

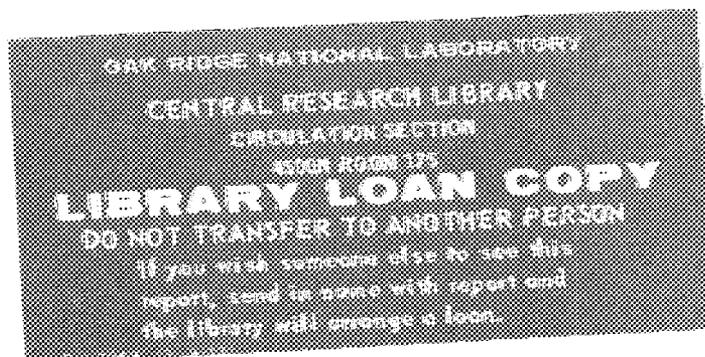
**OAK RIDGE  
NATIONAL  
LABORATORY**



**Nuclear Medicine Program  
Progress Report for  
Quarter Ending March 31, 1989**

F. F. (Russ) Knapp, Jr.

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Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT  
FOR QUARTER ENDING MARCH 31, 1989

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## SUMMARY

In this report a general route for iodination of alkynes using iodine monochloride (ICl) is described. Several alkyne substrates including pargyline and tremorine have been converted to the iodochloroalkene products in good yields. Although the stereochemistry of the addition has not yet been determined, the iodine-125-labeled products are readily prepared and this appears to be a simple general route for radioiodination of alkyne substrates.

Also in this report, the syntheses of two radioiodinated spiroperidol analogues with iodoalkenyl-substitution on the lactam nitrogen are described. The methods for preparation of these analogues include iododeboronation and iododestannylation using no carrier-added iodine-125. The N-(5-iodopenten-1-yl) and N-(3-iodopropen-1-yl) analogues of spiroperidol have been prepared.

## NEW RADIOIODINATION TECHNIQUES

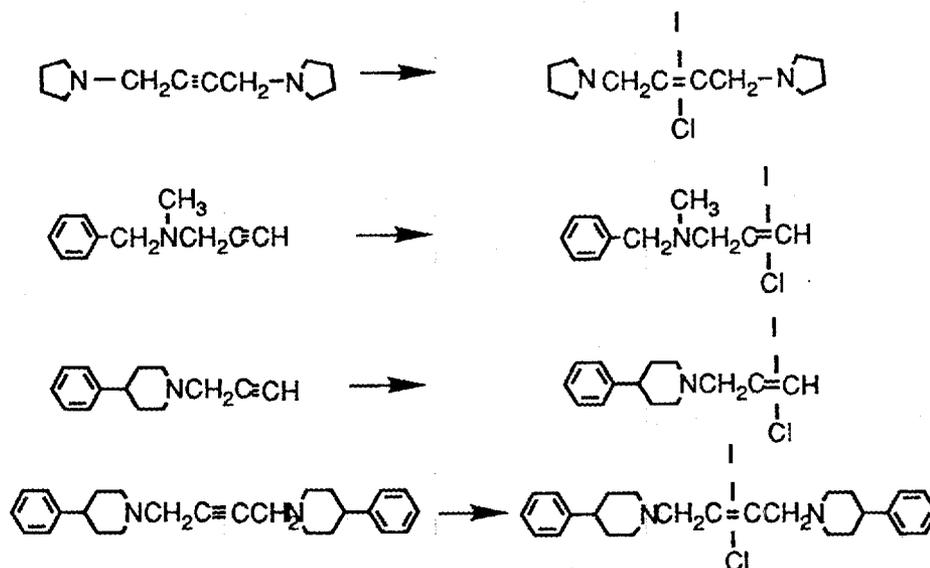
We have been interested in the development of new radioiodination techniques for incorporation of radioactive iodine in tissue specific molecules for diagnostic and therapeutic applications. We have earlier demonstrated the relative in vivo stability of aryl, alkenyl, and alkyl iodides and developed techniques which allow incorporation of iodine utilizing these functional groups. The use of organomercury and organoborane substrates have proven very useful for the synthesis of aryl and alkenyl iodides, respectively. Recently, our studies have included radioiodination of biologically active molecules containing an amine or nitrogen heterocycles. Unfortunately, problems have been encountered in attempts to prepare and radioiodinate alkenyl and aryl boronic acids containing such moieties. Consequently, we have developed an ICl halogenation procedure which readily allows introduction of iodine to an alkyne. The procedure has general application for iodination of alkynes including those attached to a heterocycle or to an amine molecule.

The formation of dihalogenated alkene (Figure 1) by the addition of iodine monochloride in THF across the triple bond of molecules containing different functional groups is rapid and proceeds in good yield with minimal side products. Analysis of the distribution of the expected regioisomer products is currently in progress.



Fig. 1.

There are very few examples of iodine monochloride additions to alkynes in the literature, and there are no reports of (I-125)-iodine monochloride additions to alkynes. The utility of this reaction has been demonstrated by labeling several molecules intended for biological testing in laboratory animals (Scheme I).



Scheme I.

Biologically active molecules (Scheme I) such as pargyline and tremorine, already contain the alkyne functional group and are thus readily available for ICl addition. For other molecules, such as the 4-phenylpiperidines, alkylation of nitrogen may be effected by using an alkynyl halide such as propargyl bromide or 1,4-dichloro-2-butyne as the alkylating agent via a simple nucleophilic substitution reaction. After the triple bond is introduced into the molecule, subsequent (I-125)-iodine monochloride addition yields the corresponding labeled compound.

Radioiodination of the compounds summarized in Scheme I were achieved by the addition of (I-125)-iodine monochloride produced in situ by the action of N-chlorosuccinimide and sodium (I-125)iodide. Sodium (I-125)iodide, when purchased from commercial suppliers, is dissolved in a solution of sodium hydroxide to prevent oxidation of (I-125)iodide. If this basic solution is not neutralized, the radiochemical yield of the labeled compound will be compromised. Therefore, an equivalent of hydrochloric acid is added to sodium (I-125)-iodide/THF solution followed by anhydrous magnesium sulfate for absorption of water. This procedure presumably yields a solution of (I-125) iodine monochloride in THF and subsequent addition of the alkyne followed by 1.5 h

of reflux produces the labeled compound in good radiochemical yield. These studies were performed as part of the doctoral research requirements (S. Lambert) in conjunction with the Chemistry Department at the University of Tennessee (Dr. G. W. Kabalka).

## SYNTHESIS OF RADIOLABELED IODOALKENYL ANALOGUES OF SPIROPERIDOL

Dopamine receptor populations have been implicated in the pathogenesis of various neurologic disorders including schizophrenia, Parkinsonism, and Huntington's chorea. Although dopamine D2 receptors are found throughout the brain, they are primarily located in the striatum putamen. With the advent of Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), it is now possible to map dopamine receptor populations in humans non-invasively. Spiroperidol (Figure 2) is a potent neuroleptic agent widely used in the treatment of schizophrenia, and has been shown to bind specifically to dopamine receptors *in vitro* and *in vivo*.

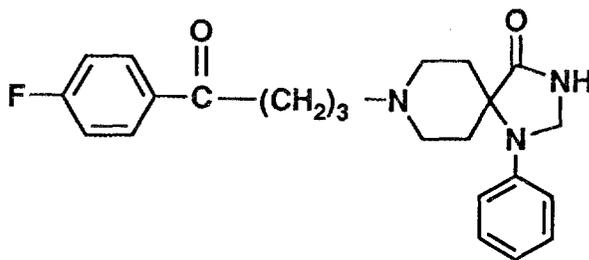


Fig. 2.

Spiroperidol and a variety of spiroperidol analogues have been radiolabeled with various radionuclides (F-18, C-11, Br-77, I-125, I-123) and evaluated as potential dopamine imaging agents for both PET and SPECT imaging studies. The spiroperidol analogues labeled with radioisotopes of iodine often lose selectivity for dopamine receptor binding. In addition, the necessary high

specific activity cannot be obtained with many of the synthetic procedures that are currently used, such as iodide exchange procedures. Since dopamine receptors are present in cerebral tissue at nanomolar concentrations, they are easily saturated at relatively low concentrations of the tracer molecules. The availability of methods to prepare spiroperidol analogues at no-carrier-added (NCA) levels with radioiodine is therefore important. We have synthesized two spiroperidol analogues in which radioiodine is attached to an alkenyl moiety on the lactam nitrogen (Figure 3). This approach allows radiolabeling of the spiroperidol analogue utilizing NCA iodine-125 and results in the stable attachment of the radioiodine thus minimizing *in vivo* deiodination.

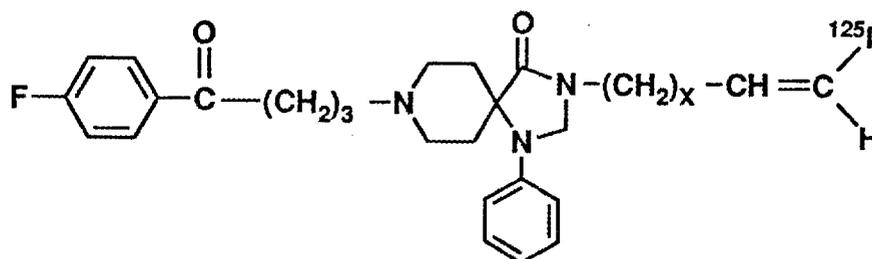
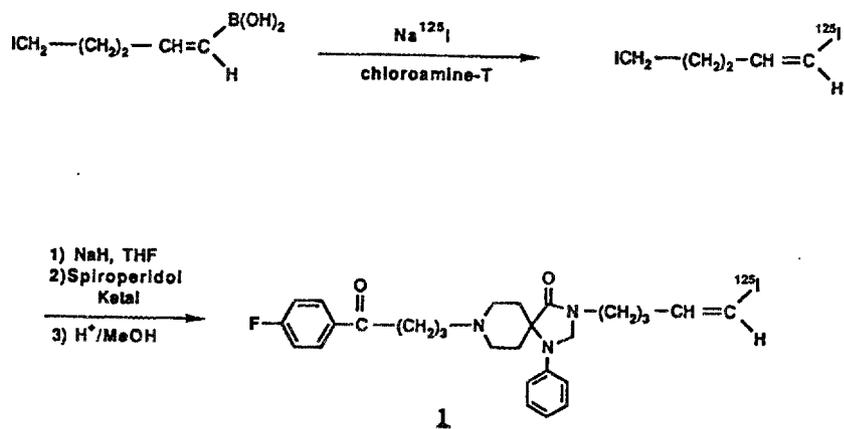


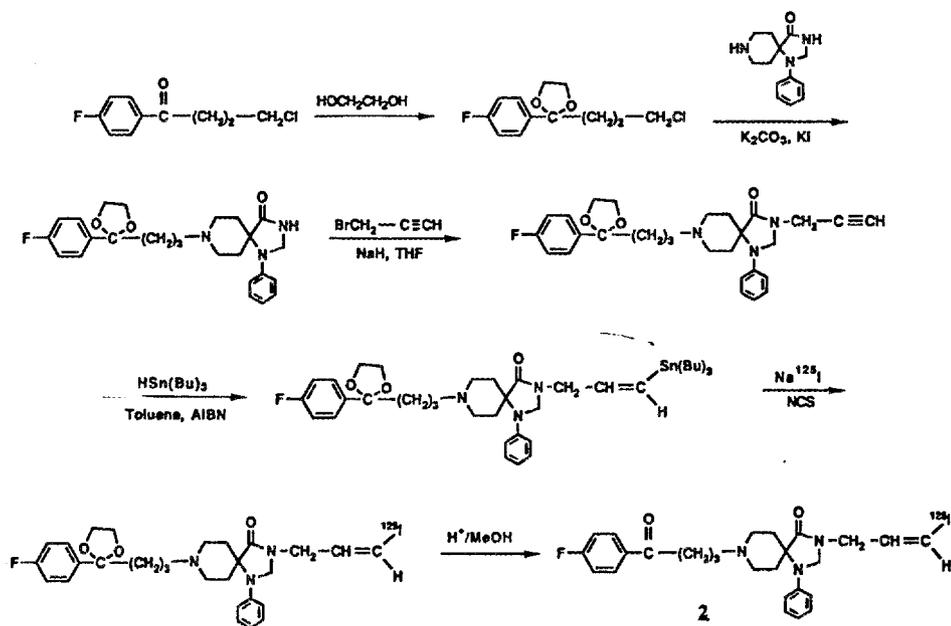
Figure 3.

Preparation of these analogues has been performed by the two routes shown in Schemes II and III. The first method (Scheme II) involves displacement of boronic acid with (NCA) I-125 with subsequent alkylation of the ketal of spiroperidol with the radiolabeled iodoalkenyliodine-moiety. Hydrolysis of the ketal group with acid readily affords I-125-iodopentenyl spiroperidol (1). The second procedure (Scheme III) was developed to overcome the decomposition of the propenyl boronic acid ( $X=1$ ) intermediate that we observed under the reaction conditions utilized in the first approach. The ketal of spiroperidol was first alkylated with propargyl bromide with subsequent conversion to the tributyltin analogue. Iododestannylation was performed utilizing iodine in the presence of *N*-chlorosuccinimide. Iodopropenylspiroperidol (2) was then purified by HPLC following removal of the ketal by acid hydrolysis.

We are currently evaluating the brain uptake, the dopamine D2 receptor specificity and *in vivo* stability of these iodoalkenyl spiroperidol analogues.



Scheme II.



Scheme III.

## AGENTS FOR MEDICAL COOPERATIVES

One shipment of iodine-125-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) was shipped to Brookhaven National Laboratory (Dr. P. Som). Four shipments of fatty acid substrates for I-123 radiolabeling were made to Crawford Long Hospital in Atlanta (Dr. R. Patterson). One shipment of I-123-labeled BMIPP was made to the University of Bonn, West Germany (Dr. J. Kropp) for isolated heart studies.

## OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Ambrose, K. R., Owen, B. A., Callahan, A. P., Goodman, M. M., and Knapp, F. F., Jr. "Effects of Fasting on the Myocardial Subcellular Distribution and Lipid Distribution of Terminal p-Iodophenyl-Substituted Fatty Acids in Rats," Nucl. Med. Biol., 15, 695-700 (1988).

Brihaye, C., Dewez, S., Guillaume, M., Callahan, A. P., Rice, D. E., and Knapp, F. F., Jr. "Reactor Production and Purification of Osmium-191 for Use in a New Os-191/Ir-191m Radionuclide Generator System," Appl. Rad. and Isotopes (Part A), 40, 183-191 (1989).

Callahan, A. P., Rice, D. E., and Knapp, F. F., Jr. "Availability of Rhenium-188 (Re-188,  $T_{1/2}$  16.9 h) from a Tungsten-188/Rhenium-188 Generator System for Therapeutic Applications," NucCompact – European/American Communications in Nuclear Medicine, 20, 3-6 (1989).

Knapp, F. F., Jr., and Callahan, A. P. "Biomedical Radioisotope Technology Development - Ensuring the Availability of Radioisotopes of Biomedical Interest from ORNL," Isotope News, 18, 4-6 (1989).



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