Table 2. Therapeutic efficiency of dexetimide plus obidoxime in treating organophosphate intoxications of rabbits

Organophosphate	Number of animals	LD_{50} mg/kg b.wt (controls)	Dose range of organophosphates mg/kg b.wt*	Dose range of dexetimite mg/kg b.wt	Dose range of obidoxime mg/kg b.wt	Therapeutic factor
Paraoxone s.c.	11	0.4	2.0 –24	0.8– 8.0	7.2	60
Paraoxone i.v.	10	0.3	0.45–15	8.0–16	3.6–7.2	50
DFP s.c.	7	1.0	40 –80	0.8– 8.0	7.2	80
OMPA i.v.	5	–	10 –40	All animals died in spite of treatment		

The therapeutic factor has been calculated from the highest dose of organophosphate which could be overcome by the antidotes i.v. injected at the onset of intoxication (therapeutic factor $= \left(\frac{\text{dose of organophosphate}}{LD_{50} \text{ controls}}\right)$.

The LD_{50} values were taken from literature (Wescoe et al.[6], Karlog[7]) and their applicability to our animal batch was checked. * Dose range which was survived by the combined treatment.

mine, this result is supported by the reports of other authors[6,7]. Because of the risk for the experimentators of becoming intoxicated, it was not possible to determine the protective potency of scopolamine or dexetimide against still higher doses of DFP.

In a second series of experiments, the therapeutic potency of dexetimide plus obidoxime was investigated in rabbits poisoned with organophosphates. For the sake of comparison with atropine, and for checking the LD_{50}-values, a total of 82 rabbits (hybrids, 1900–3500 g) were poisoned with organophosphates. The organophosphates diethyl-paranitrophenylphosphate (paraoxone), DFP and octa-methyl-pyrophosphoramide (OMPA) were applied to rabbits i.v. or s.c. Dexetimide plus obidoxime were given i.v. as soon as the intoxication became evident. The therapy was regarded successful when the animals survived at least 72 h after application of the poison. When treated with 20 or 40 μmoles dexetimide/kg b.wt plus 20 μmoles obidoxime/kg b.wt, the animals survived 60 times the LD_{50} of DFP s.c., 50 times the LD_{50} of paraoxon i.v., and 80 times the LD_{50} of paraoxone s.c. (see table 2). An intoxication by OMPA which is considered to act entirely peripherally could not be influenced by the therapeutic procedure. In contrast to the repeated application of atropine, necessary for the treatment of organophosphate intoxication, one single application of dexetimide proved to be sufficient to overcome the intoxication completely. The results of our animal experiments demonstrate that the combination of dexetimide and obidoxime is superior to the combination of atropine and obidoxime recommended for the therapy of organophosphate intoxication in man.

In consequence of the results reported here we suggest the use of dexetimide or scopolamine in the treatment of organophosphate intoxication to improve the rate of recovery. Dexetimide is used for treatment of parkinsonism, and is commercially available in some European countries.

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

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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

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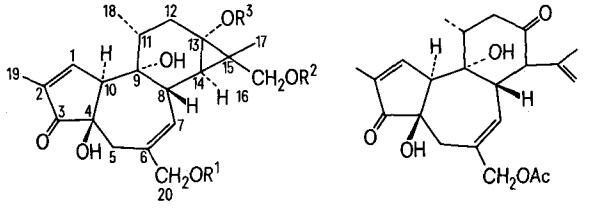
the form of two aliphatic esters. The candletoxins A and B represent the first aromatic derivatives of this parent diterpene to be isolated from natural sources.

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) δ 7.51 b s 1H; δ 7.23 s 5H; δ 5.60 d (J = 4.8 Hz) 1H; δ 4.38 s 2H; δ 3.90 q (AB, J = 11 Hz) 2H; δ 3.98 s 2H; δ 3.20 m 1H; δ 3.08 m 1H; δ 2.54 m 1H; δ 2.34 b s 2H; δ 2.00 s 3H; δ 1.77 dd (J = 1.5 Hz) 3H; δ 1.54 m 2H; δ 1.26 s 3H; δ 1.16 d (J = 6 Hz) 3H; δ 0.93 complex 7H; δ 2.03 and δ 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), δ 7.55 b s 1H; δ 7.24 s 5H; δ 5.59 d (J = 5 Hz) 1H; δ 3.98 s 2H; δ 3.95 q (AB, J = 11 Hz) 2H; δ 3.58 s 2H; δ 3.26 m 1H; δ 3.02 m 1H; δ 2.47 b s 2H; δ 2.38 m 1H; δ 1.77 dd (J = 1.6 Hz) 3H; δ 1.53 m 2H; δ 1.25 s 3H; δ 1.16 d (J = 6 Hz) 3H; δ 0.93 complex 7H; δ 5.32, δ 2.17 and δ 1.5 3 OH (deuterium exchange) ppm. The absence of a 3H singlet at about δ 2.00 ppm and the diamagnetic shift of the 2H singlet of the C-20 position from δ 3.98 in **1** to δ 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 δ 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**)

Methiothepin and a 5-HT pathway to rat substantia nigra[1]

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Summary. Methiothepin reduced both median-raphe evoked and exogenous 5-HT depression of single substantia nigra neurones. While this is compatible with a serotonin releasing pathway, additional interactions of methiothepin with exogenous dopamine suggest the need for further pharmacological confirmation.

Recent evidence suggests the existence of a possible monosynaptic pathway from the median-raphe nucleus (MRN) to the substantia nigra (SN) of the rat[2,4]. Electrical stimulation of the MRN produces mainly depression of cell activity in the SN and this effect is well correlated with the response of the same neurones to electrophoretically administered 5-HT[4]. To establish further the identity of 5-HT as the inhibitory neurotransmitter we have