The Crystal Structure of Viomycin, a Tuberculostatic Antibiotic

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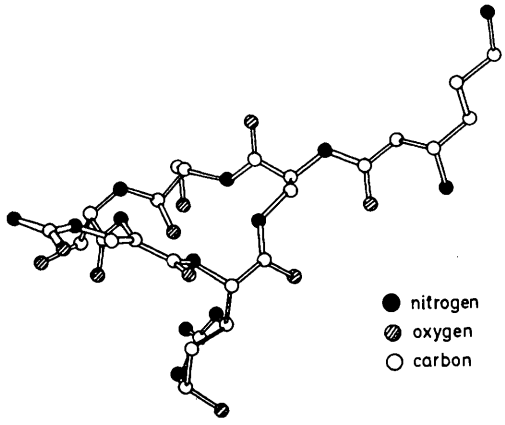
Summary The structure of the tuberculostatic antibiotic viomycin has been determined by *X*-ray techniques and the conformation of the molecule in the crystalline state is discussed in relation to other cyclic peptides.

THE structure of the antitubercular *Streptomyces* antibiotic viomycin[1] has been the subject of considerable controversy. In order to substantiate our structural proposals,[2] made on the basis of extensive chemical evidence, the suitability of a number of derivatives for *X*-ray crystallographic examination was investigated.



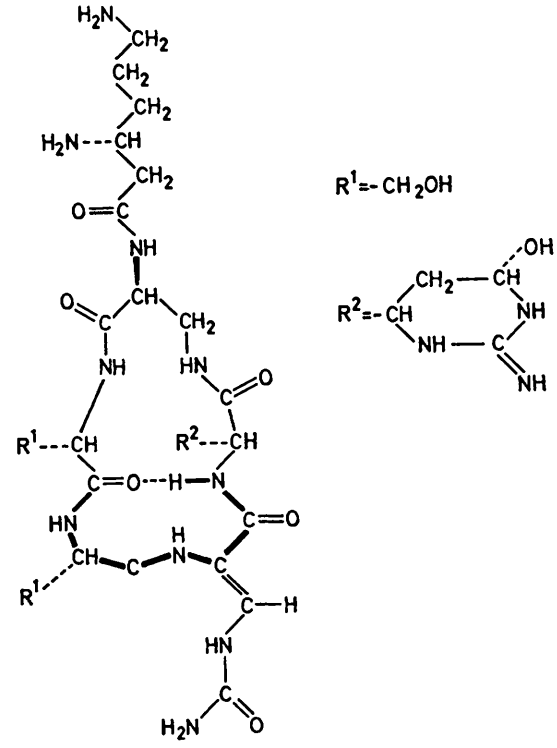
FIGURE

Crystals of viomycin dihydrobromide hydrochloride $C_{25}H_{43}N_{13}O_{10}\cdot 2HBr\cdot HCl\cdot 3H_2O$, monoclinic, space group C_2 with cell dimensions $a = 20{\cdot}70 \pm 0{\cdot}03$, $b = 15{\cdot}79 \pm 0{\cdot}03$, $c = 13{\cdot}93 \pm 0{\cdot}03$Å, $\beta = 106{\cdot}17°$, were subsequently prepared and the intensities of 1525 independent reflexions recorded on a Hilger and Watts linear diffractometer using Mo-K_α radiation. Initial co-ordinates for the two bromide and chloride anions were obtained from a three dimensional Patterson synthesis and several successive rounds of structure factor calculations and Fourier syntheses phased on these ions revealed the molecular structure shown in the Figure.

The water molecules were located by difference Fourier synthesis and in the final stages of refinement the halogen anions were treated anisotropically resulting in the present *R* value of 0·14.

The structure (I) confirms the presence of the novel dehydroserine ureide, the guanidine carbinol system, and the sixteen membered peptide ring suggested by us but necessitates an amendment to our suggested amino-acid sequence.[3]

Since the L-configuration of the α-amino-acids has already been determined the absolute configuration of the



(I)

whole molecule is also established. A significant feature of viomycin in the crystalline state is the hydrogen bonded ring (I, heavy lines), the conformation of which is similar to the β-turn structure common to many other cyclic peptides.[4] The corner positions of the β-turn in cyclic peptides are normally occupied by the α-carbon atoms of a D- and L-amino-acid residue respectively. Conformational energy considerations[5] accord with the established stability of this type of system and there is abundant evidence to suggest that the β-turn conformation is retained in solution.[5,6]

In viomycin these corner positions are occupied by L-serine and the dehydroserine ureide which replaces the usual D-amino-acid residue [Figure and (I)]. The

presence of the same β-turn structure in the closely related antiobiotic tuberactinomycin has also been established by an *X*-ray crystallographic analysis.[7] This interesting conformational feature may be relevant to our views[8] concerning the possible relationship of D-amino-acids and dehydroamino-acids in microbial peptide antibiotics, as well as to the mode of action of this novel antibiotic.

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