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ANGUSTIFOLIN, A COUMARIN FROM *RUTA ANGUSTIFOLIA*

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Key Word Index—*Ruta angustifolia*; Rutaceae; coumarins; angustifolin; scoparone; 6,7,8-trimethoxycoumarin; alkaloid; graveolin

Abstract—From the aerial parts of *Ruta angustifolia*, a new natural coumarin, angustifolin, was obtained. Two other coumarins (scoparone and 6,7,8-trimethoxycoumarin) and the alkaloid graveolin were also isolated.

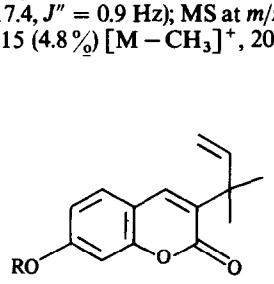
From the chloroform extract of 2.1 kg of aerial parts of *Ruta angustifolia* Pers., collected in San Agustín de Guadalix, Madrid province, Spain, a new natural coumarin, angustifolin (**1**) has been isolated. This coumarin was found in a very small amounts (about 15 mg and it could not be crystallized) together with the alkaloid graveolin (**2**) and the two coumarins scoparone (**3**) and 6,7,8-trimethoxycoumarin (**4**), from which it was separated by flash chromatography.

Angustifolin shows blue fluorescence in UV light; it absorbs at λ_{max}^{EtOH} nm (ε): 325 (4.01), 297 (h, 3.83), 269 (3.64) and 258 (h, 3.66); IR ν_{max}^{KBr} cm^{-1}: 3400, 1740, 1630; ^{1}H NMR ($CDCl_3$): δ7.53 (*s*, H, β-coumarin proton), aromatic protons H-5, H-8 and H-6 at 7.30 (*d*, H, J = 7 Hz), 6.94 (*d*, H, J = 2 Hz) and 6.80 (*dd*, H, J = 7, J' = 2 Hz) respectively, and 1.47 (*s*, 6H, gem-dimethyl), vinylic group signals at 6.15 (*dd*, H, J = 17.4, J' = 10.5 Hz), 5.09 (*dd*, H, J' = 10.5, J'' = 0.9) and 5.08 (*dd*, H, J = 17.4, J'' = 0.9 Hz); MS at *m/z* (rel. int.): 230 (3.7%) $[M]^+$, 215 (4.8%) $[M-CH_3]^+$, 202 (8.8%) $[M-CO]^+$ and 161 (5.1%) $[M-CMe_2\ CH{=}CH_2]^+$.

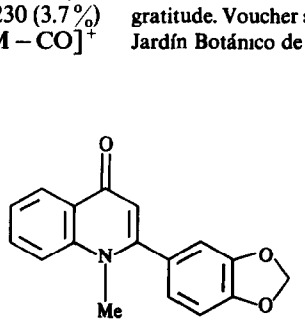
These data suggest that angustifolin must be 3-(1′,1′-dimethylallyl)-7-hydroxycoumarin (**1**), which possibly has been produced in the plant from 7-(3′,3′-dimethylallyloxy)-coumarin through a multiple rearrangement. The structure was confirmed by treatment of **1** with Me_2SO_4–K_2CO_3–Me_2CO, yielding **5**, a substance obtained before from *Ruta graveolens* roots [1] and later synthesized [2]. Compound **5** was identified by its ^{1}H NMR spectrum.

EXPERIMENTAL

Material was collected by the authors during the plant's flowering season, in June, 1982. The plant was classified by Dr J Fernández Casas, of the Departamento de Botánica, Universidad Autónoma de Madrid, to whom the authors express their gratitude. Voucher specimens were deposited in the Herbario del Jardín Botánico de Madrid, where they are classified with n° of



1 R = H
5 R = Me



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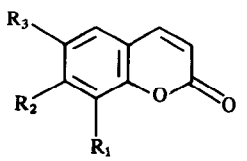

3 R_1 = H, R_2 = R_3 = OMe
4 R_1 = R_2 = R_3 = OMe

M.A 243201.

The ABX system of the vinyl in **1** was solved with help of LAOCON III program. The ^{1}H NMR signals of **5** were: δ7.53 (*s*, H), 7.34 (*dd*, H, J = 8.9, J' = 1 Hz), 6.84–6.79 (*m*, 2H), 6.15 (*dd*, H, J = 10.5, J' = 17.4 Hz), 5.08 (*dd*, H, J = 10.5, J'' = 0.9 Hz), 5.07 (*dd*, H, J' = 17 4, J'' = 0 9 Hz), 3 86 (*s*, 3H) and 1 84 (*s*, 6H).

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METHYL *p*-COUMARATE: A CYTOTOXIC CONSTITUENT FROM *COMPTONIA PEREGRINA*

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Key Word Index—*Comptonia peregrina*, Myricaceae; sweet fern; cytotoxicity, toxicology; methyl *p*-coumarate.

Abstract—Methyl *p*-coumarate has been isolated from the roots and stems of *Comptonia peregrina*, a plant used by North American Indians, settlers and herbalists to treat a variety of skin conditions. Pharmacological testing has proven this compound to be cytotoxic.

INTRODUCTION

Among those screened as part of an ongoing study of medicinal plants used by the Maritime native peoples [1, 2] was *Comptonia peregrina* (L.) Coult. This shrub, commonly known as sweet fern, grows abundantly in poor soil in eastern North America. A literature search reveals that the only constituents characterized from this plant are essential oils [3] and flavonoids [4]. Indians of the Canadian Maritimes employed the leaves of *C. peregrina* in the treatment of sprains, swellings, and the inflammation caused by poison ivy [5]. Other North American Indians used this plant for a variety of dermatological problems as did the European settlers, who also used the plant for 'skin cancer' [4, 6]. Locally, a concoction of sweet fern roots has been reported of use against 'psoriasis' and 'eczema'.

RESULTS AND DISCUSSION

A phytochemical screening of *C. peregrina* indicated several components of possible medicinal interest [1, 2]. During the phytochemical analysis methyl *p*-coumarate was isolated in small amounts (< 0.0002%) from the ammonium hydroxide–methanol extract. Identification of the isolated compound was based upon chemical analysis, melting point, IR, ^{1}H NMR and ^{13}C NMR and GC/MS.

p-Coumaric acid, isolated first in 1865 by Hlasiwetz and synthesized in 1918 by Konek, is a well known and widely distributed plant constituent [7]. Methyl *p*-coumarate, however, has been reported only rarely as a natural product [8, 9] and there are few studies on biological effects. Among those effects reported are chlorophyll-degrading activity [10], marked inhibition of bacterial growth [11, 12] and possibily, coffee rust self-inhibition [13].

In vitro pharmacological testing of methyl *p*-coumarate against mouse TLX5 lymphoma cells demonstrated a significant inhibitory activity. The LD_{50} dose of the compound was 15 μg/ml. *In vivo* testing against P388 tumor indicated that the compound was inactive at doses of 400 mg/kg or less and toxic at doses of 800 mg/kg and greater. We believe this is the first report of cytotoxicity for this compound. Although nonselective, when administered topically, this compound may well account for the reported success of *C. peregrina* in the treatment of various dermatological problems. This is also the first report of methyl *p*-coumarate in the Myricaceae.

EXPERIMENTAL

C. peregrina was harvested in Nova Scotia in summer and air dried. Leaves were removed and the roots and stems ground in a Wiley mill (mesh size 5 mm) and extracted successively with petrol × 2, $CHCl_3$ × 3 and 10% NH_4OH in MeOH × 3. Methyl *p*-coumarate was obtained from the combined, partially reduced in volume, MeOH extracts by alternately partitioning between acid (HCl) and base (NH_4OH) with $CHCl_3$ as the organic solvent. Final recrystallization was from 5% HCl, mp 136–137° (lit 137° [14]). It was possible to monitor the isolation by GC of the $CHCl_3$ extract [9]. Methyl *p*-coumarate (Found C, 67 4; H, 5.6. Calc. for $C_{10}H_{10}O_3$, C, 67.4, H, 5 7%). EIMS (direct interface) 70 eV, *m/z* 178 $[M]^+$ ($C_{10}H_{10}O_3$), 147 $[M-OMe]^+$ and 119 $[M-CO_2Me]^+$ [15]. Spectra were in agreement with