INGOL ESTERS, CYTOTOXIC AGENTS OF THE MACROCYCLIC TYPE

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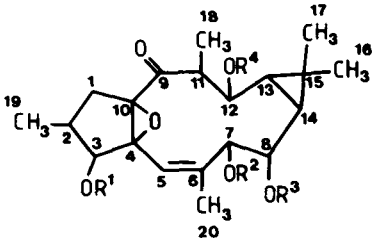
Euphorbia kamerunica Pax. contains tetracyclic diterpenes which are closely related to the tumour-promoting and pro-inflammatory phorbol agents of other Euphorbia species (Evans & Kinghorn 1975). However, it has been reported that Euphorbia plants are used as anti-tumour drugs in native medicine (Hartwell 1969). The ether soluble extract of E. kamerunica latex was tested in vivo for induction of erythema (Evans & Schmidt 1979) and in vitro for cytotoxic activity (Phillipson & Darwish 1979). The extract was fractionated by gradient elution column chromatography and several fractions which did not possess pro-inflammatory activity, characteristic of tetracyclic diterpenes, were cytotoxic agents in vitro. Three macrocyclic ester diterpenes (Fig. 1) were isolated from these fractions by adsorption and partition thin-layer chromatography.

FIGURE 1



Ingol esters	R^1	R^2	R^3	R^4
1	H	H	H	H
2	acetate	acetate	acetate	tigliate
3	—"—	—"—	H	—"—
4	—"—	—"—	acetate	acetate

Complete hydrolysis of these esters with 0.5M KOH in methanol afforded ingol 1 (TLC, M.S., ^{1}H-NMR). The i.r., u.v., m.s. and ^{1}H-NMR spectra of 2, 3 and 4 demonstrated that these compounds were tigliate and acetate esters of ingol. Decoupling experiments of the 250 MHZ ^{1}H-NMR spectra assisted in the assignment of the signals for the protons adjacent to the secondary acyl groups at C-3, 7, 8 and 12 of ingol 1. Mild hydrolysis of 2, 3 and 4 with 0.1M potassium methoxide in methanol produced a series of products for each compound. From the shift in 1H signals in the ^{1}H-NMR spectra of these products for the protons at C-3, 7, 8 and 12 due to removal of acyl substituents, the macrocyclic esters were assigned as 3, 7, 8-triacetyl-ingol-12-tigliate 2, 3,7-diacetyl-ingol-12-tigliate 3 and ingol-tetra-acetate 4. Compounds 2 and 3 are new ingol esters, whilst 4, which has been produced synthetically from ingol 1, has not previously been shown to be a natural product.

Evans, F.J. & Kinghorn, A.D. (1975) Lloydia, 38: 363-365
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Hartwell, J.L. (1969) Lloydia, 32: 153-205
Phillipson, J.D. & Darwish, F.A. (1979) Planta Medica, 35: 308-315

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