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Nuclear Medicine Program Progress Report for Quarter Ending December 31, 1995

F. F. Knapp, Jr.
K. R. Ambrose
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ORNL/TM-6916
ORNL/TM-6958
ORNL/TM-7072
ORNL/TM-7223
ORNL/TM-7411
ORNL/TM-7482
ORNL/TM-7605
ORNL/TM-7685
ORNL/TM-7775
ORNL/TM-7918
ORNL/TM-8123
ORNL/TM-8186
ORNL/TM-8363
ORNL/TM-8428
ORNL/TM-8533
ORNL/TM-8619
ORNL/TM-8746
ORNL/TM-8827
ORNL/TM-8966
ORNL/TM-9037
ORNL/TM-9124
ORNL/TM-9343
ORNL/TM-9394
ORNL/TM-9480
ORNL/TM-9609
ORNL/TM-9707
ORNL/TM-9784
ORNL/TM-9937
ORNL/TM-10082
ORNL/TM-10238
ORNL/TM-10294
ORNL/TM-10377
ORNL/TM-10441
ORNL/TM-10618
ORNL/TM-10711
ORNL/TM-10839
ORNL/TM-11014
ORNL/TM-11043
ORNL/TM-11145
ORNL/TM-11224
ORNL/TM-11304
ORNL/TM-11377
ORNL/TM-11427
ORNL/TM-11550
ORNL/TM-11570
ORNL/TM-11721
ORNL/TM-11755
ORNL/TM-11830
ORNL/TM-11881
ORNL/TM-11992
ORNL/TM-12054
ORNL/TM-12110
ORNL/TM-12159
ORNL/TM-12222
ORNL/TM-12312
ORNL/TM-12343
ORNL/TM-12411
ORNL/TM-12485
ORNL/TM-12661
ORNL/TM-12707
ORNL/TM-12789
ORNL/TM-12875
ORNL/TM-12909
ORNL/TM-12965
ORNL/TM-13053
ORNL/TM-13107

CONTENTS

SUMMARY

In this report we describe the first resolution of the 3R-(+)- and 3S-(-)-methyl BMIPP methyl-branched fatty acid stereoisomers and biodistribution of the radioiodinated isomers in rats to investigate the effects of the configuration of the 3(β)-methyl group on the organ distribution and myocardial uptake and release kinetics. Synthesesis of 3R-(+)BMIPP was accompanied by initial acylation of the thiophene template with the acid chloride of ethyl 3R-methylglutarate. The amide of the synthetic 3R-BMIPP isomer prepared from S-(-)-α-methylbenzylamine exhibited identical spectral and chromatographic properties with the chromatographically more polar isomer (TLC and HPLC) which was separated from the mixture of amides prepared from reaction of the acid chloride of racemic BMIPP with the S-(-)-α-methylbenzylamine. The second less chromatographically polar amide isomer was thus assigned the 3S-(-)-methyl configuration. The free acids were obtained by acid hydrolysis of the amides and converted to the radioiodinated analogues. While biodistribution studies in separate groups of rats demonstrated greater myocardial uptake of 3R-BMIPP compared with the 3S-isomer (30 min, Mean % ID/gm heart: 3R = 4.02; 3S = 2.81), values for most other tissues evaluated (blood, lungs, kidneys and thyroid) were similar, whereas the 3S-BMIPP isomer consistently showed higher liver uptake. These results were confirmed in a [I-131]-3S-BMIPP/[I-125]-3R-BMIPP dual label study (30 min: 3R = 4.37; 3S = 3.44) and both isomers had similar myocardial wash-out curves (5-180 min). These studies suggest that [I-123]-3R-BMIPP is a candidate for clinical evaluation and may show greater myocardial uptake than the 3S-isomer and thus may require a reduced injected dose compared to racemic BMIPP.

Also during this period several radioisotopes and tungsten-188/rhenium-188 generators were provided to collaborators through the ORNL Isotope Distribution Office (IDO). Tungsten-188/rhenium-188 generators were provided to collaborators at the Kent and Canterbury Hospital for initial clinical Phase I studies to evaluate the osseous uptake of rhenium-188(V)-labeled DMSA as a potential new palliative agent for treatment of bone pain from cancer metastases.

Generators were also provided to the Paul Scherrer Institute in Switzerland for a collaborative project evaluating Re(I) compounds, and to the Institute for Nuclear Energy Research (INER) in Lung-Tan, Taiwan for collaborative development of new Re-188-labeled radiopharmaceuticals. Tungsten-188/rhenium-188 generators were also provided on a cost-recovery basis through the ORNL IDO to CIS Bio-International in France, and ANSTO in Sydney, Australia. A processed tungsten-188 solution was provided to Sorin Biomedica for preparation of generators to provide rhenium-188 to label MDP for a collaborative program with the Catholic University Hospital in Rome, Italy, for treatment of bone pain.

Samples of high specific rhenium-186 produced in the ORNL HFIR were provided to Mallinckrodt, Inc. in St. Louis, Missouri and Petten, Holland, and NeoRx, Inc., in Seattle, Washington, to evaluate the purity and use of this radioisotope from ORNL for preparation of therapeutic agents. One sample of tin-117m was provided on a cost-recovery basis to Golden Pharmaceuticals for preparation of the tin-117m-DTPA agent for bone pain treatment in a program in conjunction with Diatech, Inc. and the Medical Department at the Brookhaven National Laboratory.

Resolution and Evaluation in Rat Tissues of the Radioiodinated 3R- and 3S-Isomers of 15-(p-iodophenyl)-3-methylpentadecanoic Acid ("BMIPP")

The clinical use of iodine-123-labeled fatty acids is currently primarily focussed on myocardial imaging with the ORNL-developed agent, 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP; Figure 1).[1-3] The clinical protocols which are currently most widely used involve comparison of the regional uptake of [I-123]-BMIPP with the distribution of flow tracers such as thallium-201[4-6] or [Tc-99m]-Sestamibi.[7-9] The combined results from studies conducted in patients at several centers have clearly demonstrated that important information on myocardial viability can be determined by evaluation of the "mis-match" ratio between BMIPP and flow tracer distribution (i.e. BMIPP < flow = viable but threatened myocardium).

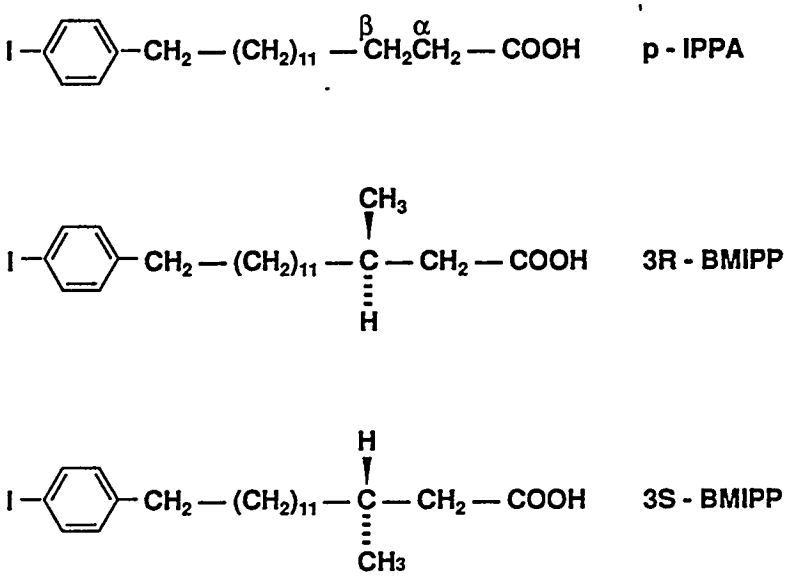

Figure 1. Fatty Acid Structures. The 3-methyl group of BMIPP results in prolonged myocardial retention. Racemic BMIPP is commercially available as "Cardiodine" as a clinical agent in Japan, and consists of an equal mixture of the 3R- and 3S-BMIPP isomers.

The preparation of [I-123]-BMIPP for current clinical studies involves radioiodination of the racemic BMIPP mixture which is based on our original synthesis of BMIPP reported in 1985[10] which involved the synthesis of the racemic BMPPA substrate (i.e. 3R-BMPPA and 3S-BMPPA). Although the potential importance of the effects of the absolute configuration of the 3-methyl group on myocardial uptake and release kinetics had been recognized,[10-12] the expected difficulties in obtaining the requisite optically active methyl-substituted substrates required for preparation of the 3R- and/or 3S-methyl enantiomers of BMPPA could not be justified at that time. Through 1995, however, over 70,000 clinical studies have been completed with [I-123]-BMIPP in Japan alone, where this agent is marketed as "Cardiodine" by Nihon Medi-Physics, Inc. In addition, clinical studies with [I-123]-BMIPP are being conducted at several institutions in Europe, including the Free University Hospital in Brussels, Belgium (P. Franken, M.D.), the University of Dresden, Germany (J. Kropp, M.D.) and the University of Bonn, Germany (H.-J. Biersack, M.D., *et al.*). Now that the widespread clinical use of [I-123]-BMIPP has demonstrated the usefulness of this agent, we have initiated an investigation of the effects of isomerism at the C-3 carbon of BMIPP on the biological properties of radioiodinated BMIPP.

We report here the first synthesis of the authentic 3R-methyl BMPPA isomer which has been used to identify the 3(R)-isomer obtained by chromatographic separation of the isomers of the amides prepared from reaction of the racemic mixture of BMPPA with S-(-)-α-methylbenzylamine. The synthetic studies were conducted by Qun Lin, Ph.D., from the Chemistry Department at Xavier University, in New Orleans, Louisiana, who worked at ORNL with the Nuclear Medicine Group for the June - August 1995 period, and was supported by funds from the DOE Program for Historically Black Colleges and Universities (HBCU). Purification and acid hydrolysis of the amides and characterization of the 3R- and 3S-BMPPA and BMIPP isomers by HPLC and ^{1}H and ^{13}C were conducted by Mr. Florian Mokler, a medical student from the University of Mainz, Germany, who is working with the ORNL Nuclear Medicine Group for a six-month period beginning in September 1995. The results of these studies will form the basis for his "Dr.

med." research thesis for the University of Mainz (Prof. Dr. Dr. A. Bockisch, research coordinator). These studies provided the 3(R)- and 3(S)-methyl isomers of BMPPA which were isolated and characterized by optical rotation and spectral data and the radioiodinated analogues have been prepared and evaluated in fasted female Fischer rats by comparison with the biodistribution of racemic BMIPP.

The 3R-methyl isomer of 15-phenyl-3R-methylpentadecanoic acid (3R-BMPPA) was synthesized as shown in Figure 2 using a thiophene template for carbon-carbon bond formation as described earlier.[10] The initial steps involved Friedel-Crafts coupling of phenylhexanoyl chloride (**2**) with thiophene as developed earlier for preparation of the racemic BMPPA mixture (**8A** and **8B**). Following Wolff-Kishner reduction of (**3**), commercially available ethyl-3R-methylglutarate was converted to the acid chloride (**5**) which was then condensed with the phenylhexyl-substituted thiophene (**4**) to provide intermediate (**6**) which was reduced to give the disubstituted thiophene (**7**). The thiophene ring of the Wolff-Kishner reduction product (**7**) was then opened by Raney Nickel reduction to provide 15-phenyl-3R-methylpentadecanoic acid (3R-BMPPA). *Para* thallation-iodination then provided authentic 3R-BMIPP (**9A**).

Since the requisite optically active methyl-substituted substrate required for preparation of 3S-BMIPP (3S-BMPPA; **8A**) was not available, a different route was pursued which involved chromatographic separation of the diastereomeric mixture of amides prepared from racemic BMPPA by reaction with optically pure (S)-(-)-methylbenzylamine, as shown in Figure 3. The racemic BMPPA mixture (**8**)[10] was converted to the acid chloride and then reacted with (S)-(-)-methylbenzylamine to provide the mixture of amides (**10**). The (R,S)- (**10A**) and (S,S)-diastereomers (**10B**) formed from the 3R- and 3S-methyl components of the racemic mixture readily separated and could be purified by preparative TLC, HPLC or column chromatography. For this (R,S) and (S,S) notation, the fatty acid asymmetric center is designated first and the α-methylbenzylamine asymmetric center second. The amides formed from reaction of (S)-(-)-methylbenzylamine with 3R-BMPPA or 3R-BMIPP isomers synthesized as shown in Figure 2 had

identical spectral and chromatographic properties as the more polar amides formed from the racemic BMPPA and BMIPP mixtures, respectively. From a chromatographic comparison it was thus deduced that the less polar amide from the racemic mixture must therefore represent the 3S-BMPPA isomer (**10A**). The 3S-BMPPA (**8A**) was then obtained following acid hydrolysis of amide (**10A**) which had been purified by column chromatography from the racemic mixture. Subsequent thallation-iodination then provided the 3S-BMIPP isomer (**9A**).

The ^{1}H-NMR spectra of the purified 3R- and 3S-BMPPA and BMIPP amides provided an unanticipated and important bonus which helped confirm assignment of the R configuration to the chromatographically more polar components isolated from the BMPPA and BMIPP amide mixtures. The chemical shift values for the methyl doublet representing the methyl group at the C-3 chiral center of the fatty acid moietiy of the amide were slightly further downfield in the ^{1}H-NMR spectra of the R-metryl amide as compared to the S-methyl-amides (Table 2). As shown in Figure 4, the doublet for the amide of 3R-methyl BMPPA is the downfield component of the multiplet in this region of the proton NMR spectrum. The 0-2 ppm regions of the proton NMR spectra of the amides formed from (S)-(-)-α-methylbenzylamine and racemic 3-R,S-, 3R- and 3S-methyl isomers of both BMPPA and BMIPP (Figure 4) clearly illustrate the differences in the chemical shift values for the angular methyl group doublet. This chemical shift difference is therefore an important tool which can be used to help assignment of the configuration of this methyl group in the fatty acid chain of the amides.

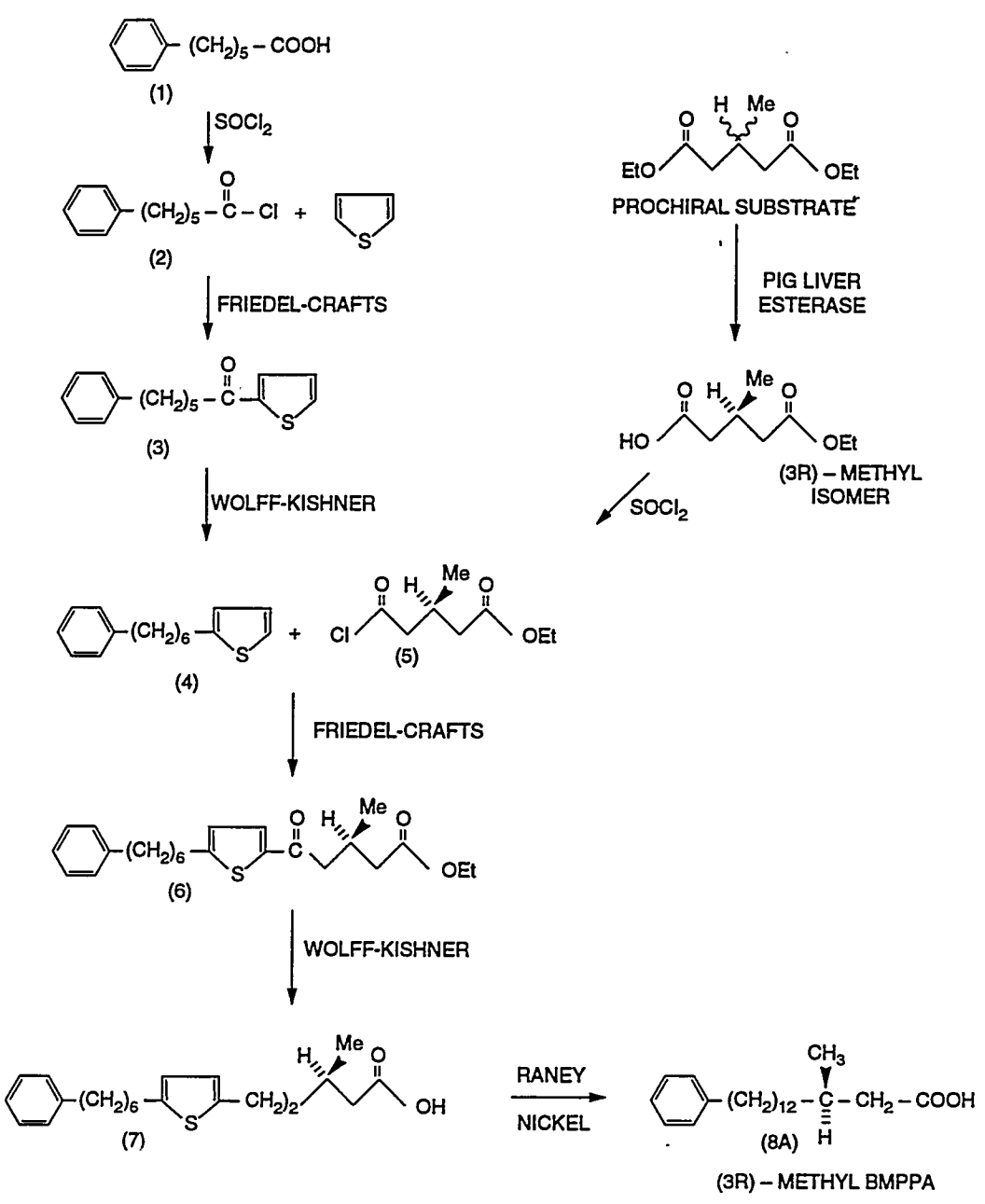

Figure 2. Synthesis of 3R-BMPPA and 3R-BMIPP using commercially available ethyl-3R-methylglutarate.

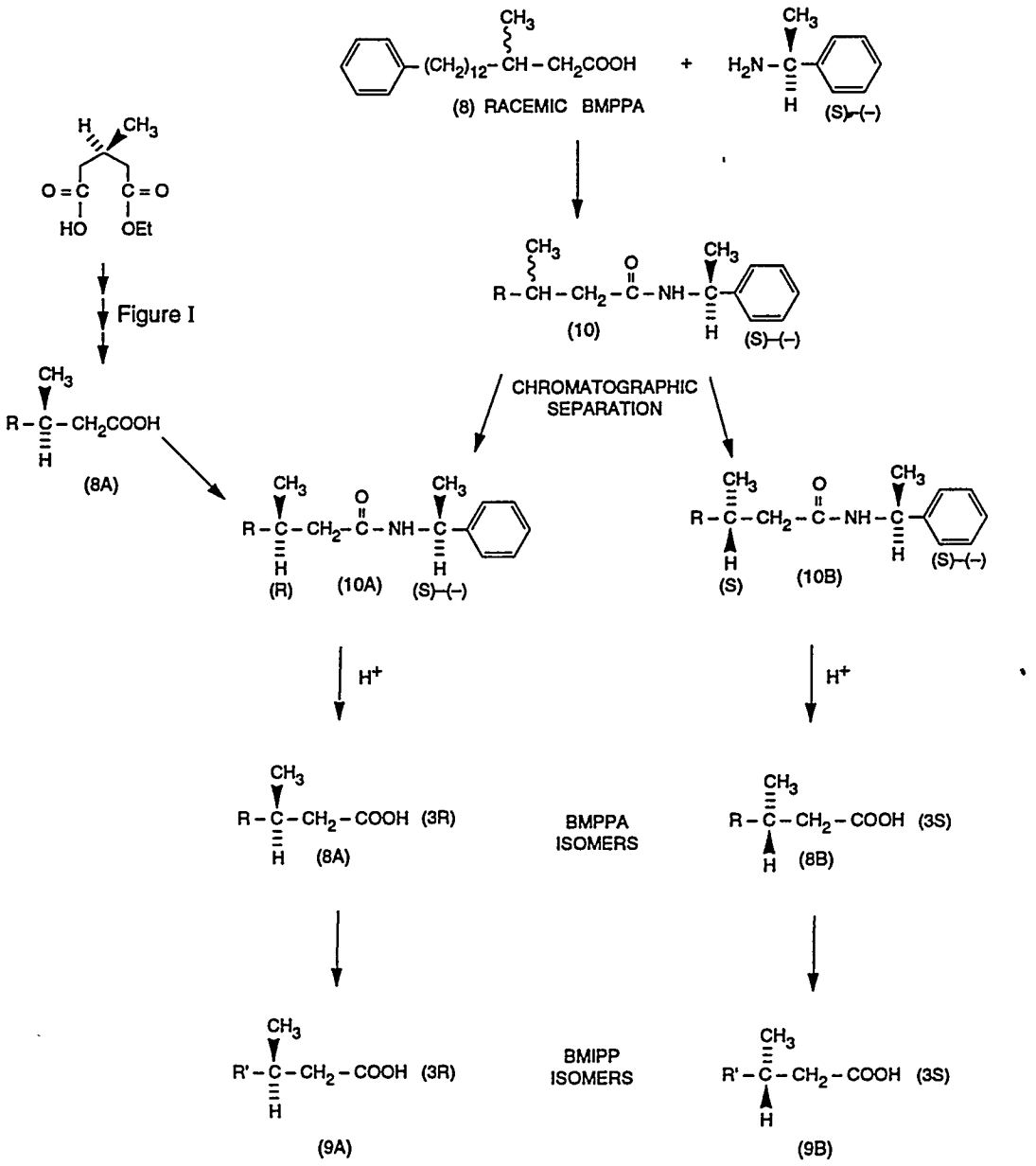

Figure 3. Resolution of the amides of 3R- and 3S-methyl BMPPA and BMIPP by reaction of the acyl chlorides of the racemic BMPPA and racemic BMIPP mixtures with (S)-(-)-α-methylbenzylamine.

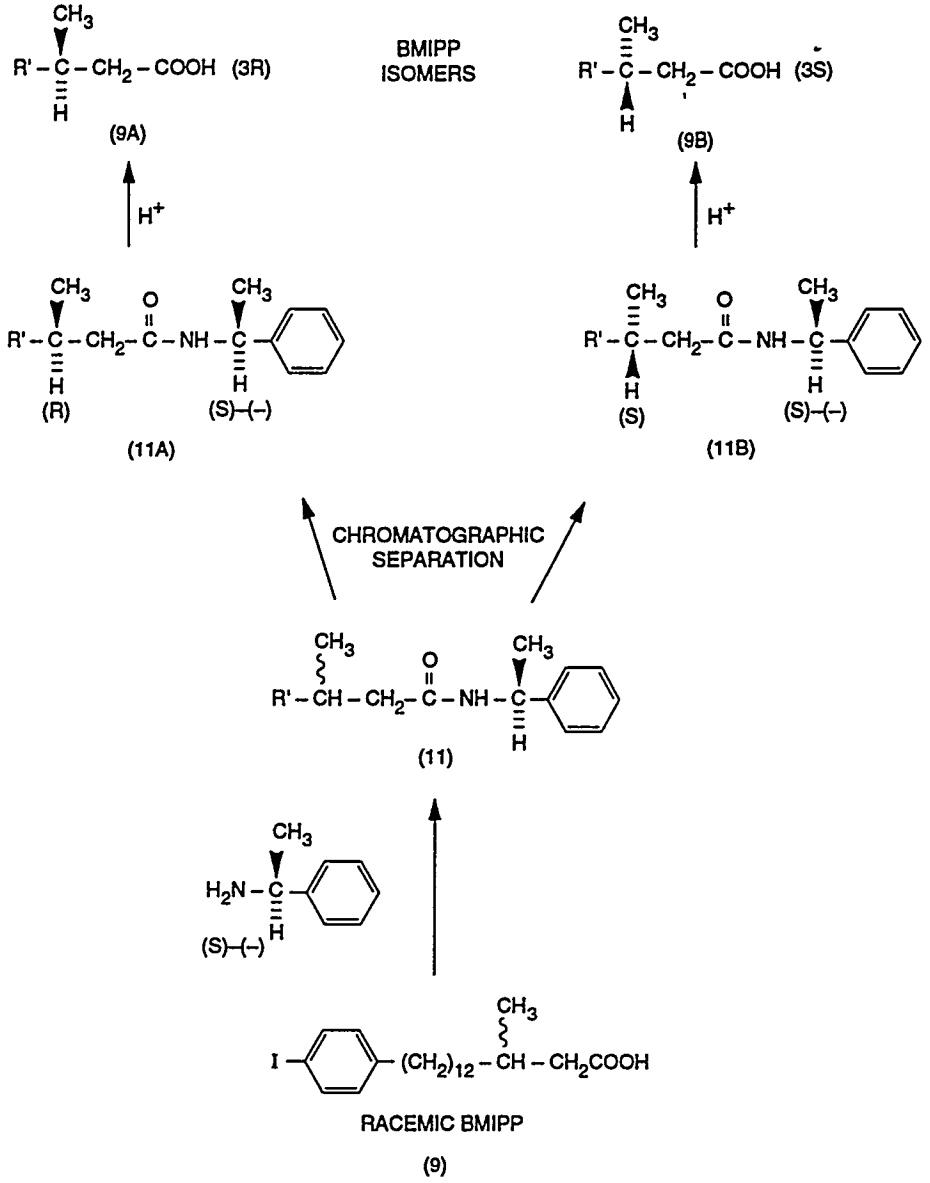

Figure 3, Continued

Resolution of the amides of 3R- and 3S-methyl BMPPA and BMIPP by reaction of the acyl chlorides of the racemic BMPPA and racemic BMIPP mixtures with (S)-(-)-α-methylbenzylamine.

The 3S-methyl and 3R-methyl isomers were freed from the (R,S) and (S,S) diastereomeric amides by acid treatment. To determine the optimal conditions for acid hydrolysis of the amides, 5 mg aliquots of the amide of 3R-BMPPA were heated with 1-2 ml of concentrated HCl in a Teflon-lined bomb in a oven for two hours at temperatures beginning at 100 °C increasing in 25 ° increments to 200 °C. The products were analyzed by TLC and proton NMR. Since the doublet for the β-methyl group of the free acid resonated downfield from the doublets for either amide (Table 2 and Figure 4), integration of this region provided an estimate of the degree of hydrolysis. Based on these systematic studies, a hydrolysis temperature of 175 °C for two hours was chosen for preparative-scale hydrolysis of the 3S-BMPPA-amide. The specific rotation values determined for the two BMPPA isomers, while of low magnitude (Table 1), have opposite magnitude. Because of the relatively small amounts of the free acids which were available from these studies and the very low specific rotation values, the optical rotations for the free acids were difficult to measure accurately. As expected, proton NMR analysis demonstrated that the doublet for the secondary methyl substituent had the essentially same chemical shift value for both BMPPA isomers (Table 2). The iodinated BMIPP isomers were prepared from the purified 3R- and 3S-methyl isomers and exhibited spectral properties which were consistent with the proposed structures.

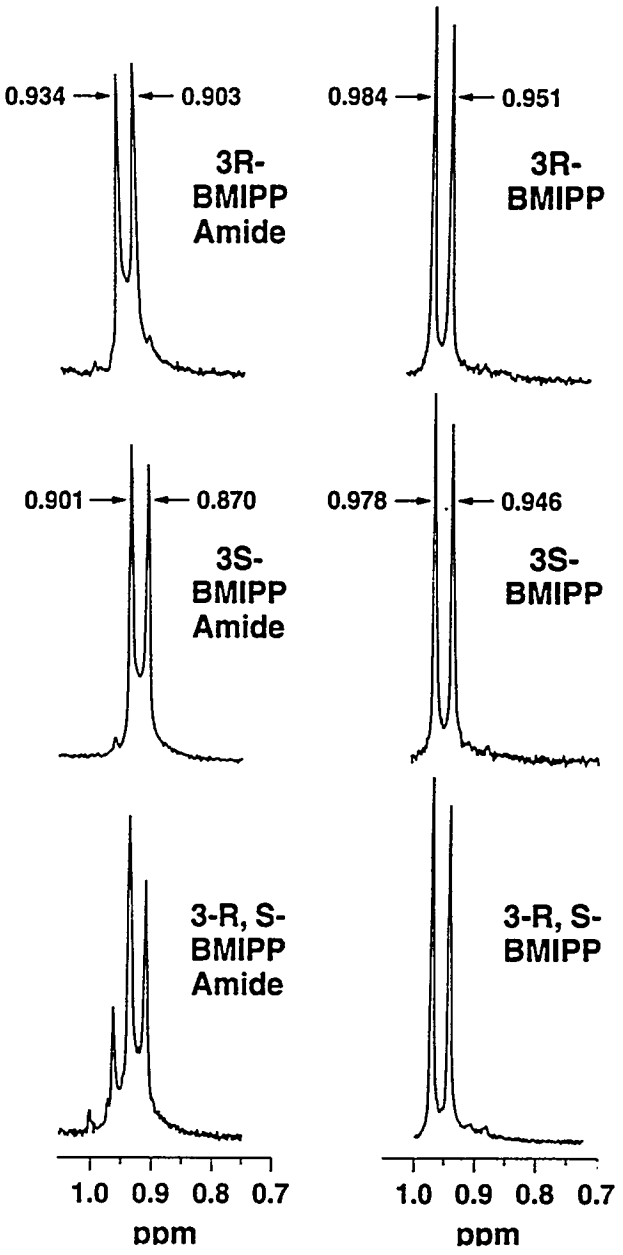

Figure 4. Illustration of the differences in the chemical shift values of the doublet representing the secondary methyl group of BMPPA and BMIPP in diastereomeric amides formed by reaction of the BMPPA and BMIPP enantiomeric acyl chlorides with (S)-(-)-α-methylbenzylamine observed in the proton spectra.

Table 1. Specific Rotation [α_D] Values (c = g/ml, chloroform) for theFree Acid and Amides. Amides Were Prepared by Reaction of the Corresponding Acid Chloride with (S)-(-)-α-Methylbenzylamine. *

Compound	Free Acid Degrees Rotation	Amide Degrees Rotation
3-(R,S)-BMPPA	0	0
3R-BMPPA		
Synthetic	+ 1.47 °	- 44.95 °
From Amide Mixt.	+ 4.49 °	- 49.59 °
3S-BMPPA	- 3.90 °	- 49.65 °
3-(R,S)-BMIPP	0	0
3R-BMIPP		
Synthetic	+ 0.74 °	- 41.74 °
From Amide Mixt.	+ 1.94 °	- 39.60 °
3S-BMIPP	- 2.50 °	- 40.69 °

* The specific rotation for the commercial ethyl-3R-methylglutarate $[\alpha]_D$ = - 1.51 ° (Literature = - 1.50 °).

Table 2. Proton NMR Spectra Chemical Shifts of Methyl Doublets (ppm) for Free Acids and Amides.

Compound	Free Fatty Acid		Amide	
	Downfield	Upfield	Downfield	Upfield
3R-BMPPA:				
Synthetic	0.979	0.946	...	...
From Amide	0.979	0.946	0.935	0.904
3S-BMPPA (From Amide)	0.977	0.944	0.907	0.876
3R-BMIPP:				
Synthetic	0.979	0.946	...	...
From Amide	0.977	0.946	0.937	0.906
3S-BMIPP	0.977	0.945	0.906	0.875

* All samples were analyzed in $CDCl_3$ and resonances are reported downfield from the TMS internal standard. Amides prepared from reaction of acid chlorides with S-(-)-α-Methylbenzylamine. The doublet for the N-methyl group had essentially the same chemical shift value for all free acids and for the amides.

Table 3. Summary of High Pressure Liquid Chromatographic (HPLC) Retention Times of BMIPP and BMPPA Free Acids and Amides Prepared from (S)-(-)-α-Methylbenzylamine.

Compound	Free Acid * Retention Time, min (C18 Column)	Amide ** Retention Time, min (Silica Gel Column)
3-(R,S)-BMPPA	2.856	...
3R-BMPPA		
Synthetic	2.855	...
From Amide Mixture	2.849	1.590 ± 0.018
3S-BMPPA	2.859	1.485 ± 0.014
3-(R,S)-BMIPP	3.685	...
3R-BMIPP		
Synthetic	3.693	...
From Amide Mixture	3.693	1.568 ± 0.006
3S-BMIPP	3.689	1.471 ± 0.007

* Relative to the acetone solvent peak.

** Relative to the chloroform solvent peak.

The radioiodinated 3R- and 3S-BMIPP isomers were prepared and evaluated in fasted female Fisher rats by comparison with the tissue distribution of activity with the racemic mixture. In our initial experiment (Table 4), iodine-125-labeled 3S-, 3R- and racemic BMIPP were evaluated in separate groups of fasted female Fisher rats. The results from this study demonstrated that the 3R-BMIPP isomer had greater myocardial uptake than the 3S-isomer, although levels of radioactivity in other tissues evaluated were similar, except for greater hepatic uptake of the 3S-BMIPP isomer. To further evaluate the relative tissue uptake values at various time intervals, [I-131]-3S-BMIPP and [I-125]-3R-BMIPP were synthesized and purified by preparative HPLC. The purified samples (Figure 5) were then formulated together in 6% BSA solution and the dual-labeled mixture then administered to groups of fasted rats. In this manner, each rat served as a control to eliminate differences between groups of rats. The results (Table 5) confirmed the earlier study and clearly demonstrated greater myocardial uptake of the 3R-BMIPP isomer compared to 3S-BMIPP. The per cent dose per gram values were similar for the other tissues evaluated. One group of rats was also individually housed in metabolism cages and the urine and feces collected daily. Both isomers showed similar excretory patterns (Figure 5).

Table 4 Comparison of the Distribution of Radioactivity in Tissues of Separate Groups of Fasted Female Fisher Rats Following Intravenous Administration of [I-125]-3R-BMIPP, [I-131]-3S-BMIPP or [I-125]-3-R,S-BMIPP *

Per Cent Injected Dose Per Gram of Tissue Values						
Minutes After Injection	BMIPP Isomer	Blood	Heart	Liver	Lungs	Thyroid
30 Minutes	3R-	2.44 ± 0.24	**4.02** ± 0.75	3.78 ± 0.65	1.57 ± 0.18	32.56 ± 27.2
	3S-	2.25 ± 0.04	**2.81** ± 0.20	2.92 ± 0.14	1.49 ± 0.11	35.13 ± 3.6
	3-R,S-	2.05 ± 0.80	**3.95** ± 1.42	2.89 ± 1.34	1.44 ± 0.57	33.91 ± 14.5
60 Minutes	3R-	1.98 ± 0.08	**3.75** ± 1.04	2.03 ± 0.56	1.04 ± 0.14	44.45 ± 10.5
	3S-	1.97 ± 0.18	**2.28** ± 0.73	2.29 ± 0.49	1.25 ± 0.13	16.21 ± 10.8
	3-R,S-	2.25 ± 0.10	**2.82** ± 0.22	2.94 ± 0.15	1.50 ± 0.08	24.74 ± 10.9

* Each animal was injected with 0.5 ml 6% BSA solution to which had been complexed the following injected doses: [I-125]-3R-BMIPP = 3.2 μCi/rat; [I-125]-3S-BMIPP = 3.85 μCi/rat; 3-R,S-BMIPP = 2.3 μCi/rat.

Table 5.Comparison of the Distribution of Radioactivity in Tissues of Groups of Fasted Female Fisher Rats Following Intravenous Administration of a Dual-Labeled Mixture of [I-125]-3R-BMIPP and [I-131]-3S-BMIPP *

Per Cent Injected Dose Per Gram of Tissue Values ± S.D.						
Minutes After Injection	BMIPP Isomer	Blood	Heart	Liver	Lungs	Thyroid
5	[I-125]-3R	2.27 ± 0.13	**5.25** ± 0.77	6.41 ± 0.81	2.06 ± 0.15	18.79 ± 9.3
	[I-131]-3S	2.16 ± 0.20	**4.51** ± 0.50	7.18 ± 0.92	1.98 ± 0.10	17.42 ± 8.7
30	[I-125]-3R	2.09 ± 0.15	**4.37** ± 1.22	2.70 ± 0.28	1.51 ± 0.15	21.12 ± 8.9
	[I-131]-3S	2.07 ± 0.19	**3.44** ± 0.79	2.76 ± 0.29	1.53 ± 0.12	18.73 ± 8.2
60	[I-125]-3R	2.12 ± 0.14	**3.36** ± 0.61	2.02 ± 0.21	1.33 ± 0.14	20.60 ± 8.0
	[I-131]-3S	2.09 ± 0.13	**2.51** ± 0.29	2.03 ± 0.19	1.36 ± 0.13	19.41 ± 8.9
180	[I-125]-3R	1.70 ± 0.10	**2.31** ± 0.51	1.03 ± 0.06	1.23 ± 0.09	16.85 ± 10.4
	[I-131]-3S	1.69 ± 0.09	**1.78** ± 0.26	1.05 ± 0.05	1.22 ± 0.09	15.45 ± 9.2

* Five fasted rats were studied for each group. Each rat was injected via a lateral tail vein with a mixture of 3.95 μCi [I-125]-3-R-BMIPP and 1.07 μCi [I-131]-3-BMIPP complexed to a 6% BSA solution.

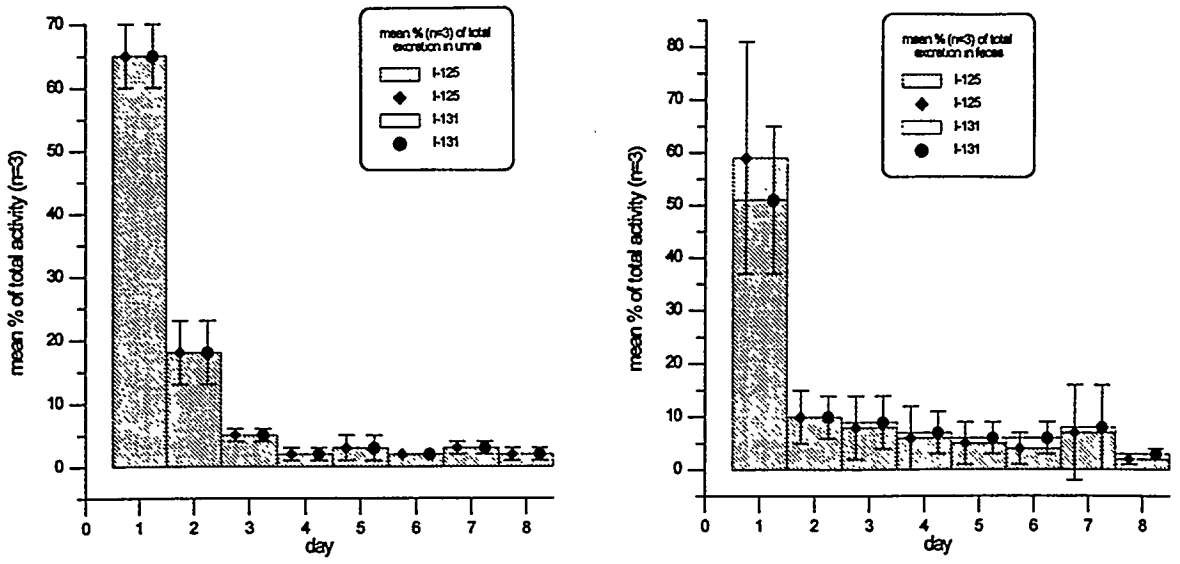

Figure 5. Relative excretion of radioactivity in the urine and feces of fasted rats after intravenous administration of a mixture of [I-125]-3R-BMIPP and [I-131]-3S-BMIPP.

These studies have demonstrated that the 3R-BMIPP isomer has greater myocardial uptake in rats compared to the 3S-BMIPP isomer. Although it may have been expected that only one BMIPP isomer would have significant myocardial extraction and/or that the myocardial release kinetics for the isomers would be drastically different, the results demonstrate that the observed difference is reflected in the myocardial extraction of the two radioiodinated BMIPP isomers. The slopes of the curves observed for myocardial for release of radioactivity are essentially the same (Figure 5), and may reflect differences in myocardial extraction of the two isomers. Although an error in determination of the injected dose values would increase or decrease the experimental values, the

per cent injected dose per gram values for the other tissue examined were similar for the two isomers (Table 5), which provides further evidence for the differences in absolute myocardial extraction for the two isomers. Future studies will determine if the relative incorporation of the two BMIPP isomers into intracellular lipids is similar as described earlier for the racemic BMIPP[13]. In addition, evaluation of the relative formation of the p-iodophenylacetic acid metabolite and other expected oxidative products which have been identified from the racemic 3-R,S-BMIPP mixture [14] will be evaluated.

The potential relevance of these results to clinical studies must await the evaluation of the iodine-123-labeled 3S- and 3R-BMIPP stereoisomers in humans. Although the relative myocardial uptake and pharmacokinetic behavior of these isomers in humans cannot be predicted, significantly increased myocardial uptake and/or different pharmacokinetic properties of one isomer may have certain benefits. If the relative uptake and properties of the 3R-BMIPP and 3S-BMIPP observed in animal studies are reproduced in humans, then [I-123]-3R-BMIPP may represent the preferred isomer for expanded clinical studies focussed on the use of iodine-123-BMIPP in comparison with flow tracers for the evaluation of myocardial viability. Of course the differences in behavior of the 3R- and 3S-BMIPP may be more or less pronounced in humans. The advantages of increased myocardial specificity of one BMIPP isomer are important since the costs associated with iodine-123 could be reduced. Increased retention would permit better statistics for serial SPECT at later time periods. In addition, the radiation exposure would be reduced and lower relative non-target tissue uptake in humans would improve visualization of the myocardium for example, if the relative myocardial/hepatic ratio were increased, visualization of the inferior myocardial wall may be improved.

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Other Nuclear Medicine Group Activities

F. F. (Russ) Knapp, Jr., ORNL Nuclear Medicine Group Leader, accepted an invitation to serve as sub-chairman for the halogen radiopharmaceutical papers for the Annual Meeting of the Society of Nuclear Medicine to be held in "Denver, Colorado, on June 2-6, 1996.

Publications

D. W. McPherson, C. R. Lambert, K. Jahn, V. Sood, R. C. McRee, B. Zeeberg R. C. Reba and F. F. Knapp, Jr., "Resolution and *In Vitro* and *In Vivo* Evaluation of Isomers of Iodine-125-Labeled 1-Azabicyclo-[2.2.2]oct-3-yl-α-Hydroxy-α-(1-iodo-1-propen-3-yl)-α-phenyl acetate: A High Affinity Ligand for the Muscarinic Receptor," J. Med. Chem., 38, 3908-3917 (1995).

Members of the ORNL Nuclear Medicine Group have co-authored two sections in the recently published 2nd edition of "Principles of Nuclear Medicine," edited by Henry Wagner, Z. Szabo and J. W. Buchanan, editors, published by W. B. Saunders Co. (1,300 pages). The first edition of this book was published in 1968 and is the most widely recognized comprehensive textbook and reference book on both the basic science and clinical aspects of nuclear medicine.

F. F. Knapp, Jr. and S. Mirzadeh, "Reactor Production of Medical Radioisotopes," pp. 135-143.

F. F. Knapp, Jr., C. Brihaye and A. P. Callahan, "Radionuclide Generators for Nuclear Medicine Applications." pp. 150-165.

F. F. Knapp, Jr., "Radionuclide Generator Systems," Chapter 10, pp. 203-213, In, Nuclear Medicine - Diagnosis and Therapy, J. C. Harbert, W. C. Eckelman, R. D. Neuman, Editors, Thieme Medical Publishers, Inc., New York, 1995, 1256 pages.

Presentations

On December 15, 1995, F. F. (Russ) Knapp, Jr., presented an invited "ORNL Showcase Lecture," entitled, "From Twinkling Atoms to Glowing Hearts - Nuclear Medicine Research at ORNL," which presented an opportunity to discuss the history of nuclear medicine research at ORNL, and in particular, recent advances in the development of imaging agents to evaluate myocardial viability and cerebral neuroreceptor activity being developed by the nuclear medicine program.

Medical Cooperative Programs

In a cooperative study with collaborators at the Canterbury and Kent Hospital in Canterbury, England (P. J. Blower, Ph.D., and M. O'Doherty, M.D., *et al.)* initial tracer targeting studies have demonstrated excellent uptake of the Re(V)-188-DMSA complex in skeletal lesions in patients with metastases from prostate and bronchial cancer. Because of the expected significantly reduced costs of rhenium-188 from the ORNL tungsten-188/rhenium-188 in comparison with other radioisotopes proposed for bone palliation, there is broad interest in the use of rhenium-188. Since these initial studies have shown excellent uptake in metatheses and low liver and kidney uptake, therapeutic studies with larger amounts of the Re(V)-188 DMSA agent have been planned for early in 1996 to assess the effectiveness of this agent in relieving the bone pain associated with skeletal metastases.

Distribution of Radioisotopes By Cost Recovery Through the ORNL Isotopes Distribution Office (IDO)

Several radioisotopes and tungsten-188/rhenium-188 generators were provided to customers on a cost-recovery basis through the ORNL Isotope Distribution Office (IDO), and included tungsten-188/rhenium-188 generators provided to CIS Bio-International in France, and ANSTO in Sydney, Australia. One sample of tim-117m was provided on a cost-recovery basis to Golden Pharmaceuticals for preparation of tin-117m for bone pain treatment in a program in conjunction with Diatech, Inc. and the Medical Department at BNL. In addition, samples of high specific rhenium-186

produced in the ORNL HFIR were provided to Mallinckrodt, Inc. in St. Louis, Missouri and Petten, Holland, and NeoRx, Inc. in Seattle, Washington, to evaluate the purity and use of this radioisotope from ORNL for preparation of therapeutic agents.

Visitors and Guest Assignment

Several visitors and guests during this period included Prof. Lon Wilson, from the Chemistry Department at Rice University in Houston, Texas, who visited on October 16, 1995, to discuss and coordinate collaborative studies for the development of radiometal-labeled metallo endofullerenes. On October 16, 1995, Dr. Susan Smith, visited from ANSTO, in Sydney, Australia, to discuss continuing collaborative projects with ORNL. On October 25, 1995, Dr. M. Yacama, Director of the Mexican Nuclear Institute, visited with the ORNL Nuclear Medicine Group for a tour of facilities and an overview of current areas of research at ORNL and potential areas of collaborative research. On December 4, 1995, Drs. Jeff Wu and Akira Mackawa, U.S. representatives from Nihon Medi-Physics, Inc., located in Emeryville, California visited for a tour and discussions of areas of mutual interest.

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EXTERNAL DISTRIBUTION

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