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THE STRUCTURE OF RYRIDOMYCIN

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Pyridomycin is an antibiotic produced by Streptomyces albidofuscus Okami et Umezawa[1] and it inhibits the growth of Mycobacteria and also some species of Gram negative bacteria[2]. Although the chemical studies of this antibiotic were carried out[3,4], the total structure of the molecule has not been elucidated successfully. In the present paper, the authors report the structure including the stereochemistry of pyridomycin determined by X-ray analysis.

Crystals of dihydrobromide of pyridomycin recrystallized from the mixed solution of ethyl acetate, acetone and water are colorless prisms which contain one molecule of ethyl acetate and one molecule of water as the crystal solvent. The analytical data coincide with the formula of $C_{27}H_{32}N_4O_8 \cdot 2HBr \cdot H_2O \cdot CH_3COOC_2H_5$. m.w. 808.7 (813.6 by X-ray method) m.p. 203-205°C (under decomposition).

The crystal belongs to the monoclinic system, space group $P2_1$, with two structure units in the unit cell of dimensions a=19.23Å, b=8.02Å, c=12.20Å, β=103.6° which were determined from the precession photographs of 0kℓ, h0ℓ and hk0 taken with CuK_α radiation (λ =1.5418Å). The density measured by floatation in the mixed solution of chloroform and methylene chloride is 1.477 g.cm^{-3}; the density calculated for two molecules in the unit cell is 1.468 g.cm^{-3}. Three-dimensional intensity data were collected from the equi-inclination Weissenberg photographs. The layers hk0 ~ hkl and h0ℓ ~ h6ℓ were taken by CuK_α radiation using the

multiple film technique. The intensities were estimated visually using a calibrated intensity scale. Totally 2115 independent structure factors of $F_o \neq 0$ were evaluated for the analysis.

Two- and three-dimensional Patterson syntheses were calculated and the positions of two bromine atoms were determined. A three-dimensional Fourier synthesis was then computed using the phases of Fourier coefficients determined by the two bromine atoms (R=36.9 %). The resulting electron density map was very difficult to interpret. There appeared 132 prominent peaks in the asymmetric unit and 93 of them were later found to be spurious. Several trial Fourier and difference Fourier syntheses were then calculated. Comparing these trial electron density maps, a planar dipeptide group could be recognized. A subsequent difference Fourier map synthesized with two bromine and 19 light atoms (R=30.9%) showed 15 well defined peaks. A six-membered ring which could be assigned to one of two pyridine nuclei shown by the chemical study[3] was recognized at this stage of the analysis. Successive calculations of difference Fourier synthesis revealed the whole structure and the reliability factor dropped to 23.9%. The structure was refined by the three-dimensional Fourier and least squares methods. At the present stage of refinement, the R factor is 15.3%.

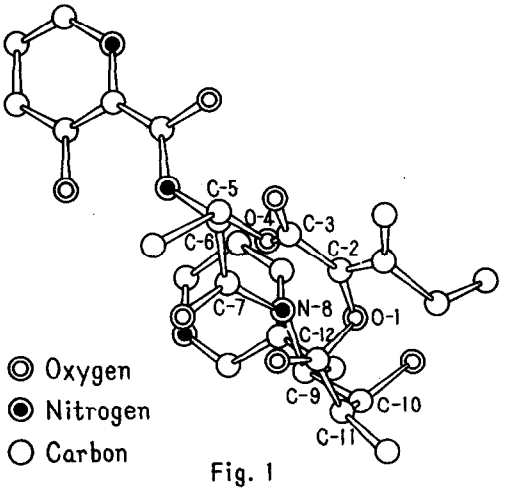
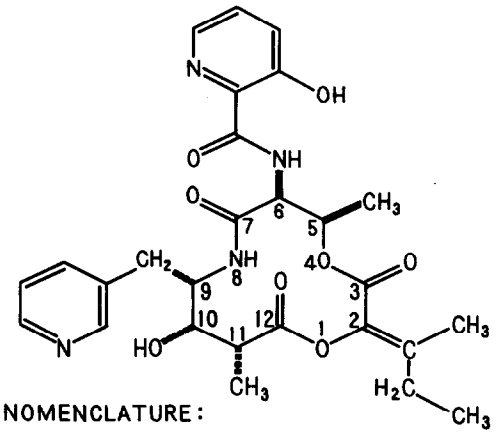


Fig. 1

The molecular structure of pyridomycin is shwon in Fig. 1. It is seen that the molecule consists of a novel hetero-dodecane ring system containing unique exocyclic 1-methyl-propylidene and 3-pyridylmethyl groups. The present study on the crystal structure of pyridomycin provides not only the structural formula, but also the stereochemistry of carbon atoms at C-5, C-6, C-9, C-10 and C-11 in the absolute sense. The absolute configuration was determined by the use of the anomalous dispersion effect due to the bromine atoms and is presented in Fig. 1. This result is compatible with the chemical observation that L_s-(-)-threonine is obtained by degradation of pyridomycin[3].

Thus, the chemical structure of pyridomycin molecule found in the crystal of its dihydrobromide is established as follows;



NOMENCLATURE:
10-hydroxy-6-(3-hydroxypicolinamido)-5,11-dimethyl-2-(1-methylpropylidene)-9-(3-pyridylmethyl)-8-aza-1,4-dioxa-cyclododecane-3,7,12-trione

The bond distances and angles calculated in the molecule are normal. The structure of pyridomycin presented here is in agreement with all physical and chemical data[3].

The calculations in the present study were performed on the HITAC 5020E computor at the University of Tokyo.

Further crystallographical details will be published later.

References

1. Y. Okami, K. Maeda and H. Umezawa, J. Antibiotics, 7A, 55 (1954).

2. K. Maeda, H. Kosaka, Y. Okami and H. Umezawa, J. Antibiotics, 6A, 140 (1953).

3. K. Maeda, J. Antibiotics, 10A, 94 (1957).

4. N. Sugiyama and K. Hori, 5th Symposium on the Chemistry of Natural Products, Symposium Papers, 2-1, Sendai, October (1961).