

The Cytochalasins, a New Class of Biologically Active Mould Metabolites

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WE report a new class of mould products for which the name cytochalasins (*cytos* = cell, *chalsis* = relaxation) has been proposed as descriptive of their novel biological effects¹ which were observed by Dr. S. B. Carter of these laboratories. We have isolated four cytochalasins—A and B from *Helminthosporium dematioides* and C and D from *Metarrhizium anisopliae*—and cytochalasin-like biological activity has been observed in filtrates from fermentations of several other moulds.

Our work on cytochalasin A (C₂₈H₃₅NO₅) and cytochalasin B (C₂₉H₃₇NO₅), the key features of which are summarized here, leads us to suggest structures (Ia) and (Ib) respectively for the compounds.

The relationship between cytochalasins A and B was established by oxidation of the latter to the former with manganese dioxide. The presence of the R : C-CH^t=CH-CO₂R system could be deduced from the n.m.r. spectra of the compounds, and was

confirmed by reduction of cytochalasin B with sodium borohydride to a dihydro-compound, treatment of which with alkali and then acid gave an isomeric γ -lactone (II), whose formation also revealed the presence of a large-ring lactone involving a tertiary hydroxyl group in cytochalasins A and B.

Ozonolysis of the γ -lactone (II) gave formaldehyde and the aldehyde (III); we were unable to isolate any pure fragment from the remainder of the molecule. The n.m.r. spectrum of cytochalasin B revealed the presence of sequence (IV) and hydrogenation of the γ -lactone (II) to compounds (V), (VI), and (VII) permitted this sequence to be extended to (VIII).

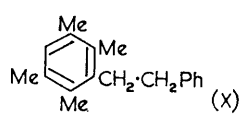
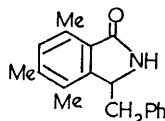
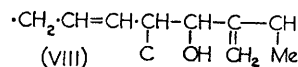
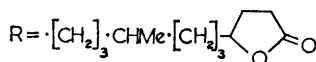
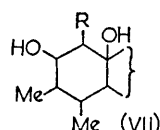
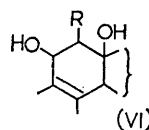
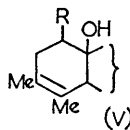
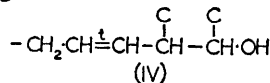
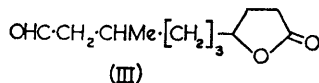
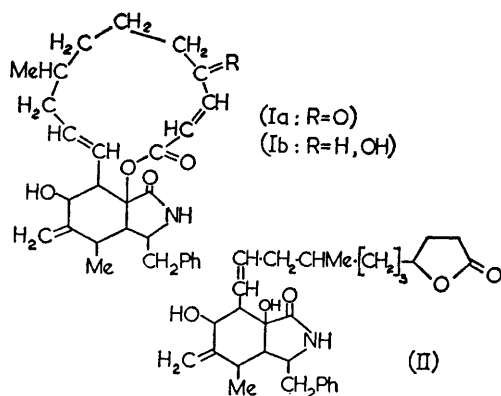
The presence of a benzyl group in cytochalasins A and B was deduced from n.m.r. and mass spectroscopy, and from the formation of benzoic acid on oxidation of cytochalasin B. That the benzyl group was part of a phenylethylamine system was indicated by the presence of an ion

$C_8H_{10}N^+$ in the mass spectrum of the cytochalasins and their derivatives, replaced by $C_8H_{16}N^+$ in compounds in which the benzene ring had been reduced. The (neutral) nitrogen atom was allocated to a γ -lactam ring on the basis of the resistance of the compounds to acid hydrolysis and the presence of a band at about 1695 cm^{-1} in the infrared spectra of the cytochalasins and their derivatives. The presence of the γ -lactam group was confirmed by the formation of the phthalimidine (IX) by fusion of the γ -lactone (II) with alkali. The orientation of the substituents in phthalimidine (IX), and hence the orientation of the γ -lactam in the cytochalasins, was established by degrading it to the hydrocarbon (X) which was synthesized from durene.

The above facts permit the unique structures (Ia) and (Ib) to be assigned to cytochalasins A and B and these structures are in accord with other degradative and spectroscopic evidence.

Recently Professor Ch. Tamm (Basel) suggested² that cytochalasin B might be identical with phomin which he has isolated from a *Phoma* sp., and comparison of the two compounds has proved this to be so. Professor Tamm has independently, and by different reasoning, arrived at structure (Ib) for phomin and a preliminary account of his work has now appeared.^{3*}

Cytochalasins C and D are isomers, $C_{30}H_{37}NO_6$, whose relationship to each other has not been established. Cytochalasin C does not possess a large lactone ring; on alkaline hydrolysis it yields a carboxylic acid, $C_{23}H_{29}NO_4$, which (on spectroscopic evidence) contains sequence (IV), a phenylethylamine moiety, a lactam ring, and a secondary methyl group. In addition to their qualitatively identical biological activity, therefore, the cytochalasins form a structurally related class of compounds, though considerable differences are apparent.



(Received, November 17th, 1966; Com. 903.)

* We are indebted to Professor Tamm for drawing our attention to his work and for permitting us to see his manuscript before publication.

¹ Cf. *New Scientist*, 1966, **33**, 170.

² Ch. Tamm, personal communication.

³ W. Rothweiler and Ch. Tamm, *Experientia*, 1966, **22**, 750.