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NEW 5-METHYLCOUMARIN DERIVATIVES FROM *ETHULIA CONYZOIDES**

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Key Word Index—*Ethulia conyzoides*; Compositae; coumarins; terpene derivatives; 5-methyl coumarins; eucarvone derivative.

Abstract—A reinvestigation of the aerial parts of *E. conyzoides* L. afforded three new 5-methyl coumarins and a degraded *nor* compound with an eucarvone part. The structures were elucidated using spectral methods and some chemical transformations. The biogenetic relationships of these compounds are discussed.

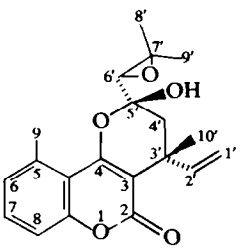
INTRODUCTION

Ethulia conyzoides (Compositae, tribe Vernonieae) has been investigated before [1], but the amount of material was very limited. Therefore, a reinvestigation of this plant was worthwhile. In addition to the 5-methyl coumarin **1**, several other compounds of this type are present. Their structures could be elucidated by spectral methods and few chemical transformations.

RESULTS AND DISCUSSION

The ether extract of the aerial parts of *E. conyzoides* afforded 4 isomeric 5-methyl coumarin compounds. One of them is the already known ethuliacoumarin **1** [1] and the others were accordingly named isoethuliacoumarin A–C. In the ^{1}H NMR (Table 1) isoethuliacoumarin A displays additional signals of vinylic protons with one of the methyl singlets missing and another one is olefinic [*s*(*br*) 1.86]. Double resonance experiments clearly show a coupling of the vinyl protons with this methyl group. While most of the other ^{1}H NMR signals are very similar to those of **1** a doublet at 4.38 ppm replaces the singlet at 3.05 in the spectrum of **1**. Decoupling shows that the doublet couples with a doublet at 2.34 which is due to a hydroxyl proton. Consequently this signal disappears after exchange with D_2O and the doublet at 4.38 collapses to a singlet. These results are in good agreement with structure **2**. On treating with periodate this isomer afforded the same lactone **5** previously obtained from **1** after methanolysis and periodate treatment and thus confirming the proposed structure **2**. The relative configuration at C-3′ and C-5′ in **1** could be proposed from the different chemical shifts of 10′-H and 2′-H in the C-5′-isomers [1]. As **2** shows the same shifts this may be an indication that the relative configuration is the same, while the absolute configuration and that at C-6′ could not be clarified.

The second isomer isoethuliacoumarin B, shows a ^{1}H NMR spectrum again very similar to **1** (Table 1). However, there are some characteristic differences which can only be explained if we assume structure **3**



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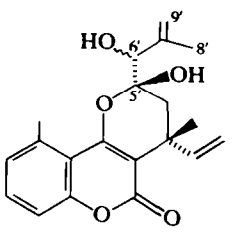

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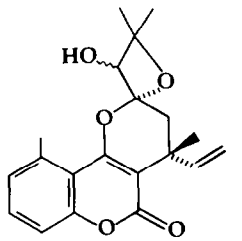

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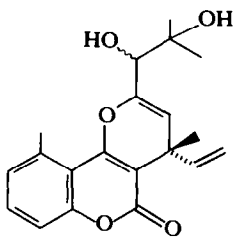

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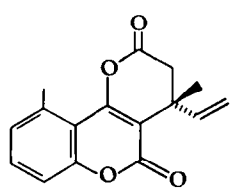

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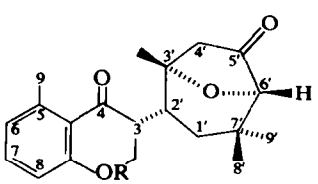


6a R = H
6b R = Ac

* Part 266 in the series "Naturally Occurring Terpene Derivatives". For Part 265 see Bohlmann, F., Zdero, C., Cuatrecasas, J., King, R. M. and Robinson, H. (1980) *Phytochemistry* **19**, 1145.

Table 1. ^{1}H NMR data of **1–4** (270 MHz, TMS as int. standard, $CDCl_3$)

	1[1]	**2***	**3**	**4**
6-H	7.02 *d*(*br*)	7.01 *d*(*br*)	7.02 *d*(*br*)	7.04 *d*(*br*)
7-H	7.35 *dd*	7.33 *dd*	7.33 *dd*	7.36 *dd*
8-H	7.15 *d*(*br*)	7.14 *d*(*br*)	7.14 *d*(*br*)	7.15 *d*(*br*)
9-H	2.74 *s*(*br*)	2.75 *s*(*br*)	2.80 *s*(*br*)	2.75 *s*(*br*)
1′-H	5.10 *d*	5.11 *m*	5.18 *d*	5.07 *dd*
1′*c*-H	5.15 *d*		5.08 *d*	5.22 *dd*
2′-H	6.10 *dd*	6.11 *dd*	6.26 *dd*	6.47 *dd*
$4'_1$-H	2.23 *d*(*br*)	1.89 *d*(*br*)	2.39 *d*	
$4'_2$-H	2.03 *d*	1.81 *d*	2.04 *d*	5.04 *s*
6′-H	3.05 *s*	4.38 *d*	4.57 *d*	4.08 *d*
8′-H	1.50 *s*	1.86 *s*(*br*)	1.53 *s*	1.38 *s*
		4.50 *d*		
9′-H	1.39 *s*		1.41 *s*	1.32 *s*
		5.11 *m*		
10′-H	1.70 *s*	1.73 *s*	1.61 *s*	1.64 *s*
OH		2.34 *d*	2.28 *s*	2.68 *d*

* In C_6D_6—$CDCl_3$ (1:2): 6.03 (*d*, 1′*t*-H); 5.01(*d*, 1′*c*-H); 4.89 and 4.85 (*s*(*br*), 9′H). *J*(Hz): 6.7 = 7,8 = 8; $4'_1$, 4_2 = 14; 1′*t*,2′ = 17; 1′*c*,2′ = 10; **3**: 6′.OH = 5; **4**: 1′*t*, 1′*c* = 1; 6′OH = 3.5.

with an oxetane ring. A doublet at 4.57 ppm can be assigned to 6′-H. D_2O-exchange shows that the doublet splitting is due to a coupling with the OH-proton (2.28, *d*). The shift differences of the signals for 2′-H and 10′-H in the spectra of **1** and **3** indicate a different configuration at C-5′ (see above), while again that at C-6′ is not clear. Also the MS of **3** is in good agreement with the proposed structure, both, elimination of acetone and of $HOCH{=}CMe_2$ can be observed, which is typical for oxetanes.

The third compound, isoethuliacoumarin C, also shows some characteristic differences in the ^{1}H NMR spectrum from **1** (Table 1). The doublets for 4′-H are replaced by an olefinic singlet at 5.04 ppm, while again a doublet at 4.08 (collapsing to a singlet after exchange with D_2O) must be assigned to the proton at C-6′ bearing a hydroxyl. All data can only be explained if we assume structure **4** for this isomer. The MS is also in good agreement with this assumption. Elimination of acetone directly and after loss of

Table 2. NMR data of **6a** and **6b** (270 MHz, $CDCl_3$ and 25.2 MHz for ^{13}C NMR)

	6a	Δ	**6b**	**6a** ^{13}C
3-H	2.92 *dd*	0.10	2.73 *dd*	C-3 46.9 *t*
3′-H	2.34 *dd*	0.11	2.36 *dd*	C-4 206.4 *s*
6-H	6.83 *d*(*br*)	0.07	7.08 *d*(*br*)	C-5 133.8 *s*
7-H	7.27 *dd*	0.02	7.30 *dd*	C-6, C-7 123.4 *d*
8-H	6.74 *d*(*br*)	0.02	6.97 *d*(*br*)	
9-H	2.52 *s*(*br*)	0.03	2.26 *s*(*br*)	C-8 116.1 *d*
$1'_1$-H	1.00 *dd*	0.20	0.97 *dd*	C-9 23.4 *q*
$1'_2$-H	1.58 *ddd*	0.13	1.77 *ddd*	C-10 160.0 *s*
2′β-H	2.75 *dddd*	0.11	2.67 *dddd*	C-11 137.7 *s*
$4'_1$-H	2.31 *d*	0.27	2.23 *d*	C-1′ 39.5 *t*
$4'_2$-H	2.14 *d*(*br*)	0.28	2.10 *d*	C-2′ 37.5 *d*
6′-H	3.52 *s*(*br*)	0.29	3.53 *s*(*br*)	C-3′ 82.0 *s*
8′-H	0.91 *s*	0.18	0.93 *s*	C-4′ 43.7 *t*
9′-H	1.19 *s*	0.09	1.22 *s*	C-5′ 214.6 *s*
10-H	1.45 *s*	0.05	1.45 *s*	C-6′ 86.3 *d*
OH	10.64 *s*	0.22	—	C-7′ 33.8 *s*
OAc	—	—	2.24 *s*	C-8′ 24.5 *q*
				C-9′ 24.8 *q*
				C-10′ 25.0 *q*

J(Hz): 2′, 3_1 = 4.5; 2′, 3_2 = 8.5; 3_1, 3_2 = 16; 6,7 = 7,8 = 8; 1_1, 2′ = 12; $1'_2$, 2′ = 4.5; $1'_1$, $1'_2$ = 14; $1'_1$, 6′ = 2; $4'_1$, $4'_2$ = 18; 6′, $4'_2$ ~ 1.5.

methyl leads to prominent peaks. This behaviour is typical for such an arrangement. The loss of the methyl at C-3′ produces the highly stabilized pyrylium cation and consequently the M^+ ion is very small.

The petrol extract, on the other hand, afforded a compound which reveals significant differences from the previous isomers. The molecular formula ($C_{19}H_{24}O_4$) indicates together with the spectral data that we are dealing with a compound which is not a coumarin. Most probably C-2 is missing. Consequently there is a hydrogen bridge between a phenolic hydroxyl and an aromatic keto group (IR and ^{1}H NMR spectrum), which disappears after acetylation giving a monoacetate. The ^{1}H NMR (Table 2) further shows that the aromatic part still has the same substitution pattern as in **1–4**. Therefore, this compound must be a terpene substituted by 3-methyl-*o*-hydroxy acetophenone. Intensive double-resonance experiments, also with addition of Eu(fod)$_3$, led to the structure **6a**, which could be further established by the ^{1}H NMR data of the acetate **6b** (Table 2) and by the ^{13}C-NMR data of **6a**. In the ^{1}H NMR spectrum of **6a** irradiation of the four-fold doublet at 2.75 collapses the two double-doublets at 2.95 and 2.54, as well as those at 1.0, and the three-fold doublet at 1.58 to doublets respectively to a double-doublet (1.58). Further decoupling experiments show that irradiation at 3.52 changes the signal at 1.58 to a double-doublet and sharpens the broadened doublet at 2.14 indicating two *W*-couplings. Together with the observed coupling constants this also establishes the configurations at C-2′, C-3′ and C-6′, while the absolute configuration is unknown. The ^{13}C-NMR data (Table 2) clearly show that we are dealing with an *o*-hydroxy acetophenone and a compound with an ether ring (86.3, *d*) and 82.0, *s*). The only position for the keto group is at C-5′. An IR band at 1760 cm^{-1} already indicates a five-membered ring ketone. **6a** is a derivative of eucarvone for which the name ethuliconyzone is proposed.

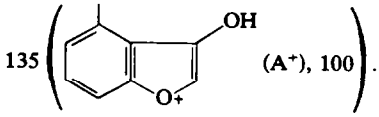
If we look at the compounds isolated from this *Ethulia* species, a biogenetic pathway starting with the keto acid **7** and the monoterpene **8** can be proposed. If **7** reacts with **8** at C-2′ after protonating the epoxide oxygen, the intermediate **9** would result, which by internal addition of the hydroxyl at C-6′ to the conjugated ketone would lead to **10**. Decarboxylation finally could afford **6a**. If **7**, on the other hand, reacts with **8** at C-3′ a compound would be obtained which after cyclization to a coumarin and ring closure between the oxygen at C-4 and C-5′ would result in the formation of **1**. The further transformations of **1** to **2–4** are obvious.

So far the compounds isolated from the monotypic genus *Ethulia* are unique. However, 5-methylcoumarins are also present in other genera of the tribe Vernonieae [2, 3] and also in *Gerbera* belonging to the Mutisieae [4, 5]. Further investigations of the complex tribe are necessary to see whether these compounds are chemotaxonomically important.

EXPERIMENTAL

IR: $CHCl_3$, KBr; ^{1}H NMR: 270 MHz, TMS as int. standard; ^{13}C-NMR: 25.2 MHz, TMS as int. standard; MS: 70 eV; optical rotation: $CHCl_3$. Air-dried aerial parts (3 kg) (collected on canal banks near Mansoura in Summer 1978, identified by Dr. N. El-Hadidi, Dept. of Botany, Cairo University, Voucher sample being deposited in the Dept. of Pharmacognosy, Mansoura University) were powdered and first extracted with petrol (A) and further with Et_2O (B). *A* was separated by column chromatography using Al_2O_3 and C_6H_6—EtOAc and further by prep. TLC on Si gel. One third of *A* afforded with C_6H_6—EtOAc (1:1) 95 mg **6a**. *B* was treated with charcoal then separated by column chromatography using Si gel and Et_2O–petrol (E–P) to afford 750 mg **1** (E–P, 1:7), 3.6 g **2** (E–P, 1:4), 100 mg **3** (E–P, 1:3) and 600 mg **4** (E–P, 2:3).

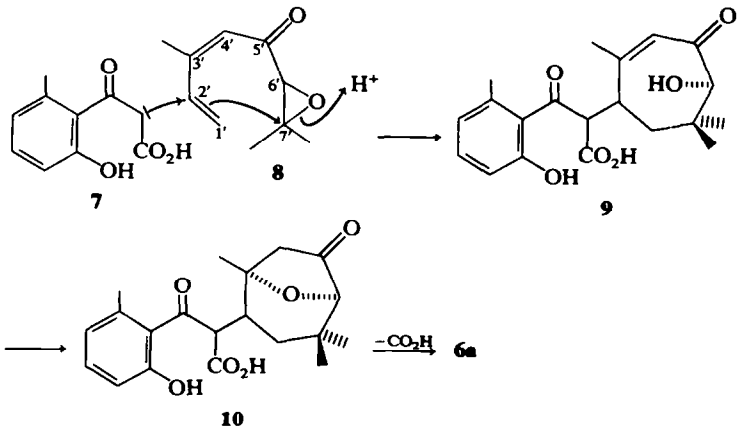
Isoethyliacoumarin A (**2**). Colourless crystals from E–P, mp 156–57°. IR (KBr) cm^{-1}: 3480 (OH), 1695 (C=O), 1600, 1563 (aromatic); MS: *m/e* (rel. int.): 342.147 (M^+, 4%) ($C_{20}H_{22}O_5$); 324 ($M^+ - H_2O$, 5); 271 (M^+ – HOCHC(Me)CH_2. 44); 243 (271 –CO, 25): 229 (271 – C_2H_2O, 65):



UV (Et_2O) nm: 323, 308, 288, 275 (ε = 4700, 6800, 11 900, 12 100)

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\ \text{nm}}{-20.4 \quad -21.7 \quad -26.0 \quad -55.0} \ (c = 1.61).$$

To 5 mg **2** in 0.5 ml MeOH 10 mg $NaIO_4$ in 0.1 ml MeOH was added. After 30 min the reaction product was extracted



with Et_2O and the residue was crystallized from E–P, colourless crystals, mp 148°(2.5 mg), identical with an authentic sample (mp, ^1H NMR).

Isoethyliacoumarin B (**3**). Colourless crystals from E–P, mp 267–268°. IR (KBr) cm^{-1}: 3500 (OH), 1700 (C=O), 1607 (aromatic). UV (Et_2O)nm: 323, 308, 288, 275(ε = 4800, 6800, 11 800, 12 100); MS: *m/e* (rel. int.): 342.147 (M^+, 9%) ($C_{20}H_{22}O_5$); 327 ($M^+ - Me$, 2); 324 ($M^+ - H_2O$, 2); 284 ($M^+ - Me_2CO$, 6); 270 ($M^+ - HOCH{=}CMe_2$, 22); 309 (324 – Me, 4); 255 (327 – $HOCH{=}CMe_2$, 42); 288 (255 – $CH{=}CH_2$, 79); 135 (A^+, 100).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\ nm}{+47.1 \quad +50.0 \quad +57.9 \quad +112.9} (c = 0.14).$$

Isoethuliacoumarin C (**4**). Colourless crystals from E–P, mp 153–154°. IR (KBr) cm^{-1}: 3490 (OH), 1715 (C=O), 1605 (aromatic); UV (Et_2O) nm: (330) 315, 303, (270), 259; MS: *m/e* (rel. int.) 342 (M^+, 0.3%); 327.123 ($M^+ - {}^{\cdot}Me$, 41) ($C_{19}H_{19}O_5$); 284 ($M^+ - O{=}CMe_2$, 17); 309 (327 – H_2O, 10); 269 (327 – $O{=}CMe_2$, 100); 257 (284 – $CH{=}CH_2$, 28); 135 (A^+, 30).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\ nm}{+30.7 \quad +32.9 \quad +37.1 \quad +75.6} (c = 0.45).$$

Ethuliconyzone (**6a**). Colourless crystals from MeOH, mp 166–167°. IR (CCl_4), cm^{-1}: 3500 – 2700 (OH), 1760 (C=O), 1638, 1610 (aromatic ketone, hydrogen bridge); UV (Et_2O)nm: 288, (280), (246), 218; MS: *m/e*(rel. int.) 316.167 (M^+, 24%) ($C_{19}H_{24}O_4$); 298 ($M^+ - H_2O$, 16); 163 (298 – C_6H_3 (Me) (OH) $CO^{\cdot}$, 14); 135 (A^+, 100).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\ nm}{-17.0 \quad -17.9 \quad -21.1 \quad -48.5} (c = 0.81).$$

To 2 mg **6a** in 0.5 ml CH_2Cl_2 and 0.05 ml Ac_2O, 5 mg 4-pyrrolidino pyridine [6] was added. After heating for 30 min to 70° the soln was washed with dil H_2SO_4 and $NaHCO_3$ soln. After TLC (E–P, 1:1)2 mg **6b** were obtained, ^1H NMR see Table 2.

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