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NEW CLERODANES FROM *SYMPHIOPAPPUS ITATIAYENSIS*[*]

WALTER VICHNEWSKI†, RAMASWAMY MURARI‡ and WERNER HERZ‡§

†Nucleo de Pesquisas de Productos Naturais do Faculdade de Farmácia e Odontologia, 14.100 Ribeirão Preto, São Paulo, Brasil;
‡Department of Chemistry, The Florida State University, Tallahassee, FL 32306, U.S.A.

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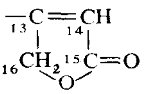
Key Word Index—*Symphiopappus itatiayensis*; Eupatorieae; Compositae; clerodanes; diterpenoids.

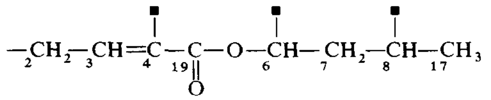
Abstract—The isolation and structure determinations of two new *ent-cis*-clerodane dilactones from *Symphiopappus itatiayensis* are reported.

In the course of our work on constituents of Brazilian Compositae, we have isolated from the hexane–EtOAc (10:1) extract of *Symphiopappus itatiayensis*, tribe Eupatorieae, Disynaphia group [2], two new clerodane dilactones whose structures **1a** and **2** are reported herewith.

The four oxygen atoms of **1a**, mp 150°, $C_{20}H_{26}O_4$ (elementary analysis and high resolution MS) were those of two conjugated lactone functions as indicated by the empirical formula, the absence of hydroxyl groups and by IR bands at 1750 (very strong) and 1650 cm^{-1}. NMR analysis showed that these were included in partial structures **A** and **B** (numbering as in final formula). Chemical shifts of C-13, C-14, C-15, and C-16 at 170.1, 115.2, 172.3, and 72.9 ppm, with H-14 at 5.85 being long-range coupled ($J = 1.5$) to the two proton doublet of H-16 at 4.75 ppm, were essentially identical with those found in an *ent-trans*-clerodane from *Baccharis trimera* [3] containing a similar lactone system (also see [4]); likewise, chemical shifts and coupling constants of H-2 (buried in a four proton multiplet at 2.35 ppm), H-3 (*t* at 6.83 ppm, $J = 3.5$ Hz) and H-6 (*dd* at 4.32 ppm, $J = 10.5$, 7 Hz) were essentially identical with H-2, H-3, and H-6 of **1b** from *Solidago arguta* [5]. Signals of C-3, C-4, and C-19, C-6 were located at 133.3, 135.9, 169.5, and 84.8 ppm, respectively. Spin-decoupling experiments permitted identification of H-7a and H-7b as two multiplets at 1.92 and 1.32 ppm, each being coupled to a multiplet at 1.52 ppm (H-8) which was in turn responsible for splitting the signal of H-17 at 0.85 ppm.



A



$$-\underset{2}{CH_2}-\underset{3}{CH}=\overset{\blacksquare}{\underset{4}{C}}-\underset{19}{C}(=O)-O-\overset{\blacksquare}{\underset{6}{CH}}-\underset{7}{CH_2}-\overset{\blacksquare}{\underset{8}{CH}}-\underset{17}{CH_3}$$

B

■ indicates quaternary carbon

Two methyl singlets at 1.26 and 0.77 ppm and consideration of the ^{13}C-NMR spectrum which exhibited upfield methylene triplets (including those of C-2 and C-7) at 22.0, 24.5, 30.5, 34.7 and 35.0 ppm, two upfield methine doublets at 32.0 (C-8) and 41.4 (C-10) and two quaternary carbons at 30.0 and 30.4 (C-5 and C-9), as well as three quartets at 15.2, 16.2, and 17.6 ppm completed the argument leading to gross structure **1a**, which was supported by the appearance in the high resolution MS of important peaks at *m/e* 219 ($C_{14}H_{19}O_2$) corresponding to loss of the six carbon side chain and 111 ($C_6H_7O_2$) corresponding to the side chain itself.

Because of the coincidence of the relevant NMR signals with those exhibited by **1b** whose structure has been established by X-ray crystallography [6], we deduced that the new dilactone was the *ent-cis*-clerodane **1a**. Several attempts to correlate **1a** and **1b** by reduction of **1a** with $(iso\text{-}Bu)_2AlH$ to a diol previously [5] obtained from **1b** resulted in mixtures which could not be separated satisfactorily; however, a solvent shift study of the two substances (Table 2) showed that $\Delta\delta$s for H-3, H-6, and H-18 were essentially identical. Since the somewhat larger differences in $\Delta\delta$ for H-17 and H-20 are easily attributable to the proximity of these protons to the lactone and furanoid side chains of **1a** and **1b** respectively, we conclude that the relative stereochemistry of the two substances is indeed the same. The absolute stereochemistry as depicted is consonant with the strongly negative Cotton effect ($[\theta]_{250}$ −23 900).

A second substance **2**, mp 229–230°, $C_{20}H_{28}O_5$ (high resolution MS) which was isolated in very small amounts only differed from **1a** in possessing a saturated γ-lactone function in the side chain (MS and NMR, see Table 1) and an extra hydroxyl group (IR) which was located on C-2 (*m* at 4.63 ppm which was spin coupled to H-3 and to signals at 2.26 and 1.91 ppm—H-1 a, b). The similarity of chemical shifts and coupling constants where appropriate (Table 1) shows that the stereochemistry of **2** corresponds to that of **1a** as does its absolute configuration ($[\theta]_{250}$ −6500). The magnitude of the coupling constants involving H-2 requires that the hydroxyl group on C-2 be

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§To whom inquiries concerning this article should be addressed.

Table 1. 270 MHz NMR spectra of compounds **1a** and **2***

	1a	**2**
H-1	†	2.26 *m* 1.91 *m*
H-2	2.35 *m*‡	4.63 *ddd* ($J_{1a,2} = 9$, $J_{1b,2} = 6$)
H-3	6.83 *t* (3.5)	6.79 *d* (3)
H-6	4.32 *dd* (10.5, 7)	4.25 (10.5, 7.5)
H-7a	1.97 *m*	1.91 *m*
7b	1.32 *m*	1.34 *m*
H-8	1.52 *m*	1.34
H-10	†	1.91 *m*
H-11	†	†
H-12	†	†
H-13	—	2.44 *m*
H-14	5.84 m	2.64 *dd* (16.6, 8) 2.16 (16.6, 8)
H-16	4.75 *d* (1.5)‡	4.40 *dd* (9, 6) 3.90 *dd* (9, 6)
H-17§	0.85 *d* (6.5)	0.80 *d* (6.5)
H-18§	1.26	1.27
H-20§	0.77	0.69

* Run in $CDCl_3$. Chemical shifts in ppm. Coupling constants in hertz. Unmarked signals are singlets.

† Obscured signal.

‡ Intensity two protons.

§ Intensity three protons.

Table 2. Solvent shifts of compounds **1a** and **1b***

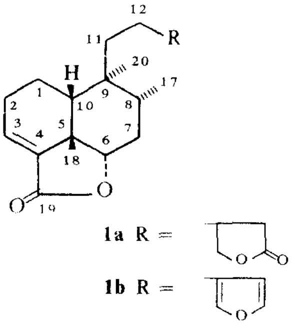
	$CDCl_3$		C_6D_6		Δδ	
	1a	**1b**	**1a**	**1b**	**1a**	**1b**
H-3	6.83	6.85	6.67	6.65	+0.20	+0.20
H-6	4.32	4.35	3.88	3.87	+0.44	+0.48
H-17	0.85	0.88	0.32	0.49	+0.53	+0.39
H-18	1.26	1.27	0.93	0.94	+0.33	+0.34
H-20	0.77	0.74†	0.25	0.34	+0.52	+0.40

* Run at 270 MHz. Values in ppm.

† This value differed significantly from the value of 0.59 ppm given in ref. [5].

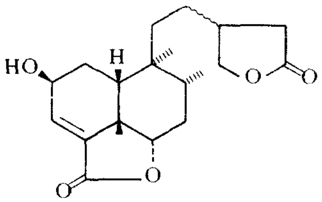
In all other respects the spectrum was the same as that reported by McCrindle *et al.* [5].

quasiequatorial. Its configuration depends on the conformation of ring A; if the latter is a half-chair, the hydroxyl group must be β, if a half-boat, α. While inspection of the models does not permit a facile choice between the two possibilities, the crystal structure of **1b** [6] indicates a half-chair conformation for ring A of **1b** in the solid state and presumably therefore also for ring A of **2**. Consequently, the hydroxyl group of **2** should be β, subject to the proviso that the conformations in solution and in the solid state are the same.



1a R =

1b R =



EXPERIMENTAL

Aerial parts of *Symphiopappus itatiayensis* (Hieron.) King & Robinson (5.2 kg) collected by Dr. Hermogenes de Freitas Leitão Filho in Campos do Jordão (Pico de Itapeva), São Paulo State, Brazil in March 1974 were extracted with hexane–EtOAc (10:1), giving 129 g of extract which was worked up in the usual manner. The crude gum (30 g) was chromatographed over 270 g Si gel. 250 ml fractions were eluted in the following order: 1–7 (hexane), 8–12 (hexane–EtOAc, 20:1), 13–15 (hexane–EtOAc, 10:1), 16–17 (5:1), 18–50 (3.3:1), 51–55 (2:1), 56–60 (1.4:1), 61–64 (EtOAc), 65–66 (EtOAc–EtOH, 21:1), 67–78 (EtOAc–EtOH, 10:1), 79–84 (3.3:1), 85–87 (2:1), 83–93 (EtOH). Fractions 41 and 42 contained 0.3 g of crude **1a** which was purified by TLC (Si gel PF 254–366; EtOAc–C_6H_6, 1:3), mp 150°, IR ν_{max}^{KBr} cm^{-1}: 1780 (weak), 1750 (very strong), 1695 (weak) and 1640, $[\alpha]_D$ 9.62° (c 0.97, $CHCl_3$), CD curve $[\theta]_{250}^{CHCl_3}$ −23900, UV λ_{max}^{MeOH} 216 nm (ε 10300), significant peaks in the high resolution MS at *m/e* (rel. int.) 330 (M^+), 315 ($M^+ - CH_3$, 16.9), 297 ($M^+ - CH_3 - H_2O$, 13.5), 219 ($C_{14}H_{19}O_2$, 25.3), 111 ($C_6H_7O_2$, 24.9). (Calc. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93; O, 19.37; MW, 330.1830. Found: C, 72.27; H, 7.89; O, 20.02%; MW (MS), 330.1845).

Fraction 58 contains 12 mg of solid which gave after purification by TLC (hexane–EtOAc, 3:1) and elution of the major spot with $CHCl_3$–MeOH (50:1) 7 mg of **2**, mp 229–230°, IR ν_{max}^{KBr} cm^{-1}: 3520, 1760 (very strong, sh at 1720, and 1630, CD curve $[\theta]_{256}$ −6500, UV λ_{max}^{MeOH} 213 nm (ε 7700) significant peaks in the high resolutions MS at *m/e* (rel. int.) 348 (M^+, 0.5) 333 ($M^+ - CH_3$, 100), 315 ($M^+ - CH_3 - H_2O$, 77.5). (Calc for $C_{20}H_{28}O_5$: MW, 348.1935: Found: MW (MS), 348.1956).

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