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REDUCED ACETOPHENONE DERIVATIVES FROM *CALEA CUNEIFOLIA**

TÂNIA O. LOURENÇO,† GOKITHI AKISUE‡ and NÍDIA F. ROQUE†

† Instituto de Química, Universidade de São Paulo, C.P. 20780, 05508 São Paulo, SP, Brazil;
‡ Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, Brazil

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Key Word Index—*Calea cuneifolia*; Compositae; reduced acetophenone derivatives; acetylsarracinic acid; chromanone.

Abstract—Six reduced *p*-hydroxyacetophenones, a *p*-hydroxyvinylbenzene derivative, a chromanone, and acetylsarracinic acid were isolated from the xylopodium of *Calea cuneifolia*. The constitutions were elucidated by spectroscopic methods and a few chemical transformations.

INTRODUCTION

In continuation of the phytochemical investigations of the genus *Calea* (Compositae) [1] we now report the isolation and characterization of sitosterol, acetylsarracinic acid, 6-hydroxy-2,2-dimethylchroman-4-one, 2-senecionyl-4-(1-hydroxyethyl)-phenol and five new derivatives of this last substance from the hexane extract of *Calea cuneifolia* DC. This appears to be the first report of acetylsarracinic as a free acid in plants.

RESULTS AND DISCUSSION

The spectral data (UV, IR, ^{1}H NMR and MS) of the aromatic constituents (**1**–**4**) of the hexane extract of *C. cuneifolia* show very similar features. All, except **4**, present IR absorption characteristics of an *o*-hydroxyacetophenone (ν_{max} 1640 cm^{-1}). The ^{1}H NMR spectra show the trisubstituted pattern for these substances (Table 1). The major compound (**1a**) has ^{1}H NMR, IR, MS and $[\alpha]_D$ data similar to those of 2-senecionyl-4-(1-hydroxyethyl)-phenol isolated before from *Ageratina altisima* [2]. The obtention of acetophenone [3], diacetyl and dihydro derivatives confirmed the constitution.

Compounds **1b** and **1c** have the same molecular formula ($C_{26}H_{30}O_5$), established by high resolution MS, UV and IR spectra but different mps, R_f on TLC and $[\alpha]_D$. These observations and the slight differences in the chemical shifts of the bands in the ^{1}H NMR spectra of these two substances could only be explained by the assumption that they are epimers. The absence of the hydroxyl bands in the ^{1}H NMR (present in **1a**), the fragmentation shown in the MS and the obtention of only a phenol acetate agree with the constitution proposed for **1b** and **1c**. Compound **1b** has $[\alpha]_D^{24}$ −11.6, C-7 and C-7′ having therefore the same absolute configuration. **1c**, with $[\alpha]_D^{24}$ 0, is the meso compound.

In the ^{1}H NMR spectra of **1d** and **1e** this signal of H-7 is shifted downfield relative to that in **1a**. These substances are the corresponding acetate and acetylsarracinate of **1a**. Compound **2** presents in the ^{1}H NMR spectrum a singlet at 1.29 ppm equivalent to 6H and a singlet at 3.07 ppm (2H) instead of the two methyl bands at 2.02 and 2.20 ppm and the 6.70 ppm multiplet (1H) of **1a**. These differences fit very well with its formulation as the hydration product of **1a**. The structure of the vinyl compound **3** was easily established by ^{1}H NMR data.

Compound **4** does not present the spectral absorptions characteristic of the senecionyl and hydroxyethyl moieties present in the spectra of the other compounds. The chroman structure was suggested by the ^{1}H NMR spectrum. This compound has been described before as a synthetic product [4].

The IR spectrum of **5** show absorptions characteristic of ester and acid functions. The strong similarity between the ^{1}H NMR spectrum of this compound and that of the acid moiety of compound **1e** indicated that it is acetylsarracinic acid. The other spectral data confirmed this suggestion. As far as we know, this is the first report of the occurrence of free acetylsarracinic acid.

The dimeric compounds (**1a** and **1c**) and the vinyl compound (**3**) could be artifacts. This possibility is suggested by the presence of an acidic compound (**5**) in the hexane extract of the xylopodium of *Calea cuneifolia* and by the small amounts of these compounds in addition to large amounts of **1a**. The absence of optical activity strongly supports this probability in the case of **1c**.

Isoprenylated acetophenones are common in species of the Compositae. Reduced acetophenones, however, have been found previously only in species of the tribes Inuleae, Heliantheae and Eupatorieae.

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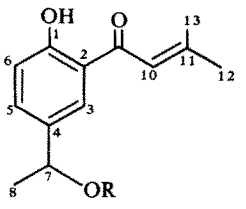
† To whom correspondence should be addressed.

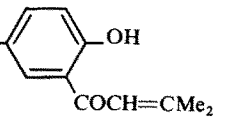
Table 1. ^{1}H NMR of aromatic constituents of *C. cuneifolia* (CCl_4, 60 MHz, δ, J in Hz)

	1a	**1b**	**1c**	**1d**	**1e**	**2**	**3**	**4***
H-3	7,60 (*d*, J = 2, 1 H)	7,46 (*d*, J = 2, 2 H)	7,40 (*d*, J = 2, 2 H)	7,67 (*d*, J = 2, 1 H)	7,75 (*d*, J = 2, 1 H)	7,68 (*d*, J = 2, 1 H)	7,60 (*d*, J = 2, 1 H)	2,69 (*s*, 2 H)
H-5	7,30 (*dd*, J = 8 and 2, 1 H)	7,40 (*dd*, J = 8 and 2, 2 H)	7,32 (*dd*, J = 8 and 2, 2 H)	7,41 (*dd*, J = 8 and 2, 1 H)	7,43 (*dd*, J = 8 and 2, 1 H)	7,39 (*dd*, J = 8 and 2, 1 H)	7,50 (*dd*, J = 8 and 2, 1 H)	7,40 (*d*, J = 2, 1 H)
H-6	6,77 (*d*, J = 8, 1 H)	6,92 (*d*, J = 8, 2 H)	6,85 (*d*, J = 8, 2 H)	6,89 (*d*, J = 8, 1 H)	6,88 (*d*, J = 8, 1 H)	6,85 (*d*, J = 8, 1 H)	6,89 (*d*, J = 8, 1 H)	7,09 (*dd*, J = 8 and 2, 1 H)
H-7	4,70 (*q*, J = 6, 1 H)	4,15 (*q*, J = 6, 2 H)	4,40 (*q*, J = 6, 2 H)	5,83 (*q*, J = 6, 1 H)	5,89 (*q*, J = 6, 1 H)	4,73 (*q*, J = 6, 1 H)	6,63 (*dd*, J = 18 e 10, 1 H)	6,83 (*d*, J = 8, 1 H)
H-8 and H-8′	1,37 (*d*, J = 6, 3 H)	1,32 (*d*, J = 6, 6 H)	1,42 (*d*, J = 6, 6 H)	1,52 (*d*, J = 6, 3 H)	1,53 (*d*, J = 6, 3 H)	1,40 (*d*, J = 6, 3 H)	5.16 (*d*, J = 10, 1 H): 5.53 (*d*, J = 18, 1 H)	
H-10	6,72 (*m*, 1 H)	6,70 (*m*, 2 H)	6,47 (*m*, 2 H)	6,73 (*m*, 1 H)	6,80 (*m*, 1 H)	3,07 (*s*, 2 H)	6,80 (*m*, 1 H)	1,45 (*s*, 6 H)
H-11								
H-12	2,03 (*d*, J = 2, 3 H)	2,02 (*d*, J = 2, 6 H)	1,92 (*d*, J = 2, 6 H)	2,02 (*d*, J = 2, 3 H)	2,02 (*d*, J = 2, 3 H)	1,29 (*s*, 6 H)	2,00 (*d*, J = 2, 3 H)	
H-13	2,20 (*d*, J = 2, 3 H)	2,20 (*d*, J = 2, 6 H)	2,15 (*d*, J = 2, 6 H)	2,20 (*d*, J = 2, 3 H)	2,20 (*d*, J = 2, 3 H)		2,23 (*d*, J = 1, 3 H)	
Ar-O<u>H</u>	12,55 (*s*, 1 H)	12,57 (*s*, 2 H)	12,53 (*s*, 2 H)	12,53 (*s*, 1 H)	12,58 (*s*, 1 H)	12,00 (*s*, 1 H)	12,58 (*s*, 1 H)	6,09 (*s*, 1 H)
R-O<u>H</u>	2,00 (*s*, 1 H)					3,07 (*s*, 2 H)		
H-16					6,37 (*q*, J = 6, 1 H)			
H-17					2,09 (*d*, J = 6, 3 H)			
H-18					4,69 (*s*, 2 H)			
H-20					1,92 (*s*, 3 H)			
$ROCOCH_3$				1,88 (*s*, 3 H)				

* Spectrum in $CDCl_3$.



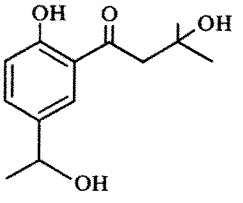
1a R = H

1b R = CHMe– 

1c = **1b**

1d R = Ac

1e R = $COC(CH_2OAc)CHMe$



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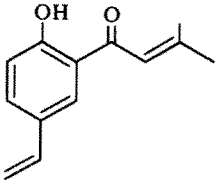

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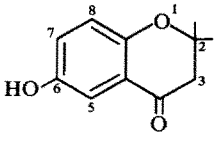

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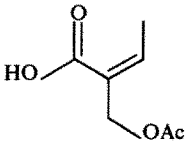

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EXPERIMENTAL

Plant material. Calea cuneifolia DC. was collected in Mogi-Mirim, São Paulo, Brazil. A voucher specimen, no. 145512 was deposited in the Herbarium of Instituto de Botânica, Universidade de São Paulo.

Extraction and isolation of the constituents. Air dried xylopodium (5200 g) was extracted with *n*-hexane, the solvent being removed under vac. to give a dark brown oil (115 g). A part of the hexane extract (10 g) was directly chromatographed on Si gel (300 g) using *n*-hexane–EtOAc gradient to give 35 fractions. Investigation of these fractions revealed several mixtures which were subsequently separated by chromatographic column, prep. TLC, or crystallization. The mixture eluted with 10% EtOAc gave **1a** (1.7 g), **1b** (33 mg), **1c** (5 mg), **3** (13 mg) and **1d** (5 mg). Elution with 20% EtOAc provided **1e** (70 mg). The fraction eluted with 30% EtOAc gave **4** (2.5 mg) and sitosterol (60 mg). Elution with EtOAc provided **2** (5 mg) and **5** (2 mg).

2-*Senecionyl*-4-(1-*hydroxyethyl*)-*phenol* (**1a**). Yellow oil. Calc. for $C_{13}H_{16}O_3$: MW 220.1099, Found MW (MS) 220.1158. ν_{max}^{film} cm^{-1}: 3450, 2950, 1640, 1580, 1490, $[\alpha]_D^{24}$ −8,7 (C = 29,5 × 10^{-3}). λ_{max}^{MeOH} nm (ε_{max}): 340 (7265), 275 (26420), 220 (28408). Low resolution MS *m/e* (rel. int.): 220 (M^+, 13), 206 (21), 205 (100), 165 (20), 149 (47), 147 (12), 91 (26), 83 (41), 65 (59), 55 (59). Acetylation: **1a** (70 mg) by the usual procedures gave the diacetate (60 mg), ν_{max}^{film} cm^{-1}: 2950, 1760, 1740, 1660, 1610, 1240, 1200, 1190, 1070. MS: *m/e* (rel. int.) 304 (M^+, 5), 260 (70), 195 (100), 151 (47), 83 (16), 43 (87). ^1H NMR (CCl_4, 60 MHz, δ, *J* in Hz): 7.60 (*d*, *J* = 2), 7.42 (*d*, *d*, *J* = 8 and 2), 7.00 (*d*, *J* = 8), 5.85 (*q*, *J* = 6), 1.50 (*d*, *J* = 6), 6.45 (*m*), 2.02 (*d*, *J* = 2), 2.20 (*d*, *J* = 2), 2.25 (*s*), 2.05 (*s*). Hydrogenation: by PtO_2: **1a** (97 mg) in EtOH (6 ml) were hydrogenated in the presence of PtO_2 (1.5 mg) at room temp. for 5 hr. Filtration, evapn and chromatographic purification gave 50 mg of a colourless oil, ν_{max}^{film} cm^{-1}: 3500, 2940, 1640, 1480, 1260, 960, 920. MS *m/e* (rel. int.) 222 (M^+, 14), 207 (30), 165 (100), 149 (10), 121 (12), 91 (21), 85 (6). ^1H NMR (CCl_4, 60 MHz, δ, *J* = Hz): 7.62 (*d*, *J* = 2), 7.34 (*dd*, *J* = 8 and 2), 6.80 (*d*, *J* = 8), 4.73 (*q*, *J* = 6), 1.40 (*d*, *J* = 6), 2.80 (*d*, *J* = 6), 2.0–2.5 (*m*), 1.03 (*d*, *J* = 6), Jones oxidation: **1a** (98 mg) gave 4-hydroxy-3-senecionyl-acetophenone (50 mg) [3].

1,1′-*Bis*-[2-*senecionyl*-4-(1-*ethyl*)-*phenoxy*]*ether* (**1b**). Yellow crystals mp 139–42° (light petrol). Calc. for $C_{26}H_{30}O_5$: MW 422.20931, found MW (MS) 422.2258. ν_{max}^{KBr} cm^{-1}: 3300–2700, 1640, 1580, 1480. $[\alpha]_D^{24}$ −11,6 (C = 3,9 × 10^{-3}). λ_{max}^{MeOH} nm (ε_{max}): 340 (11010), 275 (42660), 220 (52290). Low resolution MS *m/e* (rel. int.) 422 (M^+, 38), 407 (75), 351 (28), 205 (20), 204 (48), 203 (98), 196 (48), 189 (28), 187 (22), 149 (28), 148 (28), 147 (100), 91 (48), 83 (37), 65 (30), 55 (30). Acetylation: **1b** (15 mg) with Ac_2O–Py at room temp. overnight gave the monoacetate (14 mg), ν_{max}^{film} cm^{-1}: 2940, 1760, 1660, 1610, 1480, 1190, 1080, MS *m/e* (rel. int.) 506 (M^+, 27), 449 (14), 407 (26), 351 (8), 203 (45), 187 (15), 147 (100), 91 (34), 83 (29), 55 (26), ^1H NMR (CCl_4, 60 MHz, δ, *J* = Hz): 7.48 (*d*, *J* = 2), 7.40 (*dd*, *J* = 8 and 2), 7.02 (*d*, *J* = 2), 4.30 (*q*, *J* = 6), 1.40 (*d*, *J* = 6), 6.40 (*m*), 1.98 (*d*, *J* = 2), 2.18 (*d*, *J* = 2), 2.22 (*s*).

Meso-1,1′-*bis*-[2-*senecionyl*-4-(1-*ethyl*)-*phenoxy*]*ether* (**1c**). Yellow crystals, mp 109–11° (light petrol). Calc. for $C_{26}H_{30}O_5$: MW 422.2093, Found MW (MS) 422.2026. ν_{max}^{KBr} cm^{-1}: 3300–2700, 1640, 1580, 1480. $[\alpha]_D^{24}$ 0. λ_{max}^{MeOH} nm (ε_{max}): 340 (13560), 275 (44840), 220 (54260). Low resolution MS *m/e* (rel. int.) 422 (M^+, 20), 407 (40), 351 (30), 205 (23), 196 (21), 187 (20), 149 (20), 147 (100), 91 (34), 83 (29), 55 (21).

2-*Senecionyl*-4-(1-*acetoxyethyl*)-*phenol* (**1d**). Yellow oil. ν_{max}^{film} cm^{-1}: 3300–2700, 1720, 1640, 1230. λ_{max}^{MeOH} (ε_{max}): 340 (3070), 260 (14640), 220 (23200). $[\alpha]_D^{24}$ −6.7 ($C = 3 \times 10^{-3}$). Low resolution MS: *m/e* (rel. int.) M^+ −43 (10), 203 (40), 187 (96), 147 (100), 91 (33), 83 (50), 55 (78).

2-*Senecionyl*-4-(1-*acetylsarracinoyloxyethyl*)-*phenol* (**1e**). Yellow oil. Calc. for $C_{20}H_{24}O_6$: MW 360.1573, Found MW (MS) 360.1666. ν_{max}^{film} cm^{-1}: 3300–2700, 1720, 1750, 1640, 1580, 1490, 1230. λ_{max}^{MeOH} nm (ε_{max}): 340 (2780), 275 (15560), 220 (22780). $[\alpha]_D^{24}$ −20 ($C = 6 \times 10^{-3}$). Low resolution MS: *m/e* 360 (M^+, 2), 345 (21), 203 (19), 187 (100), 147 (58), 83 (12), 55 (14).

2-(3-*Methyl*-3-*hydroxybutanoyl*-1)-4-(1-*hydroxyethyl*)-*phenol* (**2**). Yellow oil. Calc. for $C_{13}H_{18}O_4$: MW 238.1205, Found MW (MS) 238.1173: ν_{max}^{film} cm^{-1}: 3500, 3010, 1640, 1610, 1490. λ_{max}^{MeOH} nm (ε_{max}): 330 (3885), 256 (9375), 220 (19830). $[\alpha]_D^{24}$ −9 ($C = 7{,}6 \times 10^{-3}$). Low resolution MS: *m/e* (rel. int.) 238 (M^+, 6), 220 (9), 205 (84), 165 (100), 164 (31), 163 (30), 147 (42), 149 (97), 91 (52), 83 (19), 55 (18).

2-*Senecionyl*-4-*vinylphenol* (**3**). Yellow oil. Calc. for $C_{13}H_{13}O_2$: 202.0994, Found MW (MS) 202.0994. ν_{max}^{film} cm^{-1}: 3300–2700, 1640, 1580, 1480, 990, 910. λ_{max}^{MeOH} nm (ε_{max}): 340 (1465), 265 (18810), 245 (19050), 210 (7185). Low resolution MS: *m/e* 202 (M^+, 21), 189 (25), 188 (20), 187 (100), 149 (16), 147 (40), 91 (16), 83 (18), 55 (14).

6-*Hydroxy*-2,2-*dimethylchroman*-4-*one* (**4**). Crystals (carbon tetrachloride), mp 154–6°. Calc for $C_{11}H_{12}O_3$: MW 192.0786, Found MW (MS) 192.0531. ν_{max}^{KBr} cm^{-1}: 3400, 2990, 1670, 1610, 1490. λ_{max}^{MeOH} nm (ε_{max}): 350 (4080), 255 (8650), 225 (24040). Low resolution MS: *m/e* 192 (M^+, 42), 177 (100), 137 (89), 136 (95), 108 (47), 81 (26), 80 (42), 55 (32), 53 (74), 52 (89).

Acetylsarracinic acid (**5**). Yellow oil. ν_{max}^{film} cm^{-1}: 3500–2500, 1390, 1250, 1030, 860, ^1H NMR (CCl_4, 60 MHz, δ, J = Hz): 2.0 (*s*), 2.15 (*d*, J = 7), 4.70 (*s*), 6.55 (*q*, J = 7). Low resolution MS: M-43 (10), 99(13), 98 (67), 97 (59), 70 (32), 69 (36), 55 (30), 53 (51), 43 (100), 41 (44), 39 (60).

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