



# International Isotope Society

9th Central US Chapter Meeting, June 6-7, 1996 in Chicago, Illinois

..ORAL PRESENTATIONS..POSTER PRESENTATIONS..

## **ORAL PRESENTATIONS**

- [Ion Chemistry Initiated by Nuclear Decay in Tritiated Molecules](#)
- [Synthesis and Preliminary Evaluation of Boronated Agents Labeled with Positron Emitting Isotopes For Use In Boron Neutron Capture Therapy Treatment](#)
- [Strategies For Radiolabeling Biological Molecules](#)
- [Stereospecific Radiosynthesis of U-101387, A Dopamine D4 Antagonist With Potential Antipsychotic Activity. Part 1: Tritium Labeling](#)
- [Stereospecific Radiosynthesis of U-101387, A Dopamine D4 Antagonist With Potential Antipsychotic Activity. Part 2:  \$^{14}\text{C}\$  Labeling](#)
- [Current Trends in Stable Isotope Technology: Pharmacokinetics, Metabolism and Beyond](#)
- [Successful Problem Solving in the Synthesis and Analysis of  \$^{14}\text{C}\$  Compounds](#)
- [Synthesis of \(R\)-a\[ \$^{14}\text{C}\$ \]Methyltryptophan Methyl Ester and Its Conversion to PD 145942 and PD 154075](#)

## **POSTER PRESENTATIONS**

- [Syntheses of Carbon-14 Labeled Leukotriene  \$A\_4\$  Hydrolase Inhibitor Compound](#)
- [A Circuitous Synthesis of Olanzapine Suitable for the Preparation of Its Tritiated Isotopomer](#)
- [Synthesis of 8b-Methylthiomethyl-6-\[N-\[\(4-hydroxy-3-iodophenyl\)propionyl\]- \(3-aminopropyl\)\]Ergoline-\[ \$^{125}\text{I}\$ \]. A Radioligand Potentially Useful in the RIA of Pergolide Mesylate](#)
- [What's New at the NTLF?](#)
- [Synthesis of  \$^3\text{H}\$  and  \$^{14}\text{C}\$  Labelled SCH 48461](#)
- [Synthesis of  \$^{14}\text{C}\$  Labelled Antioxidant Pyrrolopyrimidine Compounds](#)

### **Ion Chemistry Initiated by Nuclear Decay in Tritiated Molecules**

Maurizio Speranza, University of Rome

The spontaneous decay of covalently bonded tritium atoms in tritiated molecules, taking place under carefully controlled conditions, affords a route to ions of well-defined structure and charge location, free of counterions. The nuclear nature of the ionization process makes it insensitive to environmental effects, so that exactly the same charged species can be generated, and its reactivity investigated, in widely varying media, from low-pressure gases to liquid and to solids. The tritium decay technique, which often involves elaborate synthetic and appropriate storage procedures, are used in studies of the production of otherwise inaccessible species, the structural characterization of free ions, and the comparative evaluation of their reactivity in different environments, in particular, gas phase and solution.

---

## SYNTHESIS AND PRELIMINARY EVALUATION OF BORONATED AGENTS LABELED WITH POSITRON EMITTING ISOTOPES FOR USE IN BORON NEUTRON CAPTURE THERAPY TREATMENT

George W. Kabalka, N. Kesavulu Reddy, Rajiv Srivastava, Chatla Narayana  
Biomedical Imaging Center  
The University of Tennessee, Knoxville, Tennessee USA

4-Boronophenylalanine-fructose (BPA-F) is currently being used in Phase II clinical trials to validate boron neutron capture therapy (BNCT) as a treatment for glioblastoma multiforme and melanoma. Successful BNCT is dependent on knowledge of the distribution of boron in the tumor versus normal tissue. Currently BNCT treatment planning is hampered by the necessity of determining boron distribution by analyzing tissue samples obtained during the pre-therapy removal of the tumor. Our laboratory developed boron-MRI for potential use in determining the *in vivo* distribution of BNCT agents.<sup>1,2</sup> The technique has met with limited success but it has been used experimentally to evaluate the distribution of a BNCT agent in a human.<sup>3</sup> An alternative approach to non-invasively studying the kinetics and biodistribution of BNCT agents is positron emission tomography (PET).<sup>4</sup> We have extensive experience in the use of amino acids labeled with positron emitting isotopes to evaluate tumors using PET.<sup>5</sup> We wish to report the synthesis of BPA-F labeled with the positron emitting isotopes: fluorine-18 and carbon-11. We also wish to report the use of PET to determine the pharmacokinetics of the fluorine-18 labeled analogue of BPA-F in glioblastoma multiforme patients. Our results indicate that PET may prove valuable in the evaluation of new boronated agents for use in BNCT, as well as in BNCT treatment planning.

### ACKNOWLEDGMENTS

We wish to acknowledge research support from the U.S. Department of Energy and the Robert H. Cole Foundation.

### REFERENCES:

1. Kabalka GW, Davis M, Bendel P, *J Magn. Reson. Med.* 8:231,1988.
2. Kabalka GW, Cheng CQ, Bendel P, Micca PL, Slatkin DN *J. Magn. Reson. Imag.* 9:969,1991
3. Bradshaw KM, Schweizer MP, Glover GH, Hadley JR, Tippets R, Tang PP, Davis WL, Heilbrun MP, Johnson S, Ghanem T, *Magn. Reson. Med.* 34:48,1995
4. Ishiwata K, iso T, Kawamura M, Kubota K, ichihashi M, Mishima Y, *Nucl. Med. Biol.* 18:745,1991
5. Hubner KF, Smith GT, Thie JA, Stephens TS, Buonocore E, *J Nucl. Med.* 33:1992,1992

---

### Strategies For Radiolabelling Biological Molecules

Barry Kent and Martin James  
Ligand Development Service, Amersham International plc  
Cardiff Laboratories, Forest Farm, Whitchurch, UK

There are an increasing number of chemical leads being generated by the use of high

throughput biological screening in drug discovery programs. This has led to an increase in the number and range of radiolabelled biological molecules required for use in the screens. Radiochemists are now being asked to provide new and improved labelling routes to these complex molecules.

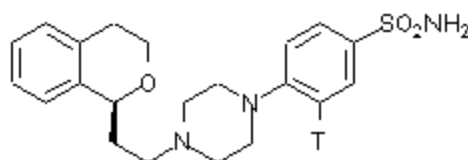
In this overview, we will look at a range of radiolabelling strategies focusing on peptides, proteins and oligonucleotides. We will review established labelling options, including related problems and limitations. We will also discuss alternative labelling methods that we have developed to overcome many of the traditional problems associated with these radiolabelled biological molecules.

---

## STEREOSPECIFIC RADIOSYNTHESIS OF U-101387, A DOPAMINE D<sub>4</sub> ANTAGONIST WITH POTENTIAL ANTIPSYCHOTIC ACTIVITY. PART 1: TRITIUM LABELING

Wayne T. Stolle, John A. Easter, Ruth E. TenBrink, Carol L. Bergh,  
Iain J. Martin, and Richard S.P. Hsi  
Pharmacia & Upjohn, Inc. PPC-US  
Kalamazoo, MI 49001

(S)-4[4-[2-(3,4-Dihydro-1H-2-benzopyran-1-yl)ethyl]-1-piperazinyl]-benzenesulfonamide (U-101387) is a highly bioavailable compound with excellent binding selectivity for mammalian dopamine D<sub>4</sub> receptors. It is under investigation as a potential antipsychotic for treating schizophrenia. Radioactive forms of U-101387 have been prepared to conduct drug metabolism and receptor binding studies with this compound. (Phenyl-<sup>3</sup>H)U-101387 was prepared by catalytic reduction, with tritium gas, of the corresponding phenyl 2-bromo derivative of U-101387, resulting in a product with specific activity (SA) of 5.41 mCi/mg and radiochemical purity (RCP) of 99%. Development of regiospecific tritiation conditions utilizing the IN/US TriSorber manifold, which led to the production of benzylic tritium free [<sup>3</sup>H]U-101387, will be discussed.



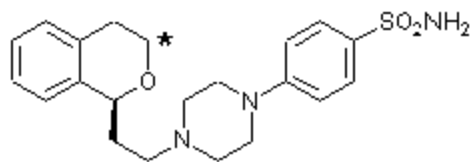
[<sup>3</sup>H]U-101387

---

## STEREOSPECIFIC RADIOSYNTHESIS OF U-101387, A DOPAMINE D<sub>4</sub> ANTAGONIST WITH POTENTIAL ANTIPSYCHOTIC ACTIVITY. PART 2: CARBON-14 LABELING

John A. Easter, Wayne T. Stolle, Ruth E. Tenbrink, Carol L. Bergh, Arthur O. Romero,  
John C. Sih, and Richard S.P. Hsi  
Pharmacia & Upjohn, Inc. PPC-US  
Kalamazoo, MI 49001

(U-101387) is a highly bioavailable compound with excellent binding selectivity for mammalian dopamine  $D_4$  receptors. It is under investigation as a potential antipsychotic for treating schizophrenia. Radioactive forms of U-101387 have been prepared to conduct drug metabolism and receptor binding studies with this compound. For the synthesis of [ $^{14}\text{C}$ ]U-101387, we first prepared ethyl [ $^{14}\text{C}$ ]iso-chroman-1-yl]acetate in 4 steps from potassium [ $^{14}\text{C}$ ]cyanide and benzyl bromide. The labeled racemic ester was kinetically resolved through lipase mediated hydrolysis to afford the desired levorotatory [3- $^{14}\text{C}$ ]isochromanylacetic acid. The unhydrolyzed intact antipode ester was recycled through base catalyzed racemization and farther lipase directed hydrolytic resolution. The synthesis was completed by amide formation between the chiral carbon-14 labeled isochromanylacetic acid and 4-(4-sulfonamido)-phenylpiperazine, followed by reduction of the resulting amide to the labeled free base U-101387, which was isolated as the monomethanesulfonic acid salt U-101387G, with SA of 45.8 uCi/mg and RCP of 98.9%. Chiral HPLC analysis of the product showed no detectable level of its antipode. Using the same synthetic route, we also prepared stable isotope labeled U-101387G, with carbon-13 bearing two deuterium atoms at the 3-position of the isochroman ring structure, by substituting  $\text{K}^{13}\text{CN}$  for  $\text{K}^{14}\text{CN}$  and reducing the intermediate C-13 labeled phenylacetic acid with deuterated borane.



[ $^{14}\text{C}$ ] U-101387

\* =  $^{14}\text{C}$

---

### Current Trends in Stable Isotope Technology: Pharmacokinetics, Metabolism and Beyond.

Daniel L. Bolt and Ronald Trolard  
Cambridge Isotope Laboratories, Inc.  
50 Frontage Road  
Andover MA 01810

For nearly 65 years, stable isotopes of all kinds have been invaluable tools for scientific investigators. As probes of metabolic pathways, solvents for nuclear magnetic resonance (NMR) investigations and analytical surrogates in precise quantitative studies, these heavy isotopes of carbon, nitrogen, oxygen and hydrogen have become staples of modern chemical research. More recently, specifically and uniformly labeled compounds have been used in combination with multi-dimensional NMR techniques and high resolution mass spectrometric techniques to elucidate three dimensional structures of biomolecules, as diagnostic imaging tools and as substrates in the identification of inherited and acquired diseases. The results of such investigations have led to advances in many disciplines including; rational drug design, composition and delivery of nutritional supplements and the treatment of certain diseases such as gastric ulcers.

A review of these varied applications of isotopically labeled compounds will be presented. Particular emphasis will be placed on emerging technologies surrounding pharmacokinetics,

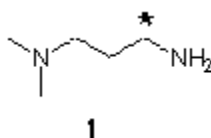
metabolism, nucleic acid conformational studies, neurochemistry and diagnostic medicine.

---

### Successful Problem-Solving in the Synthesis and Analysis of $^{14}\text{C}$ Compounds

Crist Filer, Zhigang Jian, Puliur Srinivasan and Christopher Wright  
DuPont-NEN Products, Boston, Massachusetts

Useful problem-solving techniques, essential to the synthesis of radiochemicals, will be described and illustrated by the preparation of 3-Dimethylamino[1- $^{14}\text{C}$ ]propylamine **1**, a deceptively simple molecule. Problem-solving in analysis will be demonstrated through the development of NMR techniques for accurate and consistent determination of the specific activity of  $^{14}\text{C}$  compounds.

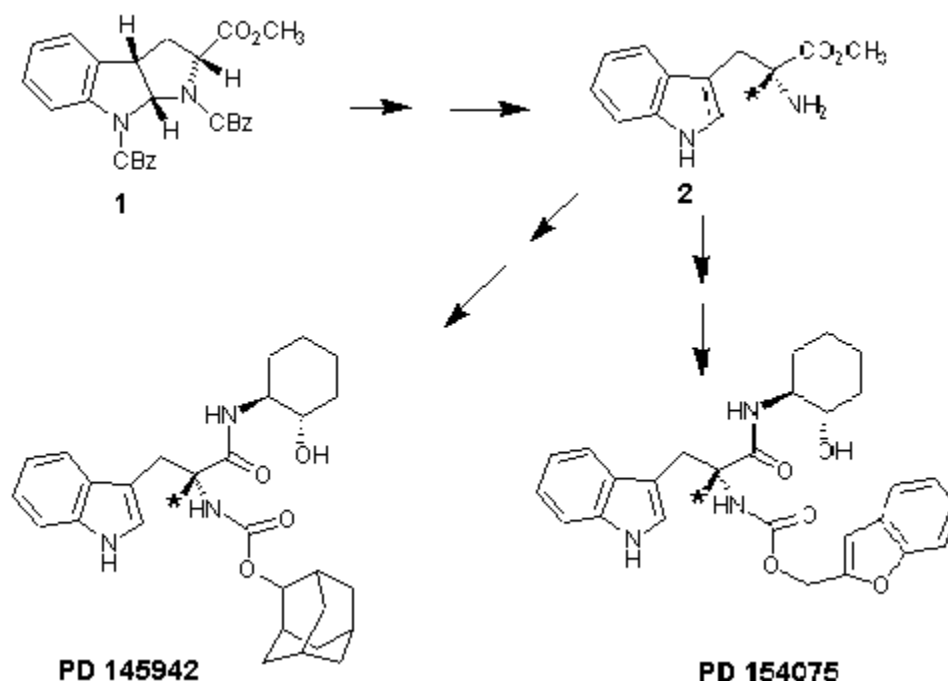


---

### SYNTHESIS OF (R)- $\alpha$ -[ $^{14}\text{C}$ ]METHYLTRYPTOPHAN METHYL ESTER, AND ITS CONVERSION TO PD 145942 AND PD 154075

I. Victor Ekhato  
Department of Chemical Development  
Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company  
Ann Arbor, Michigan 48105.

Carbon-14 labeled PD 145942 and PD 154075 were synthesized from (R)- $\alpha$ -[ $^{14}\text{C}$ ]methyl tryptophan methyl ester **2**. Radiolabelled compound **2** was prepared enantioselectively from [ $^{14}\text{C}$ ]methyl iodide. Both PD 145942 and 154075 are in pre-clinical study, and are being developed as potential drug candidates for the treatment of anxiety and emesis, respectively.



The preparation of [2R-(2a, 3b, 8b)]-2,3,3a,8a-tetrahydro-pyrrolo [2,3-b]indole- 1 ,2,8-tricarboxylic acid-1,8- dibenzyl ester 2-methyl ester **1**, and its application in a simple, enantioselective, and high yielding route to (R)- $\alpha$ -[ $^{14}\text{C}$ ]methyltryptophan methyl ester will be presented. In addition, the talk will describe the utilization of this labeled synthon in the asymmetric preparation of PD 145942 and PD 154075.

### Syntheses of Carbon-14 Labeled Leukotriene A<sub>4</sub> Hydrolase Inhibitor Compounds

Verinder K. Mahindroo, Christian H. Huber, Scott R. Harring and Charles S. Markos  
G. D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077

LTA<sub>4</sub> is a requisite enzyme in the biosynthetic pathway leading to formation of proinflammatory LTB<sub>4</sub>. The goal of the Leukotriene A<sub>4</sub> Hydrolase Inhibitors Project is to identify low molecular weight inhibitors of LTB<sub>4</sub> biosynthesis as orally active antiinflammatory compounds. Three lead compounds SC-55683, SC-56938 and SC-57461A were to be labeled with carbon- 14 to select the best compound based on PK studies. The unlabeled syntheses of all the three compounds used 4-hydroxydiphenylmethane as the common intermediate. [ $^{14}\text{C}$ ]4-Hydroxydiphenylmethane was synthesized in five steps and 32% overall radiochemical yield starting with carbon-14 labeled barium carbonate and utilized in the syntheses of [ $^{14}\text{C}$ ] SC-55683, [ $^{14}\text{C}$ ]SC-56938 and [ $^{14}\text{C}$ ]SC-57461A. Of these three lead compounds, SC-57461A was selected as the best candidate and was studied extensively. In order to determine the metabolic pathway of SC-57461A, the compound was also labeled at two alternate sites (carboxyl function and methyl group). Its carbon-14 labeled metabolites [ $^{14}\text{C}$ ]SC-66430 (N-oxide derivative) and [ $^{14}\text{C}$ ]SC-67105 (hydroxylamine derivative) were synthesized.

### A CIRCUITOUS SYNTHESIS OF OLANZAPINE SUITABLE FOR THE PREPARATION OF

## ITS TRITIATED ISOTOPOMER

Delise M. Douglas, William J. Wheeler  
Lilly Research Laboratories, A Division of Eli Lilly & Co.  
Indianapolis, IN 46285

Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b]-benzodiazapine, is a potent dopamine antagonist that is currently under investigation for use in the treatment of schizophrenia. In addition to action at the D-1 and D-2 receptors, olanzapine has also shown anticholinergic and serotonin blocking behavior.

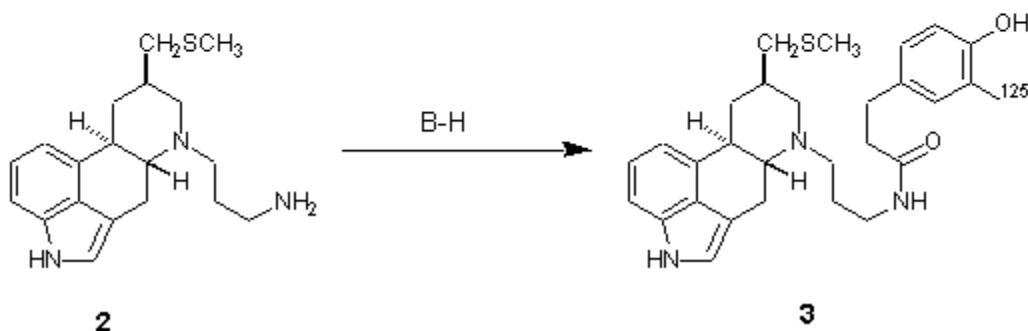
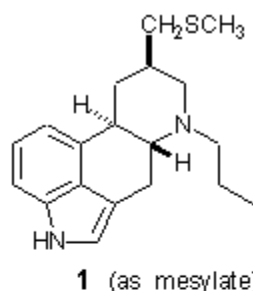
High specific activity tritiated olanzapine was needed for a number of mechanism and receptor binding studies. Both C-14 and deuterium labeled olanzapine have been previously prepared; however, the synthetic route for the deuterium labeled material was not amenable to the preparation of the tritiated isotopomer, since the introduction of the label occurred very early in the synthetic sequence. We have devised a novel circuitous synthetic route useful in the preparation of tritiated olanzapine that allows the introduction of tritium in the last step. There are many reagents used in von Braun type chemistry which effect the two step demethylation of tert-amines (i.e., BrCN, TCEOCOCI, phenylchloroformate). Frequently, removal of the carbamate to elaborate the sec-amine requires vigorous conditions. More recently, a method has been devised, allowing the removal of the methyl group without isolation of the intermediate carbamate. Thus, olanzapine was demethylated by reaction with  $\alpha$ -chloro-ethyl chloroformate (ACE-Cl) followed by treatment of the resulting carbamate with methanol. Desmethylolanzapine was in turn re-methylated by reaction with methyl-[ $^2\text{H}_3$ ] iodide or methyl-[ $^3\text{H}_3$ ] iodide in the presence of Hunig's base to yield the corresponding olanzapine isotopomers.

---

## THE SYNTHESIS OF 8-beta-METHYLTHIOMETHYL-6-[N-[(4-HYDROXY-3- IODOPHENYL) PROPIONYL]-(3-AMINOPROPYL)]ERGOLINE-[125I], A RADIOLIGAND POTENTIALLY USEFUL IN THE RADIOIMMUNOASSAY OF PERGOLIDE MESYLATE

William J. Wheeler, Delise Douglas, W.Edwin Legan  
Lilly Research Laboratories, A Division of Eli Lilly and Company  
Indianapolis, IN 46285

A radioimmunoassay for pergolide (**1**) has been developed using pergolide-[ $^3\text{H}$ ] mesylate, but problems have arisen concerning the long term stability of this radioligand. It was felt that a radioiodinated ligand should give better sensitivity because of the much higher specific activity, but also be more convenient. We have synthesized a substrate (**2**) which can be conveniently acylated with the Bolton-Hunter reagent to provide an appropriate  $^{125}\text{I}$ -labeled radioligand (**3**). This radioligand should be viable for 6-8 weeks and can be freshly prepared on an "as needed" basis. This poster details the synthesis of the precursor as well as the preparation and characterization of the radioiodinated ligand.



### WHAT'S NEW AT THE NTLF?

Hiromi Morimoto, Chit Than, Manouchehr Saljoughian, Mervin Long and Philip G. Williams  
 National Tritium Labelling Facility  
 Lawrence Berkeley National Laboratory  
 One Cyclotron Road -MS 75 123  
 Berkeley, CA 94720-1000

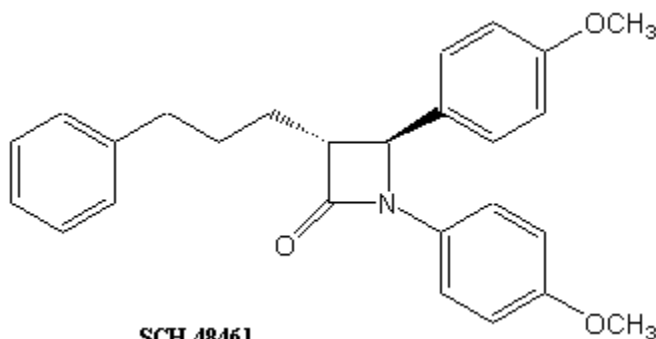
The recent advances in tritium labeling developed at the NTLF. are discussed. The improved labeling of alkali metal borohydrides,  $\text{NaBT}_4$ ,  $\text{LiBT}_4$ , and  $\text{BT}_3$  are demonstrated. These reagents are characterized by boron, tritium and proton NMR. The utility of these reagents in labeling reactions is confirmed by exemplary reductions yielding specifically highly labeled products.

A high specific activity acetylation reagent, N-tritioacetoxyphthalimide is discussed. This reagent is shown to be reactive in DMSO, water or methanol, and is highly specific. Representative reactions are shown.

### SYNTHESIS OF $^3\text{H}$ AND $^{14}\text{C}$ LABELLED SCH 48461

D.Hesk. C. Bowlen, S. Hendershot, D. Koharski, P. McNamara, D. Rettig, and S. Saluja.  
 Schering Plough Research Institute, 2015 Galloping Hill Road  
 Kenilworth NJ 07033. USA.

Sch 48461 is a drug candidate currently under development as an absorption inhibitor of cholesterol.



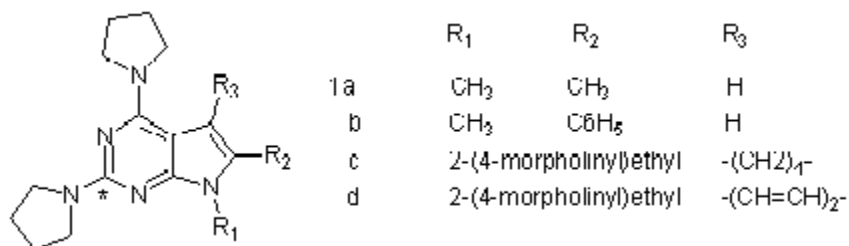
During the early discovery phase, the tritiated racemate,  $^3\text{H}$ -SCH 47949 was prepared at a specific activity of 40 mCi/mmol by Pt catalysed exchange with tritiated water to conduct preliminary AME studies in rats and mice. Subsequently after the compound had progressed to the development phase, all work was carried out on the single enantiomer, Sch 48461. Hence  $^{14}\text{C}$ -SCH 48461 was prepared in 8 steps from 14 potassium cyanide in overall radiochemical yield of 18.5% for the development program. In addition high specific activity  $^3\text{H}$ -Sch 48461 was prepared, at a specific activity of 64.6 Ci/mmol, by a Pd/C catalysed reduction of an olefinic intermediate for protein binding studies. The paper describes the synthesis of each labeled form.

### Synthesis of Carbon-14 Labeled Antioxidant Pyrrolopyrimidine Compounds

W.T. Stolle and R.S.P. Hsi

Pharmacia & Upjohn PPC - US, Kalamazoo, Michigan 49001

Several pyrrolo[2,3-d]pyrimidines are under investigation as potential orally active antioxidant compounds for treating asthma and a variety of chronic neurodegenerative disorders. Four members of this series, compounds **1a-d**, have been radiolabeled with carbon-14 for conducting drug metabolism studies. A common carbon-14 labeled intermediate, 4-chloro-2,6-di-1-pyrrolidinyl-[2- $^{14}\text{C}$ ]pyrimidine, was prepared in three steps from [ $^{14}\text{C}$ ]urea. Conversion of this intermediate to **1a**, **1b**, and **1c** was each carried out in two steps: treatment with an appropriate amine, followed by reaction with an alpha-bromoketone. Dehydrogenation of **1c** provided **1d**. Because of their antioxidant properties, these compounds and their precursors all showed sensitivity towards oxygen, and often required handling in a nitrogen atmosphere, particularly when in solution.



[Return to the main page.](#)