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Progress in the Chemistry of Organic Natural Products

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L. Zechmeister

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Naturally Occurring Plant Coumarins

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Contents

I. Scope of the Review

This review of plant coumarins discovered between 1989 and early 1996 has been compiled on the premise that the reader has access to the two previous reviews in this series by the reviewer, those of 1978 in Vol. 35 (*171*) and 1991 in Vol. 58 (*172*). With these other two reviews to hand, the reader will have immediate access to every plant coumarin ever known and should readily be able to determine, for example, if a coumarin just isolated is indeed a new natural plant product.

In the 1978 review, the 502 naturally occurring monomeric plant coumarins known at that time were tabulated principally according to the number and orientation of oxygen atoms on the benzenoid ring and then by the oxidation level of the substituent. For every entry, leading references were given to the isolation, structure determination, stereochemistry assignment where relevant and synthesis, where effected, of the coumarin. A similar format was adopted in 1991 and for comparability the reviewer has here again presented the data in the style used earlier.

The 1978 review specifically excluded aryl-substituted and biscoumarins even though examples were known. This was rectified in the 1991 review with the inclusion of a further 750 monomeric coumarins which included 111 aryl-substituted coumarins and coumestans. Data on 34 biscoumarins and one triscoumarin were also given. A similar format to that of the 1991 review has been adopted here but aflatoxins, benzocoumarins and ellagic acid derivatives have again been excluded.

II. Progress in the Past Six Years

Comparison of the entries in each of Tables 1–8 of the 1991 review with those of the 1978 review revealed that the numbers of each type of coumarin discovered during 1978–1989 were almost identical with those found during the previous 158 years since the first isolation of coumarin in 1820. Now, some six years later, comparison of the 1996 entries in Tables 1–8 with those of 1991 shows that the number of new coumarins has approximately halved indicating a similar rate of isolation. In the opinion of the reviewer, however, the numbers of new coumarins reported are, not surprisingly, beginning to fall. Compared with the period 1978–1989, there has been a relative increase in 5,7- and 6,7-dioxygenated coumarins (Tables 2 and 3) with a corresponding decrease in ethers of 7-hydroxycoumarin (Table 1) while there has been a marked increase in 5,6,7,8-tetraoxygenated coumarins (Table 8). Thirty biscoumarins, many from *Citrus* plants and hybrids have been newly reported (Table 12) and three triscoumarins (Table 13).

The power of modern spectrometric techniques, especially nuclear magnetic resonance, has been elegantly displayed in many of the structural elucidations, some on extremely small amounts of material. Apart from many isolation procedures to be found in the leading references on specific coumarins, the reader's attention is directed towards additional publications on solvent extraction studies (*31*) and ultrasound-assisted furanocoumarin extraction (*37*) and separation methods using capillary electrophoresis (*182*), micellar electrokinetic capillary chromatography (*40*), centrifugal partition chromatography (*157*) and two-dimensional planar chromatography (*81*). A review has appeared on high-performance liquid chromatography of coumarins (*231*) with additional publications on analysis by high-performance liquid chromatography (*21, 29, 75, 83, 181, 226, 229*) micro high-performance liquid chromatography-mass spectrometry (*34*) and capillary gas chromatography-mass spectrometry (*23*). An easy and absolute diagnosis for coumarin/chromone discrimination used ^{17}O n.m.r. spectroscopy at natural abundance (*173*).

Many of the new coumarins isolated in the past six years could well have been anticipated as natural products being, for example, glycosides of a known aglycone with a different sugar, an alcohol acylated with a different acid or a coumarin with a known side chain but at a higher oxidation level. However, some structures would have been much less easy to predict such as microminutin (**83**), the initially proposed structure (*197*) being shown to be incorrect and later elegantly found to contain a five-carbon bicyclic moiety (*198*), and the unstable dihydroquinone (**250**), a supposed intermediate in the biosynthesis of miroestrol (*45*).

While esters of (−)-*cis*-khellactone (**90**) and (+)-*trans*-khellactone (**91**) are known, bioactivity-guided fractionation has led to the isolation of the cytotoxic parent diols (*62*, *63*). Anti-HIV bioassay-guided fractionation has also been instrumental in the isolation of calanolide A (**264**) and B (**262**) and related 4,6,8-trisubstituted-5,7-dioxygenated coumarins from *Calophyllum lanigerum* (*122*). The structures assigned to calanolide C and D were subsequently shown to be incorrect (*163*, *191*) and the two compounds have been renamed pseudocalanolide C (**260**) and D (**261**).

There has been a marked increase in the number of acrimarines, naturally-occurring acridone-coumarin dimers, from three to 13, isolated in Japan mainly from *Citrus* hybrids (Table 1.1) along with five neoacrimarines. The structure originally proposed (*242*) for acrimarine-L is not given in the Tables since the compound was later shown to be identical with acrimarine-C (**360**) and the name acrimarine-L removed (*246*). Two further coumarin-naphthoquinone dimers, pummeloquinone (**80**) (*109*) and toddacoumaquinone (**158**) (*98*, *102*) have been reported.

The simple, albeit unexpected, 4-allyloxycoumarin structure assigned to setarin (**277**) has been confirmed by its thermal rearrangement to 3-allyl-4-hydroxycoumarin (*112*). On the other hand, the structure assigned to yuehgesin-A (**65**) (*143*) is most surprising in that it would appear to be unambiguously confirmed by a variety of ^{1}H n.m.r. techniques yet it is an acyclic hemiketal of a tertiary alcohol and acetone and should not be stable.

In the Amendments/Additions Tables which update data in the two earlier reviews many of the entries refer to synthesis. However, supposedly new coumarins continue to be reported but later have their structures revised to those of known coumarins, such as asacoumarin B = galbanic acid (**350**) (*13*) and bakuchicin (*124*) = angelicin (**367**) (*164*).

In an elegant piece of work using supercritical carbon dioxide extraction of *Toddalia asiatica*, the diol toddalolactone (**379**) has been shown to be a genuine natural coumarin but in the original 1933 studies it had been isolated principally as an artifact derived from aculeatin (**377**) during extraction (*101*). The structure of the 6,7,8-trioxygenated coumarin obtusifol (**407**) has been revised for a second and, it is hoped, final time (*27*).

III. Introduction to Tables

The arbitrary but biogenetically-related classification used for tabulating coumarins in the two earlier reviews (*171*, *172*) has once again been employed in order to assist the reader. It is based primarily on the number, and then position, of oxygen atoms attached directly to the coumarin nucleus. Thereafter, within each table, entries are presented in the following order: (i) coumarins with acyclic substituents, (ii) dihydrofuranocoumarins, (iii) furanocoumarins, (iv) dihydropyranocoumarins, (v) pyranocoumarins. The coumarins of each subclass are listed in order of increasing number of carbon atoms in the substituent and in increasing oxidation level within that group. Phenols are considered before their ethers and glycosides while alcohols precede their glycosides and esters.

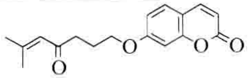
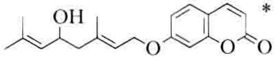
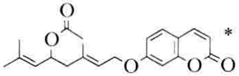
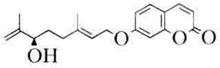
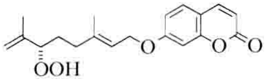
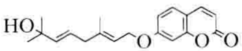
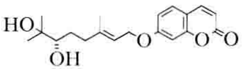
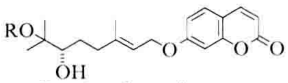
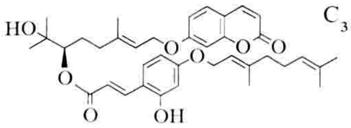
For each entry, the trivial name if one has been coined, is given first followed by the year of isolation, the structure and molecular formula. The melting point of crystalline coumarins is quoted; alternatively, the physical form as an oil or gum or amorphous (amorph.) is reported. The $[\alpha]^t_\lambda$ and solvent columns refer to the specific rotation at t°C in the given solvent at a given wavelength, λ (nm). Where no wavelength is quoted, as in most cases, the rotation has been measured at 589 nm. The plant source from which the coumarin was first isolated is then given. Where more than one plant source is quoted, the later reference has provided additional information such as another trivial name and/or different physical constants.

The naturally occurring aryl-substituted coumarins which were not discussed in the 1978 review (*171*), even though a number were then known, but were incorporated in the 1991 review (*172*) are again to be found in Tables 9.1, 10.1 and 11.1, with data on six new coumestans presented in Table 11.2.

An asterisk (*) in the top right of the structure column indicates that some aspect of the stereochemistry remains to be defined. In cases where the relative stereochemistry is shown the asterisk implies that the absolute stereochemistry has not yet been defined; *racemic* substances are so indicated.

In the later tables giving amendments/additions to data in the two earlier reviews, the compound numbers given in parenthesis below numbers (**344**–**434**) inclusive are those which appeared in the 1978 review while those numbers in square brackets refer to the compound entry numbers in the 1991 review.

Table 1. *7-Oxygenated Coumarins*

	Trivial name(s)	Year isolated	Structure	Formula	M.p.	$[\alpha]_\lambda^t$	Solvent	Plant sources	Leading references
1	Crellisin-B	1995		$C_{17}H_{18}O_4$				*Cremantho-dium ellisi*	*(265)*
2	Anisocoumarin H	1989		$C_{19}H_{22}O_4$	oil	-20.5^{25}	$CHCl_3$	*Clausena anisata*	*(176)*
3	Acetoxyaurapten	1995		$C_{21}H_{24}O_5$	53–55	-30.0^{23}	$CHCl_3$	*Zanthoxylum schinifolium*	*(42)*
4		1992		$C_{19}H_{22}O_4$	75	10^{26}	$CHCl_3$	*Citrus hassaku*	*(158)*
5		1992		$C_{19}H_{22}O_5$	gum	-11	$CHCl_3$	*Phebalium filifolium*	*(210)*
6		1992		$C_{19}H_{22}O_4$	oil	24	$CHCl_3$	*Phebalium anceps*	*(196)*
7	(−)-(*S*)-*trans*-Marmin	1995		$C_{19}H_{24}O_5$	117–118	-11^{26}	MeOH	*Pituranthos triradiatus*	*(78)*
8	Pituranthoside	1995	 R = β-D-glucosyl	$C_{25}H_{34}O_{10}$	185–186	12^{26}	MeOH	*Pituranthos triradiatus*	*(78)*
9		1992		$C_{38}H_{46}O_8$	oil	72^{26}	EtOH	*Citrus hassaku*	*(158)*

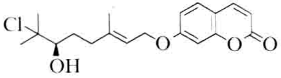
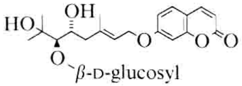
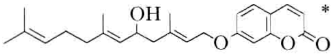
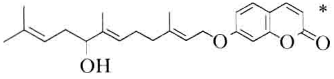
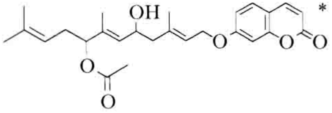
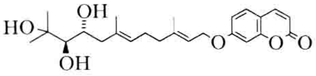
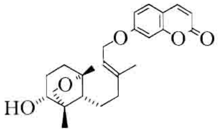
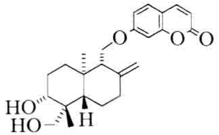
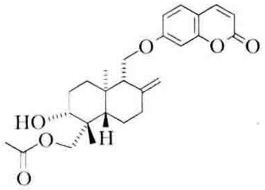
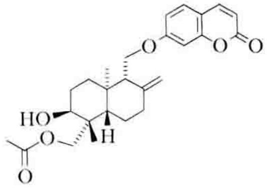
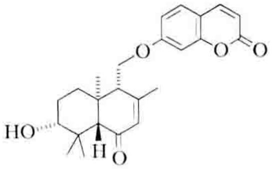
10	Chloromarmin	1995		$C_{19}H_{23}ClO_4$	oil	27.3^{23}	EtOH	*Aegle marmelos*	*(183)*
11	Aeglin	1995		$C_{25}H_{34}O_{11}$	218–219	25.9^{24}	EtOH	*Aegle marmelos*	*(183)*
12		1994		* $C_{24}H_{30}O_4$	53	-3.8^{25}	CH_2Cl_2	*Ferula assafoetida*	*(13)*
13		1994		* $C_{24}H_{30}O_4$	oil	-2.4^{25}	CH_2Cl_2	*Ferula assafoetida*	*(13)*
14		1994		* $C_{26}H_{32}O_6$	oil	-2.8^{25}	CH_2Cl_2	*Ferula assafoetida*	*(13)*
15		1992		$C_{24}H_{32}O_6$	oil	-14.3^{25}	CH_2Cl_2	*Heptaptera anisoptera*	*(11)*
16	Ligupersin B	1991		$C_{24}H_{30}O_5$	oil	-8^{24}	$CHCl_3$	*Ligularia persica*	*(156)*
17		1992		$C_{24}H_{30}O_5$	220	-37.4^{25}	CH_2Cl_2	*Heptaptera anisoptera*	*(12)*

Table 1 (*continued*)

	Trivial name(s)	Year isolated	Structure	Formula	M.p.	$[\alpha]^t_\lambda$	Solvent	Plant sources	Leading references
18		1992		$C_{26}H_{32}O_6$	120	-31.5^{25}	CH_2Cl_2	*Heptatera anisoptera*	(*12*)
19		1992		$C_{26}H_{32}O_6$	oil	-22.0^{25}	CH_2Cl_2	*Heptaptera anisoptera*	(*12*)
20	Ligupersin A	1991		$C_{24}H_{28}O_5$	oil	-70^{24}	$CHCl_3$	*Ligularia persica*	(*156*)