

Salinomycin *p*-iodophenacyl ester, $C_{50}H_{75}O_{12}I$, M.W. 995·1, m.p. 191·5–192·5°C. Orthorhombic, $a=20{\cdot}981(2)$, $b=22{\cdot}761(2)$, $c=10{\cdot}493(1)$ Å, $U=5010{\cdot}7$ Å^3, $D_m=1{\cdot}32$ g cm^{-3}, by flotation in an aqueous solution of sodium potassium tartrate, $Z=4$, $D_x=1{\cdot}32$ g cm^{-3}, $F(000)=2096$, linear absorption coefficient for Mo $K\alpha$ ($\lambda=0{\cdot}7107$ Å), $\mu=7{\cdot}27$ cm^{-1}, space group, $P2_12_12_1$, from absent reflexions.

A crystal approximately 0·35 × 0·35 × 0·40 mm was used to collect data on the Rigaku automated four-circle diffractometer. Integrated intensities were measured for $2\theta \le 50°$ by the θ–2θ scan technique with Mo $K\alpha$ radiation at a scan speed of 2θ 4° min^{-1}. Backgrounds were counted at the beginning and the end of each scan for 10 s. In this way 4936 reflexions were recorded, of which 3288 gave intensities greater than three times their standard deviations. Three reflexions were measured as references every fifty reflexions: the net count of these reflexions reduced by about 4% over the period of data collection. All the data were corrected for this effect. They were also corrected for Lorentz and polarization factors, but not for absorption.

Structure determination and refinement

The structure was solved by the heavy-atom method. The position of the iodine atom was easily deduced from a three-dimensional Patterson map. A set of structure factors was calculated for 1708 reflexions up to $2\theta = 35°$, and the electron-density map was computed with the phases based on the iodine atom alone. The initial R value was 0·43 and the positions of 16 lighter atoms were located from this map.

Subsequent calculation of structure factors and electron-density maps yielded 43 atomic positions and

Table 1. *Final atomic parameters* ($\times 10^4$)

The thermal factors are of the form $T = \exp\,[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
I	1947·6 (0·6)	2127·1 (0·4)	676·2 (1·1)	44·3 (0·3)	21·2 (0·2)	147·7 (1·1)	−2·6 (0·3)	13·8 (0·7)	−0·4 (0·5)
C(1)	1929 (7)	3047 (5)	374 (12)	29 (4)	18 (3)	111 (15)	−1 (3)	4 (7)	−8 (5)
C(2)	1529 (8)	3366 (6)	1146 (17)	48 (6)	21 (3)	192 (25)	−1 (4)	51 (10)	−4 (8)
C(3)	1544 (8)	4004 (6)	1022 (17)	51 (6)	19 (3)	186 (26)	0 (4)	45 (10)	−12 (7)
C(4)	1937 (7)	4246 (5)	77 (12)	27 (4)	19 (3)	92 (13)	−0 (3)	8 (7)	3 (5)
C(5)	2281 (6)	3901 (6)	−749 (14)	32 (4)	24 (3)	87 (14)	−2 (3)	15 (7)	−18 (7)
C(6)	2300 (7)	3296 (5)	−537 (15)	33 (4)	19 (3)	127 (18)	−6 (3)	23 (8)	−12 (7)
C(7)	1960 (7)	4899 (6)	−94 (13)	24 (4)	23 (3)	125 (16)	1 (3)	14 (8)	−8 (6)
C(8)	1866 (9)	5251 (5)	1199 (13)	50 (6)	18 (3)	98 (15)	3 (4)	12 (9)	−7 (5)
O(9)	1867 (4)	5881 (3)	964 (8)	28 (3)	17 (2)	118 (11)	4 (2)	4 (5)	−7 (4)
C(10)	1293 (6)	6110 (6)	615 (13)	22 (3)	28 (3)	80 (13)	−0 (3)	11 (7)	−12 (6)
C(11)	1299 (6)	6768 (5)	572 (13)	28 (4)	18 (2)	74 (13)	1 (3)	−7 (7)	7 (5)
C(12)	1601 (5)	7027 (5)	1793 (11)	19 (3)	15 (3)	70 (11)	−4 (2)	−4 (5)	8 (5)
O(13)	1375 (3)	6724 (3)	2920 (7)	17 (2)	13 (2)	82 (9)	−2 (1)	−2 (4)	8 (3)
C(14)	721 (6)	6819 (5)	3291 (11)	24 (3)	11 (2)	74 (12)	1 (2)	5 (6)	−1 (4)
C(15)	595 (7)	7485 (5)	3537 (14)	32 (4)	14 (3)	120 (17)	3 (3)	14 (7)	6 (6)
C(16)	785 (7)	7833 (6)	2296 (12)	41 (5)	15 (3)	95 (14)	5 (3)	4 (7)	−1 (6)
C(17)	1487 (7)	7700 (5)	1935 (14)	35 (4)	13 (3)	120 (17)	−3 (3)	13 (7)	9 (5)
C(18)	622 (6)	6443 (5)	4472 (12)	24 (3)	15 (2)	74 (13)	−1 (2)	7 (6)	4 (5)
C(19)	702 (6)	5786 (5)	4041 (11)	25 (3)	15 (2)	67 (13)	−4 (2)	4 (6)	2 (5)
C(20)	689 (6)	5335 (5)	5152 (11)	27 (4)	11 (2)	69 (12)	−3 (2)	−8 (6)	4 (4)
C(21)	853 (6)	4742 (5)	4618 (12)	20 (3)	19 (3)	96 (15)	−1 (2)	6 (6)	8 (5)
C(22)	747 (6)	4180 (5)	5450 (13)	24 (3)	15 (2)	104 (15)	0 (2)	10 (6)	11 (5)
C(23)	57 (5)	4191 (5)	5977 (11)	15 (3)	19 (3)	61 (12)	−1 (2)	−3 (5)	9 (5)
O(24)	−354 (4)	4243 (3)	4892 (7)	20 (2)	16 (2)	63 (8)	0 (2)	5 (3)	1 (3)
C(25)	−1019 (6)	4317 (5)	5226 (11)	21 (3)	15 (2)	60 (12)	0 (2)	4 (5)	1 (4)
C(26)	−1228 (6)	3774 (6)	6024 (12)	21 (3)	24 (3)	86 (15)	−7 (3)	12 (6)	9 (6)
C(27)	−803 (6)	3699 (6)	7209 (12)	27 (4)	27 (3)	61 (12)	1 (3)	4 (6)	13 (6)
C(28)	−99 (6)	3633 (6)	6751 (13)	21 (3)	24 (3)	85 (14)	1 (3)	7 (6)	20 (6)
O(29)	−1349 (4)	4247 (3)	4049 (7)	22 (2)	16 (2)	54 (8)	−3 (2)	−1 (3)	0 (3)
C(30)	−1484 (6)	4764 (5)	3295 (12)	19 (3)	16 (3)	81 (13)	1 (2)	−2 (6)	−1 (5)
C(31)	−1843 (6)	5228 (5)	4100 (12)	27 (4)	24 (3)	83 (14)	11 (3)	6 (7)	−10 (5)
C(32)	−1480 (6)	5322 (5)	5383 (11)	22 (3)	20 (3)	64 (13)	0 (2)	13 (5)	−5 (5)
C(33)	−1109 (6)	4905 (5)	5866 (12)	22 (3)	17 (2)	72 (13)	3 (2)	12 (6)	4 (5)
O(34)	−926 (3)	5007 (3)	2800 (7)	18 (2)	13 (1)	52 (7)	−2 (1)	−1 (3)	−1 (3)
C(35)	−813 (6)	4820 (5)	1504 (11)	24 (3)	15 (2)	54 (11)	−1 (2)	6 (5)	−1 (4)
C(36)	−1421 (6)	4464 (6)	1103 (12)	28 (4)	21 (3)	79 (14)	−8 (3)	7 (6)	−9 (5)
C(37)	−1900 (7)	4556 (6)	2162 (12)	22 (3)	31 (3)	69 (12)	−6 (3)	−6 (7)	−5 (6)
C(38)	−705 (5)	5396 (5)	765 (11)	16 (3)	21 (2)	51 (11)	2 (2)	1 (5)	3 (5)
O(39)	−1305 (3)	5729 (3)	862 (7)	18 (2)	17 (2)	61 (8)	−1 (1)	2 (4)	6 (3)
C(40)	−1271 (6)	6318 (5)	330 (11)	21 (3)	18 (3)	78 (14)	2 (3)	−2 (6)	6 (5)
C(41)	−1139 (6)	6262 (6)	−1128 (11)	24 (4)	22 (3)	66 (13)	−3 (3)	−9 (6)	3 (5)
C(42)	−521 (7)	5908 (6)	−1364 (12)	33 (4)	22 (3)	55 (12)	1 (3)	10 (6)	10 (5)
C(43)	−546 (6)	5297 (5)	−676 (13)	36 (4)	19 (3)	54 (11)	1 (3)	15 (7)	3 (6)
O(44)	2067 (5)	5136 (4)	−1089 (9)	52 (4)	22 (2)	105 (11)	−2 (2)	28 (6)	4 (4)
O(45)	842 (4)	5811 (4)	357 (11)	28 (3)	26 (2)	170 (15)	−4 (2)	−5 (5)	−6 (5)
C(46)	1699 (7)	6989 (6)	−623 (14)	44 (5)	28 (4)	86 (14)	1 (3)	18 (8)	10 (7)
C(47)	1375 (14)	6870 (10)	−1833 (17)	138 (14)	52 (7)	79 (19)	−40 (9)	−12 (15)	1 (10)
C(48)	991 (8)	7716 (5)	4705 (13)	62 (7)	14 (3)	96 (17)	−1 (3)	4 (8)	−16 (5)
C(49)	−51 (8)	6536 (7)	5071 (16)	36 (5)	27 (4)	155 (21)	7 (4)	42 (9)	16 (7)
O(50)	201 (5)	5654 (4)	3152 (10)	45 (4)	24 (2)	119 (12)	−16 (2)	−43 (6)	15 (4)
C(51)	1166 (10)	5490 (7)	6210 (16)	66 (7)	27 (4)	125 (20)	−12 (5)	−46 (11)	15 (7)
O(52)	1085 (6)	4680 (5)	3582 (11)	70 (5)	27 (3)	138 (14)	13 (3)	53 (7)	20 (5)
C(53)	910 (6)	3607 (6)	4645 (19)	20 (4)	17 (3)	269 (30)	6 (3)	34 (9)	5 (8)
C(54)	1657 (7)	3545 (7)	4592 (21)	27 (4)	36 (4)	257 (32)	12 (4)	26 (11)	10 (11)
C(55)	−1950 (7)	3836 (7)	6439 (16)	20 (4)	38 (4)	178 (21)	−7 (4)	22 (9)	26 (8)
C(56)	353 (7)	3583 (7)	7944 (15)	28 (4)	40 (5)	126 (19)	−3 (4)	−16 (9)	44 (8)
O(57)	−1856 (5)	5779 (4)	3423 (9)	41 (3)	22 (2)	107 (10)	15 (2)	−6 (5)	1 (4)
C(58)	−185 (6)	4446 (6)	1456 (13)	22 (4)	20 (3)	98 (15)	6 (3)	14 (6)	9 (6)
C(59)	−776 (7)	6700 (5)	1029 (13)	35 (4)	18 (3)	106 (17)	−7 (3)	−18 (7)	5 (5)
O(60)	−1687 (4)	5933 (4)	−1628 (9)	31 (3)	35 (3)	101 (11)	−6 (2)	−24 (5)	−3 (5)
C(61)	−1091 (7)	6840 (6)	−1839 (14)	35 (5)	20 (3)	113 (17)	4 (3)	−5 (8)	25 (6)
C(62)	−1696 (8)	7225 (7)	−1677 (16)	44 (6)	27 (4)	141 (19)	4 (4)	−9 (9)	10 (8)

R became 0·36. However the benzene ring attached directly to the iodine atom could not be recognized easily. Block-diagonal least-squares refinements with isotropic thermal factors followed by Fourier syntheses were repeated. *R* became 0·28 but did not decrease further. Then with all the 3288 observed reflexions, the least-squares refinements were repeated. The benzene ring and the ether rings could be assigned and all the positions of the non-hydrogen atoms were fixed except for the terminal methyl groups of the ethyl side chains. *R* was reduced to 0·13. The coordinates were finally refined by the block-diagonal least-squares method with anisotropic thermal factors. All the non-hydrogen atoms were then fixed and distinguished, including the terminal methyl groups, C(47) and C(62). *R* was 0·066 for the 3288 observed reflexions. At the final stage of refinement all the shifts of atomic coordinates were less than one ninth of their standard deviations. Unit weight was given to all the reflexions. The atomic scattering factors and the corrections for the anomalous dispersion of the iodine atom ($\Delta f' = -0{\cdot}5$, $\Delta f'' = 2{\cdot}4$) for Mo *Kα* radiation were taken from *International Tables for X-ray Crystallography* (1962).

The final atomic parameters are given in Table 1 together with their estimated standard deviations.*

Table 2. *Comparison of the calculated and observed intensity differences used for the establishment of absolute configuration*

h	k	l	$\lvert F_c(hkl)\rvert$	Obs.	$\lvert F_c(\bar{h}\bar{k}\bar{l})\rvert$
1	2	1	30·0	<	43·5
1	5	1	35·5	>	18·3
1	8	1	103·0	<	127·1
1	12	1	35·4	>	22·7
1	15	1	48·2	>	41·2
2	2	1	68·2	<	84·9
2	3	1	140·5	>	110·9
2	13	1	79·5	>	62·3
3	3	1	44·8	<	72·9
3	4	1	28·9	>	13·3
3	8	1	38·2	<	50·1
3	9	1	107·0	>	93·3
4	2	1	107·8	>	72·2
4	3	1	62·7	<	76·8

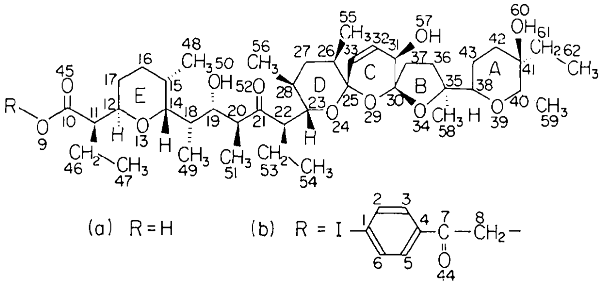

Fig. 1. The chemical structures and the absolute configurations of (*a*) salinomycin and (*b*) salinomycin *p*-iodophenacyl ester.

Determination of the absolute configuration

The absolute configuration was determined by the use of the anomalous dispersion effect of the iodine atom ($\Delta f' = -1{\cdot}1$, $\Delta f'' = 7{\cdot}2$) for Cu *Kα* radiation (*International Tables for X-ray Crystallography*, 1962). The structure factors for the Friedel pairs of reflexions were evaluated by assuming that the coordinates of the atoms were derived from a right-handed set of axes. Some calculated and observed relations are listed in Table 2. From the agreement in Table 2, it can be concluded that the set of atomic coordinates given in Table 1 correctly represents the absolute configuration of the molecule referred to the right-handed set of axes. All the figures shown in this paper are drawn with the correct absolute configuration.

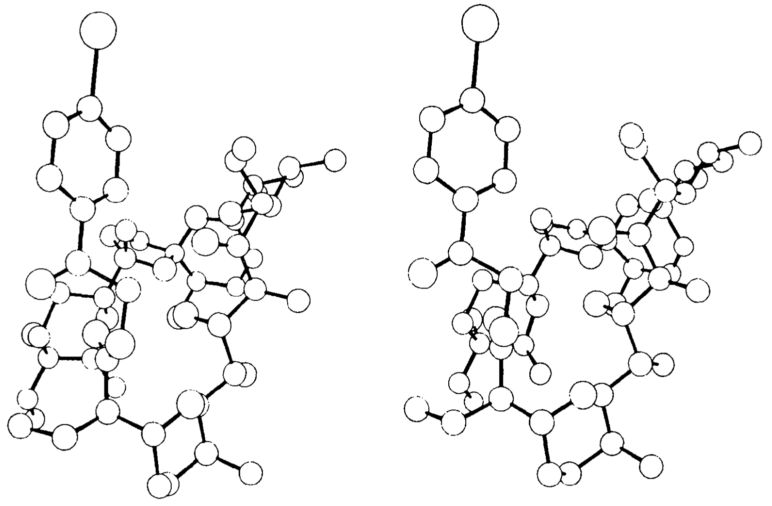

Fig. 2. A stereoscopic picture of the molecule of salinomycin *p*-iodophenacyl ester viewed along the *a* axis.

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31028 (21 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Description of the structure and discussion

The molecular structure

The chemical structure and the absolute configuration of salinomycin *p*-iodophenacyl ester is shown in Fig. 1(*b*). The structure proposed for salinomycin is therefore that shown in Fig. 1(*a*). It is now well established that salinomycin is a new member of the polyether antibiotics containing four six-membered rings (*A*, *C*, *D* and *E*) and one five-membered ring *B*. Rings *B*, *C* and *D* form a unique tricyclic spiroketal ring system. Salinomycin is also the first example of polyether antibiotics containing an unsaturated *C* ring in the molecule. The moieties of ring *A* and the *β*-ketol are identical with those of X-537A, a member of the polyether antibiotics, with respect to the substituents as well as their absolute configurations (Westley, Evans, Williams & Stempel, 1970).

A stereoscopic view of the molecule of salinomycin *p*-iodophenacyl ester along the *a* axis is shown in Fig. 2. It correctly represents the absolute configuration. The bond lengths and angles in the molecule calculated from the coordinates given in Table 1 are shown in Figs. 3 and 4 respectively. They do not differ significantly from normal values. The mean estimated standard deviations in all the bond lengths and angles in the molecule are 0·02 Å and 1·1 ° respectively. The arrangements of atoms around C(25) and C(30) are tetrahedral, so that the junctions between rings *C* and *D* and between *B* and *C* are of the spiro type. The C(32)–C(33) bond of length 1·33 Å indicates a double bond between these atoms.

Unlike other polyether antibiotics, the terminal hydroxyl O(60)H and the ester carbonyl group are too distant to form a hydrogen bond. Ring *A* is oriented down the ester carbonyl group; thus the whole molecule takes a helical conformation rather than the circular structure adopted by other polyether antibiotics. This may be attributed to the difference in property between the ester used for the present analysis and metal salts in other cases. From the interatomic distances and angles the other two hydroxyl groups O(50)H and O(57)H seem to be involved in intramolecular hydrogen bonding. O(50)· · ·O(34) and O(57)· · ·O(39) are 2·81 and 2·93 Å, respectively. The C(19)O(50)O(34) and C(31)O(57)O(39) angles are 144·1 and 114·3 ° respectively. O(50) and O(52) in the *β*-ketol may not form a hydrogen bond because the angle C(19)O(50)O(52) is 66·0 °. These two hydrogen bonds seem to reinforce the helical conformation of the molecule. Most of the oxygen atoms are hidden in the interior of the molecule and the exterior surface of the molecule is hydrophilic. In view of this salinomycin is likely to form metal complexes containing a metal ion in the centre of the molecule, like other polyether antibiotics.

The planarity and the conformation of each ring are evident from Table 3. The five-membered ring *B* takes an envelope conformation with C(37) 0·34 Å out of

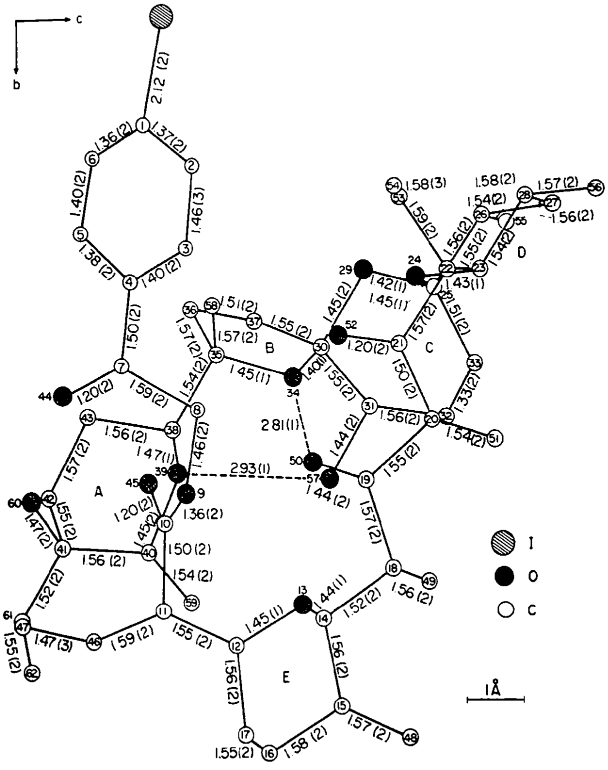

Fig. 3. Bond lengths and their standard deviations (Å). Hydrogen bonds are shown by broken lines.

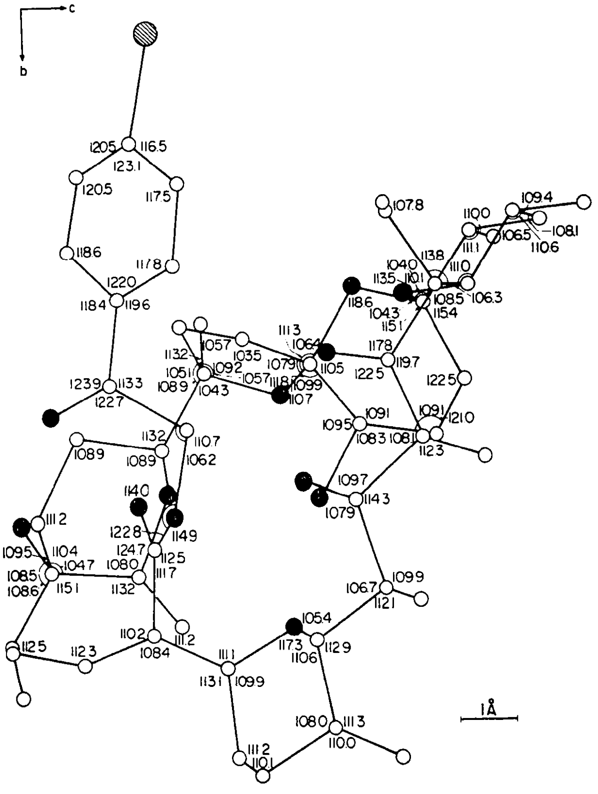

Fig. 4. Bond angles (°).

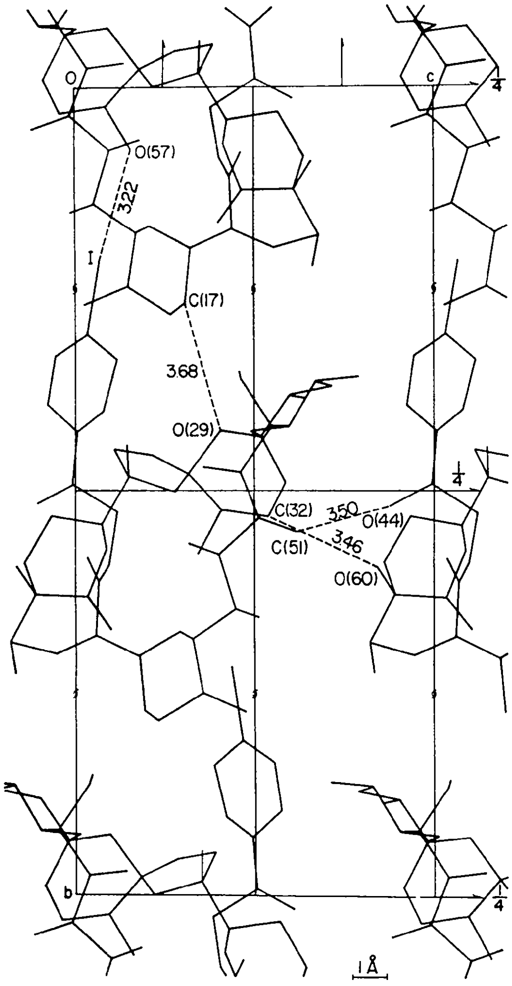

Fig. 5. The crystal structure of salinomycin *p*-iodophenacyl ester. Half the unit cell is shown along the *a* axis. Some of the short contacts between molecules are shown by broken lines (Å).

the least-squares plane through the other four atoms of the ring. The other three six-membered rings *A*, *D* and *F* adopt chair conformations, while ring *C* takes the half-chair conformation owing to the double bond in the ring. For ring *A*, C(35) and C(61) are equatorial, whereas C(59) and O(60) are axial. For ring *C*, C(26), C(37) and O(57) are pseudo-equatorial, while O(24) and O(34) are pseudo-axial. For ring *D* all the substituents are equatorial except C(33) which is axial. For ring *E*, C(18) is equatorial and C(11) and C(48) are axial.

The crystal structure

A projection of the crystal structure viewed along the *a* axis is presented in Fig. 5. Intermolecular short contacts less than 3·8 Å are listed in Table 4. The molecules are packed together by van der Waals forces. There are no unusual short contacts between the molecules.

Calculations were carried out on FACOM 270-30 of this Institute and on HITAC 8700/8800 at the Computer Centre of this University.

Table 3. *Least-squares planes and the deviations of the atoms from the planes*

Ring *A*		Ring *B*		Ring *C*	
C(38)	−0·021 Å	C(30)	0·022	C(31)	0·001
O(39)	0·022	O(34)	−0·037	C(32)	−0·003
C(41)	−0·022	C(35)	0·033	C(33)	0·003
C(42)	0·021	C(36)	−0·018	C(25)	−0·001
C(40)	−0·708*	C(37)	−0·345*	O(29)	0·022*
C(43)	0·698*			C(30)	0·631*
Ring *D*		Ring *E*		Benzene ring	
C(23)	−0·016	O(13)	0·002	C(1)	−0·015
C(25)	0·015	C(14)	−0·002	C(2)	0·037
C(26)	−0·015	C(16)	0·002	C(3)	−0·012
C(28)	0·015	C(17)	−0·002	C(4)	−0·032
O(24)	0·654*	C(12)	0·632*	C(5)	0·047
C(27)	−0·732*	C(15)	−0·718*	C(6)	−0·024
				I	−0·092*
				C(7)	−0·065*

* Not included in the calculation of the plane.

Table 4. *Intermolecular contacts less than* 3·8 Å

C(32)–O(60^{i})	3·46	C(5)—O(13^{iii})	3·45
C(33)–O(60^{i})	3·72	C(6)—C(12^{iii})	3·70
C(51)–O(44^{i})	3·50	C(6)—O(13^{iii})	3·22
C(51)–C(47^{i})	3·78	O(9)—C(54^{iii})	3·66
I———O(57^{ii})	3·22	O(44)–C(8^{iii})	3·73
O(29)–C(16^{ii})	3·71	C(46)–C(54^{iii})	3·66
O(29)–C(17^{ii})	3·68	C(37)–O(60^{iv})	3·41
C(54)–C(62^{ii})	3·72	C(55)–O(57^{iv})	3·37

Symmetry code

(i)	x	y	$1+z$
(ii)	$-x$	$-\frac{1}{2}+y$	$\frac{1}{2}-z$
(iii)	$\frac{1}{2}-x$	$1-y$	$-\frac{1}{2}+z$
(iv)	$-\frac{1}{2}-x$	$1-y$	$\frac{1}{2}+z$

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