

## SYNTHESIS AND BIOSYNTHESIS OF PHYTOXANTHONES

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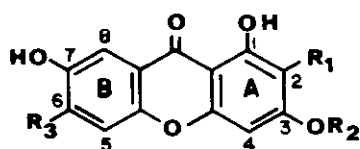
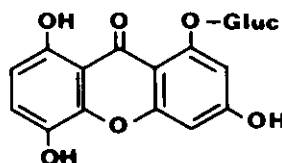
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Chemotherapeutic and taxonomic values of natural xanthenes are appraised.

Synthesis and biosynthesis of phytoxanthenes is reviewed.

Gentisin (1,7-dihydroxy-3-methoxyxanthone; 1) is the first xanthone isolated from a plant source, *Gentiana lutea* in 1821<sup>1</sup>. More recently a number of xanthenes 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<sup>2-16</sup>. Nearly over one hundred and fifty naturally occurring xanthenes have been isolated from higher plants and fungi.

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

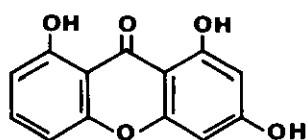
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Chemotherapeutic Value:

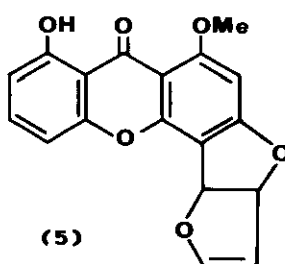
Naturally occurring xanthenes are considered important molecules, since in recent years such compounds are shown<sup>17-20</sup> to produce remarkable pharmacological and other biological activities, as well as they are of chemotaxonomic value<sup>6,21-24</sup>. Thus mangiferin (1,3,6,7-tetrahydroxyxanthone- $C_2$ - $\beta$ -glucoside; 2), a major metabolite of *Canscora decussata* (Gentianaceae)<sup>25-29</sup>, *Swertia chirata*<sup>17</sup> and other species<sup>30-36</sup> showed monoamine oxidase inhibitor, cardiovascular stimulant, anticonvulsant and choleric activities<sup>17,18,37</sup>. Norswertianolin (3,5,8-trihydroxyxanthone-1-0-

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

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



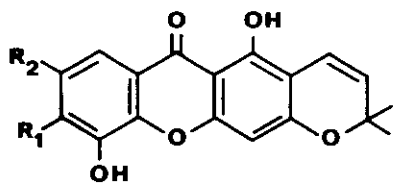
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(5)

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

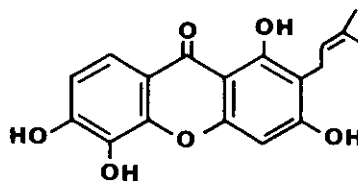
The total xanthone-O-glucosides of *C. decussata*<sup>18,37</sup> are reported to produce marked anti-psychotic effects. Whereas the xanthone-O-glucosides of *S. purpurascens* Wall are known to produce<sup>39,43</sup> signs of central nervous system (CNS) depression in albino mice and rats. However the 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. Xanthenes of *S. chirata* are also reported<sup>17</sup> to have similar effects as that of *S. purpurascens*. 1,3- and 1,6-dihydroxyxanthenes, closely related to the many naturally occurring xanthenes isolated from *Mammea americana* (Gentianaceae), exhibit some degree of growth-inhibiting activity against Sarcoma 180 tumor cell<sup>44</sup>.



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

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

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



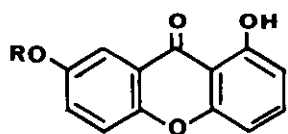
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#### Chemotaxonomic Value:

Xanthones are also known to be of chemotaxonomic value. Thus Scheinmann *et al*<sup>6</sup> have postulated that jacareubin (6)<sup>21,45,46a,48,51-69</sup> or its putative isoprenyl<sup>48,51b,53,55,56,66,67</sup> 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*<sup>45,46</sup>. Sultanbawa and co-worker<sup>21</sup> have reported that jacareubin (6) is found only in older timber of the genus *Calophyllum*. This has provided a good explanation 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.

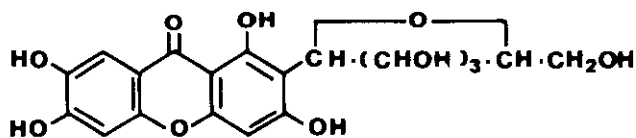
The taxonomic implications of the occurrence of euxanthone (1,7-dihydroxyxanthone; 8) in *Guttiferae* has been pointed out by Scheinmann<sup>70</sup>. A 1,7-dihydroxyxanthone derivative, euxanthic acid (9) is believed<sup>71,72</sup> to be a metabolic degradation product; it is found in the urine of the cows fed with mango leaves (*Mangifera indica*) of which mangiferin<sup>73</sup>, 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)<sup>74</sup>.

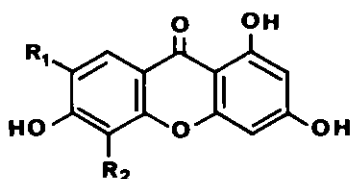


(8): R = H

(9): R = Gluc

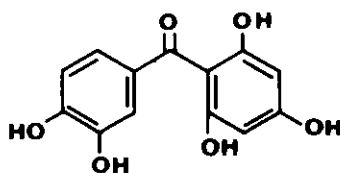


(10)



(11): R<sub>1</sub> = OH; R<sub>2</sub> = H

(12): R<sub>1</sub> = H; R<sub>2</sub> = OH



(13)

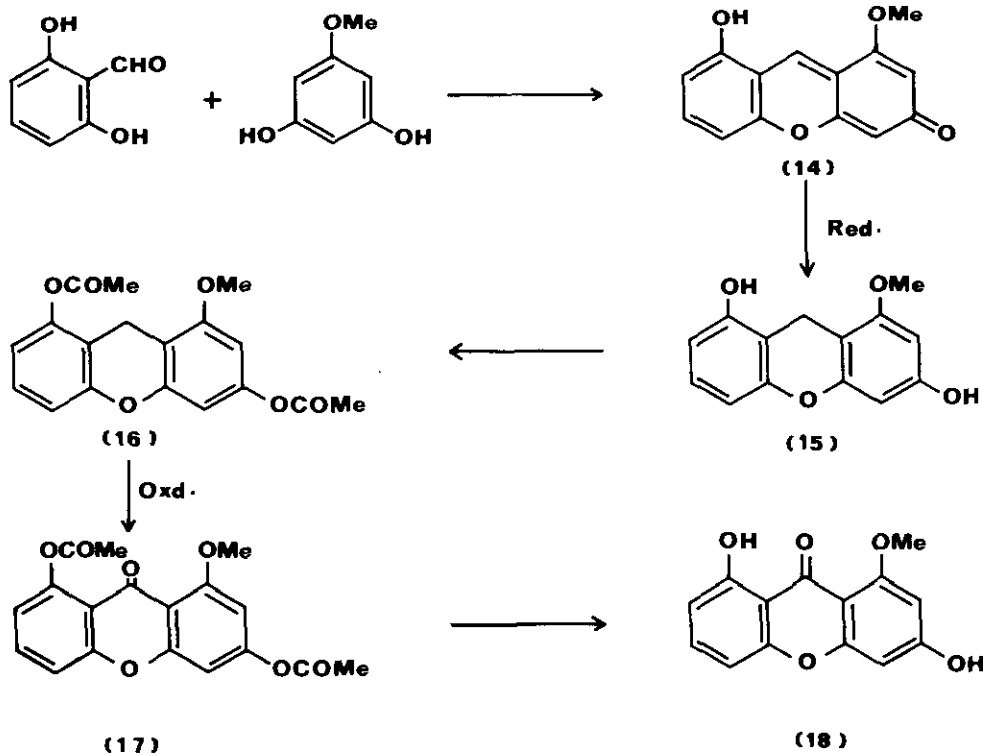
Stout and Fries have noticed<sup>75</sup> a close relationship between the xanthenes of *Halenia* and those of the various *Frasera* species, which is of significance since both genera are initially identified with *Swertia*<sup>76,77</sup>. Although *Swertia* has been regarded as the nearest genus<sup>76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

#### Synthetic Methods:

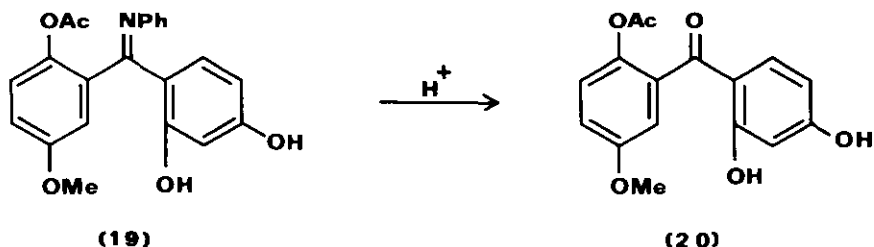
Polyoxygenated xanthenes of potential therapeutic and taxonomic value and many other xanthenes have been synthesized by a number of methods. Although the method described by Grover, Shah and Shah<sup>78</sup> has serious limitations, it is still used extensively for the synthesis of phytoxanthenes. An *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 xanthenes as final products along with other unwanted materials. The following phytoxanthenes or their derivatives have been prepared by this method: Scriblitifolic acid-*O*-methyl ether<sup>79-81</sup>, monomethoxy-dihydro-osajaxanthone<sup>82,83</sup>, 1,5-dihydroxy-<sup>16</sup>, 1,7-dihydroxy-<sup>84,85</sup>, 1,3-dihydroxy-5-methoxy-<sup>86</sup>, 1,3,5-trihydroxy-<sup>87-89</sup>, 1,5-dihydroxy-3-methoxy-<sup>89</sup>, 1,3,5-trimethoxy<sup>88,89</sup>, 1,3,7-trihydroxy-<sup>78</sup>, 1,3-dihydroxy-7-methoxy-<sup>78</sup>, 1-hydroxy-3,7-dimethoxy-4-isoprenyl-<sup>90,91</sup>, 1,3,5,6-tetrahydroxy-<sup>78,92,93</sup>, 1,3,6,7-tetrahydroxy-<sup>94</sup>, 1,3,5-trihydroxy-6-methoxy-<sup>96</sup>, 1,3,8-trihydroxy-5-meth-

oxy<sup>15</sup>, 1,3-dimethoxy-6,7-dihydroxy<sup>94</sup>, 1,3,6-trihydroxy-7-methoxy<sup>94</sup> and 1,3-dihydroxy-6,7-dimethoxyxanthone<sup>94</sup>. 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 xanthenes by the method of Michael-Kostanecki. Euxanthone<sup>44,49,52,55,66,67,72,74,88,101-109</sup> has been synthesized by this method<sup>97</sup>.

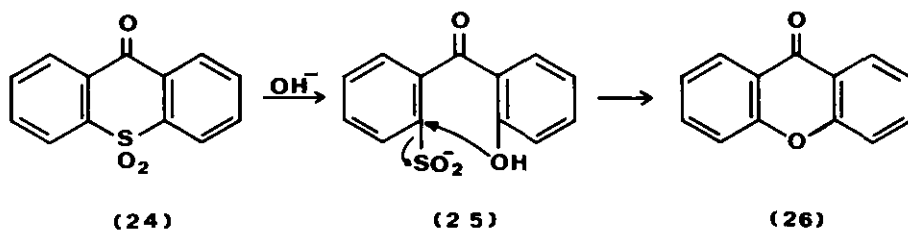
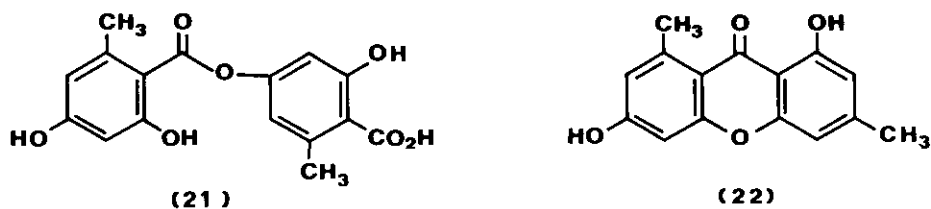
Asahina and Tanase's route<sup>110,111</sup> for the synthesis of xanthenes involves an *o*-hydroxybenzaldehyde which is condensed with a phenol to give 9H-xanthen-3-one (14). Upon methylation or reduction, this gives a 9H-xanthene derivative (15) which can then be oxidised to a xanthone derivative (17).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



Xanthenes involving ketimine intermediates of the type (19) have been synthesized by Robinson and Nishikawa<sup>112,113</sup>. Recently Whalley et al<sup>95</sup> have used this method for the synthesis of a number of benzophenone intermediates which upon oxidation could yield xanthenes.



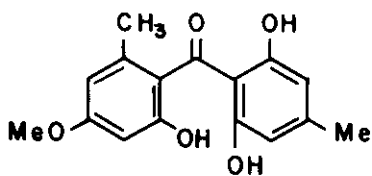
Salicylaldehyde copper complexes<sup>114,115</sup> when reacted with aromatic halides are reported to give xanthenone in good yields<sup>116</sup>. Some xanthenes have been prepared by pyrolysis of aryl esters of *o*-hydroxybenzoic acids. An example is the pyrolysis of lecanoric acid (21) which gives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



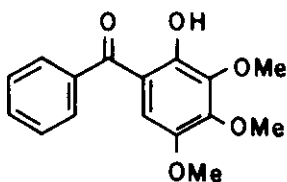
Mono- and dioxygenated xanthenes have been mostly prepared by Ullmann synthesis of diphenyl-ether intermediates which cyclize by phosgene, or alternatively through diphenyl ether 2-carboxylic acids which cyclize by an intramolecular acid catalysed acylation<sup>111,125-128</sup>. However more convenient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

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

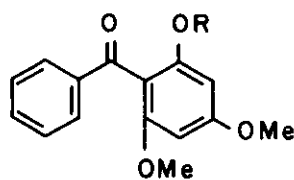
Xanthone synthesis by this method is largely concerned with orientation control, selective methylation, and demethylation of phenolic hydroxyl groups<sup>3</sup>. The synthesis of benzophenones, suitable as precursors for cyclization to xanthenes, has been conveniently achieved at room temperature by Friedel-Crafts acylation of methoxybenzene derivatives, with 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<sup>132</sup> scleroin (27), whereas acylation of 1,3,5-trimethoxybenzene gives either natural benzophenone hydrocotoain (2-hydroxy-4,6-dimethoxybenzophenone; (28) or cometabolite methylhydrocotoain<sup>134,135</sup> (29),



(23)



(27)

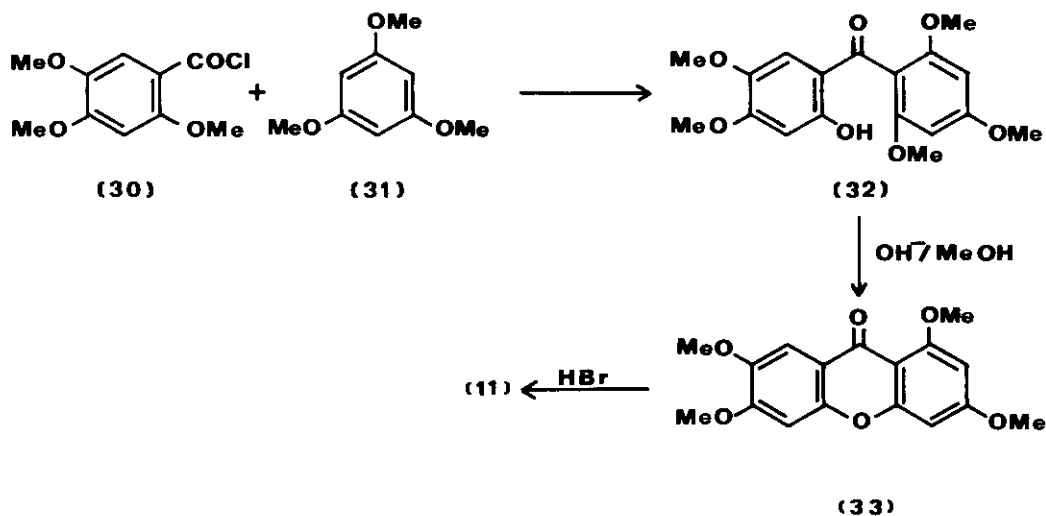


(28): R = H

(29): R = Me

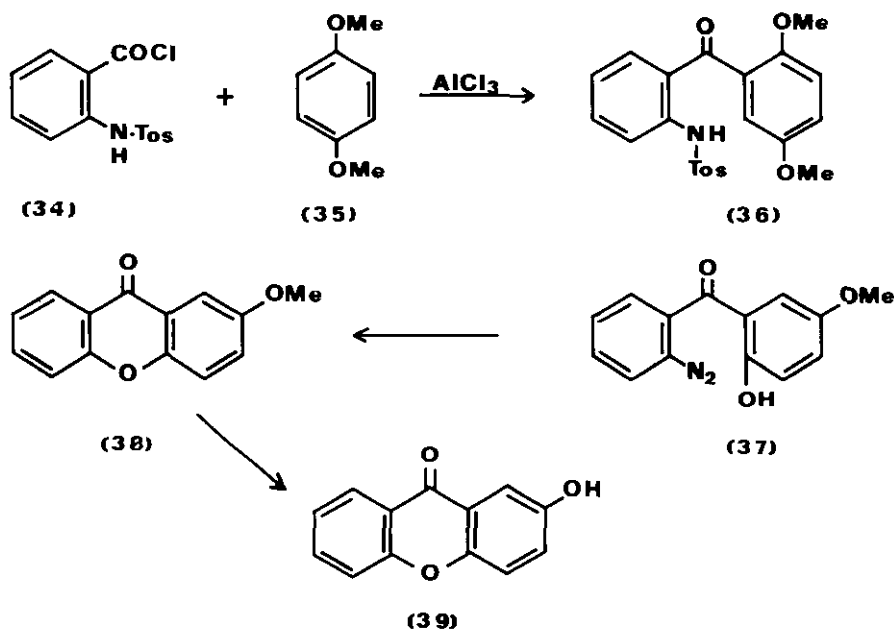
according to the duration of the reaction. Hydrocotoin is of some considerable chemotherapeutic interest<sup>135,136</sup> and was initially isolated in 1879 from the barks of *Aniba pseudocoto* (Rusby) *Kostermans* (Lauracea). The fact that extended reaction time causes ortho-monodemethylation has led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

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



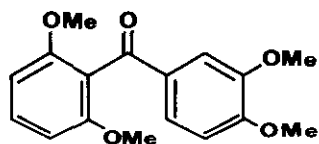


2-N-Tosyl-2'-hydroxybenzophenones are also reported to undergo cyclisation via elimination process. In vivo the synthesis of a xanthone nucleus could involve a similar mechanistic pathway, with a phosphate group participating in the displacement<sup>152</sup>. Thus the following synthesis of 2-hydroxyxanthone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

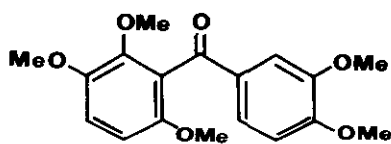


#### Selective Demethylation of Xanthenes:

Selective demethylation of preformed methoxybenzophenones and xanthenes has proved to be a very useful tool in the total synthesis of phyto-xanthenes. 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<sup>140,145,154,155</sup>. Boron trichloride also selectively demethylates a methoxy-group adjacent to a carbonyl group<sup>156</sup>. 1-Hydroxy-5-methoxyxanthone, a metabolite of *Mesua ferrea* L<sup>107</sup> has been prepared from 1,5-dimethoxyxanthone<sup>107,157</sup>. Locksley and Murray<sup>158</sup> have used boron tribromide<sup>159,160</sup> in methylene chloride or benzene for the demethylation of 2,3',4',6-tetramethoxybenzophenone (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-

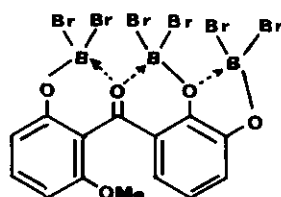


(40)



(41)

6-methoxybenzophenone. Locksley and Murray<sup>158</sup> have proposed a planar 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<sup>160</sup> and phosphorus oxychloride in the presence of zinc chloride<sup>129</sup> have also been used for selective demethylation reactions of xanthenes.

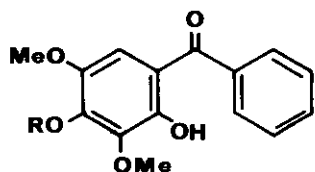


(42)

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

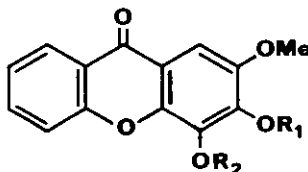
Scheinmann *et al.*<sup>129</sup> have shown that a methoxy-group buttressed<sup>139</sup> by two ether functions is demethylated next under acidic conditions followed by methoxy-groups not para to a carbonyl function. The final methoxy-group to be demethylated, under these conditions, is para to the 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 presence of aqueous piperidine to give 2,4-dihydroxy-3,5-dimethoxy benzophenone<sup>45</sup>. Also refluxing 2,3,4-trimethoxyxanthone (45) with either aqueous piperidine or tetramethylammonium hydroxide is shown to give 3-hydroxy-2,4-dimethoxyxanthone<sup>129</sup> (46).



(43): R = Me

(44): R = H



(45): R = R<sub>2</sub> = Me

(46): R<sub>1</sub> = H ; R<sub>2</sub> = Me

(47): R<sub>1</sub> = Me ; R<sub>2</sub> = H

(48): R<sub>1</sub> = R<sub>2</sub> = H

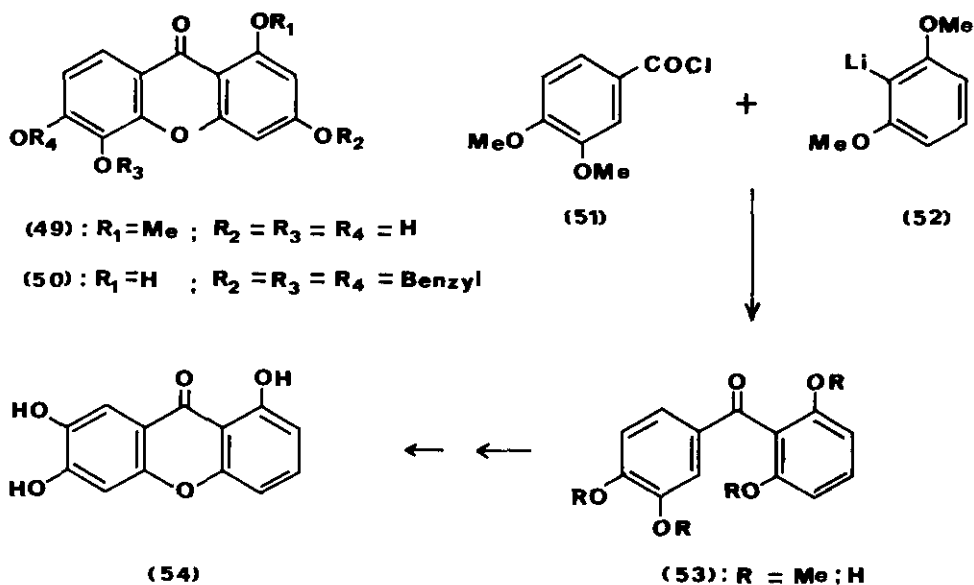
Contrary to these results Chaudhuri and coworkers<sup>166</sup> have shown that demethylation of 1-methoxy-, 1,3-dimethoxy-, and those xanthenes containing added methoxy-group(s) in the B ring (5- and/or 7- position) takes place preferentially at the 1- position with aqueous piperidine, followed by demethylation 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 xanthenes, 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.*<sup>129</sup> 2,4-Dimethoxy-3-hydroxy-<sup>129</sup>, 1,3-dihydroxy-4,7-dimethoxy-<sup>129</sup> and 1-hydroxy-3,5,6,7-tetramethoxyxanthenes<sup>25</sup> have been prepared by this method. A number of other xanthenes with interesting oxygenation pattern have also been obtained by this route. The use of sodium ethanethiolate<sup>143,167,168</sup> has also been mentioned as a versatile demethylating method for aryl ethers.

#### Selective Methylation of Xanthenes:

Some of the phytoxanthenes have been prepared by selective methylation of preformed hydroxy-xanthenes. 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

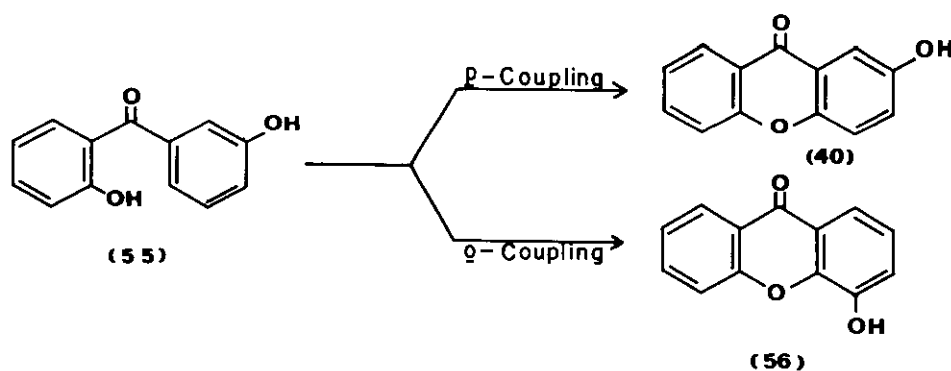
*Guttiferae* species<sup>6,46a,140,154,169,171,172</sup>, has been prepared by selective methylation of 3,4-dihydroxy-2-methoxyxanthone (48) by dimethyl sulphate and potassium carbonate. The phytoxanthone 1-methoxy-3,5,6-trihydroxyxanthone (49) has been obtained<sup>66</sup> by benzylation of 1,3,5,6-tetrahydroxyxanthone (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-<sup>157</sup>; 1-hydroxy-7-methoxy-<sup>103,105,107,145,173</sup>; 2,3-dimethoxy-4-hydroxy-<sup>129</sup>; 1,5-dihydroxy-3-methoxy-<sup>89</sup>; 1,3,5-trimethoxy-<sup>142</sup>; 1-methoxy-3,5-dihydroxy<sup>174</sup>; 1,3,7-trimethoxy-<sup>129</sup>; 1,7-dihydroxy-3-methoxy-<sup>175</sup>; 1-hydroxy-3,7-dimethoxy-<sup>66,176</sup>; 1-methoxy-3,4,5-trihydroxy-<sup>66</sup>; 1,5,6-trihydroxy-3-methoxy-<sup>27</sup>; 1,5,8-trihydroxy-3-methoxy<sup>9</sup>; 1-hydroxy-3,5,8-trimethoxy-<sup>8</sup>; 1-hydroxy-3,7,8-trimethoxyxanthone<sup>161-164</sup>.

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



Oxidative Cyclization of Benzophenones:

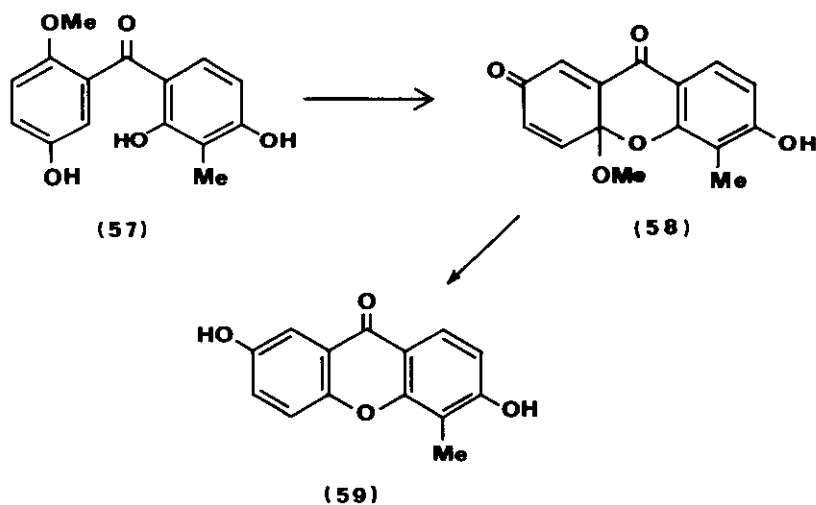
Apart from the base catalysed cyclization of polyoxygenated benzophenones to the corresponding xanthenes, biogenetic type of oxidative cyclization has been extensively used. Lewis<sup>182</sup> first proposed that naturally occurring xanthenes may be generated by an oxidative cyclization of an appropriately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



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

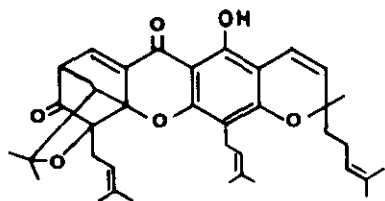
Several oxidants have been used to convert the polyhydroxybenzophenones into their respective xanthenes by oxidative cyclization. Thus photochemical oxidation<sup>68</sup>, manganese (III) tris (acetylacetonate)<sup>158,183,184</sup>, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)<sup>126</sup>, ceric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

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

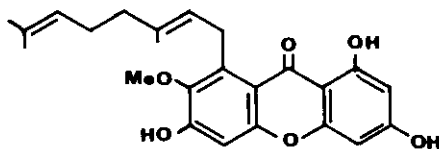


Geranyl substituents have been reported in xanthenes obtained from the genus *Garcinia*. In the case of gambogic acid<sup>186,239</sup> (60), this substituent is cyclised but in the cases of rubraxanthone<sup>187</sup> (61), cowaxanthone<sup>188</sup> (62), and its congeners, the geranyl side-chain is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

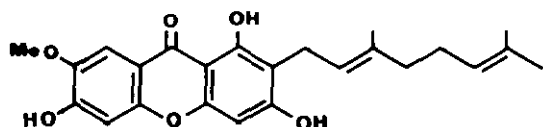
Interesting biogenetic type synthesis of xanthenes has been mentioned by Douglas and Money<sup>198</sup>. The ortho-substituents on the aryl rings of methyl 7-(4-*orcynyl*)-3,5,7-trioxoheptanoate



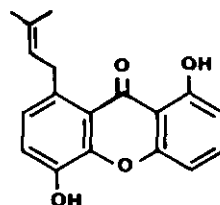
(60)



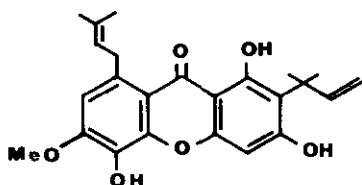
(61)



(62)



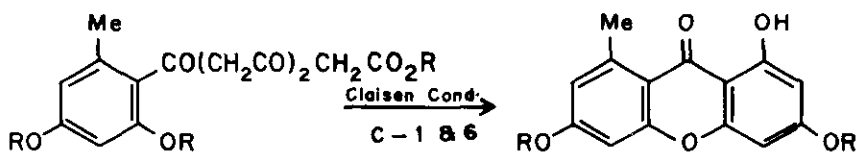
(63)



(64)

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

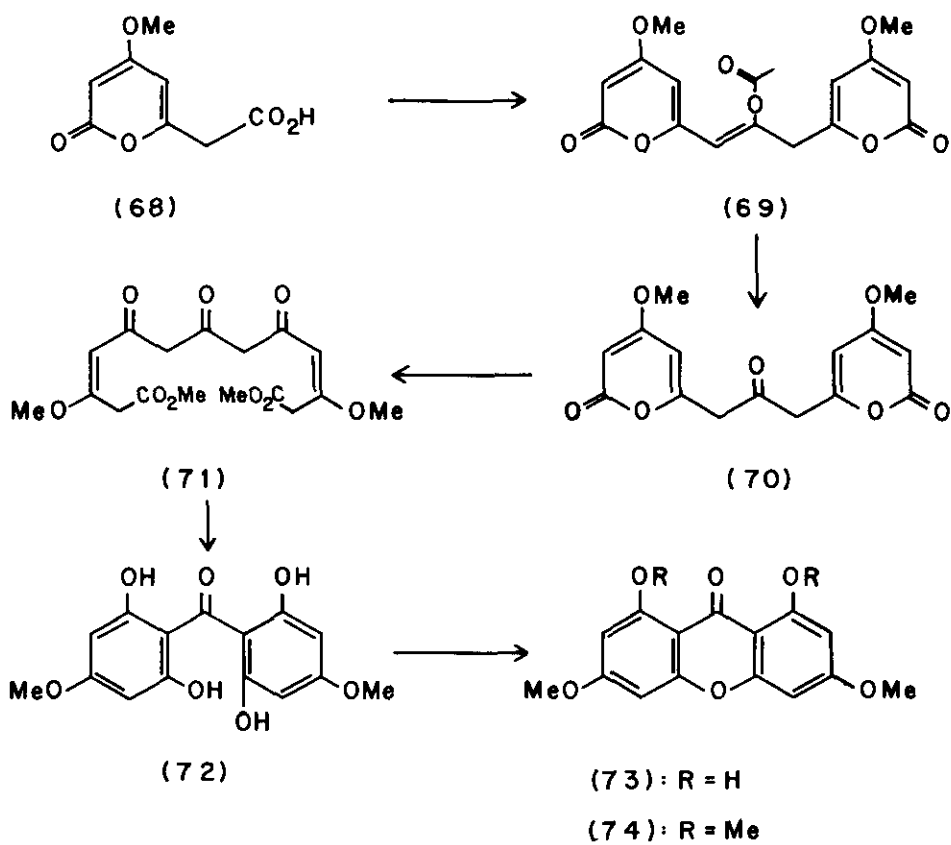
Synthesis of xanthenes from extended poly- $\beta$ -ketide chains, in which control of cyclisation and reductive sequences, paralleling those of nature, is described by Scott *et al*<sup>201</sup>. Thus decarboxylative dimerisation of the acid (68) is shown to give ketone (70) via intermediate (69). This system constitutes a source of the polyhydroxyxanthenes as shown on next page:-



(65): R = H

(67): R = Me

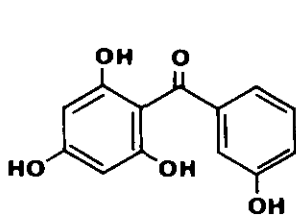
(66): R = Me



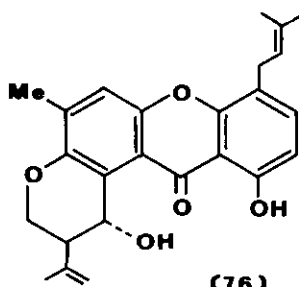


Biosynthesis:

The possible interrelationship between hydroxybenzophenones and xanthenes was first suggested<sup>182</sup> in 1963. This has been supported by the co-existence of polyhydroxybenzophenones and related xanthenes in a number of plants like *Symphonia globulifera*<sup>4,6</sup>, *Chorophora tinctoria*<sup>68,69</sup>, *Allanblakia floribunda* Oliver<sup>6,101,108</sup> and in fungus *Penicillium patulam*<sup>202</sup>. Conversion of polyhydroxybenzophenones into naturally occurring xanthenes 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*<sup>182</sup> and rapid assimilation of sodium acetate-2-<sup>14</sup>C, by the plant to form both labelled benzophenone and the xanthone, provided strong support for the formation of xanthenes 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 penduculata*<sup>146</sup>, supports the view that xanthenes are formed from hydroxybenzophenones. Maclaurin (13) co-occurs with 1,3,6,7-tetrahydroxy-, 1,3,5,6-tetrahydroxyxanthenes (11) and (12) respectively in *Symphonia globulifera* L.<sup>108</sup> and their mangostin derivatives have been isolated from many plant species<sup>74,91,108,147,203</sup>.



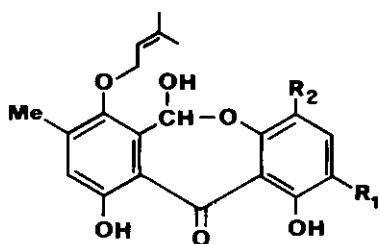
(75)



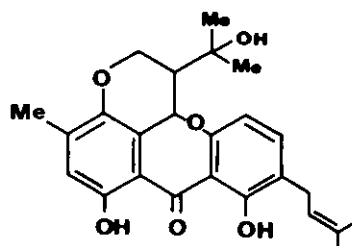
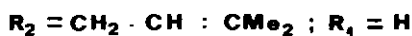
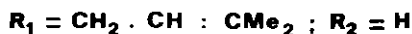
(76)

By means of tritium incorporation studies, Gupta and Lewis have established<sup>4</sup>, 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 xanthenes present in *Pentapthalangium Solomonse* Warb<sup>148</sup>, and *Calophyllum scriblitifolium* Henderson and Wyatt Smith<sup>48</sup>. Anthraquinone intermediates are most likely involved in the formation of several fungal benzophenones and xanthenes<sup>204-206</sup>. Thus shamixanthone (76)<sup>207,208</sup>, tajixanthone (79)<sup>207,208</sup> and arugosins (77, 78)<sup>209-212</sup> 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<sup>214</sup>. 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 transformation of an acetate-derived anthracene intermediate<sup>213</sup>.



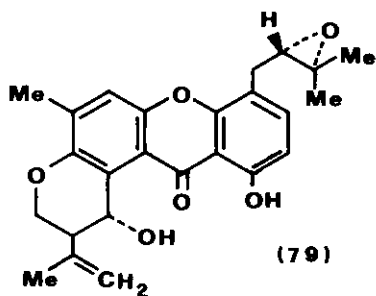
(77)



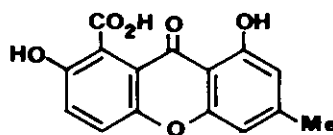
(78)

Compounds with a benzophenone skeleton are biosynthesized by two routes<sup>215</sup>: (a) wholly acetate-polyketide, (b) shikimate-polyketide ( $\text{C}_6\text{C}_1$  plus 3  $\text{C}_2$  and  $\text{C}_6\text{C}_3$  plus 2  $\text{C}_2$ ). In the case of naturally occurring xanthenes, it has been shown in biosynthetic studies that the former route is probably operating in fungi and the latter in higher plants<sup>4,6,209,215,216</sup>.

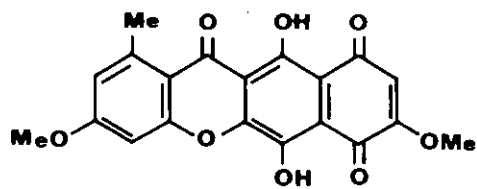
Vining and his co-workers<sup>216</sup> have shown from doubly labelled experiments that the fungal xanthone bikaverin (81) is derived via the folding of a single polyketide chain without a anthraquinone intermediate. The xanthone ravenelin (82) is a metabolite of *Helminthosporium ravenelli*<sup>217</sup> and *H. turcicum*<sup>244</sup> passerin. Birch *et al*<sup>217</sup> 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<sup>205,218</sup> and ergot pigments<sup>219</sup> have also been suggested to be derived from a single polyketide chain. Sterigmatocystin<sup>205,218</sup> and ergot pigments<sup>219</sup> have also been suggested to be derived from a single polyketide chain.



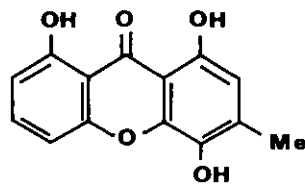
(79)



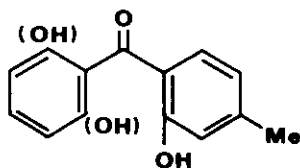
(80)



(81)

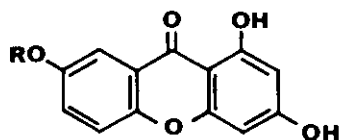


(82)



(83)

In case of plant derived xanthenes the biogenetic route is relatively simpler since benzophenones show hydroxylation patterns suggesting their derivation from acetate and shikimate. Lewis and Frank have shown<sup>14,206,220</sup> that both the shikimate and acetate routes, for biogenesis of aromatic compounds, are involved in the biogenesis of the plant xanthenes 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<sup>221</sup> (b) the direct involvement of shikimic acid or some other related C<sub>6</sub>-C<sub>1</sub> precursor such as (86) with three molecules of acetic acid or malonic acid<sup>6,141,176,222</sup>.



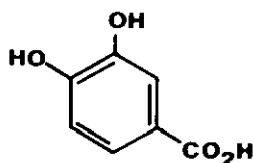
(84) : R = Me

(85) : R = H

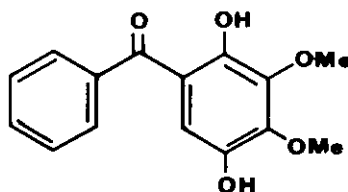
It has been suggested that the co-occurrence of sclerion (87) and cearoin (88) with neoflavonoids supports route (a). *Gentiana lutea* metabolises phenylalanine and acetic acid to give 2,3',4,6-tetrahydroxybenzophenone (75) together with several derived 1,3,7-trioxygenated xanthenes<sup>245</sup>.

This has suggested a more direct biosynthetic route, involving shikimic acid<sup>145</sup>, to benzophenones than suggested by route (a).

The co-occurrence of oxygenated benzophenone hydrocotoin (28) and 2,3'-dihydroxy-4,6-dimethoxybenzophenone (89) with xanthenes<sup>101</sup> in *Allanblackia floribunda* Oliver and earlier<sup>6,108</sup> 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<sup>141,176,222</sup>.

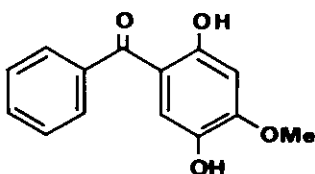


(86)

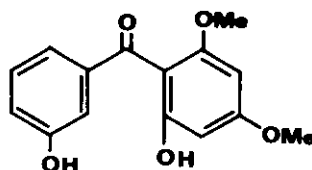


(87)

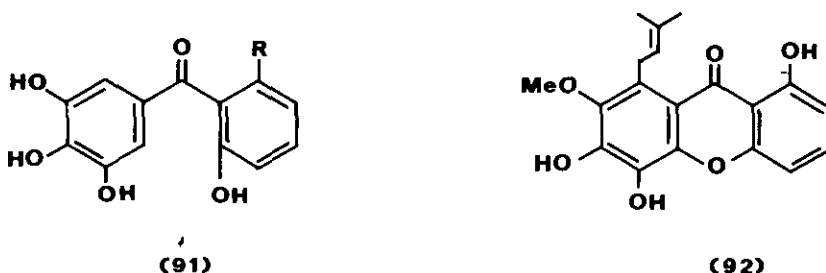
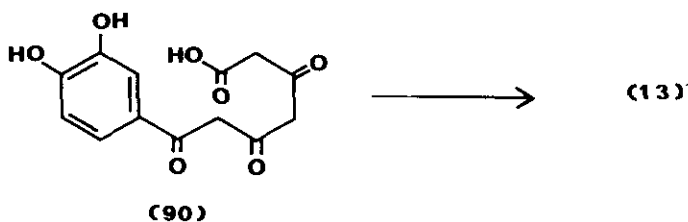
Roberts<sup>2</sup> has suggested biosynthesis of xanthenes involving the condensation of an aromatic acid with three acetate units to a  $\beta$ -polyketo-acid which then cyclizes to a benzophenone precursor. Thus 3,4-dihydroxybenzoic acid (86), derived from shikimic acid, could condense with acetate to the  $\beta$ -polyketo-acid<sup>93,223</sup> (90) which then cyclises to form maclaurin (13), a precursor for 1,3,5,6- and 1,3,6,7-tetrahydroxyxanthenes and other xanthenes with a similar oxygenation pattern. Celebixanthone<sup>224</sup> (92) and other 2,3,4-oxygenated xanthenes<sup>140</sup> 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<sup>225,226</sup>. They are led to suggest that gallic acid is formed by direct aromatisation of dehydroshikimic acid rather than by catabolic breakdown of phenylalanine.



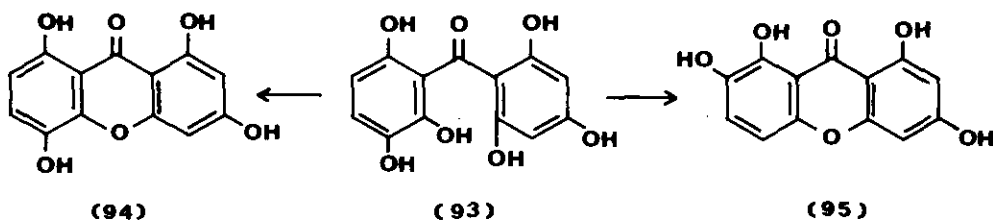
(88)



(89)



Natural xanthenes fall into two groups which reflect different modes of biogenesis<sup>220</sup>. 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<sup>217,220</sup>, and used by Markham<sup>10</sup> 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 xanthenes in the species of Gentianaceae. 2,2'-dihydroxybenzophenones have been dehydratively cyclized under a variety of conditions<sup>202,227-229</sup>. *In vivo* the synthesis of the xanthone nucleus could involve a similar mechanistic pathway, a phosphate group participating in the displacement<sup>152</sup>. The co-occurrence of 5,8- (94) and 7,8-oxygenated xanthenes (95) provides strong support for the hypothesis that they are synthesised from a common benzophenone precursor such as (93) involving elimination process.



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

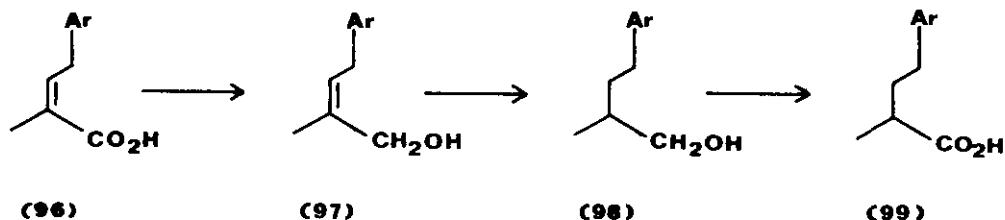
The isolation of 1,2,3-trioxygenated xanthone from *Frasera carolinensis*<sup>142</sup>, 1,3,5- and 1,3,7-trioxygenated xanthenes from *Calophyllum scriblitifolium* Henderson and Wyatt-Smith<sup>48</sup> and *Pentaplangium solomonense* Warb.<sup>148</sup>, the co-occurrence of 1,5,6- and 1,6,7-trihydroxyxanthone in *Garcinia eugeniifolia* Wall.<sup>102</sup>, 5- and 7- hydroxylated xanthenes in *Mammea americana*<sup>84,85</sup> (two pairs) and in *Mammea africana*<sup>49</sup> (three pairs), are all in accordance with the oxidative coupling mechanism of xanthenes. The isolation of these xanthenes 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<sup>222,233</sup> by Lewis.

*In vivo*, oxidation of hydroxybenzophenones has been suggested<sup>141</sup> 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<sup>234</sup>. Lewis *et al* have reported<sup>141</sup> the oxidation of benzophenones *in vivo* by peroxidase and laccase from *Polystictus virsicolor* to give xanthenes. A mechanism of parallel type, involving radical intermediates in these enzyme induced oxidations<sup>235</sup>, has been formulated to give xanthenes.

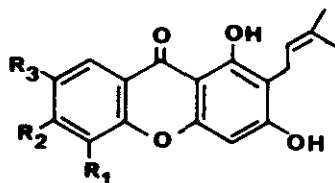
The dimethylallyl side chain is suggested to be introduced into a preformed hydroxylated xanthone nucleus which is produced from an appropriate hydroxylated benzophenone. The presence of 1,1-dimethylallyl group in natural xanthenes is of biogenetic importance, and indicates that an aromatic precursor attacks " $\gamma,\gamma$ -dimethylallyl pyrophosphate" in a manner analogous to an  $SN_2$ ,<sup>93,246</sup> substitution. An *ortho*-Claisen-type rearrangement of an *O*-3,3-dimethylallyl precursor to an *C*-1,1-dimethylallyl compound has been demonstrated<sup>236</sup>. Several *O*-3,3-dimethylallyl compounds have been isolated from natural sources<sup>93,205</sup> 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<sup>90</sup>.

The suggestion that the pyrone ring in natural xanthone<sup>230,237,238</sup> 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-dimethylallylxanthonones, (100) and (101) in *C. scriblitifolium* Henderson and Wyatt-Smith .



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 step-wise modification of a 3,3-dimethylallyl group at C-6. Scheinman and coworkers have suggested<sup>192</sup> 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) :  $R_1 = R_2 = H$  ;  $R_3 = OH$

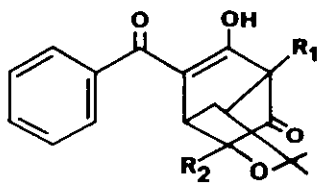


(102) :  $R_2 = -CH_2 \cdot CH_2 \cdot \overset{\overset{CH_3}{|}}{CH} \cdot CO_2H$

(103) :  $R_2 = -CH_2 \cdot CH_2 \cdot \overset{\overset{CH_3}{|}}{CH} \cdot CH_2OH$

(104) :  $R_2 = -CH_2 \cdot \overset{\overset{CH_3}{|}}{CH} \cdot C \cdot CH_2OH$

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

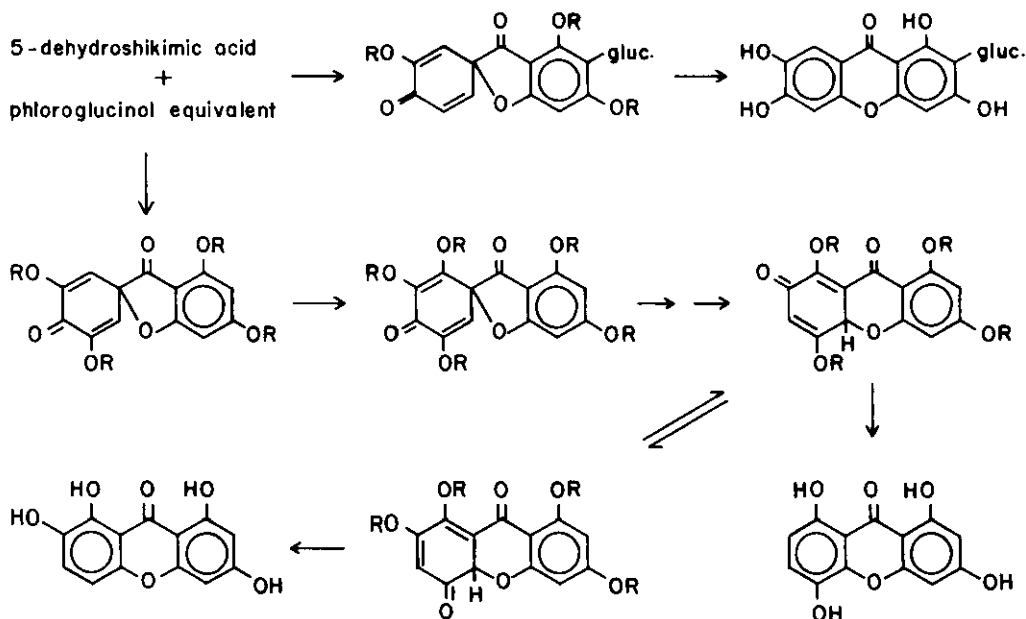


(105)

$R_2 = \text{Geranyl}$

$R_1 = \text{Farnesyl}$

Ghosal et al have proposed the biosynthesis of tetraoxygenated xanthenes of *Swertia chirata*<sup>17</sup>. The absence of 1,3,5- and 1,3,7-trioxygenated xanthenes which were previously suggested to be precursors of tetraoxygenated xanthenes by further oxidation at one of the activated sites  $C_6$  or  $C_8$  has led Ghosal *et al.* to propose that tetraoxygenated xanthenes (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 cooccurrence of polyoxygenated xanthenes 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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