Phytochemistry, Vol 23, No 7, pp 1503–1505, 1984
Printed in Great Britain

0031-9422/84 $3 00+0 00

PYRROLIDINE AND PIPERIDINE AMIDES FROM *ACHILLEA*

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(*Received* 11 *November* 1983)

Key Word Index—*Achillea nana*, *A macrophylla*, *A ligustica*, Compositae, unsaturated aliphatic acid amides, pyrrolidides, isobutyl amides, piperidide, chemosystematics

Abstract—The underground parts of three *Achillea* species afforded, in addition to known unsaturated aliphatic acid isobutyl amides, four new pyrrolidides and one new piperidide The structures were established by spectroscopic evidence The chemosystematic importance of the amide accumulation is discussed

INTRODUCTION

In connection with a comparative computerized UV–IR data screening program on secondary constituents within the tribe Anthemideae (Compositae), the accumulation of olefinic and acetylenic amides has been shown to be a typical chemical trend of the genus *Achillea* [1–5] This biogenetic capacity has also been observed in the probably related genera *Leucocyclus* [3], *Anacyclus* [2, 6, 7] and *Otanthus* [2], as well as in *Cladanthus* [2] and *Chamaemelum* [8] Moreover, from *Argyranthemum* species, a thienyl-hexadien-isobutyl amide has been isolated [9, 10] which, to date, could not be detected in the above genera but has recently been found in the North African annual *Matricaria pubescens* [11]

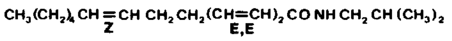
In continuation of these studies, we have now investigated the amide pattern of the underground parts of *Achillea nana* and *A macrophylla*, as well as an amide from *A ligustica* whose UV spectrum suggests a new chromophore in the acid moiety

RESULTS AND DISCUSSION

The polar fractions of the petrol–ether extract of *A nana* afforded a complex mixture of unsaturated amides which were separated by repeated TLC Finally, the isobutyl amides **1** [3], **2** [3], **3** [4], **4** and **5** [12, 13], as well as the pyrrolidides **6–9**, were isolated The structures of **1–5** followed from their spectral data, which agreed with those of authentic material

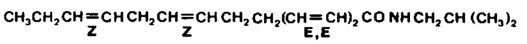
The UV spectra of **6–9** indicated the presence of dienoic acid amides although in the case of **9** the typical UV maximum was overlapped by the characteristic maxima of an endiyne chromophore The spectral data of **6** clearly indicated the presence of a dienamide with a pyrrolidine ring, while the molecular formula showed that a tetradecadienoic acid amide has to be assumed From the ^{1}H NMR spectrum of **7** (Table 1), again a conjugated amide structure with a pyrrolidine ring could be deduced from the typical pair of triplets at δ 3 53 and 3 51 and the corresponding pair of triplets of triplets The remaining signals were assigned by spin decoupling The *Z*-configuration of the Δ^{10}-double bond followed from the couplings observed The molecular formula of **8** ($C_{18}H_{25}NO$) already indicated that this amide differed from **7** by the degree of unsaturation As can be deduced from the ^{1}H NMR spectrum (Table 1), an 8,10-diyne has replaced the enyne group of **7** Thus **8** is related to anacyclin, the corresponding isobutyl amide **4** [12, 13] Similarly, all the data of **9** clearly showed that it is an amide, where the isobutyl amide group of 12,13-dehydroanacyclin (**5**) [13] is replaced by a pyrrolidide residue Accordingly, most of the ^{1}H NMR signals were similar However, as in other pyrrolidides, the nature of the amide group caused a considerable shift in the 2-H signal.

Achillea nana



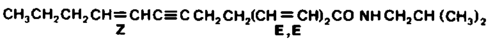
$\mathrm{CH_3(CH_2)_4CH\underset{Z}{=}CH\,CH_2CH_2(CH\underset{E,E}{=}CH)_2CO\,NH\,CH_2CH(CH_3)_2}$

1



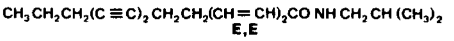
$\mathrm{CH_3CH_2CH\underset{Z}{=}CH\,CH_2CH\underset{Z}{=}CH\,CH_2CH_2(CH\underset{E,E}{=}CH)_2CO\,NH\,CH_2CH(CH_3)_2}$

2



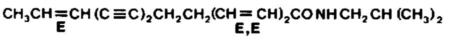
$\mathrm{CH_3CH_2CH_2CH\underset{Z}{=}CHC{\equiv}C\,CH_2CH_2(CH\underset{E,E}{=}CH)_2CO\,NH\,CH_2CH(CH_3)_2}$

3



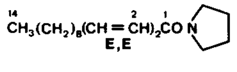
$\mathrm{CH_3CH_2CH_2(C{\equiv}C)_2CH_2CH_2(CH\underset{E,E}{=}CH)_2CO\,NH\,CH_2CH(CH_3)_2}$

4

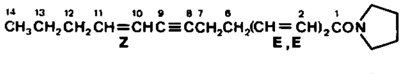


$\mathrm{CH_3CH\underset{E}{=}CH(C{\equiv}C)_2CH_2CH_2(CH\underset{E,E}{=}CH)_2CONH\,CH_2CH(CH_3)_2}$

5



6



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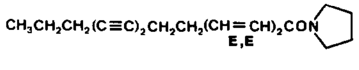

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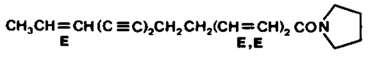
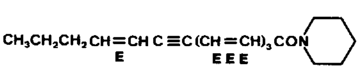


9

Achillea ligustica



10

Table 1 ^{1}H NMR spectral data of compounds **6**–**10** (400 MHz, TMS as internal standard)

	6	7	8	9	10
2-H	6 10 *d*	6 12 *d*	6 13 *d*	6 14 *d*	6 40 *d*
3-H	7 26 *dd*	7 27 *dd*	7 27 *dd*	7 27 *dd*	7 28 *dd*
4-H	6 20 *dd*	6 26 *dd br*	6 24 *dd br*	6 24 *dd br*	6 38 *dd*
5-H	6 09 *dt*	6 13 *dt*	6 08 *dt*	6 08 *dt*	6 53 *dd*
6-H	2 16 *dt*	2 41 *dt br*	2 38 *d**	2 44 *m*	6 60 *dd*
7-H		2 46 *t br*		2 40 *m*	5 85 *dd*
10-H	1 4–1 3 *m*	5 43 *dt*	—	—	5 64 *ddt*
11-H		5 87 *dt*	—	—	6 18 *dt*
12-H		2 25 *dq*	2 23 *t*	5 50 *dq*	2 12 *dq*
13-H		1 42 *tq*	1 55 *tq*	6 30 *dq*	1 44 *tq*
14-H	0 88 *t*	0 92 *t*	0 99 *t*	1 80 *dd*	0 92 *t*
N<	3 54 *t*	3 53 *t*	3 55 *t*	3 54 *t*	3 62 *m* (2H)
	3 52 *t*	3 51 *t*	3 53 *t*	3 52 *t*	3 49 *m* (2H)
	1 96 *tt*	1 96 *tt*	1 97 *tt*	1 97 *tt*	1 58 *m* (4H)
	1 86 *tt*	1 86 *tt*	1 87 *tt*	1 87 *tt*	1 65 *m* (2H)

*Not first order

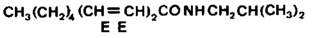
J (Hz) 2, 3 = 4, 5 = 15, 3, 4 = 10 5, 5, 6 = 6, 7 = 7, 11, 12 = 12, 13 = 13, 14 = 7 5, 2′, 3′ = 3′, 4′ = 4′, 5′ ~ 7, compound **7** 7, 10 = 10, 12 ~ 1 5, 10, 11 = 10 5, compound **8** 12, 13 = 7, compound **9** 12, 13 = 16, 12, 14 = 1 7, 13, 14 = 7, compound **10** 2, 3 = 4, 5 = 6, 7 = 15, 3, 4 = 5, 6 = 11, 7, 10 = 10, 12 ~ 1 5, 10, 11 = 15 5, 11, 12 = 7

A ligustica also contains a complex mixture of different amides from which one has been suggested to be new on the basis of UV comparison The molecular formula of this amide is $C_{19}H_{25}NO$ indicating a high degree of unsaturation, which was also supported by the UV maxima at 355 and 340 nm The nature of the amine group followed from the mass spectrum (*m/z* 84, $C_5H_{10}N^+$) and from the ^{1}H NMR spectrum (Table 1), which showed typical multiplets at δ 3 62, 3 49, 1 58 and 1 65 Spin decoupling allowed the assignment of all signals Starting with the 2-H signal (δ 6 40, *d*), the sequence of 2-H–7-H clearly could be established The presence of a long-range coupling between 7-H and 10-H allowed the completion of the sequence The nature of the end group (C-11–C-14) was easily deduced from the corresponding ^{1}H NMR signal, thus leading to structure **10** Its chromophore to date has not been observed

The amide pattern of *A macrophylla* is characterized by the known isobutyl amides **11** [12], **12** [2] and **13** [14] The compounds were identified by comparison of ^{1}H NMR, mass spectra, IR and UV data with authentic samples

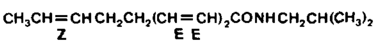
The present data again show that amide accumulation represents a significant chemical character of *Achillea* In addition to the more widespread isobutyl amides, the genus is particularly characterized by the frequent occurrence of piperidides and pyrrolidides Apart from the different amine parts, trends towards different carbon chain lengths as well as different levels of unsaturation within the acid moieties may serve as further chemosystematic criteria which most likely contribute to an infrageneric classification of *Achillea* Extensive chromatographic and spectroscopic comparisons of the petrol–ether extracts of other species exhibited a further series of probably new amides The isolation and structure elucidation of these compounds is currently under investigation in our laboratories

Achillea macrophylla



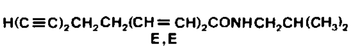
$\underset{E\ E}{CH_3(CH_2)_4(CH{=}CH)_2}CONHCH_2CH(CH_3)_2$

11



$CH_3\underset{Z}{CH{=}CH}CH_2CH_2\underset{E\ E}{(CH{=}CH)_2}CONHCH_2CH(CH_3)_2$

12



$H(C{\equiv}C)_2CH_2CH_2\underset{E,E}{(CH{=}CH)_2}CONHCH_2CH(CH_3)_2$

13

EXPERIMENTAL

Plant material *A nana* L was collected in Aosta valley, *ca* 2200 m, N W Italy, 29 July 1983, by L Schratt, *A macrophylla* L was collected in Kanton Valais, Furka Pass, *ca* 2000 m, Switzerland, 19 July 1982, by K Valant-Vetschera, *A ligustica* A22 was collected near Sparta, Peloponnesus, Greece, 29 June 1979, by K Vallant-Vetschera Voucher specimens are deposited at the Herbarium of the Institute of Botany, University of Vienna (WU)

Air-dried underground parts were cut into small pieces and extracted with petrol–Et_2O (2 1) for several days at room temp The resulting extracts were roughly fractionated by CC (silica gel), eluted with petrol–Et_2O mixtures, with Et_2O increasing from 0 to 100% and finally with 3–10% MeOH in Et_2O The polar fractions (100% Et_2O–10% MeOH in Et_2O) were separated by repeated TLC (silica gel and partly $AgNO_3$) using petrol–Et_2O mixtures and CH_2Cl_2–Et_2O (19 1) as solvents

A nana (33 g) afforded 26 mg **1**, 19 mg **2**, 6 mg **3**, 21 mg **4**, 2 mg **5**, 2 mg **6**, 10 mg **7**, 30 mg **8** and 5 mg **9**, *A macrophylla* (30 g) afforded 16 mg **11**, 9 mg **12** and 15 mg **13**, *A ligustica* (100 g) afforded 4 mg **10** MS were determined at 70 eV by direct insertion and ^{1}H NMR at 400 MHz Mps are uncorr

*Tetradeca-*2E,4E*-dienoic acid pyrrolidide* (**6**) Colourless oil, UV λ_{Et_2O} nm 254, IR $\nu_{\max}^{CCl_4}$ cm^{-1} 1625, 1600, 995 [(CH=CH)$_2$*E*,*E*], 1652 (CON<), MS *m/z* (rel int) 227 140 (8)

$[M]^+$ (calc for $C_{18}H_{31}NO$ 277 140), 165 (26) $[M-C_8H_{16}]^+$, 164 (26) $[M-C_8H_{17}]^+$, 150 (45) $[M-C_9H_{19}]^+$, 98 (62) $[C_4H_8NCO]^+$, 55 (100)

Tetradeca-2E,4E,10Z-*trien*-8-*ynoic acid pyrrolidide* (7) Colourless oil, UV λ_{Et_2O} nm 254, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1626, 1601, 996 [(CH=CH)$_2$*E*,*E*], 1652 (CON<), MS *m/z* (rel int.) 271 193 (4) $[M]^+$ (calc for $C_{18}H_{25}NO$ 271 193), 270 (6) $[M-1]^+$, 256 (1) $[M-Me]^+$, 242 (1) $[M-Et]^+$, 98 (28) $[C_4H_8NCO]^+$, 91 (100) $[C_7H_7]^+$, 79 (64) $[C_6H_7]^+$, 67 (48) $[C_5H_7]^+$

Tetradeca-2E,4E-*dien*-8,10-*diynoic acid pyrrolidide* (8) Colourless crystals, mp 88–89°, UV λ_{Et_2O} nm 255, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1628, 1602, 996 [(CH=CH)$_2$*E*,*E*], 1653 (CON<), MS *m/z* (rel int) 269 177 (14) $[M]^+$ (calc for $C_{18}H_{23}NO$ 269 177), 254 (6) $[M-Me]^+$, 240 (4) $[M-Et]^+$, 98 (26) $[C_4H_8NCO]^+$, 71 (50) $[C_4H_8NH]^+$, 55 (100) $[C_4H_7]^+$

Tetradeca-2E,4E,12E-*trien*-8,10-*diynoic acid pyrrolidide* (9) Colourless crystals, mp 107–10°, UV λ_{Et_2O} nm 282, 266, 253, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1627, 1602, 996 [(CH=CH)$_2$*E*,*E*], 1653 (CON<), MS *m/z* (rel int) 267 162 (32) $[M]^+$ (calc for $C_{18}H_{21}NO$ 267 162), 165 (21) $[M-C_8H_6]^+$, 98 (44) $[C_4H_8NCO]^+$, 55 (100) $[C_4H_7]^+$

Tetradeca-2E,4E,6E,10E-*tetraen*-8-*ynoic acid piperidide* (**10**) Yellow crystals, mp 98–102°, UV λ_{Et_2O} nm 355, 340; IR $\nu_{max}^{CCl_4}$ cm^{-1} 1603, 998 [(CH=CH)$_3$*E*,*E*,*E*], 1638 (CON<), 953 (CH=CH,*E*), MS *m/z* (rel int) 283 193 (63) $[M]^+$ (calc for $C_{19}H_{25}NO$ 283 193), 254 (28) $[M-Et]^+$, 186 (22), 129 (45), 128 (48), 112 (88), 91 (56), 84 (64) $[C_5H_{10}N]^+$, 69 (100)

Acknowledgements—We are indebted to Mrs L Schratt and Dr K Valant-Vetschera for providing the plant material Support by the Österreichischer Fonds zur Forderung der wissenschaftlichen Forschung (project No 4837) is gratefully acknowledged

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