The Structure and Stereochemistry of Phorbol, Diterpene Parent of Co-carcinogens of Croton Oil

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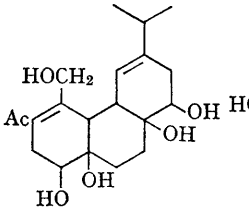
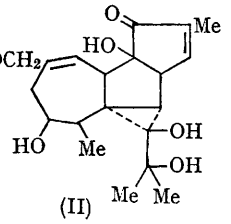
PHORBOL, $C_{20}H_{28}O_6$, can be isolated[1] from croton oil, a vesiccant oil from the seeds of *Croton tiglium* L. The latter contains a group of potent co-carcinogens in which phorbol is esterified with various fatty acid pairs, one short- and one long-chain.[2-4] On the basis of spectroscopic and degradative evidence, phorbol has been variously reported as (I),[3] (II),[5] and (III).[6] Several aspects of all these structures are chemically unsatisfactory† and a three-dimensional *X*-ray analysis of a suitable phorbol derivative was undertaken to settle the matter.

Our *X*-ray analysis of crystals of a 5-bromofuroate derivative‡ of phorbol unambiguously establishes that the derivative has the constitution and relative stereochemistry shown in (IV). The constitution and relative stereochemistry of phorbol is thus (V).§ On the basis of chemical information[4] the active esters are then (VI).

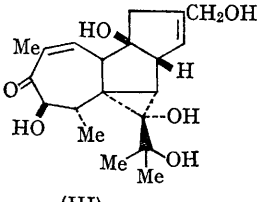
Phorbol 5-bromofuroate crystallises from chloroform with two formula units of $C_{25}H_{29}O_8Br,CHCl_3$ in a unit cell of dimensions $a = 10{\cdot}54$, $b = 10{\cdot}35$, $c = 13{\cdot}80$ Å, $\beta = 107{\cdot}6°$. The crystals are unstable in the *X*-ray beam at 20° but decompose only slowly when irradiated at −160°. At this temperature some 1600 three-dimensional *X*-ray intensity data were recorded on equi-inclination Weissenberg photographs using Cu-K_α radiation and crystals rotating about *b*. The intensities were estimated visually and the structure was solved by the phase-determining heavy-atom method.[7] The hydroxyl oxygen atoms were distinguished from methyl carbon atoms by the



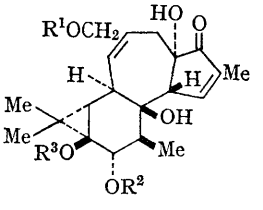
(I)



(II)



(III)



(IV) R^1=Br  CO, $R^2=R^3$=H
(V) $R^1=R^2=R^3$=H
(VI) R^1=H, $R^2=R^4$CO, $R^3=R^5$CO

† Details will be published elsewhere.
‡ The ninth phorbol derivative prepared and examined by us for this purpose since June 1965.
§ Constitution (V) is in agreement with suggestion made by Professor E. Hecker in a lecture at the Chester Beatty Research Institute in London on 11th January, 1967, *cf. Naturwiss.*, 1967, **54**, 282.

fact that they enter into an O–H · · · O intermolecular hydrogen-bond network in the crystal and also by their greater integrated peak density in the electron-density distributions (when allowed for as carbon atoms). Refinement by Fourier and least-squares methods has lowered R to 0·16. Further refinement by least-squares calculations¶ is in progress; full details will be reported in due course.

One of us (R.C.P.) is indebted to the United States Institutes of Health for a post-doctoral fellowship. We thank the British Empire Cancer Campaign for financial support.

(*Received, June 9th,* 1967; *Com.* 580.)

¶ Using programs devised by Professor D. W. J. Cruickshank, Drs. K. W. Muir and J. G. Sime, and D. R. Pollard and D. McGregor.

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