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PIPERIDIDES AND OTHER AMIDES FROM *ACHILLEA* SPECIES*

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Key Word Index—*Achillea spinulifolia*; *A. grandifolia*; *A. lycaonica*; *A. tomentosa*; Compositae; Anthemideae; amides; piperidides; pyrrolidides; acetylenes.

Abstract—The investigation of the roots of four *Achillea* species afforded, in addition to known ones eight new amides most of them being piperidides. The structures were elucidated by spectrocopic methods. The chemotaxonomic importance of the amides is discussed briefly.

INTRODUCTION

So far the chemical investigations of 13 *Achillea* species have shown that acetylenic compounds with an amide grouping are characteristic for this genus[1–4]. These compounds have also been isolated from members of the genera *Anacyclus*[5], *Otanthus*[5] and *Leucocyclus*[4] which are probably closely related to *Achillea*. We have now investigated three further species and re-investigated *A. tomentosa*. Several known and eight new amides were isolated.

RESULTS AND DISCUSSION

The roots of *Achillea spinulifolia* Fenzl. ex Boiss. afforded the *iso*-butyl-amides **8**[1], **9**[6] and **12**[7] as well as two further ones, the acetylenic piperidides **1** and **3**. The structure of **1** followed from the spectroscopic data. The UV maximum indicated the presence of a dienamide, which was established by the ^1H NMR data (Table 1) and which further indicated that this amide was a piperidide as followed from the typical multiplets at δ 3.79, 3.67, 1.64 and 1.56. The nature of the unconjugated side chain was also deduced from the ^1H NMR data. The presence of a *cis*-double bond followed from the coupling of the olefinic signals, while the propyl end group was deduced by spin decoupling. Also the fragmentation pattern in the mass spectrum supported the structure (see Experimental). This was also true for the structure of **3**, where the fragments at m/z 101 $[Me(C{\equiv}C)_3CH_2]^+$ and $[M-101]^+$ clearly indicated the nature of the unsaturation. The ^1H NMR data (Table 1) in part were similar to those of **1**. However, the H-6 and H-7 signals were an overlapping multiplet and the H-14 signal was a sharp singlet, indicating that more than two triple bonds must be present. The roots of *A. grandifolia* Friv. afforded two amides, the enediyne **10** and a second diyne, which could be separated from **10** only with difficulty. Its molecular formula showed that this amide had two hydrogens less than **10**. The UV spectrum was similar to that of an enediyne triene carboxylate[8], while the ^1H NMR data (Table 1) led to structure **11**, as was deduced from spin decoupling experiments. Starting with the H-2 signal the H-3 signal could be assigned, which was partly obscured by the chloroform signal. However, in C_6D_6 this signal could be observed. Further decoupling allowed the assignment of H-4 through H-7, while the nature of the end group directly followed from the typical signals of a propenyl group linked to an acetylenic bond. The configuration of the double bond followed from the coupling constants observed. Compound **11** is the first fully conjugated C_{14}-amide.

The roots of *A. lycaonica* Boiss. et Heldr. afforded two amide fractions, which both crystallized easily. The mass spectra as well as the ^1H NMR spectra, however, showed that both were mixtures of two amides, differing by two hydrogens. Inspection of the ^1H NMR data led to the proposal each time that we were dealing with an α,β-unsaturated and the corresponding saturated amide. Consequently a separation with silver nitrate impregnated Si gel was possible to produce four amides with the molecular formulae $C_{23}H_{43}O_2$, $C_{23}H_{41}NO_2$, $C_{22}H_{41}O_2$ and $C_{21}H_{39}NO_2$. The ^1H NMR data (Table 1) indicated that the first pair were piperidides with and without a 2,3-*trans*-double bond, while the second one were pyrrolidides also differing in saturation. The nature of the second oxygen function followed from the IR spectra, while its position was deduced from the mass spectra, which in all cases showed elimination of $Me^{\cdot}$, $Et^{\cdot}$, $C_3H_7^{\cdot}$, $C_4H_{13}^{\cdot}$. The last fragment showed loss of a

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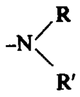
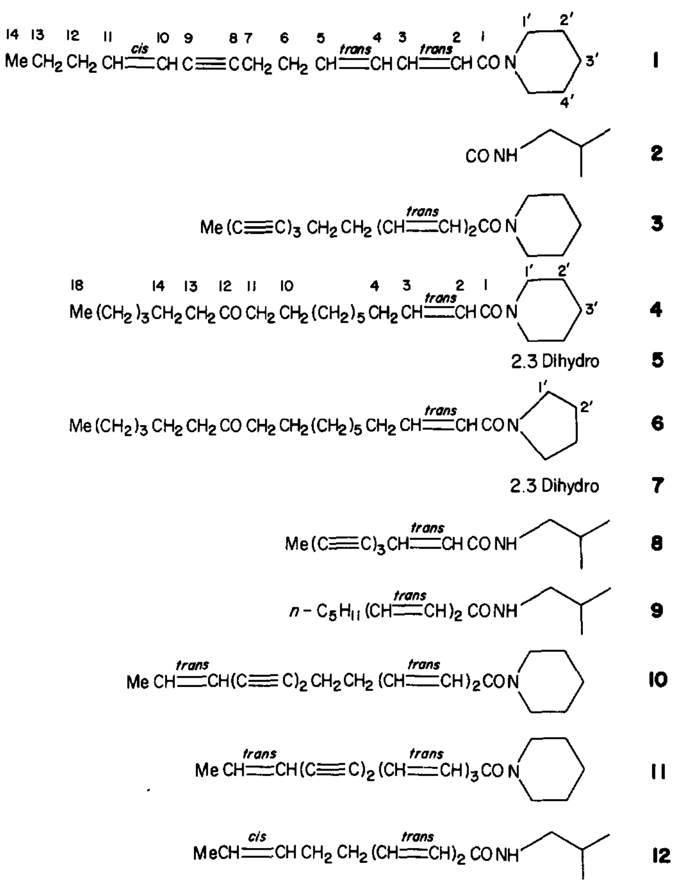
*Part 261 in the series "Polyacetylenic Compounds". For Part 260 see Greger, H., Grenz, M. and Bohlmann, F. (1981) *Phytochemistry* **20**, 2579.

Table 1. ^{1}H NMR spectral data of compounds **1–7** and **11** (400 MHz, $CDCl_3$, TMS as int. standard)

	1	**2**	**3**	**4**	**5**	**6**	**7**	**11**
H-2	6.28 *br d*	5.78 *br d*	6.31 *br d*	6.24 *dt*	2.30 *t*	6.08 *dt*	2.25 *t*	6.43 *d*
H-3	7.22 *dd*	7.19 *dd*	7.21 *dd*	6.82 *dt*	1.54 *m*	6.91 *de*	1.63 *m*	7.27 *dd*
H-4	6.24 *br dd*	6.20 *br dd*	6.23 *br dd*	2.18 *ddt*	1.29 *m*	2.19 *ddt*		6.73 *dd*
H-5	6.08 *br dt*	6.10 *br dt*	6.01 *br dt*	1.20 *m*		1.27 *m*	1.27 *m*	6.38 *dd*
H-6	2.40 *br dt*	2.40 *br dt*	2.40 *m*					6.52 *dd*
H-7	2.46 *br t*	2.47 *br dt*						5.80 *br d*
H-8, H-9	—	—	—					—
H-10	5.43 *dtt*	5.43 *br d*	—	1.57 *m*	1.54 *m*	1.55 *m*	1.55 *m*	—
H-11	5.83 *dt*	5.83 *dt*	—	2.38 *t*	2.38 *t*	2.38 *t*	2.38 *t*	—
H-12	2.25 *ddt*	2.24 *ddt*	—	—	—	—	—	—
H-13	1.42 *tq*	1.41 *tq*	—	2.38 *t*	2.38 *t*	2.38 *t*	2.38 *t*	—
H-14	0.91 *t*	0.91 *t*	1.95 *s*	1.57 *m*	1.57 *m*	1.55 *m*	1.53 *m*	—
H-15–H-17	—	—	—	1.29 *m*	1.29 *m*	1.29 *m*	1.29 *m*	5.60 *br d*, 6.33 *tq*
H-18	—	—	—	0.88 *t*	0.88 *t*	0.87 *t*	0.87 *t*	3.61 *m*
	3.79 *m*	—	3.61 *m*	3.59 *m*	3.53 *t*	3.52 *t*	3.46 *t*	3.61 *m*
	3.67 *m*	—	3.49 *m*	3.48 *m*	3.38 *t*		3.41 *t*	3.49 *m*
	1.56 *m*	—	1.57 *m*	1.57 *m*	1.54 *m*	1.96 *tt*	1.84 *tt*	1.57 *m*
	1.64 *m*	—	1.64 *m*	1.65 *m*	1.61 *m*	1.82 *tt*	1.94 *tt*	1.65 *m*

J(Hz): Compounds **1–3**: 2,3 = 4,5 = 15; 3,4 = 10.5; 5,6 = 6,7 = 7; compounds **1** and **2**: 10,11 = 10; 10,12 = 1.5; 11,12 = 13,14 = 7; compounds **4–7**: 10,11 = 13,14 = 17,18 = 7; compounds **4** and **6**: 2,3 = 15; 2,4 = 1.5; 3,4 = 4,5 = 7; compounds **5** and **7**: 2,3 = 7; compound **11**: 2,3 = 4.5 = 6,7 = 16,17 = 15; 3,4 = 5,6 = 10; 16,18 = 1.5; 17,18 = 7; NH*i*Bu: 1′, NH = 1′,2′ = 2′,3′ = 2′,4′ = 7; pyrrolidides 1′,2′ = 7.



Scheme 1.

carbonyl, indicating that the keto group could only be at C-12. Furthermore the corresponding peaks from a McLafferty fragmentation were visible (*m*/*z* 295, 293, 281 and 279 respectively). The other fragments were formed by splitting all single bonds of C-1 through C-11, though some fragments were more intensive indicating some preferences (Scheme 1). As all compounds also showed a prominent fragment, due to the corresponding acetyl amide, migration of the double bond must also have taken place which probably led to the favoured formation of some ions. All data were in agreement with structures **4**–**7**. The clear difference in polarity of the pairs **4**, **5** and **6**, **7** is interesting. The ^1H NMR data of H-2 and H-3, as well as those of the amide part, were also typically different. We have named the acid corresponding to **5** and **7** lycaonic acid.

A re-investigation of the extract of the roots of *A. tomentosa* L. afforded a further compound, the isobutylamide **2**. Its structure clearly followed from the ^1H NMR data (Table 1), which were similar to those of **1**, except for the amide part. These results again showed that different types of amides are typical for *Achillea* species. Further investigations are required to show to what extent these compounds may contribute to a species grouping within the genus.

EXPERIMENTAL

The roots were extracted with Et_2O–petrol (1:2) and the resulting extracts were separated first by CC (Si gel) and the polar fractions (Et_2O–petrol, 1:1 and Et_2O) further by repeated TLC (Si gel and partly $AgNO_3$–Si gel). Specimen vouchers are deposited in the Herbarium of the Institute of Botany, University of Vienna.

Achillea lycaonica (*voucher A*-1542). The roots (238 g) afforded 40 mg **3** and **4** (*ca* 1:1) as well as 40 mg **5** and **6** (*ca* 1:1). Separation on $AgNO_3$–Si gel (Et_2O–petrol, 7:3, ×3) gave the pure compounds.

Achillea spinulifolia (*voucher A*-1540). The roots (83 g) afforded 75 mg **1**, 8.4 mg **3**, 20 mg **8**, 95 mg **9** and 10 mg **12**.

Achillea grandifolia (*voucher A*-1443). The roots (130 g) afforded 5 mg **10** and **11** (*ca* 3:2), which could be separated by TLC on $AgNO_3$–Si gel, but only 1 mg pure **11** was obtained.

Achillea tomentosa (*voucher A*-1602). The roots (31 g) afforded in addition to the amides reported earlier[4] 5 mg **2** ($AgNO_3$–Si gel, Et_2O–petrol, 4:1).

Tetradeca-2t, 4t, 10c-*trien*-8-*ynoic-piperidide* (**1**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}; 2230 ($C\equiv C$), 1655, 1630, 1605 (C=CCON$\langle$); UV $\lambda_{max}^{Et_2O}$ nm: 257; MS *m*/*z* (rel. int.): 285.209 $[M]^+$ (11)($C_{19}H_{27}NO$), 284 $[M-H]^+$ (12), 270 $[M-Me]^+$ (3), 256 $[M-Et]^+$ (6), 242 $[M-C_3H_7]^+$ (2), 179 $[M-C_8H_9]^+$ (41) (McLafferty), 178 $[M-C_3H_7CH{=}CHCCH_2]^+$ (30), 164 $[179-Me]^+$ (14), 112 $[CONC_5H_{10}]^+$ (100), 84 $[112-CO]^+$ (93).

Tetradeca - 2t, 4t, 10c - *trien* - 8 - *ynoic* - *iso* - *butylamide* (**2**). Colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3440, 1670, 1620 (CH=CHCONH); UV $\lambda_{max}^{Et_2O}$ nm: 252; MS *m*/*z* (rel. int.):

273.204 $[M]^+$ (6) ($C_{18}H_{27}NO$), 272 $[M-H]^+$ (5), 201 $[M-NHR]^+$ (5), 173 $[201-CO]^+$ (20), 57 $[C_4H_9]^+$ (100).

Tetradeca - 2t, 4t - *diene* - 8,18,12 - *triynoic piperidide* (**3**). Colourless crystals, mp 115°; IR $\nu_{max}^{CCl_4}$ cm^{-1}; 2230 ($C\equiv C$), 1650, 1625, 1605 ($C{=}CCOH<$); UV $\lambda_{max}^{Et_2O}$ nm: 253; MS *m/z* (rel. int.): 279.162 $[M]^+$ (84) ($C_{19}H_{21}NO$), 264 $[M-Me]^+$ (2), 205 $[M-{}^{\cdot}NC_5H_{10}]^+$ (17), 178 $[M-Me(C\equiv C)_3CH_2]^+$ (41), 101 $[Me(C\equiv C)_3CH_2]^+$ (81), 84 $[NC_5H_{10}]^+$ (100).

2,3-*Dehydrolycaonic acid piperidide* (**4**). Colourless crystals, mp 43°; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1715 ($C{=}O$), 1660, 1620 ($C{=}CCON<$); MS *m/z* (rel. int.): 363.314 $[M]^+$ (2) ($C_{23}H_{41}NO_2$), 348 $[M-Me]^+$ (0.3), 334 $[M-Et]^+$ (0.5), 320 $[M-C_3H_7]^+$ (0.5), 306 $[M-C_4H_9]^+$ (3), 293 $[M-C_5H_{10}]^+$ (2) (McLafferty), 278 $[M-C_6H_{13}]^+$ (2), 250 $[278-CO]^+$ (6), 236 $[M-CH_2COC_6H_{13}]^+$ (14), 222 (3), 208 (4), 194 (4), 180 (7), 166 (20), 138 $[CH{=}CHCONC_5H_{10}]^+$ (100), 127 $[MeCON]^+$ (12), 112 $[138-C_2H_2]^+$ (10), 84 $[NC_5H_{10}]^+$ (24).

Lycaonic acid piperidide (**5**). Colourless crystals, mp 41°; IR $\nu_{max}^{CCl_4}$ cm^{-1} 1715 ($C{=}O$), 1645 ($CON<$); MS *m/z* (rel. int.): 365.329 $[M]^+$ (4) ($C_{23}H_{43}NO_2$), 350 $[M-Me]^+$ (0.2), 336 $[M-Et]^+$ (0.2), 322 $[M-C_3H_7]^+$ (0.2), 308 $[M-C_4H_9]^+$ (2), 295 $[M-C_5H_{10}]^+$ (1.5) (McLafferty), 280 $[M-C_6H_{13}]^+$ (4), 252 $[280-CO]^+$ (6), 238 $[M-CH_2COC_6H_{13}]^+$ (27), 224 (2), 210 (2), 196 (4), 182 (6), 168 (4), 154 (8), 140 (27), 127 $[MeCONC_5H_{10}]^+$ (100), 112 $[CONC_5H_{10}]^+$ (16), 84 $[NC_5H_{10}]^+$ (21).

2,3-*Dehydrolycaonic acid pyrrolidide* (**6**). Colourless crystals, mp 64°; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1715 ($C{=}O$), 1660, 1615 ($C{=}CCON<$); MS *m/z* (rel. int.): 349.297 $[M]^+$ (18) ($C_{22}H_{39}NO_2$), 306 $[M-C_3H_7]^+$ (1), 292 $[M-C_4H_9]^+$ (8), 279 $[M-C_5H_{10}]^+$ (4) (McLafferty), 264 $[M-C_4H_9]^+$ (6), 236 $[252-CO]^+$ (34), 222 $[M-CH_2COC_6H_{13}]^+$ (95), 208 (7), 194 (8), 180 (8), 166 (10), 102 (100), 124 (60), 113 $[MeCONC_5H_{10}]^+$ (83), 98 $[124-C_2H_2]^+$ (30), 70 $[98-CO]^+$ (72).

Lycaonic acid pyrrolidide (**7**). Colourless crystals, mp 44°; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1715 ($C{=}O$), 1645 ($CON<$); MS *m/z* (rel. int.): 351.314 $[M]^+$ (2) ($C_{22}H_{41}NO_2$), 336 $[M-Me]^+$ (0.3), 294 $[M-C_4H_9]^+$ (2), 281 $[M-C_5H_{10}]^+$ (2) (McLafferty), 266 $[M-C_6H_{13}]^+$ (3), 238 $[266-CO]^+$ (4), 224 (18), 210 (2), 196 (4), 182 (4), 168 (4), 126 (20), 113 (100), 70 (30).

Tetradeca - 2t,4t,6t,12t - *tetraene* - 8,10 - *diynoic piperidide* (**11**). Unstable, yellow gum, UV $\nu_{max}^{Et_2O}$ nm: 372, 348, 266; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2220 ($C\equiv C$), 1650 ($CON<$); MS *m/z* (rel. int.): 279.162 $[M]^+$ (19) ($C_{19}H_{21}MO$), 278 $[M-H]^+$ (9), 264 $[M-Me]^+$ (6), 195 $[M-NC_5H_{10}]^+$ (11), 167 $[195-CO]^+$ (24), 165 $[195-H_2]^+$ (60), 84 $[NC_5H_{10}]^+$ (100).

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