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THE STRUCTURE OF SPORIDESMIN: CAUSATIVE AGENT OF FACIAL ECZEMA IN SHEEP

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In 1958, after almost 60 years of investigation in New Zealand[1], the cause of the hepatotoxic disease in sheep, facial eczema, was finally tracked down to a saprophytic mould growing on pasture grasses[2]. The toxic principle was isolated, purified and characterised by Synge and White[3], who named it sporidesmin, from the then-current name of the fungus, Sporidesmium bakeri Sydow, subsequently renamed Pithomyces chartarum (Berk. and Curt.) Ellis.

The determination of the molecular structure of sporidesmin, $C_{18}H_{20-22}O_6N_3S_2Cl$[4], by chemical methods posed considerable problems (vide White and Synge[5]), and it was considered that X-ray methods[6] would be of assistance in this respect. We have been fortunate in that Dr. R. L. M. Synge aroused our interest in this problem and are extremely grateful to

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[1]Footnote: Outbreaks of facial eczema have also occurred in Australia since 1956, with a more severe incidence in 1959, vide B. S. Janes, Nature 184, 1327 (1959).

[2]G. C. Thornton and R. H. Percival, Nature 182, 1095 (1958); 183, 63 (1959).

[3]R. L. M. Synge and E. P. White, Chem. and Ind. 1546 (1959).

[4]Empirical formula as on Sept., 1961. This differs slightly from that recorded in (3) and (5).

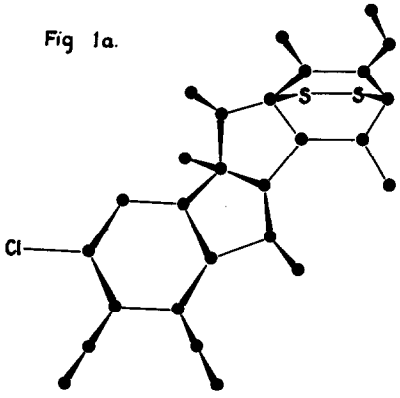
[5]E. P. White and R. L. M. Synge, First I.U.P.A.C. Symposium on Natural Products, Australia (1960) Abstracts p.53.

[6]A. McL. Mathieson, Pure and Applied Chemistry 2, 505 (1961).

Dr. E. P. White for his kind cooperation in preparing for us suitable derivatives in crystalline form. From one of these derivatives, the methylene dibromide adduct, we have succeeded in solving the structure of sporidesmin; although the structure is not yet fully refined, interest in this compound has prompted us to present the result, since it may be of some significance in relation to current physiological studies of facial eczema[7] and of liver damage in general[8].

Sporidesmin methylene dibromide crystallizes in space group $P2_12_12_1$ with cell dimensions $\underline{a}$ = 9.681, $\underline{b}$ = 10.629, $\underline{c}$ = 23.358 Å at - 150°C. Unit cell contents, for the sample used in the analysis were 4 x ($C_{18}H_{20-22}O_6N_3S_2Cl$ · 0.65 CH_2Br_2). X-ray analysis was based on 0 - 7 layers

Fig 1a.



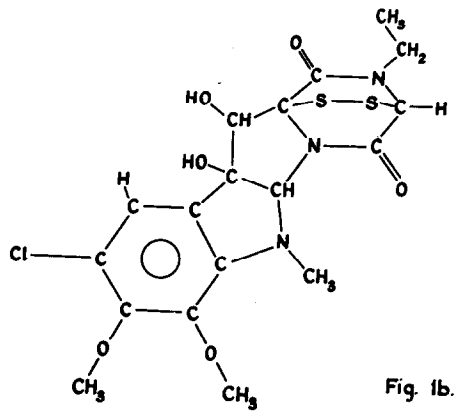


Fig. 1b.

[7](a) D. McFarlane, J. V. Evans and S. C. V. Reid, N.Z.J. agric. Res. 2, 194 (1959).

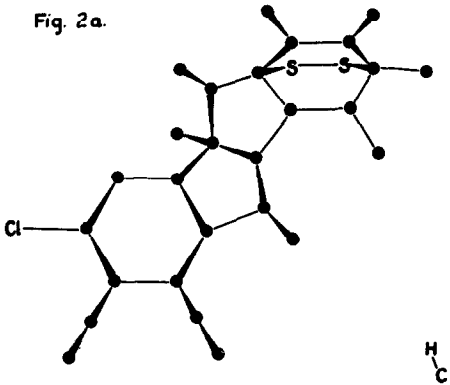
(b) J. Done, P. H. Mortimer and A. Taylor, Res. vet. Sci. 1, 76 (1960).

[8]L. B. Bull, Australian Vet. J. 37, 126 (1961).

about the a axis (1925 reflections of 2450 theoretically possible). The structure was derived mainly from the electron-density distribution, phased by means of the two 0.65 Br atoms, the two S atoms and the Cl atom. The molecular skeleton deduced in this way is shown in Fig. 1a, as viewed along the b axis of the cell. By reference (a) to the differentiation of atoms into C, N and O from the diffraction evidence, (b) to the stereo-chemical arrangement of adjacent atoms and (c) to bond lengths, we interpreted the molecular skeleton to accord with the structure for which the conventional chemical formula is given in Fig. 1b, the empirical formula for this being $C_{18}H_{20}O_6N_3S_2Cl$.

At this stage the above information was passed to our colleagues in New Zealand and subsequent discussion regarding their N.M.R. results[9] led to the conclusion that the $-CH_2-CH_3$ group could not be substantiated, but rather that there ought to be five $-CH_3$ groups. Since the atom site corresponding to the $-CH_3$ of the $-CH_2-CH_3$ group was one of the last two

Fig. 2a.



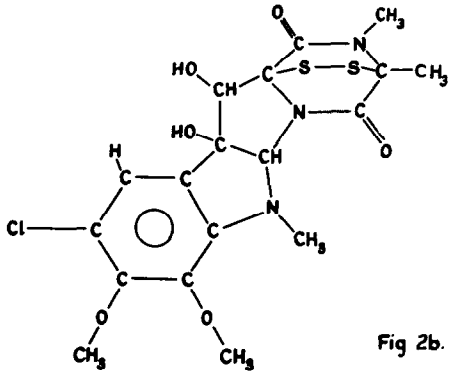


Fig 2b.

[9] A. Taylor and E. P. White, private communication.

atom sites allocated in the X-ray study, this side-group atom was less well authenticated than those constituting the main skeleton. Hence a close investigation of the available electron-density distributions was made at the four remaining sites for the presence of a possible atom. Only one alternative was revealed and further calculations supported this alternative choice as more satisfactory than our earlier allocation. The corresponding skeleton structure for sporidesmin is given in Fig. 2a with the relative configuration as shown. The interpretation in terms of differentiation of the skeletal atoms into C, N and O with the resultant allocation of H atoms, giving the complete structure of sporidesmin, is shown in Fig. 2b.

A full description of the X-ray analysis and dicussion of the structure and stereo-chemistry will be given at a later date. One point which may prove worthy of note at the moment is the structural similarity of sporidesmin and gliotoxin with respect to the bird-cage ring system[10].

Acknowledgments:- We are grateful to the New Zealand Department of Agriculture for the opportunity to tackle this investigation, especially to Dr. E. P. White of that Department for provision of crystals of sporidesmin derivatives and to Drs. E. P. White and A. Taylor for their kindness in bringing to our notice the critical N.M.R. information. We wish also to express our gratitude to Professor G. A. Barclay of the Chemistry Department of the University of New South Wales for assistance with computations at a very opportune moment.

[10] R. M. Bell, J. R. Johnson, B. S. Wildi and R. B. Woodward, J. Amer. Chem. Soc. 80, 1001 (1958).