ORNL/TM-6916

Nuclear Medicine Technology Progress Report for Quarter Ending March 31, 1979

F. F. Knapp, Jr.

HEALTH AND SAFETY RESEARCH DIVISION
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NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT FOR QUARTER ENDING MARCH 31, 1979

F. F. Knapp, Jr.

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SUMMARY

In this report, we describe the preparation of a unique class of trimethyltin-substituted steroids that were designed because of the potential use of the ^{117m}Sn-labeled analogs for adrenal imaging. Several steroids were prepared that contained various structural modifications of both the nucleus and sidechain. The physical properties of these stable, crystalline products were consistent with the proposed structures. The trimethyltin-substituted steroids were readily prepared on the microscale in yields ranging from 40-80%, which indicate that this methodology should be applicable for the preparation of the ^{117m}Sn-labeled steroids.

Studies with the ^{123m}Te-labeled fatty acids have continued, and radiolabeled 6-telluraheptadecanoic acid and 11-telluraheptadecanoic acid have shown pronounced heart uptake in rats similar to that reported earlier for ^{123m}Te-labeled 9-telluraheptadecanoic acid. These combined results suggest that the position of the tellurium heteroatom has little effect on the heart uptake of the telluraheptadecanoic acids and that the pronounced heart uptake observed with ^{123m}Te-labeled 9-telluraheptadecanoic acid is therefore not simply a consequence of its isosteric similarity with oleic acid (9-octadecenoic acid).

As a result of our interest in the potential use of ^{73}Se-labeled agents for tomographic imaging applications, we have prepared several ^{75}Se-labeled compounds for preliminary tissue distribution studies in rats. Significant heart uptake was observed with ^{75}Se-labeled-9-selenoheptadecanoic acid, suggesting that the various structural features affecting heart uptake of seleno fatty acids should also be

explored. In addition, ^{75}Se-labeled 24-(isopropyl seleno)-chol-5-en-3β-ol was prepared and showed pronounced adrenal uptake in rats.

In this progress report, we also describe the results of continuing studies with ^{11}C-labeled amino acids in a collaborative project with the Oak Ridge Associated Universities (ORAU). Recent patient studies at ORAU have established that ^{11}C-DL-tryptophan is superior to ^{11}C-DL-valine for pancreatic visualization by positron emission tomography. Nitrogen-13 ($T_{1/2}$ = 10 min) was prepared for the first time in the ORNL 86-inch cyclotron and converted to ^{13}N-ammonia that was used successfully to visualize dog hearts.

TIN-117*m*

F. F. Knapp, Jr., T. A. Butler, and K. R. Ambrose

In an earlier report (ORNL/TM-6638), we described the properties of ^{117m}Sn that make this radionuclide an attractive candidate for incorporation into various tissue-specific radiopharmaceuticals. More recently, we have described the preparation of ^{117m}Sn-labeled 12,12-dimethyl-12-stannahexadecanoic acid as well as the results of tissue distribution studies in rats with this potential myocardial imaging agent (ORNL/TM-6639). Additional studies are now in progress to determine the effect of both the total chain length and the position of the dimethyltin moiety on the heart uptake of a series of ^{117m}Sn-labeled fatty acids.

We are also interested in the preparation of various other ^{117m}Sn-labeled radiopharmaceuticals, and we have how explored the preparation of a novel series of steroids containing the trimethyltin moiety

in the sidechain. While a variety of synthetic strategies were considered for the preparation of such compounds, we chose to investigate the reaction of trimethyltin-alkali metal salts with steroid substrates brominated in the sidechain, primarily because of the ready availability of the latter compounds that were used earlier to prepare the ^{123m}Te-labeled adrenal imaging agents (ORNL/TM-6044). In addition, we had developed an efficient route for the preparation of the Me_3Sn-Cl (ORNL/TM-6638), which forms the crucial Me_3Sn-Li intermediate that readily reacts with halogenated substrates. We were therefore ready to attempt the preparation of novel trimethyltin-substituted steroids. We found that commercial Me_3Sn-Cl formed the reactive Me_3Sn-Li intermediate by reaction with metallic lithium in either liquid ammonia or dry tetrahydrofuran. Addition of the brominated steroid substrates resulted in rapid, high-yield conversion to the trimethyltin-substituted steroids at room temperature. The structures of the steroids prepared in this manner are shown in Fig. 1 and include the following structural modifications: I, 24-(trimethyl stanna)-chol-5-en-3β-ol (analog of cholesterol); II, 3β-methoxy-24-(trimethyl stanna)-chol-5-ene (hydrophobic C-3 substituent); III, 23-(trimethyl stanna)-5α-cholan-3β-ol (saturated nucleus containing the *trans* A/B ring juncture); IV, 23-(trimethyl stanna)-5β-cholan-3α-ol (saturated nucleus containing the *cis* A/B ring juncture); and V, 17β-[(trimethyl stanna) methyl]-androst-5-en-3β-ol (short sidechain). In the next quarter, the ^{117m}Sn-labeled steroids will be prepared, and tissue distribution experiments will be performed in rats in an attempt to define the important structural features required for the adrenal uptake of such compounds.

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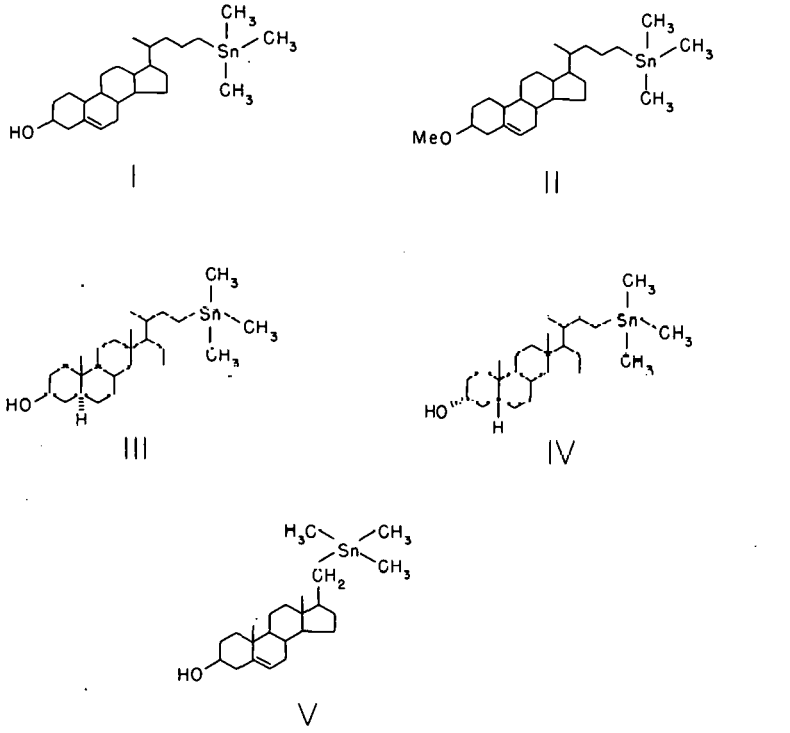

Fig. 1. The structure of steroids containing the trimethyltin moiety in the sidechain: I, 24-(trimethyl stanna)-chol-5-en-3β-ol; II, 3β-methoxy-24-(trimethyl stanna)-chol-5-ene; III, 23-(trimethyl stanna)-24-nor-5α-cholan-3β-ol; IV, 23-(trimethyl stanna)-24-nor-5β-cholan-3α-ol; V, 17β-[(trimethyl stanna)methyl]-androst-5-en-3β-ol.

TELLURIUM-123*m*

F. F. Knapp, Jr. and K. R. Ambrose

We have continued our studies with ^{123m}Te-labeled-9-telluraheptadecanoic acid. An extensive tissue-distribution study in rats was completed for periods ranging from 2 minutes to 7 days after injection of the radiolabeled agent. The results (Fig. 2) indicate that the rapid heart uptake of radioactivity remains high for at least an hour after injection. The implications of these results are discussed in detail under the *Selenium-75* section of this report *(vide post)*.

In earlier studies (ORNL/TM-6638), we had investigated the effect of structure on heart uptake in rats of a variety of ^{123m}Te-labeled

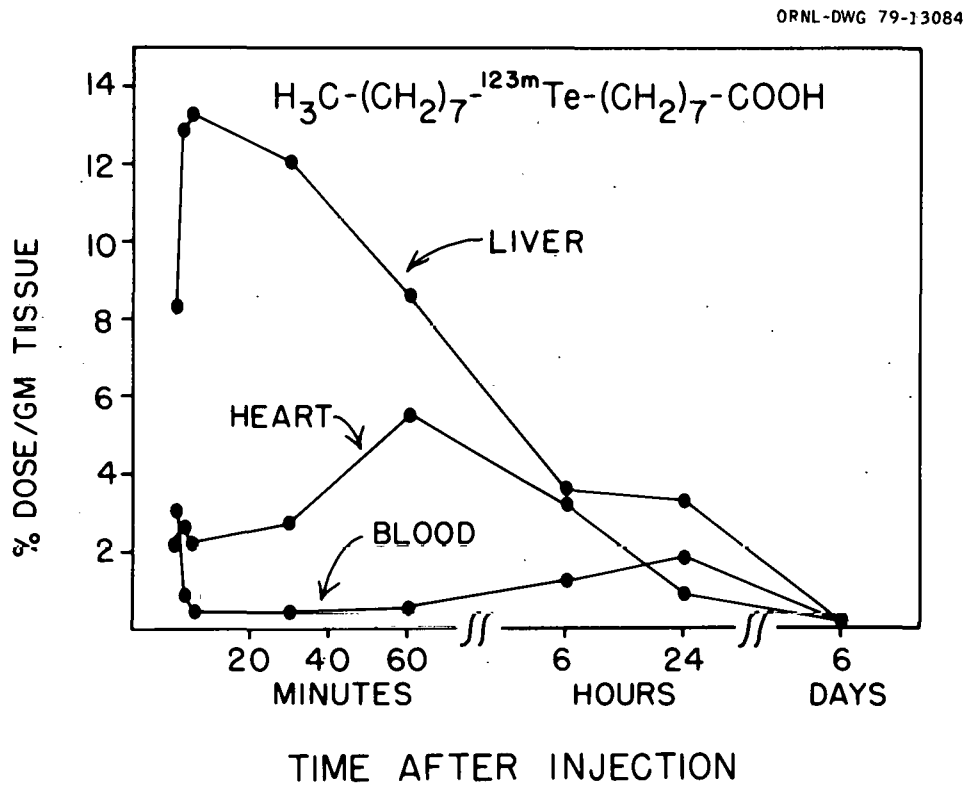

Fig. 2. Tissue distribution of radioactivity following intravenous administration of ^{123m}Te-labeled 9-telluraheptadecanoic acid to rats.

telluro fatty acids. The structural variations included compounds in which both the total chain length and the position of the tellurium heteroatom were altered. The results of these studies indicated that while ^{123m}Te-labeled 9-telluraheptadecanoic acid showed significant heart uptake, the radiolabeled 6-telluraheptadecanoic acid did not. It was not clear from these results if the decreased heart uptake of the latter compound was a result of the shorter chain length or the altered position of the tellurium heteroatom. For these reasons, we have now studied the tissue distribution of the following three ^{123m}Te-labeled fatty acids: 9-telluratridecanoic acid (I), 11-telluraheptadecanoic acid (II) and 6-telluraheptadecanoic acid (III). Radiolabeled-(I) was prepared by basic hydrolysis of the methyl ester prepared by coupling of sodium butyl tellurol with methyl-8-bromooctanoate, and radiolabeled (II) was similarly generated following coupling of sodium hexyl tellurol with methy-10-bromooctanoate. For these two syntheses and all previously discussed preparations, the tellurols were generated by sodium borohydride reduction of dialkyl ditellurides, which were prepared by alkyl halide alkylation of sodium ditelluride generated in liquid ammonia. Because of the insolubility of n-alkyl iodides larger than octyl iodide in this medium, an alternative method was required for the synthesis of diundecyl ditelluride used for the synthesis of (III). The diundecyl ditelluride was prepared by a simple method involving undecyl iodide alkylation of sodium ditelluride prepared by the reaction of sodium metal with tellurium in ethylene-diamine (R. A. Grigsby and K. J. Irgolic, personal communication). The details of this method of preparation of sodium ditelluride will be described in a future report. Methyl-6-telluraheptadecanoate was

prepared by coupling sodium undecyl tellurol with methyl-5-bromo-pentanoate and then converting to the free acid (III) by basic hydrolysis.

The results of tissue distribution studies with these three ^{123m}Te-labeled fatty acids are illustrated in Figs. 3-5. While 9-telluratridecanoic acid did not show pronounced heart uptake (Fig. 3), the 6-tellura- and 11-tellura isomers of 9-telluraheptadecanoic acid showed significant heart uptake (Figs. 4 and 5). These studies indicate that total chain length is more important than the position of the tellurium heteroatom for heart uptake of ^{123m}Te-labeled fatty acids. Furthermore, the pronounced heart uptake originally observed with ^{123m}Te-labeled 9-telluraheptadecanoic acid must not simply result from the isosteric similarity between this compound and oleic acid as was originally suggested.

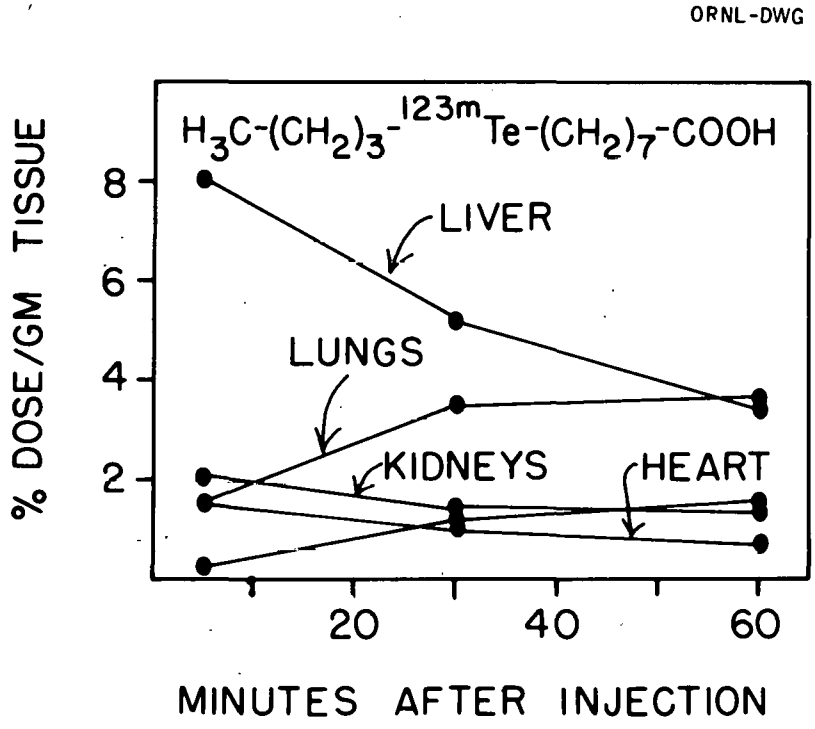

Fig. 3. Tissue distribution of radioactivity following intravenous administration of ^{123m}Te-labeled 9-telluratridecanoic acid to rats.

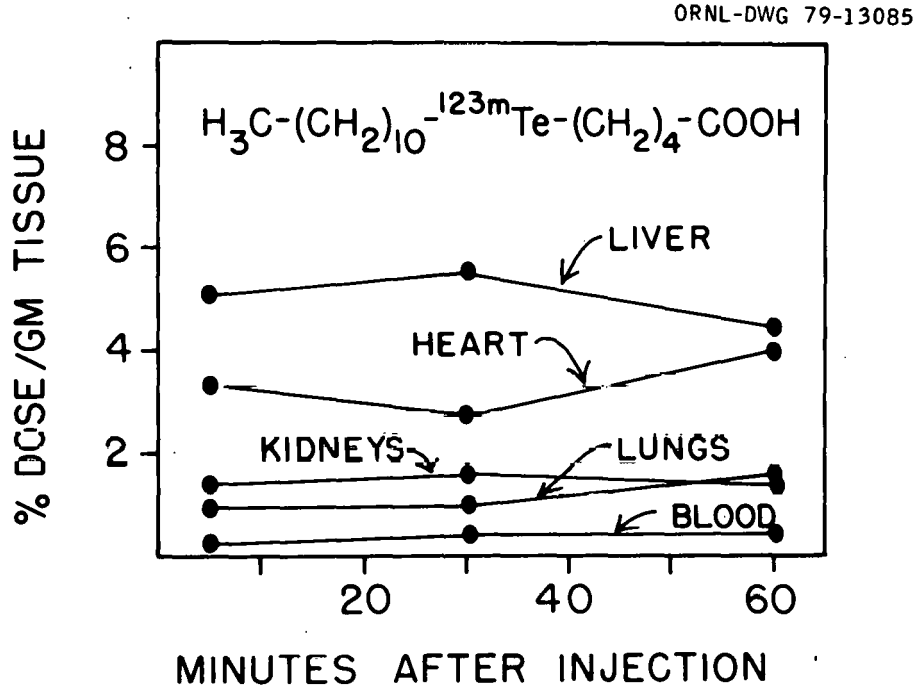

Fig. 4. Tissue distribution of radioactivity following intravenous administration of ^{123m}Te-labeled 6-telluraheptadecanoic acid to rats.

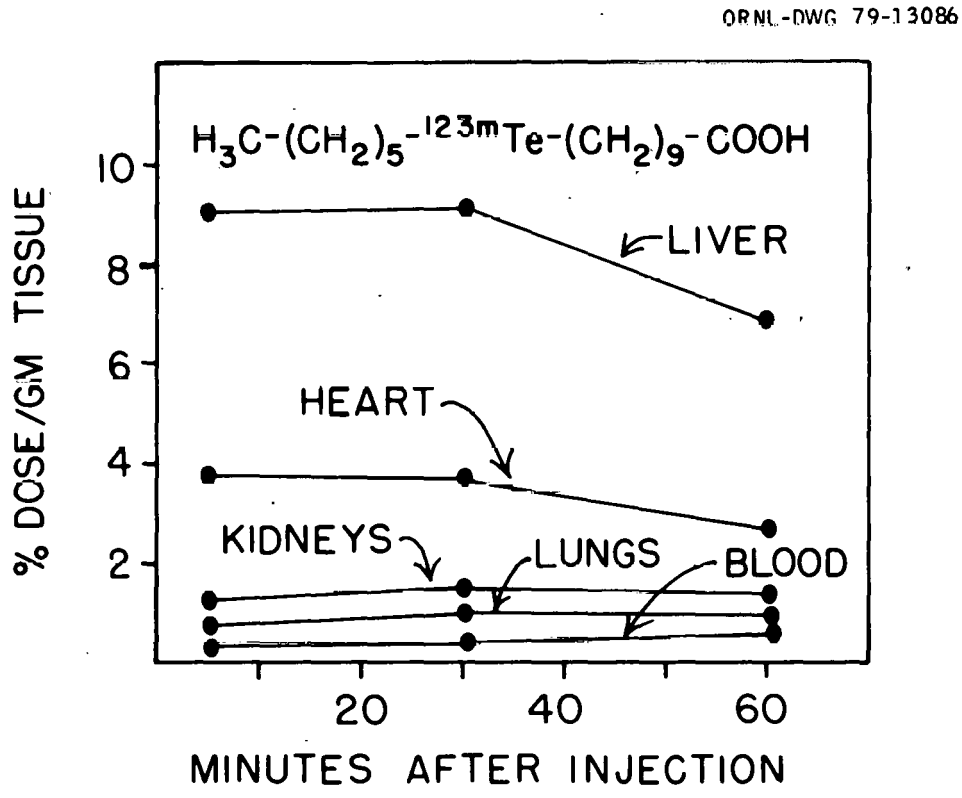

Fig. 5. Tissue distribution of radioactivity following intravenous administration of ^{123m}Te-labeled 11-telluraheptadecanoic acid to rats.

SELENIUM-75

F. F. Knapp, Jr., T. A. Butler, and K. R. Ambrose

In ORNL/TM-6638, we described in detail the development of ^{123m}Te-labeled fatty acids as a unique class of potential myocardial-imaging agents. Tissue distribution studies with ^{123m}Te-labeled 9-telluraheptanoic acid demonstrated pronounced heart uptake of radioactivity following the intravenous administration of this agent in rats *(vide ante)*. More recently, rat hearts have been clearly imaged following injection of ^{123m}Te-labeled 9-telluraheptadecanoic acid (ORNL/TM-6639). Because of the relative instability of the radiolabeled telluro fatty acids, we have now initiated a series of experiments to investigate the effect of structure on heart uptake of ^{75}Se-labeled fatty acids. Although the radionuclidic properties of ^{75}Se are not as attractive as those exhibited by ^{123m}Te, the anticipated greater stability of the seleno fatty acids coupled with the potential use of ^{73}Se-labeled fatty acids for tomographic imaging of the myocardium has stimulated our interest in preparing and studying such compounds. Since extensive studies have been completed on ^{123m}Te-labeled 9-telluraheptadecanoic acid, we chose to prepare ^{75}Se-labeled 9-selenaheptadecanoic acid as the initial member of this potentially useful class of compounds. Methyl-9-selenaheptadecanoate [H_3C-$(CH_2)_7$-Se-$(CH_2)_7$-COOMe] was prepared in high yield by coupling excess sodium octyl selenol with methyl-8-bromooctanoate in the usual manner. The methyl ester was fully characterized by the usual series of spectral measurements and was converted to 9-selenaheptadecanoic acid by ethanolic basic hydrolysis. While 9-tellurahepta-

decanoic acid readily decomposes after formation, the 9-selenaheptadecanoic acid is much more stable and can be handled for several hours after generation. Detailed studies of the stability of seleno fatty acids are now in progress. The ^{75}Se-labeled 9-selenaheptadecanoic acid was prepared in the same manner by using ^{75}Se-labeled diooctyl diselenide, which was generated by octyl iodide alkylation of the radiolabeled sodium diselenide. The results of tissue distribution studies in rats (Fig. 6) indicated significant heart uptake of radioactivity after intravenous administration of ^{75}Se-labeled 9-selenaheptadecanoic acid. The concentration of radioactivity in the heart tissue, however, was not as pronounced as that found following injection of ^{123m}Te-9-telluraheptadecanoic acid. This result was unexpected in light of the greater chemical sta-

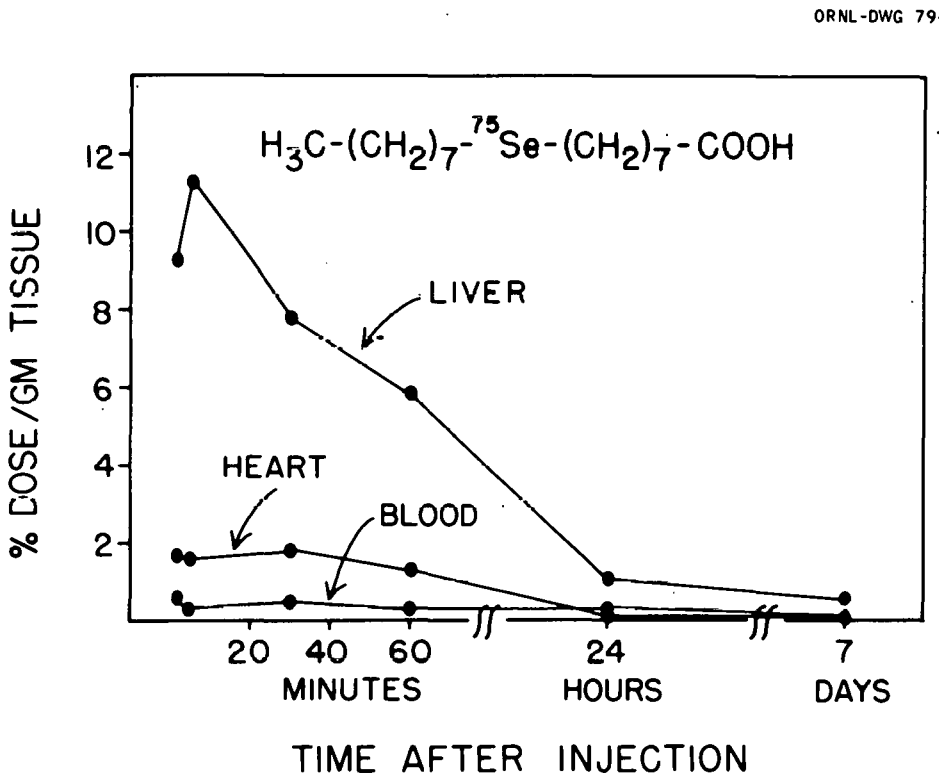

Fig. 6. Tissue distribution of radioactivity following intravenous administration of ^{75}Se-labeled 9-selenaheptadecanoic acid to rats.

bility of the seleno fatty acid and may indicate that the telluro and seleno fatty acids are not metabolized similarly, as was originally expected. In addition, maximal heart uptake of the seleno fatty acids may be exhibited by an isomer of 9-selenaheptadecanoic acid. In the next quarter, a series of ^{75}Se-labeled fatty acids will be prepared and tested in rats.

The results of tissue distribution studies with the radiolabeled 9-selena- and 9-telluraheptadecanoic acids have demonstrated that the significant levels of radioactivity in the heart remain relatively constant over at least the first hour after intravenous administration of these agents. In contrast, the initial pronounced heart uptake of alkanoic acids such as ^{11}C-labeled palmitic acid and radioiodinated ω-iodoheptadecanoic acid rapidly decreases as the radioactivity "washes out" of the heart tissue. The presence of the selenium or tellurium heteroatom appears to increase the residence time of such fatty acids in the heart tissue. This finding could be of considerable importance in the design of new radiolabeled fatty acids for myocardial imaging studies since one could envision the preparation of ^{11}C-labeled or terminally radioiodinated fatty acids containing either stable selenium or tellurium in the fatty acid alkyl chain. The presence of the heteroatom would presumably increase the residence time of the radiolabeled fatty acids in the heart tissue resulting in longer counting periods during which greater diagnostic information could be obtained. During the next quarter, synthetic strategies will be developed for the preparation of such compounds.

As a result of our continuing interest in the potential use of the 7.1 hr half-life ^{73}Se positron emitter for tomographic imaging of the adrenal glands, we have prepared ^{75}Se-24-(isopropyl seleno)-chol-5-en-3β-ol by the reaction of ^{75}Se-labeled isopropyl selenol with 3β-acetoxy-24-bromo-chol-5-ene. Tissue distribution studies with this new agent in rats demonstrated significant adrenal uptake within 24 hr after administration (Fig. 7).

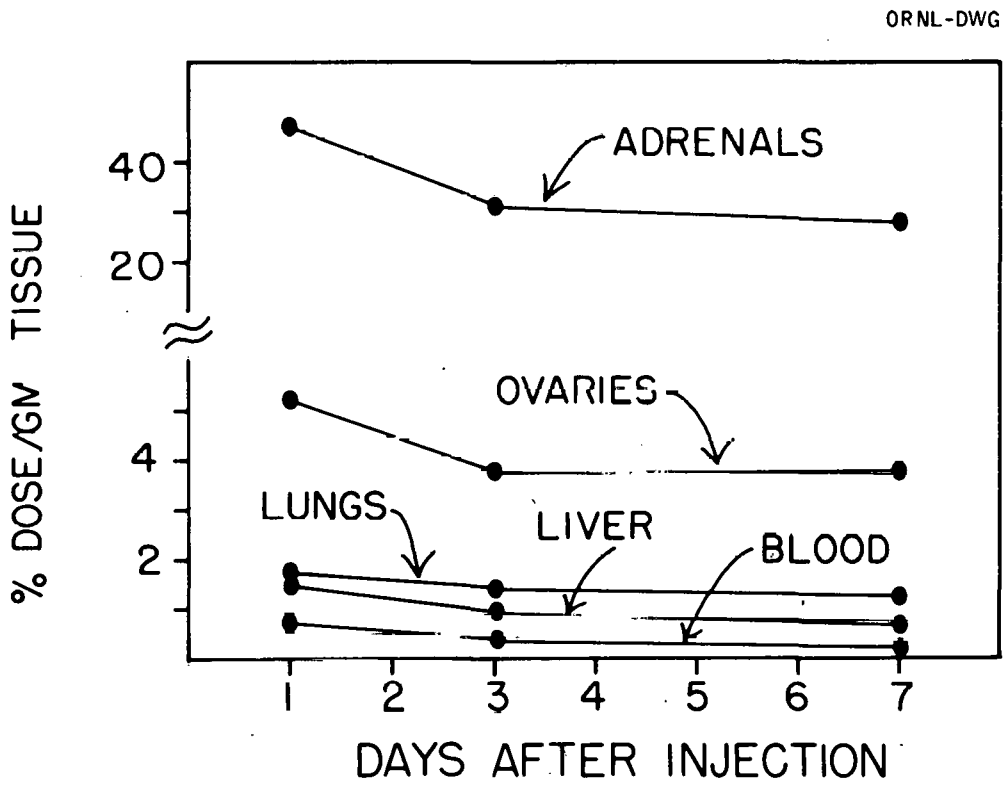

Fig. 7. The distribution of radioactivity in rat tissues following intravenous administration of ^{75}Se-labeled 24-(isopropyl seleno)-chol-5-en-3β-ol.

RADIONUCLIDES FOR MEDICAL COOPERATIVE PROGRAMS

F. F. Knapp, Jr., J. D. Hoeschele, and T. A. Butler

Carbon-11

Four ^{11}C production runs were made for the Medical Cooperative Program with Oak Ridge Associated Universities (ORAU) to study the application of ^{11}C-labeled amino acids for tumor localization and pancreas imaging in human patients. Preparations of ^{11}C-DL-valine, ^{11}C-DL-tryptophan, and ^{11}C-1-aminocyclobutanecarboxylic acid (^{11}C-ACBC) were utilized in 12 human patient studies at ORAU using positron emission tomography for organ visualization. The results of these studies definitely indicated that ^{11}C-DL-tryptophan was superior to ^{11}C-DL-valine as a pancreatic imaging agent in these human subjects. Carbon-11-labeled carbon monoxide was also prepared during this quarter for preclinical inhalation studies in dogs at ORAU.

Nitrogen-13

As part of our continuing Medical Cooperative Program with ORAU to study the application of short-lived positron emitting radionuclides in nuclear medicine, ^{13}N ($T_{1/2}$ = 10 min) was prepared for the first time in the ORNL 86-inch cyclotron by the $^{16}O(p,\alpha)^{13}N$ nuclear reaction and converted to $^{13}NH_3$, which is an attractive candidate for tomographic heart imaging applications. Two cyclotron runs resulted in 45 mCi and 90 mCi products, which were used by ORAU to scan successfully the hearts of two dogs.

Platinum-195*m*

Three shipments of ^{195m}Pt-labeled Na_2PtCl_6 were made to the University of Kentucky Medical Center as part of the continuing Medical Cooperative Program to study platinum antitumor compounds. Three shipments of ^{195m}Pt-labeled *cis*-$[Pt(NH_3)_2Cl_2]$(*cis*-DDP) were made to the University of Southern California. A Medical Cooperative was also established with Dr. S. J. Lippard from the Chemistry Department of Columbia University to investigate the relative nucleosome binding of ^{195m}Pt-labeled *cis*- and *trans*-DDP. Dr. Lippard performed these studies at the Medical Research Council Laboratory of Molecular Biology at Cambridge, England, where he was supplied with two shipments of ^{195m}Pt-labeled *cis*-DDP and one shipment of the radiolabeled *trans*-isomer.

OTHER NUCLEAR MEDICINE TECHNOLOGY GROUP ACTIVITIES

J. D. Hoeschele and F. F. Knapp, Jr. attended the Second International Symposium on Radiopharmaceuticals at Seattle, Washington, on March 19-22.

Visitors for this period included Dr. K. J. Irgolic from the Chemistry Department at Texas A & M University who presented a seminar on March 28 describing the biological formation of various organic compounds of arsenic. A research and development subcontract has been initiated with Dr. Irgolic to investigate the chemical synthesis of organic compounds of tellurium and tin that are of biological interest. On April 16 and 17, R. A. Grigsby, a graduate student with Dr. Irgolic, visited to consult on various aspects of these studies. On March 13,

Dr. A. Oberman, director of the Division of Preventive Medicine at the University of Alabama in Birmingham, was briefed on the research activities of the Nuclear Medicine Technology Program in an effort to explore the possibility of establishing cooperative projects between the two institutions. On March 8, a group of physicians, nurses, and technicians attending an ORAU course entitled *Medical Planning and Care in Radiation Accidents* visited the facilities.

Potassium-43 was supplied to several institutions on a cost-recovery basis. Five shipments of ^{43}K were made to the University of Mississippi Medical Center for coronary disease studies in human patients. In addition, four shipments were made to the V. A. Center at Wood, Wisconsin, for investigations of the potassium uptake in the hearts of stressed rats. Two shipments were made to the Shields Warren Radiation Laboratory of the Harvard Medical School at the Children's Hospital Medical Complex at Boston, Massachusetts, for microdosimetric studies. Single shipments were also made to the National Institute for Environmental Health Sciences at Research Triangle Park, North Carolina, and the University of Connecticut Health Center.

PAPERS AND PUBLICATIONS

Papers

J. D. Hoeschele, T. A. Butler, and J. A. Roberts, "Microscale Synthesis and Biodistribution Studies of Pt-195*m*-Labeled *Cis*-Dichlorodiammine-platinum (II), *cis*-DDP," 2nd International Symposium on Radio-pharmaceuticals, Seattle, Washington, March 19-22, 1979.

F. F. Knapp, Jr., K. R. Ambrose, A. P. Callahan, R. A. Grigsby, and K. J. Irgolic, "Te-123*m*-Labeled Isosteres of Palmitoleic and Oleic Acids Show High Myocardial Uptake," 2nd International Symposium on Radiopharmaceuticals, Seattle, Washington, March 19-22, 1970.

D. V. Woo, F. F. Knapp, Jr., A. P. Callahan, and T. A. Butler, "An Efficient Microscale Preparation of Sn-117*m*-Tin Tetrachloride-A Pivotal Intermediate for the Synthesis of Sn-117*m*-Labeled Radiopharmaceuticals," 2nd International Symposium on Radio-pharmaceuticals, Seattle, Washington, March 19-22, 1979.

Publications

J. D. Hoeschele, T. A. Butler, and J. A. Roberts, "Microscale Synthesis and Biodistribution Studies of Pt-195*m*-Labeled *Cis*-Dichloro-diammineplatinum(II), *Cis*-DDP," *Am. J. Roentgenol.*, 132, 488, 1979 (Abstract).

F. F. Knapp, Jr., "Telluroamino Acids-The Synthesis of Telluromethionine," *J. Org. Chem.*, 44, 1007, 1979.

F. F. Knapp, Jr., "The Modified Hunsdiecker Degradation of Bile Acids and Related Compounds," *Steroids*, 33, 245, 1979.

F. F. Knapp, Jr., K. R. Ambrose, A. P. Callahan, R. A. Grigsby, and K. J. Irgolic, "Tellurium-123*m*-Labeled Isosteres of Oleic and Palmitoleic Acids Show High Myocardial Uptake," *Am. J. Roentgenol.*, 132, 487, 1979 (Abstract).

D. V. Woo, F. F. Knapp, Jr., A. P. Callahan, and T. A. Butler, "An Efficient Microscale Preparation of Sn-117*m*-Tin Tetrachloride -- A Pivotal Intermediate for the Synthesis of Sn-117*m*-Labeled Radiopharmaceuticals," *Am. J. Roentgenol.*, 132, 487, 1979 (Abstract).

Reports

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