Biogenetic-type Syntheses of Heptaketide Natural Products: Alternariol and Lichexanthone

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Summary The *ortho*-substituents on the aryl rings of methyl 7-(4-orcinyl)-3,5,7-trioxoheptanoate and its dimethyl ether, respectively, direct intramolecular aldol and Claisen condensations of the triketo-esters to give biogenetic-type syntheses of alternariol and lichexanthone.

The natural products, alternariol (I) and lichexanthone (II) are thought to have a common biogenesis involving linear combination of seven acetate moieties to give hexaketo-acid (III).[1] This putative intermediate has never been detected and may, in fact, be covalently bound to an enzyme or cofactor. Formation of (I) from (III) requires carbocyclic ring closures by aldol condensations of position 2 with 7 and position 8 with 13; whereas formation of (II) from (III) requires aldol condensation of position 8 with 13 and Claisen condensation of position 6 with 1. The sequences of these cyclizations are unknown; however, if the 8:13 closure occurs first in the formation of both (I) and (II), then triketo-acid (IV) will be common to both pathways.

We sought to test the chemical basis of this suggestion by examining the cyclization of simple derivatives of (IV) with the expectation that the mode of cyclization of esters of (IV) could be controlled by appropriate choices of reaction parameters. Conditions for effecting selectively aldol and Claisen cyclizations of a similar triketo-ester, methyl 3,5,7-trioxo-7-phenylheptanoate, had previously been developed in this laboratory.[2]

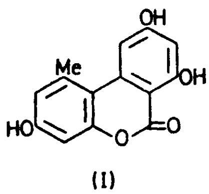
For the preparation of ester (V), the dibenzyl ether of methyl orsellinate was condensed with dilithioacetylacetone in tetrahydrofuran.[2,3] The resulting triketone was carboxylated in the presence of lithium di-isopropylamide[3] and the product was esterified with diazomethane to give (VI). Hydrogenolysis of (VI) gave (V), which cyclized spontaneously to chroman (VII). Cyclization to (VII) appeared (n.m.r. and u.v.) to be quantitative; however, hemiacetal formation is a reversible reaction. As a consequence, (VII) can serve as a source of (V) for cyclization reactions.

Treatment of (VII) with methanolic sodium acetate (1 M)–acetic acid (1 M) gave a mixture of alternariol (I) (52%) and coumarin (VIII) (46%). Under more basic conditions, the yield of (VIII) increased at the expense of (I). The formation of (I) from (VII) requires opening of the hemiacetal ring, aldol cyclization of (V), dehydration, and lactonization. None of the intermediates was observed; neither were any Claisen products of (V) detected.

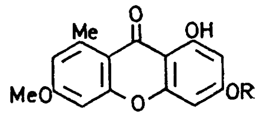
Next, triketo-ester (IX) was prepared by the procedure used for (VI). The ester underwent cyclization in aqueous potassium hydroxide to give 25% of benzophenone (X) and 5% of xanthone (XI); methanolic potassium hydroxide converted (X) into (XI). Methylation of (XI) with diazomethane gave lichexanthone (II). Aldol products were not observed in this reaction of (IX) or in reactions attempted under less basic conditions.

It is evident from these results that the mode of cyclization or aryltriketo-esters is dependent not only upon the reaction conditions but also upon the nature of the *ortho*-substituents on the aromatic ring. With (IX), the two substituents provide steric hindrance to nucleophilic attack at the 7-carbonyl group and/or the subsequent dehydration of (XII); consequently, the intramolecular Claisen reaction leading to (XI) is the only cyclization observed. With (V), the *o*-hydroxy-group hydrogen-bonds with the 7-carbonyl group, holding the carbonyl group coplanar with the aromatic ring. This sterically and electronically facilitates aldol condensation to give (XIII) and ultimately (I).

The cyclization preferences of model compounds (V) and (IX) may also obtain in biological systems. Griseofulvin is formed from seven acetate units, presumably *via* (III). As in the formation of (II), an 8:13 aldol condensation and a 6:1 Claisen condensation are required. In this pathway the most primitive aromatic intermediate to be identified is griseophenone C (XIV), in which the *o*-hydroxy-group of the orcinol ring is methylated.[4] One can speculate that in this case the 8:13 cyclization occurs first and that methylation of the *o*-hydroxy-group occurs prior to the Claisen cyclization. Birch has similarly suggested that this *O*-methyl group is introduced after aldol closure, but prior to formation of (IV) by dehydration.[5] Both suggestions receive support from the observation by Jackson and his co-workers that the metabolic origin of the 2′-methoxy-group of griseofulvin differs from that of the 4- and 6-methoxy-groups.[6]



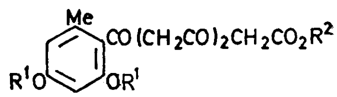
(I)



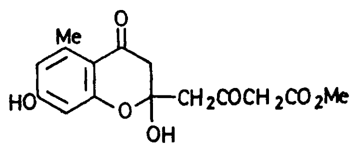
(II) R = Me
(XI) R = H

MeCO(CH$_2$CO)$_5$CH$_2$CO$_2$H

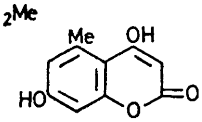
(III)



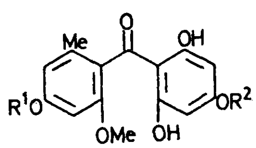
(IV) $R^1 = R^2 = H$
(V) $R^1 = H, R^2 = Me$
(VI) $R^1 = PhCH_2, R^2 = Me$
(IX) $R^1 = R^2 = Me$



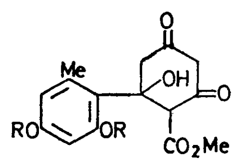
(VII)



(VIII)



(X) $R^1 = Me, R^2 = H$
(XIV) $R^1 = H, R^2 = Me$



(XII) R = Me
(XIII) R = H

Scott and his co-workers have investigated biogenetic-type synthetic approaches to (I) and (II) based on cleavage

and recyclization of pyrones. By this method they have prepared a xanthone[7] but their attempt to prepare the alternariol ring system was not successful.[8]

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