

Communications to the editor

VERTISPORIN, A NEW ANTIBIOTIC FROM
VERTICIMONOSPORIUM DIFFRACTUM

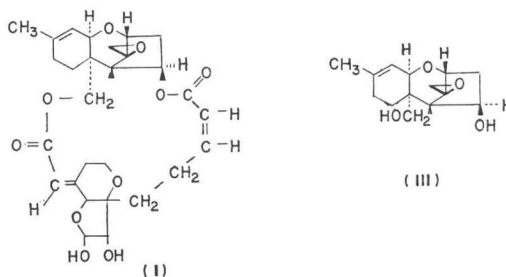
Sir:

In a continuing search for fungal metabolites with cytotoxic activity, we have found that the fungus *Verticimonosporium diffractum* strains TM-2098 and TM-2492 produced a new cytotoxic antibiotic, vertisporin (I). The fungi were isolated from a dead leaf and identified according to MATSUSHIMA¹. Fermentations with strain TM-2098 were conducted under submerged culture conditions for 5 days at 28°C in a medium containing 2% glucose, 1% peptone, 0.5% meat extract and 0.3% sodium chloride. The pH was adjusted to 6.8 prior to sterilization. Twenty liters of medium were used and the culture broth was treated as follows:

The culture broth was filtered and the filtrate was extracted with ethyl acetate with stirring at room temperature. The extract (1.52 g) was chromatographed on silica gel (Merck, 60 g) to give crude vertisporin (530 mg), which was purified by preparative t.l.c. on silica gel (solvent system: chloroform-methanol (20:1), R_f 0.40) affording a light yellow viscous oil (348 mg).

Vertisporin (I) was obtained from isopropyl ether as a colourless amorphous powder, C₂₉H₃₈O₁₀, M⁺ 544, m.p. 176~183°C, [α]_D²⁰ +62.5° (±1.5°). It showed an absorption maximum at 216 nm (ε 19,500) in the u.v. and absorption bands at 1723 and 1717 cm⁻¹ in the i.r. spectra. Moreover, as a dicarboxylic acid (II) C₁₄H₁₈O₈, m.p. 219~232°, was obtained by hydrolysis with potassium hydrogen carbonate, vertisporin has two α, β-unsaturated carboxyl-systems. On acetylation with acetic anhydride in pyridine, (I) gave a diacetate, m.p. 145~155°C. Vertisporin has therefore two hydroxy-groups. From these results, it was assumed that the remaining four oxygen atoms in vertisporin are present in ether-linkages.

On hydrolysis of vertisporin with an alkali, it gave a diol (III), C₁₈H₂₂O₄, m.p. 159~161.5°C, as well as the above-mentioned dicarboxylic acid (II). The former afforded a



diacetate, m.p. 84~86.5°C.

The diol (III) and its diacetate were clarified to be identical with verrucarol^{2,3} and its diacetate, respectively, by comparison of the i.r. and the n.m.r. spectra. Therefore, vertisporin is a new cytotoxic compound belonging to the roridin group⁴⁻⁸, and assumed to be represented by the formula (I). Structural elucidation of vertisporin will be described in the following paper.

Vertisporin showed limited antifungal activity and inhibited only the growth of *Trichophyton asteroides* at the concentration of 10 mcg/ml.

The cytotoxic effect (ED₅₀) against HeLa cells was 0.001 mcg/ml (ED₅₀ of verrucarol A was 0.0007 mcg/ml).

During the isolation of this antibiotic, one of the researchers suffered from skin irritation 24 hours after contact with solvent extracts. A solution, 0.05 ml (100 mcg/site), of vertisporin in acetone was painted on the dehaired skin of mouse, rat, and guinea pig. In every case, a red ring of hyperemic edema was observed within 24 hours, which changed to a necrosis after 3 days.

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