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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: JAN 27 1983

SUBJECT: Comments on the Draft Protocol of the Metabolism, Distribution and Excretion of Tritium and Carbon-14 Labeled Avermectin B1a in Rats. EPA I.D. No. 618-EUP-10. Tox. Chem. No. 63AB

TO: George LaRocca
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THRU: William Butler, Jr., Head
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and
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William Butler 1-25-83

Sponsor and Testing Facility (Applicant):

Merck, Sharp and Dohme Research Laborties
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Comments: The submitted draft protocol for this study can be considered acceptable in principle. However, a few suggestions are herewith made for the applicant's consideration to be incorporated in their final study procedures.

Suggestions:

(1) Avermectin B1 is a mixtue of two compounds belonging to the Avermectin family, namely Avermectin B1a ($R = C_2H_5$) and Avermectin B1b ($R = CH_3$). Avermectin B1 is a product that contains at least 80% of the compound in which R in its structure is the ethyl group and less then 20% of the compound in which R is the methyl group at the 25-carbon position of the molecular structure (see attachment). Therefore, the purity of this test compound must be assured by chemical analysis prior to the study.

(1)

(2) We are not in a position to make a decision about the dose-range of test material used in this study. Since the experimental data, which were previously submitted, indicated Oral LD_{50} of C-076(B1a) for young male CRCD rats was 10.6 (7.67 - 14.51) mg/kg and the same for females was 11.3 (7.48-17.1) mg/kg (Willam Dystra's review, dated 2/8/82; Tox Chem. # 63AB), a dose-range of 0, 0.15, 0.75, 1.50 and 3.00 (0, 1, 5, 10 and 20X) mg/kg may be used. Thus, the detemination of any possible bioaccumulation and/or bioretention of compound and/or metabolite(s) as a function of doses may be mapped out. Furthermore, an exaggerated dose (e.g., 3.00 mg/kg) may provide a better chance for extraction and characterization of residues and possibly metabolites in the biological samples taken during and after the dosing periods.

(3) In the case of ^{14}C-labeled Avermectin B1a, the samples of urine and plasma (from blood) may be placed in Insta-Gel (Packard) for direct liquid scintilation counting of radioactivity, while other tissue/organ samples by liquid scintilation counting following the combustion process.

(4) Avermectin B1a is a relatively new compound of complicated structure and its toxicity study is incomplete at present. Since the applicant indicated that the results from this study will help to understand the safety of Avermectin in consideration of its intended uses and anticipated human exposure, identification of the residues or metabolites is definitely worth of effort to pursue.

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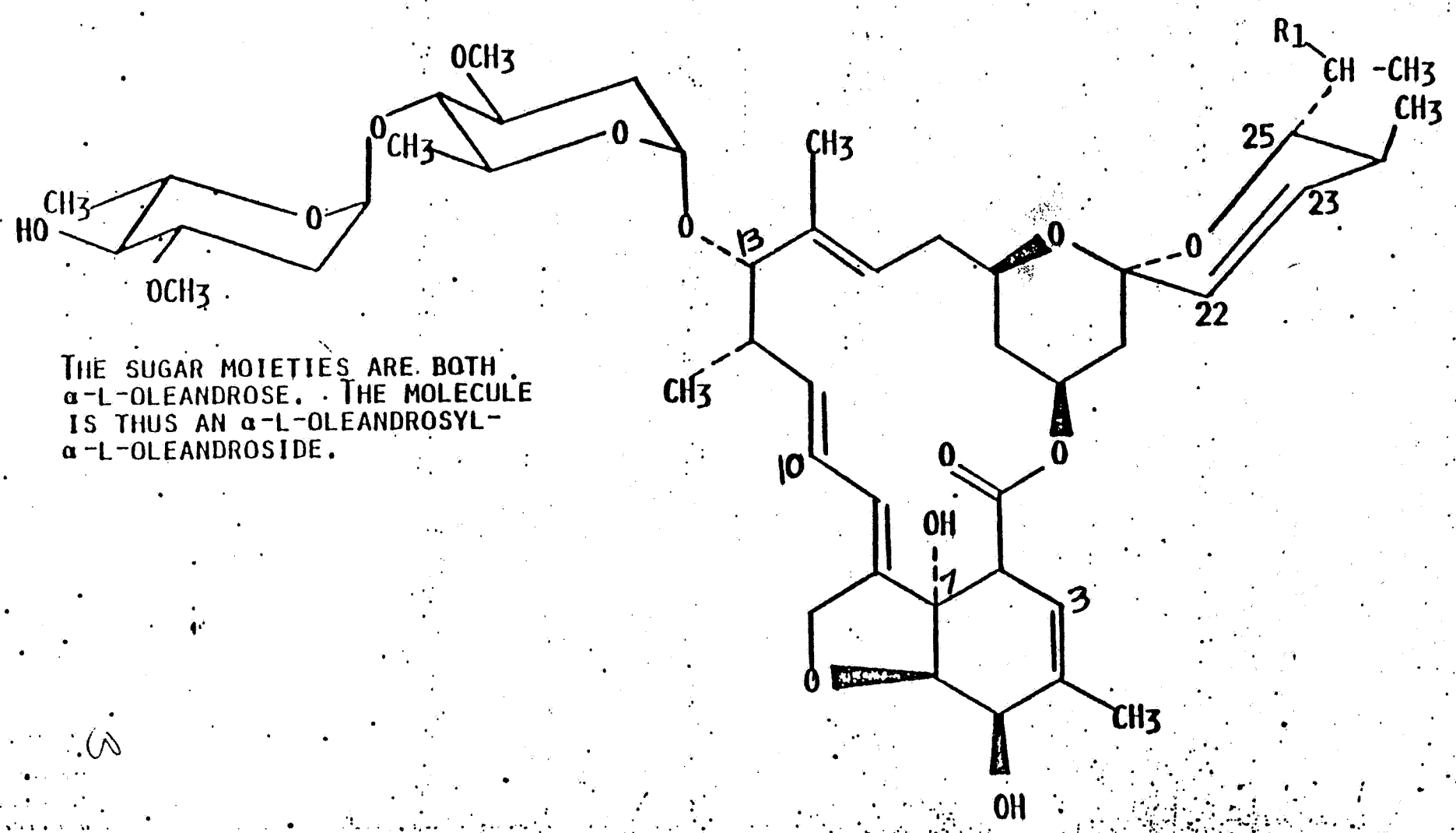
MK-936

AVERMECTIN B_1

L-676,863



THE SUGAR MOIETIES ARE BOTH α-L-OLEANDROSE. THE MOLECULE IS THUS AN α-L-OLEANDROSYL-α-L-OLEANDROSIDE.

R_1 = C_2H_5 ≥ 80% (AVERMECTIN B_{1a}, L-676,895)