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

CASWELL FILE

MAR 12 1990

MEMORANDUM

SUBJECT: Classification of Tetrahydroazadirachtin as a Biochemical Pesticide

TO: Phil Hutton/Willie Nelson (PM-17)
Registration Division (H7505C)

FROM: J. Thomas McClintock, Ph.D., Microbiologist
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

THROUGH: Reto Engler, Ph.D., Chief
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

ACTION REQUESTED: SACB and the OPP Biotechnology Workgroup have been asked to classify tetrahydroazadirachtin as a conventional chemical or biochemical pesticide.

BACKGROUND INFORMATION: Azadirachtin is a naturally occurring insecticide which is extracted from the Neem tree seed. Azadirachtin is currently classified by the Agency as a biochemical pesticide. Native Plants, Inc. (NPI) has developed an extraction and hydrogenation process which yields tetrahydroazadirachtin, a hydrogenated compound which is less susceptible to ultraviolet photodegradation. In a previous coorespondence (see 2/16/90 memorandum from J. T. McClintock to P. Hutton) SACB requested supplemental information from NPI on the manufacturing process and for comparative purposes the chemical structure of both compounds (azadirachtin and tetrahydroazadirachtin).

DISCUSSION/CONCLUSION: On behalf of NPI, E.R. Butts International, Inc. submitted information on the chemical structure of azadirachtin and tetrahydroazadirachtin, the hydrogenated form. A side-by-side comparison of the compounds revealed similar, if not, nearly identical chemical structures. A review of the manufacturing process confirmed that only a simple hydrogenated product would result. Briefly, azadirachtin is suspended in ethanol and mixed with palladium on alumina at 20°C under hydrogen (10 atmosphere) for 3 hr. The reaction mixture is filtered, evaporated (rotary vacuum), and purified by preparative HPLC (solvents - 2-propanol-n-hexane; methanol-water) to give tetrahydroazadirachtin.

Based on the recent and previous information, SACB would recommend that tetrahydroazadirachtin be classified as a biochemical pesticide. Tetrahydroazadirachtin is structurally similar to azadirachtin, the naturally occurring compound, displaying similar insecticide activity.



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WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Classification of Azadirachtin and Tetrahydroazadirachtin
as Conventional Chemicals or Biochemical Pesticides

TO: Phil Hutton/Willie Nelson (PM-17)
Registration Division (H7505C)

FROM: J. Thomas McClintock, Ph.D., Microbiologist
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

THROUGH: Reto Engler, Ph.D., Chief
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

ACTION REQUESTED: Native Plants, Inc. (NPI) has asked the Agency to classify azadirachtin and tetrahydroazadirachtin as biochemical pesticides in order to initiate a registration program. SACB and the OPP Biotechnology Workgroup have been asked to classify the above-referenced compounds as either conventional chemicals or as biochemical pesticides.

GENERAL INFORMATION: Azadirachtin is a naturally occurring insecticide which is extracted from the Neem tree seed. Azadirachtin is an insect growth regulator which is used at low doses for insect control. The precise mode of action is not very well understood. However, current theory suggests that azadirachtin disrupts molting and metamorphosis during the larval or immature stages by functioning as a molting hormone analog or by inhibiting the release of the ecdysis hormone. Even though azadirachtin appears to be a promising candidate for insect control the material is susceptible to ultraviolet photodegradation following extraction.

The registrant has developed an extraction and hydrogenation process which yields tetrahydroazadirachtin, a hydrogenated form of azadirachtin with identical properties. The hydrogenated compound is less susceptible to ultraviolet photodegradation than azadirachtin. However, no information was provided on the manufacturing process for either compound.

NPI submitted information and/or data on the natural occurrence of azadirachtin, the proposed mode of action as an insect growth regulator and feeding deterrent, a comparison of the stability of azadirachtin and tetrahydroazadirachtin following exposure to ultraviolet radiation and a brief summary of laboratory, greenhouse and field studies.

SACB CONCLUSION: Azadirachtin is currently registered by the Agency as a biochemical pesticide. Presumably, NPI's analagous compound would also be classified as a biochemical pesticide providing that during the manufacturing process the subject-compound is unaltered. Before SACB can consider tetrahydroazadirachtin as a biochemical pesticide NPI should submit a detailed description of the extraction and hydrogenation process. In addition, SACB recommends that NPI submit information on the chemical structure of both compounds. A structural comparison would enable SACB to verify the similarities between both compounds.

E.R. BUTTS INTERNATIONAL, INC.

555 Clinton Avenue
P.O. Box 3337
Bridgeport, CT 06605-0337

Telephone: (203)333-4943
Telex: 9102507473 ERBUTTS
Fax: (203)334-0654

Sent via UPS Overnight

February 23, 1990

Mr. Willie Nelson (PM-17)
Registration Division (H7505C)
Environmental Protection Agency
Crystal Mall, Building 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Subject: Tetrahydroazadirachtin - Supplemental Information to
Support Its Biochemical Determination Assessment

Dear Mr. Nelson:

During my discussion with Dr. Tom McKlintock regarding NPI-720 (azadirachtin), he requested additional information to assist in the determination of whether or not NPI-724 (tetrahydroazadirachtin) is a biochemical. That information is as follows:

1. Structures of tetrahydroazadirachtin and azadirachtin
2. Manufacturing process for tetrahydroazadirachtin

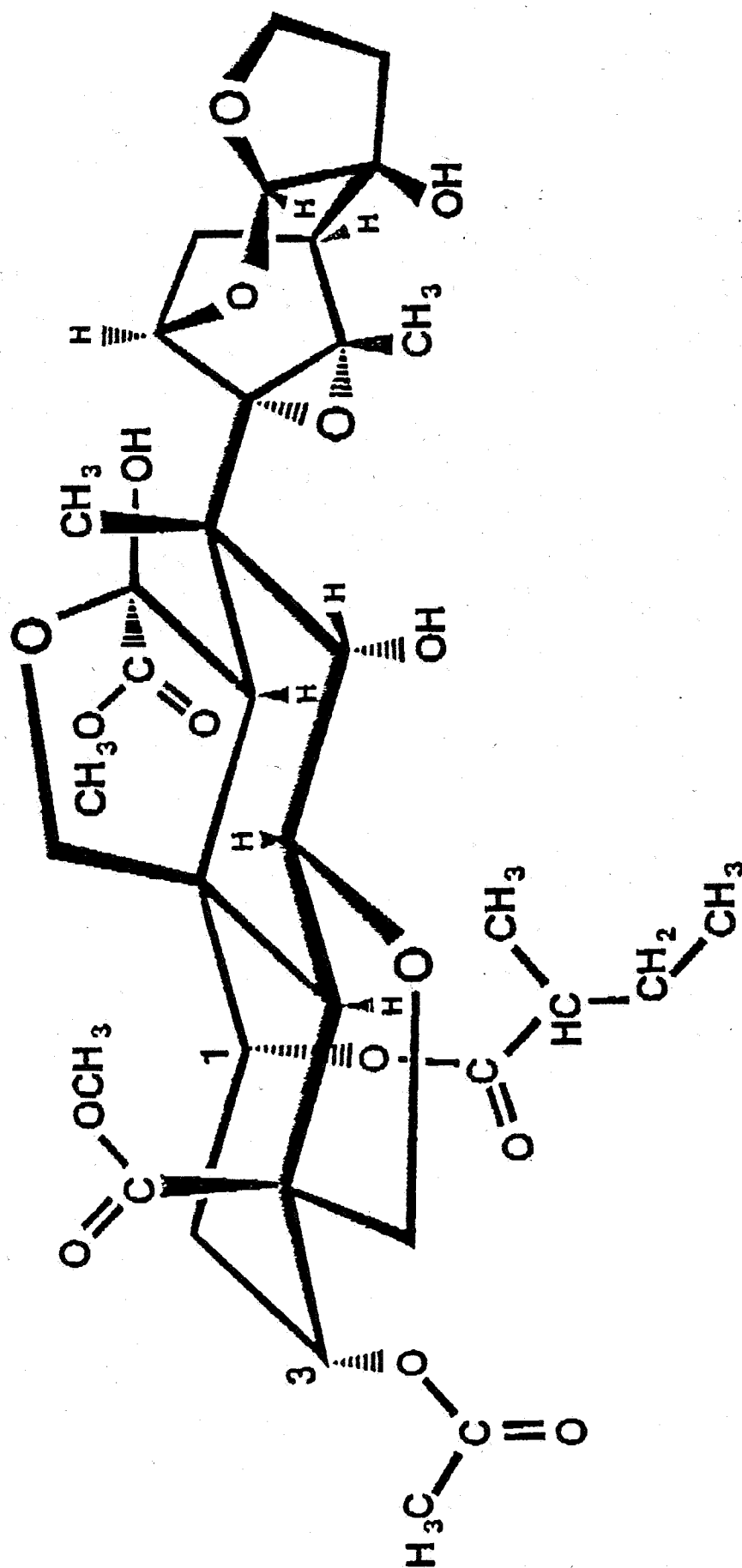
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If additional information is required, please advise.

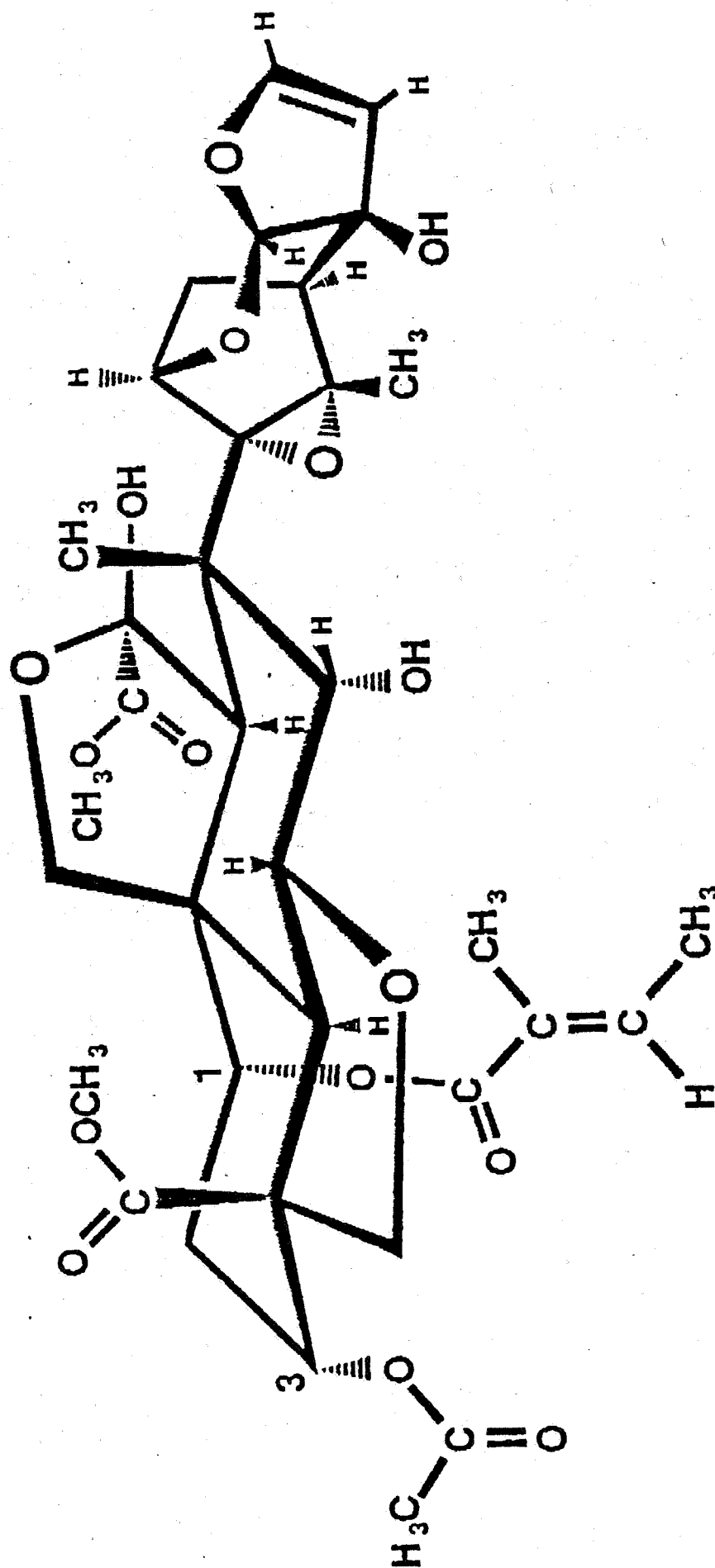
Sincerely,

Edgar R. Butts, Ph.D.
President

cc: Dr. Tom McKlintock w/enclosures
Enclosures



2', 3', 22, 33-tetrahydroazadirachtin



Azadirachtin
MW 720



Manufacturing Process for
2',3',22,23-tetrahydroazadirachtin

117 W. 10th Way
Salt Lake City, Utah 84108
(801) 562-0141
TELE FAX (801) 562-2045

METHODS

2',3',22,23-tetrahydroazadirachtin is made by hydrogenating azadirachtin, using the following simple process:

Hydrogenation:

30 mg (0.042 mmol) of azadirachtin in 0.5 mL of ethanol is stirred with 20 mg of 5% palladium on alumina at 20 deg. C under hydrogen (10 atm) for 3 hr. The reaction mixture is then filtered and rotary evaporated in vacuo. The crude product is purified by silica gel preparative HPLC (solvent 2-propanol-n-hexane, 17:83, v/v), followed by ODS preparative HPLC (solvent methanol-water, 1:1, v/v) to give 2',3',22,23-tetrahydroazadirachtin.

MATERIALS

Solvents used for high-performance liquid chromatography (HPLC) should be HPLC grade. Other chemicals should be of reagent grade or better and can be used without further purification.