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MARTIN MARIETTA

Nuclear Medicine Program Progress Report for Quarter Ending December 31,1991

F. F. Knapp, Jr.

K. R. Ambrose
A. P. Callahan
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P. C. Srivastava
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Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING DECEMBER 31, 1991

F. F. Knapp, Jr., Group Leader

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CONTENTS

SUMMARY

We have developed a new improved synthesis of carrier-free rhenium-188-labeled Re(V) dimercaptosuccinic acid (DMSA) complex as a potential therapeutic agent for treatment of thyroid medullary carcinoma. These studies were prompted by the unique localization reported for the analogous technetium-99m-labeled Tc(V) complex used for diagnosis of this disease. Such therapeutic applications of Re-188 complement our earlier development of an efficient tungsten-188/rhenium-188 generator system. Rather than the use of traditional reducing agents, our new method uses triphenylphosphine (TPP) for the facile reduction of the Re(VIII) rhenium-188 generator eluant to Re(V). Rhenium-188 Re(V) DMSA was then formed in high yield by treatment of the intermediary Re(V)$OCl_3(TPP)_3$ complex with DMSA.

The *in vivo* imaging of cerebral serotonin S_2 receptors by nuclear medicine techniques is of interest for the study of aging and also for the evaluation of Alzheimer disease and dementias. Altanserine binds with high selectivity and specificity to the cerebral serotonin S_2 receptors. This project was directed toward the synthesis and evaluation of a series of iodine-125-labeled analogues of altanserine. Our strategy involved preparation of a series of stannylated derivatives of altanserine which would be used for the incorporation of iodine. The first syntheses were therefore directed to the preparation of the necessary bromo derivatives of altanserine. Once these were prepared, we investigated the replacement of the brominated substituent with the trialkylstannyl group and the subsequent iododestannylation reaction to give the desired iodinated analogues. The stannylation of these intermediates under a variety of different reaction conditions, however, did not proceed to give the desired product due to the presence of the sulfur moiety. We then investigated introducing the trialkylstannyl group on other intermediates in the reaction scheme before the introduction of the sulfur moiety. Although we were able to introduce the trialkylstannyl group, the iododestannylation reaction did not proceed due to the deactivation of the phenyl ring by the carbonyl group. This allowed us to explore a number of potential routes, however we have been unable to synthesize the target molecules. One possible route for the synthesis of the iodinated intermediate which we expect will be pursued by collaborators will involve "masking"

of the carbonyl group as a ketal. This should "activate" the phenyl ring and thus overcome the problem of the iododestannylation reaction encountered above.

Also during this period, several ORNL agents were supplied to Medical Cooperative Programs for further collaborative preclinical and clinical studies.

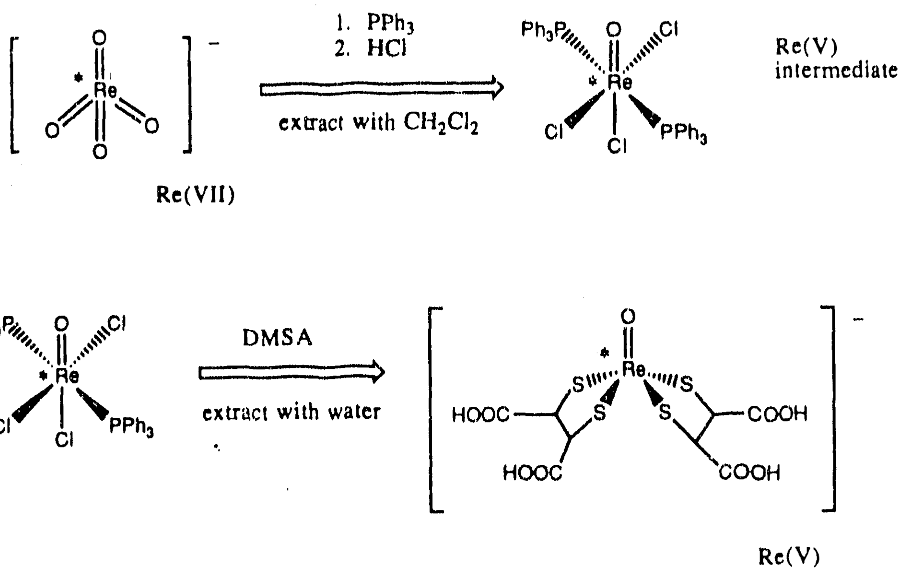
SYNTHESIS OF CARRIER-FREE RHENIUM-188 LABELED Re(V) DMSA USING TRIPHENYLPHOSPHINE AS A FACILE REDUCING AGENT

A unique diagnostic application of the technetium-99m-labeled Tc(V) complex of dimercaptosuccinic acid (DMSA) is for the imaging of thyroid medullary carcinoma. For unknown reasons, Tc(V)-DMSA often accumulated in these tumors and other tumors of the head and neck. Since these tumors are often nonresectable, the availability of tumor specific agents radiolabeled with therapeutic radionuclides is of interest. Since rhenium is in the same transition metal group as technetium, the Re(V) DMSA complex would be expected to be prepared in a similar manner. Our interest in this area developed as a result of our development of a tungsten-188/rhenium-188 generator which provides carrier-free rhenium-188 (ORNL/TM-10531). Other investigators have demonstrated the preparation of the rhenium(V) and Re-186(V) DMSA complexes by treatment of perrhenate with commercially available kits developed for the preparation of the Tc-(III) DMSA renal perfusion agent.[1] By increasing the reaction time and temperature, the Re(V) DMSA is formed in an analogous manner as Tc(III)DMSA.[2]

As an alternative route which could be conveniently conducted at room temperature in a short time period, we have explored the use of triphenylphosphine (TPP) as a facile agent for the reduction of perrhenate [e.g., Re(VIII)] to the requisite Re(V) oxidation state. These studies have been pursued in conjunction with E. C. Lisic, Ph.D., Assistant Professor of Chemistry at the Tennessee Technological University in Cookeville, Tennessee, who is a visiting scientist at ORNL through support through the ORAU Participation Agreement Program.

For this new facile synthesis of Re(V) DMSA (Scheme I), perrhenate was reduced with triphenylphosphine (TPP) in an aqueous solution containing HCl, by a modification of the method of Chatt et al.,[3] to provide the $ReOCl_3(TPP)_3$ [e.g., Re(V)] intermediate which is extracted into methylene chloride. The Re(V) DMSA is then readily formed by treatment of this intermediate with DMSA in methylene chloride-ethanol (1:1) solution. Following dilution with water, the orange-colored Re(V) DMSA is then extracted into the aqueous layer. Following evaporation, the product was identified by proton and carbon NMR, infrared spectroscopy, thin layer chromatography, and elemental analysis.

REACTION OF PERRHENATE ION
TO FORM A REACTIVE INTERMEDIATE



Scheme I

The carrier-free rhenium-188-labeled Re(V) DMSA was prepared on a scale up to 7 mCi in >80% overall yield. In a typical preparation, the physiological saline eluant containing Na[^{188}Re]perrhenate from the tungsten-188/rhenium-188 generator (1 ml) was treated with a biphasic mixture of methylene chloride and aqueous HCl containing 1-5 mg of triphenyl phosphine. After shaking for 5 min at room temperature, the organic layer was separated to yield the $ReOCl_3(TPP)_3$ intermediate. Treatment of this solution with 3 mg of

DMSA in a 10% ethanol/water solution formed the Re(V) DMSA complex. The product was conveniently and rapidly purified by passing this solution through an amine SepPak®. After washing with ethanol and 0.01 N HCl, the product was removed with 5 ml of water.

The product formed by this method shows a single component on TLC analysis with the mobility of an authentic Re(V) DMSA sample. This simple, high yield method for the preparation of high specific activity Re(V) DMSA should allow an evaluation of the usefulness of this agent for the potential treatment of patients with thyroid medullary carcinoma.

APPROACHES FOR SYNTHESIS OF 2'-IODOALTANSERINE

Receptors are molecular structures within or on the surface of cells characterized by selective binding of a specific substance or a structural analogue and a specific physiological effect that accompanies the binding. Such receptors in the brain play a central role in neurotransmission for a variety of cerebral processes. The various classes of serotoninergic binding sites, notably the S_2 receptor site, have been well characterized in pharmacological and physiological terms and have been implicated in several neurological conditions such as aging, Alzheimer's disease, and personality disorders. These observations have generated an increased interest among researchers for the potential non-invasive imaging of the serotonin receptor. The population or activity of receptor binding can be conveniently determined by evaluating the degree of uptake of radiolabeled receptor specific agents. In *in vivo* studies such uptake can be evaluated non-invasively using nuclear medicine imaging procedures by injecting radiolabeled receptor agents whose cerebral localization can be determined by measuring the emitted radiation.

This project was directed toward the synthesis and evaluation of a series of iodinated altanserine derivatives for use in the *in vivo* imaging of serotonin receptor populations by Single Photon Emission Computed Tomography (SPECT). Altanserine (**1**) is structurally related to ketanserine (**2**), a ligand which has been radiolabeled and evaluated as a potential candidate for the imaging of serotonin S_2 receptor. However, ketanserine has been shown to have a very high non-specific binding to other receptor sites and therefore would produce low quality images. In contrast to ketanserine, altanserine contains a thioamide (sulfur replaces oxygen) group as a component of the heterocyclic ring system and this change dramatically enhances the S_2 receptor specificity.

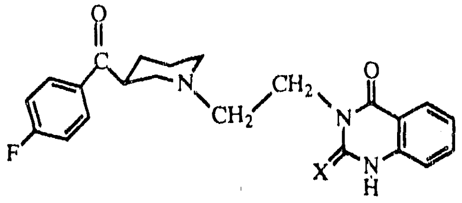
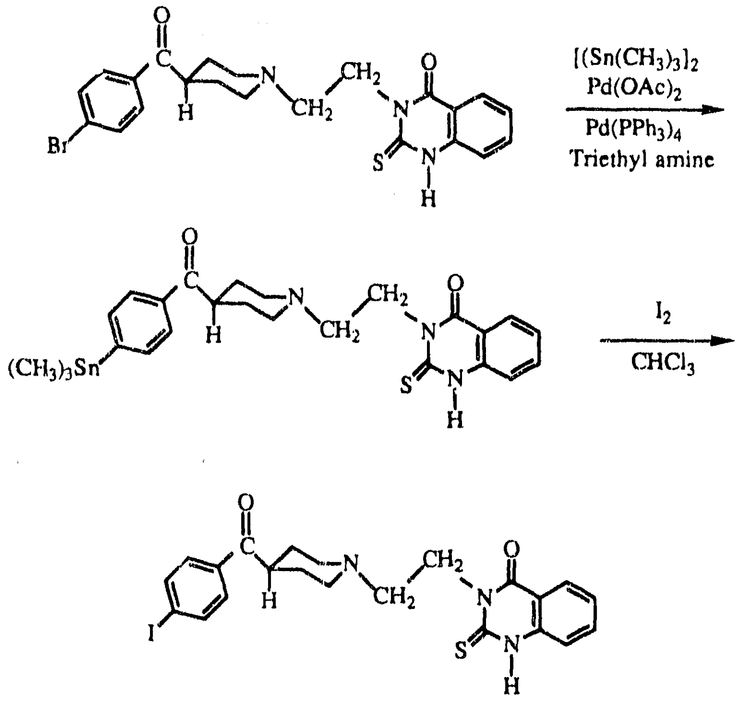


Figure 1.

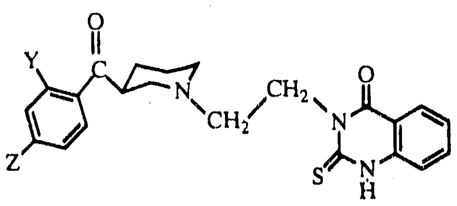
1) Altanserine X=S
2) Ketanserine X=O

Ketanserine has been reported to be labeled with iodine-123 in the 2 position via the copper(I) assisted halogen exchange utilizing the brominated precursor in sufficient yield.[4] When this same procedure was used for the radiolabeling of 1, the compound undergoes decomposition due to the presence of the sulfur moiety with no radiolabeled product being isolated. In this project we proposed the labeling of altanserine via the trialkylstannyl derivatives as shown in Scheme II.



Scheme II.

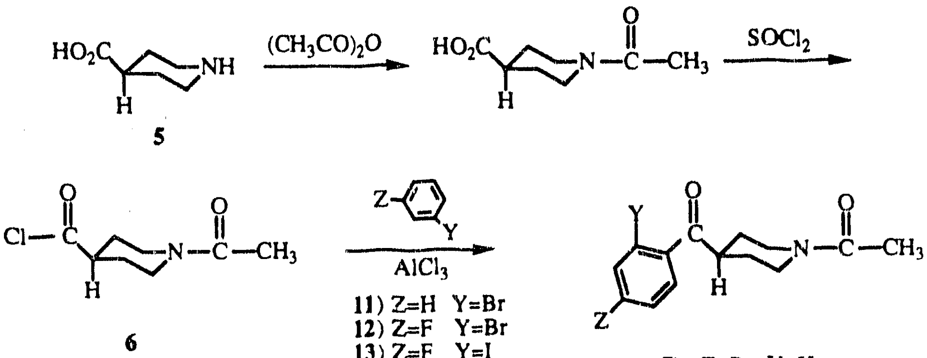
This route involves the preparation of a series of brominated derivatives as the target molecules. The derivatives that we initially proposed to synthesize are shown in Figure 2. These are the p-iodo (**3**) and p-fluoro-o-iodo (**4**) analogues. Compound **3** is analogous to that prepared for ketanserine, and compound **4** was chosen from the data observed with similar ligands which showed that placement of the iodine in the position meta to the fluorine atom allows the molecule to retain its affinity for the receptor binding site.



3) Z=I Y=H
4) Z=F Y=I

Figure 2.

The initial step for the synthesis of the target molecules involves the preparation of the substituted phenyliperidine ketones. This was accomplished by the route as shown in Scheme III and involves the protection of the amine portion of 4-piperidinecarboxylic acid (**5**) with acetic anhydride and the subsequent formation of the acid chloride by treatment with thionyl chloride to afford compound **6**. The final step involves the Friedel-Crafts acylation of **6** with the substituted benzene derivative in the presence of aluminum chloride. For the p-bromo derivative (**7**) bromobenzene (**11**) was used and the desired compound was obtained.



5

6

11) Z=H Y=Br
12) Z=F Y=Br
13) Z=F Y=I

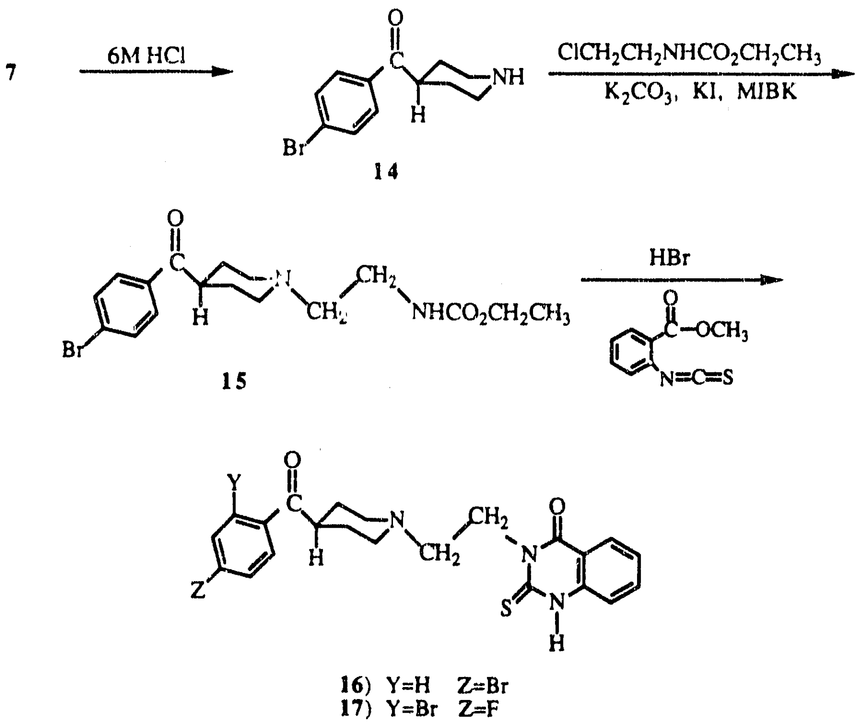
7) Z=Br Y=H
8) Z=F Y=Br
9) Z=Br Y=F
10) Z=F Y=H

Scheme III.

For the p-fluoro-o-bromo compound (**8**), 1-fluoro-3-bromobenzene (**12**) was used and in addition to compound **8**, the p-bromo-o-fluoro isomer (**9**) was also obtained in the reaction mixture. Compounds **8** and **9** were obtained in pure form after repeated column purification and recrystallization. Initially, the reaction was attempted with 1-fluoro-3-iodobenzene (**13**) to synthesize compound **4** for use as a cold standard and to optimize the subsequent synthetic steps to the target molecules. Under the reaction conditions of the Friedel-Crafts acylation, however, the molecule lost iodine and only the p-fluoro analogue (**10**) was obtained. Compound **10** was utilized in the subsequent steps to confirm the reaction pathway and to afford a standard sample of altanserine (**1**) for use as a blocking agent in future animal studies.

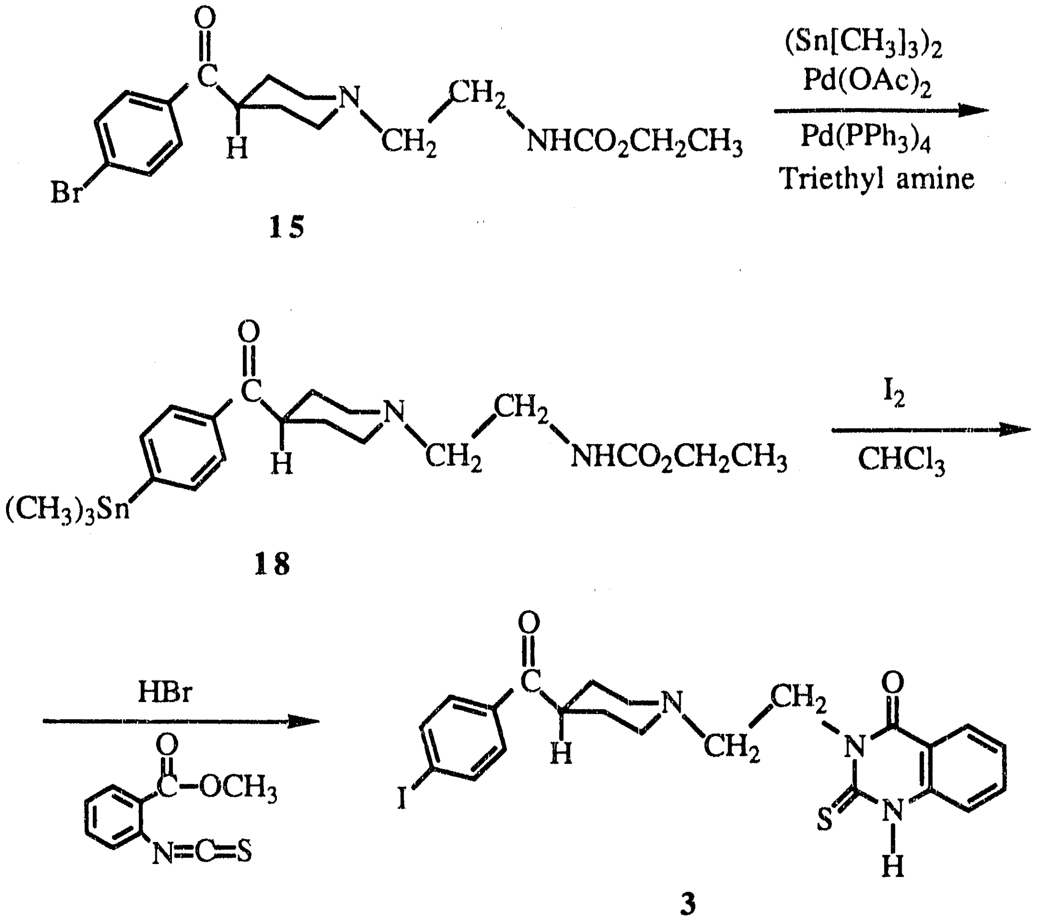
The final steps of the reaction sequence employed are shown in Scheme IV using **7** as an example. This involves the removal of the N-acetyl group in 6 M HCl solution to afford compound **14** followed immediately by the alkylation of **14** with ß-chloroethyl-ethylcarbamate to give the desired compound, N-1-(2-ethoxycarbonylaminoethyl)-4-(4-bromobenzoyl)-piperidine (**15**). The ethylcarbamate group was then removed in the presence of HBr followed by the addition of methyl 2-isothiocyanatobenzoate to yield the brominated analogue (**16**) of altanserine. The p-fluoro-o-bromo analogue (**17**) was prepared in an analogous manner. Compound **16** was then reacted under a variety of conditions with either bistributyltin or hexamethylditin in either anhydrous triethylamine or dioxane as shown in Scheme II. In all cases, however, **16** was recovered from the reaction mixture. In the reactions where triethylamine was used as the solvent, **16** was insoluble and when dioxane was used as the solvent the sulfur moiety of **16** interfered with the palladium catalysts that were used. The replacement of bromine for trialkytin was also attempted on compound **17** and as before the desired product was not isolated.

This lead us to investigate the addition of the trialkyltin group before the sulfur moiety was introduced into the molecule which would presumably eliminate the sulfur interfering with the palladium catalysts employed in the reaction mixture. The reaction of **15**



Scheme IV.

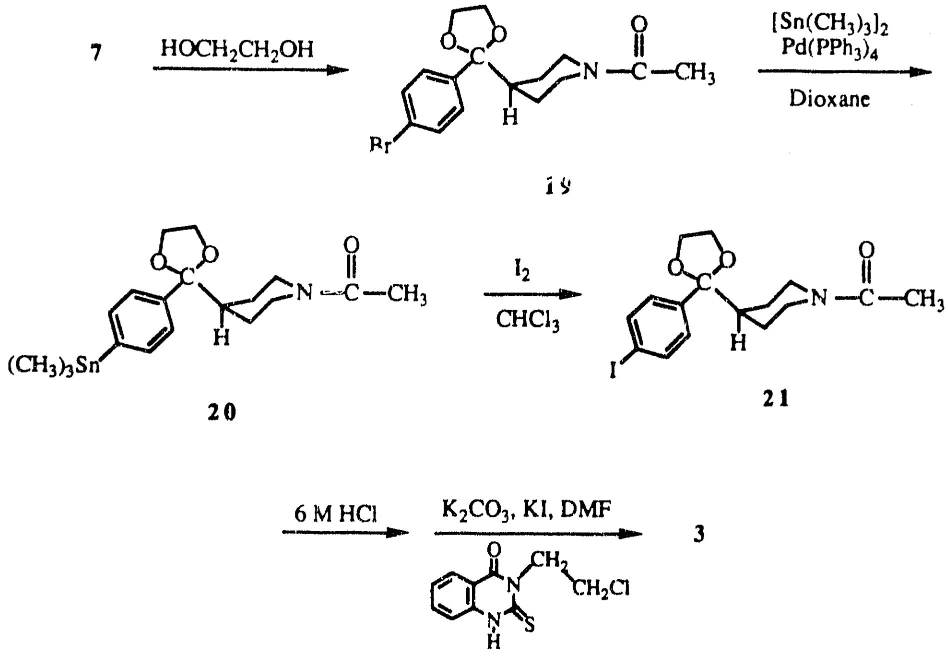
with hexamethylditin was carried out as shown in Scheme V. This involved refluxing **15** and hexamethylditin in anhydrous triethylamine in the presence of the palladium catalysts to afford the trimethyltin derivative (**18**). However, the desired iodinated derivative (**3**) was not obtained when **18** was reacted with iodine with chloroform as the solvent. The reaction was also performed using the p-fluoro-o-bromo analogue of **15**. Again the iodinated intermediate was not isolated, and the crude reaction product was used in the ring closure step. In this case the only product that was formed was altanserine (**1**) as determined by NMR analysis. The iodination was also carried out with sodium iodide with chloramine-T as the oxidizing agent, and as before, **3** was not formed in the reaction mixture. The iodination at this point did not proceed to give the desired product since the aromatic ring which contains the trimethyltin group is deactivated and this prevents the electrophilic displacement of the trimethyltin group by iodine.



Scheme V.

The ring closure was also attempted on compound **18** as shown in Scheme V. The N-ethylcarbamate group of **18** was removed by treatment with HBr followed by ring closure with methyl 2-isothiocyanatobenzoate. In this reaction the unsubstituted analogue of **1**, where the trimethyltin group was displaced by a hydrogen atom, was the only product isolated, and this approach was therefore abandoned.

A phenyl ring containing halogen or the trialkyltin substituent is deactivated due to the presence of the α-carbonyl group. This led us to investigate the use of a blocking group which could later be used to mask the deactivating character of the carbonyl group and could later be readily removed. We chose the ketal group to block the carbonyl due to its ease of removal in acidic solutions, as shown in Scheme VI for the preparation of compound **3**. This reaction scheme is based on the preparation of various neuroleptics similar to altanserine (**1**). Compound **7** is reacted with ethylene glycol with p-toluene sulfonic acid as a catalyst to afford the desired ketal (**19**), which is then reacted with hexamethylditin in the presence of tetrakis(triphenylphosphine)palladium(0) in anhydrous dioxane to give compound **20**. When **20** is reacted with iodine, the desired iodinated compound (**21**) is isolated. Therefore, the masking of the carbonyl group as a ketal does activate the aromatic ring and allows the electrophilic substitution with iodine to proceed. When **21** is treated with 6 M HCl, the ketal and the acetyl groups are both removed. When this intermediate is alkylated with the substituted chloroethylamine, however, the desired product is not isolated. The substituted chloroethylamine compound is recovered from the reaction mixture indicating that the problem with this reaction is the solubility of the chloroethylamine.



Scheme VI.

The reaction utilizing compound **15** and performing analogous chemistry as discussed previously is possible since the ketal protecting group can be removed by treatment with HBr, and we have already demonstrated that the ring closure proceeds readily. In addition, this pathway will allow the compound to be radiolabeled in a suitable time frame. If this route is successful for the preparation of the desired analogues of altanserine by our collaborators in Belgium, we expect to prepare a grant application for the National Institute of Health (NIH). Arrangements have also been made with our collaborators at the University of Liege, Liege, Belgium (Dr. M. Guillaume and colleagues) to test the selectivity and specificity of our new altanserine analogues using animal models with fluorine-18 labeled altanserine, which they routinely produce.

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AGENTS FOR MEDICAL COOPERATIVES

During this period three shipments each of the tungsten-188/rhenium-188 generator were made to Immunomedics, Newark, New Jersey (Dr. Gary Griffiths), Guy's Hospital, London, England (Dr. C. Lazarus), and the Nuclear Medicine Institute, Shanghai, P. R. China (Dr. T. Zhu).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Presentations

F. F. Knapp, Jr., presented an invited lecture entitled "Radioisotopes for Radioimmunodetection (RAID) and Radioimmunotherapy (RAIT) - Current and New Perspectives," in the Continuing Education Lectures at the Annual Meeting of the Southeastern Chapter Meeting of the Society of Nuclear Medicine in Hollywood, Florida, on October 11-13, 1991.

Members of the Nuclear Medicine Group co-authored two papers at the "Third International Symposium on Lipid Metabolism in the Normoxic and Ischemic Heart," which was held in Rotterdam, The Netherlands, on September 9-10, 1991.

> Sloof, G. W., Visser, F. C., Teerlink, T., Comans, E. F. I., van Eenige, M. J., van der Vusse, G. J., and Knapp, F. F., Jr. "Phospholipid Distribution of Radioiodinated Fatty Acids After Intravenous Injection in Normoxic Canine Myocardium."
>
> Visser, F. C., Sloof, G. W., van Eenige, M. J., Comans, E. F. I., Teerlink, T., Herscheid, K., and Knapp, F. F., Jr. "Comparison of Uptake, Oxidation, and Lipid Distribution of IHA, IPPA, and DMIPP Fatty Acid Analogues in Normal Canine Myocardium."

Textbook Chapter

F. F. Knapp, Jr., C. Brihaye (Liege, Belgium), A. P. Callahan, and S. Mirzadeh will author the two sections entitled "Radionuclide Generators for Nuclear Medicine Applications" and "Reactor Production of Medical Radioisotopes," for the second edition of the classic textbook entitled, "Principles of Nuclear Medicine," edited by H. N. Wagner, Jr., M.D. (W. B. Saunders, publishers). The first 896 page edition was published in 1968 and is widely recognized as the only comprehensive and authorative text on the principles and practice of nuclear medicine. The second edition is scheduled for publication in 1993, on the 25th anniversary of the publication of the first edition.

Miscellaneous

Kathleen R. Ambrose has been appointed as Chairperson of the ORNL Animal Care and Use Committee (ORNL-ACUC). The Committee's responsibilities include review and approval of all procedures and proposals involving the care and use of animals for experimental purposes at ORNL, as well as routine inspections of ORNL animal facilities. Ms. Ambrose attended a workshop entitled "Dilemmas in Rodent Research: Scientific, Regulatory, Ethical Perspectives," in Houston, Texas, December 5-6, 1991.

P. C. Srivastava received a Distinguished Scientist Award given by the United Nations World Development Program and visited research scientists in India to help in India's developmental endeavors in the areas of biomedical and molecular nuclear medicine technologies. Under the World Program, the United Nations will also allow the Council of Scientific and Industrial Research Scientists from India to come to visit the Oak Ridge regional area to interact with scientists for development of new collaborations and technology transfer programs.

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