

STRUCTURE OF KIDAMYCIN : X-RAY ANALYSIS
OF ISOKIDAMYCIN DERIVATIVES

Minoru Furukawa

Research Institute, Daiichi Seiyaku Co., Ltd., Edogawaku, Tokyo, Japan

Yoichi Iitaka

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Tokyo, Japan

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In a previous communication we reported the crystal and molecular structure (Ia) of a methanolysis product of acetylkidamycin methiodide⁽¹⁾, from which a few possible structures for kidamycin were deducible. Convincing evidence for the structure of kidamycin has now been provided by crystallographic studies of isokidamycin bis-m-iodobenzoate (IIb) and its apparently isomorphous bromo derivative (IIc), which discloses the structure (IIa) of isokidamycin and clarifies the chemistry of kidamycin.

Although the crystal of IIc contains 142 non-hydrogen atoms in an asymmetric unit, the structure was solved by the successive use of Fourier and difference Fourier syntheses coupled with least-squares calculations. The method of isomorphous replacement was tried in which the phase determination was aided by the use of anomalous dispersion data for the iodo derivative, but it was not successful due to the fact that the crystals of IIb and IIc are not rigorously isomorphous with regard to the heavy atom positions.

Treatment of kidamycin in refluxing CHCl_3 with TsOH gave an isomerized product, isokidamycin from which its bis-m-iodobenzoate $\text{C}_{53}\text{H}_{54}\text{O}_{11}\text{N}_2\text{I}_2$ was prepared and crystallized from benzene-acetone-n-hexane to give large prismatic crystals. The crystal belongs to the orthorhombic system with the lattice constants $a=19.38_9$, $b=41.70_3$, $c=14.02_4$. The space group was determined to be $P2_12_12_1$. The corresponding bis-m-bromobenzoate was prepared similarly and obtained as the crystal of $a=19.27_0$, $b=41.33_9$, $c=13.93_3$. The lattice constants

and three dimensional intensity data were collected from the measurement using a Rigaku Denki computer-controlled four circle diffractometer with Ni-filtered Cu-K α radiation. A total of 1546 independent reflexions of the iodo derivative and 3033 independent reflexions of the bromo derivative, having net intensities above three times of their standard deviations, were obtained by the θ - 2θ scan method with the scan speed of 4° 2 θ /min. The density was calculated as 1.309 g/ml assuming the content of an asymmetric unit to be C₁₀₆H₁₀₈O₂₂N₄Br₄.C₆H₆. The presence of benzene molecules as a solvent of crystallization was confirmed later by the X-ray analysis. An approximate structure of the iodo derivative was at first determined by starting with the phase angles obtained by the iodine atom contributions. The coordinates of the four iodine atoms in an asymmetric unit were determined by comparing the two kinds of Patterson functions, one synthesized with $|F_H|^2$ as coefficient and the other with $(|F_{H+}| - |F_{H-}|)^2$, where $|F_{H+}|$ and $|F_{H-}|$ denote the magnitude of the observed structure factors of $h k \ell$ and $\bar{h} \bar{k} \bar{\ell}$ reflexions, respectively. Repeated cycles of structure factors and Fourier, difference Fourier calculations yielded the most probable locations of 60 atoms.

Although the dispositions of atoms thus obtained could not be interpreted as a reasonable molecular model — they only indicated several fragment of the molecule —, these atomic coordinates were transferred to the bromo derivative. Structure determination was further continued for the bromo derivative using the 3033 observed structure factors.

At the final stage of analysis, the disorder of a *m*-bromobenzoyl group was noticed as shown in Fig 1 ; the ratio of the peak heights Br(A) to Br(B) was 2:1. The site occupancy factors for the A and B sites were fixed to be 0.66 and 0.34, respectively. Finally, the structure was refined by the method of block-diagonal least-squares, in which anisotropic thermal parameters were taken into account for the atoms involved in the four bromobenzene moieties. The final R value was 0.113. The absolute configuration was determined by the anomalous dispersion method. Dispersion corrections for the scattering factor of the bromine atom for Cu-K α were taken as $\Delta f' = -0.9$, $\Delta f'' = 1.5$. Comparison of the observed intensities of 543 Friedel pairs of reflexion of the bromo deri-

vative with the calculated values clearly indicated the absolute configuration as shown in Fig 2. The structure of the molecules involved in an asymmetric unit is shown in Fig 1 excluding the solvent benzene molecule. It is seen that the chromophores of isokidamycin bis-m-bromobenzoate are stacked along the c-axis and the tetrahydropyrane moieties are projected radially from the stacked unit.

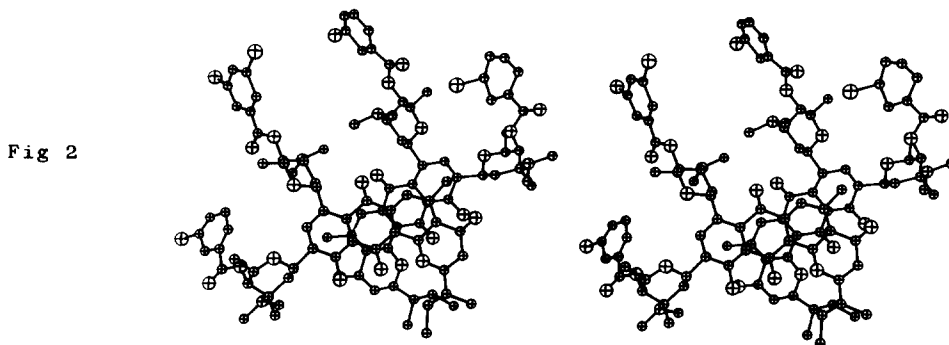
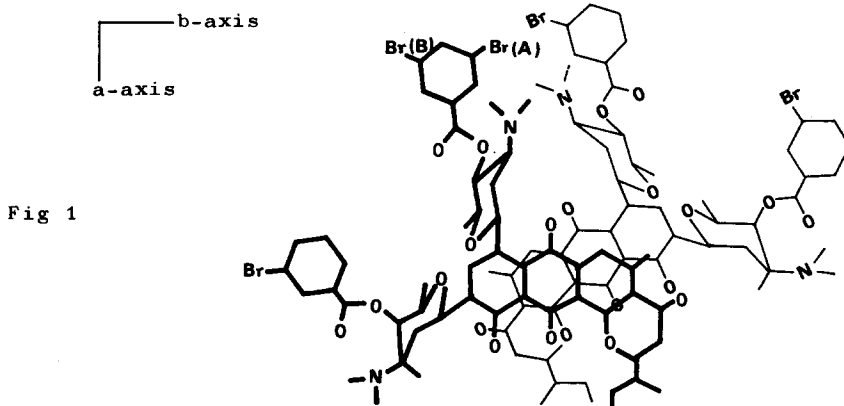


Fig 2 shows a stereoscopic view of the molecules of isokidamycin bis-m-bromobenzoate drawn by the plotter program ORTEP by Johnson⁽²⁾. The atoms are represented by the spheres of varying size with increasing order of atomic numbers.

The constitution of isokidamycin is now represented as IIa, which together with structure Ia of the methanolysis product, makes it possible to assign the structure Ib for kidamycin. These structures are fully consistent with the chemical and spectral evidence. The most striking difference in the struc-

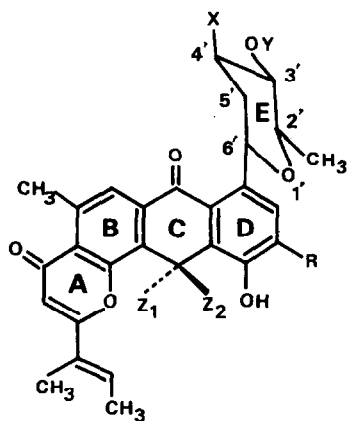
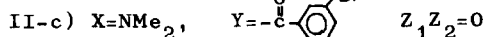
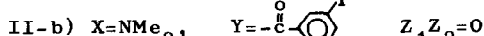
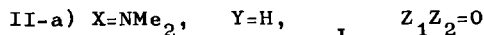
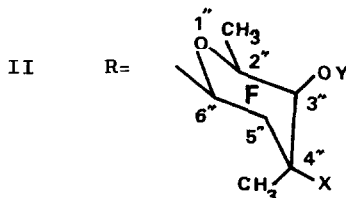
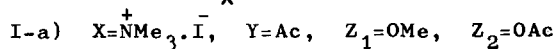
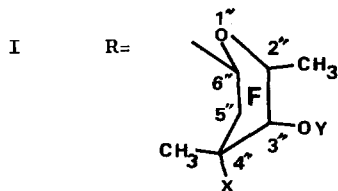


Fig 3



tures of kidamycin and isokidamycin is found in ring F : the configurations of ring F are 2''S, 3''S, 4''S, 6''R, in kidamycin while 2''S, 3''S, 4''S, 6''S, in isokidamycin. The isomerization occurs at C-6'' which can be explained in terms of protonation at the 1'' ethereal oxygen of Ib, followed by ring opening and recyclization accompanying the transformation of ring F from boat to chair. Kidamycin and isokidamycin reveal the same UV spectra indicating that they have the same chromophore. Formation of the methanolysis product (Ia) is explained by the migration of the phenoxy-O-acetyl group, accompanied by methoxylation, to the neighbouring carbonyl group.

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