THE STRUCTURE OF CEPHALORIDINE HYDROCHLORIDE MONOHYDRATE

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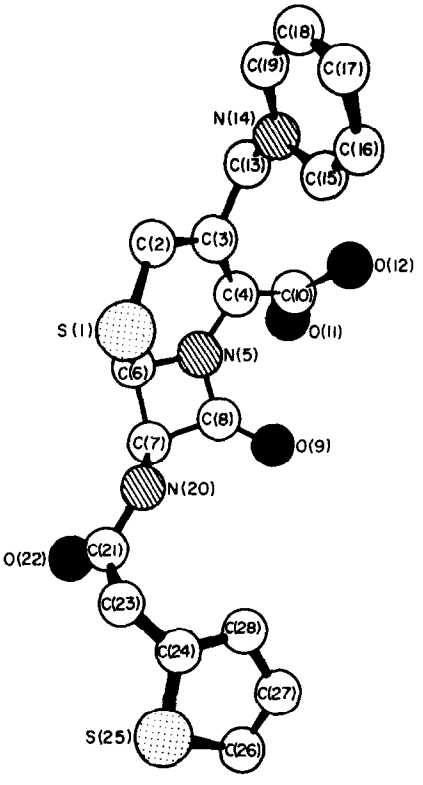
SUMMARY

The crystal and molecular structure of cephaloridine hydrochloride monohydrate (Fig. 1), an antibiotic inhibiting the synthesis of bacterial



Cephaloridine hydrochloride monohydrate

$C_{19}H_{17}O_4N_3S_2 \cdot HCl \cdot H_2O$

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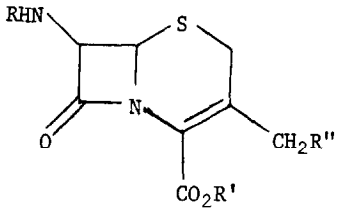
cell walls in a fashion similar to that of the penicillins, has been determined by three-dimensional, single crystal X-ray diffraction methods. The central part of the molecule is found to be similar to that of cephalosporin C.

RESULTS

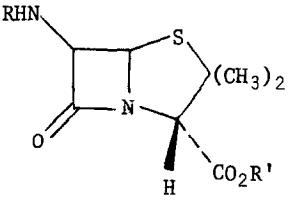
In order to make detailed stereochemical comparisons among the β-lactam antibiotics (viz., the cephalosporins and penicillins) which seem to be active at the same enzymatic site in inhibiting bacterial cell wall synthesis, accurate structural information must be available. It is to this end that we have begun crystal structure analyses of several derivatives of the cephalosporin antibiotics. The mechanism of action of the penicillins and cephalosporins has only recently been clarified. These antibiotics have been shown to inhibit the terminal reaction in bacterial cell wall synthesis, a transpeptidation in which linear peptidoglycan strands are crosslinked to form a three-dimensional network. It has been proposed that in Staphylococcus aureus this inhibition is a consequence of the structural similarity of these antibiotics to a possible conformation of the D-alanyl-D-alanine end of the uncross linked unit in the cell wall. Because the enzyme accepts the antibiotic as an analog of D-ala-D-ala, the β-lactam ring is cleaved and there is a resultant acylation of the enzyme (Tipper and Strominger, 1965; Strominger, et al., 1967; and references cited therein).

Crystals of cephaloridine hydrochloride monohydrate (I, R = CO-CH_2-2-thiophene, R' = HCl, R'' = N-pyridyl) are orthorhombic with four $C_{19}H_{17}O_4N_3S_2 \cdot HCl \cdot H_2O$ species in a unit cell of symmetry $P2_12_12_1$, and dimensions a = 11.22, b = 17.73, and c = 11.12 Å. The structure was solved and refined to an unweighted R value of 13% based on 2244 independent diffraction maxima obtained photographically.

The molecular nucleus, of which all cephalosporins are derivatives, is Δ^3-7-aminocephalosporanic acid (I, R = R' = H, R'' = OAc), abbreviated Δ^3-7-ACA.



I



II

Comparison of the molecular parameters of this nucleus from cephaloridine to the ones from that of cephalosporin C (I, R = CO-$(CH_2)_3$-$CH(NH_2)CO_2H$, R' = Na, R'' = OAc) (Hodgkin and Maslen, 1961), shows that they are similar within the accuracy of the two refinements. Comparison of Δ^3-7-ACA with the 6-amino-penicillanic acid (II, R = R' = H) nucleus of the penicillins shows that the conformations around the β-lactam rings are quite similar, while those at the carboxyl group exocyclic to the dihydrothiazine and thiazolidine rings respectively are different. This leads one to believe that if the ability of the antibiotic to bind to the enzyme is dependent upon the stereochemistry of this molecular nucleus as Tipper and Strominger suggest, a rather wide range of conformations at the carboxyl group is acceptable. Details of the structural features of cephaloridine · HCl · H_2O and its stereochemical relationship to the structure and activity of the penicillins will be forthcoming.

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