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DOE/ER/60434--5

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BORON IN NUCLEAR MEDICINE: NEW SYNTHETIC APPROACHES TO PET, SPECT, AND BNCT AGENTS

Progress Report

March 1, 1990 - February 28, 1991

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OCTOBER 1990

PREPARED FOR THE U. S. DEPARTMENT OF ENERGY
UNDER GRANT NUMBER DE-FG05-86ER60434

DISCLAIMER

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I. OBJECTIVE

The primary objective of the D.O.E. Nuclear Medicine Program at The University of Tennessee is the creation of new methods for introducing short-lived isotopes into agents for use in PET and SPECT. A small, but significant portion of our effort is directed toward the design of boron-containing neutron therapy agents. The uniqueness of the U.T. program is its focus on the design of new chemistry (molecular architecture) and technology as opposed to the application of known reactions to the synthesis of specific radiopharmaceuticals. The new technology is then utilized in nuclear medicine research at the U.T. Biomedical Imaging Center and in collaboration with colleagues at other D.O.E. facilities (Brookhaven National Laboratory, Oak Ridge National Laboratory, Los Alamos National Laboratory, and Oak Ridge Associated Universities).

An important goal of the D.O.E. Nuclear Medicine Program at U.T. is to provide training for students (predoctoral and postdoctoral) in the scientific aspects of nuclear medicine. The University of Tennessee is one of the very few institutions in the world where students have "hands-on" access to all modern nuclear medicine modalities: PET, SPECT and MRI. The academic nature of the program facilitates collaborative interactions with other D.O.E. nuclear medicine programs and helps to insure the continued availability of skilled scientists dedicated to the advancement of nuclear medicine.

II. RESEARCH ACCOMPLISHMENTS

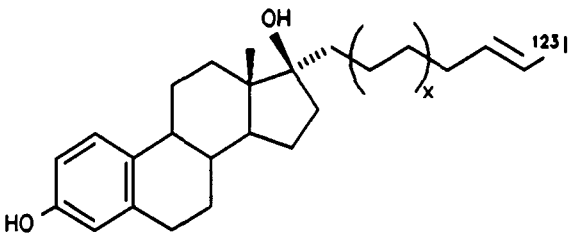
I am pleased to report that this has been a productive year for the D.O.E. Program at Tennessee. Fifteen journal articles appeared in print since our last progress report. In addition, fourteen research abstracts of oral presentations have been published.

A. New Isotope Incorporation Reactions

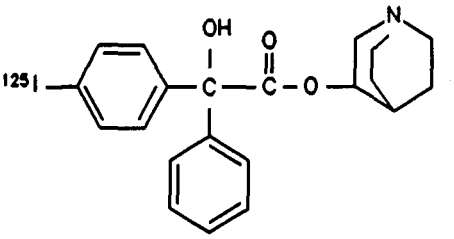
1. Iodination: We have continued to develop new routes for radioiodinating physiologically active agents. The most versatile route involves the direct reaction of no-carrier-added sodium [^{123}I]-iodide with organoboranes. Utilizing this new methodology, we have synthesized a variety of radioiodinated agents for use in nuclear medicine. Since our last progress report, we have reported the syntheses of

$$RB(OH)_2 \xrightarrow[[O]]{Na^{123}I} R-^{123}I$$

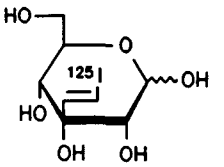
a new series of radioiodinated α-iodovinylestradiols (I) an improved preparation of 3-QNB (II), and a new allose derivative (II).



I



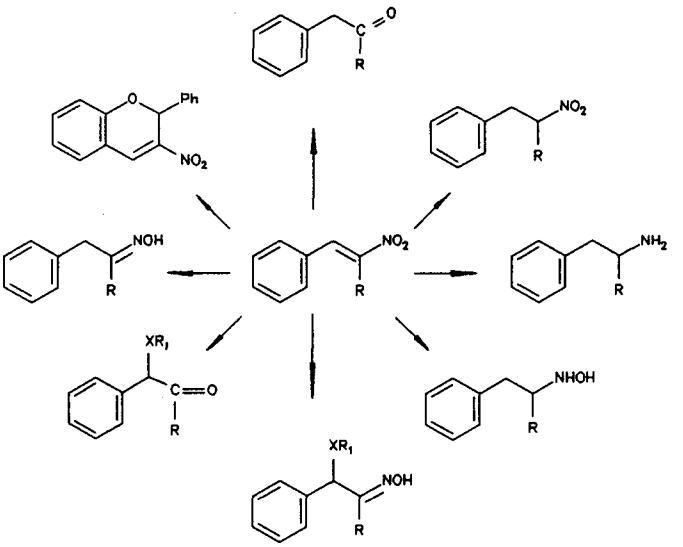
II



III

[Section IIIa, articles 1, 3, and 11; Section IIIb, abstracts 1, 3, 4, 6, 10 and 13].

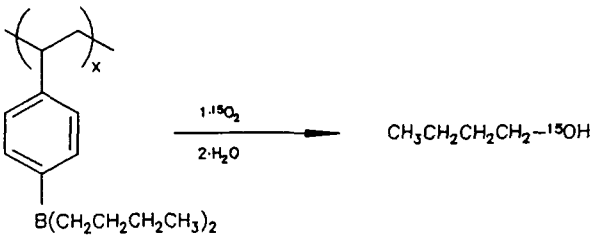
The synthesis of iodoamphetamine derivatives, such as IV, via the corresponding boronic acid involved the development of new reduction sequences some of which are illustrated below. This year, we investigated the use of polymer bound reducing agents and free metals to achieve these reductions.



[Section IIIa, articles 5, 6 and 15].

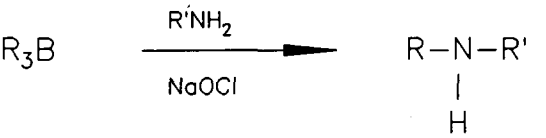
2. Oxygen-15: We have continued to develop a new oxygen-15 ($t_{1/2}$ = 2 min) incorporation route involving the direct

reaction of organo-boranes with [^{15}O]-O_2. We synthesized polystyrene reagents with butylborane groups attached.

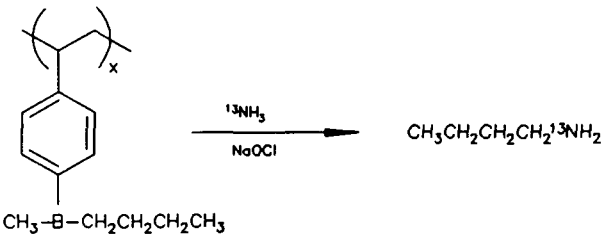


Preliminary experiments demonstrate that butanol (a PET blood flow agent) can be produced by simply passing oxygen gas over the surface. Current research efforts are also focused on the development of a flow through module (a "kit") containing butylborane on alumina which can be directly attached to The University of Tennessee, 11 MeV, clinical cyclotron to generate oxygen-15 labeled butanol "on-line." Microprocessor controlled systems are also being examined in an effort to reduce radiation exposure to personnel. [Section IIIa, articles 2, 8, 10, and 11; Section IIIb, abstracts 1, 2 and 12.]

3. Nitrogen-13: We continue to develop new routes for incorporating nitrogen into organic molecules. We are investigating the syntheses of unsymmetrical dialkylamines:



We also reported the use of polymeric reagents for the synthesis of nitrogen-13 labeled amines. The procedure has the advantage that no soluble byproducts contaminate the desired product.



Microprocessor controlled units are currently under development.

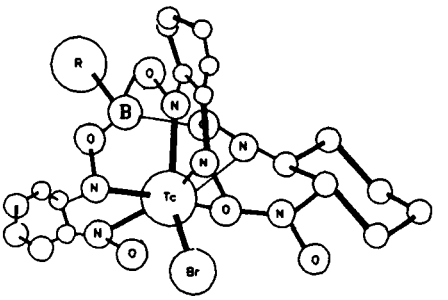
[Section IIIa, articles 7, 9, and 11; Section IIIb, abstracts 5 and 7.]

4. Carbon-11: We continue to investigate the potential use of carbon-11 in the synthesis of labeled steroids and amino acids for possible use in clinical PET.

[Section IIIb, abstracts 1 and 11.]

B. Technetium-Boron Complexes

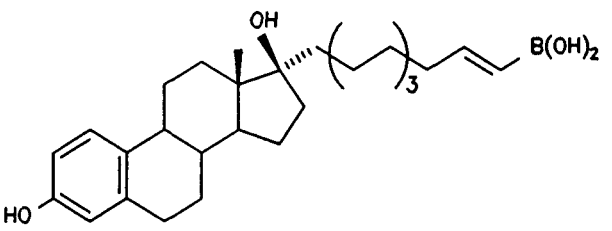
Boronic acid derivatives of technetium-dioxime complexes, such as IV, have great potential as a single photon agents (SPECT) in nuclear medicine:



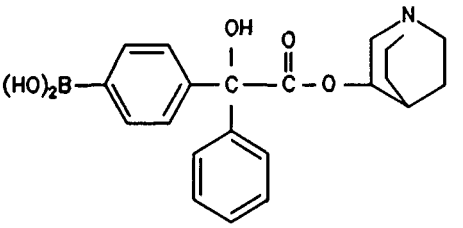
$TcBr(cyclohexanedione\ dioxime)_3$

IV

The preparation of functionally substituted boronic acids, $RB(OH)_2$, could result in organ specific technetium-labeled agents which parallel successful PET agents. Our group is experienced in boronic acid technology and we are currently attempting to synthesize a variety of functionally substituted boronic acids for use in complexes such as IV. We are also in the process of developing boronic acid analogs of estradiol (V) and QNB (VI).



V



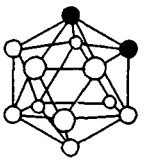
VI

[Section IIIa, article 1; Section IIIb, abstracts 3 and 6.]

C. Boron-Neutron-Capture

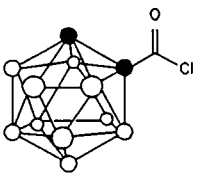
We have collaborated with the Brookhaven National Laboratory Group (Dr. Dan Slatkin) for nearly seven years in the area of

BNCT. To date, the interaction has been focused on designing new BCNT agents. Agents of current interest involve ortho-carboranes which are rich in boron but behave like phenyl groups in organic

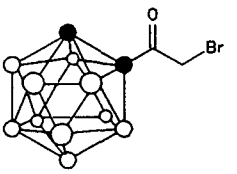


[where: ○ = BH and ● = CH]

synthesis. Our group is currently investigating the syntheses of reagents such as VII and VIII which could be used to label monoclonol antibodies by attachment to terminal amino or thio functional groups.



VII



VIII

[Section IIIb, abstract 4.]

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IV. GRADUATE AND POSTDOCTORAL STUDENTS

Four postdoctoral students and three graduate students were supported during this period by the Department of Energy Nuclear Medicine Program.

a. Postdoctoral Students

Dr. Timothy Shoup

Dr. Laila H. M. Guindi

Dr. Chatla Narayana

b. Graduate Students

Mark A. Davis (Ph.D. candidate - Ph.D. 1990)

R. David Pace (Ph.D. candidate)

Stephen J. Lambert (Ph.D. candidate)

Elizabeth Zippi (Ph.D. candidate)