

THE STRUCTURE OF NIGERICIN

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Received August 9, 1968

SUMMARY

The molecular structure and the cation binding of nigericin, an antibiotic affecting ion transport and ATPase activity in mitochondria, has been determined by single crystal X-ray crystallography. The molecule is found to be similar to monensin, another antibiotic of similar properties.

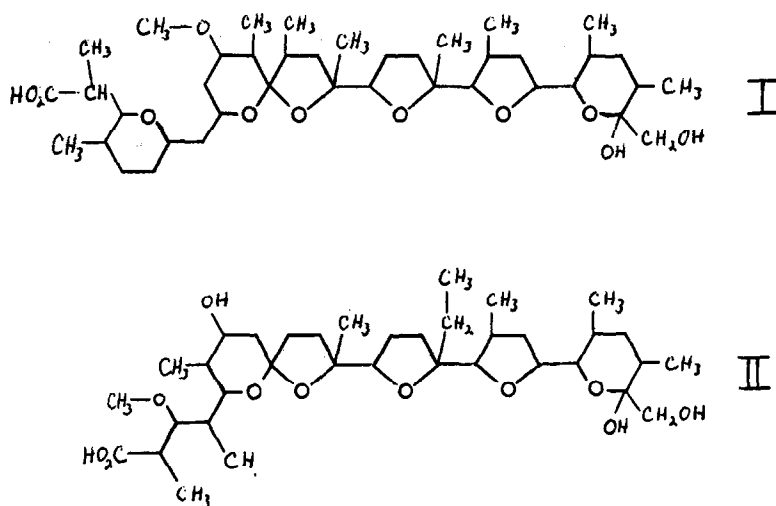
RESULTS

Among the antibiotics which affect the transport of alkali metal ions in mitochondria, nigericin (Harned, Hidy, Corum and Jones, 1950) is one of the most extensively studied (Lardy, Johnson and McMurray, 1958; McMurray and Begg, 1959; Graven, Estrada-O and Lardy, 1966; Estrada-O, Graven and Lardy, 1967), but the structure up to now has been unknown. There are considerable difficulties in the investigation of the molecular configuration and conformation of this type of antibiotic by most conventional methods. The structure determination by X-ray crystallography of a salt of nigericin is therefore highly attractive, particularly since the conformation of the antibiotic with the cation may be determined at the same time.

Silver was used as a heavy atom crystallographically, since the Ag^+ cation is monovalent and has a radius between Na^+ and K^+ , which are the two alkali cations with which nigericin is most active. Crystals of the silver salt and of the sodium salt were grown by diluting ethanol solutions with equal volumes of water and allowing the mixtures to evaporate slowly. The silver salt and the sodium salt are isomorphous crystallographically, which is an almost certain indication that the two salts have configuration and conformation.

The crystals were orthorhombic, space group $\text{P2}_1\text{2}_1\text{2}_1$, with $a = 14.59$, $b = 23.67$, and $c = 12.06$ Å. Approximately 2,200 independent data of the silver salt were recorded on a Supper-Pace Autodiffractometer.

The structure was solved by conventional heavy atom methods.



The molecule of nigericin (I) is seen to be very similar to, but not identical to that of monensin (II), previously determined by us (Agtarap, Chamberlin, Pinkerton and Steinrauf, 1967). The molecule of the antibiotic is wrapped completely around the silver ion and coordinated to it by five of the oxygen atoms. This produces a hydrocarbon-like exterior, which can account for the low water solubility of salts of nigericin. The coordination of the silver ion by monensin did not involve the carboxyl

group, but the coordination of silver by nigericin does. This difference we feel could be sufficient to give the two antibiotics slightly different specificity toward alkali metal cations.

This work has been supported by a grant from the National Science Foundation (GB7047), by assistance from the Heart Research Center, Grant HE06308 from the National Heart Institute, U. S. Public Health Service, and by computer time from the Research Computation Center, which is supported by Public Health Research Grant FR00162.

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