# Candletoxins A and B, 2 new aromatic esters of 12-deoxy-16-hydroxy-phorbol, from the irritant latex of Euphorbia poisonii Pax

**ARTICLE** *in* CELLULAR AND MOLECULAR LIFE SCIENCES CMLS · AUGUST 1977

Impact Factor: 5.81 · DOI: 10.1007/BF01922325

Separatum EXPERIENTIA *33*, 1197 (1977)
Birkhäuser Verlag, Basel (Schweiz)

Experientia 33(9): 1197-1198 (1977)
[ISSN 0014-4754]

# Candletoxins A and B, 2 new aromatic esters of 12-deoxy-16-hydroxy-phorbol, from the irritant latex of Euphorbia poisonii Pax.

R. J. Schmidt and F. J. Evans[1]

*Department of Pharmacognosy, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX (England), 18 February 1977*

*Summary.* 2 new aromatic esters of 12-deoxy-16-hydroxy-phorbol, known as candletoxins A and B, were isolated from the irritant latex of Euphorbia poisonii Pax. Compound A was identified as 12-deoxy-phorbol-13-O-phenylacetate-16-O-α-methyl-butyrate-20-acetate, and compound B was the C-20 desacetyl analogue.

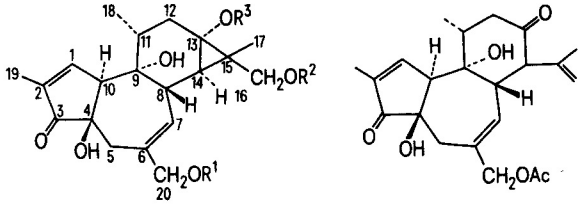
Euphorbia poisonii Pax. latex was collected by one of us in West Africa and has been shown to produce acute inflammation of mice ears[2]. From the ether fraction of the extract, biologically active esters of 12-deoxyphorbol and resiniferol[3–5] were isolated together with 2 minor compounds which we propose to call candletoxins A and B. Both of these toxins are aromatic esters of 12-deoxy-16-hydroxy-phorbol. This tigliane derivative was initially isolated from E. cooperi[6] where it occurred naturally in

1 Acknowledgments. F. J. E. is grateful to the Central Research Fund of the University of London for a travel grant to visit West Africa, and R.J.S. is indebted to the Science Research Council for a research studentship.

2 F. J. Evans and A. D. Kinghorn, Lloydia *38*, 363 (1975).
3 R. J. Schmidt and F. J. Evans, J. Pharm. Pharmac. *27*, 50P (1975).
4 F. J. Evans and R. J. Schmidt, Phytochemistry *15*, 333 (1976).
5 R. J. Schmidt and F. J. Evans, Phytochemistry *15*, 1778 (1976).
6 M. Gschwendt and E. Hecker, Z. Krebsforsch. *80*, 335 (1973).

the form of two aliphatic esters. The candletoxins A and B represent the first aromatic derivatives of this parent diterpene to be isolated from natural sources.

Candletoxin A (**1**) was a glassy resin, $hR_f$ 71 (Kieselgur G, 750 μm, coated with digol by developing their full length in 20% digol in acetone and air drying before use, solvent 25% ethylacetate in cyclohexane). Spectral data suggested that it was a triester of 12-deoxy-16-hydroxy-phorbol; IR (solid film KBr discs) $V_{max}$, 3420, 1730, 1630, 1605 $cm^{-1}$; CD (methanol), 335 nm ($\Delta\epsilon=-1.0$); 274 nm ($\Delta\epsilon=-0.67$); 227 nm ($\Delta\epsilon=+14.03$); 205 nm ($\Delta\epsilon=-16.70$): MS, an $M^{+\cdot}$ ion at m/e 608.2971 ($C_{35}H_{44}O_9$, error −2.5%) and fragment ions at m/e 590 (0.2%); 548 (2.0%); 530 (0.2%); 506 (2.5%); 499 (3.0%); 472 (5%); 446 (11%); 430(7%); 412 (10%); 394 (5%); 388 (5%); 370 (15%); 357 (10%); 352 (12%); 328 (15%); 310 (35%); 292 (10%); 282 (5%); 241 (12%); 223 (15%); 208 (35%); 179 (40%); 168 (25%); 161 (15%); 121 (45%); 109 (30%); 91 (100%): NMR-spectrum ($CCl_4$, 100 MHz) $\delta$ 7.51 b s 1H; $\delta$ 7.23 s 5H; $\delta$ 5.60 d (J = 4.8 Hz) 1H; $\delta$ 4.38 s 2H; $\delta$ 3.90 q (AB, J = 11 Hz) 2H; $\delta$ 3.98 s 2H; $\delta$ 3.20 m 1H; $\delta$ 3.08 m 1H; $\delta$ 2.54 m 1H; $\delta$ 2.34 b s 2H; $\delta$ 2.00 s 3H; $\delta$ 1.77 dd (J = 1.5 Hz) 3H; $\delta$ 1.54 m 2H; $\delta$ 1.26 s 3H; $\delta$ 1.16 d (J = 6 Hz) 3H; $\delta$ 0.93 complex 7H; $\delta$ 2.03 and $\delta$ 5.32 2 OH (deuterium exchange) ppm. The splitting of the allylic 2H signal of C(16) as a quartet can be understood by the proximity of the aromatic ring at C(13) (figure). Acid catalyzed transesterification of candletoxin A (**1**) (1% $HClO_4$ in $CH_3OH$) resulted in the production of candletoxin B (**2**) the C-20 hydroxy diester.




Candletoxin B (**2**) was also resinous, $hR_f$ 24 in the same TLC system as before. This compound exhibited the following spectral data: IR $V_{max}$ at 3420, 1730 (broad); 1630; 1605 $cm^{-1}$; C.D. (methanol), 337 nm ($\Delta\epsilon=-0.40$); 269 nm ($\Delta\epsilon=-0.8$); 227 nm ($\Delta\epsilon=+21.16$); 202 nm ($\Delta\epsilon=-24.60$); MS an $M^{+\cdot}$ ion at m/e 566.2859 ($C_{33}H_{42}O_9$, error −3.7%) and fragment ions at m/e 548 (4%); 530 (2%); 475 (1.5%); 463 (3%); 457 (12%); 446 (4%); 430 (12%); 412 (24%); 394 (16%); 373 (4%); 355 (8%); 346 (20%); 337 (4%); 328 (80%); 310 (84%); 292 (28%); 241 (40%); 223 (48%); 208 (88%); 179 (80%); 168 (68%); 161 (64%); 121 (88%); 120 (92%); 109 (84%); 95 (64%); 91 (100%); NMR-spectrum ($CDCl_3$ 100 $MH_z$), $\delta$ 7.55 b s 1H; $\delta$ 7.24 s 5H; $\delta$ 5.59 d (J = 5 Hz) 1H; $\delta$ 3.98 s 2H; $\delta$ 3.95 q (AB, J = 11 Hz) 2H; $\delta$ 3.58 s 2H; $\delta$ 3.26 m 1H; $\delta$ 3.02 m 1H; $\delta$ 2.47 b s 2H; $\delta$ 2.38 m 1H; $\delta$ 1.77 dd (J = 1.6 Hz) 3H; $\delta$ 1.53 m 2H; $\delta$ 1.25 s 3H; $\delta$ 1.16 d (J = 6 Hz) 3H; $\delta$ 0.93 complex 7H; $\delta$ 5.32, $\delta$ 2.17 and $\delta$ 1.5 3 OH (deuterium exchange) ppm. The absence of a 3H singlet at about $\delta$ 2.00 ppm and the diamagnetic shift of the 2H singlet of the C-20 position from $\delta$ 3.98 in **1** to $\delta$ 3.58 in **2** suggested that the C(20) acetyl moiety was absent in candletoxin B. Alkaline hydrolysis of **2** (0.5 M KOH in $CH_3OH$) produced a tetrol **3** which was converted to a diacetate **4**. (Acetic anhydride in pyridine (4:1).) MS an $M^{+\cdot}$ ion at m/e 566 (0.5%) and significant fragment ions at m/e 506 (2.5%); 426 (10%); 430 (5%); 310 (50%). The NMR-spectrum was similar to candletoxin (A) with the exception that signals due to the protons of α-methyl-butyrate were absent and an extra 3H singlet was exhibited at $\delta$ 2.01 ppm, thereby confirming the position of α-methyl-butyrate as C(16) in **1** and **2**.

Candletoxin B (**2**) was synthesized from the tetrol **3** by reaction with α-methyl-butyric anhydride in pyridine followed by acid catalyzed transesterification. Acetylation of **2** produced candletoxin A (**1**), thereby confirming that the phenylacetate moiety of **1** and **2** was present at C(13) of the tigliane nucleus. Complete hydrolysis of **1** and **2** (saturated barium hydroxide in methanol), followed by acetylation of the product produced a monoacetate which was recrystallized from acetone (m.p. 104–5 °C). The product **5** was identified as crotophorbolone monoacetate from its spectral data: IR $V_{max}^{CHCl_3}$ 3540; 3360; 1735; 1710; 1630 $cm^{-1}$: CD ($CH_3OH$), 210 nm ($\Delta\epsilon=-0.85$); 230 nm ($\Delta\epsilon=-4.76$); 273 nm ($\Delta\epsilon=+0.32$); 339 nm ($\Delta\epsilon=-0.40$); MS an $M^{+\cdot}$ ion at m/e 388 ($C_{22}H_{28}O_6$, 2%); 370 (2%); 328 (12%); 310 (17%); 292 (6%); 241 (21%); 208 (67%); 207 (81.5%); 179 (83.5%); 137 (33%); 122 (85%); 121 (77%); 91 (75%); 83 (100%). Base catalyzed elimination of the C(16) ester group with consequent formation of crotophorbolene confirms the nature of the parent diterpene as 12-deoxy-16-hydroxy-phorbol[6].

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **1** | $CH_3CO$ | $CH_3 \cdot CH_2 \cdot CH(CH_3) \cdot CO$ | $CO \cdot CH_2 \cdot$  |
| **2** | H | $CH_3 \cdot CH_2 \cdot CH(CH_3) \cdot CO$ | $CO \cdot CH_2 \cdot$ |
| **3** | H | H | $CO \cdot CH_2 \cdot$ |
| **4** | $CH_3CO$ | $CH_3CO$ | $CO \cdot CH_2 \cdot$ |

Crotophorbolone monoacetate (**5**)