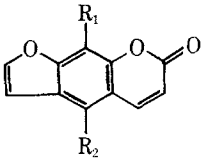
Natural Coumarins XII: Umbelliprenin, a Constituent of *Ammi majus* L. Fruits

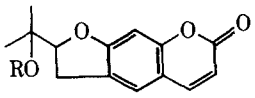
E. A. ABU-MUSTAFA, F. K. A. EL-BAY, and M. B. E. FAYEZ

Abstract □ The hitherto known free coumarins of *Ammi majus* L. fruits (xanthotoxin, imperatorin, bergapten, isopimpinellin, and isoimperatorin) are all psoralene derivatives. Umbelliprenin represents the first nonfuranoid coumarin to be found in this source, and its isolation is reported in this article.

Keyphrases □ Umbelliprenin, a nonfuranoid coumarin—isolation from *Ammi majus* L. fruits □ Coumarins, natural—isolation of umbelliprenin from *Ammi majus* L. fruits □ TLC—separation, identification

The well-established pharmaceutical utility of *Ammi majus* L. fruits, essentially as a source for photodynamically active agents used in the treatment of leucodermia (vitiligo) (1), made it one of the most important economic drug plants of Egypt. Five furocoumarin products—xanthotoxin (I) (2), imperatorin (II) (3), bergapten (III) (3), isopimpinellin (IV) (4), and isoimperatorin (V) (5)—and one dihydrofurocoumarin—marmesin (VI) (6), occurring naturally as the glucoside





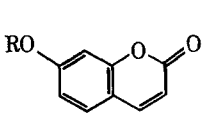
VI: R = H; VII: R = glucose

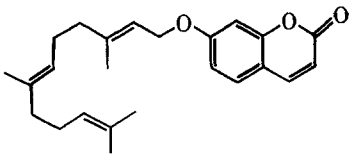
I: R_1 = OCH_3, R_2 = H
II: R_1 = $OCH_2CH{=}C(CH_3)_2$, R_2 = H
III: R_1 = H, R_2 = OCH_3
IV: R_1 = R_2 = OCH_3
V: R_1 = H, R_2 = $OCH_2CH{=}C(CH_3)_2$

marmesinin (VII) (7)—have so far been isolated from this umbelliferous plant which may be regarded as the richest known source for coumarins.

From TLC evidence, the presence of at least one additional product in the free (nonglycosidic) coumarin fraction of *A. majus* L. fruits has been suspected for some time. The isolation, from preparative chromatoplates, of yet another constituent of the drug is now reported. The product (m.p. 60–61°, optically inactive) was obtained in extremely small amounts and was shown to be a nonhydroxylic coumarin. The UV spectrum (showing one principal peak at 325 nm.) precluded the presence of a furanoid moiety (a feature in all the hitherto known coumarins of *A. majus* L.) since no perceptible absorption was observed in the 240–280-nm. region (7, 8).

The nature of the isolated product was revealed by mild treatment with mineral acid, which readily afforded a phenol identified as umbelliferone (VIII) and subsequently methylated to give herniarin (IX). By direct comparison, it was established that the compound was actually umbelliprenin [the *trans,trans*-farnesyl ether (9) of umbelliferone] (X), a rare product which had previ-





VIII: R = H; IX: R = CH_3 X

ously been isolated from *Angelica archangelica* (10). The mass spectrum[1] (Fig. 1) of umbelliprenin showed that the molecular ion (*m/e* 366) suffers an initial loss of 56 mass units, which may be attributed to expulsion of C_4H_8 giving ion formulated as *a* (measured *m/e* 310.1521, calculated for $C_{20}H_{22}O_3$ *m/e* 310.1565) (Scheme I) rather than to expulsion of two carbon monoxide particles (calculated for $C_{22}H_{30}O$ *m/e* 310.2294). This type of expulsion obviously occurs from the sesquiterpenoid side chain and is also observed to take place from other fragment ions. Elision of the entire farnesyl side chain, with transfer of a hydrogen atom favorably accommodated in a six-membered cyclic arrangement, leads to umbelliferone ion (*m/e* 162) and fragment *b* (*m/e* 204), which subsequently loses 43 mass units to give an ion at *m/e* 161. The more intense peaks in the spectrum result by fragmentations in the farnesyl group. These include ions *c*, *d*, and *e* showing at *m/e* 69, 137, and 205, respectively; the last two undergo further degradation by loss of C_4H_8 to give ions at *m/e* 81 and 149, respectively. The genesis of the ions resulting by loss of C_4H_8 may be difficult to envisage, although rearrangement may well be involved; *f* and *g* are not unlikely for ions *m/e* 81 and 149, respectively. The assigned structures are all substantiated by high resolution measurement of the respective peaks.

Umbelliprenin is the first nonfuranoid coumarin to be found in *A. majus* L. Its presence among the major furocoumarins may have biogenetic significance. It indicates that ether isoprenylation at C-7 (presumably with farnesyl pyrophosphate) may occur, though to a limited degree, prior to the more extensive and biogenetically favored carbon alkylation at C-6 which is considered, by the very reasonable postulations of Aneja *et al.* (11), to lead to the α-(hydroxyisopropyl)-dihydro-

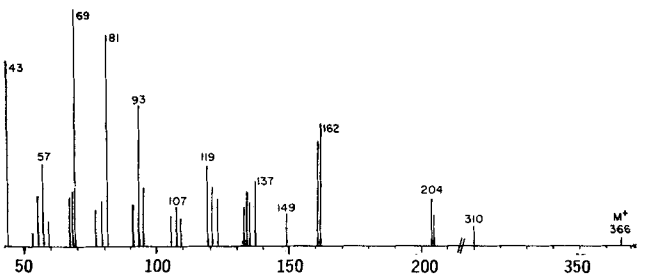
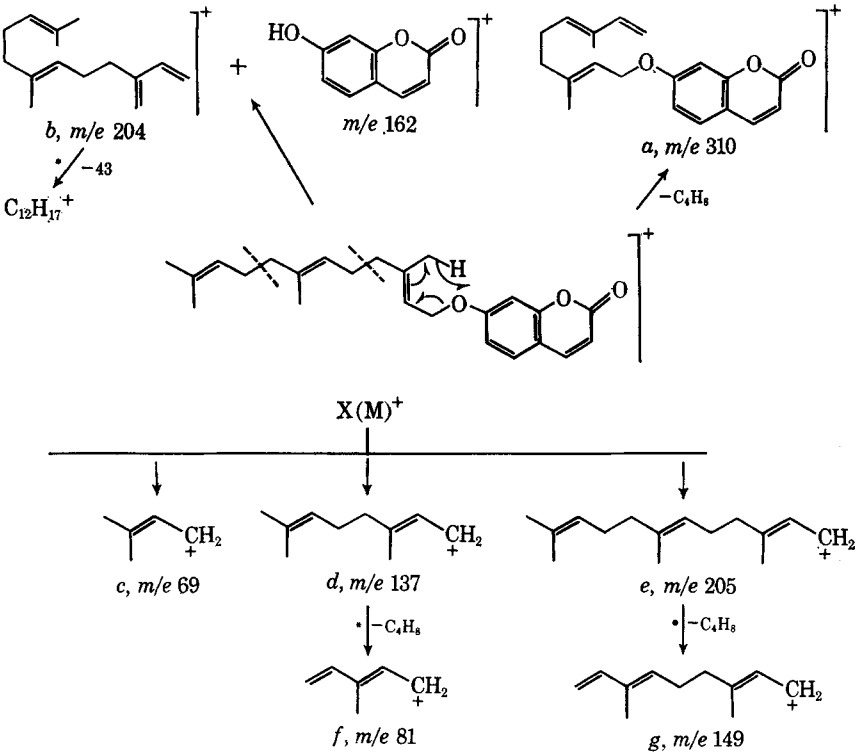


Figure 1—*Mass spectrum of umbelliprenin (X).*

[1] In Scheme I, the transitions supported by the observation of appropriate metastable ions are distinguished by an asterisk.



Scheme I

furan residue (as in marmesin, VI) and ultimately to the unsubstituted furan system (as in the psoralene derivatives, I–V). In fact, it appears particularly attractive to envision all oxygen and carbon isoprenylations as events that occur early in the biogenetic pathway of *A. majus* L. coumarins, quite possibly before the complete elaboration of the α-pyrone system[2].

EXPERIMENTAL

Isolation of Umbelliprenin from *A. majus* L.—The processing of 3.5 kg. of *A. majus* L. fruits for free coumarins, as previously described (5), afforded a crude mixture (18 g.) in which isopimpinellin, xanthotoxin, bergapten, imperatorin, and isoimperatorin were detected (R_f 0.36, 0.39, 0.42, 0.49, and 0.62, respectively) on silica gel G chromatoplates developed with benzene–ethyl acetate (9:1). In addition, a minor product showed up at R_f 0.63, giving brilliant violet fluorescence under UV light and orange, blue, and light-pink colors with the iodine–potassium iodide, 10% sodium hydroxide, and 50% stannous chloride spray reagents, respectively. It was isolated by repeated preparative layer chromatography, and the material collected was crystallized from ethanol–water to give a small amount (8 mg.) of yellowish needles, m.p. 60–61°. The new product was soluble in ethanolic alkali to give a yellowish solution (fluorescent in UV light) from which it was precipitated by acidification. The compound gave negative tests for methoxyl and phenol groups. The UV spectrum exhibited a principal absorption at 325 nm. ($\log \epsilon = 4.15$). Direct comparison (TLC, mixed melting point, and IR spectra) of the isolated material with authentic umbelliprenin revealed its identity.

Boiling the natural product for 2 hr. in 10% ethanolic hydrochloric acid solution, followed by the usual work-up, gave a residue (positive phenol reaction) from which umbelliferone (melting point and mixed m.p. 218–220°) was isolated. The latter was treated with methyl iodide in acetone solution containing sodium carbonate under reflux for 3 hr., and the product was shown to be herniarin. The identities of these two reaction products were established by direct comparison with authentic materials on the chromatoplates, using several solvent systems and spray reagents.

[2] In a recent report, Paikert and Floss (12) proposed that isoprenylation may take place at an early stage in the pathway of furocoumarin biosynthesis in *Pimpinella magna*.

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