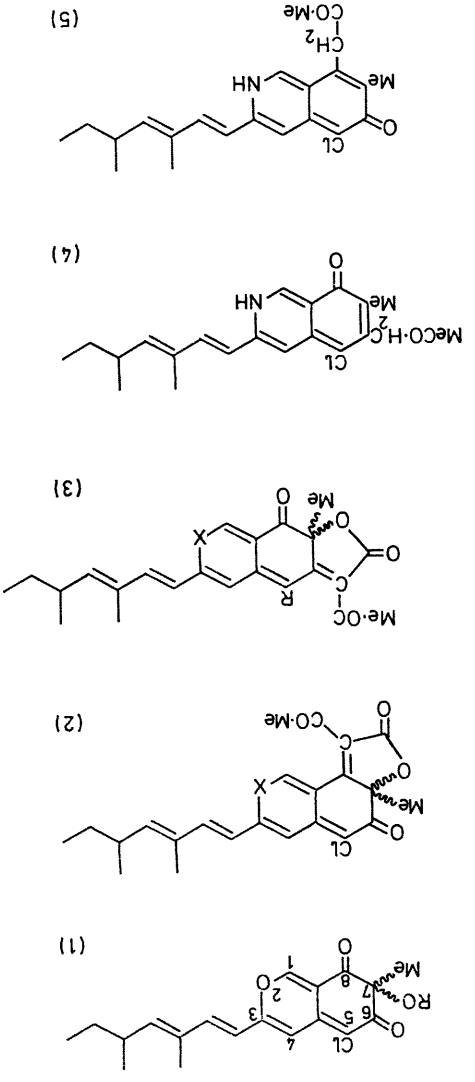
(−)-7-Epi-5-chloroisorotiorin, a Novel Metabolite of the Sclerotiorin Group

By R. W. GRAY and W. B. WHALLEY*

(*The School of Pharmacy, The University, 29–39 Brunswick Square, London, W.C.*1)

Summary The constitution of 7-epi-5-chloroisorotiorin, the first angular azaphilone, has been established: the total synthesis of the metabolite is reported.

IN addition to (−)-sclerotiorin, [7-epi-(+)-sclerotiorin][1] (1; R = Ac), it has been reported[2] that *Penicillium hirayamae* Udagawa elaborates a red pigment of uncertain molecular formula and of unknown constitution. We now report definition of the structure of this metabolite as (−)-7-epi-5-chloroisorotiorin (2; X = O) and record its total synthesis.



Mass spectrometry defined the molecular formula as $C_{23}H_{23}ClO_5$ which is the equivalent of a chloro-rotiorin or chloro-isorotiorin. The general spectral properties of the new metabolite were compatible with this view, but although very similar to, it was not identical with (+)-5-chloroisorotiorin (2; X = O) derived[3] from (+)-deacetyl-sclerotiorin. Chlorination, (sulphuryl chloride) of (+)-rotiorin[4] (3; R = H, X = O) furnished (+)-5-chlororotiorin (3; R = Cl, X = O) which was not identical with the new metabolite. The constitution of (3; R = Cl, X = O) follows from the n.m.r. spectrum and from the oxidation[4] (with nitric acid) of (+)-5-chlororotioramine (3; R = Cl, X = NH) to berberonic acid. In addition, aromatisation[4] of (3; R = Cl, X = NH) furnished 5-chloroaporotioramine (4).

Condensation of (−)-deacetysclerotiorin (1; R = H) [prepared from (−)-sclerotiorin] with diketen gave (−)-7-epi-5-chloroisorotiorin (2; X = O), which was identical (rotation, m.p., mixed m.p., t.l.c., i.r., u.v., n.m.r., and mass spectra) with the natural material. Since (−)-sclerotiorin has been synthesised[3] this constitutes a total synthesis of (−)-7-epi-5-chloroisorotiorin.

Chemical confirmation of structure (2; X = O) for the metabolite was provided. Thus, (+)-5-chloroisorotiorin (2; X = O) gave the corresponding rotioramine (2; X = NH) which was isomeric, but not identical, with (−)-7-epi-5-chloroisorotioramine (2; X = NH). However, as required by our conclusions, aromatisation of these two epimeric 5-chloroisorotioramines, (2; X = NH) furnished the *same* (m.p., mixed m.p., i.r., u.v., n.m.r., and mass spectrum) 5-chloroisoaporotioramine (5).

(−)-7-Epi-5-chloroisorotiorin is the first naturally occurring angular member of the sclerotiorin (azaphilone) group of fungal metabolites to be characterised.

The stereochemistry of the asymmetric centre in the side-chain of this novel pigment is not defined unequivocally but since (+)- and (−)-sclerotiorin and (+)-rotiorin each have identical absolute stereochemistry at this centre, it is likely that the new metabolite belongs to the same stereochemical series.

All new compounds had the appropriate spectral and analytical characteristics.

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[1] G. A. Ellestad and W. B. Whalley, *J. Chem. Soc.*, 1965, 7260.
[2] S. Udagawa, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 366.
[3] R. Chong, R. R. King, and W. B. Whalley, *Chem. Comm.*, 1969, 1512.
[4] J. S. E. Holker, J. Staunton, and W. B. Whalley, *J. Chem. Soc.*, 1963, 3641.