Journal of Natural Products
Vol. 58, No. 3, pp. 432-437, March 1995

SESQUITERPENE LACTONES AND OTHER CONSTITUENTS OF *ALLAGOPAPPUS* SPECIES

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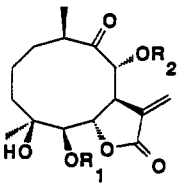
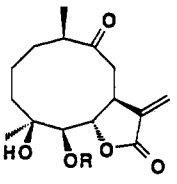
ABSTRACT.—Analysis of the aerial parts of two *Allagopappus* species has yielded several known compounds and new sesquiterpene lactones related to the ineupatorolides: compound **3** was obtained from *A. viscosissimus*, compound **12** from *A. dichotomus* ssp. *latifolius*, and compounds **20**, **21**, and a mixture of **22** and **23** from *A. dichotomus* ssp. *dichotomus*. New thymol derivatives were isolated from *A. dichotomus* ssp. *latifolius* [**5**] and *A. dichotomus* ssp. *dichotomus* [**5** and **16**]. The structures of these new natural products were established by spectroscopy, and the chemotaxonomy of the genus as a whole is briefly discussed.

The genus *Allagopappus* belongs to the subtribe Inulinae (*Inula* group, Compositae) (1). It is endemic to the Canary Islands and consists of two species, *A. viscosissimus* Bolle (endemic to Gran Canaria) and *A. dichotomus* (L.) Cass. The latter species is more widely distributed than the former and has two subspecies, *latifolius* (endemic to Gran Canaria) and *dichotomus* (predominating in Tenerife and the more westerly islands) (2). An earlier paper dealt with the isolation of several germacranolide-type sesquiterpene lactones closely related to the ineupatorolides from *A. viscosissimus* (3). A phytochemical study of an *Allogopappus* species collected in Tenerife, on the other hand, did not result in the isolation of any sesquiterpene lactones (4). The findings of an investigation on the minor constituents of *A. viscosissimus* from Gran Canaria as well as those of the two subspecies of *A. dichotomus* collected in Gran Canaria and Tenerife are summarized below.

The aerial parts of *A. viscosissimus* yielded the sesquiterpene lactones **1** (5), **2** (5), and **3**, in addition to the products cited by Gonzalez *et al.* (3). The aerial parts of *A. dichotomus* ssp. *latifolius* afforded the flavonoids 5,7-dihydroxy-3,3′,4′-trimethoxyflavone (6), quercetin 3,3′-dimethyl ether (7), and naringenin (8), the thymol derivatives **4** (9) and **5**, the sesquiterpene lactones aguerin A (10), the ineupatorolide derivatives **6** and **7**





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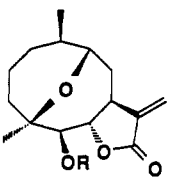
19 $R_1=$MeBu; $R_2=$H
20 $R_1=$Sen; $R_2=$H
20a $R_1=$Sen; $R_2=$Ac
22 $R_1=$Sen; $R_2=$iBu
23 $R_1=$Tigl; $R_2=$iBu

6 R=MeBu
7 R=iBu



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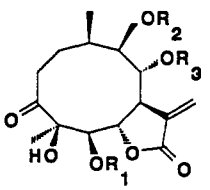
9 R=iBu



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17 $R_1=R_2=$iBu; $R_3=$H
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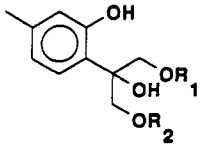

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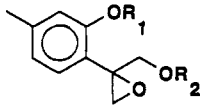

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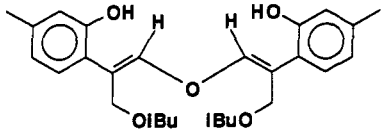

16

(11), the dittrichiolide derivatives **8** and **9** (12), the incaspitolide derivatives **10** (3) and **11** (13), and a new ineupatorolide derivative, **12**, together with other compounds (see Experimental).

Various compounds (see Experimental) were obtained from the aerial parts of *A. dichotomus* ssp. *dichotomus* including the flavonoids 4′,5,7-trihydroxy-3,6-dimethoxyflavone (14), kaempferol 3-methyl ether (14), betuletol 3-methyl ether (15), chrysoeriol (16), and eriodyctiol (17), the thymol derivatives **4** (9), **5**, **13** (18), **14** (18), **15** (9), the dimer **16**, the sesquiterpene lactones **1** (5), **2** (5), **6** (11), **11** (13), **17** (5), **18** (12), **19** (12), **20**, **21**, and an inseparable mixture of **22** and **23**.

Compound **3**, empirical formula $C_{24}H_{34}O_8$, showed a characteristic ms fragmentation for the presence of both isobutyrate and angelate groups, as confirmed by ^{1}H-nmr spectroscopy (Table 1). Other ^{1}H-nmr signals closely resembled those of **1** (5), with the compounds differing only in that one of the isobutyrate groups in **1** was replaced by an angelate group in **3**. The angelate moiety was located at C-5 from the observation of the 0.11 ppm downfield shift of the H-5 signal in **3** as compared to **1**.

The structure of **5** could be deduced from its ^{1}H-nmr spectrum (Table 2), which resembled that of **4** (9), with the only differences being the signals for a 2-methylbutyrate group in **5** instead of those of an isobutyrate group as in **4**, in agreement with its ms fragmentation pattern.

The structure of **12** was deduced from its ^{1}H-nmr and ms spectra (Table 1) and differed from **1** (5) only in having 2-methylbutyrate groups instead of isobutyrate groups at C-5 and C-8.

The ^{1}H-nmr spectrum of **16** (Table 2) contained characteristic signals for a thymol derivative similar to those of **5**, with methylenes each bearing an isobutyrate group on a double bond (δ 5.04), and vinyl protons geminal to an ether group (δ 6.32). Ir, ^{1}H-nmr, and ms data indicated a thymol dimer structure for this compound, similar to that of glechonin A (19) but with an isobutyrate group instead of an acetate.

The ^{1}H-nmr spectrum of **20** (Table 1) was closely related to that of **18** (12), but with a senecionate group in place of the methylsenecionate group. A hydroxy group on C-8 (δ 2.70) was confirmed when the acetyl derivative **20a** was obtained. The structure of **21** (Table 1) greatly resembled that of **17** (5), the difference being that the esters displayed typical isobutyrate and 2-methylbutyrate signals. When **21** was treated with Ac_2O in pyridine, a monoacetate **21a** was obtained, enabling the isobutyrate to be placed at C-9, contiguous to the hydroxy group, as a consequence of the upfield shift (0.11 ppm) of the tertiary proton of this group, which was also observed when substances **10** and **17** were acetylated.

The ^{1}H-nmr spectral data of the inseparable mixture of **22** and **23** (Table 1) showed these compounds to be sesquiterpene lactones in the form of isomeric diesters, distinguishable from **1** only by

TABLE 1. ^{1}H-Nmr Spectral Data of Compounds **3**, **12**, **20**, **20a**, **21**, **21a**, **22**, and **23**.[a]

Proton	Compound						
	3	**12**	**20**	**20a**	**21**	**21a**	**22/23**
2					3.75 m	3.85 m	
					2.28 m	2.28 m	
5	4.73 d (6)	4.66 m	4.69 d (6.5)	4.67 d (6.5)	5.39 m	5.30 d (10)	4.69 d (6)
6	4.69 dd (6,1.5)	4.66 m	4.57 m	4.65 s	4.70 m	4.70 m	4.65 dd (6,1.5)
7	3.50 dd (11,1.5)	3.47 dd (11,1.5)	3.34 dd (11,1.5)	3.47 d (11)	3.05 m	3.09 m	3.50 dd (11,1.5)
8	4.86 d (11)	4.84 d (11)	3.86 dd (11,1.5)	4.89 d (11)	4.30 m	5.71 d (10)	4.87 d (11)
9					5.03 dd (10.5,1.5)	5.23 dd (10.5,1.5)	
10	3.04 m	3.04 m	3.18 m	3.06 m	2.28 m	2.28 m	2.05 m
13	6.41 d (1.5)	6.40 d (1.5)	6.44 d (2)	6.39 d (1.5)	6.46 d (3)	6.46 d (2.7)	6.41 d (2)
13′	5.95 d (1.5)	5.92 d (1.5)	6.06 d (1.6)	5.92 d (1.5)	5.65 d (2.5)	5.71 d (2.5)	5.94 d (1.5)
14	1.04 d (7)	1.04 d (7)	1.19 d (7)	1.05 d (7)	0.97 d (7)	0.99 d (7)	1.04 d (7)
15	1.16 s	1.14 s	1.16 s	1.14 s	1.31 s	1.32 s	1.14 s
5-OR	6.17 qq (1,1.5)	2.48 m	5.77 s	5.77 d (1)	2.49 sext. (7)	2.47 sext. (7)	5.77 s/6.91 m
	1.95 dd (7,1.5)	1.17 d (7)	2.14 d (1.5)	2.12 d (1)	1.22 d (7)	1.14 d (7)	2.13 d (1)/1.84 s
	1.94 s	0.93 t (7.5)	1.94 d (1.5)	1.92 s	0.96 t (7.5)	0.95 t (7.5)	1.93 d (1)/1.71 d (6)
8-OR	2.64 hept. (7)	2.46 m	2.70 m	2.15 s		1.93 s	2.64 hept. (7)
	1.23 d (7)	1.19 d (7)					1.23 d (7)
	1.21 d (7)	0.90 t (7.5)					1.20 d (7)
9-OR					2.67 sext. (7)	2.56 sext. (7)	
					1.24 d (7)	1.23 d (7)	
					1.22 d (7)	1.21 d (7)	

[a]Run at 200 MHz, in $CDCl_3$, with TMS as internal standard. Values in parentheses are coupling constants in Hz.

TABLE 2. ^{1}H-Nmr Spectral Data of Compounds **5** and **16**.[a]

Proton	Compound	
	5	**16**
2	6.70 d (1.5)	6.70 s
5	6.90 d (8)	6.93 d (8)
6	6.65 dd (8,1.5)	6.70 d (8)
7	2.27 s	2.30 s
9	4.48 d (12)	6.32 br s
9'	4.41 d (12)	—
10	4.50 d (12)	5.04 br s
10'	4.42 d (12)	—
OH-Ar	8.75 s	6.20 s
OMeBu ...	2.35 sext. (7)	—
	1.11 d (7)	—
	0.84 t (7.5)	—
OiBu	2.57 sext. (7)	2.51 sext. (7)
	1.13 d (7)	1.07 d (7)

[a]Run at 200 MHz, in $CDCl_3$, with TMS as internal standard. Values in parentheses are coupling constants in Hz.

their isobutyrate, tiglate, and senecioate ester groups (ms, see Experimental). The siting of the various ester groups could be deduced as there were no obvious differences in the signals of the tertiary protons of the isobutyl groups (5), and the chemical shift of H-5 was similar to that observed in similar substances when geminal to an unsaturated ester.

The phytochemistry of the species of the genus *Allagopappus* shows close affinities to those of *Inula eupatorioides* (11), *I. cuspidata* (5), and *I. cappa* (13) as well as that of *Dittrichia viscosa* (12), when collected in Tenerife, inasmuch as sesquiterpene lactones with a germacrane skeleton similar to that of ineupatorolide [**6**] are present in all. It would be of interest to conduct taxonomic studies to determine the relationship between the species containing this type of sesquiterpene lactone, especially as the two genera *Allagopappus* and *Inula* belong to the same group *Inula* of the subtribe *Inulinae* (1).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were taken on a Gallenkamp 4AO865 apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer model 141 polarimeter. Ir and uv spectra were run on Perkin-Elmer 783 and Shimadzu IV-240 spectrophotometers, respectively. The ^{1}H-nmr spectra were recorded by a Bruker WP-200 SY spectrometer, and ms spectra on a Hewlett-Packard Model 5930 instrument, using a direct inlet system at 70 eV.

PLANT MATERIAL.—The plant material was identified by Prof. Consuelo Padrón of the Department of Botany of the University of La Laguna, where voucher specimens are on file with the following numbers: *A. viscosissimus* gathered at Mogan (Gran Canaria) in June 1986, TFC 36411; *A. dichotomus* ssp. *latifolius* collected at Agüimes (Gran Canaria) in May 1985, TFC 36410; *A. dichotomus* ssp. *dichotomus* collected at Tabaiba, Tenerife, in June 1991, TFC 36409).

EXTRACTION AND ISOLATION.—The aerial parts (2 kg) of *A. viscosissimus* were extracted and fractionated in a Si gel column as described in Ref. (3). The hexane-Me_2CO (4:1)-eluted fractions obtained after additional Si gel cc and prep. tlc (Si gel) gave a series of known compounds (3), **1** (10 mg), **2** (14 mg), and **3** (11 mg). The aerial parts (3 kg) of *A. dichotomus* ssp. *latifolius* were extracted with hot EtOH. The solvent was removed under reduced pressure, giving a syrupy residue (448 g) that was percolated with Me_2CO to give 235 g of an extract that was then chromatographed on Si gel with hexane and mixtures of hexane/EtOAc. The fractions eluted with hexane-EtOAc (9:1) were re-chromatographed over Si gel with the same solvent and then by prep. tlc (Si gel) with benzene-EtOAc (9:1), yielding **4** (75 mg) and **5** (52 mg) from the more polar fractions. The stock was concentrated, acetylated, and chromatographed to yield acetyl aguerin A (21 mg), **6** (55 mg) and, after prep. tlc (Si gel), **7** (23 mg). The less polar fractions gave **8** (21 mg) and **9** (39 mg). The next fractions were crystallized in hexane/EtOAc to give a mixture of substances, which were then chromatographed on a Si gel column with hexane-EtOAc (4:1) as eluent, affording **10** (80 mg) and **11** (112 mg). The fractions eluted with hexane-EtOAc (4:1) were rechromatographed on Si gel and subjected to prep. tlc (Si gel) with hexane-EtOAc (9:1) to give **12** (15 mg) and, after crystallization in hexane/EtOAc, 5,7-dihydroxy-3,3',4'-trimethoxyflavone (65 mg) was obtained. The more polar fractions yielded quercetin 3,3'-dimethyl ether (125 mg) when crystallized in hexane/EtOAc. The hexane-EtOAc (2:1)-eluted fractions, when crystallized in hexane/EtOAc, gave naringenin (23 mg) and the fractions eluted with hexane-EtOAc (2:3) afforded sitosterol-β-D-glucoside (135 mg).

The aerial parts (2.5 kg) of *A. dichotomus* ssp. *dichotomus* were extracted with hot EtOH. The solvent was extracted under reduced pressure,

giving a syrupy residue (295 g) which was chromatographed as described above. The fractions eluted with hexane-EtOAc (9:1) were rechromatographed over Si gel with the same solvent to give **13** (27 mg); crystallization with hexane/Me_2CO furnished stigmasterol (170 mg) and prep. tlc (Si gel) with hexane-EtOAc (9:1) resulted in pure **14** (21 mg) and **16** (11 mg). The fractions eluted with hexane-EtOAc (4:1) crystallized to give betuletol 3-methyl ether (80 mg), and, when rechromatographed on hexane-EtOAc (9:1), **4** (75 mg) and **5** (47 mg) were obtained. Prep. tlc (Si gel) with $CHCl_3$-EtOAc (4:1) yielded vanillin (25 mg) and 4-formylbenzamide (10 mg). From the less polar fraction, elution with hexane-EtOAc (7:3) and rechromatography on Si gel with hexane-EtOAc (4:1) resulted in **2** (57 mg) and prep. tlc (Si gel) with the same eluent, led to pure **1** (14 mg), **6** (11 mg), and a mixture of **22** and **23** (21 mg). The more polar fractions afforded **11** (139 mg), **15** (35 mg), **18** (76 mg), and **19** (53 mg); by prep. tlc (Si gel) with C_6H_6-EtOAc (9:1), **17** (48 mg), and **21** (35 mg) resulted, and by crystallization in hexane/EtOAc, 4′,5,7-trihydroxy-3,6-dimethoxyflavone (53 mg) and kaempferol 3-methyl ether (80 mg) were obtained. The fractions eluted with hexane-EtOAc (3:2), rechromatographed on Si gel with hexane-EtOAc (7:3), yielded **20** (84 mg), and chrysoeriol (25 mg), eriodyctiol (31 mg), and scopoletin (13 mg) were obtained from the more polar fractions. The fractions treated with hexane-EtOAc (2:3) gave sitosterol-β-D-glucoside (115 mg).

8α-Isobutyryloxyineupatorolide B [**3**].—Oil; $[\alpha]^{20}D$ −18.6° (*c*=0.43, $CHCl_3$); ir ν max ($CHCl_3$) 3426, 2930, 1769, 1732, 1709, 1460, 1379, 1278, 1138, 972, 945 cm^{-1}; ^1H-nmr data, see Table 1; ms *m/z* $[M]^+$ (not visible), 351 (1), 264 (17), 246 (6), 218 (5), 193 (13), 151 (15), 148 (18), 141 (20), 83 (70), 71 (50), 57 (100); hreims *m/z* $[M]^+$ 450.2240 ($C_{24}H_{34}O_8$ requires 450.2254).

9-(2-Methylbutyryloxy)-10-isobutyryloxy-8-hydroxythymol [**5**].—Oil; $[\alpha]^{20}D$ +15.38° (*c*=0.26, $CHCl_3$); ir ν max ($CHCl_3$) 3250, 2890, 1710, 1605, 1560, 1500, 1440, 1370, 1235, 1170, 1130, 1060, 990 cm^{-1}; ^1H-nmr data, see Table 2; ms *m/z* $[M]^+$ 352 (2), 310 (14), 282 (2), 267 (11), 264 (3), 251 (7), 250 (2), 237 (12), 235 (14), 162 (9), 135 (30), 85 (53), 71 (63), 57 (100); hreims *m/z* $[M]^+$ 352.1884 ($C_{19}H_{28}O_6$ requires 352.1886).

8α-(2-Methylbutyryloxy)ineupatorolide A [**12**].—Oil; $[\alpha]^{20}D$ +25.0° (*c*=0.28, $CHCl_3$); ir ν max ($CHCl_3$) 3560, 2950, 1765, 1730, 1715, 1630, 1450, 1370, 1260, 1115, 950 cm^{-1}; ^1H-nmr data, see Table 1; ms *m/z* $[M]^+$ (not visible), 348 (1), 264 (8), 246 (4), 193 (9), 151 (10), 141 (15), 113 (22), 85 (75), 71 (48), 57 (100); hreims *m/z* $[M-C_{10}H_{20}O_4]^+$ 262.1201 ($C_{15}H_{18}O_4$ requires 262.1205).

Desacylglechonin A-10-10′-bis-isobutyrate [**16**].—Oil; optically inactive; ir ν max ($CHCl_3$) 3400, 2920, 1720, 1602, 1514, 1460, 1379, 1221, 1155, 1080, 930 cm^{-1}; ^1H-nmr data, see Table 1; eims *m/z* $[M]^+$ not visible, 268 (6), 232 (12), 184 (14), 162 (46), 152 (1), 151 (2), 145 (100), 117 (10), 115 (31), 91 (33), 71 (46), 57 (33); hreims, not clear.

8α-Hydroxyineupatorolide D [**20**].—Needles; mp 198–200° (hexane/EtOAc); $[\alpha]^{20}D$ +78.94° (*c*=0.19, $CHCl_3$); ir ν max ($CHCl_3$) 3605, 2931, 1775, 1715, 1651, 1454, 1379, 1271, 1136, 1080, 941 cm^{-1}; ^1H-nmr data, see Table 1; ms *m/z* $[M]^+$ (not visible), 362 (1), 334 (3), 305 (2), 234 (2), 184 (3), 165 (5), 139 (7), 126 (13), 97 (19), 83 (100), 71 (22), 69 (27), 57 (15), 55 (41); hreims *m/z* $[M]^+$ 380.1845 ($C_{20}H_{28}O_7$ requires 380.1835).

A solution of **20** (30 mg) in Ac_2O-pyridine (1:1) was allowed to stand at room temperature overnight. The reaction mixture was treated in the usual way and the product was recrystallized from *n*-hexane/EtOAc to give **20a** (17 mg) as needles: mp 148–150°; ir ν max ($CHCl_3$) 3590, 2936, 1776, 1718, 1647, 1452, 1377, 1230, 1134, 1039, 898 cm^{-1}; ^1H-nmr data, see Table 1; ms *m/z* $[M]^+$ 422 (1), 404 (2), 363 (5), 262 (6), 245 (6), 149 (92), 111 (26), 97 (31), 83 (100), 71 (40), 69 (45), 57 (57), 55 (58).

5-Desacylincaspitolide D-5-O-(2-methylburytrate) [**21**].—Needles; mp 177–179° (hexane/EtOAc); $[\alpha]^{20}D$ −58.33° (*c*=0.12, $CHCl_3$); ir ν max ($CHCl_3$) 3426, 2930, 1770, 1723, 1626, 1462, 1384, 1289, 1138, 1076, 977 cm^{-1}; ^1H-nmr data, see Table 1; ms *m/z* $[M]^+$ (not visible), 280 (1), 250 (1), 207 (1), 194 (2), 111 (12), 85 (20), 83 (32), 71 (38), 69 (55), 57 (81), 55 (100); hreims *m/z* $[M]^+$ 468.2359 ($C_{24}H_{36}O_9$ requires 468.2359).

Compound **21** (20 mg) was acetylated with Ac_2O-pyridine (1:1) at room temperature overnight. Normal work-up and recrystallization from hexane/EtOAc gave **21a** (18 mg): mp 183–185°; ir ν max ($CHCl_3$) 3599, 2931, 1770, 1743, 1662, 1460, 1373, 1234, 1138, 1024, 979 cm^{-1}; ^1H-nmr data, see Table 1; ms *m/z* $[M]^+$ (not visible), 380 (1), 278 (2), 260 (3), 250 (8), 233 (8), 207 (7), 194 (6), 111 (8), 85 (69), 83 (52), 71 (58), 57 (100), 55 (35).

8α-Isobutyryloxyineupatorolide D [**22**] *and 8α-Isobutyryloxy-5-desacylineupatorolide D-5-O-tiglate* [**23**].—Oil; $[\alpha]^{20}D$ +55.57° (*c*=0.28, $CHCl_3$); ir ν max ($CHCl_3$) 3597, 2935, 1776, 1747, 1718, 1649, 1469, 1458, 1379, 1269, 1125, 1084, 956 cm^{-1}; ^1H-nmr data, see Table 1; ms *m/z* $[M]^+$ (not visible), 432 (1), 363 (4), 263 (5), 245 (4), 215 (3), 165 (4), 149 (16), 109 (8), 97 (13), 83 (100), 71 (97), 57 (42), 55 (88); hreims *m/z* $[M]^+$ 450.2257 ($C_{24}H_{34}O_8$ requires 450.2254).

ACKNOWLEDGMENTS

This work has been partly financed by a grant from CICYT (PB91-0049). J.B.B. and J.T.M. are indebted to the Consejería de Educación del Gobierno de Canarias (P28/08.03.90 and 93/08.03.90), and A.G.G. to the Colegio Libre de Eméritos (Spain).

LITERATURE CITED

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Received 2 June 1994