X-Ray Determination of the Structure and Absolute Configuration of a Novel Sesquiterpenoid, Melampodin

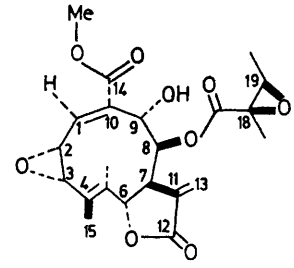
By S. NEIDLE
(*Department of Chemistry, Queen Mary College, Mile End Road, London E.*1)
and D. ROGERS*
(*Chemical Crystallography Laboratory, Imperial College, London* SW7 2AY)

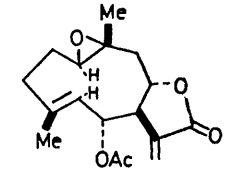
Summary The structure and absolute configuration of the recently isolated sesquiterpenoid lactone, melampodin, have been determined by *X*-ray crystallography using direct statistical methods; a revised constitutional formula is also given for heliangine.

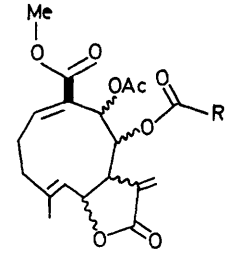
A CRYSTALLINE lactone, $C_{21}H_{24}O_9$, was recently isolated by Fischer *et al.*[1] from *Melampodium leucanthum* and called melampodin. Shortage of material and the complexity of the spectra suggested that an *X*-ray study offered the best prospect of determining the structure, so a few crystals were kindly supplied by Dr. N. H. Fischer. Recently, however, he and his colleagues have been able, using Eu(dpm)$_3$-expanded n.m.r. spectra, to make much more detailed deductions concerning the structure and conformation of this molecule in solution. Their results, which are described in the preceding communication,[1] tally well with the results of the X-ray work.

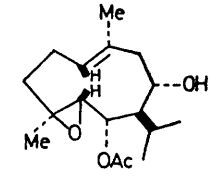
Melampodin crystallises as well formed, colourless, orthorhombic prisms, space group $P2_12_12_1$, $a = 8{\cdot}990$, $b = 14{\cdot}352$, $c = 16{\cdot}294$ Å; $Z = 4$ ($C_{21}H_{24}O_9$ units). The intensities of 1773 statistically significant reflections, to a limit of $\theta = 60°$, were measured on a Siemens AED diffractometer using Cu-K_α radiation. The structure was solved by direct methods,[2] assuming no prior knowledge of the molecular structure. Four origin- and enantiomorph-defining phases were chosen by inspection, and two terms to be given symbolic phases were selected by a program written by Motherwell and Isaacs.[3] Tangent refinement on the 196 *E* values greater than 1·5 produced one solution for the two symbolic phases markedly better than any other; it gave an R_{KARLE} value[2] of 0·20. The corresponding *E* map revealed 25 chemically sensible peaks, and subsequent difference Fouriers revealed five more. The presence of nine oxygen atoms in the molecule, and their positions, were readily established by standard crystallographic methods. The present value of the conventional *R* factor is 0·037, with the effects of absorption allowed for. The absolute configuration of the molecule was determined with a confidence level exceeding 0·995 by means of the anomalous scattering from oxygen and carbon atoms.[4]

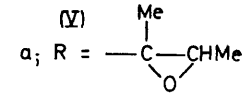
Our study has shown melampodin to have the structure and absolute configuration (I) (see also the Figure for details of the conformation), and it is thus a sesquiterpenoid, specifically a germacradienolide lactone. The configurations at the dissymmetric atoms are 2*R*, 3*S*, 6*R*, 7*S*, 8*S*, 9*S*, 18*R*, 19*R*. The absolute configuration at C(7) is thus in agreement with that for pyrethrosin (II)[5] (from optical evidence), shiromodiol (III)[6] and elephantol[6] (from *X*-ray fluorescence), mikanolide (IV),[7] scandenolide,[7] cnicin,[8] and isabelin[9] (all from chemical and n.m.r. correlations).

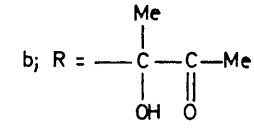

(I)

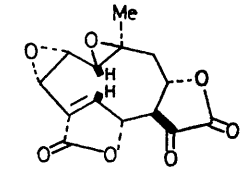

(II)

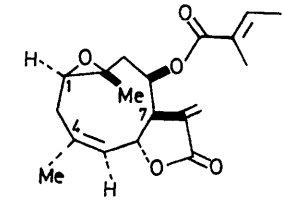

(V)


(III)

a; R = 

b; R = 


(IV)


(VI)

† Uvedalin 4-5 epoxide has recently been equated with enhydrin.[10]

‡ The constitutional formula given in ref. 12 is in error as it shows Δ^4 *trans*, whereas both the co-ordinate list and the pictorial representation in the same paper show it to be *cis*. Mathieson,[13] in a review which predates the appearance of ref. 12, gave a correct drawing for dihydrohelianginol, but it seems not to be generally known. Formula (VI) here shows the correct constitution of heliangine.

TABLE

		Δ^4	$\Delta^{1(10)}$	Examples
Group 1	Germacrolides	*trans*	*trans*	(II)—(IV)
Group 2	Melampolides	*trans*	*cis*	(I), (Va), (Vb)
Group 3	Heliangolides	*cis*	*trans*	(VI), erioflorin[14]

The nearest known relatives to melampodin seem to be uvedalin (Va)† and polydalin (Vb), recently isolated from another member of the genus *Melampodium*,[11] heliangine (VI)[12]‡ and the related erioflorin.[14] For none of these molecules is the absolute configuration known.

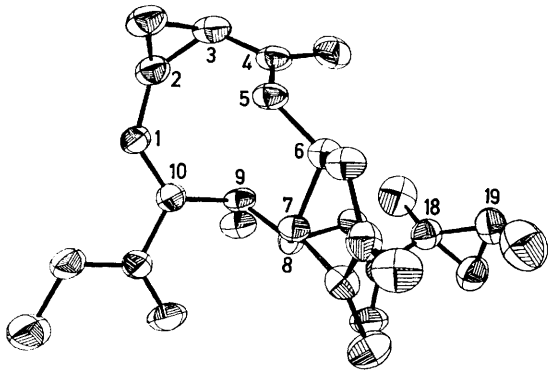


Figure. *View of the α-face of the molecule of melampodin.*

Comparison of the endocyclic double bonds or their epoxide equivalents in formulae (I)—(VI) shows that the germacradienolides may be grouped, and suggests that it may be useful to name the subgroups in the Table. Evidently, it is no longer possible tacitly to assume that a new germacranolide will be *trans, trans*. Under appropriate conditions (*e.g.* the influence of light), *trans–cis*-isomerism could occur, so that the proposed groups may not be immutable. However, such isomerisation is virtually impossible for the many compounds containing highly constrained rings, and the subgroups are then stable. These differences raise an interesting question as to what point in each of the biosyntheses of the melampolides and heliangolides the *cis* double bond is generated: is it at the farnesyl pyrophosphate stage or later? The recently reported selective incorporation of *cis–cis* farnesol into the sesquiterpene, gossypol,[15] supports such an idea, and suggests that a fourth group of *cis,cis*-germacradienolides may yet be found.

The ten-membered ring in melampodin is very contorted owing to the concurrence of *cis*- and *trans*-double bonds and fusions with the lactone and epoxide rings. The torsion angles around the double bonds are 24° (Δ^4, *trans*) and 8° ($\Delta^{1(10)}$, *cis*). The plane of the *trans* double bond is roughly perpendicular to the macrocycle as in most other unsaturated rings of a similar size and in agreement with the n.m.r. observations,[1] but the plane of the *cis* double bond is less steeply inclined to that of the ring. Consequently it becomes possible to talk of C(14) and C(15) as lying α or β to the macrocycle.§ They are *syn* (sometimes both α, sometimes both β) in all the germacrolides so far reported (*e.g.* refs. 5, 6, 18). However, in both melampodin and heliangine they are *anti*, with the substituent on the *cis* double bond being α. This is probably a consequence of the ring constraints, for, as was shown by an *X*-ray study of *cis,trans*-cyclodeca-1,5-diene[19] (which contains a similar but unconstrained ring), the hydrogens corresponding to C(14) and C(15) are *syn*. Sim *et al.*[6] suggest that a *syn* arrangement is probably the energetically favoured conformation of the cationic intermediate in the biogenesis of the germacrolides from *trans,trans*-farnesyl pyrophosphate. (See also ref. 20.) The *anti* arrangement in melampodin and heliangine may thus provide further evidence for different biogenetic pathways.

We are grateful to Drs. N. H. Fischer, and G. P. Moss, and Professors J. K. Sutherland and W. Herz for discussions. One of us (S.N.) is grateful to the University of London for an I.C.I. Research Fellowship.

(*Received, September 29th*, 1971; *Com.* 1697.)

§ Kupchan, Kelsey and Sim[16] proposed a convention for defining α and β faces of the ring and for numbering it. As their assignment is ambiguous until the absolute configuration is known, we have, after discussion with colleagues, made fresh proposals in the following communication.[17] Formulae (I)–(VI) are drawn in the present note to comply with our convention regardless of how they appeared in the original publications. Our novel use of —— and ..... bonds attached to endocyclic double bonds is explained in ref. 17.

[1] N. H. Fischer, R. Wiley, and J. D. Wander, preceding communication.
[2] J. Karle and I. L. Karle, *Acta Cryst.*, 1966, **21**, 849.
[3] We are grateful to Drs. W. D. S. Motherwell and N. W. Isaacs for use of their program (to be published in *Acta Cryst.*).
[4] S. Neidle and D. Rogers, *Nature*, 1970, **225**, 376; D. W. Engel, K. Zechmeister, M. Röhrl, F. Brandl, P. Narayan, and W. Hoppe, *Nature (Physical Science)*, 1971, **229**, 28.
[5] E. J. Gabe, S. Neidle, D. Rogers, and C. E. Nordman, *Chem. Comm.*, 1971, 559.
[6] R. J. McClure, G. A. Sim, P. Coggon, and A. T. McPhail, *Chem. Comm.*, 1970, 128.
[7] W. Herz, P. S. Subramaniam, P. S. Santhanam, K. Aota, and A. L. Hall, *J. Org. Chem.*, 1970, **35**, 1453.
[8] Z. Samek, M. Holub, V. Herout, and F. Šorm, *Tetrahedron Letters*, 1969, 2931.
[9] H. Yoshioka, T. J. Mabry, and H. E. Miller, *Chem. Comm.*, 1968, 1679; H. Yoshioka and T. J. Mabry, *Tetrahedron*, 1969, **25**, 4767.
[10] B. S. Joshi, V. N. Kamat, and H. Fuhrer, *Tetrahedron Letters*, 1971, 2373.
[11] W. Herz and S. V. Bhat, *J. Org. Chem.*, 1970, **35**, 2605
[12] N. Nishikawa, K. Kamiya, A. Takabake, H. Oshio, Y. Tomiie, and I. Nitta, *Tetrahedron*, 1966, **22**, 3601.
[13] A. McL. Mathieson, Perspectives in Structural Chemistry, 1967, Vol. 1, Wiley, New York, p. 76.
[14] S. J. Torrance, T. A. Geissman, and M. R. Chedekel, *Phytochemistry*, 1969, **8**, 2381.
[15] P. F. Heinstein, D. L. Herman, S. B. Tove, and F. H. Smith, *J. Biol. Chem.*, 1970, **245**, 4658.
[16] S. M. Kupchan, J. E. Kelsey and G. A. Sim, *Tetrahedron Letters*, 1967, 2863.
[17] D. Rogers, G. P. Moss and S. Neidle, *Chem. Comm.*, following communication.
[18] F. H. Allen and D. Rogers, *J. Chem. Soc.* (*B*), 1971, 257.
[19] D. Rogers and M. L. Smart, *Acta Cryst.*, 1969, Congress Abstracts, S149, XIII-62.
[20] W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev.*, 1967, **21**, 331.