The Biosynthesis of Sterigmatocystin

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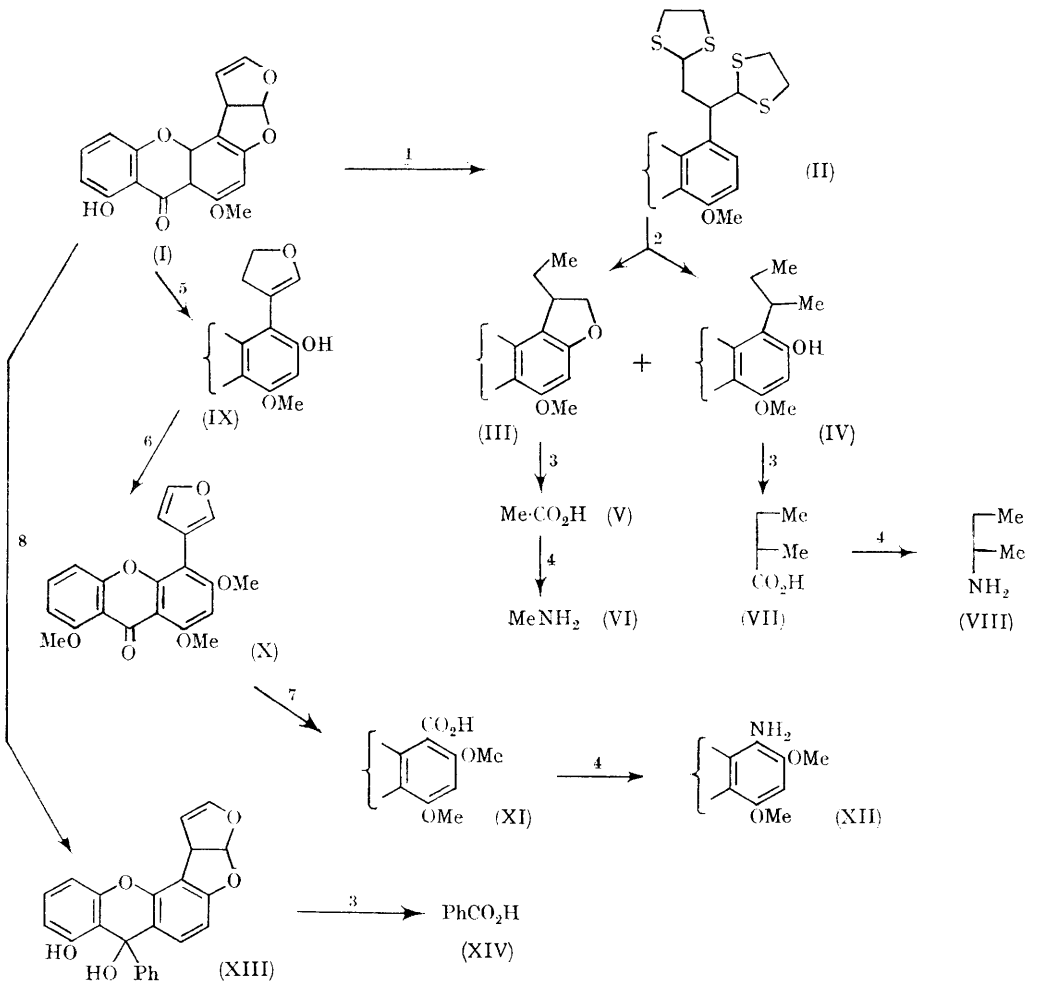
IN the previous Communication[1] we suggested that the xanthone, sterigmatocystin (I)[2] may be derived biogenetically from the anthraquinone, although the origin of the branched four-carbon unit in the bis-furan system is obscure.

To provide direct evidence, sterigmatocystin has been isolated from a culture of *Aspergillus versicolor* containing [1-^{14}C]acetate. The metabolite, which incorporated 0·5% of the radioactivity, has

SCHEME



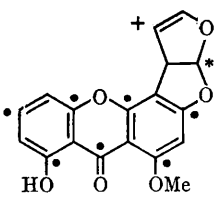
Reagents: 1, $(CH_2SH)_2$–*p*-Me·C_6H_4·SO_3H; 2, Raney Ni; 3, CrO_3–H_2SO_4; 4, NaN_3–H_2SO_4; 5, KOH; Me_2SO_4–K_2CO_3; 7, O_3–H_2O; 8, PhMgBr.

versicolorin A.[3] Structural considerations suggest that the acetate–malonate pathway is probably involved in the biosynthesis of these metabolites,

Distribution of label

Compound	Activity (μc/mmole) Found	Calc. for distribution shown
(I)[2]	0·515	0·515
(II)	0·516	0·515
(III)	0·512	0·515
(IV)	0·516	0·515
(V) as *p*-bromophenacyl ester	0·054	0·053
(VI) as *p*-bromobenzoyl derivative ..	0·003	0·002
(VII) as *p*-bromophenacyl ester	0·105	0·105
(VIII) as *p*-bromobenzoyl derivative ..	0·103	0·103
(IX)[2]	0·514	0·515
(X)[2]	0·512	0·515
(XI) as methyl ester[2]	0·410	0·414
(XII)	0·406	0·412
(XIII)	0·507	0·515
(XIV) as *p*-bromophenacyl ester ..	0·056	0·056

been subjected to the degradations outlined in the Scheme, and the activities of the individual products† are shown in the Table. The distribution of label given by these results is as follows:



Carbons labelled ● have 10·9% of total activity.
Carbon labelled + has 9·9% of total activity.
Carbon labelled * has 9·3% of total activity.
Unlabelled carbons each have 0·4% of total activity.

This distribution of radioactivity supports the acetate–malonate hypothesis for the origin of the xanthone ring system in sterigmatocystin. Although the four-carbon unit of the bis-furan system appears to be similarly derived by head-to-tail linkage of two acetate units, the C–C bond joining this moiety to the xanthone system is apparently formed between two carbon atoms, both of which originated in the methyl groups of acetate. This head-to-head linkage of two acetate units is not readily accommodated by any of the usual biogenetic pathways. Furthermore, the level of radioactivity in the branched side-chain is significantly lower than that in the xanthone system. Hence, it appears that sterigmatocystin is biogenetically derived from two separate preformed ketide units. The mechanism of combination of these two units is at present obscure although experiments are in hand to test various possible theories.

Recently the absolute configuration of aflatoxin B has been determined by degradation to (*S*)-2-methylbutanoic acid.[4] A similar sequence of reactions on sterigmatocystin, (I) → (II) → (IV) → (VII), similarly leads to (*S*)-2-methylbutanoic acid, isolated as its *p*-bromophenacyl ester, $[\alpha]_D$ + 15° (*c* 1·4 in $CHCl_3$). Hence aflatoxin B and sterigmatocystin have the same absolute configuration.

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† All new compounds have been fully characterised by the usual spectroscopic methods and satisfactory elemental analysis.

[1] J. S. E. Holker and S. A. Kagal, proceding Communication.
[2] E. Bullock, J. C. Roberts, and J. G. Underwood, *J. Chem. Soc.*, 1962, 4179.
[3] T. Hamasaki, Y. Hatsuda, N. Terrashima, and N. Renbutsu, *Agric. and Biol. Chem.* (*Japan*), 1965, **29**, 166.
[4] S. Brechbühler, G. Büchi, and G. Milne, *J. Amer. Chem. Soc.*, 1967, **89**, 2641.