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Nuclear Medicine Progress Report for Quarter Ending December 31, 1987

F. F. Knapp, Jr.
J. F. Allred
K. R. Ambrose
S. L. Blystone
A. P. Callahan
E. C. Lisic
D. W. McPherson
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Printed in the United States of America. Available from
National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road, Springfield, Virginia 22161
NTIS price codes—Printed Copy: A03; Microfiche A01

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ORNL/TM-10711

Contract No. DE-AC05-84OR21400

Health and Safety Research Division

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Work sponsored by
DOE Office of Health and
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Date Published - July 1988

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SUMMARY

The production of osmium-191 by thermal neutron irradiation of enriched osmium-190 has been further evaluated at neutron flux values from 4×10^{14} to 2.5×10^{15} neutrons/cm^2·sec. In order to obtain osmium-191 with a specific activity of 250 mCi per mg of enriched osmium-190, irradiation periods at neutron flux values lower than 2.5×10^{15} neutrons/cm^2·sec have to be extended up to 2-4 weeks. This results in significantly increased levels of the undesirable iridium-192. The iridium-192 is produced by capture of a neutron by iridium-191, which is formed by decay of the short-lived 4.96 sec iridium-191m daughter produced by β^- decay of osmium-191. Elution of even small levels of iridium-192 from the Os-191/Ir-191m generator results in a large proportion of the total absorbed radiation dose from the generator eluate. Two efficient methods for purification of osmium-191 by conversion to osmium tetroxide and isolation by both distillation and solvent extraction methods have been developed for removal of iridium-192.

During this period, iodination of model nucleoside substrates has also been pursued. The reaction of iodine monochloride with the imidazole nucleoside, 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide, provided the unexpected 2-chloroimidazolenucleoside in good yield. This could be a useful method for preparation of other chlorinated imidazoles.

OSMIUM-191/IRIDIUM-191m GENERATOR STUDIES: PURIFICATION OF OSMIUM-191 BY DISTILLATION AND SOLVENT EXTRACTION

The use of ultra-short lived single photon emitting radionuclides for radionuclide angiography (first-pass) offers several advantages including the opportunity to perform rapid repeat studies and a significantly reduced radiation exposure to both patient and personnel. The development of a new osmium-191/iridium-191m radionuclide generator system which utilizes specially heat-treated activated carbon adsorbent has recently been described.[1,2] Using this system, the iridium-191m daughter is obtained in 12-18% yield by elution with 0.9% saline solution at pH 2 containing 0.025% potassium iodide. The generator eluant is neutralized at the outlet during elution with pH 8.4 TRIS buffer to give an isotonic solution at physiological pH for rapid intravenous injection. This generator system exhibits a long useful shelf-life with reproducible performance over a 2-3 week period, and over 600 patient studies have now been conducted by collaborators in Belgium with no adverse effects.

Because of the potential for widespread use of this generator system, the principal goals of the current work were to evaluate the production of the osmium-191 by neutron irradiation of enriched osmium-190 and to study the effect of neutron flux on the production of iridium-192. The production of osmium-191 and iridium-192 in the High Flux Isotope Reactor (HFIR) at the Oak Ridge National Laboratory (ORNL) has been previously described.[3,4] Elution of even low levels of iridium-192 results in a major contribution to the total absorbed radiation dose.[5] Minimization of this by-product radionuclide, which is formed by secondary neutron capture by iridium-191 produced from the decay in the reactor of the 4.96 second ultra-short lived iridium-191m, is thus required. Since several nuclear reactors of moderate neutron flux are available for production of osmium-191, two practical methods have been developed for purification of osmium-191 by removing undesired iridium-192. The availability of these methods will allow the production of osmium-191 in reactors of moderate flux.

One of the goals of the present study was to compare the experimental production values for Os-191 and Ir-192 (Fig. 1) in three reactors with different neutron fluxes (Table 1) with the theoretical values calculated using cross section values available in the literature and calculated from production studies in the HFIR. This work has been pursued in conjunction with Claude Brihaye, Ph.D., and Marcel Guillaume, Ph.D. through

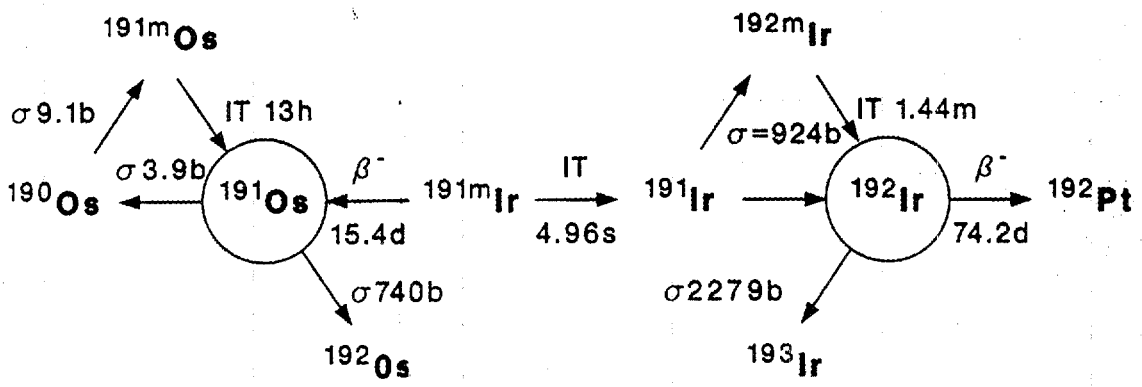


Fig. 1. Production and decay modes for radionuclides produced during neutron irradiation of enriched osmium-190.

collaboration with the University of Liege, Belgium. Dr. Brihaye worked at ORNL for six-month periods during 1983 and 1987, and a close collaboration has continued. In this study, the literature values[8] of the cross sections for the Os-190(n,γ)Os-191m and Os-190(n,γ)Os-191 reactions have been adopted and are 9.1 and 3.9 barns, respectively. The minimal specific activity requirement for the current activated carbon generator is about 250 mCi/mg. This value is required to prepare generators with enough ^{191}Os activity (1-2 Ci) to provide sufficient levels of iridium-191m in small bolus volumes (<3 ml).

Table 1. Summary of Thermal Neutron Flux Values of Reactors Used for Production Studies

Reactor	Thermal Neutron Flux (thermal neutrons/$cm^2 \cdot sec$)
HFIR (ORNL)	2.5×10^{15}
HFBR (BNL)	5×10^{14}
BR2 (Mol, Belgium)	8×10^{14}

Data from earlier HFIR studies clearly demonstrate that production of Os-191 from enriched Os-190 is linearly proportional with time for about 6 days and then deviates for longer irradiation periods.[3,4] Because the Os-191 product has a long physical half-life of 15.4 days, the decrease in production yields with increasing time periods apparently results from a burn-up reaction of the osmium-191 product by further neutron capture. Using the Os-191 production experimental data from the HFIR, a cross section value (Table 2) of 740 barns was calculated for the Os-191(n,γ)-Os-192 reaction using the Bateman equations and a SIMPLEX program (Courtesy of C. Brihaye, Cyclotron Center, University of Liege, Belgium).[9] Direct experimental verification of this value was not possible since Os-192 is a stable isotope and is present in only 1.86% abundance in the enriched Os-190 used for these studies. The accuracy of the Os-191 production scheme was evaluated, however, by a comparison of the experimental production values of Os-191 at neutron fluxes in the HFIR of 2.2×10^{14}, 8.5×10^{14} and 2.5×10^{15} for various irradiation time periods with the expected yields calculated on the base of the production scheme. Figure 2 illustrates that the experimental values fall on the calculated production curve using the calculated burn-up cross section and demonstrates that the production of Os-191 at various neutron flux values can be accurately estimated using this approach.

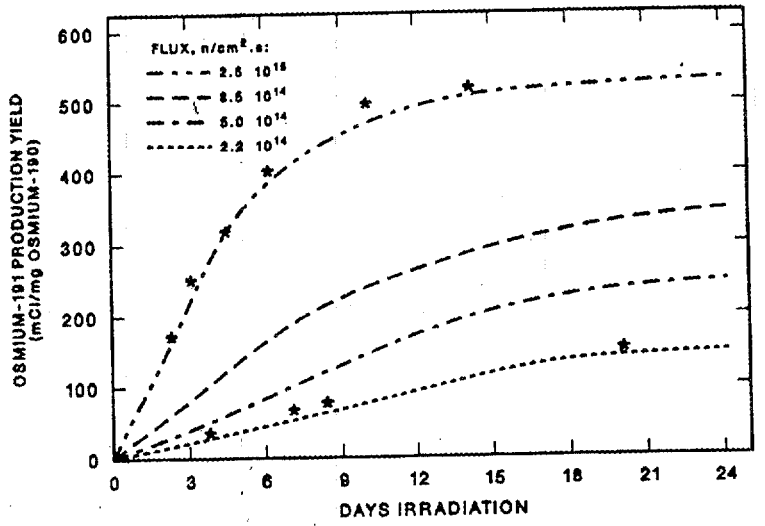


Fig. 2. Osmium-191 production yield from enriched metallic osmium-190 as a function of irradiation time at different thermal neutron fluxes. The curves represent calculated production yields and the stars are experimental data.

Table 2. Neutron Cross-Section Values Used for Radionuclide Production Calculations

(n,γ) Reaction		
Target	Product	Cross-Section (barns)
Os-191	Os-192	740
Os-190	Os-191m	9.1 (ref. 8)
Os-190	Os-191	3.9 (ref. 8)
Ir-191	Ir-192	
Ir-191	Ir-192m	924
Ir-192	Ir-193	2273

A similar approach was used to approximate the production of Ir-192 at various neutron flux values. Earlier studies in the HFIR had demonstrated that Ir-192 production yields increased exponentially with time as would be expected because of the rapid formation of Ir-191 from decay of the ultra-short-lived Ir-191m (4.96 sec) growing in from decay of Os-191 (Fig. 1) and the high neutron cross section for the Ir-191(n,γ)Ir-192 reaction.[3,4] A

cross section value of 924 barns was calculated for the direct Ir-191(n,γ)Ir-192 reaction and through the decay of metastable Ir-192m isomer, and a value of 2273 was found for the Ir-192(n,γ)Ir-193 reaction. The values for Ir-192 production calculated from the cross section values are shown in Fig. 3 and agree very well with the experimental data.

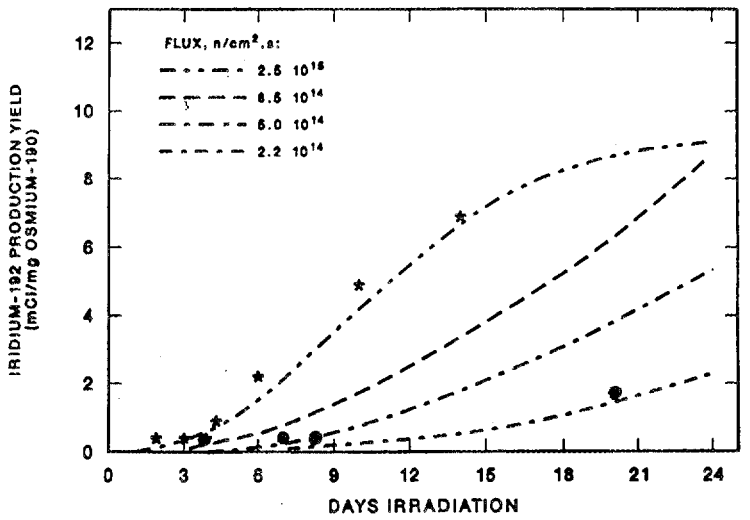


Fig. 3 Iridium-192 production yield from enriched metallic osmium-190 as a function of irradiation time. The curves are the calculated production yields and the stars represent experimental data obtained at 2.5 x 10^{15} n·cm^2/sec and the curves represent experimental data obtained at 2.2 x 10^{14} n·cm^2/sec.

The purification of osmium-191 involves either distillation or solvent extraction of OsO_4 formed via acidification of potassium perosmate (Fig. 4). Distillation of OsO_4 is a well-known procedure in analytical chemistry for the separation of trace levels of osmium from other metals. An alternative method is based on the extraction of osmium tetroxide from aqueous solution by carbon tetrachloride or chloroform.[7] After extraction and separation of the two phases, the organic solvent is shaken with a sulfuric acid solution of thiourea to form the red $Os(NH_2CSNH_2)_6^{3+}$ complex whose color intensity is measured photometrically.[2] Both methods (Fig. 4) for the separation of osmium-191 as the tetroxide from iridium-192 have been evaluated. The separation is based on the reactivity of OsO_4 with potassium hydroxide in aqueous solution form $K_2OsO_4(OH)_2$. In this manner, OsO_4 is back-extracted from the organic phase into aqueous phase

where Os-191 is then recovered in the same chemical form as the starting material.

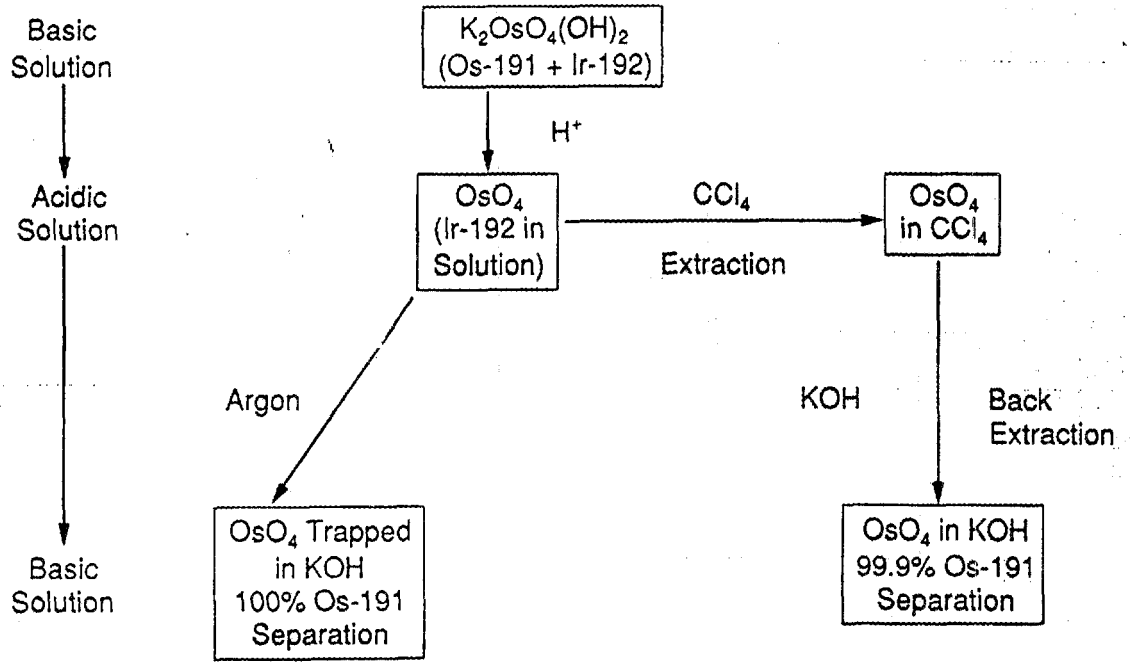


Fig. 4. Schematic of purification of osmium-191 by distillation or extraction of osmium tetroxide.

For the distillation method a special glass system designed for hot cell use has been developed (Fig. 5). The potassium perosmate solution is acidified with nitric acid or sulfuric acid which converts the potassium perosmate to the volatile osmium tetroxide. The osmium-191 is then distilled at a temperature between 50 and 60°C with an argon gas sweep into a KOH solution where the osmium-191 is trapped as potassium perosmate. The discharge of the apparatus is passed through a KOH scrubber and then a charcoal trap to prevent the release of radioactive material. The dark brown colored osmium-191 potassium perosmate solution is added in the aerator vessel by way of the addition funnel and the solution gradually turns clear after acidification. The osmium tetroxide solution is heated with a heat lamp to 55°C and the distillation requires 4 h. The column trapping solution will turn yellow as the osmium-191 is trapped. After completion of distillation, the osmium-191 is discharged into the collection reservoir with air pressure. This is the preferred method for

the purification of Os-191 at ORNL. The results from several experiments are illustrated in Table 3 and demonstrate the efficiency of this method.

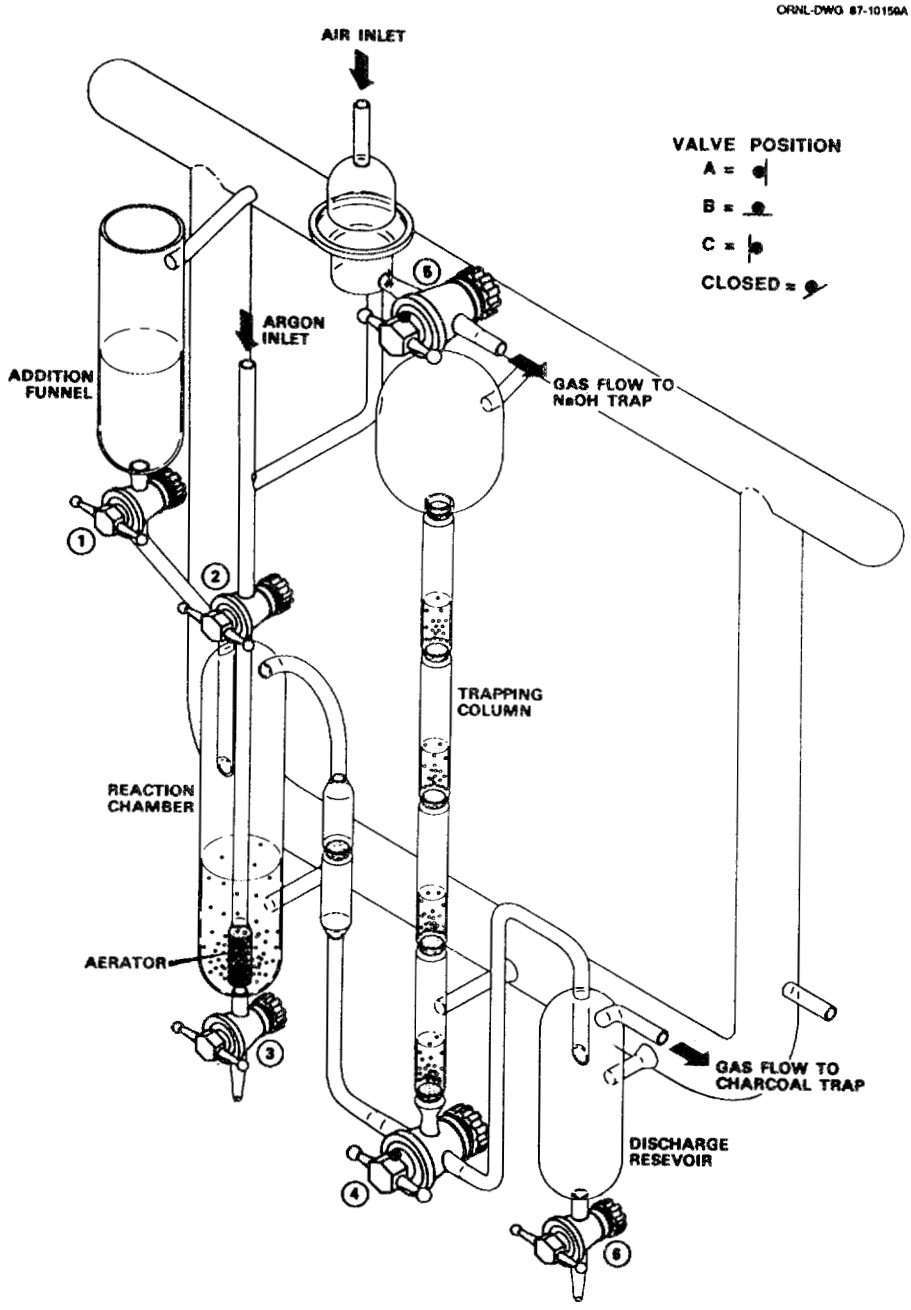


Fig. 5. Apparatus for purification of osmium-191 by distillation of OsO_4.

Table 3. Results of Osmium-191 Distillation Studies

Exp. #	Os-191 Source	Os-191 Initial	Os-191 Product	Ir-192 Initial	Ir-192 Product	% Os-191 Recovered	Elapse Time
1	^{191}Os-ORNL	2985.7 mCi	2635.4 Ci	169.4 Ci		88.3%	3.0 h
2	^{191}Os-ORNL	2650.0 Ci	1834.4 Ci	2.1 Ci		69.2%	2.5 h*
3	^{191}Os-ORNL	3497.3 mCi	3456.3 mCi	6.86 mCi		98.82%	3.5 h
4	^{191}Os-BNL #2	4940.2 mCi	4770.0 mCi	17.12 mCi	None Detected	96.5%	3.75 h
5	^{191}Os-BNL #3	5877.5 mCi	5830.5 mCi	19.8 mCi		99.2%	4.0 h
6	^{191}Os-BNL #6	7227.5 mCi	6841.3 mCi	205.3 mCi		94.7%	4.0 h

*Re-distilled Os-191 from Exp. #1 to evaluate time effect of Os recovery.

As an alternative, the solvent extraction method involves acidification of the basic potassium perosmate solution with sulfuric acid, and osmium is oxidized to the oxidation state VIII (OsO_4) with hydrogen peroxide. OsO_4 is then extracted twice with carbon tetrachloride. After discarding the aqueous phase containing iridium-192, OsO_4 is back extracted three times with a 0.75 N KOH solution. The apparatus utilized for this procedure is illustrated in Figure 6. This is the preferred routine method used at the Cyclotron Center in Liege, Belgium (C. Brihaye and M. Guillaume). A 0.75 N KOH solution is introduced into the extraction chamber, and the extraction is performed for

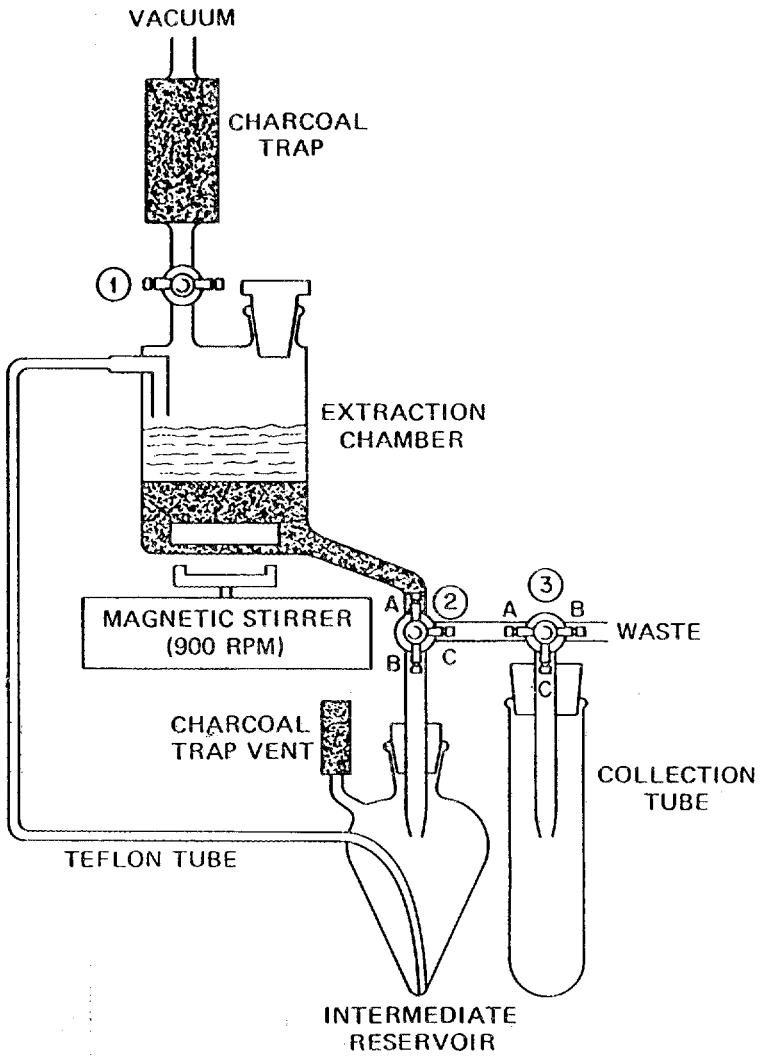


Fig. 6. Apparatus for purification of osmium-191 by extraction of OsO_4. (Courtesy of C. Brihaye, University of Liege, Belgium).

5 min. After separation of the phases, the organic phase is collected in the intermediate reservoir as described above, and the aqueous solution of perosmate is collected. The organic phase is aspirated back into the extraction chamber. Back extractions are performed twice more with 0.75 N KOH solution following the same procedure.

Table 4. Yields (%) of back extraction of OsO_4 in CCl_4 with KOH solutions of different concentration.

KOH concentration (mole/l)	Yield (%)
0.1	40.0
0.25	70.5
0.50	81.1
1.0	90.7

Both methods for the removal of Ir-192 are based on the inertness of Ir-192 during the facile conversion of potassium perosmate to osmium tetroxide with acid. The distillation method has a separation efficiency between Os-191 and Ir-192 of 100% when conducted in the apparatus shown in Fig. 5. The total recovery yield of Os-191 is 95% and the total time required for completion of this procedure is about 4 h. The extraction method is easier to perform and the separation efficiency between Os-191 and Ir-192 is 99.9%. The final recovery yield of Os-191 is between 92 and 95%. This procedure, including the extraction and the back extraction is accomplished in about 1 h.

These studies have demonstrated that the production of Os-191 and the undesirable Ir-192 by-product can be accurately predicted at thermal neutron flux values from 2.2×10^{14} to 2.5×10^{15} neutrons/cm^2·sec. The published cross section value for the Os-191(n,γ)Os-192 reaction is 383 barns .[10] The experimental data for Os-191 production at a flux of 2.5×10^{15} n/cm^2·sec do not agree with the calculated values using this literature value of 383 b. The total cross section value (924 b) for the Ir-191(n,γ)Ir-192 reaction calculated in the present work agrees very well with the published value of

954 b.[8] For the Ir-192(n,γ)Ir-193 reaction, the observed 2273 b value is different from the published value of 1420 b.[8] In the present work, the presence of other reactions such as Ir-193(n,γ)Ir-194 were not taken into account.

Purification of Os-191 by distillation of OsO_4 presents the advantage that the separation between Os-191 and Ir-192 is complete. The separation by the solvent extraction method is 99.9%. For a generator loaded with 1.0 Ci of Os-191 produced by irradiation of Os-190 at a flux of 8.5×10^{14} n/cm^2·sec for a period of 24 d, about 250 mCi of Ir-192 is present on the generator. Since about 0.02% of the Ir-192 activity is eluted in a 2.5 ml bolus, Ir-192 activity of 0.01 mCi is eluted with the Ir-191m, which contributes only a small amount to the total absorbed radiation dose.

As an illustration of the importance of removing Ir-192 from Os-191 produced in lower flux reactors, the estimated absorbed dose values to the liver for a bolus from a generator prepared from Os-191 produced at either 2.5×10^{15} or 5×10^{14} neutrons/cm^2·sec is illustrated in Table 5. For these calculations, the analysis of sequential gamma camera frames to evaluate the vascular passage of a bolus in a typical patient study was used. Values are calculated for the expected 100 of mCi injected Ir-191m activity the average percent Ir-192 elution from generators used over the last two years in clinical studies in Belgium.

Table 5. Iridium-192 significantly increases the total absorbed dose.

	Liver absorbed dose in mRad		
Flux n/cm^2·sec	Ir-191m	Os-191m	Ir-192
2.5×10^{15} (HFIR)	1.2 mR (100 mCi)	4.1 mR (5 mCi)	5.3 mR (0.7 mCi)
5×10^{14} (HFBR)	1.2 mR (100 mCi)	4.1 mR (5 mCi)	53 mR (7.0 mCi)

The longer irradiation periods at the lower neutron flux result in a ten-fold increase in the levels of Ir-192 that are produced and thus eluted with the bolus. The ten-fold increase (53 mRad) in the absorbed dose, as

illustrated for the liver, is unacceptable and demonstrates the necessity of Ir-192 removal. The absorbed dose values for a bolus elution of Ir-191m from a generator prepared from a processed solution from which the Ir-192 had been removed are summarized in Table 7. The usual 2 x 10^{-4}% breakthrough of Os-191 contributes to the principal portion of the target organ absorbed dose values. These values are greatly reduced from the absorbed values for a typical 20 mCi first-pass study with Tc-99m human serum albumin.

Table 7. Comparison of expected absorbed dose values for first-pass studies.

	Absorbed dose (Mrads)	
Organ	100 mCi Ir-191m (+ Os-191)	20 mCi Tc-99m Human Serum Albumin
Heart wall	49.0 (+0.7)	200
Liver	1.2 (+4.1)	520
Kidneys	3.1 (+7.5)	700
Total body	0.7 (+1.5)	200

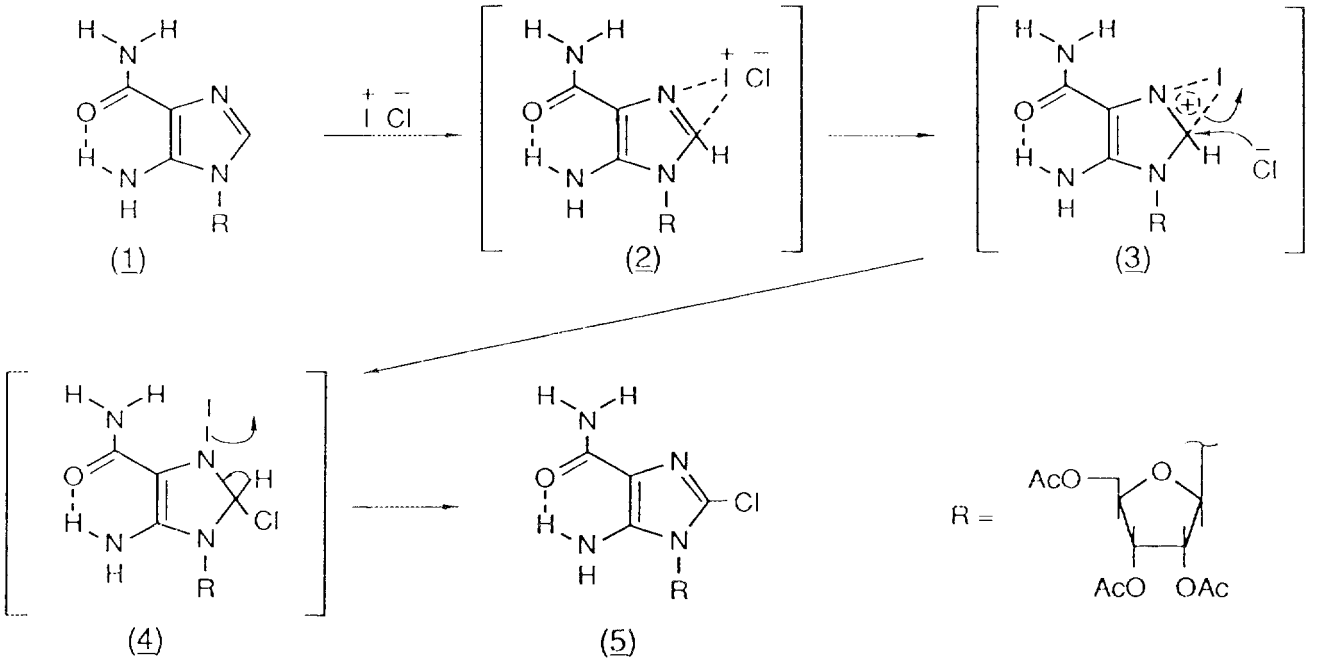
AN UNUSUAL IODINE MONOCHLORIDE CHLORINATION OF AN IMIDAZOLE NUCLEOSIDE

Iodine monochloride (ICl) is an iodinating agent[12] commonly employed for effecting the electrophilic iodination of aromatic moieties of amino acids such as tyrosine and histidine residues of proteins[13-16] and of other biological substrates.[17] However, the possibility of concurrent chlorination when employing this agent has not been investigated. In this study we describe the formation of an unexpected product from a novel ICl[18] reaction of 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide[19] (1) in anhydrous tetrahydrofuran at -5°C. The reaction predominately (60%) provides the chlorinated product, 5-amino-2-chloro-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (5), rather than the expected 2-iodo derivative. The product 5 was isolated by silica gel column chromatography, and the structure determined by ^{1}H NMR spectroscopy. The original signal for the proton at the 2-position of 1 is absent indicating that position-2 is the site of halogenation. The mass spectrum of 5 exhibits molecular ion peaks

the site of halogenation. The mass spectrum of 5 exhibits molecular ion peaks at m/z = 418 (^{35}Cl) and m/z = 420 (^{37}Cl) for the chlorinated compound. Further proof for structure of 5 was evident from its mp: 188-189°C (lit.[20] mp: 189-190°C) and its TLC mobility which was identical to that of the authentic sample prepared by a procedure described in the literature.[20]

A possible mechanism for the formation of the observed chlorination product is outlined in Scheme I based on a polarized iodine-chlorine bond with a partial positive charge on the iodine in ICl. The hydrogen bonded structure of nucleoside 1 would be a favorable substrate for ICl addition on the C^2,N^3-double bond resulting in intermediate formation of the iodonium ion 2. Subsequent attack of chloride (Cl^-) on 2 would provide intermediate 3 which could undergo aromatization via elimination of HI to yield the 2-chloro product 5.

Although the formation of 5 by ICl treatment of 1 is rather unusual, it indicates that care should be exercised to account for a similar potential side reaction while performing ICl iodinations for biological evaluations. Potential use of ICl as chlorinating agent for other imidazole containing molecules such as purine nucleosides and histidine merits investigation.



Scheme I

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AGENTS FOR MEDICAL COOPERATIVES

One shipment of I-131 was supplied to the University of Bonn (Dr. Kropp) and a prototype W-188/Re-188 generator system was supplied to NeoRx, Seattle, WA (Dr. Fitzberg).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Following the completion of toxicity testing, Nihon Medi-Physics, Inc., has announced they will establish multicenter clinical trials in Japan for testing of the iodine-123-labeled methyl-branched fatty acid (BMIPP) developed by the Nuclear Medicine Program at ORNL. The BMIPP agent contains methyl-branching which interferes with catabolism resulting in significantly prolonged retention by the heart muscle which is optimal for the increased imaging periods required by SPECT.

Meetings and Lectures

K. R. Ambrose was appointed Technical Program Coordinator for the Xth Health and Safety Research Division Information Meeting held at ORNL on October 27-28, 1987. P. C. Srivastava presented a talk entitled "New Approaches for Protein Radiolabeling for Diagnostic and Therapeutic Applications in Nuclear Medicine." This presentation described the new maleimide approach which is an improved method for radioiodination of

antibodies and other proteins. The development of the new tungsten-188/-rhenium-188 generator was also described.

F. F. Knapp, Jr., visited NeoRx Corporation in Seattle, Washington on October 20, and presented a seminar on the development of therapeutic agents at ORNL. NeoRx is involved in the commercialization of radiolabeled and therapeutic applications in the use of rhenium-188 from the Tungsten-188/Rhenium-188 Generator System recently developed in the Nuclear Medicine Program at ORNL. He also presented an overview of the ORNL Nuclear Medicine Program to the U.S. Department of Energy Nuclear Medicine Review Committee on Radiopharmacology at Bethesda, Maryland on November 3, and on November 4 presented an invited seminar describing the development of radioiodinated fatty acids at the Medical Department of Brookhaven National Laboratory. He visited the Institute for Clinical and Experimental Nuclear Medicine at the University of Bonn, West Germany, and the Cyclotron Research Center at the University of Liege, Belgium, to coordinate collaborative research projects on November 23-24. He was an invited speaker at the Fourth International Symposium on the Development of Radioiodinated Fatty Acids in Amsterdam, the Netherlands on November 25-26.

P. C. Srivastava departed for a 2-month guest assignment at the Central Drug Research Institute, Lucknow, India. He was awarded a TOKTEN Distinguished Scientist Award through the United Nations.

Papers

Members of the Nuclear Medicine Program also co-authored an abstract at the recent meeting of the International Society of Heart Research in Budapest, Hungary, on September 13-16, 1987. This work described the kinetic and metabolic properties of the dimethyl-branched DMIPP fatty acid developed at ORNL in comparison with other fatty acids used for heart research and clinical applications. These collaborative studies were initiated in Amsterdam while F. F. Knapp, Jr. was on guest assignment in West Germany in 1986 and are continuing.

"Comparison of kinetics between I-123-heptadecanoic acid (IHDA), I-125-phenylpentadecanoic acid (IPPA) and I-131-dimethylphenylpentadecanoic acid (DMIPPA) in the normal dog heart."

F. C. Visser, C. M. B. Duwel, M. J. Eenige van, M. M. Goodman, F. F. Knapp, Jr., S. N. Reske, J. P. Roos.

K. R. Ambrose, D. E. Rice, M. M. Goodman, and F. F. Knapp, Jr. "Effect of 3-Methyl-Branching on the Metabolism in Rat Hearts of Radioiodinated Iodovinyl Long Chain Fatty Acids," Eur. J. Nuc. Med., 13(7), 374-379 (1987).

New Staff

In November Ed C. Lisic, Ph.D., began working with the Nuclear Medicine Group as a post-doctoral fellow.

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