Biosynthesis of Cochlioquniones

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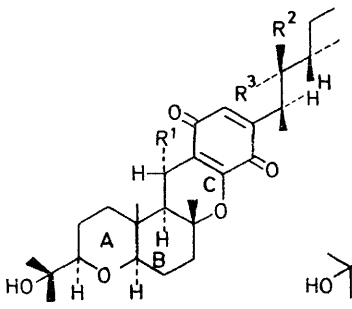
Summary The mixed biosynthesis of cochlioquinones A (I) and B (II) in *Cochliobolus miyabeanus* occurs through the introduction of a farnesyl unit onto an aromatic precursor whose secondary methyl groups derive from methionine.

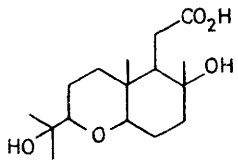
COCHLIOQUINONES A (I) and B (II) are metabolites isolable from a strain of *Cochliobolus miyabeanus*.[1] Their structures have been determined by chemical, spectroscopic, and crystallographic evidence.[2]

[2-^{14}C]Mevalonolactone is incorporated into cochlioquinones A (15%) and B (3%) exclusively into the C_{15} terpenoid unit (rings A, B, and C). This is shown by treatment of (II) with alkaline H_2O_2. The acid (III)[2] thus obtained has the same molar radioactivity as the starting material. Chromic oxidation in acetic acid of the γ-lactone,[2] obtained by dehydration of (III) with acetic anhydride, yields acetone containing one third of the radioactivity of the starting material.

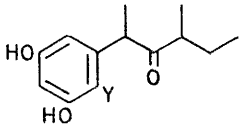
These data indicate that the biosynthesis of (I) and (II) occurs through the introduction of a farnesyl unit onto a precursor of non-terpenoid origin. The formation of this precursor occurs through the intervention of methionine. In fact, [*Me*-^{14}C]methionine is incorporated into (I) (1·59%) and (II) (0·86%). Furthermore, oxidation of (I) thus obtained with alkaline $KMnO_4$ yields (IV),[2] isolated by t.l.c. as its *p*-bromophenacyl ester, whose radioactivity has 96·5% of the radioactivity of (I); however (III) prepared



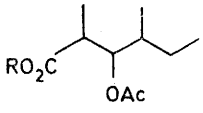
(I) R^1 = OH, R^2 = H, R^3 = OAc
(II) R^1 = H, R^2, R^3 = O



(III)



(VI)



(IV) R=H
(V) R=*p*-$BrC_6H_4COCH_2$

from (II) contains only 2% of the original radioactivity. Since the possibility of a small incorporation of [*Me*-^{14}C]-methionine into terpenoids is known,[3] it can be concluded that, the two secondary methyl groups of the open side-chain of (I) or (II) derive from methionine.

Feeding of [3-^{14}C]propionic acid gives 0·85% incorporation into (I) and 0·41% into (II). Treatment of these samples as before yields (III) (93% retention of the radioactivity) and (V) (4% retention) indicating that incorporation of the radioactive methyl group of propionic acid is more efficient on the terpenoid part of the molecule of cochlioquinones. Hence it can be thought that propionic acid undergoes a rapid degradation to acetic acid which is rapidly transformed into farnesol and slowly incorporated into the second biosynthetic intermediate of the cochlioquinone molecule.

This intermediate could be (VI) (Y = CO_2H or H), deriving from the double methylation of an esaketide by adenosylmethionine.

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[2] J. R. Carruthers, S. Cerrini, W. Fedeli, C. G. Casinovi, C. Galeffi, A. M. Torracca Vaccaro, and A. Scala, *Chem. Comm.*, 1971, 164.
[3] A. K. Bose, K. S. Khanchandani, and B. L. Hungund, *Experientia*, 1971, 1403.