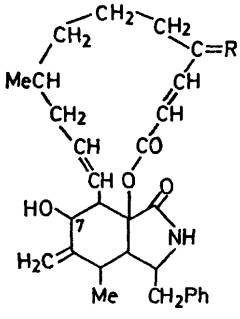
The Structures of the Fungal Metabolites Cytochalasins E and F

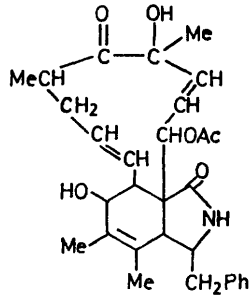
By D. C. ALDRIDGE, B. F. BURROWS, and W. B. TURNER*
(*Imperial Chemical Industries Ltd., Pharmaceutical Division, P.O. Box 25, Mereside, Alderley Park, Macclesfield, Cheshire* SK10 4TG)

Summary Cytochalasin E, a metabolite of *Rosellinia necatrix*, is shown to have structure (**6a**); cytochalasin F, a minor metabolite of *Helminthosporium dematioideum*, is shown to have structure (**4**).

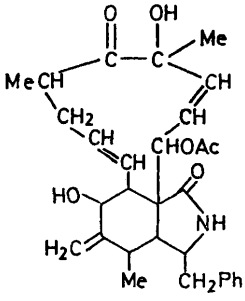
THE cytochalasins are a biosynthetically related group of fungal metabolites which produce unusual and interesting effects on mammalian cells in tissue-culture.[1] Cytochalasins A (**1a**) and B (**1b**) are metabolites of *Helminthosporium dematioideum*[2] and of a *Phoma* sp.[3] Cytochalasins C (**2**) and D (**3**) are metabolites of *Metarrhizium anisopliae*,[4] cytochalasin D having also been isolated from *Zygosporium masonii*[5] along with several closely related compounds.[6] We now report the structures of two new members of the class.



(1a; R = O)
(1b; R = H,OH)



(2)



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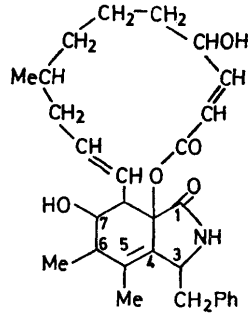
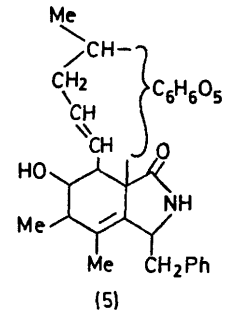
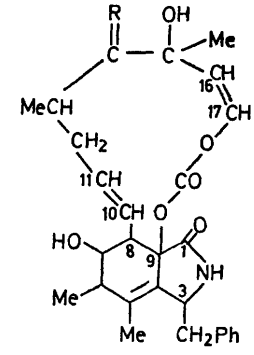


(4)

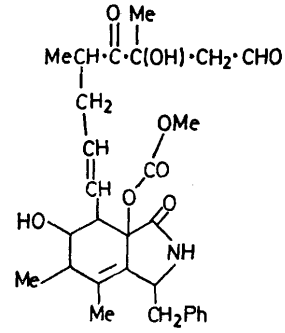
Cytochalasin F, $C_{29}H_{37}NO_5$, a minor metabolite of *H. dematioideum*, is isomeric with cytochalasin B. Its n.m.r. spectrum shows most of the features of the spectrum of cytochalasin B, the significant differences being (i) the absence of signals due to an exocyclic methylene group, (ii) the presence of a signal due to a vinylic methyl group, and (iii) a change in the pattern of the signal due to H-7. These features of the n.m.r. spectrum of cytochalasin F are consistent with structure (**4**), and this structure was confirmed by mild treatment of cytochalasin F with acid to give cytochalasin B (**1b**) and the $\Delta^{5,6}$-isomer of (**4**) whose n.m.r. spectrum reveals the presence of two vinylic methyl groups [*cf.* cytochalasin C (**2**)]. Compound (**1b**) and the $\Delta^{5,6}$-isomer of (**4**) are stable to acid, so that the formation of the exocyclic methylene group must involve a hydride shift.



(5)



(6a; R = O)
(6b; R = H, OH)



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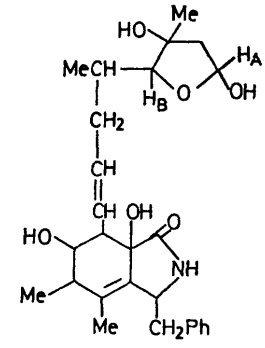

(8)

Cytochalasin E, $C_{28}H_{33}NO_7$, is produced by *Rosellinia necatrix*.[7] Comparison of its n.m.r. spectrum with that of cytochalasin F reveals the presence of the part-structure (**5**), and cytochalasin E undergoes acid-catalysed rearrangement to give compounds analogous to those derived from cytochalasin F. In addition to the signals arising from part-structure (**5**), the n.m.r. spectrum of cytochalasin E shows signals due to a tertiary methyl group, a tertiary hydroxy-group, and a *cis*-disubstituted double bond (sharp AB quartet). A structure which accommodates these features is (**6a**), containing an unusual vinyl carbonate residue. Structure (**6a**) is consistent with i.r. bands at 1765 (vinyl ethyl carbonate absorbs[8] at 1765) and 1720 cm^{-1} (ketone)

and with the chemical shift of the tertiary methyl group (τ 8·5, *cf.* cytochalasins C and D[4]), and was proved by the following reactions. Hydrogenation of cytochalasin E over Pd–C yielded the $\Delta^{16,17}$-dihydro-derivative in which the band originally present at 1765 now appears at 1747 cm^{-1} (diethyl carbonate absorbs[8] at 1745 cm^{-1}), and the AB quartet of the disubstituted double bond is replaced by a two-proton multiplet at τ 5·8. Treatment of cytochalasin E with sodium bicarbonate in aqueous methanol yields the aldehyde (**7**) (τ 1·3, t). Reduction of cytochalasin E with $LiAlH_4$ yields the secondary alcohol (**6b**) and the lactol (**8**) $C_{27}H_{37}NO_6$. The i.r. spectrum of the lactol shows a single carbonyl band (1700 cm^{-1}) due to the lactam, and its n.m.r. spectrum shows signals due to H_A (τ 4·75, m) and H_B (τ 6·28, d, J 9 Hz).

We have already suggested[4] that the macrolide ring of cytochalasins A and B might be derived from a carbocyclic precursor. The structure of cytochalasin E raises the possibility that the carbonate group might be formed by insertion of two oxygen atoms into a carbon chain; this possibility is made more likely by the similarity of the large ring of cytochalasin E and that of cytochalasins C and D. The position of the double bond in the cyclohexane ring of cytochalasins E and F, and its ready migration to positions where it appears in cytochalasins A, B, C, and D, suggests that the latter compounds are derived from a precursor which has a double bond arranged as in E and F.

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