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STRUCTURE OF ISOFERPRENIN, A 4-HYDROXYCOUMARIN
DERIVATIVE FROM *FERULA COMMUNIS* VAR. *GENUINA*

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ABSTRACT.—A new 4-hydroxycoumarin, isoferprenin [**1**], has been isolated from *Ferula communis* var. *genuina* and its structure elucidated from spectroscopic studies including ir, ms, and nmr.

Ferula communis varieties (Apiaceae) are widespread plants all around the Mediterranean area and are responsible for an intoxication in livestock, known as ferulosis. Ferulosis is characterized by hemorrhagic symptoms similar to those of poisoning from fermented sweet clover. Previous studies on this species led to the isolation of daucane sesquiterpenes (1–5) and farnesyl-coumarins: ferulenol and 12'- and 15'-hydroxyferulenols (6–9). Some of these coumarins have been shown to have hemorrhagic activity (10). On continuation of our work on toxic substances produced by *F. communis* L. var. *genuina*, which is most common in Morocco, we have isolated a new coumarin derivative **1**, which is structurally related to ferulenol and for which we propose the name isoferprenin. We present here its isolation and structure elucidation.

RESULTS AND DISCUSSION

Isoferprenin [**1**] was extracted from the root sap of *F. communis* var. *genuina*, purified by Si gel cc, and obtained as a colorless oil.

The cims of isoferprenin showed the protonated pseudomolecular ion $[MH]^+$ at m/z 365. Hrms (ei) gave the molecular ion at m/z 364.2065, calculated 364.2038 for $C_{24}H_{28}O_3$. Its ir spectrum indicated that the molecule contained a carbonyl group of an unsaturated δ -lactone (ν 1716 and 1697 cm^{-1}) and aromatic double bonds (ν 1637, 1613, 1494 cm^{-1}). In the ^{13}C -nmr spectrum all the 24 individual resonances were exhibited, and a ^{13}C APT experiment revealed 16 carbons attached to a total of 28 hydrogen atoms. Observed were one carbonyl, 14 sp_2 carbon atoms among which two bore an oxygen atom and eight a hydrogen atom, 9 sp_3 carbon atoms shared among four methyls, four methylenes, and one quaternary carbon atom (Table 1). From the 1H - 1H COSY spectrum, the following substructures could be defined: one ortho-disubstituted aromatic ring, two $-CH_2-CH_2-$ systems, one disubstituted and two trisubstituted carbon-carbon double bonds, and four methyl groups. The protonated carbon atoms were assigned through a 1H - ^{13}C heteronuclear correla-

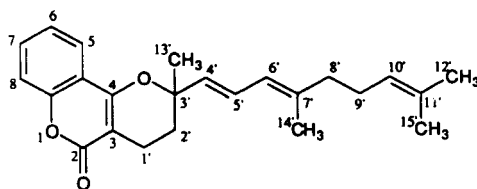


TABLE 1. ^{13}C - and ^1H -nmr Data for Isoferprenin [1].

Position	δ_{C}	δ_{H}	$J(\text{Hz})$
2	163.09 s		
3	100.44 s		
4	158.93 s		
4a	115.94 s		
5	122.20 d	7.834 dd	7.7, 1.4
6	123.68 d	7.254 ddd	8.3, 7.7, 1.3
7	131.19 d	7.479 ddd	8.3, 7.3, 1.4
8	116.49 d	7.290 dd	7.3, 1.3
8a	152.34 s		
1'eq	17.38 t	2.583 ddd	-17.4, 5.9, 5.9
ax		2.474 ddd	-17.4, 9.2, 6.4
2'eq	31.39 t	2.024 ddd	-14.7, 6.4, 5.9
ax		1.883 ddd	-14.7, 9.2, 5.9
3'	79.82 s		
4'	131.98 d	5.600 d	15.3
5'	125.80 d	6.364 dd	15.3, 10.8
6'	123.32 d	5.783 dq	10.8, -1.3
7'	140.58 s		
8'	39.84 t	1.95-2.10 m	
9'	26.40 t	1.95-2.10 m	
10'	123.72 d	5.049 tq	6.8, -1.2
11'	131.55 s		
12'	25.63 q	1.647 brs	
13'	26.58 q	1.541 s	
14'	16.68 q	1.619 d	-1.3
15'	17.62 q	1.562 d	-1.2

tion experiment, and the quaternary carbon atoms were assigned through a long range ^1H - ^{13}C heteronuclear correlation experiment (XHCORR), optimized for a $J_{\text{C-H}}$ coupling constant value of 7 Hz.

The spectral data, compared to that of ferulenol, suggested the presence of a 4-hydroxycoumarin moiety substituted in position 3, which was in agreement with the mass spectral fragmentations.

The ^1H - ^1H COSY spectrum, enhancing the long range couplings (LR COSY), allowed connection of these substructures and definition of an isoprenoid chain. The ethylenic proton at 5.049 ppm (H-10'), which was vicinal to the methylene protons at 1.95-2.10 ppm, gave cross peaks with signals of methyl protons at 1.647 (H-12') and 1.562 ppm (H-15'). The ethylenic proton at 5.783 ppm, H-6', gave correlation spots with methyl protons at 1.619 ppm (H-14') and methylene protons at

1.95-2.10 ppm. This proton H-6' is coupled ($J = 10.8$ Hz) with the proton at 6.364 ppm (H-5'), which in turn gave a trans ethylenic coupling ($J = 15.3$ Hz) with the proton at 5.600 ppm (H-4'). This latter proton (H-4') gave cross peaks, on the ^1H - ^1H LR-COSY, with Me-13' (1.541 ppm) and also with the methylene that gave the signals at 1.883 and 2.024 ppm (C-2'); these results lead to the linkage of C-2', C-4', and C-13' to the remaining methinoxy carbon atom (79.82 ppm, C-3'). As the molecule does not include any hydroxyl groups, the oxygen atom linked to C-3' must be also linked to the C-4 of the hydroxycoumarin. The methylene group, which gave the deshielded signals at $\delta_{\text{H}} = 2.474$ and 2.583 ppm and which is thus linked to C-3 of the coumarin, is strongly coupled to the methylene C-2'. The high vicinal coupling constant value ($J = 9.2$ Hz) between two of them is characteristic of a

trans diaxial relative disposition, in agreement with their involvement in a six-membered cycle.

Finally, nOe difference measurements confirmed the proposed structure and gave information on the conformation in solution. Strong nOe's were observed between: H-4' and H-6' (13.0%), H-6' and H-8' (8.5%), H-8' and H-10' (6.5%), H-5' and Me-14' (12.5%), and H-10' and Me-12' (9.5%), indicating that they are in a cis relative disposition. Irradiation of H-4' enhanced the signals of Me-13' (5.5%), H-5 (4.0%), and H-1'ax (2.5%), and irradiation of H-13' increased the signal of H-2'ax (5.0%); these data show the flexibility of the non-aromatic ring and of the isoprenyl chain.

These results lead to structure **1** (relative configuration) for isoferprenin, which is thus an isomer of ferprenin recently isolated from *F. communis* (8,9). From a biosynthetic point of view, this new compound is related to ferulenol (3-farnesyl-4-hydroxycoumarin), from which it may be derived by cycloaddition of the 4-hydroxyl group of the coumarin ring on the C-2'-C-3' double bond of the farnesyl chain, and dehydrogenation of the C-4'-C-5' bond.

EXPERIMENTAL

GENERAL METHODS.—¹H- and ¹³C-nmr spectra (CDCl₃) were obtained on an AC 300 Bruker spectrometer operating at 300 MHz and 75 MHz, respectively. Chemical shifts, given in δ (ppm) relative to TMS, and coupling constant values of proton-coupled systems have been determined after simulation of the calculated values with the PANIC program (Bruker). The ir spectrum was registered on a Perkin-Elmer 881 ir spectrophotometer, the uv spectrum was recorded on an Uvikon 810 Kontron spectrophotometer, and the optical rotation was measured on a Perkin-Elmer 141 polarimeter. Eims and cims were obtained with a Nermag Sidar V 3.0 mass spectrometer. Hrms was obtained with a V.G. Analytical MM ZAB-HF mass spectrometer.

ISOLATION OF ISOFERPRENIN.—The root sap of *F. communis* var. *genuina* was dissolved in

CH₂Cl₂, filtered to eliminate soil and plant particles, and concentrated under reduced pressure. The residue (10 g) was chromatographed on a Si gel column, and elution was started with CH₂Cl₂ and followed with increasing proportions of EtOAc. The first collected fractions (2 g) were further purified by repetitive Si gel cc [*n*-hexane-EtOAc (3:7)] to give isoferprenin [**1**] (200 mg).

ISOFERPRENIN [1].—C₂₄H₂₈O₃, colorless oil, [α]_D²² +0.4° (c = 1.8, CHCl₃); ir (liquid film, ν cm⁻¹) no -OH absorption, 2966, 2928, 2056, 1716, 1697, 1637, 1613, 1494, 1459, 1395, 1328, 1110, 1075, 1051, 753; uv λ max (EtOH, log ε) 318 (4.7), 304 (4.9), 281 (5.0), 236 (5.4), 242 (5.4); cims (NH₃) *m/z* [M + H]⁺ 365; eims (70 eV, 200°) *m/z* (%) [M + H]⁺ 365 (100), [M]⁺ 364 (29), 203 (3), 190 (28), 189 (15), 175 (49), 147 (8), 133 (4), 121 (67), 107 (7), 105 (15), 93 (16), 69 (16); hrms (ei) *m/z* [M]⁺ 364.2065, calcd 364.2038 for C₂₄H₂₈O₃.

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