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STRUCTURE AND STEREOCHEMISTRY OF THE EPOXIDE OF PHANTOMOLIN, A NOVEL CYTOTOXIC SESQUITERPENE LACTONE FROM *ELEPHANTOPUS MOLLIS*

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An earlier examination of the whole plant of *Elephantopus mollis* H. S. K. harvested in the early spring yielded molephantin[1] (I) as a novel cytotoxic agent. We now report that the winter collection of this same plant[2] yields phantomolin (II) as the major cytotoxic[3] component (0.023%) in addition to traces of molephantin (0.0007%). Phantomolin is a novel germacranolide $\Delta^{3(4)}$ *cis*, $\Delta^{1(10)}$ *cis*-diene[5].

Phantomolin was isolated as a colorless oil from the chloroform extract of *E. mollis* according to an exact literature procedure[1]. Phantomolin [II; $C_{21}H_{26}O_6$ (M^+ 388.1880); ν_{max} ($CHCl_3$) 1770 (γ-lactone), 1725, 1719 (C=O), 1664 and 1640 cm^{-1} (C=C); δ ($CDCl_3$) 6.33 (1H, d, J = 3.0 Hz, 13-H), 5.80 (1H, d, J = 3.0 Hz, 13-H), 3.47 (2H, q, J = 7.5 Hz, H-20), 1.18 (3H, t, J = 7.5 Hz, H-21), and 2.00 (3H, d, J = 1.5 Hz), 1.79 (3H, m) and 1.73 (3H, m) (three vinyl methyl groups)] gave upon treatment with *m*-chloroperbenzoic acid in chloroform, a 1,10-*cis*-epoxide [III; $C_{22}H_{28}H_7$ (M^+ 404.1835); m.p. 172°; δ ($CDCl_3$) 1.41 (3H, s, 15-H)]. Colorless prisms of (III) belong to the monoclinic system, space group $C2(C_2^3)$, a = 21.11(1), b = 10.28(1), c = 10.00(1)Å, β = 106.12(10)°, Z = 4. From intensity data measured on an Enraf-Nonius CAD-3 diffractometer with Zr-filtered Mo-K_α radiation 827 statistically significant reflexions were obtained. The crystal structure was solved by direct phase-determining methods using the MULTAN[6] program. Refinement of the atomic positional and thermal parameters by full-matrix least-squares calculations to R = 0.055 led to the structure and relative stereochemistry

(III) for the epoxide from which it follows that phantomolin must be represented by (II).

Although the absolute configuration of phantomolin was not determined independently it is probably correctly represented by (II) from correlation with that established earlier for molephantin. Neither (I) nor (II) can be assigned unambiguously to the recently proposed germacranolide sub-groups[7,8] for the cis-trans nature of the normal reference $\Delta^{4(5)}$ double bond or its equivalent is obscured in both sesquiterpenes.

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References and Footnotes

1. K. H. Lee, H. Furukawa, M. Kozuka, H. C. Huang, P. A. Luhan, and A. T. McPhail, J.C.S. Chem. Comm., 476 (1973).

2. Specimens were gathered in January, 1973, in Chia-Sen, Kaohsiung, Taiwan.

3. Phantomolin showed significant inhibitory activity of the *in vitro* growth of tissue culture cells originating from human epidermoid carcinoma of larynx (H. Ep. -2) at 0.66 µg/ml. Cytotoxicity was assayed by Dr. E. S. Huang, Department of Bacteriology and Immunology, School of Medicine, University of North Carolina at Chapel Hill by literature method.[4]

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5. The presence of an ethyl ether is also novel and appears to represent the first example in naturally-occurring sesquiterpene lactones. Although EtOH was not used during the isolation and extraction procedure it is possible, though improbable, that the ethyl group was introduced as an artifact from traces of EtOH present in the $CHCl_3$ (0.75% in Baker Analysed Reagent Chloroform, J. T. Baker Chemical Company, Phillipsburg, New Jersey). It has been verified, however, that molephantin does not transform to phantomolin either under the conditions used for the extraction or when subjected to more rigorous conditions. The origin of the ethyl group can only be fully clarified by future studies when fresh plant material collected in the same season becomes available.

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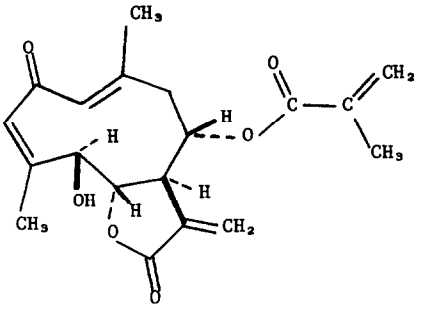
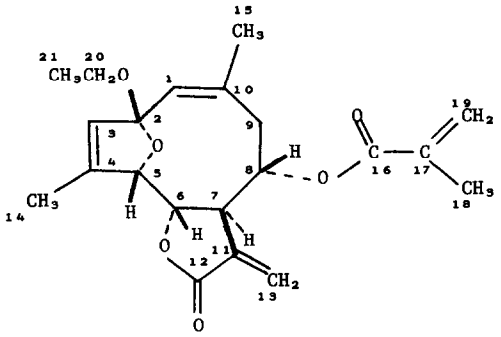
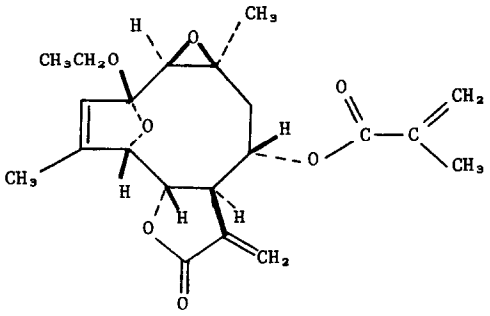


(I)



(II)



(III)