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TRIOXYGENATED NATURALLY OCCURRING XANTHONES*

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Key Word Index—xanthones; pharmacological activity; higher plants; fungus; lichen; biosynthesis.

Abstract—This review discusses the chemistry of 127 trioxxygenated xanthones occurring in six families, 37 genera and 107 species of higher plants, and 55 which are fungal or lichen metabolites. The value of these substances in connection with their pharmacological activity and the therapeutic use of some species is considered. The structural formulae of 130 compounds and their natural distribution are given. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Xanthones are secondary metabolites commonly occurring in a few higher plant families, fungi and lichen (Table 1). Their high taxonomic value in such families and their pharmacological properties have provoked great interest [1]. The symmetrical nature of the xanthone nucleus, coupled with its mixed biogenetic origin in higher plants necessitates that the carbons be numbered according to a biosynthetic convention. Carbons 1–4 are assigned to the acetate-derived ring A, and carbons 5–8 to the shikimate-derived ring B [2]. The numbering system is based on xanthene-9-one (Fig. 1) as the basic skeleton [3] and in cases where only ring B is oxygenated the lowest numbers are used, except in the biosynthetic discussion [2].

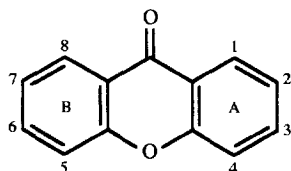


Fig. 1. Xanthone basic skeleton.

Classification

The xanthones isolated to date may be classified into five major groups: simple oxygenated xanthones, xanthone glycosides, prenylated and related xanthones, xanthonolignoids and miscellaneous [4]. The simple oxygenated xanthones can further be subdivided into six groups, according to the degree of oxygenation. Simple trioxxygenated xanthones, along with prenylated and related xanthones with the same degree of oxygenation, are listed in this review (Tables 2–10).

METHODS OF ISOLATION AND STRUCTURAL INVESTIGATION

Xanthones are commonly separated by chromatography on silica gel, using different solvent mixtures [5]. Xanthones are also separated and identified by comparison with authentic samples by TLC [6] and HPLC [7,8]. The structures of the simple oxygenated xanthones have been derived mainly from the UV, IR, mass spectral and NMR data of these compounds [9–12].

Xanthones can be detected by their colours in UV light with and without ammonia or by using a general phenolic spray [5]. The UV spectrum varies in a characteristic manner depending on the oxygenation pattern and, with the availability of a considerable amount of data, assignments can be readily made. In addition to the use of AlCl_3 shifts for chelated hydroxyl groups, sodium acetate, sodium hydroxide and boric acid shifts provide considerable information on the

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Table 1. Natural sources of trioxxygenated xanthenes

Gentianaceae		<i>Caraipa</i>	<i>C. costata</i> [94]
<i>Canscora</i>	<i>C. decussata</i> [42–44]		<i>C. grandifolia</i> [94]
<i>Centaurium</i>	<i>C. erythraeae</i> [259]	<i>Cratoxylon</i>	<i>C. cochinchinense</i> [95]
	<i>C. littorale</i> [259]	<i>Garcinia</i>	<i>G. buehneri</i> [96]
<i>Chironia</i>	<i>C. krebsii</i> [45]		<i>G. cowa</i> [97]
<i>Eustoma</i>	<i>E. grandiflorum</i> [46]		<i>G. eugenifolia</i> [80, 98]
<i>Fraseria</i>	<i>F. albicaulis</i> [47]		<i>G. forbesii</i> [99]
	<i>F. albomarginata</i> [48]		<i>G. gerrardii</i> [40]
<i>Gentiana</i>	<i>G. ciliata</i> [49]		<i>G. livingstonei</i> [100]
	<i>G. lutea</i> [50–54]		<i>G. mangostana</i> [101–107]
<i>Halenia</i>	<i>H. campanulata</i> [55]		<i>G. quadrifaria</i> [108]
<i>Hoppea</i>	<i>H. dichotoma</i> [56]		<i>G. subelliptica</i> [37, 109, 110, 260]
<i>Schultesia</i>	<i>S. lisianthoides</i> [261]		<i>G. xanthochymus</i> [111]
<i>Swertia</i>	<i>S. calycina</i> [258]	<i>Haploclathra</i>	<i>H. leiantha</i> [112]
	<i>S. chirata</i> [57]		<i>H. paniculata</i> [113, 114]
	<i>S. davida</i> [38]	<i>Hypericum</i>	<i>H. androsaemum</i> [115, 116]
	<i>S. hookeri</i> [58]		<i>H. balearicum</i> [117]
	<i>S. japonica</i> [59]		<i>H. brasiliense</i> [118]
	<i>S. mussotii</i> [60]		<i>H. calycinum</i> [115]
	<i>S. petiolata</i> [61]		<i>H. canariensis</i> [119]
	<i>S. patens</i> [62]		<i>H. degenii</i> [120]
	<i>S. speciosa</i> [63]		<i>H. ericoides</i> [121, 122]
			<i>H. inodorum</i> [123]
Guttiferae			<i>H. maculatum</i> [115]
<i>Allanblackia</i>	<i>A. floribunda</i> [64]		<i>H. mysorensis</i> [124–126]
<i>Bonnetia</i>	<i>B. dinizii</i> [65]		<i>H. perforatum</i> [115]
	<i>B. stricta</i> [66]		<i>H. reflexum</i> [1]
<i>Calophyllum</i>	<i>C. bracteatum</i> [67, 68]		<i>H. sampsonii</i> [127]
	<i>C. brasiliense</i> [69–71]	<i>Kielmeyera</i>	<i>K. candidissima</i> [128]
	<i>C. calaba</i> [67, 68, 72]		<i>K. coriacea</i> [26, 129, 130–134]
	<i>C. canum</i> [73]		<i>K. corymbosa</i> [71, 131, 132, 135]
	<i>C. cordato-oblongum</i> [74]		<i>K. excelsa</i> [136]
	<i>C. cuneifolium</i> [75]		<i>K. ferruginea</i> [132]
	<i>C. fragrans</i> [76]		<i>K. petiolaris</i> [136, 137]
	<i>C. inophyllum</i> [77–81]		<i>K. rubriflora</i> [133, 138]
	<i>C. neo-ebudicum</i> [82]		<i>K. rupestris</i> [139, 140]
	<i>C. ramiflorum</i> [83]		<i>K. speciosa</i> [71, 132, 133, 141–143]
	<i>C. scribblifolium</i> [84]	<i>Mammea</i>	<i>M. africana</i> [144]
	<i>C. soulattri</i> [75]	<i>Mesua</i>	<i>M. ferrea</i> [145–147]
	<i>C. thwaitesii</i> [67, 85]		<i>M. thwaitesii</i> [148]
	<i>C. tomentosum</i> [32, 86]	<i>Ochrocarpos</i>	<i>O. odoratus</i> [149]
	<i>C. trapezifolium</i> [87–89]	<i>Pentaphalangium</i>	<i>P. solomonse</i> [150]
	<i>C. walkeri</i> [85, 90]	<i>Pentadesma</i>	<i>P. butyracea</i> [151]
	<i>C. wightianum</i> [91]	<i>Platonia</i>	<i>P. insignis</i> [94]
	<i>C. zeylanicum</i> [92, 93]	<i>Psorospermum</i>	<i>P. febrifugum</i> [35, 36, 152–155]

position of hydroxyl groups in other locations [9, 13].

The use of IR spectroscopy in xanthone chemistry is limited in detecting the carbonyl stretching frequency [10, 14]. The effect of chelation on the IR carbonyl frequency of hydroxy-xanthenes may be useful in spectra of some substituted and extended xanthenes [15, 16]. The use of IR for detecting other functional groups, such as unchelated hydroxyl and methyl groups does not require comment [10, 17, 18].

By introducing lichen samples in a mass spectrometer via a direct inlet system, Santesson [19] obtained mass spectra of the volatile lichen substances. The method is well suited to the tentative identification of lichen xanthenes [18, 19]. Apart from discussion of the

mass spectra of lichen xanthenes, no systematic investigation on the electron-impact-induced fragmentation of xanthenes appears to have been made; however Arends *et al.* [12] did discuss this in the study of electron-impact-induced fragmentation of monohydroxy- and monomethoxyxanthenes [12]. Mass spectrometry has not been applied extensively to the study of naturally occurring xanthenes, but the mass spectral data have been very valuable for a preliminary examination [20].

The data obtained in proton magnetic resonance spectra should be of great value in characterizing and identifying naturally occurring xanthenes [21]. ¹H NMR spectroscopy has been used for determining the struc-

Table 1. (Continued)

<i>Rheedia</i>	<i>R. brasiliensis</i> [156]		<i>D. australiensis</i> [199]
	<i>R. gardneriana</i> [157–159]	<i>Haematomma</i>	<i>H. erythromma</i> [200]
<i>Symphonia</i>	<i>S. globulifera</i> [160–162]	<i>Lecanora</i>	<i>Lecanora</i> sp. [199]
<i>Tovomita</i>	<i>T. choisyana</i> [163]		<i>L. andrewii</i> [196]
	<i>T. excelsa</i> [164]		<i>L. behringii</i> [199, 201]
	<i>T. pyrifolium</i> [165]		<i>L. bolanderi</i> [196]
<i>Vismia</i>	<i>V. guaramirangae</i> [166]		<i>L. brocchia</i> [195, 199, 202]
	<i>V. micrantha</i> [167]		<i>L. capistrata</i> [196]
			<i>L. contractula</i> [199, 201]
Loganiaceae			<i>L. dispersa</i> [203]
<i>Anthocleista</i>	<i>A. djalonensis</i> [168]		<i>L. flavidopallens</i> [196]
			<i>L. flavo-pallencens</i> [196, 204]
Moraceae			<i>L. ingae</i> [196]
<i>Cudrania</i>	<i>C. cochinchinensis</i> [169–171]		<i>L. novomexicana</i> [19]
	<i>C. tricuspidata</i> [172–175]		<i>L. pinguis</i> [19]
<i>Maclura</i>	<i>M. aurantica</i> [176]		<i>L. populicola</i> [199, 201]
	<i>M. pomifera</i> [177–180]		<i>L. pruinosa</i> [196]
<i>Morus</i>	<i>M. insignis</i> [181]		<i>L. reuteri</i> [205]
			<i>L. rupicola</i> [19, 206]
Podostemaceae			<i>L. salina</i> [199, 201]
<i>Mourera</i>	<i>M. fluviatilis</i> [182]		<i>L. straminea</i> [205, 207–209]
			<i>L. sulphurata</i> [196, 199, 204]
			<i>L. vinetorum</i> [199]
Polygalaceae			<i>L. carpathica</i> [19]
<i>Monnina</i>	<i>M. obtusifolia</i> [183]	<i>Lecidea</i>	<i>L. querneae</i> [19]
<i>Polygala</i>	<i>P. arillata</i> [184]		<i>L. asema</i> [195]
	<i>P. nyikensis</i> [41]	<i>Lecidella</i>	<i>L. meiococca</i> [199]
	<i>P. tenuifolia</i> [185, 186]		<i>L. subalpica</i> [195]
	<i>P. triphylla</i> [187]		<i>L. vorax</i> [199]
	Fungi	<i>Melanaria</i>	<i>M. melanospora</i> [196]
	<i>Aspergillus versicolor</i> [188–190]	<i>Micarea</i>	<i>M. austrotemaria</i> [204]
	<i>Bipolaris sorokinian</i> [191]		<i>M. isabellina</i> [199, 204, 210]
	<i>Helminthosporium ravenelii</i> [192]	<i>Parmelia</i>	<i>P. formosana</i> [211]
	<i>H. turcicum</i> [192]	<i>Pertusaria</i>	<i>Pertusaria</i> sp. [196, 200]
	<i>Penicillium patulum</i> [193]		<i>P. cicatricosa</i> [199]
			<i>P. flavicans</i> [212]
	Lichen		<i>P. hymeneae</i> [19]
<i>Arthothelium</i>	<i>A. pacificum</i> [19]		<i>P. lutescens</i> [19]
<i>Buellia</i>	<i>Buellia</i> sp. [194, 195]		<i>P. pycnothelia</i> [199]
	<i>B. glaziouana</i> [196]		<i>P. sulphurata</i> [213]
<i>Dimelaena</i>	<i>Dimelaena</i> sp. [197, 198]	<i>Rinodina</i>	<i>R. thiomela</i> [210, 214]

ture of substituents and for locating aromatic protons by comparison with reference data and by analysis of spin–spin coupling. A closer scrutiny of chemical shifts of the aromatic protons allows prediction of the oxygenation pattern [22]. There are detailed NMR results for this class of compounds [23].

^1H and ^{13}C NMR spectroscopies are the most useful tools in structure elucidation of xanthenes [24]. The ^{13}C NMR spectra of a great number of naturally occurring xanthenes are reported and all chemical shifts assigned [23, 25, 26]. Hambloch and Frahm [27] introduced a computer program called SEOX 1, which rapidly identifies unknown xanthenes with the help of additivity rules that represents a remarkable facility in structure elucidation.

BIOACTIVITIES OF XANTHONES

The study of xanthenes is interesting not only for the

chemosystematic investigation but also from the pharmacological point of view. Xanthenes possess an antidepressant action and an antitubercular activity, while xanthone glycosides have a depressant action. A choleric, diuretic, antimicrobial, antiviral and cardiotonic action of some xanthenes has also been established [28–31]. The inhibition of Type A and Type B monoamine oxidases by a number of xanthenes has also been observed [29, 30]. Xanthenes, despite their restricted occurrence in the plant kingdom, are reported to possess antileukaemic, antitumour, antiulcer, antimicrobial, antihepatotoxic and CNS-depressant activities [32]. Recently, the various bioactivities of xanthenes that have been described include cytotoxic and antitumour activity, anti-inflammatory activity, antifungal activity, enhancement of choline acetyltransferase activity and inhibition of lipid peroxidase [33]. In 1994, Mehta *et al.* [34] reported the total synthesis of the novel xanthone antibiotics cervinomycins A_1 and

A₂, which have promising activity against anaerobic bacteria, mycoplasma and some Gram-positive bacteria.

The significant antitumour and cytotoxic activities associated with the ethanolic extract of *Psorospermum febrifugum* have promoted a detailed chemical investigation of the plant extract, and routes to the synthesis of the parent antileukaemic furanoxanthone, psorospermin have been described [35]. Psorospermin was demonstrated to have significant antitumour activity in the P 388 *in vivo* system as well as cytotoxicity against a cell culture derived from a human epidermoid carcinoma of the nasopharynx (KB) *in vitro* system [36]. Garcinaxanthone B was found to enhance greatly choline acetyltransferase activity on a cultured neuronal cell of foetal rat brain hemisphere [37]. Gentsine, the 1,7-dihydroxy-3-methoxyxanthone, isolated from medicinal plant *Swertia davida*, is used for treatment of hepatitis and enteritis [38]. As a result of QSAR analysis, the tuberculostatic activities of polyhydroxyxanthones have been assessed: 1,3,7-trihydroxyxanthone showed the highest tuberculostatic activity [39]. 1,4,5-Trihydroxy-2-(1,1-dimethylallyl)xanthone found in the root bark extracts of *Garcinia gerrardii* is fungicidal against *Cladosporium cucumerinum* [40]. 1,7-Dihydroxy-4-methoxyxanthone exhibits antifungal activity against the plant pathogenic fungus *C. cucumerinum* [41].

USES OF PLANTS WHICH CONTAIN TRIOXYGENATED XANTHONES

Anthocleista djalensis (A. Chev.) and *A. vogelli* (Planch), Loganiaceae, are small trees which grow in the tropical rain forest areas of west Africa. The stem bark is used in local medicine for curing fever, stomach-ache and as a purgative [168].

Among *Calophyllum* species, *C. inophyllum* is the most widespread and in Malaysia has superior timber qualities [79]. The balsam from the bark of *C. inophyllum* 'Alexandrian Laurel' is called an 'oleo-resin' and used as a cicatrisant; an infusion or decoction of the leaves has been traditionally used as an eye remedy in Asian medicine [33]. Xanthones from *C. inophyllum* produce CNS depression in rats and mice [2]. The tropical American tree *C. brasiliense* produces a strong and durable timber known as Santa Maria or jacareuba [215].

Canscora decussata Schult, an erect annual plant 0.6 m high, has found use in the Indian system of medicine for a variety of purposes. The roots are used as a laxative and nerve tonic and in tuberculosis and fevers, while the aerial portions are used in insanity, epilepsy and nervous debility [42]. The extract of *C. decussata* is used in the treatment of certain mental disorders and of tuberculosis in Indian medicine [43].

The botanical source of the Taiwan folk remedy 'Hwang-jin-guey' is the root and stem of *Cudrania cochinchinensis* (Lour.) Kudo & Masamune var. *gerontogea* (S. & Z.) Kudo & Masamune [169]. It was used in the treatment of neuralgia, rheumatics, hepatitis and

contused wounds [171]. The ethanolic extract of roots of this species also showed significant anti-inflammatory and liver protective effects [262]. *Cudrania tricuspidata* (Carr.) Bur. (Japanese name 'Hariguwa') is a deciduous tree and the cortex as well as the root bark has been used as a Chinese crude drug [173].

Plant extracts obtained from genera *Eustoma* are used to treat various ailments including constipation, nervous debility, tuberculosis, fever and anorexia [46].

Garcinia livingstonei is a small to medium-sized tree that produces edible fruits and grows at low altitudes. It is found, particularly in South Africa, in riverine fringes and in open woodland. Extracts of the leaves and flowers are reported to exhibit antibiotic properties [100]. The fruit hull of *G. mangostana* L., the mangosteen tree, is used in Thai folk medicine for healing skin infection and wounds and for the relief of diarrhoea [101]. *Garcinia subelliptica* is a small shrub 4–5 m in height or a large tree sometimes reaching 15–20 m, and has been extensively cultivated as a windbreak in the Yaeyama islands of Japan, the bark has been utilized as a source of a yellow-coloured dye [37].

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 [10].

Hoppea dichotoma Willd. is used in the Ayurvedic system of medicine in the treatment of haemorrhoids, in cardiac dropsy and in certain mental disorders [56].

A number of species of the genus *Hypericum* have been found to possess various biological properties. Among the activities is the inhibition of monoamine oxidase (MAO; E.C. 1.4.3.4). MAO, which exists as two isoenzymes, MAO-A and MAO-B, plays a key role in the regulation of some physiological amines and is the target of inhibitors used as antidepressive drugs. The xanthones of *H. brasiliense* inhibit MAO activity [118]. The leaves and young twigs of *H. balearicum* exude lipophilic products [117]. The ethanol extract of aerial parts of *H. mysorensense* showed antifungal function [124]. The stems, leaves and flowers of *Hypericum ericoides* are used in Valentian folk medicine [121]. *H. sampsonii* Hance is known as a tumour inhibitory plant in Formosan folk medicine [127].

Mesua ferrea is commonly called ironwood in Malaya. The hard and durable trunk-wood is used widely in agricultural tools and vehicles in the south-east Asian countries [145]. Two crystalline antibiotic principles, mesuol and mesuone [146] have been isolated from the expressed oil of its seeds. In contrast to mangiferin, which is reported to be a CNS stimulant [216], xanthones from *M. ferrea* produces CNS depression in rats and mice [2]. *Mesua thwaitesii* is endemic in Ceylon and found generally in the wet zone forests of Ceylon. The tree has good timber properties [148].

Monnina obtusifolia is used in the folk medicine of Equador as an antifungal, antitumoral, antipyrorrhoeal, antiseptic and as a skin cleanser [183].

Polygala arillata Benth & Ham, native to the

mountains of the Western Himalayas, is a small plant used in the indigenous system of medicine for a variety of purposes [184]. *Polygala triphylla* Buch.-Ham. is a small herb which grows abundantly in the Kumaon region of the Western Himalayas up to altitudes of 2133 m. Its extract is used as a tonic and in chest ailments in popular medicine [187]. The roots of *P. tenuifolia* are used as an expectorant, tonic and sedative agent under the names 'Onji' in Japan and 'Yuan zhi' in China [185, 217]. It is also effectively inhibits congestive oedema in rats [186].

Psorospermum febrifugum is a woody plant of tropical Africa which has been used as a febrifuge, a leprosy treatment, a poison antidote and a purgative. An ethanolic extract of *P. febrifugum* was found to have antileukaemic activity *in vivo* in P388 lymphocytic leukaemia in mice and *in vitro* in the KB cell culture system used as a control [36]. From the extract, six compounds were found to exhibit significant *in vitro* cytotoxic activity against 9PS cells in culture and another exhibited both *in vitro* cytotoxic and *in vivo* antitumour activity [35, 152, 153]. One of these six xanthenes exhibited significant cytotoxicity in the HT-29 human colon adenocarcinoma *in vitro* cell line [154]. In addition, the xanthone psorospermin, isolated from *P. febrifugum* exhibited cytotoxic and *in vivo* antitumour activity in the P388 mouse leukaemia, mammary (CD) and colon (C6) models [155].

Both methanolic and dichloromethane extracts of *Swertia calycina* exhibited a strong antifungal activity against *Cladosporium cucumerinum* and *Candida albicans* [258]. An extract of *S. hookeri* is used by people of the north-eastern Himalayas for the treatment of microbial infections in man, in hypertension, and as a mood elevator [58]. *Swertia petiolata* has a bitter taste and is used for its laxative and antimalarial properties in the folk medicine of the high altitude Himalayan region [61]. *Swertia japonica* Makino, a popular medicinal herb in Japan, usually grows in a cold climate. The whole plant has been widely used as a folk medicine for stomach complaints because of the characteristic bitter taste. The swertia herb has also been widely used in Ayurveda and Unani medicines as an anthelmintic, febrifuge and bitter tonic. The aqueous ethanolic extract of *S. japonica* and its fractions showed a potent hypoglycaemic activity in streptozotocin (STZ)-induced diabetic rats, by both oral and intraperitoneal administration [59, 257].

By using chemiluminescence assays (CL) Ashida *et al.* [218] have recently reported that a natural Japanese folk medicine for a peptic, named Senburi (*Swertia japonica* Makino), contained some components with antioxidative activity. Antioxidative activities of the isolated components, which are six xanthone derivatives, are compared with α -tocopherol and BHT. In India, a *S. chirata* decoction is a commonly used household remedy for constipation and weak liver function in children. An infusion of the plant has been used by Hindu physicians as a bitter tonic, stomachic, febrifuge and anthelmintic. Its use has been also

reported in Unani medicine as a substitute for official gentiana preparations. *S. chirata* found a place among useful medicinal plants of east and southeast Asia as a bitter tonic, febrifuge, stomachic, laxative and blood purifier [219].

Vismia micrantha (Guttiferae) is used in traditional medicine as purgative, tonic, febrifuge and anti-rheumatic [167].

The fungus *Helminthosporium ravenelii* is a plant pathogen that parasitizes the grass *Sporobolus indicus*; *H. turcicum* is the causative agent of leaf blight disease of maize *Zea mays* [192].

TRIOXYGENATED XANTHONES

The first naturally occurring trioxxygenated xanthone to be discovered was gentisin (1,7-dihydroxy-3-methoxyxanthone), isolated from *Gentiana lutea* in 1821 by Henry and Caventou [220]. A large number of naturally occurring trioxxygenated xanthenes have now been isolated from higher plants, ferns, fungi and lichens [4].

The review by Roberts [10] refers to the natural occurrence of six trioxxygenated xanthenes: gentisin and isogentisin in *G. lutea* [52, 220], griseoxanthone C in *Penicillium patulum* [193], lichexanthone in *Parmelia formosana* [211], ravenelin in *Helminthosporium ravenelii* and *H. turcicum* [192] and sterigmatocystin in *Aspergillus versicolor* [188, 189, 221]. A later review, by Afzal *et al.* [222], included 38 trioxxygenated xanthenes isolated from higher plants, and described some as fungal and lichen metabolites; by 1979 the number of characterized natural trioxxygenated xanthenes had considerably increased. The review by Sultanbawa [9] included 35 trioxxygenated xanthenes (some previously described) from tropical plants, with a dramatic increase in the number of known natural trioxxygenated xanthenes.

In a review of the *Hypericum* genus, Kitanov and Blinova [28] listed five trioxxygenated xanthenes: kielcorin, 1,3,7-trihydroxyxanthone, 1-hydroxy-6,7-dimethoxyxanthone, 3-hydroxy-2,5-dimethoxyxanthone and 2,3,4-trimethoxyxanthone. Two years later in a review of xanthenes from Guttiferae, Bennett and Lee [2] listed 23 simple trioxxygenated xanthenes, 11 mono-C5-trioxxygenated xanthenes, 12 di-C5-trioxxygenated xanthenes and five more complex xanthenes from *Guttiferae* species. Finally, in a review by Mandal *et al.* [4] 21 simple trioxxygenated xanthenes and 33 prenylated and related xanthenes are listed. Mandal *et al.* [4] enlarged the list of Bennett and Lee with eight simple trioxxygenated xanthenes and 19 prenylated and related xanthenes. Bennett and Lee [2] enlarged the list of Sultanbawa with 14 simple trioxxygenated xanthenes and 23 prenylated, chromenoxanthenes and more complex xanthenes.

During the period 1821 to mid-1995, approximately 82 trioxxygenated naturally occurring xanthenes were described in review articles. In this review, 182 of the

Table 2. Simple trioxxygenated naturally occurring xanthenes

1 1-Hydroxy-2,3-dimethoxyxanthone <i>Polygala arillata</i> [184] <i>P. triphylla</i> [187]	13 4-Hydroxy-2,3-dethylenedioxyxanthone <i>Kielmeyera coriacea</i> [131] <i>K. corymbosa</i> [131, 135] <i>K. rubriflora</i> [138] <i>K. speciosa</i> [141, 142]
2 1-Hydroxy-2,3-methylenedioxyxanthone <i>Polygala arillata</i> [184] <i>P. triphylla</i> [187]	14 5-Hydroxy-1,3-dimethoxyxanthone <i>Kielmeyera candidissima</i> [128] <i>K. coriacea</i> [130, 131] <i>K. corymbosa</i> [131, 135] <i>K. ferruginea</i> [132] <i>K. rupestris</i> [139, 140] <i>K. speciosa</i> [141, 142] <i>Mesua thwaitesii</i> [148]
3 1-Hydroxy-3,5-dimethoxyxanthone <i>Canscora decussata</i> [42, 43] <i>Chironia krebsii</i> [45] <i>Eustoma grandiflorum</i> [46] <i>Frasera albomarginata</i> [48] <i>Hoppea dichotoma</i> [56] <i>Schultesia lisianthoides</i> [261] <i>Swertia calycina</i> [258] <i>S. hookeri</i> [58] <i>S. mussotii</i> [60] <i>S. patens</i> [62]	15 8-hydroxy-1,2-dimethoxyxanthone <i>Kielmeyera petiolaris</i> [136, 137]
4 1-Hydroxy-3,7-dimethoxyxanthone (methylgentisin) <i>Calophyllum brasiliense</i> [69] <i>Eustoma grandiflorum</i> [46] <i>Frasera albicaulis</i> [47] <i>F. albomarginata</i> [48] <i>Gentiana ciliata</i> [49] <i>G. lutea</i> [50, 51] <i>Polygala tenuifolia</i> [186] <i>Swertia japonica</i> [59] <i>S. speciosa</i> [63]	16 1,2-Dihydroxy-5-methoxyxanthone <i>Garcinia xanthochymus</i> [111]
5 1-Hydroxy-6,7-dimethoxyxanthone <i>Calophyllum ramiflorum</i> [83] <i>Hypericum mysorensense</i> [124, 125]	17 1,3-Dihydroxy-2-methoxyxanthone <i>Vismia guaramirangae</i> [166]
6 2-Hydroxy-1,8-dimethoxyxanthone <i>Calophyllum calaba</i> [68, 72]	18 1,3-Dihydroxy-5-methoxyxanthone <i>Calophyllum brasiliense</i> [70]
7 2-Hydroxy-3,4-dimethoxyxanthone <i>Hypericum sampsonii</i> [127] <i>K. rubriflora</i> [133] <i>Kielmeyera speciosa</i> [133]	19 1,3-Dihydroxy-7-methoxyxanthone (isogentisin) <i>Gentiana ciliata</i> [49] <i>G. lutea</i> [50–53] <i>Swertia petiolata</i> [61] <i>S. speciosa</i> [63]
8 3-Hydroxy-1,2-dimethoxyxanthone <i>Kielmeyera rupestris</i> [139, 140] <i>K. speciosa</i> [141, 143]	20 1,5-Dihydroxy-2-methoxyxanthone <i>Garcinia xanthochymus</i> [111]
9 3-Hydroxy-2,4-dimethoxyxanthone <i>Hypericum canariensis</i> [119] <i>H. reflexum</i> [1] <i>Kielmeyera coriacea</i> [129, 130] <i>K. rubriflora</i> [138] <i>K. speciosa</i> [141, 143]	21 1,5-Dihydroxy-3-methoxyxanthone (mesuaxanthone A) <i>Canscora decussata</i> [42, 43] <i>Centaurium erythraea</i> [259] <i>C. littorale</i> [259] <i>Chironia krebsii</i> [45] <i>Garcinia xanthochymus</i> [111] <i>Hoppea dichotoma</i> [56] <i>Hypericum mysorensense</i> [124] <i>Kielmeyera coriacea</i> [130, 131] <i>K. corymbosa</i> [131, 135] <i>K. rupestris</i> [139, 140] <i>K. speciosa</i> [141, 142] <i>Mesua ferrea</i> [145, 146] <i>Monnina obtusifolia</i> [183] <i>Schultesia lisianthoides</i> [261] <i>Vismia guaramirangae</i> [166]
10 3-Hydroxy-2,5-dimethoxyxanthone <i>Hypericum androsaemum</i> [116]	22 1,5-Dihydroxy-4-methoxyxanthone <i>Vismia guaramirangae</i> [166]
11 3-Hydroxy-2,8-dimethoxyxanthone <i>Polygala tenuifolia</i> [186]	23 1,5-Dihydroxy-6-methoxyxanthone <i>Tovomitia excelsa</i> [164]
12 4-Hydroxy-2,3-dimethoxyxanthone <i>Hypericum reflexum</i> [1] <i>Kielmeyera coriacea</i> [131, 133] <i>K. corymbosa</i> [131, 135] <i>K. ferruginea</i> [132] <i>K. rubriflora</i> [138] <i>K. rupestris</i> [139, 140] <i>K. speciosa</i> [141, 142]	24 1,5-Dihydroxy-8-methoxyxanthone <i>Vismia guaramirangae</i> [166]
	25 1,6-Dihydroxy-5-methoxyxanthone (buchanoxanthone) <i>Calophyllum calaba</i> [68, 72] <i>C. cordato-oblongum</i> [74] <i>C. cuneifolium</i> [75] <i>C. fragrans</i> [76]

Table 2. (Continued)

<i>C. inophyllum</i> [77]	<i>Garcinia xantochymus</i> [111]
<i>C. soulattri</i> [75]	38 1,3,7-Trihydroxyxanthone (gentisein)
<i>C. tomentosum</i> [86]	<i>Gentiana ciliata</i> [49]
<i>C. trapezifolium</i> [89]	<i>G. lutea</i> [50, 51]
<i>C. zeylanicum</i> [92]	<i>Haploclathra paniculata</i> [113]
<i>Garcinia buchananii</i> [96]	<i>Hypericum degenii</i> [120]
<i>Rheedia gardneriana</i> [159]	<i>Swertia chirata</i> [57]
<i>Tovomita excelsa</i> [164]	39 1,4,5-Trihydroxyxanthone
26 1,7-Dihydroxy-3-methoxyxanthone (gentisin)	<i>Garcinia subelliptica</i> [223]
<i>Calophyllum brasiliense</i> [69]	40 1,5,6-Trihydroxyxanthone (mesuaxantone B)
<i>Chironia krebsii</i> [45]	<i>Calophyllum calaba</i> [68, 72]
<i>Garcinia eugenifolia</i> [98]	<i>C. cordato-oblongum</i> [75]
<i>Gentiana ciliata</i> [49]	<i>C. fragrans</i> [76]
<i>G. lutea</i> [50–52, 54]	<i>C. inophyllum</i> [77, 78]
<i>Polygala tenuifolia</i> [185]	<i>C. scriblitifolium</i> [84]
<i>Swertia davida</i> [38]	<i>Garcinia buchananii</i> [96]
<i>S. petiolata</i> [61]	<i>G. eugenifolia</i> [80]
<i>S. speciosa</i> [63]	<i>Mesua ferrea</i> [146, 147]
27 1,7-Dihydroxy-4-methoxyxanthone	<i>M. thwaitesii</i> [148]
<i>Hypericum inodorum</i> [123]	<i>Ochrocarpos odoratus</i> [149]
<i>Polygala nyikensis</i> [41]	<i>Symphonia globulifera</i> [160]
<i>Vismia guaramirangae</i> [166]	41 1,6,7-Trihydroxyxanthone
<i>V. micrantha</i> [167]	<i>Garcinia eugenifolia</i> [80]
28 1,7-Dihydroxy-6-methoxyxanthone	<i>Platonia insignis</i> [94]
<i>Tovomita excelsa</i> [164]	42 2,3,4-Trihydroxyxanthone
29 1,7-Dihydroxy-8-methoxyxanthone	<i>Ochrocarpos odoratus</i> [149]
<i>Calophyllum calaba</i> [68, 72]	43 1-Methoxy-2,3-methylenedioxyxanthone
<i>Kielmeyera excelsa</i> [136]	<i>Polygal arillata</i> [184]
<i>K. ferruginosa</i> [132]	<i>P. triphylla</i> [187]
<i>K. petiolaris</i> [136, 137]	44 4-Methoxy-2,3-methylenedioxyxanthone
30 2,3-Dihydroxy-1-methoxyxanthone	<i>Kielmeyera coriacea</i> [130, 131]
<i>Kielmeyera speciosa</i> [141, 143]	<i>K. corymbosa</i> [131, 135]
30a 2,5-Dihydroxy-1-methoxyxanthone	<i>K. rubriflora</i> [138]
<i>Garcinia subelliptica</i> [260]	<i>K. rupestris</i> [139, 140]
31 2,7-Dihydroxy-1-methoxyxanthone (clathraxanthone)	45 1,2,3-Trimethoxyxanthone
<i>Haploclathra paniculata</i> [114]	<i>Polygala arillata</i> [184]
32 3,4-Dihydroxy-2-methoxyxanthone	<i>P. triphylla</i> [187]
<i>Hypericum reflexum</i> [1]	46 1,3,4-Trimethoxyxanthone
<i>Kielmeyera coriacea</i> [131]	<i>Polygala arillata</i> [184]
<i>K. corymbosa</i> [131, 135]	47 1,3,5-Trimethoxyxanthone
33 3,5-Dihydroxy-1-methoxyxanthone	<i>Frasera albicaulis</i> [47]
<i>Canscora decussata</i> [44]	<i>Haploclathra paniculata</i> [113]
34 3,6-Dihydroxy-2-methoxyxanthone	<i>Mesua ferrea</i> [146]
<i>Hypericum reflexum</i> [1]	48 1,3,7-Trimethoxyxanthone
35 5,6-Dihydroxy-1-methoxyxanthone	<i>Frasera albicaulis</i> [47]
<i>Tovomita excelsa</i> [164]	<i>Gentiana lutea</i> [50, 51]
36 1,2,5-Trihydroxyxanthone	49 2,3,4-Trimethoxyxanthone
<i>Garcinia subelliptica</i> [110]	<i>Hypericum ericoides</i> [121]
<i>Hypericum balearicum</i> [117]	50 2,3,5-Trimethoxyxanthone
37 1,3,5-Trihydroxyxanthone	<i>Halenia campanulata</i> [55]
<i>Allanblackia floribunda</i> [64]	51 2,3,8-Trimethoxyxanthone
<i>Canscora decussata</i> [43]	<i>Polygala tenuifolia</i> [186]

compounds found in the literature, are now listed (Tables 2–10).

SYNTHESIS AND BIOSYNTHESIS OF XANTHONES

Selective demethylation of 1,2,3-, 2,3,4-, and 1,3,5-trimethoxyxanthone led to the synthesis of the following constituents: 2,3-dihydroxy-4-methoxyxanthone

(and also the derivatives 2,3-methylenedioxy-4-methoxyxanthone and 2,3-methylenedioxy-4-hydroxyxanthone), 3-hydroxy-2,4-dimethoxyxanthone, 4-hydroxy-2,3-dimethoxyxanthone, 3-hydroxy-1,2-dimethoxyxanthone and 1,5-dihydroxy-3-methoxyxanthone [224].

Some authors have reported the preparation of hydroxyxanthenes [225–230] but the first xanthone synthesis was proposed by Kostanecki [231, 232] and

Table 3. Mono-C₅-trioxygenated naturally occurring xanthenes

52 5'-Hydroxyisopsorofebrin
Psorospermum febrifugum [153, 154]

53 1-Hydroxy-3,5-dimethoxy-4-(3-methylbut-2-enyl)xanthone
Pentaplangium solomonse [150]

54 1-Hydroxy-3,7-dimethoxy-2-(3-methylbut-2-enyl)xanthone
Allanblackia floribunda [64]

55 Psorospermin
Psorospermum febrifugum [36, 155]

56 3',4'-Deoxypsorospermin
Psorospermum febrifugum [155]

57 3',4'-Deoxy-4'-choropsorospermin-3'-ol
Psorospermum febrifugum [155]

58 Psorofebrin
Sorospermum febrifugum [153, 154]

59 3',4'-Deoxyisopsorospermin-3',4',5'-triol
Psorospermum febrifugum [152]

60 *O*⁴-Methyl-3',4'-deoxypsorospermin-3',4'-diol
Psorospermum febrifugum [152]

61 3',4'-Deoxypsorospermin-3',4'-diol
Psorospermum febrifugum [155]

62 *O*⁴-Ethyl-3',4'-deoxypsorospermin-3',4'-diol
Psorospermum febrifugum [152]

63 5'-Hydroxypsorospermin
Psorospermum febrifugum [152]

64 4'-*O*-Acetyl-3',4'-deoxypsorospermin-3',4'-diol
Psorospermum febrifugum [154]

65 3',4'-Deoxypsorospermin-3',4',5'-triol
Psorospermum febrifugum [154]

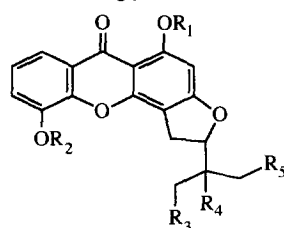
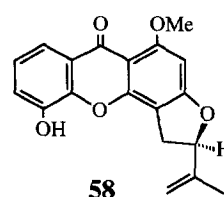
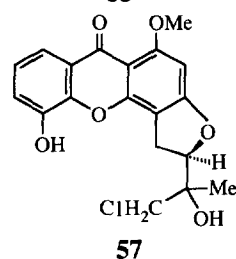
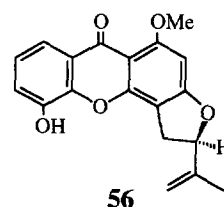
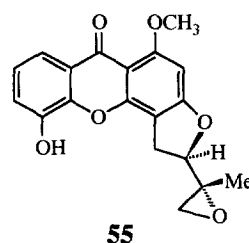
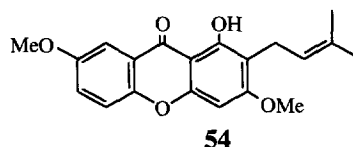
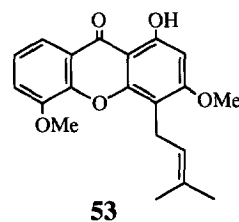
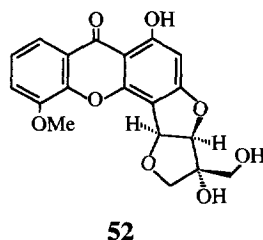
66 *O*¹-Demethyl-3',4'-deoxypsorospermin-3',4'-diol
Psorospermum febrifugum [152]

67 *O*⁵-Methyl-3',4'-Deoxypsorospermin-3',4'-diol
Psorospermum febrifugum [152]

68 *O*⁵-Methyl-3',4'-deoxypsorospermin-3'-ol
Psorospermum febrifugum [155]

69 4'-Chloro-5-*O*-methyl-3',4'-deoxypsorospermin-3',5'-diol
Psorospermum febrifugum [152]

70 1,5-Dihydroxy-3-methoxy-2-(3-methylbut-2-enyl)xanthone
Garcinia mangostana [103]



	R ¹	R ²	R ³	R ⁴	R ⁵
59	H	Me	OH	OH	OH
60	Me	H	OMe	OH	H
61	Me	H	OH	OH	H
62	Me	H	OEt	OH	H
63	Me	H	-----O-----	OH	
64	Me	H	OAc	OH	OH
65	Me	H	OH	OH	OH
66	H	H	OH	OH	H
67	Me	Me	OH	OH	H
68	Me	Me	H	OH	H
69	Me	Me	Cl	OH	OH

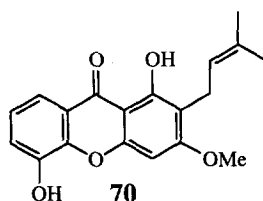


Table 3. (Continued)

71 6-Deoxyjacareubin or 6-dehydroxyjacareubin

Calophyllum bracteatum [68]

C. brasiliense [69, 71]

C. calaba [68, 72]

C. cuneifolium [75]

C. fragrans [76]

C. inophyllum [77, 79–81]

C. neo-ebudicum [82]

C. scriblitfolium [84]

C. soulattri [75]

C. tomentosum [86]

C. trapezifolium [88]

C. zeylanicum [92]

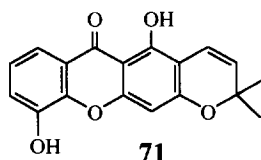
Hypericum brasiliense [118]

Kielmeyera ferruginea [132]

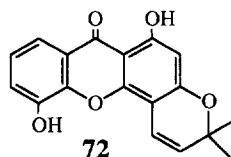
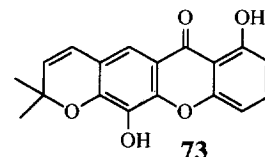
K. speciosa [71, 141, 142]

Maclura aurantica [176]

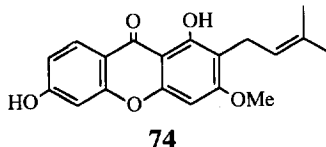
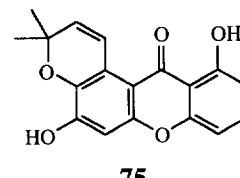
M. pomifera [177]

Mourera fluviatilis [182]

71
72 6-Deoxyisojacareubin

Garcinia livingstonei [100]

Pentaphalangium solomonse [150]

72

73
73 Rheediachromenoxanthone

Rheedia brasiliensis [156]

R. gardneriana [157]

74

75
74 1,6-Dihydroxy-3-methoxy-2-(3-methylbut-2-enyl)xanthone

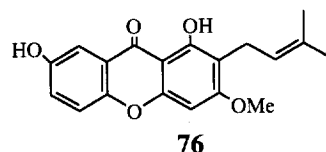
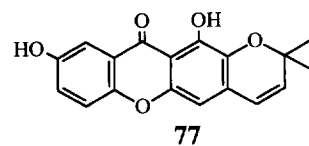
Garcinia mangostana [105]

75 Tovoxanthone

Maclura aurantica [176]

Tovomita choisyana [163]

76 1,7-Dihydroxy-3-methoxy-2-(3-methylbut-2-enyl)xanthone

Garcinia mangostana [101, 103]

76

77
77 Osajaxanthone

Calophyllum brasiliense [71]

C. canum [73]

C. scriblitfolium [84]

Cudrania cochinchinensis [169]

Kielmeyera corymbosa [71, 135]

K. ferruginea [132]

Maclura aurantica [176]

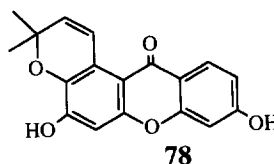
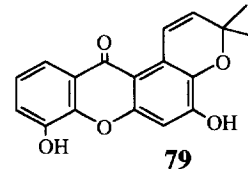
M. pomifera [177–179]

Pentadesma butyracea [151]

Tovomita pyrifolium [165]

78 Hyperxanthone

Hypericum reflexum [1]

H. sampsonii [127]

78

79
79 Hypericanarin

Hypericum canariensis [119]

80 Globuxanthone

Garcinia subelliptica [37, 109]

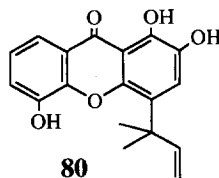
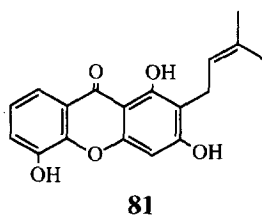
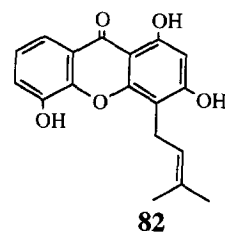
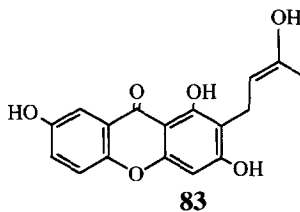
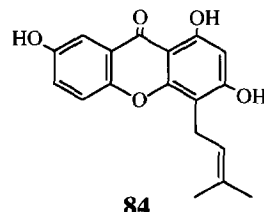
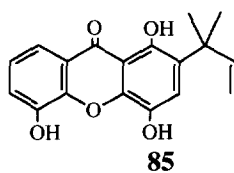
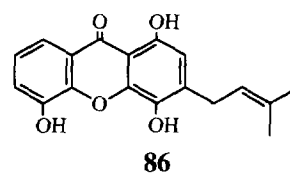
Symphonia globulifera [161]

80

Table 3. (Continued)

81 1,3,5-Trihydroxy-2-(3-methylbut-2-enyl)xanthone*Calophyllum cuneifolium* [75]*C. inophyllum* [77, 79]*C. scriblitifolium* [84]*C. soulattri* [75]*C. thwaitesii* [85]*C. tomentosum* [86]*C. walkeri* [85]**81****82****82** 1,3,5-Trihydroxy-4-(3-methylbut-2-enyl)xanthone*Pentaphalangium solomonse* [150]**83** 1,3,7-Trihydroxy-2-(3-methylbut-2-enyl)xanthone*Calophyllum canum* [73]*C. scriblitifolium* [84]*Cudrania cochinchinensis* [171]*Garcinia forbesii* [99]*Pentaphalangium solomonse* [150]**83****84****84** Mbaraxanthone*Symphonia globulifera* [162]**85** 1,4,5-Trihydroxy-2-(1,1-dimethylallyl)xanthone*Garcinia gerrardii* [40]*G. livingstonei* [100]*G. subelliptica* [109]**85****86****86** 1,4,5-Trihydroxy-3-(3-methylbut-2-enyl)xanthone*Garcinia livingstonei* [100]

the test by Ravi *et al.* [233], with a new route to xanthone synthesis and Vitale *et al.* [234] with a novel route for the preparation of xanthones and chromanones.

The preparation of 1-formyl-2-hydroxyxanthone was proposed by Davies *et al.* [235], and 1-methoxyxanthone was synthesized first by Tambor [236]. The total synthesis of lichen xanthones [237], synthesis of furanoxanthones [238,239], synthesis of new xanthones [240], a new one-step method [241] and general study for synthesis of dioxygenated xanthones have been reported recently by Lin *et al.* [242].

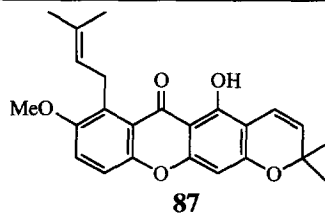
The biosynthetic pathways to xanthones have been discussed in recent years. Initially, these attempted to relate the observed oxygen pattern of natural xanthones and correlate them with recognized oxygenation patterns. In general, it appears that ring A and attached carbonyl group are provided by the shikimic acid pathway, whereas ring B arises via the acetate-malonate polyketide route [9, 243, 244]. Thus, Locksley *et al.* [245] reported the significance of maclurin in xanthone biosynthesis and the biogenetic-type synthesis of xanthones from their benzophenone precursors [246]. Gottlieb [3, 247] showed biogenetic proposals for xanthones, and Bhanu *et al.* [248] related the biogenetic implications in the conversion of 4-phenylcoumarins into xanthones. More recently the biosynthetic route of tajixanthone and shamixanthone has been studied [249].

Some xanthones in lower plants have been proved to be totally acetate derived, from seven acetate units [193, 250]. However, the oxygenation patterns of all xanthones in higher plants suggest that these are formed by a mixed shikimate-acetate pathway. This involves the condensation of shikimate and acetate-derived moieties to form benzophenones or benzophenone-like intermediates, which then react intramolecularly to form xanthones. Mechanisms for this intramolecular reaction have been postulated involving either direct phenol oxidative coupling [251], quinone addition [252], dehydration between hydroxyl groups on the acetate and shikimate-derived rings [253], or spirodienone formation and subsequent rearrangement to form the xanthone [3, 254].

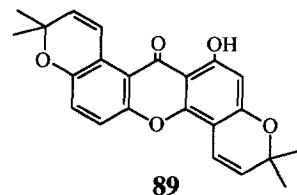
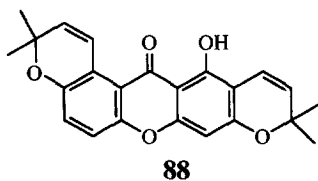
Concerning lichen and fungi biosynthesis, it is important to state that the many secondary metabolites found in the lichen-forming fungi play a dominant role in the systematics of these organisms because of the extensive parallels with morphology and their clear ecological significance. Despite their common occurrence in a number of important genera, lichen xanthones have not featured prominently in the repertoire of lichen taxonomists for several reasons. Nevertheless, with the availability of more sensitive methods of detection and synthetic materials for comparison these compounds have been employed effectively in recent systematic studies of lichens [199, 203, 255]. Elix *et al.* [255] reported the unambiguous total synthesis of 17

Table 4. Di-C₅-trioxygenated naturally occurring xanthenes

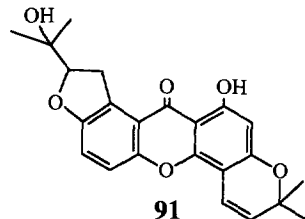
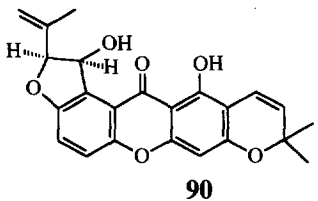
87 Calabaxanthone
Calophyllum bracteatum [67, 68]
C. calaba [67, 68, 72]
C. cuneifolium [75]
C. tomentosum [86]
C. trapezifolium [87]
C. walkeri [85]



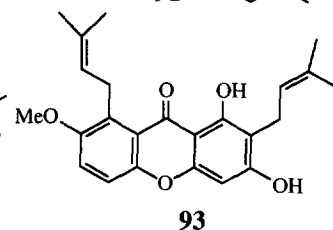
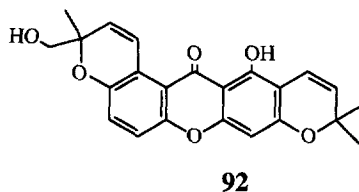
C. zeylanicum [92]
Garcinia mangostana [101]
88 Thwaitesixanthone
Calophyllum thwaitesii [67, 85]
C. walkeri [90]
89 Cudraxanthone A
Cudrania cochinchinensis [169]
C. tricuspidata [175]



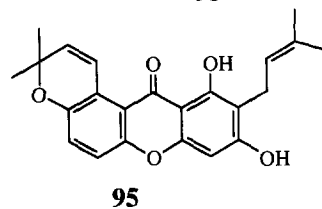
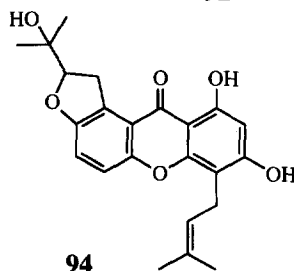
90 2''-Isopropenyl-3''-hydroxydihydrofurano-
 demethylcalabaxanthone
Calophyllum walkeri [90]
91 Cudraxanthone O
Cudrania tricuspidata [174]



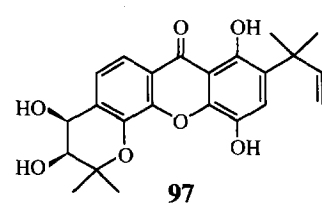
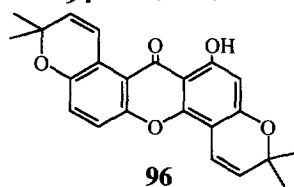
92 Thwaitesixanthanol
Calophyllum walkeri [90]
93 Calocalabaxanthone or 6-deoxymangostin
Calophyllum bracteatum [67]
C. calaba [67, 72]



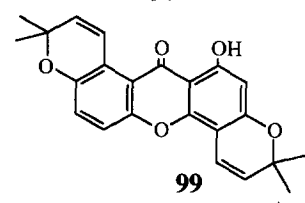
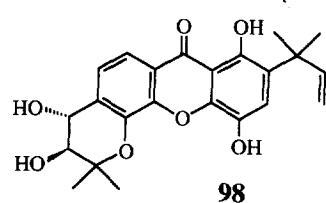
94 Cudraxanthone J
Cudrania tricuspidata [173]
95 Calothwaitesixanthone
Calophyllum thwaitesii [67]



96 Garcinixanthone B
Garcinia subelliptica [37]
97 Garcigerrin A
Garcinia gerrardii [40]



98 Garcigerrin B
Garcinia gerrardii [40]
G. subelliptica [109]
99 Cudraxanthone G
Cudrania tricuspidata [172]



100 Morusignin G
Morus insignis [181]
101 Morusignin H
Morus insignis [181]

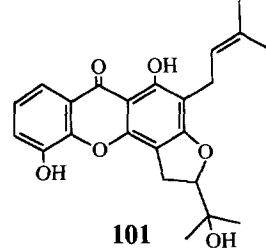
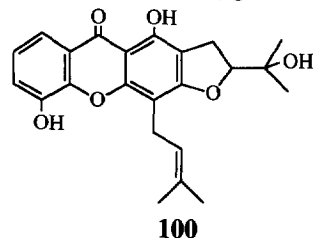


Table 4. (Continued)

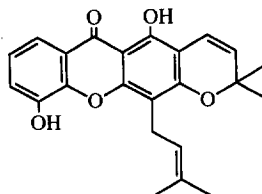
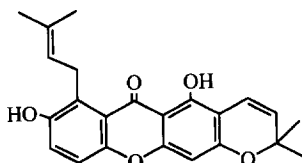
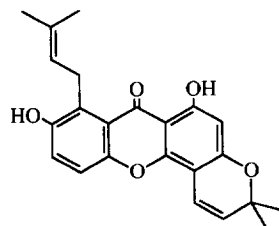
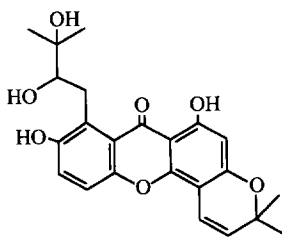
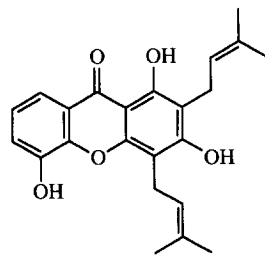
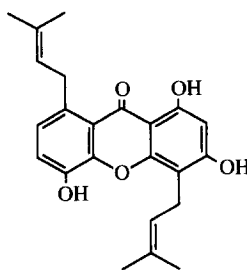
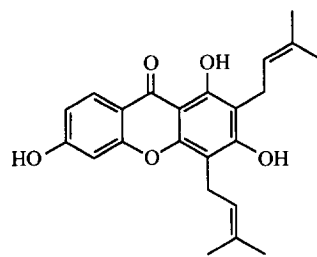
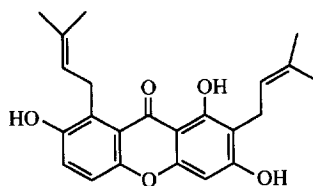
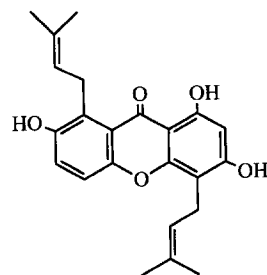
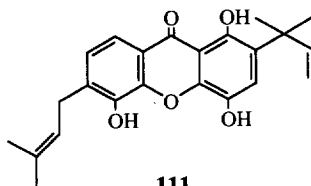
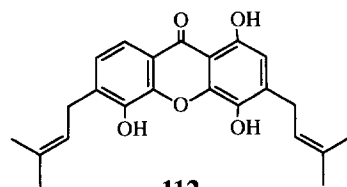
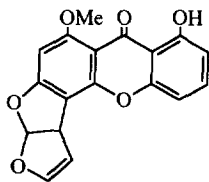
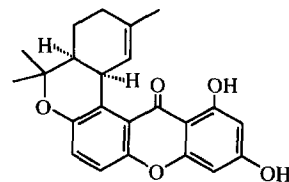
102 Toxyloxanthone A or trapezifolixanthone*Calophyllum calaba* [67]*C. cuneifolium* [75]*C. trapezifolium* [86]*Maclura pomifera* [177]*Mourera fluvialis* [182]**102****103** Demethylcalabaxanthone*Calophyllum walkeri* [90]*Garcinia mangostana* [101]**103****104** Cudraxanthone I*Cudrania tricuspidata* [173]**104****105** Cudraxanthone N*Cudrania tricuspidata* [174]**105****106** 8-Deoxygartanin*Garcinia mangostana* [106, 107]*Maclura pomifera* [177]*Rheedia brasiliensis* [156]*R. gardneriana* [158]**106****107** 1,3,5-Trihydroxy-4,8-bis(3-methylbut-2-enyl)xanthone*Garcinia quadrifaria* [108]**107****108****108** Garcinone A*Garcinia mangostana* [102, 104]**109** 6-Deoxy-γ-mangostin*Calophyllum thwaitesii* [67]*Garcinia mangostana* [101]**109****110****110** Gerontoxanthone H or cudraxanthone H*Cudrania cochinchinensis* [170]*C. tricuspidata* [172]**111** Garciniaxanthone A*Garcinia subelliptica* [37]**111****112****112** Garciniaxanthone C*Garcinia subelliptica* [110]

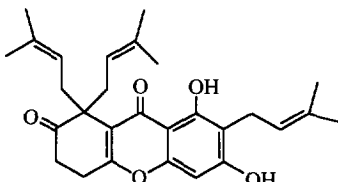
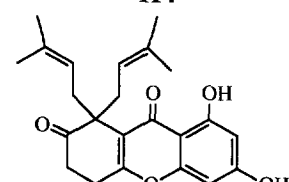
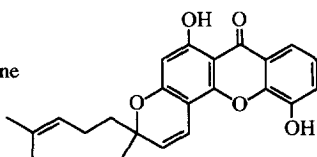
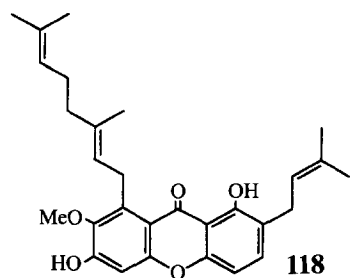
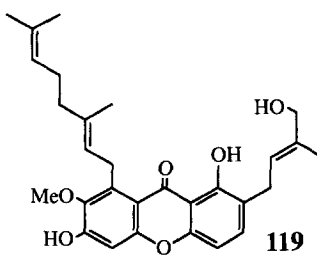
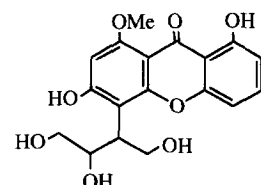
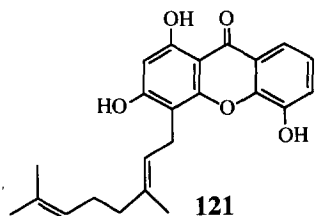
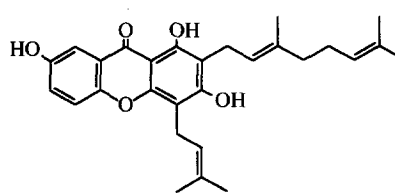
Table 5. More complex trioxygenated naturally occurring xanthenes

113 Sterigmatocystin
Aspergillus versicolor [188–190]

Bipolaris sorokiniana [191]

113
114 Calozyloxanthone
Calophyllum tomentosum [32]

C. zeylanicum [92]

114
115 Zeyloxanthone or wightianone
Calophyllum tomentosum [32]

C. wightianum [91]

C. zeylanicum [92, 93]

115

116
117 1,5-Dihydroxy-6'-methyl-
6'[(4"-methyl)-3"-pentenyl]pyranoxanthone
Garcinia livingstonei [100]

117
118 Cowanin
Garcinia cowa [97]

118
119 Cowanol
Garcinia cowa [97]

119
120 1,6-Dihydroxy-8-methoxy-
5-(2,3-dihydroxy-1-hydroxymethylpropyl)xanthone
Bipolaris sorokiniana [191]

120
121 1,3,5-Trihydroxy-4-(3',7'-dimethyl-2',6'-
octadienyl)xanthone
Garcinia livingstonei [100]

121
122 1,3,6-Trihydroxy-4-(3-methylbut-
2-enyl)-2-geranylxanthone
Cratogeomys cochinchinense [95]

122
123 Kielcorin
Hypericum androsaemum [115, 116]

H. calycinum [115]

H. canariensis [119]

H. ericoides [122]

H. maculatum [115]

H. perforatum [115]

H. reflexum [1]

Kielmeyera coriacea [26, 132]

K. corymbosa [132]

K. ferruginea [132]

K. speciosa [132]

Psorospermum febrifugum [35]

Vismia guaramirangae [166]

124 Cadensin D or hypericorin
Hypericum canariensis [119]

H. mysorensense [126]

Psorospermum febrifugum [35]

125 Kielcorin B
Kielmeyera coriacea [134]

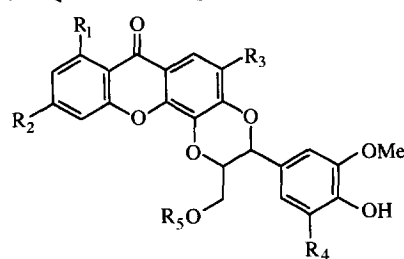
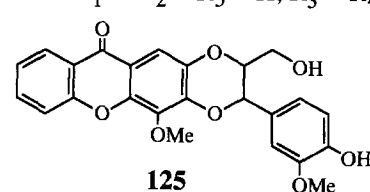
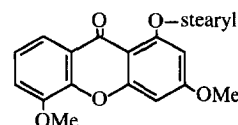
126 3,5-Dimethoxy-1-O-stearylxanthone
Swertia hookeri [58]

123 $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OMe$
124 $R_1 = R_2 = R_5 = H$; $R_3 = R_4 = OMe$

125

126

Table 6. Trioxxygenated xanthenes detected in lichens—lichexanthone derivatives

127 Lichexanthone	
<i>Athocleista djalensis</i> [168]	
<i>Parmelia formosana</i> [211]	
<i>Pertusaria</i> sp. [196]	
<i>P. sulphurata</i> [213]	
128 2-Chlorolichexanthone	
<i>Lecanora</i> sp. [199]	
<i>Pertusaria cicatricosa</i> [199]	
<i>P. sulphurata</i> [213]	
129 5-Chlorolichexanthone	
<i>Lecanora contractula</i> [199]	
130 2,4-Dichlorolichexanthone or 2,4-dichloro-3,6-di- <i>O</i> -methylnorlichexanthone	
<i>Dimelaena australiensis</i> [199]	
<i>Pertusaria</i> sp. [200]	127 $R_2 = R_4 = R_5 = R_7 = H$
<i>P. cicaticosa</i> [199]	128 $R_2 = Cl; R_4 = R_5 = R_7 = H$
131 2,5-Dichlorolichexanthone or 2,5-dichloro-3,6-di- <i>O</i> -methylnorlichexanthone	129 $R_2 = R_4 = R_7 = H; R_5 = Cl$
<i>Dimelaena australiensis</i> [199]	130 $R_2 = R_4 = Cl; R_5 = R_7 = H$
<i>Pertusaria</i> sp. [200]	131 $R_2 = R_5 = Cl; R_4 = R_7 = H$
<i>P. cicaticosa</i> [199]	132 $R_2 = R_7 = Cl; R_4 = R_5 = H$
132 2,7-Dichlorolichexanthone	133 $R_2 = R_7 = H; R_4 = R_5 = Cl$
<i>Buellia glaziouana</i> [196]	134 $R_2 = R_4 = R_5 = Cl; R_7 = H$
<i>Lecanora behringii</i> [199, 201]	135 $R_2 = R_5 = R_7 = Cl; R_4 = H$
<i>L. dispersa</i> [203]	
<i>L. populicola</i> [199, 201]	
<i>L. salina</i> [199, 201]	
133 4,5-Dichlorolichexanthone or coronatone	
<i>Dimelaena australiensis</i> [199]	
<i>Pertusaria cicaticosa</i> [199]	
134 2,4,5-Trichlorolichexanthone or 2,4,5-trichloro-3,6-di- <i>O</i> -methylnorlichexanthone	
<i>Dimelaena</i> sp. [197]	
<i>D. australiensis</i> [199]	
<i>Pertusaria</i> sp. [200]	
<i>P. cicaticosa</i> [199]	
135 2,5,7-Trichlorolichexanthone	
<i>Dimelaena australiensis</i> [199]	
<i>Lecanora broccha</i> [199]	

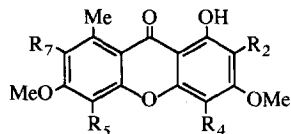
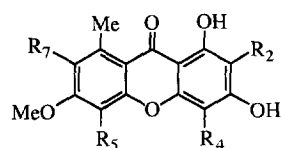


Table 7. Trioxxygenated xanthenes detected in lichens—6-*O*-methylnorlichexanthone derivatives

136 2-Chloro-6-*O*-methylnorlichexanthone
Lecanora salina [199]
Pertusaria cicatricosa [199]
P. sulphurata [213]
137 4-Chloro-6-*O*-methylnorlichexanthone
Pertusaria sulphurata [213]
138 5-Chloro-6-*O*-methylnorlichexanthone
Lecanora contractula [199]
139 7-Chloro-6-*O*-methylnorlichexanthone
Lecanora populicola [199]
L. salina [199]
140 Thiophaninic acid
Buellia sp. [198]
Dimelaena sp. [198]
D. australiensis [199]
Lecanora broccha [195]
L. novomexicana [19]
L. rupicola [19]
Lecidea quernei [19]
Lecidella asema [195]
L. subalpida [195]
Pertusaria flavicans [212]
P. hymenea [19]
P. lutescens [19]
P. sulphurata [213]
141 2,5-Dichloro-6-*O*-methylnorlichexanthone
Dimelaena sp. [198]
D. australiensis [199]
Lecanora contractula [199]
Pertusaria cicatricosa [199]
142 2,7-Dichloro-6-*O*-methylnorlichexanthone
Lecanora behringii [199]
L. opulicola [199]
L. salina [199]
143 4,5-Dichloro-6-*O*-methylnorlichexanthone
Dimelaena sp. [198]
D. australiensis [199]
144 6-*O*-Methylarthothelin
Dimelaena sp. [197]
D. australiensis [199]
Micarea isabellina [199]
Pertusaria pycnothelia [199]
145 6-*O*-Methylasemone
Pertusaria pycnothelia [199]
146 6-*O*-Methylthiophanic acid
Micarea isabellina [199]



- 136** $R_2 = Cl; R_4 = R_5 = R_7 = H$
137 $R_2 = R_5 = R_7 = H; R_4 = Cl$
138 $R_2 = R_4 = R_7 = H; R_5 = Cl$
139 $R_2 = R_4 = R_5 = H; R_7 = Cl$
140 $R_2 = R_4 = Cl; R_5 = R_7 = H$
141 $R_2 = R_5 = Cl; R_4 = R_7 = H$
142 $R_2 = R_7 = Cl; R_4 = R_5 = H$
143 $R_2 = R_7 = H; R_4 = R_5 = Cl$
144 $R_2 = R_4 = R_5 = Cl; R_7 = H$
145 $R_2 = H; R_4 = R_5 = R_7 = Cl$
146 $R_2 = R_4 = R_5 = R_7 = Cl$

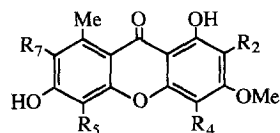
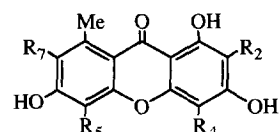
Table 8. Trioxxygenated xanthenes detected in lichens—3-*O*-methylnorlichexanthone derivatives**147** 3-*O*-Methylnorlichexanthone or griseoxanthone C*Lecanora vinetorum* [199]*Penicillium patulum* [193]**148** 5-Chloro-3-*O*-metilnorlichexanthone or vinetorin*Lecanora vinetorum* [199]*Pertusaria* sp. [200]**149** 2,5-Dichloro-3-*O*-methylnorlichexanthone*Lecanora behringii* [201]*L. contractula* [201]*L. populicola* [201]*L. salina* [201]**150** 2,7-Dichloro-3-*O*-methylnorlichexanthone*Lecanora behringii* [199]*L. salina* [199]**151** 5,7-Dichloro-3-*O*-methylnorlichexanthone*Buellia* sp. [195]*Lecanora broccha* [195, 199, 202]*L. vinetorum* [199]*Lecidella asema* [195]*L. meiococca* [199]*L. subalpicida* [195]*L. vorax* [199]**152** 2,4,5-Trichloro-3-*O*-methylnorlichexanthone or thuringione*Lecanora pinguis* [19]*Lecidea carpathica* [19]*Pertusaria* sp. [200]**153** 2,5,7-Trichloro-3-*O*-methylnorlichexanthone*Buellia* sp. [195]*Lecanora broccha* [195, 199, 202]*L. capistrata* [196]*Lecidella asema* [195]*L. meiococca* [199]*L. subalpicida* [195]*L. vorax* [199]**154** 4,5,7-Trichloro-3-*O*-methylnorlichexanthone or 3-*O*-methylasemone*Buellia* sp. [195]*Lecanora broccha* [195, 199, 202]*Lecidella asema* [195]*L. capistrata* [195]*L. capistrata* [196]*L. meiococca* [199]*L. subalpicida* [195]*L. vorax* [199]**155** 3-*O*-Methylthiophanic acid*Lecidella meiococca* [199]**147** $R_2 = R_4 = R_5 = R_7 = H$ **148** $R_2 = R_4 = R_7 = H; R_5 = Cl$ **149** $R_2 = R_5 = Cl; R_4 = R_7 = H$ **150** $R_2 = R_7 = Cl; R_4 = R_5 = H$ **151** $R_2 = R_4 = H; R_5 = R_7 = Cl$ **152** $R_2 = R_4 = R_5 = Cl; R_7 = H$ **153** $R_2 = R_5 = R_7 = Cl; R_4 = H$ **154** $R_2 = H; R_4 = R_5 = R_7 = Cl$ **155** $R_2 = R_4 = R_5 = R_7 = Cl$

Table 9. Trioxygenated xanthenes detected in lichens—norlichexanthone derivatives

156 Norlichexanthone
<i>Lecanora reuteri</i> [205]
<i>L. straminea</i> [209]
157 2-Chloronorlichexanthone
<i>Lecanora populicola</i> [199]
<i>L. salina</i> [199]
<i>L. straminea</i> [209]
<i>L. vorax</i> [199]
158 7-Chloronorlichexanthone
<i>Lecanora populicola</i> [199]
159 2,4-Dichloronorlichexanthone
<i>Buellia</i> sp. [195]
<i>Lecanora broccha</i> [195]
<i>L. straminea</i> [209]
<i>Lecidella asema</i> [195]
<i>L. subalpida</i> [195]
<i>L. vorax</i> [199]
160 2,5-Dichloronorlichexanthone
<i>Buellia</i> sp. [195]
<i>Lecanora broccha</i> [195, 199]
<i>Lecidella asema</i> [195]
<i>L. meiococca</i> [199]
<i>L. subalpida</i> [195]
<i>L. vorax</i> [199]
161 2,7-Dichloronorlichexanthone
<i>Buellia</i> sp. [195]
<i>Lecanora andrewii</i> [196]
<i>L. behringii</i> [199]
<i>L. broccha</i> [195, 199]
<i>L. ingae</i> [196]
<i>L. populicola</i> [199]
<i>L. pruinosa</i> [196]
<i>L. salina</i> [199]
<i>L. straminea</i> [208]
<i>L. sulphurata</i> [196]
<i>Lecidella asema</i> [195]
<i>L. meiococca</i> [199]
<i>L. subalpida</i> [195]
<i>Melanaria melanospora</i> [196]
162 4,5-Dichloronorlichexanthone
<i>Buellia</i> sp. [195]
<i>Lecanora broccha</i> [195]
<i>L. flavo-pallescent</i> [204]
<i>Lecidella asema</i> [195]
<i>L. subalpida</i> [195]
<i>L. vorax</i> [199]
<i>Micarea austroternaria</i> [204]
<i>M. isabellina</i> [199]
<i>Pertusaria pycnothelia</i> [199]
163 4,7-Dichloronorlichexanthone
<i>Buellia</i> sp. [195]
<i>Lecanora broccha</i> [195]
<i>Lecidella asema</i> [195]
<i>L. meiococca</i> [199]
<i>L. subalpida</i> [195]
164 5,7-Dichloronorlichexanthone
<i>Buellia</i> sp. [195]
<i>Lecanora broccha</i> [195, 199]
<i>Lecidella asema</i> [195]
<i>L. subalpida</i> [195]
<i>L. vorax</i> [199]



- 156** $R_2 = R_4 = R_5 = R_7 = H$
157 $R_2 = Cl; R_4 = R_5 = R_7 = H$
158 $R_2 = R_4 = R_5 = H; R_7 = Cl$
159 $R_2 = R_4 Cl; R_5 = R_7 = H$
160 $R_2 = R_5 = Cl; R_4 = R_7 = H$
161 $R_2 = R_7 = Cl; R_4 = R_5 = H$
162 $R_2 = R_7 = H; R_4 = R_5 = Cl$
163 $R_2 = R_5 = H; R_4 = R_7 = Cl$
164 $R_2 = R_4 = H; R_5 = R_7 = Cl$

Table 9. (Continued)

165 2,4,5-Trichloronorlichexanthone or arthothelin*Arthothelium pacificum* [19]*Buellia* sp. [194, 195]*Dimelaena australiensis* [199]*Lecanora andrewii* [196]*Lecanora andrewii* [196]*L. bolanderi* [196]*L. broccha* [195]*L. flavidopallens* [196]*L. flavo-pallescent* [204]*L. ingae* [196]*L. pinguis* [19]*L. pruinosa* [196]*L. straminea* [19]*L. sulphurata* [199, 204]*Lecidea quemea* [19]*Lecidella asema* [195]*L. meiococca* [199]*L. subalpicida* [195]*L. vorax* [199]*Melanaria melanospora* [196]*Micarea austroternaria* [204]*M. isabellina* [199]*Pertusaria* spp. [200]*P. pycnothelia* [199]**166** 2,4,7-Trichloronorlichexanthone*Lecanora flavo-pallescent* [204]*L. reuteri* [205]*L. sulphurata* [199, 204]**167** 2,5,7-Trichloronorlichexanthone or isoarthothelin*Buellia* sp. [194, 195]*Lecanora broccha* [195, 199]*L. flavo-pallens* [196]*L. sulphurata* [196, 199, 204]*Lecidella asema* [195]*L. meiococca* [199]*L. subalpicida* [195]*L. vorax* [199]**168** 4,5,7-Trichloronorlichexanthone or asemone*Buellia* sp. [195]*Lecanora broccha* [195, 199]*Lecidella asema* [195]*L. subalpicida* [195]*Micarea austroternaria* [204]*M. isabellina* [204, 210]*Pertusaria pycnothelia* [199]**169** Thiophanic acid*Lecanora bolanderi* [196]*L. flavo-pallescent* [196, 204]*L. rupicola* [206]*L. straminea* [207]*L. sulphurata* [196, 199, 204]*Lecidella meiococca* [199]*L. vorax* [199]*Micarea austroternaria* [204]*M. isabellina* [199]*Pertusaria pycnotelia* [199]**165** $R_2 = R_4 = R_5 = Cl; R_7 = H$ **166** $R_2 = R_4 = R_7 = Cl; R_5 = H$ **167** $R_2 = R_5 = R_7 = Cl; R_4 = H$ **168** $R_2 = H; R_4 = R_5 = R_7 = Cl$ **169** $R_2 = R_4 = R_5 = R_7 = Cl$

Table 10. Other trioxygenated xanthenes detected in lichens and fungi

170 3,6-Di-*O*-acetyl-1-hydroxy-2,4,5-trichloronorlichexanthone or erythrommone

Haematomma erythromma [200]

171 4-Dechloro-8-*O*-methylthiomelin

Rinodina thiomela [214]

172 2-Dechloro-8-*O*-methylthiomelin

Rinodina thiomela [214]

173 8-*O*-Methylthiomelin

Rinodina thiomela [214]

174 2-Dechlorothiomelin

Rinodina thiomela [210]

175 4-Dechlorothiomelin

Rinodina thiomela [214]

176 Thiomelin

Rinodina thiomela [214]

177 Ravenelin

Helminthosporium ravenelii [192]

H. turcicum [192]

178 Northiomelin

Rinodina thiomela [210]

179 1,3,6-Trimethoxy-8-methylxanthone

Parmelia formosana [211]

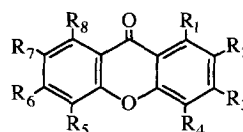
180 1,3,6-Tri-*O*-methylarthothelin

Dimelaena sp. [197]

D. australiensis [199]

181 1,4,6-Trimethoxy-3-methylxanthone

Parmelia formosana [211]



	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈
170	OH	Cl	OAc	Cl	Cl	OAc	H	H
171	OH	Cl	H	H	OMe	Me	H	OMe
172	OH	H	H	Cl	OMe	Me	H	OMe
173	OH	Cl	H	Cl	OMe	Me	H	OMe
174	OH	H	H	Cl	OMe	Me	H	OH
175	OH	Cl	H	H	OMe	Me	H	OH
176	OH	Cl	H	Cl	OMe	Me	H	OH
177	OH	H	Me	OH	H	H	H	OH
178	OH	H	Me	OH	Cl	H	Cl	OH
179	OMe	H	OMe	H	H	OMe	H	Me
180	OMe	Cl	OMe	Cl	Cl	OMe	H	Me
181	OMe	H	Me	OMe	H	OMe	H	H

chlorine-containing derivatives of norlichexanthone, achieved by using the condensation of an appropriately substituted methyl or ethyl orsellinate and phloroglucinol or 2-chlorophloroglucinol in the key step; previously Elix *et al.* reported the synthesis of several trioxygenated lichen xanthenes [256].

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