Tetrahedron Letters Vol. 21, pp 1905 - 1908
©Pergamon Press Ltd. 1980. Printed in Great Britain

0040-4039/80/0502-1905$02.00/0

THE STRUCTURE OF CHAETOGLOBOSIN K.

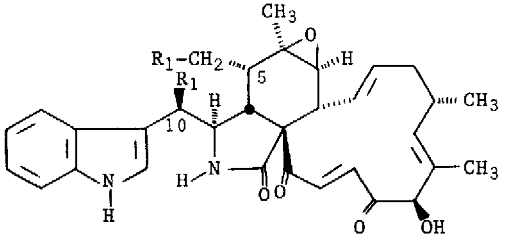
James P. Springer*
Merck Sharp & Dohme Research Laboratories
Rahway, New Jersey 07065

Richard H. Cox
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina 27709

Horace G. Cutler and Farrist G. Crumley
U. S. Department of Agriculture
Science and Education Administration, Agricultural Research
Georgia Coastal Plain Experiment Station
Tifton, Georgia 31794

Summary: The structure of chaetoglobosin K, a toxic metabolite from *Diplodia macrospora*, has been determined by single crystal X-ray analysis.

The cytochalasins are a group of cytostatically-active fungal metabolites which were first isolated in 1966, but which are generating interest both as mycotoxins and as research tools in cellular biology.[1,2] In addition to the unique responses triggered by these compounds in animal cells, selective responses in plants have also been described.[3] A new fungal metabolite, chaetoglobosin K (1), isolated from *Diplodia macrospora* (ATCC No. 36896), inhibits growth in wheat coleoptiles at 10^{-7}M and has an LD_{50} in day-old chicks of 25-62.5 mg/kg.[4]



1 $R_1 = CH_3$

2 $R_1 = H$

Previously reported mass spectral data indicated that chaetoglobosin K (1) has a formula of $C_{34}H_{40}N_2O_5$. Mass spectral fragmentation, U.V. and I.R. absorptions revealed the presence of a 3-substituted indole moiety. Initial analysis of both the ^1H and ^{13}C NMR spectra indicated that 1 was a chaetoglobosin; however, additional resonances and shifted resonances precluded a straightforward interpretation of the data. As a consequence, single crystal X-ray diffraction experiments were undertaken to completely define the structure and stereochemistry.

Suitable crystals of 1 formed from acetone solutions as skewed parallelepipeds with symmetry P1 and a = 10.302(6), b = 10.569(4), c = 9.689(4)Å, α = 116.23(3), β = 103.29(4) and γ = 100.80(4)°. For Z = 1 the calculated density was 1.14 g/cc with one molecule of acetone in the unit cell (*vide infra*). Of the 2358 reflections measured with graphite-monochromated CuKα (λ = 1.5418Å) radiation having $2\theta \leq 114°$, 2047 (87%) were observed ($I \geq 3\sigma I$). The structure was solved using a multi-solution tangent formula approach.[5] After a number of attempts, a recognizable fragment was expanded using tangent formula refinement[6] to give coordinates for most of the atoms. Fourier difference maps using all of the data gave coordinates for the remainder of the atoms in the molecule as well as for a solvated molecule of acetone. The structure was refined using full matrix least squares techniques by minimizing $\Sigma w\ (|F_o| - |F_c|)^2$ with $w = (1/\sigma F_o)^2$ and including anisotropic temperature parameters for the nonhydrogen atoms and fixed isotopic temperature parameters for the hydrogens to give a final R factor of .051.[7] Figure 1 is a perspective drawing of the molecule generated from the final coordinates.[8] The absolute configuration of the figure is drawn to conform with the previously described cytochalasins.[9,10]

Tables I, II and III containing the fractional coordinates and temperature parameters, bond distances and bond angles are available.[11] O1' is involved in two intermolecular hydrogen bonds, one of length 2.96Å with N1' and the other of length 2.65Å with O19'. Curiously, the solvent molecule of acetone is not in a position to hydrogen bond since there are no suitable contacts less than 3.5Å.

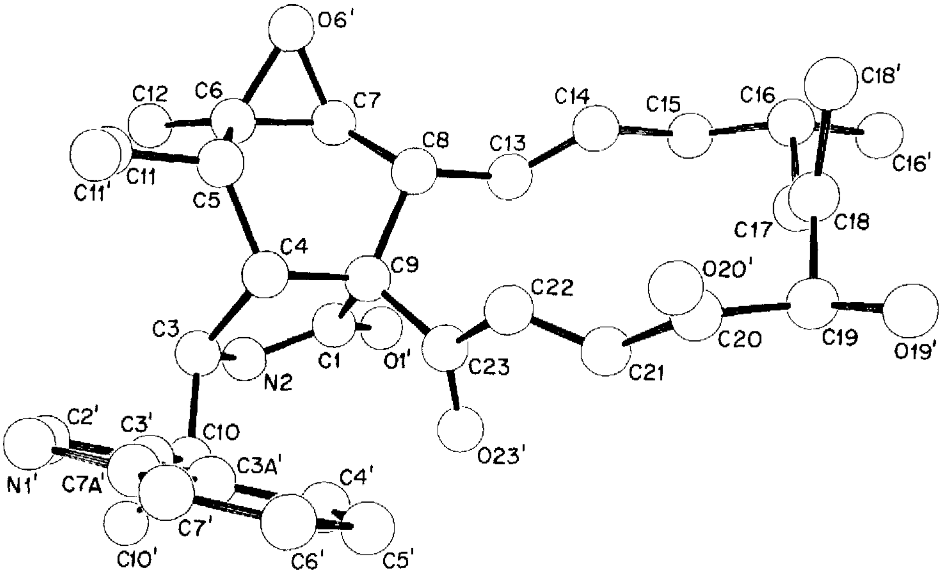


Figure 1. A computer generated perspective drawing of chaetoglobosin K (1). Hydrogens have been omitted for clarity.

Chaetoglobosin K (1) is found to be an indol-3-yl [13] cytochalasin similar to chaetoglobosin A (2)[10,12] with additional unique features. Instead of a methyl substituent at C5, 1 has an ethyl group; an additional methyl substituent is also found on C10. Since none of the more than 20 cytochalasins described in the literature has these additional methyl groups, an interesting biosynthetic question is raised. Biogenesis of the cytochalasins has been shown to result from the union of an aromatic amino acid, a 16- or 18-membered polyketide and several additional carbons from the C_1 pool.[2] The methyl group C10' undoubtedly came from the C_1 pool; however, the additional carbon C11' could have come from methionine, degradation and reduction of a 20-membered polyketide, or most likely from a propionate starting unit on the polyketide chain.

REFERENCES AND NOTES

1. S. B. Carter, Endeavour *31*, 77 (1972).
2. M. Binder and Ch. Tamm, Angew. Chem. Internat. Edit. *12*, 370 (1973).
3. W. Herth, W. W. Franke and W. J. Vanderwoude, Naturwissenshaften *59*, 38 (1972). J. M. Wells, H. G. Cutler and R. J. Cole, Can. J. Microbiol. *22*, 1137 (1976).
4. H. G. Cutler, F. G. Crumley, R. H. Cox, R. J. Cole, J. W. Dorner, J. P. Springer, F. M. Latterell, J. E. Thean and A. E. Rossi, J. Agri. Food Chem. (1980).
5. P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, "MULTAN 78, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data", Universities: York, England; Louvain, Belgium (1978).
6. J. Karle, Acta Cryst. *B24*, 182 (1968).
7. J. M. Stewart, J. G. Kruger, H. L. Ammon, D. Dickinson and S. R. Hall, "The X-Ray System, Version of June, 1972", TR-192, Computer Science Center, University of Maryland, College Park, Maryland (1972).
8. C. K. Johnson, "ORTEP-II: A FORTRAN Thermal Ellipsoid Plot Program for Crystal Structure Illustrations", U. S. Atomic Energy Commission, Report ORNL-3794 (2nd Rev., with Supplemental Instructions), Oak Ridge National Laboratory, Oak Ridge, Tennessee (1970).
9. G. M. McLaughlin, G. A. Sim, J. R. Kiechel and Ch. Tamm, J. Chem. Soc., Chem. Commun. 1398 (1970).
10. J. V. Silverton, C. Kabuto and T. Akiyama, Acta Cryst. *B34*, 588 (1978).
11. Contact the Directory of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
12. S. Sekita, K. Yoshihira, S. Natori and H. Kuwano, Tetrahedron Lett. 2109 (1973).

(Received in USA 13 February 1980)