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# STRUCTURES OF CHAETOGLOBOSINS C, D, E, AND F, CYTOTOXIC INDOL-3-YL-[13]CYTOCHALASANS FROM *Chaetomium globosum*[1)]

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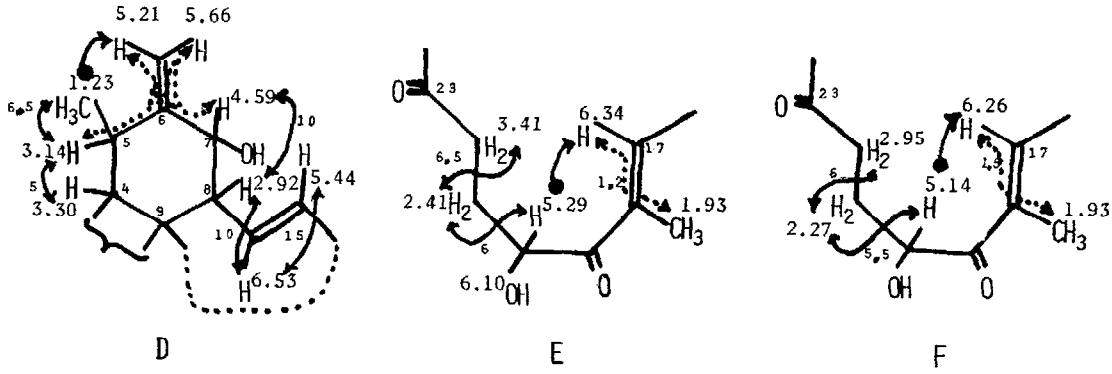
CHAETOGLOBOSINS A - F are cytotoxic metabolites of *Chaetomium globosum*.[2)] The structures of chaetoglobosins A and B, proposed in the previous communication[3)] from the chemical and spectroscopic evidences, have been verified by the X-ray analysis of chaetoglobosin A and the relative stereochemistry of the compounds A and B is now established as I and II.[4)] The compounds belong to novel type [13]cytochalasans[5)] containing tryptophan units. This communication concerns the structures of other four metabolites, isolated by chromatography of chloroform extracts of the mold cultured on polished rice grains and designated as chaetoglobosins C, D, E, and F.

Chaetoglobosin D (III), mp 216°, $[\alpha]_D$ -269° (MeOH), pale yellow prisms from $CHCl_3$, has the same molecular formula $C_{32}H_{36}O_5N_2$ ($M^+$ 528.261 m/e, calcd. 528.262) as A and B and shows similar spectral properties ($\lambda_{max}^{EtOH}$ 221, 273, 281, 290 nm (log ε 4.64, 3.96, 3.96, 3.88), $\nu_{max}^{KBr}$ 3421, 3280, 2945, 2918, 2880, 1686(s), 1606, 1430, 1250, 1052, 972, 908, 750 $cm^{-1}$), suggesting an isomeric relationship to A and B. As in the case of A and B the examination of the structure by $^1$H-NMR decoupling experiments was precisely carried out. All the protons show entirely the same chemical shifts and coupling patterns as those of A and B except those on the cyclohexane or the cyclohexene nucleus; i.e. the two olefinic methyl groups at $C_5$ and $C_6$[6)] in B are replaced by one secondary methyl group and one terminal methylene group (the group is also suggested by IR) as shown in the partial formula (Chart 1).[7)] Indeed acetylation of D with $Ac_2O$-pyridine gave an acetate, which was identified with B diacetate. When chaetoglobosin A (I) was treated with $BF_3$-etherate in $CHCl_3$, D was formed along with B. The coupling constant (10 Hz) of the $C_7$-carbinyl proton and $C_8$-proton suggests the trans-diaxial relation of the protons. Thus the



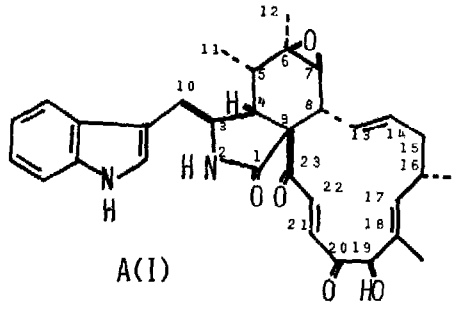

D E F

The chemical shifts are δ values in ppm from TMS in pyridine-$d_5$.
The coupling constants are in Hz.
vicinal coupling, long range coupling, NOE.

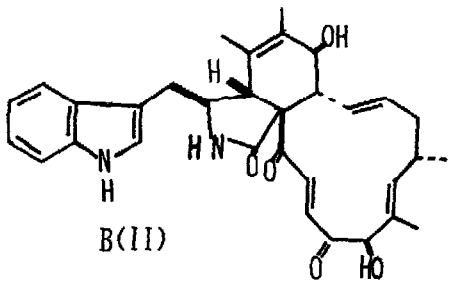
Chart 1

structure of chaetoglobosin D was proved to be the formula III.

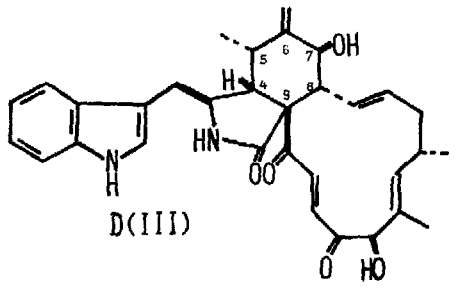
Chaetoglobosin C (IV), mp 260-263°, $[\alpha]_D$ -30° (MeOH), colorless leaflets from acetone, has again the same molecular formula $C_{32}H_{36}O_5N_2$ ($M^+$ 528.264 m/e, calcd. 528.262) and shows similar spectral properties ($\lambda_{max}^{MeOH}$ 222, 273, 281, 291 nm (log ε 4.56, 3.83, 3.83, 3.76), $\nu_{max}^{KBr}$ 3445, 3305, 2915, 1697(s), 1642, 1441, 1327, 1099, 1056, 986, 851, 832, 745 $cm^{-1}$), suggesting isomeric to chaetoglobosins A, B, and D. The compound recovered unchanged by acetylation. The $^1$H-NMR spectrum shows the entirely same pattern as that of A in the indolyl group to the $C_{16}$-methyl group including the vicinity of the epoxide ring ($C_5$-Me, δ 1.08, d, $J$ = 7 Hz; $C_5$-H, δ 2.02, m; $C_6$-Me, δ 1.28, s; $C_7$-H, δ 3.06, d, $J$ = 5 Hz). However it lacks the typical $C_{21}$-$C_{22}$ double bond signals which appear at lower fields with A and B, integration of the methylene protons at δ 2.2-3.6 region increases for four protons instead, and the $C_{17}$-olefinic proton (δ 6.31, br. d) and the $C_{18}$-methyl protons (δ 1.90, d)($J_{16\text{-}17}$ 10 Hz, $J_{17\text{-}18Me}$ 1.2 Hz) appear at lower field than those of A. As shown in the previous communication[3] the treatment of A with triethylamine in methanol gave B and C. The isomerization of A to C occurs in a better yield when A was treated with the amine in pyridine. The same isomerization reactions were observed for chaetoglobosins B and D under the same conditions and the products exhibit the same change in $^1$H-NMR spectra, in which the presence of a group ■-$CH_2$-$CH_2$-■ (δ 3.6 and 2.6, each 2H) was proved by decoupling experiments. The tetrazolium salt reactions, positive for A, B, and D, are negative in the case of C and the isomers from B and D. Although further reactions to confirm the structure of C are now under investigation, a tentative structure (IV) is proposed for the compound to suffice the



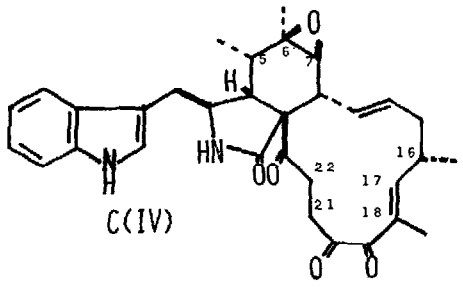
A(I)



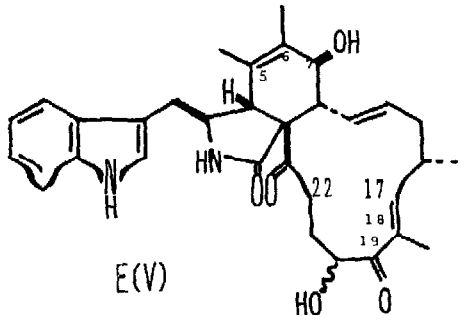
B(II)



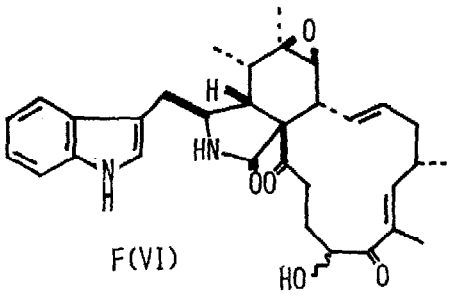
D(III)



C(IV)



E(V)



F(VI)

chemical and spectral properties and the formation from A by a series of keto-enol tautomerizations.[8]

Chaetoglobosin E (V), mp 279-280°, $[\alpha]_D$ +158° (MeOH), colorless needles from MeOH, and F (VI), mp 177-178°, $[\alpha]_D$ -69° ($CHCl_3$), colorless leaflets from benzene, exhibit also similar spectral properties (V, $\lambda_{max}^{EtOH}$ 221, 275, 281, 291 nm (log ε 4.75, 3.85, 3.85, 3.80), $\nu_{max}^{KBr}$ 3410, 2885, 1704(s), 1676, 1455, 1048, 746 $cm^{-1}$; VI, $\lambda_{max}^{EtOH}$ 222, 276, 283, 292 nm (log ε 4.68, 3.84, 3.83, 3.78), $\nu_{max}^{KBr}$ 3346, 2955, 2920, 1676(s), 1618, 1430, 1385, 1260, 1110, 979, 879, 740 $cm^{-1}$). However the molecular formulae $C_{32}H_{38}O_5N_2$ (V, $M^+$ 530.275 m/e, VI, $M^+$ 530.275 m/e, calcd. 530.278) suggested the compounds to be the dihydro derivatives of chaetoglobosins A - D. Chaetoglobosin F forms a monoacetate, while E gives a diacetate. Precise $^1$H-NMR examinations were again per-

formed on the two compounds and the acetates, revealing that the framework of E ($C_5$-Me, δ 1.49, br. s; $C_6$-Me, δ 1.90, br. s; $C_7$-H, δ 4.56, dd, $J$ = 6 and 9 Hz; $C_7$-OH, δ 5.97, d, $J$ = 6 Hz) is identical with B (II) and that of F ($C_5$-Me, δ 0.97, d, $J$ = 6.5 Hz; $C_5$-H, δ 2.01, m; $C_6$-Me, δ 1.25, s; $C_7$-H, δ 3.12, d, $J$ = 5 Hz) with A except for $C_{19}$-$C_{22}$. The typical AB type signals of the $C_{21}$-$C_{22}$ double bonds appearing at lower fields for A, B, and D disappear and the presence of a group ■-$CH_2$-$CH_2$-$\underset{OH}{CH}$-■ was shown instead (Chart 1). The carbinyl protons in the group exhibit NOE on the $C_{17}$-olefinic protons in E anf F and the chemical shifts of the protons and the $C_{18}$-methyl protons shift to lower fields as in the case of chaetoglobosin C. The presence of α-ketol groups in the compounds was suggested by the positive tetrazolium salt reactions. Although the chemical correlation of the compounds to chaetoglobosins A - D series has not been carried out due to the scarcity of the materials, the formulae V and VI are proposed respectively for chaetoglobosins E and F as the most preferable formulations.

Further work is now in progress in our laboratory.

## References and Notes


1) The work has been carried out by the collaboration with Drs. H. Kurata, S. Udagawa, and F. Sakabe, this Institute (Mycology) and Professor M. Saito and Drs. M. Umeda and K. Ohtsubo, Institute of Medical Sciences, University of Tokyo (Pathology).[2] The authors are indebted to Fermentation Research Laboratories, Sankyo Co., Ltd., for a large scale fermentation.

2) M. Umeda, K. Ohtsubo, M. Saito, S. Sekita, K. Yoshihira, S. Natori, S. Udagawa, F. Sakabe, and H. Kurata, *Experientia*, 31, 435 (1975).

3) S. Sekita, K. Yoshihira, S. Natori, and H. Kuwano, *Tetrahedron Letters*, 1973, 2109.

4) J. V. Silverton, T. Akiyama, C. Kabuto, S. Sekita, K. Yoshihira, and S. Natori, the preceding paper.

5) M. Binder and Ch. Tamm, *Angew. Chem., Intern. Ed.*, 12, 370 (1973).

6) In this paper the systematic numbering proposed for cytochalasans[5] and different from that used in the previous paper[3] is adopted for the conveniance for the comparison for other papers.

7) All the NMR data in this paper are those in pyridine-$d_5$ solution at 100 MHz.

8) The same compound has been isolated from *Penicillium aurantio-virens* and the identity has been established by the direct comparison of the specimens (Professor J. Clardy, private communication). The X-ray analysis carried out by the American group revealed the correctness of the proposed structure (J. P. Springer, J. Clardy, J. M. Wells, R. J. Cole, J. W. Kirksey, R. D. Macfarlane, and D. F. Torgerson, the paper submitted simultaneously to *Tetrahedron Letter*).