Phytochemistry, Vol. 28, No. 9, pp. 2363–2368, 1989.
Printed in Great Britain.

0031-9422/89 $3.00+0.00

POLYENOIC ACID PIPERIDEIDES AND OTHER ALKAMIDES FROM *ACHILLEA MILLEFOLIUM*

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(*Received* 14 *December* 1988)

Key Word Index—*Achillea millefolium*; Asteraceae–Anthemideae; olefinic piperideides; alkamides; stereochemistry.

Abstract—From the lipophilic extract of subterranean parts of *Achillea millefolium* s.str. 17 different alkamides together with (+)-sesamin were separated by CC, MPLC, TLC, and identified by spectroscopic methods. The stereochemistries of the fully conjugated decatetraenoic acid piperideides were established for the first time by using the lanthanide-induced shift technique. Besides a rare decadienoic acid tyramide and the corresponding novel *p*-methoxy derivative the amide pattern is especially characterized by the dominating olefinic piperideides.

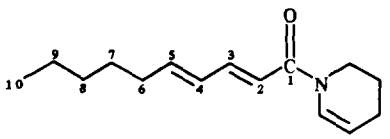
INTRODUCTION

The genus *Achillea* (Asteraceae–Anthemideae) is known to produce a wide variety of olefinic and acetylenic alkamides which are mainly accumulated in the subterranean parts. It is especially rich in derivatives with cyclic amide moieties. Besides the more widespread saturated ring amides (piperidides, pyrrolidides), the genus is particularly characterized by the additional occurrence of the corresponding dehydro derivatives (piperideides, pyrrolideides, pyrrolides) [1–4]. Extensive comparative HPLC-analyses within different provenances of *A. millefolium* L. itself and closely related species have shown that the accumulation of polyenoic acid piperideides represents a typical biogenetic trend of the *A. millefolium* group [5].

A re-investigation of the underground parts of a hexaploid strain of *A. millefolium* ($2n = 54$), originating from Carinthia (Austria), yielded relatively large quantities of conjugated decatrienoic and decatetraenoic acid piperideides together with other alkamides. In addition to the rare tyramide (**11**) which is as yet only known from *Anacyclus pyrethrum*, (L.) Link [6], the novel *O*-methylated derivative (**12**) as well as the previously unknown 2*E*,4*E*,6*E*-decatrienoic piperideide (**3**) has been isolated. Using the lanthanide-induced shift technique, the stereochemistries of the very characteristic decatetraenoic piperideides **5** and **6** have been established for the first time.

RESULTS AND DISCUSSION

Combined CC, MPLC and TLC separations of the lipophilic extract led to the isolation of 17 different alkamides and (+)-sesamin. The pattern is characterized by the predominance of piperideides containing olefinic C_{10} acid moieties (**1–6**). As in most members of the *Achillea millefolium* group, the (2*E*,4*E*,6*Z*)-2,4,6-decatrienoic acid piperideide (**4**) clearly dominates as the major compound [5]. It was originally isolated from *A. millefolium* [1] and later also reported for *A. crithmifolia* Waldst. et Kit. [7]. The corresponding all-*trans* isomer



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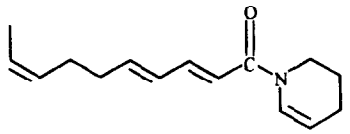

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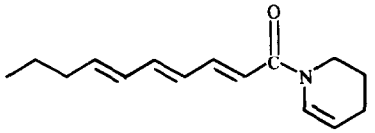

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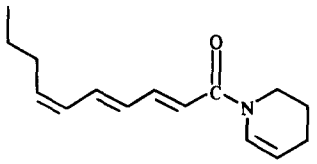

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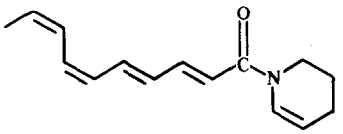

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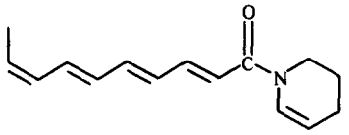

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(**3**), by contrast, occurs only in small amounts and is reported here for the first time.

The structure of the (*E,E,E*)-triene **3** was derived in a straightforward manner from its ^{1}H NMR spectrum. All six olefinic proton signals of the acid moiety are sufficiently separated to allow a clear first order interpretation. All olefinic coupling constants are in the range of typical *trans*-couplings (15 Hz, see Table 1). The UV maximum corresponds to the characteristic triene-amide chromophor (300 nm). The mass spectrum is very similar to the one of the known (*E,E,Z*)-isomer **4** [1].

The closely related deca-2*E*,4*E*-dienoic piperideide (**1**) [7], mostly accompanied by small amounts of deca-2*E*,4*E*,8*Z*-trienoic piperideide (**2**) [8], appears to be more widely distributed. Of special chemotaxonomic interest, however, is the formation of the two stereoisomeric decatetraenoic acid piperideides (**5, 6**) which may easily be separated both by reversed phase HPLC or normal phase MPLC. Based on extensive chromatographic comparisons within the genus *Achillea* it became apparent that the accumulation of these fully conjugated alkamides is obviously confined to the European representatives of the *A. millefolium* group [4, 5]. A piperideide with a decatetraenoic acid moiety has already been isolated from *A. millefolium* in a previous investigation. However, the configurations of the double bonds could not be determined [1]. In the present analysis sufficient amounts of both isomers were available, but the structures could not be elucidated by standard ^{1}H NMR methods. In this case, the quantitative evaluation of the lanthanide-induced shifts (^{1}H-LIS simulation) was used to establish the stereochemistries of the compounds.

In the NMR spectra of the tetraenes **5** and **6** several important coupling constants are obscured by overlapping resonance signals. In the case of **5** four olefinic resonances collapse in the region of δ6.30–6.55, for **6** two resonances coincide at δ6.60–6.70 and two further at δ6.30–6.40. This is the reason that in an earlier report [1] no structure elucidation concerning the configuration of the double bonds could be achieved. However, two important pieces of information may be derived from the otherwise complex resonance patterns of **5** and **6**. For both compounds the most characteristic 9-H (*dq*) at relatively high field shows coupling constants of ~ 10 and 7 Hz indicating a (*Z*)-configuration for the C-8, C-9 double bond, and the significant 3-H (*dd*) at rather low field with coupling constants of 15 and ~ 11 Hz indicating an (*E*)-configuration of the C-2, C-3 double bond. Thus, the (2*E*) and (8*Z*)-double bonds are common to both isomers **5** and **6**, whereas the configurations of the C-4, C-5 and C-6, C-7 double bonds remain open. In this case, further conclusive assignments of resonances and coupling constants could be derived from the ^{1}H LIS data.

In a recent paper [8] we have reported on the conformational analysis of (*E,E*)-2,4-decadienoic acid piperideide (**1**) by means of LIS calculations. In that paper the two observable rotamers, originating from the hindered

Table 1. ^{1}H NMR data of alkamides **3–6** and **11**, **12** (250 MHz, δ/ppm, $CDCl_3$)

H	3	4*	5	6	11	12
2	6.32 *d*	6.35 *d*	6.38 *d*	6.36 *d*	5.70 *d*	5.68 *d*
3	7.34 *dd*	7.38 *dd*	7.40 *dd*	7.37 *dd*	7.20 *dd*	7.19 *dd*
4	6.25 *dd*	6.32 *dd*	6.36 *dd*	6.35 *dd*	6.11 *m*†	6.11 *m*†
5	6.53 *dd*	6.85 *dd*	7.03 *dd*	6.63 *dd*	6.07 *m*†	6.07 *m*†
6	6.14 *dd*	6.10 *dd*	6.10 *dd*	6.27 *dd*	2.15 *dt*	2.14 *dt*
7	5.92 *dt*	5.65 *dt*	6.44 *dd*	6.70 *dd*	1.40 *m*	1.41 *m*
8	2.12 *dt*	2.12 *dt*	6.53 *dd*‡	6.10 *dd*‡	1.28 *m*	1.28 *m*
9	1.45 *tq*	1.45 *tq*	5.73 *dq*	5.65 *dq*	1.28 *m*	1.28 *m*
10	0.91 *t*	0.92 *t*	1.81 *d*‡	1.83 *d*‡	0.89 *t*	0.89 *t*
2'§	6.74 *d*	6.73 *d*	6.73 *d*	6.73 *d*	3.55 *dt*	3.56 *dt*
	7.27 *d*	7.27 *d*	7.27 *d*	7.27 *d*		
3'§	4.98 *dt*	4.99 *dt*	4.99 *dt*	4.98 *dt*	2.76 *t*	2.80 *t*
	5.12 *dt*	5.13 *dt*	5.13 *dt*	5.13 *dt*		
4'	2.10 m	2.10 *m*	2.10 *m*	2.10 *m*	—	—
5'	1.86 *m*	1.87 *m*	1.87 *m*	1.86 *m*	7.04 *d*	7.12 *d*
6'§	3.75 *m*	3.75 *m*	3.75 *m*	3.74 *m*	6.80 *d*	6.85 *d*
	3.68 *m*	3.68 *m*	3.69 *m*	3.69 *m*	—	—
–OMe	—	—	—	—	—	3.80 *s*

Coupling constants (Hz): **3**: 2,3 = 4,5 = 6,7 = 15; 3,4 = 5,6 = 11; 7,8 = 7.5; 8,9 = 9,10 = 7; 2',3' = 10; 3',4' = 4; **4**: 2,3 = 4,5 = 15; 6,7 = 10; 3,4 = 5,6 = 11; 7,8 = 8,9 = 9,10 = 7; 2',3' = 10; 3',4' = 4; **5**: 2,3 = 4,5 = 15; 6,7 = 8,9 = 10; 3,4 = 5,6 = 7,8 = 11; 9,10 = 7; 2',3' = 10; 3',4' = 4; **6**: 2,3 = 4,5 = 6,7 = 15; 8,9 = 11; 3,4 = 5,6 = 7,8 = 11.5; 9,10 = 7; 2',3' = 10; 3',4' = 4; **11,12**: 2,3 = 4,5 = 15; 3,4 = 11; 5,6 = 6,7 = 9,10 = 7; 5',6' = 8.5.

*Spectra of **4** in CCl_4 and C_6D_6 see ref. [1].

†Very narrow *dd* (for 4-H) and *dt* (for 5-H).

‡Broad due to long range coupling between 8-H and 10-H.

§Two signals due to two rotamers about the amide C–N bond; the first value listed corresponds to the predominant one (*ca*, 60%, shown in the formulas), the value listed below corresponds to the other rotamer [1, 8].

rotation about the C-N amide bond, have been discussed in some detail. Since the chemical shift data, including the LIS values, are almost identical for all piperideide moieties of **1** and **4–6** (Table 1 and refs [1, 8]), in the present paper we have confined ourselves to the simulation of the LIS for the protons of the acid moiety (Table 2). Using the lanthanide ion position obtained for compound **1** [8], expected values for possible configurations of tetraenes **5** and **6** may be calculated. The Eu(III) positions relative to the co-ordinating amide carbonyl functions of **1** and **5**, **6** should be almost the same in the corresponding substrate-reagent complexes. These calculations showed that only the (*E*,*E*,*Z*,*Z*)-geometry for **5** and the (*E*,*E*,*E*,*Z*)-configuration for **6** gave a good agreement between experimental and calculated LIS values. The optimized fits are summarized in Table 2. For comparison with compounds **5** and **6**, the LIS data of the well known (*E*,*E*,*Z*)-triene **4** were included as well. The lanthanide ion positions are similar for all piperideides and the R-factors (all below 5%) indicate very good fits [9, 10] (the best possible fits for wrong configurations, e.g. the (*E*,*Z*,*E*,*Z*)-geometry, gives R-factors > 15% for the experimental data of **5** or **6**).

A qualitative comparison of the experimental LIS data of the previously fully assigned proton resonances of compound **4** with the data of **5** (Table 2) demonstrates the compatibility of the results obtained. The experimental data of these two compounds, both possessing an (*E*,*E*,*Z*)-sequence of double bonds, agree very well with each other due to the similar overall geometry (compare the structural formulas). The most striking difference is the much more negative LIS value for the terminating methyl group of **4**, which is due to the more pronounced 'U' shape of the O=C....chain....Me arrangement (comp. e.g. [11]). This agreement for the protons 2-H–6-H is especially remarkable since the proton positions in the strongly negative lobe of the magnetic field of the Eu(III) point-dipole are (according to the MacConnell–Robertson relationship) in a very sensitive region where small deviations in the lanthanide ion position results in relatively large changes of the LIS values [9, 10, 12] (compare for instance 5-H and the calculated average lanthanide ion position for compound **6**).

Table 2. LIS data* for the decapolyene piperideides **4–6**

	4		**5**		**6**	
H	exp.	calc.	exp.	calc.	exp.	calc.
2	7.04	6.96	7.39	7.19	6.73	7.05
3	9.46	9.49	10.00	10.09	11.00	10.81
4	2.35	2.25	2.39	2.31	2.38	2.23
5	−1.50	−1.44	−1.47	−1.26	−0.97	−0.98
6	0.08	0.27	0.16	0.29	0.21	0.26
7	−0.42	−0.38	−0.27	−0.36	−0.92	−0.93
8	−1.23	−1.42	−1.58	−1.88	−0.12	−0.15
9	−0.85	−0.87	−0.92	−1.15	−0.24	−0.29
10	−0.88	−1.13	−0.38	−0.54	−0.41	−0.62
R†		3.27%		4.15%		3.50%
d		2.6 Å		2.6 Å		2.7 Å
ρ		18°		25°		35°
ϕ		96°		91°		89°

*In ppm, extrapolated to the 1:1 complex [$CDCl_3$, Eu(fod)$_3$]; for typical LIS values of the piperideide moiety see ref. [8].

†For definition of the R-factor and the parameters of the Eu(III) position (*d*, *ρ*, *ϕ*) see refs [9, 10].

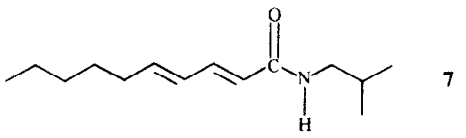
It is interesting to note that for all three compounds the negative LIS values for the more distant protons are overestimated. A separate calculation using a different model recommended for the calculation of carbonyl compounds ('two site model' [13], in contrast to the generally usable 'one site model') changed this trend but the overall simulation became worse. For a complete documentation of the LIS calculations we have included these results in the Experimental. It should be emphasized that both possible models for the LIS simulation of carbonyl compounds must necessarily lead to the same conclusions concerning the substrate geometries [14].

The mass spectra of **5** and **6** are very similar, the base peak is in both cases the acylium cation (M^+ − amine moiety, [1]). The two isomers may already be distinguished by different IR spectra in the =C-H out-of-plane region. The *E*,*E*,*Z*,*Z*,-isomer (**5**) shows a sharp band at 995 cm^{-1} together with a pronounced band at 1013 cm^{-1} (typical for piperideides [15]), whereas the *E*,*E*,*E*,*Z*-isomer (**6**) deviates by a strong band at 1000 cm^{-1} and only a weak-sized band at 1012 cm^{-1} (compare also compound **3**). There are also some minor differences in the finger print region. In the UV spectra the tetraeneamide chromophor (332 nm) is somewhat less broad for compound **5** compared to the isomer **6**. This is due to the relatively closer position of the long wavelength shoulder for **5** (a long wavelength shoulder is generally typical for piperideides).

Besides small amounts of the acetylenic C_{14} alkamides anacyclin (**15**) and dehydroanacyclin (**16**), the biogenetically directly derived C_{11} compounds **13** and **14** were found in higher concentrations. The C_{15} compound **17** which may be derived in a similar way from a corresponding C_{18} precursor [4, 19], occurs in small amounts only. It was originally isolated from *Echinacea purpurea* (L.) Moench [16] and has so far not been detected in the genus *Achillea*. However, most likely it has been overlooked in previous screenings because of its inconspicuous UV-spectrum.

All the other compounds belong to a series of closely related olefinic C_{10} amides containing a deca-2*E*,4*E*-dienoic (**7**, **9**, **11**, **12**) or a deca-2*E*,4*E*,8*Z*-trienoic (**8**, **10**) acid moiety. Whereas the two corresponding pairs of isobutylamides (**7**, **8**) and piperidides (**9**, **10**) are more widely distributed, the occurrence of the *para*-substituted phenethylamides **11** and **12** is of special systematic interest. The former belongs to the dominating derivatives of the amide pattern and has as yet only been detected in *Anacyclus pyrethrum*. In that investigation, however, it could only be isolated as a mixture with the corresponding C_{12} and C_{14} homologues. Thus, its structure had to be confirmed by synthesis [6]. The latter compound (**12**) belongs to a new type of alkamide which contains a *p*-methoxyphenethylamine moiety.

The ^1H NMR spectra of the *p*-hydroxy-and *p*-methoxy-phenethylamides **11** and **12** are relatively simple. The most characteristic signal group is the AB system of 2 × 2 H characteristic for *p*-substituted benzenes. The only problem in the interpretation of the spectra is represented by the rather narrow 4-H and 5-H protons which show no clear first order coupling constants which are necessary to derive the configuration of the C-4, C-5



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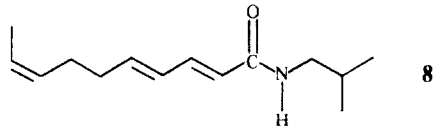

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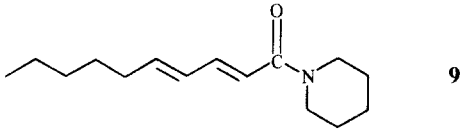

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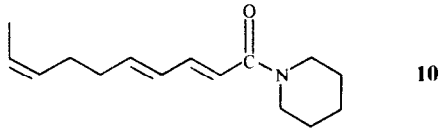

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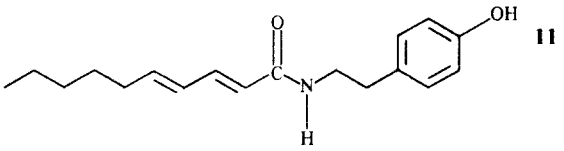

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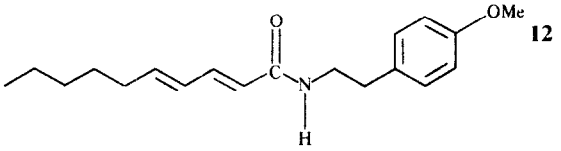

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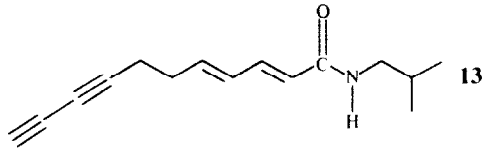

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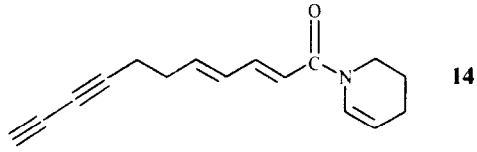

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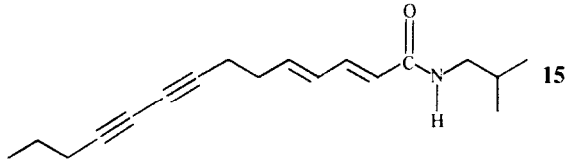

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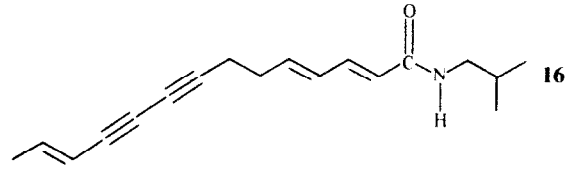

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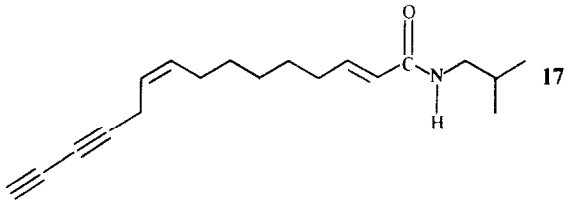

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double bond. However, all experience from the similar shift data of other amides containing the 2,4-diene-amide system (**1**, **2**, **7**–**10**, **13**–**16**) is in favour of a (2*E*,4*E*)-configuration. Unambiguous proof for this was obtained by adding a small quantity of shift reagent to the NMR sample. The sufficiently separated signals for 4-H and 5-H show the proper coupling constants of 15 Hz. Since the *p*-hydroxy-phenethylamide **11** was not soluble in carbon tetrachloride its IR spectrum was recorded in chloroform. The presence of a phenolic OH-group is indicated by an absorption at 3571 cm^{-1}. In compounds **11** and **12**, the N-H stretching at 3422 and 3438 cm^{-1} and the three bands in the N–C=O/$(C=C)_n$ stretching region from 1654 to 1605 cm^{-1} are typical for secondary amides containing a (*E*,*E*) diene adjacent to an amide group. These two *E*-orientated double bonds are also reflected with a band in the =C-H out of plane region at 994 and 991 cm^{-1}. The UV spectra are also characterized by this chromophor (252 nm). The mass spectral data of **11** and **12** are rather interesting. Both are dominated by the very characteristic base peak for the olefinic McLafferty product at *m/z* 120 (for **11**) and *m/z* 134 (for **12**), $[CH_2=CH-C_6H_4-OR]^+$. The usually prominent acylium ion is very weak, although still present (see Experimental). In the unsubstituted phenethylamides the McLafferty product is less intense (in the 30% range), the mass spectrum of these compounds are still dominated by the 100% acylium ion [17]. Obviously a *para*-oxygen has a strong stabilizing effect for the vinylbenzene cation of the McLafferty rearrangement.

Comparing the many alkamide structures which are already known from other *Achillea* species [2, 4, 5], *A. millefolium* s. str. deviates by the formation of polyenoic acid piperideides (**3**–**6**) and of the *para*-substituted phenethylamides (**11**, **12**). Whereas the deca-2*E*,4*E*,8*Z*-trienoic acid moiety (with an isolated double bond) is more widely distributed, the corresponding conjugated 2*E*,4*E*,6*Z*-isomer appears to be confined to *A. millefolium* and closely related species. Moreover, it may be of some systematic interest that a further conjugated deca-2*E*,4*Z*, 6*E*-stereoisomer, sencolaminic acid, has been shown to occur as phenethyl and isopentylamide in *Senecio colaminus* Cuatr. [18]. Up to now, this is the only report on alkamides in the tribe Senecioneae (Asteraceae). These data suggest the presence of highly stereospecific enzymes which are genetically fixed. On the other hand, the two decatetraenoic piperideides **5** and **6** are relatively unstable compounds; especially the (*E*,*E*,*Z*,*Z*)-isomer **5** isomerizes to some extent to the (*E*,*E*,*E*,*Z*)-isomer **6** during TLC separation. Based on HPLC-analyses, however, both isomers appear to be already present in the original crude extract [5].

Generally, the amide pattern of *A. millefolium* is characterized by a predominance of derivatives with short-chain

acid moieties. In the case of purely olefinic alkamides only C_{10} chains have been detected, whereas in the acetylenic representatives the C_{11} derivatives (**13**, **14**) prevail. With regard to the dominating C_{18} alkamides in *A. lycaonica* Boiss. et Heldr. and *A. chamaemelifolia* Pourr. [19], the C_{16} derivatives in *A. ageratifolia* (Sibth. et Smith) Boiss. [20], and the C_{14} derivatives in *A. nana* L. [21], these different biogenetic trends within the genus *Achillea* deserve special systematic and/or ecological attention.

EXPERIMENTAL

A hexaploid strain of *A. millefolium* s. str. ($2n = 54$) was collected near Bad St. Leonhard, Lavanttal, Carinthia, Austria (*ca* 1000 m; 3 August 1984). Voucher specimens have been deposited at the Herbarium of the Institute of Botany, University of Vienna (WU).

Fresh air-dried underground parts (190 g) were cut into small pieces and extracted with petrol (60–80°)–Et_2O (2:1) for several days at room temp. The concentrated extract was roughly fractionated first by CC (silica gel) eluted with petrol–Et_2O mixtures, with Et_2O increasing from 0 to 100%. The polar fractions obtained with petrol–Et_2O (1:1) and Et_2O were further separated by (i) MPLC with 15%, 30% and 70% (v/v) EtOAc in petrol (400 × 38 mm homemade column packed with Merck LiChroprep Si 60, 25—40 μm, *ca* 6000 theoretical plates, UV detection, 280 nm; ISCO UA-5) and (ii) prep. TLC (silica gel, CH_2Cl_2–Et_2O 19:1). The corresponding fractions were combined and yielded 12 mg **1**, 5 mg **2**, 2 mg **3**, 28 mg **4**, 18 mg **5**, 7 mg **6**, 5 mg **7**, 2 mg **8**, 6 mg **9**, 3 mg **10**, 10 mg **11**, 3 mg **12**, 7 mg **13**, 6 mg **14**, 2 mg **15**, 3 mg **16**, 3 mg **17**, and 10 mg (+)-sesamin.

(E,E,E)-2,4,6-*Decatrienoic acid piperideide* (**3**). Yellow oil; UV $\lambda_{max}^{Et_2O}$ nm: 300; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2919 *s*, 2848 w, 1631 *s*, 1598 *m*, 1579 w, 1457 w, 1402 *s*, 1375 *s*, 1350 *m*, 1315 *w*, 1302 w, 1282 *m*, 1243 *m*, 1226 *m*, 1156 *m*, 1132 w, 1070 *m*, 1012 w, 999 *s*, 940 w, 870 w, 707 w; MS (70 eV, 90°, *m/z* (rel. int.): 231 $[M]^+$ (31), 220 (28), 205 (36), 161 (10), 159 (14), 149 $[M-C_5H_8N]^+$ acylium (78), 147 (14), 145 (16), 133 (30), 131 (19), 121 (16), 120 (11), 119 (20), 108 (13), 107 $[149-C_3H_6]^+$ (84), 91 (41), 79 (36), 77 (35), 55 (100); high resolution MS: observed 231.162, $C_{15}H_{21}NO$ requires 231.1623.

(E,E,Z,Z)-2,4,6,8-*Decatetraenoic acid piperideide* (**5**). Yellow crystals, mp 91–95° (partially decomp.); UV $\lambda_{max}^{Et_2O}$ nm: 342 sh, 332; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3024 w, 2917 *m*, 2837 w, 1862 w, 1632 *s*, 1586 *m*, 1434 *m*, 1401 *s*, 1370 *s*, 1347 *s*, 1317 *m*, 1300 w, 1284 *m*, 1244 *m*, 1226 *m*, 1174 w, 1157 *m*, 1131 *m*, 1069 *m*, 1013 *s*, 995 *s*, 931 w, 915 w, 872 *m*, 706 *m*, 602 w; MS (70 eV, 90°, *m/z*) (rel. int.): 229 $[M]^+$ (28), 147 $[M-C_5H_8N]^+$ acylium (100), 119 [147 −CO] (27), 93 (31), 91 (45); high resolution MS: observed 229.147, $C_{15}H_{19}NO$ requires 229.1467.

(E,E,E,Z)-2,4,6,8-*Decatetraenoic acid piperideide* (**6**). Yellow crystals, mp 104–106°; UV $\lambda_{max}^{Et_2O}$ nm: 344 sh, 332; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3012 w, 2920 *m*, 2837 w, 1877 w, 1633 *s*, 1583 *m*, 1440 w, 1409 *s*, 1372 *s*, 1350 *s*, 1302 w, 1281 w, 1243 *m*, 1227 *m*, 1174 w, 1154 *m*, 1131 w, 1069 *m*, 1012 w, 1000 *s*, 939 w, 884 w, 872 w, 707 w, 693 w, 631 w, 605 w; MS (70 eV, 90°, *m/z*): 229 $[M]^+$ (31%), 147 $[M-C_5H_8N]^+$ acylium (100), 119 [147−CO] (28), 93 (35), 91 (51); high resolution MS: observed 229.146, $C_{15}H_{19}NO$ requires 229.1467.

(E,E)-2,4-*Decadienoic acid p-hydroxyphenethylamide* (**11**). Colourless crystals, mp 130–132° (132–133° for the synthetic product [6]); UV $\lambda_{max}^{Et_2O}$ nm: 287 sh, 253, 228 sh; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3571 *m*, 3422 *m*, 3287 *m*, 2990 w, 2912 *s*, 2845 *m*, 1654 *s*, 1624 *m*, 1605 *s*, 1492 *s*, 1438 w, 1329 *m*, 1167 *m*, 1100 w, 994 *s*; MS (70 eV, 130°, *m/z*) (rel. int.): 287 $[M]^+$ (12%), 168 (72), 151 $[M-NHCH_2CH_2C_6H_4OH]^+$ acylium (30), 121 (15), 120 $[CH_2=CH-C_6H_4OH]^+$ McLafferty product (100), 107 (15); high resolution MS: observed 287.189, $C_{18}H_{25}NO_2$ requires 287.1885.

(E,E)-2,4-*Decadienoic acid p-methoxyphenethylamide* (**12**). Colourless crystals, mp 126–128°; UV $\lambda_{max}^{Et_2O}$ nm: 284 sh, 252, 227 sh; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3438 *m*, 3299 *m*, 3020 w, 2946 w, 2918 *s*, 2847 *m*, 1668 *s*, 1631 *s*, 1607 *m*, 1494 *s*, 1458 *m*, 1435 w, 1330 w, 1313 w, 1296 *m*, 1240 *s*, 1172 *s*, 1144 *m*, 1037 *s*, 991 *s*; MS (70 eV, 130°, *m/z*) (rel. int.): 301 $[M]^+$ (5), 151 $[M-NHCH_2CH_2C_6H_4OMe]^+$ acylium (6), 135 (12), 134 $[CH_2=CH-C_6H_4OMe]^+$ McLafferty product (100), 121 (10); high resolution MS: observed 301.204, $C_{19}H_{27}NO_2$ requires 301.2042.

Calculation of lanthanide induced shifts. For the determination of ^1H LIS values increasing amounts of Eu(fod)$_3$ were added to solutions of 2–3 mg of substrate in 0.5 ml $CDCl_3$. The LIS for the concn ratio $R_0:S_0 = 1:1$ ('1:1 complex') were obtained by extrapolation of 4–6 different reagent concentrations in the range of $R_0:S_0 = 0.0$–$0.7:1$. The calculations were performed on an Apple Macintosh PC using the program COLIS (a combined COORD and LIS program), which was suited for the generally used 'one site model' and the special 'two site model' for carbonyl compounds [13]. The results using the 'OSM' are summarized in Table 2, the calculations using the 'TSM' gave comparable results: compound **4**: R = 5.29% (d = 2.8 Å, $\rho = 25°$) with a population of site 1 (*trans* to the fatty acid chain, $\Phi = 0°$): site 2 (*cis* relative to the acid rest, $\Phi = 180°$) = 60:40 and calcd values of 6.96, 9.53, 2.33, −1.74, 0.39, −0.20, −1.08, −0.55, −0.57 (listed in the same order as the experimental data in Table 2); **5**: R = 4.15% (d = 2.8 Å, $\rho = 25°$. $\Phi = 0°/180°$) site 1:site 2 = 62:38, values 7.27, 10.05, 2.49, −1.62, 0.45, −0.17, −1.56, −0.67, −0.31; **6**: R = 6.23% (d = 2.8 Å, $\rho = 20°$, $\Phi = 0°/180°$) site 1: site 2 = 64:36, values 7.22, 10.59, 2.63, −1.02, 0.55, −0.70, 0.04, −0.15, −0.44.

Acknowledgements—We thank Dr W. Silhan (^1H NMR), Univ.-Doz. Dr A. Nikoforov (high resolution MS), and Mr H. Bieler (MS) for recording spectra (Institute of Organic Chemistry, University of Vienna). Support by the Hochschuljubiläumsstiftung der Stadt Wien and the 'Österreichischer Fonds zur Förderung der wissenschaftlichen Forschung' (projects no. 4837 and 5840) is gratefully acknowledged.

REFERENCES

1. Bohlmann, F. and Zdero, C. (1973) *Chem. Ber.* **106**, 1328.
2. Greger, H. (1984) *Planta Med.* **50**, 366.
3. Kuropka, G. and Glombitza, K.-W. (1987) *Planta Med.* **53**, 440.
4. Greger, H. (1988) in *Chemistry and Biology of Naturally Occurring Acetylenes and Related Compounds* (Lam, J., Breteler, H., Arnason, T. and Hansen, L., eds), pp. 159–178. Elsevier, Amsterdam.
5. Greger, H. and Werner, A. (1989) Planta Med. (submitted).
6. Burden, R. S. and Crombie, L. (1969) *J. Chem. Soc.* (C), 2477.
7. Greger, H., Grenz, M. and Bohlmann, F. (1981) *Phytochemistry* **20**, 2579.
8. Hofer, O., Greger, H., Robien, W. and Werner, A. (1986) *Tetrahedron* **42**, 2707.
9. Willcott III, M. R., Lenkinski, R. E. and Davis, R. E. (1972) *J. Am. Chem. Soc.* **94**, 1742.
10. Davis, R. E. and Willcott III, M. R. (1972) *J. Am. Chem. Soc.* **94**, 1744.
11. Greger, H., Hofer, O. and Nikiforov, A. (1982) *J. Nat. Prod.* **45**, 455.
12. Hofer, O. (1976) in *Topics of Stereochemistry* (Allinger, N. L.

and Eliel, E. L., eds) pp. 111–197. Wiley, New York.
13. Lenkinski, R. E. and Reuben, J. (1976) *J. Am. Chem. Soc.* **98**, 4065.
14. Földesi, P. and Hofer, O. (1980) *Tetrahedron Letters* **21**, 2137.
15. Greger, H. (1985) *Pl. Syst. Evol.* **150**, 1.
16. Bohlmann, F. and Hoffmann, H. (1983) *Phytochemistry* **22**, 1173.
17. Greger, H. and Hofer, O. (1987) *J. Nat. Prod.* **50**, 1100.
18. Bohlmann, F. and Zdero, C. (1979) *Phytochemistry* **18**, 125.
19. Greger, H., Hofer, O. and Werner, A. (1987) *Phytochemistry* **26**, 2235.
20. Greger, H., Zdero, C. and Bohlmann, F. (1987) *Phytochemistry* **26**, 2289.
21. Greger, H., Zdero, C. and Bohlmann, F. (1984) *Phytochemistry* **23**, 1503.