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FOETIDIN, A SESQUITERPENOID COUMARIN FROM *FERULA ASSA-FOETIDA*

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Key Word Index—*Ferula assa-foetida*; Umbelliferae; root extract; sesquiterpenoid coumarin; 4-hydroxycoumarin; foetidin.

Abstract—A new sesquiterpenoid coumarin, foetidin, has been isolated from the roots of *Ferula assa-foetida*.

Extracts of *Ferula* spp. are well known in the Mediterranean area as medicines and as food additives (spice). Extracts of *Ferula assa-foetida L.* are used as an anti-spasmodic, a diuretic, a vermifuge and an anti-algetic [1–3]. A characteristic feature of this plant is the presence of sesquiterpenoid coumarins [4]. We now report on a new constituent called foetidin (**1**), which represents a new sesquiterpenoid coumarin.

The dried roots of *F. assa-foetida* were extracted with ethanol–water (19:1) to give a syrup, the fractionation of which by column chromatography yielded foetidin (**1**) as colourless plates, mp 176–178°, $[\alpha]_D^{20}$ $-39.8°$ (ethanol). The compound displayed a behaviour typical of coumarin derivatives in dissolving in dilute alkali from which it was precipitated on addition of an acid. Cleavage by hydroiodic acid in acetic acid gave 4-hydroxycoumarin as shown by cochromatography.

The structure of foetidin was established by comparison of its ^{13}C NMR spectrum with those of colladonin (**2**) [5] and 4-methoxycoumarin (**3**) [6]. The chemical shifts of the coumarin and sesquiterpene moieties agreed well with those of 4-methoxycoumarin and the sesquiterpene moiety of colladonin, respectively. Thus foetidin had the same sesquiterpene moiety (including all stereochemical implications) as colladonin, the sesquiterpene being, however, attached to oxygen at C-4 of coumarin.

The proposed structure is in accord with the IR spectrum (OH band at 3400 cm^{-1}, further bands in the region 1685–1610 cm^{-1} due to different double bonds) and with the UV spectrum (double bands at 265/277 and 303/315 nm typical for 4-alkoxycoumarins [7]). It also agreed well with the ^{1}H NMR spectrum, which revealed an axial $C\underline{H}OH$ ($J = 11.0$ Hz), an exocyclic methylene group at δ4.54 and 4.92[*], three methyl groups linked with quaternary C atoms at *ca* 1 ppm, a CH_2–O group at δ4.35. A singlet at δ5.72 was typical for a coumarin with an alkoxy group at C-4 [9]. The M_r was established by EI mass spectrometry of the compound and its monoacetate (*m/z* 382 and 424, respectively). The fragmentation pattern was in agreement with the deduced structure, although the base signal at *m/z* 163 was due to the coumarin moiety with two additional hydrogens, as shown by accurate mass measurement ($C_9H_7O_3$). The same unusual rearrangement [10] is observed in the spectrum of colladonin (sample kindly provided by Prof. Pinar, Madrid), *m/z* 163

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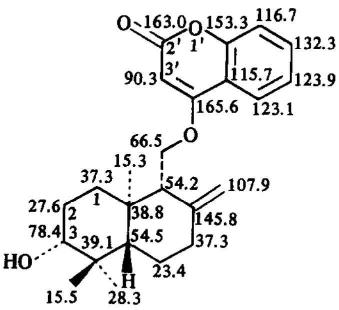
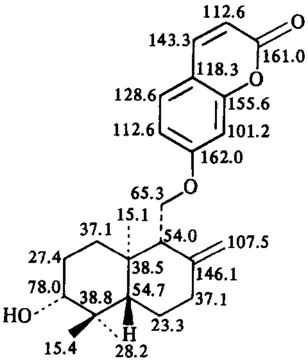
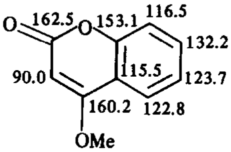
[*] The same signals are observed in coladonin which is identical with colladonin [8].



1 Foetidin



2 Colladonin



3 4 – Methoxycoumarin

(65 %); migration of only one hydrogen gave rise to the base signal at *m/z* 162. On negative ion FAB mass spectrometry of foetidin, no rearrangement occurred and the signal at *m/z* 161 was recorded.

The absolute configuration of foetidin is not known. It is supposed that foetidin has the same absolute configuration as colladonin (**2**) [8, 11].

F. assa-foetida has been reported [12–14] to contain the three compounds farnesiferols A, B and C, all sesquiterpenoid coumarins derived from umbelliferone (7-hydroxycoumarin). The structure of foetidin resembles that of farnesiferol A. However, the C-9 substituent in foetidin is equatorial (as shown by almost the same ^{13}C chemical shift of the C-10 methyl not only as in colladonin, but also as in primaradiene [15]) and the sesquiterpene moiety is attached to the hydroxyl group of 4-hydroxycoumarin. 4-Alkoxycoumarins, like foetidin, are very rare; the two compounds hitherto known [4] (ekersenin and gerberacoumarin) have an additional group attached to C-5. Thus foetidin is the first example of a naturally occurring 4-alkoxycoumarin with no additional groups at the coumarin moiety.

EXPERIMENTAL

Dried powdered roots (400 g) of *F. assa-foetida* were exhaustively extracted with EtOH–H_2O (19:1) and processed as described before [16] to give 20 g of a coumarin fraction. The fraction was separated on a column containing 800 g alumina by eluting successively with the solvents *n*-hexane, *n*-hexane–C_6H_6 (1:1), C_6H_6 and MeOH–C_6H_6 (99.5:0.5). The MeOH–C_6H_6 fraction was crystallized from MeOH to give 0.2 g colourless plates, mp 176–178°. R_f (TLC) 0.23 (C_6H_6–EtOAc, 9:1); no colour under UV; deep violet colour when sprayed with I_2. EI MS (accurate mass measurement) *m/z* (rel. int.): 382 $[M]^+$ (7, $C_{24}H_{30}O_4$), 220 (16, $C_{15}H_{24}O$), 202 (17, $C_{15}H_{22}$), 187 (15, $C_{14}H_{19}$), 163 (100, $C_9H_7O_3$), 159 (22, $C_{12}H_{15}$); IR ν_{max}^{KBr} cm^{-1}: 3400 (s, OH), 3040–3100 (w), 2800–3000 (s), 1685 (s), 1650 (w), 1620 (s), 1610 (s); UV λ_{max}^{MeOH} nm: two double bands at 265/277 and 303/315; ^1H NMR (270 MHz, $CDCl_3$, assignments achieved on the basis of coupling constants, decoupling experiments and shifts induced by adding Eu(fod)$_3$: δ0.83 (*s*, Me-10), 0.88 (*s*, Me_{ax}-4), 1.04 (*s*, Me_{eq}-4), 1.2–1.9 (*m*, H_{ax}-1, H_{eq}-1, H_{ax}-2, H_{eq}-2, H-5, H_{ax}-6, H_{eq}-6, OH), 2.12 (*m*, H_{ax}-7), 2.31 (*t*, *J* = 5.4 Hz, H-9), 2.49 (*m*, H_{eq}-7), 3.33 (*dd*, *J* = 11.0 and 4.0 Hz, H_{ax}-3), 4.35 (*m*, –CH_2–O), 4.54 and 4.92 (each *s*, exomethylenic H's), 5.72 (*s*, H-3'), 7.2–7.4 (*m*, H-6', H-8'), 7.6 (*m*, H-7'), 7.8 (*dd*, *J* = 8.5 and 2.1 Hz, H-5').

Acetylation. Foetidin (50 mg) was refluxed in 6 ml Ac_2O–C_5H_5N (1:1) for 2 hr. The mixture was worked up by standard methods to give 50 mg colourless crystals of acetylated foetidin, mp 189–192° (MeOH). EIMS *m/z* (rel. int.): 424 $[M]^+$ (12), 163 (100).

Hydrolysis. Foetidin was refluxed in a mixture of HI–HOAc (1:1) for 1 hr. Separation of the reaction mixture by TLC revealed the formation of 4-hydroxycoumarin (same R_f value and same behaviour under UV light as an authentic sample).

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