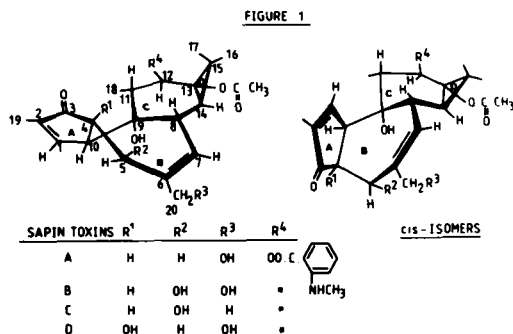


THE SAPINTOXINS: NITROGEN CONTAINING PHORBOLS OF PHARMACOLOGICAL INTEREST

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Tumour-promoting and pro-inflammatory phorbol esters are the toxic constituents of Croton and Euphorbia species (Evans & Soper 1978). Interest has recently been shown in the mechanism of action of these agents (Blumberg 1980). Phorbol occurs naturally as a series of aliphatic esters. Sapium indicum L. is a poisonous Indian plant of the family Euphorbiaceae (Chopra et al 1958). From the oil of the dried fruits, four aromatic nitrogen containing phorbol derivatives were obtained, known as Sapintoxins A, B, C and D (Fig. 1).



These u.v. fluorescent esters were isolated by a combination of centrifugal-liquid chromatography and thin-layer chromatography. The assignment of N-methylamino-benzoate to C-12 and acetate to C-13 in each compound was facilitated by selective hydrolysis reactions. The nucleus of Sapintoxin A was assigned as 4-deoxy-phorbol, B as 4-deoxy-5-OH-phorbol, C as 4,20-dideoxy-5-OH-phorbol and D as phorbol by m.s., i.r., u.v., C.D. and ¹H-NMR together with decoupling experiments. Sapintoxins A and C were accompanied in the extract by their AB-cis isomers. When exposed to alkali the AB-trans junction of the Sapintoxins was converted to the cis form. This conversion was monitored by their C.D. and ¹H-NMR spectra. Sapintoxins A, B and D caused erythema of skin (Evans & Schmidt 1979) in doses of 1×10^{-2} μg to 5×10^{-1} μg , and induced aggregation of human and rabbit platelets (Westwick et al 1980) in doses of 5×10^{-3} μg to 1×10^{-1} μg . The AB-cis isomers were inactive in these tests as was Sapintoxin C, the 20-deoxy derivative. The AB-trans junction and the C-20 hydroxy group are necessary for activity of Sapintoxins in vivo and in vitro, whilst the C-4 hydroxy group is not. The Sapintoxins are the first biologically active nitrogen containing phorbol esters to be isolated from natural sources.

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