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Natural Xanthones

O.A.Denisova-Dyatlova and V.I.Glyzin

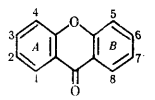
The available information on the abundance of natural xanthones in nature and the methods for the determination of their structure, biogenesis, and pharmacological properties is surveyed and described systematically.
The bibliography includes 151 references.

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I. INTRODUCTION

The term "xanthone" denotes a chemical compound with the dibenzo-γ-pyrone structure:



The unsubstituted xanthone has not been discovered in nature but its numerous derivatives have been isolated from representatives of higher plants, lichens, and lower fungi.

The first review on natural xanthones, published in 1961,[1] describes only 17 compounds of which 11 have been detected in various parts of flowering plants, 5 are metabolic products of lower fungi, and one has been isolated from lichen species.

Eight years later Carpenter et al.[2] examined the chemotaxonomic aspect of more than 70 natural xanthones and surveyed the available information about the possible ways of their biogenesis in plants. Chemotaxonomic problems were subsequently considered in greater depth in connection with xanthones from tropical plants[3].

In 1977 Hostettmann and Wagner[4] described one of the extensive groups of natural xanthones—xanthone glycosides.

The sharp growth of interest in natural xanthones in recent years can be readily accounted for by the fact that the first studies in the field of the pharmacological properties of xanthone derivatives already indicated that compounds of this class show promise.

The enormous amount of information accumulated during the last 20 years requires a clear-cut systematic treatment as regards questions concerning primarily the qualitative composition and physicochemical and pharmacological properties of natural xanthones. The employment of synthetic chemical methods for the preparation of highly efficient medicinal agents based on natural xanthones is also of considerable interest. However, the reviews published in recent years deal mainly with problems associated with the chemotaxonomy and biogenesis of xanthones. The aim of the present review is therefore to give a systematic account of the data on the qualitative composition, the methods for the determination of structure, and the pharmacological properties of natural xanthones.

II. CLASSIFICATION OF NATURAL XANTHONES

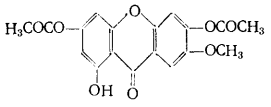
The qualitative composition of natural xanthones is extremely varied. The earlier classification of xanthones was based on the principle adopted in the classification of coumarins and chromones (derivatives of 5,6-benzo-α-pyrone and 5,6-benzo-γ-pyrone respectively).[5] However, in recent years compounds which do not fit within the framework of the proposed classification have been discovered. We believe that all the natural xanthones known at the present time should be divided into the following three groups:

1. Xanthones proper substituted by alkoxy-, alkyl, and alkenyl groups, *C*- and *O*-glycosidic residues, and chlorine atoms in positions *1–8*.
2. Pyrano- and dihydropyrano-xanthones.
3. Furano- and dihydrofurano-xanthones.

1. Xanthones Proper

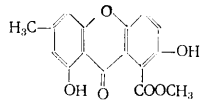
The majority of the xanthones discovered in nature are hydroxy- or methoxy-derivatives of xanthone. Tri- and tetra-substituted xanthones are most abundant. A characteristic feature of the tetrasubstituted xanthones is the presence, as a rule, of substituents in the 1- and 3-positions in the xanthone nucleus and in the main these are xanthones with substituents in the 1,3,5,8-, 1,3,7,8-, and 1,3,6,7-positions[2,4]. Pentasubstituted xanthones are encountered quite frequently. These are as a rule partly or fully methoxylated compounds containing in most instances between three and four methoxy-groups. Xanthones with one or two substituents are encountered somewhat more rarely and among the disubstituted xanthones those having substituents in the 1,5- and 1,7-positions are most abundant[3,5], Several hexasubstituted xanthones have been described. These are mainly either fully methoxylated compounds or compounds containing five methoxy-groups[5,6].

Xanthones with a greater number of substituents have not been detected in nature. Acetoxy-derivatives of xanthones are encountered in nature extremely rarely, especially among higher plants. A compound of this type [compound (I)] has been isolated from *Lawsonia inermis* (Lythraceae):[7]

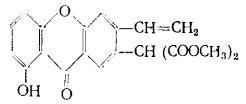


(I)

Several methoxycarbonyl derivatives of xanthone have been described. Among higher plants, *Cassia occidentalis* (Fabaceae), for example, contains methoxycarbonylxanthones (II).[8] Methoxycarbonylxanthones (III) have also been found in certain lower fungi—in the mycelium of *Mycosphaerella rosigena*:[9]

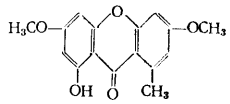


(II)

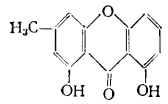


(III)

Methylated xanthones are encountered mainly in lichens, in the mycelia of certain fungi [compounds (IV)], and extremely rarely in certain higher plants [compounds (V)].[10]

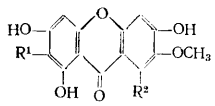


(IV)



(V)

Xanthones containing the isopropenyl group constitute a fairly extensive set of compounds distributed mainly among plants of the family Guttiferae [structures of type (VI, a and b)].[2,3,5] Substituents with a longer aliphatic chain are not characteristic of xanthones, but a xanthone containing the diene substituent geranyl has been isolated from the stems of *Garcinia cowa* (Guttiferae) [compound (VIc)]:[11]



(VI)

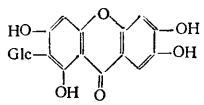
(a) R^1=H, R^2=$CH_2CH{=}C(CH_3)_2$; (b) R^1=R^2=$CH_2CH{=}C(CH_3)_2$; (c) R^1=H, R^2=geranyl.

Chloroxanthones constitute a special group among xanthones proper, since they are the products of the vital activity of lichens and have not been detected in higher plants.

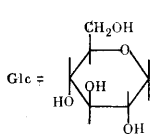
Xanthones containing in their molecule a carbohydrate substituent—xanthone glycosides—merit special attention. They can be divided into two groups: *C*-glycosides and *O*-glycosides. In contrast to the *O*-glycosides, the *C*-glycosides are resistant to acid and enzymatic hydrolysis, since the sugar component is attached to the aglycone by a C–C bond. The xanthone *C*-glycosides are encountered in nature comparatively rarely and have as a rule isotypical structures.

The aglycones of xanthone *C*-glycosides are hydroxy-derivatives of xanthone with substituents in the 1,3,6,7- or 1,3,5,6-positions in the xanthone nucleus. The carbohydrate component of the *C*-glycosides consist of glucose or glucobiose residues.

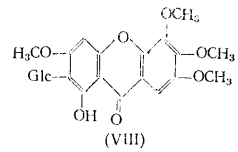
Mangiferin (VII),[12–16] which has the structure of 2-*C*-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone, is the most abundant representative of the *C*-glycosides:



(VII)

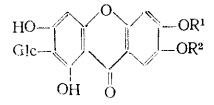


In plants mangiferin is as a rule accompanied by its isomer isomangeriferin, which has the structure of 4-*C*-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone[17]. Among the derivatives of 1,3,6,7-tetrahydroxyxanthone, the 3-methyl ether of mangeriferin[18], glucomangiferin (2-*C*-β-D-glucobiosyl-1,3,6,7-tetrahydroxyxanthone), and glucoisomangiferin (4-*C*-β-D-glucobiosyl-1,3,6,7-tetrahydroxyxanthone) have also been discovered in nature[19]. The xanthone *C*-glycosides with substituents in the 1,3,5,6-positions in the aglycones are encountered more rarely. 2-*C*-β-D-glycosyl-1,3,5,6-tetrahydroxyxanthone[20], its 5-methyl ether, called iris-xanthone, since it was first isolated from the roots of *Iris florentina* L.,[21] and its 3,5,6-trimethyl ether, obtained from *Hoppea dichotoma*,[22] have now been described. The only *C*-glycoside of a penta-substituted xanthone [compound (VIII)] known at the present time has also been isolated from *Hoppea dichotoma*:[22]



(VIII)

The discovery in nature of compounds having two carbohydrate substituents, one of which is linked to the aglycone by a C–C bond and the other by a C–O bond, made an important contribution to the study of xanthone glycosides. Thus acid hydrolysis of these compounds can yield the corresponding sugar and the *C*-glycoside. An example is provided by the *O*-glycosides of mangiferin isolated from *Gentiana asclepiadea* L. [compounds (IX) and (X)].[23]

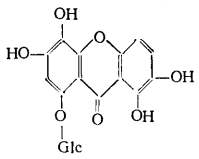


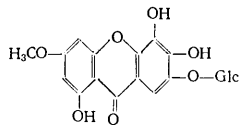
(IX) R^1=H, R^2=β-D-glucosyl;
(X) R^1-β-D-glucosyl, R^2=H.

Xanthone *O*-glycosides are encountered in plants much more frequently than the *C*-glycosides and have a more varied qualitative composition. Both *O*-monosides and *O*-biosides have been described. The monosaccharide *O*-glycosides of xanthones contain only β-D-glucose as the carbohydrate substituent[3]. Disaccharides are formed as a rule by primeverose (β-D-xylopyranosyl-β-D-glucopyranose) and rutinose (α-L-rhamnopyranosyl-β-D-glucopyranose).

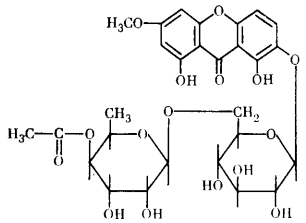
The aglycones of xanthone *O*-glycosides are tri-, tetra-, and penta-hydroxy-xanthones. The glycosides of tetra-substituted xanthones with oxygen-containing substituents in the 1,3,7,8-positions are most widely distributed. The glycosides of trihydroxyxanthones are encountered more rarely. Hitherto only two such compounds have been described in the literature: 1-hydroxy-7-methoxy-3-*O*-primeverosylxanthone, detected in the roots of the various *Gentiana* species[24], and 5-hydroxy-1-methoxy-3-*O*-rutinosylxanthone, isolated from *Canscora decussata* Schult[25]. Of the pentahydroxyxanthone glycosides, 1-*O*-β-D-glucopyranosyl-3,8-dihydroxy-4,5-dimethoxy-xanthone, detected in the leaves of *Gentiana campestris* L.,[26] 1-*O*-glucosyl-3,4,7,8-tetrahydroxyxanthone from the aerial part of *Swertia angustifolia* Buch.-Ham. [compound (XI)],[27] and 7-*O*-glycosyl-1,5,6-trihydroxy-3-methoxyxanthone from *Hoppea dichotoma* [compound (XII)] [22] have now been

described.

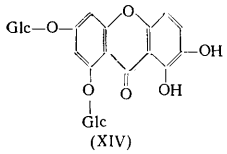

(XI)


(XII)

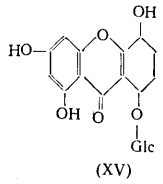
The only xanthone acyl-*O*-glycoside known hitherto, which was discovered in the leaves of *Gentiana bavarica* L.,[28] has the structure of 7-*O*-acetylrutinosyl-1,8-dihydroxy-3-methoxyxanthone (XIII).[29]


(XIII)

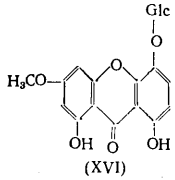
The xanthone diglucoside having the structure of 1,3-di-*O*-glucosyl-7,8-dihydroxyxanthone (XIV) was isolated in 1977 from *Swertia perennis* L.[30].


(XIV)

A novel xanthone *O*-glycoside, whose *B* ring is partly hydrogenated [compound (XV)] has been isolated from the aerial part of *Gentiana campestris* L.[31].


(XV)

The carbohydrate substituent in xanthone *O*-glycosides usually occupies the 1-position, glycosides with substituents in the 3-, 7- and 8-positions being encountered somewhat more rarely. The first and hitherto only xanthone *O*-glycoside having the carbohydrate substituent in the 5-position was isolated by the present authors from the aerial part of *Swertia iberica* Fish et May[32] and subsequently also from *Swertia connata* Schrenk[33]. The compound called bellidifoloside has the structure of 5-*O*-β-D-glucopyranosyl-1,8-dihydroxy-3-methoxyxanthone (XVI).

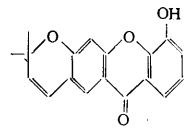

(XVI)

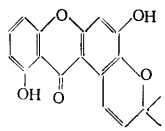
It is of interest to note that, whereas the presence of the carbohydrate substituent in the 2- and 4-positions is characteristic of the xanthone *C*-glucosides, not a single *O*-glycoside with substituents in these positions has been described hitherto. Furthermore, all the xanthone glycosides discovered in nature contain only hydroxy- and methoxy-xanthones as aglycones and not a single glycoside has been found whose aglycone contains alkyl substituents and pyran or furan rings.

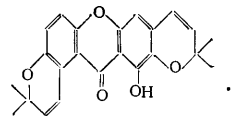
Pyrano- and Furano-Derivatives of Xanthone

Xanthones containing pyran or furan substituents in the molecule have a limited distribution in nature. They have been detected in plants of the families Guttiferae and Polygalacae and also in certain lower fungi.[3,5]

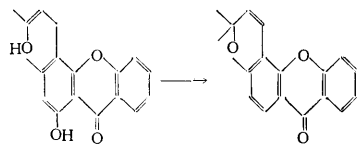
Compounds with one or two pyran rings having the linear and angular structures (XVII)–(XIX) have been described:


(XVII)

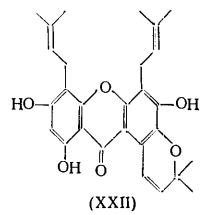

(XVIII)


(XIX)

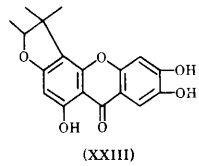
The pyranoxanthones in plants are always accompanied by xanthones with isoprenyl substituents, which are their biogenetic precursors [compounds (XX) and (XXI)]:[34]

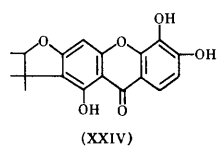

(XX) (XXI)

Partial cyclisation of the isoprenyl chain can lead to the formation of compounds containing simultaneously both the pyran ring and an alkenyl substituent [compound (XII)]:[35]

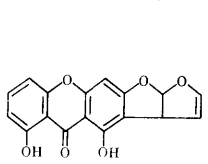

(XXII)

Furanoxanthones have been discovered in nature at the beginning of the 1970's. They have a very limited distribution and have been isolated from certain plants of the family Guttiferae and also from the mycelia of lower fungi. Mainly dihydrofuranoxanthones with a single furan ring [compounds (XXIII) and (XXIV)] are encountered in plants of the family Guttiferae[36,37]:

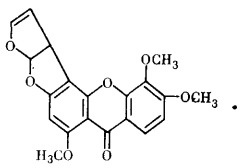

(XXIII)


(XXIV)

The mycelia of lower fungi (certain *Aspergillus* species) contain condensed furanoxanthones [compounds (XXV) and (XXVI)]:[38,39]



(XXV)



(XXVI)

This class of natural xanthones is at present only just beginning to be investigated.

III. CHEMOTAXONOMY OF NATURAL XANTHONES

The distribution and quantitative compositions of natural xanthones have chemotaxonomic importance. A correlation has been found for higher plants between the nature of the substituents in the xanthone ring, their relative positions, and the assignment of the plants to specific families[3,40,41].

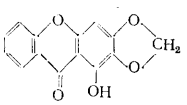
The distribution of xanthones in the family Gentianacae has been studied in greatest detail from this standpoint. Thus the presence of xanthones is characteristic of plants of the genera *Enicostemma, Hoppea, Canscora, Gentiana, Swertia, Halenia, Eustoma, and Frasera.*[42–45].

The importance of polyhydroxyxanthones as a chemotaxonomic marker is mainly limited to the genera *Swertia* and *Gentiana*, where xanthones are encountered most frequently. Thus the distribution of xanthone glycosides has been investigated in very great detail within the limits of individual sub-families of the genus *Gentiana*. Studies have shown that the plants belonging to different sub-families have as a rule a specific set of xanthones and in addition individual plant species within the limits of one sub-family can contain a xanthone glycoside specific only to the given species. For example, the presence of 7,8-dihydroxy-3-methoxy-1-*O*-primeverosylxanthone, 7-hydroxy-3,8-dimethoxy-1-*O*-primeverosylxanthone, and 3,7,8-trimethoxy-1-*O*-primeverosylxanthone is characteristic of the majority of plants in the *Cyclostigma* section. At the same time gentiabavarutinoside (7-*O*-acetylrutinosyl-1,8-dihydroxy-3-methoxyxanthone), discovered in *Gentiana bavarica* L., is absent from the other species of the *Cyclostigma* section investigated. At the same time *Gentiana verna* L. contains 8-*O*-glucosyl-1,7-dihydroxy-3-methoxyxanthone, the only glycoside with the carbohydrate substituent in the 8-position within the limits of the sub-family[3,30,46]. The mode of substitution in the xanthone ring is specific to each sub-family. Thus xanthones with substituents in the 1,3,7,8-positions predominate in the *Cyclostigma* sub-family, whereas 1,3,5,8- and 1,3,4,5,8-substituted xanthones predominate, for example, in plants of the *Amarella* sub-family[47]. The presence of 1-hydroxy-7-methoxy-3-*O*-primeverosylxanthone is characteristic of plants of the sub-family *Coelanthe*[48].

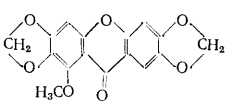
An extremely important chemotaxonomic feature of plants in the family Guttiferae is the presence of pyranoxanthones and xanthones with isoprenyl substituents.

The quantitative compositions of xanthones in plants of the genera *Garcinia*[49], *Calophyllum*, and *Kielmeyera*[50,51] have been studied in greatest detail.

Xanthones containing the methylenedioxy-group are encountered in nature comparatively rarely and their presence in plants is an extremely interesting chemotaxonomic feature. Xanthones with the methylenedioxy-group have been discovered in plants of the families Polygalaceae and Guttiferae. In plants, xanthones with this structure are accompanied as a rule by polyhydroxyxanthones which are partially or completely methylated. In the family Polygalaceae, mono- and bis-methylenedioxy-derivatives of xanthone have been discovered in plants of the genus *Polygala* [compounds (XXVII) and (XXVIII)]:[52–55]

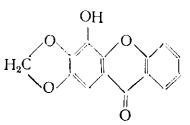


(XXVII)

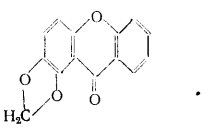


(XXVIII)

In the family Guttiferae xanthones with this structure are encountered in representatives of the genera *Caraipa*[56,57] and Kilelmeyera,[58–61] xanthones with the methylenedioxy-group in the *A* ring predominating in plants of the genus *Kilelmeyera* [compounds (XXIX) and (XXX)]:



(XXIX)



(XXX)

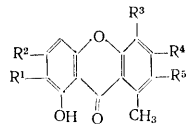
Among all the xanthone glycosides known at the present time, mangiferin is most widely distributed in nature. It has been discovered in plants of almost 20 families[1,v,62,63]. Plants of the families Gentianaceae, Fabaceae, and Iridaceae have the highest content of mangiferin. However, the attempts to establish a regularity in the distribution of mangiferin in plants within the limits of the sub-families of the genus *Gentiana* have not been successful, since mangiferin has been discovered in plants of almost all the sub-families.

Among plants of the family Iridaceae, mangiferin has been sought in various Iris species[64,65]. Although specimens with a very high mangiferin content (1–2.7%) are encountered among the plants of the Iris species investigated, its presence in plants of individual sections shows no particular regularity[64]. The studies on plants of the genus *Hedysarum* (the family Fabaceae) were more successful. Investigations were made of 26 different species belonging to five sub-families of the genus *Hedysarum* (representatives of the sub-family *Spinosissima* were not investigated, since they are virtually not encountered on the territory of the USSR). Mangiferin was detected in 12 plant species belonging to the sub-family *Obscura* and in one plant species belonging to the sub-family *Subacaulia*[62]. Among plants of this sub-family, mangiferin was also detected in *Hedysarum denticulatus* Rgl.[66]. Thus, among plants of the genus *Hedysarum*, a relation is observed between the content of mangiferin and the assignment of the plant to a particular sub-family.

It is also of particular interest to note that, among all the plants of the family Guttiferae investigated at the present time, mangiferin is present mainly in plants of the genus *Hypericum*[63,67]. The systematic study of the mangiferin content in plants of this species is only just beginning.

The structural features of lichen xanthones exhibit a definite regularity: the substituents in the xanthone ring are in the 1-, 3-, 6-, and 8-positions, the 8-position is occupied by the methyl group, the 1-position is occupied by the hydroxy-group, and the 3- and 6-positions are occupied by methoxy-groups [compound (XXXIa)]. In the study of lower plants, lichens were found to possess a novel property consisting in their ability to biosynthesise chloro-xanthones. Chlorine atoms occupy the 2-, 4-, 5-, and 7-positions in the xanthone ring. Di- and tri-chloro-xanthones are encountered most frequently, the tetra- and mono-chloro-derivatives being rarer [compounds (XXXI, b

and c)]:[68-71]



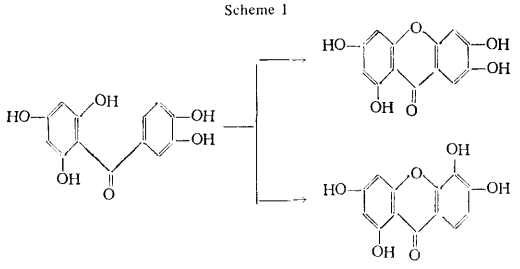
(XXXI)

(a) $R^1=R^3=R^5=H$, $R^2=OCH_3$, $R^4=OH$;
(b) $R^1=R^5=Cl$, $R^3=H$, $R^2=R^4=OCH_3$;
(c) $R^1=R^3=R^5=Cl$, $R^2=OCH_3$, $R^4=OH$.

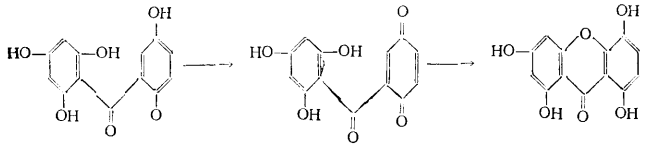
IV. BIOGENESIS OF XANTHONES

At the present time numerous studies on the biogenesis of xanthones have been described in the literature[2,3,72-74]. In higher plants the xanthone compounds with oxygen-containing substituents are biosynthesised by a mixed shikimate–acetate pathway, i.e. intermediates based on shikimic and acetic acid are condensed with formation of polyhydroxybenzophenones, the intramolecular transformations of which lead to the formation of xanthones. The possible mechanisms of such intramolecular transformations are presented in Schemes 1–4.

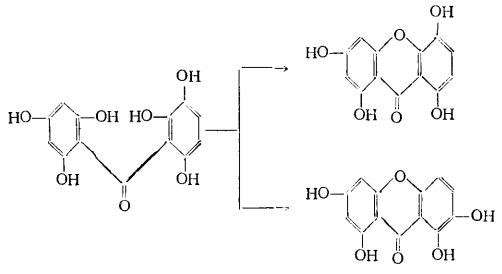
Scheme 1



Scheme 2

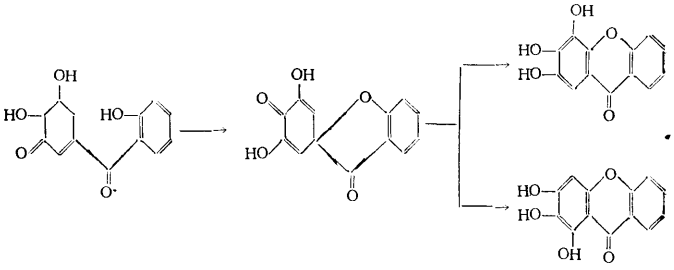


Scheme 3



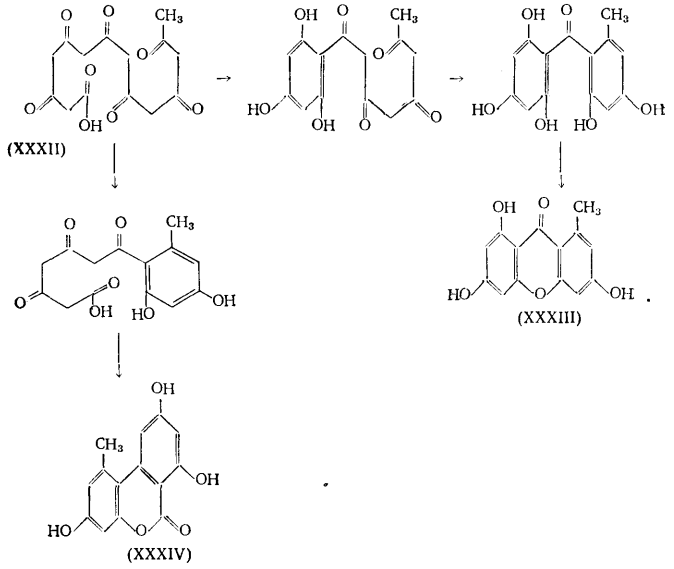
Thus the xanthone structures can be obtained from benzophenones via direct phenolic oxidative addition (Scheme 1), via a quinone stage (Scheme 2), by the dehydration reaction between the OH groups of the ring formed by the acetate mechanism and the ring formed by the shikimate mechanism (Scheme 3), and finally via a spirodiene structure with its subsequent transformation into the xanthone (Scheme 4).

Scheme 4



There exist data showing that direct phenolic oxidation of hydroxybenzophenones predominates in higher plants. The formation of xanthones from compounds having the spirodiene structure is more characteristic of certain microorganisms, which is confirmed by the joint presence of spirans and xanthones in the latter[50]. In higher plants xanthones have not been isolated together with spirans[2].

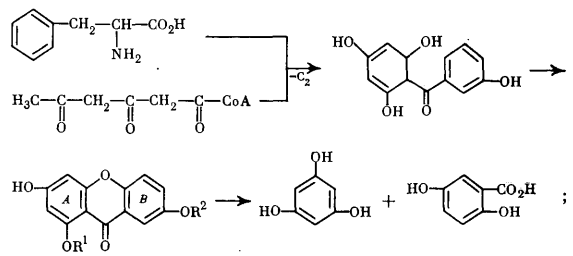
The same workers pointed out previously[2] the possible involvement of compounds of the polyketone type in the mechanism of the formation of hydroxybenzophenones. In the study of the biogenesis of lichen xanthones by the chemical synthetic method, the involvement of the poly-β-ketone structure (XXXII) in the formation of norlichexanthone (XXXIII) was demonstrated[75]:



The above scheme shows that there exist two possible reaction pathways for compound (XXXII): as a result of one of these there is a possibility of the formation of the pyranocoumarin (XXXIV), while the other leads to norlichexanthone (XXXIII). However, in the lichens investigated a pyranocoumarin having the above structure was not detected and the intramolecular transformations of compound (XXXII) in lichens therefore lead to the formation of the xanthone structure.

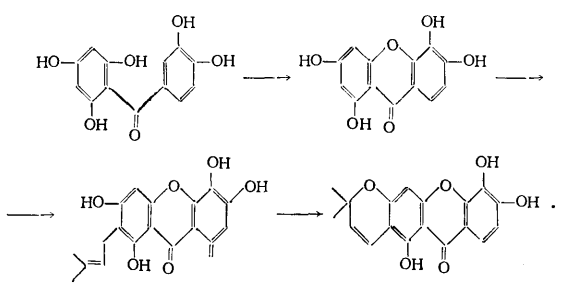
In order to demonstrate the validity of the hypothesis that hydroxybenzophenones are biosynthesised from shikimic acid derivatives and polyhydroxyphenols formed via the acetate pathway, [^{14}C]phenylalanine was injected into *Gentiana lutea* L.[72]. The xanthone derivatives gentisin (XXXV) and isogentisin (XXXVI), containing, as shown by

the analysis of the pyrolysis products, the radioactive label in the *B* ring, were then isolated from the plant:



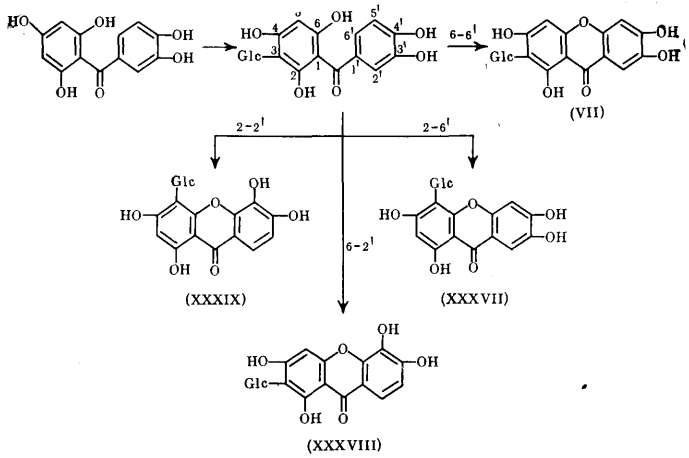
CoA = coenzyme A, $R^1 = CH_3$, $R^2 = H$; $R^1 = H$, $R^2 = CH_3$.

In the study of the biogenesis of pyranoxanthones and xanthones containing isoprenyl derivatives, it was established that the isoprenyl substituent is introduced in the *ortho*- or *para*-position relative to the OH group after the formation of the xanthone structure, this being followed by the closure of the isoprenyl chain at the neighbouring hydroxy-group, which leads to the formation of a pyran ring:



The validity of the assumptions made is confirmed by the simultaneous presence in plants of benzophenone precursors and the corresponding "daughter" xanthones with isoprenyl substituents and pyran rings[34,51,76].

The possible pathways in the biosynthesis of xanthone glycosides have been investigated by introducing labelled precursors of the intermediate benzophenones into *Anemarrhena asphodeloides* Bunge[73]. It was found that glycosylation precedes the formation of the xanthone structure; there is then a possibility of four versions of the closure of the γ-pyrone ring (see below). The proposed mechanism has been confirmed by the isolation of mangeriferin and isomangeriferin (XXXVII) from *Anemarrhena asphodeloides* Bunge[17] and of 2-*C*-β-D-glucopyranosyl-1,3,5,6-tetrahydroxyxanthone (XXXVIII);[20] only 4-*C*-glucosyl-1,3-5,6-tetrahydroxyxanthone (XXXIX) has not so far been detected in nature.



V. METHODS FOR THE DETERMINATION OF THE STRUCTURES OF XANTHONES

For the isolation of xanthones, the plant starting material is ground and extracted by the usual methods using, as a rule, solvents with increasing polarity: petroleum ether, chloroform, and methanol[77-79], hexane and acetone[80], ether, acetone, and ethanol[81], etc. Xanthones are extracted usually from lichens using acetone as the solvent, this being followed by treatment of the evaporated extracts with alkali[82-84].

When the starting material is treated with non-polar solvents, mainly the aglycones are extracted. Glycosides are usually extracted with polar solvents after the separation of the total aglycones. The compounds are purified by recrystallisation and also by column and thin-layer chromatography[3]. Apart from thin-layer and column chromatography, gas–liquid chromatography of the TMS-derivatives of xanthones[89] as well as high-pressure liquid chromatography[90,91] have been used successfully for the qualitative and quantitative analysis. The separation by liquid chromatography has been investigated in relation to the compounds obtained from plants of the genus *Gentiana*. A satisfactory separation of the positional isomers has been achieved.

The structures of xanthones are nowadays determined using extensively physicochemical methods such as ultraviolet and infrared spectroscopy, ^1H NMR, mass spectrometry, and X-ray diffraction analysis[39,92].

1. Ultraviolet Spectroscopy

This method is used mainly to determine the positions of the OH groups in the xanthone nucleus. It has been established that the ultraviolet spectra of all natural xanthones are characterised by four intense bands regardless of structural differences: $\lambda_{max}(E)$ = 230–260 nm (20000 – 50000), 260–350 nm (6000 – 28000), 285–300 nm (3000 – 10000), and 325–395 nm (3000 – 12000) [4] (Fig.1).

Sometimes the number of bands increases to five or diminishes to three, but the characteristic spectrum with a specific ratio of the intensities of the short-wavelength and long-wavelength maxima is in general retained. Thus, a given substance can be assigned to the class of xanthones

on the basis of the nature of the absorption in the ultraviolet. In order to determine the location of the OH groups, ionising and complex-forming additives are employed. The ionising additives are usually sodium acetate, methoxide, or ethoxide or caustic alkalis. Thus, in the presence of a free OH group in the 3- or 6-position, the ultraviolet spectrum of the compound in the presence of sodium acetate exhibits a bathochromic shift of the long-wavelength maximum in the range 300–330 nm.

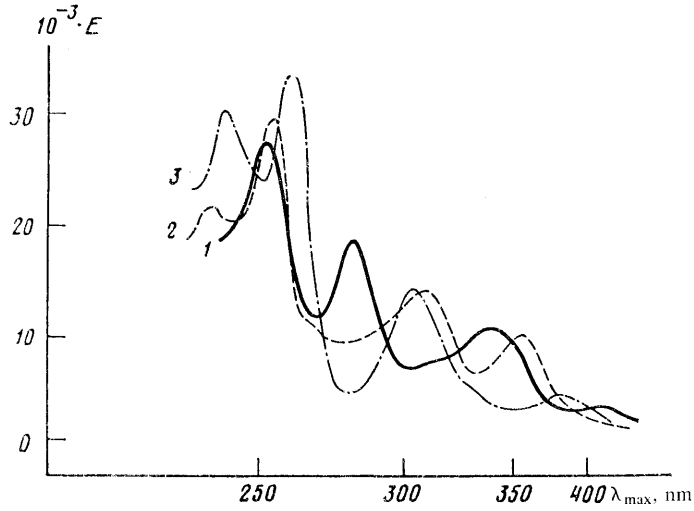


Figure 1. Ultraviolet spectra of xanthones with different modes of substitution in the nucleus (solvent–methanol): *1*) 1,5,8-trihydroxy-3-methoxyxanthone; *2*) 1,3,6,7-tetrahydroxyxanthone; *3*) 1-hydroxy-3,7,8-trimethoxyxanthone.

The OH groups in the 1- and 8-positions can be detected and the presence of the *ortho*-dioxy-group in the molecule can be demonstrated with the aid of complex-forming additives. $AlCl_3$ and boric acid in the presence of sodium acetate are most widely employed for such purposes. The presence of OH groups in the 1- and 8-positions is indicated by the bathochromic shift of the short-wavelength maximum in the range 260–335 nm by approximately 20 nm in the presence of $AlCl_3$. Despite the fact that in the presence of $AlCl_3$ the bathochromic shift of the long-wavelength maximum is about 60 nm, the more intense short-wavelength maximum is used in the test for the presence of the OH groups in the 1- and 8-positions[93,94]. The *ortho*-dioxy-groups also form a compound with $AlCl_3$, but such a complex decomposes in the presence of hydrochloric acid. Boric acid in the presence of sodium acetate, which causes a bathochromic shift of the long-wavelength maximum, is used in the test for the *ortho*-dioxy-groups.

The addition of sodium methoxide to an analytical solution of xanthones can be used to detect vicinal OH groups. This constitutes the optical version of the Bargellini reaction and is manifested by the absence from the ultraviolet spectrum of the four absorption maxima characteristic of the xanthone structure[95,96] (Fig. 2).

2. ^{1}H NMR

^{1}H NMR is a method which yields most information for the determination of the structures of xanthones as regards the nature and relative positions of the substituents. There have been a number of studies in which the proton spectra of hydroxy- and methoxy-xanthones, recorded in different solvents, were analysed[97–99].

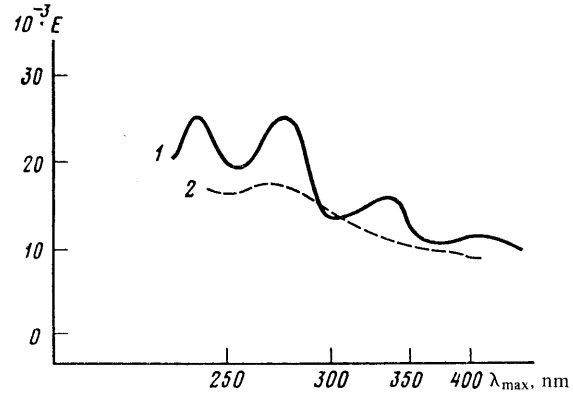


Figure 2. Changes in the ultraviolet spectrum of swertiaperennin (1,2,3-trihydroxy-7,8-dimethoxyxanthone) in the presence of $NaOCH_3$ (solvent–methanol): *1*) swertiaperennin; *2*) ditto plus $NaOCH_3$.

The aromatic protons of xanthones are manifested in the range 6.00–8.05 p.p.m. If the compound is a glycoside, then also the aliphatic protons of the carbohydrate substituents are observed in the range 3.00–5.60 p.p.m.[79] The protons of the aromatic methoxy-groups give rise to signals in the range 3.80–4.10 p.p.m. The ^{1}H NMR spectrum of a hydroxyxanthone recorded in dimethyl sulphoxide exhibits in the range 12–14 p.p.m. the signal of the protons of the OH groups in the 1- and 8-positions, while the proton signals of the OH groups in the other positions of the xanthone nucleus are displaced upfield to 9–11 p.p.m. The ^{1}H NMR of acetylxanthones has been used successfully recently for the determination of the structures of xanthones[79,100]. Thus signals in the range 2.40–2.50 p.p.m. (solvent–chloroform) indicate the presence of the acetyl substituent in the 1- and 8-positions, while the acetyl substituents in the other positions of the aromatic nucleus are manifested in the range 2.30–2.35 p.p.m. The signals of the protons of the aliphatic acetyl groups are displaced to a still stronger field—1.90–2.20 p.p.m. (Fig. 3).

The protons of the aromatic ring containing the chelate hydroxyl (OH groups in the 1- or 8-position) give rise to signals in a stronger field than the corresponding protons of the ring without a chelate hydroxyl. This can be accounted for by the higher electron density in the ring owing to chelation. In the case of glycosides this effect is observed most effectively in solution in deuteriated DMSO.[4]

The signals of the protons of the methyl groups of the isopropenyl substituent in the xanthone molecules are usually manifested as three-proton singlets in the range 1.1 to

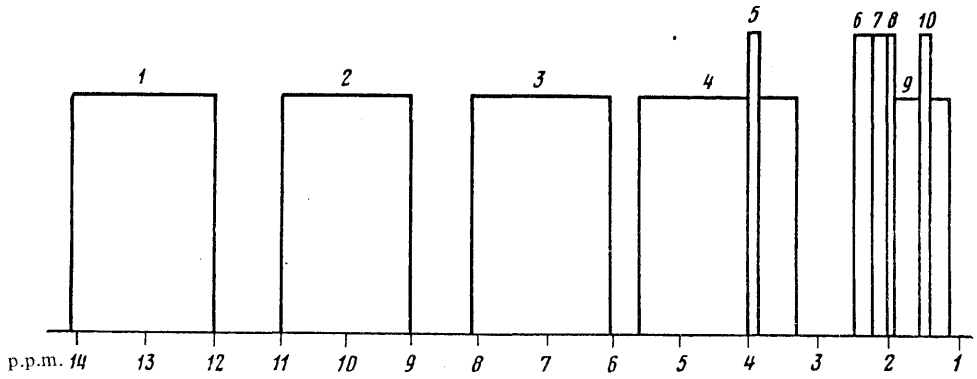


Figure 3. The proton chemical shifts in the ^1H NMR spectra of xanthone derivatives: *1*) OH groups in the 1- and 8-positions; *2*) OH groups in the 2–7-positions; *3*) aromatic protons; *4*) aliphatic protons; *5*) protons of aromatic CH_3O groups; *6*) protons of the CH_3OCO group in the 1- and 8-positions; *7*) protons of the CH_3OCO group in the 2–7-positions; *8*) protons of the carbohydrate component; *9*) protons of the $(CH_3)_2C=$ group; *10*) protons of the $(CH_3)_2C$ group.

1.8 p.p.m.[5]. The signals of the protons in the angular methyl groups in the molecule of a pyranoxanthone are observed in the range 1.4–1.5 p.p.m. (Fig.4).

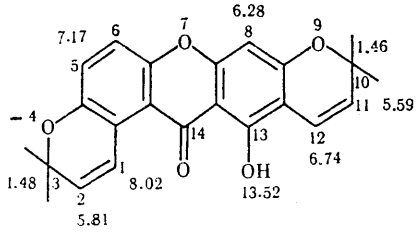


Figure 4. Distribution of the proton chemical shifts (p.p.m.) in pyranoxanthone[101].

Fig.4 shows that the chemical shifts of the protons in the 2- and 11-positions of the pyran ring are displaced upfield relative to the signals of the protons in the 1- and 12-positions, which can be accounted for by the electron-donating influence of the protons of the angular methyl groups at the C(3) and C(10) atoms.

The problem of the site where the carbohydrate component is attached frequently arises in the determination of the structures of xanthone glycosides. The exhaustive methylation method with subsequent hydrolysis of the glycosides proved to be extremely effective for the solution of this problem. Furthermore, direct comparison of the spectra of the glycosides and their aglycones yields information about the site of addition of the carbohydrate component to the xanthone nucleus. The spin–spin interaction constant for the signal of the anomeric protons of the glycosidic centre yields information about the nature of the glycosidic linkage.

The Overhauser effect has also been used to elucidate the positions of the substituents in the xanthone nucleus[102].

^{13}C NMR has been used successfully in recent years for the determination of the structures of xanthones[103–105]. The ^{13}C NMR spectra of polyhydroxyxanthones (aglycones, *O*- and *C*-glycosides) have been investigated. ^{13}C NMR spectroscopy is of special diagnostic importance for the determination of the nature of the relative positions of the monosaccharides in diglycosidic substituents[4].

3. Infrared Spectroscopy

The assignments in the infrared spectra of xanthones are complicated by the strong interaction of the vibration of the carbonyl group and the C=C bonds of the γ-pyrone ring. According to some data[106], the highest-frequency 1660 to 1670 cm^{-1} band in the range 1500–1700 cm^{-1} has been assigned to the vibrations of the carbonyl group. However, further investigations showed that this band is due to the vibrations of the C=C bonds of the γ-pyrone ring, while the vibrations of the C=O group give rise to a band in the range 1620–1640 cm^{-1}.[4,107]

Santesson[108] investigated the infrared spectra of lichen polyhydroxyxanthones in the range 1500–1700 cm^{-1}.[108] It was found that the frequency of the band corresponding to the C=O group is reduced by 15–25 cm^{-1} after the introduction of an OH group in the 1-position. This effect is evidently due to chelation, since alkylation or esterification of the OH group returns the frequency of the C=O group to its previous value.

Klimenko et al.[109] carried out a theoretical calculation of the vibrations of the xanthone molecule; the symmetry of certain vibrations was determined from the dichroism of the infrared bands.

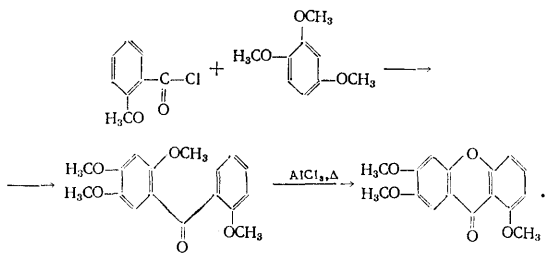
The band in the range 3200–3500 cm^{-1} in the infrared spectra of hydroxyxanthones is due to the vibrations of the chelate hydroxyls, while the bands in the range 1500 to 1600 cm^{-1} are assigned to the vibrations of the aromatic C=C bonds. The region below 1500 cm^{-1} is specific to each compound and can be used successfully for the identification of xanthones.

Mass spectrometry has been used widely in recent years for the determination of the structures of xanthones. Aritomi et al.[110] used this method in the study of the fully acetylated derivatives of mangiferin and isomangiferin. The mass spectra of xanthone *O*-glycosides do not contain the characteristic molecular peak, but the molecular peak of the aglycone (M^+) and the nature of its fragmentation yield information about the structure of the substance. Thus the mass spectra of hydroxyxanthones usually exhibit signals due to the fragments (M^+-OH), (M^+-CO), and (M^+-CHO). When one or several methoxy-groups are introduced into the xanthone, its mass spectrum shows signals due to the fragments (M^+-CH_3), (M^+-CH_2O), and (M^+-CH_3CO).[111,112] The presence of a weak molecular peak has been noted in the fully methylated derivatives of xanthone *O*-glycosides[4].

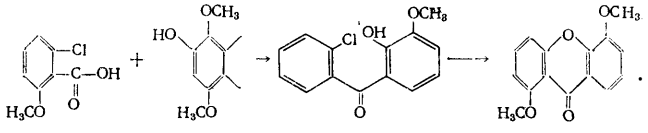
VI. SYNTHETIC CHEMICAL METHODS IN THE STUDY OF NATURAL XANTHONES

The preparation of synthetic xanthone derivatives was used previously only to confirm the structures of natural xanthones[1]. At the present time the applications of synthesis in the study of natural xanthones have expanded and make it possible to solve certain biogenetic problems. Furthermore, chemical synthesis is used to prepare biologically active natural xanthones.

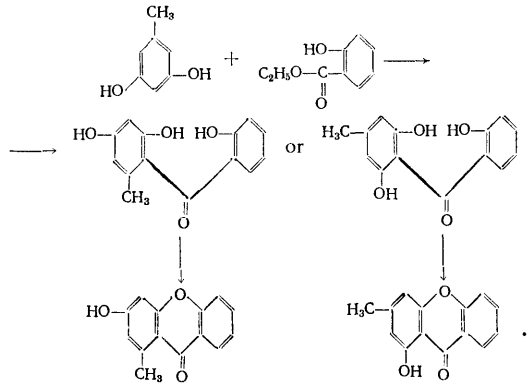
One of the common reactions used to synthesise xanthones is the Friedel–Crafts reaction between aromatic carboxylic acid chlorides and polyhydroxyphenols[113–116]. The corresponding benzophenone is an intermediate. The benzophenone cyclises to the xanthone on heating the reaction mixture to 200–220 °C.[117] If polymethoxyphenols are involved in the reaction, then the benzophenone formed as an intermediate undergoes partial demethylation in the *o*-position relative to the carbonyl group. Aluminium chloride is usually employed as the dimethylating agent[113,118]:



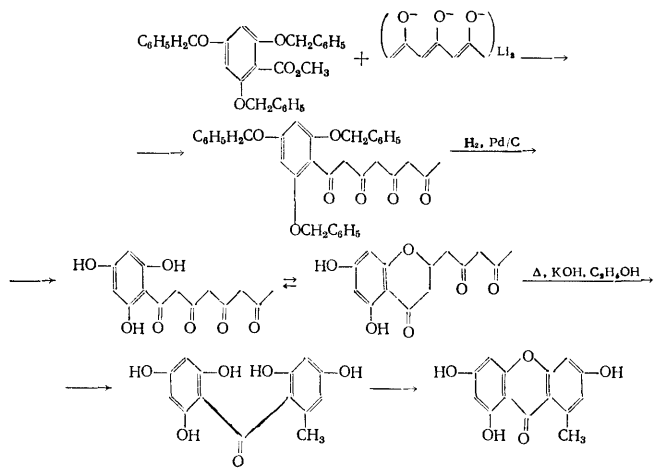
If *o*-chlorobenzoic acids are used in the reaction, then the cyclisation of benzophenone to the xanthone takes place under milder conditions[117]:



Xanthones can be obtained by the cyclocondensation of phenols with methyl or ethyl *o*-hydroxyarenecarboxylates in diphenyl ether[119]:



In the modelling of processes occurring in the biogenesis of xanthones in lichens, an aldol-type cyclisation of 1-(2,4,6-trihydroxyphenyl)octane-1,3,5,7-tetraone was used to prepare natural xanthones. The corresponding benzophenone is formed as an intermediate, undergoing subsequent dehydration[75]:



(XXIX)

The acid-catalysed cyclocondensation of hydroxy-derivatives of diphenyl ether and phosgene[120] and also the intramolecular cyclisation of 2-carboxy-derivatives of diphenyl ether[121] can be used to synthesise polyhydroxy-xanthones.

A reaction involving the synthesis of xanthones from ω-acetoxy-2-acylcyclohexanones has been described[122].

The most convenient method of synthesising pyrano-xanthones has been developed by Locksley and coworkers[123–126]. It is based on the synthesis of 2-alkyl-1-hydroxyxanthones from 1-allyloxyxanthones by the Claisen rearrangement with subsequent modification of its side chain. The derivatives of 1-hydroxy(3-methylbut-2-enyl)xanthones obtained in this way are treated with hydrobromic or hydriodic acid. Depending on the reaction conditions, angular or linear pyranoxanthones are obtained.

The syntheses of xanthone glycosides have been investigated. The addition of the glycosidic residue to the aglycone takes place via a reaction involving the condensation of the aglycone with acetyl-α-D-glycosyl bromide, the formation of both *C*- and *O*-glycosides being possible depending on the reaction conditions. Thus, when the

reaction is carried out in methanol in the presence of sodium methoxide, the hydrocarbon substituent adds to the aglycone via a C—C bond[118]. *O*-Glycosides are formed when the reaction is carried out in pyridine in the presence of silver carbonate[127,128].

VII. PHARMACOLOGY OF XANTHONES

Plants containing xanthones have been used for a long time in Soviet medicine[129,130]. Current research has shown that xanthones exhibit an extremely wide variety of pharmacological activities. Antidepressant, antimicrobial, cardiotonic, diuretic, and antiviral activities of xanthones have been noted.

The stimulating activity on the central nervous system (CNS) and the antitubercular activity of certain natural and synthetic derivatives of xanthones have been investigated in greatest detail.

The search for natural compounds with antidepressant activity has been prosecuted mainly among plants of the family Gentianaceae[131]. Xanthones differing in the number and relative positions of hydroxy- and methoxy-groups have been the object of study. It was noted that the aglycones[130] and also the xanthone *C*-glycoside mangiferin[132] have the most marked antidepressant activity. The fact that the xanthone *O*-glycosides have in fact a depressant activity on the CNS and an anticonvulsant activity proved to be of very great interest[133]. However, natural xanthones do not exhibit a clear-cut relation between the nature of the antidepressant activity and structure. In order to investigate in greater detail the dependence of the nature and strength of the antidepressant effect on the structure, a series of semisynthetic methoxy-amino- and chloro-xanthones substituted in the 2-, 3-, 4-, and 6-positions were screened[134,135]. The introduction of the hydroxy-group in the 3-position increased the activity of the xanthone compound and substitution of the 6-position by a chlorine atom greatly altered the nature of the antidepressant activity and increased the toxicity of the compound.

The studies on the antitubercular activity of natural xanthones proved to be extremely fruitful[136,137]. Thus, in the investigation of xanthones from the ethanol extract of *Canscora decussata* Achult, it was observed that the sum of the aglycones has a more marked tuberculostatic activity than the xanthones and the glycoside mangiferin[138]. In order to investigate in greater detail this behaviour, a study was made of fourteen natural and semisynthetic xanthones differing in the positions of the hydroxy- and methoxy-groups and in the presence or absence of a carbohydrate substituent[139]. Experimental results revealed a definite relation between the type of substitution in the xanthone nucleus and the tuberculostatic activity: the activity of xanthones is manifested in the presence of hydroxy- or methoxy-groups in the 1,3,5,6- or 1,3,8-positions in the xanthone nucleus. With increase of the number of hydroxy-groups in the above positions, the activity rises. Thus 1,3,5,6,7- and 1,3,6,7,8-pentahydroxyxanthones proved to be the most active. When a carbohydrate substituent is introduced into the molecule, the activity falls.

3,6,8-Trihydroxy-1-methylxanthone, with appreciable antibacterial activity, has been isolated from the metabolic products of *Penicillium patulum*.[140]

Studies on the antitumour activity of natural xanthones have been started in recent years. Thus 1,6-dihydroxy-xanthones and 1,3-dihydroxyxanthones among the 18 natural xanthones isolated from *Mammeae americana* were found to have an appreciable inhibiting activity in relation to sarcoma 180.[141]

1,8-Dihydroxy-3-methylxanthone, which exhibits an antifungal activity, was obtained from the defatted seeds of *Cassia tora*. The compound manifested an activity in relation to certain *Trichophyton*, *Microsporum*, and *Geatrichum* species in the presence of 100 mg ml^{-1} of L-ascorbic acid as the antioxidant[10]. An antifungal activity in relation to certain *Fusarium* species has also been noted in mangiferin[142,143].

Mangiferin is the most thoroughly investigated xanthone derivative from both physicochemical and pharmacological points of view. Apart from its stimulating effect on the CNS,[132] it exhibits cardiotonic and diuretic effects[144], influences the water metabolism[145], and has some anti-tubercular activity[138,142,143]. Medicinal forms of this substance have been developed: tablets, suppositories, and solutions for injection[144].

The results of a pharmacological study of mangostin [3,6,8-trihydroxy-2-methoxy-1,7-di(3-methylbut-2-enyl)-xanthone] and its derivatives were published in 1979.[146] Almost all the compounds have a depressant effect on the CNS and in addition the 3,6-di-*O*-glucoside of mangostin has a stimulating effect on heart muscle and increases blood pressure. Mangostin, 1-isomangostin, and mangostin triacetate have an appreciable anti-inflammatory activity, manifested even in the case of bilateral adrenalectomy in rats; mangostin has also been found to have an antiulcer activity.

Together with the study of natural xanthones, investigations have been made in recent years of the pharmacological properties of synthetic xanthone derivatives in order to carry out specific syntheses of compounds with a specified spectrum of pharmacological activity.

The synthesis of various alkylaminoxanthones constitutes the most interesting trend. Thus Fleming and coworkers[147] synthesised a series of di(aminoacetyl)xanthones which act against certain viruses affecting warm-blooded animals, including the viruses of encephalomyocarditis, the viruses of the herpes group, etc.

Baum[148] investigated the antiarrhythmic activity of bis(dialkylamino)ethoxyxanthones in experiments on dogs. The highest activity was noted in 1,6-bis-2-di-(isopropenylamino)ethoxyxanthone.

Studies on the pharmacological activity of various derivatives of xanthone-2-carboxylic acid, which proved to be active in asthmatic conditions, have been of very great interest[149]

* * *

The studies carried out hitherto on natural xanthones undoubtedly demonstrate their enormous value as regards the creation of new medicinal preparations. The continually growing interest in this type of compound is indicated by the fact that in recent years studies have begun on the mechanism of the pharmacological activity of xanthones at the biochemical level. Thus, in connection with the investigation of the stimulating effect of natural xanthones on the CNS, detailed studies have been made of the mechanism of the inhibition of monoamino-oxidase by isogentisin and its 3-*O*-glucoside.[150] The relation between the structures of xanthones and their ability to inhibit AMP phosphodiesterase has been investigated[151].

There is no doubt that further more profound studies on these lines will extend the pharmacological applications of natural xanthones.

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Department of Pharmacognosy,
Sechenov Ist Moscow Medical Institute