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ARTANOMALOIDE, A DIMERIC GUAIANOLIDE AND PHENYLALANINE DERIVATIVES FROM *ARTEMISIA ANOMALA*

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Key Word Index—*Artemisia anomala*; Compositae; sesquiterpene lactones; guaianolides; dimeric guaianolide; phenylalanine derivatives.

Abstract—The aerial parts of *Artemisia anomala* afforded in addition to umbelliferone, herniarin and salvigenin the eudesmanolides, reynosin and armexifolin, the guaianolides dehydromatricarin and its desacetyl derivative, two secoguaianolides, a dimeric guaianolide and two derivatives of phenylalanine. The structures were elucidated by spectroscopic methods.

INTRODUCTION

Artemisia anomala S. Moore has been used for centuries in Chinese folk medicine for its function as an analgesic, haemostatic, antibiotic and for curing wounds. So far nothing is known on the chemistry of this species. We therefore have studied a sample collected in autumn 1985 in China. The results are discussed in this paper.

RESULTS AND DISCUSSION

The extract of the aerial parts of *A. anomala* afforded, in addition to widespread compounds (see Experimental), the sesquiterpene lactones reynosin [1], armexifolin [2], dehydromatricarin [3], its desacetyl derivative [4], secotanapartholide (**5**) [5], the isomeric lactone **6** [6] and the dimeric lactone **4** as well as the phenylalanine derivatives **7** and **8**.

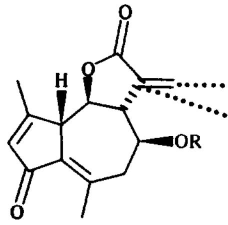
Table 1. ^{1}H NMR spectral data of **4** (400 MHz, $CDCl_3$, δ-values)

Hydrogen		Hydrogen	
2	6.39 *br d*	3′	6.19 *dq*
3	5.81 *br d*	5′	3.49 *br d*
5	1.94 *br dd*	6′	3.71 *dd*
6	4.18 *dd*	7′	2.88 *dd*
7	3.07 *m*	8′	5.03 *ddd*
8	2.21 *m*	$9'_1$	2.77 *dd*
	1.50 *m*	$9'_2$	2.34 *dd*
9	2.21 *m*	$13'_1$	2.33 *d*
13_1	6.12 *d*	$13'_2$	1.57 *d*
13_2	5.39 *d*	14′	2.41 *br s*
14	1.31 *s*	15′	2.31 *br s*
15	1.57 *s*	OAc	2.04 *s*

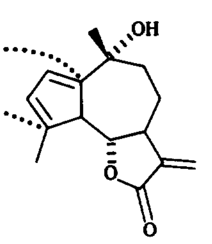
J[Hz]: 2,3 = 5.5; 5,6 = 6,7 = 10; 7,13 = 7,13′ = 3.5; 3′,5′ = 3′15′ = 1.2; 5′,6′ = 6′,7′ = 7′,8′ = 8′,$9'_1$ = 10; 8′$9'_2$ = 2.5; $9'_1 9'_2$ = 13; $13'_1 13'_2$ = 11.5.

The molecular formula of **4** was determined by high resolution mass spectroscopy as $C_{32}H_{36}O_8$. Intense fragments were *m/z* 302 and 246. As the sum of these fragments agreed with the molecular formula, it is likely that they are formed by RDA. The presence of an acetoxy group followed from *m/z* 488 [M − HOAc] and of a hydroxy group from *m/z* 228 (246 − H_2O). These groups also could be deduced from the ^{1}H NMR spectrum (Table 1) which was in part similar to that of **1** and 8-desoxycumambrin B [7]. However, the exomethylene protons of **1** were replaced by a pair of doublets at δ2.33 and 1.57. Furthermore a pair of broadened doublets at δ6.39 and 5.18 (*J* = 5.5 Hz) indicated the presence of a double bond in a five membered ring. As no vicinal couplings were present this double bond must have two neighbouring quaternary carbons. Spin decoupling allowed the assignment of all signals. Accordingly, all data indicate the presence of a dimeric lactone formed by Diels–Alder reaction of **1** with the not yet isolated diene **3**. The stereochemistry of **4**, which we have named artanomaloide, was established by NOE difference spectroscopy which also allowed the assignment of those signals which showed no coupling. Saturation of H-15 gave NOE's with H-3 (10%), H-5 (2%), H-6 (3%) and H-7′ (12%). The latter effect required that the cycloaddition of **1** has taken place from the α-face leading to β-methyl group at a C-4. Further NOE's were observed between H-5, H-7 (8%) and H-8′(5%), between H-14, H-2 (9%) and H-$13_2'$ (6%), between H-6′, H-8′ (4%) and H-$13_1'$, (4%), between H-7′, H-5′ (8%) and H-15 (6%) as well as between H-8′, H-5 (6%), H-6′ (4%) and H-$13'_1$ (8%). The ^{13}C NMR spectrum supported the proposed structure. The secoguaianolides **5** and **6** are probably formed from a dihydroxy guaianolide which could also be the precursor of **3**.

The structure of **7** followed from the ^{1}H NMR data (see Experimental) and from the fragmentation pattern in the mass spectrum. The presence of two benzamide groups followed from the typical ^{1}H NMR signals as well as from the fragments *m/z* 385 [M − $PhCONH_2$, McLafferty] and *m/z* 105 $[PhCO]^+$. The phenylalanine moiety could be deduced from the corresponding ^{1}H NMR signals, which were close to those of *N*-acyl derivatives of phenylalanine [8]. All data therefore agreed with the



1 R = Ac
2 R = H



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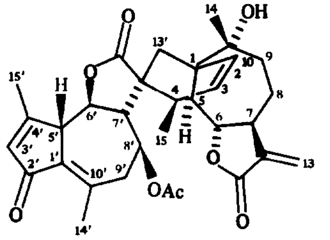

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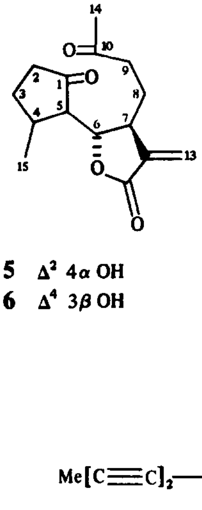
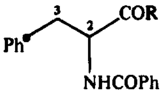
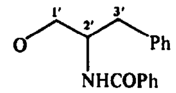


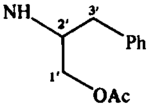
5 Δ^2 4α OH
6 Δ^4 3β OH

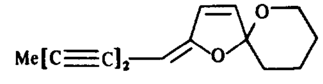


7 R =



8 R =





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presence of an ester of phenylalanine-*N*-benzoate with the corresponding alcohol, previously isolated from an *Anaphalis* species [9]. Since the spectral data for this compound are incomplete, we have added the ^{1}H NMR data in the Experimental. The spectral data of **8** are in part close to those of **7**. However, the ^{1}H NMR spectrum (see Experimental) indicated that one benzamide group was replaced by an acetate group which must be present as an *O*-acetate as the mass spectrum clearly showed elimination of acetic acid. All data therefore agree with the presence of an amide of phenylalanine-*N*-benzoate formed by reaction of the acid with the amino group of the acetylated phenylalaninol. Compound **8** we have named anomalamide. As the optical rotation of **8** has the same sign, a derivative of L-phenylalanine can be assumed. The roots afforded, like many other *Artemisia* species, the spiroketal enolether polyine **9** [10].

Most of the constituents of *A. anomala* are common in *Artemisia* species except the amides **7** and **8** and the dimeric lactone **4**. However, other dimeric lactones like absinthin and related compounds have been reported from several species [11, 12].

EXPERIMENTAL

The air-dried aerial parts (500 g, collected in autumn 1985 near Shanghai, V.R. China) were extracted with EtOH and the extract obtained was worked-up as reported previously [13]. CC (SiO_2) and TLC (Et_2O–petrol-mixtures) gave 83 mg sitosterol, 76 mg herniarin, 26 mg **1**, 17 mg **2**, 50 mg reynosin, 14 mg salvigenin, 18 mg umbelliferone, 27 mg **5**, 30 mg **6**, 18 mg armexifolin, 16 mg **4** [TLC ($CHCl_3$–MeOH, 10:1, R_f 0.45)], 20 mg **7** [TLC ($CHCl_3$–MeOH, 40:1, × 3, R_f 0.3)] and 25 mg **8** [TLC (same solvent, R_f 0.28)]. The roots (1 kg) gave by CC and TLC 50 mg nerylisovalerate and 800 mg **9**. Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material.

Artanomaloide (**4**). Colourless gum; IR $\nu_{\max}^{CHCl_3}$, cm^{-1}: 3600 (OH) 1780, 1770 (γ-lactone), 1740 (OAc), 1695 (C=CC=O); MS m/z (rel. int.): 548.241 $[M]^+$ (2) (calc. for $C_{32}H_{36}O_8$: 548.241), 530 $[M-H_2O]^+$ (1), 488 $[M-HOAc]^+$ (2), 302 (70) and 246 (60) (RDA), 260 $[302-\text{ketene}]^+$ (20), 242 $[302-HOAc]^+$ (50), 228 $[246-H_2O]^+$ (100); ^{13}C NMR ($CDCl_3$, signals not assigned): 14.5, 20.0, 20.3, 21.7 and 29.9 *q*; 23.7, 34.9, 36.7, 43.6 and 119.4 *t*; 43.4, 50.3, 56.6, 66.2, 66.4, 79.2, 79.5, 131.9, 136.2 and 142.9 *d*; 57.3, 59.9, 63.1, 72.7, 134.3, 140.7, 143.4, 170.1, 170.4, 170.2, 176.2 and 194.7 *s*; $[\alpha]_D^{24°} - 17$ ($CHCl_3$; *c* 0.2).

(−)-*Anabellamide* (**7**). Colourless crystals, mp. 204°, (Lit. [9] 202°); IR $\nu_{\max}^{CHCl_3}$, cm^{-1}: 1740 (CO_2R), 1640 (CONH); MS *m/z* (rel. int.): 506.220 $[M]^+$ (0.6) (calc. for $C_{32}H_{30}O_4N_2$: 506.220), 415 $[M-C_7H_7]^+$ (6), 294 $[415-PhCONH_2]^+$ (4), 252 $[C_{16}H_{14}O_2N]^+$ (8), 224 $[C_{15}H_{14}ON]^+$ (7), 148 $[PhCH{=}CHCO_2H]^+$ (25), 146 $[294-PhCH{=}CHCO_2H]^+$, 118 $[C_9H_{10}]^+$ (11), 105 $[PhCO]^+$ (100), 91 $[C_7H_7]^+$ (43), 77 $[105-CO]^+$ (38); ^{1}H NMR (400 MHz, $CDCl_3$): PhCONH-R: δ7.70 (*d*, 2H), 7.72 (*d*, 2H), 7.40 (*t*, 2H), 7.45 (*t*, 2H), 7.51 (*t*), 7.53 (*t*); C_6H_5: 7.23 and 7.29 (*m*, 10H), 4.91 (*br q*, H-2), 3.30 and 3.22 (*dd*, H-3), 6.56 and 6.67 (*d*, NH), 4.55 and 4.04 (*dd*, H-1′), 4.62 (*m*, H-2′), 3.01 and 2.90 (*dd*, H-3′); $[\alpha]_D^{24°} - 35$ ($CHCl_3$; *c* 0.05).

Anomalamide (**8**). Colourless crystals, mp 185°; IR $\nu_{\max}^{CHCl_3}$, cm^{-1}: 1740 (CO_2R), 1640 (CONH); *m/z* (rel. int.): 444.205 $[M]^+$ (1.8) (calc. for $C_{27}H_{28}O_4N$: 444.205), 384 $[M-HOAc]^+$ (3), 353 $[M-C_7H_7]^+$ (3), 323 $[M-PhCONH_2]^+$ (2), 293 $[353-HOAc]^+$ (4), 252 $[C_{16}H_{14}O_2N_2]^+$ (42), 224 $[C_{15}H_{14}ON]^+$ (26), 105 $[PhCO]^+$ (100); ^{1}H NMR ($CDCl_3$): PhCONH-R: 7.72 (*d*, 2H), 7.45 (*t*, 2H), 7.53 (*d*); Ph: 7.15–7.3 (*m*, 10H), 4.77 (*ddd*, H-2), 3.23 and 3.06 (*dd*, H-3), 6.75 and 5.92 (*d*, NH), 3.93 and 3.81 (*dd*, H-1′), 4.34 (*m*, H-2′), 2.77 and 2.73 (*dd*, H-3′) (*J* [Hz]: $2,3_1 = 6; 2,3_2 = 9; 2,NH = 7; 3_1,3_2 = 14; 1'_1,1'_2 = 11; 1'_1,2' = 1'_2,2' = 5; 2',3'_1 = 2', 3'_2 = 7; 2', NH = 9; 3'_1, 3'_2 = 13$); $[\alpha]_D^{24°} - 38$ ($CHCl_3$; *c* 0.1).

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