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

Progress Report

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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. The new methodology is based on reactive boron-containing precursors containing organic functional groups responsible for physiologic responses. 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 such as Brookhaven National Laboratory and Oak Ridge National Laboratory. New radiopharmaceuticals are evaluated preclinically by colleagues at U.T. and other PET centers (e.g., The University of Pennsylvania) as well as by contract laboratories such as Nova Screen.

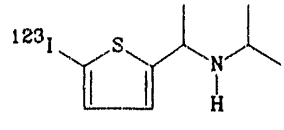
An important goal of the D.O.E. Nuclear Medicine Program at U.T. is to provide training for students (predoctoral and postdoctoral) in the scientific aspects of nuclear medicine. The University of Tennessee is one of the very few institutions in the world where students have "hands-on" access to all 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

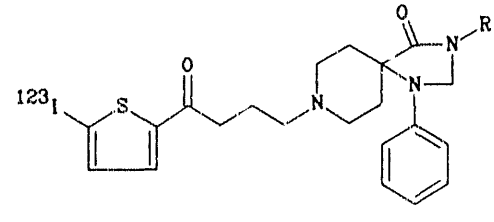
I am pleased to report that this has been a productive year for the D.O.E. Program at Tennessee. Fifteen journal articles have appeared in print, or are in press, since our last progress report. Fourteen research abstracts of oral presentations have been published. In addition, I was invited to chair scientific sessions at two international meetings and to present ten lectures at universities and national scientific meetings.

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]-iodine 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 a new radioiodinated

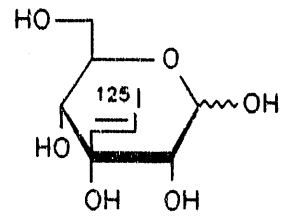


I



II

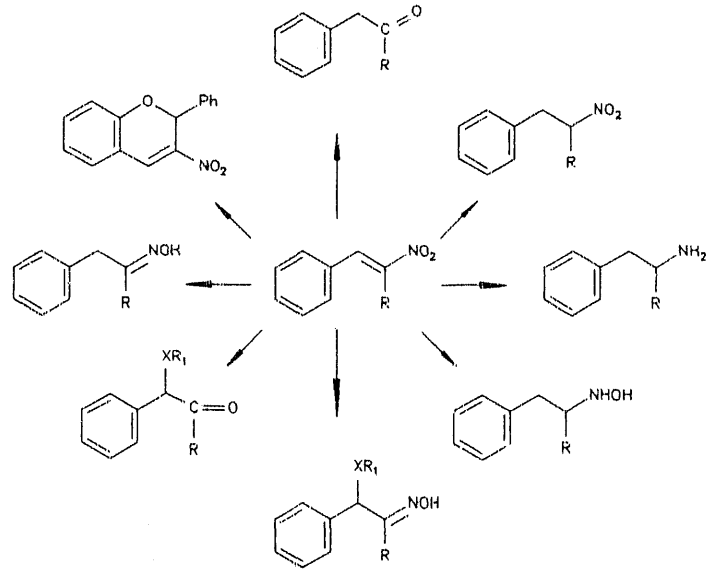
thienylamphetamine (I) an improved preparation of thienylbutyrophenones (II), and a new allose derivative (III).



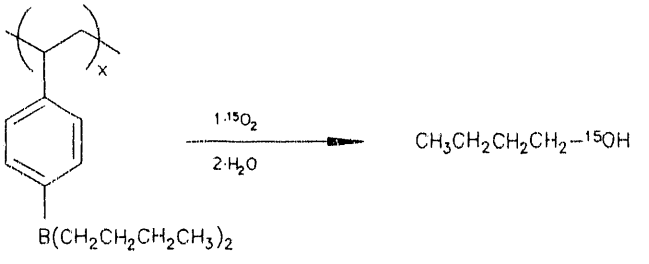
III

[Section IIIa, articles 2, 8, and 11; Section IIIb, abstracts 2, 8, and 12]

The synthesis of iodoamphetamine derivatives 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.



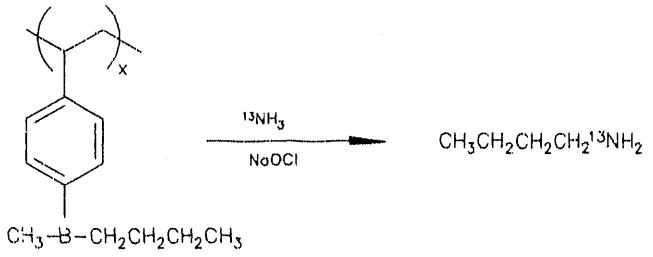
2. Oxygen-15: We have begun to develop a new oxygen-15 ($t_{1/2}$ = 2 min) incorporation route involving the direct reaction of organoboranes with $[^{15}O]O_2$. We synthesized polystyrene reagents with butylborane groups attached and then utilized them to incorporate oxygen-15 into physiologically active agents.



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 ("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 a effort to reduce radiation exposure to personnel. [Section IIIa, article 7; Section IIIb, abstract 8.]

3. Nitrogen-13: We continued to develop new routes for incorporating nitrogen into organic molecules.

We reported the initial 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 1, 7, and 14; Section IIIb, abstracts 1 and 4.]

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 IIIa, article 10; Section IIIb, abstract 8.]

5. Fluorine-18: We have been investigating the use of organoboranes for incorporation of fluorine-18. To date, we have relied on traditional fluoride displacement reactions to achieve fluorination. However, fluorine-18 targets are now commercially available and one is being installed on our cyclotron. We propose to investigate the direct fluorine-18 fluorination of

boronic acids as a means to prepare a variety of physiologically active compounds.

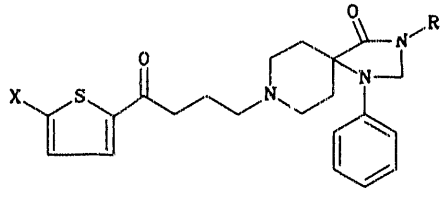
$$R{-}B(OH)_2 \xrightarrow[2.\ H_2O]{1.\ {}^{18}F_2} R{-}{}^{18}F + B(OH)_3$$

The reaction would be based on our earlier studies which demonstrated that boron reagents react readily with halogen molecules but not with halide ions.

B. Preclinical Evaluation of New Agents

The U. S. Department of Energy Project Review Panel which was convened by The Office of Program Analysis (May, 1992) recommended continued support of our program. The Panel also recommended integrating our radiotracer development with enhanced preclinical evaluations. We have actively pursued preclinical evaluation of promising new agents via routes that are funded by the other government agencies; these include collaboration with other PET centers and commercial screening controls. [This DOE project does not support biological testing.]

Nova-Screen Corporation has provided binding assay data for seven of our new butyrothiophenones of the general structural type:



The preliminary data presented below demonstrates that all of the new reagents are receptor site active.

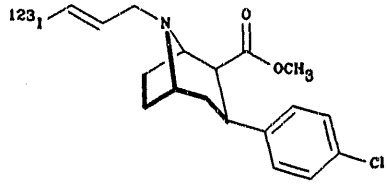
Nova-Screen Binding Assay Data

Compound		**% Inhibition at [10^{-5}M]		
X	Y	*D2(dopamine)	S1(seratonin)	S2(seratonin)
-H	-H	100.2		104.6
-H	$-CH_3$	100.5		104.2
-H	$-CH_2CH_3$	99.5		102.3
-H	$-(CH_2)_2CH_3$	100.5		103.6
-I	-H	100.9		92.7
-I	$-CH_2Ch_3$	100.0	42.5	93.9
-I	$-(CH_2)_3CH_3$	100.8		95.8

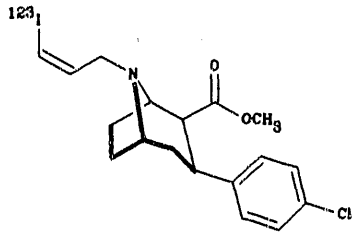
*The parentheses denote the reference compounds. **A % inhibition greater than 90.0 means that saturation occurred.

We are now negotiating with Nova-Screen to test the compounds at more dilute ($10^{-9}M$) concentrations.

We are also collaborating with Dr. Hank Kung at The University of Pennsylvania in Philadelphia who is helping to evaluate our new neuroreceptor agents in both mice and baboons. DR. Kung carried out a complete receptor-site radiographic analysis on our two new cocaine analogs, IV and V.



IV



V

Baboon studies reveal that both reagents are active but the *Syn* [IMMG 142(Z)] isomer, V, demonstrated unexpected affinity for the D2 receptor sites. The data for the uptake of V is presented below. Further evaluation of these agents are related fluorine-18 labeled agents is currently underway.

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2. "The Synthesis of Radioiodinated Vinyl Iodines Via Organoborane Chemistry", IXth International Symposium on Radiopharmaceutical Chemistry", G. W. Kabalka, Paris, France (April, 1992).

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12. "Isotope Incorporation Via Organoborane Chemistry", International Isotope Society Fifth Regional Meeting, Kalamazoo, MI, (May, 1992).

13. "Boron in Medical Imaging", Institute of Electrical and Electronics Engineers, Knoxville, TN, (May, 1992).

14. "Synthesis of Pharmaceuticals Via Borane Chemistry", University of California, Los Angeles (June, 1992).

IV. GRADUATE AND POSTDOCTORAL STUDENTS

One postdoctoral student and two graduate students were supported during this period by the Department of Energy Nuclear Medicine Program.

A. Postdoctoral Students

Dr. Chatla Narayana

B. Graduate Students

Stephen J. Lambert (Ph.D. Candidate)

Elizabeth Zippi (Ph.D., 1992)

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