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3-ISOPRENYLCOUMARINS

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Key Word Index—3-Isoprenylcoumarins; biogenesis; biological activity; synthesis.

Abstract—Natural and synthetic 3-isoprenylcoumarins are reviewed. Their biogenesis and biological activities are also considered.

INTRODUCTION

The term coumarin is applied to a large group of naturally occurring compounds possesing a 2H-1-benzopyran-2-one nucleus. Most coumarins are biogenetically derived from the shikimic acid pathway [1], but a significant number appear to be formed from a mixed shikimic acid/acetate pathway (4-phenylcoumarins) or totally from the acetate route (4-*n*-propyl-coumarins) [2].

The major feature in the diversification of simple coumarins is the widespread incorporation of prenyl units. Prenylation has been demonstrated to occur at the umbelliferone stage [3]. C-3 prenylated coumarins form an interesting group due to the biological activities that they show. The isoprene unit at C-3 usually appears as 1,1-dimethylallyl group rather than the 3,3-dimethylallyl moiety commonly found in other compounds. The aim of this review is to summarize the structures of all natural and synthetic 3-isoprenylcoumarins and their biological activities.

BIOGENESIS

A seemingly attractive hypothesis [4] about the biosynthesis of this group of coumarins is the suggestion that the 3-(1,1-dimethylallyl) coumarins arise via triple rearrangement from a 7-(3,3-dimethylallyloxy) coumarin precursor (Scheme 1). The co-occurrence, in some species, of the rearranged product with the 7-(3,3-dimethylallyloxy) coumarin (ramosin and ramosinin from *Haplophyllum ramosissimum* [5], obtisitsin [6] and obtusidin [7] from *Haplophyllum obtusifolium*) provides support for this proposal.

As rutamarin is a well known metabolite belonging to this group, experimental work has been carried out on this compound. As marmesin is not incorporated into the biogenetical pathway of rutamarin [8], it appears that the 1,1-dimethylallyl substituent is introduced before the formation of the dihydrofuran ring. 7-Hydroxycoumarin is a precursor of rutamarin but not of 7-(3,3-dimethylallyloxy) coumarin or the 6-prenyl derivative. Thus, these results do not support a pathway to rutamarin involving rearrangements of a 7-prenyloxycoumarin.

An alternative route to rutamarin and related compounds involves formation and Claisen rearrangement of a 4-prenyloxycoumarin (Scheme 2). This proposal was tested by tracer feeding experiments with *Ruta graveolens* [9,10]. The labelled compound [3-^{14}C]-4,7-dihydroxycoumarin was incorporated into rutamarin involving a rearrangement of the chain of the 4-prenyloxycoumarin. Although these 4,7-dioxygenated coumarins are obviously precursors of rutamarin, their acceptance as natural intermediates must await the demonstration of their occurrence as constituents of *R. graveolens*.

BIOLOGICAL ACTIVITY

3-Isoprenylcoumarins possess a wide range of biological properties (Table 1). The few studies on the relation-

Table 1. Biological activities of 3-isoprenylcoumarins

Coumarin	Biological activity	Ref.
9	Spasmolytic action	11
13	Cytostatic activity	12
	Molluscicidal activity	13, 14
15	Cytostatic activity	12
	Antispasmogenic effect	15, 16, 17
	Antihistaminic effect	18
17	Molluscicidal activity	14
	Antifertility effect	19
	Cytostatic activity	12, 20
	Photobinding DNA capacity	21
21	Molluscicidal activity	14
	Photobinding DNA capacity	21
19, 20	Spasmolytic action	22, 23
21	Inhibition of frijol seed germination capacity	24

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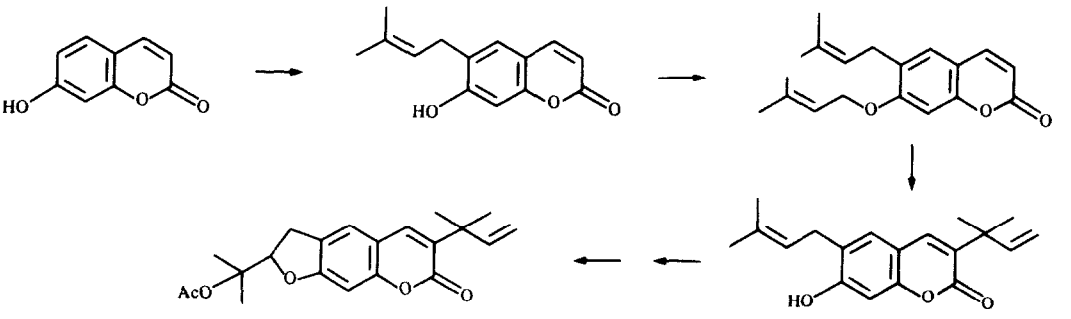
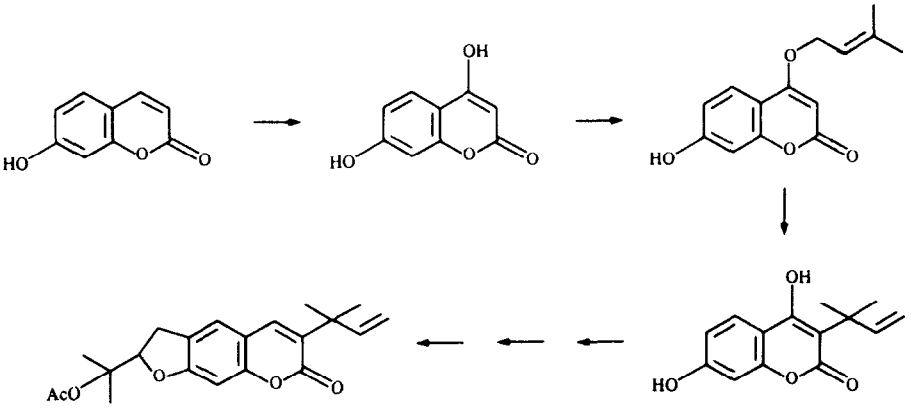
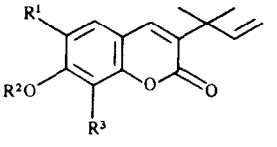


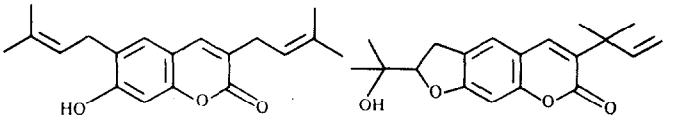
Scheme 1.



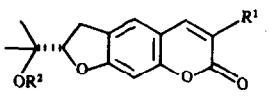
Scheme 2.



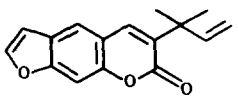
	R^1	R^2	R^3
1	H	H	H
2	H	Me	H
3	CH_2OH	Me	H
4	CHO	Me	H
5	$CH(OMe)_2$	Me	H
6	CH_2CHO	Me	H
7	$CH_2CH{=}C(Me)_2$	H	H
9	$CH_2CH{=}C(Me)_2$	Me	H
10	H	Me	$CH{=}CHC(Me){=}CH_2$
11	H	Me	$CH_2CH{=}C(Me)_2$
12	$CH_2CHOHCOH(Me)_2$	Me	H



8 **13**



	R^1	R^2
14	$C(Me)_2CH{=}CH_2$	H
15	$C(Me)_2CH{=}CH_2$	Ac
16	$CH_2CH{=}C(Me)_2$	H



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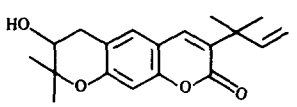

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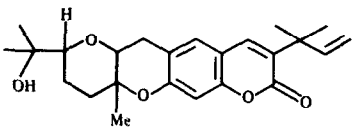

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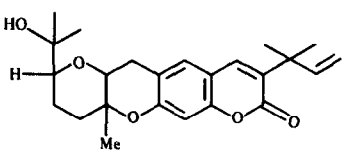

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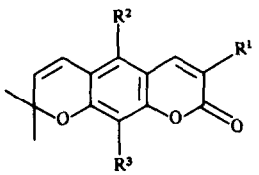
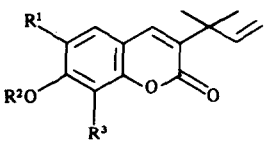
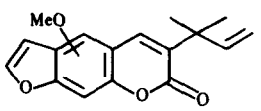


	R^1	R^2	R^3
21	$C(Me)_2CH{=}CH_2$	H	H
22	$CH_2CH{=}C(Me)_2$	H	H
23	$C(Me)_2CH{=}CH_2$	H	$CH_2CH{=}C(Me)_2$
24	$C(Me)_2CH{=}CH_2$	OH	$C(Me)_2CH{=}CH_2$



	R^1	R^2	R^3
25	OMe	H	H
26	OMe	Me	H
27	H	Me	OH
28	H	Me	OMe
29	$CH_2CH{=}C(Me)_2$	H	OMe
31	OMe	H	OH



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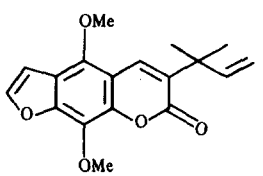

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Table 2. Natural 3-isoprenylcoumarins

Compound	Trivial name(s)	Original isolation [Ref.]	Synthesis ref.
1	Angustifolin	*Ruta angustifolia* [25]	26, 27
2	Coumarin Rr_8	*Ruta graveolens* [28]	26, 29
3	Pinnaterin	*Ruta pinnata* [30]	
4		*Ruta* sp. tene 29662 [31]	
5		*Ruta* sp. tene 29662 [31]	
6	Anisocoumarin A	*Clausena anisata* [32]	
7	Gravelliferone	*Ruta graveolens* [33]	34, 35, 36
8	Balsamiferone	*Amyris balsamifera* [37]	35, 38
9	Coumarin Rr_7	*Ruta graveolens* [28]	
10	Obtusifolin	*Haplophyllum obtusifolium* [39]	
11	Ramosinin	*Haplophyllum ramosissimum* [40]	41
12	Swietenocoumarin I	*Chloroxylon swietenia* [42]	
13	Heliettin	*Helietta longifoliata*	
	(racemic)	Britt. [43]	34
14	Chalepin	*Ruta chalepensis* [44]	36
15	Rutamarin	*Ruta chalepensis* [44]	36
		Ruta graveolens [45]	
16		*Amyris elemifera* DC. [46]	
17	Chalepensin	*Ruta chalepensis* [44]	
		Clausena indica Oliv. [48]	
	Xylotenin	*Chloroxylon swietenia* DC. [47]	
	Coumarin Rr_6	*Ruta graveolens* [28]	
18	Ulismoncadina	*Helietta parviflora* (Barr.) [24]	49
19	Clausmarin A	*Clausena pentaphylla* (Roxb.) DC. [23]	
20	Clausmarin B	*Clausena pentaphylla* (Roxb.) DC. [23]	
21		*Boenninghausenia albiflora* [50]	49, 51
22		*Amyris simplicifolia* [52]	53
23		*Ruta graveolens* [54]	34, 41
24	Clausarin	*Clausena pentaphylla*	
		(Roxb.) DC. [55]	56, 57
25	Diversin	*Ruta graveolens* [58]	4, 59
26	Rutacultin	*Ruta graveolens* [60]	4
27		*Ruta* tene sp. 29662 [61]	
28		*Ruta graveolens* [54]	
29	8-methoxygravelliferone	*Ruta graveolens* [54]	
30	Methoxychalepensin	*Ruta graveolens* [62]	
31	Obtusidin	*Haplophyllum obtusifolium* [7]	
32	Dimethoxychalepensin	*Ruta graveolens* [62]	
33		*Bothriocline laxa* [63]	
34–38		*Bothriocline eupatorioides* [64]	
39	Cyclolongipesin	*Bothriocline eupatoriodes* [64]	
		Bothriocline longipes [64]	
40, 41, 42		*Bothriocline eupatorioides* [64]	
		Bothriocline longipes [64]	
43, 44		*Bothriocline laxa* [63]	65

ship between biological activity and structure suggest that the nature of the side chain, its location in the coumarinic skeleton and the presence of additional furan or pyran rings are important requirements for the activity.

THE KNOWN 3-ISOPRENYL COUMARINS

We have summarized the literature on all natural and synthetic 3-isoprenylcoumarins up to middle of 1989 (Tables 2 and 3). This Review is scheduled as follows: list of natural 3-isoprenylcoumarins, with the plant(s) from which they have been isolated for the first time, their reference and their synthesis; list of synthetic 3-isoprenylcoumarins with their synthesis reference. The structures of all sixty-six coumarins **1–66** are illustrated.

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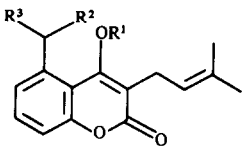
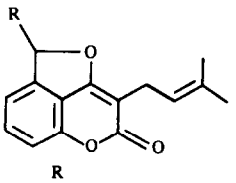
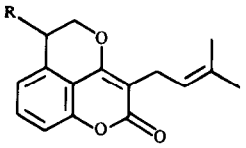


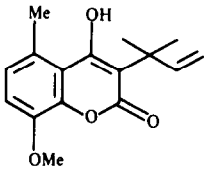
	R^1	R^2	R^3
33	H	H	Me
34	H	OAc	H
35	H	OPr	H
36	H	OH	Me
37	H	OAc	Me
38	Pr	OAc	Me



	R
39	H
40	Me



	R
41	OAc
42	OPr



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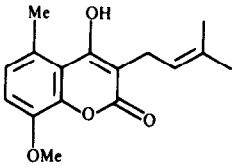

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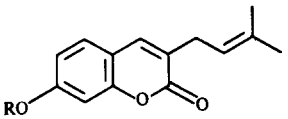
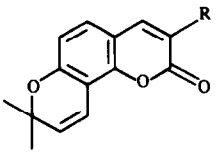
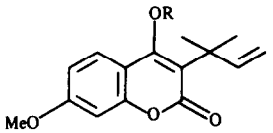


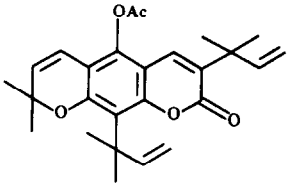
	R
45	H
46	Me



	R
47	$C(Me)CH{=}CH_2$
48	$CH_2CH{=}C(Me)_2$



	R
49	Ac
50	Ts



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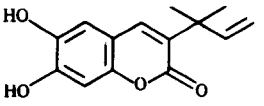

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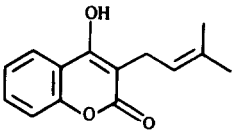

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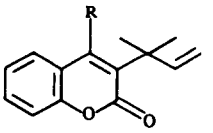
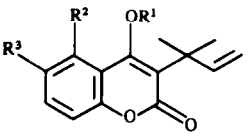
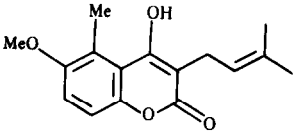


	R
53	H
54	OH



	R^1	R^2	R^3
56	Ac	H	H
57	Ts	H	H
58	H	Me	H
59	Me	Me	H
60	Ac	Me	H
61	H	Me	OMe
62	Me	Me	OMe
63	Ac	Me	OMe



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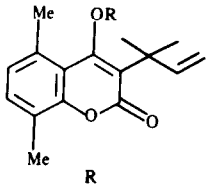

	R
65	Ac
66	Me

Table 3. Synthetic 3-isoprenylcoumarins

Compound	Synthesis reference
45	53, 66
46	66
47	27
48	53
49, 50	29
51	56, 57
52	67
53	29
54	68, 69
55	70, 71
56	29, 71
57	29
58–66	65

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