SYNTHESIS AND BIOSYNTHESIS OF PHYTOXANTHONES

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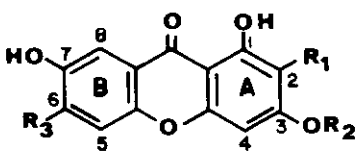
Chemotherapeutic and taxonomic values of natural xanthones are appraised.

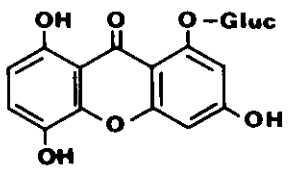
Synthesis and biosynthesis of phytoxanthones is reviewed.

Gentisin (1,7-dihydroxy-3-methoxyxanthone; 1) is the first xanthone isolated from a plant source, Gentiana lutea in 1821[1]. More recently a number of xanthones have been isolated from various plant species and microbial sources. Among the plants, Guttiferae and Gentianaceae represent the principal sources containing a diversified nature of xanthone derivatives with different degree of oxygenation pattern and isopentenyl side chains[2-16]. Nearly over one hundred and fifty naturally occurrring xanthones have been isolated from higher plants and fungi.



(1): $R_1 = R_3 = H$; $R_2 = Me$

(2): $R_2 = H$; $R_3 = OH$; $R_1 = \beta$-D-Gluc



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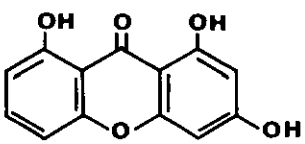
Chemotherapeutic Value:

Naturally occurring xanthones are considered important molecules, since in recent years such compounds are shown[17-20] to produce remarkable pharmacological and other biological activities, as well as they are of chemotaxonomic value[6,21-24]. Thus mangiferin (1,3,6,7-tetrahydroxyxanthone-C_2-β-glucoside; 2), a major metabolite of Canscora decussata (Gentianaceae)[25-29], Swertia chirata[17] and other species[30-36] showed monoamine oxidase inhibitor, cardiovascular stimulant, anticonvulsant and choleretic activities[17,18,37]. Norswertianolin (3,5,8-trihydroxyxanthone-1-O-

glucoside; 3), a metabolite of Swertia randaiensis[38] and S. purpurascens Wall[39], has been reported to produce significant antitubercular activity[38-40]. The Swertia plant extracts are known for their therapeutic uses in the treatment of tuberculosis[40].

Antitubercular activity was first reported for 1,3,8-trihydroxyxanthone (4), a degradation product of sterigmatocystin (5), a metabolite of Aspergillus versicolor[20]. Some antitubercular folklore medicines are also found to contain polyoxygenated xanthones as their major chemical component[41]. The extract of Canscora decussata Schult (Gentianaceae) is reported[41] to be useful



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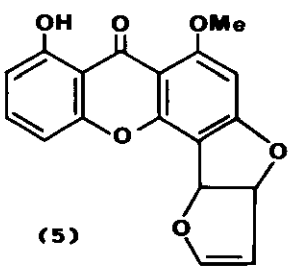
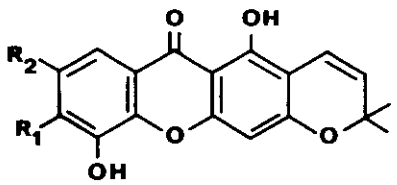
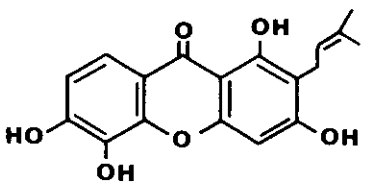


(5)

in the treatment of certain mental disorders and tuberculosis. This plant has yielded, in addition to mangiferin (2), three; 1,3,5-trioxygenated xanthones, four; 1,3,5,6-tetraoxygneated xanthones and four; 1,3,5,6,7-pentaoxygenated xanthones. The antitubercular activity of the total xanthone aglycones of C. decussata has been demonstrated in vitro[42].

The total xanthone-O-glucosides of C. decussata[18,37] are reported to produce marked antipsychotic effects. Whereas the xanthone-O-glucosides of S. purpurascens Wall are known to produce[39,43] signs of central nervous system (CNS) depression in albino mice and rats. However the xanthone aglycones are shown to produce dose-dependant weak CNS stimulant activities. The effect on CNS system is known to be manifested by an initial transient hyperactivity followed by moderate to deep depression, intact reflexes and response to external stimuli, potentiation of hexobarbital hypnosis in albino mice and complete protection against amphetamine and 5-methoxy-N,N-dimethyltryptamine induced toxicities. Xanthones of S. chirata are also reported[17] to have similar effects as that of S. purpurascens. 1,3- and 1,6-dihydroxyxanthones, closely related to the many naturally occurring xanthones isolated from Mammea americana (Gentianaceae), exhibit some degree of growth-inhibiting activity against Sarcoma 180 tumor cell[44].





(7)

(6) : $R_1 = OH$; $R_2 = H$

(6A) : $R_2 = OH$; $R_1 = H$

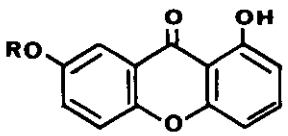
(6B) : $R_1 = R_2 = H$

Chemotaxonomic Value:

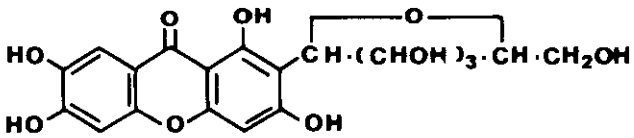
Xanthones are also known to be of chemotaxonomic value. Thus Scheinmann et al[6] have postulated that jacareubin (6)[21,45,46a,48,51-69] or its putative isoprenyl[48,51b,53,55,56,66,67] precursor (7) may be a taxonomic marker for the genus Calophyllum owing to its presence in almost all the species investigated, regardless of the geographic origin of the sample. None the less jacareubin has also been observed in some species of the genera Kielmeyera, Pentadesma and Mesua[45,46]. Sultanbawa and co-worker[21] have reported that jacareubin (6) is found only in older timber of the genus Calophyllum. This has provided a good explaination for the reported absence of jacareubin (6) in South Indian sample of Calophyllum inophyllum. Consequently this leads to the conclusion that if jacareubin (6) is to be accepted as chemotaxonomic marker for Calophyllum, age factor of the timber should also be considered.

The taxonomic implications of the occurrence of euxanthone (1,7-dihydroxyxanthone; 8) in Guttiferae has been pointed out by Scheinmann[70]. A, 1,7-dihydroxyxanthone derivative, euxanthic acid (9) is believed[71,72] to be a metabolic degradation product; it is found in the urine of the cows fed with mango leaves (Mangifera indica) of which mangiferin[73], a glucoside of 1,3,6,7-tetrahydroxyxanthone (10) is a constituent. This relationship between 1,7-dihydroxyxanthone (8) and 1,3,6,7-tetrahydroxyxanthone (11) is also suggested to occur in plant metabolism because of the co-occurrence of 1,3,6,7-tetrahydroxyxanthone (11) and 1,3,5,6-tetrahydroxyxanthone (12) in

Symphonia globulifera L., formed from a common precursor maclaurin (13)[74].



(8): R=H
(9): R=Gluc



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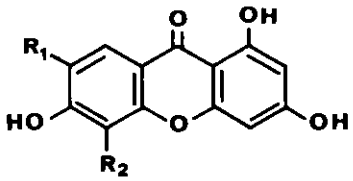
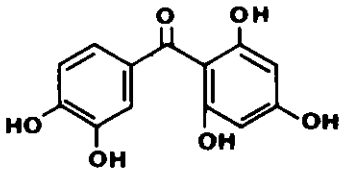


(11): R_1=OH; R_2=H
(12): R_1=H ; R_2=OH



(13)

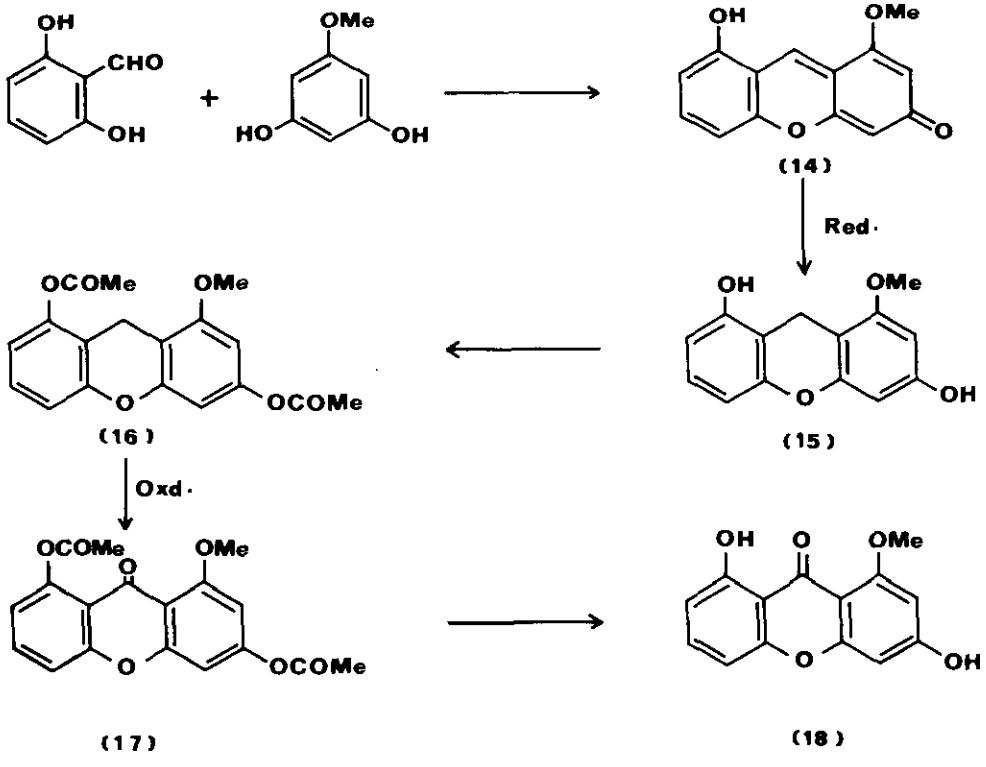
Stout and Fries have noticed[75] a close relationship between the xanthones of Halenia and those of the various Frasera species, which is of significance since both genera are initially identified with Swertia[76,77]. Although Swertia has been regarded as the nearest genus[76] to Halenia. Stout and Fries have suggested a closer phytochemical relationship between Halenia and Frasera than between either and Swertia since the latter produces xanthones of quite different substitution pattern and are of chemotherapeutic value[46].

Synthetic Methods:

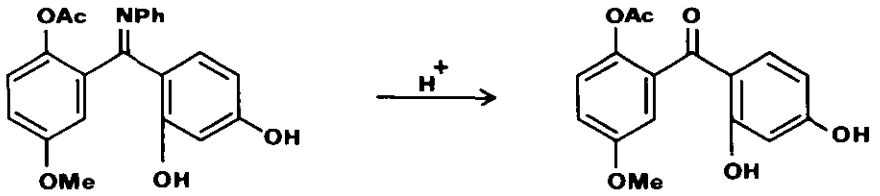
Polyoxygenated xanthones of potential therapeutic and taxonomic value and many other xanthones have been synthesized by a number of methods. Although the method described by Grover, Shah and Shah[78] has serious limitations, it is still used extensively for the synthesis of phytoxanthones. An o-hydroxybenzoic acid is condensed with a reactive phenol in the presence of zinc chloride and phosphorus oxychloride which usually results in the formation of intermediate benzophenones and xanthones as final products along with other unwanted materials. The following phytoxanthones or their derivatives have been prepared by this method: Scriblitifolic acid-O-methyl ether [79-81], monomethoxy-dihydro-osajaxanthone[82,83], 1,5-dihydroxy-[16], 1,7-dihydroxy-[84,85], 1,3-dihydroxy-5-methoxy-[86], 1,3,5-trihydroxy-[87-89], 1,5-dihydroxy-3-methoxy-[89], 1,3,5-trimethoxy[88,89], 1,3,7-trihydroxy-[78], 1,3-dihydroxy-7-methoxy-[78], 1-hydroxy-3,7-dimethoxy-4-isoprenyl-[90,91], 1,3,5,6-tetrahydroxy-[78,92,93], 1,3,6,7-tetrahydroxy-[94], 1,3,5-trihydroxy-6-methoxy-[96], 1,3,8-trihydroxy-5-meth-

oxy-[15], 1,3-dimethoxy-6,7-dihydroxy-[94], 1,3,6-trihydroxy-7-methoxy-[94] and 1,3-dihydroxy-6,7-dimethoxyxanthone[94]. A polyhydric phenol, when heated with o-hydroxybenzoic acid in the presence of a dehydrating agent such as acetic anhydride or zinc chloride also gives xanthones by the method of Michael-Kostanecki. Euxanthone[44,49,52,55,66,67,72,74,88,101-109] has been synthesized by this method[97].

Asahina and Tanase's route[110,111] for the synthesis of xanthones involves an o-hydroxybenzaldehyde which is condensed with a phenol to give 9H-xanthene-3-one (14). Upon methylation or reduction, this gives a 9H-xanthene derivative (15) which can then be oxidised to a xanthone derivative (17). 3,8-Dihydroxy-1-methoxyxanthone (18), a degradation product of sterigmatocystin (5), has been synthesised by this method[8,20].

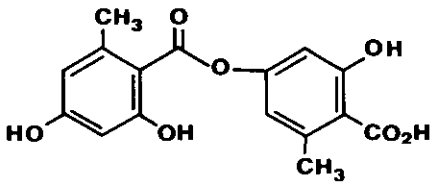


Xanthones involving ketimine intermediates of the type (19) have been synthesized by Robinson and Nishikawa[112,113]. Recently Whalley et al[95] have used this method for the synthesis of a number of benzophenone intermediates which upon oxidation could yield xanthones.



(19) (20)

Salicyaldehyde copper complexes[114,115] when reacted with aromatic halides are reported to give xanthone in good yields[116]. Some xanthones have been prepared by pyrolysis of aryl esters of o-hydroxybenzoic acids. An example is the pyrolysis of lecanoric acid (21) which gives 1,6-dihydroxy-3,8-dimethylxanthone[117] (22). Photo Fries rearrangement of aryl esters is also known to give complex benzophenone intermediates useful in the synthesis of xanthones and other compounds[124]. 2,2',6'-Trihydroxy-6,4'-dimethyl-4-methoxybenzophenone (23) has been obtained in this way[124]. Bennet and coworkers[118] have claimed the synthesis of xanthones, in good yields, from thioxenthene-9-one-10, 10-dioxide nucleus[118-123] in alkaline media. This conversion is believed to take place through intermediate formation of hydroxybenzophenonesulfinic acids of the type (25).



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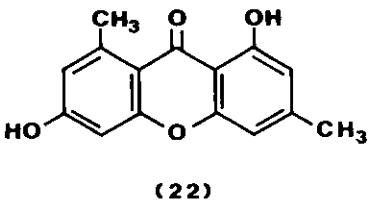

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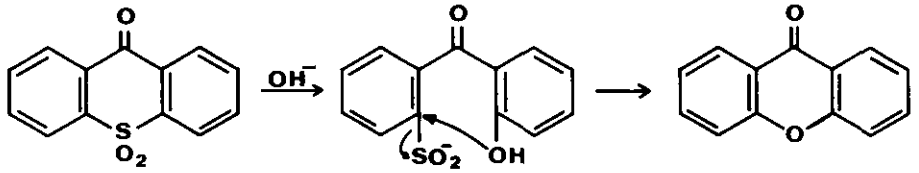
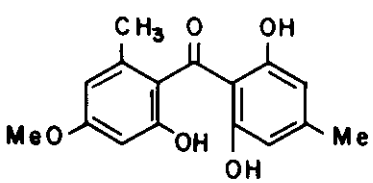


(24) (25) (26)

Mono- and dioxygenated xanthones have been mostly prepared by Ullmann synthesis of diphenyl-ether intermediates which cyclize by phosgene, or alternatively through diphenyl ether 2-carboxylic acids which cyclize by an intramolecular acid catalysed acylation[111,125-128]. However more convenient syntheses of these xanthones have been reported by Scheinmann et al, involving Friedel-Crafts method.[129] 4-Hydroxy-[128], 2-hydroxy-[64], 1,5-dihydroxy-[6,130] and 1,7-dihydroxyxanthones[131], all four isolated from Guttiferae species, have been synthesised through a diphenyl ether intermediate.

The foregoing methods for the synthesis of phytoxanthones, however, do not always give the required products[66,74] and the reactions are accompanied by unwanted demethylation and/or multiplicity of products[89,129]. Most of the phytoxanthones have been synthesized by using milder Friedel-Crafts reaction conditions, via, benzophenone intermediates.

Xanthone synthesis by this method is largely concerned with orientation control, selective methylation, and demethylation of phenolic hydroxyl groups[3]. The synthesis of benzophenones, suitable as precursors for cyclization to xanthones, has been conveniently achieved at room temperature by Friedel-Crafts acylation of methoxybenzene derivatives, whith appropriately substituted benzoyl chloride in the presence of aluminium chloride in ether. That preferential para acylation occurs under these conditions is shown by the reaction of benzoyl chloride and veratrole which gives 3,4-dimethoxybenzophenone. However where acylation occurs adjacent to a methoxy- group, selective demethylation is shown to occur at a site adjacent to the carbonyl group. The reaction of benzoyl chloride with 1,2,3,4-tetramethoxybenzene gives the monomethyl ether of natural benzophenone[132] scleroin (27), whereas acylation of 1,3,5-trimethoxybenzene gives either natural benzophenone hydrocotoain (2-hydroxy-4,6-dimethoxybenzophenone; (28) or cometabolite methylhydrocotoin[134,135] (29),



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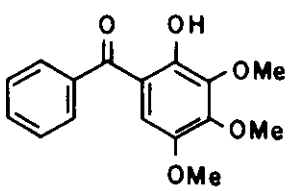

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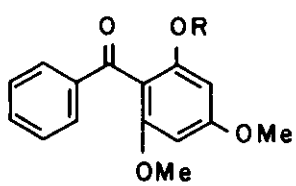
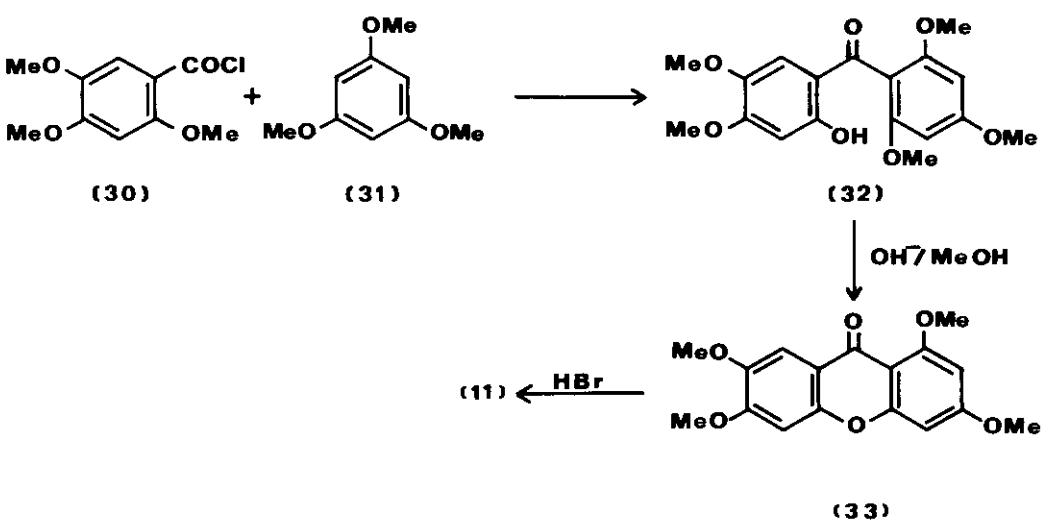


(28): R = H

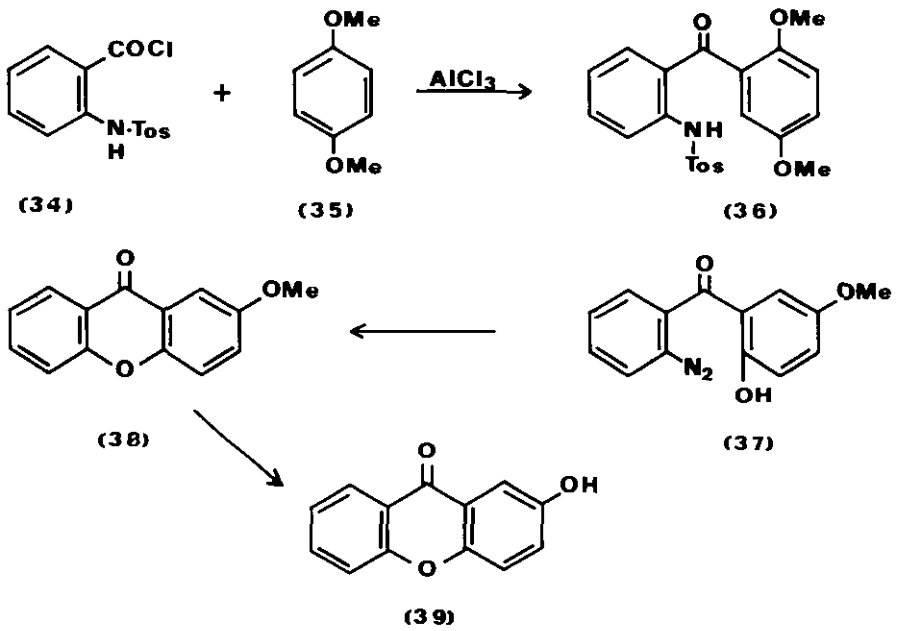
(29): R = Me

according to the duration of the reaction. Hydrocotoin is of some considerable chemotherapeutic interest[135,136] and was initially isolated in 1879 from the barks of Aniba pseudocoto (Rusby) Kostermans (Lauracea). The fact that extended reaction time causes ortho-monodemethylation has led to convenient syntheses of 2-hydroxy-2'-methoxybenzophenones suitable for cyclization to xanthones by base catalysed elimination of methanol.

2-Mono-[125,126] and 2,3-dioxygenated xanthones[111,127], previously prepared by Ullman method have been conveniently synthesized using Friedel-Crafts reaction conditions[129], involving benzophenone as intermediates. A number of highly oxygenated phytoxanthones have been obtained through the corresponding benzophenone intermediates synthesized under Friedel-Crafts reaction conditions. The 2-hydroxy-2'- alkoxybenzophenone intermediates thus obtained are cyclized under a variety of reaction conditions which involve the use of aqueous alkali hydroxides, ike sodium, potassium and tetramethylammonium hydroxydes or aqueous piperidine[129]. The following phytoxanthones have been synthesised by this method:- 2-methoxy-[129,137]; 1,7-dihydroxy-[129]; 3-hydroxy-2-methoxy-[138]; 2-hydroxy-3-methoxy-[129]; 2,3,4-trihydroxy-[129,140,142]; 1,5,6-trihydroxy-[129]; 1,6,7-trihydroxy-[129]; 1,3,7-trimethoxy-[129]; 1,3,6,7-tetrahydroxy-[129]; 1,3,5,6-tetrahydroxy-[129]; 1,5,6-trihydroxy-5-methoxy-2-(1',1'-dimethylallyl) (as trimethyl ether)-[139]; 1,5-dihydroxy-6,7-dimethoxy-[129]; 1-hydroxy-3,5-dimethoxy-[140]; 1,3,7-trihydroxy-[141]; 1,3,4,7-tetramethoxy-[129]; 1-hydroxy-3,5,7- trimethoxy-[25]; 1-hydroxy-2,3,4,5-tetramethoxy-[46b,142,143]; 1-hydroxy-2,3,4,7-tetramethoxy-[46b,142,144]; 1,3,6,7,8-pentamethoxyxanthone[145]. An example for the synthesis of 1,3,6,7-tetrahydroxyxanthone (11) a metabolite of many Guttiferae species[27,49,68,69,74,101,109,138,146-151] is outlined below:-

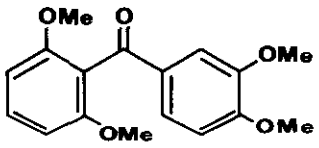


2-N-Tosyl-2'-hydroxybenzophenones are also reported to undergo cyclisation *via* elimination process. *In vivo* the synthesis of a xanthone nucleus could involve a similar mechanistic pathway, with a phosphate group participating in the displacement[152]. Thus the following synthesis of 2-hydroxyxanthone[153] has been achieved:



Selective Demethylation of Xanthones:

Selective demethylation of preformed methoxybenzophenones and xanthones has proved to be a very useful tool in the total synthesis of phytoxanthones. This is possible in either acidic or alkaline media. Different products are obtained depending on conditions used. Demethylation by conventional methods involving hydrogen bromide in acetic acid or sulphuric acid demethylates a methoxyl group preferentially adjacent to a carbonyl group[140,145,154,155]. Boron trichloride also selectively demethylates a methoxy- group adjacent to a carbonyl group[156]. 1-Hydroxy-5-methoxyxanthone, a metabolite of *Mesua ferrea L*[107] has been prepared from 1,5-dimethoxyxanthone[107,157]. Locksley and Murray[158] have used boron tribromide[159,160] in methylene chloride or benzene for the demethylation of 2,3',4',6-tetramethoxy-benzophenone (40) and 2,3,3',4',6-pentamethoxybenzophenone (41) to give the corresponding tetra- and pentahydroxybenzophenones, respectively. However 2,2',3',6-tetramethoxybenzophenone when demethylated under the same conditions, is shown to give the corresponding tetrahydroxybenzophenone as a minor product, while the major product is 2,2',3'-trihydroxy-



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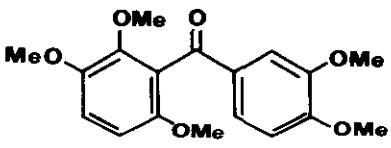
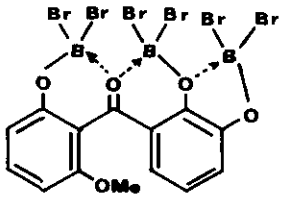


(41)

6-methoxybenzophenone. Locksley and Murray[158] have proposed a plannar complex (42) which would inhibit the demethylation of the methoxy-group at C-6 due to its steric inaccessibility for further attack by the reagent. Boron trifluoride[160] and phosphorus oxychloride in the presence of zinc chloride[129] have also been used for selective demethylation reactions of xanthones.

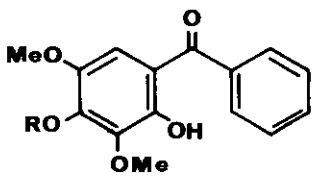


(42)

Aluminium chloride has also found its use in selective demethylation of methoxybenzophenones and xanthones as mentioned earlier. Demethylation under controlled conditions takes place preferentially at methoxy- group adjacent to a carbonyl group. Thus the following phytoxanthones have been prepared by this method:- 1,3,5-trihydroxy-[140]; 1,3,7-trihydroxy-[103]; 1,7-dihydroxy-3,8-dimethoxy-[160-165]; 1-hydroxy-2,3,7-trimethoxy[46b]; 1-hydroxy-3,4,5-trimethoxy[46b]; 1-hydroxy-2,3,4,5-tetramethoxy-[46b,142,143]; 1-hydroxy-2,3,4,7-tetramethoxyxanthone[46b,142-144].

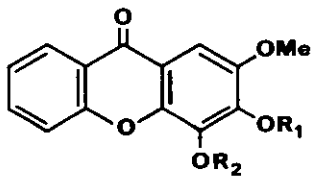
Scheinmann et al.[129] have shown that a methoxy-group buttressed[139] by two ether functions is demethylated next under acidic conditions followed by methoxy-groups not para to a carbonyl function. The final methoxy- group to be demethylated, under these conditions, is para to the carbonyl group. These workers have further suggested that demethylation occur more readily at the C-7 methoxy-group on account of its higher electron density.

However the sequence of demethylation reactions is shown to reverse under alkaline conditions. Thus demethylation of methoxy- group para to a carbonyl function is known to occur first under alkaline conditions. The alkaline demethylation of 2-hydroxy-3,4,5-trimethoxybenzophenone (43) is shown to occur in the presnece of aqueous piperidine to give 2,4-dihydroxy-3,5-dimethoxy benzophenone[45]. Also refluxing 2,3,4-trimethoxyxanthone (45) with either aqueous piperidine or tetramethylammonium hydroxide is shown to give 3-hydroxy-2,4-dimethoxyxanthone[129] (46).



(43): R = Me

(44): R = H



(45): $R = R_2 = Me$

(46): R_1=H ; R_2 =Me

(47): R_1=Me ; R_2=H

(48): $R_1 = R_2$ = H

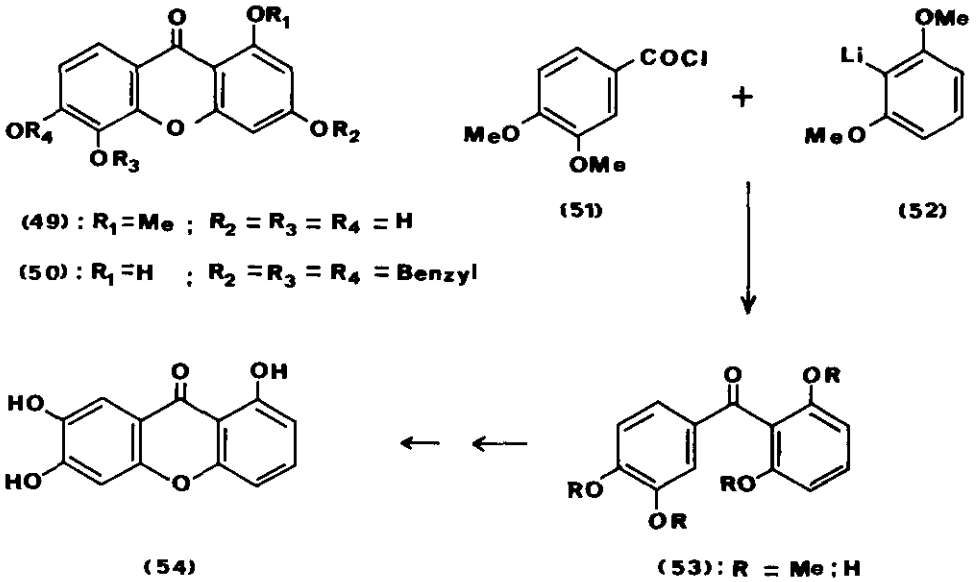
Contrary to these results Chaudhuri and coworkers[166] have shown that demethylation of 1-methoxy-, 1,3-dimethoxy-, and those xanthones containing added methoxy-group(s) in the B ring (5- and/or 7- position) takes place preferentially at the 1- position with aqueous piperidine, followed by demethylation at positions C-3 and C-6. This group of workers have further shown that compounds having substitution at three or four adjacent carbon atoms of xanthones, demethylation predominantly takes place at C-2, which is flanked by C-1 and C-3 methoxy- groups. This is in accordance with the observations previously reported by Scheinmann et al.[129] 2,4-Dimethoxy-3-hydroxy-[129], 1, 3-dihydroxy-4,7-dimethoxy-[129] and 1-hydroxy-3,5,6,7-tetramethoxyxanthones[25] have been prepared by this method. A number of other xanthones with interesting oxygenation pattern have also been obtained by this route. The use of sodium ethanethiolate[143,167,168] has also been mentioned as a versatile demethylating method for aryl ethers.

Selective Methylation of Xanthones:

Some of the phytoxanthones have been prepared by selective methylation of preformed hydroxy-xanthones. In this endeavour, use has been made of difference in acidity of the various phenolic hydroxy- groups which can either undergo selective methylation or alternatively protection followed by methylation and deprotection. Thus, 2,3-dimethoxy-4-hydroxyxanthone (47), a metabolite of many

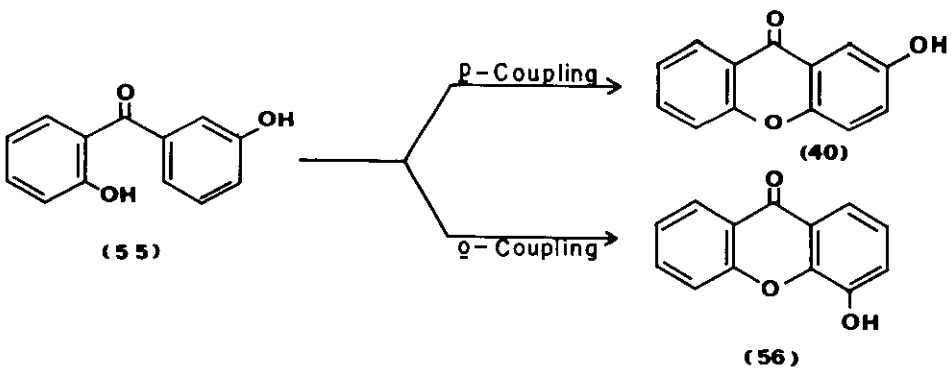
Guttiferae species[6,46a,140,154,169,171,172], has been prepared by selective methylation of 3,4-dihydroxy-2-methoxyxanthone (48) by dimethyl sulphate and potassium carbonate. The phytoxanthone 1-methoxy-3,5,6-trihydroxyxanthone (49) has been obtained[66] by benzylation of 1,3,5,6-tetrahydroxyxanthone (12) to give 1-hydroxy-3,5,6-tribenzyloxyxanthone (50) which is then methylated and debenzylated to give the natural product (49). The following phytoxanthones have been obtained by selective methylation process:- 1-Methoxy-5-hydroxy-[157]; 1-hydroxy-7-methoxy-[103,105,107,145,173]; 2,3-dimethoxy-4-hydroxy-[129]; 1,5-dihydroxy-3-methoxy-[89]; 1,3,5-trimethoxy-[142]; 1-methoxy-3,5-dihydroxy[174]; 1,3,7-trimethoxy-[129]; 1,7-dihydroxy-3-methoxy-[175]; 1-hydroxy-3,7-dimethoxy-[66,176]; 1-methoxy-3,4,5-trihydroxy-[66]; 1,5,6-trihydroxy-3-methoxy-[27]; 1,5,8-trihydroxy-3-methoxy[9]; 1-hydroxy-3,5,8-trimethoxy-[8]; 1-hydroxy-3,7,8-trimethoxyxanthone[161-164].

The intermediate benzophenone derivatives are also accessible through condensation of appropriately substituted benzoyl chlorides with lithium salts of phenolic ethers. The 1,5-dihydroxyxanthone[130], 1,6,7-trihydroxyxanthone[158] (54) (Guttiferae); and 1,3,5-trihydroxy-8-methoxyxanthone[160] (Gentianaceae) have been prepared by this method. Similar routes to the synthesis of highly oxygenated benzophenone and xanthones have been adopted[124,160,177-179] involving trifluoroacetic anhydride. Thus 1-hydroxy-2,3,5-trimethoxy-[140-142]; 1-hydroxy-2,3,7-trimethoxy[142]; and 1,3,4,5-tetramethoxyxanthones[180] (all Gentianacea)[46b,140,142,181] have been synthesized by this method.



Oxidative Cyclization of Benzophenones:

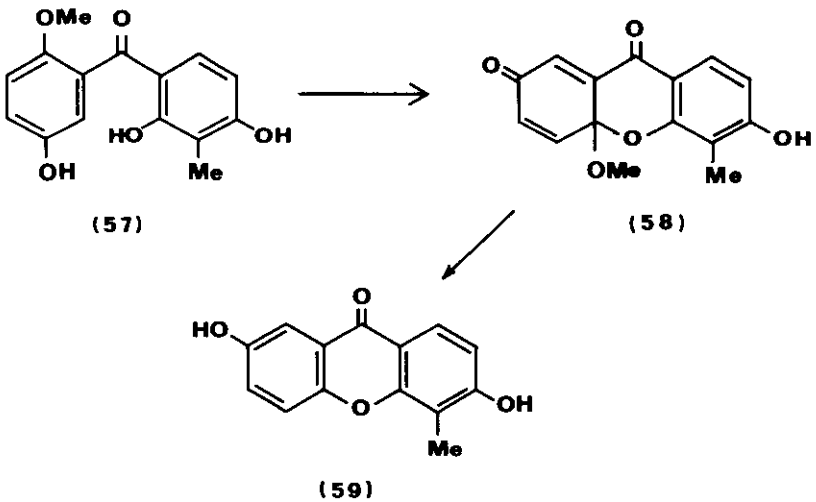
Apart from the base catalysed cyclization of polyoxygenated benzophenones to the corresponding xanthones, biogenetic type of oxidative cyclization has been extensively used. Lewis[182] first proposed that naturally occurring xanthones may be generated by an oxidative cyclization of an appropriately hydroxylated benzophenone precursors. In vitro studies have supported this proposal and many naturally occurring xanthones have been synthesized from their corresponding hydroxybenzophenones by oxidative coupling. Both ortho- and para- coupling are possible[84].



Whalley et al[95] have been successful in synthesizing xanthones by oxidative coupling of benzophenones of the type (57) to give dienone intermediate (58) which could then undergo base catalysed elimination to xanthones.

Several oxidants have been used to convert the polyhydroxybenzophenones into their respective xanthones by oxidative cyclization. Thus photochemical oxidation[68], manganese (III) tris (acetonylacetone)[158,183,184], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[126], ceric ammonium sulphate[185], permanganate[141], ferricyanide[141,68], persulphate[9], and potassium hexacyanoferrate (III)[95] have been used for the oxidative cyclisation of benzophenones to xanthones. The following phytoxanthones have been prepared by oxidative coupling of respective benzophenones:- 1,7-dihydroxy-[141,158]; jacareubin[68,69]; 1,3,5,8-tetrahydroxy-[9]; 1,3,5,6-tetrahydroxy-[69]; 1,3,6,7-tetrahydroxy-[141]; 1,3,5,6-tetrahydroxy-4-isoprenyl-[91] and 1-hydroxy-3,4,8-tetramethoxyxanthone[45].

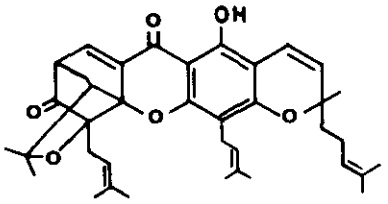
Isopentenyl and geranyl substituents are found in many xanthones isolated from Guttiferae.



(57) (58) (59)

Geranyl substituents have been reported in xanthones obtained from the genus Garcinia. In the case of gambogic acid[186,239] (60), this substituent is cyclised but in the cases of rubraxanthone[187] (61), cowaxanthone[188] (62), and its congeners, the geranyl side-chain is unfolded. Isopentenyl substituents are common in Guttiferae and Moraceae but are occassionally modified by terminal oxidation or by cyclization involving ortho- hydroxy groups. Nearly fifty phytoxanthones have been isolated so far, with 3,3-dimethylallyl-; 1,1-dimethylallyl-; or dimethylpyrano substituents. In some cases phytoxanthones with more than one of these substituents have been isolated. 8-Deoxygartanin[189], trapezifolixanthone[190], calabaxanthone[80,190], twaitesixanthone[104], normangostin[189,191], are only a few example to mention. The dimethylallyl moiety has been introduced into the preformed xanthone nucleus by Claisen rearrangement of the corresponding para- dimethylallyl ether[139]. Thus isoguanin[157] (63) and alvaxanthone dimethylallyl ether[157] (64) have been synthesized by this method. The following phytoxanthones have been synthesized accordingly:- dehydroxycloguanandin[157], scriblitifolic acid[192], tovoxanthone-6-methyl ether, 5-methoxy-6-deoxyjacareubin[86], 1,3,5-trihydroxy-4-isoprenyl-[86,148], 8-deoxygartanin[86,194], trapezifolixanthone[194], 1,3,7-trihydroxy-2-isoprenyl (as 7-O-methyl ether)[194], 3,7-dimethoxymbaraxanthone[139,195], bicylogartanin[86], 5-methoxycelebixanthone [155], toxyloxanthone dimethyl ether[196] and osajaxanthone[197].

Interesting biogenetic type synthesis of xanthones has been mentioned by Dougles and Money[198]. The ortho- substituents on the aryl rings of methyl 7-(4-orcinyl)-3,5,7-trioxoheptanoate



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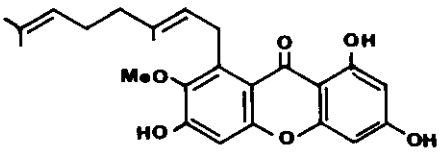

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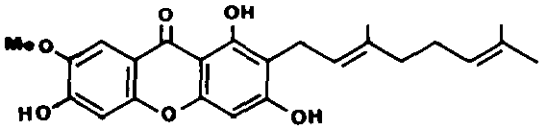

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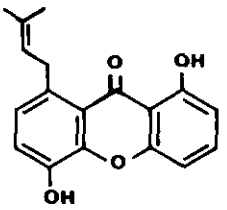

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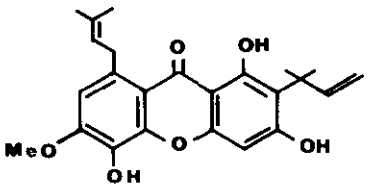
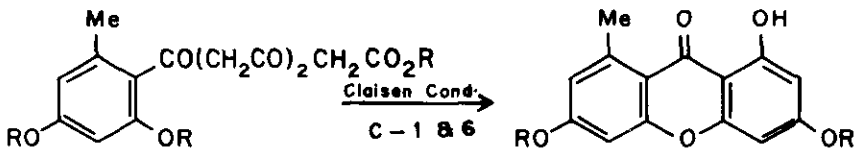


(64)

(65), and its dimethyl ether (66) respectively are shown[200] to direct intramolecular Claisen condensation of the triketo-ester to give lichexanthone (67).

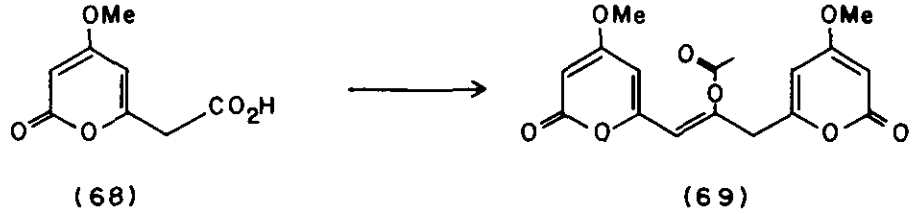
Synthesis of xanthones from extended poly-ß-ketide chains, in which control of cyclisation and reductive sequences, paralleling those of nature, is described by Scott et al[201]. Thus decarboxylative dimerisation of the acid (68) is shown to give ketone (70) via intermediate (69). This system constitutes a source of the polyhydroxyxanthones as shown on next page:-



(65) : R = H

(66) : R = Me

(67) : R = Me



(68)

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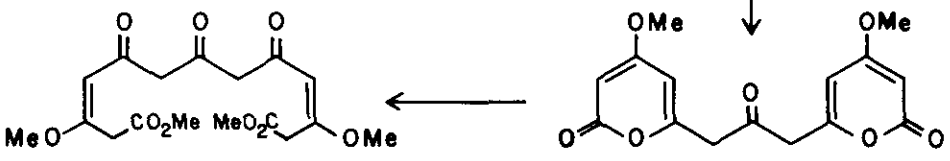
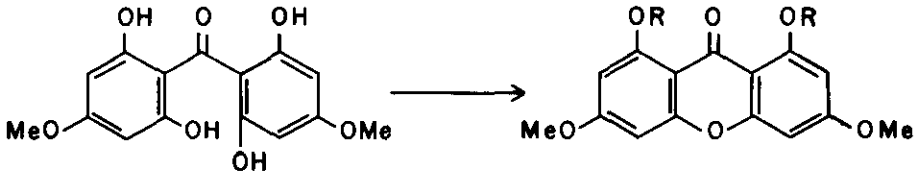


(71)

(70)



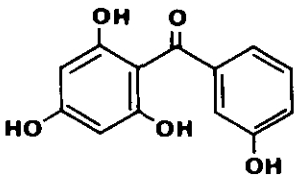
(72)

(73) : R = H

(74) : R = Me

Biosynthesis:

The possible interrelationship between hydroxybenzophenones and xanthones was first suggested[182] in 1963. This has been supported by the co-existence of polyhydroxybenzophenones and related xanthones in a number of plants like Symphonia globulifera[4,6], Chorophora tinctoria[68,69], Allanblakia floribunda Oliver[6,101,108] and in fungus Pencillium patulam[202]. Conversion of polyhydroxybenzophenones into naturally occurring xanthones has been proved by labelling studies in vivo. Thus the co-occurrence of 2,3',4,6-tetrahydroxybenzophenone and 1,3,7-trihydroxyxanthone in Gentiana lutea[182] and rapid assimilation of sodium acetate-2-^{14}C, by the plant to form both labelled benzophenone and the xanthone, provided strong support for the formation of xanthones from related benzophenones. Similarly co-occurrence of 2,3',4,5',6-pentahydroxybenzophenone and 1,3,5,7-tetrahydroxyxanthone along with 1,3,6,7-tetrahydroxyxanthone (11) in Garcinia pendunculata[146], supports the view that xanthones are formed from hydroxybenzophenones. Maclaurin (13) co-occurs with 1,3,6,7-tetrahydroxy-, 1,3,5,6-tetrahydroxyxanthones (11) and (12) respectively in Symphonia globulifera L.[108] and their mangostin derivatives have been isolated from many plant species[74,91,108,147,203].



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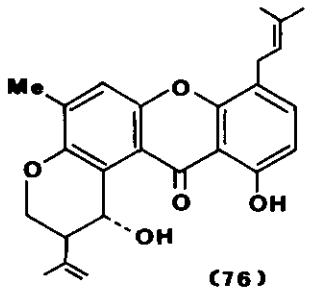
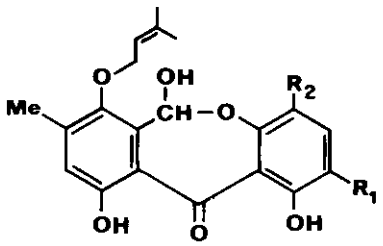


(76)

By means of tritium incorporation studies, Gupta and Lewis have established[4], that 2,3',6-tetrahydroxybenzophenone (75) is a precursor to gentisin (1). The benzophenone (75) has also been suggested to be a common precursor for co-occurring 1,3,5- and 1,3,7-trioxygenated xanthones present in Pentaphalangium Solomonse Warb[148], and Calophyllum scriblitifolium Henderson and Wyatt Smith[48]. Anthraquinone intermediates are most likely involved in the formation of several fungal benzophenones and xanthones[204-206]. Thus shamixanthone (76)[207,208], tajixanthone (79)[207,208] and arugosins (77, 78)[209-212] are suggested to be biogenetically derived from crysophanol anthrone by oxidative ring fission and introduction of O- and C- prenyl units from mevalonate, to give the O-formylbenzophenone, from which arugosins and shamixanthone are derived. Ring fission is also

involved in the formation of pinselic acid (80) derived from helminthosporin anthrone[214]. Similarly ergot pigments are also proposed to arise from ring fission of anthrone or/ anthraquinone derivatives via benzophenone formation. The ergochromes, which have a reduced xanthone skeleton and co-occur with anthraquinone derivatives, have also been suggested to be formed by transforation of an acetate-derived anthracene intermediate[213].



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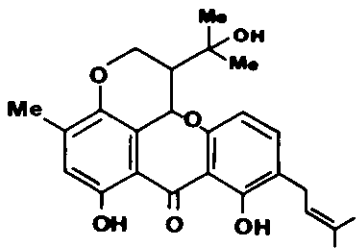


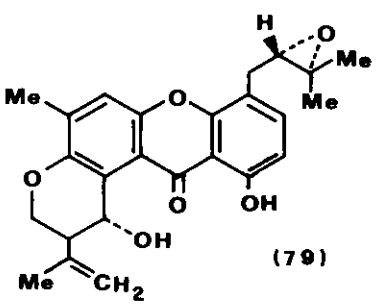
(78)

$R_1 = CH_2 \cdot CH : CMe_2$; $R_2 = H$

$R_2 = CH_2 \cdot CH : CMe_2$; $R_1 = H$

Compounds with a benzophenone skelton are biosynthesized by two routes[215]: (a) wholly acetate-polyketide, (b) shikmate-polyketide (C_6C_1 plus 3 C_2 and C_6C_3 plus 2 C_2). In the case of naturally occurring xanthones, it has been shown in biosynthetic studies that the former route is probably operating in fungi and the latter in higher plants[4,6,209,215,216].

Vining and his co-workers[216] have shown from doubly labelled experiments that the fungal xanthone bikaverin (81) is derived via the folding of a single polyketide chain without a anthraquinone intermediate. The xanthone ravenelin (82) is a metabolite of Helminthosporium ravenelli[217] and H. turcicum[244] passerin. Birch et-al[217] have recently shown by labelling experiments, that it is derived from a single acetate chain and an oxygenated benzophenone derivative such as (83) is an intermediate in the biosynthetic pathway. Sterigmatocystin[205,218] and ergot pigments[219] have also been suggested to be derived from a single polyketide chain. Sterigmatocytin[205,218] and ergot pigments[219] have also been suggested to be derived from a single polyketide chain.



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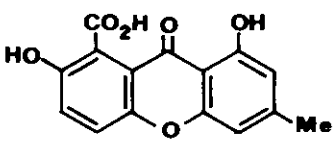

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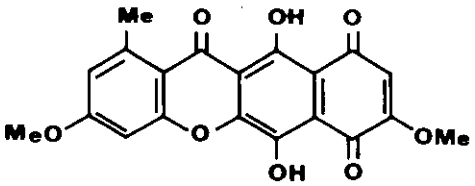

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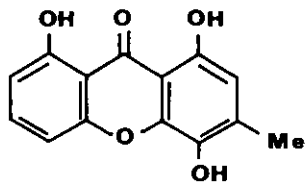

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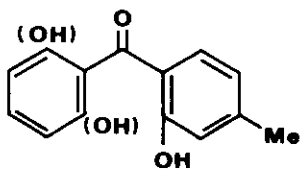
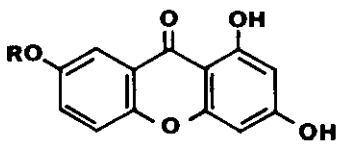


(83)

In case of plant derived xanthones the biogenetic route is relatively simpler since benzophenones show hydroxylation patterns suggesting their derivation from acetate and shikimate. Lewis and Frank have shown[14,206,220] that both the shikimate and acetate routes, for biogenesis of aromatic compounds, are involved in the biogenesis of the plant xanthones gentisin (1), isogentisin (84) and gentisein (85). Fifteen benzophenone derivatives have been so far isolated from higher plants. Two main theories have been advanced to explain the origin of natural benzophenones in higher plants: (a) the catabolism of dalbergins and related compounds[221] (b) the direct involvement of shikimic acid or some other related C_6-C_1 precursor such as (86) with three molecules of acetic acid or malonic acid[6,141,176,222].



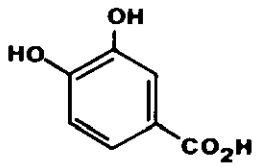
(84) : R = Me

(85) : R = H

It has been suggested that the co-occurrence of sclerion (87) and cearoin (88) with neoflavonoids supports route (a). Gentiana lutea metabolises phenylalanine and acetic acid to give 2,3', 4,6-tetrahydroxybenzophenone (75) together with several derived 1,3,7-trioxygenated xanthones[245].

This has suggested a more direct biosynthetic route, involving shikimic acid[145], to benzophenones than suggested by route (a).

The co-occurrence of oxygenated benzophenone hydrocotoin (28) and 2,3'-dihydroxy-4,6-dimethoxybenzophenone (89) with xanthones[101] in Allanblackia floribunda Oliver and earlier[6,108] isolation of both types of molecules from the same source have suggested that the former are biogenetic precursors of the latter and this has been confirmed by the recent labelling studies[141,176,222].



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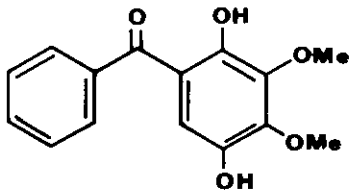
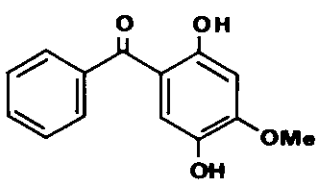


(87)

Roberts[2] has suggested biosynthesis of xanthones involving the condensation of an aromatic acid with three acetate units to a β-polyketo-acid which then cyclizes to a benzophenone precursor. Thus 3,4-dihydroxybenzoic acid (86), derived from shikimic acid, could condense with acetate to the β-polyketo-acid[93,223] (90) which then cyclises to form maclaurin (13), a precursor for 1,3,5,6- and 1,3,6,7-tetrahydroxyxanthones and other xanthones with a similar oxygenation pattern. Celebixanthone[224] (92) and other 2,3,4-oxygenated xanthones[140] can be envisaged to arise from a benzophenone precursor such as (91) involving one ring derived from gallic acid. Dewick and Haslam have shown that, for certain plants producing gallic acid, shikimic acid is more efficiently incorporated than phenylalanine[225,226]. They are led to suggest that gallic acid is formed by direct aromatisation of dehydroshikimic acid rather than by catabolic breakdown of phenylalanine.



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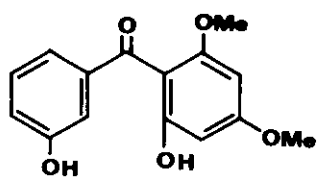
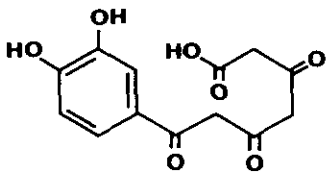


(89)



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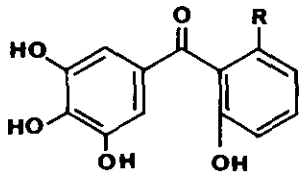

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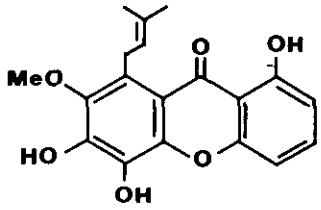
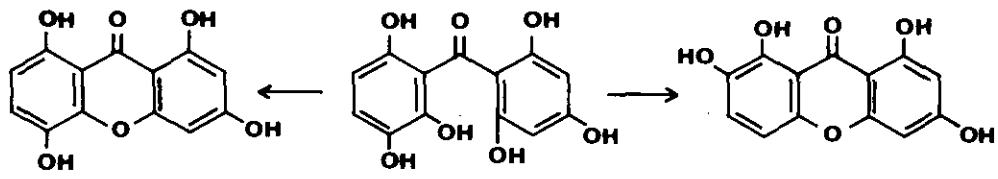


(92)

Natural xanthones fall into two groups which reflect different modes of biogenesis[220]. The first group consists of those apparently derived from an appropriate 2,2'-dihydroxybenzophenone by a cyclodehydration sequence. The elimination of a C-(2) hydroxyl as a pyrophosphate anion from a polyhydroxylated benzophenone precursor has been suggested[217,220], and used by Markham[10] to account for the appearance of 1,3,5,8- and 1,3,7,8-tetraoxygenated and possibly of 1,3,4,5,8- and 1,3,4,7,8- pentaoxygenated xanthones in the species of Gentianaceae. 2,2'-dihydroxybenzophenones have been dehydratively cyclized under a variety of conditions[202,227-229]. In vivo the synthesis of the xanthone nucleus could involve a similar mechanistic pathway, a phosphate group participating in the displacement [152]. The co-occurrence of 5,8- (94) and 7,8-oxygenated xanthones (95) provides strong support for the hypothesis that they are synthesised from a common benzophenone precursor such as (93) involving elimination process.



(94) (93) (95)

The second group of xanthones comprises of those conveniently regarded as arising from hydroxybenzophenones by oxidative coupling. Lewis[182] was the first to suggest the biogenesis of xanthones by oxidative coupling of o-hydroxybenzophenones. This has been subsequently supported by a statistical analysis of xanthones found in higher plants. Thus the co-existence of pairs of xanthones like 2- and 4-hydroxyisomers and 1,5- and 1,7-dihydroxyxanthones in Mesua ferra L[107], 1,3,6,7- and 1,3,5,6-tetrahydroxyxanthones (11 and 12 respectively) in Symphonia globulifera L.[108] are in accord with their respective derivation by oxidative coupling from common benzophenone precursors[231]. Oxidative coupling as a ready means for the synthesis of xanthones under "physiological type" conditions has been carried out by a number of workers[68,69,108,220,222,232,233].

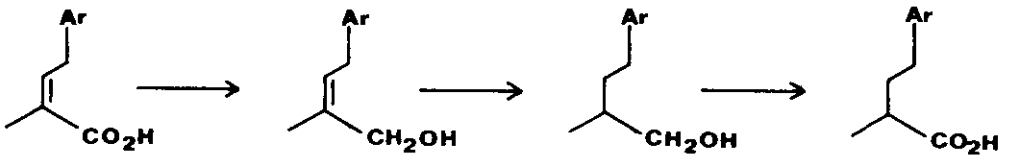
The isolation of 1,2,3-trioxygenated xanthone from Frasera caroliniens[142], 1,3,5- and 1,3,7-trioxygenated xanthones from Calophyllium scriblitifolium Henderson and Wyatt-Smith[48] and Pentaphalangium solomonse Warb[148], the co-occurrence of 1,5,6- and 1,6,7-trihydroxyxanthone in Garcinia eugeniifolia Wall[102], 5- and 7- hydroxylated xanthones in Mammea americana[84,85] (two pairs) and in Mammea africana[49] (three pairs), are all in accordance with the oxidative coupling mechanism of xanthones. The isolation of these xanthones has revealed the fact that there is no absolute requirement for a 3'-hydroxyl group on a benzophenone precursor to give xanthone, as was first suggested[222,233] by Lewis.

In vivo, oxidation of hydroxybenzophenones has been suggested[141] to take place via enzyme participation and the action of the enzymes on phenols has been reported in several cases to give the same cyclization as found for inorganic oxidants[234]. Lewis et al have reported[141] the oxidation of benzophenones in vivo by peroxidase and laccase from Polystictus virsicolor to give xanthones. A mechanism of parallel type, involving radical intermediates in these enzyme induced oxdations[235], has been formulated to give xanthones.

The dimethylallyl side chain is suggested to be introduced into a preformed hydroxylated xanthone nucleus which is produced from an appropriate hydroxylated benzophenone. The presence of 1,1-dimethylallyl group in natural xanthones is of biogenetic importance, and indicates that an aromatic precursor attacks "γ,γ-dimethylallyl pyrophosphate" in a manner analogous to an SN_2,[93,246] substitution. An ortho-Claisen-type rearrangement of an O-3,3-dimethylallyl precursor to an C-1,1-dimethylallyl compound has been demonstrated[236]. Several O-3,3-dimethylallyl compounds have been isolated from natural sources[93,205] and Claisen type of rearrangement has been shown to take place under mild conditions. Thus 3,3-dimethylallyl phenolic ethers have been rearranged to ortho and para positions during purifications procedures of the ethers on a silica-gel column[90].

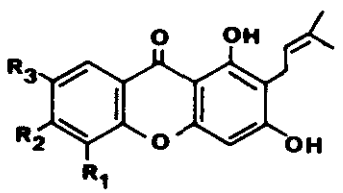
The suggestion that the pyrone ring in natural xanthone[230,237,238] is derived from the one

stage oxidative cyclisation of a dimethylallyl side chain is supported by the co-occurrence of pyranoxanthone jacareubin (6), osajaxanthone (6A), 6-deoxyjacareubin (6B) and 3,3-dimethylallylxanthones, (100) and (101) in C. scriblitifolium Henderson and Wyatt-Smith .



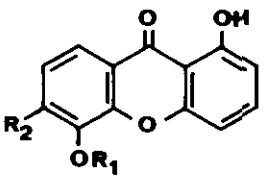
(96) (97) (98) (99)

The presence of a 2-methylbutanoic acid side chain in scriblitifolic acid (102; R_1=Me) and oxidised chains in its cometabolites (103,104; R_1=H) (C. scriblitifolium) is an instance of stepwise modification of a 3,3-dimethylallyl group at C-6. Scheinman and coworkers have suggested[192] the steps (96 - 99) in the biosynthesis of this side chain. The presence of a side chain closely



(100) : $R_2 = R_3 = H$; $R_1 = OH$

(101) : $R_1 = R_2 = H$; $R_3 = OH$

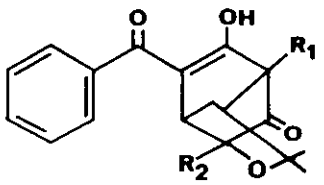


(102): $R_2 = -CH_2 \cdot CH_2 \cdot CH(CH_3) \cdot CO_2H$

(103): $R_2 = -CH_2 \cdot CH_2 \cdot CH(CH_3) \cdot CH_2OH$

(104): $R_2 = -CH_2 \cdot CH : C(CH_3) - CH_2OH$

related to 2-methylbutanoic acid has also been reported in gambogic acid[240], morellin[241,242], isomorellin[243] and cometabolites[186,239]. Isolation of brominonone (105), a modified benzophenone from Garcinia hombromiana Pierre[221] suggests that isoprenylation can occur at the benzophenone stage of biosynthesis. Spiranic intermediates in the biosynthesis of naturally occurring xanthones, have been postulated by Gottlieb[4] and Ghosal[17].

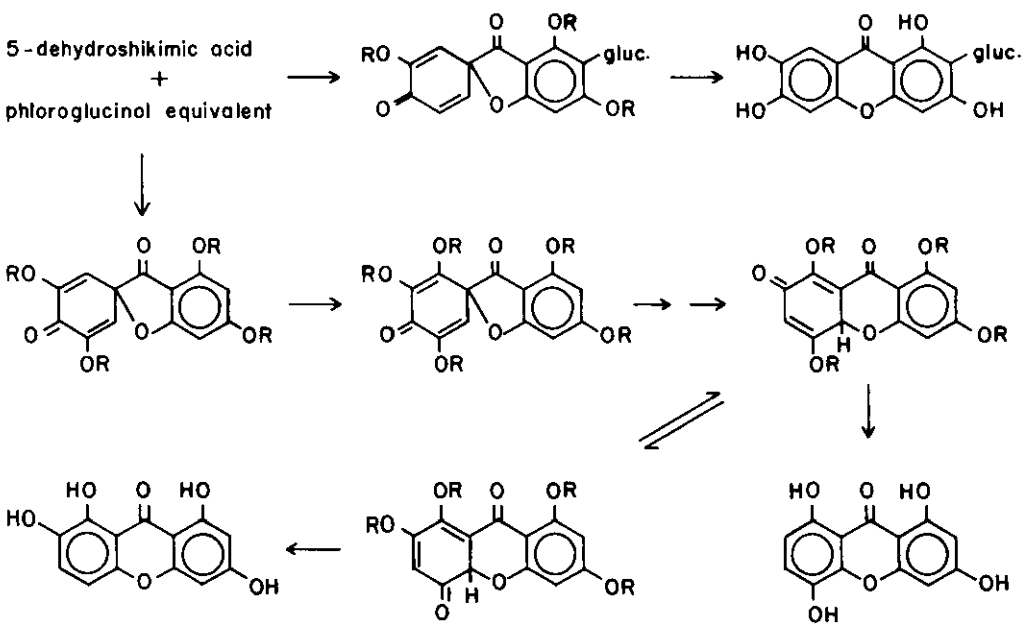


(105)

R_2 = Geranyl

R_1 = Farnesyl

Ghosal et al have proposed the biosynthesis of tetraoxygenated xanthones of Swertia chirata.[17] The absence of 1,3,5- and 1,3,7-trioxygenated xanthones which were previously suggested to be precursors of tetraoxygenated xanthones by further oxidation at one of the activated sites C_6 or C_8 has led Ghosal et al to propose that tetraoxygenated xanthones (1,3,5,8- and 1,3,7,8-) in S. chirata are derived by a different biogenetic route involving spiran intermediates as put down under:-



However cooccurence of polyoxygenated xanthones along with their corresponding spiran derivatives in higher plants has not been demonstrated in vivo and experimental evidence for this biogenetically important conversion is still awaited.

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