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DITERPENOIDS OF *NEPETA TUBEROSA* SUBSP. *RETICULATA*

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Key Word Index—*Nepeta tuberosa* subsp. *reticulata*; Labiatae; diterpenoids; new isopimarane and nepetalactone derivatives.

Abstract—Seven new isopimarane and nepetalactone derivatives were isolated from *Nepeta tuberosa* subsp. *reticulata* and their structures elucidated by spectroscopic and chemical methods. They were identified as isopimaryl 2β[(1′-methyl-2′-al)ethyl]-5α-methyl-cyclopentane-β-carboxylate; isopimaryl-2β-acetyl-5α-methyl-cyclopentane-β-carboxylate; 3α-isopimaryloxy-4α,4aα,7α,7aα-dihydronepetalactone; isopimaryl-4β[(3′α-methyl-2′β-methoxycarbonyl) cyclopentyl]-2-pentenoate; isopimaryl 3β-methylencarboxylate-4α,4aα,7α,7aα-dihydronepetalactone; isopimaryl 3α-methylencarboxylate-4α,4aα,7α,7aα-dihydronepetalactone and isopimaryl 3-methylencarboxylate-4-hydroxy-4aα,7α,7aα-dihydronepetalactone.

INTRODUCTION

Some species from the genus *Nepeta* are important medicinal plants [1] or they have euphoric effects on cats [2]. *Nepeta tuberosa* (subsp. *reticulata*) [3] is a Labiate relatively abundant in the Iberian Peninsula. In this paper we report the isolation and structural determination of some components of a hexane extract of *Nepeta tuberosa* subsp. *reticulata*, that are derived from isopimarol and nepetalactone and some of their hydrolysis products.

RESULTS AND DISCUSSION

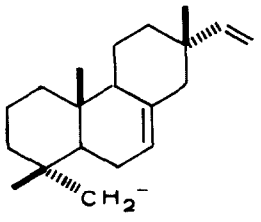
Apart from the compounds described previously [4, 5], from the MeOH-soluble extract of the non-volatile part of the hexane extract of *N. tuberosa* the following compounds were determined: six isopimaryl esters (**1**, **2**, **4**–**7**) with acids derived from nepetalactones and an acetal (**3**) of isopimarol with dihydronepetalactone. Compounds **1**–**7** have ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) showing signals of –CH=CH_2, CH=C, C–CH_2O and three Me–C groupings, characteristic of an isopimaryl group (*R*) substituted at C-18 [4].

Compound **2** has ^{1}H and ^{13}C NMR spectra which, apart from the signals of *R*, also exhibit a singlet of an acetyl group Me–CO (2.15 ppm, 3H, *s*) and a Me–CH doublet (1.12, *d*, 3H, J=6.5 Hz). Its ^{13}C NMR spectrum, apart from the signals of *R*, shows the signals of nine carbon atoms: two methyls, two methylenes, three methynes and two sp^2 quaternary carbon atoms (174.85 and 208.48 ppm). Hydrolysis of **2** affords isopimarol and the nepetonic acid **2a** (Table 3) [6, 7].

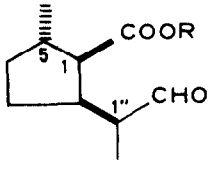
Compound **1**, which is present in very small amounts, has a ^{1}H NMR spectrum which shows, apart from the signals of *R*, methyl doublets (1.06, J=6.8 Hz) and a doublet at 9.60 ppm (J=1.1 Hz) of the hydrogen of a formyl group. Apart from the signals of *R*, its ^{13}C NMR spectrum shows signals of a further 10 carbon atoms: two methyls, two methylenes, four methynes and two sp^2 quaternary carbons (174.85 and 201.8 ppm). Biogenetically, compound **1** would arise from the cleavage of a nepetalactone present in the volatile part [4]. Although it has not been possible to isolate **1a** described for *N. cataria* (**6**), comparison of the spectroscopic data (^{13}C) with those of the nepetalactones isolated [4, 6, 7] permits the assignation of **1** to the proposed structure.

As well as the above-described signals characteristic of an isopimaryloxy moiety, compound **3** also shows those corresponding to a dihydronepetalactone substituted at C-3 [4, 8]. In this case the methylene 18 of *R* is bound to the oxygen of an ether and not to an ester as in the previous cases, since it appears upfield. The correspondence of the shifts of the signals in the ^{13}C NMR spectrum of **3** with those of **3a** [4, 8] is total.

The ester **4** shows in its ^{1}H NMR spectrum (Table 1) signals of a disubstituted double bond with an *E* configuration (6.80 ppm, *dd*, J=15.6 and 8.8 Hz and 5.70 ppm, *dd*, J=15.6 and 0.9 Hz); one singlet (3H) of a methoxycarbonyl group (COOMe) and two doublets of methyl groups at 1.03 (J=6.6) and 1.02 (J=6.6). Its ^{13}C NMR spectrum (Table 2) shows signals for 13 carbon atoms as well as those corresponding to the isopimaryloxy group: three methyls, two methylenes, six methynes (2 of them sp^2) and two carbonylic atoms of esters. Comparison the spectra of **4** with those of the nepetalactones [6, 7] suggests the structure shown in the figure which could have arisen biogenetically from condensation of **1a** with isopimaryl malonate, also present among the components of *N. tuberosa* [5] and later elimination of the carboxylic group. Hydrolysis of **4** affords isopimarol and an acid which after treatment with diazomethane yields the diester **4a** (Table 3) which



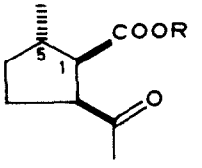
R (Isp)



R

1 Isp

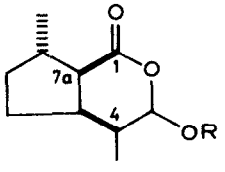
1a H



R

2 Isp

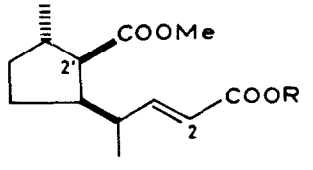
2a H



R

3 Isp

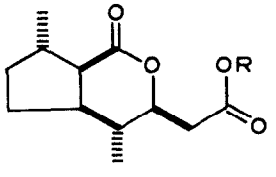
3a H



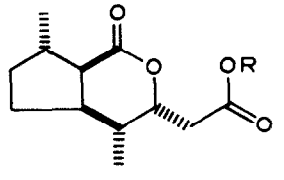
R

4 Isp

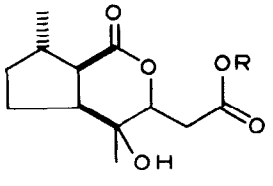
4a Me



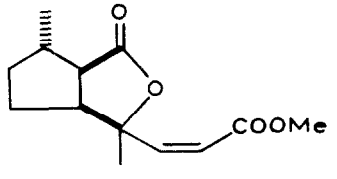
5 R = Isp



6 R = Isp



7 R = Isp



7a

has a positive NOE in the H–C_2, when the Me C_3, is irradiated.

As well as the 20 carbon atoms of the *R*, compounds **5** and **6** have a further 12 carbon atoms: two methyls, three methylenes, five methynes and two quaternary carbon atoms (Table 2). Of these carbon atoms, 10 belong to a dihydronepetalactone substituted at the 3 position; the other two belong to a CH_2–COO grouping. Hydrolysis of both **5** and **6** followed by treatment with diazomethane yields **4a**, showing that **5** and **6** must be epimers at the 3 position of the dihydronepetalactone. According to two-dimensional $^1H/^1H$ correlation and double irradiation experiments, the presence of a –CH(Me)–CH(OCO–)–CH_2–COO– grouping is confirmed.

In compound **5** the H–C_3 appears at 4.41 ppm (*ddd*, J = 4.6, 7.1 and 9.2 Hz) corresponding to an equatorial substituent at C–3 and a methyl, also equatorial, at C–4, while in the ^1H NMR spectrum of **6**, the H–C_3 appears at 4.85 ppm (*ddd*, J = 7.6, 6.1 and 2.1 Hz) corresponding to a *cis* stereochemistry [8] of the two hydrogens at C-3 and C-4. Comparison of the shifts of the rest of the signals of

Table 1. ^{1}H NMR data of compounds 1–7

H		1	2	3	5	6	7	4	H
1		—	2.70 *dd* (8.8, 9.0)	—	—	—	—	—	
2		—	3.30 *ddd* (8.8, 8.8, 7.5)	—	—	—	—	5.70 *dd* (15.6, 0.9)	2
3		—	—	4.91 *d* (2.4)	4.41 *ddd* (4.6, 7.1, 9.2)	4.85 *ddd* (7.6, 6.1, 2.1)	4.32 *t* (6.2)	6.80 *dd* (15.6, 8.8)	3
Me-5		1.06 *d* (6.8)	1.12 *d* (6.5)	—	—	—	—	1.03 *d* (6.6)	Me-4
7a		—	—	—	—	—	2.82 *dd* (8.6, 4.1)	1.02 *d* (6.59)	Me-3′
8		—	—	1.00 *d* (6.7)	0.98 *d* (6.8)	0.97 *d* (6.0)	1.35 *s*	—	
9		—	—	1.22 *d* (6.4)	1.20 *d* (6.4)	1.20 *d* (6.4)	1.14 *d* (6.9)	—	
7′		5.33 *br s*	5.33 *br s*	5.32 *br s*	5.34 *br s*	5.33 *br s*	5.33 *br s*	5.31 *br s*	7″
15′		5.80 *dd* (17.6, 10.6)	5.80 *dd* (17.5, 10.5)	5.80 *dd* (17.5, 10.7)	5.81 *dd* (17.6, 10.7)	5.81 *dd* (17.5, 10.7)	5.79 *dd* (17.5, 10.7)	5.79 *dd* (17.6, 10.7)	15″
16′	a	4.93 *dd* (17.6, 1.4)	4.92 dd (17.5, 1.3)	4.92 *dd* (17.5, 1.5)	4.92 *dd* (17.6, 1.4)	4.93 *dd* (17.5, 1.4)	4.92 *dd* (17.5, 1.5)	4.91 *dd* (17.6, 1.4)	16″
	b	4.86 *dd* (10.6, 1.4)	4.86 *dd* (10.5, 1.3)	4.85 *dd* (10.7, 1.5)	4.86 *dd* (10.7, 1.4)	4.86 *dd* (10.7, 1.4)	4.85 *dd* (10.7, 1 5)	4.85 *dd* (10.7, 1.4)	
17′		0.86 s	0.86 s	0.89 s	0.86 s	0.86 s	0.85 s	0.85 *s*	17″
18′	a	3.77 *d*	3.85 *d*	3.50 *d*	3.81 *s*	3.94 *d*	3.88 *d*	3.85 *d*	18″
	b	3.63 *d* (10.9)	3.69 *d* (10.9)	3.12 *d* (9.2)		3.66 *d* (10.9)	3.74 *d* (10.9)	3.69 *d* (11.0)	
19′		0.94 *s*	0.95 *s*	0.86 *s*	0.96 *s*	0.94 *s*	0.95 *s*	0.96 *s*	19″
20′		0.90 *s*	0.90 *s*	0.91 *s*	0.90 *s*	0.90 *s*	0.89 *s*	0.90 *s*	20″
Me-1″		1.06 *d* (6.8)	—	—	—	—	—		
CHO		9.60 d (1.1)	—	—	—	—	—	3.54 s	–COOMe
Me–CO–R		—	2.15 *s*	—	—	—	—		
$-CH_2-COOisp$		—	—	—	2.72 *dd* (16.1, 4.6) 2.60 *dd* (16.1, 7.1)	2.78 *dd* (15.9, 7.6) 2.55 *dd* (15.9. 6.1)	2.40 *d* (6.2)		

the ^{13}C NMR spectrum with the data in the literature [7, 8] confirms the stereochemistry proposed.

Apart from the signals of *R*, the ^{1}H NMR spectrum of **7** (Table 1) shows signals corresponding to a methyl geminal to a hydroxyl group Me–COH (1.35. 3H, *s*), of a Me–CH (1.14 ppm, *d*, 3H, $J=6.9$ Hz) and of a C(=O)–$CHCH_2$–COO– grouping (4.32, 1H, *t*, $J=6.2$; 2.40, 2H, *d*, $J=6.2$ Hz). The ^{13}C NMR spectrum of **7** (Table 2), apart from the signals of *R*, shows signals of a further twelve carbon atoms that can be assigned to a dihydronepetalactone [7, 8] with a hydroxyl at C-4 and substituted with a CH_2–COOR group at C-3. Hydrolysis of **7** yields a γ-lactone **7a** (IR 1770 cm^{-1}) ^{1}H NMR and ^{13}C NMR in Table 3.

EXPERIMENTAL

^{1}H NMR: 200 MHz, $CDCl_3$, TMS int. st; ^{13}C NMR: 50.3 MHz.

Extraction and isolation. Plant material was collected in Ciudad Rodrigo (Salamanca) in July 1987. The dried plant (5.7 kg) was extd with *n*-hexane at room temp. for 4 weeks. After evapn of solvent, 148.1 g of ext was obtained. This was subjected to a vapour-current distn yielding 8.1 g (volatile fraction) and 140.0 g (non-volatile fraction). The composition of volatile fraction were reported in previous papers. The non volatile fraction was dewaxed with MeOH yielding 76.3 g of dewaxed ext and CC or prep. TLC yielded compounds **1** to **7**, besides other compounds reported in previous papers.

Isopimaryl 2β[(1′-methyl-2′-al)ethyl]-5α-methyl-cyclopenta-β-carboxylate (**1**). Colourless oil. $C_{30}H_{46}NO_3$. $[\alpha]_D=+2.6°$ ($CHCl_3$; *c*, 0.27). IR ν_{max}^{film} cm^{-1}: 3050, 2860, 1740, 1720, 1650, 1470, 1390, 920. ^{1}H NMR see Table 1. ^{13}C NMR see Table 2.

Isopimaryl 2β-acetyl-5α-methyl-cyclopenta-β-carboxylate (**2**). Colourless oil. $C_{29}H_{44}O_3$. $[\alpha]_D=+7.3°$ ($CHCl_3$; *c*, 0.33). IR ν_{max}^{film} cm^{-1}: 3090, 1740, 1660, 1480, 1390, 920. ^{1}H NMR see Table 1. ^{13}C NMR see Table 2.

Hydrolysis of **2**; **2a**: *2β-acetyl-5α-methyl-cyclopenta-β-carboxylic acid.* **2** (100 mg) was treated with 4 ml of a soln of 0.5 N KOH–MeOH. After standing 24 hr at room temp. it was extracted with Et_2O. The Et_2O was dried (Na_2SO_4) and evapd to dryness, yielding 70 mg of isopimarol, identified by TLC. The alkaline soln was acidified with HCl and extracted with Et_2O. This was dried (Na_2SO_4) and evapd to dryness, providing 20 mg

Table 2. ^{13}C NMR data of compounds (1–7)

C	1	2	3	5	6	7	4	C
1′	39.46	39.43	39.61	39.35	39.36	39.83	39.41	1″
2′	18.10	18.07	18.14	18.04	18.02	18.02	18.09	2″
3′	36.25	36.23	36.59	36.26	36.26	36.29	36.26	3″
4′	36.90	36.51	37.15	36.47	36.45	36.48	36.48	4″
5′	44.50	44.61	44.90	44.87	44.63	44.87	44.78	5″
6′	23.55	23.56	23.73	23.62	23.58	23.62	23.59	6″
7′	121.02	121.11	121.06	121.18	121.08	121.08	121.22	7″
8′	135.64	135.64	135.65	135.62	135.72	135.74	135.57	8″
9′	52.03	52.00	52.10	51.98	51.95	52.06	51.97	9″
10′	35.32	35.36	35.30	35.36	35.38	35.69	35.36	10″
11′	20.29	20.25	20.28	20.24	20.24	20.25	20.23	11″
12′	36.42	36.33	36.88	36.26	36.26	36.35	36.84	12″
13′	36.80	36.84	36.28	36.88	36.87	36.85	36.26	13″
14′	46.20	46.18	46.19	46.18	46.22	46.19	46.19	14″
15′	150.43	150.39	150.47	150.44	150.41	150.34	150.37	15″
16′	109.29	109.27	109.22	109.27	109.30	109.30	109.27	16″
17′	21.59	21.57	21.59	21.58	21.56	21.57	21.56	17″
18′	72.96	73.23	79.59	73.71	73.50	73.69	72.93	18″
19′	18.22	18.17	18.35	18.14	18.12	18.11	18.21	19″
20′	15.54	15.50	15.51	15.53	15.49	15.45	15.49	20″
1	54.01	53.30	174.59	170.30	170.16	171.06	166.84	1
2	42.62	55.62	—	—	—	—	120.06	2
3	29.74	28.19	105.41	79.74	74.80	70.85	153.23	3
4	33.72	34.16	39.74	45.23	42.86	87.05	47.88	4
5	38.72	39.73	—	—	—	—	19.04	5
Me–5	21.34	19.45	—	—	—	—	39.49	1′
1″	48.01	—	—	—	—	—	53.80	2′
Me–1″	12.75	—	—	—	—	—	38.27	3′
–OCO–	174.85	174.85	—	—	—	—	33.67	4′
Me–CO–	—	29.03	—	—	—	—	30.44	5′
Me–CO–	—	208.48	—	—	—	—	21.36	Me–3′
4a	—	—	39.55	40.12	41.26	54.09	175.88	–COOMe
5	—	—	32.27	32.28	32.37	26.62	50.98	–COOMe
6	—	—	34.56	34.47	35.15	35.35		
7	—	—	38.56	38.05	36.33	37.42		
7a	—	—	49.43	49.41	48.70	48.92		
8	—	—	15.26	15.53	14.80	21.14		
9	—	—	20.63	20.66	19.13	21.14		
–CH_2–COOR	—	—	—	38.22	37.45	37.42		
–C–COOR	—	—	—	174.45	173.58	178.69		

of **2a**: Colourless oil. $C_9H_{14}O_3$. IR ν_{max}^{film} cm^{-1}: 3080, 1740, 1660, 1480, 1380, 920. ^1H NMR and ^{13}C NMR see Table 3.

3α-Isopimaryloxi-4α, 4aα, 7α, 7aα-Dihydronepetalactone (**3**). Colourless oil. $C_{30}H_{46}O_3$. $[\alpha]_D = +33.2°$ ($CHCl_3$; *c*, 1.24). IR ν_{max}^{film} cm^{-1}: 3090, 1750, 1650, 1470, 1390, 1200, 1000, 920. ^1H NMR see Table 1; ^{13}C NMR see Table 2.

Isopimaryl 4β[(3′α-methyl-2′β-methoxycarbonyl) cyclopenthyl]-2-penthenoate (**4**). Colourless oil. $C_{33}H_{50}O_4$. $[\alpha]_D = -23.3°$ ($CHCl_3$, *c* 3.21). IR ν_{max}^{film} cm^{-1}; 3100, 1730, 1650, 1455, 1380, 1170, 1000, 910. ^1H NMR see Table 1; ^{13}C NMR see Table 2.

Hydrolysis of **4** *and treatment with* CH_2N_2, **4a**: *methyl 4β[(3′α-methyl-2′β-methyoxycarbonyl) cyclopenthyl]-2-pentenoate.* To a soln of **4** (50 mg) in MeOH (4 ml) and 3 drops of H_2O were added 85 mg of K_2CO_3, and the mixt. stirred for 24 hr at room temp. After evapn of solvent and diln with H_2O, the soln was extd with EtOAc. The EtOAc ext. was dried (Na_2SO_4) and evapd to dryness, yielding 35 mg of isopimarol, identified by TLC. The aq soln was acidified with HCl and extd with EtOAc as above, yielding 10 mg of **4a**; Colourless oil. $C_{14}H_{22}O_4$. $[\alpha]_D = -35.9°$ ($CHCl_3$, *c* 0.83). IR ν_{max}^{film} cm^{-1};: 2940, 2845, 1730, 1715, 1660, 1460, 1440, 1380, 930, 900, 870. ^1H NMR and ^{13}C NMR see Table 3.

Isopimaryl 3β-methylene carboxylate-4α,4aα,7α,7aα-Dihydronepetalactone (**5**). Colourless oil. $C_{32}H_{48}O_4$. $[\alpha]_D = -13.5°$ ($CHCl_3$; *c* 1.3). IR ν_{max}^{film} cm^{-1}: 3090, 1735, 1640, 1450, 1380, 1180, 1030, 900. ^1H NMR see Table 1. ^{13}C NMR see Table 2.

Hydrolysis of **5** *and treatment with* CH_2N_2: **4a**. **5** (100 mg) was treated with 4 ml of 0.5 N KOH–MeOH for 24 hr at room temp. Usual work-up and extn with Et_2O yielded 65 mg of neutral product (isopimarol) and 26 mg of acid product, which when treated with CH_2N_2 provided a product whose properties were identical to **4a**.

Isopimaryl 3α-methylenecarboxylate-4α,4aα,7α,7aα-dihydro-

Table 3. ^{1}H and ^{13}C NMR data of compounds **2a**, **4a** and **7a**

C	**2a** ^{1}H NMR	^{13}C NMR	C	**4a** ^{1}H NMR	^{13}C NMR	C	**7a** ^{1}H NMR	^{13}C NMR
1	2.72 *d*	52.81	1	—	167.14	1	—	170.20
	(9.8, 8.3)		(1)–COOMe	3.59 *s*	51.26	3	—	89.12
2	3.30 *m*	55.55	2	5.71 *dd*	119.73	3a	—	50.16
3	—	28.21		(15.7, 0.9)		4	—	26.72
4	—	34.08	3	6.83 *dd*	153.45	5	—	32.39
5	—	39.68		(15.7, 8.6)		6	—	37.35
Me–5	1.15 *d*	19.33	4	—	47.78	6a	—	52.25
	(6.7)		Me-4	1.04 *d*	18.96	Me-3	1.51 *s*	24.15
–CO–Me	2.20 *s*	29.03		(6.7)		Me–6	1.01 *d*	22.12
–CO–Me	—	208.98	1′	—	39.20		(6.8)	
–COOH	—	180.35	2′	—	53.99	1′	7.37 *d*	159.13
			3′	—	38.13		(5.9)	
			4′	—	33.52	2′	5.96 *d*	120.23
			5′	—	30.13		(5.9)	
			Me–3′	1.02 *d*	21.35	–COOMe	3.67 *s*	51.52
				(6.8)		–COOMe	—	166.12
			–COOMe	3.72	50.94			
			–COOMe	—	175.72			

nepetalactone (**6**). Colourless oil. $C_{32}H_{48}O_4$. $[\alpha]_D = +20.96°$ ($CHCl_3$; *c* 1.65). IR ν_{max}^{film} cm^{-1}: 3100, 1750, 1730, 1720, 1635, 1460, 1440, 1400, 1250, 1000, 910, 830. ^{1}H NMR see Table 1. ^{13}C NMR see Table 2.

Hydrolysis of **6** *and treatment with* CH_2N_2: **4a**. **6** (100 mg) was treated with 4 ml of 0.5 N KOH–MeOH for 24 hr at room temp. Usual work-up and extn with Et_2O yielded 63 mg of neutral product (isopimarol) and 25 mg of acid product, which when treated with CH_2N_2 provided a compound identical to **4a**.

Isopimaryl 3-methylenecarboxylate-4-hydroxy-4aα,7α,7aα-dihydronepetalactone (**7**). Colourless oil. $C_{42}H_{48}O_5$. $[\alpha]_D = -6.0°$ ($CHCl_3$; *c* 1.83). IR ν_{max}^{film} cm^{-1}: 3500, 3090, 1750, 1650, 1490, 1390, 910. ^{1}H NMR see Table 1. ^{13}C NMR see Table 2.

Hydrolysis of **7** *and treatment with* CH_2N_2: **7a**. **7** (100 mg) was dissolved in 8 ml of MeOH containing some H_2O and 170 mg of K_2CO_3 added. The soln was stirred for 24 hr at room temp. Usual work-up and extn with EtOAc yielded 60 mg of acid product, which when treated with CH_2N_2 provided compound **7a**: Colourless oil $C_{13}H_{18}O_4$. IR ν_{max}^{film} cm^{-1}: 3090, 1770, 1715, 1640, 1460, 1390. ^{1}H NMR and ^{13}C NMR see Table 3.

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