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20-NOR-ABIETANE AND REARRANGED ABIETANE DITERPENOIDS FROM THE ROOT OF *SALVIA ARGENTEA*

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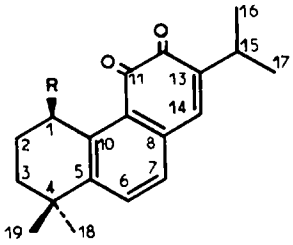
Key Word Index—*Salvia argentea*; Labiatae; diterpenoids; 20-nor-abietanes; 4,5-seco-5,10-*friedo*-abietanes; 1*R*-hydroxymiltirone; arucadiol; 1-keto-aethiopinone.

Abstract—From the root of *Salvia argentea* three new abietane diterpenoids, 1*R*-hydroxymiltirone, arucadiol and 1-keto-aethiopinone, have been isolated, together with the previously known diterpenes isopimara-8(9),15-diene, salvipisone, ferruginol and aethiopinone. The structures of the new compounds were established by spectroscopic means.

INTRODUCTION

In continuation of our studies on the diterpenoids from *Salvia* spp. [1–4], we have now investigated the root of *S. argentea* L. From this material seven diterpenoid compounds have been isolated, four of which are the previously known isopimara-8(9),15-diene [5–7], ferruginol [8–10], salvipisone [11] and aethiopinone (**4**) [11, 12]. The other three are new substances, whose structures are established as 1*R*-hydroxy-20-nor-5(10),6,8,13-abietatetraene-11,12-dione (**1**, 1*R*-hydroxymiltirone), 11,12-dihydroxy-20-nor-5(10), 6,8,11,13-abietapentaen-1-one (**2**, arucadiol) and 4,5-seco-5,10-*friedo*-4(18), 5(10),6,8,13-abietapentaene-1,11,12-trione (**3**, 1-keto-aethiopinone).



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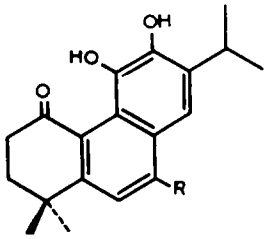
5 R = H



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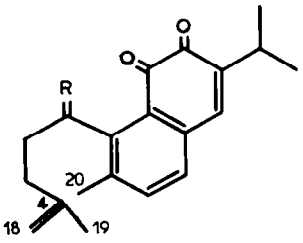
6 R = OH



3 R = O
4 R = H_2

RESULTS AND DISCUSSION

The first of the new diterpenoids (1*R*-hydroxymiltirone, **1**), $C_{19}H_{22}O_3$, had an IR spectrum which showed hydroxyl (3510 cm^{-1}) and *ortho*-quinone (1675, 1660, 1633 cm^{-1}) [12–14] absorptions. Its UV spectrum (Table 1) was almost identical with that of miltirone (**5**) [13], a 20-nor-abietane diterpenoid previously isolated from *S. miltiorrhiza* and whose structure was firmly established by total synthesis [15]. The ^1H NMR spectra of the new diterpenoid (**1**, Table 2) and miltirone (**5**) [13, 15] were very similar. The only difference was the presence in the former of a one-proton triplet (J = 3.1 Hz) at δ4.98, which was assigned to the geminal proton of a secondary hydroxyl group placed between a fully substituted carbon atom and a methylene grouping. Thus, this alcohol function could be placed at the C-1 or C-3 position of miltirone. However, the chemical shift of the geminal proton of the hydroxyl group (δ4.98) was in agreement with a benzylic alcohol [16] and not with the value (δ3.67) reported for 3α-hydroxytanshinone II A [17].

Therefore, this new diterpenoid possesses the structure depicted in formula **1**, in which the 1*R* absolute configuration was established by application of Horeau's method [18] (see Experimental).

Another of the new diterpenoids, arucadiol (**2**), had a molecular formula $C_{19}H_{22}O_3$, and its IR spectrum showed phenolic (3490, 3400–2500 cm^{-1}, broad) and aryl-ketone (3060, 1640, 1590, 1555, 1510 cm^{-1}) absorptions. The presence of a *o*-diphenol moiety conjugated with a ketone function in compound **2** was revealed by its UV spectra obtained after addition of base, aluminium chloride and boric acid (Table 1), which showed the characteristic band shifts of this chromophore [1, 14]. The ^1H NMR spectrum of arucadiol (Table 2) was consistent with the structure depicted in formula **2**, showing signals of an isopropyl group attached to an aromatic ring (δ3.43, 1H, *br septet*, J = 6.9 Hz, H-15, and 1.34, 6H, *d*, J = 6.9 Hz, Me-16 and Me-17), two *ortho* aromatic protons (δ7.32, *d*, and 7.94, *d*, J_{ortho} = 8.7 Hz, H-6 and H-7, respectively), another aromatic proton at δ7.26 (*br* s, H-14) and two hydrogen bonded phenolic functions (δ10.63,

Table 1. UV spectra of compounds 1–3 [λ_{max} nm (log ε)]

Compound	MeOH	+NaOMe	+H_3BO_3	+$AlCl_3$
1	226 (4.37)	220 (4.20)	*	*
	264 (4.24)	257 (4.38)		
	280 sh (4.04)	275 sh (4.00)		
	356 (3.20)	335 (3.14)		
	422 (3.38)	430 (2.60)		
2	228 (4.58)	225 (4.49)	228 (4.58)	230 (4.57)
	242 sh (4.39)	244 (4.40)	270 sh (4.29)	269 (4.23)
	270 (4.25)	252 sh (4.39)	279 (4.30)	280 (4.21)
	278 (4.24)	260 sh (4.35)	360 (3.47)	458 (3.47)
	362 (3.54)	325 (3.47)	416 (3.60)	
	410 (3.65)			
3	261.5 (4.20)	†	*	*
	330 (2.69)			
	428 (2.77)			

*Not measured.
†No change was observed.

Table 2. ^{1}H NMR data of compounds 1–3 (300 MHz, $CDCl_3$, TMS as internal standard)*

	1	2	3
H-1	4.98 *t*	—	—
2H-2	1.90 *m* (1H), 1.53 *m* (1H)	2.92 *t*	2.65 *m*
2H-3	†	2.07 *t*	2.65 *m*
H-6	7.22 *d*	7.32 *d*	7.25 *d*
H-7	7.68 *d*	7.94 *d*	7.48 *d*
H-14	7.10 *br s*	7.26 *br s*	7.16 *d*
H-15	3.01 *br septet*	3.43 *br septet*	3.03 *br septet*
Me-16 / Me-17	1.17 *d*	1.34 *d*	1.16 *d*
Me-18	1.24 *s*	1.44 *s*	—
Me-19	1.38 *s*		1.77 *t*
2H-18	—	—	4.70 *br s* ($W_{1/2}$ = 3.5 Hz)
Me-20	—	—	2.24 *s*
OH‡	4.55 *br*	10.63 *s*	—
	—	6.87 *s*	—
J (Hz)			
1α,2α	3.1	—	—
1α,2β	3.1	—	—
2,3	†	6.9	†
6,7	8.0	8.7	7.8
14,15	< 0.3	< 0.3	1.0
15,16(17)	6.7	6.9	7.0
18,19	—	—	0.9

*The majority of these assignments have been confirmed by double resonance experiments.
†Not identified.
‡Disappeared after addition of D_2O.

s, and 6.87, *s*, disappeared after addition of D_2O) [1, 4]. The ^{1}H NMR spectrum of arucadiol (2) also showed signals for a (C)–CO–CH_2–CH_2–CMe_2– unit (δ2.92, 2H, *t*, *J* = 6.9 Hz, 2H-2; 2.07, 2H, *t*, *J* = 6.9 Hz, 2H-3; and 1.44, 6H, *s*, Me-18 and Me-19), identical with that found [19] in arucatriol (6), a 20-nor-abietane diterpenoid previously isolated from *S. canariensis*. From all the above data, it was clear that arucadiol (2) is the 7-deoxyderivative of arucatriol (6) [19].

The last diterpenoid (3) is the 1-oxo-derivative of aethiopinone (4) [12]. It had a molecular formula $C_{20}H_{22}O_3$ and its IR spectrum showed conjugated ketone (1700 cm^{-1}) and *ortho*-quinone (1675, 1660, 1625 cm^{-1}) [12–14] absorptions. Its ^{1}H NMR spectrum (Table 2) was almost identical with that of aethiopinone (4) [12], showing the signal of the protons of the exocyclic methylene group (δ4.70, 2H, *br s*, $W_{1/2}$ = 3.5 Hz) at the same field as aethiopinone (4, δ4.7, 2H, *br s*) [12]; thus

establishing that the ketone function must be placed at the benzylic C-1 position. Moreover, comparison of the UV spectra of compound **3** (λ_{max} 261.5 nm, log ε 4.20, Table 1) and aethiopinone (**4**, λ_{max} 250 nm, log ε 4.18) [12] confirmed that the ketone function was conjugated with the 1,2-naphthaquinone moiety and not with the exocyclic methylene grouping. This conclusion was also in agreement with the fact that the ^{1}H NMR spectrum of compound **3** (see Table 2) was devoid of signals attributable to the benzylic C-1 protons of aethiopinone (**4**, at δ 2.8–3.1, *m*) [12].

It is important to note that 4,5-seco-5,10-*friedo*-abietane derivatives are chemically obtained from suitable abietane derivatives by acid catalysis [4, 20]. However, this transformation yields 4-hydroxy and/or 3,4-dehydro derivatives instead of 4,18-dehydro derivatives such as compounds **3** and **4**. Thus, it is reasonable to assume that these rearranged abietane diterpenoids ([11, 12] and this work) are not artefacts.

From a chemotaxonomic point of view it is interesting to note that this is the first report of isopimara-8(9),15-diene and only the second report [10] of ferruginol in plants belonging to the *Salvia* genus.

EXPERIMENTAL

Mps are uncorr. For general details on methods see refs [1–4, 11, 14]. Plant materials were collected in June 1985, near Arganda (Madrid, Spain), and voucher specimens were deposited in the Herbarium of the Faculty of Pharmacy (Madrid 'Complutense' University).

Extraction and isolation of the diterpenoids. Dried and finely powdered *S. argentea* roots (960 g) were extracted with Me_2CO (4 l.) at room temp. for 1 week. After filtration, the solvent was evaporated yielding a red gum (32 g) which was subjected to dry CC over silica gel (600 g, Merck No. 7734, deactivated with 10% H_2O). Elution with *n*-hexane and *n*-hexane–EtOAc mixtures yielded the following compounds in order of elution: isopimara-8(9), 15-diene (56 mg) [5–7], salvipisone (530 mg) [11], ferruginol (980 mg) [8–10], aethiopinone (**4**, 9.5 g) [11, 12], arucadiol (**2**, 6 mg), 1-keto-aethiopinone (**3**, 68 mg) and 1*R*-hydroxymiltirone (**1**, 65 mg). The previously known diterpenoids were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, UV, ^{1}H NMR, MS) data and by comparison (mmp, TLC) with authentic samples.

1*R*-*Hydroxymiltirone* (**1**). Mp 130–133° (*n*-hexane); $[\alpha]_D^{24}$ + 989.1° ($CHCl_3$; *c* 0.101); IR ν_{max}^{KBr} cm^{-1}: 3510, 3080, 3030, 2970, 2940, 2880, 1675, 1660, 1633, 1580, 1560, 1460, 1390, 1265, 1200, 1080, 1045, 950, 925, 905, 855; UV: see Table 1; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 2; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 298 $[M]^+$ (15), 283 (2), 282 (5), 280 (2), 270 (41), 255 (47), 252 (46), 237 (100), 227 (9), 222 (16), 214 (19), 209 (20), 194 (17), 179 (39), 178 (32), 165 (37), 152 (25), 128 (14), 115 (15), 89 (15), 76 (12), 57 (9), 43 (21). (Found: C, 76.31; H, 7.36. $C_{19}H_{22}O_3$ requires: C, 76.48; H, 7.43%.)

Application of Horeau's method to compound **1**. Performed in the usual manner [18]. Compound **1** (0.134 mmol), (±)-α-phenylbutyric anhydride (0.362 mmol) in pyridine soln (2.0 ml): $\alpha_1 = +0.520$; $\alpha_2 = +0.386$; $\alpha_1 - 1.1\alpha_2 = +0.095$; configuration 1*R*.

Arucadiol (**2**). Red oil; IR ν_{max}^{NaCl} cm^{-1}: 3490, 3400–2500 (br), 3060, 2970, 2930, 2880, 1640, 1590, 1555, 1510, 1465, 1425, 1335, 1180, 1040, 965, 870, 775; UV: see Table 1; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 2; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 298 $[M]^+$ (100), 283 (7), 281 (3), 269 (3), 195 (10), 178 (5), 165 (8), 128 (5), 89 (4), 69 (8), 57 (5), 55 (5), 43 (7). $C_{19}H_{22}O_3$ *M*, 298.

1-*Keto-aethiopinone* (**3**). Mp 96–99° (*n*-hexane); $[\alpha]_D^{24}$ 0.0° ($CHCl_3$; *c* 0.134); IR ν_{max}^{KBr} cm^{-1}: 3080, 3060, 2970, 2930, 2880, 1700, 1675, 1660, 1625, 1590, 1565, 1465, 1420, 1380, 1270, 1170, 1075, 950, 880, 820, 675; UV: see Table 1; ^{1}H NMR (300 MHz, $CDCl_3$): see Table 2; EIMS (direct inlet) 70 eV, *m/z* (rel. int.): 310 $[M]^+$ (14), 282 (5), 255 (100), 242 (15), 227 (39), 213 (89), 199 (13), 183 (24), 141 (39), 128 (21), 115 (28), 91 (5), 77 (6), 55 (9), 43 (10). (Found: C, 77.51; H, 7.06. $C_{20}H_{22}O_3$ requires: C, 77.39; H, 7.14%.)

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