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THE STRUCTURE AND ABSOLUTE CONFIGURATION OF GLIOTOXIN AND THE ABSOLUTE CONFIGURATION OF SPORIDESMIN

by

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Gliotoxin, an antibiotic from Gliocardium fimbriatum, isolated by Weindling (1) was studied extensively by Johnson and his coworkers (2). A structure was proposed by Woodward, Johnson et al. (3) in 1958 without specification of configurational detail and this proposal has not received confirmation or subsequent elaboration. The determination of the structure of sporidesmin (4), also fungal in origin, indicated similarities to the proposed structure for gliotoxin in certain structural features. Gliotoxin has therefore been analysed by X-rays to clarify its structure and configurational detail and also because of the inherent interest in the 1,3-cyclohexadiene system for which accurate dimensional details are lacking (5).

Crystal data, taken with CuKα radiation and calibrated against an internal standard (6), are compared in the Table with the earlier values of Crowfoot and Rogers-Low (7). The density, measured at room temperature, is in accord with the total cell contents being 4 molecules, i.e., the asymmetric unit corresponds to 2 molecules of $C_{13}H_{14}N_2O_4S_2$.

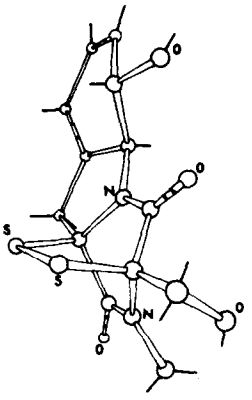
TABLE

Gliotoxin, monoclinic, space group $P2_1$

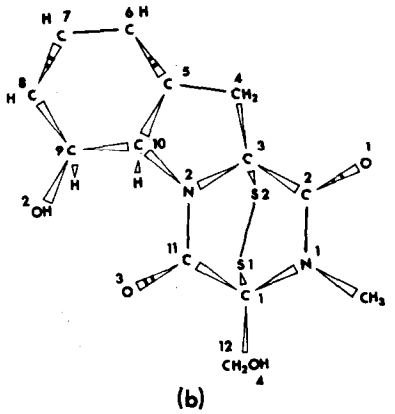
	BFM (at 150°C)	BFM (at 20°C)	CR-L (7)
a	10.17	10.25	10.36Å
b	7.49	7.52	7.59Å
c	18.28	18.46	18.74Å
β	100.7°	100.7°	100.0°

Intensity data were recorded at -150°C under conditions outlined previously (8). Location of the 4 S atoms in the asymmetric unit proved possible and the first electron-density distribution, phased on these, permitted deduction of all atom locations in both molecules, the redundancy involved in dealing with 2 molecules in the asymmetric unit providing useful internal checks against misleading conclusions (9). Refinement carried out by least-squares procedures has reduced the reliability index R to 0.09 for the 2859 measured reflexions. The hydrogen atoms, located from a difference distribution, are incorporated in the calculation.

Peterson (10) has shown the feasibility of using the small but detectable component f" for Cl at the CuKα wavelength to define absolute configuration following Bijvoet's proposal (11). Using the f" component of the S atoms, we have been able to define the absolute configuration of gliotoxin, using the photographic technique at -150°C by careful selection of pairs of reflexions to suit the most appropriate conditions (12). The resultant conclusion for gliotoxin is represented by the space formula in Fig. 1a with the more conventional representation in Fig. 1b.



(a)

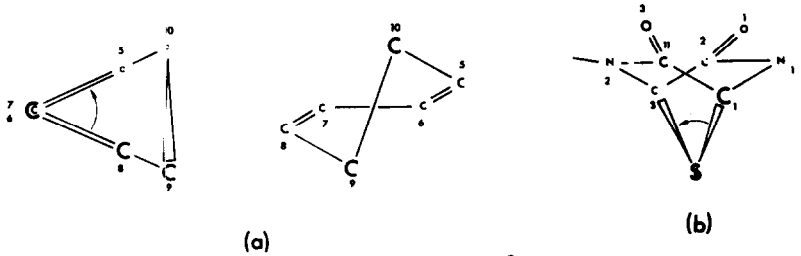


(b)

Fig.1

The structure, ignoring configurational detail, accords with the conclusion of Woodward, Johnson et al. (3). Apart from the disposition of the hydroxyl group O4 with different orientations in the two molecules, only one of which is depicted in Fig. 1a, the two crystallographically independent molecules are identical within experimental error. The identity in detail is in accord with the molecular framework being relatively rigid and this is confirmed by the corresponding Dreiding model. This rigidity holds in specific mutual orientation the structural features which are of interest as chromophores and hence the structural details derived from the crystal analysis can be carried over directly to discussion of structural studies by spectroscopic techniques in solution (13). Full details of bond lengths and angles will be given in another place but certain structural features are worthy of comment here.

(a) The 1,3-cyclohexadiene system: This system is identical in the two independent molecules, the conformation of ring A being a skew-chair. The groups C6,7,8,9 and C10,5,6,7 are individually coplanar and the mean value of the dihedral angle C5,6,7/C6,7,8 is 14°, while for the dihedral angle C8,9,10/C9,10,5 it is 44.8°. These values are in reasonable agreement with the less-directly derived parameters of a recent microwave investigation (14) of 1,3-cyclohexadiene itself. The sense of the skew-diene system in gliotoxin is left-handed, Fig. 2a. The implications of this result with regard to the circular dichroism of this group are treated in the accompanying paper (15).



(a) (b)

Fig. 2

(b) The 1,4-disulphide bridged 2,5-piperazinedione system: The attachment of the disulphide group to C1 and C3 restricts the normal open-chain dihedral angle (circa 100°) to the low (mean) value of 12.3° for ∠ C1S1S2/S1S2C3. The chirality of the group C-S-S-C is, presumably, determined by the substituents in the piperazinedione ring at C1, N1, N2 and C3. It, also, is left-handed, Fig. 2b.

(c) Configurations at C1 and C3: As noted earlier (3), the bridged bicyclic structure requires that the absolute configurations at C1 and C3 be the same. The present result reveals that, if originally derived from amino acids — serine and phenylalanine (16) — these would have been in the L-form if no inversion occurred during the natural synthesis of gliotoxin.

Sporidesmin

Although decomposition of the crystals of sporidesmin in the earlier work (4) had prevented the extension of the X-ray analysis to define the absolute configuration, the availability of the structure analyses of the two compounds and the definition of the absolute configuration of one of these provides an opportunity to resolve the question by reference to the configurational evidence of their circular dichroism (C.D.) curves. Comparison of the two structures, on the basis merely of relative configuration indicates dimensional and angular identity not only in the bridged piperazinedione system, including the skewness of the disulphide bridge, but extending also to the associated 5-membered ring at N2C3. Only at C10 do the relative configurations differ, cf. Figs. 1 and 3. Herrmann, Hodges and Taylor (17) have determined the C.D. of gliotoxin and sporidesmin and we have repeated this work. Gliotoxin shows two weak negative maxima at circa 310 mμ and at 340 mμ probably due to the disulphide absorption (18) and possibly reflecting both the sense and magnitude of the skewness of that system (see (15)). If the transitions concerned are active in sporidesmin, their effect is masked by positive dichroism associated with the dihydroindole chromophore of the molecule. Below 260 mμ, however, both compounds exhibit strong

negative dichroism peaking at 233 mμ and this feature is shared by dehydroglictoxin, sporidesmin-B and anhydrosporidesmin-B (17). The disulphide-bridged piperasinedione systems exists unmodified in all five of these compounds and, for this reason, as well as from the nature of the chromophore, we identify it as the source of the short wavelength dichroism. It follows that the absolute configuration of this common structural unit is the same in gliotoxin and sporidesmin and in their alteration products mentioned above.

The absolute configuration of sporidesmin is that depicted by the space formula, Fig. 3a and the more conventional representation in Fig. 3b.

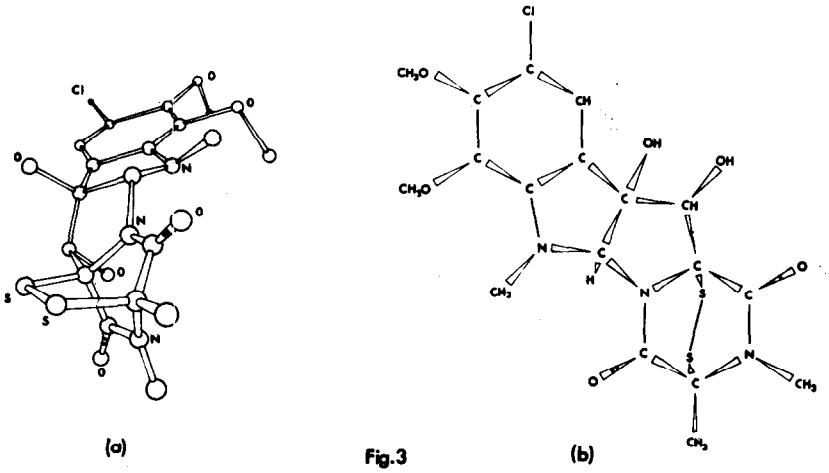


Fig.3

The opposite configuration of C10 in gliotoxin and the corresponding atom in sporidesmin is reflected in the overall shapes of the two molecules, cf. Figs. 1 and 3.

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