constrictor activity in the spinal cat preparation[11] (i.v. injection). d) The oxytocic activity using the uterus of non-pregnant rabbit in spontaneous oestrus[12,13]. e) The antifertile activity in rats after s.c. injection on day 5 post coitum (spermatozoa control; autopsy at day 12 p.c.). f) The acute toxicity in rabbits after i.v. injection ($LD_{50}$ Probit-method[14]).

The results are given in table 2. 2 comparisons were calculated: 1. Activities in percent of those of ergotamine = 100. 2. Activities of the β-alkaloid in percent of those of the α-alkaloid = 100. Additionally absolute values are given for ergotamine.

Table 2 shows that the activity profiles of the ergot alkaloids under investigation are qualitatively similar but differ quantitatively. No systematic difference exists between the α- and β-alkaloids with the exception of serotonin-antagonism which is more potent in the β-alkaloids. The greatest quantitative difference was found between α- and β-ergoptine concerning uterotonic activity (factor 8) followed by the serotonin-antagonism (factor 3), and between α- and β-ergokryptine in the antifertile activity (factor 3). All other differences in activity are smaller.

The results compare well with those reported earlier for α- and β-ergokryptine[15].

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## New tigliane and daphnane derivatives from *Pimelea prostrata* and *Pimelea simplex*

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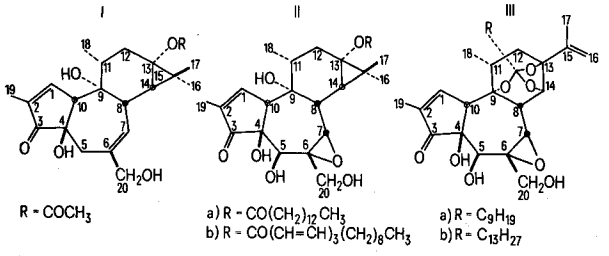
*Summary.* From the methanol extract of *Pimelea prostrata*, prostratin (**I**) and 2 autoxidation products have been isolated. They are tigliane derivatives and relatively nonirritant on the mouse ear. The irritant pimelea factor $P_5$ (**IIa**) also with a tigliane skeleton and related to mancinellin (**IIb**), as well as the irritant diterpene ester pimelea factor $P_1$ (**IIa**, simplexin) with daphnane skeleton, were found to be present in both *P. prostrata* and *P. simplex*. Further the irritant homologue of simplexin, pimela factor **IIIb** was detected in *P. prostrata*. Some biogenetic consequences of these findings are discussed.

A large number of species of the Euphorbiaceae are known to contain toxic, irritant and cocarcinogenic diterpene esters of the tigliane and/or daphnane as well as of the ingenane type[4]. From species of the Thymelaeaceae, the toxic and irritant diterpene esters isolated until recently[4a] were of the daphnane type, e.g. mezerein[5] from *Daphne mezereum* L. (spurge laurel) and simplexin[6] from *Pimelea simplex* F. Muell. (desert rice flower). Both toxins are cocarcinogenic[4,7,8] in mouse skin. Moreover, mezerein[9] and crude extracts of *P. simplex*[10] were shown to exhibit antileucemic activity. The first tigliane derivative from the Thymelaeaceae family, prostratin [13-O-acetyl-12-deoxyphorbol (**I**)], was isolated recently from the strathmore weed *Pimelea prostrata* Willd.[11]. This plant is a small endemic New Zealand shrub known to be toxic to livestock[12], extracts of which were reported to exhibit antitumor activity[11]. Now we wish to report on further new tigliane and daphnane derivatives isolated from *P. prostrata* and *P. simplex* (figure).

From methanol extracts of different air-dried parts of *P. prostrata*, by a combination of counter current distribution and chromatographic methods, besides the main constituent prostratin (**I**)[11], some oxidation products derived from it, as well as the new pimelea factors $P_1$, $P_4$ and $P_5$, were obtained (for irritancy and some other data see table).

$\Delta^{5,6}$-7-Hydroperoxide of **I** (table): IR ($CH_2Cl_2$): 3380, 3560 (OH); 1705 (CO); 1620 $cm^{-1}$ (C=C); UV (MeOH):




Structures of prostratin (**I**), mancinellin (**IIb**) and simplexin (pimelea factor $P_1$, **IIIa**) together with the new pimelea factors $P_5$ (**IIa**) and $P_4$ (**IIIb**) isolated from *Pimelea prostrata*.

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Data of the diterpene esters isolated from *Pimela simplex* and *Pimela prostrata* as compared to croton oil factor $A_1$ [12-O-tetradecanoylphorbol-13-acetate (TPA)]

| Factor/compound | Structure | Yield (%)[a] | Molecular ion $M^+$ (m/e) | Irritancy ($ID_{50}$) (nmoles/ear)[d] |
|---|---|---|---|---|
| TPA (see loc. cit. [4,7]) | – | – | 616 | 0.016 |
| Prostratin | **I** | 0.05[b] | 390 | >100 |
| $\Delta^{5,6}$-7-Hydroperoxide of **I** | – | 0.01[b] | 386 ($M^+$–36) | > 50 |
| $\Delta^{5,6}$-7-Ketone of **I** | – | 0.01[b] | 404 | > 50 |
| $P_5$ | **IIa** | 0.005[b] | 590 | 0.09 |
| $P_1$ | **IIIa** | 0.002[c] | 532 | 0.03 |
| | | 0.02[b] | | |
| $P_4$ | **IIIb** | 0.002–0.007[b] | 588 | 0.03 |

[a] By weight from methanol extract, [b] from roots and stems, [c] from leaves, [d] $\sigma$ : 1.3, $\alpha$ = 0.05, for procedure see loc. cit.[13].

$\lambda_{max}$ 194, 241, 324 nm ($\varepsilon_{max}$ 7830, 5500, 120); NMR ($CDCl_3$, $\delta$): 1-H: 7.6 (s, br.); 5-H: 6.34 (s, br.); 7-H: 4.75 (d, J=8 Hz); 20-$H_2$: 4.27 ± 0.09 ($J_{AB}$=12 Hz); 10-H: 2.94 (m); 8-H: 2.6 (dd, J=8Hz, 5 Hz); acetyl: 2.06 (s); 19-$H_3$: 1.78 (m); 14-H: 1.4 (d, J=5 Hz); 16-$H_3$ and 17-$H_3$: 1.24 and 1.02 (2 s); 18-$H_3$: 0.88 ppm (d, J=6 Hz). Upon treatment with triphenylphosphine in ether, this compound is converted to the corresponding 7-OH derivative: NMR ($CDCl_3$): 1-H: 7.55 (s, br.); 5-H: 6.04 (s, br.); 7-H: 4.76 (d, J=6 Hz); 20-$H_2$:4.3 (s); 10-H: 3.02 (m); 8-H: 2.25 (dd, J=6 Hz, 5 Hz); acetyl: 2.08 (s); 19-$H_3$: 1.8 (m); 16-$H_3$ and 17-$H_3$: 1.18 and 1.02 (2 s); 18-$H_3$: 0.9 (d, J=6 Hz); 14-H: 0.82 ppm (d, J=5 Hz). Acetylation with acetic anhydride in pyridine affords a triacetate, ms: ($M^+$-18) at m/e = 430; NMR ($CDCl_3$): 2.09, 2.06, 2.04 ppm (acetyl signals).

$\Delta^{5,6}$-7-Ketone of **I** (table): IR ($CH_2Cl_2$): 3600, 3570, 3380 (OH); 1710, 1670 (CO); 1620 $cm^{-1}$ (C=C); UV (MeOH): $\lambda_{max}$ 194, 223, 250, 327 nm ($\varepsilon_{max}$ 5020, 8920, 5260, 140); NMR ($CDCl_3$): 1-H: 7.62 (s, br.); 5-H: 6.88 (s, br.); 20-$H_2$: 4.32 ± 0.06 ($J_{AB}$ =12 Hz); 8-H: 3.5 (d, J=5 Hz); 10-H: 3.25 (m); acetyl: 2.08 (s); 19-$H_3$: 1.8 (m); 14-H: 1.6 (d, J=5 Hz); 16-$H_3$ and 17-$H_3$: 1,14 and 1.0 (2 s); 18-$H_3$: 0.92 ppm (d, J=6 Hz). From these data the structures 13-O-acetyl-7-hydroperoxy-4, 9, 20-trihydroxy-1,5-tigliadien-3-one and 13-O-acetyl-4, 9, 20-trihydroxy-1,5-tigliadien-3,7-dione may be derived, respectively. They are considered as products of autoxidation of prostratin (**I**) formed perhaps during the drying process of the plant material used. Analogous compounds are known to result from autoxidation of phorbol esters[13]. On the mouse ear prostratin, and the 2 oxidation products thereof, are practically nonirritant as compared to croton oil factor $A_1$[13] (table).

From roots and stems of *P. prostrata*, as well as from roots of *P. simplex*, the first highly irritant pimelea factor with tigliane skeleton $P_5$ (**IIa**, table) was isolated: IR ($CH_2Cl_2$): 3400 (OH); 1730, 1680 (CO); 1620 $cm^{-1}$ (C=C); UV (MeOH): $\lambda_{max}$ 193, 235 nm ($\varepsilon_{max}$ 11020, 4340); NMR ($CDCl_3$): 1-H: 7.7 (s, br.); 5-H: 4.22 (s); 10-H: 3.9 (m); 20-$H_2$: 3.8 (s); 7-H: 3.24 (s); 8-H: 2.8 (d, J=8 Hz); 19-$H_3$: 1.8 (m); 16-$H_3$ and 17-$H_3$: 1,18 and 1.08 (2 s); 18-$H_3$: 0.92 ppm (d, J=5 Hz). The position of the signal of 14-H could be detemined by decoupling experiments (1.21 ppm). These data suggest the structure of 12-deoxy-5$\beta$-hydroxy-13-tetradecanoylphorbol-6$\alpha$,7$\alpha$-oxide (**IIa**). It is related to mancinellin (**IIb**), one of the irritant principles of *Hippomane mancinella* (Euphorbiaceae)[14]. The daphnane derivative Pimelea factor $P_1$ (**IIIa**, table), 3 times as irritant as **IIa**, was obtained from different parts of *P. simplex* as well as from *P. prostrata*: IR ($CH_2Cl_2$): 3600, 3470 (OH); 1680 (CO); 1620 $cm^{-1}$ (C=C); UV (MeOH): $\lambda_{max}$ 194, 241, 328 ($\varepsilon_{max}$ 10900, 7090, 110); NMR ($CDCl_3$): 1-H: 7.62 (s, br.); 16-$H_2$: 5.0 (s) and 4.88 (s, br.); 14-H: 4.35 (d, J=3 Hz); 5-H: 4.23 (s); 20-$H_2$: 3.82 (s); 10-H: 3.75 (m); 7-H: 3.44 (s); 8-H: 2.9 (d, J=3 Hz); 17-$H_3$ and 19-$H_3$: 1.8 (s); 18-$H_3$: 1.15 ppm (d, J=7 Hz). The spectral data suggest the structure **IIIa** identical with simplexin, isolated also from *P. simplex* by Roberts et al.[6].

Further, a highly irritant pimelea factor $P_4$ (**IIIb**, table) was isolated from *P. prostrata*: IR ($CH_2Cl_2$): 3510 (OH); 1690 (CO); 1620 $cm^{-1}$ (C=C); UV (MeOH): $\lambda_{max}$ 194, 241, 340 nm ($\varepsilon_{max}$ 6660, 5730, 150); NMR ($CDCl_3$): 1-H: 7.66 (s, br.); 16-$H_2$: 5.04 (s) and 4.92 (s, br.); 14-H: 4.4 (d, J=3 Hz); 5-H: 4.22 (s); 20-$H_2$: 3.81 ± 0.03 ($J_{AB}$ = 12 Hz); 10-H: 3.75 (m); 7-H: 3.44 (s); 8-H: 2.9 (d, J=3 Hz); 17-$H_3$ and 19-$H_3$: 1.8 (s); 18-$H_3$: 1.14 ppm (d, J=7 Hz). Upon treatment with acetone and p-toluenesulfonic acid, $P_4$ affords an acetonide which cannot be further acetylated by acetic anhydride in pyridine (ms: parent ion at m/e = 628; NMR ($CDCl_3$): 1.44 ppm (s, 6 protons)), indicating acetonide formation with 5-OH/20-OH. The spectral data, and in particular the proton magnetic resonance of $P_4$, closely resemble those of **IIIa**. Also the major fragment ions in the mass spectrum of $P_4$ show striking similarities to those of **IIIa** and confirm the presence of the $C_{14}$-orthoester residue. Hence $P_4$ is assigned the structure **IIIb**, homologous to simplexin (**IIIa**).

The simultaneous occurrence in *P. prostrata* of the tigliane derivatives (**I, II**) and of daphnane derivatives (**IIIa, b**) supports the biogenetic relationship proposed for these classes of diterpenes[4,7,8]. Since cocarcinogenic[4,7,8], as well as antileucemic[4,8,9,15] activities, are reported in the literature for a number of individual tigliane and daphnane derivatives, we are presently investigating the new constituents isolated for both of these biological activities.

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