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PYRANOCOUMARIN DERIVATIVES FROM *SESELI TORTUOSUM**

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Key Word Index—*Seseli tortuosum*; Umbelliferae; coumarins; pyranocoumarins; khellactones; khellactone esters.

Abstract—*Trans*-khellactone, *cis*-khellactone, 3′-senecioyl-*cis*-khellactone, 3′-senecioyl-4′-acetyl-*cis*-khellactone, 4′-senecioyl-*cis*-khellactone, 3′-acetyl-4′-senecioyl-*cis*-khellactone, 3′,4′-di-*iso*valeryl-*cis*-khellactone, 3′,4′-disenecioyl-*cis*-khellactone, 3′-angeloyl-4′-*iso*valeryl-*cis*-khellactone and 3′-*iso*valeryl-4′-angeloyl-*cis*-khellactone were obtained from the aerial part of *Seseli tortuosum*.

INTRODUCTION

In a previous paper [1], the isolation and identification of twelve simple coumarins from an ethanolic extract of the aerial part of *Seseli tortuosum* was reported, as well as a possible biogenetic route accounting for the formation of the different types of coumarins in the genus *Seseli*. From the same ethanolic extract, a number of angular pyranocoumarins closed at C-8 have now been obtained. Compounds of this type have been found in varying amounts in seven of the fifteen *Seseli* species studied before 1976 [2].

RESULTS AND DISCUSSION

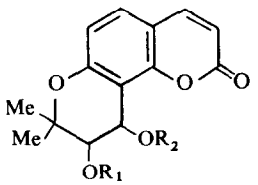
Trans-khellactone (**1**), *cis*-khellactone (**2**), 3′-senecioyl-*cis*-khellactone (**10**), 3′-senecioyl-4′-acetyl-*cis*-khellactone (samidin) (**11**), 4′-senecioyl-*cis*-khellactone (**12**), 3′-acetyl-4′-senecioyl-*cis*-khellactone (**13**), 3′,4′-di-*iso*valeryl-*cis*-khellactone (**16**), 3′,4′-disenecioyl-*cis*-khellactone (**17**), 3′-angeloyl-4′-*iso*valeryl-*cis*-khellactone (**18**) and 3′-*iso*valeryl-4′-angeloyl-*cis*-khellactone (**19**) were obtained from the aerial part of *Seseli tortuosum*. Compounds **10** and **12** have not been reported previously.

When the ether mixture was treated with NaOH diluted in water, *cis*-khellactone (**2**) and *trans*-khellactone (**1**) were separated and when this reaction was repeated using NaOH in methanol, not only was a mixture of *cis*- and *trans*-khellactones obtained, but also *trans*- (**5**) and *cis*- (**7**) 4′-monomethyl-khellactones, *trans*-dimethyl-khellactone (**9**) and a mixture of the hydroxyester methyl derivatives (**14**) and (**15**).

It seems likely that the *cis*-khellactone derivatives occur naturally in the plant while the *trans* derivatives are the result of epimerization at C-4′ during the isolation process or the basic treatment. This phenomenon has been recorded before [3, 4].

The structure of these compounds was determined by comparing their spectral data with those of their acetyl derivatives as it was not possible to purify all the substances to the point where their physical constants could be ascertained. The spectra studied in some cases were of mixtures such as the pairs **14**–**15** and **18**–**19**.

The UV absorptions of these compounds (Table 1) were typical of coumarins with alkyloxy moieties at C-7, the first three bands being practically the same as for 7-alkyloxy-8-alkyl-coumarins [3, 5] although the wavelengths of the fifth band were slightly longer. IR signals at 1745–1710, 1650–1610, 1610–1600 cm^{-1} indicated that these substances were lactones and/or esters. NMR in $CDCl_3$ (Table 2) showed H-3 and H-4 as AB quartets with the coupling constant J_{AB} = 9.6–10.2 Hz. H-4 appeared as a doublet centred between δ 7.68 and 7.58 and H-3 ranged from δ 6.27 to 6.16. H-5 and H-6 were



1 $R_1 = R_2 = H$; *trans*
2 $R_1 = R_2 = H$; *cis*
3 $R_1 = R_2 = COMe$; *cis*
4 $R_1 = R_2 = COMe$; *trans*
5 $R_1 = H$, $R_2 = Me$; *trans*
6 $R_1 = COMe$; $R_2 = Me$; *trans*
7 $R_1 = H$, $R_2 = Me$; *cis*
8 $R_1 = COMe$; $R_2 = Me$; *cis*
9 $R_1 = R_2 = Me$; *trans*
10 $R_1 = COCH{=}C(Me)_2$; $R_2 = H$; *cis*
11 $R_1 = COCH{=}C(Me)_2$; $R_2 = COMe$; *cis*
12 $R_1 = H$; $R_2 = COCH{=}C(Me)_2$; *cis*
13 $R_1 = COMe$; $R_2 = COCH{=}C(Me)_2$; *cis*
14 $R_1 = COC(Me){=}CHMe$; $R_2 = Me$
15 $R_1 = COCH{=}C(Me)_2$; $R_2 = Me$
16 $R_1 = R_2 = COCH_2CH(Me)_2$; *cis*
17 $R_1 = R_2 = COCH{=}C(Me)_2$; *cis*
18 $R_1 = COC(Me){=}CHMe$; $R_2 = COCH_2CH(Me)_2$
19 $R_1 = COCH_2CH(Me)_2$; $R_2 = COC(Me){=}CHMe$

* Part 21 in the series "Constituents of the Umbelliferae". For Part 20 see González, A. G., Barroso, J. T., López-Dorta, H., Luis, J. R. and Rodríguez-Luis, F. (1978) *An. Quim.* **74**, 832.

Table 1. UV absorptions (λ_{max}^{EtOH})

Compound	Band 1	Band 2	Band 3	Band 4	Band 5	Band 6
1	221(sh)	246	260	—	330	348(sh)
2	222(sh)	248(sh)	260	300(inf)	330	350(sh)
3	219(sh)	246(sh)	257	297(inf)	325	—
4	220(sh)	248	259	300(inf)	330	—
5	221(sh)	248	260	—	329	—
6	219(sh)	246	257	300	327	—
7	221(sh)	246	259	—	328	—
8	221(sh)	248(sh)	260	300(inf)	330	—
9	220(sh)	246(sh)	257	—	326	—
10	220(sh)	242(sh)	258	301	327	—
11	216(sh)	246(sh)	256	297(sh)	324	—
12	221(sh)	246(sh)	258(sh)	298(sh)	327	—
13	218(sh)	245(sh)	257	298(sh)	325	—
14/15	220(sh)	247(sh)	258(sh)	299(sh)	329	—

found between δ 7.46 and 7.30, and H-6, between δ 6.68 and 6.76. These values for the coumarin and benzene protons are those proper to khellactone derivatives and to simple coumarins with an alkyl chain at C-8 and an alkyloxy one at C-7 [1, 6, 7].

The relative *trans* configuration of compounds **1**, **4**, **5**, **6** and **9** and the *cis* configuration of **2**, **3**, **7**, **8**, **10**–**13** and **16**–**19** were assigned on the basis of the coupling constant $J_{3',4'}$ which was between 2.4 and 3 Hz for the *trans* compounds (except for khellactone and khellactone diacetate [4] and between 4.1 and 5 Hz for the *cis* compounds. The dihydropropane gem-dimethyl signals generally appear as separate doublets in *trans*, and as a rather broad singlet or two singlets close together in *cis* compounds [4] (Table 3). This latter fact is not, however, particularly conclusive.

The relative stereochemistry of **14** and **15** could not be established because H-3 and H-4 of the mixture appeared as multiplets. Since the gem-dimethyl was shown as a singlet it is likely that both compounds are *cis*[4]. The positions of the alkyl and acyl moieties attached to khellactones were determined from the NMR chemical shifts of H-3′ and H-4′. H-3′ was found between δ 4.46 and 3.78 and H-4′, between δ 5.21 and

Table 2. ^{1}H NMR signals in $CDCl_3$ for coumarinic and aromatic protons

Compound	H-3	H-4	H-5	H-6
1	6.20(9.6)	7.60(9.6)	7.25(8.4)	6.72(8.4)
2	6.24(10.2)	7.66(10.2)	7.46(9)	6.77(9)
3	6.21(10.2)	7.64(10.2)	7.39(9)	6.80(9)
4	6.21(10.2)	7.59(10.2)	7.34(9)	6.80(9)
5	6.20(9.6)	7.58(9.6)	7.30(9.6)	6.77(9.6)
6	6.22(10.2)	7.62(10.2)	7.33(9)	6.76(9)
7	6.22(9.6)	7.62(9.6)	7.30(8.4)	6.73(8.4)
8	6.20(10.2)	7.59(10.2)	7.30(9)	6.72(9)
9	6.25(9.6)	7.62(9.6)	7.35(8.4)	6.78(8.4)
10	6.22(9.6)	7.65(9.6)	7.34(8.4)	6.77(8.4)
11	6.22(10.2)	7.65(10.2)	7.42(9)	6.82(9)
12	6.16(9.6)	7.60(9.6)	7.35(8.4)	6.78(8.4)
13	6.24(9.6)	7.65(9.6)	7.42(8.4)	6.84(8.4)
14/15	6.26(9.6)	7.64(9.6)	7.36(9)	6.80(9)
16	6.22(9.6)	7.62(9.6)	7.38(8.4)	6.81(8.4)
17	6.23(9.6)	7.68(9.6)	7.43(8.4)	6.86(8.4)
18/19	6.23(10.2)	7.61(10.2)	7.38(9.6)	6.82(9.6)

Table 3. ^{1}H NMR signals in $CDCl_3$ for pyranic protons

Compound	H-3′	H-4′	gem-Dimethyl
1	3.78(6)	4.93(6)	1.45 and 1.22
4	5.30(5)	6.52(5)	1.47 and 1.28
5	3.92(3)	4.58(3)	1.48 and 1.43
6	5.21(2.4)	4.45(2.4)	1.51 and 1.49
9	4.46(2.4)	5.21(2.4)	1.45
2	3.84(5)	5.18(5)	1.43
3	5.28(4.2)	6.20(4.2)	1.45 and 1.37
7	3.80(*m*)	4.68(5.4)	1.38
8	5.18(4.2)	4.80(4.2)	1.49 and 1.40
10	5.42(5)	5.16(5)	1.48 and 1.39
11	5.32(5)	6.62(5)	1.47 and 1.42
12	4.05(5)	6.46(5)	1.42
13	5.33(5)	6.62(5)	1.45 and 1.42
14/15	5.38–5.15(*m*)	4.52(*m*)	1.51
16	5.32(5)	6.56(5)	1.42
17	5.39(4.1)	6.66(4.1)	1.51 and 1.47
18	5.39(4.1)	6.66(4.1)	1.44
19	5.32(5)	6.56(5)	1.44

4.93 in khellactones **1** and **2** and in the methyl-khellactones **5**, **7** and **9**. In **12**, H-3′ proved to be vicinal to an ester at δ 4.05. H-4′ was located between δ 5.16 and 4.45 when vicinal to an ester as in **6**, **8**, **10**, **14** and **15**. The shift tended to be smaller when the proton was geminal to an ether rather than to a hydroxyl. H-3′ was geminal to an ester and vicinal to ethers or hydroxyls and had a δ value of between 5.42 and 5.18 in compounds **6**, **8**, **10**, **14** and **15**. If H-3′ was geminal to senecioyl, it was between δ 5.42 and 5.32. Where H-4′ was geminal to an ester and vicinal to a hydroxyl, as in **12**, a senecioyl ester, its observed value was δ 6.46. Lastly, when H-3′ and H-4′ were geminal and vicinal to esters or khellactone diesters, their values were in the range 5.32–5.28 for H-3′ and 6.66–6.20 for H-4′.

The angeloyl, methyl, senecioyl, *iso*valeryl and acetate moieties attached to the khellactones were identified by NMR, the spectra coinciding with those already reported [4, 7, 8].

MS of **16** and **17** revealed the formation of the coumarinopyrilium ion showing that these compounds could not be angular dihydrofurocoumarins or derivatives [9, 10].

The khellactone derivative content of *Seseli tortuosum* was similar to that of *S. libanotis* [4, 9] and, even more, to that of *S. gummiferum* which yielded not only khellactone diesters, but also a complex mixture of *cis*-khellactone monoesters and angelic, senecioic and *iso*valeric acid which could not be studied [8].

EXPERIMENTAL

Mps were taken on a Kofler block and are uncorr. The ^{1}H NMR chemical shifts are expressed in terms of δ with TMS as internal reference. The coupling constants are given in Hz. MS were determined at 70 eV. Chromatography was carried out using Merck Si gel.

Extraction and separation of products. 13.625 kg of the dried aerial part of *Seseli tortuosum* LBS Eur. was gathered in Adanero (Avila, Spain) in September 1970 and a further 13.545 kg in Riaza (Segovia, Spain) in September 1971. This material was extracted and treated as described [1]. Preparative column and TLC gave the following: 15 mg *trans*-khellactone (**1**), 20 mg *cis*-khellactone (**2**), 60 mg 3′-senecioyl-*cis*-khellactone (**10**),

100 mg 3′-senecioyl-4′-acetyl-*cis*-khellactone (**11**), 130 mg 4′-senecioyl-*cis*-khellactone (**12**), 120 mg 3′-acetyl-4′-senecioyl-*cis*-khellactone (**13**), 1.5 g 3′,4′-di-*iso*valeryl-*cis*-khellactone (**16**), 540 mg 3′,4′-disenecioyl-*cis*-khellactone (**17**), 120 mg of a mixture of 3′-angeloyl-4′-*iso*valeryl-*cis*-khellactone (**18**) and 3′-*iso*valeryl-4′-angeloyl-*cis*-khellactone (**19**).

Characterization of products. Trans-*khellactone* (**1**): mp 187–188° (EtOAc–petrol); IR ν_{max}^{KBr} cm^{-1}: 1710 (br), 1600, 1560. 30 mg of **1** was treated with Ac_2O–Py in the usual way affording 25 mg *trans*-khellactone diacetate (**4**). Cis-*khellactone* (**2**): mp 174–175° (EtOAc–petrol), $[\alpha]_D$ +89.4° (*c* 0.228 $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 1615, 1595. (ref. [41] +75° and refs. cited therein, +81°). 30 mg of **2** dissolved in Py was treated with Ac_2O yielding *cis*-khellactone diacetate (**3**). Cis-*khellactone diacetate* (**3**) (oil): $[\alpha]_D$ −3.8° (*c* 1.16 $CHCl_3$). Trans-*khellactone diacetate* (**4**): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (br), 1605. 4′-*Methyl*-trans-*khellactone* (5): mp 162–164° (EtOAc–petrol), $[\alpha]_D$ −32.9° (*c* 0.334 $CHCl_3$). (ref. [4]: mp 162–162.5°, $[\alpha]_D$ −30°). 40 mg of **5** was treated as usual to form 4′-methyl-*trans*-khellactone acetate (**6**): mp 162–164°, $[\alpha]_D$ +13.1° (*c* 2.06 $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2985, 2920, 1820, 1720, 1600, 1565. 4′-*Methyl*-cis-*khellactone* (**7**); mp 124–127° (EtOAc–petrol), $[\alpha]_D$ +60.3° (*c* 1.48 $CHCl_3$). (ref. [4]: mp 125.5–126.5°, $[\alpha]_D$ +80°). 40 mg of **7** was treated with Ac_2O–Py to give 4′-methyl-*cis*-khellactone acetate (**8**): $[\alpha]_D$ −41.7° (*c* 1.38 $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 2930, 2730, 1725 (br), 1625, 1605. Trans-*dimethyl-khellactone* (**9**) (*oily*): $[\alpha]_D$ +18.6° (*c* 0.204 $CHCl_3$). 3′-*Senecioyl*-cis-*khellactone* (**10**) (*oily*): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3420, 2910, 1720, 1640, 1600, 1490, 1440, 1400, 1370, 1350, 1280, 1140, 1115, 1085, 1000, 890, 840. 3′-*Senecioyl-4′-acetyl*-cis-*khellactone* (**11**) (*oily*): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3030, 2980, 1735 (br), 1650, 1610, 4′-*Senecioyl*-cis-*khellactone* (**12**) (*oily*): MW (MS) 344; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600–3300, 2980, 2930, 2860, 1730, 1645, 1625, 1605, 1490, 1440, 1405, 1380, 1370, 1355, 1300, 1275, 1250–1170, 1110, 1075, 1010, 985, 895, 870, 840. 20 mg of 12 was treated with Ac_2O–Py forming 3′-acetyl-4′-senecioyl-*cis*-khellactone (**13**) (oily): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (br), 1650, 1630, 1600. (ref. [5]: mp 120.5–121°). 3′-*Angeloyl-4′-methyl-khellactone* (**14**) occurred in a mixture with **15**, as an oil: IR of the mixture $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1650, 1620, 1600. 3′-*Senecioyl-4′-methyl-khellactone* (**15**) was in a mixture with **14**. 3′,4′-*Di-isovaleryl-cis-khellactone* (**16**) (*oily*): MW (MS) 430. (ref. [5]: mp 88–89°). **16** mixed with **17** and other esters (5 g) was treated with 50 ml 10% NaOH in H_2O for 24 hr. Khellactones **1** and **2** were obtained. Unpurified **16** (3.1 g) was treated with 0.5 N NaOH in MeOH for 3 hr, acidified with HCl and extracted with Et_2O. 35 mg *trans*-khellactone (**1**), 70 mg *cis*-khellactone (**2**), 32 mg 4′-methyl-*trans*-khellactone (**5**), 17 mg 4′-methyl-*cis*-khellactone (**7**), 34 mg 3′,4′-dimethyl-*trans*-khellactone (**9**), 43 mg of a mixture of 3′-angeloyl-4′-methyl-khallactone (**14**) and 3′-senecioyl-4′-methyl-khellactone (**15**) were separated, together with some unreacted starting material. 3′,4′-*Di-senecioyl*-cis-*khellactone* (**17**) (*oily*): $[\alpha]_D$ −16.3° (*c* 0.98 $CHCl_3$). (ref [5] mp 112–113°, $[\alpha]_D$ −47.7°; ref [4]: mp 108–108.5°, $[\alpha]_D$ +15.8°). 3′-*Angeloyl*-4′-iso*valeryl*-cis-*khellactone* (**18**) was found together with **19** (120 g). MW (MS) 428. Characterized by ^1H NMR of the mixture. 3′-Iso*valeryl*-4′-*angeloyl*-cis-*khellactone* (**19**) could not be separated from the mixture with **18**.

All products described above showed blue fluorescence in UV. The most important UV and ^1H NMR findings are set out in the main text.

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