

## Constituents of Umbelliferous Plants

### XV.\* Coumarins from *Thapsia garganica* L. The Structure of a New Coumarin

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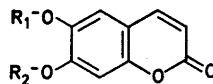
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The roots of *Thapsia garganica* L. var. *sylyphium* (Viv.) Asch. ap. Rohlfs (= *Th. sylyphium* Viv.), a perennial herb distributed in the southern part of the Mediterranean region, afforded a rather complex mixture of yellow- and blue-fluorescent compounds, most of which occurred only in trace amounts. Besides scopoletin (II), which was identified by comparison with an authentic sample, a new coumarin (III) was obtained. From the UV-, <sup>1</sup>H-NMR, and mass spectra (III) appeared to be a di-*O*-alkyl derivative of aesculetin (I), the alkyl groups being methyl and 3,7-dimethyl-2,6-octadienyl. (III) was shown, by synthesis, to be 6-methoxy-7-geranyloxycoumarin. Furthermore, the *cis*-isomer, 6-methoxy-7-neryloxycoumarin (IV), was synthesized.

The isomeric coumarins (III) and collinin (7-geranyloxy-8-methoxycoumarin)<sup>1</sup> are quite similar in their mass spectral fragmentations. Furthermore, the mass spectrum of (III) by comparison with the spectra of auraptene (7-geranyloxy-coumarin) and bergamottin (5-geranyloxy-psoralen) showed the fragmentation expected for a geranyloxycoumarin with other features superimposed by substitution.

Usually an intense M-15 peak provides a ready means of demonstrating the presence of a 6-methoxy substituent in simple coumarins.<sup>3</sup> In the case of (III), however, the M-15 peak was missing. The absence of this ion and the presence of a minimal parent peak seem to be reflections of the facile fragmentation of the allylic aliphatic side chain.<sup>1</sup>

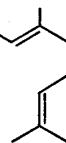
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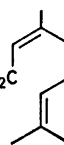
I R<sub>1</sub>=R<sub>2</sub>=-H

II R<sub>1</sub>=-CH<sub>3</sub>, R<sub>2</sub>=-H

III R<sub>1</sub>=-CH<sub>3</sub>, R<sub>2</sub>=-H<sub>2</sub>C



IV R<sub>1</sub>=-CH<sub>3</sub>, R<sub>2</sub>=-H<sub>2</sub>C



The ethanol extract of the roots of *Thapsia garganica* L. var. *sylyphium* caused a strongly itching rash when getting into touch with the human skin. The coumarins, isolated from this extract, were shown not to be responsible for this property. However, a rather polar fraction, bringing about the above mentioned skin eruption in very small concentrations, was isolated. The IR- and <sup>1</sup>H-NMR-spectra showed very complex patterns and demonstrated the non-aromatic nature of this fraction. Further investigations of this fraction by chemical and biological methods are under consideration.

*Experimental.* Melting points were determined as in a previous paper.<sup>4</sup> IR-, UV-, and mass spectra were recorded as earlier described.<sup>5</sup> <sup>1</sup>H-NMR-spectra (CDCl<sub>3</sub>) were measured on a JEOL JNM-C-60HL instrument. Silica gel and silica gel, impregnated with silver nitrate, used in column chromatographic separations, was prepared as earlier described (Ref. 6 and 5, respectively).

*The plant material* was collected in May 1969 in Libya (Cyrenaica peninsula).

*Isolation of 6-methoxy-7-geranyloxycoumarin (III) and scopoletin (II).* The roots were extracted with ethanol and evaporation of the extract afforded an oily residue. The residue (10 g) was extracted repeatedly with methylene chloride, until the residue displayed only a faint fluorescence, when exposed to long-wave UV-light. The combined methylene chloride phase were evaporated, affording 4.0 g of an oily residue, which was chromatographed

on silica gel (200 g). As the eluent was used methylene chloride, to which increasing amounts of ethyl acetate were added. The following fractions were collected.

a. Elution with 1.5–8 % of ethyl acetate in methylene chloride afforded 450 mg of a fraction containing (III). This fraction was rechromatographed twice on silica gel (75 g and 25 g) using tetrachloromethane-methylene chloride-ethyl acetate mixtures and benzene-ethyl acetate mixtures, respectively, as the eluents. 36 mg of (III), m.p. 84.0–84.5° (ether-petroleum ether) were obtained. (Found: C 73.29; H 7.48. Calc. for  $C_{20}H_{24}O_4$ : C 73.14; H 7.37). The IR-, UV-,  $^1H$ -NMR-, and mass spectra were consistent with the structural assignments. Prominent peaks (and the parent peak) in the mass spectrum of (III) (*m/e*): 328 ( $M^+$ , ca. 0.5 %), 193 (22 %), 192 (100 %), 177 (11 %), 164 (5 %), 149 (5 %), 137 (5 %), 136 (8 %), 93 (17 %), 81 (18 %), 69 (83 %), 68 (8 %), 67 (6 %), 55 (6 %), 53 (6 %), and 41 (39 %).

b. Elution with 16–25 % of ethyl acetate in methylene chloride afforded 360 mg of a fraction containing scopoletin (II). Rechromatography two times on silica gel (60 g and 11 g), using benzene-ethyl acetate (4:1), to which increasing amounts of methanol were added, as the eluents, afforded 1 mg of scopoletin (II), m.p. 202.0–203.0° (water) (Ref. 7, m.p. 205°). The IR-spectrum was identical with that of an authentic sample.

c. Finally, elution with methanol afforded 600 mg of a non-fluorescent fraction which was rechromatographed on silica gel (55 g), using benzene-ethyl acetate (4:1), to which increasing amounts of methanol were added, as the eluent. Obtained were 290 mg of a glassy substance, which was homogeneous on silica gel plates [ $R_F$  0.50 (benzene-ethyl acetate-methanol, 15:4:1)]. This fraction caused a vigorous skin eruption when getting into touch with the human skin.

*Synthesis of (III)*. 77 mg of scopoletin (II) were dissolved in 6 ml of dimethylformamide. Potassium carbonate (69 mg) was added to the solution and the mixture stirred for 4 h. Then 3.5 ml of an ether solution of geranyl bromide, prepared as described by Bates *et al.*<sup>8</sup> were added. The mixture was stirred at room temperature for further 17 h. Water (25 ml) was added and the mixture extracted with methylene chloride. Upon evaporation of the solvent an oily residue remained. Chromatography on silica gel (26 g), using benzene-ethyl acetate mixtures as the eluents, afforded 100 mg of (III), m.p. 83.5–84.0° (ether-petroleum ether). Except for a few

differences in the abundance ratios the mass spectra of (III) and natural (III) were identical. The IR-, UV-, and  $^1H$ -NMR-spectra were identical with those of natural (III).

*Synthesis of (IV)*. Coumarin (IV) was synthesized as described above for (III), using 3.5 ml of an ether solution of neryl bromide.<sup>9</sup> Chromatography of the reaction mixture on TLC-plates, using silica gel, impregnated with 3.3 % of silver nitrate and 3.3 % of boric acid, as the adsorbent,<sup>9</sup> revealed the presence of small amounts of an impurity, which cochromatographed with (III). As the eluent was used benzene-ethyl acetate (4:1). Column chromatography on silica gel, impregnated with 5 % of silver nitrate, (67 g), using benzene-ethyl acetate mixtures as the eluents, afforded 58 mg of (IV), m.p. 45.0–46.0° (methanol). (Found: C 73.26; H 7.23. Calc. for  $C_{20}H_{24}O_4$ : C 73.14; H 7.37). IR-,  $^1H$ -NMR-, and mass spectra were consistent with the structural assignments and were shown to be different from those of (III). Prominent peaks (and the parent peak) in the mass spectrum of (IV) (*m/e*): 328 ( $M^+$ , ca. 0.5 %), 193 (28 %), 192 (100 %), 177 (9 %), 137 (10 %), 136 (10 %), 95 (8 %), 93 (9 %), 81 (40 %), 69 (60 %), 68 (5 %), 67 (5 %), 55 (5 %), and 41 (29 %).

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