A new Toxic Metabolite of *Pithomyces chartarum* related to the Sporidesmins

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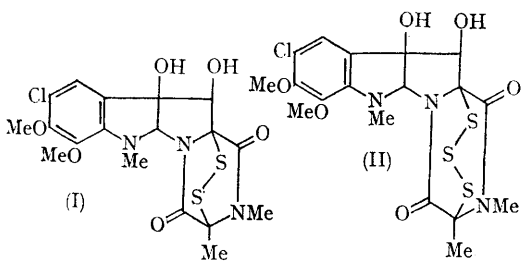
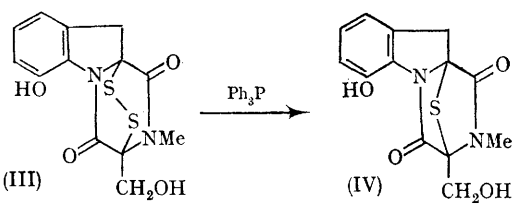
WE have reported[1] that *Pithomyces chartarum* produces several sulphur-containing metabolites other than sporidesmin (I). A further example has now been isolated by chromatography (silica gel) of the sporidesmin fraction[2] with the solvent n-pentane–t-butyl alcohol (17 : 3). Early fractions from this column contained the new metabolite (named sporidesmin-E) which separated from ether as the etherate, m.p. 155—165°, $[\theta]_{306}$ + 2920°; $[\theta]_{263}$ −44,000° (*c* 0·46, MeOH), *m/e* 505, and 507. Elemental analysis of the solvate gave values which agreed with the molecular formula $C_{18}H_{20}ClN_3O_6S_3$. Sporidesmin-E formed a diacetate and on treatment with sodium borohydride and methyl iodide gave sporidesmin-D.[1] Treatment of sporidesmin (I) with an excess of sulphur and phosphorous pentasulphide in carbon disulphide gave sporidesmin-E in 40% yield. Sporidesmin-E[1] reacted with triphenylphosphine in ether to give sporidesmin[2] the corresponding disulphide in 50% yield, thus providing additional evidence for proposed structure (II).



Dehydrogliotoxin (III)[3] also reacted smoothly with triphenylphosphine in tetrahydrofuran to give a product (70%, m.p. 114—115°), *m/e* 292·0519 ($C_{13}H_{12}N_2O_4S$ requires 292·0518). Its n.m.r. spectrum was similar to that of dehydrogliotoxin *i.e.* τ ($CDCl_3$) 5·60 (-CH_2OH) and 5·95 and 6·71 p.p.m. (d, J_{AB} — 21 c./sec., benzylic methylene). Its i.r. and u.v. spectra (λ_{max} 2850 Å, log ϵ 3·64) were also analogous to those of dehydrogliotoxin. The formula (IV) is therefore proposed for this product.

The n.m.r. spectrum of sporidesmin-E [τ, ($CDCl_3$) 2·92, 2·93 (intensity 1), 4·59, 4·71 (intensity 1), 5·38, 5·48 (intensity 1), 6·10, 6·13, 6·17 (intensity 6), 6·50, 6·67, 6·86, 6·98 (intensity 6), 8·00, and 8·05 (intensity 3)] suggested that it was a mixture of isomers. The chemical evidence given above requires that this isomerisation involves only the sulphur function. Cyclic trisulphides are known to exist in different stable conformations,[4] and we consider this the most likely explanation for these n.m.r. results.

The toxicity of sporidesmin-E to cultures of HeLa cells has been examined by the method used previously for sporidesmin.[5] No cytotoxic activity was observed in the case of sporidesmin at concentrations less than 1 mμg./ml., whereas the end-point found for sporidesmin-E in strictly comparable tests was 0·1 mμg./ml. Thus sporidesmin-E is the most cytotoxic mould metabolite described so far.



The stepwise desulphurisation of these natural products is clearly of diagnostic and biological interest and other examples are currently under investigation. It has been found that the monosulphide (IV) at 65 μg./ml. inhibits the growth of *Bacillus subtilis*.

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