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**Nuclear Medicine Program Progress
Report for Quarter Ending
December 31, 1990**

F. F. Knapp, Jr.
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A. P. Callahan
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NUCLEAR MEDICINE PROGRAM PROGRESS REPORT
FOR QUARTER ENDING DECEMBER 31, 1990

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SUMMARY

In this report the development of a solvent extraction technique for the efficient separation of iridium radioisotopes from osmium radioisotopes is described. Although this technique would be most useful for the separation of iridium-194 (Ir-194, $t_{1/2}$ 19 h) from the osmium-194 (Os-194, $t_{1/2}$ 5.9 years) parent, for these developmental studies a mixture of Os-191 ($t_{1/2}$ 15 d) and Ir-192 ($t_{1/2}$ 74 d) was used. The Os-191 (Os-VIII) was efficiently separated from iridium-192 by extraction of a 1 M HCl solution with $< 10^{-2}$ M tetrahexylamine (THA) in methyl isobutyl ketone. Over 99% of the osmium is extracted in one step, leaving the radioactive iridium in the aqueous acidic solution. This simple extraction technique may be useful for the development of a new Os-194/Ir-194 generator prototype which is currently being explored.

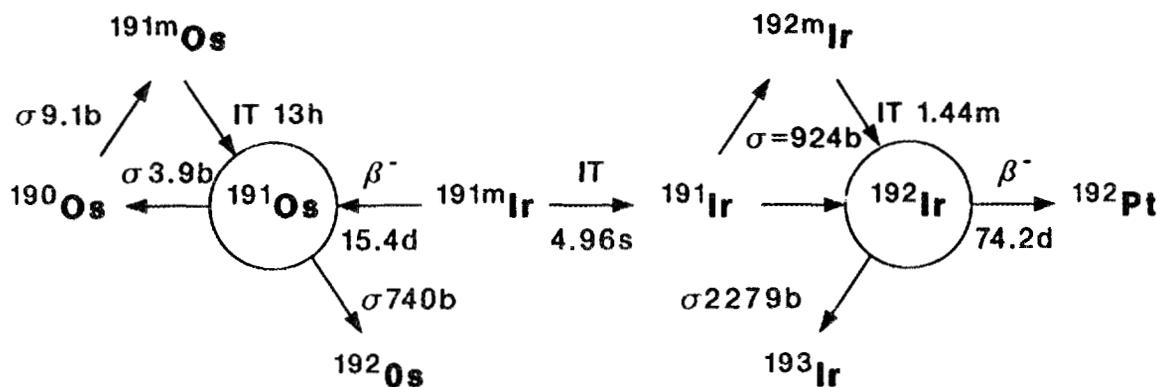
Also in this report, biodistribution studies of the two iodine-125 (I-125)-labeled spiroperidol analogues, E-3-N-(iodo-1-propen-3-yl)- and E-3-N-(iodo-1-penten-5-yl)spiroperidol in male Balb C mice are described. Groups of 5 mice each were administered the test agents intravenously and sacrificed after 30, 120 and 300 min. The brains were removed and the regional distribution of radioactivity in the dopamine-rich striatal and the control cerebellar regions then determined. The highest ratios were only 1.5:1 to 2.3:1, observed after 300 min, indicating that the iodoalkenyl nitrogen substituent probably increases the lipophilicity resulting in greater non-specific cerebral uptake.

Several samples were supplied for collaborative research projects during this period and included I-125 and I-131 methyl-branched fatty acids which were supplied to investigators at the Brookhaven National Laboratory (BNL) and the Clinic for Nuclear Medicine in Bonn, Germany. In addition, samples of tin-177m (Sn-177m), gold-199 (Au-199) and scandium-47 (Sc-47) produced in the ORNL High Flux Isotope Reactor (HFIR) were supplied to investigators at BNL to assist them in their research projects during the period the BNL High Flux Beam Reactor (HFBR) is not operating.

EXTRACTION OF OSMIUM-191 AND CARRIER-FREE IRIDIUM-192
IN ISOBUTYLKETONE (MIBK) AS THE TETRAHEXYLAMINE
(THA) COMPLEX

The methylisobutyl ketone (MIBK) extraction of metallic ions with quaternary amines from aqueous media has been shown to be an effective method for separation of many elements.¹ We have explored the applicability of this technique for separation of carrier-free iridium-192 (Ir-192) from a neutron irradiated osmium-190 (Os-190) target. In dilute basic, neutral, and dilute acidic solutions, we found that Os is quantitatively extracted into methyl isobutyl ketone (MIBK) as the tetrahexylamine (THA) complex, while carrier-free Ir-192 is essentially retained in the aqueous solution. Based on these data, a possible extraction method is proposed for a prototype Os-194 ($t_{1/2}=6$ y)/Ir-194 ($t_{1/2}=19.2$ h) generator system.

For these preliminary studies Os-191 and Ir-192 were used. The Os-191 ($t_{1/2}=15.4$ d) and carrier-free Ir-192 ($t_{1/2}=74.2$ d) were produced according to the following Scheme²:



Scheme I

Subsequent to irradiation of highly enriched Os-190 in the ORNL-HFIR, the target material was dissolved according to the previously described procedure,³ which involved mixing the target with a KOH/KNO₃ flux in a tantalum crucible and fusion at elevated temperature (approximately 650°C). After cooling, the product cake was dissolved in water to yield an approximately 1 mg/ml solution of Os with a specific activity of 50 $\mu\text{Ci}/\text{mg}$ for Os-191 at the time of the studies. The activity of carrier-free Ir-192 in this solution was

approximately 100 μCi and the total Ir concentration was $\leq 10^{-6}$ M. This value was extrapolated from spectrographic analysis of the target material.

In a typical experiment, 10 μL of Os target solution was added to a mixture of 5 ml of 1 M HCl and 5 ml of 10^{-2} M THA reagent. The THA reagent was prepared by dissolving 480 mg of tetrahexylamine in 100 ml of MIBK. A 15 ml centrifuge cone fitted with ground glass stopper was used as a convenient extraction vessel. The mixture was vigorously shaken for 2 min, and prior to separation of phases, centrifuged for 2 min. Both aqueous and organic phases were assayed for radioactivity, and the percent extraction is reported relative to the content of an external radioactive standard. The activity of Os-191 and Ir-192 was quantitated using gamma spectrometry by analysis of the 129 (25%) and 316 (82%) keV gamma-rays, respectively, in a calibrated high purity germanium detector.

The results are summarized in Table 1 and indicate that under the experimental conditions using a concentration of $[\text{THA}] = 10^{-2}$ M, 95.4% of Os-191 was extracted into the organic layer while 99% of carrier-free Ir-192 remained in the aqueous layer. When the concentration of the THA reagent was decreased by 100 fold, it was still possible to quantitatively separate these two radioisotopes within two minutes. Various aqueous solutions were tested for back-extraction of Os from the organic layer, and no suitable conditions were found. The fractions of Os back-extracted into strong NH_4OH (6 M) were about 50% as shown in Table 1. These preliminary results will provide the basis for development of an extraction-based Os-194/Ir-194 generator system.

Table 1. Extraction of Os-191 and Carrier-free Ir-192 in Methyl Isobutyl Ketone (MIBK) as Tetrahexyl Amine (THA) Complex From 1.0 M HCl Solution

Fraction of Activity Extracted, Per Cent						
Phases	[THA]=10 ⁻² M		[THA]=10 ⁻³ M		[THA]=10 ⁻⁴ M	
	Os-191	Ir-192	Os-191	Ir-192	Os-191	Ir-192
Aqueous	4.6	99.8	3.1	100.0	4.3	99.5
Organic	95.0	1.2	96.1	0.1	95.4	0.8
Total	99.6	101.0	99.2	100.1	99.7	100.3
Back-extraction with 6 M NH ₄ OH						
Aqueous	58.1	-	41.0	-	46.8	-
Organic	42.9	-	59.8	-	51.2	-
Total	101.0	-	100.8	-	98.0	-

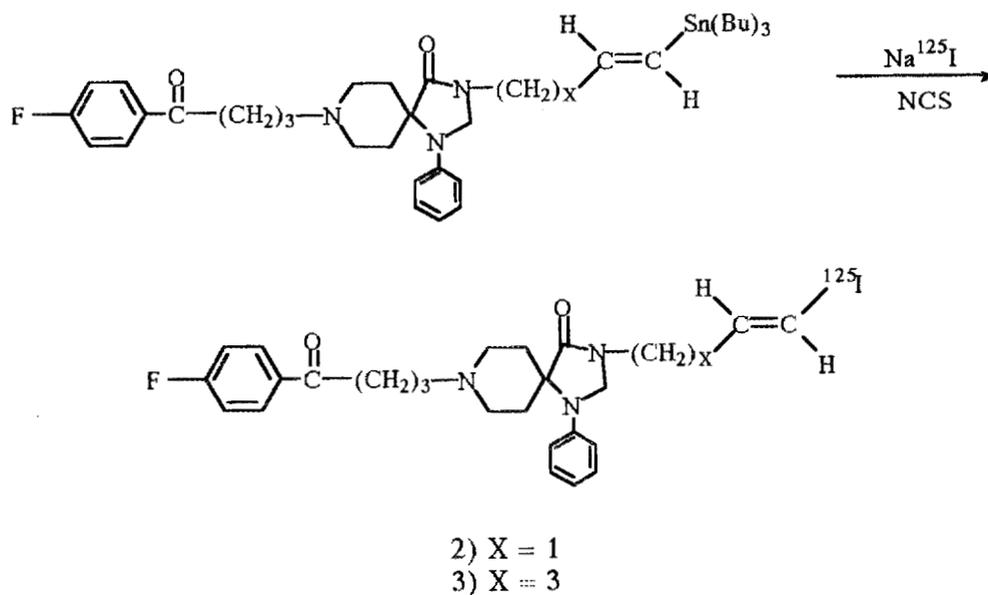
BRAIN DISTRIBUTION OF RADIOLABELED IODOALKENYL
ANALOGUES OF SPIROPERIDOL

The ability to image dopamine-rich areas of the brain by single photon emission computerized tomography (SPECT) has enhanced the need for new, improved receptor-specific radiopharmaceuticals labeled with short-lived radionuclides. Spiroperidol (1, Figure 1) is used for the treatment of neuropsychiatric disorders and has high specificity for dopamine D2 receptors, thus making radiolabeled analogues of this ligand attractive candidates for imaging studies. Studies have demonstrated that substitution on the lactam nitrogen increases the lipophilicity and therefore the brain uptake of spiroperidol analogues. We have investigated analogues in which an iodoalkenyl group radiolabeled with iodine-125 is placed in this position. We previously reported (ORNL/TM-11224) preparation of analogues in which a E-3-iodo-2-propenyl (2) and E-5-iodo-4-pentenyl (3) group has been introduced on the lactim nitrogen of 1 (Figure 1).

The reaction of the tributylstannyl intermediate (4) and (5) with sodium iodide-125 in the presence of N-chlorosuccinimide (NCS) followed by heating in acidic methanol as shown in Scheme II. This procedure afforded radioiodinated 2 and 3, respectively, in good yield after semi-preparative HPLC purification. The TLC and HPLC properties were identical to those of the unlabeled standard. The results of the brain uptake studies in male Balb-C mice with compounds 2 and 3 are shown in Tables 1 and 2. Groups of 5 mice received intravenous injections of 2 or 3 and were killed at 30, 120 and 300 min after injection. The striatum and cerebellum, in addition to the remainder of the brain tissue, were assayed for radioactivity.

While this work was in progress, the preparation and dopamine D2 receptor selectivity and specificity *in vitro* and *in vivo* of E- and Z-2 labeled with iodine-125 were reported and concluded that 2 is a potential ligand for the imaging of dopamine D2 receptors.⁴ We therefore studied the relative uptake of 2 and 3 into the dopamine rich area (striatum) as compared to the receptor poor area (cerebellum). These studies allowed a comparison of the uptake of 3 into dopamine D2 receptor rich areas and allowed the use of 2 as a control. As shown in Tables 2 and 3, compound 3 has lower global brain uptake and a corresponding lower striatal to cerebellar ratio indicating a higher nonspecific binding relative to dopamine

D2 receptor sites. These data therefore suggest that **2** is a better ligand for the recognition of the dopamine D2 receptor populations *in vivo*.



Scheme II

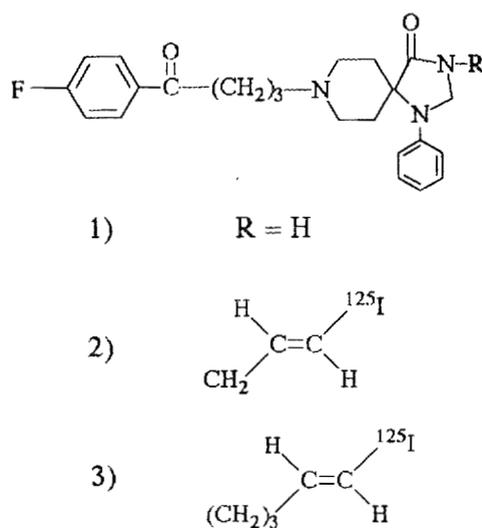


Figure 1.

Studies with radiobrominated analogues of spiroperidol have demonstrated that as the lipophilicity of the analogue increases, a point for maximum brain uptake is reached and the binding to the blood proteins interferes with blood clearance, thereby lowering the brain to blood ratio.⁵ It was also reported in the same study that nonspecific binding occurs as lipophilicity increases. One possible reason for the lower specificity of 3 for dopamine rich regions of the brain may thus be that the iodopentenyl group increases the lipophilicity of the molecule to a greater extent than the iodopropenyl group and results in the greater non specific binding which is observed.

Table 2. Tissue distribution (mean % injected dose/g \pm SD) of E-3-N-(1-[¹²⁵I]iodo-1-propen-3-yl)spiroperidol (2) in male Balb-C mice (n=5).

Organ	Time after injection (min)		
	30	120	300
Brain	0.26 \pm 0.09	0.17 \pm 0.02	0.13 \pm 0.02
Striatum (S)	0.29 \pm 0.14	0.23 \pm 0.04	0.18 \pm 0.06
Cerebellum (C)	0.26 \pm 0.11	0.15 \pm 0.02	0.08 \pm 0.03
S/C ratio	1.1	1.5	2.3

Table 3. Tissue distribution (mean % injected dose/g \pm SD) of E-3-N-(1-[¹²⁵I]iodo-1-penten-5-yl)spiroperidol (3) in male Balb-C mice (n=5).

Organ	Time after injection (min)		
	30	120	300
Brain	0.05 \pm 0.02	0.06 \pm 0.02	0.05 \pm 0.02
Striatum (S)	0.01 \pm 0.05	0.04 \pm 0.08	0.06 \pm 0.11
Cerebellum (C)	0.05 \pm 0.02	0.04 \pm 0.02	0.04 \pm 0.02
S/C Ratio	0.2	1.0	1.5

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AGENTS FOR MEDICAL COOPERATIVES

One shipment each of I-125 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP), I-131 BMIPP, and I-125 15-(p-iodophenyl)-3,3-dimethylpentadecanoic acid (DMIPP) were supplied for a collaborative program with Brookhaven National Laboratory (P. Som, D.V.M.) to study the effects of cocaine on myocardial uptake and metabolism of fatty acid energy substrates in a rat model. One shipment each of I-125 BMIPP and I-125 DMIPP were also supplied to the University of Bonn, Germany (J. Kropp, M.D.) for continuing studies of fatty acid metabolism in an isolated rat heart model which are being conducted in conjunction with patient studies with I-123 BMIPP in Bonn. Samples of Sn-117m, Au-199, and Sc-47 from the HFIR were supplied to Brookhaven National Laboratory (L. Mausner, Ph.D.).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Coursey, B., Calhoun, J. M., Cessna, J., Hoppes, D. D., Schima, F. J., Unterweger, M. P., Golas, D. B., Callahan, A. P., Mirzadeh, S., and Knapp, F. F., Jr. "Assay of the Eluent from the Alumina-Based Tungsten-188/Rhenium-188 Generator," *Radioactivity and Radiochemistry*, 3:38-49 (1990).

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Srivastava, P. C., Knapp, F. F., Jr., Callahan, A. P., and Goldstein, B. M. "Myocardial Imaging Agents: Synthesis, Characterization, and Evaluation of [(Z) and (Z,E)-1-(⁸²Br)Bromo-1-penten-5-yl]triphenylphosphonium Cations," *J. Label. Compds. Radiopharm.*, 28, 1161-1170 (1990).

Collaboration on Clinical Trials

The first patient studies using Sn-117m-DTPA for the palliative treatment of bone pain were initiated in a collaborative program with investigators in the Medical Department at the Brookhaven National Laboratory (BNL) and at the State University of New York at Stony Brook. The initial Sn-117m production studies by irradiation of enriched Sn-116 (n, γ) in the HFIR and subsequent chemical processing were conducted at ORNL during the 1983-1985 period, and the preparation and testing of Sn-117m-DTPA was conducted at BNL. The results showed very high cortical bone uptake, and dose radiation dose calculations indicated that the short-range conversion electrons and Auger electrons would deliver a bone dose as high as 21 rads/mCi. These results identified this new agent as a good candidate for the treatment of bone pain associated with the metastasis of primary tumors to the skeleton, particularly from the ovaries and prostate. The Sn-117m has now been produced by the (n,n', γ) reaction on enriched Sn-117 and shipped to BNL for preparation of this agent. Initial Phase I studies at BNL will involve the administration of tracer levels of the Sn-117m-DTPA to cancer patient volunteers. The goal is to confirm the expected high skeletal uptake by gamma camera imaging. Successful completion of these initial studies will form the basis for additional therapeutic studies at Stony Brook.

Grants

F. F. Knapp, Jr. has received a NATO Collaborative Research Grant as project coordinator in conjunction with J. Kropp, M.D., at the Clinic for Nuclear Medicine at the University of Bonn, Germany, entitled "Metabolism of Radioiodinated Fatty Acids Used for Heart Imaging." The grant will support collaboration on the preclinical and clinical evaluation in patients in Bonn of the I-123 BMIPP modified fatty acid cardiac imaging agent developed at ORNL.

Miscellaneous

P. C. Srivastava visited institutions in India during the November 24-December 29 period under support of a United Nations Developmental Award for Distinguished Scientists. He presented lectures at the Central Drug Research Institute in Lucknow and at the Bhabha Atomic Research Center in Bombay. He also attended the Annual Conference of the Indo-American Society of Nuclear Medicine in Calcutta on December 10-17 and discussed collaborative projects on nucleosides and protein labeling with the maleimide technique with colleagues at several institutions.

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