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STRUCTURES OF CHAETOGLOBOSIN A AND B, CYTOTOXIC METABOLITES OF CHAETOMIUM GLOBOSUM[1)]

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IN our course of screening program on toxic mold metabolites,[1)] strains of Chaetomium globosum Kuntze ex Fries were noticed by the production of toxic metabolite(s) causing polynuclear cells in cultured HeLa cells.[2)] From the mycelial extract the metabolites, named chaetoglobosin A (I), mp 168-170°, $[\alpha]_D$-270°(MeOH), yellow prisms from CH_2Cl_2, chaetoglobosin B (II), mp 186-187°, $[\alpha]_D$-176°(MeOH), pale yellow needles from benzene, and chaetoglobosin C (III), mp 259-261°, colorless powder from acetone, were isolated by chromatography. The three compounds showed the same molecular formula, $C_{32}H_{36}O_5N_2$, in high resolution mass spectra (observed for I, 528.263, II, 528.265, and III, 528.264 m/e; calcd. 528.262). This communication concerns with the structures of I and II.

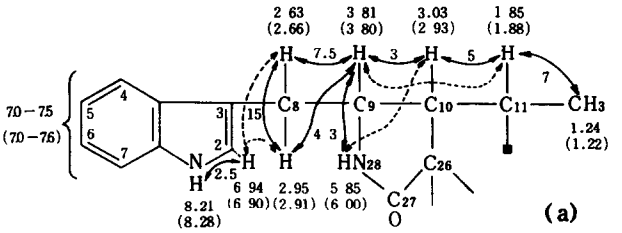
The IR spectra of I (ν_{max}^{KBr} cm^{-1}: 3438, 3259, 2960, 1689 (br., s.), 1615, 1432, 1248, 1052, 983, 969, 760) and II (ν_{max}^{KBr} cm^{-1}: 3440, 2950, 2900, 1690 (br., s.), 1620, 1245, 1040, 972, 746) suggest the presence of -NH, -OH, =CO, aromatic rings, and trans -CH=CH- in the molecules. I forms monoacetate (I'), mp 252°, $C_{34}H_{38}O_6N_2$, while II gives diacetate (II'), mp 257-258°, $C_{36}H_{40}O_7N_2$. The NMR spectra disclosed the presence of one secondary alcohol in I and two in II. The UV spectra of I, I', II, and II' are nearly superimposable (I, λ_{max}^{EtOH} nm (log ε): 223, 245(sh), 274, 282, 292 (4.61, 3.96, 3.82, 3.82, 3.73), II, λ_{max}^{EtOH} nm (log ε): 222, 245(sh), 274, 281, 290 (4.64, 3.99, 3.90,

3.90, 3.83)), indicating the presence of an indole chromophore in I and II. The positive Ehrlich reaction, the strong peak at m/e 130 in the mass spectra, and the NMR data also suggest the presence of the indole moiety in I and II. The other NH was assumed to be that in γ-lactam from the non-basic nature, the IR (the strong absorption around 1690 cm^{-1} devoid of amide II band)[3-5] and the NMR.

The precise decoupling experiments performed on I and I' in $CDCl_3$ and in d_5-pyridine revealed the presence of the groups (a), (b), and (c) in the molecule of I (Chart 1). The summation of these fragments leaves only C_2O_3 in I. The trans-olefinic proton resonances at C_{23} and C_{24} in the fragment (c) appearing in low field and the subtraction of the UV absorption of the indole chromophore from that of I (λ_{max} ca. 240 nm (log ε ca. 3.9)) suggest the presence of a group, -CO-CH=CH-CO-.

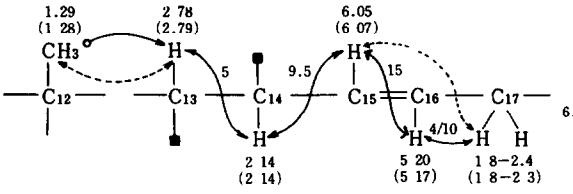
When I was treated with triethylamine or kept in chloroform solution, isomerization occurred to afford II and III. The precise comparison of the NMR spectra of II and the acetate (II') with I and I' revealed that the secondary methyl group at C-11 (fragment (a)) and the tertiary methyl group at C-12 (fragement (b)) in I change into two allyllic methyl groups in II and a secondary alcohol newly appears in II, but the other part of the molecules is essentially the same. The decoupling experiments clearly disclosed the interrelationship of the groups as shown in Chart 2 and the difference between I and II could be explained by the cleavage of an epoxide at C-12-C-13 in I. Thus the sequence C_{11}-C_{12}-C_{13} was established and all the atoms in I and II were revealed.

The presence of an α-ketol group in I and II was suggested by the positive tetrazolium salt reaction and the chemical shift of the carbinyl proton in the fragment (c). There exist weak long range couplings between the carbinyl proton and the C-19, C-23, and C-24 protons respectively. Furthermore the irradiation at the carbinyl proton resulted in the observation of NOE at C-19 and C-23 protons. The influence of acetylation (I→I', II→II') on chemical shifts was also observed for these protons (Chart 1).

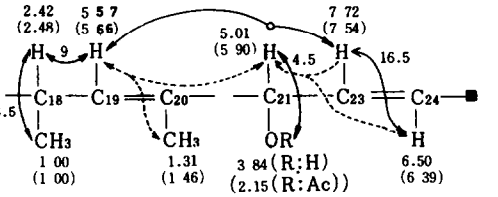


(a)

N_1-H is exchangeable with D_2O very slowly. N_{28}-H is exchangeable rather slowly.



(b)



(c)

The assignments for C_{23}-H and C_{24}-H are alternative.

Chart 1 THE PARTIAL STRUCTURES AND NMR PARAMETERS OF CHAETOGLOBOSIN A (I) AND THE ACETATE (I')

The data are those in $CDCl_3$. The chemical shifts in parentheses are those for I'. ⌒ indicates geminal or vicinal coupling, ⌒ long range coupling, and ⌒ NOE.

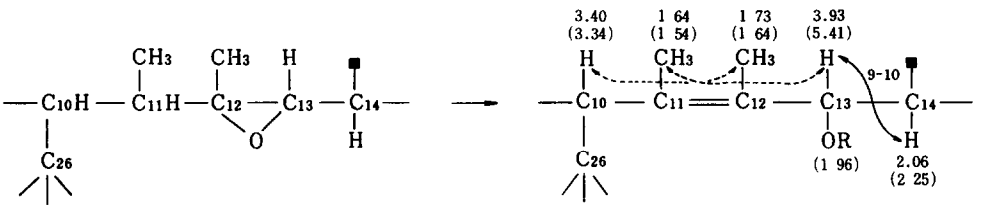
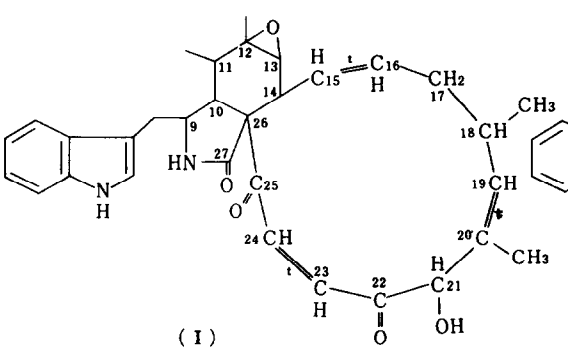
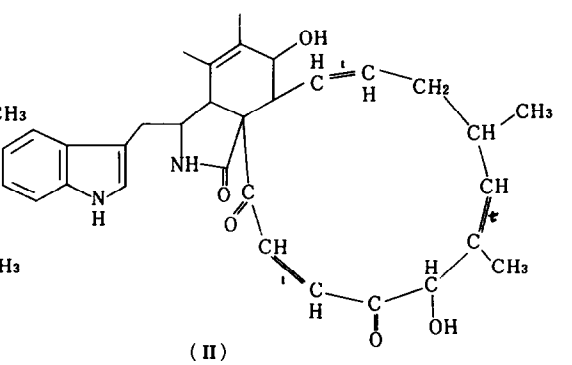


Chart 2 THE PARTIAL STRUCTURE AND NMR PARAMETERS OF CHAETOGLOBOSIN B (II) AND THE ACETATE (II')



(I)



(II)

Thus the sequence C_{20}-C_{21}-C_{22}O-C_{23}=C_{24}-C_{25}=O was suggested. Although the first order analysis was impossible due to the complicated couplings, the coupling patterns of C-17 and C-18 protons suggest that these must be vicinal. Thus the remaining bonds at C-14, C-25, and C-26 (two) must be linked each other.

From these findings the structures (I and II) were put forward for chaetoglobosin A and B as most preferable formulations. The fragmentations in the mass spectra also support the structures. These formulae are analogous to cytotoxic mold metabolites, phomins,[3] zygosporins,[4] and cytochalasins,[5] whose phenylalanine unit is replaced by tryptophane in the formulae I and II. The structures are also in good accord with the biosyntheses from one unit of tryptophane, nine units of acetate-malonates, and three C_1 units.[6]

Further confirmation of the structures including the stereochemistry is now in progress.

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