X-Ray Crystallographic Determination of the Stereochemistry of the Tetrathio-bridge in Sporidesmin G

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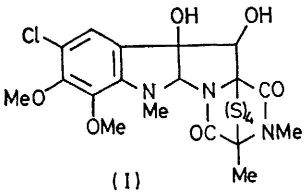
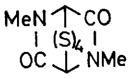
Summary A single-crystal *X*-ray study of sporidesmin G revealed that the stereochemistry of the tetrathio-bridge is closely similar to that in *NN′*-dimethyl-3,6-epitetrathiopiperazine-2,5-dione.

WE have reported the production of the tetrasulphide sporidesmin G[1] by *Pithomyces chartarum*. The tetrasulphide structure (I) was suggested for sporidesmin G on the basis of its chemical and spectroscopic properties. The c.d. and n.m.r. of the natural product were identical with those of a cyclic tetrasulphide, prepared from sporidesmin, a disulphide, by its reaction with dihydrogen disulphide. The conformation of the sulphur bridge, however, could not be assigned and we report the solution of this problem by *X*-ray crystallography.



(I)



(II)

A number of conformations of the sulphur bridge across the dioxopiperazine ring appeared possible, including the existence of conformers having a low dihedral angle for the central S–S bond, because of the stability of this type of disulphide in sporidesmin, aranotin, and gliotoxin. In addition, since in proteins disulphide bridges are found,[2] which are mirror images of each other, the biosynthesis of the tetrasulphide was expected to be stereo-indiscriminate producing a mixture of forms. However, our n.m.r. and c.d. studies indicate that sporidesmin G exists in solution in a single form and the results of the *X*-ray analysis reported here confirmed the presence of a single conformation in a crystal.

Crystal data: Sporidesmin G etherate, $C_{18}H_{20}O_6N_3S_4Cl\cdot(C_2H_5)_2O$, orthorhombic, space group $P2_12_12_1$; $a = 15{\cdot}160$, $b = 21{\cdot}369$, $c = 8{\cdot}978$ Å; $U = 2908{\cdot}5$ Å^3, $D_m = 1{\cdot}403$, $D_c = 1{\cdot}398$ g cm^{-3}, $Z = 4$, $M = 612{\cdot}23$.

Three-dimensional data consisting of 2152 independent observed reflections were collected with a Picker automatic diffractometer. The structure was solved by the direct-phasing method. The E map calculated with 263 values $\geqslant 1{\cdot}51$ gave the location of the five heavy atoms. The

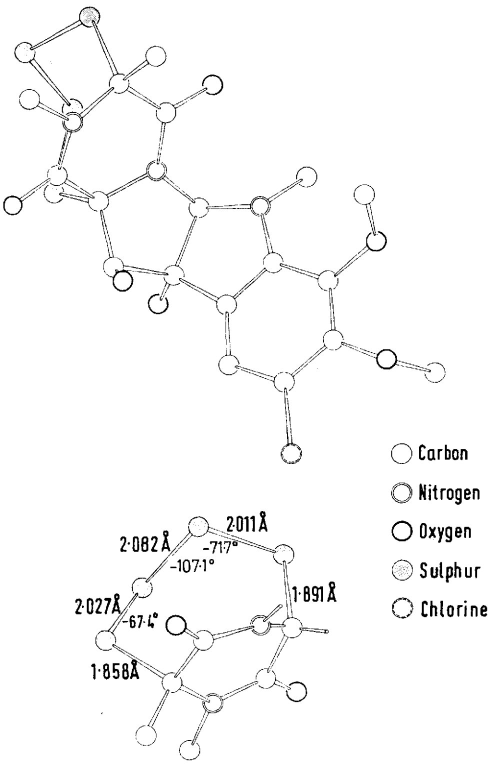


FIGURE. *Perspective drawing of the molecule of sporidesmin G projected down the* c *axis and a view of the tetrathio-piperazinedione portion down the* b *axis. The e.s.d's of the* S–S *and* S–C *bonds are* 0·004 *and* 0·008 Å, *respectively. The dihedral angles for the* S–S *bonds are also given.*

remaining atoms were obtained from Fourier syntheses. The atomic parameters were refined by the block-diagonal approximation of the least-squares method and the *R* factor of 0·057 was reached.

The structure of sporidesmin G and the final S–S and S–C bond lengths are shown in the Figure. The structure of sporidesmin was determined by *X*-ray methods by Fridrichsons and Mathieson[3] and its absolute configuration was reported by Beecham *et al.*[4] The absolute configuration of sporidesmin G was therefore not determined but it was assumed to be identical with that of sporidesmin.

Recently, Davis and Bernal[5] reported the results of the *X*-ray analysis of *NN'*-dimethyl-3,6-epitetrathiopiperazine-2,5-dione (II). This compound was also prepared by the reaction of dihydrogen disulphide with the corresponding disulphide of piperazinedione.[1] The tetrathiopiperazinedione part of sporidesmin G was found to be the enantiomer and closely resembling the structure described by Davis and Bernal.

It can, therefore, be concluded that the biosynthesis of sporidesmin G by *P. chartarum* and the reaction of sporidesmin and of *NN'*-dimethyl-3,6-epidithiopiperazine-2,5-dione with dihydrogen disulphide giving the tetrathio-derivatives proceed stereospecifically with respect to sulphur.

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