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Naturally Occurring Sesquiterpene-Coumarin Ethers, VI.* New Sesquiterpene-Isofraxidin Ethers from *Achillea depressa*

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The roots of *Achillea depressa* afforded in addition to known sesquiterpene-isofraxidin ethers three new derivatives: the bicyclic drimenol derived albartol and the monocyclic derivatives deparnol and acetyldeparnol. The compounds were characterized by ^{1}H-NMR, MS, UV, IR, and CD data.

(Keywords: Achillea depressa; Compositae-Anthemideae; Sesquiterpene-Isofraxidin Ethers; Circular dichroism)

Natürlich vorkommende Sesquiterpen-Cumarin-Ether, 6. Mitt.: Neue Sesquiterpen-Isofraxidin-Ether aus Achillea depressa

Aus den Wurzeln von *Achillea depressa* wurden zusätzlich zu bereits bekannten Sesquiterpen-Isofraxidin-Ethern drei neue Derivate isoliert: das vom bicyclischen Drimenol abgeleitete Albartol und die monocyclischen Derivate Deparnol und Acetyldeparnol. Die Verbindungen wurden mittels ^{1}H-NMR-, MS-, UV-, IR- und CD-Daten charakterisiert.

Introduction

Sesquiterpene-coumarin ethers have been detected so far only in two plant families: the *Umbelliferae* and the *Compositae*. Hence, their distribution within these families deserves special chemosystematic interest. Up to now especially umbelliferone (7-hydroxycoumarin) derived ethers[1] are well known and have been extensively documented mainly by Russian authors[2]. Most of these derivatives have been isolated from the umbelliferous genus *Ferula*.

In contrast, comparative analyses within the *Compositae* tribe *Anthemideae* have shown that in the genera *Artemisia, Achillea* and

* Herrn Prof. Dr. *U. Schmidt* mit den besten Wünschen zum 60. Geburtstag gewidmet.

Anthemis another series of sesquiterpene ethers dominate which are all derived from isofraxidin (7-hydroxy-6,8-dimethoxycoumarin). From the roots of several *Artemisia* and *Achillea* species we have already isolated 16 isofraxidin ethers with different sesquiterpene moieties, sometimes in rather high yields[3–6]. Beyond that in *Artemisia* we recently found a third series of sesquiterpene ethers which are derived from scopoletin (7-hydroxy-6-methoxycoumarin). It has been shown that these compounds occur very often as minor constituents accompanied by the corresponding isofraxidin analogues[7].

In this paper a complete analysis of the sesquiterpene-coumarin ethers from the roots of *Achillea depressa* Janka is presented. Eleven different compounds—all belonging to the isofraxidin series—were identified. Three compounds were new: the bicyclic sesquiterpenoid derivative albartol proved to be the corresponding alcohol to the previously isolated albartin[4]; the two monocyclic derivatives deparnol and acetyldeparnol close a gap in the biosynthetic path[8] within the isofraxidin series, representing the step between the open chain farnesyl derivatives and the bicyclic drimenyl derivatives.

According to morphological characters these chemical findings also support the close alliance between *A. depressa* and the *A. ochroleuca—A. pseudopectinata* complex[3,5,6].

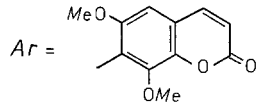
Results and Discussion

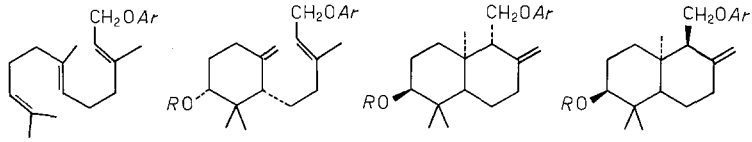
The coumarin derivative containing column fractions (see Exp.) were subjected to TLC (ether : petrolether = 9 : 1) yielding six well separated bands of blue fluorescence in UV. NMR analysis (250 MHz) of the fractions revealed that fraction 1 was pure farnochrol (**1**), fract. 2 was an unknown compound (**2**), all other fractions were either mixtures of known compounds (fract. 3 and 4) or contained in addition to already known components new compounds as well (fract. 5 and 6) (see Table 1). The fractions containing known sesquiterpene-isofraxidin ethers were not separated into the pure components; the integrations of significant NMR signals were taken as an analytical measure for the contents of the single compounds. Fractions 5 and 6 were further separated by repeated TLC ($CH_2Cl_2 : Et_2O = 98.5 : 1.5$). Fraction 5 yielded pectachol (**9**) and an unknown compound **8**, fraction 6 yielded drimartol B (**11**) and unknown **10**.

The UV spectra of all new compounds **2**, **8**, and **10** were almost identical and typical for isofraxidin derivatives[3–6]. The mass spectra gave small but still significant molecular ions of $m/e = 442$ for **8** and **10**, and $m/e = 484$ for **2**; the base peak was in all cases $m/e = 222$

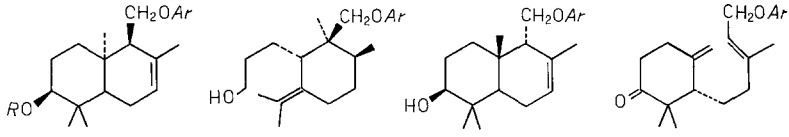
representing the isofraxidin ion. A mass of 442 is common to all monooxygenated sesquiterpene-isofraxidin ethers, 484 for corresponding acetyl derivatives[3–6].

The ^{1}H-NMR spectra of **2** and **8** established that **2** is the acetyl derivative of **8**: in the spectrum of **2** an additional acetylmethyl group is found and the >CHOH proton is shifted from 3.66 ppm (**8**) to 4.88 for >CHOCO*Me* (**2**). The coupling pattern of this proton—geminal to OH and OCO*Me*, resp.—is indicative for an equatorial O*R*: the





1 | **2** *R* = Ac, **8** *R* = H | **3** *R* = Ac, **10** *R* = H | **4** *R* = Ac, **9** *R* = H



5 *R* = Ac, **7** *R* = H | **6** | **11** | **12**

corresponding axial proton shows an ax-ax vicinal coupling of 10 Hz and an ax-eq coupling of 4 Hz. All these data agree very well with corresponding data for the A ring of bicyclic drimenyl derived sesquiterpene ethers[3–5]. On the other hand a dublet of 2 H at about 4.70 ppm is diagnostic for an open chain sesquiterpene ether [*Ar*O–CH_2–CH=; for instance 4.68 ppm for farnochrol (**1**); 4.70 for **2** and 4.69 for **8**]. Obviously the B ring has not been closed. From the biosynthetic point of view **8** is the product of acid catalyzed cyclization of 10,11-epoxyfarnochrol (already isolated from *Achillea ochroleuca*[5]) with loss of a proton at the monocyclic stage[8,9]. Thereby an exomethylene at the A ring is formed (=CH_2 at 4.60 and 4.83 ppm for **2**, 4.57 and 4.81 ppm for **8**). The proposed structure is supported by all other ^{1}H-NMR resonances as well. The compounds were designated as deparnol (**2**) and acetyldeparnol (**8**); **8** is the isofraxidin analog of the umbelliferone derived farnesiferol B[8].

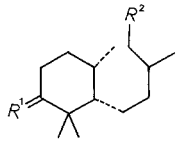
Table 1. *Complete analysis of the coumarin fractions isolated from 105 g roots of Achillea depressa*

Fract.	Compd.	Name	Yield/mg	*Rf**
1	**1**	Farnochrol[3]	6.5	0.60
2	**2**	Acetyldeparnol	7.0	0.47
3	**3**	Albartin[4]	4.5	0.42
	4	Acetylpectachol[3]	4.5	0.40
	5	Acetyldrimartol A[4]	3.0	0.38
4	**6**	Secodriol[6]	0.5	0.34
	7	Drimartol A[3]	4.0	0.32
5	**8**	Deparnol	1.5	0.26
	9	Pectachol[3]	3.0	0.25
6	**10**	Albartol	2.0	0.21
	11	Drimartol B[3]	1.5	0.20
1–6			38.0	

* *Rf* in ether : petrolether = 4 : 1, silicagel 60 F 254 (Merck).

The absolute stereochemistry of acetyldeparnol (**2**) was correlated with the absolute configuration of farnesiferol B by chemical degradation[8] and transformation into (−)-**14** (see Exp.). The absolute configurations of (1 *S*, 4 *R*) for **2** and **8** (correlated with each other by acetylation of **8**) are further supported by the CD spectrum of the oxo-derivative of **8**. The *Cotton* effect of the $n \rightarrow \pi^*$ carbonyl transition of the oxo-product **12** is $\Delta\varepsilon_{295} = -1.3$. The negative sign of the effect of this 1,2-*gem.*-dimethyl substituted monocyclic keton agrees with the predictions according to the octant rule—in contrast to comparable bicyclic sesquiterpenoid ketones where the equatorial β-substituent is part of the second ring[10–12].

The ^{1}H-NMR spectrum of **10**, designated as albartol, is typical for a bicyclic sesquiterpene-isofraxidin ether of the exo-methylene series: $=CH_2$ at 5.08 and 5.02 ppm and 3 *Me* resonances at 0.78, 0.87, and 1.00 ppm. The hydroxyl group at C 6 is axial since the corresponding



13 R^1 = H, OH R^2 = CH_2OH
14 R^1 = O R^2 = COOMe

geminal (equatorial) proton shows only small eq-ax and eq-eq couplings to C 7 H_2 and appears therefore as a relatively sharp signal ($w_{1/2} = 6$ Hz at 3.46 ppm). The $-CH_2OAr$ moiety is attached equatorially to the *trans* decaline system of the terpenic unit because the corresponding $>CH-CH_2-OAr$ protons are represented by an almost undisturbed pseudo dublet close to an $A_2(X)$ type signal (axial $-CH_2OAr$ groups are always indicated by clear ABX patterns with $\Delta\delta_{AB} > 0.1$ ppm; $\Delta\delta_{AB}$ for **10** is < 0.01 ppm). **10** is therefore the parent alcohol to albartin (**3**), previously isolated from *Artemisia alba*[4]. This was also confirmed by acetylation of **10** giving a product which was identical with albartin in all respects (^{1}H-NMR, CD).

The optical rotation of **10** is low and no accurate value can be given due to the small amount of material isolated. For the acetyl derivative albartin (**3**)[4] $[\alpha]_D = +2°$ and $[\alpha]_{436} = -3°$, indicating that the ORD is very flat in this wave length region. However, the CD spectra allow an absolutely safe chiroptical correlation. The absolute configuration shown in the formula has been determined recently by chemical degradation of albartin[10].

Acknowledgements

We are grateful to Dr. *K. Valant-Vetschera* for collecting the plant material and to Dr. *W. Silhan* and Mr. *H. Bieler* for recording NMR and mass spectra. Thanks are further due to Prof. *H. Falk*. University of Linz, Austria, for access to the dichrograph Mark V. Support by the "Fonds zur Förderung der wissenschaftlichen Forschung in Österreich" (projects 4009 and 4837) is gratefully acknowledged.

Experimental Part

Instruments: Optical rotation: Perkin-Elmer 241 polarimeter; Circular dichroism: Jobin-Yvon Mark V; IR: Perkin-Elmer 398; UV: Perkin-Elmer "Lambda 5"; MS: Varian MAT CH-7; NMR: Bruker WM 250.

Plant Material: Achillea depressa Janka was collected near Niš, Yugoslavia. Voucher specimens are deposited at the herbarium of the Institute of Botany, University of Vienna (WU).

Isolation of the Compounds

105 g of fresh air dried roots were cut into small pieces and extracted with petrol ether (60–80°) : ether (2 : 1) for two days at room temperature. The concentrated extract was roughly fractionated on a silica gel column with solvent mixtures as eluents starting with petrol ether—ether (Et_2O increasing from 0% to 100%) and finally Et_2O—$MeOH$ ($MeOH$ increasing from 0% to 10%). The coumarin derivative containing fractions (Et_2O and Et_2O—$MeOH$) were detected by UV spectroscopy and were further separated by TLC on 1 mm thick layers of silica gel GF 254 (Merck) using Et_2O-petrol ether (4 : 1) as solvent to give six fractions (s. Tab. 1). Fraction 2 was pure Acetyldeparnol (**2**), fractions 5 and 6 were again repeatedly chromatographed by TLC using CH_2Cl_2—$EtOH$ (98.5 : 1.5) as solvent to give pure deparnol (**8**) and albartol (**10**).

Acetyldeparnol (**2**), *(1S,4R)-7-[5-(4-acetyloxy-5,5-dimethyl-2-methylene-cyclohexyl)-3-methylpent-2-enyloxy]-6,8-dimethoxy-2H-1-benzopyran-2-one*

Colourless oil; IR (CCl_4): 2955, 1745, 1560, 1470, 1420, 1405, 1290, 1150, 1125, 1045, 835; UV (*Et*OH): 340 nm ($\varepsilon = 7850$), 297 (11300), 226 (23400, sh), 206 (50500, sh); CD (*Et*OH): 340 nm ($\Delta\varepsilon = +0.1$, sh), 295 (-0.55), 235 ($+1.9$), at 210 nm steep negative slope: MS (70 eV, 100 °C): *m/e* 484 (M^+, 1.5%), 223 (42), 222 (100), 221 (15), 133 (12), 119 (11), 107 (10), 95 (10), 93 (12), 91 (18); NMR ($CDCl_3$): 7.63 (d, 1H, $J = 9.5$ Hz, isofrax. C4-H), 6.67 (s, 1H, isofrax. C5-H), 6.35 (d, 1H, $J = 9.5$ Hz, isofrax. C3-H), 5.55 (broad t, $J = 7$ Hz, $=$C**H**$-$CH$_2$O*Ar*), 4.88 (dd, 1H, $J = 10$ and 4 Hz, $>$CHO*Ac*), 4.83 (broad s, 1H, exo-methylene, $w_{1/2} = 4$ Hz), 4.70 (d, 2H, $J = 7$ Hz, $-$CH$_2$O*Ar*), 4.60 (broad s, 1H, exo-methylene, $w_{1/2} = 4$ Hz), 4.05 (s, 3H, C8-O*Me*), 3.90 (s, 3H, C6-O*Me*), 2.14–2.19 (m, 2H), 2.04–2.09 (m, 2H), 2.06 (s, 3H, *Me*$-$CO$-$O$-$), 1.3–1.9 (m, 5H), 1.69 (broad s, 3H, olefin. *Me*), 0.93 (s, 3H, *Me*), 0.87 (s, 3H, *Me*).

Deparnol (**8**), *(1S,4R)-7-[5-(4-hydroxy-5,5-dimethyl-2-methylen-cyclohexyl)-3-methylpent-2-enyloxy]-6,8-dimethoxy-2H-1-benzopyran-2-one*

Colourless oil; IR (CCl_4): 3635, 2950, 1745, 1560, 1475, 1420, 1410, 1290, 1150, 1130, 1045, 840; UV (*Et*OH): 338 nm ($\varepsilon = 7700$), 297 (10900), 227 (22800, sh), 206 (48000, sh); CD (*Et*OH): 350 nm ($\Delta\varepsilon = -0.04$), 300 ($+0.35$), 235 ($-0.7$), at 210 nm steep negative slope; MS (70 eV, 100 °C): *m/e* 442 (M^+, 1%), 223 (35), 222 (100), 221 (10), 119 (10), 107 (16), 95 (12), 93 (12), 91 (15); NMR ($CDCl_3$): 7.62 (d, 1H, $J = 9.5$ Hz, isofrax. C4-H), 6.66 (s, 1H, isofrax. C5-H), 6.35 (d, 1H, $J = 9.5$ Hz, isofrax. C3-H), 5.53 (broad t, 1H, $J = 7$ Hz, $=$C**H**$-$CH$_2$O*Ar*), 4.81 (broad s, 1H, $w_{1/2} = 5$ Hz, exo-methylene), 4.69 (d, 2H, $J = 7$ Hz, $-$CH$_2$O*Ar*), 4.57 (broad s, 1H, $w_{1/2} = 4$ Hz, exo-methylene), 4.04 (s, 3H, C8-O*Me*), 3.89 (s, 3H, C6-O*Me*), 3.66 (dd, 1H, $J = 10$ and 4 Hz, $>$C**H**OH), 2.13–2.19 (m, 2H), 1.93–2.00 (m, 2H), 1.3–1.9 (m, 5H), 1.66 (broad s, 3H, olefin. *Me*), 0.94 (s, 3H, *Me*), 0.87 (s, 3H, *Me*).

Albartol (**10**), *(1R,4aS,6S,8aR)-7-[(6-hydroxy-decahydro-5,5,8a-trimethyl-2-methylene-1-naphthalenyl)methoxy]-6,8-dimethoxy-2H-1-benzopyran-2-one*

Colourless oil; IR (CCl_4): 3640, 2930, 1745, 1560, 1465, 1420, 1405, 1290, 1240, 1150, 1120, 1040, 835; UV (*Et*OH): 339 nm ($\varepsilon = 7800$), 296 (11200), 228 (23500, sh), 206 (48000, sh); CD (*Et*OH): 360 nm ($\Delta\varepsilon = -0.01$?), 304 ($+0.35$), 217 (-3.8); MS (70 eV, 100 °C): *m/e* 442 (M^+, 3%), 223 (23), 222 (100), 203 (45), 161 (10), 147 (16), 133 (20), 121 (13), 119 (12), 109 (13), 107 (20), 105 (15), 95 (22), 93 (19), 91 (16); NMR ($CDCl_3$): 7.60 (d, 1H, $J = 9.5$ Hz, isofrax. C4-H), 6.65 (s, 1H, isofrax. C5-H), 6.35 (d, 1H, $J = 9.5$ Hz, isofrax. C3-H), 5.08 (broad s, 1H, $w_{1/2} = 5$ Hz, exo-methylene), 5.02 (broad s, 1H, $w_{1/2} = 5$ Hz, exo-methylene), 4.26 (pseudo d, 2H, $J = 6$ Hz, CH$_2$O*Ar*), 4.00 (s, 3H, C8-O*Me*), 3.88 (s, 3H, C6-O*Me*), 3.46 (broad s, 1H, $w_{1/2} = 6$ Hz, C6-H), 2.50 (ddd, 1H, $J = 14$, 4, and 3 Hz, C3-H eq), 2.41 (t, 1H, $J = 6$ Hz, C1-H ax), 2.18 (ddd, 1H, $J = 14$, 13, and 4 Hz, C3-H ax), 1.96 (dddd, 1H, $J = 14$, 13, 4, and 3 Hz, C8-H ax), 1.30–1.85 (m, 6H), 1.00 (s, 3H, *Me*), 0.87 (s, 3H, *Me*), 0.78 (s, 3H, *Me*).

Acetylation of **10**

0.2 ml of acetic anhydride was added to 1 mg **10** and the solution kept at 60° for 8 h. Evaporation of excess anhydride and preparative TLC gave albartin which was identical with the natural product isolated from *Artemisia alba*[4] (*Rf*, NMR, CD).

Oxo-Derivative of **8**

A mixture of 1 mg **8** and 10 mg CrO_3 in 0.5 ml of dry pyridine was stirred for 15 h at room temperature. Then 10 ml of ether and a few drops of 2 n HCl were added to obtain an acidic aqueous layer. The ether layer was washed neutral, dried over $MgSO_4$, the ether evaporated and the keton **12** purified by TLC (CH_2Cl_2 : *Et*OH = 98.5 : 1.5).

12: UV (*Et*OH): 340 (8000), 297 (11500), 227 (23000, sh), 206 (49000, sh); CD (*Et*OH): 295 nm ($\Delta\varepsilon = -1.3$); NMR ($CDCl_3$): 7.62 (d, 1 H, $J = 9.5$ Hz, isofrax. C 4-H), 6.65 (s, 1 H, isofrax. C 5-H), 6.34 (d, 1 H, $J = 9.5$ Hz, isofrax. C 3-H), 5.50 (broad t, 1 H, $w_{1/2} = 18$ Hz, $=CH-CH_2OAr$), 5.00 (broad s, 1 H, $w_{1/2} = 5$ Hz, exo-methylene), 4.80 (broad s, 1 H, $w_{1/2} = 5$ Hz, exo-methylene), 4.68 (d, 2 H, $J = 7$ Hz, $-CH_2OAr$), 4.04 (s, 3 H, C 8-O*Me*), 3.89 (s, 3 H, C 6-O*Me*), 1.85–2.45 (m, 7 H), 1.4–1.6 (m, 2 H), 1.65 (broad s, 3 H, olefin. *Me*), 1.19 (s, 3 H, *Me*), 1.02 (s, 3 H, *Me*).

Transformation of **2** *to Keto-acid Methylester* **14**

4 mg **2** in 10 ml *Et*OH–*Ac*OH (3 : 1) were hydrogenated with Pt/H_2 (10 mg PtO_2, roomtemp., atm. pressure, 12 h). The catalyst was removed, the solvent evaporated and the remaining oil was subjected to hydrolyzation with 5% KOH in *Me*OH/H_2O (2 : 1). The neutral products were isolated by extraction with ether yielding the crude diol **13**. An excess of *Jones* reagent was added to a solution of the diol in 0.5 ml acetone. After 10 min 10 ml ether was added and the acidic products were isolated. The crude keto-acid was converted to its methylester with an etheric solution of diazomethane. The material isolated (ca. 0.5 mg) was not enough for further purification. However, the crude methylester **14**—dissolved in 1.2 ml $CHCl_3$—gave a polarimeter reading of $-0.006 \pm 0.001°$. This agree very well with the methylester isolated by *Caglioti* et al.[8] ($[\alpha]_D^{20} = -17°$).

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