Two New Anthraquinones from *Digitalis cariensis*

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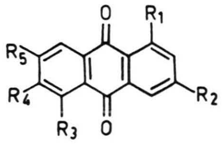
Two new minor anthraquinones, ω-hydroxydigitoemodin (**1**) and ω-hydroxyziganein-1-methyl ether (**4**), have been isolated from *Digitalis cariensis.* Their structures were elucidated on the basis of spectral analysis and **1** was also confirmed by synthesis.

Introduction

It is well known that *Digitalis* plants contain anthraquinone and flavanoid pigments. In the course of our investigations of pigments from *Digitalis* species growing wild in Turkey we have isolated several new minor anthraquinones (Thomson, 1971, 1987) and some known flavanoids (Imre *et al.,* 1984). We examined an uninvestigated species, *Digitalis cariensis* Jaup. *et* Spach and have isolated two new anthraquinones ω-hydroxydigitoemodin (**1**) and ω-hydroxyziganein-1-methyl ether (**4**).



	R_1	R_2	R_3	R_4	R_5
1	OH	CH_2OH	H	OH	H
2	OH	CH_3	H	OH	H
3	OH	CH_3	H	H	OH
4	OCH_3	CH_2OH	OH	H	H
5	OH	CH_2OH	OH	H	H

Results and Discussion

From the EtOH extract of the roots of *D. cariensis* we have isolated the pigments **1** and **4** in very low yields by extensive column chromatography and preparative TLC. Compound **1** has the molecular formula of $C_{15}H_{10}O_5$ obtained by HREIMS. Its IR spectrum showed a free (1655 cm^{-1}) and a hydrogen-bonded (1628 cm^{-1}) carbonyl absorption and ^1H NMR spectrum indicated the presence of a *peri*-OH (δ 12.83) and a $-CH_2OH$ (δ 4.79, 2 H) group and five aromatic protons (δ 7.33–8.24, 5 H). The assignment of the aromatic protons by spin decoupling experiment led us to assume that **1** must be 1,6-dihydroxy-3-hydroxymethylanthraquinone. To confirm this structure by synthesis we first prepared digitoemodin (**2**) from 4-hydroxyphthalic anhydride and *m*-cresol (Imre and Ersoy, 1978) and separated it by preparative TLC from wrong isomer **3** and obtained **2** in poor yield. Then we converted **2** by the usual way (Imre and Ersoy, 1973) into its ω-hydroxy derivative and obtained the desired compound in minute amount by preparative TLC. Direct comparison (m.p., TLC, UV, IR) with the natural compound confirmed the structure proposed for **1.** We have also isolated compound **1** from anthraquinone containing clean-up residues, which were obtained during the isolation of cardiac glycosides from the EtOH extract of *D. cariensis* leaves (Imre and Yurdun, 1987).

Compound **4,** $C_{16}H_{12}O_5$ exhibited a molecular ion peak at *m/z* 284 as base peak in the EIMS. The IR spectrum has a free (1660 cm^{-1}) and a hydrogen-bonded (1640 cm^{-1}) carbonyl absorption. The ^1H NMR spectrum indicated that **4** contains a *peri*-OH (δ 12.29), a $-CH_2OH$ (δ 4.67, 2 H; 5.47, 1 H) and a $-OMe$ (δ 3.96, 3 H) group and five aromatic protons (δ 7.30–7.87, 5 H). Thus **4** is an α-hydroxy-methoxy-hydroxymethylanthraquinone.
The demethylation of **4** afforded an anthraquinone **5** which contains in its IR spectrum only a hydrogen-bonded carbonyl absorption (1622 cm^{-1}). A direct comparison (m.p., TLC, UV, IR) with an authentic sample showed that **5** was identical with ω-hydroxyziganein (Imre *et al.,* 1976). Therefore, compound **4** is a monomethyl ether of ω-hydroxyziganein. Irradiating the methoxy group at δ 3.96 in DNOE spectrum (in $CDCl_3$) caused only a great enhancement of the H-2 singlet at δ 7.45. Thus compound **4** must be ω-hydroxyziganein-1-

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methyl ether. With the isolation of these two new pigments the number of *Digitalis* anthraquinones increased to 33.

Experimental

General procedure

Melting points were determined on a melting point microscope (Reichert) and are uncorrected. The IR and UV spectra were recorded on Perkin-Elmer 577 and Shimadzu 160 A spectrophotometer respectively. Mass spectra were taken at 70 eV on AEI MS 30 and Kratos MS 50. ^{1}H NMR and DNOE spectra were recorded on 200 MHz Bruker and 400 MHz JOEL apparatus respectively. Silica gel Merck (0.063–0.200 mm) and Ultramid B 12 were used for column chromatography. Solvent systems for silica gel both analytical (pre-coated silica gel 60, Merck) and preparative (silica gel G, Merck) TLC: petroleum ether–EtOAc–HOAc (75:24:1) and for polyamide TLC (pre-coated, Merck): MeOH.

Plant material

The roots and leaves of *Digitalis cariensis* were collected in Karabelköy near Fethiye, southwest Turkey. A voucher specimen is deposited at the herbarium of Faculty of Pharmacy, University of Istanbul (ISTE 40185).

Isolation of **1** *and* **4**

The coarsely powdered roots (2.2 kg) were exhaustively percolated with 96% EtOH. After removal of the solvent, H_2O (1 l) was added and extracted with Et_2O. The residue of the Et_2O extract was chromatographed on silica gel column ($CHCl_3$ containing increasing amounts of MeOH) and 91×40 ml fractions were collected. The pure compound **1** and the impure compound **4** were obtained from the fractions 49–51 ($CHCl_3$–MeOH, 3:1) and 69–91 ($CHCl_3$–MeOH, 1:1) by preparative silica gel TLC respectively. **4** was obtained in pure state by repeated polyamide column chromatography.

ω-Hydroxydigitoemodin (**1**)

Red needles (from MeOH, 8 mg), m.p. 273–275 °C, UV λ_{max} (MeOH) (log ε) 220 (4.00), 269 (3.84), 409 (3.21) nm; IR ν_{max} (KBr) 1655, 1628 cm^{-1}; ^{1}H NMR [$(CD_3)_2CO$] δ 12.83 (1 H, br s, 1-OH), 8.24 (1 H, d, 8.5 Hz, 8-H), 7.78 (1 H, d, 1.5 Hz, 4-H), 7.64 (1 H, d, 2.3 Hz, 5-H), 7.33 (1 H, dd, 8.5, 2.8 Hz, H-7), 7.33 (1 H, d, 1.5 Hz, 2-H), 4.79 (2 H, s, $-CH_2OH$); EIMS *m/z* (rel. int.) $[M]^+$ 270.0527 (100) [$C_{15}H_{10}O_5$, calcd. 270.0528], 254 (8), 241 (86), 225 (9), 213 (13), 197 (8), 168 (7), 155 (8), 139 (10), 121 (13).

Synthesis of **1**

4-Hydroxyphthalic anhydride (200 mg) and *m*-cresol (0.35 ml) were condensed in a melt of $AlCl_3$ (6 g) and NaCl (1 g) at 180 °C and 30 mg digitoemodin (**2**) were isolated from the reaction mixture. After acetylation we converted **2** acetate (22 mg) into its ω-hydroxy derivative as described in Imre and Ersoy (1973). We obtained from the reaction mixture 5 mg **1** by preparative silica gel TLC. Synthetic **1** was identical with the natural compound (m.p., TLC, UV, IR).

ω-Hydroxyziganein-1-methyl ether (**4**)

Red needles (from MeOH, 3 mg), m.p. 223–225 °C; UV λ_{max} (MeOH) (log ε) 224 (4.14), 254 (3.78), 2.85 sh (3.59), 405 (3.35) nm; IR ν_{max} (KBr) 1660, 1640 cm^{-1}; ^{1}H NMR (DMSO) δ 12.29 (1 H, s, 5-OH), 7.87 (1 H, s, 4-H), 7.78 (1 H, t, 7.7, 7.8 Hz, H-7), 7.63 (1 H, d, 7.4 Hz, 8-H), 7.54 (1 H, s, 2-H), 7.30 (1 H, d, 8.1 Hz, 6-H), 5.48 (1 H, t, 5.9, 5.4 Hz, $-CH_2OH$), 4.67 (2 H, d, 5.7 Hz, $-CH_2OH$), 3.96 (3 H, s, $-OCH_3$); EIMS *m/z* (rel. int.) $[M]^+$ 284 (100), 267 (35), 255 (28), 237 (24), 225 (67), 209 (22), 197 (20), 181 (20), 168 (11), 152 (22), 139 (27).

Demethylation of **4**

Compound **4** (2 mg) was demethylated with $AlCl_3$ in hot C_6H_6 (5 ml) to give ω-hydroxyziganein, red needles, m.p. 233–235 °C (Imre *et al.*, 1976; 232–234 °C). TLC, UV and IR comparison with an authentic sample confirmed the identity.

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