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FOR QUARTER ENDING JUNE 30, 1989

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SUMMARY

In this report the development of a simple and inexpensive spectrophotometric technique to determine the specific activity of spallation-produced copper-67 (Cu-67) is described. The method is based upon the well-known strong absorption at 480 nm of the orange-colored copper(II) complexes with bis-thiosemicarbazone (TSC) ligands. We have used the Cu(II) complex of phenylglyoxal (PC-TSC) and determined a calibration curve in an acidic ethanol-acetate buffer which is linear up to a concentration of 40 ppm (40 $\mu\text{gm/ml}$) with a lower limit of detection of about 0.4 ppm.

Also in this report, the results of the synthesis and tissue distribution in fasted rats of a series of five analogues of 3,3-dimethyl-substituted terminal para-iodophenyl fatty acids to determine the effects of total chain length on myocardial uptake and retention properties are summarized. The C-11, C-12, C-13, C-14, C-15 (3,3-DMIPP) and C-19 analogues were evaluated. The C-15 analogue showed the highest heart uptake. The shorter C-11 \rightarrow C-14 and the C-19 chain lengths showed much lower heart uptake and heart:blood values. These studies clearly demonstrate that the position of dimethyl-branching and the total chain length are both important factors which affect myocardial uptake.

During this period several shipments of iodine-125-labeled agents were made to collaborators including the iodopentenylspiropiperidol analogue to H. Kung, Ph.D., at the University of Pennsylvania for dopamine receptor uptake studies, and several fatty acid analogues to J. Kropp, M.D., in Bonn, West Germany, and F. Visser, M.D., in Amsterdam, The Netherlands. In addition, several substrate mixtures for preparation of iodine-123 fatty acids were made to R. Patterson, M.D., at the Cardiology Department, Crawford Long Hospital of Emory University in Atlanta, for evaluation of uptake in "stunned" myocardium in an open chest canine model. Platinum-195m-labeled *cis*-dichlorodiammineplatinum(II) was prepared and distributed on a cost-recovery basis through the ORNL Isotope Distribution Office (IDO).

DEVELOPMENT OF A SIMPLE COLORIMETRIC ASSAY TO DETERMINE THE SPECIFIC ACTIVITY OF COPPER-67

Copper-67 (Cu-67), one of several radionuclides of interest for radionuclide therapy, is available through high energy (spallation) cyclotron production at Brookhaven National Laboratory (BNL)¹ and Los Alamos Scientific Laboratory (LASL). There is widespread interest in the use of Cu-67 for various therapeutic applications,²⁻⁴ particularly for radiolabeling tumor-specific antibodies. In fact, patient trials are currently being pursued using Cu-67-labeled tumor specific antibodies.⁵ Toward such applications, a variety of bifunctional approaches are being developed for the attachment of either Cu-67 for therapy or Cu-64 for potential diagnostic applications using positron emission tomography (PET). We have recently described (ORNL/TM-11014) the development of a bifunctional ligand utilizing terminal bis-thiosemicarbazone (TSC) derivatives of short-chain carboxylic acids (Figure 1). While the TSC moiety can be used to bind Cu(II), the carboxyl group can be activated for coupling with the lysine residues in antibodies with radiolabeling yields as high as 40% (ORNL/TM-11043).

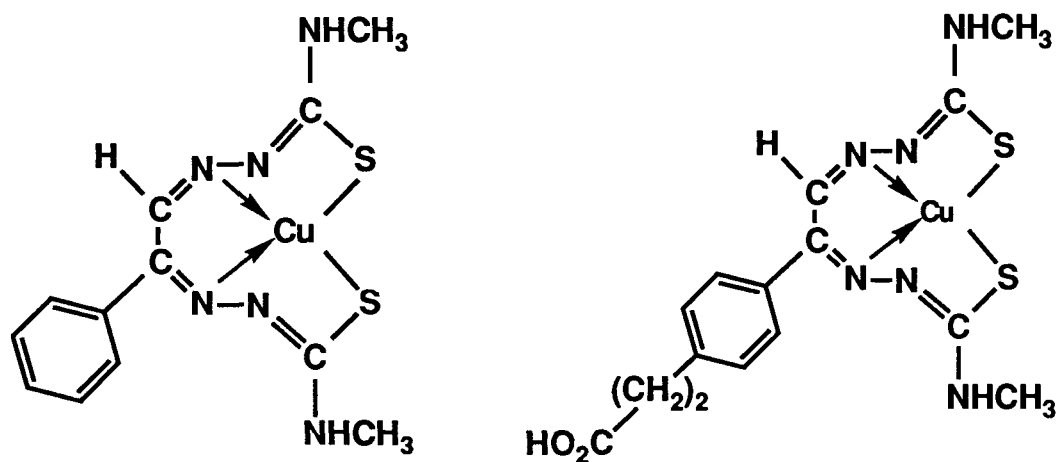


Figure 1.

Because high specific activity Cu-67 is usually required for antibody radiolabeling, we have now developed a simple, and accurate method to estimate the specific activity of Cu-67 by a colormetric technique utilizing a monofunctional TSC chelate (Figure 1). This assay has many advantages over the usual isotope coupling plasma (ICP) and atomic adsorption (AA) techniques which can be expensive, require special sample preparation, and require a long decay period before analysis, since only low levels of radioactivity can normally be analyzed. Our new method utilizes the formation of orange-colored complexes of Cu(II) with the organic bis-thiosemicarbazone (TSC) complexes. We have adapted this process using a reagent which is the TSC derivative of phenylglyoxal (Figure 1). While the TSC reagent exhibits a principal adsorption in the ultraviolet region at 350 nm, the Cu(II) chelate exhibits a strong adsorption at 480 nm (Figure 2; Spectra in ethanol-HCl-acetate buffer of A = Cu(II)PG-TSC chelate, B = Zn(II) PG-TSC chelate, C = PG-TSC ligand). Thus, excess ligand can be used to bind all of the Cu(II) added to the test solution and the adsorption of the reagent does not interfere with the 480 nm adsorption. Evaluation of

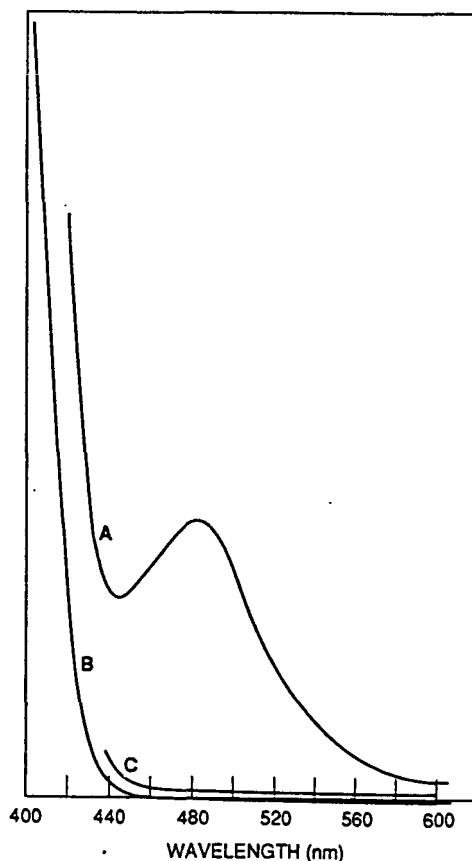


Figure 2.

standards (Figure 3) demonstrates that the calibration curve ($r = >0.99-1.00$) is linear up to about 40 $\mu\text{g}/\text{mL}$ (40 ppm). The lower limit of detection is about 0.4 ppm using a 1 cm path length cell with a Carey 219 spectrophotometer. An additional important feature is our demonstration of no interference at 480 nm from the presence of up to 100 equivalents of zinc(II) chloride, which is important since Zn is the spallation target and is known to be an impurity in the Cu-67 solutions. The radioactive Cu(II) solutions are supplied in 2 N HCl and the samples can be measured directly by simply adding to the reagent and reading the adsorbance at 480 nm after several minutes.

The next stage of our studies will be the evaluation of Cu-67 samples produced at BNL and LASL to determine the expected usefulness of this method. The availability of this simple technique should allow the rapid, inexpensive analysis of Cu(II) solutions with readily available reagents, using a simple spectrophotometer without any sample preparation.

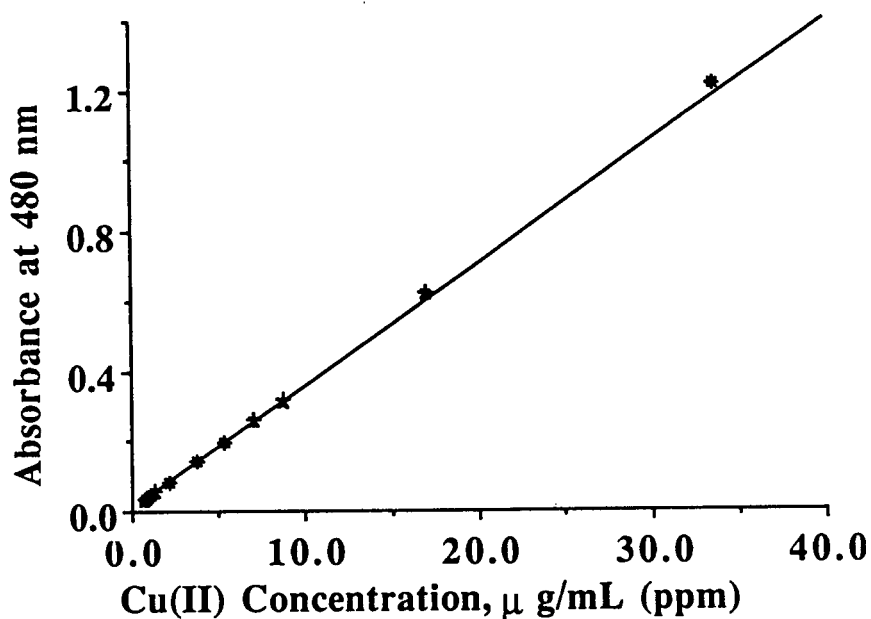


Figure 3.

EFFECTS OF TOTAL CHAIN LENGTH ON THE MYOCARDIAL UPTAKE AND
RETENTION KINETICS IN RATS OF 3,3-DIMETHYL-BRANCHED TERMINAL
p-[I-125]IODOPHENYL-SUBSTITUTED FATTY ACIDS

Since our original demonstration that the introduction of the 3-methyl group in 15-(p-iodophenyl)pentadecanoic acid (IPPA) to form 15-(p-iodophenyl)-3-R,S-methyl-pentadecanoic acid (BMIPP) results in considerable decrease in the rate of myocardial clearance (ORNL/TM-9343), we have also investigated the effects of geminal 3,3-dimethyl-substitution (DMIPP, Figure 4) and found that this structural change resulted in even more marked retention with similar myocardial extraction and subsequent heart:blood ratios as with BMIPP (ORNL/TM-9609 and -10082).⁶

The goal of these studies is to optimize the structural features which would result in prolonged retention by investigating the effects of the position of dimethyl-branching and chain length on uptake and retention. In two earlier reports, we had described the effects of the position of geminal dimethyl-branching on the heart uptake and retention of iodine-125-labeled terminal 15-(p-iodophenyl)pentadecanoic acid analogues (DMIPP) in rats in vivo (ORNL/TM-10294 and -10377). We found that the 3,3- and 4,4-DMIPP analogues

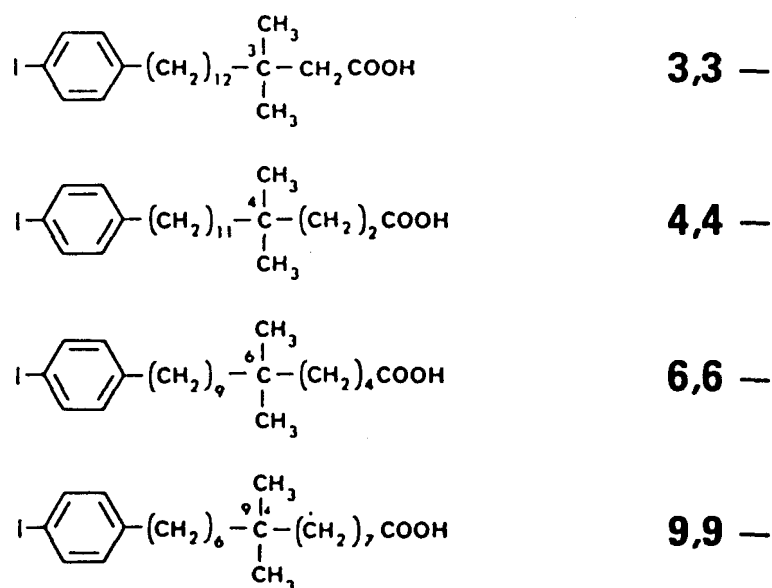


Figure 4.

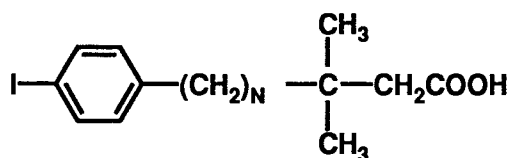
(Figure 4) showed high uptake and good retention while the 6,6- and 9,9-DMIPP analogues showed much lower heart specificity and significantly lower heart:blood ratios (Table 1). These studies demonstrated that the position of dimethyl-branching is an important structural parameter which affects heart uptake in this series of compounds.

Table 1. Comparison of tissue distribution results in Fischer rats with the 3,3-, 4,4-, 6,6-, and 9,9-DMIPP analogues.*

Tissue	Time (min)	Mean values of dimethyl analogues of 15-(p-iodophenyl)pentadecanoic acid			
		3,3-	4,4-	6,6-	9,9-
Heart	5	4.67	7.33	2.36	3.13
	30	5.06	8.03	2.26	3.06
	60	4.49	8.68	1.83	1.90
Blood	5	1.48	0.81	1.40	1.20
	30	0.42	0.48	0.73	1.09
	60	0.36	0.50	0.55	0.90
Lungs	5	2.15	2.02	1.78	1.81
	30	1.42	1.83	1.26	1.28
	60	1.17	1.85	0.92	1.17
Mean Heart: Blood Ratios	5	3:1	9:1	2:1	3:1
	30	12:1	16:1	3:1	3:1
	60	12:1	17:1	3:1	2:1

*Mean values for five fasted female rats.

As a second aspect of this project, we have now evaluated the effect of total chain length on the heart uptake and retention in rats of five iodine-125-labeled 3,3-dimethyl-substituted terminal p-iodophenyl-substituted fatty acid analogues. The synthesis of these new analogues was initiated in conjunction with Professor Gilbert Kirsch, from the University of Metz, France, during his guest assignment at ORNL during the June-December 1988 period. In this project, the terminal p-iodophenyl- and 3,3-dimethyl-substitution patterns were the same in each molecule allowing an evaluation of the specific contribution of total chain length.

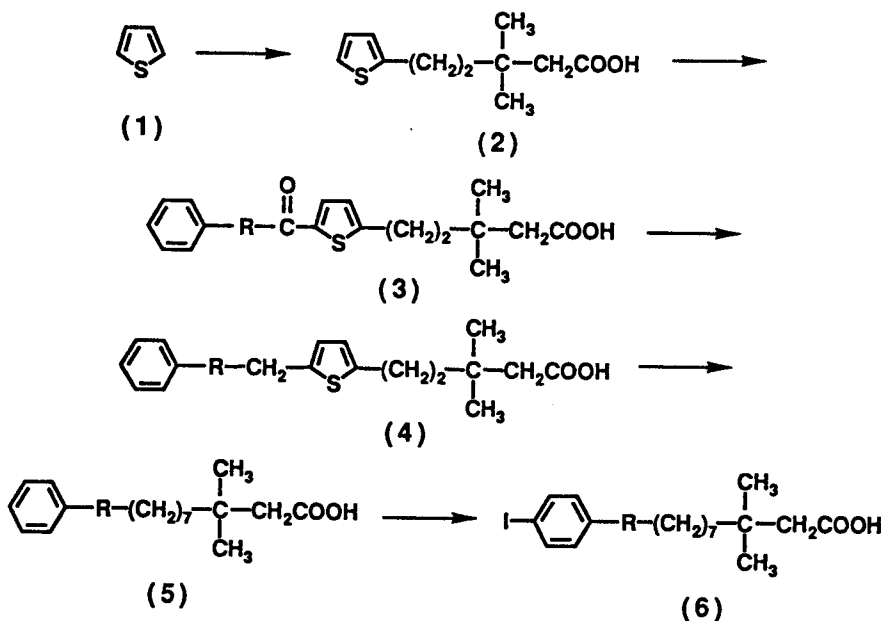


<u>Analogue</u>	<u>N</u>
6a, C-11	8
6b, C-12	9
6c, C-13	10
6d, C-14	11
6e, C-15	12
6f, C-19	16

Figure 5.

Five 3,3-dimethyl analogues (Figure 5) with C-11, C-12, C-13, C-14, C-15 (the original "3,3-DMIPP" analogue reported earlier) and C-19 carbon chain lengths were synthesized from the common 2-(3,3-dimethyl-1-hydroxypentanoyl)thiophene intermediate (2, Scheme I). By choice of the appropriate -phenylalkanoyl chloride, the various analogues were readily prepared by acylation of (2) followed by Wolff-Kishner deoxygenation of the disubstituted thiophene product (3) and sulfur extrusion of (4) with Raney Nickel. Iodine was then introduced into the para-position of (5) by the usual thallation-potassium iodide route to provide the final product (6). The iodine-125-labeled analogues were prepared for tissue distribution studies in fasted rats in the same manner using iodine-125.

The results of tissue distribution studies in fasted female Fischer rats are summarized in Table 2 and demonstrate that total chain length is an important structural parameter. This would be expected from earlier results of studies which evaluated the relative



Scheme I. Synthesis of 3,3-dimethyl-(15-p-iodophenyl)-substituted fatty acid analogues.

extraction of alkanolic acids by arterial-venous differences in vivo. Furthermore, the higher extraction of C-15 analogues with chain lengths similar to natural fatty acids demonstrate that these radioiodinated modified fatty acid analogues mimic natural fatty acids in their uptake. The recent demonstration of the decreased uptake of 3,3-dimethylheptadecanoic acid demonstrate that not only total chain length is an important factor, but that the terminal substitution pattern is also obviously important.⁷ Furthermore, the combined effects of these structural factors cannot be predicted, and empirical evaluation is the only means to determine the optimal combination of structural parameters of any type of analogue. The 3,3- and 4,4-DMIPP analogues exhibit the best heart uptake and heart/blood ratios and appear to be the best candidates for further study.

Table 2. Comparison of tissue distribution data from female Fischer rats following intravenous administration of iodine-125-labeled 3,3-dimethyl terminal (p-iodophenyl)-substituted fatty acid analogues with various chain lengths.*

Tissue	Time (Minutes)	Mean per cent injected dose values \pm SD for each analogue					
		Chain length					
		C-11	C-12	C-13	C-14	C-15	C-19
Heart	5	1.65	1.78	1.15	2.38	4.67	1.91
	30	0.70	1.25	0.47	1.63	5.06	1.29
	60	0.47	0.86	0.42	1.33	4.49	0.88
Blood	5	2.01	4.64	3.30	1.17	1.48	2.08
	30	0.70	1.82	0.52	0.46	0.42	1.57
	60	0.59	1.16	0.35	0.34	0.36	1.10
Liver	5	9.64	5.97	6.96	5.43	8.32	10.21
	30	8.38	5.53	4.21	4.71	3.66	8.82
	60	6.49	4.62	3.43	3.57	1.92	7.95
Lungs	5	1.80	2.22	1.91	1.64	2.15	1.31
	30	0.75	1.29	0.62	0.74	1.42	1.19
	60	0.54	0.87	0.44	0.62	1.17	0.87
Mean Heart: Blood Ratio	5	0.82:1	0.38:1	0.35:1	2.03:1	9.01:1	0.92:1
	30	1.00:1	0.68:1	0.90:1	3.54:1	16.70:1	0.82:1
	60	0.79:1	0.74:1	1.20:1	3.91:1	12.50:1	0.80:1

*Mean values for 5 fasted rats.

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AGENTS FOR MEDICAL COOPERATIVES

One shipment of a new iodine-125-labeled spiroperidol analogue was made to the University of Pennsylvania, Philadelphia, Pennsylvania (Dr. H. Kung). Four shipments of the thallated substrate mixture for preparation of 15-(p-iodophenyl)pentadecanoic acid (IPPA) were sent to Crawford Long Hospital, Atlanta, Georgia, for evaluation of the use of iodine-123-labeled fatty acids to identify salvaged myocardial zones in a reperfused canine heart model (Dr. R. Patterson). One shipment each of [I-125]BMIPP was made to the University of Bonn, West Germany (Dr. J. Kropp), and Amsterdam, The Netherlands (Dr. F. Visser). Dr. Visser also received a shipment of [I-125]DMIPP and two shipments of [I-131]IPPA for studies of fatty acid metabolism in an ischemic canine heart model. On a cost recovery basis, one shipment each of [Pt-195m]-cis-DDP was made to the University of Utah, Duke University, New York Medical Center, and Ram Bam, Israel.

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Callahan, A. P., Rice, D. E., and Knapp, F. F., Jr. "Rhenium-188 for Therapeutic Applications from an Alumina-Based Tungsten-188/Rhenium-188 Generator," NucCompact – European/American Communications in Nuclear Medicine, 20:3-6 (1989).

Franken, P. R., Dobbeleir, A., Ham, H. R., Brihaye, C., Guillaume, M., Knapp, F. F., Jr., and Vandevivere, J. "Ultrashort-Lived Iridium-191m from a New Carbon-Based Generator System for Left Ventricular First-Pass Angiocardiology," Journal of Nuclear Medicine, 30: 1025-1031 (1989).

Srivastava, P. C. "New Antibody Radiolabeling Agent Developed," Isotope News, 19: 6-8 (1989).

Patents

Goodman, M. M., and Knapp, F. F., Jr. "Radiohalogenated Branched Carbohydrates," Patent 4,826,966, May 2, 1989.

Knapp, F. F., and Goodman, M. M. "Radioiodinated Dimethyl-Branched Fatty Acids for Heart Imaging," U.S. Patent 4,764,358, Patent Gazette, p. 1331, August 16, 1988.

Srivastava, P. C. "Precursors to Radiopharmaceutical Agents for Tissue Imaging," U.S. Patent 4,764,598, Patent Gazette, p. 1393, August 16, 1988.

Miscellaneous

Davy Lee, Ph.D., a radiochemist from the Institute of Nuclear Energy Research in Lung-Tan, Taiwan, joined the Nuclear Medicine Program in April for a three-month guest assignment through the "Civil Nuclear Cooperative Active Working Agreement" between the U.S. and Taiwan. He worked on the development of a colorimetric assay technique which can be used for the routine determination of the specific activity of copper-67

produced by spallation and radioisotopes of copper reactor produced by the $^{67}\text{Zn}(\text{n,p})^{67}\text{Cu}$ and $^{64}\text{Zn}(\text{n,p})^{64}\text{Cu}$ routes.

Members of the Nuclear Medicine Group recently co-authored an abstract presented at the Fourth International Conference on Monoclonal Antibody Immunoconjugates for Cancer, March 30 - April 1, 1989.

Srivastava, P. C., Kennel, S. J., Allred, J. F., and Buchsbaum, D. J. "Synthesis and Evaluation of Radioiodinated Iodophenylmaleimides as Potential Antibody Radioimmunoconjugates."

F. F. Knapp, Jr., was co-organizer of the "Workshop on Clinical Use of the Iridium-191m from the Carbon-Base Osmium-191/Iridium-191m" at the Cyclotron Research Center at the University of Liege, Belgium, on April 14, 1989. In addition to Liege, he also visited the Institute for Clinical and Experimental Nuclear Medicine at the University of Bonn, West Germany, to review collaborative projects and plan and coordinate various research projects.

Visitors

On June 9, 1989, Jukka Hiltunen from the Reactor Research Institute in Espoo, Finland visited the Nuclear Medicine Group to discuss collaboration on initiating patient studies at several hospitals in Finland with the osmium-191/iridium-191m generator system. On June 19, 1989, J. Kropp, M.D., and Bernd Boelte visited from the Institute for Clinical and Experimental Nuclear Medicine at the University of Bonn, West Germany.

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