The Biosynthesis of Brefeldin A

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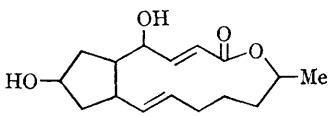
THE occurrence of the fungal metabolite brefeldin A (I), $C_{16}H_{24}O_4$, has been reported from four different species of fungi and also from *Curvularia lunata*. This compound which has significant cytotoxic and antifungal activity has a cyclopentane ring structure whose biogenetic origin is not obvious from an examination of the structural formula.

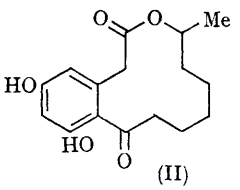
Labelling experiments discussed below indicate that brefeldin A is wholly acetate derived and is structurally similar to the macrolide curvularin (II), $C_{16}H_{20}O_5$, also isolated from a *Curvularia sp.* and acetate derived.[1]

The literature has revealed only a small number of nonterpenoid cyclopentane structures, the prostaglandins, calythrone, and terrein being examples, and for this reason the biosynthetic origin of the cyclopentane ring in brefeldin A was investigated.

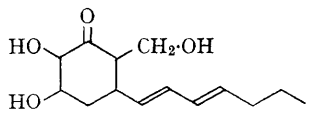
The five-membered ring in brefeldin A could arise by a direct oxidative condensation of a polyketide structure or by a ring contraction of a six-membered ring intermediate of the palitantin (III) type.



(I)



(II)



(III)

Palitantin and frequentin are co-metabolites with brefeldin A in *Penicillium berfeldianum*. [1-^{14}C]-acetate-labelling experiments with brefeldin A isolated from *Curvularia lunata* are summarised in

TABLE

[1-^{14}C]*Acetate-labelled brefedlin A*

	Average RMA (10^{-3})	% Label	Theoretical %
Brefeldin A	435·5, 427·5	100·0, 100·0	100·0
Hexane-1,5-diol di-*p*-nitrobenzoate	150·4, 159·0	34·6, 37·2	37·5
Ethyleneglycol di-*p*-nitrobenzoate	48·4, 53·75	11·3, 12·5	12·5
3,4-Dihydroxymethylcyclopentan-1-ol tri-*p*-nitrobenzoate	159·5, 166·5	36·7, 39·0	37·5
Acetic acid(Kuhn–Roth)	53·2 54·3,	12·2, 12·5	12·5

the Table. The degradative products were obtained by a modified reductive ozonolysis as described by Sigg.[2] These results indicate that brefeldin A is formed from eight acetate units and that the cyclopentane ring has not been produced from a palitantin precursor by a ring contraction since if this were the case the 3,4-dihydroxymethylcyclopentan-1-ol ester obtained by degradation would be expected to contain four labels and have 50% of the initial activity. The results are consistant with a direct oxidative condensation, although it is not possible to exclude a ring contraction of a non-palitantin precursor. This last possibility is unlikely when the co-production of acylorcinol metabolites, palitantin, frequentin and brefedlin A by *P. brefeldianum* are considered.

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[1] A. J. Birch, O. C. Musgrave, R. W. Rickards, and H. Smith, *J. Chem. Soc.*, 1959, 3146.
[2] H. P. von Sigg, *Helv. Chim. Acta*, 1964, **47**, 1401.