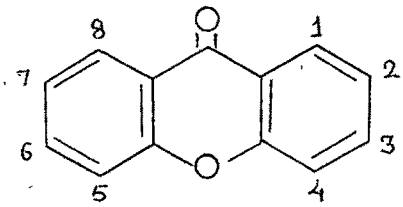
CHAPTER I

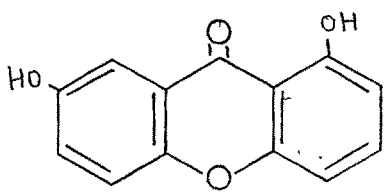
GENERAL INTRODUCTION

The term xanthone, from the Greek, meaning yellow, designates the chemical compound dibenzo-γ-pyrone (I).



(I)

Many xanthones have been isolated from plants and other sources. In plants they occur either in combination with glucose or xylose or both or in an uncombined state. A few representative members occurring in nature are given below. Euxanthone[1] (II) is a yellow pigment present in the heartwood of Plantonia insignis Mart. Swertinin[2] (III) and Decussatin[2] (IV) are found in Swertia decussata, the former being located in the stem and the latter in the flowers.



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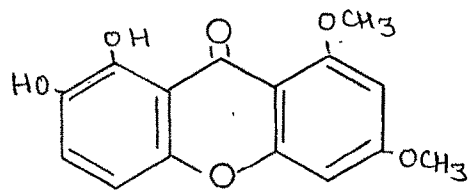

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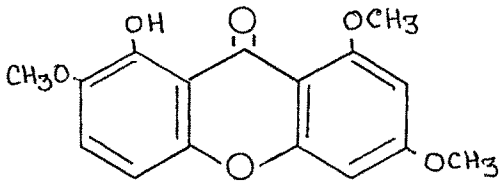

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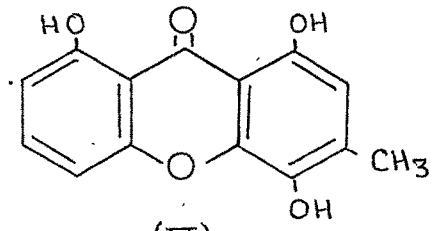

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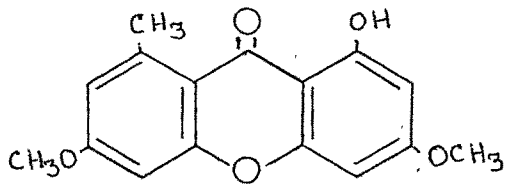

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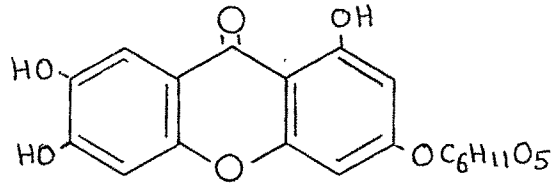
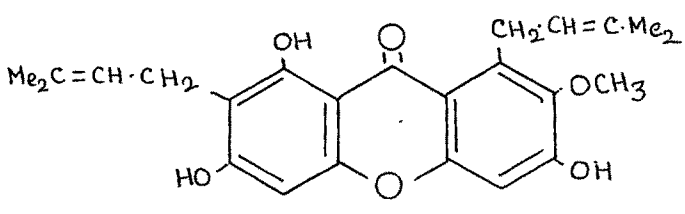


(VII)

Ravenelin[3] (V) is a fungal metabolite, while Lichexanthone[4] (VI) is a yellow pigment found in the lichen Parmelia formosana. Mangiferin[5] (VII) is a pigment present in the bark of the tree, Mangifera indica. Mangostin[6] (VIII) is a major pigment latex of the mangosteen tree, Garcinia mangostana L.



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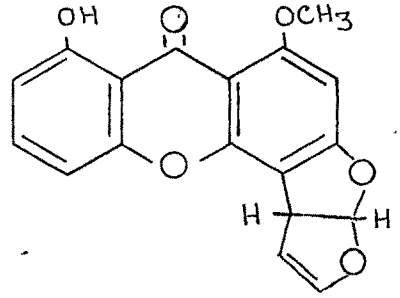

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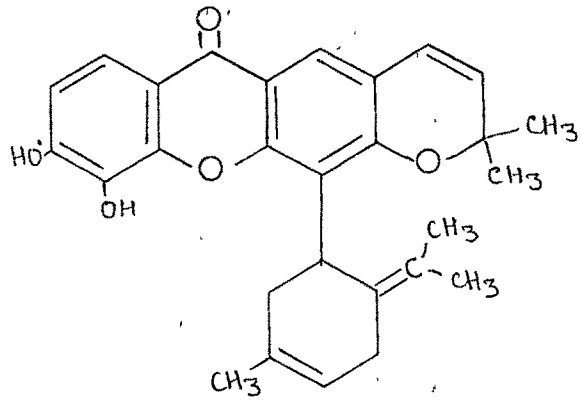


(X)

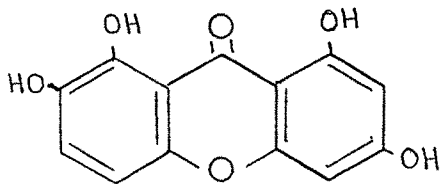
Sterigmatocystin[7] (IX) is a metabolite of Aspergillus versicolour (Vuillemin) Tiraboschi, while Maculatoxanthone[8] (X) is a xanthone with a monoterpene side chain isolated from roots of Hypericum maculatum.

Naturally occurring xanthones have been reviewed by Roberts[9]. Recently many workers have isolated xanthones from plants like Brazilian Guttifereae[10], Guttifereae[11], Gentianacea[12], Mammea amerikana[13], etc. and have used modern techniques for arriving at the structures.

Xanthones have diverse pharmacological properties. They are used as insecticides[14,15] and in the control of codling moth[16]; mites[16,17,18], chicken-louse[19], acarid[20] and cabbage insect[21]. Xanthones have been tried in termite control[22,23] and have been found to act as a termite deterrant in wood[24].

Bromoxanthones have been found to act as urinary antiseptics[25], while some of the aminoxanthones possess antibacterial activity[26]. Antibiotic activity was shown by some

nitro- and amino-[27,28] as well as hydroxyxanthones[29]. Xanthones such as (XI) and its methyl ether are active anti-tubercular agents[30] and Miracil A (XII) is active against bilharziasis (schistosomiasis).



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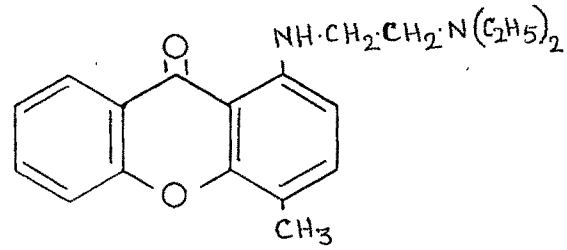
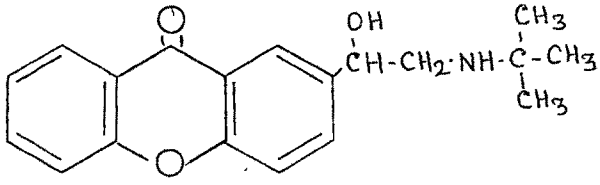


(XII)

Xanthones with antiinflammatory[31,32,33], anti-secretory[31] and antiulcerogenic[31] properties have also been reported. Substituted xanthones suitad for the treatment of extrinsic asthma, hay fever, nettle rash, eczema and allergic dermatitis are reported[34]. 2-Substituted xanthones such as (XIII) showed β-adrenergic blocking potency[35,36]. Xanthones containing a tetrazole ring such as (XIV) are useful as antiallergics, especially in the treatment of asthma[37]. Monopotassium salts of xanthones such as (XV) and (XVI) are found to be plant-growth regulators[38]. Xanthone carboxylic acids and esters have been used as anti-histemines[30,40,41,42]. Da Re et al.[43,44,45,46] have synthesised a large number of Mannich bases from xanthones. They report[46] that 3-methoxy-4-diethylaminoxanthone (XVII) was the most active, with favourable therapeutic index. Goldberg and Walker[47] have prepared some N-substituted xanthones possessing anti-malarial activity. Finnegan et al.[48] have reported that out



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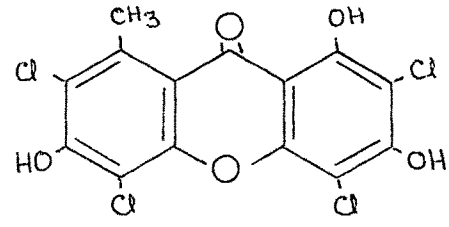

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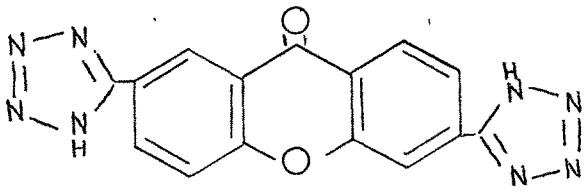

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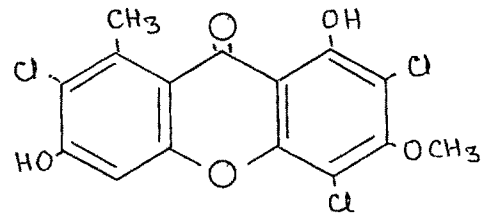

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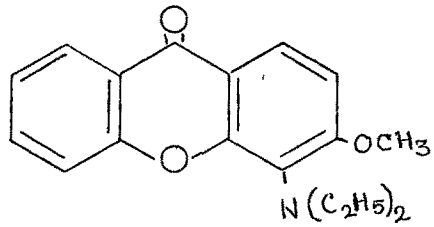


(XVII)

of eighteen xanthones from Mammea amerikana, 1,6-dihydroxy- and 1,3-dihydroxyxanthone were the most potent inhibitors of sarcoma-180 in vitro.

Xanthones have also been used in the detection of Fluoride[49] and in the determination of Thorium[50,51] and Uranium[50]. Similarly 1-hydroxyxanthone[52] is used in the detection of Copper and Beryllium, spectrophotometrically. Xanthones such as 1,3-dihydroxyxanthone are also used as chromatographic spraying reagents for qualitative analysis of inorganic cations[53].

METHODS FOR THE SYNTHESIS OF XANTHONES

A number of methods have been developed for the synthesis of xanthones and these are briefly reviewed here. These methods grouped under five main headings are described below :-

1. From benzophenone derivatives :-

A suitable benzophenone derivative obtained by any one of the following methods can be cyclised further to get the desired xanthone.

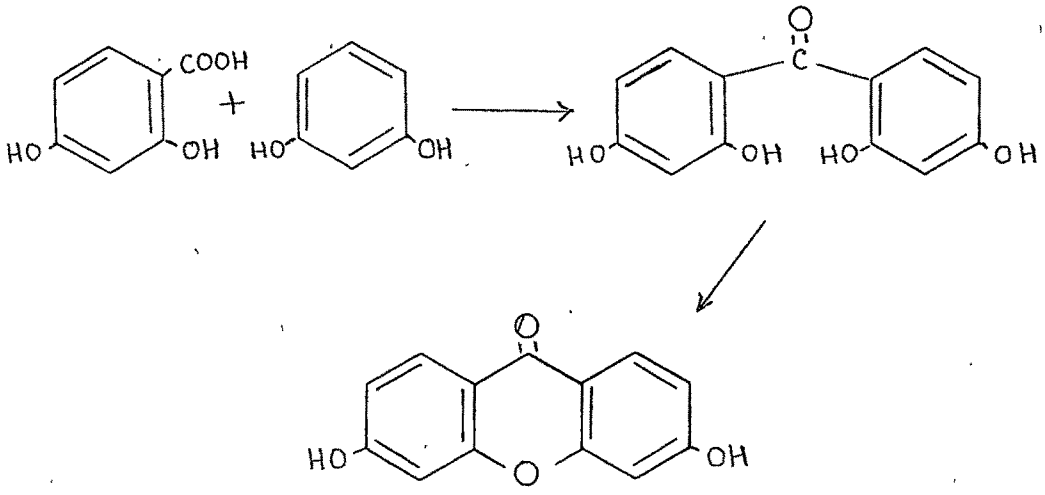
(A) Michael-Kostanecki method :-

In this method equimolecular propertions of a polyhydroxyphenol and a 2-hydroxybenzoic acid are heated with a dehydrating agent such as acetic anhydride[54] or zinc chloride[55,56,57,58] to get 2,2'-dihydroxybenzophenone. A modification of this method by Grover and Shah[59] consists in the use of a mixture of phosphorus oxychloride and zinc chloride as condensing agent. It has the advantage that the required reaction temperature is lower and the product is free from the polymeric products. Scheinmann et al.[60] suggested the use of aluminium chloride alongwith zinc chloride and phosphorus oxychloride, when the latter two condensing agents failed.

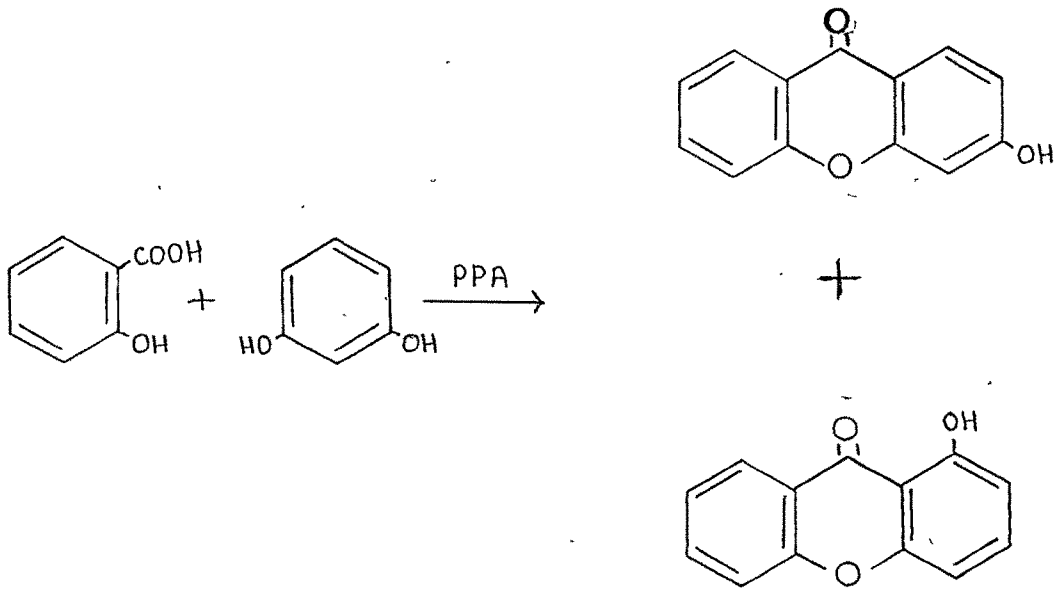
Various reagents have been reported for the cyclisation of these benzophenones such as, dilute acids[61], conc. sulphuric acid[62], aluminium chloride[3], water at 200-20° (in an autoclave)[63] or acetic anhydride in pyridine[64].

The synthesis of 3,6-dihydroxyxanthone may be taken

as an example to illustrate this method,

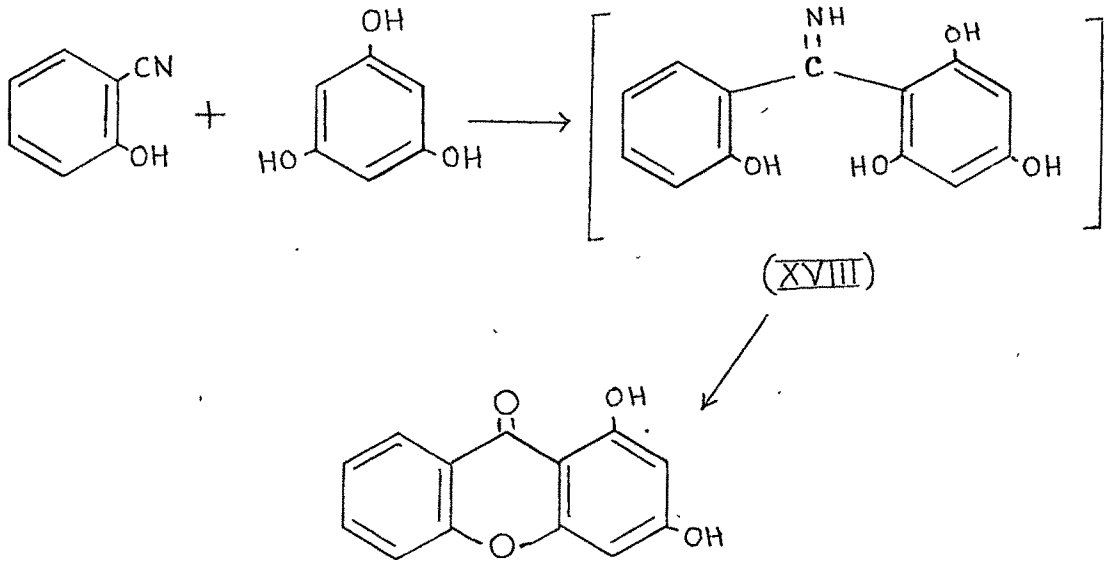


Polyphosphoric acid as the condensing agent for getting xanthones from 2-hydroxybenzoic acids and polyhydroxyphenols, has been suggested by Desai et al.[65] The intermediate benzophenones are not obtained here.



(B) Robinson-Nishikawa method :-

This method[61,66], a variant of Hoesch synthesis, proceeds through a ketimino compound (XVIII). 2,2'-Dihydroxybenzophenone obtained by alkaline hydrolysis of the ketimino compound can be cyclised to xanthone by one of those reagents discussed before. Thus salicylonitrile and pholoroglucinol can be condensed to get 1,3-dihydroxyxanthone.

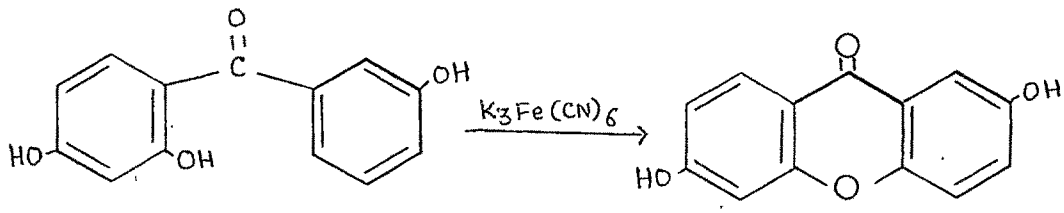


(XVIII)

(C) Oxidative coupling method :-

Lewis[64] has reported that 2,3',4-trihydroxybenzophenone (XIX) can be cyclised to 2,6-dihydroxyxanthone (XX) in high yield by oxidative coupling with potassium ferricyanide. Thus 2-hydroxybenzophenones can be cyclised to xanthones by this method.

Lewis et al.[67] have also suggested the use of DDQ for oxidative coupling and have explained the coupling on the basis of formation of phenoxonium ion as an intermediate.

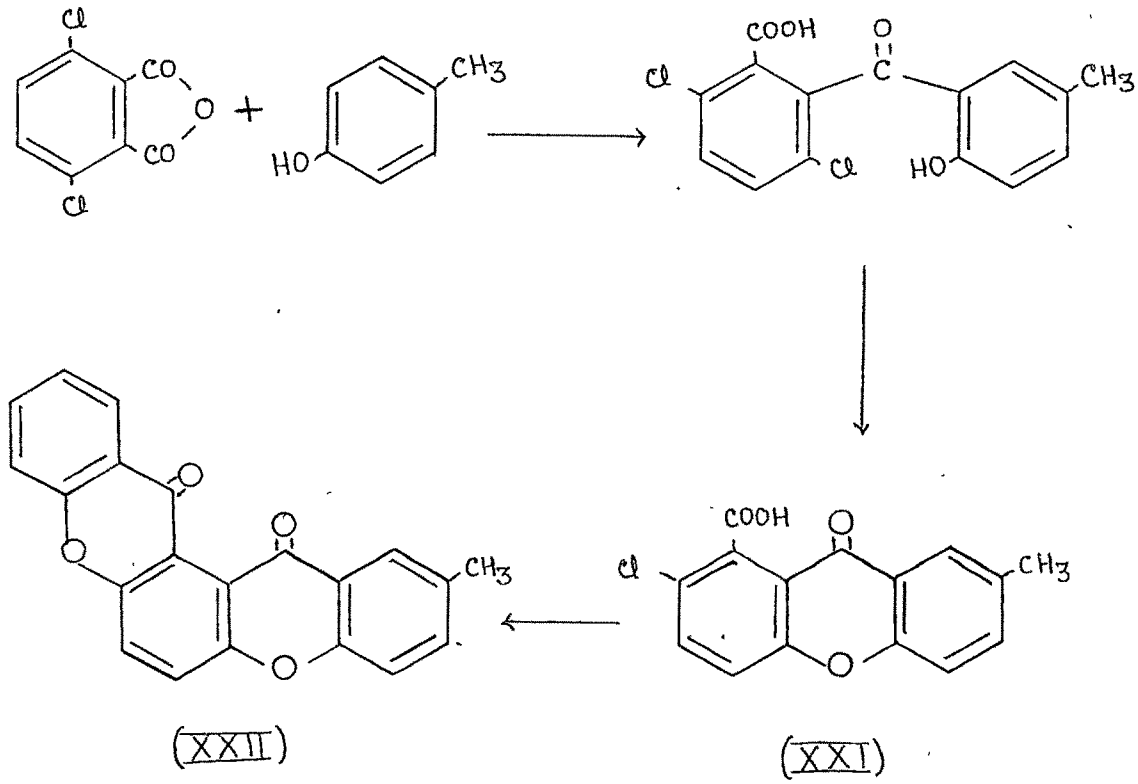


(XIX) (XX)

They[68] extended this method to cyclise 3'-amino-2-hydroxy-benzophenone by potassium ferricyanide and potassium dichromate and studied the reaction over pH range of 0-14. Locksley and Murray[69] have suggested the use of DDQ, manganese(III)-tris(acetonylacetonate), and manganese dioxide for oxidative coupling.

(D) From 2-halo-2'-hydroxy (or methoxy) benzophenones :-

Ullmann and Schmidt[70] have prepared 2-methyl-



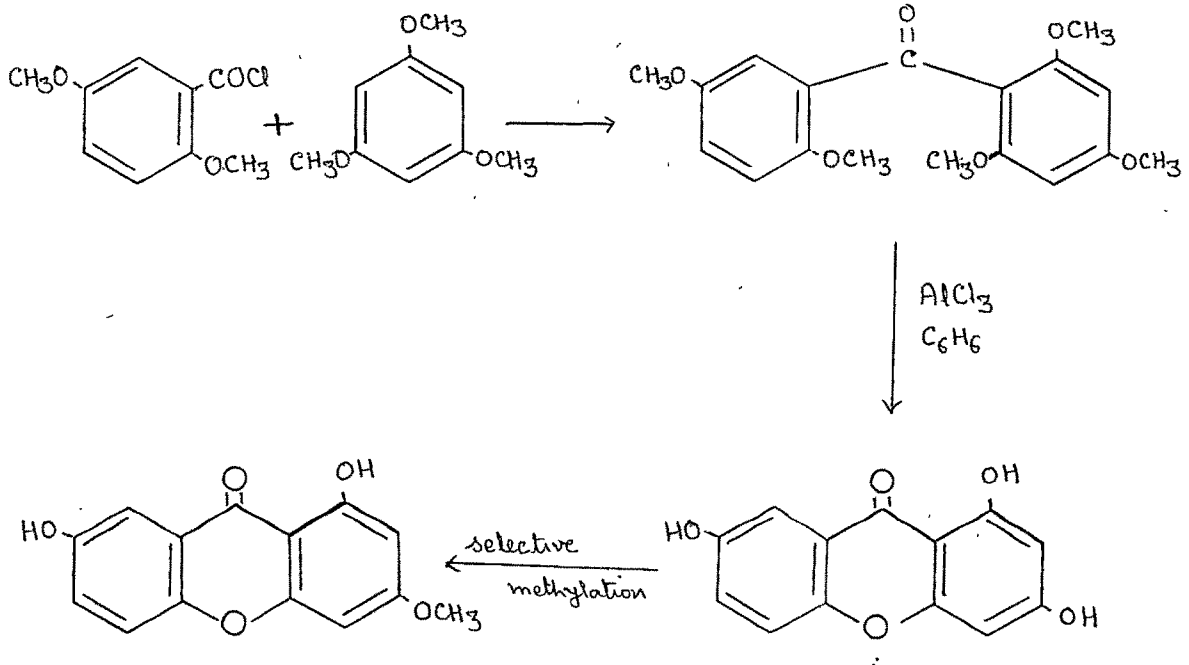
(XXII) (XXI)

5,6,7-trichloroxanthone-8-carboxylic acid from 2,3,4,5-tetrachloro-6-carboxy-2-hydroxy-5-methylbenzophenone by cyclising the latter with 33 % sodium hydroxide solution. Anna Marie and Ullmann[71] have prepared 2-methyl-7-chloroxanthone-8-carboxylic acid (XXI) and further 2-methyldixanthone (XXII) from the latter by the same method.

Royer et al.[72] have reported the synthesis of many xanthones such as 2-hydroxy-, 2-methyl-, 2-methyl-6-nitro-, and 3-hydroxy-6-chloroxanthone from the corresponding 2-halo (chloro or bromo)-2'-methoxybenzophenones. The cyclisation was induced by pyridine-hydrochloride.

(E) By Friedel-Crafts method :-

Gentisin (XXIII) has been synthesised[73] by Friedel-Crafts method. In this method a suitable 2-methoxy-



(XXIII)

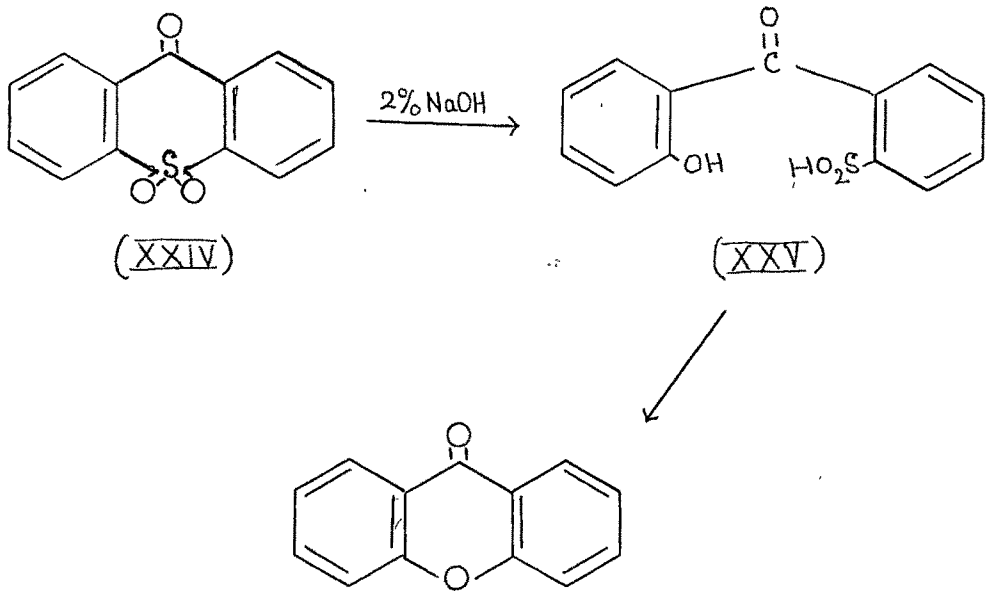
benzoyl chloride is condensed with fully methylated phenol in the presence of aluminium chloride. The benzophenone is demethylated and simultaneously cyclised by aluminium chloride in benzene.

Stout et al.[74,75] have prepared polyoxygenated xanthones by this method. The intermediate 2-hydroxy-2'-methoxybenzophenone obtained was cyclised by the action of tetramethylammonium hydroxide in pyridine by elimination of methanol. Recently, Scheinmann and Quillinan[76] have prepared many oxygenated xanthones by Friedel-Crafts method. For cyclising the intermediate 2-hydroxy-2'-methoxybenzophenone, they have used different alkaline agents such as, aqueous sodium hydroxide in methanol, piperidine, aqueous potassium carbonate in methanol or tetramethylammonium hydroxide in aqueous pyridine. They have also discussed some effective reagents such as boron trichloride, pyridine and DDQ - in methanol for the preparation of xanthones with hydroxy and methoxy functions. 2-Hydroxy-2'-methoxybenzophenones can be cyclised by other alkaline reagents such as 2 % alcoholic potassium hydroxide[77] and 1 N potassium hydroxide in nitrogen atmosphere[78].

Finnegan and Merkel[79] have prepared 2,5-dihydroxy- and 4,5-dihydroxyxanthones, for which the benzophenones were obtained by photo-Fries migration.

(F) <u>From 2-hydroxybenzophenone-2-sulphinic acids</u> :-

Bennet et al.[80] have reported a method to convert 2-hydroxybenzophenone-2'-sulphinic acid (XXV) into xanthone



(XXIV) (XXV)

by refluxing it with 3 % sodium hydroxide. The 2-hydroxybenzophenone-2'-sulphinic acid was prepared from thioxanthen--9-one-10,10-dioxide (XXIV) by hydrolysing the latter by 2 % sodium hydroxide in aqueous dioxane (65 %). 2,6-Dicarboxylic-, 2-chloro-, 2-methyl-, 2-methoxyxanthone have been prepared by this method.

2. <u>From diphenylether derivatives</u> :-

Xanthones can be obtained from two types of diphenyl ethers, (A) from diphenyl ether-2-carboxylic acids and (B) from diphenylethers in which 2,2'-positions are not occupied (Asahina-Tanase method).

(A) <u>From diphenyl ether-2-carboxylic acids</u> :-

In this method a diphenyl ether-2-carboxylic acid is first prepared by reaction between a phenol and a 2-chlorobenzoic acid, and this is then cyclised to a xanthone. Diphenyl-

ether-2-carboxylic acid can be directly prepared either by Ullmann[81] reaction or by treating 2-diazonium chloride benzoic acid with phenol[82]. The method has very wide applications and has been used for preparing unsymmetrical xanthones.

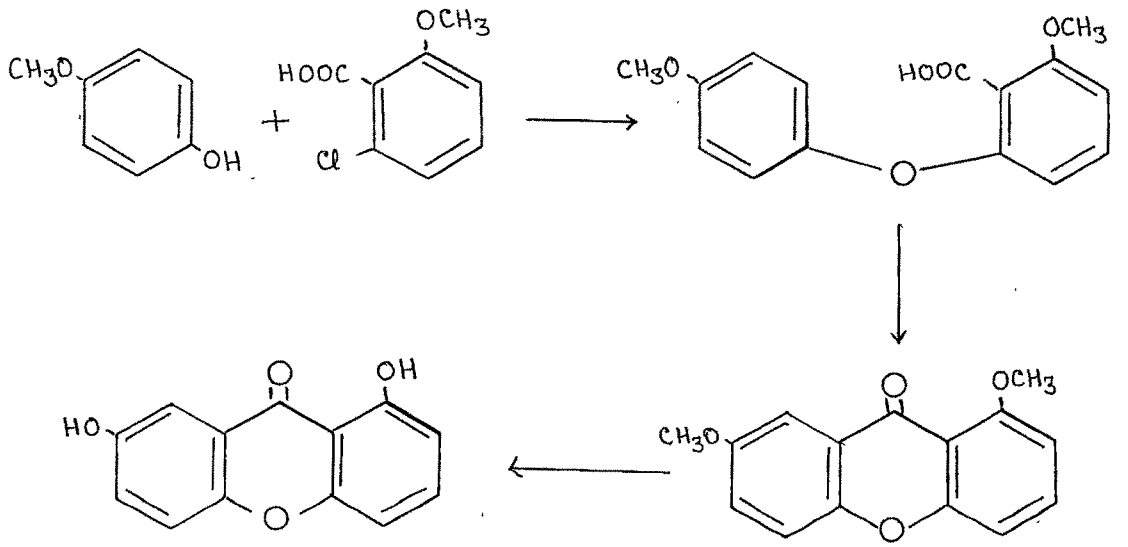
Koelsch and Lucht[83] carried out the condensation between 2-chlorobenzoic acid and 3-nitrophenol in amyl alcohol as a solvent and copper bronze and cuprous iodide as catalysts. Goldberg and Walker[84] reported nitrobenzene, hexyl alcohol and anisole as suitable solvents, because they can be easily removed from the reaction mixture by steam distillation.

Davies et al.[85] prepared 2-hydroxyxanthone in a better yield from 4-methoxyphenol and 2-chlorobenzoic acid using pentyl alcohol as a solvent. Goldberg and Wragg[86] prepared 3'-methoxydiphenylether-2-carboxylic acid by stirring continuously 2-chlorobenzoic acid, 3-methoxyphenol, potassium carbonate, copper bronze and cuprous iodide in nitrobenzene at 160° for 6 hr.

Mauthner[87] also synthesised 3'-methoxydiphenylether-2-carboxylic acid from sodium-2-chlorobenzoate and 3-methoxyphenol, using copper powder and sodium methoxide. This method has been further used by many workers like Rajagopal et al.[88-93], Allen et al.[94] and Arends and Helboe[95].

Cyclisation of the diphenylether-2-carboxylic acid to xanthone can be carried out in excellent yields by heat or with acidic reagents such as sulphuric acid[96], acetyl

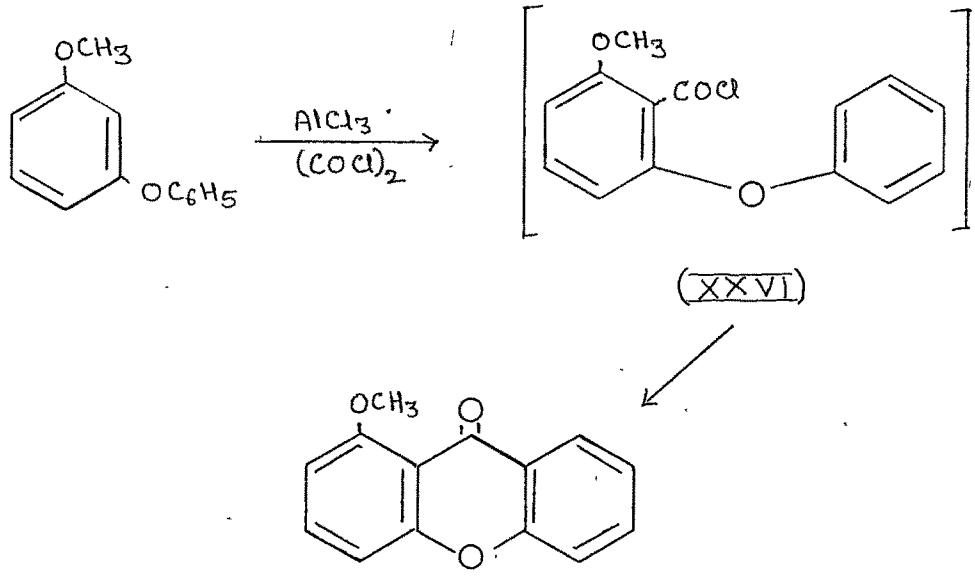
chloride[97], a mixture of these[98], thionyl chloride, phosphorus pentachloride[99], oxalic acid[100], oxalyl chloride[101], phosphorus pentoxide[102], phosphorus oxychloride[103,104], stannic chloride[105] and phosphorus pentachloride-aluminium chloride in benzene[87]. Cyclisation of the acid chloride with aluminium chloride[106] has also been carried out. Many nitro-[27] and aminoxanthones[28,107] have been prepared by this method. With sulphuric acid as cyclising agent, 3'-acetamidodiphenylether-2-carboxylic acids cyclised almost exclusively in the 6'-position[28] in contrast to 3'-nitro derivatives, which cyclised in the 2'-position. Gunter[108] has reported the use of 84 % polyphosphoric acid for getting the optimum yield of xanthone from 2-phenoxybenzoic acid. The synthesis of euxanthone[109] (II) may be taken as an example of this method.



(II)

(B) Asahina-Tanase method :-

Asahina and Tanase have cyclised substituted diphenylethers to xanthones by oxalyl chloride in the presence of aluminium chloride[110,111]. 2-Phenoxybenzoyl chloride (XXVI) must be the intermediate in the formation of xanthone by this method, since oxalyl chloride is decomposed by aluminium chloride into phosgene and carbon monoxide[112]. The reaction may be illustrated by the example of 1-methoxyxanthone.

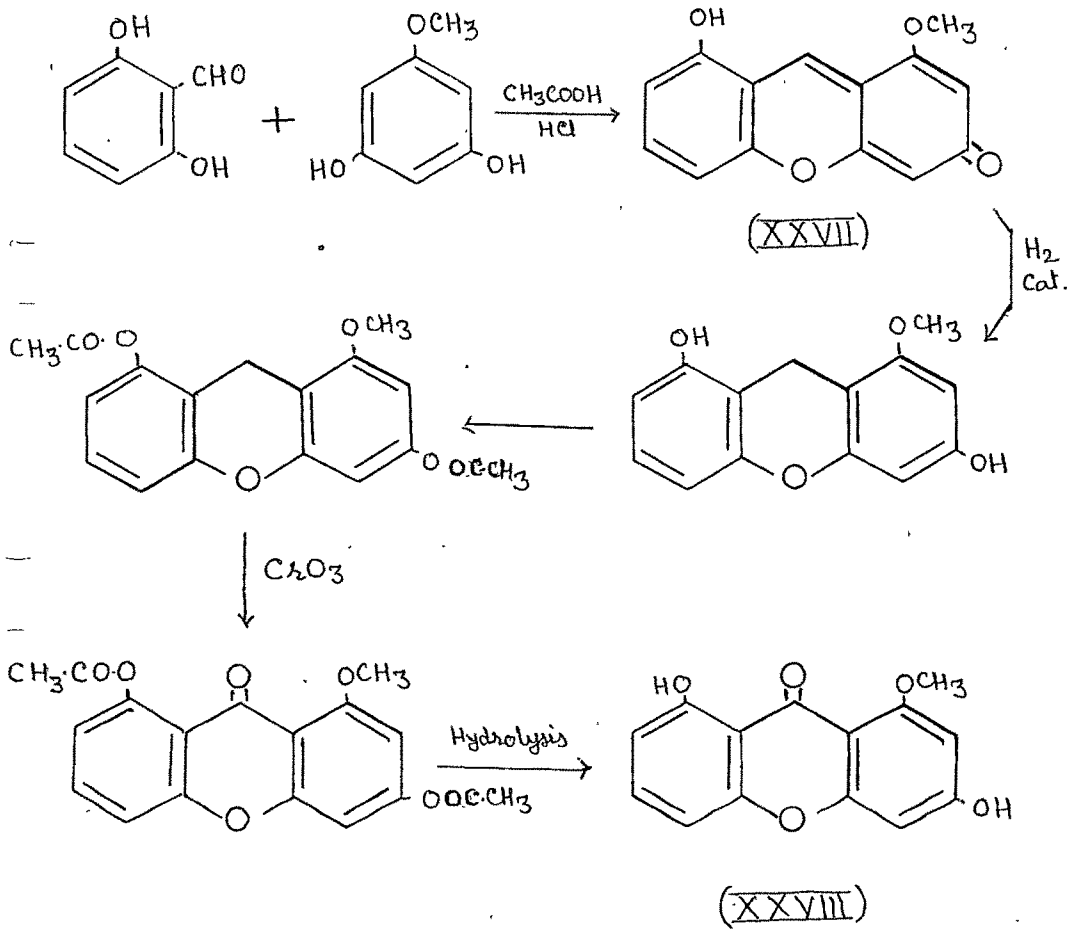


The method has been used for the preparation of 3-methoxy-, 3-methyl-, 2,3-dimethoxy-, 3,6-dimethyl- and 2,6-dimethoxyxanthone. Recently, Granoth et al.[113] have prepared 6-bromo-2-chloro and 6-bromo-2-fluoroxanthone by this method.

3. From 3H-xanthen-3-one derivatives (Tanase method) :-

In this method a suitable benzaldehyde is condensed

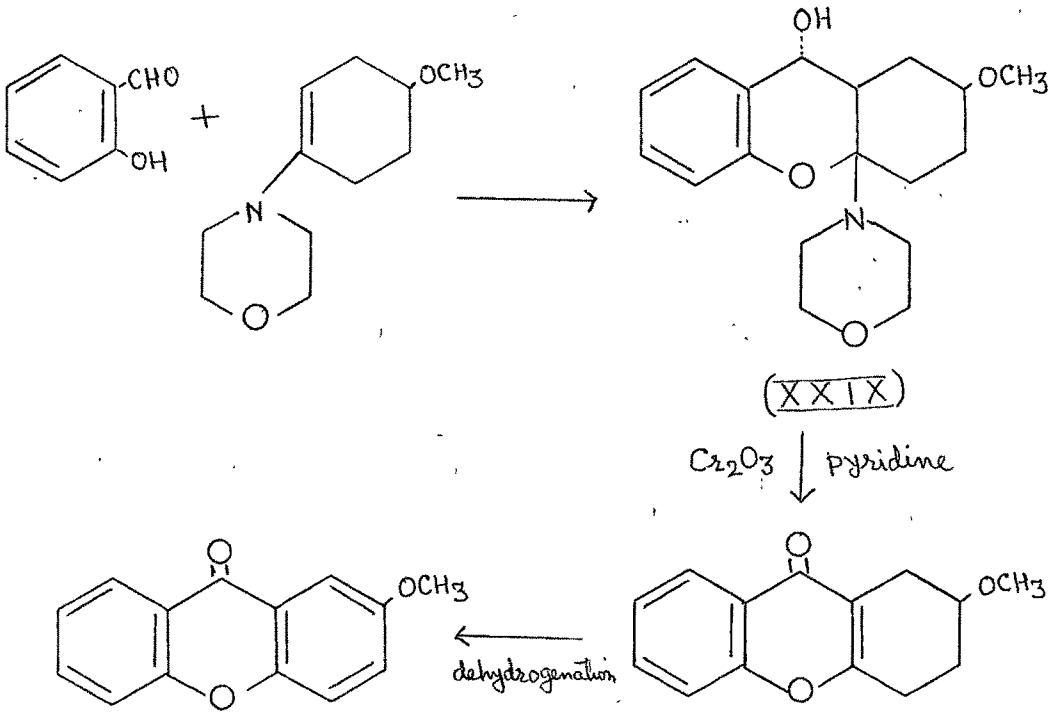
with a reactive phenol such as phloroglucinol in the presence of hydrochloric acid, which gives 3H-xanthen-3--one (XXVII). This xanthen-3-one can be converted into xanthene by reduction and then into xanthone by oxidation. This method[111] is used for the preparation of partially methylated polyhydroxyxanthones, in which the orientation of the substituents is unequivocally established. For example, it has been used[7,114] to synthesise 3,8-dihydroxy--1-methoxyxanthone (XXVIII) which is not obtainable by any other known method.



4. From 1,2,3,4-tetrahydroxanthone derivatives :-

A suitable 1,2,3,4-tetrahydroxanthone can be prepared either by enamine-salicylaldehyde condensation or by Simonis reaction. Further dehydrogenation of the tetrahydroxanthone provides the xanthone.

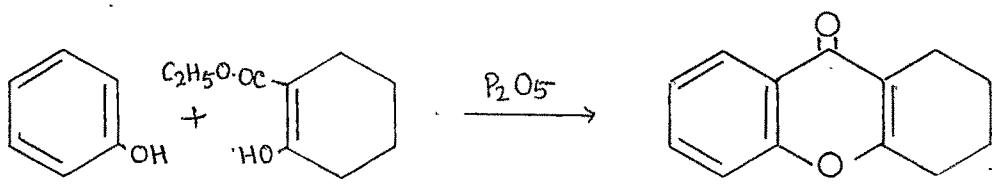
The enamine-salicylaldehyde condensation method



reported by Paquette and Stucki[115] consists in condensing salicylaldehyde with a suitable 1-morpholinocyclohexene derivative (XXIX). Oxidation of the pyran derivative with chromium trioxide in pyridine gives the tetrahydroxanthone, dehydrogenation of which gives the xanthone. Preparation of 2-methoxyxanthone may be taken as an example as shown above.

The Simonis reaction has been applied by Hall

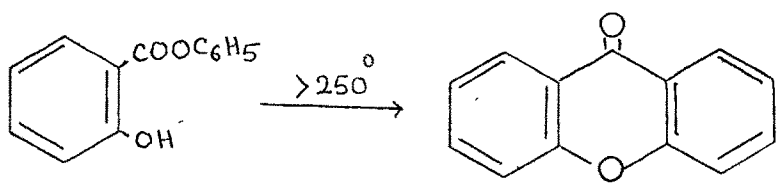
and Plant[116]. They have condensed 2-carbethoxycyclohexanone with phenol in the presence of phosphorus pentoxide and obtained 1,2,3,4-tetrahydroxanthone.



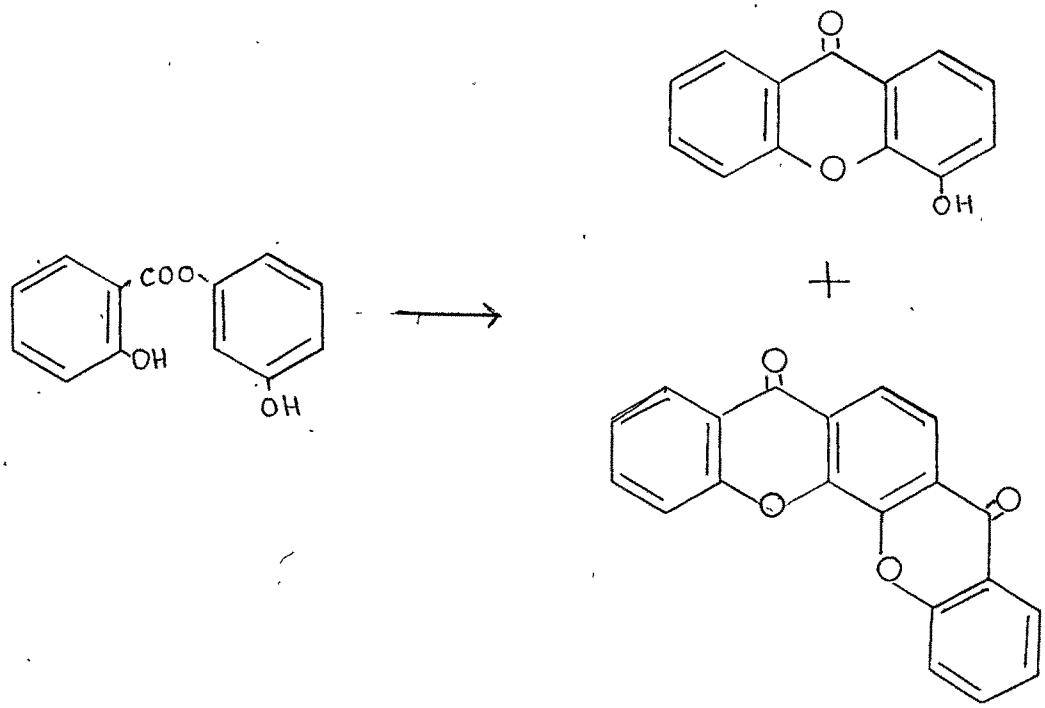
5. From benzoic acid derivatives by pyrolysis :-

Xanthones can be obtained by pyrolysis of either 2-hydroxybenzoic acid or its arylesters or alkali salts of 2-halobenzoic acids.

2-Hydroxybenzoic acids and 2-hydroxynaphthoic acids are converted into xanthones and benzoxanthones by atmospheric distillation of the acid either alone[117] or in the presence of tungsten oxide or vanadium pentoxide[118] and the distillation of the aryl esters[119] or the acetates[120]. Preparation of simple xanthone from salol[119] by its distillation is the best example of this method.



Many dibenzoxanthones have been prepared by this method. Kamel and Shoeb[121] have prepared 1,2,5,6-dibenzoxanthone and 2,3,5,6-dibenzoxanthone by heating 1-hydroxy-2-(2'-naphthyl)naphthoate and 3-hydroxy-2-(1-naphthyl)-naphthoate respectively at 300-25° for 45-60 min. Parija et al.[122] have also prepared similarly 3,4,5,6-dibenzoxanthone. In the preparation of hydroxyxanthones by this method dixanthones (XXX) are often produced as by products[123]. Moreover, side reactions like decarboxylation and auto-condensation are also possible.

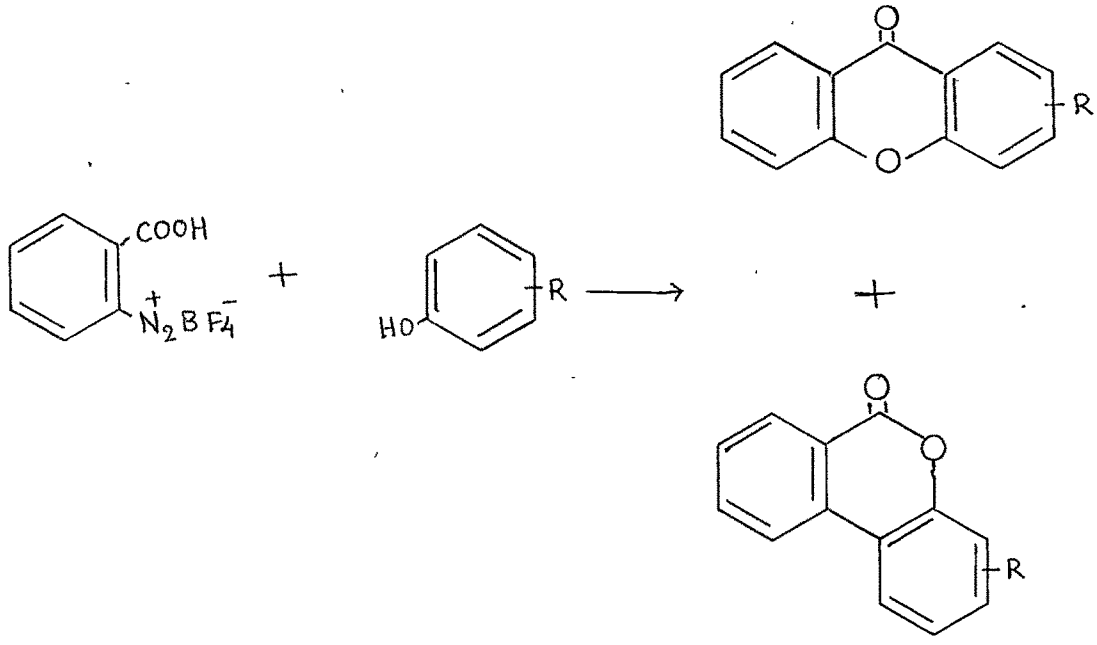


(XXX)

Kochi[124] has reported that the alkali salts of 2-halobenzoic acids decompose smoothly at 325-80° in vacuo to produce xanthones in 50 to 70 % yield. Sartori and

Weidenbruch[125] have prepared octafluoroxanthone by pyrolysing sodium pentafluorobenzoate at 275°. Alkali salts of dihalobenzoic acids are found to give dihaloxanthones[126], through the benzyne intermediates[127].

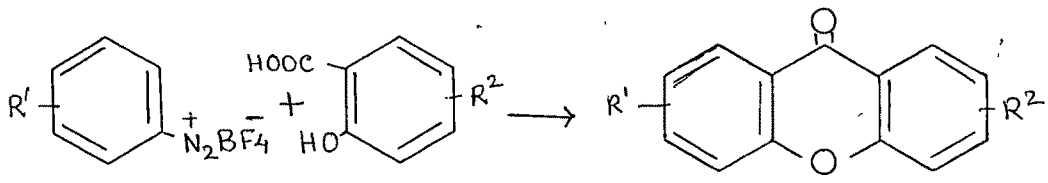
Sellers and Suschitzky[128] have developed a novel pyrolysis method for the preparation of xanthones, by decomposing 2-carboxyphenyldiazonium tetrafluoroborate in phenols and by thermolysis of aryldiazonium tetrafluoroborate in salicylic acids. In some cases xanthones are accompanied by 3,4-benzocoumarins (XXXI). Thermolysis in phenols can be illustrated as follows :-



(XXXI)

Thermolysis of aryldiazonium tetrafluoroborate

in salicylic acid proceeds as follows :-



In this method the reaction temperature must be above or at least near the decomposition temperature of the diazonium salt. Substituted xanthones such as 2-methyl-, 4-methyl-, 2-methoxy-, 4-methoxy-, 1-methoxy and 2-fluoro- have been prepared by this method.

SUBSTITUTION IN XANTHONES

As the present work deals mainly with substitution in xanthones, some of the previous work on substitution in simple and hydroxyxanthones is discussed here.

1. Halogenation :-

Fluorination :- No direct fluorination is known in the case of xanthones, however, some of the fluoroxanthones have been synthesised indirectly. Allen et al.[129] have prepared all the four monofluoroxanthones starting from the mono-fluorophenols and also by Balz-Scheinmann reaction from the corresponding aminoxanthones. Many fluoroxanthones such as octafluoroxanthone[125], 2-fluoroxanthone[128], 6-fluoro-2-methoxyxanthone[32], 2,7-difluoroxanthone[130], 6-bromo-2-fluoro-

xanthone[113] and 1,2,3,4-tetrafluoroxanthone[131] have been synthesised.

Chlorination :- Chlorination of simple xanthone in acetic acid at 110° in the presence of iodine gives mainly 2,7-dichloroxanthone[132]. A more highly halogenated product such as octachloroxanthone may be obtained with antimony pentachloride[133]. Hall and Plant[116] have chlorinated 1,2,3,4-tetrahydroxanthone and 7-methyl-2,3,4-tetrahydroxanthone with chlorine in carbon tetrachloride and obtained the 10,11-dichlorohexahydroxanthone derivatives. Recently, Jayalakshmi et al.[134] have chlorinated 1,3,6-trimethoxy-8-methylxanthone and obtained 1,3,6-trimethoxy-2,4,5,7-tetrachloro-8-methylxanthone. Santesson and Sundholm[135], on chlorination of 1,3,6-trihydroxy-8-methylxanthone with slighly less amount of chlorine than that required for the tetrachloro, obtained a mixture containing 1,3,6-trihydroxy-2,4,7-trichloro-8-methyl- and 1,3,6-trihydroxy-2,4-dichloro-8-methylxanthone. Kurdukar and Subba Rao[136] have chlorinated 3,6-dihydroxyxanthone with sulphuryl chloride and obtained 3,6-dihydroxy-2,4,5,7-tetrachloroxanthone. No other work on direct chlorination of xanthones appears to have been reported. A number of chloroxanthones have been, however, synthesised by other methods.

Bromination :- When xanthone in acetic acid is heated with one mole of bromine and a trace of iodine 3-bromoxanthone is obtained[137] but when conc.sulphuric acid is used as a solvent instead of acetic acid, the product is 2-bromoxanthone. Each of these bromo compounds when heated with bromine passes

easily into the same 2,7-dibromo derivative. When temperature and amount of bromine are increased, tetrabromo-, and hexa-bromoxanthone are formed but the structures have not been determined. Although xanthone is brominated in sulphuric acid solution by liquid bromine, it is not attacked by the mixture of potassium bromide and potassium bromate in sulphuric acid[54]. Lespagnol and Dupas[138] have brominated simple xanthone, when they obtained 2,7-dibromoxanthone. Bromination of 3,6-dihydroxyxanthone gave 3,6-dihydroxy-2,4,5,7-tetrabromoxanthone[136]. Most of the bromoxanthones have been made by synthetic means or from amino derivatives or by mercuration followed by bromination[139].

Iodination :- Direct iodination of xanthones is not reported so far. The work undertaken by the present author is discussed in Chapter II.

2. Nitration :-

Simple xanthone is nitrated fairly readily in the 2- and 7- positions. Dhar has reported that when the xanthone was added to a mixture of sulphuric acid and nitric acid, it gave a mixture of α- and β-dinitroxanthone[137], but when it was dissolved in sulphuric acid and nitric acid was added, it gave 3-nitro- and β-dinitroxanthone[54]. α-Dinitroxanthone was found to be a mixture of 2,4-dinitro- and 2,8-dinitroxanthones,[141] while β-dinitroxanthone was found to be 2,7-dinitroxanthone. These dinitroxanthones have been synthesised by Perkin[140]. Xanthone with cold fuming nitric acid gives the benzene soluble 2,4,7-trinitroxanthone and benzene insoluble 2,7-dinitroxanthone[141,84a].

The latter compound is also obtained in 90 % yield by nitration of xanthone with nitric acid and sulphuric acid[142]. By careful nitration of xanthone in sulphuric acid with fuming nitric acid (1 mole) it is possible to obtain 2-nitroxanthone[84a]. All the four mononitroxanthones, viz. 1-nitro-[54], 2-nitro-[54], 3-nitro-[54,143] and 4-nitro-[54] have been synthesised. These can be nitrated more easily than xanthone itself. 1-Nitro- and 4-nitroxanthone form tetranitroxanthones of unknown orientation, while nitration of 2-nitroxanthone gives 2,7-dinitroxanthone and 2,3,7-trinitroxanthone, which could also be obtained by nitration of 3-nitroxanthone[54]. Goldberg and Walker[27] nitrated 3-nitroxanthone and obtained 2,6-dinitroxanthone, whereas 4-nitroxanthone gave 2,5-dinitro- and 2,4,7-trinitroxanthone. Dhar has nitrated some bromoxanthones[54], but the structures of the bromonitroxanthones obtained are not established. Haase[144] has prepared 1-hydroxy-2-nitroxanthone by nitrating 1-hydroxyxanthone in cold acetic acid with conc. nitric acid. Kurdukar and Subba Rao[137] have nitrated 3,6-dihydroxyxanthone, when they obtained 3,6-dihydroxy-2,4,5,7-tetranitroxanthone. Kiyoshi[145] has reported the nitration of xanthone, 2-chloroxanthone, 2-methylxanthone and 3-chloroxanthone forming 2-nitroxanthone, 2-chloro-7-nitroxanthone, 2-methyl-7-nitroxanthone and 3-chloro-7-nitroxanthone respectively. The structure of the mononitroxanthone obtained by nitration of 4-methylxanthone is, however, not established. Kudav et al.[146] have recently reported the nitration of 1,3-dimethoxy-,

1,3-dimethoxy-6-methyl-, 1,3-dimethoxy-5-methylxanthone forming in all cases 4-substituted mononitroxanthones.

3. Formylation of hydroxyxanthones :-

Considerable work on the formylation of hydroxyxanthones has been reported. Mustafa et al.[147] prepared 2-hydroxy-1-formylxanthone by Duff reaction on 2-hydroxyxanthone and by Sommelet reaction on 2-hydroxy-1-dimethylaminomethylxanthone. This was also prepared by Davies et al.[85] by Duff as well as by Reimer-Tiemann reaction on 2-hydroxyxanthone. Scheinmann and Suschitzky[148] have prepared 1-hydroxy-2-formylxanthone by Duff reaction and have reported qualitatively the presence of another isomer. 1-Hydroxy-2-formyl-7-methoxyxanthone has been prepared by the Duff method by Philbin et al.[149] Puranik and Rajagopal[150] report that 1,3-dihydroxyxanthone when treated with hexamine and acetic acid under conditions of Duff reaction did not yield the formyl derivative but the Gattermann reaction on 1,3-dihydroxyxanthone and 1,3-dihydroxy-6-methylxanthone worked well and resulted in about 50 % yield of the 4-formyl derivative. Duff reaction on 1-hydroxy-3-methoxyxanthone and 1-hydroxy-3-carbomethoxyxanthone resulted in the formation of 2-formyl derivatives in very poor yields. Similarly, formylation of 1-methoxy-3-hydroxyxanthone by the Duff as well as by the Reimer-Tiemann method did not give any encouraging results. Roberts and Underwood[151] prepared 1,8-dimethoxy-3-hydroxy-4-formylxanthone by Reimer-Tiemann reaction in about 9 % yield. Puranik and Rajagopal[152] have

formylated 3-hydroxyxanthone and obtained 3-hydroxy-4-formylxanthone by both the Duff and the Reimer-Tiemann reaction. Similarly, 3-hydroxy-6-methylxanthone[153] with hexamine gave the 4-formyl derivative.

4. Friedel-Crafts acetylation and Fries rearrangement :-

Mustafa et al.[154] have studied the Fries rearrangement and Friedel-Crafts acylation in the xanthones in a systematic way. They prepared 2-acetyl-1-hydroxyxanthone by both, Fries migration of 1-acetoxyxanthone and Friedel-Crafts acetylation of 1-hydroxyxanthone. Similarly, 2-benzoyl--1-hydroxyxanthone was prepared by the Friedel-Crafts benzoylation of 1-hydroxyxanthone. When a 1-benzoyloxy-xanthone was allowed to undergo Friedel-Crafts acetylation with acetic anhydrided, the benzoyl group was eliminated and 2-acetyl-1-hydroxyxanthone was obtained in 71 % yield. Similarly, Friedel-Crafts acylation using benzoyl chloride and benzenesulphonyl chloride, under the same conditions, gave 2-benzoyl and 2-benzenesulphonyl-1-hydroxyxanthone. Fries rearrangement carried out with p-nitrobenzoyl and p-nitrosulphonyl ester of 1-hydroxyxanthone and 1-hydroxy-3-methylxanthone gave 2-substituted xanthones. Fries rearrangement of benzoyl and benzenesulphonyl derivatives of 1-hydroxy-6,7-benzoxanthone yielded 2-benzoyl and 2-benzene-sulphonyl derivatives respectively. But when 1-(β-naphthyloxy) xanthone was allowed to undergo Fries rearrangement, the β-naphthyl group was eliminated and 1-hydroxyxanthone was obtained quantitatively. Similar elimination occurred when

4-benzoyloxyxanthone was subjected to Fries rearrangement. 3-Methyl-2-benzoyloxyxanthone was recovered almost quantitatively, when treated with aluminium chloride under similar conditions. Davies et al.[155] and Scheinmann and Suschitzky[148] have studied the Fries rearrangement of 1-acetoxyxanthone and the Friedel-Crafts acetylation of 1-hydroxyxanthone with acetyl chloride. They isolated 1-hydroxy-2-acetylxanthone as well as 1-hydroxy-4-acetylxanthone.

Lamb and Suschitzky[156] found that 2-hydroxyxanthone does not undergo acetylation. Mustafa et al.[157] successfully carried out the Friedel-Crafts acylation on 1-hydroxyxanthone and prepared 2-propionyl-, 2-phenylacetyl-, and 2-cinnamoyl-1-hydroxyxanthone. Da Re and others[43] have prepared 4-propionyl--3-hydroxyxanthone by carrying out Fries rearrangement of 3-propionoxyxanthone.

Rajagopal and his coworkers have done extensive work in this field. They have prepared 3-hydroxy-4-acetylxanthone[158], 3-hydroxy-4-acetyl-6-methylxanthone[158], 3-hydroxy-4-acetyl-8-methylxanthone[90], 3-hydroxy-4-acetyl--7-methylxanthone[90], 1-hydroxy-2-acetyl-3-methylxanthone[159] and 1-hydroxy-2-acetyl-3,6-dimethylxanthone[159] by Friedel-Crafts acylation of the corresponding hydroxyxanthones using acetyl chloride in the presence of aluminium chloride. They also prepared[159] 1-hydroxy-2-benzoyl-3-methylxanthone and 1-hydroxy-2-benzoyl-3,6-dimethylxanthone by Fries migration of the corresponding 1-benzoyloxy derivative. Acetylation

of 1,3-dihydroxyxanthone[160] under Friedel-Crafts and Fries conditions resulted in a mixture of products, but when this xanthone was acetylated by the Nenki method, only 1,3-dihydroxy-2-acetylxanthone was obtained. Acetylation[161] of 1-hydroxy-3-methyl-6,7-benzoxanthone gave 2-acetyl derivative. They also prepared 3-hydroxy-4-acetyl-7,8-benzoxanthone[164]. Fries rearrangement of 3-benzoyloxyxanthone and 3-benzoyloxy--6-methylxanthone resulted in the 4-benzoyl derivatives[165].

5. Mannich reaction and chloromethylation :-

Mustafa et al.[147] have chloromethylated 1-hydroxyxanthone and 2-hydroxyxanthone and obtained 1-hydroxy-4-chloromethyl- and 2-hydroxy-1-chloromethylxanthone, from which they prepared Mannich bases. They also carried out Mannich reaction on 1-hydroxyxanthone and 1-hydroxy-3-methylxanthone and obtained the 2-substituted derivatives. In the case of Mannich reaction on 2-hydroxyxanthone, the substitution was [illegible] at 1-position as in the case of chloromethylation. They prepared Mannich bases with secondary amines such as morpholine, piperidine, dimethylamine, diethylamine, diethanolamine, etc.

Rajagopal and his coworkers[88,164] have prepared the 4-alkylamino derivatives of 3-hydroxyxanthone by Mannich reaction using formaldehyde and secondary amines such as dimethylamine, piperidine and morpholine. Mannich reaction on 3-hydroxy-6-methyl- and 3-hydroxy-7-methylxanthone also gave the 4-aminomethyl derivatives.

Chloromethylation of 3-methoxyxanthone, 3-methoxy-

-6-chloroxanthone and 3,6-dimethoxyxanthone by formaldehyde and hydrogen chloride gas or by monochloromethylether is reported by Da Re and his coworkers[43]. 3-Methoxyxanthone gave the 2- and 4-chloromethyl-3-methoxyxanthone, whereas 3-methoxy-6-chloroxanthone gave only the 4-chloromethyl derivative. In the chloromethylation of 3,6-dimethoxyxanthone a mixture of isomers was obtained, from which only 4,5-dichloromethyl-3,6-dimethoxyxanthone could be isolated. Mannich reaction on 3,6-dihydroxyxanthone with morpholine and piperidine resulted, however, purely in 3,6-dihydroxy-4,5--bis(morpholinomethyl)xanthone and 3,6-dihydroxy-4,5-bis--(piperidinomethyl)xanthone.

6. Claisen rearrangement :-

Allylation :- Mustafa et al.[154] have prepared 1-allyloxyxanthone. Scheinmann and Suschitzky[148] carried out the Claisen rearrangement on 1-allyloxyxanthone and obtained 2-allyl-1-hydroxyxanthone. Mustafa et al.[157] have prepared 1-allyl-2-hydroxyxanthone and 3-allyl-4-hydroxyxanthone from 2-allyloxy- and 4-allyloxyxanthone respectively. Burling et al.[165] have carried out allyl migration of 1-allyloxy-3,5,6-trimethoxyxanthone, when they obtained 1-hydroxy-2-allyl-3,5,6-trimethoxyxanthone. Allyl migration of 3-allyloxy and 3-allyloxy--6-methylxanthones gave the 4-allyl- derivatives[166]. Agasimundin and Rajagopal[167] prepared 3-hydroxy-2-allyl-4-acetyl- and 3-hydroxy-2-allyl-4-acetyl-7-methylxanthones by blocking the 4-position by first acetylation and then by carrying out the allyl migration. They have also prepared 5-allyl-6-hydroxy-

1-methyl- and 5-allyl-6-hydroxy-2-methylxanthone[90] from the corresponding allyloxy derivatives. Scheinmann et al.[168] prepared 1-allyloxy-3,5,6-trimethoxyxanthone which gave 2-allyl-1-hydroxy-3,5,6-trimethoxyxanthone on refluxing in dimethyl aniline. Agasimundin and Rajagopal[169] reported the preparation of 2-allyl-3-hydroxy-4-methylxanthone and 2-allyl--3-hydroxy-4,7-dimethylxanthone from the corresponding allyloxyxanthones. Haynes and Taylor[170] prepared 1-allyloxy-3,6,7-trimethoxyxanthone, which on rearrangement gave 2-allyl-1-hydroxy-3,6,7-trimethoxyxanthone. Bhatia et al.[171] prepared 2-allyl-1,3,6,7-tetramethoxyxanthone in a similar way. Jackson et al.[172] prepared 5-allyl-6-hydroxy-1-methoxyxanthone and 6-allyl-1,5-dihydroxyxanthone from 6-allyloxy-1-methoxyxanthone and 5-allyloxy-1-hydroxyxanthone respectively.

Nuclear allylation of 1,3-dihydroxyxanthone[173] using methanolic potash and allyl bromide gave 2-allyl-1,3-dihydroxyxanthone, its 3-O-allylether, 2,4-diallyl-1,3-dihydroxyxanthone, 4-allyl-1,3-dihydroxyxanthone, its 3-O-allylether and 3-allyloxy-1-hydroxyxanthone.

1-Hydroxy-2-allyl-3,5-dimethoxyxanthone was prepared from 1-allyloxy-3,5-dimethoxyxanthone by Claisen migration by Locksley et al.[60]. Angadiyavar and Rajagopal[159] prepared 1-hydroxy-2-allyl-3-methylxanthone and 1-hydroxy-2-allyl-3,6-dimethylxanthone from the corresponding 1-allyloxy-derivatives. Goud and Rajagopal[161] have successfully carried

out allyl migration of 1-allyloxy-3-methyl-6,7-benzoxanthone and obtained the 2-allyl derivative. Goud and Rajagopal[174] have partially tosylated 1,3-dihydroxy-6,7-benzoxanthone to obtain the 3-tosylated derivative and then further allylated it to obtain 1-allyloxy-3-tosyl-6,7-benzoxanthone, which on detosylation gave 1-allyloxy-3-hydroxy-6,7-benzoxanthone. This was methylated and subjected to allyl migration, when 1-hydroxy-2-allyl-3-methoxy-6,7-benzoxanthone was obtained.

Prenylation :- Recently many xanthones with prenyl substituents have been isolated[175-183]. Among naturally occurring isoprenylxanthones the C_5 unit is generally present as either isoprenyl or as condensed 2,2'-dimethyl-pyran[184-185]. The C_5 unit can also be present as 1,1-dimethylallyl, which is formed by Claisen rearrangement of the isoprenyloxyxanthone. Such isoprene units have been introduced into hydroxyxanthone in a variety of ways[186-193].

Prenylation of 1-hydroxy-3,7-dimethoxyxanthone[194] with isoprenyl bromide gave a mixture containing 2-prenyl-, 4-prenyl- and 2,4-diprenyl-1-hydroxy-3,7-dimethoxyxanthone. Pure prenyloxyether in dimethylaniline gave 2-prenyl- and 4-prenyl- derivatives. Burling et al.[171] obtained both 2- and 4- rearranged products, when they subjected the prenyl-ether of 1-hydroxy-3,5,6-trimethoxyxanthone and 1,5-dihydroxy--3,6-dimethoxyxanthone to Claisen rearrangement. Dyer et al.[192] have shown by isotope labelling technique that the p-Claisen rearrangement proceeds largely by an intramolecular pathways.

Anand and Jain[196] reported that 1-hydroxy-7-methoxy-

-3-prenyloxyxanthone at 200° gave 1,3-dihydroxy-7-methoxyxanthone the angular 4',4',5'-trimethyldihydrofurano xanthone and its linear isomer. 1-Hydroxy-3-prenyloxyxanthone rearranged similarly, whereas 1-hydroxy-5-methoxy-3-prenyloxy-xanthone gave 1,3-dihydroxy-5-methoxyxanthone, the linear 4'4',5'-trimethyldihydrofurano xanthone and a xanthone with prenyl and dihydrofurano units.

Anand and Jain[192] also reported that 1,3,7-trihydroxyxanthone with prenyl bromide, gave C-prenylated, and O-prenylated xanthones of which 2-prenyl-1,3,7-trihydroxy-xanthone was cyclised further when dihydroosajaxanthone and dihydroisoosajaxanthone were obtained. Reaction of 1,3,7-trihydroxyxanthone with prenyl bromide in the presence of methanolic sodium methoxide[197] yielded four compounds, which have been identified on the basis of spectral data as 1,3,7-trihydroxy-2-prenylxanthone, its 7-prenylether, 1,3,7-trihydroxy-2,4-diprenylxanthone and its 7-prenylether. Reaction of 1,3-dihydroxyxanthone, with 2-hydroxy-2-methyl-3-butene in the presence of boron-trifluoride etherate[198] gave a mixture of 1,3-dihydroxy-4-prenylxanthone, 1,3-dihydroxy-2-prenylxanthone and 1,3-dihydroxy-2,4-diprenylxanthone.

Claisen rearrangement of 1-hydroxy-3-prenyloxy-xanthone, its 7-methoxy and 6-methoxy derivatives at 200-10° in vacuo[199] yielded a mixture of the corresponding dealkenylated xanthones, angularly condensed 4',4',5'-trimethyldihydrofurano derivatives and their linear isomers. However, 1-hydroxy-5-methoxy-3-prenyloxyxanthone afforded, besides the dealkenylated

xanthone, only the linearly condensed 4',4',5'-trimethyldihydrofuranoxanthone and its 4-prenylated derivative.

Burling et al.[165] have reported the prenyl migration of 1-prenyloxy-3,5,6-trimethoxyxanthone in dimethylaniline. They obtained 4-prenyl-1-hydroxy-3,5,6-trimethoxyxanthone, the furanoxanthone, the normal 2-prenyl- migration product and the dealkenylated xanthone. In another experiment 2,4-diprenyl-3,5,6-trimethoxyxanthone was also obtained.

The present work deals mainly with the substitution reactions on some hydroxyxanthones and with the synthesis of pyrano- and furanoxanthones.

Chapter II deals with the work on the iodination of 2-hydroxy-, 3-hydroxy-, 3-hydroxy-6-methoxy- and 3,6-dihydroxyxanthone and the conversion of these iodoxanthones into the cyanoxanthones by Rosenmund-von Braun reaction and into bixanthonyls by the Ullmann reaction.

Chapter III deals with the nitration of 2-hydroxy-, 3-hydroxy-, 3-hydroxy-6-methoxy- and 3,6-dihydroxyxanthone and coupling of these xanthones with phenyldiazonium chloride. Both the nitro- and the phenylazoxanthones have been reduced to the corresponding aminoxanthones.

In Chapter IV the work on the synthesis of [illegible] pyronoxanthones from 3,6-dihydroxy-2,5-diacetylxanthone by the Baker-Venkataraman transformation and by cyanoethylation of 2-hydroxy- and 3-hydroxyxanthone has been discussed. The synthesis of angular furanoxanthones from 3-hydroxy-6-methoxyxanthone and 3,6-dihydroxyxanthone through the intermediate 4-allyl and 4,5-diallyl derivatives is also discussed in this Chapter.

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