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BIOGENETIC PROPOSALS REGARDING AUCUPARINS AND XANTHONES[1]

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Abstract—The co-occurrence of aucuparins and xanthones in plants, as well as the oxygenation pattern of the natural representatives of these classes of compounds, become understandable, if their biosynthesis is considered to involve interaction of 5-dehydroshikimic acid with activated acetic acid units through Michael type addition and acylation, respectively.

THE considerable number of xanthones discovered since the publication of the review paper by Roberts[2] or the chapter in Dean's book[3] calls for a new formulation of ideas on the biosynthesis of this class of natural compounds. They represent an unusually interesting case for such studies, since two routes are available for the construction of their skeleton. Thus, like the benzophenones, the xanthones produced by micro-organisms are polyketides. This is revealed not only through inspection of the substitution pattern (Table 1), but has actually been proved by direct experimentation, at least in the case of *Penicillium patulum* Bainier-Thom.[4–7]

Only comparative biochemistry can be adduced to show that xanthones produced by higher plants are polyketi-shikimides[8] (Table 2). The acetate–malonate-derived portion of the molecule (ring A) most frequently shows the phloroglucinol pattern (1,3-substitution,[9] present in thirty-one representatives). All known xanthones which possess a mono-oxygenated A-ring, bear the function at C-1 (thirteen representatives) and, indeed, laboratory analogy shows preferential occurrence of nuclear reduction at position 3.[10] This points to

[1] For a preliminary report see O. R. GOTTLIEB and M. TAVEIRA MAGALHÃES, *Anais Acad. Brasil. Ciênc.* **38,** 439 (1966).

[2] J. C. ROBERTS, *Chem. Rev.* **61,** 591 (1961).

[3] F. M. DEAN, *Naturally Occurring Oxygen Ring Compounds*, p. 266. Butterworths, London (1963).

[4] A. J. BIRCH, R. A. MASSY-WESTROPP, R. W. RICKARDS and H. SMITH, *J. Chem. Soc.* 360 (1958).

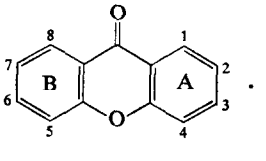
[5] W. J. MCMASTER, A. I. SCOTT and S. TRIPETT, *J. Chem. Soc.* 4628 (1960).

[6] A. RHODES, B. BOOTHROYD, M. P. MCGONAGLE and G. A. SOMMERFIELD, *Biochem. J.* **81,** 28 (1961).

[7] A. J. BIRCH, *Proc. Chem. Soc.* 1 (1962).

[8] For designations and a classification of natural compounds see O. R. GOTTLIEB and W. B. MORS, *Planta Med.* **11,** 377 (1963).

[9] The numbering system is based on xanthene-9-one as the basic skeleton, following the rules given in *Handbook for Chemical Society Authors*, Special Publication No. 14. The Chemical Society, London (1960); the letters are added for convenience (see text):



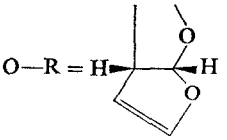
[10] A. C. JAIN, O. P. MITTAL and T. R. SESHADRI, *J. Sci. Ind. Res.* (*India*) **12B,** 647 (1953).

an order of the reduction sequence, since totally reduced acetate-derived xanthone rings also occur (eleven representatives). It is considered that 1,3,4- and 1,2,3,4-oxygenated A-rings (three representatives) arise through additional oxidation of phloroglucinol types, whereas 1,2- and 1,2,4-oxygenated A-rings derive in an analogous manner from 1-hydroxyxanthones (three representatives). Clearly, however, the arbitrary elements inherent to such a classification (Table 2) will not be lost on the reader.

The major question in relation to the remaining part of the molecule (ring B *plus* carbonyl) concerns the point of the shikimate pathway at which the $C_6 \cdot C_1$ fragment derives. Recent findings seem to provide clues to the answer.

TABLE 1. BENZOPHENONES AND XANTHONES ISOLATED FROM MYCOPHYTA

Benzophenone	Substitution pattern 2	3	4	5	6	2′	3′	4′	5′	6′	Occurrence
Griseophenone A	OMe		OMe	Cl	OH	OMe		OH		Me	As I[5]
Griseophenone B	OH		OMe	Cl	OH	OMe		OH		Me	As I[5]
Griseophenone C	OH		OMe		OH	OMe		OH		Me	As I[5]
Griseophenone Y	OMe		Me	Cl	OH	OMe		OH		Me	As I[5]
Sulochrin	OH		Me		OH	OMe		OH		COOMe	MoI[35]
Xanthone	**1**	**2**	**3**	**4**			**5**	**6**	**7**	**8**	
Griseoxanthone C	OH		OMe					OH		Me	As I[36]
Pinsellin	OH		Me						OH	COOMe	As II[36]
Pinsellic acid	OH		Me						OH	COOH	As II[36]
Sterigmatocystin	OMe		O—R							OH	De I[36]
Ravenelin	OH		Me	OH						OH	De II,[36] III[36]
Lichexanthone	OH		OMe					OMe		Me	Pa I[36]
Thiophanic acid	OH	Cl	OH	Cl			Cl	OH	Cl	Me	Le I[37]



Key to plant sources:

FUNGI—As, Aspergillaceae: I, *Penicillium patulum* Bainier-Thom.; II, *P. amarum*. Mo, Moniliaceae: I, *Oöspora sulphurea-ochracea*. De, Dematiaceae: I, *Aspergillus versicolor*; II, *Helminthosporium Ravenelii*; III, *H. turcicum*.

LICHENS—Pa, Parmeliaceae: I, *Parmelia formosana*. Le, Lecanoraceae: Le, *Lecanora rupicola* (L.) Zahlbr.

Ellagic acid (I) is a common constituent of the Theaceae, Dipterocarpaceae, Elatinaceae, Frankeniaceae, Tamaricaceae and Cistaceae, families belonging to the plant order Parietales *sensu latissimo* Emberger.[11] It has not yet been located in the Guttiferae, a somewhat surprising fact, in view of the close morphological relationship of this family with the former ones. The Guttiferae are characterized by the presence of xanthones. *Kielmeyera* species,

[11] P. LEBRETON and M.-P. BOUCHEZ, *4th Int. Symp. Chemistry of Natural Products*. International Union of Pure and Applied Chemistry, Royal Institute of Technology, Stockholm (1966); *apud* Abstract Book.

[35] H. NISHIKAWA, *Acta Phytochim. (Japan)* **11**, 167 (1939); *apud Chem. Abstr.* **34**, 4386 (1940).

[36] For reference to the original literature see Ref. 2.

[37] S. HUNECK, *Tetrahedron Letters* 3547 (1966).

TABLE 2. XANTHONES ISOLATED FROM TRACHEOPHYTA, ARRANGED ACCORDING TO THE OXYGENATION PATTERN OF THE SHIKIMATE-DERIVED RING B

	Substitution pattern								
	A-ring				B-ring				
Trivial name	1	2	3	4	5	6	7	8	Occurrence
Mono-oxygenation									
	OH		OMe		OH				Gu I,[13] II,[13] III,[15] VII[38]
	OH		OH		OMe				Gu IX[43]
	OMe		OMe		OH				Gu I,[13] II,[13] III[15]
6-Dehydroxyjacareubin	OH	P—O			OH				Gu III,[39] IX,[39] sp[19]
	OH	S	OH		OH				Gu sp[19]
Globuxanthone	OH	OH		T	OH				Gu XV[40]
	OH				OH				Gu VIII,[41] sp[19]
Guanandin	OH				OH	S			Gu IX,[39] sp[19]
Dehydrocycloguanandin	OH				O—P				Gu IX[39]
Isoguanandin	OH				OH			S	Gu IX[39]
Scriblitifolic acid	OH				OMe	U			Gu XI[42]
	OH				OH	V			Gu sp[19]
	OH				OH	W			Gu sp[19]
					OH				Gu IX,[43] VIII[41]
Polygalaxanthone B	OMe	OMe	OMe	OMe			OMe		Po I[44]
Gentisin	OH		OMe				OH		Gu IX[43]; Ge I[36]
Isogentisin	OH		OH				OMe		Ge I[36]
	OH		OMe				OMe		Gu IX[43]
Mbarraxanthone	OH		OH	S			OH		Gu XV[45]
Osajaxanthone	OH	P—O					OH		Gu II,[39] sp[19]; Mo I[46]
	OH	S	OH				OH		Gu sp[19]
Euxanthone	OH						OH		Gu V,[47] VII,[38] VIII,[41] X,[48] XV[49], XVI[36]
	OH						OMe		GU II,[47] V[50]
							OH		Gu III,[15] V,[50] VIII[51]
							OMe		Gu I,[12] II,[14] VIII[52]
Di-oxygenation									
	OH		OH		OH	OH			Gu X,[48] XV,[49] sp[19]; Mo II [722]
	OMe		OH		OH	OH			Gu X[48]
	OH	S	OH		OH	OH			Gu X[48]

[38] T. R. GOVINDACHARI, B. R. PAI, P. S. SUBRAMANIAM, U. R. RAO and M. MUTHUKUMARASWAMY, *Tetrahedron* **23**, 243 (1966).

[39] O. R. GOTTLIEB, M. TAVEIRA MAGALHÃES, M. OTTONI DA SILVA PEREIRA, A. A. LINS MESQUITA, D. DE BARROS CORRÊA and G. G. DE OLIVEIRA, *Tetrahedron*, in press.

[40] H. D. LOCKSLEY, I. MOORE and F. SCHEINMANN, *J. Chem. Soc.* (C) 2186 (1966).

[41] R. A. FINNEGAN, J. K. PATEL and P. L. BACHMAN, *Tetrahedron Letters* 6087 (1966).

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[44] J. MORON, J. POLONSKY and H. POURRAT, *Bull. Soc. Chim.* 130 (1967).

[45] H. D. LOCKSLEY, I. MOORE and F. SCHEINMANN, *J. Chem. Soc.* (C) 2265 (1966).

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[48] B. JACKSON, H. D. LOCKSLEY and F. SCHEINMANN, *J. Chem. Soc.* (C) 178 (1966).

[49] H. D. LOCKSLEY, I. MOORE and F. SCHEINMANN, *J. Chem. Soc.* (C) 430 (1966).

[50] G. M. STEFANI, O. R. GOTTLIEB and M. TAVEIRA MAGALHÃES, Unpublished work.

[51] R. A. FINNEGAN and P. L. BACHMAN, *J. Pharm. Sci.* **54**, 633 (1965).

[52] L. CROMBIE, D. E. GAMES and A. MCCORMICK, *Tetrahedron Letters* 145 (1966).

TABLE 2—*continued*

Trivial name	Substitution pattern: A-ring 1	2	3	4	B-ring 5	6	7	8	Occurrence
Di-oxygenation—*continued*									
Jacareubin	OH	P—O			OH	OH			Gu IX,[36] X[48]
Macluraxanthone	OH	P—O		S	OH	OH			Mo I[18]
Alvaxanthone	OH	S	OH		OH	OH			Mo I[53]
Ugaxanthone	OH		OH	S	OH	OH			Gu XV[45]
Morellin	OH	P—O		S	(O)	=O	*		Gu XIII[26,54]
Dihydroisomorellin	OH	R—O		S	(O)	=O	*		Gu XIII[54]
Desoxymorellin	OH	P—O		S	(O)	=O	*		Gu XIII[54]
Gambogic acid	OH	Q—O		S	(O)	=O	*		Gu XIII,[55] XIV[27]
Morellic acid	OH	P—O		S	(O)	=O	*		Gu XIII[54]
Isomorellic acid	OH	P—O		S	(O)	=O	*		Gu XIII[54]
Symphoxanthone	OH	OH		T	OH	OH			Gu XV[40]
	OH				OH	OH			Gu VII,[38] XV[49]
Norathyriol	OH		OH			OH	OH		Gu XV,[49] sp[19]; As I[56]; Mo I[57]
Athyriol	OH		OMe			OH	OH		As I[56]
Isoathyriol	OH		OH			OH	OMe		As I[56]
Mangiferin	OH	G	OH			OH	OH		As I[56]; Ir I, II, III, IV[29]; Li I[58]; Le I[59]; An I[36]; Hi I[60]; Bi I[61]; Sa I[62]
Mangostin	OH	S	OH			OH	OMe	S	Gu XII[36]
Polygalaxanthone A	OMe	OMe		OMe		OCH_2	O		Po I[44]
Swertinin	OMe		OMe				OH	OH	Ge IV[36]
Decussatin	OMe		OMe				OMe	OH	Ge IV[36]
4,7-Dimethoxybellidin	OH		OH	OMe			OMe	OH	Ge II[63]
	OH						OH	OMe	Gu IV,[64] V[65]
	OH						OMe	OMe	Gu IV[64]
							OH	OMe	Gu III,[15] V[50]
Desmethylbellidifolin	OH		OH		OH			OH	Ge II[63]
Bellidifolin	OH		OMe		OH			OH	Ge II[63]
Isobellidifolin	OH		OH		OMe			OH	Ge II[63]

* For a type-formula see (XII), for specific derivatives, Refs. 26, 27, 54, 55.

[53] M. L. WOLFROM, F. KOMITSKY, JR., and P. M. MUNDELL, *J. Org. Chem.* **30,** 1088 (1965).
[54] C. G. KARANJGAONKAR, P. M. NAIR and K. VENKATARAMAN, *Tetrahedron Letters* 687 (1966).
[55] P. YATES, S. S. KARMARKAR, D. ROSENTHAL, G. H. STOUT and V. F. STOUT, *Tetrahedron Letters* 1623 (1963).
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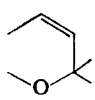
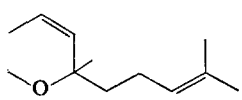
[63] K. R. MARKHAM, *Tetrahedron* **21,** 3687 (1965).
[64] O. R. GOTTLIEB, M. TAVEIRA MAGALHÃES and G. M. STEFANI, *Tetrahedron* **22,** 1785 (1966).
[65] L. D. ANTONACCIO, G. M. STEFANI, O. R. GOTTLIEB and M. TAVEIRA MAGALHÃES, *Anais Acad. Brasil. Ciênc.* **37,** 231 (1965).

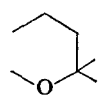
TABLE 2—*continued*

Trivial name	Substitution pattern: A-ring 1	2	3	4	B-ring 5	6	7	8	Occurrence
Di-oxygenation—*continued*									
Swerchirin	OH		OMe		OMe			OH	Ge III,[63] V[36]
Swertianol	OH		OH		OH			OMe	Ge VI,[36] VII[36]
Corymbiferin	OH		OH	OMe	OMe			OH	Ge II,[63] III[36, 63]
Tri-oxygenation									
Celebixanthone	OH				OH	OH	OMe	S	Gu VI[66]
					OH	OH	OMe		Gu II[13]
					OH	OMe	OMe		Gu I, II,[13] III[15]
					OMe	OH	OMe		Gu III[15]
					OH	OCH_2	O		Gu II,[13] III[15]
					OMe	OCH_2	O		Gu I, II[13]
						OH	OH	OMe	Gu III[15]
						OH	OMe	OMe	Gu III[15]

Special substituents:


P--O


Q--O

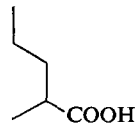

R--O

glucose

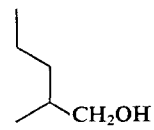
G


S

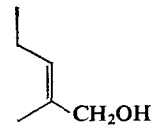

T



U



V



W

Key to plant sources:

FILICINEAE—As, Aspidiaceae: I, *Athyrium mesosorum* Makino.

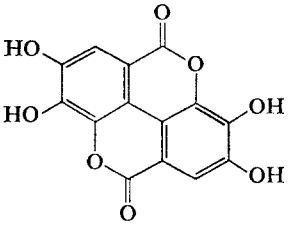
ANGIOSPERMAE. MONOCOTYLEDONEAE—Ir, Iridaceae: I, *Iris*, all spp. of the Pogoniris section; II, *Iris pseudocorus* Fischer; III, *I. dichotoma* Pallas; IV, *Belamcanda chinensis* (L.) Leman. Li, Liliaceae: I, *Smilax glycyphylla*.

ANGIOSPERMAE. DICOTYLEDONEAE. ARCHICHLAMYDEAE—Mo, Moraceae: I, *Maclura pomifera* Raf.; II, *Chlorophora tinctoria* L. Le, Leguminosae-Papilionatae: I, *Hedysarum obscurum* L. Po, Polygalaceae: I, *Polygala paenea* L. An, Anacardiaceae: I, *Mangifera indica* L. Hi, Hippocrateaceae: I, *Salacia prinoides* L. Gu, Guttiferae: I, *Kielmeyera coriacea* Mart.; II, *K. corymbosa* (Spr.) Mart.; III, *K. speciosa* St. Hil.; IV, *K. petiolaris* (Spr.) Mart.; V, *K. excelsa* Camb.; VI, *Cratoxylon celebicum* Blume; VII, *Mesua ferrea* L.; VIII, *Mammea americana* L.; IX, *Calophyllum brasiliense* Camb.; X, *C. sclerophyllum* Vesq.; XI, *C. scriblitifolium* Hend. & Wyatt Smith; XII, *Garcinia mangostana*; XIII, *G. morella*; XIV, *G. Hanburryi*; XV, *Symphonia globulifera* L.; XVI, *Platonia insignis* Mart. Bi, Bixaceae: I, *Aphlota madagascariensis* Clos.

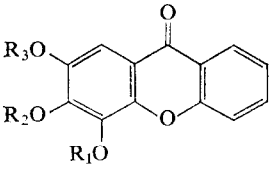
ANGIOSPERMAE. DICOTYLEDONEAE. SYMPETALAE—Sa, Sapotaceae: I, *Madhuca utilis* (Ridley) Lam. Ge, Gentianaceae: I, *Gentiana lutea*; II, *G. bellidifolia*; III, *G. corymbifera* T. Kirk; IV, *Swertia decussata*; V, *S. chirata*; VI, *S. japonica* Makino; VII, *S. tosaensis*.

[66] G. H. STOUT, V. F. STOUT and M. J. WELSH, *Tetrahedron* **19**, 667 (1963).

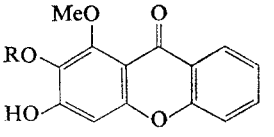
for instance, contain, among others, the five xanthones (II)[12–15] and the two xanthones (III),[15] together with the aucuparin (IVa).[14, 16] Both the relationship of the organisms which produce these substances and the oxygenation pattern of (I), (II), (III) and (IV) suggest that ellagic acid, xanthones and aucuparins possess a common precursor. Since in the case of ellagic acid this is clearly gallic acid, and hence[17] 5-dehydroshikimic acid (V), it seems



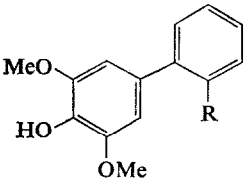
(I)



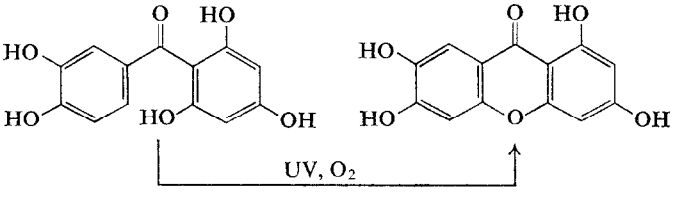
(II) a, $R_1=R_2=H$, $R_3=Me$
b, $R_1=H$, $R_2=R_3=Me$
c, $R_1=R_3=Me$, $R_2=H$
d, $R_1=H$, $R_2—R_3=CH_2$
e, $R_1=Me$, $R_2—R_3=CH_2$



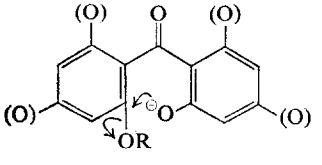
(III) a, R=H
b, R=Me



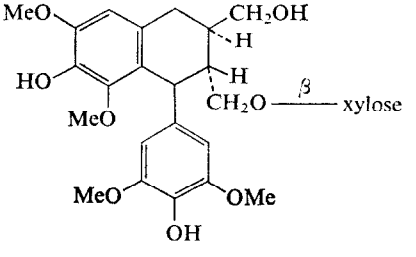
(IV) a, R=H
b, R=OMe



(IX) (X)



(XI)



(XIII)

[12] A. PIMENTA, A. A. LINS MESQUITA, M. CAMEY, O. R. GOTTLIEB and M. TAVEIRA MAGALHÃES, *Anais Acad. Brasil. Ciênc.* **36,** 39 (1964).
[13] O. R. GOTTLIEB, M. TAVEIRA MAGALHÃES, M. CAMEY, A. A. LINS MESQUITA and D. DE BARROS CORRÊA, *Tetrahedron* **22,** 1777 (1966).
[14] D. DE BARROS CORRÊA, O. R. GOTTLIEB and M. TAVEIRA MAGALHÃES, *Anais Acad. Brasil. Ciênc.* **38,** 296 (1966).
[15] G. G. DE OLIVEIRA, A. A. LINS MESQUITA, O. R. GOTTLIEB and M. TAVEIRA MAGALHÃES, *Anais Acad. Brasil. Ciênc.* **38,** 421 (1966); **39,** in press.
[16] A. PIMENTA, A. A. LINS MESQUITA, M. CAMEY, O. R. GOTTLIEB and M. TAVEIRA MAGALHÃES, *Anais Acad. Brasil. Ciênc.* **36,** 283 (1964).
[17] E. HASLAM, R. D. HAWORTH and P. F. KNOWLES, *J. Chem. Soc.* 1854 (1961).

reasonable to assume that xanthones and aucuparins are also derived basically from this metabolite.

According to the suggestion contained in Chart 1, 5-dehydroshikimic acid (V) acts as the initiator of a reaction by which it condenses successively with three activated acetic (malonic) acid units. Since it is impossible to judge at which stage cyclization and eventual loss or gain of hydroxy-groups of the acetate-derived portion occurs, this is represented symbolically as the phenol (VI). If the precursors (V) and (VI) interacted by a Michael type addition (route 1), biphenyl derivatives of the aucuparin type (IV) would result and if acylation was involved (route 2), xanthones would result.

TABLE 3. BENZOPHENONES ISOLATED FROM TRACHEOPHYTA

Benzophenone	Substitution pattern 2	3	4	5	6	2′	3′	4′	5′	6′	Occurrence
Cotoin	OH		OMe		OH						La I,[67] III[68]
Hydrocotoin	OH		OMe		OMe						La II[67]
Methylhydrocotoin	OMe		OMe		OMe						La II[67]; Rh I[67]
Protocotoin	OH		OMe		OMe		OCH_2 O				La II[67]
Methylprotocotoin	OMe		OMe		OMe		OCH_2 O				La II[67]
	OH		OH		OH			OH			Mo I[69]
Maclurin	OH		OH		OH		OH	OH			Mo II[70]; Gu I[19]
	OH		OMe	Me	OMe						My I[71]
	OMe		OMe	Me	OH						My I[71]
Scleroin	OH	OMe	OMe	OH							Le I[23]
Cearoin	OH		OMe	OH							Le II,[32] III[32]
			OH								Ma I[72]
			OMe								Zi I[73]

Key to plant sources:

ANGIOSPERMAE. MONOCOTYLEDONEAE—Zi, Zingiberaceae: I, *Costus speciosus* Smith.

DICOTYLEDONEAE. ARCHICHLAMYDEAE—La, Lauraceae: I, *Aniba coto* (Rusby) Kostermans; II, *A. pseudocoto* (Rusby) Kostermans; III, *A. Duckei* Kostermans. Rh, Rhamnaceae: I, *Rhamnus purshiana.* Mo, Moraceae: I, *Morus alba*; II, *Chlorophora tinctoria* (L.) Gaud. Gu, Guttiferae: I, *Symphonia globulifera* L. My, Myrtaceae: I, *Leptospermum Luehmanni.* Le, Leguminosae-Papilionatae: I, *Machaerium scleroxylon* Tul.; II, *Dalbergia cearensis* Ducke; III, *D. violacea* (Vog.) Malme. Ma, Magnoliaceae: I, *Talauma mexicana.*

Formulation of the spiranic intermediates (VII) and (VIII) is attractive on several counts:

(1) The mechanism of their formation (Chart 1) provides an explanation for the activating function of hydroxyl in the shikimate derived ring. In the absence of such a group, ring closure does not seem to occur. It appears indeed significant that most of the natural benzophenones (Table 3) and neoflavanoids (Chart 2) lack a free hydroxyl at the correct position in the shikimate moiety. Of the two known exceptions to this rule, 2,4,4′,6-tetrahydroxybenzophenone and maclurin (IX) (Table 3), the latter one is notable exactly because of its

[67] For reference to the original literature see W. KARRER, *Konstitution und Vorkommen der organischen Pflanzenstoffe.* Birkhäuser, Basel (1958).

[68] O. R. GOTTLIEB and W. MORS, *J. Am. Chem. Soc.* **80,** 2263 (1958).

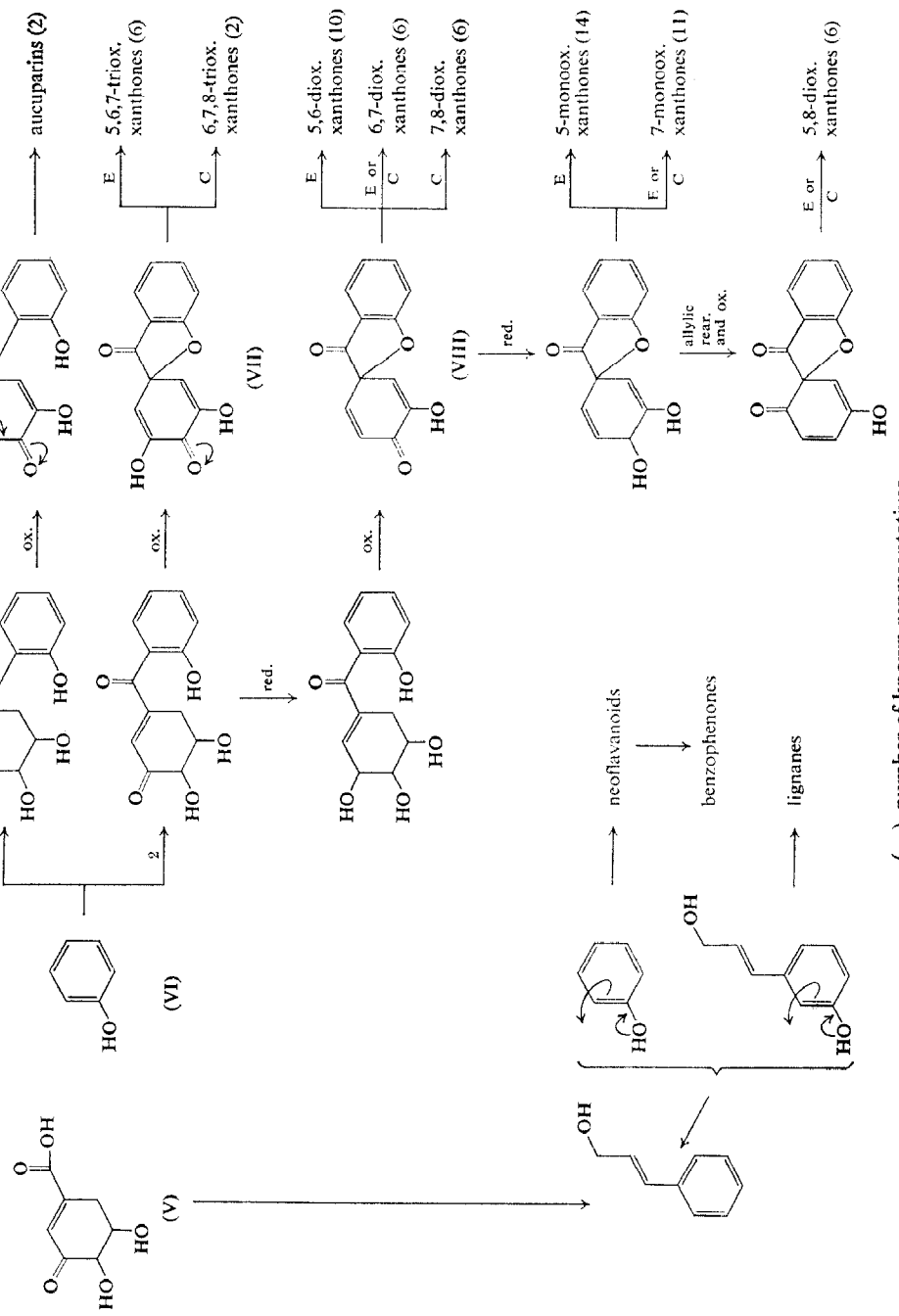
[69] A. SPADA, R. CAMERONI and M. T. BERNABEI, *Gazz. Chim. Ital.* **86,** 46 (1956).

[70] A. KOMAROWSKY and S. VON KOSTANECKI, *Chem. Ber.* **27,** 1997 (1894).

[71] V. H. POWELL and M. D. SUTHERLAND, *Australian J. Chem.* **16,** 281 (1963).

[72] E. S. PALLARES and H. M. GARZA, *Chem. Abstr.* **42,** 2730 (1948).

[73] M. L. SHARMA, M. C. NIGAM and K. L. HANDE, *Perfumery Essent. Oil Record* **54,** 579 (1963).



( ), number of known representatives.

CHART 1. PROPOSED BIOSYNTHETIC ROUTES.

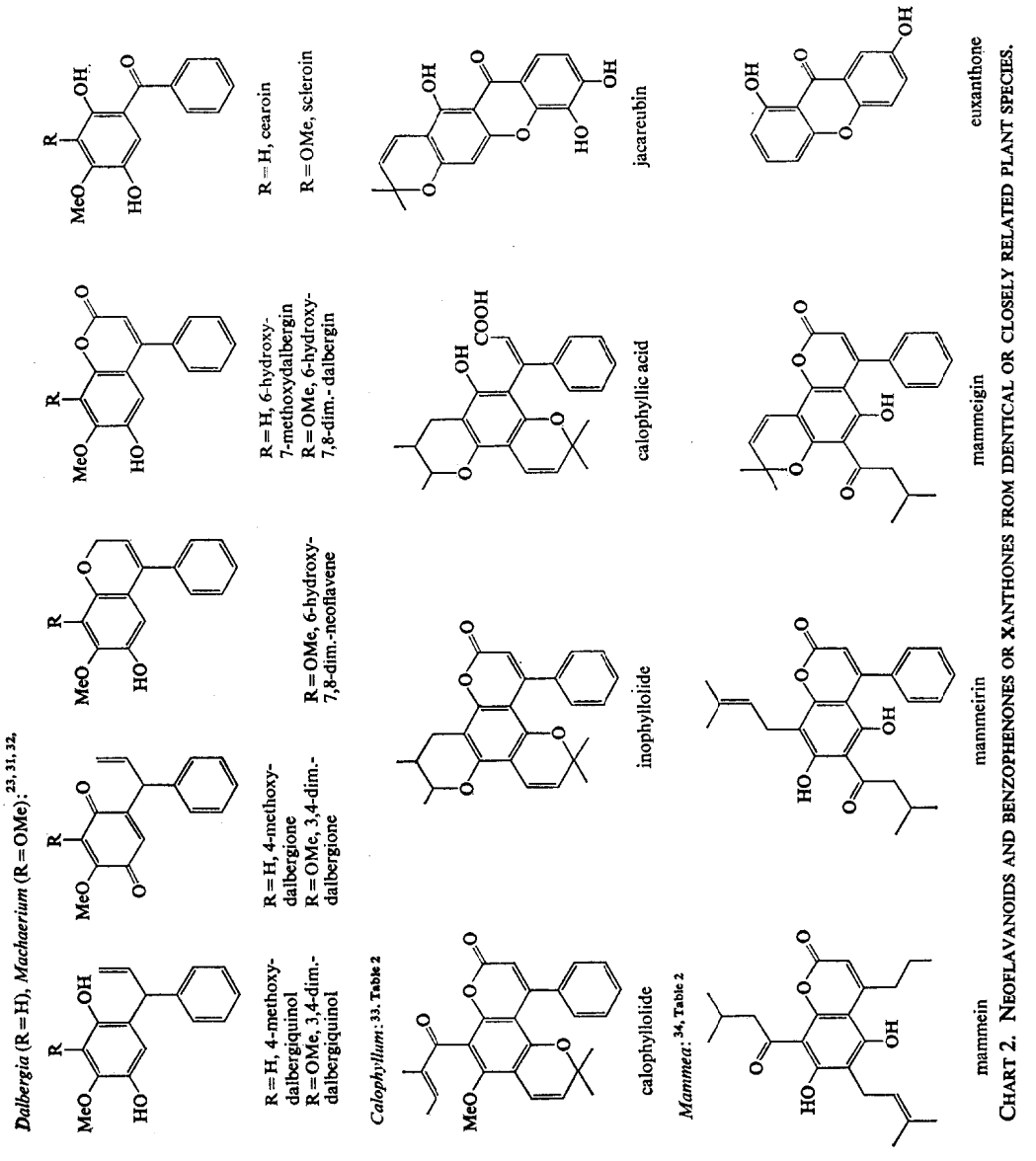


CHART 2. NEOFLAVANOIDS AND BENZOPHENONES OR XANTHONES FROM IDENTICAL OR CLOSELY RELATED PLANT SPECIES.

[31] W. B. EYTON, W. D. OLLIS, I. O. SUTHERLAND, O. R. GOTTLIEB, M. TAVEIRA MAGALHÃES and L. M. JACKMAN, *Tetrahedron* **21**, 2683 (1965).

[32] W. D. OLLIS, In *Recent Advances in Phytochemistry* (edited by T. MABRY, R. E. ALSTON and V. C. RUNECKLES). Appleton-Century-Crofts, New York (1967).

[33] J. POLONSKY, *Bull. Soc. Chim.* **24**, 1079 (1957).

[34] R. A. FINNEGAN and W. H. MUELLER, *J. Org. Chem.* **30**, 2342 (1965).

co-occurrence with 1,3,5,6- and 1,3,6,7-tetraoxygenated xanthones in Moraceae species.[18, 19,*] The relationship of neoflavanoids and benzophenones has been commented previously.[23]

(2) The mechanisms of transformation of the spiranic intermediates (VII) and (VIII) would account for the special features which can be noted in the oxygenation pattern of natural xanthones (Table 2). Clearly, in xanthones position 6 may appear unsubstituted, in contrast to the usual shikimate-derived molecules or parts of molecules where oxygenation usually occurs at the *para* position to the side chain whatever the remaining substitution pattern may be. Indeed, all observed oxygenation patterns can be deduced by the pathways summarized in Chart 1. The final step requires in all cases either a dienone–phenol or a dienol–benzene rearrangement. This does seem to occur more frequently through a nucleophilic attack by the ether bridge (route E), than through an electrophilic attack by the carbonyl bridge (route C).

(3) The existence of such spiranic intermediates has been in fact proved in micro-organisms which produce griseoxanthone.[4–7] It should be noted, however, that the cyclization mechanism here probably involves nucleophilic displacement of an intermediate with a good leaving group, such as pyrophosphate (XI, $R = P_2O_6H_3$),[24] for which laboratory models exist.[20, 21, 25] The oxygenation pattern of the xanthone precursors in higher plants precludes the possibility of cyclization by the same mechanism.

(4) Lastly, an additional argument in favour of the formulation of a dienone intermediate in xanthone biosynthesis is the fact that it allows the formation of the morellins (modified xanthones of type (XII), see also Table 2) to be rationalized through isoprenylation reactions (Chart 3) with greater simplicity than has hitherto been possible.[26, 27]

In Guttiferae species, xanthones co-occur with neoflavanoids (Chart 2, *Calophyllum*, *Mammea*). In accordance with the proposed scheme, the pathway to these compounds would diverge at the point where 5-dehydroshikimic acid reacts with acetic acid, either directly (to yield xanthones) or after transformation to a cinnamyl derivative (to yield neoflavanoids and benzophenones).[23] Analogous explanations would fit the interesting cases of the apparently substitutive presence of either mangiferin (a glycoxanthone, see Table 2) or glycyphyllin (a dihydrochalcone) in two forms of *Smilax glycyphylla* (Liliaceae)[28] and of either mangiferin or glycoflavones in different sections of the genus *Iris* (Iridaceae).[29]

* This fact, together with the possibility of transforming certain benzophenones into xanthones by chemical[20,21] and photochemical[22] oxidations (IX→X), has led very recently to the suggestion that oxidative coupling is responsible for the biosynthesis of xanthones in higher plants.[19] It should be emphasized, however, that this postulate was based on the occurrence of 5,6- 6,7- (and 5,6,7-) ring B oxygenated xanthones. It does not explain reasonably the peculiarities of the oxygenation pattern of any others. The intermediary existence of benzophenones in xanthone biosynthesis seems, consequently, at most restricted to special cases.

[18] M. L. WOLFROM, F. KOMITSKY, JR., G. FRAENKEL, J. H. LOOKER, E. E. DICKEY, P. MCWAIN, A. THOMSON, F. M. MUNDELL and O. M. WINDRATH, *J. Org. Chem.* **29**, 692 (1964).
[19] H. D. LOCKSLEY, I. MOORE and F. SCHEINMANN, *Tetrahedron* **23**, 2229 (1967).
[20] J. R. LEWIS and B. H. WARRINGTON, *J. Chem. Soc.* 5074 (1964).
[21] J. R. LEWIS, *Proc. Chem. Soc.* 373 (1963).
[22] A. JEFFERSON and F. SCHEINMANN, *Nature* **207**, 1193 (1965).
[23] W. B. EYTON, W. D. OLLIS, M. FINEBERG, O. R. GOTTLIEB, I. SALIGNAC DE SOUZA GUIMARÃES and M. TAVEIRA MAGALHÃES, *Tetrahedron* **21**, 2697 (1965).
[24] A. JEFFERSON and F. SCHEINMANN, *J. Chem. Soc.* (C) 175 (1966).
[25] D. H. R. BARTON and A. I. SCOTT, *J. Chem. Soc.* 1767 (1958).
[26] G. KARTHA, G. N. RAMACHANDRAN, B. H. BHAT, P. M. NAIR, V. K. V. RAGHAVAN and K. VENKATARAMAN, *Tetrahedron Letters* 459 (1963).
[27] W. D. OLLIS, M. V. J. RAMSAY, I. O. SUTHERLAND and S. MONGKOLSUK, *Tetrahedron* **21**, 1453 (1965).
[28] A. H. WILLIAMS, In *Comparative Phytochemistry* (edited by T. SWAIN), p. 302. Academic Press, New York (1966).
[29] E. C. BATE-SMITH and J. B. HARBORNE, *Nature* **198**, 1307 (1963).

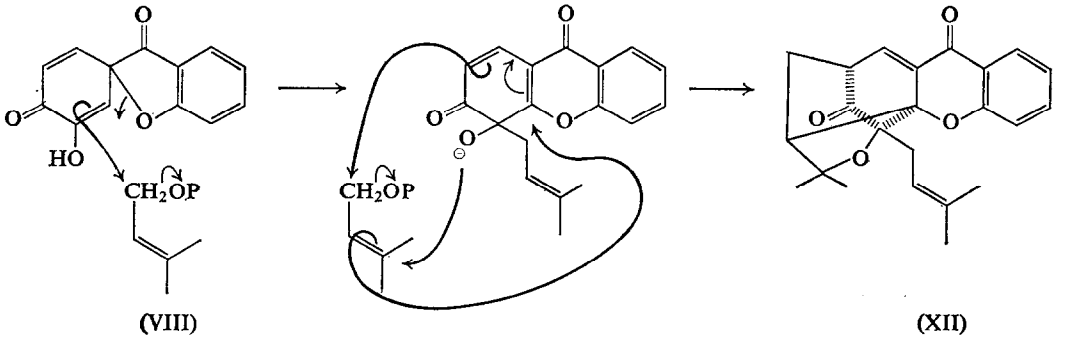


CHART 3. PROPOSED BIOSYNTHETIC ROUTE TO THE MORELLINS.

In *Sorbus* species (family Rosaceae), aucuparins co-occur with lyonia-xyloside (XIII).[30] Here, consequently, 5-dehydroshikimic acid may either condense with acetic acid (to yield aucuparins) or again lead to a cinnamyl derivative. If dimerization of this precursor to lignane is formulated as a nucleophilic attack of an activated aromatic ring of one cinnamyl unit upon the side-chain α-carbon of another one, it recalls closely the recently proposed mechanism of the formation of neoflavanoids.[23] A unified pattern (Chart 1) thus emerges for the biosynthesis of several classes of phenolic compounds.

[30] H. ERDTMAN, In *Chemical Plant Taxonomy* (edited by T. SWAIN), p. 103. Academic Press, New York (1963).