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Nuclear Medicine Progress Report for Quarter Ending September 30, 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 SEPTEMBER 30, 1986

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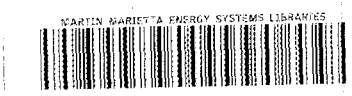

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SUMMARY

In this report the synthesis of two new dimethyl-branched analogues of 15-(p-iodophenyl)-3,3'-dimethylpentadecanoic acid (DMIPP) is described. Methyl-branching was introduced into the 6- and 9-positions to determine the effect of the position of dimethyl-branching on myocardial uptake and clearance kinetics in rats. The goal of these studies is to maximize heart uptake and retention and minimize blood and liver uptake. The 6,6'-dimethyl- (6,6'-DMIPP) and 9,9'-dimethyl- (9,9'-DMIPP) analogues were prepared by multi-step sequences involving successive Friedel-Crafts/Wolf Kishner reactions on thiophene. Regiospecific para-iodination using thallation and treatment with iodide provided the two new analogues. The 9,9'-[I-125]DMIPP was evaluated in rats and showed somewhat lower uptake than 3,3'-DMIPP (3.13 dose/gm at 5 min versus 4.18) and more rapid clearance (~ 30% at 1 h). In addition the heart:blood ratios were lower for the 9,9'-dimethyl isomer. These studies have demonstrated the effects of the position of dimethyl substitution on uptake and retention. The 6,6'-dimethyl and other new analogues will be evaluated in future studies.

The new N-iodophenyl-substituted maleimide protein labeling agent N-(p-iodophenyl)maleimide (IPM) has been further evaluated in conjunction with collaborators at Temple University (Dr. David C. B. Mills). Studies of platelet aggregation demonstrated that IPM may specifically react with the thiol groups associated with the inhibitory effect of adenosine diphosphate (ADP). Incubation of [I-125]IPM with human platelets followed by analysis and electrophoretic analysis demonstrated binding of the new reagent with a variety of intracellular proteins.

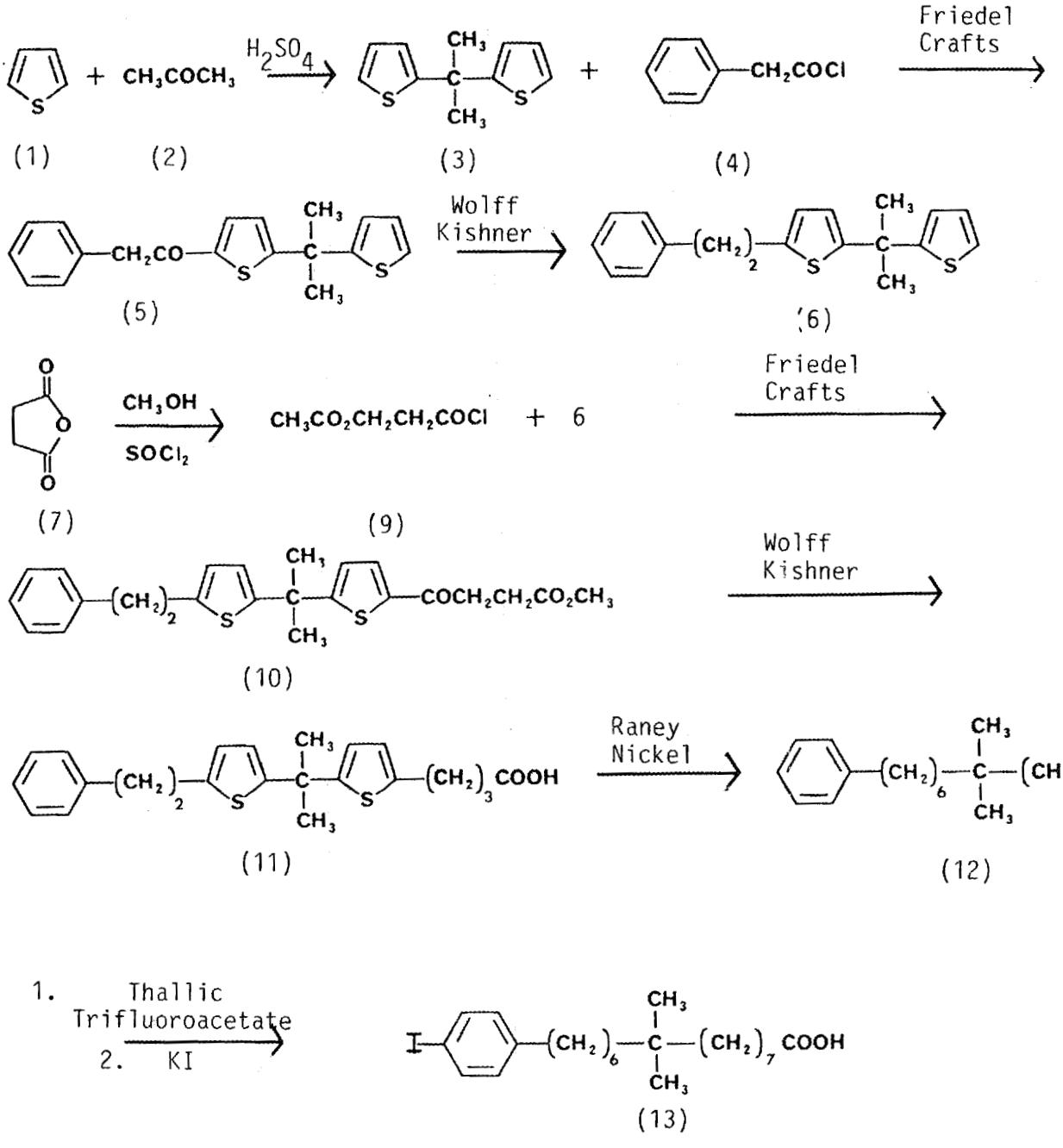
During this period a variety of agents were also supplied to Medical Cooperative investigators, including five shipments of osmium-191 for fabrication of osmium-191/iridium-191m generators and one shipment of copper-64. In addition, four shipments of platinum-195m cis-DDP were made through the ORNL Isotopes Distribution Office on a cost recovery basis.

SYNTHESIS AND EVALUATION OF TWO NEW DIMETHYL-SUBSTITUTED ANALOGUES OF 15-(p-IODOPHENYL)PENTADECANOIC ACID

In a recent report (ORNL/TM-9609) it was demonstrated that the introduction of dimethyl-branching at the 3-position of 15-(p-iodophenyl)-pentadecanoic acid resulted in rapid and pronounced myocardial uptake in rats with irreversible retention 60 min following i.v. administration. More recently, the model agent, 15-(p-iodophenyl)-3,3'-dimethylpentadecanoic acid (DMIPP) has been radiolabeled with iodine-123 and evaluated in patients at the University of Bonn, Federal Republic of Germany (ORNL/TM-10082). Single photon emission computerized tomographs (SPECT) of patients with multi-vessel coronary artery disease at 60 min following i.v. administration of [I-125]DMIPP showed clear visualization of the myocardium. Serial SPECT images taken shortly after administration of [I-125]DMIPP indicated a gradual clearance of activity from the plasma which resulted in moderate heart to background ratios. These results were confirmed by the analysis of serial blood samples drawn from patients (n=4) following administration of [I-123]DMIPP. Since these preliminary clinical studies with the model iodophenyl fatty acid DMIPP agent showed a longer than optimal for plasma clearance ($t_{1/2}$ = 8-10 min), the effect of dimethyl-branching at various positions along the fatty acid chain of 15-(p-iodophenyl)pentadecanoic acid (IPP) on myocardial uptake, retention, and heart:blood ratios has now been investigated. In this report the preparation and preliminary biological evalaution of two model dimethyl analogues of IPP, 15-(p-iodophenyl)-6,6'-dimethylpentadecanoic acid (6,6'-DMIPP) and 15-(p-iodophenyl)-9,9'-dimethylpentadecanoic acid (9,9'-DMIPP) are described.

The model dimethyl-branched analogues were synthesized from a key synthetic intermediate, bis(thienyl)propane (3) utilizing the thiophene elongation synthesis for long chain fatty acids (Scheme I). By selection of the substituents introduced into the 2- and 2'-positions of the thiophene ring of bis(thienyl)propane, a variety of dimethyl-branched fatty acids with branching at positions 6 through 10 can be prepared. In this synthetic approach, the starting material bis(thienyl)propane (3) was

prepared by treatment of thiophene (1) and acetone (2) with 75% sulfuric acid. The synthesis of the analogue 9,9'-DMIPP was accomplished in a 9-step sequence of reactions (Scheme I). Utilizing this approach we

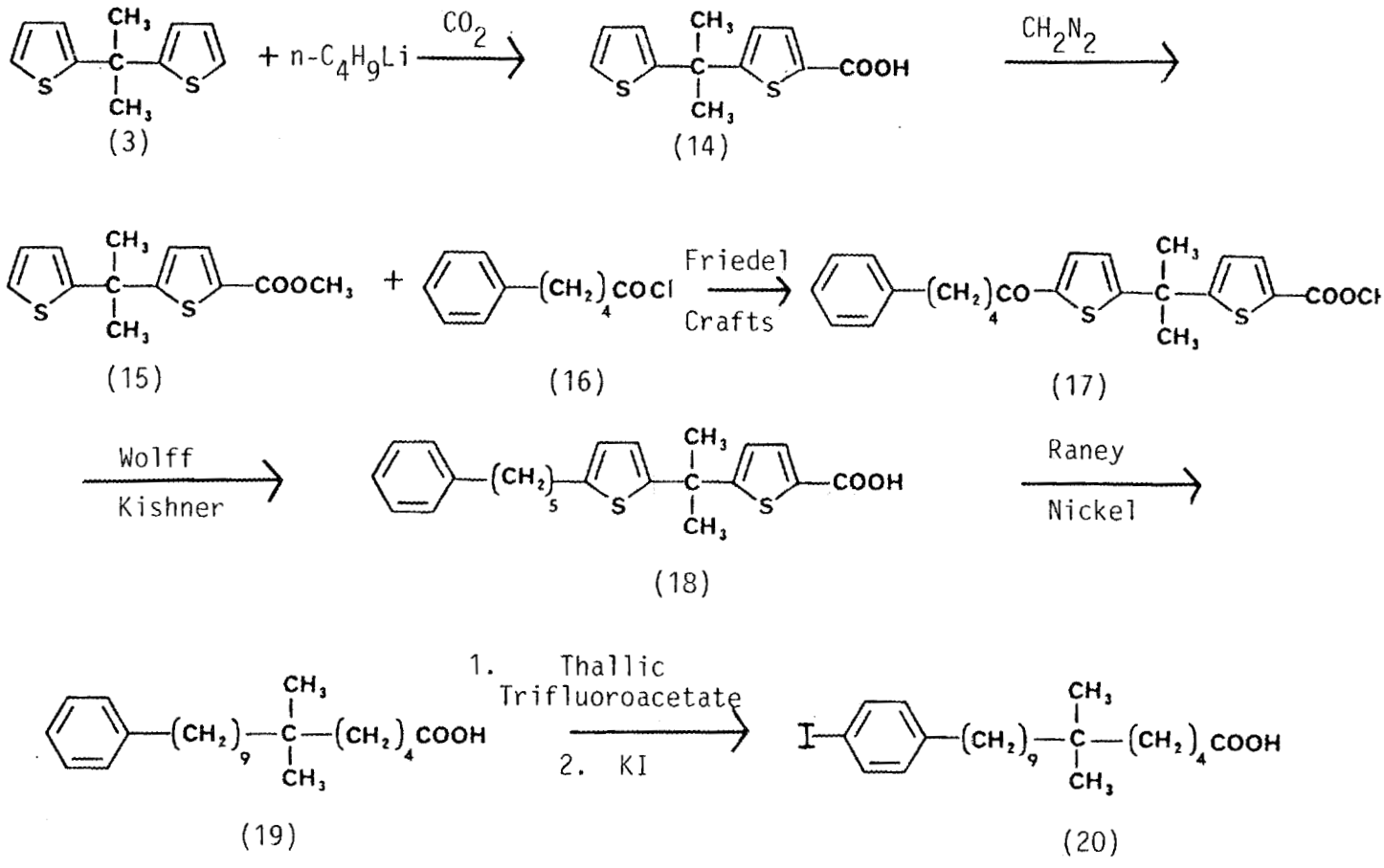


(1) (2) (3) (4) (5) (6) (7) (9) (10) (11) (12) (13)

Scheme I

coupled commerically available phenylacetyl chloride (4) with bis(thienyl)-propane (3) by treatment with tin(IV) chloride in dichloromethane which gave 2-(2-phenyl-1-oxoethyl)bis(thienyl)-propane (5). Wolff-Kishner reduction of the ketone gave 2-(2-phenylethyl)bis(thienyl)propane (6). The carboxylic acid moiety was introduced into the 2'-thienyl position by acylation of the half ester acid chloride of succinic anhydride. The 3-carbomethoxypropionyl chloride (9) was prepared from commercially available succinic anhydride (7) by treatment with methanol followed by thionyl chloride. The thienyl derivative (6) was subjected to Friedel-Crafts condensation with the acyl chloride (9) to afford 2-[2-phenyl-ethyl]-2'-(1-oxo-3-carbomethoxypropyl)bis(thienyl)propane (10). Wolff-Kishner reduction of the keto ester (10) gave 2-[2-phenylethyl]-2'(3-hydroxypropionyl)bis(thienyl)propane (11). The pivotal step in the synthesis involved the Raney nickel desulfurization of the acid (11) followed by subsequent treatment with thallium (III) trifluoroacetate and potassium iodide to give 9,9'-DMIPP (13).

The preparation of 15-(p-iodophenyl)-6,6'-dimethylpentadecanoic acid (6,6'-DMIPP) was achieved in a manner analogous to the 9,9'-analogue (Scheme II). Bis(thienyl)propane was converted to the 2-lithio derivative using n-butyllithium and then reacted with dry ice to give 2-bis(thienyl)propane carboxylic acid (14). The carboxylic acid was then treated with diazomethane to give the corresponding methyl ester (15). The resulting ester and 5-phenylpentanoyl chloride (16) were subjected to Friedel-Crafts acylation to afford 2-(methoxycarbonyl)-2'-(1-oxo-5-phenylpentyl)bis(thienyl)propane (17). Wolff-Kishner reduction of the ketone gave 2-(hydroxycarbonyl)-2'-(5-phenylpentyl)bis(thienyl)thiophene (18). Raney nickel desulfurization of the thienyl acid and subsequent iodination using thallium (III) trifluoroacetate and potassium iodide afforded 6,6'-DMIPP (20). The 9,9'-DMIPP was radioiodinated with [iodine-125] sodium iodide and the radioiodinated agent evaluated in fasted female Fischer rats. The results of this preliminary biological evaluation are summarized in Table 1. The level of accumulation of radioactivity in the myocardium after injection of 9,9'-DMIPP was significant. The blood levels of activity were moderate resulting in modest heart:blood ratios (3:1). This analogue thus appears to show lower



(3) (14) (15) (16) (17) (18) (19) (20)

Scheme II

heart uptake, more rapid myocardial washout, and higher blood levels than the original 3,3'-DMIPP analogue. Since the chain length is the same, these results suggest that the position of dimethyl-branching is an

important structural feature. The agent exhibited excellent (>95%) retention in the heart at 30 min following injection which decreased to 67% at 60 min. The 6,6'-DMIPP and other positional isomers will be studied in an effort to increase both H:B ratios and retention.

Table 1. Tissue distribution of [I-125]-9,9'-DMIPP in fasted female rats (3 animals, mean ± SD)

Tissue	5 min	30 min	1 hr
Blood	1.20 ± 0.09	1.09 ± 0.17	0.90 ± 0.05
Liver	8.51 ± 0.57	6.54 ± 0.81	5.00 ± 0.16
Kidney	1.36 ± 0.06	1.28 ± 0.22	1.25 ± 0.02
Heart	3.13 ± 0.53	3.06 ± 0.79	1.90 ± 0.26
Lung	1.81 ± 0.13	1.28 ± 0.23	1.17 ± 0.09
Thyroid	11.53 ± 2.97	12.52 ± 3.08	14.72 ± 1.09
Heart/Blood	2.63 ± 0.65	2.77 ± 0.30	2.09 ± 0.19

RADIOIODINATED N-SUBSTITUTED MALEIMIDES — NEW SULFHYDRYL BINDING PROTEIN-LABELING AGENTS

In the last report in this series (ORNL/TM-10238), the synthesis and biological properties of a new protein-labeling agent (IPM), were described. The IPM has more recently been tested on the adenylate cyclase system in blood platelets by a collaborator at the Thrombosis Research Center, Temple University, Philadelphia (Dr. David C. B. Mills). The IPM was incubated for 10 min with washed human blood platelets in which the metabolic adenine nucleotides had been pre-labeled with [3H]-adenine. The platelets were then incubated with prostaglandin (PGI_2), a stimulator of adenylate cyclase, either alone or with adenosine diphosphate (ADP) or epinephrine (Epi) at concentrations that inhibit the action of PGI_2. The radioactive cyclic adenosine monophosphate (cAMP) was then separated from other labeled nucleotides. Accumulation of cAMP is related to the stimulation of adenglate cyclase in platelets. In this system, thiol reagents of the maleimide type interfere with the inhibitory effect of ADP. Compounds like N-ethylmaleimide have little effect on the inhibitory response to epinephrine under these conditions.[1] At higher concentrations, compounds that penetrate the cell membrane also inhibit adenylate

cyclase. Figure 1 shows the results of an experiment using IPM. The results are similar to those that are generally seen with N-ethylmaleimide or with N-phenylmaleimide, only the iodinated compound appears to be at least four times as active as N-phenylmaleimide. It appears that IPM may react specifically with the thiol group(s) associated with the inhibitory effect of ADP, which may be intimately associated with the ADP receptor.

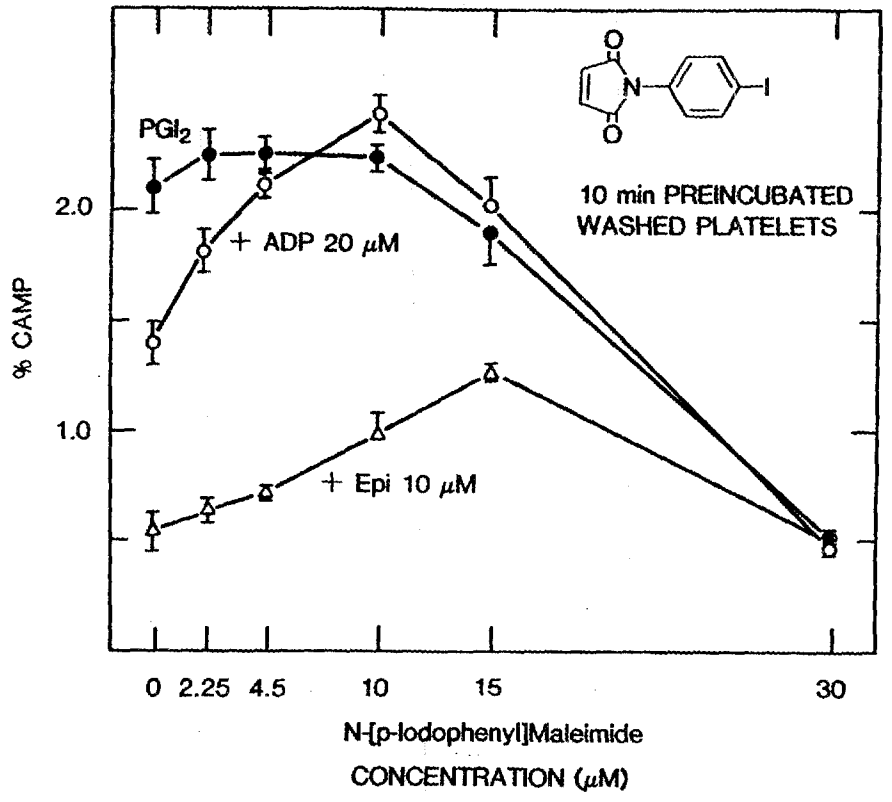


Figure 1. Effect of IPM on the response of platelet adenylate cyclase to PGI_2* in the presence and absence of ADP or Epi. Results are given as percent of intracellular radioactivity found as cAMP. (Courtesy of David C. B. Mills, Ph.D., Thrombosis Research Center, Philadelphia).

High specific activity of [I-125]IPM has also been evaluated in human platelets. Samples of washed platelets were exposed to different reagents for 32 min at 37°C and then to aproximately 100 μM [I-125]IPM for another 2 min. The platelets were lysed in SDS-mercaptoethanol and the samples

then applied to lanes 2-13 of a 15 well 12.5% polyacrylamide gel electrophoresis (PAGE) slab and run overnight. The slab was fixed and stained with Coomassie blue (CB) and photographed (Fig. 2). An autoradiography was developed with intensifying screens for 23 h (Fig. 3). The samples are identified in Table 2. The reagent reacts with almost all of the proteins identifiable by CB staining, regardless of their intracellular location, e.g., actin (Mr 42k) and myosin (heavy chain Mr 200k and light chain Mr 20k) and alpha-actinin (Mr 220k). There was not detectable protection of any of the bands by pretreatment with any of the non-penetrating reagents.

Table 2. Data for samples of washed platelets exposed to different reagents for 32 min at 37° before treatment with [I-125]IPM. Electrophoretic results are illustrated in Figures 2 and 3. (Courtesy of David C. B. Mills, Thrombosis Research Center, Philadelphia).

Platelet	Reagents	Lanes
1 & 2	1 mM 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB)	2 & 3
3 & 4		
5 & 6	80 μM cytochalasin A	6 & 7
7 & 8	1 mM p-chloromercurybenzene sulphonate (pCMBS)	8 & 9
9 & 10	1 mM taurine maleimide	10 & 11
11 & 12	No addition	12 & 13

These combined studies have thus demonstrated that N-(p-[^{125}I]iodophenyl)maleimide can be prepared in high specific activity in a three-step process. Tissue distribution studies in rats indicate preferential retention of [I-125]IPM with cellular blood components (ORNL/TM-10238). This new agent also appears to bind with IgG, albumin and platelet proteins. The technology could be developed for labeling of a variety of biological substrates with suitable radiohalogens for radiopharmaceutical applications.

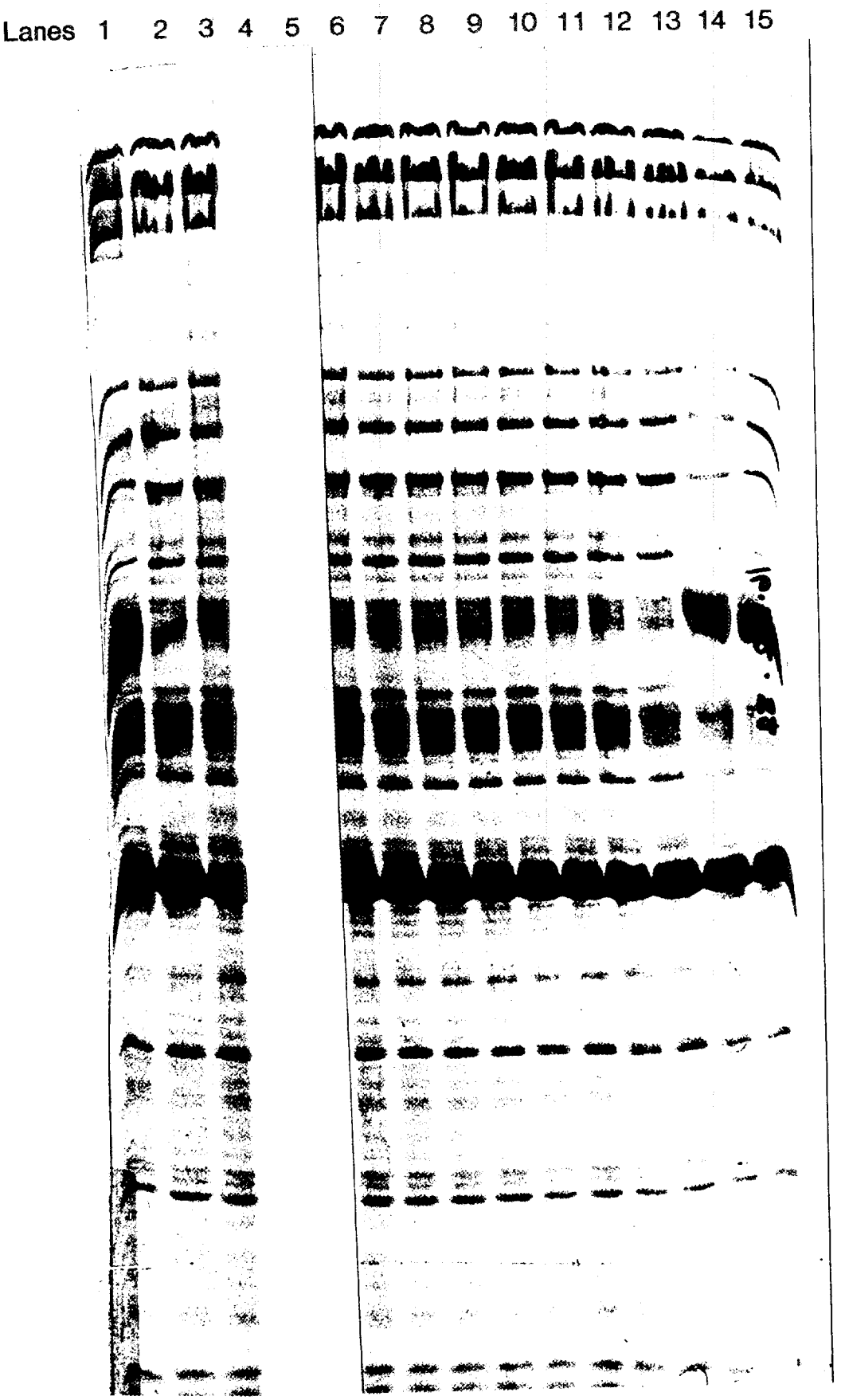


Figure 2. Coomassie blue stained photograph after the samples of washed platelets were exposed to different reagents for 32 min at 37° and then to approximately 100 μM [I-125]IPM for another 2 min analysis. (Courtesy of David C. B. Mills, Thrombosis Research Center, Philadelphia).

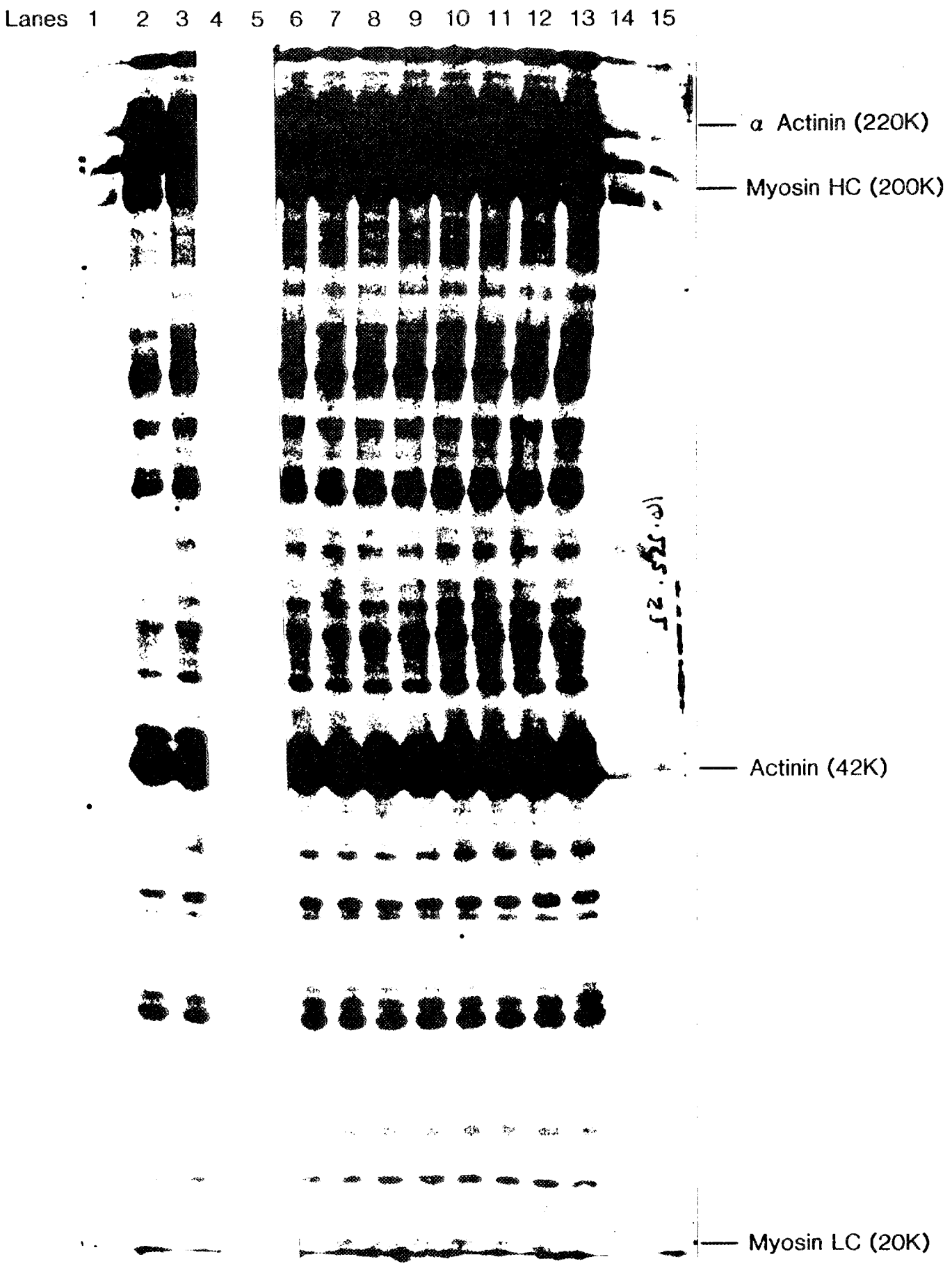


Figure 3. Autoradiograph after the samples of washed platelets were exposed to different reagents for 32 min at 37° and then to approximately 100 μM [I-125]IPM for another 2 min analysis. (Courtesy of David C. B. Mills, Thrombosis Research Center, Philadelphia)

REFERENCE

1. Abbott, R. E. and Schachter, D. J. Biol. Chem., 251, 7176 (1976).

AGENTS FOR MEDICAL COOPERATIVE PROGRAMS

Osmium-191

Five shipments of osmium-191 were made during this reporting period. Two shipments went 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); and one shipment to Yale University, New Haven, CT (Dr. K. K. Turekian).

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

Four 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, Bethesda, MD (Dr. C. Litterst), University of Medicine and Denistry of New Jersey, Newark, NJ (Dr. V. V. Rao), Shields Warren Radiation Laboratory, Boston, MA (Dr. A. I. Kassis); and the University of California - San Diego, La Jolla, CA (Dr. P. Andrews).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

B. M. Goldstein, P. C. Srivastava, F. F. Knapp, Jr. "Cis/Trans Disorder in (5-Bromo-4-pentenyl)triphenylphosphonium Iodide," Acta Cryst., C42, 570-573 (1986).

F. F. Knapp, Jr., P. C. Srivastava "Potential Approaches for the Development of Brain Imaging Agents for Single-Photon Applications," in, Amphetamines and pH-Shift Agents for Brain Imaging, H.-J. Biersack and C. Winkler, editors, pp. 71-84, de Gruyter, Berlin, 1986.

F. F. Knapp, Jr. "New Agents to Detect Heart Disease," IAEA Bulletin, Vol. 28, Summer Issue, pp. 26-32, 1986.

P. C. Srivastava, M. L. Tedjamulia, F. F. Knapp, Jr. "Potential Cerebral Perfusion Agents," J. Heterocycl. Chem., 23, 1167 (1986).

K. Yamamoto, P. Som, A. B. Brill, Y. Yonekura, Suresh C. Srivastava, G. E. Meinken, J. Iwai, M. M. Goodman, F. F., Knapp, Jr., D. R. Elmaleh, E. Livni, H. W. Strauss "Dual Tracer Autoradiographic Study of β-Methylpentadecanoic Acid in Normotensive and Hypertensive Rats," J. Nucl. Med., 27, 1178-1183 (1986).

Visitors

Dr. Jean-Louis Piette, Chemistry Department, University of Liege, Belgium, visited the Nuclear Medicine Group facilities on July 8, 1986, and discussed research work of mutual interest.

Jorn Kolkmeier and Sigurd-Wilhelm Kohlen, medical students at the University of Bonn, Federal Republic of Germany, joined the ORNL Nuclear Medicine summer research program on July 16, 1986.

Frans Visser, M.D., and Michael Van Eenige, Ph.D., from the Cardiology Department at the Free University in Amsterdam, The Netherlands, visited

on September 20-24, 1986. They presented seminars describing clinical studies with iodine-123-labeled fatty acids and the evaluation in special animal models of new radioiodinated heart imaging agents developed at ORNL. Drs. Visser and Van Eenige worked with F. F. Knapp while he was on foreign assignment in Germany during the July 1985 – August 1986 period, and these collaborative studies are continuing. They also used this opportunity to discuss these joint projects and plan and review present and future experiments.

Meetings

M. M. Goodman and P. C. Srivastava attended the Sixth International Symposium on Radiopharmaceutical Chemistry, Boston, June 29–July 3, 1986. Members of the ORNL Nuclear Medicine Group presented papers and authored three abstracts at the meeting.

P. C. Srivastava, F. F. Knapp, Jr. "Design, Synthesis and Evaluation of Redox Radiopharmaceuticals: A Potential New Approach for the Development of Brain Imaging Agents."

M. M. Goodman, A. P. Callahan, F. F. Knapp, Jr. "Design, Synthesis and Evaluation of 2-Deoxy-2-Iodovinyl-Branched Carbohydrates as Potential Brain Imaging Agents."

M. M. Goodman, K. R. Ambrose, K. H. Neff, F. F. Knapp, Jr. "Synthesis and Biological Evaluation of (E)-19-Iodo-3,3-Dimethyl-18-Nonadecenoic Acid, A New Dimethyl-Branched Long-Chain Fatty Acid to Evaluate Regional Myocardial Fatty Acid Uptake."

Several papers co-authored by members of the Nuclear Medicine Group were presented at the European Nuclear Medicine Congress, Goslar, FRG, September 2-5, 1986.

S. N. Reske, F. F. Knapp, Jr., R. Knoop, C. Winkler "First Pass Ventrikulographie mit dem Ultrakurzlebigen Radionuklid Ir-191m."

S. N. Reske, F. F. Knapp, Jr., W. Schmitt, C. Winkler "Effect of Glucose-Insulin Treatment on Cardiac Turnover of I-123 Phenylpentadecanoic Acid (IP) and C-14 Palmitic Acid (PA)."

S. N. Reske, F. F. Knapp, Jr., A. Kropp, K. Reichmann, J. Nitsch, C. Winkler "Regional Stress-Induced Inhomogeneity of Cardiac (I-123) Phenyl Fatty Acid (IP) Metabolism in CAD by SPECT."

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