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X-RAY ANALYSIS OF DIBROMOGRISEUSIN A, REVISED ABSOLUTE CONFIGURATION OF GRISEUSINS

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Abstract: The molecular structure and the absolute configuration of griseusin A were unequivocally determined by X-ray crystal analysis of its dibromo derivative.

Griseusins A and B are antibiotics of the isochromanquinone group isolated from metabolites of a strain of Streptomyces griseus,[1] and their structures, including the absolute configuration inferred from CD spectra, have been elucidated as enantiomeric to structures 1 and 2 (Fig. 1) in the previous paper.[2]

Recently we received a letter from Professor E. Yoshii informing us that his group had synthesized a compound presumably corresponding 8-deoxygriseusin B using a synthone which includes the $C_{3'}$, $C_{5'}$ and $C_{6'}$ carbon atoms of established absolute configurations, and unexpectedly, the CD spectrum of the product showed a Cotton curve opposite to those of griseusins A and B.[3]

Since their 8-deoxy compound has not been correlated chemically to the natural product, the identity of the molecular conformations of both specimens is not clear enough, and we decided to reexamine the absolute molecular structure of griseusins by X-ray analysis.

In order to obtain a crystalline bromo derivative, griseusin A (1) (10 mg) in AcOH (0.5 ml) was treated with Br_2 (55 mg) at 22° for 1 hr. The products were not resolved on TLC but successfully separated by preparative HPLC [Nucleosil-7-C_{18} (4.0φ x 200 mm); solvent, 60% MeOH aq.:AcOH = 99:1] to give 5-bromo- (3) (2.5 mg), 7-bromo- (4) (trace) and 5,7-dibromogriseusin A (5) (10 mg) and their structures were easily deduced by ^{1}H NMR. All the bromides, retained the antibacterial activity, were crystalline and 5,7-dibromide, dec. 239-240°, orange crystal ($CHCl_3$-n-hexane) was found to be suitable for X-ray analysis.

Crystal data: $C_{22}H_{18}O_{10}Br_2 \cdot 1/2CHCl_3$; triclinic; space group P1; a = 10.610(4), b = 13.398(4), c = 10.359(3) Å, α = 101.29(4), β = 118.08(2), γ = 84.99(4)°; Z = 2. Intensity data were collected by the ω-2θ scan technique with a Rigaku diffractometer using graphite-monochromatized Mo Kα radiation and

a crystal of dimensions 0.15 x 0.2 x 0.2 mm. The 3338 independent intensities were measured in the range θ ≦ 22.5° and corrected for Lorentz and polarization factors. The structure was solved by the heavy-atom method and refined by the block-diagonal least-squares method to the R-value of 0.063 (for 2577 reflections) excluding all the hydrogen atoms. The absolute configuration of the molecule was determined by the anomalous dispersion method ($\Delta f' = -0.374$ and $\Delta f'' = 2.456$ for bromine): the configurations at the respective asymmetric carbons are 1R, 3R, 4R, 3'R, 5'R and 6'R as shown in Figs. 1 and 2.*

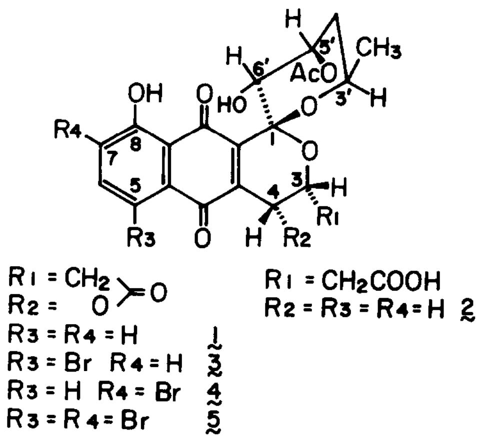

Fig. 1

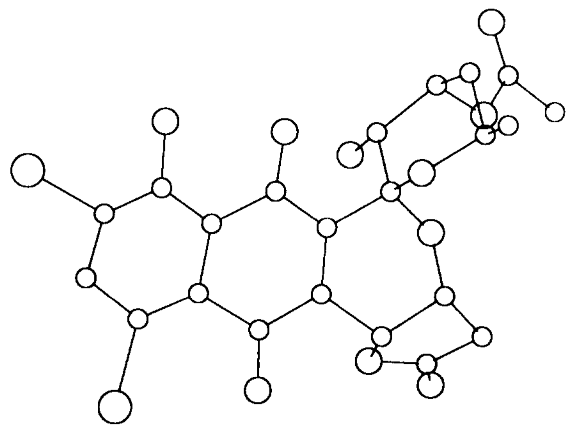

Fig. 2

The absolute configuration obtained is opposite to that inferred previously from comparison of the Cotton curves with those of known isochromanquinone antibiotics. Therefore, the CD spectrum of griseusin is not merely due to the chirality of the dihydropyran ring but is more intensely affected by the conformation of the spiroketal ring system unprecedented in this antibiotic family.

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* Atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre.

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