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New clerodane diterpenoid and flavonol-3-methyl ethers from *Dodonaea viscosa*

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Chromatographic separation of the extract of the aerial parts of *Dodonaea viscosa* L. (family Sapindaceae) afforded β -sitosterol, stigmasterol, the flavone acacetin-7-methyl ether, the flavonol-3-methyl ethers 4',5,7-trihydroxy-3,6-dimethoxyflavone and penduletin, as well as a new clerodane diterpenoid which was identified by spectral means as 15,16-epoxy-5,9-diepicleroda-3,13(16),14-trien-20,19-olide.

1. Introduction

Dodonaea viscosa L. (family Sapindaceae) is an erect up to five meters high, evergreen shrub, widespread in Eastern Australia, parts of Asia, Africa and central America [1]. It can be considered as highland indicator, widespread in Southern Saudi Arabia on altitudes up to 2500 meters above sea level [2].

Two recent reviews [1, 3] summarized the use of *D. viscosa* by indigenous people from various countries as spasmolytic, antimicrobial, febrifuge, anti-inflammatory, cathartic, discutient, anodyne, alterative, tonic, antipruritic, hypotensive and antiviral. Rojas et al. [4] identified four active spasmolytic principles from *D. viscosa*.

These activities in turn appear to correlate with the active constituents isolated previously from *D. viscosa*. Pengelly [3] reported the presence of flavonoids (isorhamnetin, penduletin, quercetin, doviscogenin, sakuranetin, quercetol, hyperin, kaempferol, rutin and cyanidin), saponins (dodanone A, B), triterpenes, resin consisting mainly of bicyclic diterpenes, diterpenoids (hautriwaic acid, ent-labdane furan and ent-clerodane furan), phenols (tannins, shikimic acid and caffeic acid), coumarins, essential oil, fixed oil and β -sitosterol.

Given its lack of toxicity [3] and the widespread availability, *D. viscosa* is one of the most promising herbs for adapting to clinical use.

In this article, we report the isolation of a new clerodane diterpenoid, together with some known compounds from *D. viscosa* that was collected from Saudi Arabia.

2. Investigations, results and discussion

Chromatographic separation of the extract of the aerial parts of *D. viscosa* afforded β -sitosterol and stigmasterol [5], the flavone acacetin-7-methyl ether **2** [6], the flavonol-3-methyl ethers 4',5,7-trihydroxy-3,6-dimethoxyflavone **3** [7] and penduletin **4** [8], as well as a new clerodane diterpenoid **1**. The known compounds were identified by comparing their NMR spectra with literature data. Rojas et al. [4] identified 6-hydroxykaempferol-3,7-dimethyl ether, closely related to compounds **3** and **4**, as an active spasmolytic principle from *D. viscosa*. Compounds **3** and **4** belong to a group of compounds (4'-hydroxy-3-methoxyflavones) known to be potent and specific inhibitors of picornaviral replication [9]. These compounds inhibit the replication of rhinoviruses, the most frequent causative agent of the common cold.

The structure of compound **1** followed from its ^1H NMR spectrum (Table). The typical down-field signals at δ 7.35, 7.20 and 6.25 ppm indicate the presence of a β -substituted

Table: ^1H and ^{13}C NMR data of compound **1** (400 MHz for ^1H and 100 MHz for ^{13}C , CDCl_3)

| Atom No. | δ -value of ^1H , multiplicity (J Hz) | δ -value of ^{13}C , multiplicity* |
|----------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------|
| 1 | α , 1.63, <i>m</i> β , 1.71, <i>m</i> | 38.49 <i>t</i> |
| 2 | α , 2.44, <i>m</i> β , 2.30, <i>m</i> | 18.26 <i>t</i> |
| 3 | 6.76 <i>t</i> (3.6) | 139.56 <i>d</i> |
| 4 | — | 128.84 <i>s</i> |
| 5 | — | 41.93 <i>s</i> |
| 6 | α , 2.13, <i>ddd</i> (5.6, 12.3, 12.3) β , 1.18, <i>ddd</i> (5.4, 12.3, 12.3) | 31.22 <i>t</i> |
| 7 | α , 1.41, <i>m</i> β , 1.46, <i>m</i> | 26.69 <i>t</i> |
| 8 | 1.60, <i>m</i> | 36.19 <i>d</i> |
| 9 | — | 38.75 <i>s</i> |
| 10 | 1.57, <i>m</i> | 46.27 <i>d</i> |
| 11 | 1.72, <i>m</i> , 1.56 <i>m</i> | 16.97 <i>t</i> |
| 12 | 2.38, <i>m</i> , 2.28 <i>m</i> | 26.76 <i>t</i> |
| 13 | — | 125.23 <i>s</i> |
| 14 | 6.25, <i>br s</i> | 110.92 <i>d</i> |
| 15 | 7.35, <i>br s</i> | 142.82 <i>d</i> |
| 16 | 7.20, <i>br s</i> | 138.42 <i>d</i> |
| 17 | 0.85 <i>d</i> (6.7) | 18.61 <i>q</i> |
| 18 | 0.75, <i>s</i> | 15.85 <i>q</i> |
| 19 | 4.21, <i>d</i> (10.1), 3.77, <i>d</i> (10.1) | 65.88 <i>t</i> |
| 20 | — | 171.36 <i>s</i> |

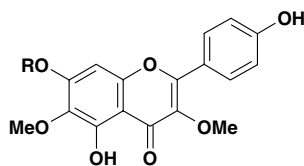
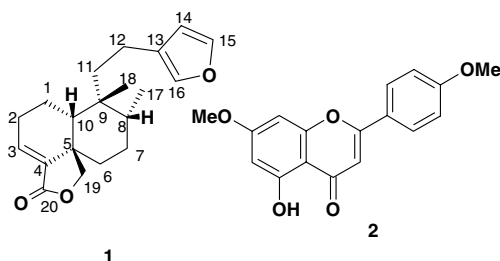
* multiplicity was concluded from DEPT 90 and DEPT 135 experiments

furan [10]. The presence of two doublets with geminal coupling of 10.1 Hz at δ 4.21 and 3.77 ppm is in agreement with a γ -lactone group in a clerodan-20,19-olide [10, 11]. The ^{13}C NMR and DEPT spectra (Table) indicate the presence of two methyl-, seven methylene, six methine and five quaternary carbons. This supported the presence of C_{20} diterpenoid. Considering two O atoms in the lactone function and one in the furan ring, thus the molecular formula $\text{C}_{20}\text{H}_{26}\text{O}_3$ could be deduced. Consistently, a molecular ion peak M^+ at m/z 314 was observed in the MS (Experimental). The molecular formula indicated the presence of eight degrees of unsaturation, hence a third double bond should be present. It was located at C-3 on the basis of a triplet at δ 6.76 in the ^1H NMR as well as a methine and a quaternary carbon at δ 139.56 and 128.84 respectively in the ^{13}C NMR. NMR data were assigned on the basis of H,H-COSY, H,C-COSY and HMBC experiments.

Comparison of NMR data with those of closely related clerodane derivatives isolated by Bohlmann et al. from *Baccharis* species [11] and from *Conyza podocephala*

[10] revealed some differences in coupling constant values and chemical shifts of both H and C, specially in ring A and in the lactone ring, indicating the *cis* fusion between rings A and B instead of the *trans* fusion. A NOESY experiment showed NOE effects between H-19 and H-18 as well as H-10, indicating the presence of a 5,9-diepiclerodane. No effects were observed between H-17 and H-18. On the other hand, there was an NOE effect between H-17 and H-11. Thus **1** was identified as 15,16-epoxy-5,9-diepicleroda-3,13(16),14-trien-20,19-olide. However, this formula does not imply the absolute stereochemistry of **1**.

Although the majority of clerodane diterpenoids having 5 α , 8 α , 9 α , 10 β configuration [12], there are few with A-B *cis* fusion [13] and some are epimers at C-5 and C-9 [14].



3; R = H

4; R = Me

3. Experimental

3.1. General

GC/MS spectra were taken on a QP-7000 Shimadzu, with fused silica capillary column (30 m \times 0.25 mm ID), film (5% phenyl, 95% methylsilicon) thickness 0.25 μ m, and the output of an IBM computer with software Class 500 and NIST library for comparison; NMR spectra were recorded on Bruker FT-400 MHz; IR spectra were taken on a Nicolet Magenta 550 FT IR spectrometer.

3.2. Plant material

Dodonaea viscosa L. (Sapindaceae) was collected in October 1999 from AtTaief-AlBaha road 30 km apart from AlTaief, K.S.A., and identified by Prof. Dr. Abdulaziz Faied, Botany Department, Faculty of Science, King Abdulaziz University. A voucher specimen was deposited at the Herbarium of King Abdulaziz University.

3.3. Processing of the plant material

The dried, grinded aerial parts (1500 g) of *D. viscosa* were extracted by soaking at RT in petrol-Et₂O-MeOH (1:1:1) for 24 h. The crude extract (60.5 g) was defatted using cold MeOH.

3.4. Separation of the compounds

The defatted extract (41.7 g) was separated by CC on silica gel into four fractions. Fraction I (12.1 g, eluted with petrol-Et₂O, 3:1) was re-separated on flash silica gel CC into 13 subfractions. Subfractions 1–12 (eluted with petrol-Et₂O, 4:1) contained fat. Subfraction 13 (eluted with petrol-Et₂O, 3:1) gave the flavone **2** (1.2 g). Fraction II (8.3 g, eluted with petrol-Et₂O, 1:1) was further separated on flash silica gel CC into 8 subfractions. Subfraction 1 (eluted with petrol-Et₂O, 3:2) gave a mixture of β -sitosterol and stigmasterol (0.7 g, 6:1). Subfraction 5 gave the flavone **4** (2.3 g). Fraction III (9.4 g, eluted by Et₂O) gave by flash CC (silica gel, petrol-Et₂O, 1:4) six subfractions. Subfraction 1 (2.8 g) contained mainly the diterpenoid **1**, which was purified by TLC (silica gel, petrol-Et₂O, 1:9) to give **1** at R_f 0.38 (yield 92.8%). Subfraction 4 (3.4 g) gave by TLC, 20 mg of which, (silica gel, petrol-Et₂O, 1:9) **4** (6 mg, R_f 0.66) and **3** (8 mg, R_f 0.63). Fraction IV (5.2 g, eluted with Et₂O-MeOH, 9:1) contained a complex mixture of flavonoids and fat.

3.5. 15,16-Epoxy-5,9-diepicleroda-3,13(16),14-trien-20,19-olide (**1**)

White foamy solid; IR, $\nu_{\text{max}}^{\text{CHCl}_3}$, cm⁻¹: 2960.5, 2873.5 (str. CH₃, CH₂, CH), 1732.2 (γ -lactone), 1608.0 (C=C), 1470.4, 1365.3, 1280.7, 1215.5, 1175.9, 756.3; ¹H NMR: (Table); ¹³C NMR: (Table); MS, m/z (rel. int.): 314 [M]⁺ (7.8) (corresponding to C₂₀H₂₆O₃), 220 (14.1), 189 (9.4), 149 (12.5), 95 (100), 81 (53.1), 53 (48.4); [α]_D = -2 (CHCl₃, c = 1.4).

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