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NEW SESQUITERPENES FROM *FERULA SINAICA*

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ABSTRACT.—The CH_2Cl_2 extract of *Ferula sinaica* afforded twelve sesquiterpenes including three new daucanes, 14-hydroxyvaginatin [**6**], 4β,8β,9α-trihydroxy-6α-*p*-hydroxybenzoyloxydaucane [**7**], and isolancerotriol [**8**].

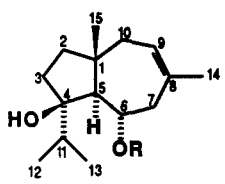
The large genus *Ferula* (Umbelliferae) is represented by about 150 species worldwide (1). Extracts of some species of *Ferula* have been used in folk medicine for treating various diseases (2). More than seventy species have been studied chemically, and these investigations have shown that germacranes, humulanes, carotanes, himachalanes, and guaianes represent the main sesquiterpene constituents of the genus. Previous work on *Ferula sinaica* Boiss. led to the isolation of a coumarin, two sesquiterpenes, and a propiophenone (3).

RESULTS AND DISCUSSION

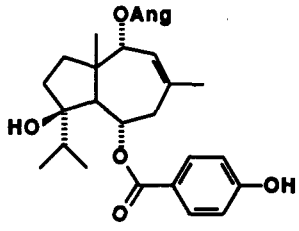
Re-investigation of the CH_2Cl_2 extract of the roots of *F. sinaica* afforded twelve sesquiterpene compounds, including three new daucanes. The known compounds were identified as jaeschkeanadiol [**1**] (4), jaeschkeanadiol benzoate [**2**] (5), jaeschkeanadiol *p*-hydroxybenzoate [**3**] (6), jaeschkeanadiol *p*-methoxybenzoate (3), 4β-hydroxy-6α(*p*-hydroxybenzoyloxy)-10α-angeloxydauc-7-ene [**4**] (7), 5-*p*-hydroxybenzoyl ester of ferutiol [**5**] (8), isosamarcandin [**9**] (9), coladonin [**10**] (10), and feselol [**11**] (9). The known compounds were identified by comparison of their ^{1}H-nmr, mass, and ir spectra with those reported in the literature.

The ^{1}H-nmr spectral data of compound **6** were very similar to those of vaginatin (12). In addition to signals of an olefinic proton at δ 5.94 and a proton geminal to an ester group at δ 5.34, those of a tertiary methyl and isopropyl group were observed. The downfield chemical shift of the tertiary methyl and the isopropyl group at δ 1.07, 1.06, and 1.00 were typical for daucane with a 1,5-cis skeleton and an isopropyl group with a β-orientation, respectively (11–13). Moreover, the coupling constant of H-10 with 9 Hz indicated a H-10β. On the other hand, the signals at δ 6.06 qq, 1.97 dq, and 1.83 q indicated the presence of an angelate group. The absence of a signal for an olefinic methyl group and the presence of a broad two-proton singlet at δ 4.03 suggested the presence of a hydroxyl group at C-14. Spin decoupling allowed the assignment of all signals, and the resulting sequences indicated the position of the functional groups. The ms showed a molecular ion $[M]^+$ ($C_{20}H_{30}O_5$) at *m/z* 350, loss of an H_2O molecule to give *m/z*332, loss of an isopropyl group to give *m/z* 307, loss of an angelate to give *m/z* 267, and the angelate group at *m/z* 83. On the other hand, the ^{13}C spectrum of **6** showed the presence of a keto group at δ 220, a double bond at δ 148.4 and 119.7, and carbons bearing primary, secondary, and tertiary hydroxyl groups at δ 67.7, 75.2, and 82.4, respectively. Also, the angelate group gave signals at δ 166, 140, 126.6, 20.7, and 15.8. Comparison of the ^{13}C-nmr data with those of carotol, a compound with established stereochemistry, confirmed the configuration at C-1, C-4, and C-5 (13).

The ms of the sesquiterpene **7** indicated a typical fragmentation pattern of daucane, loss of an isopropyl group at *m/z* 349 $[M-43]^+$, and loss of *p*-hydroxybenzoic acid at *m/z* 254 $[M-138]^+$. The ^{1}H-nmr spectrum of **7** showed a two-proton doublet at δ 7.89 coupled to a



1 R=H
2 R=benzoate
3 R=*p*-hydroxybenzoate



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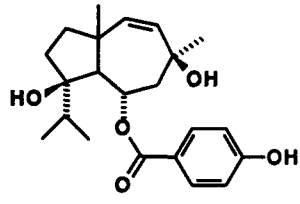

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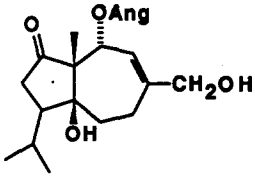

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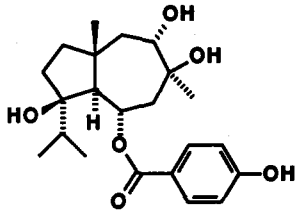

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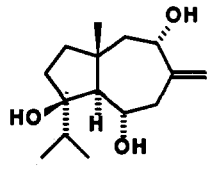

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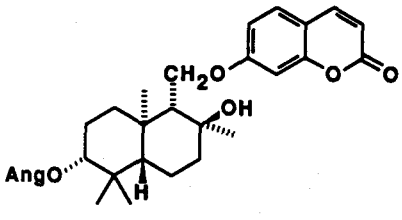

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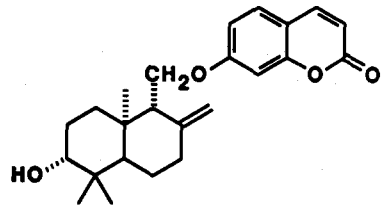

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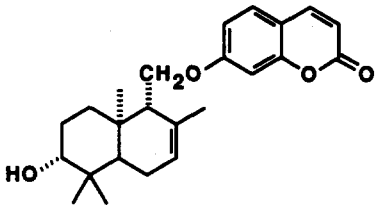

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doublet at δ 6.84, confirming the presence of a *p*-hydroxybenzoyl group. The proton geminal to the ester group appeared at δ 5.54 as a ddd with coupling constants of 10 Hz with H-5, and 6 Hz and 2 Hz with H-7β and H-7α; indicating a β orientation for H-6 and an α orientation for H-5. The upfield signals at δ 0.73 and δ 0.78 agreed with the presence of an isopropyl group. Compound **7** was synthesized by treatment of **3** with *m*-perchlorobenzoic acid to form the 8,9-epoxide and reaction of this epoxide with perchloric acid to give **7**; it is known that this sequence of reactions yields the diol stereochemistry shown (14). The chemical shifts of H-14 and H-9 as well as the coupling constant of H-9 of the synthetic compound were identical to those of **7**. Therefore, the hydroxyl groups at C-8 and C-9 must have the β and α configurations, respectively. Additionally, the broad triplet at δ 3.66 supported the α orientation of the hydroxyl group at C-9.

The ^{1}H-nmr spectrum of **8** was essen-

tially identical to those of isolancerotriol esters (14,15), except that the proton geminal to the hydroxyl group at the 6-position was shifted upfield at δ 4.04. This indicated the presence of a free hydroxyl group at C-6. Again, the chemical shift of H-9 at δ 4.22 and the coupling constant with H-10α and H-10β were identical to those reported for the lancerotriol ester which was isolated from *Ferula linkii* (15), supporting the β-configuration of H-9. Similarly, the α orientation of H-5 was deduced from the chemical shift and the coupling constant. In eims, compound **8** gave no molecular ion, but a clear $[M+1]^+$ ion was observed by chemical ionization at *m/z* 255 ($C_{15}H_{26}O_3$). Other fragments due to loss of one, two, and three molecules of H_2O gave ions *m/z* 237, 219, and 201, respectively. ^{13}C-nmr data were very close to those of lancerotriol and provided further support for the structure.

EXPERIMENTAL

PLANT MATERIAL.—The roots of *F. sinaica* were collected from North Sinai in March 1987. A voucher specimen (A. Ahmed 110) is deposited in the Department of Botany, El-Minia University.

EXTRACTION AND ISOLATION OF TERPENOIDS.—Dried and powdered roots of *F. sinaica* (2 kg) were extracted with CH_2Cl_2 at room temperature and gave 200 g of viscous oil. The resulting extract was roughly fractionated by cc (Si gel) using petroleum ether with increasing amounts of Et_2O. The fraction eluted with 20% Et_2O (25 g) was separated into two parts. From the less polar portion (5 g), 2 g was again separated by cc (Si gel) using CH_2Cl_2, which gave 700 mg of **1**, 30 mg of **2**, 20 mg of **3**, and 15 mg of **4**. The latter fraction (50 g) was jaeschkeanadiol *p*-methoxybenzoate, previously reported (3). The fraction eluted with 80% Et_2O gave 25 g; 50 mg of that fraction could be separated by hplc [RP8, ca. 100 bar, either MeOH-H_2O (7:3) or MeOH-H_2O (1:1)] and afforded 4 mg of **5**, 3 mg of **6**, 5 mg of **7**, 10 mg of **8**, 15 mg of **9**, 11 mg of **10**, and 8 mg of **11**. All compounds have been purified by hplc (RP8, ca. 100 bar).

14-HYDROXYVAGINATIN [**6**].—Ir ν max (CHCl) cm^{-1} 3560, 3400, 2940, 2360, 1700, 1680, 1160; ^1H nmr (400 MHz, $CDCl_3$, TMS as internal standard) δ 6.06 (1H, qq, *J* = 7.0 and 1.5 Hz, H-3′), 5.94 (1H, br d, *J* = 9 Hz, H-9), 5.34 (1H, *J* = 9 Hz, H-10), 4.03 (2H, br s, H-14), 1.97 (3H, dq, *J* = 7.0 and 1.5 Hz, H-4′), 1.83 (3H, q, H-5′), 1.07 (3H, s, H-15), 1.06 (3H, d, *J* = 7 Hz, H-12), 1.00 (3H, d, *J* = 7 Hz, H-13); ^{13}C nmr (400 MHz, $CDCl_3$), δ 220 (s, C-2), 166.0 (s, C-1′), 148.4 (s, C-8), 140.0 (d, C-3′), 126.6 (s, C-2′), 119.7 (d, C-9), 82.4 (s, C-5), 75.2 (d, C-10), 67.7 (t, C-14), 59.9 (s, C-1), 50.5 (d, C-4), 38.5 (t, C-6), 37.0 (t, C-3), 26.3 (d, C-11), 24.6 (q, C-13), 24.2 (t, C-7), 21.2 (q, C-12), 20.7 (q, C-4′), 18.0 (q, C-15), 15.8 (q, C-5′); ms *m/z* (% rel. int.), $[C_{20}H_{30}O_5]^+$ 350 (5), $[M-H_2O]^+$ 332 (2), $[M-C_3H_7]^+$ 307 (3), $[M-C_5H_7O]^+$ 267 (38), [angelate]$^+$ 83 (100).

4β,8β,9α-TRIHYDROXY-6α-*p*-HYDROXYBENZOYLOXYDAUCANE [**7**].—$[\alpha]^{24}D$ +15.8 (*c* = 0.5, MeOH); ir ν ($CHCl_3$) max cm^{-1} 3700, 3620, 3480, 3000, 2440, 1700, 1640, 1580, 1160, 1050; ^1H nmr (400 MHz, $CDCl_3$, TMS as internal standard) δ 7.89 (2H, d, *J* = 9 Hz H-3′, -7′), 6.84 (2H, d, *J* = 9 Hz, H-4′, -6′), 5.54 (1H, ddd, *J* = 10, 6, and 2 Hz, H-6), 3.66 (1H, br t, *J* = 4 Hz, H-9), 1.87 (1H, dd, *J* = 15 and 4 Hz, H-10a), 1.78 (1H, dd, *J* = 10 and 4 Hz, H-10b), 1.18 (3H, s, H-14), 1.16 (3H, s, H-15), 0.78 (3H, d, *J* = 7 Hz, H-12), 0.73 (3H, d, *J* = 7 Hz, H-13); ^{13}C nmr (400 MHz, $CDCl_3$) δ 166.1, (s, C-1′), 161.6 (s, C-5′), 131.7 (d, C-3′, -7′), 121.2 (s, C-2′), 115.2 (d, C-4′, -6′), 86.0 (s, C-4), 78.7 (d, C-6), 75.1 (s, C-8), 68.2 (d, C-9), 56.2 (d, C-5), 43.2 (t, C-10), 42.6 (t, C-7), 42.3 (s, C-1), 42.1 (t, C-3), 37.0 (d, C-11), 31.3 (t, C-2), 30.5 (q, C-14), 21.2 (q, C-15); ms *m/z* (% rel. int.) $[M-43]^+$ 349 (3), $[M-138]^+$ 254 (3), $[M-181]^+$ 211 (10), [benzoate]$^+$ 121 (100).

SYNTHESIS OF **7**.—Jaeschkeanadiol *p*-hydroxybenzoate [**3**] (50 mg) was dissolved in $CHCl_3$ (5 ml) and added to a solution of *m*-chloroperbenzoic acid (20 mg) in $CHCl_3$ (5 ml). After 2 h, the reaction mixture was washed with a saturated solution of $NaHCO_3$. The formed epoxide was extracted with CH_2Cl_2, treated with aqueous 3% perchloric acid at room temperature for 2 days, and worked up as mentioned to give a crude oil, which was purified by hplc [MeOH-H_2O (6:4)] and gave 15 mg of **7**.

ISOLANCEROTRIOL [**8**].—$[\alpha]^{24}D$ +63 (*c* = 0.31, MeOH); ir ν max ($CHCl_3$) cm^{-1} 3560, 3420; ^1H nmr δ 5.22 (1H, br s, H-14_a), 5.04 (1H, br s, H-14_b), 4.22 (1H, dd, *J* = 10 and 6 Hz, H-9), 4.04 (1H, ddd, *J* = 11, 6, and 6 Hz, H-6), 2.65 (1H, dd, *J* = 16 and 6 Hz, H-7_a), 2.49 (1H, dd, *J* = 16 and 6 Hz, H-7_b), 2.15 (1H, dd, *J* = 13 and 6 Hz, H-10_a), 1.75 (1H, d, *J* = 11 Hz, H-5), 1.30 (1H, dd, *J* = 13 and 11 Hz, H-10_b), 1.06 (3H, s, H-15), 0.96 (3H, d, *J* = 7 Hz, H-12), 0.88 (3H, d, *J* = 7 Hz, H-13); ^{13}C nmr (400 MHz, $CDCl_3$), δ 149.2 (s, C-8),

114.1 (t, C-14), 86.3 (s, C-4), 72.7 (d, C-9), 70.1 (d, C-6), 58.2 (d, C-5), 50.1 (t, C-10), 43.1 (t, C-7), 42.9 (t, C-3), 41.5 (s, C-1), 38.2 (d, C-11), 32.2 (t, C-2), 20.3 (q, C-15), 18.3 (q, C-13), 17.1 (q, C-12); cims *m/z* (% rel. int.) $[M+H]^+$ 255 (3), $[M-18]^+$ 237 (10), $[M-36]^+$ 219 (60), $[M-54)]^+$ 201 (100).

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