Tetrahedron Letters No. 49, pp 4955 - 4958, 1973. Pergamon Press. Printed in Great Britain.

THE STRUCTURE OF SALINOMYCIN, A NEW MEMBER OF THE POLYETHER ANTIBIOTICS

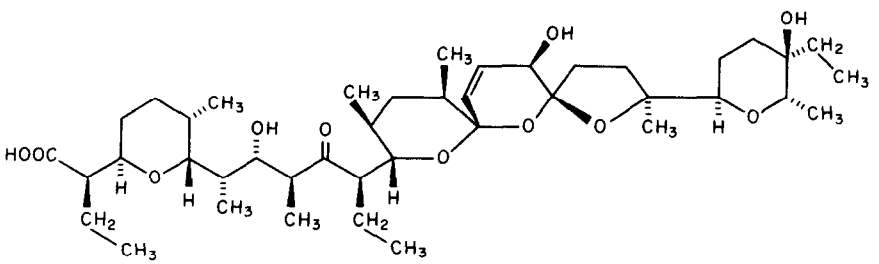
Haruyasu Kinashi, Noboru Ōtake and Hiroshi Yonehara
Institute of Applied Microbiology, The University of Tokyo
Shoichi Sato and Yoshihiko Saito
Institute for Solid State Physics, The University of Tokyo
Tokyo, Japan

(Received in Japan 3 October 1973; received in UK for publication 29 October 1973)

Salinomycin[1] is a new antibiotic elaborated by the strain of *Streptomyces albus* and has an antimicrobial activity against Gram-positive bacteria, mycobacteria and fungi. Furthermore, salinomycin is effective in the treatment of coccidial infections in poultry.

In light of its biological activity coupled with the physicochemical properties and spectral data, the antibiotic is assumed to belong to a new member of the polyether antibiotics.

In this communication, we wish to report the structural elucidation of salinomycin p-iodophenacyl ester by X-ray analysis as depicted formula (I).



(I)

Salinomycin is a monocarboxylic acid of m.p. 112.5-113.5°C, pKa' 6.4 (DMF), $[\alpha]_D^{25}$-63° (c 1, ethanol), λmax 284 nm (ε126 in ethanol-water, 2:1), $\nu_{max}^{CHCl_3}$ 3520, 1718, 1710 cm^{-1}.

The molecular formula $C_{42}H_{70}O_{11}$ for salinomycin was established on the basis of elemental analysis and its mass spectrum (M^+, m/e 750 and two dehydration peaks at m/e 732 and m/e 714).

The nmr spectrum ($CDCl_3$) showed the presence of a number of C-methyl groups as unresolved peaks in the range of δ 0.7-1.5, two unsplitted vinyl protons at around δ 6.0 and no methoxy group in the molecule. This spectral information gave a distinct evidence to differentiate the antibiotic from the known naturally occuring polyether antibiotics hitherto recorded such as monensin[2], nigericin[3], X-537A[4], grisorixin[5], X-206[6], dianemycin[7] and A204A[8].

The methyl ester of salinomycin, $C_{43}H_{72}O_{11}$, obtained by the treatment with diazomethane crystallized as well-defined needles of m.p. 99-101°C, $[\alpha]_D^{25}$ -74° (c 1 in ethanol). The mass spectrum showed the molecular ion peak at m/e 764, and two dehydration peaks at m/e 746 and 728.

Unlike the known polyether antibiotics, salinomycin gave no crystallizable metal salts suitable for X-ray analysis. Accordingly an effort was directed to prepare the carboxylic acid ester derivatives bearing a heavy atom.

Fortunately, it gave the crystalline p-iodophenacyl ester by the reaction of salinomycin with p-iodo-α-diazoacetophenone in dioxane in the presence of cupric chloride as a catalyst .

The p-iodophenacyl ester of salinomycin, recrystallized from ethanol gave colorless needles 191.5-192.5°C $[\alpha]_D^{25}$ -51° (c 1, ethanol). In its mass spectrum, the molecular ion peak could be observed at m/e 994 which was consistent to the molecular formula $C_{50}H_{75}O_{12}I$.

Salinomycin p-iodophenacyl ester crystallizes in the orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell of dimensions: a=20.981(2), b=22.761(2) and c=10.492(1) Å. The intensity data were collected with Mo Kα radiation on an automated four-circle diffractometer(λ=0.7107 Å). The structure was solved by the heavy-atom method and the positional and thermal parameters were refined by the method of least-squares, using anisotropic temperature factors for the non-hydrogen atoms. The final R value for 3288 reflexions used in the refinement process was 0.066.

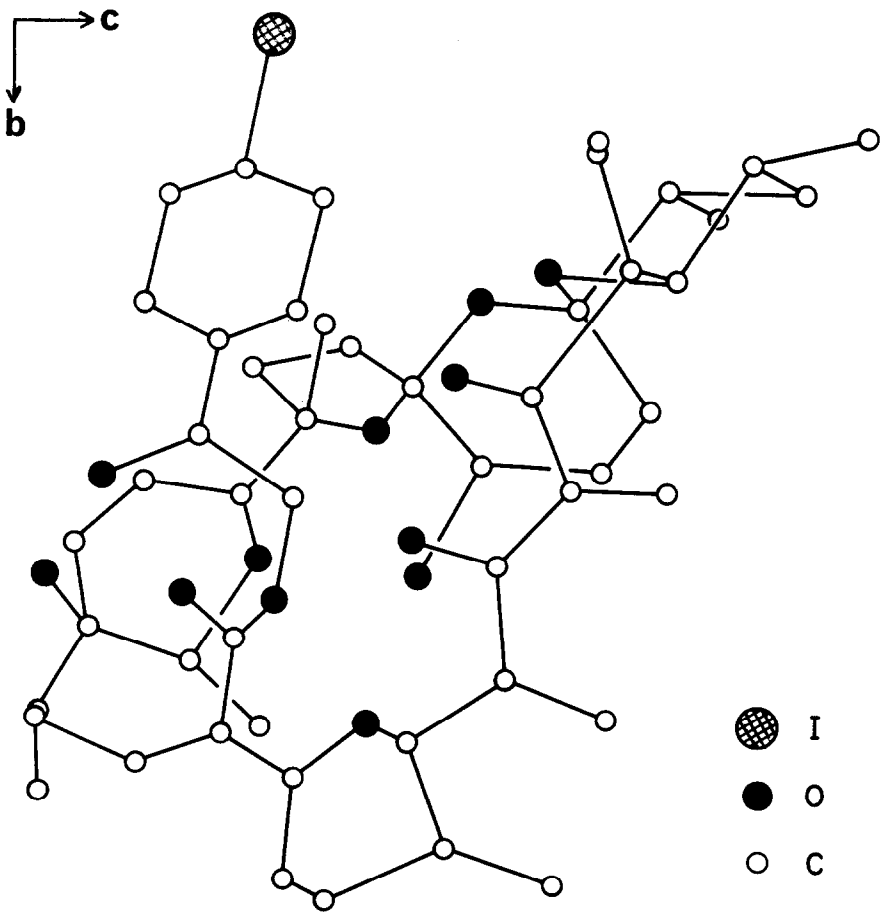
The absolute configuration was determined by use of the anomalous scattering effect of the iodine atom for Cu Kα radiation(λ=1.5418 Å). An equi-inclination photograph was taken of the first layer-line around the c axis. The difference in intensity between the reflexions and the counter reflexions was clearly observable, as shown in Table 1.

The resulting molecular structure of salinomycin p-iodophenacyl ester viewed along the a axis is illustrated in Fig. 1. It correctly represents the absolute configuration.

Table 1. Determination of the Absolute Configuration

hkl	Fc(hkl)	Obs.	Fc($\bar{h}$kl)
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



It is noteworthy that salinomycin has a unique tricyclic spiroketal ring system and an unsaturated six-membered ring in the molecule. Unlike the other polyether antibiotics, the terminal hydroxyl and the ester carbonyl of salinomycin are oriented too far to form a hydrogen bonding. This may be attributable to the difference in property between the ester used in our case and metal salts used in other cases.

Acknowledgement

We are indebted to the Kaken Chemical Co. Ltd. for the supply of salinomycin.

References

1. Y. Miyazaki, M. Shibuya, H. Sugawara, O. Kawaguchi, C. Hirose, J. Nagatsu and S. Esumi, J. Antibiot., in press
2. A. Agtarap, J. W. Chamberlin, M. Pinkerton and L. Steinrauf, J. Amer. Chem. Soc., 89 5737 (1967)
3. L. K. Steinrauf, M. Pinkerton and J. W. Chamberlin, Biochem. Biophys. Res. Comm., 33 29 (1968) T. Kubota, S. Matsutani, M. Shiro and H. Koyama, Chem. Comm., 1541 (1968)
4. J. W. Westley, R. H. Evans, Jr., T. Williams and A. Stempel, Chem. Comm., 71 (1970)
5. P. Gachon, A. Kergomard and H. Veschambre, Chem. Comm., 1421 (1970)
6. J. F. Blount and J. W. Westley, Chem. Comm., 927 (1971)
7. E. W. Czerwinski and L. K. Steinrauf, Biochem. Biophys. Res. Comm., 45 1284 (1971)
8. N. D. Jones, M. O. Chaney, J. W. Chamberlin, R. L. Hamill and Sue Chen, J. Amer. Chem. Soc., 95 3399 (1973)
9. J. L. E. Erickson, J. M. Dechary and M. R. Kesling, J. Amer. Chem. Soc., 73 5301 (1951)