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Paralinones A and B, Novel Diterpene Esters from *Euphorbia paralias*

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Abstract- Two tetracyclic diterpene polyesters, paralinones A and B, with a new carbon framework, were isolated from an acetone extract of the whole plant of *Euphorbia paralias*. The structures of the compounds were elucidated by high field spectroscopic methods, including 2D NMR techniques and X-ray crystallography.

INTRODUCTION

Euphorbia paralias L. (Euphorbiaceae) is one of the most common species of the *Euphorbia* growing in Turkey. Chemical constituents of this species have been investigated previously and the presence of three irritant and cytotoxic ingenane diterpenoids[1], as well as triterpenoids and flavonoids,[2-4] have been established. As a part of our ongoing study to search for biologically active compounds from the Turkish Euphorbiaceae, we have reported previously some new macrocyclic diterpene polyesters from *Euphorbia* species.[5,6] We now report herein the isolation, characterization and structural elucidation of two new tetracyclic diterpene polyesters, paralinone A (**1**) and paralinone B (**2**) with a novel skeleton. The structures have been identified spectroscopically and chemically, and by X-ray crystallography for compound **1**.

RESULTS AND DISCUSSION

Paralinone **A** (**1**) was isolated from the acetone extract of the whole plant of *Euphorbia paralias* and crystallized as colorless needles from methanol-water. Its molecular formula was assigned as $C_{37}H_{46}O_{14}$ by HREIMS (obsd. *m/z* 714.28872). The IR spectrum exhibited characteristic absorptions for hydroxyl (3545 cm^{-1}) and carbonyl (1720, 1735, 1745 cm^{-1}) groups and an aromatic ring (1600, 1580, 1490 cm^{-1}). In the EIMS spectrum, the prominent fragment peaks at *m/z* 105 [C_6H_5-CO], 121 [C_6H_5-COO] and 593 [M^+-121] were compatible with the presence of a benzoyl moiety in the molecule. This was further confirmed by the ^1H and ^{13}C NMR (Table 1) spectra which displayed resonances at δ 7.82 (2H, dd, δ 129.2), 7.55 (1H, dt, δ 133.4) and 7.45 (2H, t, δ 128.8). The ions at *m/z* 654 and 594 indicated the sequential loss of acetic acid moieties from the molecular ion at *m/z* 714.

Apart from the signals for the ester groups, the ^1H NMR spectrum in $CDCl_3$ showed four oxymethine proton signals geminal to ester functions as two singlets at δ 6.41 and 5.20, a doublet at δ 5.51 (d, *J*=11 Hz) and a triplet at δ 5.76 (t, *J*=4 Hz) for H-17, H-14, H-5 and H-3, respectively. The spectrum also showed the four methyl groups of a diterpene skeleton comprised of a secondary methyl doublet at δ 0.91 (d, *J*=6.8 Hz), three tertiary methyl singlets at δ 1.00, 1.05 and 1.12, and four acetoxy methyl singlets at δ 2.00, 2.04, 2.05 and 2.15. In addition, AB signals at δ 4.55 (d, *J*=16 Hz) and 4.43 (d, *J*=16 Hz) suggested the presence of an isolated -CH_2OR group. This was assigned to a CH_2OAc moiety because its chemical shifts remained unchanged after acetylation. All of the vicinal relationships of the proton resonances were determined by extensive spin-decoupling in C_6D_6 and in ^1H-^1H COSY experiments.

Through decoupling experiments on **1** in C_6D_6, the sequence H-1α through H-5 was easily deduced by irradiation of the double doublet at δ 3.73 (*J*=4,11 Hz, H-4). Irradiation of the triplet of doublets at δ 3.93 (*J*=3,13,14 Hz, H-8) collapsed the dd at δ 3.03 (*J*=4,13 Hz, H-7β) to a doublet (*J*=13 Hz), the br triplet at δ 2.12 (*J*=13 Hz) to a br doublet (*J*=13 Hz, H-7α), and simplified the ddd at δ 1.94 (*J*=8,12,14 Hz, H-12) to a doublet of doublets (*J* =8,12 Hz). On the other hand, irradiation of H-12 (δ 1.94) simplified the signals of C-11 protons at δ 1.63 and 1.38 and turned the ddd of H-8 at δ 3.93 to a double doublet.

The ^{13}C NMR (APT) and DEPT spectra of **1** showed 37 carbon atoms, including, eight CH_3, four CH_2, thirteen CH and twelve quaternary carbons, of which nine are oxygenated (one ketone, two tertiary alcohols and six ester carbonyls). All of the proton-bearing carbons were assigned by a HETCOR experiment. In addition to the signal of the benzoyl carbonyl at δ 165.8, the ^{13}C NMR spectrum revealed five carbonyl resonances of the ester moieties at δ 170.4, 170.0, 169.9, 169.4 and 167.1. However, from the ^1H NMR spectrum, the presence of only four acetoxy groups was apparent as ester functions in **1**. Attempted acetylation of **1** under normal conditions failed, although, under drastic conditions **1** afforded a monoacetyl derivative **3** which showed an additional acetoxy methyl singlet at δ 2.07, while the chemical shifts of the other protons remained nearly the same indicating the presence of a hydroxyl group at C-15. Hence the remaining carbonyl signal was assigned to the carbonyl carbon of

Table 1: Spectral Properties of Compound **1** (in $CDCl_3$)

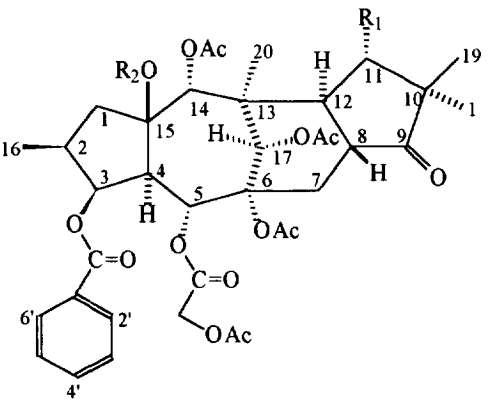
H	^1H	^1H (C_6D_6)	^{13}C*	HMBC	NOESY
1α	2.35 dd	2.38 dd	49.9 t	16-H_3	
1β	1.53 dd	1.35 dd			
2	2.10 dq	1.71 m	37.2 d	16-H_3	
3	5.76 t	6.06 t	80.9 d	1-H, 16-H_3	4-H
4	3.39 dd	3.73 dd	47.5 d	5-H, 14-H	17-H, 3-H
5	5.51 d	6.00 d	69.1 d	4-H, 7-H_2	7β-H, 8-H
6			83.2 s	4-H, 7-H_2, 8-H, 17-H	
7α	1.72 dd	2.12 dd	30.8 t	5-H, 17-H	7β-H
7β	2.31 dd	3.03 dd			
8	3.65 ddd	3.93 ddd	46.2 d		5-H, 2',6'-Hs
9			219.3 s	18-H_3, 19-H_3	
10			45.5 s	18-H_3, 19-H_3	
11α	1.83 m	1.63 m	32.0 t	18-H_3, 19-H_3	11β-H
11β	1.83 m	1.38 m			11α-H, 14-H
12	1.94 ddd	1.94 ddd	42.8 d		
13			46.0 s	20-H_3	
14	5.20 s	5.39 s	75.9 d	1-H_2, 17-H, 20-H_3	11β-H
15			82.3 s	3-H, 5-H, 14-H	
16	0.91 d	0.75 d	14.3 q		
17	6.41 s	6.83 s	70.2 d	14-H, 20-H	4-H
18	1.05 s[a]	1.14 s	24.9 q[b]	11-H_2	
19	1.12 s[a]	1.05 s	26.7 q[b]	11-H_2	
20	1.00 s	0.99 s	25.8 q	14-H	
CO<u>CH_2</u>OR	4.55 d	4.70 s br	60.4 t		
	4.43 d	-			
CO<u>CH_3</u>	2.00 s	1.98 s	20.3q		
	2.04 s	1.76 s	20.6 q		
	2.05 s	1.64 s	21.0 q		
	2.15 s	1.60 s	21.0 q		
6-<u>CO</u>CH_3			169.9		
14- <u>CO</u>CH_3			170.0	14-H	
17- <u>CO</u>CH_3			169.4	17-H	
5- <u>CO</u>CH_2-			170.4	5-H, -CH_2O-	
5-CH_2-O<u>CO</u>-			167.1	-CH_2O	
OBz					
1'			129.4 s	2',3',4',5',6'-Hs	
2',6'	7.82 dd	7.94 dd	129.2 d	2',3',4',5',6'-Hs	8-H
3',5'	7.45 t	6.99 t	128.8 d	2',3',4',5',6'-H	
4'	7.55 td	7.02 td	133.4 d	2',6'-Hs	
7'			165.8 s	3-H, 2',6'-Hs	
OH[c]	2.60 br s	2.43 br s			

J (Hz) in C_6D_6, **1**: 1α,1β=15; 1α,2=8; 1β,2=11; 2,3=4; 3,4=4; 4,5=11; 8,7=13; 8,7=4; 8,12=14; 7,7=13; 12,11=8; 12,11=12; 11,11=14; 16,2=6.8; -CH_2O=16; 2',3'=7.3 and 2',4'=1.1; 3',4'=7.3.

*Assignments from ^1H-^{13}C-COSY and DEPT spectra; a,b signals are interchangeable; c D_2O exchangeable.

an unusual acetoacetic acid moiety (-$OCOCH_2OAc$). Integration of these data, the observed molecular ion peak at *m/z* 714 and the fifteen degrees of unsaturation supported the presence of a tetracyclic diterpene moiety $C_{20}H_{32}O_7$ esterified with three acetic acid, one benzoic acid and one acetoacetic acid group. The issues to be resolved were therefore the nature of the diterpene skeleton and the respective locations of the esterifying groups.

The coupling constants of H-1α, H-3 and H-5 were nearly identical to those reported for lathyrane derivatives[7], and to those of compounds previously isolated from *Euphorbia aleppica* by us[6]. The diterpene moiety of **1** was similar to that of a new parent alcohol obtained by Adolf *et al.*[8] from the lathyrane skeleton by transannular cyclization and chemical rearrangement. In the ^{13}C NMR spectrum of **1**, a quaternary carbon resonating at δ 45.5 suggested the presence of a five-membered ring with a geminal di-methyl group. From these spectral data, the parent alcohol of **1** was considered to be a rearranged lathyrol (Figure 1).



1 R_1=R_2=H

2 R_1=OAc; R_2=H

3 R_1=OAc; R_2=Ac

Figure 1

Further assignment of the location of the acylating groups in **1** was established by a ^1H-^{13}C long-range COSY experiment (COLOC). Cross-peaks between the carbonyl carbons at δ 169.4 ($COCH_3$), 170.0 ($COCH_3$), 167.1 ($COCH_3$), 170.4 ($COCH_3$) and 165.8 (OBz) with the protons at δ 6.41 (H-17), 5.20 (H-14), 4.55 and 4.43 (-CH_2OCO), 5.51 (H-5) and 5.76 (H-3), respectively, established the locations of the ester groups. Further correlations observed in the HMBC spectrum are shown in Table 1.

The stereochemistry of H-17 and H-14 were determined by nOe experiments. Irradiation of H-4 gave significant enhancements of H-17 and H-3, whereas irradiation of H-17 afforded a nOe at H-4 indicating the

proximity with H-17, also indicating that the bridge configuration is α. Furthermore, irradiation of H-16 gave nOe's for H-14 and H-5. NOESY correlations of **1** are given in Table 1. However, in spite of extensive HETCOR experiments, it was not possible to assign the skeleton to the diterpene framework.

Therefore, in order to firmly establish the structure, **1** was examined by X-ray crystallography. The X-ray diffraction study indicated that **1** is a novel tetracyclic diterpene skeleton with three acetoxy groups at C-6, C-14 and C-17, an acetylacetoxy at C-5, a benzoyloxy at C-3 and a hydroxy at C-15. The crystal structure of **1** is shown in Figure 2.

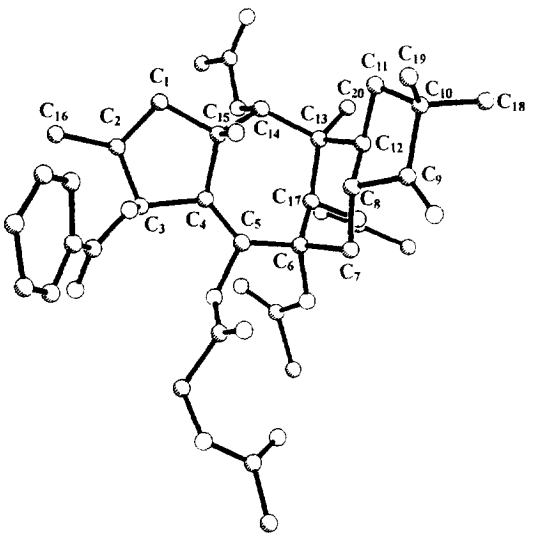


Figure 2: The Crystal structure of Paralinone A (**1**)

The spectral data of paralinone **B** (**2**) were very similar to those of **1**. Compound **2** had an additional acetoxy group as demonstrated by an increase in M^+ of 58 amu, and by a doublet with J=10 Hz at δ 5.58 in its ^1H NMR spectrum and by the signals at δ 77.3 (C-11), 21.4 and 167.3 in the ^{13}C NMR spectrum (see Experimental). Location of this group at C-11 was determined by successive spin decoupling experiments. The irradiation of the signal at δ 2.02 dd (H-12) collapsed the doublet at δ 5.58 (H-11) to a singlet, while the other signals were not affected, and irradiation of H-8 at δ 3.73 (ddd, J=3.5,13,14 Hz) transformed the signals of H_2-7, and H-12 (dd, J=10,14 Hz) into a pair of doublets (J=13 Hz) and a doublet (J=10 Hz), respectively, while the doublet of H-11 remained unchanged.

Compounds **1** and **2** were evaluated for cytotoxic activity against the human cancer cell lines BC1, LU1, Co12, KB, KB-V and LNCaP[9] and both were judged inactive (ED_{50} >20 μg/ml). The compounds were also found to be inactive as inhibitors of the HIV-1 reverse transcriptase at a concentration of 200 μg/ml.

EXPERIMENTAL

General. Solvents were distilled before use. TLC; Merck precoated silica gel 60 F-254 plates, dedection under UV light and then with spraying cerium (IV) sulfate/H_2SO_4 (cerium sulfate:H_2SO_4:H_2O; 1:5:45 v/v) at 110°. ^{1}H NMR (200, 300, 360 MHz) and ^{13}C NMR (50.32, 90.8 MHz) spectra were recorded on Bruker AC 200, Nicolet NC 360 and Varian XL-300 instruments. HMBC spectra were obtained with a GE Omega 500 instrument and NOE spectra were recorded on Varian Gemini 200 MHz instrument. δ values are given in ppm, relative to TMS as an internal standard and assignments are based on 1D and 2D NMR techniques and extensive spin-decoupling experiments. IR spectra (KBr pellet) on a Perkin-Elmer 983. LR-MS and HR-MS spectra were recorded on a VG analytical ZabSpec instrument.

Plant Material. *Euphorbia paralias* L. was collected in July, 1989 in Turkey (Ayvalık) and identified by Prof. Dr. Neriman Özhatay (University of Istanbul, Faculty of Pharmacy). A voucher specimen is deposited in the Herbarium of Faculty of Pharmacy, University of Istanbul (ISTE:60404).

Extraction and Isolation. Air-dried, whole plant material (1.3 kg) was powdered and macerated three times with MeOH at room temperature. The combined extract was concentrated under vacuum, dissolved in a small amount of MeOH-H_2O (2:1) and then partitioned against *n*-hexane, and further extracted with $CHCl_3$. The $CHCl_3$ phase was evaporated *in vacuo* below 40°. The residue (51.6 g) was chromatographed over a silica gel column (300 g) using hexane, a gradient of Me_2CO up to 100%, followed by MeOH. The collected fractions were combined after TLC control, and then further separated on small Si gel columns as necessary. Two fractions were further purified by repeated preparative TLC using hexane-Me_2CO (9:1 and 4:1) as eluants to afford compounds **1** (60 mg) and **2** (21 mg) at R*f* 0.84 and 0.89 (chloroform:acetone 95:5), respectively.

Compound 1: ^{1}H and ^{13}C data see Table 1; $[\alpha]_D = \pm 0.0°$ ($CHCl_3$; *c* 5.23 mg). IR $\lambda_{max.}$ (KBr) cm^{-1}: 3465, 3040, 2930, 1745, 1735, 1720, 1600, 1580, 1495, 1455, 1420, 1379, 1275, 1240, 1180, 1080, 1025, 975, 760. HREIMS *m/z* 714.28872 (calcd. 714.28876), $C_{37}H_{46}O_{14}$; EIMS *m/z* (rel.int.): 713 [M^+-1] (4), 654 (22), 594 (36), 536 (35), 476 (13), 476 (14), 456 (7), 432 (43), 414 (19), 372 (33), 354 (35), 330 (21), 312 (86), 294 (100), 284 (65), 276 (71), 266 (81), 256 (31), 240 (74), 228 (46), 203 (44), 189 (35), 175 (31), 151 (45), 121 (47), 105 (60), 101 (84), 77 (86), 71 (64).

Acetyl Derivative of 1 (3): Compound **1** (6 mg) was treated with pyridine (2 ml) and acetic anhydride (2 ml) and refluxed at 70° for 5 hrs to afford a monoacetyl derivative **3**. ^{1}H NMR (in $CDCl_3$) δ: 2.38 (H-1α), 1.55 (H-1β), 2.09 (H-2), 5.79 (H-3), 3.43 (H-4), 5.54 (H-5), 1.72 (H-7α), 2.30 (H-7β), 3.66 (H-8), 1.85 (H_2-11), 5.21 (H-14), 0.92 (H-16), 6.43 (H-17), 1.05 (H-18), 1.13 (H-19), 1.02 (H-20), 4.46 (-CH_2O-), 4.58 (-CH_2O-), OAc: 1.99,

2.03, 2.05, 2.07, 2.14, OBz: 7.84, 7.58, 7.47. EIMS *m/z* (rel. int.): 757 $[M+1]^+$ (3), 712 (11), 654 (29), 594 (9), 536 (38), 476 (14), 432 (40), 414 (19), 372 (29), 354 (31), 330 (18), 312 (78), 294 (100), 283 (53), 276 (57), 266 (63), 252 (28), 240 (53), 225 (51), 203 (49), 189 (28), 175 (24), 163 (35), 151 (44), 121 (43), 105 (98), 101 (74), 77 (58).

Compound 2: $[\alpha]_D = \pm 0.0^\circ$ ($CHCl_3$; *c* 8.06 mg). IR λ_{max} (KBr) cm^{-1}: 3462, 3040, 2960, 2930, 1747, 1743, 1733, 1720, 1600, 1582, 1490, 1443, 1425, 1380, 1270, 1245, 1175, 1080, 1027, 975, 760. ^1H NMR (in C_6D_6 +D_2O) δ: 6.78 (H-17), 6.05 (t, *J*=4 Hz, H-3), 5.98 (d, *J*=10 Hz, H-11β), 5.91 (d, *J*=11 Hz, H-5), 5.56 (s, H-14), 4.56 (s br, -OCH_2), 4.11 (ddd, *J*=3.5,13,14 Hz, H-8), 3.68 (dd, *J*=4,11, H-4), 3.06 (dd, *J*=3.5,13 Hz, H-7β), 2.26 (dd, *J*=10,14 Hz, H-12), 2.19 (t, *J*=13 Hz, H-7α), 2.16 (m, H-1α), 1.70 (m, H-2), 1.17 (dd, *J*=11,15 Hz, H-1β), 1.20 (s, H-20), 0.99 (s, H-18 and 19), 0.76 (d, *J*=7 Hz, H-16), OAc: 1.97 s, 1.78 s, 1.63 s, 1.61 s, 1.57 s, OBz: 8.02 (dd, *J*=1,7 Hz, H-2',6'), 7.00 (t br, *J*=7 Hz, H-3',5'), 7.03 (dt, *J*=1,7 Hz, H-4'), ^1H NMR (in $CDCl_3$) δ: 2.36 (H-1α), 1.64 (H-1β), 2.08 (H-2), 5.78 (H-3), 3.42 (H-4), 5.50 (H-5), 1.81 (H-7α), 2.35 (H-7β), 3.73 (H-8), 5.58 (H-11β), 2.02 (H-12), 5.28 (H-14), 0.94 (H-16), 6.37 (H-17), 0.97 (H-18), 1.06 (H-19), 0.97 (H-20), 4.58 (-CH_2O-), 4.47 (-CH_2O-), OAc: 2.02, 2.03, 2.07x2, 2.13, OBz: 7.85, 7.48, 7.58, 2.72 (OH). ^{13}C NMR ($CDCl_3$) δ: 49.9 (C-1), 37.3 (C-2), 80.8 (C-3), 47.6 (C-4), 68.9 (C-5), 82.7 (C-6), 30.8 (C-7), 46.2 (C-8), 214.2 (C-9), 45.9 (C-10), 77.3 (C-11), 44.7 (C-12), 49.5 (C-13), 75.4 (C-14), 82.5 (C-15), 14.3 (C-16), 70.6 (C-17), 25.4 (C-18), 27.2 (C-19), 18.3 (C-20), -$\underline{CH_2}$-O: 60.5 CO$\underline{CH_3}$: 20.3, 20.7, 21x2, 21.4, $\underline{CO}CH_3$: 170.0 x2, 170.1, 169.3, 167.3, $\underline{CO}CH_2$: 170.5, OBz: 129.4 (C-1'), 129.3 (C-2',6'), 128.8 (C-3',5'), 133.5 (C-4'), 165.8 (C-7'). EIMS *m/z* (rel. int.): 772 $[M]^+$, $C_{39}H_{48}O_{16}$, 728 $[M-1-COCH_3]^+$ (5), 713 (5), 652 (34), 594 (4), 550 (6), 534 (8), 472 (6), 446 (13) 430 (16), 412 (14), 370 (37), 352 (16), 328 (15), 310 (63), 292 (57), 282 (35), 264 (30), 239 (19), 227 (18), 211 (16), 203 (21), 189 (29), 175 (20), 161 (29), 121 (32), 105 (89), 101 (100), 91 (30), 77 (87), 71 (75).

X-ray Structure Analysis of 1: The compound was crystallized from MeOH-water (10:1) to give thin colorless prisms, size about 0.6 x 0.25 x 0.25 mm.

Crystal data: Orthorhombic space group $P2_12_12_1$, a=9.809(3), b=12.673(3), c=29.704(12) A, V=3692,5 A^3, z=4, D_c=1.286 g/cm^3. A total of 5239 reflections were measured on a Siemens R3m diffractometer (Ω-scan, scan speed 3° to 29.5°/min., scan range 3.2°, 2θ range up to 114°, Ni-filtered Cu K_a radiation). Of the 4885 independent reflections, 3522 were treated as observed with $F > 4\sigma(F)$. An absorption correction was not applied to the measurements because of the regular shape of the crystal and the low absorption coefficient (μ=0.8 mm^{-1}).

The structure was solved by direct methods using SHELXTL[10] and refined initially with isotropic and subsequently with anisotropic temperature factors. Hydrogen atoms were calculated from the positions of the heavier atoms to which they are bound. The refinement converged at wR=6.76 % (w=unit weights) for the observed and wR=7.92 % for all data. The crystal structure is shown in Figure 2. The four rings of the basic

skeleton are *trans-cis-trans* connected. The atomic coordinates, as well as distances and angles, are deposited at the Cambridge Crystallographic Data Center.

Biological Evaluation of Compounds 1 and 2. Compounds **1** and **2** were evaluated for cytotoxic activity utilizing a panel of cultured human cancer cells[9] and for their potential to inhibit HIV-1 reverse transcriptase[11] with an *in vitro* test system, as described previously. In both cases, no appreciable activity was observed.

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