# Molecular Structure of the Metabolite Lanosulin

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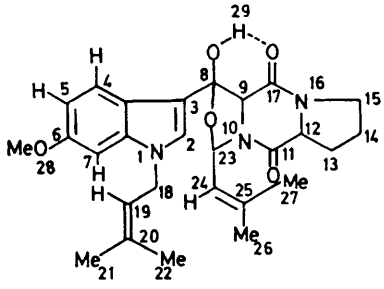
*Summary* Structure (I) has been deduced for lanosulin the major metabolite of *Penicillium lanosum* Westling.

ECHINULIN (II),[1] neoechinulin (III),[2] brevianamides-A (IV),[3] -B (V),[4] and -E (VI),[3] deoxybrevianamide-E (VII),[3,5] and austamide (VIII)[5] are a series of structurally similar metabolites which may be considered to be derived biogenetically from tryptophan, mevalonic acid, and alanine (II), glycine (III), or proline (IV)—(VIII). All formally possess an inverted $\gamma\gamma$-dimethylallyl group at C-2, the origin of which has been discussed extensively, and several mechanisms have been proposed to account for its presence. Studies with model compounds tend to exclude both a direct $S_N2'$ at the 2-position,[6] or a primary attack at C-3 followed by rearrangement,[7] but support a mechanism proceeding *via* primary attack at N-1 with subsequent rearrangement.[8]

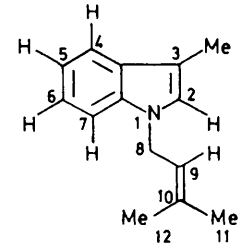
We now report the structure of lanosulin (I) the major metabolite of *Penicillium lanosum* Westling. The $\gamma\gamma$-dimethylallyl group at N-1 in lanosulin (I) presumably represents the missing biogenetic link for this group of compounds.



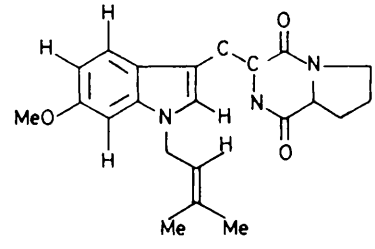
(I)

Lanosulin (I), $C_{27}H_{33}N_3O_5$, $[\alpha]_D^{25}$ + 24° (*c* 0·91, $CHCl_3$), m.p. 204—206°, forms white crystals. Its u.v. spectrum† [$\lambda_{max}$ (EtOH) 228, 278, and 295 nm ($\epsilon$ 39,960, 11,000, and 12,290)] indicated the presence of an indole nucleus,[9] and the n.m.r. data [$\delta$ 7·834 (4-H), 6·738 (5-H), and 6·650 (7-H) p.p.m.; $J_{4,7}$ 0·48, $J_{5,7}$ 2·15, $J_{4,5}$ 8·55 Hz] showed that a 5- or 6-methoxyindole was present. Comparison with the n.m.r. data for 2,3-dimethyl-5- and -6-methoxyindole suggested that the methoxy-group was at C-6, and this was confirmed by a Nuclear Overhauser effect (NOE) (6·6%) for 7-H on irradiation of the $CH_2$ part (18-H) of the $\gamma\gamma$-dimethylallyl group at N-1. A similar enhancement for 5- and 7-H ($\Sigma$ 19·9%) was observed on irradiation of 6-OMe. The 5- and 7-H resonances were also sharpened, indicative of a small coupling with 6-OMe.

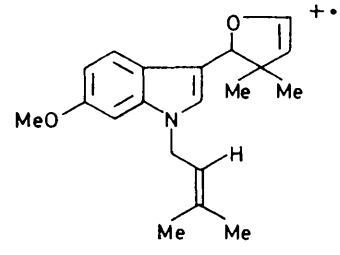
The presence of the $\gamma\gamma$-dimethylallyl group at N-1 was confirmed by comparison of the relevant n.m.r. data for (I) [$\delta$($CDCl_3$) 5·035 (19-H), 4·51 (18-H), 1·838 (22-Me), and 1·695 (21-Me) p.p.m.; $J_{18,19}$ 5·14, $J_{19,21\text{-Me}}$ 1·30 and $J_{19,22\text{-Me}}$ 0·96 Hz] with those for the indole (IX) [$\delta$ ($CDCl_3$) 5·34 (9-H), 4·53 (8-H), 1·74 (12-Me), and 1·69 (11-Me) p.p.m.; $J_{8,9}$ 7·0, $J_{9,11\text{-Me}}$ 1·32, and $J_{9,12\text{-Me}}$ 1·0 Hz]. The NOE (19-H; 9·4%) detected on irradiation of 21-Me permits differentiation between the two methyl groups at C-21 and C-22.



(IX)



(X)



(XI)

The i.r. spectrum (Nujol) of (I) possesses two intense bands at 1685 and 1645 $cm^{-1}$ which, together with the absence of amide-II bands suggested the presence of a piperazine-2,5-dione.[3] Intramolecular hydrogen bonding[10] [$\nu_{max}$ ($CCl_4$; 0·005M) 3500 $cm^{-1}$ (OH)] is responsible for the low frequency of one of the carbonyl groups. Acid hydrolysis under standard peptide conditions gave proline. A prominent fragment in the mass spectrum at *m/e* 69 ($C_4H_7N$; 62%) and n.m.r. data [$\delta$ 1·7—2·6 (13- and 14-H) and 3·533 (15-H) p.p.m.] provided further confirmation for the presence of a proline residue[3] in (I).

Assuming that the indole fragment stems from tryptophan, these results indicate (X) as a part structure for lanosulin, leaving us to account for $C_5H_{10}O_2$. The strong intramolecular hydrogen bond in (I), and the n.m.r. and

† No change with acid or base.

high-resolution mass spectral results are consistent only with structure (I).

The base peak (XI) (*m/e* 311; $C_{20}H_{25}NO_2$)‡ stems from both *m/e* 479 ($C_{27}H_{33}N_3O_5$) and *m/e* 461 ($C_{27}H_{31}N_3O_4$) by loss of the piperazinedione fragment. Further, extensive fragmentation of the base peak proceeds along well defined pathways. The loss of HO and $H_2O$ from (I) is readily accommodated. The $C_5$ unit attached to N-10 shows well defined n.m.r. resonances. Irradiation of 27-Me leads to a 11·6% enhancement of 23-H, and irradiation of 26-Me gives a 16·6% enhancement for 24-H.

We thank Professor F. McLafferty and Dr. Hans-Kaspar Wipf, Cornell University, and Mr. P. R. Briggs for mass spectra, Dr. N. Neuss, Eli Lilly, Indianapolis for n.m.r. spectra for methoxyindoles, Dr. G. Casnati, Istituto di Chimica Organica, dell' Universita di Parma, Italy, for samples, and Drs. H. Nash and R. M. Brooker of the Dow Human Health and Development Center, Zionsville, Indiana for isolation of lanosulin.

(*Received, 24th August* 1972; *Com.* 1483.)

‡ Metastable transitions are available for all of these fragmentations.

[1] A. Quilico, *Res. Progr. Org. Biol. Medicin. Chem.*, 1964, **1**, 1964.
[2] M. Barbetta, G. Casnati, A. Pochini, and A. Selva, *Tetrahedron Letters*, 1969, **4457**.
[3] A. J. Birch and J. J. Wright, *Tetrahedron*, 1970, **26**, 2329.
[4] A. J. Birch and R. A. Russell, *Tetrahedron*, 1972, **28**, 2999.
[5] P. S. Steyn, *Tetrahedron Letters*, 1971, **3331**.
[6] G. Casnati, M. Francioni, A. Guareschi, and A. Pochini, *Tetrahedron Letters*, 1969, 2485.
[7] A. H. Jackson and A. E. Smith, *Tetrahedron*, 1965, **21**, 989.
[8] G. Casnati and A. Pochini, *Chem. Comm.*, 1970, 1328.
[9] A. W. Sangster and K. L. Stuart, *Chem. Rev.*, 1965, **65**, 69.
[10] M. Tichý, *Adv. Org. Chem.*, 1965, **5**, 115.