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CYCLOHEXYL-ETHANOL DERIVATIVES FROM *ISOPLEXIS CHALCANTHA*

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Key Word Index—*Isoplexis chalcantha*; Scrophulariaceae; Digitalis of the Canary Islands; new cyclohexyl-ethanol derivatives.

Abstract—Two new cyclohexyl-ethanol derivatives were obtained as minor components from a chloroform extract of the leaves of *Isoplexis chalcantha*. Their structures were elucidated by spectroscopic methods.

INTRODUCTION

Isoplexis chalcantha [1], from the family Scrophulariaceae, is one of four species comprising the genus *Isoplexis*: *I. sceptrum*, *I. isabeliana*, *I. canariensis* and *I. chalcantha*. These species are also known as Canarian Digitalis, both differences and similarities existing with the classic Digitalis [2] from both the botanical and chemical points of view.

Two hitherto undescribed cyclohexyl-ethanol derivatives, 1-(2-hydroxyethyl)-cyclohexane-1,4α-diol (**2a**) and 1-(2-hydroxyethyl)-cyclohexane-1,4β-diol (**3a**) were isolated from the chloroform extract of the leaves of *I. chalcantha*, after separation of the major components (aglycones and glucosides).

RESULTS AND DISCUSSION

The presence of the salidroside **1** in an ethyl acetate extract of *I. chalcantha* was recently reported [3]. The co-occurrence of **1** and the cyclohexantriols **2a** and **3a** suggest that compounds such as the cyclohexadienone **5**, detected in other Scrophulariaceae [4], may act as precursors of the above-mentioned products and connect them with the metabolism of shikimic, chorismic and prefenic acids, in view of their structural resemblance.

The least polar substance, **2a**, was soluble in methanol and ethanol and slightly soluble in hot chloroform, from which it crystallized as colourless needless, mp 104–106°, without specific rotation. Acetylation under normal conditions yielded a diacetate, **2b**, that could not be crystallized.

The IR spectrum of **2a** shows a broad absorption band (3500–3200 cm^{-1}), typical of alcoholic functions, that does not disappear totally upon acetylation. In its mass spectrum the ion of highest mass appears at m/z 142. However, using chemical ionization, the $[M]^+$ can be observed at m/z 160. The ^{13}C NMR spectrum in acetone-d_6 shows only six signals, three of which correspond to oxygen-bearing carbon atoms and are found at δ59.03 (hydroxymethylene), 67.65 (C-4) and 71.59 (C-1), the remaining three corresponding to methylene groups. The general aspect of the spectrum indicates a symmetric structure as in **2a**. The ^1H NMR spectrum shows a broad signal at δ3.92 that integrates for three protons and which on acetylation unfolds into two signals that now appear at 4.92 ($W_{1/2}$ = 12 Hz), corresponding to one proton, and at 4.24 (t, J = 6.7 Hz), integrating for two protons. These signals correspond to the protons geminal to the secondary alcohol at C-4, and to the hydroxymethylene, respectively. The value of $W_{1/2}$ suggests the α-axial orientation of the hydroxyl. The rest of the signals appear in a broad zone between δ1.0 and 2.0, integrating for a total of 10 protons.

Dehydration of **2b** with thionyl chloride in pyridine at 0° yielded **4** quantitatively. Its NMR spectrum shows the signal corresponding to a single olefinic proton at δ5.33. Compound **3a** is slightly more polar than **2b**. It also crystallizes from chloroform as colourless needles, mp 114–116°. Its spectroscopic data differ very little from those of compound **2a**, a notable difference being the position of the signal for the proton at C-4, δ3.64, that appears with $W_{1/2}$ = 26.8 Hz, indicating a β-axial orientation for the hydroxyl.

EXPERIMENTAL

Mps are uncorr. IR spectra were measured in KBr or $CHCl_3$, NMR spectra in $CDCl_3$ soln unless otherwise stated at 200 MHz with TMS as int. standard. MS were recorded at 70 eV with a source temp. of 200°. CH_4 was used for CIMS. TLC was performed on Ready-Foils (Schleicher & Schüll) with $CHCl_3$–pyridine (3:1) as eluent. CC was carried out on silica gel (Merck, type 60, mesh < 0.063) at 4 atm.

Leaves of *I. chalcantha* (Svent and O'Shanahan), collected in the gardens of the Instituto de Productos Naturales Orgánicos, La Laguna, Tenerife, in June 1983, were dried (1 kg) at room temp. and later extracted in a Soxhlet with solvents of increasing polarity: hexane, $CHCl_3$, Et_2O, EtOAc and MeOH. The $CHCl_3$ extract (18 g), made up principally of glycosidic cardenolides and free genins, was submitted to CC. After separation of the cardenolides, two dark brown spots were detected on TLC with

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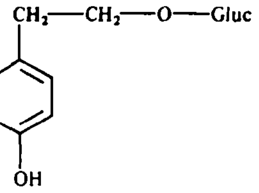

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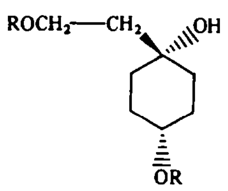
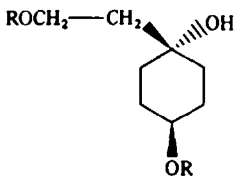


2a R = H
2b R = Ac



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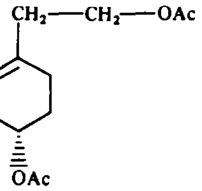
3b R = Ac



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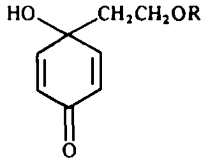

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Table 1. ^{13}C NMR data for compounds **2a**, **2b**, **3a**, **3b** and **4**

Carbon atom	**2a***	**2b**	**3a***	**3b**	**4**
1	71.59	70.27	70.48	69.92	133.87
2	34.24	32.96	36.13	35.26	120.14
3	30.86	26.12	31.52	26.96	27.59
4	67.65	69.98	70.13	72.20	69.64
5	30.86	26.12	31.52	26.96	26.45
6	34.24	32.96	36.13	35.26	30.89
1'	42.68	40.40	44.60	40.72	36.46
2'	59.03	60.85	59.18	60.92	62.89
Ac		21.17		21.19	21.09
		21.47		21.51	21.51
Ac		170.70		170.80	170.90
		171.10		171.10	171.10

*In Me_2CO-d_6.

H_2SO_4, separated in turn by CC using $CHCl_3$–pyridine (6:1), to afford **2a** and **3a**.

1-(2-*Hydroxyethyl*)-*cyclohexane*-1,4α-*diol* (**2a**). Crystallized from hot $CHCl_3$ as needles, mp 105–107°. IR ν_{max}^{KBr} cm^{-1}: 3500–3200, 1430, 1370, 1300, 1030, 1020, 1010, 980 and 960; MS *m/z* (rel int., %) CI (CH_4): 161 $[M-1]^+$, (5); EI, 70 eV: 142.0992 $[M-18]^+$ (6); calc. for $C_8H_{14}O_2$ 142.0993, 115 (37), 102 (85), 97 (100), 84 (43), 83 (42).

1-2(-*Hydroxyethyl*)-*cyclohexane*-1,4β-*diol* (**3a**). Crystallized from hot $CHCl_3$ as needles, mp 118–121°. IR ν_{max}^{KBr} cm^{-1}: 3500–3200, 1450, 1152, 1108, 1045, 1015, 960 and 938; MS *m/z* (rel. int., %) CI (CH_4): 161 $[M-1]^+$ (7); EI, 70 eV: 142.0988 $[M-18]^+$ (7), calc. for $C_8H_{14}O_2$ 142.0993, 125 (5), 115 (22), 102 (100), 97 (75), 84 (38), 83 (35).

Acetylation of **2a** *and* **3a**. Acetylations were carried out with Ac_2O and pyridine at room temp. for 18 hr.

Acetate **2b**. Oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 3450, 1725, 1440, 1365, 1030 and 970; EIMS 70 eV, *m/z* (rel. int., %): 184.1094 $[M-HOAc]^+$ (1.5), calc. for $C_{10}H_{16}O_3$ 184.1099, 157 (12), 142 (5), 124 (100), 97 (90). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ1.83 (2H, *t*, $J = 6.7$ Hz, H-1'), 2.00 (3H, *s*, OMe), 2.02 (3H, *s*, OMe), 4.24 (2H, *t*, $J = 6.7$ Hz, H-2'), 4.92 (1H, *m*, $W_{1/2} = 12$ Hz, H-4).

Acetate **3b**. Oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 3470, 1720, 1445, 1365, 1030 and 950; EIMS 70 eV, *m/z* (rel. int., %): 184.1095 $[M-HOAc]^+$ (1.5) calc. for $C_{10}H_{16}O_3$ 184.1099, 157 (10), 142 (5), 124 (100); ^{1}H NMR (200 MHz, $CDCl_3$): δ1.2–2.0 (10H), 2.01 (3H, *s*, OMe), 2.02 (3H, *s*, OMe), 4.23 (2H, *t*, $J = 6.7$ Hz, H-2'), 4.66 (1H, *m*, $W_{1/2} = 26.8$ Hz, H-4).

Dehydration of **2b**. To **2b** (10 mg) dissolved in pyridine (1 ml) and cooled to 0° were added several drops of a 1:1 soln of $SOCl_2$ and pyridine. After 1 hr the mixture was poured onto ice and H_2O and extracted × 3 with EtOAc. The combined organic extracts were washed with HCl and $NaHCO_3$ soln, dried (Na_2SO_4) and concd *in vacuo* to afford **4** (7 mg) as an oil that could not be crystallized. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1368 and 1035; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ1.4–2.4 (8H), 2.01 (6H, *s*, OMe), 4.10 (2H, *t*, $J = 6.9$ Hz, H-2'), 4.94 (1H, *m*, $W_{1/2} = 24$ Hz, H-4), 5.33 (1H, *br s*, H-2).

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