NATURALLY OCCURRING XANTHONES

JOHN C. ROBERTS

Department of Chemistry, The University, Nottingham, England

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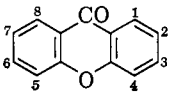
I. Introduction

The term xanthone (from the Greek ξανθός, meaning yellow) designates the chemical compound dibenzo-γ-pyrone (I). The parent substance (which forms almost



I
Dibenzo-γ-pyrone

colorless needles melting at 173–174°C.) does not, so far as is known, occur in nature, but a number of its oxygenated derivatives, which are yellow in color, have been isolated from a variety of natural sources. The xanthones bear a close structural relationship to the other naturally occurring γ-pyrone derivatives, the flavonoids (91) and the chromones (77).

The references to the literature are complete through the 1960 issues of *Chemical Abstracts* and *Current Chemical Papers*.

II. Occurrence and Distribution in Nature

The eighteen naturally occurring xanthones that have been isolated and characterized are listed in table 1. Some of these may occur in the plant as their glycosides (4, 17, 76), but these are not included in the table. Mangiferin is probably an unusual type of "glycoside" with the sugar residue linked to the xanthone nucleus by a C—C linkage (70); euxanthic acid is a glucuronide (84).

TABLE 1

Biological distribution of naturally occurring xanthones

Xanthone	Source	Family
From flowering plants:		
1. Corymbiferin	*Gentiana corymbifera*	*Gentianaceae*
2. Decussatin	*Swertia decussata*	*Gentianaceae*
3. Euxanthone	*Platonia insignis*	*Guttiferae*
4. Gentisin	*Gentiana lutea*	*Gentianaceae*
5. Isogentisin	*Gentiana lutea*	*Gentianaceae*
6. Jacareubin	*Calophyllum brasiliense*	*Guttiferae*
7. Mangiferin	*Mangifera indica*	*Anarcardiaceae*
8. Mangostin	*Garcinia mangostana*	*Guttiferae*
9. Swerchirin	*Swertia chirata*	*Gentianaceae*
10. Swertianol	*Swertia japonica* and *S. tosaensis*	*Gentianaceae*
11. Swertinin	*Swertia decussata*	*Gentianaceae*
From fungi:		
1. Griseoxanthone C	*Penicillium patulum*	
2. Pinselin	*Pencillium amarum*	
3. Pinselic acid	*Pencillium amarum*	
4. Ravenelin	*Helminthosporium spp.*	
5. Sterigmatocystin	*Aspergillus versicolor*	
From a lichen:		
1. Lichexanthone	*Parmelia formosana*	
Of animal origin:		
1. Euxanthic acid	Urine of animals fed on leaves of *Mangifera indica*	

Eleven of these xanthones occur in various parts of flowering plants belonging to the families *Gentianaceae*, *Guttiferae*, and *Anacardiaceae;* five are metabolic products of members of the lower fungi; one is of lichen origin and one, euxanthic acid, which is apparently produced by a detoxication mechanism, is found in the urine of animals which have been fed on Mango leaves.

III. Extraction, Purification, and Recognition

The xanthones, which are found in various parts of plants or in the mycelia of moulds, are generally obtained by solvent extraction (Soxhlet method) of the dried and disintegrated material. (Pinselic acid and pinselin are extracted from an aqueous substrate on which the mould has been grown.) The crude material may be purified by recrystallization, but a prior purification by chromatography (21, 53) is sometimes desirable. Most naturally occurring xanthones sublime readily (under low pressure), and this method of purification has, in one instance at least (21), proved indispensable.

Techniques for the detection of small quantities of xanthones in plant tissues have not been developed as they have been in the case of the flavonoids (27), but the separation and identification of xanthones by paper chromatography appear possible (17, 49).

A significant feature common to all the naturally occurring xanthones is the occurrence of a hydroxyl group in the 1(or equivalent 8)-position. They thus have certain properties in common with 1-hydroxyxanthone itself; e.g., they are yellow in color, the majority of them give a green color with ferric chloride in ethanolic solution, and they are colored intensely yellow on contact with 2 *N* sodium hydroxide solution. Some hydroxyxanthones (gentisin, isogentisin, corymbiferin, and jacareubin) give positive reactions in the color test (with magnesium and hydrochloric acid) for flavonoid compounds (83).

IV. General Methods of Structural Investigation

A. Physical Methods

The notable advance of physical techniques during the last two decades has led to their useful application in xanthone chemistry.

1. Infrared absorption spectroscopy

The carbonyl group in xanthones is chemically rather inert (see below) but is always easily detectable in their spectra as a strong band (stretching frequency) in the region of 1660 $cm.^{-1}$ The presence of a hydroxyl group in the 1(or 8)-position lowers the frequency, by hydrogen bonding, to a value of about 1650 $cm.^{-1}$ and a number of naturally occurring xanthones show strong bands with frequencies very close (± 5 $cm.^{-1}$)

TABLE 2

Ultraviolet absorption spectra of naturally occurring xanthones

Xanthone	Solvent	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	Reference
Corymbiferin	Ethanol	228	4.28	256	4.32	278	4.22	352	4.10	(76)
Decussatin	Ethanol	240*	4.6	260	4.6	315	4.1	380	3.7	(80)
Gentisin	Methanol	232*	4.43	260	4.32	272	4.3	410†	3.75†	(46)
Griseoxanthone C	Ethanol	242	4.57	269	3.95	309	4.36	340	3.85	(53)
Isogentisin	Not stated	234*	4.78	260	4.62	315	4.17	—	—	(17)
Jacareubin	Ethanol	240	4.09	—	—	279	4.60	334	4.26	(44)
Lichexanthone	Ethanol	242	4.55	254	4.43	306	4.35	340	3.75	(53)
Mangiferin	70% ethanol	242*	4.44	260	4.50	320	4.22	368	4.10	(41)
Mangostin	Ethanol	243	4.54	259	4.44	318	4.38	351	3.86	(96)
Ravenelin	Ethanol	234*	4.1	266	4.3	345	3.8	>400	~3.2	(55)
Sterigmatocystin	Ethanol	233	4.49	246	4.53	325	4.21	—	—	(21)
Swertinin	Ethanol	240*	4.4	267	4.5	329	4.1	390	3.5	(80)

* Values taken from a small-scale graph.
† Another maximum at 314 and 4.08.

to this latter value (21, 53, 96). It should, however, be borne in mind that substituents in the 3(or 6)-position of the xanthone nucleus may have a marked effect upon the carbonyl stretching frequency (93). According to some workers in this field, further structural information may be obtained from a knowledge of absorption bands in the region 1631–1613 $cm.^{-1}$ (96).

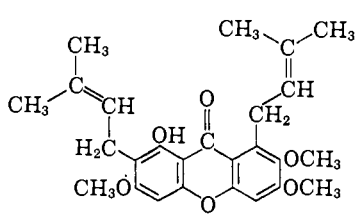
The use of infrared spectroscopy in xanthone chemistry for detecting other functional groups, such as unchelated hydroxyl. methyl groups, and vinyl ether groups, does not require special comment.

2. Ultraviolet absorption spectroscopy

Data on the absorption of ultraviolet light have proved of considerable value in a study of the naturally occurring xanthones. The spectra that have been published are listed in table 2. Three or four bands of maximum absorption are always found in the region 220–410 mμ, and it is noteworthy that all bands show a high intensity. Most of the substances show a marked absorption in the 400 mμ region, which accounts for their yellow color.

3. Nuclear magnetic resonance spectroscopy

The nuclear magnetic resonance spectrum of *O,O*-dimethylmangostin showed (96) that the *C*—CH_3 and *O*—CH_3 areas were approximately in the ratio of 4:3. Since three *O*—CH_3 groups were known to be present, it followed that the molecule contained four *C*—CH_3 groups.



O,O-Dimethylmangostin

4. X-ray crystallography

The more commonly used methods for the determination of molecular weights do not appear to give very accurate results in the case of hydroxyxanthones. The x-ray crystallographic method has been invaluable in two cases (22, 96) for fixing the molecular weights and hence the molecular formulas. The values obtainable have an accuracy of better than ±3 per cent.

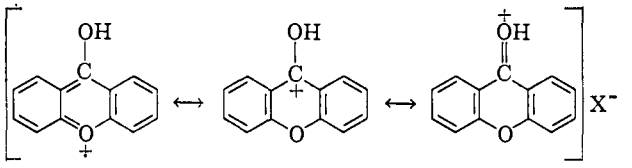
B. CHEMICAL METHODS

1. Confirmation of the presence of the carbonyl group

A characteristic property of the naturally occurring xanthones is the inertness of the carbonyl group toward reagents that ordinarily react with the carbonyl group. Xanthone itself yields an oxime under forcing conditions (16), but attempts to prepare oximes, by the standard methods, from xanthones carrying a 1(or 8)-substituent have been abortive (24). However, the following four methods can give useful information on the presence and environment of the carbonyl group.

(a) The formation of onium salts

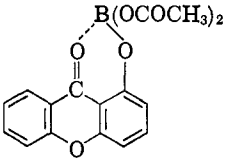
Hydroxyxanthones are not markedly basic, but the fully methylated compounds have a much enhanced basicity as shown by their solubility in concentrated hydrochloric acid with the production of onium salts which are, however, readily hydrolyzed. (For a discussion of this problem, especially in relation to xanthiones, see reference 73; in relation to flavones see reference 15.) Characterization of the fully methylated xanthones has often been achieved by the production of the crystalline and more stable ferrichlorides and perchlorates (see for example, reference 69). These onium salts may be represented by the structure:



where X^- is Cl^-, $FeCl_4^-$, or ClO_4^-.

(b) The formation of boroacetates

Compounds which possess a hydroxyl group in a position ortho to a carbonyl group react with boroacetic anhydride (23) to give boroacetates of type II.



II

If other hydroxyl groups are present in the molecule, they are acetylated. The boroacetates are readily hydrolyzed to yield the 1-hydroxyxanthone, boric acid, and acetic acid.

(c) The Grignard reaction

This reaction consists in the treatment of the fully methylated compound with phenylmagnesium bromide (69) and the isolation of the phenylxanthydrol as its ethyl ether.

(d) Reduction to the xanthene

This involves reduction of the carbonyl group, in a fully methylated hydroxyxanthone, to a methylene group with lithium aluminum hydride (58, 81) and a comparison (21) of the ultraviolet absorption spectrum of the xanthene with that of the original compound. The substituted xanthene has a spectrum which is fundamentally different from that of the xanthone.

2. Degradative methods

Three general methods are outlined below. More specialized and *ad hoc* methods are described in Section VII.

(a) Demethylation

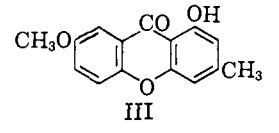
Most naturally occurring xanthones contain methoxyl groups. Demethylation may be accomplished by heating them with hydriodic acid (either alone or mixed with glacial acetic acid) or by means of aluminum chloride in boiling benzene or chlorobenzene solution. The possibility of the occurrence of a Wessely–Moser rearrangement (92) should be borne in mind (66). It should also be noted that demethylation of sterigmatocystin (XXVIII) with aluminum chloride in chlorobenzene was accompanied by the fission of an Ar—C link (21, 37), presumably by a reverse Friedel–Crafts reaction.

(b) Fusion with potassium hydroxide

High-temperature fusion of a xanthone with potassium hydroxide may lead to the identification of phenols of diagnostic value, e.g., resorcinol (14), phloroglucinol (50), etc., but difficultly separable mixtures of phenols, phenolic acids, and hydroxybenzophenones often result. These may, however, be separated and identified by paper chromatography (50).

(c) Stepwise oxidation

It has been shown (63, 79) that 1-hydroxyxanthones are convertible, by a modified Elbs persulfate oxidation, into 1,4-dihydroxyxanthones, and that the latter are susceptible to *mild* oxidation (by alkaline hydrogen peroxide), yielding salicylic acid or a substituted salicylic acid (72). For example, 1-hydroxy-7-methoxy-3-methylxanthone (III) gave 1,4-dihydroxy-7-methoxy-3-methylxanthone (IV), which was oxidized to 2-hydroxy-5-methoxybenzoic acid (VII), probably by way of V and VI.



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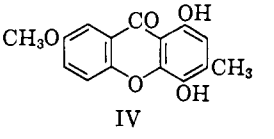
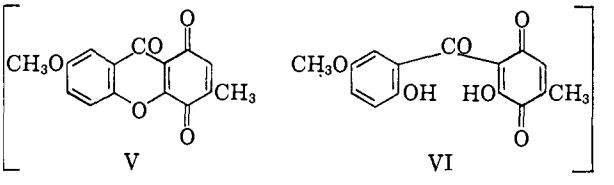
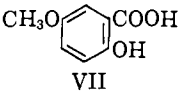


IV



V VI



VII

V. Analysis of Oxygenation Patterns in Naturally Occurring Xanthones of Known Structure

Of the eighteen xanthones listed in table 1, seventeen have oxygenation patterns which have been reasonably well established. An analysis of these patterns gives the following results:

Phenolic Nucleus	Number of Xanthones Containing This Nucleus
Phloroglucinol	12
Hydroxyquinol	7*
Quinol	6
Resorcinol	4
Orcinol	4
Pyrogallol	1

* In one instance (ravenelin) the hydroxyquinol nucleus also carries a methyl group.

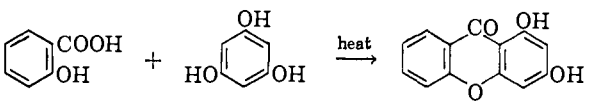
The predominance of the phloroglucinol nucleus is apparent, and it is interesting to note that all of these seventeen xanthones possess a phloroglucinol, resorcinol, or orcinol nucleus.

VI. Methods of Synthesis for Naturally Occurring Xanthones

Six general methods for synthesizing xanthone derivatives are outlined below. Selective methylation of hydroxyl groups in polyhydroxyxanthones may often be achieved (see, for example, reference 71). A hydroxyl group in the 3- or 6-position is more acidic than one in the 2- or 7-position; hence the former may be preferentially methylated. A hydroxyl group in the 1- or 8-position is hydrogen bonded to the carbonyl group and is more difficult to methylate:

A. MICHAEL–KOSTANECKI METHOD

In this method equimolecular proportions of a polyhydric phenol and an *o*-hydroxybenzoic acid are heated with a dehydrating agent such as acetic anhydride or zinc chloride (47, 51, 54, 63):

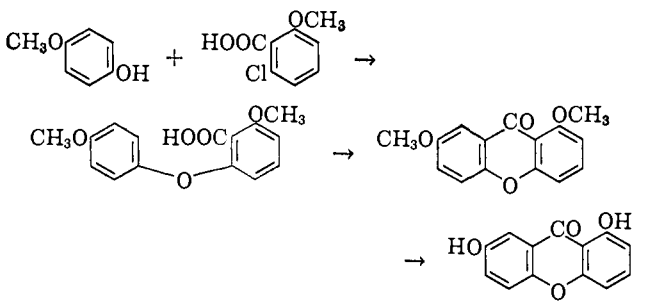


Salicylic acid Phloroglucinol 1,3-Dihydroxyxanthone

A modification of this method (32), which uses a mixture of phosphorus oxychloride and zinc chloride as condensing agent, gives good results in many cases and has the advantage that the required reaction temperature is lower.

B. ULLMANN METHOD

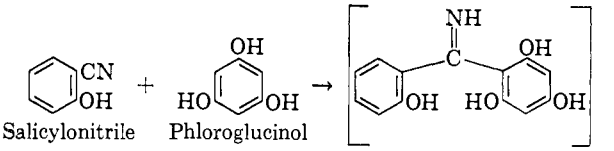
This method involves, first, the production of a diphenyl ether by reaction between a phenol and an *o*-chlorobenzoic acid, and secondly, ring-closure to the xanthone. The synthesis (90) of euxanthone (VIII) may be taken as an example:



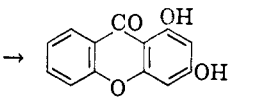
VIII
Euxanthone

C. ROBINSON–NISHIKAWA METHOD

This ingenious method (10, 62), a variant of the Hoesch synthesis, proceeds through a ketimino compound which may have the structure shown:



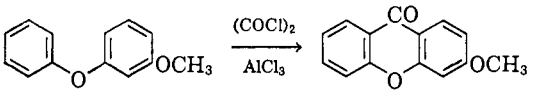
Salicylonitrile Phloroglucinol



1, 3-Dihydroxyxanthone

D. ASAHINA–TANASE METHOD

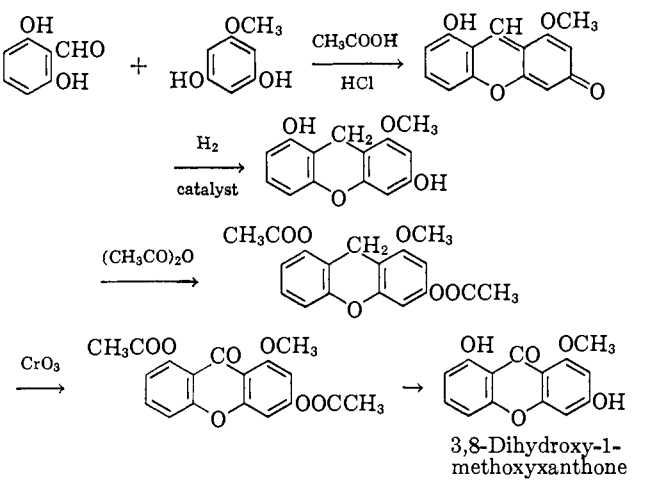
Asahina and Tanase have reported (8, 88) a useful synthesis for certain methoxylated xanthones:



3-Methoxyxanthone

E. TANASE METHOD

This elegant method (88) for synthesizing polyhydroxyxanthones has proved of special value since, in certain cases, it may be used for the preparation of partially methylated polyhydroxyxanthones in which the orientation of the substituents is unequivocally established. For example, it has been used (21, 38) to synthesize 3,8-dihydroxy-1-methoxyxanthone, which had been obtained as a degradation product of sterigmatocystin:

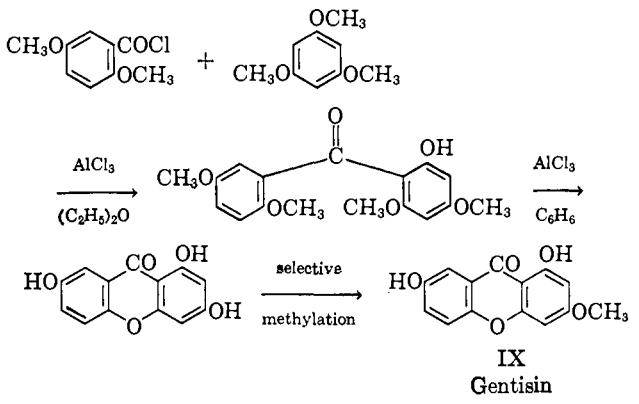


3,8-Dihydroxy-1-methoxyxanthone

This compound is not obtainable by any other known synthetic method.

F. FRIEDEL–CRAFTS METHOD

Gentisin (IX) has been synthesized (71) by the Friedel-Crafts method:



IX
Gentisin

VII. The Chemistry of the Individual, Naturally Occurring Xanthones

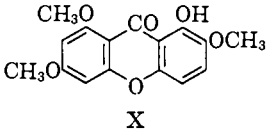
A. CORYMBIFERIN

Corymbiferin, $C_{15}H_{12}O_7$, dark yellow prisms, m.p. 268–269°C. (d.), has been obtained (76) from the roots of *Gentiana corymbifera*, a plant indigenous to New Zealand. It may exist in the plant as a glycoside which is very readily hydrolyzed.

Corymbiferin contains two methoxyl groups, dissolves in aqueous alkali (including sodium carbonate solution) to give an orange-yellow color, reduces Fehling's solution, and gives a brown-green color with ferric chloride in ethanol. It yields a triacetate, a yellow dimethyl ether (pale yellow-green color with ferric chloride in ethanol) and, under more rigorous treatment, a colorless trimethyl ether. The latter dissolves in concentrated hydrochloric acid to give an orange solution and yields a ferrichloride salt as orange prisms. Corymbiferin therefore appears to be a trihydroxydimethoxyxanthone which contains one hydroxyl group in the 1-position.

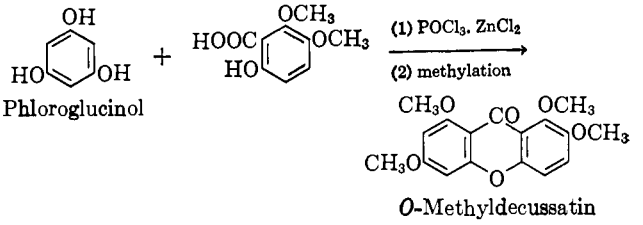
B. DECUSSATIN

Decussatin (X), $C_{16}H_{14}O_6$, yellow needles, m.p. 149–150°C., occurs in the flowers and roots of *Swertia decussata* (18).



X
Decussatin

On the basis of ultraviolet absorption data and of chemical reactions relative to swertinin (*q.v.*) it is concluded (18, 80) that decussatin has the structure shown in formula X. The oxygenation pattern has been confirmed by a synthesis of 1,3,7,8-tetramethoxyxanthone (20), which proved to be identical with *O*-methyldecussatin. The synthesis comprised a condensation of 6-hydroxy-2,3-dimethoxybenzoic acid with phloroglucinol, followed by methylation:

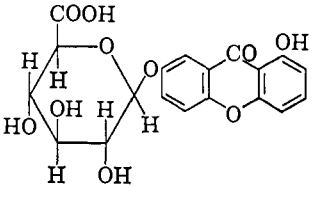


Phloroglucinol

O-Methyldecussatin

C. EUXANTHIC ACID

Euxanthic acid (XI), $C_{19}H_{16}O_{10}\cdot H_2O$, pale yellow needles, m.p. 162°C. (d.), in the form of its magnesium or calcium salt is the chief constituent of Indian Yellow. This pigment, otherwise known as Piuri,



XI
Euxanthic acid

had long been used in India for coloring walls, doors, and lattice-work and had also been used as an artist's water-color. It was obtained from the urine of cows which had been fed on Mango leaves (*Mangifera indica*) and was manufactured almost exclusively at Monghyr (Bengal) (for a detailed account see reference 30). The leaves have toxic properties and the practice is now forbidden (68).

Euxanthic acid has been isolated in crystalline form by digestion of Indian Yellow with hydrochloric acid, extraction of the residue by weak aqueous alkali, filtration, and acidification of the filtrate. Hydrolysis of euxanthic acid produces euxanthone (1,7-dihydroxyxanthone) and D-glucuronic acid (84). Methylation of euxanthic acid and hydrolysis of the product yield 7-hydroxy-1-methoxyxanthone (40, 74). Euxanthic acid therefore has the structure shown in formula XI, the glycosidic linkage being apparently of the β-type. It has been synthesized (60) by the reaction of diacetylbromoglucuronolactone with the potassium derivative of euxanthone.

D. EUXANTHONE

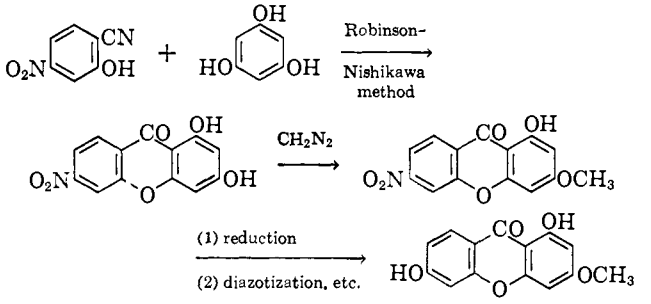
Euxanthone (VIII), $C_{13}H_8O_4$, pale yellow needles or laminae, m.p. 240°C., occurs to the extent of 1.3 per cent in the heartwood of *Platonia insignis* (85). It was first obtained (86) from euxanthic acid and its chemistry has been investigated for over a hundred years. Euxanthone is readily sublimable. On distillation with zinc dust it yields xanthene (31); fusion with alkali produces, *inter alia*, hydroquinone and resorcinol. One hydroxyl group is difficult to methylate, indicating its presence in the 1-position. A number of syntheses of euxanthone have been reported (30, 42,

48, 63, 90); of these, the synthesis of Ullmann and Panchaud (see page 595) unequivocally establishes the constitution of euxanthone as shown in formula VIII.

E. GENTISIN

Gentisin (IX), $C_{14}H_{10}O_5$, forms yellow needles melting at 274°C. Some species of gentian plants found in Europe appear to have been used in medicine since Grecian and Roman times. More recently, the roots and rhizomes of the yellow gentian (*Gentiana lutea*) have been much used for the production of a bitter tonic. Any medicinal value possessed by gentian preparations appears to be due to bitter, complex glycosides.

Gentisin, one of the coloring matters of gentian root, was first isolated (39) in 1821. This compound contains two hydroxyl groups and one methoxyl group. When fused with potassium hydroxide, it yields phloroglucinol and gentisic acid (2,5-dihydroxybenzoic acid). It was readily established (82) that gentisin was the 3- or 7-methyl ether of gentisein (1,3,7-trihydroxyxanthone), and it was deduced (64) that gentisin had the structure shown in formula IX. This deduction was supported when Shinoda (82) achieved an unambiguous synthesis of isogentisin (XIII) and showed that it was different from gentisin. An unequivocal synthesis (3) of gentisin was not achieved until 1947. This synthesis is outlined below:

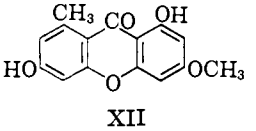


IX
Gentisin

An alternative synthesis has already been described (page 596).

F. GRISEOXANTHONE C

Griseoxanthone C (XII), $C_{15}H_{12}O_5$, buff-colored needles, m.p. 253–255°C., has recently been obtained (53) in small yield from cultures of *Penicillium patulum*. Its structure (XII) was deduced (53) from analytical

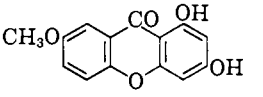


XII
Griseoxanthone C

and spectroscopic data and from the observation that, on methylation with diazomethane, it yielded lichexanthone (XVI).

G. ISOGENTISIN

Isogentisin (XIII), $C_{14}H_{10}O_5$, is obtained as yellow plates, melting at 241°C. It has recently been shown (17) that gentian root contains, in addition to gentisin,

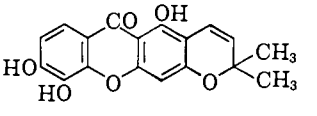


XIII
Isogentisin

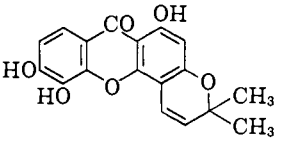
an appreciable proportion of isogentisin (XIII) and a small proportion of a glycoside, gentioside (see reference 89), which is probably 3-β-primeverosidoisogentisin. A satisfactory synthesis of isogentisin has been published (82).

H. JACAREUBIN

Jacareubin (XIV), $C_{18}H_{14}O_6$, bright yellow prisms, m.p. 256–257°C., has been isolated (in a yield of *ca.* 0.3 per cent) from the heartwood of the tropical American tree *Calophyllum brasiliense*, and its structure has been established as shown in formula XIV (44, 45).

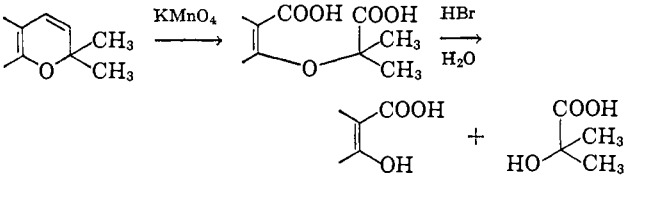


XIV
Jacareubin



XV

Jacareubin contains three phenolic hydroxyl groups and an olefinic bond. Oxidation of the trimethyl ether with potassium permanganate in acetone yielded a dicarboxylic acid, trimethyljacareubic acid, $C_{21}H_{20}O_{10}$, with the same number of carbon atoms in the molecule, thus proving the double bond to be part of a cyclic system. When trimethyljacareubic acid was boiled with hydrobromic acid, α-hydroxyisobutyric acid was liberated. These results are consistent with the degradation of a 2,2-dimethylpyran nucleus, the reactions following the course:

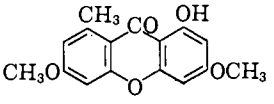


However, the principal product of the degradation of trimethyljacareubic acid was a pale yellow tetrahydric phenol, $C_{13}H_8O_6$, obviously produced by a simultaneous dealkylation and decarboxylation. From its general properties and molecular formula, and from the observation that one of the four phenolic hydroxyl groups

could be methylated only under rigorous conditions, the tetrahydric phenol was recognized as a derivative of 1-hydroxyxanthone. Further evidence concerning the orientation of the hydroxyl groups was obtained by the preparation from jacareubin of a methylene ether, thus proving the existence of a catechol grouping. Furthermore, it was apparent from the yellow color and the positive color reaction with ferric chloride of this derivative, that the chelated hydroxyl group was not one of those concerned in the formation of the methylene ether. The fourth hydroxyl group (the one formed during the destruction of the pyran ring) was assumed to form a part of a phloroglucinol nucleus (i.e., to occupy position 3), the lability of the aromatic carboxyl group in trimethyljacareubic acid being characteristic of a phloroglucinolcarboxylic acid. The tetrahydric phenol was eventually found to be identical with 1,3,5,6-tetrahydroxyxanthone, synthesized by the Tanase method (see page 595) from pyrogallol-α-aldehyde and phloroglucinol. It follows that jacareubin possesses structure XIV or XV. A decision in favor of the linear formulation (XIV) was made by the observation that 5,6-dimethyljacareubin gave a strongly positive Gibbs test (45), proving that the 4-position in jacareubin is unsubstituted. Jacareubin is the only naturally occurring pyranoxanthone known.

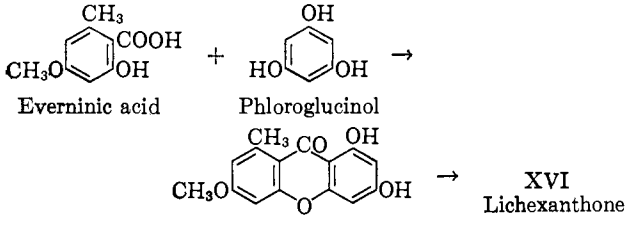
I. LICHEXANTHONE

Lichexanthone (XVI), $C_{16}H_{14}O_5$, long yellow prisms, m.p. 187°C., is at present the sole xanthone derivative known to occur in lichens. It was isolated (6, 7) from the thalli of *Parmelia formosana*, a lichen which is found in Formosa and the central regions of Japan.



XVI
Lichexanthone

The general chemical properties of this substance indicated a 1-hydroxyxanthone structure, and fusion with potassium hydroxide yielded orcinol. On the assumption that the compound also contained a phloroglucinol nucleus, it appeared likely that lichexanthone had structure XVI. This was confirmed by a synthesis (1, 6, 7) of lichexanthone from orsellinic aldehyde and phloroglucinol, using the Tanase method (see page 595). A later and simpler synthesis (33) starting from everninic acid is outlined below:

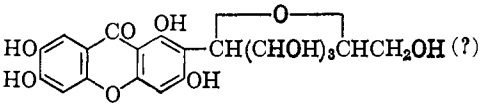


Everninic acid + Phloroglucinol → XVI Lichexanthone

An independent isolation of lichexanthone from a *Parmelia* lichen has been reported (1).

J. MANGIFERIN

Mangiferin, mangin, or euxanthogen[1] (possibly XVII), $C_{19}H_{18}O_{11}$, pale yellow needles, m.p. 271°C., occurs in the leaves and bark of *Mangifera indica*



XVII
Mangiferin

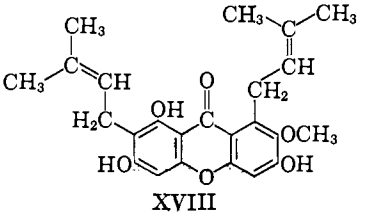
and is almost undoubtedly the precursor of the pigment known as Indian Yellow (salts of euxanthic acid).

Mangiferin gives a green color with ferric chloride in ethanol and reduces Fehling's solution on prolonged heating. Initial investigations into the chemistry of this compound (29, 94) indicated that it was built up from a polyhydroxyxanthone and a hexose, but the way in which the two moieties were combined was not established. More recently, Iseda (41) has succeeded in defining the rather special experimental conditions required for degrading mangiferin to glucose and a tetrahydroxyxanthone, which proved to be identical with a sample of 1,3,6,7-tetrahydroxyxanthone synthesized by the Tanase method (see page 595) from 2,4,5-trihydroxybenzaldehyde and phloroglucinol. Iseda claims that mangiferin is the 7-α-glucoside of 1,3,6,7-tetrahydroxyxanthone, but this structure is incompatible with the observation that the compound is very difficult to hydrolyze by means of aqueous mineral acids. Furthermore, attempts to bring about enzymic hydrolysis (94) have been unsuccessful. The most acceptable structure for this compound which has yet been put forward appears to be XVII (70).

With reference to the production of Indian yellow, a point of biochemical interest is that, in passage through the animal body, a tetrahydroxyxanthone derivative is reduced to a dihydroxyxanthone. It is worth noting, however, that a chemical reduction of a trihydroxyxanthone (gentisein) to a dihydroxyxanthone (euxanthone) has been achieved (42).

K. MANGOSTIN

Mangostin (XVIII), $C_{24}H_{26}O_6$, yellow needles, m.p. 182°C., is a yellow pigment found in various parts of

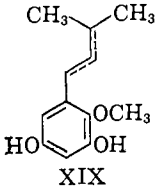


XVIII
Mangostin

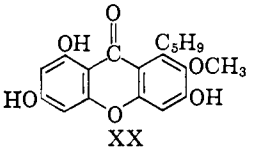
[1] It has been incorrectly stated that mangiferin is a glucoside of euxanthone (69).

the Mangosteen tree, *Garcinia mangostana*. It was first isolated in 1855 (78) but, in spite of numerous attempts, its structure was not fully elucidated until after the lapse of over one hundred years.

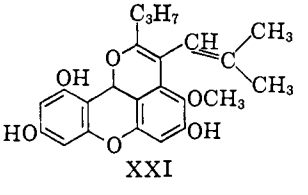
A survey of the earlier investigations into the chemistry of this compound reveals wide disagreement between the various workers with regard to its empirical and molecular formulas (57). From his own results, and from those of earlier workers, Murakami (57) concluded that mangostin had the molecular formula $C_{23}H_{24}O_6$ and possessed the following functional groups: two olefinic bonds which could be readily hydrogenated, one methoxyl group, and three hydroxyl groups of which one could be methylated only with considerable difficulty. Dragendorff (25, 26) had previously observed that mangostin formed a boroacetate, and it was concluded that the molecule possessed a carbonyl group situated in the β-position to the unreactive hydroxyl group. Further, Dragendorff found that isovaleric acid and an amyl alcohol were produced when mangostin was fused with potassium hydroxide. Also by fusion of mangostin with alkali, Yamashiro (95) had isolated, *inter alia*, isovaleric acid and a yellow phenolic compound, formulated as $C_{16}H_{16}O_5$ ("Yamashiro's phenol"), which subsequently became a key degradation product in the elucidation of the structure of mangostin. Furthermore, Yamashiro found that when the phenol was again fused with alkali, phloroglucinol and isovaleric acid were obtained. By cleavage of mangostin with ethanolic potassium hydroxide at 170–180°C. Murakami separated (from a number of other degradation products) a liquid phenol which was identified, by a number of ingenious degradative and synthetic methods, as 3,5-dihydroxy-2-methoxyisopentenylbenzene (XIX). With this knowledge, Murakami reformulated Yamashiro's phenol as $C_{19}H_{18}O_6$



XIX



XX



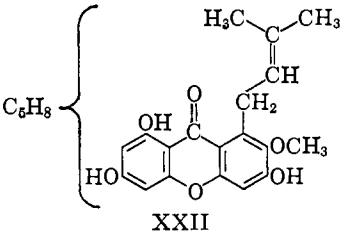
XXI

and, somewhat fortuitously, assigned to it the correct structure (XX). The molecular formula of this latter compound differed from that allocated to mangostin by C_4H_6 and Murakami was led to suggest structure XXI for mangostin.[2]

[2] The structure suggested by Murakami has twice been incorrectly represented in the literature (52, 75).

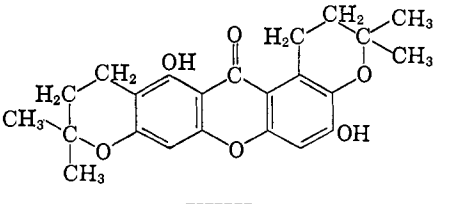
In a masterly reëxamination of this problem (for the full details of which the original paper should be consulted) Yates and Stout (96)[3] pointed out that Murakami's structure is unacceptable for a number of reasons, the most obvious being that it fails to account for the marked yellow color of the pigment and for its ultraviolet absorption spectrum (25), which shows obvious relationships to the spectra of a number of xanthone derivatives of established structure. Moreover, whereas Dragendorff had observed (25) the formation of a boroacetate from mangostin, indicating the presence in the molecule of a carbonyl group in the β-position to the unreactive hydroxyl group, Murakami's structure contains no such group. (Murakami's explanation of the formation of a boroacetate is quite unconvincing.)

Yates and Stout first corrected the molecular formula of mangostin to $C_{24}H_{26}O_6$. Secondly, they confirmed Murakami's structure (XX) for Yamashiro's phenol and, by a careful investigation of the oxidation of tetrahydromangostin, showed that isocaproic acid was produced in a quantity which undoubtedly proved the presence in the mangostin molecule of two C_5 side chains. Spectral analysis indicated that the double bonds were allocated one to each side chain, and ozonolysis of dimethylmangostin yielded acetone and a dialdehyde of the molecular formula $C_{20}H_{18}O_8$, thus confirming the existence of two isopentenyl $[(CH_3)_2C{=}CHCH_2{-}]$ side chains in mangostin. The partial structure (XXII) was thus established, and



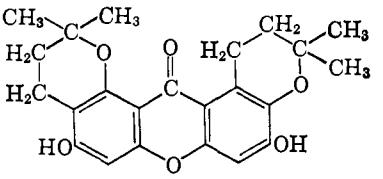
XXII

it remained only to fix the position of the second isopentenyl side chain. This was assigned to the 7-position for the reason that hydriodic acid, under different conditions, gave two different compounds (demethylmangostin and isodemethylmangostin) for which structures XXIII and XXIV, respectively, were established.



XXIII
Demethylmangostin

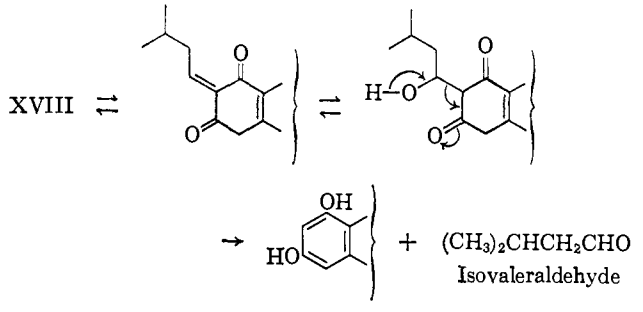
[3] These authors use a different system of numbering from that used in this review.



XXIV
Isodemethylmangostin

Had the second side chain occupied any of the other possible positions, the alternative cyclizations could not have occurred.

The production of isovaleric acid and of an amyl alcohol by fusion of mangostin with alkali is interpreted (96) thus:



Isovaleraldehyde

and

$$(CH_3)_2CHCH_2CHO \xrightarrow{\text{Cannizzaro reaction}} \underset{\text{Isovaleric acid}}{(CH_3)_2CHCH_2COOH} + \underset{\text{Amyl alcohol}}{(CH_3)_2CHCH_2CH_2OH}$$

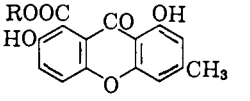
This mechanism involves double-bond shifts, hydration, and reverse aldol cleavage to give isovaleraldehyde which, by a Cannizzaro reaction, yields the experimentally observed products. The formation of Yamashiro's phenol, which retains the isopentenyl side chain at position 1, is also satisfactorily explained, for this side chain has no free hydroxyl group in the ortho or para position which might allow ketonization, hydration, and reverse aldol elimination. Repeated fusion, it is suggested, achieves demethylation at the 2-position, thus allowing the production of isovaleric acid by the above mechanism. Further degradation may then yield phloroglucinol.

The suggested structure (XVIII) (96) for mangostin so accurately interprets the experimental data that there can be virtually no doubt as to its correctness.

L. PINSELIN AND PINSELIC ACID

Pinselin (XXV: R = CH_3), $C_{16}H_{12}O_6$, golden-yellow prisms melting at 225°C., and pinselic acid (XXV: R = H), $C_{15}H_{10}O_6$, yellow needles melting at 250–252°C. (after decomposition at 195–200°C.), are two metabolites produced by a mould, *Penicillium amarum*, when it is grown on an aqueous medium containing sucrose, lactopeptone, and inorganic salts (56).

Pinselin was found to be a methyl ester hydrolyzable, with difficulty, to pinselic acid. This acid was readily

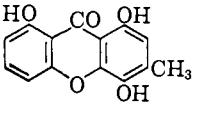


XXV
Pinselin: R = CH_3
Pinselic acid: R = H

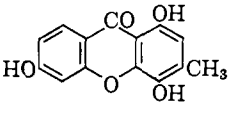
decarboxylated to produce a nonacidic dihydroxymethylxanthone, $C_{14}H_{10}O_4$, which was identified, by degradation and by comparison with a synthetic sample, as 1,7-dihydroxy-3-methylxanthone. Because of the difficulty in hydrolyzing pinselin and in esterifying pinselic acid, Munekata (56) suggested that the carboxyl group in pinselic acid occupies position 8, thus giving the above structures for the two metabolites.

M. RAVENELIN

Ravenelin (XXVI), $C_{14}H_{10}O_5$, yellow prismatic needles, m.p. 267–268°C., has been isolated (69) from the dried and defatted mycelium of two phytopathologically active members of the lower fungi, *Helminthosporium Ravenelii* and *H. turcicum*. Physical properties and chemical reactions established the formula $C_{13}H_4O_2(OH)_3CH_3$, and the possibility of a xanthone structure was indicated by the observation that the *O*-trimethyl ether readily gave a crystalline ferrichloride salt. Alkaline fusion of ravenelin yielded resorcinol. The *O*-trimethyl ether, when submitted to the Haller–Bauer reaction (34), yielded 2,5,3′-trimethoxy-3-methyldiphenyl ether, the constitution of which was established by synthesis (69). It followed that ravenelin had structure XXVI or XXVII. A compound of structure XXVII was synthesized (69) and found to be different from ravenelin. The metabolite thus has structure XXVI, a conclusion which has been rigorously proved by two independent, unambiguous syntheses.

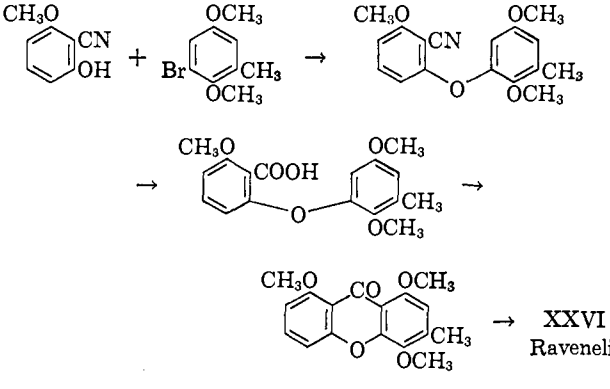


XXVI
Ravenelin



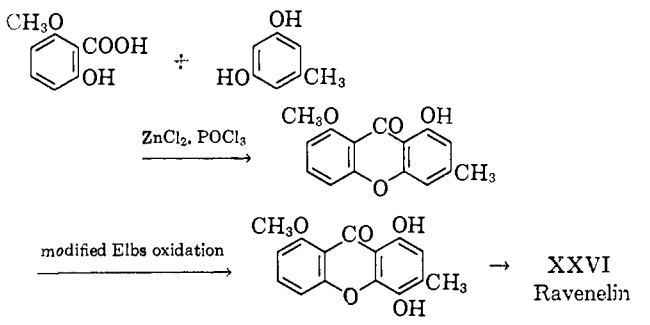
XXVII

The first synthesis (55) was accomplished thus:



XXVI
Ravenelin

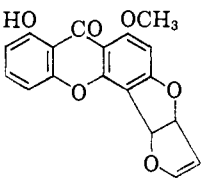
The second synthesis, published more recently (43), is outlined below:



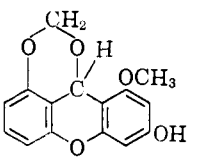
N. STERIGMATOCYSTIN

Sterigmatocystin (XXVIII), $C_{18}H_{12}O_6$, pale yellow needles, m.p. 246°C., is isolable (in a yield of *ca.* 1.3 per cent) from the dried mycelium of certain strains of the mould *Aspergillus versicolor*. Three independent isolations of this metabolite have been reported (14, 21, 22, 35).

This compound was originally assigned the molecular formula $C_{15}H_{12}O_5$ and the structural formula XXIX, but both of these formulas became untenable when it was shown (14, 21, 22) that the true molecular formula for sterigmatocystin is $C_{18}H_{12}O_6$.



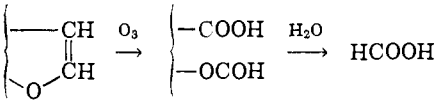
XXVIII
Sterigmatocystin



XXIX

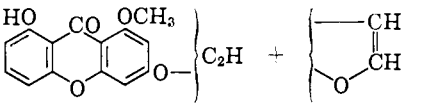
Sterigmatocystin shows the general properties and the light-absorption characteristics of a 1(or 8)-hydroxyxanthone. The compound contains one hydroxyl group and one methoxyl group. It is strongly levorotatory. It contains no methylenedioxy grouping.

Hydrogenation revealed the presence of one double bond in the molecule, and the infrared absorption spectrum indicated that this feature might be incorporated in a vinyl ether system (21). The presence of a vinyl ether grouping was confirmed by the observation that ozonolysis of *O*-methylsterigmatocystin and hydrolysis of the product led to formic acid (0.85 mole).



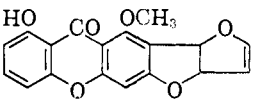
Degradation of sterigmatocystin with aluminum chloride in chlorobenzene yielded 1,3,8-trihydroxyxanthone (21, 37). The ultraviolet absorption spectrum of *O*-methylsterigmatocystin was very similar to that of 1,3,8-trimethoxyxanthone. There was therefore little doubt that sterigmatocystin was a derivative of 1,3,8-trihydroxyxanthone.

Oxidation of sterigmatocystin in acetone solution with a limited quantity of potassium permanganate yielded a carboxylic acid ($C_{14}H_9O_5COOH$) which, when pyrolyzed and sublimed, gave 3,8-dihydroxy-1-methoxyxanthone, $C_{14}H_{10}O_5$, identical with a specimen synthesized by the Tanase method (see page 595) from γ-resorcylaldehyde and *O*-monomethylphloroglucinol. The hydroxyl and methoxyl groups in the metabolite thus occupy positions 8 and 1, respectively, and the partial structure (XXX) is established. Since the ultraviolet absorption spectrum of dihydrosterigmatocystin is essentially similar to that of sterigmatocystin, the double bond cannot be in conjugation with the main chromophore. Valency analysis of dihydrosterigmatocystin indicated the presence of two rings in

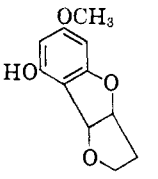


XXX

addition to those in the xanthone nucleus. Dihydrosterigmatocystin was quite stable toward moderately strong mineral acids, showing the absence of an acetal grouping in the molecule. It was therefore suggested that sterigmatocystin possesses structure XXVIII or XXXI. A decision between these two possibilities was obtained thus: Dihydrosterigmatocystin was converted by a modified Elbs persulfate oxidation (72) into dihydro-5-hydroxysterigmatocystin which, on mild oxidation with alkaline hydrogen peroxide, gave a phenol, $C_{10}H_9O_3(OCH_3)$. The analytical and spectral data and the chemical properties, including a positive Gibbs reaction (45), indicated structure XXXII for this phenol; hence sterigmatocystin has the structure shown in formula XXVIII.



XXXI

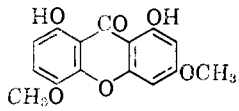


XXXII

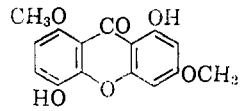
O. SWERCHIRIN

Swerchirin (XXXIII or XXXIV), $C_{15}H_{12}O_6$, yellow needles, m.p. 185–186°C., has been isolated (19) from the stems of *Swertia chirata*.

Swerchirin contains two hydroxyl groups and two methoxyl groups, and its *O*-dimethyl ether is identical with 1,3,5,8-tetramethoxyxanthone (20, 88). Since swerchirin is insoluble in sodium carbonate solution (evidence of the absence of a hydroxyl group in position 3) and gives a negative gossypetone reaction [absence of a *p*-dihydroxy grouping (65)], it is concluded



XXXIII



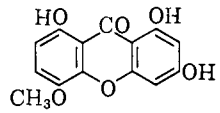
XXXIV

(20) that it is to be represented by formula XXXIII or XXXIV. Desmethylswerchirin, $C_{13}H_8O_6$, gives a positive result in the gossypetone reaction.

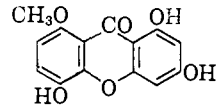
P. SWERTIANOL

Swertianol (XXXV or XXXVI), $C_{14}H_{10}O_6$, yellow needles, m.p. 263°C., has been obtained (4, 5) from *Swertia japonica*. This plant also contains swertianolin, $C_{20}H_{20}O_{11}$, which is a glycoside of swertianol.

Swertianol itself possesses three hydroxyl groups and one methoxyl group, and yields desmethylswertianol on treatment with hydriodic acid. Fusion of desmethylswertianol with potassium hydroxide yields phloroglucinol. Synthesis (88) establishes desmethylswertianol as 1,3,5,8-tetrahydroxyxanthone. Since swertianol does not give a color reaction with chloropentamminocobalt



XXXV



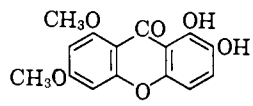
XXXVI

chloride (absence of 1,2- and 1,4-dihydroxy arrangements), it has either structure XXXV or structure XXXVI.

Swertianol and swertianolin have also been isolated from *Swertia tosaensis* (59).

Q. SWERTININ

Swertinin (XXXVII), $C_{15}H_{12}O_6$, yellow needles, m.p. 217°C., occurs in the stems of *Swertia decussata* (18). Demethylated swertinin gives phloroglucinol (50) on fusion with potassium hydroxide. Monomethylation of swertinin yields decussatin and complete methylation gives *O*-methyldecussatin.



XXXVII
Swertinin

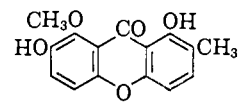
Swertinin gives a green color with ferric chloride and reduces ammoniacal silver nitrate. These observations are held to indicate that swertinin has structure XXXVII.

VIII. Asperxanthone and Rubrofusarin

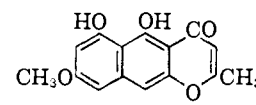
These two compounds are briefly considered here, since until very recently it was believed that they belonged to the class of naturally occurring xanthones.

Asperxanthone, $C_{16}H_{14}O_5$, primrose-yellow needles, m.p. 203°C., has been isolated (51) from the mycelium of several strains of *Aspergillus niger*. This compound possesses two methoxyl groups, one *C*-methyl group, and an unreactive carbonyl function. It yields an intense green color with ferric chloride and gives an unstable perchlorate and a boroacetate. It was therefore concluded that asperxanthone was a 1-hydroxydimethoxymethylxanthone (51). Demethylation of the compound with hydriodic acid yields a product, $C_{14}H_{10}O_5$, which is identical with demethylated rubrofusarin (24, 51). Since it is now known (see below) that rubrofusarin is a naphthapyrone, it appears that asperxanthone has been incorrectly classified and named.

Rubrofusarin, $C_{15}H_{12}O_5$, red plates, m.p. 210–211°C., has been obtained from various strains of *Fusarium culmorum* and *F. graminearum* (9, 55, 87). The first investigators of this metabolite (9) thought that rubrofusarin might be the monomethyl ether of a trihydroxymethylxanthone, and specific xanthonoid structures, e.g., XXXVIII, were suggested by later workers (55). However, convincing evidence has recently been presented (87) that rubrofusarin is a naphthapyrone of structure XXXIX.



XXXVIII



XXXIX
Rubrofusarin

IX. Biological Properties of Xanthones

The function of the naturally occurring xanthones in the metabolism of the living material in which they occur is unknown. It is possible that they are produced merely as metabolic waste products.

It has been claimed (see reference 96 and references there quoted) that mangosteen hulls have febrifuge properties, and the hulls and the bark (both of which contain mangostin) have been used for the treatment of dysentery. However, it is not known whether mangostin itself has any useful therapeutic properties.

It has been stated (36) that 1,3,8-trihydroxyxanthone ("norsterigmatocystin"), obtainable by the degradation of sterigmatocystin, is active at a dilution of 1 in 80,000 against *Mycobacterium tuberculosis*, but sterigmatocystin itself shows virtually no tuberculostatic activity (21).

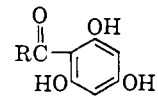
Numerous reports have appeared in the literature concerning the efficacy of xanthone, and of synthetically produced xanthone derivatives, as commercial pesticides and wood preservatives. Some synthetic xanthones (carrying basic substituents) are reported to be tuberculostatic, and some to be active in schistosomiasis (28).

X. Biogenesis of Naturally Occurring Xanthones

Ideas concerning the biogenesis of naturally occurring xanthones can be only speculative, since no experi-

mental work directly in this field appears to have been published.

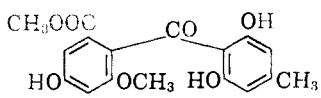
The common occurrence of the phloroglucinol nucleus is noteworthy and, since it is generally agreed that this is of "polyacetic acid" origin (12), it is concluded that xanthones, at least in part, are built up in this way. The other hydroxylation patterns encountered are of the resorcinol, quinol, hydroxyquinol, and (in one instance only, jacareubin) pyrogallol type. Robinson (75) comments on this topic: "It looks as if a number of different acids, RCO_2H, develop a polyacetic chain, $RCOCH_2COCH_2COCH_2CO_2H$." Such a compound might well yield the structure shown in formula XL, but the difficult problem of accounting for the



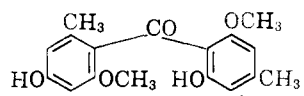
XL

formation of the diphenyl ether linkage remains unanswered. The simplest suggestion, that it is formed by elimination of the elements of water from a 2,2′-dihydroxybenzophenone, is not attractive for two reasons. First, such compounds are convertible into xanthones in the laboratory only under rigorous conditions. Secondly, if such compounds were the immediate precursors of xanthones, then it would be expected that some representatives of this type would have been isolated from natural sources. So far as the reviewer is aware, no such compounds have been detected.

It is interesting to note, however, that two 2-hydroxy-2′-methoxybenzophenones, sulochrin (XLI) (61) and griseophenone Y (XLII) (53), have been isolated from natural sources, and that both of them are convertible, under very mildly basic conditions, into xanthones.

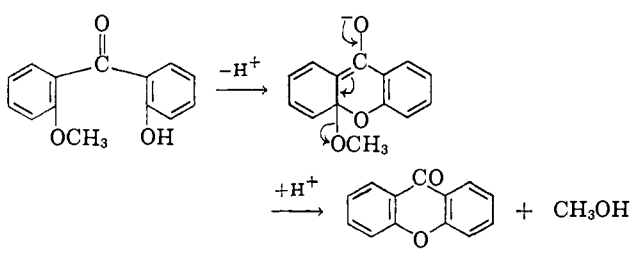


XLI
Sulochrin

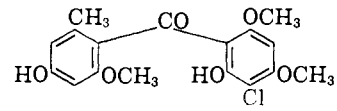


XLII
Griseophenone Y

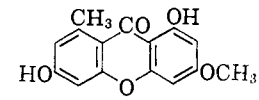
The following mechanism for this rather remarkable type of reaction has been suggested (11):



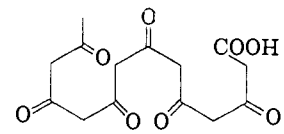
It may be significant that the benzophenone shown in formula XLIII accompanies griseoxanthone C (XII) in fermentations brought about by *Penicillium patulum* (53). A further point of interest (53) is that griseoxanthone C is theoretically derivable from seven acetate units (*cf.* formula XLIV).



XLIII



XII
Griseoxanthone C



XLIV

At what stage in the biosynthesis of naturally occurring xanthones the *O*-methylation takes place is unknown. The ubiquitous unmethylated hydroxyl group in the 1-position is noteworthy, as is also the coöccurrence in the same plant of two xanthones, decussatin (X) and swertinin (XXXVII), which differ only in their degree of *O*-methylation.

Finally, in two instances—jacareubin (XIV) and mangostin (XVIII)—isopentenyl groupings are encountered. Although these are probably of mevalonolactone origin, the mode of their introduction into the molecule is unknown (see reference 13).

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