X-Ray Crystal Structure of Cytochalasin H, a Potent New [11]Cytochalasan Toxin

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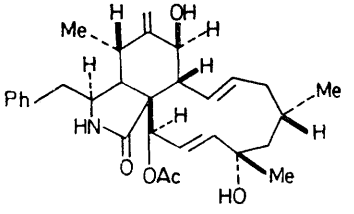
Summary A toxic fungal metabolite isolated from an unidentified species of *Phomopsis* has been unambiguously identified by *X*-ray crystallographic analysis as an [11]cytochalasan, which is very similar to cytochalasin D, differing from it only in the lack of the ketone group at C-17.

WELLS, CUTLER, and COLE have recently isolated a new mycotoxin and plant growth regulator from *Phomopsis* cultures.[1] On the basis of chemical, biological, and spectroscopic studies, this toxin was inferred to belong to the class of cytochalasans, although its chemical formula, as deduced from its chemical analysis and mass spectrum, did not appear to correspond to any known cytochalasans. It is moderately toxic to day-old cockerels and shows substantial growth inhibiting and toxic effects on a variety of crop plants.[1] Because some fungal metabolites have been found to be powerful plant growth regulators[2] and since cytochalasans as a class have unusual effects on dividing mammalian cells,[3] we have determined the constitution of this new toxin by *X*-ray crystallography.

Crystals of the toxin were grown from Et_2O. *Crystal data:* $C_{30}H_{39}NO_5$, monoclinic, space-group $P2_1$, $a = 7{\cdot}338$, $b = 13{\cdot}053$, $c = 15{\cdot}330$ Å, $\beta = 97{\cdot}24°$, $Z = 2$. Three-

dimensional intensity data were collected using a Syntex $P\bar{1}$ automated diffractometer with graphite-monochromated Mo-K_α radiation. A total of 2833 independent reflection intensities were measured, using the ω–2θ scan technique, and the structure was solved by direct methods[4,5] followed by



(I)

least-squares refinement, assuming carbon form factors for all the atoms. Inspection of the thermal parameters permitted the assignment of the nitrogen and the several oxygen atoms. The hydrogen atoms were located from difference Fourier maps, but no attempt was made to refine the hydrogen positions or thermal parameters.

Final least-squares refinement using anisotropic thermal parameters for all the non-hydrogen atoms gave a conventional R-factor of 0·049. A difference map shows no peaks $> 0{\cdot}25$ e Å^{-3}. As there are no scattering atoms heavier than oxygen in this structure, the absolute configuration cannot be reliably determined from examination of Friedel pairs. However, the close relationship with other cytochalasans whose absolute stereochemistry has been determined by chemical[6] and crystallographic[6,7] methods permits the assignment of the stereochemistry of this molecule as that in (I) and the Figure. We have assigned to this toxin the trivial name cytochalasin H. The full name, using the nomenclature proposed by Tamm is (7*S*,16*S*,18*R*,21*R*)-21-acetoxy-7,18-dihydroxy-16,18-dimethyl-10-phenyl[11]cytochalasa-6(12),13^t,19^t-trien-1-one.

Cytochalasin H (Cyt-H) is constitutionally and structurally very similar to cytochalasin D (Cyt-D), a reported anti-tumour agent,[9] the major difference being the presence of an oxo-group at C-17 in Cyt-D. Because the phenyl and alkyl groups are in very different conformations and because the two compounds have quite different peripheral substituents, the packing forces in the structures of Cyt-H and Cyt-D′ (a *p*-bromobenzoate of Cyt-D)[10] must be very different. In spite of this, the 11-membered carbocycle possesses nearly identical conformations in the two structures, and presumably must be a fairly rigid structural unit.

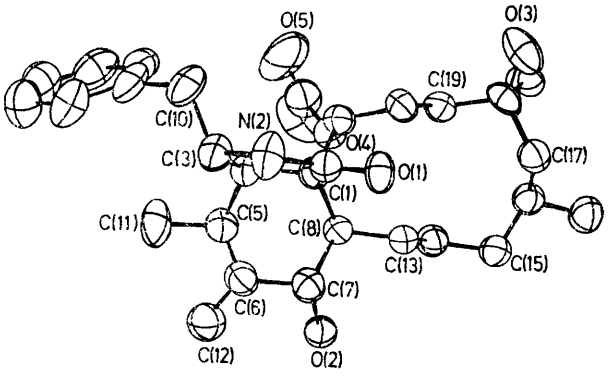


FIGURE. ORTEP diagram of cytochalasin H. The thermal ellipsoids are drawn at the 50% level and the hydrogen atoms have been eliminated for clarity. The atom numbering scheme is the same as that proposed in ref. 8.

Cyt-H is extensively hydrogen bonded in the crystal; all the possible hydrogen bond donors and nearly all the hydrogen bond acceptors are utilized. The hydrogen bonds involving the adjacent N–H and C=O functions are particularly strong. That the strong hydrogen bonds of these groups are another common feature of all the reported cytochalasan structures[10] indicates that these groups may be important to the binding of these toxic molecules to their site(s) of action and thus important for their unusual biological activity.

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