XANTHONES - A GENERAL INTRODUCTION

The xanthones constitute a very important class of plant pigments which are widely distributed in the vegetable kingdom. The term xanthone designates the chemical compound dibenzo-$\gamma$-pyrone (I). The xanthones bear a structural relationship to the other naturally occurring $\gamma$-pyrone derivatives viz., the flavonoids and chromones. The parent pyrans, the xanthones are not as yet known to occur in nature.

During the last few years there has been a revival of interest in the chemistry of xanthones. The intensive progress in this field has been thoroughly reviewed by Roberts (Chem. Rev., 1961, 61, 501), by Neelakantan and Seshadri (Current Sci. India, 1961, 30, 90), and more recently by Dean in his book "Naturally occurring Oxygen Ring Compounds" (Butterworths, London, 1963, p.366).

In view of the fact that the next chapter deals with the isolation and structure determination by degradation and
synthesis of two new xanthones from the heartwood of *Musa sapienta* L (Guttiferae) a brief account of the chemistry of xanthones is given below.

Naturally occurring xanthones in general have a hydroxyl group at position 1 and a phloroglucinol or resorcinol nucleus as one component. As the other aromatic component, the majority of xanthones have a quinol or hydroxy quinol nucleus and thereby differ markedly from all the related groups of pyrones, e.g. Coumarines (II) or flavones (III). Recently quite a few non-C-1 hydroxylated xanthones have been isolated, for example 2-hydroxyxanthone (IV) (Finnegan and Bachman, J. Pharm. Sci., 1965, 54, 683), 4-hydroxy-2,3-methylenedioxyxanthone (Va), 4-methoxy-2,3-methylenedioxyxanthone (Vb), 2,3-dimethoxy-4-hydroxyxanthone (VIa) and 3,4-dihydroxy-5-methoxyxanthone (VI b)

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\text{IV}
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\[
\text{V}
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\[
\text{VI}
\]

Structural variations in naturally occurring xanthenes arise not only from the number and disposition of the oxygen functions, but also from the presence of isoprenoid side-chains. Some examples of such complex xanthenes are jacarubin (VII) (King and Manning, J. Chem. Soc., 1963, 3032), mangostin (VIII) (Yates and Steut, J. Amer. Chem. Soc., 1968, 90, 1891).
morellin (IX) (Kerth, Namachandran, Bhat, Madhavan Nair, Raghavan and Venkataraman, Tetrahedron Letters, 1963, 459),

VII

VIII

IX

\[ \text{X} \]

\[ \text{XI} \]

\[ R_1 = \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH} = \text{C(CH}_3)_2 \]
\[ R_2 = \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH(CH}_3) \cdot \text{COOH} \]

**Occurrence in plants:**

Many of the xanthones so far reported have been found to occur in various parts of the flowering plants belonging to the
families Gentianaceae, Guttiferae and Anacardiaceae, while a few xanthonones have also been reported from lower fun-1 and lichen. Some occur as their glycosides, for example svertional \( ^{a} \) (Ashina, Asano and Uyeno, J. Pharm. Soc., Japan, 1946, 62, 221) and isogentisin (XIII) (Canonica and Palizzoni, Gaz. chim. ital., 1958, 85, 1007), Mangiferin (XIV) (Bhatia, Kamarathan and Seshadri, Tetrahedron, 1967, 23, 1363) is unusual in that it is a C-glucoside.
Isolation:

The xanthones are generally obtained by the solvent extraction of the dried, powdered plant material. The crude product thus obtained is often purified by chromatographic fractionation, or crystallisation or by partition separation technique employing aqueous solutions of sodium bicarbonate, sodium carbonate and sodium hydroxide. Further purification is also effected by sublimation under low pressure. Extensive use of thin layer chromatography must be mentioned in assessing the complexity of extracts and the purity of the compounds.

Detection:

As in the case of flavones, several colour reactions enable detection of xanthones and the hydroxylation pattern in the molecule. An alcoholic solution of a xanthone when treated with magnesium and a few drops of hydrochloric acid develops an orange, red or violet colour as in the case of flavone, flavanone or flavanol (Shinoda, J. Pharm. Soc., Japan, 1928, 48, 214). This test is not infallible, however and has been criticised (Marini-Bettolo and Ballio, Gazz. chim. ital., 1946, 76, 410).

When a xanthone is dissolved in glacial acetic acid and a drop of sulphuric acid is added, a deep orange colour appears immediately (Perkin-Ι )-pyrone test, Wolfrom, Dickey, McWain, Thompson, Looker, Windrath and Komitasky, J. Org. Chem., 1964, 29, 689). 1-Hydroxyxanthones in general, give a deep green ferric reaction and a yellow colour with a mixture of boric and citric acids (Wilson, J. Amer. Chem. Soc., 1939, 61, 2002).
p-Benzquinone gives deep red coloured compounds with 1,4-dihydroxyxanthones (Georgeson reaction, Perkin, J. Chem. Soc., 1913, 102, 657).

α-Dihydroxyxanthones on treatment with a methanolic solution of lead acetate in alcoholic solution give an immediate precipitate (Wolfson, Dicke, McWain, Thompson, Looker, Windrath and Komitsky, loc.cit.).

A methylene dioxy group is indicated by a green colour when alcoholic gallic acid is added to the solution of the substance in sulphuric acid (Labat, Bull. Soc. Chim. Biol., 1933, 15, 1344).

The Gibbs reaction (blue to green colouration and characteristic absorption in the 500–700 μ region) in borate buffer with 2,6-dichlorobenzoquinone chlorimide shows whether the position para to a hydroxyl group is unsubstituted (King, King and Manning, J. Chem. Soc., 1957, 563). The Gibbs test was however, found misleading when applied to some synthetic xanthones. Using the qualitative procedure both 2-allyl-1-hydroxy-3,5,6-trimethoxyxanthone (XV) and 1-hydroxy-3,5,6-trimethoxy-4-(3',3'-dimethylallyl) xanthone (XVI) gave results which appear positive. However, by contrast, with 1-hydroxy-3,5,6-trimethoxyxanthone (XVII) these results appear negative (Burling, Jefferson and Scheinmann, Tetrahedron, 1965, 21, 2653).
THE ROLE OF SPECTRA IN THE CHARACTERISATION AND STRUCTURE DETERMINATION OF XANTHONES:

General:

Spectroscopic methods are increasingly becoming important in elucidating the structure of naturally occurring xanthones. Yates and Stout (loc. cit.) used ultraviolet, infrared and nuclear magnetic resonance spectroscopy in elucidating the structure of mangostin (VIII). More recently Stout, Breyer and Jenson, Chem. & Ind., 1961, 289) on evidence from ultraviolet spectroscopy and X-ray methods discovered that rubrofusarin was not a xanthone. X-ray spectroscopy has helped in elucidating the structure of morellin (IX) and ergoflavin (X).

1) Infrared spectra:

The spectra of solid specimens of xanthones (either as nujol mulls or KBr pellets) have a series of bands in the region 1660-1540 cm\(^{-1}\). The band in the region 1668 cm\(^{-1}\) is attributed to the heterocyclic ring carbonyl stretching frequency and the adjacent bands at 1585-1600 cm\(^{-1}\) and 1575-1550 cm\(^{-1}\) are due to aromatic rings. Xanthone has a carbonyl absorption at 1670 cm\(^{-1}\) which is also the characteristic region for the carbonyl group in 6-methyl-2-methoxy-\(\gamma\)-pyrone and related \(\gamma\)-pyrones (Harbst, Mors, Gottlieb and Djerassi, J.Amer.Chem.Soc., 1959, 81, 2427), conjugated cyclohexadienones (Jones, Ramapriya, Leir, Dobrin, J. Amer. Chem. Soc., 1955, 77, 30) and benzophenone (Fuson, Shelton, J. Amer. Chem. Soc., 1954, 76, 2526).

The presence of a hydroxy group ortho to the ring carbonyl
causes the carbonyl stretching frequency to be lowered (moved to the higher wavelength) by 17 cm\(^{-1}\) to 35 cm\(^{-1}\). Etherification or esterification of 1-hydroxyxanthone restores the carbonyl frequency. 3-Hydroxyxanthone has the carbonyl band at 1640 cm\(^{-1}\), while 2-hydroxyxanthone has a shoulder at 1656 cm\(^{-1}\) and a very strong absorption at 1640 cm\(^{-1}\). The position of the carbonyl band in inodemethylmangostin in carbon tetrachloride was reported to be also at 1640 cm\(^{-1}\).

The increase in wavelength for the carbonyl stretching band in 1-hydroxyxanthone is due to the presence of a six membered chelate system (XVIII) (Mellamy, The Infra-red Spectra of Complex Molecules, p.143, Methuen & Co. Ltd, 1958).

![XVIII](image)

1-hydroxyxanthone shows three bands in the region between 1668 cm\(^{-1}\) and 1563 cm\(^{-1}\) and four bands when the hydroxyl group is etherified or esterified. Etherification or esterification of the 1-hydroxyl group causes the aromatic stretching band at 1613 cm\(^{-1}\) to be split into two distinct bands (Table I). It must be stressed,
however, that multiple peaks in the 1668 cm$^{-1}$ region are not specific to xanthones because such absorptions can also arise with flavones (Sondheimer and Meisels, Tetrahedron, 1960, 6, 139) and isoflavones (Crabbe, Leeming and Djerassi, J. Amer. Chem. Soc., 1958, 80, 5258; Stout and Stout, Tetrahedron, 1961, 14, 296).

Table I

Characteristic bands in 1668 cm$^{-1}$ region in the spectra of xanthones related to hydroxyxanthones.
(Scheinmann, Tetrahedron, 1962, 18, 855).

<table>
<thead>
<tr>
<th>Compound</th>
<th>cm$^{-1}$</th>
<th>cm$^{-1}$</th>
<th>cm$^{-1}$</th>
<th>cm$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthone</td>
<td>1661</td>
<td>1616</td>
<td>1608</td>
<td>1587</td>
</tr>
<tr>
<td>1-hydroxyxanthone</td>
<td>1645</td>
<td>-</td>
<td>1610</td>
<td>1570</td>
</tr>
<tr>
<td>1-methoxyxanthone</td>
<td>1668</td>
<td>1618</td>
<td>1600</td>
<td>1567</td>
</tr>
<tr>
<td>1-acetoxylxanthone</td>
<td>1667</td>
<td>1621</td>
<td>1608</td>
<td>1563</td>
</tr>
<tr>
<td>γ-pyran (2',3'-1,2) xanthone</td>
<td>1668</td>
<td>1613</td>
<td>-</td>
<td>1585</td>
</tr>
<tr>
<td>2-allyl-1-hydroxyxanthone</td>
<td>1642</td>
<td>1608</td>
<td>-</td>
<td>1580</td>
</tr>
</tbody>
</table>

The sharp hydroxyl band near 3333 cm$^{-1}$ is missing for 1-hydroxyxanthone due to strong chelation with the ring carboxyl. In the case of 2-hydroxy and 3-hydroxyxanthones, a sharp hydroxyl band occurs at 3279 cm$^{-1}$ and 3106 cm$^{-1}$ respectively, when the spectra are determined either in nujol mulls or potassium
bromide pellets. Xanthone has a weak C-H stretching vibration at 3086 cm\(^{-1}\).

ii) Ultraviolet spectra:

The ultraviolet spectra of a large number of xanthones have been studied by Yates and Stout (J. Amer. Chem. Soc., 1953, 75, 1691), Stout, Stout and Welsh, Tetrahedron, 1963, 19, 667, Jackson, Locksley and Scheinmann (J. Chem. Soc. (C), 1960, 178), Locksley, Moore and Scheinmann (ibid, 2186; ibid, 2265) and reviewed by Roberts (Chem. Rev., 1961, 61, 591) and Scott (Interpretation of the ultraviolet spectra of Natural Products, Pergamon Press, 1964).

The patterns of absorption of xanthones in the ultraviolet and visible regions are dependent on the number and positions of the hydroxyl and methoxyl groups, but, in general, there is a strong absorption above 340 m\(\mu\) and so the xanthones are usually yellow. Xanthone itself has ultraviolet absorption bands at 235, 261, 287 and 337 m\(\mu\). Usually these four bands are characteristic of xanthones. However, sometimes, there may be only three bands and sometimes five. While the position of the 235 m\(\mu\)-band may vary within 10 m\(\mu\)-irrespective of the hydroxylation pattern, the 261 m\(\mu\)-band is found to be quite sensitive to such changes. Hydroxyl ortho or meta to the carbonyl group have only slight bathochromic shifts of the 261 m\(\mu\)-band; but xanthones which have 3 and/or 6-hydroxyl groups contain an intense maximum near 310 m\(\mu\)-corresponding to the electron transfer represented below. Table II represents the
Characteristic ultraviolet absorption spectra of some known xanthones.

![Chemical structure](image)

**Table II**

<table>
<thead>
<tr>
<th>Compound</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt; in mµ (log ε)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthone</td>
<td>239(4.59), 261(4.13), 287(3.62) 337(3.80)</td>
</tr>
<tr>
<td>2-Hydroxyxanthone</td>
<td>238(4.64), 250(sh), 302(3.62) 370(3.82)</td>
</tr>
<tr>
<td>1,6-Dihydroxy-</td>
<td></td>
</tr>
<tr>
<td>xanthone</td>
<td>247(4.3), 263(4.0), 305(4.1) 355(4.8)</td>
</tr>
<tr>
<td>1,2,8-Trihydroxy-</td>
<td></td>
</tr>
<tr>
<td>xanthone</td>
<td>241(4.41), 265(4.56), 290(3.89) 338(3.94)</td>
</tr>
<tr>
<td>1,3,5,6-Tetrahydroxy-</td>
<td></td>
</tr>
<tr>
<td>xanthone</td>
<td>253(4.69), 281(4.11), 326(4.33)</td>
</tr>
<tr>
<td>2-Hydroxyxanthone</td>
<td>236(4.63), 249(4.56), 303(3.60) 355(3.86)</td>
</tr>
<tr>
<td>2,3,4-Trimethoxy-</td>
<td></td>
</tr>
<tr>
<td>xanthone</td>
<td>246(4.52), 278(3.90) 304(4.05)</td>
</tr>
<tr>
<td>4-Hydroxy-2,3-</td>
<td></td>
</tr>
<tr>
<td>methylenedioxy-</td>
<td></td>
</tr>
<tr>
<td>xanthone</td>
<td>244(4.53), 287(3.82), 328(4.11)</td>
</tr>
<tr>
<td>Jacareubin</td>
<td>241(4.58), 283(4.62), 332(4.23)</td>
</tr>
<tr>
<td>Macluraxanthone</td>
<td>242(4.31), 282(4.64) 338(4.28)</td>
</tr>
</tbody>
</table>
SPECTRA IN ALCOHOLIC SODIUM ACETATE - LOCATION OF 3( and 6) HYDROXYL IN XL: Sodium acetate is sufficiently basic to ionise hydroxyl groups present at C-3 and C-6 of the xanthone nucleus. Ionisation of a 3(6) hydroxyl produces bathochromic shifts of the order of 22 μm of the long wavelength absorption band. For example, 4,5-di-o-methylcorymbin (XIX) shows a 18 μm bathochromic shift of the long wavelength band with sodium acetate, indicating the presence of a 3 hydroxyl group (Marshall, Tetrahedron, 1965, 21, 3857).

However, Gottlieb, Tavares, McGalhaes, Camay, Lina Mesquita and de Barrows Correa (loc. cit.) have observed that 4-hydroxyxanthone also shows significant acidity, that its ultraviolet spectrum is altered if recorded in presence of sodium acetate.
SPECTRA OF ALCOHOLIC SODIUM ACETATE - BORIC ACID -

DETECTION OF o-DIHYDROXYL GROUPS. In the presence of sodium acetate, boric acid chelates with phenolic compounds containing o-dihydroxyl groups. The $\lambda_{\text{max}}$ of the long wavelength band is shifted bathochromically by 25 m$\mu$ on the addition of a mixture of boric acid and sodium acetate. For example, 1,2,8-trihydroxy-3-methoxyxanthone (XX) produces a 25 m$\mu$ bathochromic shift of the long wavelength absorption in ultraviolet, whilst no such change is observed in the spectrum of 1,4,8-trihydroxy-3-methoxyxanthone (XXI) (Markham, loc.cit.)

![Chemical structure of XX and XXI](image)

1.1) Nuclear Magnetic Resonance Spectra:

A great deal of information regarding the structure of an unknown xanthone is obtained by a careful analysis of its
N.M.R spectrum. N.M.R spectra have been widely used to elucidate the structure of many xanthones, for example, morellin (IX), macluraxanthone (XXII) (Wolfrom, Komitsky, Fraenkel, Looker, Dickey, McSwain, Thompson, Mundell and Windrath, J. Org. Chem., 1964, 29, 692), osajaxanthone (XXIII) (Wolfrom, Komitsky and Looker, J. Org. Chem., 1965, 30, 144), agaxanthone (XXIV) (Locksley, Moore and Scheinmann, J. Chem. Soc. (C), 1966, 2365),
symphoxanthone (XXV) (Lockley, Moore and Scheinmann, *ibid.*, 216), 1,2,3-trioxygenated xanthones (Gettlieb, Taveira Magalhaes and Stefani, Tetrahedron, 1966, 22, 1735), isobellidofolin (XXVI) (Markham, Tetrahedron, 1965, 21, 1449) and celebixanthone (XXVII). (Stout, Stout and Welsh, Tetrahedron, 1963, 19, 667).

An examination of the spectra of a number of 1-hydroxyxanthones reveals the presence of a very low field
signal. For example euxanthone (XXVIII) exhibits a very low

\[
\text{XXVIII}
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field signal in the region of 12.41 ppm and such a signal can be
due only to a strongly hydrogen-bonded phenolic proton. If the
C-8 and C-7 protons are present they appear as two ortho-split
doublets centred at 8.5 (J = 9 cps) and 6.31 ppm (J = 9 cps) respectively.
The C-6 proton usually appears as a doublet centred around
7.56 with a splitting constant of J = 9 cps if it has an adjacent
free C-5 or C-7 proton and otherwise as a singlet. Usually
the C-2, C-3 and C-4 protons give signals centred around 6.8 ppm
(doublet, J = 9 cps), 7.46 ppm (triplet, J = 9 cps) and 7.29 ppm (doublet,
J = 9 cps). The C-5 proton appears around 6.81 ppm. The xanthone
acetates give rise to signals around 2.3 ppm for the acetoxy groups
located at various positions, whereas the methoxy groups give
rise to sharp signals around 4 ppm.

Table III is a summary of the N.M.R. spectra of some
typical naturally occurring xanthones.
<table>
<thead>
<tr>
<th>Compound</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buxanthone</td>
<td>0H, 12.41</td>
<td>6.81</td>
<td></td>
<td>7.9</td>
<td>OH, 8.95</td>
<td>6.31 to 7.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Methoxy-2,3'-methylenedioxy xanthone</td>
<td>7.41 (s)</td>
<td>8.24 (s)</td>
<td>6.33 (s)</td>
<td></td>
<td>8.20 to 7.45 (m)</td>
<td>3.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,3-Dimethoxy-5'-hydroxyxanthone</td>
<td>0CH₃ 4.10 (s)</td>
<td>6.03 (d, J = 2.5)</td>
<td>0CH₃ 4.10</td>
<td>7.90 to 7.40 (m)</td>
<td>7.98 q J = 2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,3-Dihydroxy-1'-methoxyxanthone</td>
<td>0CH₃ 4.10 (s)</td>
<td>7.59 (d, J = 10)</td>
<td>6.91 q J = 2.5, 7.7 (t, J = 8.0), 6.92 q J = 8.5, 1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2-Dimethoxy-3'-hydroxyxanthone</td>
<td>0CH₃ 4.19 (s)</td>
<td>0CH₃ 6.00</td>
<td>7.64 (d, J = 9.6)</td>
<td>7.0 q J = 8.5, 1.0, 7.7 (t, J = 8.5), 6.84 q J = 8.5, 1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Hydroxy-3,7-dimethoxyxanthone</td>
<td>-</td>
<td>6.29 (d)</td>
<td></td>
<td>7.42 to 7.39</td>
<td>-</td>
<td>7.54 (d) Complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,3-Dihydroxy-7'-methoxyxanthone</td>
<td>-</td>
<td>6.23 (d)</td>
<td></td>
<td>7.43 to 7.39</td>
<td>-</td>
<td>7.56 (d) Complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Methoxy-3,5,6-trihydroxyxanthone</td>
<td>0CH₃ 3.59 (s)</td>
<td>5.90 (d)</td>
<td></td>
<td>7.11 (d)</td>
<td>7.97 (d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,5,6-Trihydroxy-3'-methoxyxanthone</td>
<td>12.80 (s)</td>
<td>6.28 (s)</td>
<td>4.05 (s)</td>
<td>7.96 (d)</td>
<td>7.96 (d)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DEGRADATION:

An account is presented below of the chemical degradations usually carried out on naturally occurring xanthones for their structure elucidation.

i) Fusion with potassium hydroxide:

Fusion of xanthones with alkali at high temperatures leads to the identification of phenols of diagnostic value, generally resorcinol or phloroglucinol and phenolic carboxylic acids. This useful degradative method has two limitations; methoxyl groups may suffer demethylation and hydroxyquinol nuclei are too sensitive to survive the treatment.

Xanthone (XXVIII) on alkali fusion yields vertisic acid (XXIX) and resorcinol rather than quinol and \( \gamma \)-resorcylic acid; the carbonil group being selectively detached from the more reactive phenol (Raistrick, Robinson and White, Biochem. J., 1933, 30, 1303).
When fusion was carried with jacareubin (VII) under nitrogen atmosphere 1,3,5,6-tetrahydroxyxanthone (XXX) and acetone are obtained. The production of acetone in this fusion points to the presence of a 2,2-dimethylchromene ring in jacareubin (King, King and Manning, loc.cit.).

![Diagram showing the reaction with NaOH: KOH in nitrogen to form VII and XXX with CH₃COCH₃.]

iii) Demethylation:

Most of the naturally occurring xanthones contain methoxyl groups and demethylation can be achieved by heating with hydroiodic acid in glacial acetic acid solution and also by means of aluminium chloride in benzene or chlorobenzene solution. However, there is a possibility of the molecule undergoing rearrangement also during demethylation (Wessely and Moser,
Menatsh. Chem., 1930, 55, 97; Vessely and Kallab, ibid., 1932, 62, 26). For example 1,4-dihydroxy-7-methoxyxanthone (XXXI) when treated with hydroiodic acid under pressure rearranges to give 1,2,7-trihydroxyxanthone (XXXII) (Philbin, Swirsky and Wheeler, J. Chem. Soc., 1956, 4455).

Demethylation of sterigmatocystin (XXXIII) with aluminium chloride in chlorobenzene was accompanied by the fission of the 4–c link possibly due to a reverse Friedel-Crafts reaction and yielded 1,3,8-trihydroxyxanthone (XXXIV) (Davies, Virk talky and Roberts, J. Chem. Soc., 1960, 2163).
iii) Reduction to xanthone:

The carbonyl group in a fully methylated hydroxyxanthone can be completely reduced to a methylene group with lithium aluminium hydride. The resulting xanthone has an ultraviolet spectrum which is entirely different from that of the xanthone (Mustafa and Hilmy. J. Chem. Soc., 1952, 1343).

iv) Oxidation:

Oxidation with potassium permanganate has been employed in some cases. For example, sterigmatocystin (XXXIII) when oxidised in acetone solution with a limited quantity of potassium permanganate, yielded a carboxylic acid (XXXV) which when pyrolysed and sublimed gave 3,8-dihydroxy-1-methoxyxanthone (XXXVI) (Hatsuda and Kuyama, J. Agric. Chem. Soc., Japan, 1954, 23, 399).
v) **Stepwise oxidation:**

1-Hydroxyxanthones by a modified Elb's persulphate oxidation are converted into 1,4-dihydroxyxanthones which in
turn are oxidised under mild conditions to substituted salicylic acids thus enabling the identification of the original compound. For example 1-hydroxy-7-methoxy-3-methylxanthone (XXXVII) gave 1,4-dihydroxy-7-methoxy-3-methylxanthone (XXXVIII) which was oxidised by hydrogen peroxide to 2-hydroxy-5-methoxybenzoic acid (XXXIX) (Roberts, J. Chem. Soc., 1960, 785). The hydrogen peroxide oxidation involves the attack on the sensitive quinol nucleus so produced in Elb's oxidation leaving the other benzenoid ring in the form of an easily recognisable salicylic acid. Before doing the persulphate oxidation, however on a polyhydroxynanthone
it is necessary to methylate all hydroxyl groups except the chelated one. A number of methods are available for such a partial methylation of hydroxyxanthones.

vi) Methylation of xanthones

Diazomethane does not generally methylate the chelated hydroxyl group. For the preferential methylation of the 3-hydroxyl group, dimethyl sulphate in acetone solution in the presence of sodium bicarbonate is employed (Markham, Tetrahedron, 1965, 21, 1449). Use of potassium carbonate instead of sodium bicarbonate results in complete methylation.

SYNTHESSES:

1) Michael-Kostanek method

Xanthones and their derivatives are most simply synthesised by heating a salicylic acid or its substitution products and a phenol with a dehydrating agent like acetic anhydride or zinc chloride (Kostanek and Messler, Ber., 1891, 24, 1284). It has been found that a mixture of zinc chloride and phosphorus oxychloride is a good condensing agent for the synthesis of xanthones. This method gives better yields since the temperature of the reaction is fairly low (Grover, Shah and Shah, J. Chem. Soc., 1965, 3962). For example salicylic acid condenses with phloroglucinol to give 1,3-dihydroxyxanthone (XL).
Dessai, Dessai and Dessai (J. Indian Chem. Soc., 1960, 37, 53) have found that polyphosphoric acid acts as a very efficient condensing agent for the preparation of xanthones from a mixture of salicylic acid and phenol.

ii) Ullmann method:

Xanthones can be synthesised through diphenyl ether followed by ring closure. For example 6-methoxyxanthone (XXVIII) has been synthesised by the condensation of 2-chloro-6-methoxybenzoic acid and 4-methoxy phenol, as represented by scheme I.

iii) Robinson-Hishikawa method:

This is a variant of the Boesch synthesis proceeding through a ketimine compound. 1,3-Dihydroxyxanthone (XL) is synthesised from salicylonitrile and phloroglucinol, as depicted in scheme II (J. Chem. Soc., 1962, 121, 83).
Scheme I.

Scheme II.
iv) Tanase method:

Tanase (J. Pharm. Soc. Japan 1941, 61, 341) has evolved a different route which has proved most useful for the synthesis of polyhydroxyxanthones. A salicylaldehyde is condensed with resorcinol or phloroglucinol in acid solution to give a fluoren, an anhydrobase yielding xanthyllium salts with acids. Hydrogenation of either the fluoren or the salts leads to the xanthones which are acetylated and oxidised with chrome acid to the acetoxyxanthones, deacetylation of which yields the hydroxyxanthones. For example, 1,3,6,7-tetrahydroxyxanthone (XLI) the aglycone of mangiferin is synthesised as shown in the scheme III. An important drawback of the Tanase synthesis is that the condensation cannot be controlled by chelation, since the pyrones carbonyl group is introduced only at the last step, and so resorcinsols can be converted into 3-hydroxyxanthones isomeric with 1-hydroxyxanthones.

v) Friedel-Crafts method:

Xanthones have also been synthesised by Friedel-Crafts procedure (Rao and Seshadri, Proc. Indian Acad. Sci., 1963, 71A, 710). This involves the condensation of a suitably substituted acid chloride with a methoxy phenol in the presence of aluminium chloride and ether to get a benzophenone which in turn is cyclised to the polyhydroxyxanthone with aluminium chloride in benzene solution. Scheme IV represents the synthesis of gentisin by Rao and Seshadri (loc. cit.) by this procedure.
Scheme III

\[
\text{H}^+ \\
\xrightarrow{\text{Pd/H}_2} \\
\xrightarrow{\text{AcO}}
\]

\[\text{deglycation}\]

\[\text{XLI}\]
vi) Asahina-Tanase method

Asahina and Tanase (Proc. Imp. Acad. (Tokyo) 1940, 16, 237) have reported a useful synthesis for certain methoxylated xanthones, like 3-methoxyxanthone (XLIII) in the following lines.
BIOGENESIS:

The natural xanthenes fall into two groups which reflect differing modes of biogenesis, one group consisting of those apparently derived from an appropriate 2,2'-dihydroxy-benzophenone by a cyclodehydration sequence while the other comprises those conveniently regarded as arising from a 2,3'-dihydroxybenzophenone by an oxidative coupling reaction.

The common occurrence of the phloroglucinol nucleus is noteworthy and since it is generally agreed that this is of 'polyacetic acid' origin, it is concluded that xanthenes at least in part are built up in this way. The other hydroxylation pattern encountered are of the resorcinol, quinol, hydroxyquinol and pyrogallol type. An acid, R-CHO₂H can for example develop a polyacetic chain R-CO-CH₂-CO-CH₂-CO-CH₂-CO₂H leading to the acyl phloroglucinol (XLIV) (Robinson, Structural relations of Natural Products pp.45, Oxford University Press, London, 1955).
Ndlemantan and Seshadri (Current Sci. India, Logania.) have suggested that the biogenesis of xanthones involves dehydrative cyclisation of a 2,2'-dihydroxybenzophenone. The benzophenones have been considered to be derived from 4-phenyl chromans or the corresponding coumarins which are formed from a phloroglucinol (C-6) unit (A) and a cinnamic acid (C-9) unit (B) by the process indicated below.

\[ \text{C-6 unit (A)} \quad \text{+} \quad \text{C-9 unit (B)} \rightarrow \quad \text{XLV} \]

\[ \text{XLVI} \rightarrow \quad \text{XLVII} \]
These coumarins or corresponding coumaric acids seem to act as precursors and yield the benzophenones by oxidation.

Barton and Scott (J. Chem. Soc., 1958, 1767) showed that the xanthone nucleus can be produced from a 2-hydroxy-2'-methoxybenzophenone by elimination of methanol by mild alkali at 100°. The mechanism of the reaction is given below.

\[
\text{OCH}_2\text{HO} \quad \xrightarrow{-\text{H}^+} \quad \text{OCH}_3 \\
\text{+ H}^+ \quad \longrightarrow \quad \text{O} \quad \text{+ CH}_3\text{OH}
\]

An alternative route for the biogenesis of hydroxyxanthones could arise through oxidative coupling. For geodin, ordin and griseafulvin, 2,4'-dihydroxybenzophenones are regarded as intermediates which through oxidative coupling yield dienes (Barton and Scott, loc. cit.). Consequently oxidative coupling of
2,3'-dihydroxybenzophenones should enable the ring closure of the ether bridge to give a xanthone with a hydroxyl group ortho and/or para to this ether bridge, i.e. 2-hydroxyxanthone (II) and 4-hydroxyxanthone (XLVIII) (Levis and Warrington, J. Chem. Soc., 1964, 5074).

Finnegan, Patel and Boehman (Tetrahedron Letters, 1966, 6037) believe that their observation of the coexistence not only of the 2- and 4-hydroxyxanthone isomers but also the 1,2- and
1,7-dihydroxyxanthone (XLIX & XXVIII) in the *Haplodia erucoides* L. species is in elegant accord with their respective derivation by oxidative coupling from common benzophenone precursors.

The hydroxylation pattern of celebinxanthone, derivable from 2,3',4,6'-pentahydroxybenzophenone suggests that this type of synthesis may occur in nature (Lewis and Warrington, *loc. cit.*).

Lewis and Warrington (*loc. cit.*) considered 2,3',4-trihydroxybenzophenones suitable for the study of the
oxidative coupling. The trihydroxybenzophenone in alkaline solution at room temperature with excess of potassium ferricyanide gave the dihydroxyxanthone in 83% yield after 2 hr. The identity of this and its dimethyl derivative was confirmed by comparison with authentic 2,6-dihydroxyxanthone and 2,6-dimethoxyxanthone thus indicating that oxidative coupling had taken place para to the 3'-hydroxyl group. The absence of the isomer 3,5-dihydroxyxanthone corresponding to the ortho coupling with the 3'-hydroxyl group confirmed the specificity of the oxidation. Definite evidence regarding the actual hydroxylation pattern of benzophenones and their transformation into hydroxyxanthones can only be obtained from radioactive tracer experiments.