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ISOLATION AND STRUCTURE DETERMINATION OF THE MYCOTOXIN CHAETOGLOBOSIN C, A NEW [13] CYTOCHALASIN

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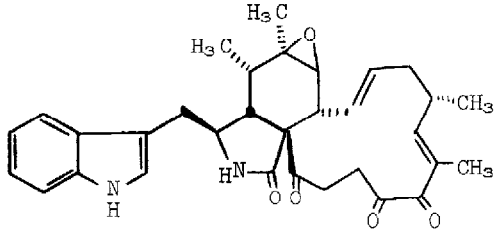
As part of our continuing program on the isolation and characterization of fungal toxins we wish to report the structure of chaetoglobosin C (1), a [13]-cytochalasin. In recent years the cytochalasins have received considerable scrutiny because of their wide range of biological effects especially cytostatic activity.[1,2]



1

Five isolates (ATCC #32000 - 32004) were taken of the fungus Penicillium aurantio-virens Biourge originally found on weevil infested pecans. The fungus was cultured on shredded wheat medium as previously described.[3] The mycelium was extracted with chloroform and after concentration subjected to an elution series on a silica gel column. Toxicity was found in the ethyl gradient elution (chloroform-ethyl acetate) was used for further purification.

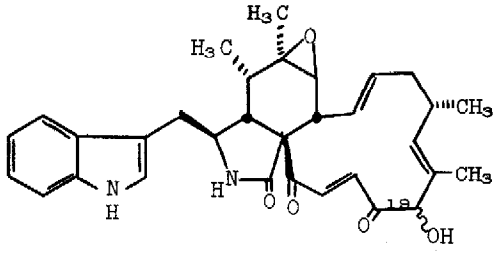
The crude toxin was crystallized from ethyl acetate to give small needles, mp. 257-259°C. Cf^{252}-plasma desorption mass spectrometry (quasi molecular ion 528) combined with microanalysis indicated the formula $C_{32}H_{36}N_2O_5$. The ir spectra (KBr) showed maxima at 3460, 3310, 1697 (broad, strong), 1641, 1621, 1096, 1044, 980 and 731 cm^{-1}. The nmr spectra (d^6-DMSO with TMS as internal standard) showed δ.92 d(3H), J = 7 Hz; δ.93 d(3H), J = 6 Hz; δ1.17 s(3H; δ1.68 s(3H); δ4.95 m(1H); δ5.8 - 6.2 m(2H); δ7.0 - 7.6 m(5H); δ8.44 s(1H) in addition to a number of unresolved peaks in the high field portion of the spectrum. A detailed analysis was frustrated by the insolubility of the compound. An X-ray diffraction experiment elucidated the complete stereostructure of 1.

Chaetoglobosin C (1) crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 13.020(4), b = 8.171(2), and c = 25.678(4). All unique reflections with $2\theta \leq 114°$ were collected utilizing an ω-scan technique on a fully automated four-circle diffractometer using monochromated CuK_α radiation (1.54178 Å). A total of 2153 pieces of data were taken and after correction for Lorentz, background, and polarization effects, 1581 (73%) were considered observed ($(F_o)^2 \geq 3\sigma\,(F_o)^2$).

The crystal structure was solved using the MULTAN series of programs.[4] After routine least squares refinements the unweighted residual index (R factor) was .035 using isotropic temperature factors for the hydrogens and anisotropic temperature factors for the remaining atoms.[5,6]

The compound can be described as a [13]cytochalasin containing a 10-(indol-3-yl) group. As can be seen in the computer generated drawing, the six and the five membered rings of the isoindolone unit are cis fused, and in addition the thirteen-membered ring is trans fused to the six-membered ring. The six membered ring adopts a slightly distorted boat conformation with C(5) and C(8) being .58 and .68Å, respectively, from the least square plane formed from C(4)-C(6)-C(7)-C(9). The thirteen membered ring contains two trans double bonds and three ketone groups including an α-diketo functionality. The dihedral angle in the solid state between these adjacent carbonyls is 108°. The relative stereochemistry is the same as the previously characterized cytochalasins and related compounds.[1,2]

There are two previous reports of cytochalasins containing the 10-(indol-3-yl) functionality.[2] The work of Natori, et al. is of particular interest. They presented structural proofs (without stereochemistry) for two mycotoxins called chaetoglobosin A (2) and B. The material we isolated has the same formula and mp as the material they previously designated chaetoglobosin C.[2] Chaetoglobosin C is known to be one of the products derived from chaetoglobosin A (2) upon treatment with triethylamine or upon letting 2 stand in chloroform.



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It is easy to imagine a series of keto-enol tautomerizations that will convert A to C. Thus, this work, which defines the relative stereochemistry of chaetoglobosin C, combined with the work of Natori, et al. on chaetoglobosins A and B provides relative stereostructures for all three mycotoxins except for the configuration of the C(19) hydroxyl in A and B. Chaetoglobosin C may be formally derived from one molecule of tryptophan, nine acetates and three C_1 residues from methionine.[7]

Acknowledgments

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5. The following crystallographic programs were used: W.R. Busing, K.O. Martin, and H.A. Levy, "ORFLS, A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965. C. Johnson "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.

6. Fractional coordinates, bond distances, bond angles and observed and calculated structure factors is available as a Supplement to Publication. To obtain a microfiche copy of the Supplement to Publication, contact the Photo Service, Iowa State University, Ames, Iowa 50011, requesting Supplement to Publication for this article and submitting $0.50 in the form of check, cash, or money order. Give your name and complete address (including zip code) for mailing.

7. See accompanying papers by S. Natori, et al. We thank Dr. Natori for an authentic sample of chaetoglobosin C and spectral data.

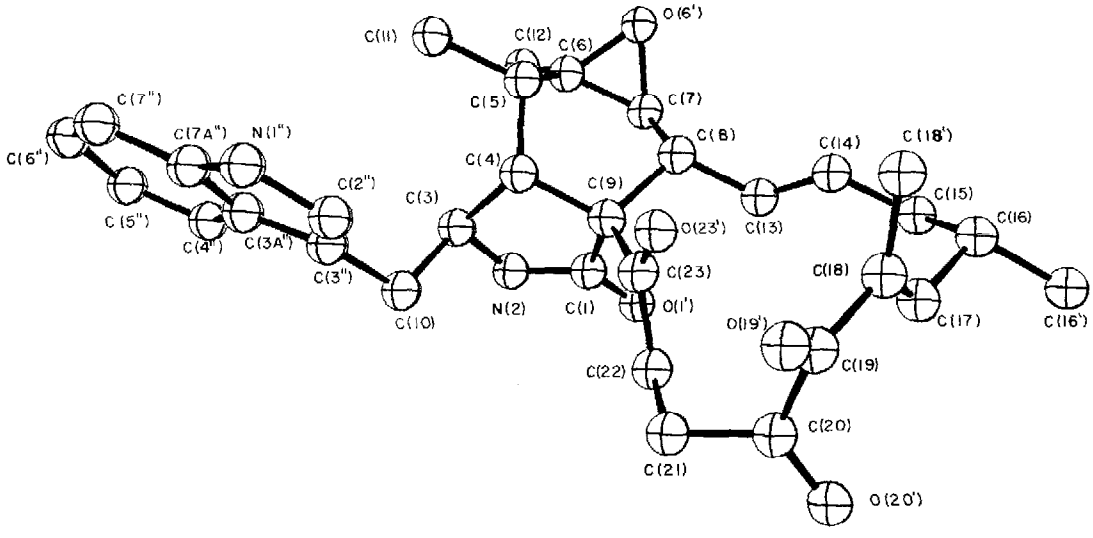

Figure 1. A computer generated perspective drawing of chaetoglobosin C (1). Hydrogens are not shown for clarity and the absolute configuration is drawn to conform with other cytochalasins.[1]