Biogenetically Modelled Synthesis of Polyketide-type Xanthones

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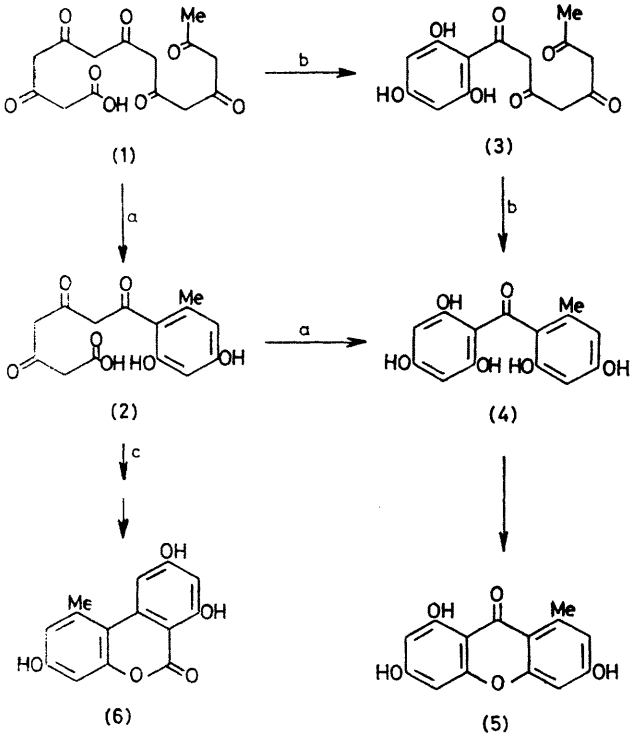
Summary Base-catalysed aldol-type cyclization of 1-(2,4,6-trihydroxyphenyl)octane-1,3,5,7-tetraone (**3**) gives a benzophenone which undergoes cyclodehydration to form norlichexanthone (**5**); the sequence mimics steps involved in the biosynthesis of this and related metabolites.

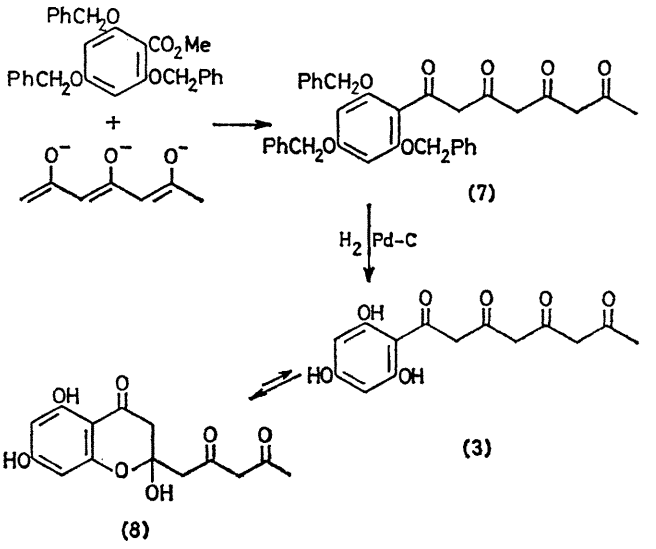
MANY of the naturally occurring xanthones arise by polyketide routes. For example, in the biosynthesis of norlichexanthone (**5**), it is generally believed that condensation of acetate with six malonates gives a β-hexaoxo acid (**1**) which undergoes an aldol and a Claisen cyclization to form the benzophenone (**4**) followed by dehydration to give (**5**).[1] The order of formation of the two benzenoid rings is of some interest. The pathway a (Scheme 1) by which



SCHEME 1

aldol cyclization occurs first would involve an aryl trioxo acid intermediate (**2**), whereas the alternative pathway b would involve an aryl tetraketone (**3**). No relevant metabolic studies have been reported, but a model study carried out by Harris and Hay[2] using the methyl ester of (**2**) failed to provide support for process a; the ester cyclized *via* another pathway (c) giving alternariol (**6**).† Although the failure of the non-enzymic reaction (**2**→**4**) does not rule out the corresponding biological process, our investigation suggests that the reaction might take place *via* pathway **b**.

The synthesis of the tetraketone (**7**) was achieved in 60% yield by the condensation of methyl 2,4,6-tribenzyloxybenzoate with the trilithium salt‡ of heptane-2,4,6-trione for 22 h at 45 °C (Scheme 2). It is noteworthy that in this



SCHEME 2

acylation the high nucleophilicity of the trianion compensated for the low reactivity of the hindered ester. Treatment of (**7**) with H_2 at atmospheric pressure in the presence of Pd–charcoal gave (**3**) in >90% yield. During chromatography on silica gel, (**3**) cyclized to the hemiacetal (**8**), m.p. 139·5—141·5 °C (ether–pentane).

Treatment of (**8**) with KOH in refluxing aqueous EtOH for 10·5 h gave norlichexanthone (**5**) in >95% yield by a pathway postulated to involve reopening of the hemiacetal ring of (**8**) to give (**3**) which cyclized to the benzophenone (**4**) and subsequently to (**5**). Neither (**3**) nor (**4**) was observed during the process; a previous study of (**4**) revealed the conversion into (**5**) to be very easy.[3]

The present investigation provides chemical support for the biosynthesis of polyketide-type xanthones occurring *via* pathway b (Scheme 1). Turner[4] has noted that none of the polyketide-type metabolites yet isolated has more uncyclized residues of the carboxy end of the polycarbonyl chain than of the methyl end. The observation that (**3**) but not the methyl ester of (**2**) can be transformed into (**8**) is consistent with his observation. This result is also relevant to the biosynthesis of griseofulvin, for which (**4**) has been proposed[3] to be one of the intermediary metabolites.

We thank the U.S. Public Health Service for financial support.

(*Received, 27th February* 1979; *Com.* 191.)

† A second biomimetic synthesis of alternariol has recently been described; it involves the opposite order for formation of the aromatic rings (F. J. Leeper and J. Staunton, *J.C.S. Chem. Comm.*, 1978, 406).

‡ Formed from the triketone and 3 equiv. of lithium di-isopropylamide in tetrahydrofuran at 0 °C.

[1] For reviews, see J. H. Richards and J. B. Hendrickson, 'The Biosynthesis of Terpenes, Steroids and Acetogonins,' Benjamin, New York, 1964; C. F. Culberson, 'Chemical and Botanical Guide to Lichen Products,' University of North Carolina Press, Chapel Hill, 1969.
[2] T. M. Harris and J. V. Hay, *J. Amer. Chem. Soc.*, 1977, **99**, 1631.
[3] C. M. Harris, J. S. Robertson, and T. M. Harris, *J. Amer. Chem. Soc.*, 1976, **98**, 5380.
[4] W. B. Turner, 'Fungal Metabolites,' Academic Press, London, 1971.