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Nuclear Medicine Progress Report for Quarter Ending December 31, 1986

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

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NUCLEAR MEDICINE PROGRESS REPORT FOR QUARTER ENDING DECEMBER 31, 1986

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SUMMARY

In this report the synthesis of the 4,4'-dimethyl analogue of the model 3,3'-dimethyl fatty acid, 15-(p-iodophenyl)-3,3-dimethylpentadecanoic acid (3,3'-DMIPP), is described. The [I-125]labeled 4,4'-DMIPP was evaluated in fasted rats and surprisingly showed higher myocardial uptake and faster blood clearance than the 3,3'-, 6,6'- and 9,9'-DMIPP analogues [heart(heart:blood), % dose/gm, 30 min: 3,3' = 5.06 (12:1), 4,4' = 8.03 (16.7:1), 6,6' = 2.26 (3.1:1), 9,9' = 3.06 (2.77)]. Since all analogues have the same chain length, differences in tissue uptake and clearance apparently result from the position of geminal dimethyl-branching.

Also described in this report is the development of a "kit" for the rapid, one-step radioiodination of N-(p-iodophenyl)maleimide. This work involved the coupling of 4-aminophenylmercuric acetate with maleic anhydride to give the acid amide which was then ring annulated with sodium acetate to give the N-(p-acetylmercuricphenyl)maleimide "kit." The crystalline kit is readily radioiodinated with $[^*I]I_2$ to give the N-(p-iodophenyl)maleimide protein labeling agent.

During this period several shipments of research products were also made to medical cooperative programs. Four shipments of osmium-191 were made to collaborators in Belgium for fabrication of osmium-191/iridium-191m radionuclide generators for clinical studies. Generators prepared at ORNL were supplied to collaborators at Boston (Dr. Strauss et al.) and Washington, D.C. (Dr. Wessels et al.) for preclinical studies. Radioiodinated methyl-branched fatty acids (Drs. Visser, Amsterdam and Drs. Kropp and Biersack, Bonn, West Germany) and the radioiodinated maleimide agents (Dr. Mills, Philadelphia) were also made for collaborative studies.

EFFECTS OF POSIITON OF DIMETHYL-BRANCHING ON HEART UPTAKE AND RETENTION AND BLOOD CLEARANCE OF DMIPP ANALOGUES

In a recent report (ORNL/TM-10294) the preparation of two model dimethyl-branched analogues of 15-(p-iodophenyl)pentadecanoic acid (IPP), 15-(p-iodophenyl)-6,6'-dimethylpentadecanoic acid (6,6'-DMIPP) and 15-(p-iodophenyl)-9,9'-dimethylpentadecanoic acid (9,9'-DMIPP), were described and preliminary tissue distribution data of the [I-125] 9,9'-DMIPP analogues were presented. The results of the preliminary biological evaluation demonstrated that the 9,9'-DMIPP analogue showed lower heart uptake, more rapid myocardial washout, and higher blood levels than 3,3'-DMIPP, an analogue which has been evaluated in patients (ORNL/TM-10082). These results suggested that the position of dimethyl-branching within the fatty acid chain is an important structural feature which effects the myocardial uptake and clearance kinetics of DMIPP analogues. In order to further study the effects of dimethyl-branching at both odd and even positions of the fatty acid chain on myocardial uptake

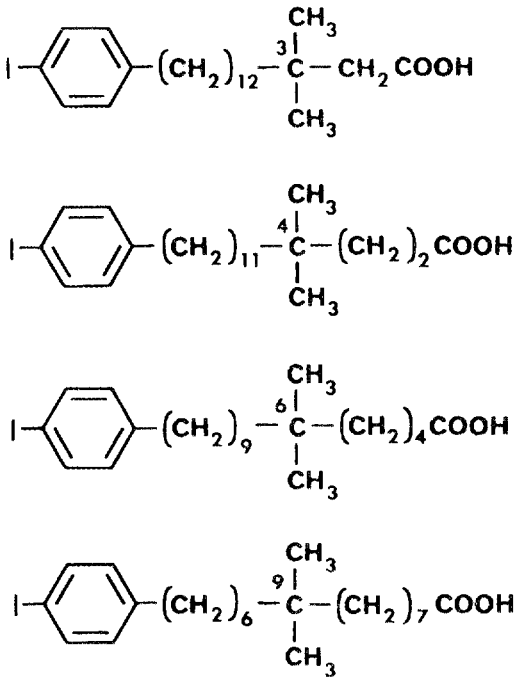
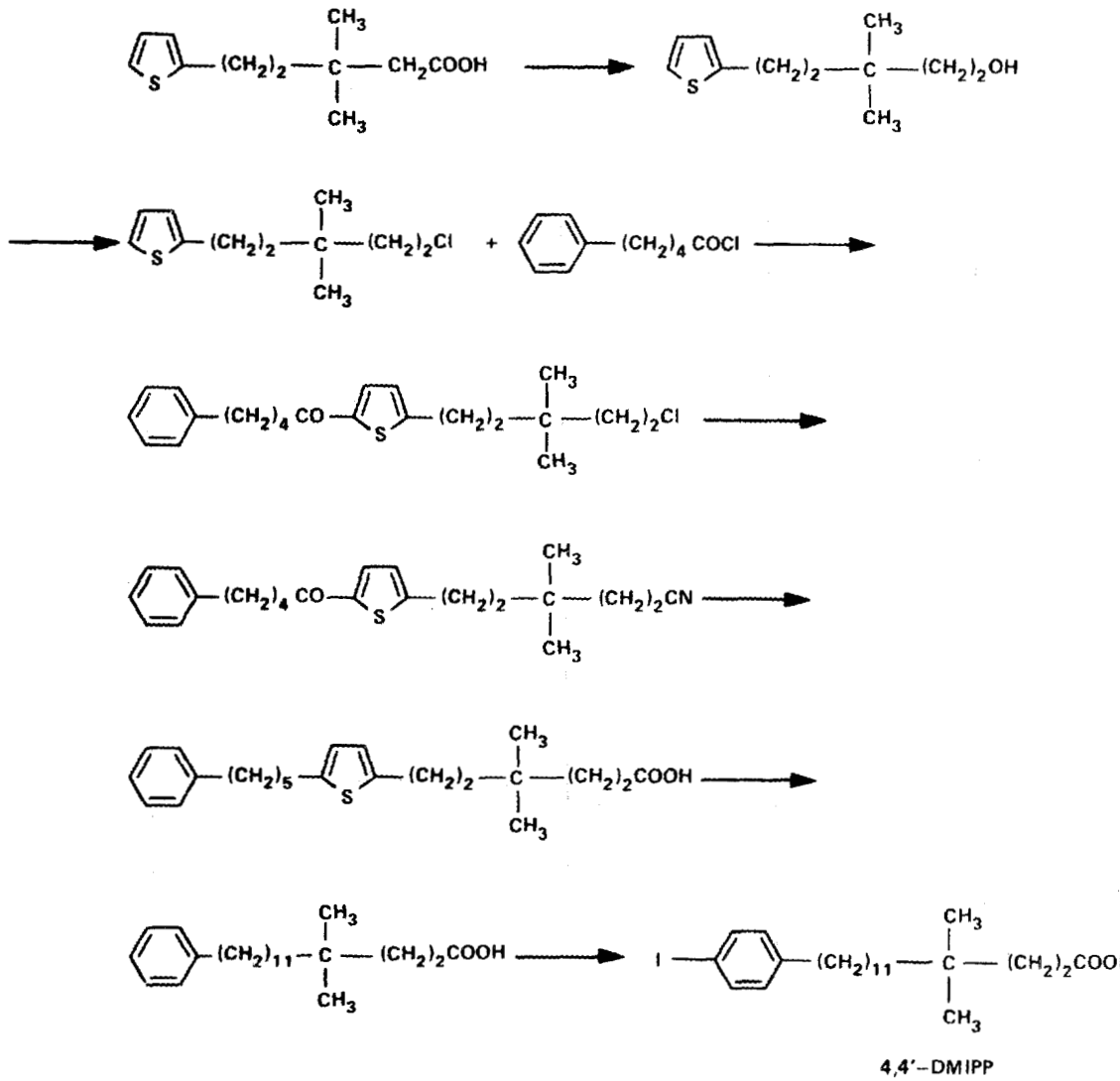


Fig. 1. Structures of the 3,3'-,4,4'-,6,6'- and 9,9'-dimethyl analogues of 15-(p-iodophenyl)pentadecanoic acid.

and clearance, the synthesis of a new dimethyl analogue 15-(p-iodophenyl)-4,4'-dimethylpentadecanoic acid (4,4'-DMIPP), is described. A comparison of the tissue distribution of the 3,3'-, 4,4'-, 6,6'-, and 9,9'-dimethyl analogues is also presented.

The 15-(p-iodophenyl)-4,4'-dimethylpentadecanoic acid (4,4'-DMIPP) was synthesized in a 7-step sequence of reactions (Scheme I) from a key



Scheme I

synthetic intermediate, 2-(3,3-dimethyl-5-hydroxypentanoyl)thiophene (1). Intermediate (1) was also utilized earlier for introduction of dimethyl-branching into the alkanoic chain for preparation of 3,3'-DMIPP (ORNL/TM-9609) and 3,3'-DMIVN (ORNL/TM-9784). In this synthetic approach, the 2-(3,3-dimethyl-5-hydroxypentanoyl)thiophene (1) starting material was reduced with $LiAlH_4$ to afford 2-(3,3-dimethyl-5-hydroxypentyl)thiophene (2). The thienyl alcohol (2) was converted to the chloride (3) by treatment with N,N'-dimethylaniline and thionyl chloride. The phenylalkyl moiety was then introduced into the 5'-thienyl position by coupling of 5-phenylpentanoyl chloride (4) with chloride (3) catalyzed by treatment with tin(IV) chloride in methylene chloride. The chloro ketone (5) was then converted to the nitrile (6) by treatment with NaCN in DMSO. The keto function of compound (6) was reduced by the Wolff-Kishner (Huang-Minlon) method which concomitantly hydrolyzed the nitrile function to give 2-(4,4'-dimethyl-6-hydroxyhexanoyl)-5-(5-phenylpenty)thiophene (7). Raney Nickel desulfurization of the thenyl acid (7) followed by subsequent treatment with thallium(III) trifluoroacetate and potassium iodide gave 4,4'-DMIPP (9).

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

Tissue	Time (min)	Mean values for dimethyl analogues of 15-(p-Iodophenyl)pentadecanoic acid			
		3,3'[b]	4,4'-	6,6'-	9,9'[c]
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
Heart: Blood	5	3:1	9:1	1.7:1	2.63
	30	12:1	16.7:1	3.1:1	2.72
	60	12.5:1	17.4:1	3.3:1	2.09

[a] mean valuses for five fasted female Fischer rats

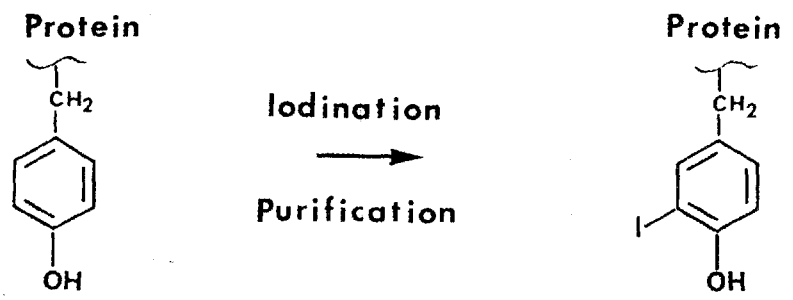
[b] from ORNL/TM-9609

[c] from ORNL/TM-10294

The 3,3'-DMIPP analogue was labeled with iodine-125 in the usual manner and administered to fasted Fischer rats. The results of these first studies (Table 1) indicated very high heart uptake, rapid blood clearance and high heart:blood ratios. These data are compared with similar data for the 3,3'-, 6,6'- and 9,9'-dimethyl analogues and suggest the 4,4'-analogue exhibits the most attractive properties. Future studies will evaluate the [I-131]3,3'-DMIPP/[I-125]4,4'-DMIPP mixture to confirm this preliminary result.

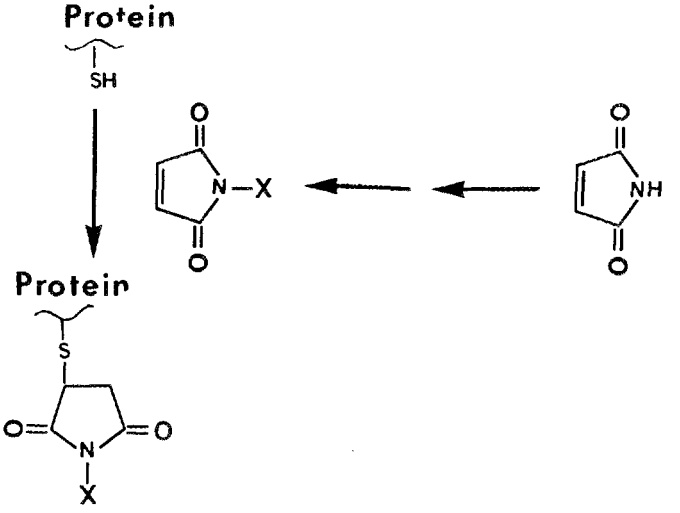
DEVELOPMENT OF A NEW "KIT" FOR FACILE RADIOIODINATION OF N-SUBSTITUTED MALEIMIDES FOR PROTEIN RADIOLABELING

Radiolabeling of antibodies with iodine-131 and iodine-123 is attractive for therapeutic and diagnostic applications. Modifications of the classical chloramine-T procedure are the most common methods for radioiodination of antibodies. The procedure is considered to radiolabel phenyl group of tyrosine residues in the protein (Scheme II). Disadvantages of this procedure include the substrate exposure to chemicals during radioiodination, the possibility of non-specific radiolabeling and denaturation of protein resulting in low yields of the radiolabeled antibody. Another major drawback is in vivo deiodination and entrapment of free radioiodine in the stomach mucosa and decreased tissue half-life of radiolabeled antibody. Further improvements and development of alternative radiolabeling techniques are therefore important.



Scheme II

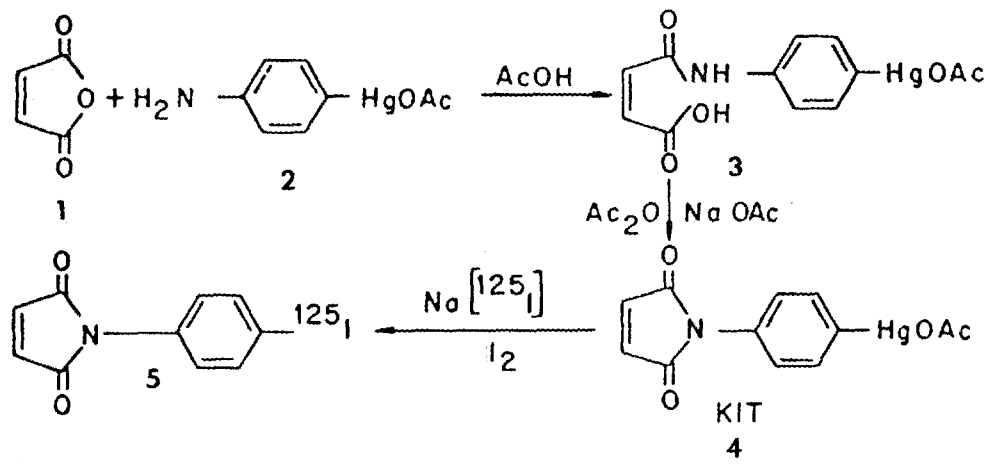
The N-substituted maleimides are attractive reagents for radiolabeling proteins, since they readily react with thiol (SH) groups of proteins under mild conditions. For proteins which do not contain a functionally unessential reactive thiol group, thiol groups can be introduced at neutral pH. Maleimides have been previously used for enzyme-labeling of insulin and rabbit antibodies. Radioligand bearing maleimides, therefore, offer significant potential for labeling proteins and antibodies for diagnostic imaging and therapeutic applications (Scheme III).



Scheme III

The synthesis of a new maleimide radioiodination agent, N-(p-[^{125}I]-iodophenyl)maleimide (IPM), has been previously described (ORNL/TM-10294), where iodine is stablized on a phenyl ring to inhibit in vivo deiodination. The agent has been labeled with iodine-125 for preliminary studies, but the ~ 8 hours required for synthesis and purification are not attractive for radioiodination with iodine-123 (13 h half-life).

To minimize the reaction time a "kit" for radiolabeling of the maleimide agent has now been prepared (Scheme IV). The kit was designed to provide the intact molecule containing a functional group, which in the last step can be readily radioiodinated to yield the desired molecule.



Scheme IV

In the "kit" synthesis of N-(p-iodophenyl)maleimide, the radionuclide is added in the last step to allow the use of the short-lived iodine-123. The starting materials, maleic anhydride (1) and 4-aminophenyl mercuric acetate (2), were condensed to form 4-[N-(p-aminophenyl(mercuric acetate)]-2-butenoic acid-4-one (3). Ring annulation of (3) with fused sodium acetate gave N-(p-acetylmercuricphenyl)maleimide (4). The mercuric acetate moiety on (4) is easily exchanged for any of the radioisotopes of iodine, depending on the particular need, to produce radiolabeled N-(p-iodophenyl)maleimide (5). The kit is a crystalline compound, stable at room temperature, and can be shipped for easy onsite radiolabeling. Other chelating functional groups can possibly be attached for potential labeling with other metallic radioisotopes.

AGENTS FOR MEDICAL COOPERATIVE PROGRAMS

Osmium-191

Seven shipments of osmium-191 were made during this period. Four shipments were supplied to collaborators to the Cyclotron Center, Liege, Belgium (Drs. C. Brihaye and M. Guillaume); one shipment to Massachusetts

General Hospital, Boston, MA (Dr. H. W. Strauss); one shipment to Children's Hospital, Boston, MA (Dr. S. Treves); one shipment to Yale University, New Haven, CT (Dr. K. K. Turekian); and one shipment to The George Washington University, Washington, D.C. (Dr. B. Wessels).

Copper-64

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

Radioiodinated Agents

Four shipments of iodine-125 labeled agents were made to collaborators. One shipment each went to Temple University, Philadelphia, PA (Dr. C. B. Mills); E.I. du Pont, North Billerica, MA (Dr. S. A. Mousa); Oak Ridge Associated Universities (Dr. J. Crook); and University of Bonn, Bonn, FRG (Drs. S. Reske and J. Kropp). One shipment of iodine-131 DMIPP was made to the Department of Cardiology (Dr. F. Visser), Amsterdam, The Netherlands.

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 National Institutes of Health, Besthesda, MD (Dr. C. Litterst); Shields Warren Radiation Laboratory, Boston, MA (Dr. A. I. Kassis); the University of California - San Diego, La Jolla, CA (Dr. P. Andrews); New York Medical Center, New York, NY (Dr. T. Reich); and Bristol-Myers Company, East Syracuse, NY (Dr. Tay).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

S. N. Reske, F. F. Knapp, Jr., and C. Winkler "Experimental Basis of Metabolic Imaging of the Myocardium with Radioiodinated Aromatic Free Fatty Acids," Am. J. Physiol. Imaging, 1, 214-229 (1986).

P. C. Srivastava, M. L. Tedjamulia, and F. F. Knapp, Jr. "Potential Cerebral Perfusion Agents. Synthesis and Evaluation of Berberine Analogues," J. Hetero. Chem., 23, 1167-1169 (1986).

Visitors

A group of 25 participants from the ORAU/REACTS "Medical Planning and Care in Radiation Accidents" visited the nuclear medicine program on November 6 for a review of current research activities.

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