

## Molephantin, a Novel Cytotoxic Germacranolide from *Elephantopus mollis*. X-Ray Crystal Structure

By KUO-HSIUNG LEE,\* HIROSHI FURUKAWA, and MUTSUO KOZUKA

(Department of Medicinal Chemistry, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27514)

HUAN-CHANG HUANG

(School of Pharmacy, Kaohsiung Medical College, Kaohsiung, Taiwan)

and PATRICIA A. LUHAN, and ANDREW T. MCPHAIL

(Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706)

**Summary** The structure and absolute configuration of molephantin, a novel cytotoxic germacranolide isolated from *Elephantopus mollis* H.S.K., have been determined on the basis of physicochemical data and X-ray crystallographic analysis.

THE search among Formosan plants for agents with potential antitumor or cytotoxic activity<sup>1</sup> has led to the isolation from *Elephantopus mollis* H.S.K.† of a novel sesquiterpene

lactone, molephantin (I), which has potent cytotoxic activity.‡ It is a germacranolide with a novel unsaturation pattern, and the first possessing a dienone ring system.

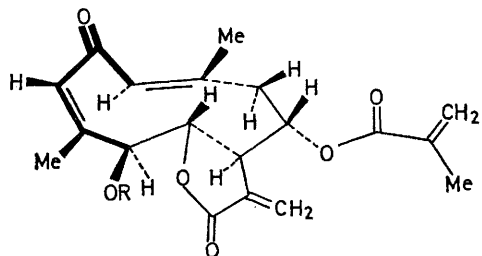
The chloroform extract of the whole plant was concentrated and partitioned between 25% aqueous methanol and hexane. Guided by the assay in H.Ep.-2 cells,§ the active principles were concentrated in the aqueous methanol layer. The aqueous methanol extract was further concentrated and extracted with chloroform. Chromatography

† Specimens were gathered in early spring, 1972, in Chia-Sen, Kaohsiung, Taiwan. *E. mollis* is also known as 'Péh-Teng-Khiã-U' in folklore.

‡ Molephantin showed significant inhibitory activity of the *in vitro* growth of tissue culture cells originating from human epidermoid carcinoma of larynx (H.Ep.-2) at 0.333 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.<sup>2</sup>

of the active chloroform extract over silica gel led to the isolation of molephantin (0.031%) as needles (from EtOH). Molephantin (I;  $C_{19}H_{22}O_6$ ;  $\eta$ ) m.p. 214–216° gave an acetate (II;  $C_{21}H_{24}O_7$ ; m.p. 159–161°), and on oxidation with Jones' reagent afforded oxomolephantin (IV;  $C_{19}H_{20}O_6$ ; m.p. 132–134°). Structures (I), (II), and (IV) were deduced from extensive electroscopic, mass spectral, and n.m.r. data which will be discussed elsewhere.



- (I) R = H  
 (II) R = COMe  
 (III) R = *p*-Br · C<sub>6</sub>H<sub>4</sub> · SO<sub>2</sub>  
 (IV) replaces OR H

Single-crystal X-ray analysis of molephantin *p*-bromobenzenesulphonate (III),  $C_{25}H_{25}BrO_8S$ , m.p. 165–167°, provided unequivocal proof of the structure, stereochemistry, and absolute configuration of molephantin. The crystals are thin orthorhombic needles, space group  $P2_12_12_1$  ( $D_2^4$ ),  $a = 11.68$ ,  $b = 27.30$ ,  $c = 8.27$  Å,  $Z = 4$ . Three-dimensional data were recorded photographically with Cu- $K_\alpha$  radiation and estimated visually. The structure was solved by the heavy-atom method and refined by full-matrix least-squares calculations (anisotropic Br, isotropic, C, O, S) incorporating anomalous dispersion corrections;  $R$  is 0.115% for 944 independent observed reflections. The conformation of (III) in the crystal is shown in the Figure, and the absolute configuration is represented by (III), in which the

$\eta$  All crystalline compounds gave satisfactory elemental analyses.

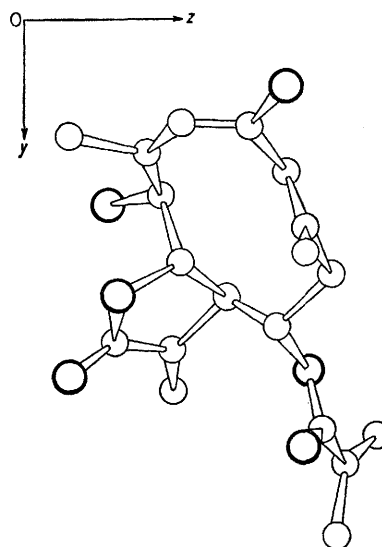
<sup>1</sup> K. H. Lee, H. C. Huang, E. S. Huang, and H. Furukawa, *J. Pharm. Sci.*, 1972, **61**, 629.

<sup>2</sup> E. S. Huang, K. H. Lee, C. Piantadosi, T. A. Geissman, and J. S. Pagano, *J. Pharm. Sci.*, 1972, **61**, 1960.

<sup>3</sup> (a) S. M. Kupchan, Y. Aynehchi, J. M. Cassidy, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *J. Amer. Chem. Soc.*, 1966, **88**, 3674; (b) S. M. Kupchan, Y. Aynehchi, J. M. Cassidy, H. K. Schnoes, and A. L. Burlingame, *J. Org. Chem.*, 1969, **34**, 3867; (c) *Elephantopus scaber* yielded deoxyelephantopin but no biological data were reported (see ref. 4).

<sup>4</sup> T. Kurokawa, K. Nakanishi, W. Wu, H. Y. Hsu, M. Maruyama, and S. M. Kupchan, *Tetrahedron Letters*, 1970, 2863.

asymmetric carbon atoms have the configurations 5*S*, 6*S*, 7*S*, and 8*S*.



FIGURE

The observed potent cytotoxic activity of molephantin accords with and extends earlier observations of antitumour and cytotoxic activities for two related sesquiterpenoids, elephantin and elephantopin, from *Elephantopus elatus*.<sup>3,4</sup>

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