Communications to the Editor

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DETHIO-TETRA(METHYLTHIO)CHETOMIN, A NEW ANTIMICROBIAL METABOLITE OF CHAETOMIUM GLOBOSUM KINZE EX FR. STRUCTURE AND PARTIAL SYNTHESIS FROM CHETOMIN

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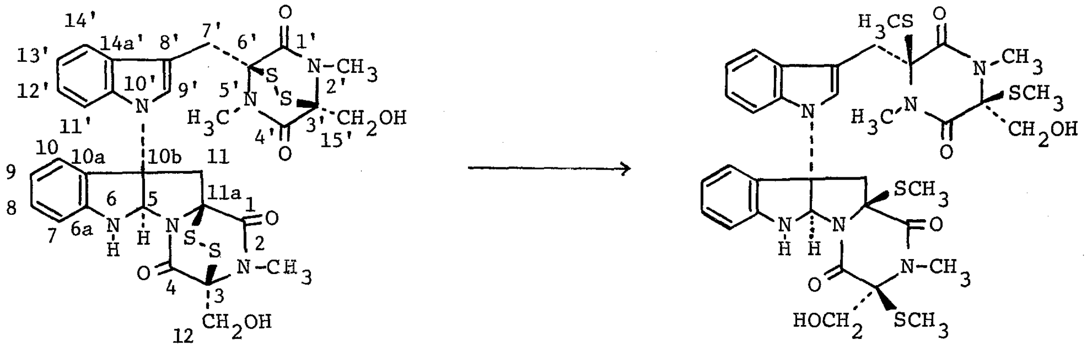
Dethio-tetra(methylthio)chetomin, a new antimicrobial metabolite, was isolated from a fungus, *Chaetomium globosum* KINZE ex FR., and its structure was determined to be 2 on the basis of chemical correlation with chetomin and X-ray crystallographic analysis.

KEYWORDS —— dethio-tetra(methylthio)chetomin; chetomin; fungal metabolite; *Chaetomium globosum*; X-ray analysis

In the preceding communication,1) we reported the identification of geosmin, a musty-smelling metabolite, from the culture of *Chaetomium globosum* KINZE ex FR., which was isolated from a soil sample collected at Suga-daira, Nagano Prefecture. This paper describes the isolation and structure elucidation of a new metabolite from the same strain of fungi.

The fungi were grown on a stationary liquid medium1) containing yeast extract and malt extract at 26°C for 24-30 days without shaking and the whole culture (48 L) was extracted with AcOEt. The extract was separated by silica gel chromatography with acetone-chloroform (1:9) and then by preparative TLC on silica gel, to give chetomin (1)2) (101 mg) and dethio-tetra(methylthio)chetomin (2) (11 mg). These metabolites showed antimicrobial activity against *Escherichia coli* W3110, *Staphylococcus aureus* 209P, and others.

Dethio-tetra(methylthio)chetomin (2), mp 191-193°C (MeOH), $[\alpha]_D$ +174° ($CHCl_3$), has the molecular formula $C_{35}H_{42}O_6N_6S_4$ (FD-MS M^+ m/z: 770) and showed a positive Ehrlich reaction, the base peak at m/z 130 in the mass spectrum, and UV absorptions at 212, 220_{sh}, 245_{sh}, 288, and 296 nm (log ε: 4.86, 4.82, 4.18, 4.00, and 4.02),3) suggesting the presence of indole group(s) in 2. Its IR (KBr) spectrum revealed a characteristic CO band at 1650 cm^{-1} and the ^1H-NMR spectrum4) gave a pattern closely similar to that of chetomin (1)2) except for additional four Me singlets at δ 2.02-



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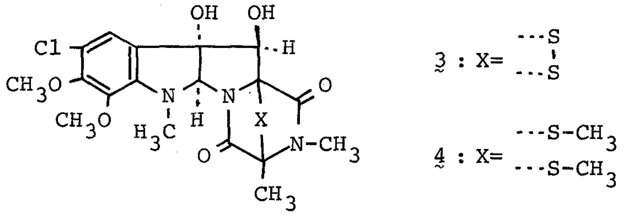

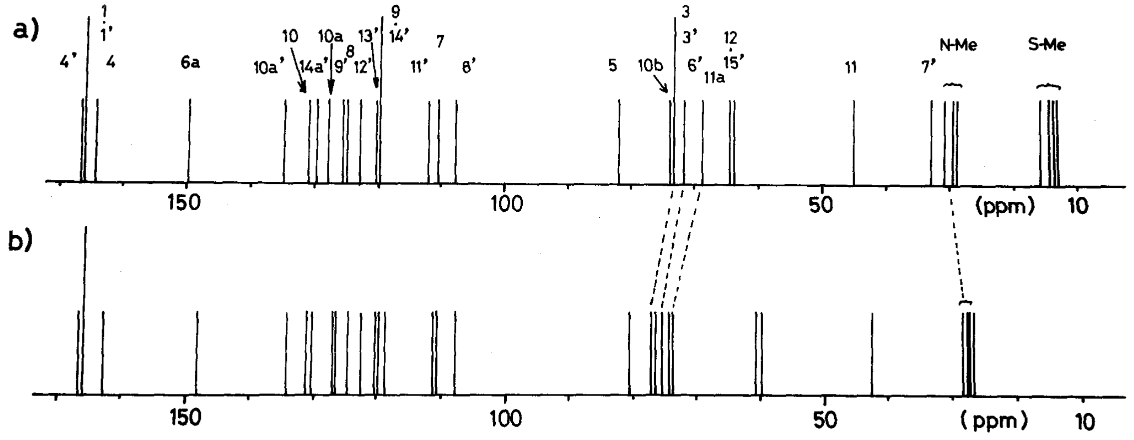

Fig. 1. The ^{13}C-NMR Spectra of a) Dethio-tetra(methylthio)chetomin (2) and b) Chetomin (1) (in $CDCl_3$, 90 MHz)

2.32, which could be ascribed to S-Me groups. Also the ^{13}C-NMR spectrum of 2 resembled that of 1 (Fig. 1), but in the former (2), four additional signals of Me carbons appeared at δ 13.3-15.7 and three Me carbon signals (δ 28.6-30.7) shifted downfield by 1.2-2.5 ppm, while signals of four quarternary sp^3 carbons (δ 68.5-73.0) moved upfield by 4-5 ppm. This behavior is comparable with that observed between sporidesmin (3) and sporidesmin-D (4).$^{5)}$

At this stage, our effort was turned to the chemical correlation of 2 with 1. Taylor et al.$^{6)}$ reported that $NaBH_4$ reduction of 1 in the presence of CH_3I and pyridine yielded solely deformyltetra-S-methylchetomin. In the present study, we re-examined this reaction under controlled conditions. Thus, treatment of 1 (5 mg) with CH_3I (0.2 ml), pyridine (0.01 ml), and $NaBH_4$ (1 mg) in THF-MeOH at 10°C for 5 min afforded the desired tetra-S-methyl compound (2) (3 mg), mp 190.5-191.5°C, FD-MS m/z: 770 (M^+). This substance was proved to be identical with the natural sample (2) by IR (KBr), MS, and ^{1}H-NMR comparisons.

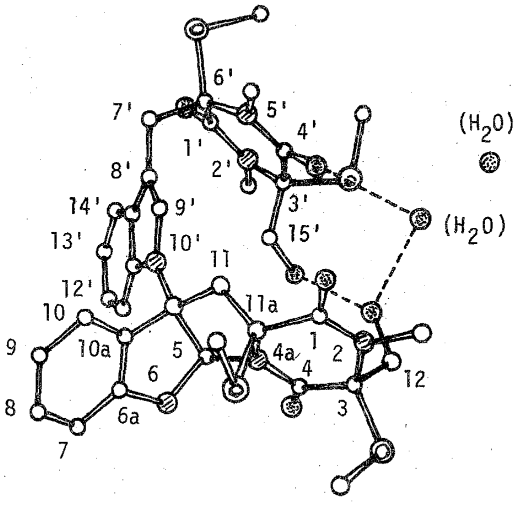

Fig. 2. A Perspective Drawing of Dethio-tetra(methylthio)-chetomin

○ Carbon
◍ Oxygen
⊘ Nitrogen
◎ Sulfur

Finally, the detailed structure and relative stereochemistry of dethio-tetra-(methylthio)chetomin (2) were established by the X-ray crystallographic study. Crystal data (crystallized from acetonitrile): $C_{35}H_{42}O_6N_6S_4 \cdot 2H_2O$; monoclinic, space group $P2_1$; a=13.380(13), b=13.767(9), c=10.796(8) Å, β=95.5(1)°; Z=2, D_{calcd}=1.354 gm/cm^3. The intensity data were collected in the 2θ-ω scan mode using a Rigaku AFC-5 diffractometer with Mo-Kα radiation (λ=0.71073 Å) and 1549 independent reflections ($Fo > 3\sigma(Fo)$) were used for the structure analysis. The structure was solved by the direct method with the aid of MULTAN. Refinement by block-diagonal least-squares calculations led to a final R value of 0.097. A computer generated perspective drawing of dethio-tetra(methylthio)chetomin (2) is shown in Fig. 2.

The absolute stereochemistry of 2 and chetomin (1) and the detailed aspect of their biological activities will be reported elsewhere.

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