Eriolangin and Eriolanin, Novel Antileukaemic *seco*-Eudesmanolides from *Eriophyllum lanatum*[1]

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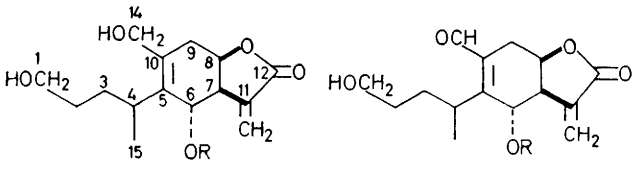
Summary The isolation and structural elucidation of eriolangin (**1**) and eriolanin (**2**), novel antileukaemic 1,10-*seco*-eudesmanolides from *Eriophyllum lanatum*, are reported.

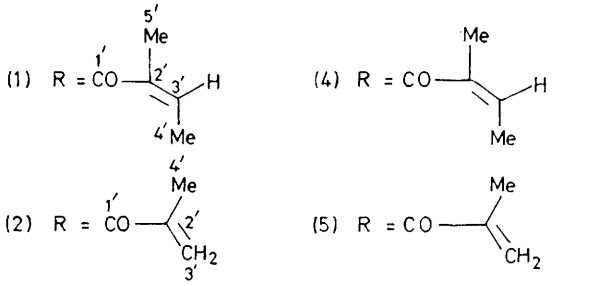
IN the course of a continuing search for tumour-inhibitory natural products, we found that chloroform extracts of *Eriophyllum lanatum* Forbes (Compositae) showed significant activity *in vivo* against the P-388 leukaemia in mice and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB).[2] We report herein the isolation and structural elucidation of eriolangin (**1**) and eriolanin (**2**), two novel antileukaemic sesquiterpene lactones. Eriolangin and eriolanin number among the small group of sesquiterpene lactones which show *in vivo* tumour inhibitory activity,[3] and are the first highly oxygenated derivatives of the rare 1,10-*seco*-eudesmanolide type.[4]

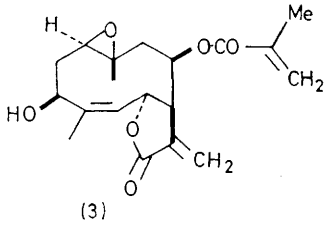
Fractionation of the chloroform extract, monitored by KB assay, revealed that the inhibitory activity was concentrated successively in the chloroform layer of a chloroform–water partition, the methanol layer of a 10% aqueous methanol–light petroleum partition, and in the chloroform layer of a chloroform–80% aqueous methanol partition. Chromatography of the latter fraction on silica gel yielded two crude cytotoxic fractions. Crystallization of the earlier fraction yielded erioflorin (**3**) (0·2%), m.p. 198—202°, $[\alpha]_D^{25}$ 104° ($CHCl_3$).[5]

Crystallization of the second fraction from chloroform–light petroleum afforded colourless crystals, m.p. 116–118° which appeared homogeneous by t.l.c. and high pressure liquid chromatography. A molecular formula $C_{19-20}H_{26-28}O_6$ was initially assigned on the basis of elemental analysis. In the mass spectrum no parent ion was observed, the highest ion having *m/e* 264 ($C_{15}H_{20}O_4$). The presence of an α-methylene-γ-lactone function could be inferred from the i.r. (5·70 μm) and n.m.r. [τ 3·48 (d, 1H, *J* 3 Hz) and 3·96 (d, 1H, *J* 3 Hz)] spectra, and that of an $\alpha\beta$-unsaturated ester group from the i.r. (6·85 μm, shifted to 5·80 μm in spectrum of the tetrahydro-derivative) spectrum. Acetylation afforded a diacetyl derivative [τ7·98, 8·01 (2s, 6H, 2 $COCH_3$)] in the n.m.r. spectrum of which two 2H signals [τ 6·0 (m, 2H) and 5·28 (AB, *J* 12 Hz)] had been shifted downfield by 0·5 p.p.m., corresponding to the acetylation of two hydroxymethyl groups. Oxidation with

manganese dioxide yielded a t.l.c.-homogeneous product (**A**), m.p. 102—103°, possessing an $\alpha\beta$-unsaturated aldehyde group [i.r. 6·0 μm, λ_{max} (EtOH) 243 nm (ϵ 13,000), τ 0·31 (s, 1H, C*H*O)] indicative of the allylic nature of one of the alcohols. However, the highest ions in the mass spectrum (C.I.) of (**A**) were observed at *m/e* 365 and 351, indicative that the substance was a mixture of two closely related compounds.







(3)

Well-formed single crystals of (**A**) were studied by *X*-ray diffraction methods. The crystals are orthorhombic, space group $P2_12_12_1$, with a = 8·115(1), b = 10·260(2), c = 22·857(3) Å, and Z = 4. By counter diffractometry with monochromatic Cu-K_α radiation the intensities of 1293 independent reflections significantly above background were measured and used in the structure analysis. The phase problem was solved by the multi-solution tangent formula procedure by use of the programme MULTAN[6] and led to the structure shown in the Figure.

Refinement, by least-squares methods, of a model corresponding to structure (**5**) gave R = 0·085, but calculation of a three-dimensional difference electron-density function showed, besides the locations of 18 hydrogen atoms, a peak corresponding to C-4′ of (**4**) present with an occupancy *ca.* 0·3 and indications of some slight disorder in the positions of C-2′ and C-3′. Coupled with the mass spectral observations, this led to a model for the crystal structure involving both (**5**) and (**4**) in the ratio 7 : 3. Complete overlap of the two structures was assumed except at C-4′ and refinement of this model, including contributions from 18 hydrogen atoms in fixed positions, led to convergence with R = 0·06. Because of the uncertainties introduced in the calculated structure factors by this model we did not try to determine the absolute configuration of the material.

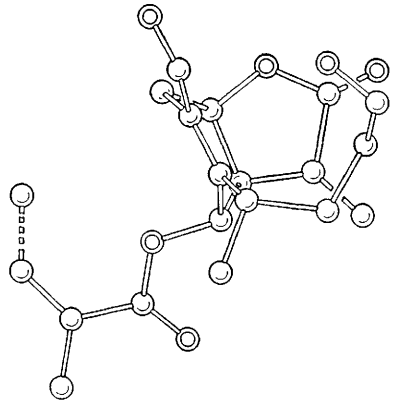


FIGURE. View of the molecular structure of (**A**) as found in the crystal. The projection is onto the plane of the lactone ring. The atomic centres for the two co-crystallising molecules coincide precisely for all atoms except for small differences in the positions of C-2′ and C-3′ and the addition of C-4′ in component (**4**) (indicated by the dashed bond). Oxygen atoms are indicated by the double circles and hydrogen atoms have been omitted for clarity.

The mixture of lactones (**1**) and (**2**) was separated by column chromatography to afford the angelate ester, eriolangin (**1**) [$C_{20}H_{28}O_6$, m.p. 94—96°, $[\alpha]_D^{25}$ − 91°(CHCl$_3$); mass spectrum (CI-CH$_4$) *m/e* 365 (M + 1)$^+$], and the methacrylate ester, eriolanin (**2**) [$C_{19}H_{26}O_6$, m.p. 126·5—128°, $[\alpha]_D^{25}$ − 93° (CHCl$_3$); mass spectrum (CI-CH$_4$) *m/e* 351 (M + 1)$^+$]. In the n.m.r. spectrum of (**1**) the resonance of the ester olefinic proton [τ 3·97 (q, J 8 Hz)] indicates the angelate nature of the ester.[7]

In view of the recent demonstration of the potential importance of nucleophilic additions to unsaturated systems for the tumour-inhibitory activity of related compounds,[8,9] it is noteworthy that (**1**) and (**2**) each contain two $\alpha\beta$-unsaturated carbonyl functions. Investigations are in progress to determine the potential significance of these, the allylic alcohol and ester, and other structural features in relation to the tumour-inhibitory activity of eriolangin and eriolanin.

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[1] For previous paper in the series "Tumor Inhibitors" see: S. M. Kupchan, *Intra-Science Chem. Rept.*, in the press.

[2] Anti-leukaemic and *in vitro* cytotoxicity were assayed under the auspices of the National Cancer Institute, by the procedures described in *Cancer Chemotherapy Reports*, 1962, **25**, 1. Eriolangin, eriolanin, and erioflorin showed significant antileukaemic activity against P-388 leukaemia in the mouse.

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