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Nuclear Medicine Progress Report for Quarter Ending March 31, 1986

F. F. Knapp, Jr.
K. R. Ambrose
M. M. Goodman
P. C. Srivastava

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Health and Safety Research Division

NUCLEAR MEDICINE PROGRESS REPORT FOR QUARTER ENDING MARCH 31, 1986

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Work sponsored by
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ORNL/TM-9937

CONTENTS

Page

Summary 1

Studies with 15-(p-[^{123}I]Iodophenyl)-3,3-dimethyl-pentadecanoic Acid (DMIPP) 3

Radioiodinated Branched Carbohydrates — Potential New Agents to Evaluate Cerebral and Myocardial Disorders 7

Radioiodinated Brain Imaging Agents — Radioiodinated Meperidine Analogue 10

Agents for Medical Cooperative Programs 13
Osmium-191 13
Iodine-125-Labeled Agents 13
Copper-64 14
Agents Distributed on Cost-Recovery Basis 14
Platinum-195m 14

SUMMARY

Completion of the first clinical studies with the new dimethyl-branched fatty acid [I-123 DMIPP] agent at the Institute for Clinical and Experimental Nuclear Medicine in Bonn, Federal Republic of Germany (S. N. Reske, M.D.) are reported. Single photon emission computerized tomographic (SPECT) studies showed clear myocardial images which were the result of slow myocardial release of DMIPP. These initial studies indicate that this agent represents a new potential technique for delineating regional myocardial fatty acid uptake patterns.

An in vitro analysis of the susceptibility of the 3,3-dimethyl-branched (DMIPP) and 3-monomethyl-branched (BMIPP) analogues, and the parent straight-chain 15-para-iodophenylpentadecanoic acid (IPP) to oxidation by an acyl CoA oxidase enzyme are described. Because of the observed differences in the degree of myocardial retention and the distribution of radioactivity in the various myocardial lipid pools, this study was initiated to assess the inhibitory effect of methyl-branching on beta oxidation. The in vitro assay demonstrated that the straight chain fatty acids which show rapid myocardial washout are also readily oxidized by an acyl CoA oxidase system. In contrast, the methyl-branched fatty acids, which exhibit prolonged retention in vivo, are apparently not oxidized by this system. Thus, the degree of myocardial retention appears to be directly related to the susceptibility to β-oxidation.

Glucose analogues labeled with single photon emitting radionuclides are desirable candidates for measuring brain glucose utilization using SPECT. Because of the attractive radionuclidic properties of iodine-123, a new deoxy-substituted iodovinyl-substituted carbohydrate has been prepared and evaluated in rats with the objective of achieving high brain uptake. The model agent, methyl-2-deoxy-2-(E)-[^{125}I]iodovinyl-2,4,6-O-tri-acetyl-β-D-altropyranoside, was prepared by a 5-step sequence of reactions. The new radioiodinated iodovinyl-branched carbohydrate showed significant brain uptake (2.31% dose/gm at 2 min), and retention (0.78% dose/gm at 60 min) in fed Fischer rats. The new carbohydrate represents the first reported transport of radioiodide stabilized onto carbon of a sugar molecule across the blood-brain barrier.

A new radioiodinated meperidine derivative was prepared to evaluate the potential for using iodine-123-labeled meperidine analogues for brain imaging. A model agent, 1-(E-1-[^{125}I]iodo-1-penten-5-yl)-4-(4-choloro-phenyl)-4-hydroxypiperidine was prepared by sodium-iodide-chloramine-T iodination of a key vinyl boronic acid intermediate. The new radioiodinated iodovinyl meperidine showed high initial brain uptake (2.38% dose/gm at 5 min) in rats followed by a gradual washout (0.58% dose/gm at 60 min). Because of the high initial brain uptake and good brain to blood values (10.3:1 at 5 min) shown with this model agent, an evaluation of additional analogues will be performed.

During the quarter ending March 31, 1986, nine osmium-191, and one copper-64 shipments were made to medical cooperative investigators. In addition, four shipments of radioiodinated fatty acid analogues (I-125-IPPA and I-125-DMIPP) were made to collaborators for collaborative studies at the Free University of Amsterdam and the University of Bonn. Five shipments of platinum-195m-labeled cis-DPP were made on a cost-recovery basis.

****

STUDIES WITH 15-(p-[^{123}I]IODOPHENYL)-3,3-DIMETHYLPENTADECANOIC ACID (DMIPP)

As described in an earlier report (ORNL/TM-9609), introduction of dimethyl-substitution in the 3-position of 15-(p-iodophenyl)pentadecanoic acid (IPP) results in considerably delayed myocardial clearance following peak uptake in rats. The increased retention of 15-(p-iodophenyl)-3,3-dimethylpentadecanoic acid (DMIPP) may result from inhibition of catabolism by the normal β-oxidative pathway at the stage of the β-hydroxy acyl-CoA intermediate (Fig. 1). Oxidation without concomitant cleavage of one carbon-carbon bond, an unexpected process, would not be possible. However, radioactive components with the expected mobility on thin layer chromatography of a β-hydroxy intermediate have not been observed by analysis of lipid extracts from rat heart tissue at various time intervals following intravenous administration of radioiodinated DMIPP (ORNL/TM-9707). Rather than the identification of polar products, the slow conversion to triglyceride storage products has been detected. Thus, it appears that DMIPP enters myocytes in the usual manner and is slowly converted to triglycerides. It is not known why "back diffusion" into the extracellular compartment is not observed despite the prolonged cellular retention of the free acid during slow conversion to storage lipids.

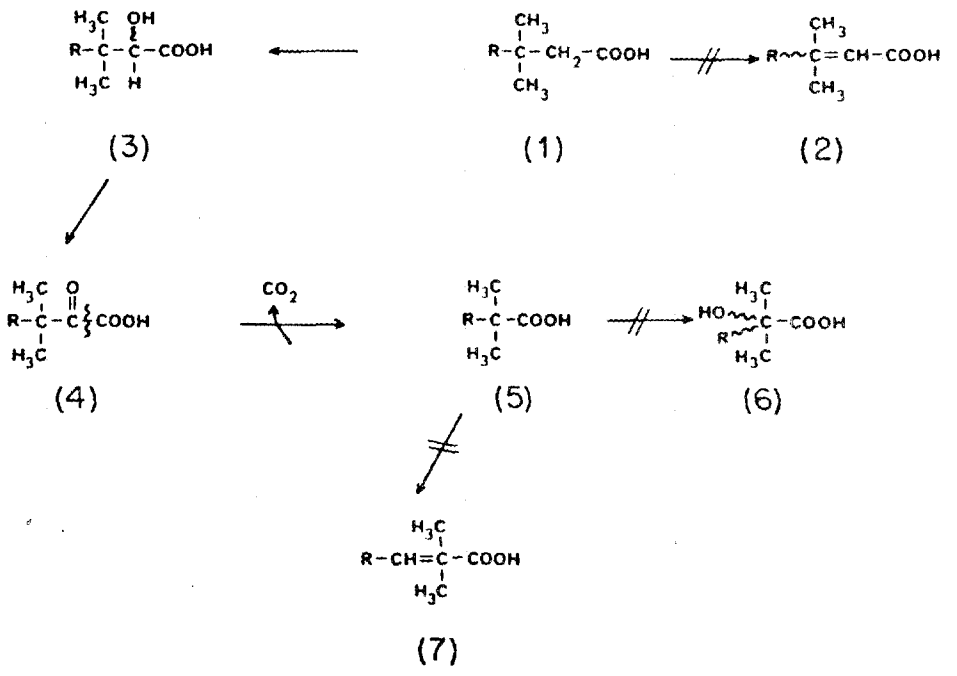


Fig. 1. Expected inhibition of β- and α-oxidation resulting from the presence of geminal dimethyl-substitution.

More recent studies with this new agent have focussed on an analysis of the oxidation of DMIPP with a commercial method ("NEFA C" TM) for the quantitative determination of unesterified fatty acids and the completion of initial clinical trials with [I-123]DMIPP at the Institute for Clinical and Experimental Nuclear Medicine in Bonn, Federal Republic of Germany.

For the fatty acid in vitro enzyme studies, a variety of other fatty acids were analyzed for comparison, including the 3-monomethyl-branched 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) analogue and several straight-chain, unbranched agents. The basis of this test (Fig. 2) involves initial enzymic formation of the fatty acyl CoA

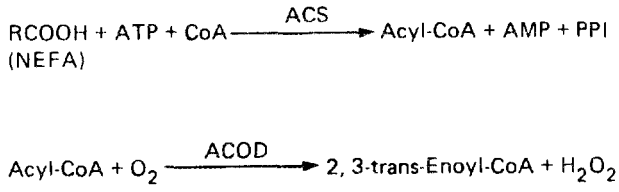


Fig. 2. Activation, oxidation and formation of colored product by treatment of fatty acids with the "NEFA C" test.

derivative by added acyl CoA synthetase followed by oxidation to the enoyl-CoA product by an acyl CoA oxidase enzyme. If oxidation occurs, the hydrogen peroxide product then participates in the presence of peroxidase with the condensation of 3-methyl-N-ethyl-N-β-hydroxylaniline (MEHA) with 4-aminoantipyrine to yield a purple (lilac) colored product with an absorption maximum of 550 nm. Formation of the colored product is directly proportional to the levels of the acyl CoA so free fatty acid levels can be accurately measured by this method. The results of these studies are summarized in Table 1 and clearly demonstrate the inhibitory effect of methyl-substitution in the β-position. This is the first in vitro demonstration of inhibition at this stage of β-oxidation by β-methyl-subsitution.

Table 1. Results of treatment of free fatty acids with the "NEFA C" fatty acid assay test.

Fatty acid	Oxidation index[a]
Straight Chain:	
Oleic	1.23
PPA	0.69
IPP	0.26
IHA	0.49
3-Monomethyl-Branched:	
BMPPA	0.015
BMIPP	0.008
3,3-Dimethyl-Branched:	
DMPPA	0.003
DMIPP	0.006

[a]Relative to μmoles oleic acid standard/ml/50 μgm fatty acid.

Initial patient studies with [I-123]DMIPP have now demonstrated the expected myocardial uptake and prolonged retention as was demonstrated in earlier animal studies (ORNL/TM-9609). These studies have been conducted at the University of Bonn, Federal Republic Germany (S. N. Reske, M.D. and co-workers) and consisted of intravenous administration of [I-123]DMIPP following submaximal exercise for 6 min. The single-photon emission computerized tomographs (SPECT) (~ 6-21 min acquisition) clearly delineated the myocardium (Fig. 3). Background

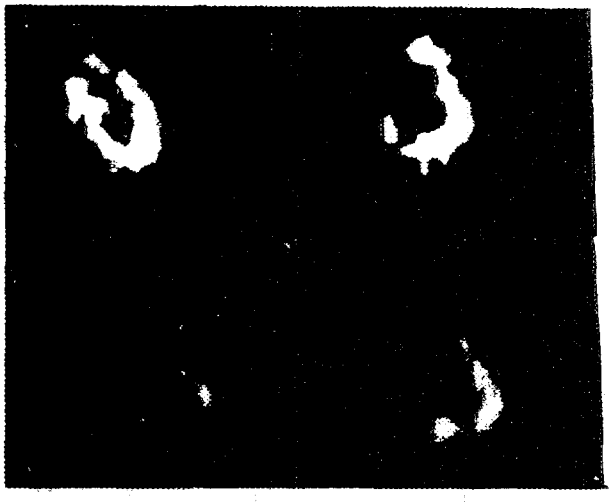


Fig. 3. Transverse single photon tomographic images from the apex to the valve plane in a patient with multi-vessel coronary artery disease after intravenous administration of 1.5 mCi of [I-123]DMIPP (courtesy of S. N. Reske, M.D., University of Bonn, Federal Republic of Germany).

activity, however, did suggest slow plasma clearance. Following a second submaximal exercise and subsequent SPECT acquisition (~ 45-60 min) the myocardium was still clearly shown with better target to non-target ratio (Fig. 3). These studies demonstrate the slow myocardial wash-out of this new agent, suggesting its potential usefulness to measure regional fatty acid uptake patterns.

Blood clearance was also evaluated in four patients from whom serial blood samples were drawn after administration of [I-123]DMIPP. These results (Fig. 4) demonstrate that DMIPP more slowly clears the plasma than was anticipated with a 8-10 min period for clearance to 50% of the maximal value and may explain the background observed in the early SPECT images. The clinical studies with [I-123]DMIPP have also been initiated at the clinical section, Center for Cyclotron Research, University of Liege, Belgium (Drs. C. DeLandsheere and P. Rigo). These collaborative studies in Bonn and Liege are continuing to evaluate the properties and usefulness for evaluating heart function in various patient groups.

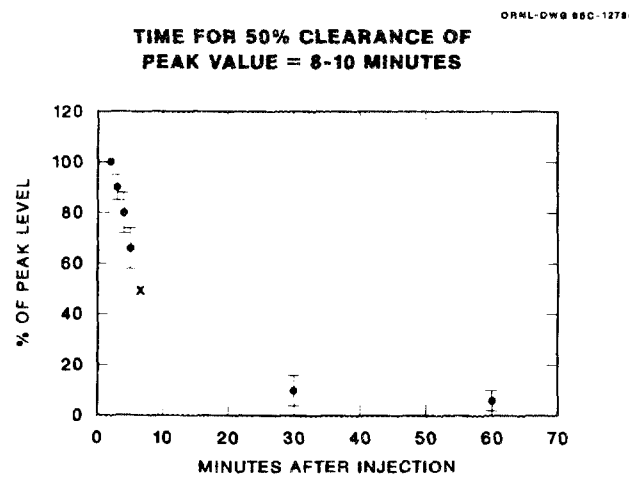


Fig. 4. Plasma clearance of radioactivity following intravenous administration of [I-123]DMIPP to four patients.

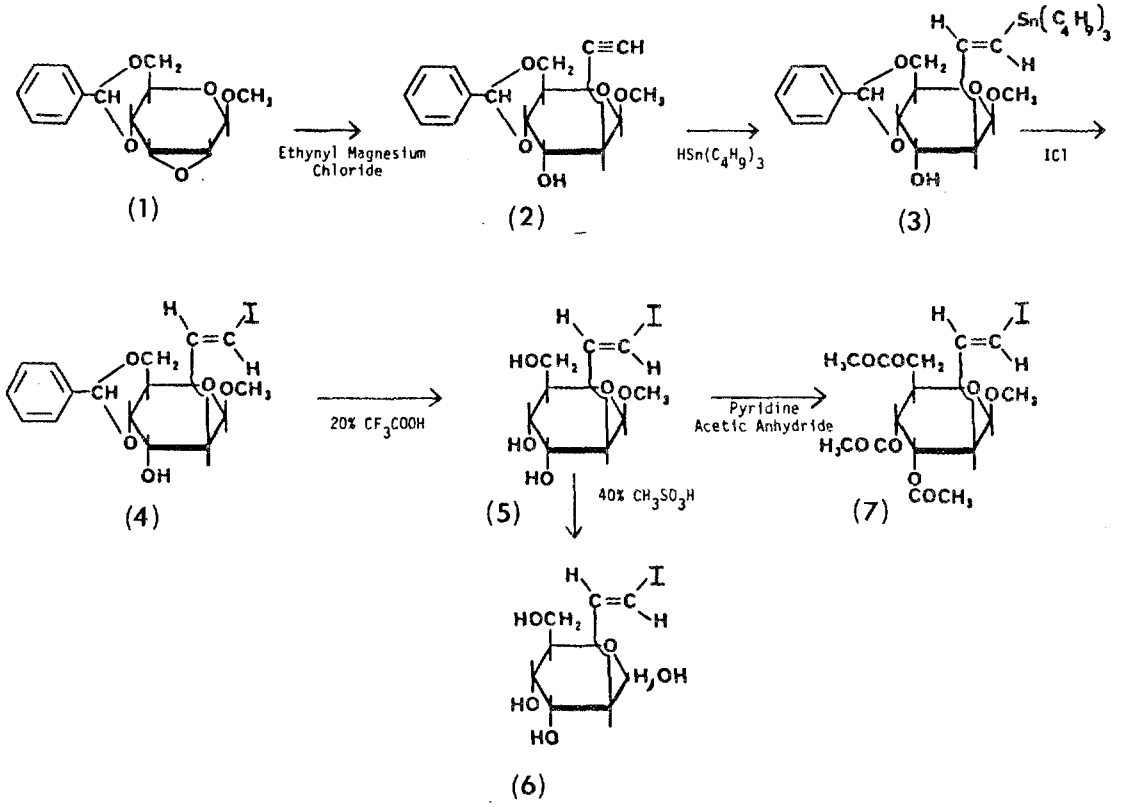
RADIOIODINATED BRANCHED CARBOHYDRATES — POTENTIAL NEW AGENTS TO EVALUATE CEREBRAL AND MYOCARDIAL DISORDERS

Clinical studies using the glucose analogue, 2-[^{18}F]-fluoro-2-deoxy-D-glucose (2-FDG), have shown that the metabolic rate for glucose utilization in the brain varies in patients with pathological disorders.[1-3] In patients with Alzheimers' disease,[4,5] Parkinsons' disease,[6] and dementia,[5,7] 2-FDG shows a characteristic distribution of reduced glucose metabolism in the parietal region of the brain. However, because carbon-11 ($t_{1/2}$ = 20 min) and fluorine-18 ($t_{1/2}$ = 110 min) are short-lived radioisotopes and because only a few regions have clinical institutions with in-house cyclotrons and positron tomorgraphic devices, only a small patient population can utilize these revolutionary diagnostic techniques available from these agents. Radioiodinated glucose analogues are better candidates for widespread clinical use because of the attractive radionuclidic properties of iodine-123, a single photon emitter (159 keV) with a 13.3 h half-life.

Radioiodinated carbohydrates such as 2-deoxy-2-iodo-D-glucose[8] and 3-deoxy-3-iodo-D-glucose[9] undergo facile chemical or in vivo deiodination which precludes their use as radiotracers of glucose metabolism in tissues. To overcome the problems resulting from in vivo deiodination, the concept of stabilizing radioiodide on a model carbohydrate, (E)-C-3-iodovinyl-D-allose[10] as an iodovinyl moiety has been explored (ORNL/TM-9480). This agent did not exhibit brain specificity but showed low in vivo deiodination which demonstrated for the first time that radioiodide can be stabilized on a carbohydrate. The goal of the current study was to develop a deoxy-branched carbohydrate with radioiodide stabilized as a vinyliodide with the objective of achieving high brain uptake.

The model agent methyl-2-deoxy-2-(E)-[^{125}I]iodovinyl-2,4,6-O-tri-acetyl-β-D-altropyranoside (7), was prepared to establish that a deoxy substituted iodovinyl carbohydrate could be delivered to the brain in significant levels with prolonged retention. The synthetic approach for the preparation of the 2-deoxy iodovinyl carbohydrate involved the scission of an anhydro sugar with a Grignard reagent. This versatile

carbon branching technique was chosen because by selecting the position of the anhydro group within the pyranose ring, a variety of 2-deoxy iodovinyl carbohydrates could be prepared. Utilizing this synthetic approach methyl-2-deoxy-2-(E) [^{125}I]iodovinyl-2,4,6-O-triacetyl β-D-altropyranoside was prepared in the sequence of reactions outlined in Scheme I.



Scheme I

In this synthetic approach, methyl-2,3-anhydro-4,6-O-benzylidene-β-D-allopyranoside (1) was treated with ethynylmagnesium chloride to give methyl 4,6-O-benzylidene-2-deoxy-2-ethynyl-β-D-altropyranoside (2).

Hydrostannylation of (2) with tributyl tin hydride [n-$(Bu)_3$-SnH] gave the key intermediate, methyl 4,6-O-benzylidene-2-deoxy-2-(E)-(n-$Bu)_3$SnHC=CH-β-D-altropyranoside (3). Iododestannylation of (3) with sodium iodide and N-chlorosuccinimide gave methyl 4,6-O-benzylidene 2-deoxy-2-(E)-IHC=CH-β-D-altropyranoside (4). Hydrolysis of (4) with 20% trifluoroacetic acid CF_3COOH followed by treatment with pyridine-Ac_2O gave the desired agent (7).

The distribution of radioactivity in tissues of female rats at 2 min, 15 min, 30 min, 45 min, 60 min and 2 h after intravenous administration of [^{125}I]-(7) is shown in Table 2. The level of accumulation of radioactivity in the brain after injection of this agent was significant. After 2 min, 2.31% injected dose/gm was detected in the brain, but the blood levels were also high resulting in brain:blood ratios of 2.18:1. This agent exhibited good brain retention, 0.78% dose/gm at 60 min which is 34% of the peak uptake detected at 2 min. The accumulation of radioactivity in the thyroid was low, only 23.0% at 60 min, which demonstrated the stability of this agent to in vivo deiodination.

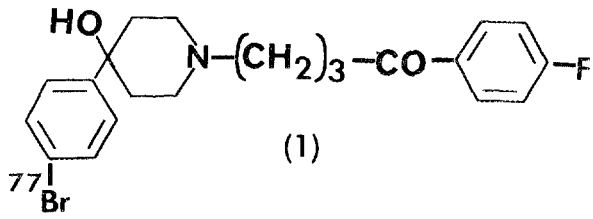
The high brain uptake of methyl 2-deoxy-2-E-iodovinyl-2,4,6-O-triacetyl β-D-altropyranoside (7) most likely results from passive diffusion, since (7) is not a substrate for the carrier system required for active sugar transport across the blood/brain barrier. Nevertheless, the brain delivery of a radioiodinated sugar with radioiodide stabilized as an iodovinyl moiety has been successfully demonstrated with the synthesis of this model agent. A series of iodovinyl deoxy sugars with active D-gluco and D-manno configurations are presently being prepared for biological evaluation.

Table 2. Distribution of radioactivity in rat tissues (% dose/gm) at various times after intravenous administration of [^{125}I]-methyl-2-deoxy-2-(E)-iodovinyl-2,4,6-O-triacetyl-β-D-altropyranoside (7)

Organ	Mean and range (% dose/gm tissue)					
	2 min	15 min	30 min	45 min	1 h	2 h
Blood	1.05 (1.01-1.12)	0.88 (0.82-0.92)	0.82 (0.76-0.90)	0.74 (0.68-0.85)	0.71 (0.64-0.76)	0.48 (0.46-0.53)
Liver	1.49 (1.44-1.59)	1.25 (1.06-1.37)	1.33 (1.20-1.37)	1.32 (1.26-1.39)	1.29 (1.16-1.39)	0.99 (0.92-1.10)
Kidney	1.43 (1.37-1.57)	1.34 (1.21-1.62)	1.72 (1.61-2.00)	1.96 (1.85-2.21)	2.32 (1.95-3.36)	1.82 (1.65-2.04)
Heart	1.27 (1.16-1.41)	1.02 (0.95-1.11)	0.89 (0.75-1.02)	0.82 (0.73-0.93)	0.75 (0.68-0.86)	0.49 (0.44-0.54)
Lung	1.30 (1.13-1.47)	0.95 (0.84-1.05)	0.84 (0.78-0.94)	0.80 (0.70-0.88)	0.73 (0.68-0.81)	0.51 (0.46-0.61)
Thyroid	20.38 (15.60-23.05)	16.06 (12.56-20.22)	15.30 (13.62-17.70)	17.56 (12.90-23.33)	23.02 (20.67-27.68)	25.96 (23.72-29.18)
Brain	2.30 (2.09-2.47)	1.19 (1.02-1.28)	0.97 (0.94-1.04)	0.84 (0.80-0.94)	0.77 (0.72-0.88)	0.49 (0.47-0.53)
Heart/Brain	1.20 (1.10-1.29)	1.15 (1.11-1.21)	1.09 (0.99-1.17)	1.09 (1.06-1.14)	1.06 (0.94-1.14)	1.02 (0.95-1.09)
Brain/Blood	2.18 (1.99-2.36)	1.34 (1.25-1.44)	1.19 (1.15-1.26)	1.13 (1.11-1.22)	1.09 (1.02-1.16)	1.01 (0.99-1.07)

RADIOIODINATED BRAIN IMAGING AGENTS — RADIOIODINATED MEPERIDINE ANALOGUE

[^{77}Br]Bromperidol (1) has been reported to show high brain uptake in rats[11] and meperidine and meperidine analogues show interesting central nervous system (CNS) properties. As a result of the potential use of



(1)

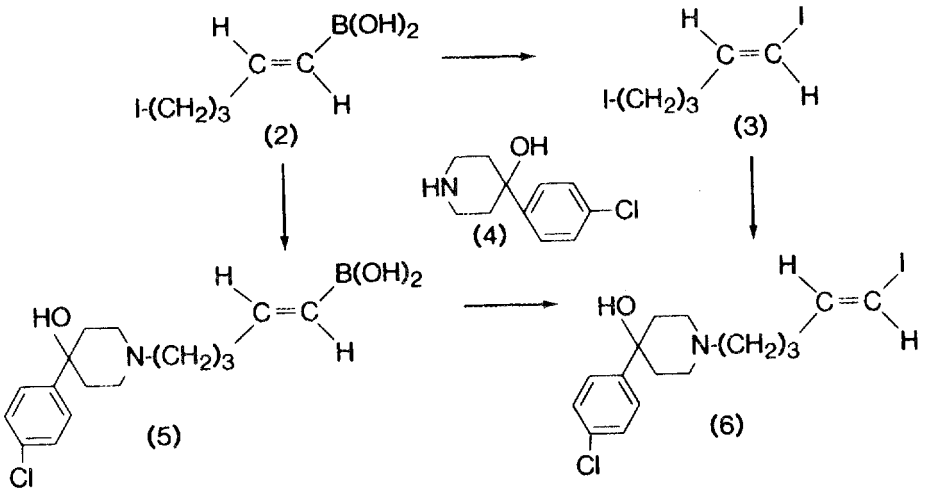
^{123}I-labeled brain imaging agents, the design and evaluation of a model iodine-123-labeled meperidine analogue has now been pursued. Such agents could be useful for brain imaging by single photon emission computerized

tomography (SPECT). For preliminary evaluation, the meperidine analogue, 1-(E-1-[^{125}I]iodo-1-penten-5-yl)-4-(4-chlorophenyl)-4-hydroxypiperidine ([^{125}I]6) has been prepared (Scheme II). The alkylating agent, (E)-1,5-diiodo-1-pentene(3), was prepared by sodium iodide-chloramine-T iodination of the corresponding boronic acid precursor, (E)-1-borono-5-iodo-1-pentene(2), as described earlier (ORNL/TM-8363), and was condensed with 4-(4-chlorophenyl)-4-hydroxypiperidine (4) to yield (6). Alternatively, (6) could be prepared by the direct sodium iodide-chloramine-T iodination of the boronic acid intermediate, 1-((E)-1-borono-1-pentene-5-yl)-4-chlorophenyl-4-hydroxypiperidine (5). The intermediate (5) was prepared in 65% yield by condensing (2) and (4) in boiling 2-butanone for 24 h. The radioiodinated compound ([^{125}I]6) was prepared similarly using Na[^{125}I], following the reaction sequence outlined in Scheme II (2→3→6). The product was purified by silica gel column chromatography and characterized by comparing with the corresponding unlabeled standard by thin-layer chromatography. Tissue distribution studies (Table 3) of iodine-125 labeled (6) in female Fischer rats showed initial high brain uptake and high brain:blood ratios with gradual washout (Fig. 5). These

Table 3. Distribution of radioactivity in tissues of female Fischer rats following intravenous administration of 1-(E)-1-[^{125}I]iodo-1-penten-5-yl)-4-(4-chlorophenyl)-4-hydroxypiperidine ([^{125}I]6).[a]

Time After Injection	Mean percent injected dose/gm (range) Tissue							Mean Brain/Blood
	Brain	Blood	Liver	Kidney	Heart	Lung	Thyroid	
5	2.38 (2.18-2.73)	0.23 (0.22-0.29)	2.28 (1.80-2.68)	3.77 (3.57-4.06)	1.48 (1.24-1.74)	12.30 (11.03-13.51)	12.23 (0.02-17.15)	10.3:1
30	1.27 (1.13-1.44)	0.36 (0.34-0.42)	1.62 (1.36-1.92)	1.45 (1.23-1.73)	0.47 (0.38-0.54)	3.68 (2.91-4.24)	40.66 (26.86-48.31)	3.5:1
60	0.58 (0.50-0.66)	0.46 (0.38-.53)	1.92 (1.85-2.07)	0.86 (0.76-0.99)	0.31 (0.29-0.37)	1.61 (1.35-1.93)	86.67 (71.82-98.83)	1.3:1

[a]Each animal (5 animals per time point) received 13 μCi of [^{125}I]6 by tail vein injection.



Scheme II

data suggest that the preparation of the corresponding iodine-123-labeled (6) for imaging studies in rats and of similar radioiodinated compounds for preliminary evaluation in laboratory animals should be pursued.

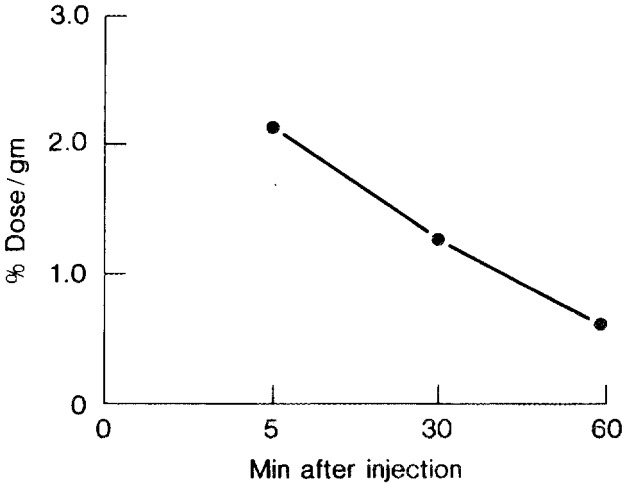


Fig. 5. Gradual washout of radioactivity from rat brains after intravenous injection of ([^{125}I]6).

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AGENTS FOR MEDICAL COOPERATIVE PROGRAMS

Osmium-191

Nine shipments of osmium-191 were made during this reporting period. Three shipments went to Cyclotron Center, Liege, Belgium (Drs. M. Guillaume and C. Brihaye); two shipments each to Massachusetts General Hospital, Boston, MA (Dr. H. W. Strauss); Children's Hospital, Boston, MA (Dr. S. Treves); and The George Washington University, Washington, DC (Dr. B. Wessels).

Iodine-125-Labeled Agents

A total of three shipments of iodine-125-labeled agents as research products were made to collaborators. One shipment each of radio-iodinated fatty acids were made to the Department of Cardiology, Free University Hospital, Amsterdam, The Netherlands (Dr. F. C. Visser); Brookhaven National Laboratory, Upton, NY (Drs. A. B. Brill and P. Som); and Massachusetts General Hospital, Boston, MA (Dr. H. W. Strauss).

Copper-64

One shipment of copper-64 was made to the Oak Ridge Associated Universities (Dr. J. Crook) during this reporting period.

AGENTS DISTRIBUTED ON COST-RECOVERY BASIS

Platinum-195m

Five shipments of ^{195m}Pt-labeled *cis*-dichlorodiammineplatinum(II) (*cis*-DDP) were made on a cost recovery basis. One shipment each was made to the University of Texas Health Science Center, San Antonio, TX (Dr. K. V. Speeg); University of Iowa (Dr. C. P. Burns); University of California, San Diego, CA (Dr. P. Andrews); City of Hope National Medical Center (Dr. K. J. Scanlon); and National Institutes of Health, Bethsda, MD (Dr. C. Litterst).

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