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CRYSTAL AND MOLECULAR STRUCTURE OF MILDIOMYCIN MONOBENZOATE HEPTAHYDRATE

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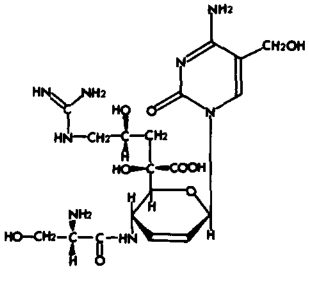
A new antibiotic mildiomycin was isolated from the culture filtrate of Streptoverticillium rimofaciens B-98891.[1a)] The antibiotic shows strong activity against powdery mildew in various plants[2)] and low toxicity in animals and fishes.[1b)] The structure I was assigned based on the physicochemical properties and degradation studies,[3)] except for the configurations at two asymmetric carbons in the guanidinopentanoic acid moiety attached to the dihydropyrane ring. We conducted X-ray analysis of the crystalline derivative of the monobenzoate[3)] to confirm the structure and establish the absolute configuration and molecular conformation.



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Colorless prisms of mildiomycin monobenzoate were obtained as the heptahydrate ($C_{26}H_{34}N_8O_{10}\cdot 7H_2O$). The crystals are orthorhombic $P2_12_12_1$ with cell dimensions of a = 14.21, b = 19.31 and c = 12.95 Å. Reflective intensities were measured on a Hilger and Watts linear diffractometer (CuKα) and with Weissenberg photographs (MoKα), and 3192 independent data were used for the analysis. The structure was elucidated by the direct method with program MULTAN.4) Based on the partial structure obtained from the resulting E-map of MULTAN, the positions of the remaining non-hydrogen atoms in the unit-cell were found by the ordinary procedure. Positional and thermal parameters were refined by the least-squares method to an R value of 0.137. A perspective view of the molecule and the atomic arrangement in the crystal are shown in Figs. 1 and 2, respectively. Since the configuration of the serine moiety had been elucidated to be L-(S),3) the configurations of the other asymmetric carbons, C(6), C(9), C(10), C(21) and C(24) were determined to be (R), (S), (S), (R) and (R), respectively, as shown

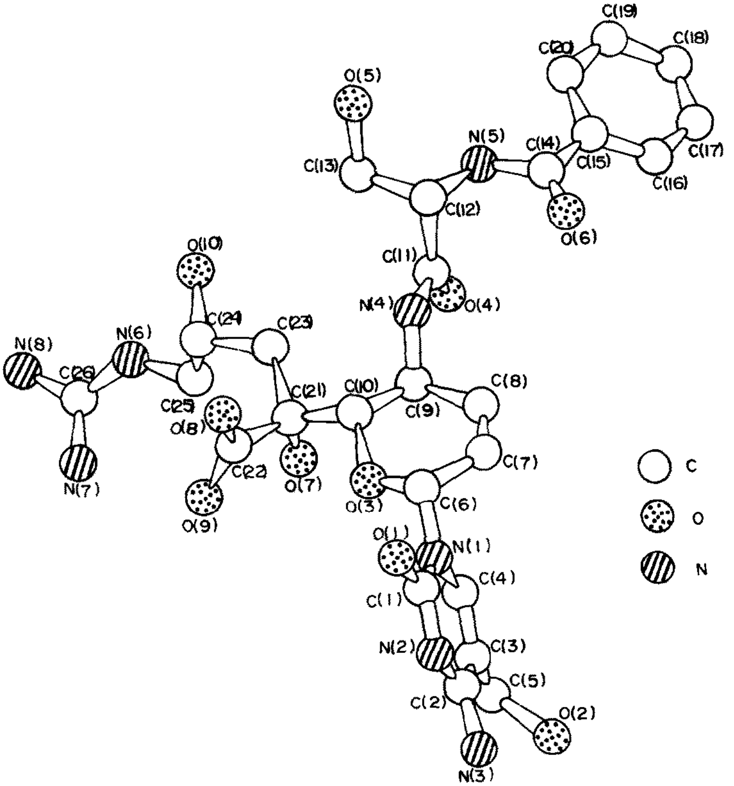

Fig. 1. Perspective view of the mildiomycin monobenzoate molecule

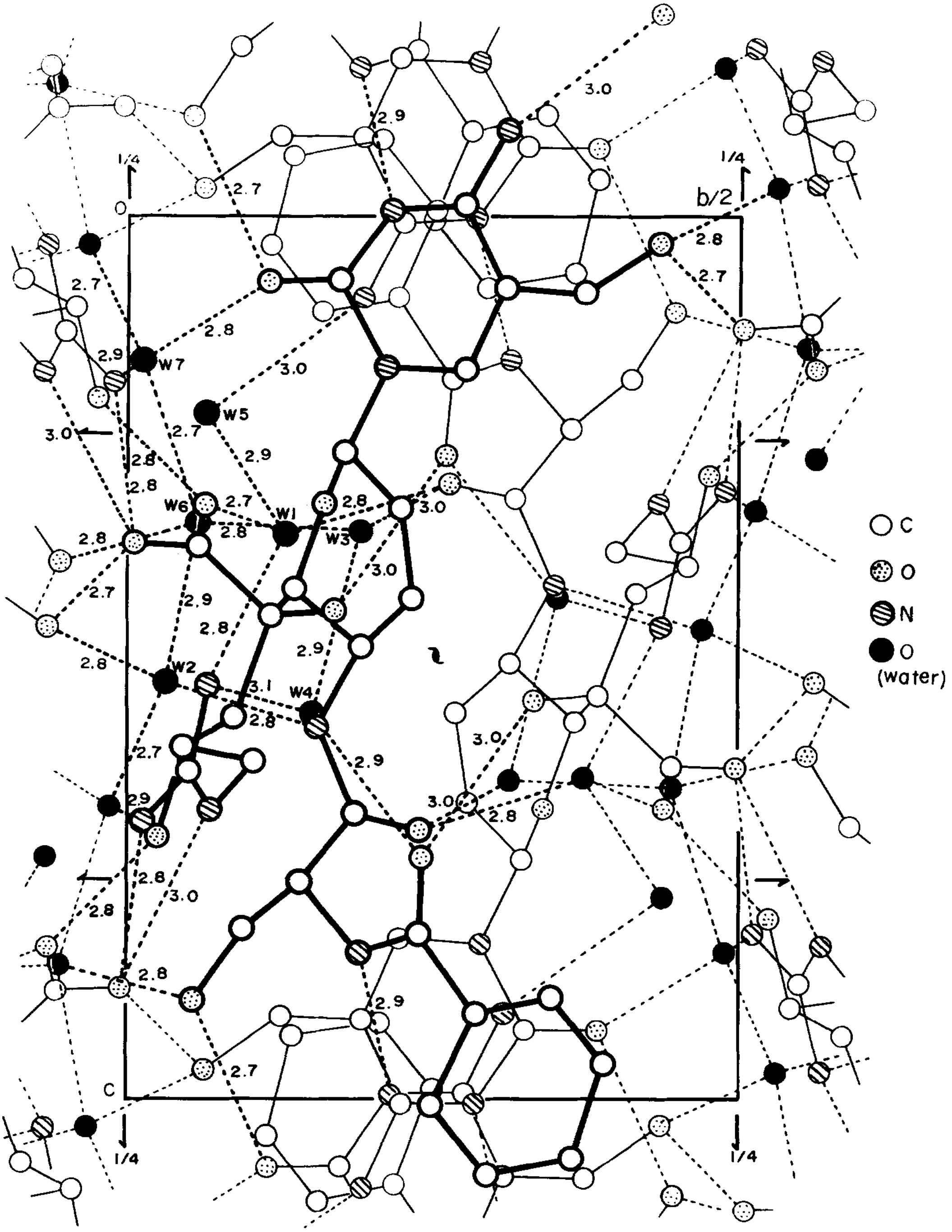

Fig. 2. Atomic arrangement in the crystal

Hydrogen bonds (broken lines) and distances between hydrogen donors and acceptors are also shown.

in Fig. 1. Consequently, the structure of mildiomycin was clarified to be I in an absolute sense. The configurations at C(21) and C(24) of the unique side chain attached to C(10), to which other methods could not be applied because of its unprecedented structure in the chemistry of natural products, were established by the present study.

The six-membered ring of hydroxymethylcytosine is planar and the four atoms attached to this ring are almost coplanar. The tortion angle (φ_{CN}), which was introduced by Donohue and Trueblood as representing the interrelationship between sugar and base moieties,[5)] is -65°. It falls in the anti range of conformation usually found in X-ray analyses of nucleosides and nucleotides. The dihydropyran ring is in the half-chair form, and the best four-atom plane of the C(7)-C(8) double bond makes a 75° angle with the cytosine ring. The least-squares plane of the guanidine group makes almost a right angle (88°) with the cytosine plane. Many hydrogen bonds, which are shown in Fig. 2 by broken lines together with the distances between hydrogen donors and acceptors, are formed in the crystal. Nitrogen and oxygen atoms, other than N(1) and O(3), all participate in the hydrogen bonding. Building infinite three-dimensional networks in the crystal, these hydrogen bonds seem to play a dominant role in the packing.

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