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THE ROLE OF MARMESIN AND COLUMBIANETIN IN THE BIOSYNTHESIS OF FURANOCOUMARINS*

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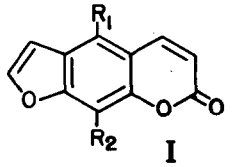
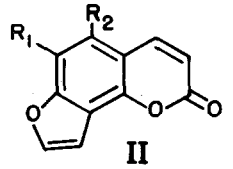
Biosynthetic pathways leading to the furanocoumarins, in contrast with those to simple coumarins (1,2), are not well understood. Floss and his co-workers have investigated the origin of several linear (I) and angular (II) furanocoumarins in the umbellifer Pimpinella magna (3,4), and in celery infected with Sclerotinia sclerotiorum (5). Their studies have established umbelliferone (7-hydroxycoumarin) and its glucoside, skimmin, as efficient furanocoumarin precursors. The two side-chain-derived carbons of the furan ring, according to their evidence, originate from C-4 and C-5 of mevalonate, and there is good reason to believe that p enylation is an early step in the conversion of umbelliferone to furanocoumarins (4,6). To date, however, no intermediate in this reaction sequence has been identified. We now present observations strongly indicating participation of two α-hydroxyisopropyldihydro-furanocoumarins, marmesin (III) and columbianetin (IV) as natural intermediates in the elaboration of linear and angular furanocoumarins, respectively.



I

a. Psoralen: $R_1=R_2=H$
b. Bergapten: $R_1=OCH_3$, $R_2=H$
c. Xanthotoxin: $R_1=H$, $R_2=OCH_3$



II

a. Angelicin: $R_1=R_2=H$
b. Isobergapten: $R_1=H$, $R_2=OCH_3$
c. Sphondin: $R_1=OCH_3$, $R_2=H$
d. Pimpinellin: $R_1=R_2=OCH_3$

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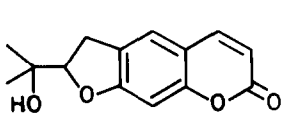
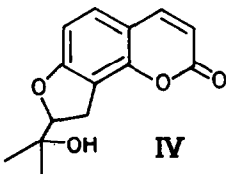


III



IV

Trapping experiments were conducted in which umbelliferone-2-C^{14} was administered to shoots of Ruta graveolens together with non-labelled marmesin, and skimmin-2-^{14}C to Heracleum lanatum together with non-labelled columbianetin. After short feeding periods residual amounts of these administered compounds could be recovered from the coumarin fractions of the plants. Some of the isolation techniques, which included column chromatography on silica and gas-liquid chromatography, have been described (7), and further details will be published elsewhere. In addition to marmesin, the linear furanocoumarins psoralen (Ia), bergapten (Ib), and xanthotoxin (Ic) were recovered from Ruta.

TABLE I

Incorporation of C^{14} from Umbelliferone into Dihydrofuranocoumarins by Ruta graveolens and Heracleum lanatum

Plant	Coumarin Recovered	Specific Activity (μCi/mmole)		Dilution Factor		% Incorporation
		Exp't A	Exp't B	A	B	A
R. graveolens	Marmesin	12	37	14	4.4	--
	Psoralen	6.5	5.6	25	29	--
	Bergapten	2.9	5.1	56	32	--
	Xanthotoxin	0.15	1.3	1100	130	--
H. lanatum	Columbianetin	11.8	--	15	--	3.1
	Angelicin	4.6	--	39	--	1.3
	Isobergapten	0.7	--	260	--	0.7
	Sphondin	1.0	--	180	--	4.8
	Pimpinellin	0.6	--	300	--	0.8

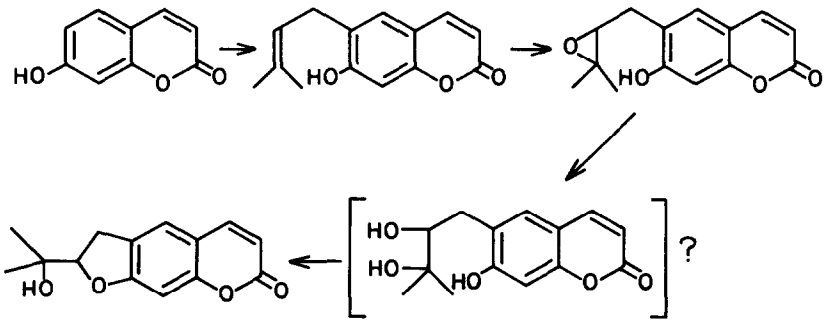
Marmesin and umbelliferone-2-C^{14} (163 μCi/mmole), 0.06 mmole of each, were administered to 27 g. of Ruta shoots for 48 hours. Columbianetin and skimmin-2-C^{14} (180 μCi/mmole), 0.02 and 0.015 mmoles resp. were administered to 50 g. of Heracleum shoots for 24 hours.

In addition to columbianetin, angelicin (IIa), isobergapten (IIb), sphondin (IIc), and pimpinellin (IId) were recovered from Heracleum.

It is clear from Table I that in each species umbelliferone has been converted to the dihydrofuranocoumarin, and the low dilution figures, 15 for columbianetin and averaging 9 for marmesin, argue for a quite direct conversion. The lower specific activities of the furanocoumarins are consistent with their formation via marmesin or columbianetin.

Direct feedings of tritiated marmesin and columbianetin have confirmed the roles of these compounds in furanocoumarin biosynthesis. Table II shows that in each case there was good conversion to the analogous unsubstituted furanocoumarin and a lower degree of tritium incorporation into the oxygenated furanocoumarins.

As umbelliferone is known to occur in Ruta graveolens (8) and in Heracleum lanatum (6) it can be regarded as a natural intermediate in furanocoumarin biosynthesis in these species. The formative route to marmesin can be envisaged as:



with an analogous sequence leading to columbianetin, but there is as yet no firm experimental evidence to support this hypothesis. The nature of the reactions leading on to psoralen and angelicin remains unclear.

The relative specific activities of the furanocoumarins in Tables I and II are consistent with the hydroxylation of the benzene rings of angelicin and psoralen and O-methylation proceeding to yield the substituted furanocoumarins, but whether these reactions do, in fact, occur is still uncertain.

TABLE II

Formation of Furanocoumarins from Marmesin and Columbianetin

Plant	Coumarin Recovered	Specific Activity (μCi/mmole)		Dilution Factor		Approx. % Incorporation	
		Exp't A	Exp't B	A	B	A	B
R. graveolens	Psoralen	730	1500	120	57	--	--
	Bergapten	170	500	510	170	--	--
	Xanthotoxin	55	45	1600	1900	--	--
H. lanatum	Angelicin	6800	189	660	24000	21	5
	Isobergapten	425	74	11000	61000	1	1
	Sphondin	90	34	50000	132000	2	7
	Pimpinellin	64	45	78000	100000	1	1

Marmesin-T (G) (0.01 mmole, 86 mCi/mmole) was administered to 33 g. of Ruta shoots for 48 hours. Columbianetin-T (G) (750 μc (A) and 100 μc (B), 4500 mCi/mmole) was administered to 50 g. Heracleum sprigs for 24 hours.

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