A NEW ANTIBIOTIC, TRICHORIN A

Sir:

In the course of screening antibiotics active against Gram-negative bacteria, we found a species of *Trichoderma* (strain K-472) produces a new antibiotic, trichorin A.

The fungus was fermented at 28°C for 72 hours on a reciprocal shaker using a Sakaguchi flask containing 100 ml of medium composed of 2% glucose, 1% peptone, 0.5% meat extract, and 0.3% sodium chloride at pH 7.0. The mycelial cake thus obtained was extracted with acetone and then ethyl acetate. The extracts were combined and evaporated *in vacuo*. The residue was dissolved in ethyl acetate, washed with 5% sodium carbonate, and evaporated *in vacuo* leaving a residue, which was dissolved in benzene and chromatographed on silica gel giving trichorin A and a small amount of trichorin B.

Trichorin A was obtained from acetone - *n*-hexane as colorless needles: $C_{20}H_{20}N_2O_8S_2$; m.p. 234~246°C (dec.); $[\alpha]_D^{24}$ −190.5° (dioxane); λ_{max}^{EtOH} 205 nm (ε 38,000), 240 sh (11,000), and 280 sh (3,100); ν_{max}^{KBr} 3490, 3330, 1715, 1685, 1606, 1508, 1215, 1101, 1025, 971, 831, 805, and 787 cm^{-1}. Its CD curve showed COTTON effects at 225 nm ([θ] −55,400) and 291 nm ([θ] +7,450), and was similar to that of dehydrogliotoxin (**I**).[1] The presence of amide bands in the IR in conjunction with the negative COTTON effect at 225 nm indicates the presence of a dioxopiperazine[2~4] moiety in trichorin A. Moreover, trichorin A triacetate shows an ion at *m/e* 64 due to loss of S_2[5] in the mass spectrum, suggesting that it has a disulfide-bridged dioxopiperazine system and is a compound belonging to the gliotoxin group.[4,6]

When trichorin A was dissolved in pyridine for NMR examination it was converted into trichorin B, which had been obtained as a minor metabolite. Therefore, we prepared trichorin A triacetate by adding a small amount of pyridine to a solution of trichorin A in acetic anhydride. The acetate was crystallized from methylene dichloride - ether - isopropyl ether to give colorless needles: $C_{26}H_{26}N_2O_{11}S_2$; m.p. 212~214°C (dec.); $\nu_{max}^{CHCl_3}$ 1780, 1729, 1609, 1088 and 1036 cm^{-1}; λ_{max}^{EtOH} 205 nm (ε 43,900), 240 sh (11,600) and 275 sh (3,600).

Trichorin B was obtained from ethanol as yellow plates: $C_{20}H_{20}N_2O_8S$; m.p. 230~238°C (dec.); ν_{max}^{KBr} 3300, 1691, 1678, 1606, 1178, 1105, 1050, 992 and 810 cm^{-1}; λ_{max}^{EtOH} 248 nm (ε *ca.* 10,000) and 341 (*ca.* 20,000). Acetylation of trichorin B gave a triacetate: yellow prisms; $C_{26}H_{26}N_2O_{11}S$; m.p. 120~125°C (from ether); $\nu_{max}^{CHCl_3}$ 3355, 1750, 1706, 1646, 1606, 1090, 1045 and 1033 cm^{-1}; λ_{max}^{EtOH} 246 nm (ε 14,100) and 327 (18,200).

The combined results of ^1H NMR and ^{13}C FT NMR examination together with evidence from chemical degradation indicate that trichorin B triacetate has partial structure **II**, two acetoxy groups and a *cis*-disubstituted ethylenic double bond. Structural elucidation of trichorins A and B will be described elsewhere. Trichorin A has a weak activity against Gram-negative bacteria (MIC 50~100 μg/ml) and B has no activity.

TERUAKI KATAYAMA
HITOSHI MINATO
KIKUO ISHII
EIJI KONDO

Shionogi Research Laboratory
Shionogi & Co., Ltd.
Fukushima-ku, Osaka, 553 Japan

(Received March 10, 1977)

References

1) LOWE, G.; A. TAYLOR & L. C. VINING: Sporidesmins. VI. Isolation and structure of dehydrogliotoxin, a metabolite of *Penicillium terlikowskii*. J. Chem. Soc. (C) 1966: 1799~1803, 1966
SAFE, S. & A. TAYLOR: Sporidesmins. XI. The reaction of triphenylphosphine with epipolythiodioxopiperazines. J. Chem. Soc. (C) 1971: 1189~1192, 1971

2) HERMANN, H.; R. HODGES & A. TAYLOR: Sporidesmins. V. The stereochemistry of the bridged dioxopiperazine ring in sporidesmins and in gliotoxins. J. Chem. Soc. 1964: 4315~4319, 1964

3) BALASUBRAMANIAN, D. & D. B. WETLASFER: Optical rotatory properties of diketopiperazines. J. Am. Chem. Soc. 88: 3449~3450, 1966
4) NAGARAJAN, R.; L. L. HUCKSTEP, D. H. LIVELY, D. C. DELONG, M. M. MARSH & N. NEUSS: Aranotin and related metabolites from *Arachniotus aureus*. I. Determination of structure. J. Am. Chem. Soc. 90: 2980~2982, 1968
5) BUDZIKIEWICZ, H.; C. DJERASSI & D. H. WILLIAMS: Structure elucidation of natural products by mass spectrometry. 2: 249~253, Holden Day, Inc., San Francisco, Calif., 1964
6) BELL, M. R.; J. R. JOHNSON, B. S. WILDI & R. B. WOODWARD: The structure of gliotoxin. J. Am. Chem. Soc. 80: 1001, 1958
BEECHAM, A. F.; J. FRIDRICHSONS & A. M. MATHIESON: The structure and absolute configuration of gliotoxin and the absolute configuration of sporidesmin. Tetrahedron Lett. 1966: 3131~3138, 1966 and references cited therein.
RAHAMN, R.; S. SAFE & A. TAYLOR: Sporidesmins. IX. Isolation and structure of sporidesmin E. J. Chem. Soc. (C) 1969: 1665~1668, 1969 and references cited therein.