PRODUCTION OF INFLAMMATION BY DITERPENE ESTERS

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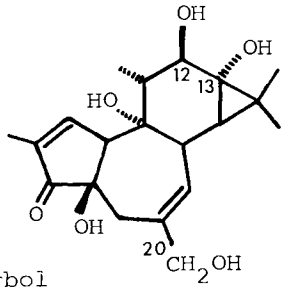
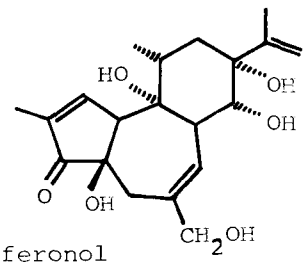
The irritant toxins of certain species of the Euphorbiaceae and Thymelaeaceae are esters of two structurally related diterpene polyols (Fig.1). Both the tumour-promoting and anti-tumour activity of the toxins have received some attention (Hecker and Schmidt 1974; Soper and Evans 1977; Kupchan and others 1976), whilst the mode of action of the irritant effects has been largely ignored.

We have observed both the time to onset and the duration of action of a series of natural and semi-synthetic esters of these polyols using a mice ear assay (Kinghorn and Evans 1975). The erythema produced appeared at time intervals after application depending upon the length of the ester side-chain at C-12 and C-13. Short chain esters exhibited activity after 1 hour, whereas longer chain esters produced erythema after a delay of up to 4 hours. In addition the persistence and intensity of the inflammation was related to the presence and structure of an ester at C-20. The irritancy of semi-synthetic esters of the C-20 hydroxy group with aromatic acids was shown to be dependent on the presence of an electronegative function in the meta or para position of the esterifying acid. These preliminary observations suggest that a study of the structure/activity relationships of further semi-synthetic and naturally occurring esters of these diterpene polyols may eventually clarify the structure of the receptor site or sites in the skin.

Fig.1



Phorbol



Resiniferonol

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