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BIOGENETIC-TYPE SYNTHESIS OF VULGARIN AND PEROXYVULGARIN

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Key Word Index—*Artemisia abyssinica*; Compositae; vulgarin; peroxyvulgarin; photo-oxygenation; biogenetic; 1-oxo-5αH,6,11βH-eudesm-3-en-6,12-olide.

Abstract—The eudesmanolides vulgarin and peroxyvulgarin were obtained via a biogenetic-type route that involved photo-oxygenation of 1-oxo-5αH,6,11βH-eudesm-3-en-6,12-olide. The α-face singlet oxygen ($^1O_2$) attack resulted in the production of peroxyvulgarin as the major product. Stannous chloride reduction of that compound readily yielded vulgarin. These two compounds, vulgarin and peroxyvulgarin, were isolated from *Artemisia abyssinica*.

INTRODUCTION

In earlier reports, biogenetic-type syntheses of santonin, chrysanolide, dihydrochrysanolide, tulirinol, arbusculin-C, tanacetin, artemin [1] and artemisinin [2] were described. In all cases, $^1O_2$-produced hydroperoxides were obtained as intermediates. This paper describes the synthesis of vulgarin and peroxyvulgarin using the same approach, and reports on the presence of both compounds in *Artemisia abyssinica*.

RESULTS AND DISCUSSION

The starting material used for the proposed biogenetic-type synthesis of vulgarin (**1**) and its peroxy-analogue peroxyvulgarin (**2**) was the β,γ-unsaturated ketone, 1-oxo-5αH,6,11βH-eudesm-3-en-6,12-olide (**3**) [3], as in this type of compound, $^1O_2$ is expected to attack the double bond from its α-face with consequent migration to form the more stable α,β-unsaturated ketone [4]. Therefore, **3**, obtained as previously described [3], was subjected to Methylene Blue sensitized photo-oxygenation. TLC analysis of the product revealed the presence of a major spot, R_f 0.46, corresponding to **2**, and a minor one, R_f 0.28, due to **1**. Flash chromatography [5] yielded **2** in 75% yield, as colourless crystals, $C_{15}H_{20}O_5$, mp 170–171° and $[\alpha]_D$ −44° (MeOH; *c* 0.1).

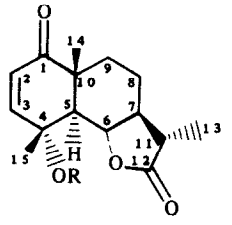
The identity of **2** was readily established from its spectral data (see Experimental), and its ^{13}C NMR assignments (Table 1) were in agreement with its structure. This compound appears to be identical with a hydroperoxide isolated from *A. judaica* [6], but was incompletely characterized (no spectral data except ^1H NMR and no physical constants). The ^1H NMR assignments reported for that compound generally agreed with those of **2**, except those for H-8a and H-9a, which were reversed. The HETCOR data for **2** clearly supported our assignments, which are listed in Experimental. Also vulgarin (**1**) was reported to be less polar than **2** upon TLC on silica gel G plates; however, in our hands, it was found to be the other way around. The minor product from the photo-oxygenation reaction was characterized as vulgarin (**1**) by direct comparison. Furthermore, it could be readily obtained from **2** by reduction with stannous chloride [1].

Table 1. ^{13}C NMR data for peroxyvulgarin (**2**)

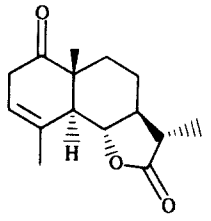
C	1
1	201.8(0)
2	127.6(1)
3	151.0(1)
4	81.3(0)
5	46.9(1)
6	79.1(1)
7	52.2(1)
8	22.6(2)
9	34.2(2)
10	46.9(0)
11	40.7(1)
12	179.7(0)
13	12.4(3)
14	20.5(3)
15	18.3(3)

Numbers in parenthesis refer to the number of attached protons as determined from the DEPTGL experiment. Assignments were based on those reported for α-santonin [13] and vulgarin [6, 14], and were verified by their 2D INADEQUATE spectra.

Vulgarin (**1**) and its peroxy-analogue **2**, now named peroxyvulgarin, were found to occur together in the local plant *A. abyssinica*. They were isolated by partitioning its hexane extract with acetonitrile followed by chromatography of the acetonitrile extract. The isolated compounds were identical to those obtained by photo-oxygenation. It is interesting to note that the ketone **3** could not be detected in the plant material, either by TLC or HPLC. One probable reason for its absence is likely to be



1 R = H
2 R = OH



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its high instability, as it fully decomposed when left in solution for several days, to give the same products as those obtained by dye-sensitized photo-oxygenation.

EXPERIMENTAL

Mps: uncorr; IR: KBr; ^{1}H NMR and ^{13}C NMR 300 and 75 MHz (Varian VXR-300) respectively, $CDCl_3$, TMS as int. standard, standard pulse sequences were used for COSY [7], HETCOR [8], DEPTGL [9] and CCC2DQ 2D-INADEQUATE [10]. TLC was performed on silica gel plates using Et_2O–petrol (9:1) as solvent and visualized under short wavelength UV light or by spraying with anisaldehyde spray reagent [11]. HPLC was performed on a μ-Porasil column using MeCN–CH_2Cl_2 (1:9) as solvent, with a UV detector set at 290 nm. The leaves of *Artemisia abyssinica* were collected in the Riyadh area in the Spring of 1986. The plant was identified locally, and a voucher specimen deposited in the herbarium of the College of Pharmacy, King Saud University. An authentic sample of vulgarin was obtained from Dr M. M. El-Sherei of the Faculty of Pharmacy, Cairo University, Cairo, Egypt.

Photo-oxygenation of 1-*oxo*-5αH,6,11βH-*eudesm*-3-*en*-6,12-*olide* (**3**). Compound **3** (330 mg), prepared as described in ref. [3], was dissolved in 16 ml dry EtOH containing 1.5 mg Methylene Blue. The soln was subjected to 650 W incandescent light while a stream of O_2 was bubbling gently through it, and its temp. was maintained at 25° by cooling. The set-up has been previously described [1]. After 2 hr, TLC showed the disappearance of **3** (R_f 0.79) and the appearance of one major spot (R_f 0.46) and a minor one (R_f 0.28), due to **2** and **1**, respectively. Flash chromatography [5] on silica gel using petrol–Et_2O (1:4) provided the following in the order of elution.

Peroxyvulgarin (**2**), 280 mg, as colourless needles from Me_2CO–Et_2O, mp 170–171°; $[\alpha]_D$ −44° (MeOH; *c* 0.1); UV: λ_{max}^{MeOH} 215 nm (ε 10 000); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200 (OH), 1770 (lactone CO) and 1675 (ketone CO), a KBr pellet showed CO bands at 1770, 1748, 1677 and 1660, apparently due to two different physical forms and not to decomposition (TLC); ^{1}H NMR ($CDCl_3$): δ 5.99 (*d*, *J* = 10.5 Hz, H-2), 6.74 (*d*, *J* = 10.5 Hz, H-3), 2.85 (*d*, *J* = 11.4 Hz, H-5), 4.12 (*dd*, *J* = 11.4, 11.4 Hz, H-6), 1.65 (*m*, H-7), 1.45 (*m*, H-8ax), 2.00 (*m*, H-8eq), 1.55 (*m*, H-9ax), 2.01 (*m*, H-9eq), 2.32 (*dq*, *J* = 6.9, 6.9 Hz, H-11), 1.20 (*d*, *J* = 6.9, C-13 Me), 1.23 (*s*, C-14 Me), 1.46 (*s*, C-15 Me) and 8.95 (*br s*, OOH, D_2O exchangeable but sample decomposed); for ^{13}C NMR ($CDCl_3$) see Table 1; CIMS (isobutane) *m/z*: 281 $[MH]^+$. (Found: C, 64.07; H, 7.07. $C_{15}H_{20}O_5$ (280) requires: C, 64.27; H, 7.19%).

Vulgarin (**1**), 12 mg, as colourless needles from Et_2O–hexane, mp 174–175° $[\alpha]_D$ +37° ($CHCl_3$; *c* 0.1), lit [3, 12]: 174–175° and +48.7°, respectively. The identity was established further by comparison with an authentic sample (same mmp and superimposable MS, IR and NMR spectra).

Reduction of peroxyvulgarin (**2**) *with* $SnCl_2$. Peroxyvulgarin (**2**, 100 mg) was stirred for 5 min in EtOAc (2 ml) with $SnCl_2$ (120 mg). Work-up [1] provided 98 mg of vulgarin (**1**), indistinguishable from a reference sample (same mp, mmp and superimposable IR and NMR spectra).

Isolation of vulgarin (**1**) *and peroxyvulgarin from* A. abyssinica *leaves*. The powdered leaves (1.2 kg) were exhaustively extracted with hexane in a Soxhlet. The solvent was removed and the residue (73 g) was partitioned between MeCN and hexane presaturated with each other. Evapn of the MeCN left 27 g of a yellowish green residue, which was subjected to flash chromatography [5] on silica gel, using petrol–Et_2O (1:4) as solvent to give vulgarin (**1**, 210 mg) and peroxyvulgarin (**2**, 47 mg) indistinguishable from the compounds obtained by photo-oxygenation (same mp, mmp and superimposable IR and NMR spectra).

Compound **3** (TLC R_f, 0.79, HPLC R_t 2.20 min) was detected neither in the hexane nor the MeCN fraction.

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