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Structure of a Novel Spiro-monoterpene-coumarin in *Ethulia conyzoides*

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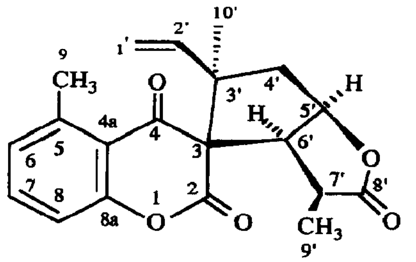
Abstract: A novel spiro-monoterpene-5-methylcoumarin, named spiro-ethuliacoumarin, was isolated from the aerial parts of *Ethulia conyzoides*. The structure was determined by spectroscopic methods and X-ray crystallography.

In continuation of our studies (A.A.A. and A.A.M.) on the terpenoid constituents of Egyptian compositaeous plants, we have isolated a spiro-monoterpene-5-methylcoumarin (**1**) from *Ethulia conyzoides* L. (Compositae). Several structurally close relatives were isolated from *E. conyzoides*,[1-4] and recently an unusual [2+2] cyclo-adduct of monoterpenoid-5-methylcoumarin has been also isolated from *E. vernonioides*.[5] Although the monoterpenoid part is usually connected to an oxygen at C-3 or C-4 in the monoterpene-5-methylcoumarin series, **1** has a different connection from these monoterpenoid-5-methylcoumarins, and then a new mode of connection is proposed here.

Compound **1** (spiro-ethuliacoumarin),[6,7] colorless needles, mp 198°C, $[\alpha]_D$ +167.39 ($CHCl_3$, *c* 1.515) was isolated from an ether fraction of the aerial parts of *E. conyzoides* extracted with Et_2O-petrol-MeOH. The high resolution electron-impact MS showed a molecular ion at *m/z* 340.1290 (calculated 340.1310 for $C_{20}H_{20}O_5$). The IR spectrum displayed characteristic absorption bands for C=O of lactone ring (1760 cm^{-1}) and α,β-unsaturated ketone (1680 cm^{-1}). The ^1H-NMR spectrum (Table 1) showed one-proton aromatic signals at δ 7.09 (d, *J*= 8 Hz), 7.48 (dd, *J*= 8, 8 Hz), and 7.00 (d, *J*= 8 Hz) and a three-proton singlet at δ 2.62, which are possibly assignable to hydrogens of a 5-methylcoumarin. The ^{13}C-NMR spectrum (Table 1) exhibited twenty carbon signals which correspond to the molecular formula composed of a 5-methylcoumarin (C_{10}) and a monoterpene (C_{10}). A partial structure of the monoterpene moiety was elucidated as follows:



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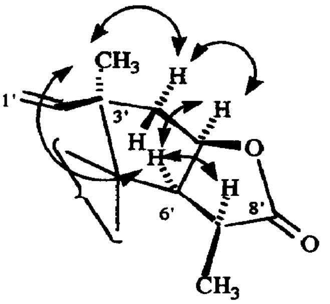

Fig. 1 NOEs observed in 1

the presence of a 7',9'-dihydro-5',8'-γ-lactone ring was inferred from the secondary methyl group signal at δ 1.04 (3H, d, J= 7.5 Hz) (H-9') which showed a coupling with a double quartet centered at δ 2.93 (1H, J= 11, 7.5 Hz) (H-7') in the ^{1}H-^{1}H COSY spectrum, and from a resonance of a carbonyl carbon at δ 177.9 ascribed

Table 1. 1D and 2D NMR Spectral Data of 1[a]

	^{13}C[b]	^{1}H[c]	^{1}H-^{1}H COSY	COLOC[d]
2	167.4 (s)			
3	70.8 (s)			
4	191.0 (s)			
4a	118.4 (s)			
5	140.9 (s)			
6	128.1 (d)	7.09 (1H, d, J= 8)	H-7	C-8
7	135.6 (d)	7.48 (1H, dd, J= 8, 8)	H-6, H-8	C-5, C-8a
8	115.2 (d)	7.00 (1H, d, J= 8)	H-7	
8a	155.2 (d)			
9	21.4 (q)	2.62 (3H, s)		C-4a, C-5, C-6
1'*trans*	117.8 (t)	4.92 (1H, d, J= 17)	H-2'	
1'*cis*	117.8 (t)	4.94 (1H, d, J= 9)	H-2'	
2'	137.8 (d)	5.51 (1H, dd, J= 17, 9)	H-1'1, H-1'2	
3'	56.4 (s)			
4'α	44.6 (t)	2.20 (1H, dd, J= 14, 7.8)	H-4'β, H-5'	
4'β		2.62 (1H, dd, J= 14, 5.4)	H-4'α, H-5'	
5'	78.4 (d)	5.09 (1H, ddd, J= 8, 7.8, 5.4)	H-4'α, H-4'β, H-6'	
6'	45.3 (d)	4.51 (1H, dd, J= 11, 8)	H-5', H-7'	C-2, C-3, C-4, C-7', C-8'
7'	36.1 (d)	2.93 (1H, dq, J= 11, 7.5)	H-6', H-9'	C-3, C-6'
8'	177.9 (s)			
9'	10.6 (q)	1.04 (3H, d, J= 7.5)	H-7'	C-7', C-8'
10'	23.1 (q)	0.99 (3H, s)		C-3, C-2', C-3', C-4'

[a]Solvent $CDCl_3$; 400 MHz; δ values from TMS, [b]Deduced from DEPT experiments and assigned by 2D hetero COSY, [c]Deduced from ^{1}H-^{1}H COSY, and J shown in Hz, [d]Long range correlation experiments; parameters optimized to 5 and 10 Hz.

to C=O of the γ-lactone in the ^{13}C-NMR spectrum. Furthermore, one oxygen-bearing methine proton signal centered at δ 5.09 (1H, ddd, J= 8, 7.8, 5.4 Hz) assignable to H-5' in the ^{1}H-NMR spectrum was correlated with a carbon signal at δ 78.4 in the ^{1}H-^{13}C COSY spectrum, and the methine proton also showed a coupling with a proton signals at δ 4.51 (1H, dd, *J*= 11, 8 Hz) assignable to H-6' which was coupled with H-7' (δ 2.93) in the ^{1}H-^{1}H COSY spectrum. These accumulated data suggested the presence of the partial structure of a Me-CH-CH-CH(OR)-CH_2- in the monoterpene moiety. In addition, the down-field proton signals at δ 5.51 (1H, dd, *J*= 17, 9 Hz), 4.94 (1H, d, *J*= 9 Hz) and 4.92 (1H, d, *J*= 17 Hz) showed correlations with carbon resonances at δ 137.8 (d) and 117.8 (t) in the ^{1}H-^{13}C COSY spectrum, indicating unequivocally the existence of a vinyl group. The assignment of the carbons in **1** was achieved by ^{1}H-^{13}C COSY except for quaternary carbons at δ 56.4 and 70.8, and carbonyl carbons at δ 167.4, 177.9 and 191.0. The COLOC experiments (Table 1) enabled the connection between all sequences of both the monoterpenoid and the 5-methylcoumarin parts through the quaternary carbons, the carbonyl carbons and the tertiary methyl groups. The most important correlations were observed between H-6' and C-2, C-3, C-4, C-7', C-8', and between each H-7', H-10' and C-3. All these results proved that **1** has a spiro moiety between the monoterpene and the 5-methylcoumarin parts and they are fused at C-3 through the central carbon. The stereochemistry of **1** was confirmed by the NOE experiments (Fig. 1). The final proof of the complete structure and the relative stereochemistry were established by the X-ray analysis of **1**[8] (Fig. 2).

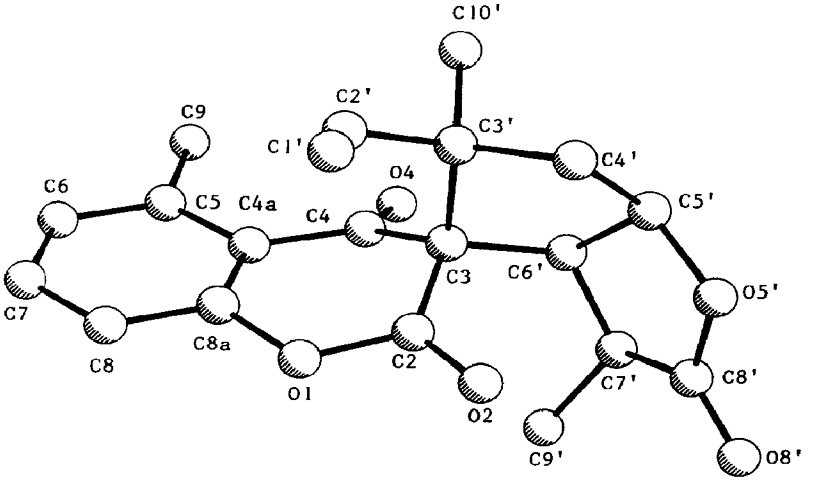

Fig. 2 The X-ray model of compound **1**

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6. *Ethulia conyzoides* was collected at Cairo-Alexandria road in Egypt. The aerial parts of the plant (1.5 kg) were air-dried, ground and extracted with Et$_2$O-petrol.-MeOH (1 : 1 : 1) at room temperature. The extract was separated by column chromatography (CC) on silica gel eluted with petrol. ether and MeOH with increasing polarity. The ether fraction was prefractionated by CC on Sephadex LH-20 eluted with CH$_2$Cl$_2$-MeOH. One of these fractions gave crude **1**, which was further purified by repeated TLC to give **1** (24 mg) in a pure form.
7. Other spectral data of **1**: EIMS *m/z* (rel. int. %): 340 [M$^+$] (11), 322 (16), 267 (22), 243 (36), 216 (100), 201 (44), 135 (96), 97 (56); IR νmax (KBr, cm^{-1}): 1760, 1680, 1605, 1575, 1475, 1380, 1320, 1280, 1180, 800, 780; UV λmax (MeOH, nm): 240, 260sh, 270, 310.
8. X-ray analysis of **1**; Crystal data: C$_{20}$H$_{20}$O$_5$, hexagonal, space group P6$_5$ (# 170), a= 12.127 (1) Å, c= 21.037 (2)Å, V=2679.2 (5)Å^3, D$_{calc}$ = 1.266 g/cm^3, Crystal dimensions (mm) 0.400 x 0.300 x 0.300. Three-dimensional intensity data were measured on a Rigaku AFC5R diffractometer using MoKα radiation (λ = 0.71069Å, μ = 0.85cm^{-1}). From a total of 10,617 measurements, those 3725 reflections (R$_{int}$ = 0.058) were merged for the analysis, and the usual Lorentz and polarization corrections were applied. The crystal structure was solved by direct methods. The non-hydrogen atoms were refined ansotropically. Least-squares refinement of atomic parameters converged to R = 0.041 over 1594 reflections. In the least-squares interactions, $\sum W(|Fo|-|Fc|)^2$ was minimized. All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Cooperation.

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