Phytochemistry, 1979, Vol. 18, pp. 331–332. © Pergamon Press Ltd. Printed in England.

0031-9422/79/0201-0331 $02.00/0

ACHILLICIN, THE FIRST PROAZULENE FROM *ACHILLEA MILLEFOLIUM*

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(*Received* 7 *July* 1978)

Key Word Index—*Achillea millefolium* ssp. *collina*; *A. collina*; Compositae; yarrow; guaianolide sesquiterpene; proazulene; 8-acetoxyartabsin.

Abstract—Achillicin, the major proazulene (prochamazulene) of *Achillea millefolium* L. ssp. *collina* Becker has been isolated and identified as 8-acetoxyartabsin. It is the first proazulene reported for the genus *Achillea* and has not been found previously in plants.

INTRODUCTION

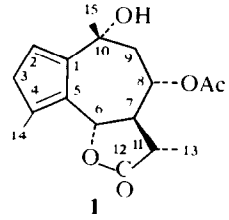
For many years, *Achillea millefolium* (yarrow, milfoil) has been known to yield proazulene-rich essential oils. Despite extensive investigations into its constituents [1–11], identification of the natural proazulenes has not been reported. Matricin, a proazulene from chamomile (*Matricaria chamomila*) has been reviewed [12] as occurring also in some *Achillea* species (*A. collina* Becker, *A. crithmifolia* W. et K., *A. pannonica* Scheel, *A. stricta* Schleid. In the paper cited [13] however, the occurrence of proazulenes in general, and not that of matricin had been stated. Similarly, the suggestion [14] that chamazulene carboxylic acid is a natural proazulene of the genus *Achillea* proved erroneous [15].

Now we report the isolation and structure elucidation of achillicin, the first natural proazulene identified for the genus *Achillea*. This compound has not been previously found in plants.

RESULTS AND DISCUSSION

Accurate mass measurements gave the molecular formula of achillicin as $C_{17}H_{22}O_5$ (306.145, requires 306.146) and MS indicated the presence of an acetoxy function (*m/e* 246.124, $C_{15}H_{18}O_3^+$, requires 246.126, M-60) and a OH group (*m/e* 228.113, $C_{15}H_{16}O_2^+$, requires 228.115, M-60-18). These were also confirmed by IR (1727 cm^{-1}, CO and 3453 cm^{-1}, OH) which, in addition, disclosed the presence of a saturated γ-lactone (1773 cm^{-1}), a tertiary OH group (1153 cm^{-1}) and two conjugated double bonds (1613 cm^{-1}). Treatment of achillicin in boiling 5% NaOH yielded chamazulene carboxylic acid (identified by IR, MS, PMR and ^{13}C NMR spectra and by transformation into chamazulene) which established the guaiazulene skeleton.

Conclusive information on the structure and stereochemistry of achillicin as **1** was inferred from PMR and ^{13}C NMR data (Tables 1 and 2). Disregarding the acetoxy group, the PMR data are in excellent agreement with values reported for artabsin [16–18]. ^1H-{^1H} double resonance experiments defined the positions of the conjugated double bonds and the acetoxy group. The stereochemistry at C-6, C-7, C-8 and C-11 was readily elucidated by ^1H-{^1H} coupling constants (see Table 1).



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The relative configuration at C-10 was inferred from consideration of ^{13}C chemical shifts indicating an equatorial orientation for the C-10 Me group (lack of 1,3 diaxial steric interactions).

EXPERIMENTAL

IR: KBr; MS: 70 eV, probe, source temp. 130°; PMR and ^{13}C NMR: 100.1 and 25.16 MHz, $CDCl_3$.

Isolation of 1. The air-dried (40 g) flowerheads of *A. mille-*

Table 1. PMR data (δ ppm from TMS) for achillicin

2-H	6.09	C-4Me	2.19
3-H	2.90	C-10Me	1.62
6-H	5.50	C-11Me	1.30
8-H	5.52	—OH	1.73
9-H_{ax}	1.66	O—CO—Me	2.09
9-H_{eq}	2.28		
11-H	2.62		

J(Hz): 2,3 = 1.5; 3,6 = 1.5; 6,7 = 10; 6,C-4Me = 2; 7,8 = 11; $8,9_{ax}$ = 10.5; 7,11 = 11; $8,9_{eq}$ = 4; $9_{ax},9_{eq}$ = 14; 11,C-11Me = 7.

Table 2. ^{13}C NMR chemical shifts (δ ppm from TMS) for achillicin

C-1	137.85	C-9	46.50
C-2	124.54	C-10	69.40
C-3	45.58	C-11	55.94
C-4	149.84	C-12	178.20
C-5	134.04	C-4Me	14.90
C-6	78.24	C-10Me	30.38
C-7	40.50	C-11Me	15.50
C-8	73.46	O—CO—Me	21.16
		O—CO	169.96

folium L., ssp. *collina* Becker collected in summer 1976 near Budapest, Hungary, were extracted with Et_2O (1.5 l.) and made alkaline with few drops of NH_4OH. Hexane (40 ml) and H_2O (400 ml) were added to the extract which was then evapd in a rotary evaporator. After filtration, the aq. filtrate was extracted with $CHCl_3$ (3 × 100 ml). The solvent was evapd under red. pres. and the resulting extracts were separated by column chromatography (Si gel 40, C_6H_6–EtOAc, hexane–EtOAc–$CHCl_3$). The fractions were analysed by TLC (Si gel G) using hexane–EtOAc–$CHCl_3$ (9:5:6) as solvent. Components were visualized by spraying with EP reagent [20], followed by heating for 10 min at 100° and subsequent spraying with EtOH for colour enhancement [15]. On removal of the solvent, the most EP-positive chromatographic fractions afforded crystalline achillicin (R_f = 0.3).

Conversion of **1** *to chamazulene carboxylic acid.* A few mg of **1** were boiled in 5% aq. NaOH (5 ml) for 15 min, cooled, neutralized with 2N H_2SO_4 and extracted with hexane. Evapn gave pure chamazulene carboxylic acid.

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Phytochemistry, 1979, Vol. 18, pp. 332–333. © Pergamon Press Ltd. Printed in England. 0031-9422/79/0201-0332 $02.00/0

NEUE EUDESMANOLIDE AUS *GAZANIA KREBSIANA**

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(*Eingegangen am* 25 *Juli* 1978)

Key Word Index—*Gazania krebsiana*; Compositae; new eudesmanolides.

Die südafrikanische Gattung *Gazania*, Tribus Arctotideae, ist chemisch noch wenig untersucht. Bisher sind lediglich Spuren von Acetylenverbindungen [1] und einige Carotinoide [2] isoliert worden. Wir haben jetzt *G. krebsiana* Less. näher untersucht. Die Wurzeln enthalten die Triperpene **1**–**4** sowie in sehr kleiner Menge zwei Sesquiterpenlactone. Die etwas weniger polare Verbindung mit der Summenformel $C_{15}H_{18}O_2$ zeigt im ^{1}H-NMR-Spektrum sehr charakteristische Signale, die nur mit der Konstitution **5** vereinbar sind (s. Tabelle 1), während es sich bei der polareren Substanz um das entsprechende 8α-Isovaleryloxy-Derivat **6** handeln muß. Doppelresonanz-Experimente zeigen klar, daß bei **5** das nicht gut aufgelöste Signal bei 5.72 dem 3-H zugeordnet werden muß. Bei Einstrahlung auf das 4-Methylsignal bei 2.00 erhält man ein klares dreifaches Dublett (J = 5.5, 3, 0.7 Hz). Das betreffende Proton koppelt also vicinal mit den 2-H (J = 5.5), sowie allyisch mit 5-H (J = 3) und 1-H (J = 0.7). Derartige Kopplungsmuster sind charakteristisch für entsprechende Cyclohexadiene. Weiterhin kann man zeigen, daß das Signal für 6β-H (*dd* 4.03) mit dem verbreiterten Dublett bei 2.68 und dem *ddddd* bei 2.54 koppelt. Letzteres ist nur dem 7α-H zuzuordnen. Entsprechend beobachtet man bei Einstrahlung auf 2.54 eine Entkopplung der Signale für 13-H und eine Veränderung der Multipletts bei 2.03 und 1.62, die zweifellos den Protonen an C-8 zuzuordnen sind. Beim Spektrum von **6** beobachtet man ein *ddd* 5.23 (J = 10, 10, 4), sowie eine geringfügige Tieffeldverschiebung der Signale für 5-, 6-, 7- und 13-H. Dieses ist charakteristisch für Lactone mit einem Esterrest in 8α-Stellung [3]. Alle übrigen Signale entsprechen weitgehend denen von **5** (s. Tabelle 1). **5** ist ein 1,2-Dehydro-α-cyclocostunolid, das wir Gazaniolid nennen möchten.

Derartige Verbindungen sind bisher noch nicht als Naturstoff isoliert worden. Evt. Vorstufen von **5** sind jedoch Santamarin [4] bzw. Douglanin [5]. Bemerkens-

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