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SIX SESQUITERPENE ALCOHOL ESTERS FROM *FERULA ELAEOCHYTRIS*

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Key Word Index—*Ferula elaeochytris*; Umbelliferae; angelic and aromatic acid esters of jaeschkeanadiol; 3-hydroxy-4,5-methylenedioxypropiophenone; sesquiterpene alcohol esters.

Abstract—Two new salicyloyl and angeloyl esters of jaeschkeanadiol, together with the known benzoic, *p*-hydroxybenzoic, *p*-methoxybenzoic and vanillic acid esters, were isolated from *Ferula elaeochytris*. A new ketone, 3-hydroxy-4,5-methylenedioxypropiophenone, was also obtained.

INTRODUCTION

This is the first chemical investigation of *Ferula elaeochytris* Korovin, the aerial parts of which are added to the diet of sheep and cattle in southeastern parts of Turkey to increase the fertility of the animals. From the benzene extract of dried roots of the plant we obtained six esters (**1a–f**) of jaeschkeanadiol (**1**); two of these compounds, **1e** and **1f**, are new. In addition, a new propiophenone, 3-hydroxy-4,5-methylenedioxypropiophenone (**2**), was isolated. The four known sesquiterpene esters were previously obtained from different *Ferula* species by Russian investigators. Compound **1a**, the benzoyl ester, was previously obtained from the fruits of *F. tenuisecta* and named teferidine [1], while the roots of the same plant yielded the vanilloyl ester, **1c** (teferin) [2]; the roots of *F. ovina* afforded the *p*-hydroxybenzoyl ester, **1b** (ferutinin) [3]; *p*-methoxybenzoyl ester **1d** (ferutidin) was obtained from the roots of *F. kuhistanica* [4]. Jaeschkeanadiol (**1**) was isolated as a free alcohol from the roots of *F. jaeschkeana* and its structure, including stereochemistry, was established [5]. Several additional aromatic acid esters of sesquiterpenes have also been reported from these and other species of *Ferula* [3, 6]. The 3-methoxy analog of the ketone **2** reported here was isolated from *Ferula ugamica* [7] and *Oenanthe crocata* L., another member of the Umbelliferae [8]. Similar propiophenones, such as 2-hydroxy-4,5-methylenedioxy- and 2-methoxy-4,5-methylenedioxypropiophenones have been found in *Piper marginatum* (Piperaceae) [9].

The IR, ^{1}H NMR and UV spectra of the esters indicated that five of them, **1a–1d** and **1f**, contained an aromatic moiety and that one, **1e**, did not. Hydrolysis of all, except one of the new ones, **1f**, could be effected with 5% aqueous potassium hydroxide; all yielded the same alcohol, jaeschkeanadiol (co-TLC and IR comparison with an authentic sample) and the following acids: benzoic (from **1a**), *p*-hydroxybenzoic (from **1b**), vanillic (from **1c**), *p*-methoxybenzoic (from **1d**) and angelic (from **1e**); all were identified by UV and TLC comparison with standard acids. The fifth aromatic ester (**1f**) did not hydrolyse under these conditions. Thus, **1f** was first acetylated to give **1g** which was then treated at room temperature with 0.1 M sodium methoxide; this reaction sequence yielded jaeschkeanadiol and the product of *trans* esterfication, namely acetyl methylsalicylate, which was identified by UV, NMR and mass spectral data. Therefore, **1f** must be the salicyloyl ester of jaeschkeanadiol. That all these compounds were esterified at the 6-hydroxyl and not the tertiary 4-hydroxyl was clearly shown in their ^{1}H NMR spectra by the δ1.4 downfield shift (δ3.92 to 5.32) of the H-6 signal in these esters relative to the free alcohol, jaeschkeanadiol [5].

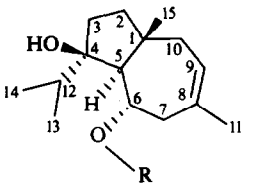
The structure of the new ketone, **2**, was determined by spectral methods. Its UV spectrum indicated that it contained an aromatic moiety and its IR spectrum exhibited absorptions for a hydroxyl group (3300 cm^{-1}) and a carbonyl function (1675 cm^{-1}). ^{1}H NMR of **2** was recorded in both acetone-d_6 and pyridine-d_5 and both spectra showed a methyl triplet at δ1.16 (J = 7 Hz), a methylene quartet at δ2.88 (J = 8 Hz) and a singlet for a methylene dioxide group at δ6.08. Two one-proton doublets for two aromatic protons appeared at δ7.05 and 7.25 in acetone-d_6 and at δ7.35 and 7.68 in pyridine-d_5 (J = 2 Hz in accordance with a *meta* relationship). The chemical shifts indicated that these aromatic protons were between a carbonyl and oxygen function as shown in **2**; in an alternative structure, **3**, the signal for the proton *ortho* to two oxygen functions should be around δ6.1–6.2 [10]. The signal for the hydroxyl proton was observed at δ7.35 in acetone-d_6. The ^{13}C NMR spectrum of **2** (in pyridine) corroborates the suggested structure (see Experimental).

EXPERIMENTAL

The plant material was collected by the senior author near Hatay in southeastern Turkey during June 1981. A voucher specimen, ISTE No. 32986, is deposited in the Herbarium on the Faculty of Pharmacy, University of Istanbul.

Isolation and identification of the compounds. Air-dried and coarsely powdered roots of *Ferula elaeochytris* (1.5 kg) were extracted in a Soxhlet successively with C_6H_6, $CHCl_3$ and EtOH. The C_6H_6 extract was concd and chromatographed over a Si gel column. Since ^{1}H NMR data of the known compounds were not previously reported, these are presented here along with spectral data for the new compounds. Where possible ^{1}H NMR assignments were based on spin–spin decoupling expts.

Teferidine (**1a**). Yield, 100 mg. ^{1}H NMR (200 MHz, $CDCl_3$): δ8.03 (2H, *dd*, J = 2 and 9 Hz, H-3′ and H-5′), 7.6 (1H, *dt*, J = 2



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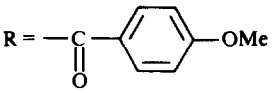
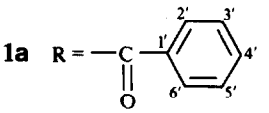
1d R = 

1a R = 

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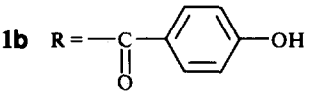
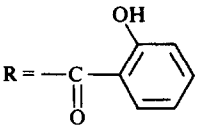
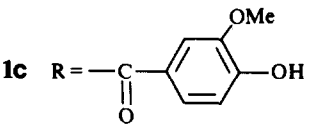
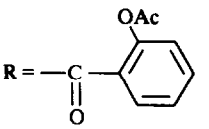
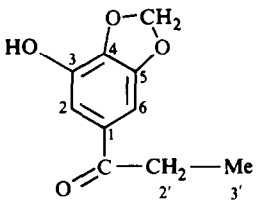
1b R = 

1f R = 

1c R = 

1g R = 



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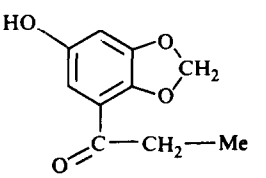

3

and 9 Hz, H-4'), 7.46 (2H, *dt*, J = 2 and 9 Hz, H-2' and H-6'), 5.56 (1H, *br t*, J = 6.5 Hz, H-9), 5.32 (1H, *dt*, J = 3 and 10 Hz, H-6), 1.85 (3H, *br s*, H-11), 1.12 (3H, *s*, H-15), 0.96 (3H, *d*, J = 7 Hz, H-13), 0.85 (3H, *d*, J = 7 Hz, H-14).

Ferutinin (**1b**). Yield, 70 mg. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.8 (2H, *d*, J = 8 Hz, H-3' and H-5'), 6.8 (2H, *d*, J = 8 Hz, H-2' and H-6'); other signals were similar to **1a**.

Teferin (**1c**). Yield, 150 mg. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.6 (2H, *br d*, J = 8 Hz, H-2' and H-6'), 6.9 (1H, *d*, J = 8 Hz, H-5'), 3.9 (3H, *s*, OMe), other signals as in **1a** and **1b**.

Ferutidin (**1d**). Yield, 10 mg. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.98 (2H, *d*, J = 8 Hz, H-3' and H-5'), 6.94 (2H, *d*, J = 8 Hz, H-2' and H-6'), 3.88 (3H, *s*, OMe), other signals as in **1a**–**1c**.

Compound **1e**. Yield 20 mg, amorphous oil. The UV spectrum (MeOH) showed only end absorption at 218 nm; IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 2960, 2860, 1705 (ester C=O), 1645, 1450, 1270, 1150, 1030, 1000, 940, 705 and 660; MS (probe) 70 eV, *m/z* (rel. int.): $[M]^+$ (not observed), 277 (8%) $[M-43]^+$, 83 (75%) [angelate acylium ion]$^+$, other fragments from the jaeschkeanadiol moiety included 220 (15) [jaeschkeanadiol $-$ (OH $-$ H)]$^+$, 202 (20) [jaeschkeanadiol $-$ 2(OH + H)]$^+$, 177 (90) [jaeschkeanadiol $-$ 43 $-$ 18]$^+$.

Compound **1f**. Yield 1.5 g, amorphous. UV λ_{max}^{MeOH} nm: 340, 280 (sh), 249 and 220; IR ν_{max}^{KBr} cm^{-1}: 3470 (OH), 3360 (OH), 2980, 2880, 1680, 1610, 1585, 1550, 1480, 1375, 1295, 1235, 1160, 1095, 950, 750 and 700; MS (probe), 70 eV, *m/z* (rel. int.): 358 (85%) $[M]^+$, 340 (5) [M $-$ (OH + H)]$^+$, 315 (88) $[M-43]^+$, 220 (20) [jaeschkeanadiol $-$ (OH + H)]$^+$, 202 (40) [jaeschkeanadiol $-$ 2(OH + H)]$^+$, 137 (95) [salicyclic acid $-$ 1]$^+$ and 121 (100) [salicyloyl acylium ion]$^+$; ^{1}H NMR (200 MHz, $CDCl_3$): δ8.65 (1H, *dd*, J = 2 and 9 Hz, H-6'), 7.94 (1H, *dd*, J = 2 and 9 Hz, H-3'), 7.52 (1H, *dt*, J = 2 and 8 Hz, H-5'), 7.07 (1H, *dt*, J = 2 and 8 Hz, H-4'), remaining signals were similar to those of **1a**. Acetylation of **1f** was carried out at room temp. in the usual manner and yielded the monoacetate **1g**, mp 168–170° (MeOH).

Compound **1g**. ^{13}C NMR (22.6 MHz, $CDCl_3$): δ169.2 (*s*, ester C=O), 168.0 (*s*, acetyl C=O), 141.9 (*s*, C-2'), 134.5 (*s*, C-8), 133.3 (*d*, C-6'), 130.3 (*d*, C-4'), 125.5 (*d*, C-9), 122.3 (*d*, C-5'), 120.2 (*d*, C-3'), 115.5 (*s*, C-1'), 86.2 (*s*, C-4), 71.8 (*d*, C-6), 59.7 (*d*, C-12), 44.1 (*s*, C-1), 41.4 (*t*, C-7), 41.1 (*t*, C-3, C-10), 36.8 (*d*, C-5), 32.2 (*t*, C-2), 26.5 (*q*, C-11), 25.4 (*q*, acetyl Me) 20.1 (*q*, C-15), 18.6 (*q*, C-14), 17.5 (*q*, C-13).

Trans *esterification of* **1g**. Compound **1g** (500 mg) was allowed to stand at room temp. in a MeOH soln of 0.1 M NaOMe for 2 hr. After neutralization with a Pi buffer (pH 7), the soln was extracted with EtOAc. This extract was then cleaned over a

Sephadex LH-20 column [11]. The 2-acetyl methylsalicylate was the only product obtained crystalline (from MeOH), mp 46–48°.

Acetylmethyl salicylate. UV λ_{max}^{MeOH} nm: 308, 247, 227; IR ν_{max}^{KBr} cm^{-1}: 2980, 2920, 1700 (acetyl C=O), 1690 (ester C=O), 1590, 1520, 1450, 1430, 1380, 1300, 1260, 1235, 1170, 1080 and 760; ^{1}H NMR (200 MHz, $CDCl_3$): δ8.7 (1H, *br d*, J = 9 Hz, H-6'), 8.02 (1H, *br d*, J = 9 Hz, H-3'), 7.55 (1H, *br t*, J = 9 Hz, H-5'), 7.05 (1H, *br t*, J = 9 Hz, H-4'), 3.95 (3H, *s*, ester Me), 2.30 (3H, *s*, acetyl Me); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ169.2 (*s*, acetyl C=O); 168.9 (*s*, ester C=O), 142.1 (*s*, C-2'), 134.8 (*d*, C-6'), 130.9 (*d*, C-4'), 122.5 (*d*, C-5'), 120.5 (*d*, C-3'), 114.9 (*s*, C-1'), 52.3 (*q*, ester Me) and 29.7 (*q*, acetyl Me).

Jaeschkeanadiol (1). ^{13}C NMR (22.6 MHz, $CDCl_3$): δ133.6 (*s*, C-8), 129.1 (*d*, C-9), 87.1 (*s*, C-4), 67.9 (*d*, C-6), 61.9 (*d*, C-12), 45.2 (*s*, C-1), 43.0 (*t*, C-7), 42.1 (*t*, C-3), 41.2 (*t*, C-10), 36.1 (*d*, C-5), 32.3 (*t*, C-2), 27.7 (*q*, C-11), 19.8 (*q*, C-15), 18.4 (*q*, C-14) and 17.2 (*q*, C-13).

3-*Hydroxy*-4,5-*methylenedioxypropiophenone* (2). Yield, 30 mg, mp 154–156°. UV λ_{max}^{MeOH} nm: 300, 275 (sh), 260, 230 (sh) and 210; IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 2900, 1675 (C=O), 1600, 1505, 1420, 1380, 1325, 1150, 1060, 1010, 920 and 800. MS (probe) 70 eV m/z (rel. int.): 194 (35%) $[M]^+$, 177 (25) $[M-17]^+$, 165 (100) $[M-Et]^+$, 137 (20) $[M-COEt]^+$, 121 (65), 107 (12), 93 (18) and 81 (20); ^{1}H NMR (200 MHz, Me_2CO-d_6 and pyridine-d_5): see text; ^{13}C NMR (22.6 MHz, pyridine-d_5): δ199.1 (*s*, C=O), 149.1 (*s*, C-5), 141.5 (*s*, C-3), 132.1 (*s*, C-4), 113.5 (*s*, C-1), 101.8 (*d*, C-2, C-6), 100.5 (*t*, O–CH_2–O), 31.5 (*t*, C-2') and 8.5 (*q*, C-3').

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