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STEREOCHEMICAL ASPECTS OF THE BIOLOGICAL OXIDATION OF ARYL ISOPRENOIDS. THE ASYMMETRIC SYNTHESIS AND ABSOLUTE CONFIGURATION OF MERANZIN AND OF MERANZIN HYDRATE

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Key Word Index—Rutaceae; Umbelliferae; coumarins; quinoline alkaloids, biosynthesis; epoxides; meranzin; meranzin hydrate.

Abstract—The role of epoxides in the biological oxidation of aryl prenyl derivatives is discussed in terms of the stereochemistry of quinoline alkaloids and coumarins found in species of the Rutaceae and Umbelliferae. Asymmetric synthesis of the epoxide, meranzin and of the diol, meranzin hydrate, have been carried out and the absolute configurations of the two coumarins have been established.

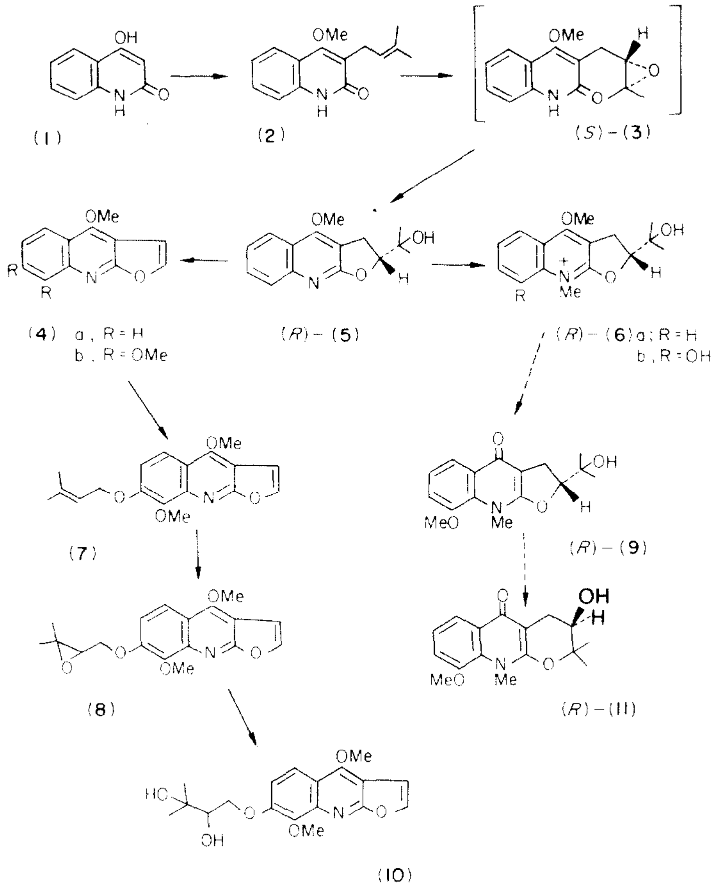
INTRODUCTION

The later stages in the biosynthesis of isoprenoid quinoline alkaloids have been studied [1] in three species of the Rutaceae, using ^{14}C-tracers and precursors doubly-labelled with ^{14}C and ^{3}H. The established pathway to platydesmine (**5**), platydesminium salt (**6**a) and dictamnine (**4**a) in *Skimmia japonica* and to dictamnine (**4**a), skimmianine (**4**b) and evoxine (**10**) in *Choisya ternata* is given in Scheme 1. Isoprenoid coumarins found mainly in species of the Umbelliferae and Rutaceae possess many of the structural features of isoprenyl quinolines. Brown, Steck and their collaborators [2,3] studied the biosynthesis of isoprenyl coumarins with generally-labelled tritiated precursors and more recently with precursors specifically-labelled with ^{14}C [4]; their conclusions and those of others [5] are included in Scheme 2.

The two biosynthetic schemes have much in common. Thus, prenylation of the heterocyclic precursors, 4-hydroxy-2-quinolone (**1**) and 7-hydroxycoumarin (**12**a) at oxygen or at carbon *ortho* to oxygen functions leads to simple derivatives, for example, 7-isopentenyloxycoumarin (**12**b), 3-isopentenyl-4-methoxy-2-quinolone (**2**) and suberosin (**13**b). Subsequent oxidation results in oxygenation of the side chain as in meranzin hydrate (**20**) or cyclization to furo- or pyrano-derivatives, i.e. platydesmine (**5**), isobalfourodine (**11**), marmesin (**21**a) and lomatin (**19**a). Furoquinolines and furocoumarins are derived by loss of the isopropyl groups from dihydrofuro-derivatives, i.e. platydesmine (**5**) → dictamnine (**4**a). In both series, aromatic hydroxylation originates late in the pathway, i.e. dictamnine (**4**a) to skimmianine (**4**b). Further prenylation and oxidation then occurs, resulting, for instance, in the formation of evoxine (**10**) and oxypeucedanin (**24**). It is the purpose of this paper to discuss certain features of Schemes 1 and 2 that have not been proved, especially the role of epoxides.

DISCUSSION

The intermediacy of epoxide (**3**) in the oxidative cyclization of the prenylquinoline (**2**) to platydesmine (**5**) is based on *in vitro* analogy; epoxidation of quinolone (**2**) leads to a mixture of platydesmine (**5**) and the isomeric pyrano compound cf. (**11**), rapid cyclization of epoxide (**3**) preventing the detection or isolation of the intermediate [6]. Similarly, the epoxide (**8**) has not been established as a precursor of the isoprenyl-1,2-diol, evoxine (**10**), although its isolation from *Evodia zanthoxyloides* [7] instead of the previously reported evoxine supports the Scheme and indeed raises the possibility that evoxine and other diols of this type, i.e.

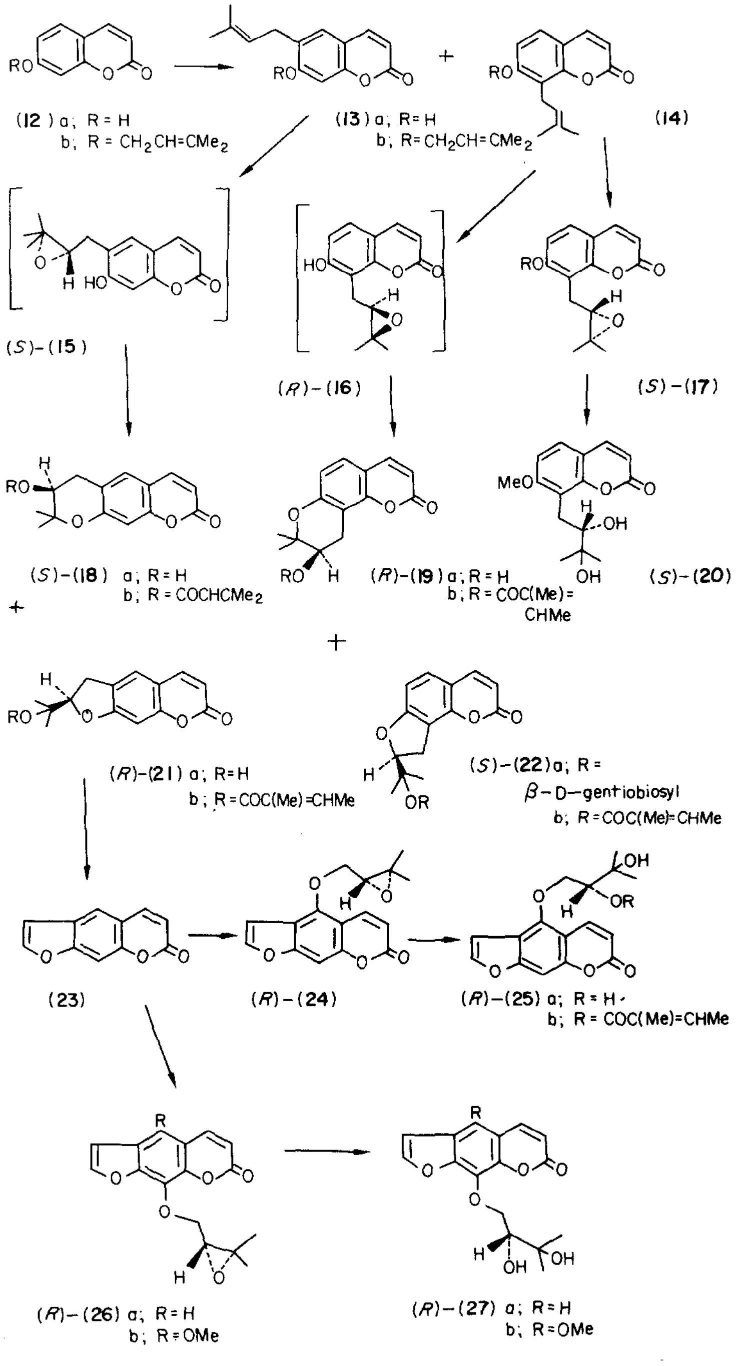


Scheme 1. Biosynthesis of prenylquinoline alkaloids.

oxypeucedanin hydrate (**25**a) are artifacts formed by hydrolysis of naturally-occurring epoxides during isolation.

We showed previously how stereochemical evidence could be used to explore the role of epoxides [8], i.e. (**3**), (**15**) and (**16**), in the biosynthesis of isomeric furo- and pyrano-derivatives, and this approach has been discussed by others [3]. Thus, the occurrence of (−)-(R)-marmesin (**21**a) and (+)-(S)-decursin (**18**b) in *Angelica decursiva* accords with their biosynthesis from the (S)-epoxide (**15**), cyclization to the furano-derivative occurring with inversion of configuration and to the pyrano-derivative without affecting the chiral centre [9]. Other known cases (Table 1, Nos. 2 and 3) support the suggestion that isomeric furo- and pyrano-coumarins are derived similarly from a chiral epoxide. In the quinoline alkaloid series enantiomeric pairs of furo–pyrano isomers occur in *Balfourodendron riedelianum* and in *Lunasia amara* (Table 1, Nos. 4 and 5); the absolute stereochemistry of the alkaloids and *in vitro* analogy suggest that the furo-derivatives originate directly from an epoxide and that the pyrano-isomers are formed subsequently by a rearrangement involving retention of configuration [9].

Since epoxides have been proposed in the biosynthesis of oxygenated C- and O-prenyl derivatives, as well as in the origin of furo- and pyrano-derivatives (Schemes 1 and 2), it appeared that a single monoxygenase showing relatively broad substrate specificity but high stereoselectivity might be responsible in a given plant species for the formation of epoxides of types (**3**), (**15**) and (**24**). The expected stereochemical consequences of this proposition are illustrated in Scheme 3 for an enzyme producing (S)-epoxides. If it is assumed that hydrolysis of the epoxides occurs through an acid-catalyzed carbonium ion mechanism not involving the chiral centres, then the "O-diols" and the "C-diols" would have (S)-configurations; on the other hand, furo-derivatives formed by cyclization of the (S)-epoxides with stereochemical inversion would have (R)-configurations. The stereochemical result might be independent of the nature of the aryl group and apply equally to coumarins and



Scheme 2. Biosynthesis of prenylcoumarins.

Table 1. Distribution of isoprenoid coumarins and quinolines of known configuration

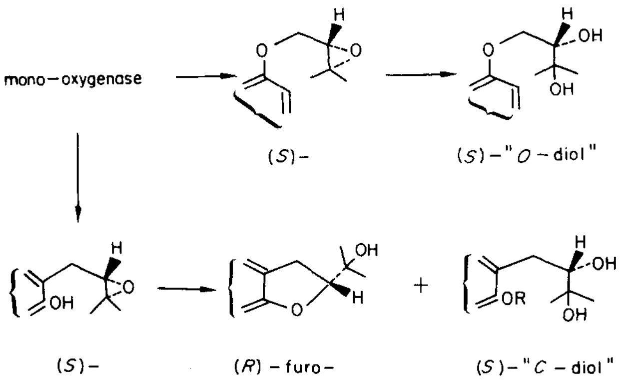
No.	Family*	Species	Compound	Probable epoxide precursor	References
1	U	*Angelica decursiva* Fr. et Sav.	(−)-(R)-Marmesin (nodakenetin) (**21**a)	(S)—(**15**)	10
			(+)-(S)-Decursin (**18**b)	(S)—(**15**)	10
2	U	*Lomatium nuttalii* (A. Gray) Macbr.	(+)-(S)-Columbianin (**22**a)	(R)—(**16**)	11
			(+)-(R)-Lomatin (**19**a)	(R)—(**16**)	11
3	U	*Seseli gummiferum* Pall.	(−)-(S)-Deltoin [(+)-marmesin angelate] (cf. **21**b)	(R)—(cf. **15**)	12
			(+)-(R)-Lomatin esters (**19**)	(R)—(**16**)	12
4	R	*Balfourodendron riedelianum* Engl.	(+)-(R)-Balfourodine (**9**)	(S)—(**3**)	13
			(+)-(R)-Isobalfourodine (**11**)		13
5	R	*Lunasia amara* Blanco	(−)-(S)-Hydroxylunacrine (cf. **9**)	(R)—(cf. **3**)	14
			(−)-(S)-Lunasia II (cf. **11**)		15
6	U	*Zozimia absinthifolia* (Vent.) DC	(−)-(S)-Deltoin [(+)-marmesin angelate] (cf. **21**b)	(R)—(cf. **15**)	16
			(+)-(S)-Columbianadin (**22**b)	(R)—(**16**)	16
7	R	*Skimmia japonica* Thunb.	(−)-(S)-Meranzin hydrate (**20**)	(S)—(**17**)	17
			(+)-(R)-Platydesminium metho-salt (**6**a)	(S)—(**3**)	18
			(+)-(R)-Oxypeucedanin (**24**)	(R)—(**24**)	17
			(+)-(R)-Oxypeucedanin hydrate (**25**a)	(R)—(**24**)	17
8	R	*Ptelea trifoliata* L.	(−)-(R)-Marmesin (nodakenetin) (**21**a)	(S)—(**15**)	19
			(+)-(R)-Pteleatinium salt (**6**b)	(S)—(**3**)	20
9	U	*Angelica ursina*	(R)-Ostruthol (**25**b)	(R)—(**24**)	21
			(+)-(R)-Byak-angelicin (**27**b)	(R)—(**26**b)	21
			(+)-(R)-Selenidin (**19**b)	(R)—(**16**)	21
10	U	*Prangos pabularia* Lindl.	(+)-(R)-Oxypeucedanin (**24**)	(R)—(**24**)	22
			(+)-(R)-Oxypeucedanin hydrate (**25**a)	(R)—(**24**)	23
			(+)-(R)-Heraclenin (**26**a)	(R)—(**26**a)	24
11	R	*Ptelea crenulata* Greene	(+)-(S)-Marmesin (cf. **21**a)	(R)—(cf. **15**)	19
			(+)-(S)-Heraclenin (cf. **26**a)	(S)—(cf. **26**a)	19
12	R	*Ruta graveolens* L.	(−)-(S)-Byak-angelicin (cf. **27**b)	(S)—(cf. **26**b)	25
			(+)-(R)-Platydesminium metho-salt (**6**a)	(S)—(**3**)	25,26
13	U	*Peucedanum ostruthium* (L.) Koch	(R)-Ostruthol (**25**b)	(R)—(**24**)	27
			(−)-(R)-Marmesin (nodakenetin) (**21**a)	(S)—(**15**)	28
14	U	*Angelica hirsutiflora* Liu, Chao et Chung	(+)-(S)-Marmesin (cf. **21**a)	(R)—(cf. **15**)	29
			(+)-(R)-Byak-angelicin (**27**b)	(R)—(**26**b)	29
15	U	*Peucedanum palustre* (L.) Moench	(+)-(S)-Columbianadin (**22**b)	(R)—(**16**)	30
			(+)-(R)-Oxypeucedanin (**24**)	(R)—(**24**)	30
			(+)-(R)-Oxypeudedanin hydrate (**25**a)	(R)—(**24**)	30

* R = Rutaceae, U = Umbelliferae.

quinolines occurring in the same plant species. We decided to test the hypothesis by carrying out a chemotaxonomic survey of isoprenoid quinoline alkaloids and coumarins of established stereochemistry; the results are summarized in Table 1 and considered under the following three headings [39].

(a) *Species containing C-prenyl derivatives* (Table 1, Nos. 6–8). The two furo-coumarins of *Zozimia absinthifolia* have the (S)-configuration and apparently are derived from the isomeric (R)-epoxides, enantiomer of (**15**) and (**16**). The conversion [20] of pteleatinium salt (**6**b) into (+)-balfourodine (**9**) of known configuration [9] indicates that both the furocoumarin and the furoquinoline of *Ptelea trifoliata* have (R)-configurations. The absolute stereochemistry of the C-prenylcoumarin, (−)-meranzin hydrate (**20**), isolated from *S. japonica*, has now been determined (see below), and presumably is formed from the (S)-epoxide (**17**). The *Skimmia* constituent, (+)-(R)-platydesminium metho-salt (**6**a) apparently is also formed from an (S)-epoxide by inversion during cyclization. Thus the stereochemistry of this group of C-prenylderivatives is consistent with Scheme 3.

(b) *Species containing O-prenyl derivatives* (Table 1, Nos. 9–10). The O-prenyl coumarins present in *A. ursina* and in *Prangos pabularia* have (R)-configurations [38], consistent with biosynthesis through a mono-oxygenase yielding (R)-epoxides of types (**24**), (**26**a) and (**26**b).



Scheme 3.

(c) *Species containing C- and O-prenyl derivatives* (Table 1, Nos. 7, 9 and 11–15). As expected on the basis of biosynthesis from (R)-epoxides, the (R)-O-prenylcoumarins of *A. hirsutiflora* and of *Peucedanum palustre* co-occur with (S)-furocoumarins. Similarly, the (S)-O-prenyldiol (**27**a) and the (R)-furoquinoline (**6**a) have been isolated from *Ruta graveolens. Angelica ursina* contains the (R)-O-prenyldiol (**27**a) and the (R)-pyranocoumarin (**19**b), the stereochemistry being consistent with an origin from (R)-epoxides.

On the other hand, the two C-prenyl derivatives, meranzin hydrate (**20**) and platydesminium metho-salt (**6**a) derived apparently from (S)-epoxides, co-occur in *S. japonica* with the (R)-epoxide, oxpeucedanin (**24**). There is also no stereochemical correlation between the furocoumarins and O-prenylderivatives present in *P. crenulata* (Table 1, No. 11) and in *Peucedanin ostruthium* (Table 1, No. 13).

CONCLUSIONS

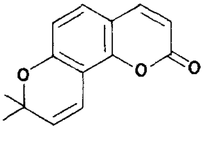
In a particular plant species, the correlation between the absolute stereochemistry of C-isoprenoid quinoline alkaloids and coumarins is consistent with stereospecific oxidation of the side-chains through epoxidation by means of a single mono-oxygenase. The same conclusion applies to O-prenyl derivatives that occur together. However, if O-prenyl and C-prenyl derivatives present in a single species are compared, there is no general stereochemical consistency between the two groups. We suggest therefore that stereospecific oxidation of the two isoprenyl types is controlled by distinct mono-oxygenases, even within one plant species; this situation may arise from different stereoelectronic requirements of groups $ArCH_2CH{=}CMe_2$ and $ArOCH_2CH{=}CMe_2$.

Our conclusions represent only a working hypothesis, since the number of plant species known to contain isoprenyl derivatives of established configuration is small. The main purpose of this discussion is to emphasize the value of this approach to biosynthetic theory and the consequent need to determine the absolute stereochemistry of other groups of aromatic isoprenoids.

Asymmetric synthesis and absolute stereochemistry of meranzin and meranzin hydrate

The absolute configurations of a number of furo- and pyrano-quinolines and coumarins have been established by ozonolysis to the hydroxy-lactone (**31**) [9,31,32], but this approach has not been applied to C-isoprenyldiols of the coumarin series. Because of our interest in comparing the configuration of isoprenoid quinolines and coumarins (see above) we chose to study (−)-meranzin hydrate (**20**) isolated from leaves of *S. japonica* together with (+)-(R)-platydesminium metho-salt (**6**a), (+)-(R)-oxypeucedanin (**24**) and (+)-(R)-oxypeucedanin hydrate (**25**a) [17]. Since insufficient of the natural coumarin was available we prepared meranzin hydrate by asymmetric synthesis.

The 3,3-dimethylallylcoumarin, osthenol (**14**; R = H), was prepared conveniently by the method described previously [33]; an alternative synthesis by reduction of the dimethylpyranocoumarin seselin (**28**), with lithium in liquid ammonia gave a lower yield. Methylation of osthenol (**14**; R = H) afforded osthol (**14**; R = Me). 8-Allyl-7-methoxycoumarin (**29**) was easily obtained from 7-hydroxycoumarin (87% yield) and was converted into the aldehyde (**30**) by ozonolysis (46%) but we were unable to prepare osthol by means of a Wittig reaction on the aldehyde.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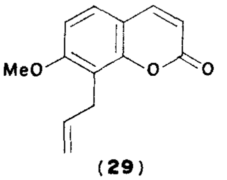
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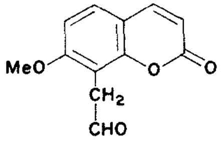

(30)

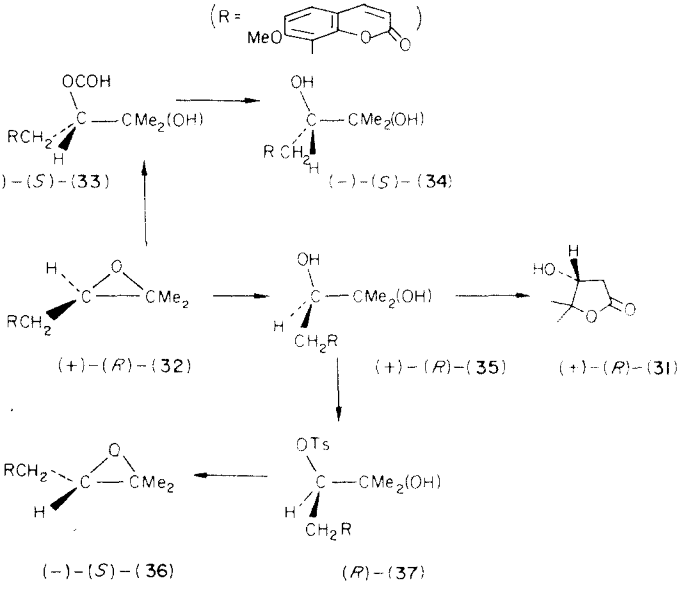
Reaction of osthol (**14**; R = Me) with (+)-peroxycamphoric acid furnished meranzin (**17**; R = Me) (84%), containing a preponderance of the (+)-enantiomer, which was converted with aqueous oxalic acid into (+)-meranzin hydrate. Ozonolysis of (+)-meranzin hydrate by the method used for analogous compounds gave the (+)-hydroxy-lactone (**31**) of known stereochemistry [31,32], thus establishing the (R)-configuration for the (+)-hydrate and the (S)-configuration for (−)-meranzin hydrate found in *S. japonica* [17] and in *Prangos ferulacea* [34].

The epoxide, (+)-meranzin (**32**), is also assigned the (R)-configuration, since acid-catalyzed hydrolysis to the (R)-hydrate (**35**) presumably occurs through a tertiary carbonium ion with retention of configuration at the chiral centre. This interpretation was confirmed by the following interconversions (Scheme 4).

The epoxide, (+)-meranzin (**32**), with HCO_2H gave the formate ester (**33**) (inversion), which was hydrolyzed to (−)-meranzin hydrate (**34**) (retention). The *p*-toluenesulphonate ester of (+)-meranzin hydrate (**37**) was converted into (−)-meranzin (**36**) (inversion). The structures of the intermediates (**33**) and (**37**) were confirmed by NMR spectroscopy (see Experimental) and the stereochemical assignments are given in Scheme 4.

EXPERIMENTAL

The NMR spectra were recorded with a Perkin–Elmer R12 spectrometer using tetramethylsilane as internal standard, and GLC with a Perkin–Elmer F11 instrument. Optical rotations were measured on a Perkin–Elmer 141 automatic digital polarimeter capable of measuring to 1×10^{-3} deg. TLC was on silica gel (Merck Kieselgel G) and light petroleum refers to the fraction b.p. 40–60 unless stated otherwise.



Scheme 4. Interconversion of meranzin and its derivatives.

A solution of osthol (**14** R = Me) (4 g) prepared by methylation of osthenol [33] (**14**, R = H) with MeI, and (+)-peroxycamphoric acid ($[\alpha]_D$ +52·5°) (8 g) in $CHCl_3$ (110 ml) was kept at ambient temp. for 4·5 days, washed with satd aq Na_2SO_3, then with aq Na_2CO_3 and evaporated. Chromatography of the product on neutral alumina and crystallization from EtOH gave (+)-meranzin in needles (3·6 g, 84%), m.p. 97–98° (lit [35], m.p. 98°), $[\alpha]_D$ +0·81° (EtOH), +1·4° ($CHCl_3$) $[\alpha]_{546}$ +0·90° (EtOH) (lit [35], $[\alpha]_D$ −33·4°), τ ($CDCl_3$) 2·09 (1 H, *d*, *J* 10 Hz), 2·36 (1 H, *d*, *J* 9·5 Hz), 2·90 (1 H, *d*, *J* 9·5 Hz), 3·55 (1 H, *d*, *J* 10 Hz), 5·91 (3 H, *s*), 6·85 (3 H, *m*), 8·44 (3 H, *s*) and 8·66 (3 H, *s*).

(+)-*Meranzin hydrate* (**35**). (+)-Meranzin (1·1 g) was refluxed for 1 hr with 1% aq oxalic acid (400 ml), and the soln was neutralized with Na_2CO_3 and extracted with $CHCl_3$. Chromatography of the product on neutral alumina and elution with light petroleum–Et_2O (3:1) gave meranzin (100 mg). Elution with Et_2O–EtOAc (10:1) afforded the hydrate separating from $CHCl_3$–light petroleum in needles (550 mg), m.p. and m.m.p. 128–129° (lit [34], m.p. 128–129°), $[\alpha]_D$ +0·9° (EtOH) [lit [28], −57° (EtOH)].

Ozonolysis of (+)-*meranzin hydrate*. By the procedure described previously for (+)-platydesminium metho-salt [32] (+)-meranzin hydrate (0·53 g, $[\alpha]_D$ + 0·90°) was converted into the hydroxy-lactone (**31**), which was purified by chromatography on silica and by preparative TLC and shown to be homogeneous by GLC; it was obtained as an oil (55 mg), b.p. 114–116°/0·8 mm., $[\alpha]_D$ +0·23° (CHCl), $[\alpha]_{436}$ +1·38 ($CHCl_3$), and shown to be identical with an authentic sample [32] (NMR and GLC).

(−)-*Meranzin* (**36**). A solution of (+)-meranzin hydrate (230 mg, $[\alpha]_D$ +0·9°) and *p*-toluenesulphonyl chloride (220 mg) in pyridine (5 ml) was kept at −5° for 5 days, added to H_2O and extracted with CH_2Cl_2. The extract was washed with N-HCl and evaporated. Chromatography of the product on alumina, and elution with light petroleum–Et_2O, gave (−)-meranzin (needles from EtOH), m.p. and m.m.p. 97–98°, $[\alpha]_{5789}$ −0·93° ($CHCl_3$) and $[\alpha]_{546}$ −1·48° ($CHCl_3$).

Crystallization of the crude product from MeOH gave the tosylate as needles, m.p. 167–168°, τ ($CDCl_3$) 4·84 (1 H, *m*) $[-CH_2-C\underline{H}(OTs)-]$, 7·10 (2 H, *d*) ($-C\underline{H}_2-CH$) and 8·62 (6 H, *s*) ($CMe_2$).

8-(2-*Formoxy*-3-*hydroxy*-3-*methylbutyl*)-7-*methoxycoumarin* (**33**). A mixture of (+)-meranzin (100 mg) ($[\alpha]_D$ +0·81°) and 90% HCO_2H (2 ml) was kept at ambient temp. for 5 hr, diluted with $CHCl_3$, washed with 2 N-Na_2CO_3 and evaporated. Chromatography of the product on silica, elution with Et_2O–EtOAc (2:1) and crystallization from EtOH at −30° gave the formate (60 mg), m.p. 135°, $[\alpha]_D$ −0·3° ($CHCl_3$), τ ($CDCl_3$) 4·72 (1 H, *m*) $[-CH_2-C\underline{H}\ (OCOH)-]$ 6·79 (2 H, *d*) ($-CH_2-CH$) and 8·60 (3 H, *s*), 8·64 (3 H, *s*) (CMe_2) (Found: C, 62·6; H, 6·0. $C_{16}H_{18}O_6$ requires: C, 62·7; H, 6·0%).

Hydrolysis of the formate with NaOH in aq MeOH at 20° and chromatography of the product on neutral alumina afforded (−)-meranzin hydrate m.p. 127–129° (needles from $CHCl_3$–light petroleum), $[\alpha]_D$ −0·71° (CHCl) and $[\alpha]_{546}$ −0·77° ($CHCl_3$).

Reduction of seselin (**28**) *with lithium in liquid ammonia*. Lithium was added to seselin (1·1 g) in liquid ammonia (100 ml) until a blue colour persisted. After 20 min, NH_4Cl and then H_2O was added and the product was obtained with $CHCl_3$ to give seselin (0·52 g). Acidification of the aq soln, extraction with Et_2O, chromatography on neutral alumina and elution with $CHCl_3$ gave osthenol (**14**; R = H), separating from MeOH in needles (0·42 g) m.p. 128–130° (lit [33], m.p. 129–131°), identical (m.m.p. and IR) with an authentic sample.

8-*Allyl*-7-*hydroxycoumarin*. The published procedure [36] gave consistently low yields of a product difficult to purify, and the following modification was used. 7-Allyloxycoumarin (16·6 g) in 2 N-dimethylaniline (30 ml) was refluxed for 2 hr in N_2. The product that separated was washed with light petroleum and recrystallized from EtOH to give 8-allyl-7-hydroxycoumarin in needles (15·5 g, 94%), m.p. 166–167° (lit [36], m.p. 165–166°).

8-*Allyl*-7-*methoxycoumarin*. A soln of 8-allyl-7-hydroxycoumarin (15 g) and MeI (28 ml) in dry acetone (225 ml) was refluxed and stirred with anhydrous K_2CO_3 (48 g) for 50 hr. Work-up in the normal way gave 8-allyl-7-methoxycoumarin (15·1 g, 94%), m.p. 142–143° (needles from MeOH) (Found: C, 72·1; H, 5·5. $C_{13}H_{12}O_3$ requires: C, 72·2; H, 5·6%).

8-*Formylmethyl*-7-*methoxycoumarin*. A mixture of ozone and O_2 was passed through a soln of 8-allyl-7-methoxycoumarin (6 g) in $CHCl_3$ (300 ml) at −78° until the starting compound had reacted (TLC). Reduction of the ozonide either with Pt/H_2 or with Me_2S, chromatography of the product on silica gel, and elution with Et_2O–EtOAc (1:1) afforded the aldehyde (2·8 g, 46%), m.p. 156–159° (from aq AcOH) (lit [37], m.p. 160°), τ ($CHCl_3$) 0·04 (1 H, *t* *J* 1·5 Hz) ($CH_2C\underline{H}O$), 2·17 (1 H, *d*, *J* 10 Hz), 2·40 (1 H, *d*, *J* 9·5 Hz), 2·97 (1 H, *d*, *J* 9·5 Hz), 3·62 (1 H, *d*, *J* 10 Hz), 5·93 (2 H, *d*, *J* 1·5 Hz) ($C\underline{H}_2CHO$) and 6·00 (3 H, *s*) (OMe).

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