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F. F. Knapp, Jr.

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NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT FOR QUARTER ENDING JUNE 30, 1981

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SUMMARY

The production of ^{191}Os for use in the ^{191}Os-^{191m}Ir generator by irradiation of natural osmium has been assessed because of limited supplies of enriched ^{190}Os. The distribution of radionuclide products has been determined after a 14-day irradiation of natural osmium (26.4% ^{190}Os) in the High Flux Isotope Reactor (HFIR) to evaluate the potential usefulness of this method of ^{191}Os production in comparison to irradiation of 97.8% enriched ^{190}Os. Because natural osmium contains several stable isotopes in addition to ^{190}Os, the following radioisotopes are formed: ^{185}Os ($T_{1/2}$, 94 d), ^{191}Os ($T_{1/2}$, 15.4 d) and ^{193}Os ($T_{1/2}$, 30.5 h). In addition, ^{192}Ir ($T_{1/2}$, 74.2 d) is formed by the ^{190}Os $\xrightarrow{n,\gamma}$ ^{191}Os → ^{191m}Ir → ^{191}Ir $\xrightarrow{n,\gamma}$ ^{192}Ir process and significant levels of ^{194}Ir ($T_{1/2}$, 19.15 h) were detected which arise by the ^{192}Os $\xrightarrow{n,\gamma}$ ^{193}Os → ^{193}Ir $\xrightarrow{n,\gamma}$ ^{194}Ir process. Studies of the relative decay of the various isotopes over a period of several weeks indicated that a decay period of at least 14 days would be necessary for the unwanted ^{185}Os and ^{193}Os radioisotopes to decay to sufficient levels that generator breakthrough of osmium would not significantly increase the radiation dose. These studies clearly indicate that neutron irradiation of natural osmium is impractical for production of ^{191}Os for clinical use and that irradiation of enriched ^{190}Os is the preferred production mode. The formation of ^{192}Ir described above is a consequence of the production mode and cannot be eliminated. Studies have shown, however, that the majority (~90%) of the ^{192}Ir contaminant can be removed from the column by successive washes (~25 column volumes) of the generator after loading.

A new tellurium fatty acid has been prepared and evaluated in rats in which radioiodine (^{131}I) has been chemically stabilized on the molecule as a vinyl iodide [I-CH=CH$_2$-(CH$_2$)$_3$-Te-(CH$_2$)$_{11}$-COOH]. The 18-iodo-13-tellura-17-octadecenoic acid was fabricated by coupling 1,5-diiodopentene with the sodium salt of methyllauryl tellurol. The 1,5[^{131}I]-diodopentene was prepared by an organoborane technique

involving $^{131}I^{+}$ treatment of the boronic acid of 1-iodopentyne [$I-(CH_2)_3-CH=CH-B(OH)_2$]. This new agent showed only marginal in vivo deiodination and significant heart:blood ratios (7:1 after 5 min). The absolute heart uptake (0.35-0.77% injected dose/gram) was only marginal, however, suggesting that this particular vinyl iodide tellurium fatty acid does not show high heart specificity. This new class of agents is under further investigation.

Several radiolabeled agents were prepared and distributed to Medical Cooperative investigators for further preclinical study and clinical evaluation. Six production runs of ^{11}C-labeled amino acids were made in conjunction with the Oak Ridge Associated Universities for tumor localization, pancreas imaging and brain scanning studies. Eight shipments of ^{191}Os for fabrication of the ^{191}Os-^{191m}Ir generator and evaluation of ^{191m}Ir for intracardiac shunt measurements and ventricular ejection fraction studies were made to Medical Cooperative Programs at Children's Hospital and the Massachusetts General Hospital in Boston, MA and Rush Presbyterian-St. Luke's Hospital in Chicago, IL. Collaborators at Brookhaven National Laboratory and John's Hopkins Medical Institutions were supplied with ^{117m}Sn in a collaborative program to determine the mechanism of red blood cell labeling with $SnCl_2$ and the potential use of ^{117m}Sn-stannous pyrophosphate and other agents for therapeutic applications in bone disease. The synthesis and purification of the ^{195m}Pt-labeled therapeutic agent *cis*-dichloro-*trans*-dihydroxy-*bis*-(isopropylamine)platinum(IV) has been completed and this agent has been supplied for investigation of pharmacological properties at St. Thomas' Hospital in London, England. Several shipments of ^{195m}Pt-labeled *cis*-dichlorodiamnineplatinum(II) (*cis*-DDP) were made to investigators in Medical Cooperative Programs for studies of pharmacokinetic and antitumor properties and for clinical applications to monitor effective therapeutic dose levels.

RADIONUCLIDE GENERATOR DEVELOPMENT — THE ^{191}Os-^{191m}Ir GENERATOR

T. A. Butler and F. F. Knapp, Jr.

Previous reports have described progress of the new program for application of ^{191m}Ir in nuclear cardiology for first-pass radionuclide angiography (ORNL/TM-7685 and -7775). Osmium-191 is currently prepared for distribution to Medical Cooperative Program collaborators for generator loading in the form of ^{191}Os-potassium osmate. The reactor production parameters for ^{191}Os yield and product quality have been established for irradiation of enriched (97.8%) ^{190}Os in the High Flux Isotope Reactor (HFIR) for periods up to 4 days. The limited supply of enriched ^{190}Os is available only through the Isotope Separations Section of the ORNL Chemical Technology Division and future enrichments of this isotope have not been scheduled before 1983. Because of the limited availability of enriched ^{190}Os, alternate methods for the production of generator-quality ^{191}Os have been investigated in the event that stocks of enriched ^{190}Os should be depleted. The results of an initial HFIR production of ^{191}Os by irradiation of natural osmium are described in this report.

Natural osmium has the following isotopic composition; 0.018% ^{184}Os, 1.58% ^{186}Os, 1.6% ^{187}Os, 13.3% ^{188}Os, 16.1% ^{189}Os, 26.4% ^{190}Os, and 41.0% ^{192}Os. A 12.376 mg target of 99.9% purity natural osmium (Alpha Products, Stock No. 00246) was irradiated in the HFIR at 2.5 x 10^{15} neutrons/(cm^2/s) for a period of 14 days. The osmium target was converted to a solution of potassium perosmate by fusion with KOH-KNO_3 in the usual manner, and the radionuclide composition determined by gamma spectroscopy (Table 1). An analysis of the radioactive decay of the product over an 18-day period indicated that the yields of ^{185}Os, ^{191}Os, and ^{193}Os were consistant with those expected from the isotopic abundances and neutron cross section values of the parent stable isotopes ^{184}Os, ^{190}Os, and ^{192}Os, respectively. An analysis of these data

Table 1. Radionuclides produced by 14-day neutron irradiation of natural osmium

Radionuclide	Half-life	Amount, mCi
^{185}Os	94.0 d	5.72
^{191}Os	15.4 d	1790
^{193}Os	30.5 h	2820
^{192}Ir	74.2 d	20
^{194}Ir	19.15 h	580

indicates that the principal mode for production of ^{192}Ir and ^{194}Ir occurs by the nuclear reaction and decay sequences summarized in Scheme I.

$$^{191}Os \xrightarrow{\beta^-} {}^{191m}Ir \xrightarrow[\text{Transition}]{\text{Isomeric}} {}^{191}Ir \xrightarrow{n,\gamma} {}^{192}Ir$$

$$^{193}Os \xrightarrow{\beta^-} {}^{193}Ir \xrightarrow{n,\gamma} {}^{194}Ir$$

Scheme I

The absence of appreciable iridium contamination in the natural osmium target material was inferred from the yield of ^{192}Ir which was even less than the amount expected from the indicated production mode by an extrapolation of calculated quantities based on previous neutron irradiations of enriched ^{190}Os for periods of 2, 3, and 4 days. As shown in Table 2, a 14-day decay period after HFIR irradiation of the natural osmium target would result in an acceptable reduction in the levels of of ^{193}Os and ^{194}Ir for the ^{191}Os-^{191m}Ir generator preparation.

Table 2. Radionuclide levels resulting from a 14-day decay of irradiated natural osmium

Radionuclide	Amount, mCi
^{185}Os	5.16
^{191}Os	1288.0
^{193}Os	1.36
^{192}Ir	17.55
^{194}Ir	0.003

Following the 14-day decay period, sufficient levels of ^{191}Os would remain for loading of two ^{191}Os-^{191m}Ir generators. The ^{185}Os radionuclide ($T_{1/2}$, 94 d) has principal gamma energies of 592 keV (1.32%), 646 keV (80.2%), 717 keV (4.08%), and 875 keV (6.54%). Thus, the presence of significant levels of ^{185}Os would increase the generator shielding requirements. In addition, the absorbed radiation dose to the patient would increase if the ^{191m}Ir eluant solution was contaminated with ^{185}Os from osmium breakthrough. The ^{192}Ir contamination can be removed from the generator prior to elution of ^{191m}Ir for clinical use as discussed in the following section. Although reactor yields of ^{191}Os can be proportionately increased by increasing the natural osmium target weight, these results clearly illustrate that use of highly enriched ^{190}Os reactor target material is preferable for production of ^{191}Os for fabrication of generators for clinical use. Use of enriched ^{190}Os avoids ^{185}Os contamination and eliminates the necessity of the long decay period prior to generator loading that is encountered after reactor irradiation of natural osmium.

The precise chemistry of the ^{191}Os-^{191m}Ir generator system is presently not well defined, and identification of the iridium species formed during the fusion process and the nature of the osmium and iridium compounds eluted from the generator are problems which are presently being investigated. Solubilization of osmium by fusion in a mixed KOH-KNO_3 salt results in the formation of water soluble osmium

perosmate, $K_2[OsO_4(OH)_2]$ with osmium oxidation state VIII. The identity and oxidation state of the iridium species formed by fusion of the trace amount of iridium present in the reactor target is not known. Either IrO_2 or $IrO_2 \cdot 2H_2O$ could be formed, perhaps in a colloidal form stabilized by the basic solution resulting from the dissolution of the fusion salt in water. These iridium (IV) species are likely candidates since it is well established that iridium V and VI oxidation states exist only as fluorides or fluro complexes. Filtration of the aqueous perosmate solution through a 0.22 μm millipore filter did not remove any ^{192}Ir radioactivity.

The next step in the preparation of the ^{191}Os solution for column loading (see ORNL/TM-7685, page 9) is reduction of the perosmate in 90% ethanol solution which precipitates potassium osmate, $K_2[OsO_2(OH)_4]$ oxidation state VI. This procedure results in complete recovery of the ^{192}Ir with the precipitate. Subsequent dissolution of the osmate solid in 4*N* HCl also solubilizes all of the ^{192}Ir activity. The resultant HCl solution is used to load the AGMP-1 ion-exchange generator column. The chemical species present are $K_2[OsO_2(OH)_2Cl_2]$ (VI), $K_2[OsO_2Cl_4]$ (VI), and perhaps $K_2[IrCl_6]$ (IV). Since the oxidation states of Os and Ir differ, it was speculated that their distribution coefficients on AGMP-1 could differ significantly and thus form the basis for a chemical separation of the ^{192}Ir prior to clincial use of the generator. The feasibility of removing ^{192}Ir from the generator in this way was confirmed experimentally. An AGMP-1 column similar to that used clinically at The Children's Hospital Medical Center, Boston (Drs. Treves and Cheng), was loaded with 5 ml of a 4*N* HCl solution containing 822 mCi of ^{191}Os and 1.79 mCi of ^{192}Ir. The initial solution was passed through the column and followed by a 4 ml rinse of 4*N* HCl to clear the container and line leading to the generator. The column was then washed six times with approximately 5 ml increments of 4*N* HCl and each of the effluent fractions analyzed for ^{191}Os and ^{192}Ir content. The results are shown in Table 3. The column of AGMP-1 appeared visually to be loaded to 40% of its length after the initial loading and rinse operation. The leading edge of the osmium band slowly moved down the column during the 4*N* HCl washes until the column appeared to be 90% loaded after the last

wash fraction. The increase in ^{191}Os content of the last two washes also indicates an approaching breakthrough of the ^{191}Os. In this preliminary experiment, it was thus shown that 90% of the ^{192}Ir contaminant could be removed from the charge solution with negligible loss of ^{191}Os. The goal of future experiments is to develop more favorable conditions for the separation of ^{192}Ir from ^{191}Os.

Table 3. ^{191}Os and ^{192}Ir radionuclides in effluents from AGMP-1 generator loading and washing experiment using 4*N* HCl solutions

Effluent	^{192}Ir, mCi	Per cent of total	^{191}Os, mCi	Per cent of total
Loading and rinse (9 ml)	0.83	46.4	3.0	0.36
Wash-1 (5 ml)	0.064	3.6	1.9	0.23
Wash-2 (5 ml)	0.172	9.6	0.19	0.02
Wash-3 (5 ml)	0.290	16.2	0.24	0.03
Wash-4 (5 ml)	0.125	7.0	0.19	0.02
Wash-5 (5 ml)	0.078	4.4	0.31	0.04
Wash-6 (5 ml)	0.052	2.9	0.43	0.05
Totals (39 ml)	1.611	90.1	6.26	0.75

Analysis of aliquots from generator eluates used for clinical applications at Children's Hospital in Boston have confirmed that the ^{192}Ir elution is significantly reduced by washing the ion-exchange column prior to clinical use. The effluents from two normal generator loadings showed 58.7% ^{192}Ir removal in one case and 50.2% removal in the second. Following a recommendation on washing the column subsequent to the normal loading operation, a column was washed with three 5 ml portions of 4*N* HCl followed by two 5 ml portions of pH 1 normal saline. Assay of the effluent fractions showed that a total of 82.6% of the ^{192}Ir had been removed.

In summary, it has been shown that ^{191}Os can be produced in multicurie amounts by irradiation of natural osmium in the HFIR. Two long-lived contaminants, ^{185}Os ($T_{1/2}$, 94 d) and ^{192}Ir ($T_{1/2}$ 74.2 d), substantially reduce the desirability of the product for loading ^{191}Os-^{191m}Ir generator systems in their present state of development because of potential contamination of the ^{191m}Ir eluate solutions. It has been further shown that the ^{192}Ir contaminant can be separated by ion-exchange chemistry and reduced by 90% with good potential for further reductions. The generator system must be improved to reduce osmium contamination of the ^{191m}Ir eluate solutions in order to minimize ^{185}Os contamination. The reactor target of choice for ^{191}Os production continues to be highly enriched ^{190}Os.

MYOCARDIAL IMAGING AGENTS — RADIOLABELED LONG-CHAIN FATTY ACIDS

F. F. Knapp, Jr. and M. M. Goodman

The development of a synthetic method for the preparation of terminal radioiodinated tellurium long-chain fatty acids (*I-R-Te-R'-COOH) was described in the last report (ORNL/TM-7775). This type of agent was envisioned as a new type of "bifunctional" radiopharmaceutical that could potentially be used to monitor regional myocardial fatty acid metabolism. The tellurium heteroatom within the fatty acid chain would result in prolonged heart uptake (ORNL/TM-6638) and the favorable radionuclidic properties of ^{123}I could then be used for myocardial imaging. Unfortunately, the model compound, 17-[^{131}I]-iodo-9-telluraheptadecanoic acid was found to suffer facile in vivo deiodination (Table 4).

The levels of radioactivity in the heart remained high for at least 2 h after administration of the ^{131}I-17-iodo-9-telluraheptadecanoic acid. The heart uptake of this agent, however, was not as pronounced (3-4% injected dose/g) as observed with the parent compound, ^{123m}Te-9-THDA (ORNL/TM-7775). Since the only structural difference is the presence in the two molecules of the terminal iodide in 17-iodo-9-THDA, these results suggest that major steric or electronic effects are introduced into the 9-THDA molecule by incorporation of the

Table 4. Distribution of radioactivity in tissues of Fischer 344 female rats following intravenous administration of ^{131}I-17-iodo-9-telluraheptadecanoic acid[a]

	Mean percent injected dose/gram (range)		
	Minutes after injection		
Tissue	2	30	60
Heart	2.39 (1.56-3.21)	1.78 (1.75-1.84)	1.86 (1.54-2.09)
Blood	1.28 (1.13-1.40)	0.72 (0.65-0.81)	0.64 (0.56-0.75)
Lungs	1.40 (1.18-1.51)	0.85 (0.81-0.88)	0.75 (0.62-0.87)
Liver	3.71 (3.17-4.00)	1.75 (1.66-1.80)	1.16 (0.92-1.32)
Kidneys	1.36 (1.22-1.46)	0.80 (0.77-0.86)	0.68 (0.60-0.79)
Thyroid	6.27 (3.35-9.51)	41.9 (31.9-49.8)	74.7 (38.3-122)

[a]Four rats were used for each time period. Other tissues that were analyzed include the pancreas, spleen, brain, and intestines.

terminal iodide. The decreased uptake of radioiodine could also result from significant in vivo deiodination of 17-iodo-9-THDA. The pronounced thyroid uptake of radioiodine after administration of 17-[^{131}I]iodo-9-THDA to rats confirms that significant deiodination of this agent does occur (ORNL/TM-7775).

To further assess the properties of myocardial uptake of 17-iodo-9-THDA, 17-iodo-9-[^{123m}Te]telluraheptadecanoic acid was prepared by the route outlined in Scheme II (*Te=^{123m}Te). The tissue distribution properties of this analog containing stable iodine and radiolabeled with ^{123m}Te could be used as an index of the myocardial specificity of the molecule independently from the deiodination. Tissue distribution

$$*Te \rightarrow Na_2{*}Te_2 + Br\text{-}(CH_2)_7\text{-}COOMe \rightarrow$$
$$MeOOC\text{-}(CH_2)_7\text{-}{*}Te\text{-}{*}Te\text{-}(CH_2)_7\text{-}COOMe \rightarrow$$
$$Na\text{-}{*}Te\text{-}(CH_2)_7\text{-}COONa + I\text{-}(CH_2)_8\text{-}I \rightarrow$$
$$I\text{-}(CH_2)_8\text{-}{*}Te\text{-}(CH_2)_7\text{-}COOH$$
(17-iodo-9-[*Te]-THDA)

Scheme II

studies after administration of the 17-iodo-9-[^{123m}Te]THDA demonstrated significant uptake and prolonged retention of radioactivity in the heart tissue of Fischer 344 rats (Table 5). These results appear to indicate

Table 5. Distribution of radioactivity in tissues of Fischer 344 male rats following intravenous administration of ^{123m}Te-17-iodo-9-telluraheptadecanoic acid[a]

	Mean percent injected dose/gram (range)		
	Minutes after injection		
Tissue	5	30	60
Heart	1.38 (1.07-1.60)	2.24 (1.49-3.22)	1.58 (1.18-1.74)
Blood	0.13 (0.10-0.17)	0.36 (0.32-0.38)	0.25 (0.23-0.27)
Lungs	0.67 (0.62-0.71)	0.62 (0.57-0.67)	0.56 (0.51-0.62)
Liver	3.33 (3.01-3.89)	2.11 (1.92-2.40)	1.65 (1.47-1.82)
Kidneys	1.17 (1.05-1.29)	1.05 (0.98-1.14)	0.99 (0.94-1.09)

[a] Four rats were used for each time period. Other tissues that were analyzed include the pancreas, spleen, brain, and intestines.

that the 17-iodo-9-THDA molecule shows myocardial specificity but then undergoes relatively rapid deiodination to a product of unknown structure. Although 17-[^{131}I]iodo-9-THDA shows significant myocardial uptake, the high blood levels of radioiodine resulting from in vivo deiodination would necessitate special substraction techniques to be used to assess the distribution properties of the radiolabeled fatty acid in the myocardium.

More recent studies have now been focussed on developing strategies to stabilize radioiodine on a model tellurium fatty acid in order to circumvent the deiodination problem described above for 17-[^{131}I]iodo-9-THDA. Since the carbon-iodine bond of vinyliodides (I-CH=CH-R) is not susceptible to facile deiodination, the synthesis of a model vinyliodide-substituted tellurium fatty acid has been developed and the tissue distribution properties of the ^{125}I- and ^{123m}Te-labeled analogs have been evaluated in rats.

The initial synthetic approach (Scheme III) involved fabrication of the intact acetylenic tellurium fatty acid, methyl-13-tellura-17-octadecynoic acid. Although this compound could be readily prepared and

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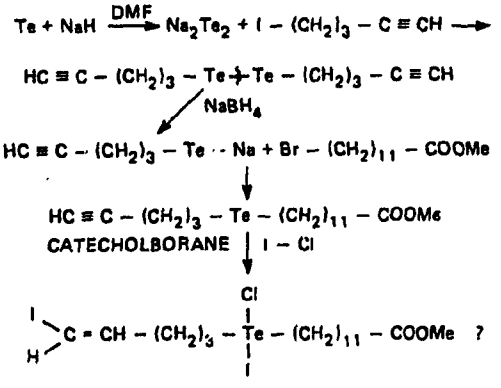
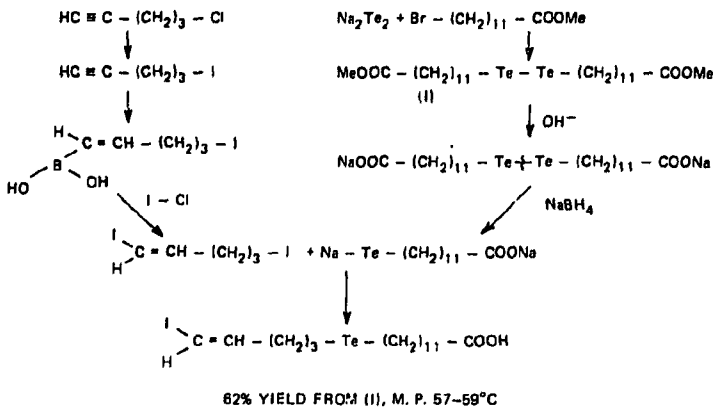


Scheme III

characterized, treatment with catecholborane followed by reaction with I-Cl did not yield a product that could be readily isolated. Presumably a telluronium compound ($R_2TeX^{\delta+}X^{\delta-}$) was formed as shown in Scheme III. The second approach involved fabrication of the 1,4-diiodopentene vinyliodide intermediate separately, prior to coupling with the fatty acid substrate.

The model terminal vinyl iodide-substituted tellurium fatty acid was prepared as shown in Scheme IV. This approach was chosen because of the commercial availability of 5-chloropentyne which was readily converted to the more reactive 5-iodopentyne. Treatment with catecholborane gave the iodopentenylboronic acid as a stable, crystalline solid. The preparation of this intermediate was developed in conjunction with collaborators in the Chemistry Department of the University of Tennessee (Drs. Kabalka and Sastry). The boronic acid intermediate was readily



Scheme IV

converted to diiodopentene by treatment with iodine monochloride (I-Cl). While the primary C-5 iodide was readily susceptible to nucleophilic displacement by the tellurol anion of the fatty acid substrate, the vinyl iodide was stable under these reaction conditions. In this manner, 18-iodo-13-tellura-17-octadecenoic acid could be prepared in 62% yield from the *bis*-(methyllauryl) ditelluride substrate (Scheme IV). The new compound readily crystallized from petroleum ether and exhibited the expected physical properties.

Tissue distribution studies showed only marginal heart uptake of the ^{125}I-labeled agent (Table 6). Although heart uptake was low, the agent did not exhibit significant thyroid uptake or high blood levels. The low heart uptake was unexpected, since the agent did not appear susceptible to in vivo deiodination. In a parallel study, the 18-iodo-13-[^{123m}Te]tellura-17-octadecenoic acid was prepared by the initial preparation of ^{123m}Te-labeled *bis*-(methyllauryl) ditelluride from alkylation of $Na_2{}^{123m}Te_2$ with methyl-17-bromolaurate. The results of tissue distribution studies with the ^{123m}Te-labeled analog (Table 7) indicated significant heart uptake, but blood levels were high. Thus, although

Table 6. Distribution of radioactivity in tissues of Fischer 344 female rats following intravenous administration of ^{125}I-18-iodo-13-tellura-17-octadecenoic acid[a]

	Mean percent injected dose/gram (range)		
	Minutes after injection		
Tissue	5	30	60
Heart	0.50 (0.35-0.77)	0.43 (0.38-0.52)	0.39 (0.31-0.54)
Blood	0.07 (0.06-0.07)	0.19 (0.17-0.32)	0.19 (0.17-0.22)
Lung	0.29 (0.21-0.34)	0.28 (0.26-0.29)	0.34 (0.31-0.37)
Liver	3.11 (2.96-3.35)	1.69 (1.55-1.90)	1.01 (0.93-1.22)
Kidneys	0.36 (0.33-0.44)	0.30 (0.27-0.35)	0.27 (0.24-0.29)
Thyroid	0.54 (0.48-0.64)	1.88 (1.69-1.99)	4.47 (3.50-5.31)

[a]Four rats were used for each time period. Other tissues that were analyzed include the pancreas, spleen, brain, and intestines.

Table 7. Distribution of radioactivity in tissues of Fischer 344 female rats following intravenous administration of ^{123m}Te-18-iodo-13-tellura-17-octadecenoic acid[a]

	Mean percent injected dose/gram (range)		
	Minutes after injection		
Tissue	5	30	60
Heart	2.09 (1.93-2.37)	1.98 (1.79-2.17)	1.92 (1.85-2.00)
Blood	0.32 (0.29-0.34)	0.84 (0.79-0.90)	0.95 (0.83-1.03)
Lungs	0.91 (0.67-1.13)	1.03 (0.96-1.10)	1.00 (0.94-1.04)
Liver	7.78 (7.18-8.03)	5.53 (5.33-5.74)	4.49 (4.03-4.84)
Kidneys	1.46 (1.42-1.56)	1.73 (1.61-1.84)	1.85 (1.71-2.03)

[a]Four rats were used for each time period. Other tissues that were analyzed include the pancreas, spleen, brain, and intestines.

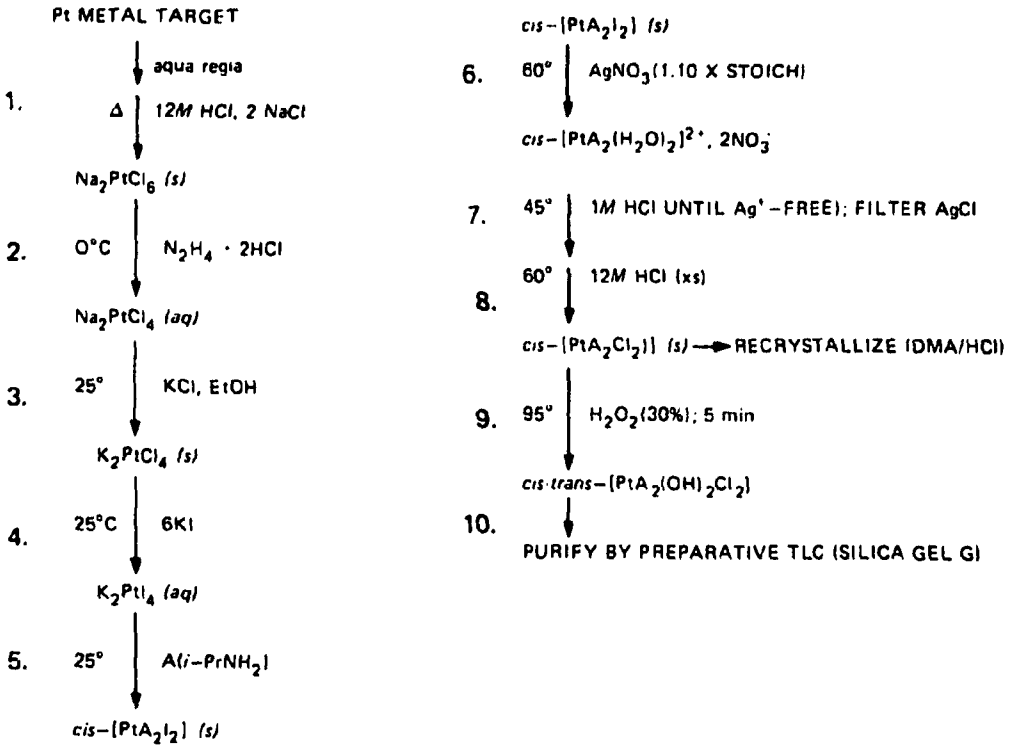
the radioiodinated 18-iodo-13-tellura-17-octadecenoic acid does not exhibit in vivo deiodination, this particular vinyl iodide-substituted tellurium fatty acid does not exhibit the high heart specificity demonstrated for 9-[^{123m}Te)THDA. The high blood levels must result from some structural feature of this unique agent. Although this agent has the optimal chain length (C_{18}) for myocardial uptake, either steric or electronic effects of the terminal vinyl iodide moiety may be the crucial factors decreasing heart specificity and leading to high blood levels. The position of the tellurium heteroatom may also have an unexpected effect, although the 6-tellura-, 9-tellura- and 11-tellura-heptadecanoic acid analogs all show similar pronounced and prolonged myocardial uptake in rats (ORNL/TM-6916). Studies now in progress are directed at preparing and evaluating other vinyliodide-substituted tellurium fatty acids and exploring other approaches for stabilization of iodine on model tellurium fatty acids.

PLATINUM ANTITUMOR AGENTS

J. D. Hoeschele and T. A. Butler

Development of the microscale synthesis of ^{195m}Pt-labeled *cis*-dichloro-*trans*-dihydroxy-*bis*-(isopropylamine)platinum(IV), ^{195m}Pt-CHIP, has been completed. The initial shipment of this radiolabeled antitumor agent has been made to collaborators at St. Thomas Hospital Medical School, London. The refined microscale synthetic scheme for ^{195m}Pt-CHIP, summarized in Scheme V, is similar to that reported earlier (ORNL/TM-7605) except for recent improvements in step 4. In step 4 of the refined scheme, Na_2PtCl_4, is prepared in situ, and then converted to K_2PtCl_4 which is subsequently precipitated with ethanol and purified by recrystallization. The purity of the *cis*-Pt(*i*-$PrNH_2)_2I_2$ and *cis*-Pt(*i*-$PrNH_2)_2Cl_2$ (CIP) precursors is increased when pure K_2PtCl_4 instead of Na_2PtCl_4 is used in step 4. The purification of ^{195m}Pt-CHIP has been accomplished by preparative thin-layer chromatography (TLC) employing silica gel G and an acetone:ethyl acetate:water (45:45:10) solvent mixture. A highly purified sample of unlabeled CHIP

ORNL–DWG 80-16070R



Scheme V

has been recently prepared and provided to collaborators at St. Thomas Hospital. This material is being evaluated in a preliminary study to determine the cytotoxic and x-ray potentiating properties of CHIP.

RADIONUCLIDES FOR MEDICAL COOPERATIVE PROGRAMS

Carbon-11

Six production runs were made for the Medical Cooperative Program with the Oak Ridge Associated Universities (ORAU) to study the application of ^{11}C-labeled amino acids for tumor localization, pancreas imaging, and brain scanning in preclinical animal studies and human patient studies. All studies this quarter were performed with the carbon-11-labeled levo isomer of valine. The levo isomer is the principal component of the DL racemic valine mixture which shows significant brain uptake. The racemic mixture is formed during the normal ^{11}C-labeled valine synthesis via a Strecker route involving the initial conversion of cyclotron produced $^{11}CO_2$ to H^{11}CN. Twelve patients with

possible brain disorders were examined by emission computerized axial tomography in the Medical and Health Sciences Division of ORAU with an excellent correlation between the distribution of radioactivity in the brain scan and the confirmed clinical diagnosis. In addition, three patients were similarly evaluated for identification of pancreatic abnormalities.

Production of $^{11}CO_2$ on the 86-inch cyclotron facility has been temporarily interrupted to permit the completion of extensive improvements requiring approximately three months for completion.

Osmium-191

F. F. Knapp, Jr. and T. A. Butler

Eight shipments of ^{191}Os potassium osmate were made as part of the growing Medical Cooperative Program to study the use of the ^{191}Os-^{191m}Ir generator system for medical application of the short-lived ($T_{1/2}$ = 4.96 s) ^{191m}Ir for first-pass radionuclide angiographic evaluation of intracardiac shunts and ventricular ejection fraction and other abnormal cardiac functions. Five shipments were made to The Children's Hospital Medical Center in Boston (Drs. S. Treves and Cheng) which were also utilized by the Massachusetts General Hospital (Dr. H. W. Strauss). Three shipments were made to the Rush-Presbyterian-St. Luke's Medical Center in Chicago (Drs. D. A. Turner and G. B. S. Rayudu) for generator development studies in preparation for preclinical animal studies for angiographic identification of the sites of onset during abnormal ventricular activation. Under these cooperatives, 9,400 mCi of ^{191}Os have been distributed to the program participants.

Platinum-195*m*

J. D. Hoeschele and T. A. Butler

Samples of ^{195m}Pt-labeled *cis*-dichlorodiammineplatinum(II) (^{195m}Pt-*cis*-DDP) were supplied to participants in Medical Cooperative Programs to study the pharmacokinetic properties and mode of antitumor activity of this antitumor agent, and to monitor the efficacy of therapeutic dose levels. Two shipments of ^{195m}Pt-*cis*-DDP were supplied to

University of Southern California (Dr. W. Wolf) and one shipment to the University of California at Los Angeles (Dr. L. C. Ford). In addition, two shipments of ^{195m}Pt-labeled Na_2PtCl_6 were supplied to University of California at Davis (Drs. D. Goodwin and C. F. Mears).

Tellurium-123$_m$

F. F. Knapp, Jr. and M. M. Goodman

One shipment each of ^{123m}Te-13-telluraheptadecanoic acid and ^{123m}Te-15-phenyl-6-tellurapentadecanoic acid was supplied to the Massachusetts General Hospital (Dr. H. W. Strauss) as part of the Medical Cooperative Program to study the potential use of these fatty acids to measure myocardial metabolism and identify abnormal heart functions. One shipment each of ^{123m}Te-*bis*[β-morpholinoethyl] telluride (MOTE) and ^{123m}Te-*bis*[β-piperidinoethyl] telluride (PIPTE) were supplied to the V. A. Medical Center, Buffalo, NY (Dr. H. Kung) as part of the Medical Cooperative Program to assess brain uptake of these compounds for potential application as agents to identify abnormal brain function. One shipment of MOTE was supplied to Oak Ridge Associated Universities (Dr. Hayes) for brain imaging studies in rabbits.

Tin-117$_m$

F. F. Knapp, Jr. and T. A. Butler

As part of the Medical Cooperative Program to determine the fate and mechanism of cellular retention of tin during the labeling of red blood cells by $SnCl_2$-pertechnetate method, three shipments of ^{117m}Sn metal were supplied to The Johns Hopkins Medical Institutions (Drs. H. N. Wagner and J. Waud) and two shipments to Brookhaven National Laboratory (Drs. J. Richards and D. C. Srivastava).

An additional goal of these studies is to determine the potential use of ^{117m}Sn-labled red blood cells as a blood pool agent to measure ventricular ejection fraction and regional wall motion.

OTHER NUCLEAR MEDICINE TECHNOLOGY GROUP ACTIVITIES

One shipment each of ^{195m}Pt-labeled *cis*-dichlorodiammineplatinum(II) was made to Baylor College of Medicine, Houston and Mount Sinai School of Medicine, New York on a cost recovery basis through the ORNL Isotopes Sales Office.

Visitors for this period included a group of nuclear medicine technology students from Vanderbilt University who visited for a program overview and tour on May 1. A group of nuclear technology students from Chattanooga State Technical Community College visited on May 7.

PAPERS AND PUBLICATIONS

Papers

A poster describing the potential use of tellurium steroids as a new class of agents to investigate sterol-phospholipid interactions in biological and artificial membranes was presented at the 72nd Annual Meeting of Biological Chemists at St. Louis, Missouri, on May 31 - June 4, 1981.

F. F. Knapp, Jr., and R. Bittman, "24-(Isopropyltelluro)-chol-5-en-3β-ol (24-ITC): A Unique Membrane Probe."

Four papers were presented at the 28th Annual Meeting of the Society of Nuclear Medicine held at the Las Vegas, Nevada Convention Center, on June 15-19, 1981.

F. F. Knapp, Jr., M. Vest, D. R. Elmaleh, R. H. Liss, H. W. Strauss, L. A. Ferren and A. P. Callahan, "Myocardial Uptake of 10-[^{14}C]-9-Telluraheptadecanoic Acid: Evidence for Retention of the Alkyl Region of 9-THDA."

R. A. Grigsby, F. F. Knapp, Jr., A. P. Callahan, L. A. Ferren and K. J. Irgolic, "New Brain Imaging Agents: Se-75 and Te-123*m*-Labeled Barbiturates."

T. Yasuda, F. F. Knapp, Jr., R. Okada, D. Elmaleh, K. A. McKusick, S. Kopiwoda and H. W. Strauss, "Extraction Fraction of 123*m*Te-9-Telluraheptadecanoic Acid By Hypertensive and Hypoxic Canine Hearts."

J. M. Waud, H. M. Drew, T. Duelfer, H. N. Wagner, Jr., and F. F. Knapp, Jr., "Sn-117*m* As a Potential Red Blood Cell Label."

Publications

M. M. Goodman, K. J. Kearfoot, D. R. Elmaleh, N. M. Alpert, and G. L. Brownell, "A Comparison of Carbon-11 and Fluorine-18 Carbohydrates," in Radiopharmaceuticals: Structure-Activity Relationships, R. Spencer, ed., Gordon and Breach, New York, Chapter 38, pp 801-833, 1981.

F. F. Knapp, Jr., K. R. Ambrose, and A. P. Callahan, "Potential Pancreatic Imaging Agents: Tellurium-123*m*-Labeled DL-α-Amino-γ-(Phenyltelluro) Butyric Acid," *J. Med. Chem.*, 24:794 (1981).

F. F. Knapp, Jr., "Selenium and Tellurium as Carbon Substitutes," in Radiopharmaceuticals: Structure-Activity Relationships, R. Spencer, ed., Gordon and Breach, New York, Chapter 16, pp 345-391, 1981.

D. L. Casey, G. A. Digenis, D. A. Wesner, L. C. Washburn, J. E. Chaney, R. L. Hayes, and A. P. Callahan, "Preparation and Preliminary Tissue Studies of Optically Active ^{11}C-D- and L-Phenylalanine," *Int. J. Appl. Radiat. Isotop.* 32: 325 (1981).

Reports

F. F. Knapp, Jr., *Nuclear Medicine Technology Progress Report for Quarter Ending March 31, 1981*, ORNL/TM-7775.