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EIGHT CAROTANE SESQUITERPENES FROM *FERULA LINKII*

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Key Word Index—*Ferula linkii*, Umbelliferae, sesquiterpenes, carotane, epoxy-jaesckeanadiol, ferulinkiol, lapiferol

Abstract—Six new carotane sesquiterpenes, the *p*-methoxybenzoate-, isovalerate- and veratrate of epoxy-jaesckeanadiol, the 1-acetate, 5-isovalerate of ferulinkiol, the 1-acetate, 5-isovalerate of lapiferol and the 1-acetate of lapiferol, and the already known *p*-methoxybenzoate of jaesckeanadiol and lapiferin have been isolated from *Ferula linkii*

INTRODUCTION

From *Ferula linkii* Webb we isolated the sesquiterpene alcohol linkiol with a carotane skeleton hydroxylated at C-6 [1] and two dienic triterpenes of the oleane type [2] We now report on the isolation and structural determination of several carotane sesquiterpenes hydroxylated at C-10 from this plant

RESULTS AND DISCUSSION

The least polar compound isolated was identified as the *p*-methoxybenzoate of jaesckeanadiol (ferutidin) (**1**), obtained previously from *Ferula kuhistanica* [3] Jaesckeanadiol (**2**) was isolated from *F jaesckeana* [4] Also isolated was a group of three new compounds with the same skeleton, the only difference between them being in the nature of the acid that was esterified to the secondary alcohol group present in the molecule All these substances gave ^{1}H NMR signals characteristic of an isopropyl group, an angular methyl group and a methyl group attached to a carbon with an oxygen function This must form part of an oxirane ring, since a proton geminal to the oxygen of this ring was observed in the spectra One of these compounds, to which structure **4** was assigned and which was named the *p*-methoxybenzoate of epoxy-jaesckeanadiol, was identical with a product obtained upon epoxidation of **1** The stereochemistry of the oxirane ring was given, because it is known that epoxidation occurs on this face [5]

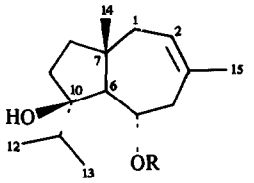
Another of these new esters was the isovalerate of epoxy-jaesckeanadiol (**5**) On hydrolysis it gave the alcohol **3** and the aldehyde **7** The latter was obtained when dilute hydrochloric acid in excess was used to neutralize the alkali Compound **7** was formed by protonation and opening of the oxirane ring, with cleavage of the C-4, C-5 bond, formation of a double bond between C-3 and C-4 and formation of a carbonyl group at C-5 On treatment of **3** with valeric anhydride in pyridine the original natural compound **5** was obtained proving that the valeric acid was esterified to the sesquiterpene alcohol The third new ester was **6** (veratrate of epoxy-jaesckeanadiol) The structure of the acid was identified as veratric acid on the basis of its ^{1}H NMR spectrum

Another new component isolated was the 1-acetate 5-isovalerate of ferulinkiol (**8**) Its structure was assigned on the basis of the following considerations its IR spectrum showed bands characteristic of alcohol and ester groups Its ^{1}H NMR spectrum presented complex signals of four methyl groups, a singlet typical of an angular methyl, a broad singlet at δ1 82 characteristic of a methyl group attached to a double bond and a doublet centred at δ2 62 and assigned to the hydrogen at C-6 This proton was coupled to the geminal hydrogen (δ5 18) of an ester group at C-5 Other signals in the spectrum were a pair of doublets at δ4 88 and 5 70 attributed to the hydrogen at C-1 and the vinylic proton at C-2 The mass spectrum of **8** showed a fragment at m/z 294 $[M - C_3H_7]^+$ This loss of an isopropyl group is typical of a carotane sesquiterpene with a hydroxylic function at C-10 [4] Losses corresponding to acetic and valeric acid were also observed in the spectrum

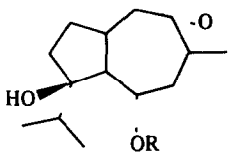
Epoxidation of **8** gave the epoxy compound **9**, identical with the new natural product reported here The assignment of the acetoxy and isovaleroxy function at C-1 and C-5 respectively was made by partial hydrolysis of **9** with methanolic sodium carbonate Thus, the isovalerate **10** and the acetate **11** were obtained, which showed coupling between the geminal protons to the esters with H-6 and H-2, respectively, in their ^{1}H NMR spectra The acetate was identical with a further compound isolated from this species and to which structure **11** was assigned The most polar compound obtained in this hydrolysis was the triol **12**

The ^{13}C NMR spectra of **9**, **11** and **12** (Table 1) were also very informative, and confirmed the existence of a tertiary alcohol group at C-10 in these compounds, the existence of an isovalerate ester, and in general the structures assigned to these products The carbon resonances of **2**, **3** and **6** are also given in the table Only partial data on the ^{13}C NMR spectra of carotane sesquiterpenes have been reported previously [6, 7]

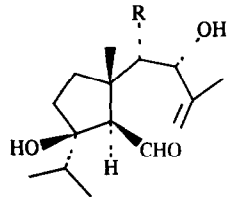
Another compound isolated from this species was the epoxide **14**, with an acetate and an angelate ester group Its structure was determined in the same way as that of **9** Thus compounds **15**, **11** and **12** were obtained by partial hydrolysis Total hydrolysis only afforded **12**, but when dilute hydrochloric acid in excess was used in the neutrali-



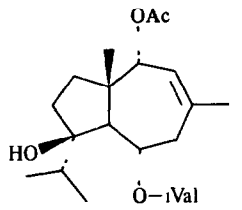
1 R = −CO−C_6H_4(OMe)
2 R = H



3 R = H
4 R = −CO−C_6H_4(OMe)
5 R = iVal
6 R = −CO−$C_6H_3(OMe)_2$



R
7 H
17 OH



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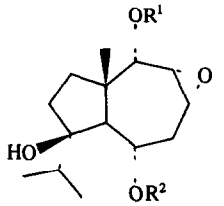

	R^1	R^2
9	Ac	iVal
10	H	iVal
11	Ac	H
12	H	H
13	Ac	Ac
14	Ac	Ang
15	H	Ang
16	H	Ac

Table 1 ^{13}C NMR data (50 32 MHz)

C	2	3	6	9	11	12	14	15
1	40 6*	41 1*	40 6*	71 4	71 4	68 8*	71 5	64 0
2	61 0	61 3	61 0	59 7	60 0	62 4	59 7	62 2
3	56 2	56 8	56 1	56 0	56 6	58 3	56 0	57 7
4	44 4	47 3	44 5	42 5	45 7	45 5	42 8	42 7
5	70 1	67 4	70 4	69 2	67 3	67 3*	69 1	69 3
6	60 9	63 4	61 0	51 0	53 4	51 7	51 4	49 7
7	44 4	43 4	44 5	47 1	46 5	48 0	47 3	48 8
8	31 8	32 2	31 8	31 4	31 6	31 9	31 1	31 2
9	41 4*	41 3*	41 4*	36 6	37 1	37 1	36 5	36 6
10	86 0	86 5	86 1	85 2	85 8	86 3	85 4	85 8
11	37 2	37 9	37 3	37 2	38 4	38 4	37 2	37 4
12	17 4†	17 1†	17 5†	17 1†	17 0†	17 1†	17 2†	17 3†
13	18 5†	18 3†	18 6†	18 3†	18 2†	18 3†	18 3†	18 5†
14	19 4	19 2	19 5	17 8	17 8	17 2†	17 9	17 5
15	23 4	24 5	23 4	23 2	24 3	24 8	23 3	23 9

*†The assignments for these signals may be reversed

zation, the aldehyde **17** was also formed in the same way as **7** from **5**

When **12** was acetylated in the usual manner only the monoacetate **16** was formed, probably because the alcohol at C-1 must be associated with the oxygen of the oxirane ring When **12** was similarly treated with isovaleric anhydride in pyridine only the monoester **10** was obtained

Russian authors [9] have recently isolated a compound with the same structure as **14** from *Ferula lapidosa* which was named lapiferin Its physical constants are identical with those of our product These authors called the alcohol **12**, obtained by hydrolysis of **14**, lapiferol We have used this name as the basis for naming the new compounds **9** and **11**, the 1-acetate,5-isovalerate of lapiferol and the 1-acetate of lapiferol, respectively

EXPERIMENTAL

Mps uncorr, IR $CHCl_3$, NMR $CDCl_3$, MS 70 eV (probe) Products were crystallized from petrol–EtOAc

Isolation of the sesquiterpenes The compounds were obtained in accordance with the experimental data reported in ref [2] and by chromatography of a complex mixture of sesquiterpenes The order of polarity and the quantities of the natural compounds isolated were **1** (150 mg), **4** (340 mg), **5** (300 mg), **8** (40 mg), **6** (100 mg), **14** (2 5 g), **9** (1 5 g) and **11** (50 mg)

Ferutidin (*p-methoxybenzoate of jaeskeanadiol*) (**1**) Mp 109–110° (lit [3] 102–103°), $[M-C_3H_7]^+$ at 329 1771 (Calc for $C_{20}H_{25}O_4$ 329 1752), ^1H NMR (90 MHz) δ0 83 and 0 93 (each 3H, *d*, *J* = 7 Hz), 1 10 (3H, *s*), 1 81 (3H, *br s*), 3 85 (3H, *s*), 5 30 (1H, *sx*, *J* = 11 and 3 Hz), 5 57 (1H, complex signals), 6 95 and 7 98 (each 2H, *d*, *J* = 9 Hz), EIMS *m/z* (rel int) 329 $[M-C_3H_7]^+$ (9), 220 (3), 202 (2), 177 (43), 159 (37)

p-Methoxybenzoate of epoxy-jaeskeanadiol (**4**) Mp 145–148°, $[M]^+$ at 388 2229 (Calc for $C_{23}H_{32}O_5$, 388 2249), IR ν_{max} cm^{-1} 3460, 3000, 2960, 2850, 1700, 1600, 1505, 1455, 1380, 1310, 1255, 1160, 1100, 1030, 955, 875, 845, ^1H NMR (90 MHz) δ0 90 (6H, *t*, *J* = 8 Hz), 1 30 and 1 51 (each 3H, *s*), 2 90 (1H, *t*), 3 91 (3H, *s*), 5 48 (1H, *t*, *J* = 11 Hz), 6 96 and 7 98 (each 2H, *d*, *J* = 9 Hz), EIMS *m/z* (rel int) 388 $[M]^+$ (0 2), 345 (5), 327 (0 3), 236 (1), 193 (10), 175 (5), 152 (23), 135 (100)

Isovalerate of epoxy-jaeskeanadiol (**5**) Mp 86–88°, $[M-C_3H_7]^+$ at 295 1907 (Calc for $C_{17}H_{27}O_4$ 295 1909), IR ν_{max} cm^{-1} 3460, 3000, 2950, 2860, 1715, 1460, 1380, 1290, 1185, 1100, 1030, 980, 960, 870, ^1H NMR (60 MHz) δ0 75–1 11 (12H, complex signal), 1 19 and 1 43 (each 3H, *s*), 2 83 (1H, *t*, *J* = 9 Hz), 5 17 (1H, *sx*, *J* = 11 and 2 Hz), EIMS *m/z* (rel int) 338 $[M]^+$ (0 7), 295 (1), 236 (3), 193 (46), 175 (54), 165 (15), 151 (26)

Veratrate of epoxy-jaeskeanadiol (**6**) Mp 187–190° $[M]^+$ at 418 2350 (Calc for $C_{24}H_{34}O_6$, 418 2355), IR ν_{max} cm^{-1} 3470, 3000, 2950, 2860, 1695, 1595, 1505, 1460, 1410, 1370, 1265, 1170, 1130, 1100, 1020, 955, 870; ^1H NMR (60 MHz) δ0 95 (6H, *t*, *J* = 6 Hz), 1 29 and 1 50 (each 3H, *s*), 2 90 (1H, *t*, *J* = 9 Hz), 3 92 and 3 95 (each 3H, *s*), 5 47 (1H, *sx*, *J* = 11 and 2 Hz), 6 93 (1H, *d*, *J* = 9 Hz), 7 58 (1H, *d*, *J* = 2 Hz), 7 77 (1H, *c*, *J* = 9 and 2 Hz), EIMS *m/z* 418 $[M]^+$, 375, 279, 236, 234, 219, 193

1-Acetate,6-isovalerate of ferulinkiol (**8**) $[M-C_3H_7-AcOH]^+$ at *m/z* 277 1761 (Calc for $C_{17}H_{25}O_3$, 277 1803) IR ν_{max} cm^{-1} 3590, 3000, 2960, 2920, 2860, 1720, 1460, 1370, 1290, 1250, 1190, 1020, 980, 950, ^1H NMR (90 MHz) δ0 98 (12H, complex signal), 1 13 and 1 82 (each 3H, *s*), 2 06 (3H, *s*), 2 62 (1H, *d*, *J* = 11 Hz), 4 88 (1H, *d*, *J* = 7 Hz), 5 18 (1H, *sx*, *J* = 11 and 3 Hz), 5 70 (1H, *d*, *J* = 7 Hz), EIMS *m/z* (rel int) 337 $[M-C_3H_7]^+$ (0 2), 295 (0 2), 277 (1 4), 264 (0 7), 251 (0 6), 235 (8), 218 (14), 193 (14), 175 (100), 157 (20), 147 (30), 132 (100)

Lapiferin (**14**) Mp 136–138° (lit [9] mp 137–138°) $[M-C_3H_7]^+$ at *m/z* 353 1963 (Calc for $C_{19}H_{29}O_6$, 353 1964) IR ν_{max} cm^{-1} 3600, 3000, 2950, 2860, 1730, 1695, 1640, 1450, 1380, 1365, 1235, 1180, 1150, 1030, 955, 940, 890, 850, ^1H NMR (90 MHz) δ0 84 and 0 91 (each 3H, *d*, *J* = 3 Hz), 1 30 and 1 44 (each 3H, *s*), 2 34 (1H, *d*, *J* = 11 Hz), 2 82 and 4 88 (each 1H, *d*, *J* = 6 Hz), 5 21 (1H, *sx*, *J* = 11 and 3 Hz), 6 11 (1H, *c*), EIMS *m/z* (rel int) 351 $[M-C_3H_7]^+$ (2), 251 (18), 209 (9), 191 (38), 163 (23), 148 (17), 135 (12), 126 (23), 107 (15)

1-Acetate,5-isovalerate of lapiferol (**9**) Mp 115–116° $[M-C_3H_7]^+$ at *m/z* 353 1963 (Calc for $C_{19}H_{29}O_6$, 353 1964) IR ν_{max} cm^{-1} 3600, 3000, 2950, 2860, 1730, 1720, 1460, 1445, 1380, 1365, 1290, 1230, 1180, 1110, 1045, 1030, 970, 940; ^1H NMR (90 MHz) δ0 83–1 01 (12H, complex signal), 1 28 and 1 45 (each 3H, *s*), 2 07 (3H, *s*), 2 36 (1H, *d*, *J* = 11 Hz), 2 97 and 4 96 (each 1H, *d*, *J* = 6 Hz), 5 16 (1H, *sx*, *J* = 11 and 3 Hz), EIMS *m/z* (rel int) 353 $[M-C_3H_7]^+$ (3), 251 (37), 209 (25), 191 (93), 173 (13), 163 (48), 152 (31), 148 (26), 135 (16)

1-Acetate of lapiferol (**11**) Mp 106–108° $[M-C_3H_7]^+$ at *m/z* 269 1396 (Calc for $C_{14}H_{21}O_5$, 269 1381) IR ν_{max} cm^{-1} 3590, 2990, 2945, 2920, 2860, 2840, 1730, 1450, 1370, 1230, 1110, 1050, 970, 940, ^1H NMR (90 MHz) δ0 88 and 0 97 (each 3H, *d*, *J* = 4 Hz), 1 21 and 1 40 (each 3H, *s*), 2 10 (3H, *s*), 2 90 (1H, *d*, *J* = 6 Hz), 4 10 (1H, *sx*, *J* = 11 and 3 Hz), 4 92 (1H, *d*, *J* = 6 Hz), EIMS *m/z* (rel int) 269 $[M-C_3H_7]^+$ (1), 251 (19), 209 (15), 191 (57), 173 (10), 163 (38), 149 (23), 139 (28) *Diacetate* (**13**) $[M-C_3H_7]^+$ at *m/z* 311 1495 (Calc for $C_{16}H_{23}O_6$, 311 1494) IR ν_{max} cm^{-1} 3590, 3000, 2950, 2920, 2880, 1720, 1600, 1450, 1370, 1240, 1045, 1025, ^1H NMR (90 MHz) δ0 90 and 0 97 (3H, *d*, *J* = 2 Hz), 1 24 and 1 44 (each 3H, *s*), 2 05 and 2 11 (each 3H, *s*), 3 38 (1H, *d*, *J* = 11 Hz), 2 95 and 4 95 (each 1H, *d*, *J* = 6 Hz), 5 18 (1H, *sx*, *J* = 11 and 3 Hz), EIMS *m/z* (rel int) 311 $[M-C_3H_7]^+$ (2), 251 (35), 209 (26), 191 (100), 175 (40), 163 (60), 149 (48), 135 (31)

Epoxidation of **1** The *p*-methoxybenzoate of jaeskeanadiol (**1**) (66 mg) in $CHCl_3$ (2 ml) was added to a soln of *m*-chloroperbenzoic acid (35 mg) in $CHCl_3$ (2 ml) The mixture was left at room temp in the dark for 75 min and then washed with a saturated soln of $NaHCO_3$ Usual work up and chromatography of the residue with petrol–EtOAc (10%) gave **4** (50 mg)

Hydrolysis of **5** The iso-valerate of jaeskeanadiol (**5**) (300 mg) was saponified with methanolic KOH (3%) (10 ml) at room temp for 2 hr TLC showed one product of hydrolysis Neutralization of the soln with HCl (5%) in excess and extraction in the usual way afforded a mixture of two components Dry CC with petrol–EtOAc (15%) gave **7** (30 mg) as a gum, IR ν_{max} cm^{-1} 3470, 3000, 2960, 2870, 2740, 1700, 1645, 1465, 1375, 1230, 1060, 905, ^1H NMR (60 MHz) δ0 90 (6H, *d*, *J* = 8 Hz), 1 24 (3H, *s*), 1 77 (3H, *br s*), 2 74 (1H, *d*, *J* = 4 Hz), 4 22 (1H, *t*, *J* = 6 Hz), 4 81 and 4 98 (each 1H, *br s*), 9 96 (1H, *d*, *J* = 4 Hz), EIMS *m/z* (rel int) 236 $[M-H_2O]^+$ (1), 221 (1), 218 (1), 211 (2), 203 (1), 193 (14), 175 (7), 166 (4), 151 (16) Further elution afforded **3** (190 mg) as a gum IR ν_{max} cm^{-1} 3470, 2960, 2880, 2830, 1708, 1600, 1450, 1360, 1280, 1250, 1150, 1130, 1090, 1055, 1030, 1010, 950, 910, 850, 830, 770, ^1H NNR (60 MHz) δ0 84 and 0 95 (each 3H, *d*, *J* = 4 Hz), 1 14 and 1 39 (each 3H, *s*), 2 81 (1H, *t*, *J* = 8 Hz), 4 05 (1H, *sx*, *J* = 11 and 2 Hz), EIMS *m/z* 211 $[M-C_3H_7]^+$, 193, 175, 165 Treatment of this latter compound (**3**) with isovaleric anhydride in pyridine gave the original natural product **5**

Epoxidation of **8** Compound **8** (40 mg) was treated as above for **1**, but for 6 hr Chromatography of the residue with petrol–EtOAc (10%) gave **9** (22 mg)

Partial hydrolysis of **9** Compound **9** (180 mg) was saponified with a saturated soln of Na_2CO_3 in MeOH (12 ml) for 5 days Extraction with EtOAc in the usual way, afforded a mixture of

four components Dry CC of the residue eluting with mixtures of petrol–EtOAc gave **10** (20 mg), ^{1}H NMR (200 MHz) δ0 88 and 0 93 (each 3H, *d*, J = 7 Hz), 1 14 and 1 46 (each 3H, *s*), 2 46 (1H, *d*, J = 11 Hz), 2 95 and 3 89 (each 1H, *d*, J = 6 Hz), 5 05 (1H, *sx*, J = 11 and 2 Hz), EIMS *m/z* 354 $[M]^+$, 311, 252, 227, 209, 191 Further elution gave the starting compound **9** (30 mg), **11** (60 mg), identical with the natural compound, and **12** (35 mg) as a gum (lit [9] 112–114°), $[M-C_3H_7]^+$ at *m/z* 227 1311 (Calc for $C_{12}H_{19}O_4$ 227 1983) IR ν_{max} cm^{-1} 3580, 2990, 2950, 2860, 1460, 1380, 1120, 1050, 1020, 910, ^{1}H NMR (90 MHz) δ0 91 and 1 00 (each 3H, *d*, J = 2 Hz), 1 16 and 1 47 (each 3H, *s*), 2 39 (1H, *d*, J = 11 Hz), 2 99 and 3 96 (each 1H, *d*, J = 6 Hz), 4 80 (1H, *sx*, J = 11 and 2 Hz), EIMS *m/z* (rel int) 227 $[M-C_3H_7]^+$ (21), 209 (15), 191 (23), 163 (20), 155 (19), 125 (100)

Partial hydrolysis of lapiferin Compound **14** (200 mg) was treated as above for **9** and the compounds **15** (60 mg), **14** (40 mg), **11** (25 mg) and **12** (45 mg) were obtained Compound **15**, mp 120–122° ^{1}H NMR (90 MHz) δ0 87, 0 95, 1 22 and 1 52 (each 3H, *s*), 2 57 (1H, *d*, J = 11 Hz), 3 01 and 3 98 (each 1H, *d*, J = 6 Hz), 5 26 (1H, *sx*, J = 11 and 4 Hz), 6 12 (1H, *c*), EIMS *m/z* 309 $[M-C_3H_7]^+$, 291, 252, 209, 191, 163

Hydrolysis of lapiferin Compound **14** (150 mg) was saponified as above for **5** The reaction time in this case was 12 hr Chromatography of the two compounds obtained with petrol–EtOAc (50%) elution gave **17** (18 mg), mp 126–128°, $[M-H_2O]^+$ at *m/z* 252 1736 (Calc for $C_{15}H_{24}O_3$ 252 1725) IR ν_{max} cm^{-1} 3590, 3000, 2960, 2880, 2730, 1700, 1690, 1640, 1470, 1380, 1370, 1300, 1235, 1050, 1010, 915, ^{1}H NMR (60 MHz) δ0 88 and 1 00 (each 3H, *d*, J = 4 Hz), 1 26 (3H, *s*), 1 81 (3H, *br s*), 9 99 (1H, *d*, J = 2 Hz), EIMS *m/z* (rel int) 252 $[M-H_2O]^+$ (2), 234 (13), 227 (11), 209 (21), 191 (14), 181 (100), 163 (34), 151 (41), 135 (66) Further elution afforded **11** (60 mg)

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