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THE BIOSYNTHESIS OF CANESCIN: A C_1-UNIT IN A CHAIN

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In accord with our predictions (1), methionine-derived C_1-units are usually found attached to aromatic rings (2) or aliphatic chains (3). The only reported examples of a C_1-unit in a carbon chain are in the ethyl group of the side-chain of sitosterols (4) which was predicted (5) by mechanistic analogy with other C-alkylation processes which it basically resembles, and in the tropone ring (6) where incorporation of the unit may well involve a rearrangement, the initial step being methylation of an aromatic system.

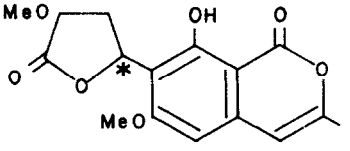
We now report a basically different type of incorporation in which a C_1-unit introduced into an aromatic ring acts as the point of attachment of a new chain. The mould metabolite canescin from Aspergillus malignus has the structure (I) (7). Incorporations of [^{14}C]-acetic acid and malonic acid, to be described elsewhere (8), confirm the expected polyketide origin of the isocoumarin nucleus. [^{14}C-Me]-Methionine introduced label into the molecule with about 20% efficiency and demethylation showed 51.6% of the radioactivity to be in the OMe. Kuhn-Roth oxidation gave inactive acetic acid, showing that the remaining radioactivity is not randomised.

Permanganate oxidation of trimethylcanescin (II) gave (III) containing 45.2% of the radioactivity. Oxidation of canescin, by the Lemieux-Rudloff method, gave methoxysuccinic acid (7) containing all of the initial radioactivity. The only common carbon in these fragments is asterisked in (I) and therefore contains approximately half of the radioactivity of the canescin. Further degradations to be described (8) amply confirm this assignment.

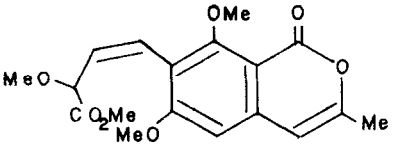
It is of interest that this methionine-derived atom is in the same position as the similarly derived carboxyl carbon in citrinin (IV). The strain of Penicillium canescens which originally gave canescin now gives only citrinin, which indicates a fairly close biogenetic relationship.

The best biosynthetic source of the remaining γ-lactone carbons so far defined by tracer incorporation is [^{14}C]-succinic acid, although [^{14}C]-malic acid is also incorporated through a symmetrical intermediate. Various mechanisms can be envisaged for the condensation, involving oxidation of introduced Me to an aldehyde group on the isocoumarin nucleus and addition of succinic or fumaric acid as the other fragment, decarboxylation occurring in the process.

Canescin is a mixture of two stereoisomers (at the benzylic lactone centre) and the γ-lactone ring may be generated by chemical, rather than enzymic, cyclisation of carboxyl on to an olefinic intermediate.



I



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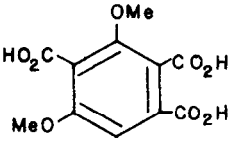
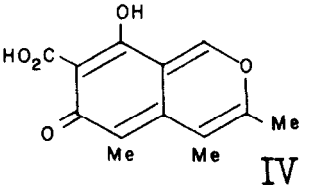


III



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REFERENCES

(1) A.J. Birch, P. Elliott and A.R. Penfold, Aust.J.Chem., 7, 169 (1954); A.J. Birch, Fortschr.Chem.org.Naturstoffe, 14, 186 (1957).

(2) A.J. Birch, R.J. English, R.A. Massy-Westropp, M. Slaytor and H. Smith, Proc.Chem.Soc., 204 (1957), J.Chem.Soc., 305 (1958); E. Schwenk, G.J. Alexander, A.M. Gold and D.F. Stevens, J.biol.Chem., 233, 1211 (1958).

(3) A.J. Birch, P. Fitton, E. Pride, A.J. Ryan, H. Smith and W.B. Whalley, J.Chem.Soc., 4576 (1958).

(4) M. Castle, G. Blondin and W.R. Nes, J.Amer.Chem.Soc., 85, 3306 (1963).

(5) At a Symposium in Milan, October 1962; A.J. Birch, Accad.Naz.dei Lincei, Roma, 64 (1964).

(6) R. Bentley, J.biol.Chem., 238, 1895 (1963).

(7) A.J. Birch, J.H. Birkinshaw, P. Chaplen, L. Mo, A.H. Manchanda, A. Pelter and M. Riano-Martin, Aust.J.Chem., in the press.

(8) A.J. Birch, F. Gager, L. Mo, A. Pelter and J.J. Wright, Aust.J.Chem., in the press.