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Nuclear Medicine Technology Progress Report for Quarter Ending September 30, 1980

F. F. Knapp, Jr.

HEALTH AND SAFETY RESEARCH DIVISION
OAK RIDGE NATIONAL LABORATORY

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NUCLEAR MEDICINE TECHNOLOGY PROGRESS REPORT FOR QUARTER ENDING SEPTEMBER 30, 1980

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SUMMARY

Of special interest in this report are the results of experiments demonstrating the pronounced brain uptake of several ^{75}Se- and ^{123m}Te-labeled barbiturates. These new agents, substituted at the C-5 position of the barbituric acid ring system with the heteroatom substituents, freely pass through the intact blood-brain barrier. Five minutes after intravenous administration the brains of rats contained from 0.46-0.94% of the injected radioactivity. The maximum uptake of radioactivity observed after 5 min decreased steadily over a 60 min period. These preliminary results demonstrate that major structural modifications at the C-5 position of the barbituric acid ring do not destroy the ability of these lipid-soluble drugs to pass through the blood-brain barrier. Barbiturates labeled with gamma-emitting radionuclides may be an attractive new class of agents for measurement of regional cerebral blood flow.

The diffusion chamber assay system (ORNL/TM-7072) has been used to assess the chronic effects of As_2O_3 toxicity. A small osmotically actuated minipump has been used to deliver aqueous As_2O_3 at a continuous delivery rate to animals having intraperitoneally implanted diffusion chambers containing human lung cells (Flow 2000). The proliferation of the target cells was measured over a five-day period as a function of As_2O_3 release from the subcutaneously implanted minipumps. In these preliminary studies, a 49-53% inhibition of cell growth was observed over a five-day period when animals received As_2O_3 at a dose of 1.7-2 mg (kg-d). These initial studies suggest that the minipump may be a useful means of studying the chronic effects of substances on cell proliferation in conjunction with the diffusion chamber assay system.

A microscale synthesis of gold antirheumatoid agents has been developed. This method involves reaction of thiohexose derivatives such as thioglucosetetraacetate (β-D-TGTA) with trialkylphosphinegold halide intermediates (R_3PAu-Cl) in the presence of pyridine to give the coupling products R_3PAu(β-D-TGTA) in good yield (>75%). Using this method, the triethyl analog Et_3PAu(β-D-TGTA) and triphenyl analog

[ϕ_3PAu(β-D-TGTA)] have been prepared and characterized. This method will be used to prepare the ^{195}Au-labeled agents. The platinum antitumor agent *cis*-dichloro-*trans*-dihydroxy-*bis*-(isopropylamine)-platinum(IV) (CHIP) has been purified by a thin-layer chromatographic system using silica gel G plates developed with ethyl acetate:acetone:1 *N* HCl (45:45:10). This system is efficient for separation of CHIP from impurities produced during the synthetic sequence and will be used to prepare ^{195m}Pt-CHIP for biological evaluation.

In the Medical Cooperative Programs, a variety of ^{11}C-labeled racemic amino acids including leucine, tryptophan, and valine were prepared for evaluation at the Oak Ridge Associated Universities for tumor localization, pancreatic imaging, and brain uptake studies. Five shipments of ^{195m}Pt-*cis*-dichlorodiammineplatinum(II) (^{195m}Pt-*cis*-DDP) were made to collaborators at the University of Southern California, the University of Arizona, and the University of California at Los Angeles. Samples of ^{75}Se and ^{123m}Te-labeled fatty acids were supplied for biological evaluation to investigators at several institutions.

NEW CEREBRAL BLOOD PERFUSION AGENTS — RADIOLABELED BARBITURATES

F. F. Knapp, Jr.

Investigations of new selenium- and tellurium-substituted barbiturates (ORNL/TM-7482) have continued, and several ^{75}Se- and ^{123m}Te-labeled barbiturates have been prepared and preliminary tissue distribution studies performed in normal rats to determine the brain uptake of these new agents. The radiolabeled barbiturates (Fig. 1) were synthesized by the general synthetic method described in detail earlier (ORNL/TM-7482) and involved coupling ^{75}Se-selenols or ^{123m}Te-tellurols

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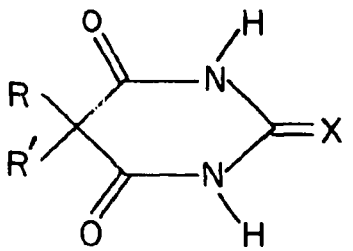

COMPOUND	R	R′	X
I	CH_3CH_2	$CH_3(CH_2)_3{}^{123m}Te(CH_2)_3$	O
II	CH_3CH_2	$C_6H_5{}^{123m}Te(CH_2)_4$	O
III	CH_3CH_2	$CH_3(CH_2)_3{}^{75}Se(CH_2)_3$	O
IV	CH_3CH_2	$C_6H_5{}^{75}Se(CH_2)_4$	O
V	CH_3CH_2	$C_6H_5{}^{75}Se(CH_2)_4$	S
VI	C_6H_5	$CH_3(CH_2)_2{}^{75}Se(CH_2)_3$	S

Fig. 1. Structures of ^{123m}Te-5-ethyl-5-[(butyltelluro)propyl] barbituric acid (I), ^{123m}Te-5-ethyl-5-[(phenyltelluro)butyl] barbituric acid (II), ^{75}Se-5-ethyl-5-[(butylseleno)propyl]barbituric acid (III), ^{75}Se-5-ethyl-5-[(phenylseleno)propyl]barbituric acid (IV), ^{75}Se-5-ethyl-5-[(phenylseleno)propyl]thiobarbituric acid (V), ^{75}Se-5-phenyl-5-[(butylseleno)propyl]barbituric acid (VI).

with 2-(ω-bromoalkyl)-2-alkyl diethylmalonates. Following absorption column chromatographic purification, ring closure of the radiolabeled diethylmalonates was achieved by treatment with potassium tertiary butoxide and urea in dimethylsulphoxide. The radiolabeled barbiturates were then purified by column chromatography and administered in 0.8% saline containing 4% ethanol and 1% Tween 80 to female Fischer-344 rats by injection in a lateral tail-vein. The results of preliminary tissue distribution studies using three rats for each study (Table 1)

Table 1. Distribution of radioactivity in tissues of Fischer 344 female rats at various time periods after intravenous injection of ^{75}Se- and ^{123m}Te-labeled barbiturates[a]

Agent, Tissue	Mean percent injected dose/gm (range)		
	Minutes after injection		
	5	30	60
I, Brain	0.46 (0.44-0.48)	0.33 (0.31-0.36)	0.26 (0.25-0.28)
Blood	1.67 (1.63-1.78)	1.39 (1.35-1.45)	1.43 (1.39-1.47)
Liver	2.47 (2.41-2.51)	1.63 (1.53-1.73)	1.25 (1.19-1.30)
II, Brain	0.94 (0.88-1.00)	0.53 (0.50-0.58)	0.44 (0.41-0.45)
Blood	1.14 (1.10-1.10)	0.67 (0.63-0.73)	0.52 (0.51-0.55)
Liver	3.86 (3.71-4.00)	2.82 (2.59-3.06)	2.35 (2.28-2.40)
III, Brain	0.82 (0.78-0.85)	0.37 (0.35-0.43)	0.26 (0.23-0.28)
Blood	0.64 (0.61-0.70)	0.42 (0.40-0.45)	0.34 (0.28-0.39)
Liver	2.84 (2.67-3.03)	1.61 (1.48-1.79)	1.09 (0.96-1.20)
IV, Brain	0.81 (0.71-0.95)	0.33 (0.30-0.37)	0.24 (0.23-0.26)
Blood	0.72 (0.67-0.76)	0.48 (0.44-0.53)	0.34 (0.32-0.36)
Liver	2.63 (2.52-2.71)	2.33 (2.15-2.50)	2.32 (2.23-2.40)
V, Brain	0.58 (0.55-0.62)	0.14 (0.13-0.15)	0.07 (0.06-0.08)
Blood	0.85 (0.76-0.98)	0.43 (0.41-0.44)	0.30 (0.26-0.36)
Liver	3.86 (3.56-4.33)	3.81 (3.66-4.02)	3.26 (3.11-3.54)
VI, Brain	0.28 (0.24-0.31)	0.12 (0.12-0.12)	0.11 (0.11-0.12)
Blood	0.81 (0.73-0.87)	0.58 (0.57-0.59)	0.46 (0.44-0.48)
Liver	3.81 (3.41-4.21)	3.27 (3.16-3.38)	2.69 (2.64-2.77)

[a]Three rats were used for each group. Other tissues analyzed included the heart, intestines, kidneys, lungs, and spleen, and a fat sample from the thigh.

demonstrated rapid and pronounced brain uptake of radioactivity after intravenous administration of the ^{75}Se- and ^{123m}Te-labeled barbiturates. Uptake varied from 0.46% to 0.94% of the injected dose within 5 min after administration indicating that the ability of these agents to enter the brain is related to the barbiturate structure. The 5-ethyl-5-[(phenyltelluro)butyl] barbituric acid (II), 5-ethyl-5-[(butylseleno)propyl] barbituric acid (III) and 5-ethyl-5-[(phenylseleno)propyl] barbituric acid (IV) showed the highest brain uptake of the compounds studied. These studies indicate that dramatic structural modification at C-5 of the ring system, such an attachment of the bulky phenylselenopropyl- or phenyltelluropropyl substituents, does not destroy the ability of the modified barbiturates to pass freely through the intact blood-brain barrier.

Since brain uptake of liphophilic drugs that are not actively transported is a function of their lipid solubility and ability to cross the blood-brain barrier, the differences in brain uptake of compounds I-VI may be correlated with their lipid solubility. Studies during the next quarter will be directed at determining the chloroform-water partition coefficients for these compounds and determining if the differences in brain uptake can be correlated with lipid solubility. Partition coefficients and brain uptake data will also be analyzed to determine if the various structural features present in compounds I-VI can be assigned values that can then be used to predict the potential brain uptake of barbiturates and design agents that show maximum brain uptake.

MYOCARDIAL IMAGING AGENTS — RADIOLABELED LONG-CHAIN FATTY ACIDS

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

The pronounced and prolonged myocardial uptake of 9-tellurahexadecanoic acid [9-THDA = R-Te-$(CH_2)_7$-COOH, R = $(CH_2)_7$-CH_3] has suggested that labeling of the alkyl (R) region of this compound may be an effective means of "trapping" radiohalogens with favorable physical properties in the heart tissue to assess myocardial function (ORNL/TM-7411).

Recently 10-[^{14}C]-9-THDA has been prepared, and tissue distribution studies performed in rats demonstrated that myocardial retention of ^{14}C from 10-[^{14}C]-9-THDA was similar to retention of ^{123m}Te observed after administration of 9-[^{123m}Te]-THDA (ORNL/TM-7482). More recently, autoradiographic analyses have been performed on rats after intravenous administration of 10-[^{14}C]-9-THDA. These studies of sagittal cross sections of the treated animals have been performed in conjunction with collaborators at the Massachusetts General Hospital (Drs. Elmaleh and Strauss) and Arthur D. Little Corporation in Boston, Massachusetts (R. H. Liss). The results of these studies (Fig. 2) dramatically substantiate the specific and pronounced myocardial uptake of radioactivity one hour after injection of 10-[^{14}C]-9-THDA. The ventricular myocardium is

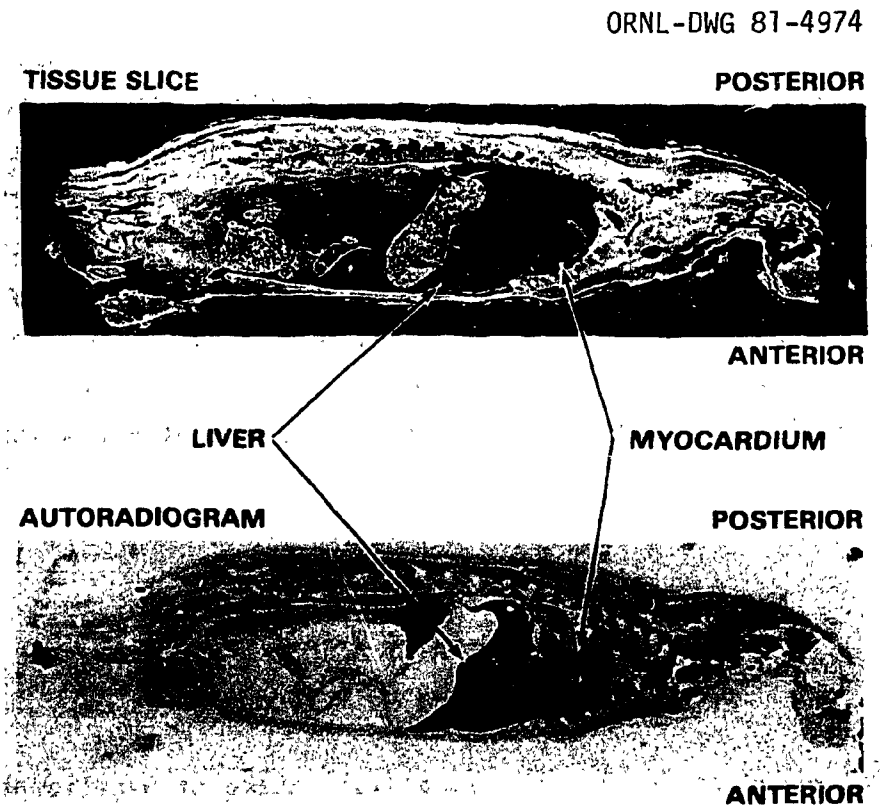

Fig. 2. Autoradiogram of a mid-line sagittal slice from a rat 1 h following intravenous injection of 10-[^{14}C]-9-telluraheptadecanoic acid (10-[^{14}C]-9-THDA). Source: R. H. Liss, Arthur D. Little, Boston, MA.

clearly visualized above the liver, while the blood pool within the heart chambers is shown to contain very little radioactivity.

These results clearly suggest that the intact alkyl group (R) of 9-THDA is retained in the myocardium and that labeling of this region of the molecule with radiohalogens should be pursued. These results also illustrate the detailed resolution that can be achieved with autoradiography of tissue slices following the *in vivo* administration of agents labeled with β-emitting nuclides. This tool could be very useful to investigate the metabolic fate of various regions of the 9-THDA molecule. Future studies will be directed at preparing carboxy-^{14}C-labeled 9-THDA [H_3C-$(CH_2)_7$-Te-$(CH_2)_7{}^{14}COOH$, 1-^{14}C-9-THDA] and methyl-^{14}C-labeled 9-THDA [$^{14}CH_3$-$(CH_2)_7$-Te-$(CH_2)_7$-COOH, 17-^{14}C-9-THDA]. Autoradiographic analyses of rat tissue slices after injection of these ^{14}C-labeled analogs could be a simple and effective method of determining the anatomical distribution of radioactivity and will provide insight into the metabolic fate of the carboxyl and methyl termini of 9-THDA.

BIOHAZARDS FROM ENERGY TECHNOLOGIES — ARSENIC TOXICITY

K. R. Ambrose

Previous studies on the toxicity of arsenic for human lung cells in vivo used a model of acute exposure in which the animal hosts for the diffusion chambers containing the human target cells received a single injection of arsenic trioxide (As_2O_3) by either the intraperitoneal, intravenous, or oral route (ORNL/TM-7482). In addressing potential health problems from energy technology pollutants, it is equally important and perhaps more relevant to investigate the effects of chronic exposure. Chronic arsenic exposure studies have been performed traditionally by administration of arsenic in the drinking water of the chosen test animal. In this system, however, it is often difficult to monitor the dose to the animal. Other methodologies for chronic exposure studies in animals include multiple injections or continuous

catheter infusion. Recently the Alza Corporation (Palo Alto, Calif.) has developed a means of achieving zero order continuous infusion rates of a test substance without the immobilization necessary with catheterization. The Alzet osmotic minipump consists of a collapsible reservoir of impermeable material surrounded by a second reservoir containing a hypertonic solution. The walls of the outer reservoir are semipermeable so that the hypertonicity of the aqueous reservoir imbibes water through the semipermeable membrane. The hydrostatic pressure that is generated causes compression of the inner flexible chamber resulting in a constant flow of its contents through a delivery portal. The inner reservoir is sealed from the outer chamber so that only the material placed in the inner reservoir exits from the pump. The minipump's delivery rate is predetermined by the manufacturer, and each lot is tested in vitro for actual delivery rates. The small size of the minipump (3.0 cm length, 0.7 cm diam) allows it to be implanted subcutaneously or intraperitoneally in small laboratory animals.

Prior to the animal studies using the minipump for chronic As_2O_3 exposure, the minipump was tested in vitro to establish the delivery of As_2O_3. A Model 2001 minipump was filled with 205 µl of ^{74}As-labeled As_2O_3 solution (3.76 mg/ml water). At 24 h intervals the pump was transferred to a fresh vial of saline, and the old vial of saline assayed for ^{74}As activity. At the manufacturer's determined pumping rate of 0.89 µl/h (±0.05) the percentage of the original dose (radioactivity) delivered in any 24 h period should have been 10.42%. With the $^{74}As_2O_3$ solution a 24 h delivery of 10.32% (±0.24) was determined, thus establishing the compatibility of As_2O_3 with the minipump delivery system.

In the chronic As_2O_3 exposure studies, hamsters received subcutaneous or intraperitoneal implants of minipumps containing As_2O_3 or $^{74}As_2O_3$ in aqueous solution. In some studies, the hamsters with subcutaneous implanted minipumps also received intraperitoneal implants of diffusion chambers containing human lung cells (Flow 2000). These chronic studies are presently continuing and were designed to determine (1) the gross health effects of chronic low level arsenic exposure in hamsters, (2) the effect of chronic arsenic exposure on the growth of

human cells in diffusion chambers, and (3) the metabolism and excretion of chronically administered arsenic in hamsters.

In recent studies, hamsters have been exposed to As_2O_3 in dosage levels ranging from 0.2 mg to 2 mg/(kg-d) and for time periods up to 20 d. The highest cumulative As_2O_3 dosage was 22 mg/kg. Other than a local inflammatory reaction in the area surrounding the delivery portal of the subcutaneous implanted minipumps, no gross adverse effects have been observed at these dosage levels. In some early experiments where $^{74}As_2O_3$-exposed hamsters were housed in metabolism cages equipped with aluminum food hoppers, many of the animals became ill with polyuria and diarrhea, and several animals died. These deaths were later attributed to aluminum toxicity from gnawing on the food hoppers. When glass food hoppers were used, no mortality or morbidity was observed in the arsenic exposed hamsters.

Preliminary studies on the effect of chronic As_2O_3 exposure on human lung cell growth in diffusion chambers have shown the necessity of longer assay times than those used in the acute studies. In the acute studies, a growth inhibition was observed within 24 h after As_2O_3 exposures at dosage levels of 2.5 mg/kg. In the chronic studies with hamsters receiving 1.7 mg(kg-d) from subcutaneously implanted minipumps, no growth inhibition of the human target cells was observed within 3 days after chamber implantation. By the fifth day, however, the arsenic-exposed target cells showed a 53% inhibition in growth in comparison to cells in chambers of control animals. In another experiment in hamsters receiving 2 mg/(kg-d) again from subcutaneous minipumps, the target cell numbers at day 5 reflected a 49% growth inhibition. It is expected that lower levels of circulating arsenic are responsible for this delayed growth inhibitory effect; however, studies monitoring the levels of ^{74}As activity in the chambers of chronically exposed hamsters are necessary to establish this relationship.

Studies of chronic arsenic exposure are still in progress and are expected to yield information on the excretion, tissue distribution, and metabolism of As_2O_3 as well as further information on the cytotoxicity induced in the human target cells. Comparison can then be made between the chronic and acute exposure models for arsenic trioxide toxicity in hamsters.

ANTIRHEUMATOID GOLD COMPLEXES

J. D. Hoeschele

Investigation of the synthesis of a series of gold antirheumatoid complexes (Fig. 3) is continuing (ORNL/TM-7223). These complexes are of interest as a result of the established clinical effectiveness of the orally active drug Auranofin (R=ethyl). The goals of the studies described in this report are to prepare a series of ^{95}Au-complexes and to obtain tissue-distribution data with these agents in rats. Correlation of tissue distribution results with pharmacological structure activity data may be useful in elucidating the mechanism of action of these agents.

The general scheme used for preparation of the R_3PAuCl and R_3PAu(β-D-TGTA) complexes is summarized in Fig. 4. Both the ethyl (Et)- and phenyl(Φ)-substituted analogs of these complexes have been prepared and characterized. The intermediate R_3PAuCl complexes were

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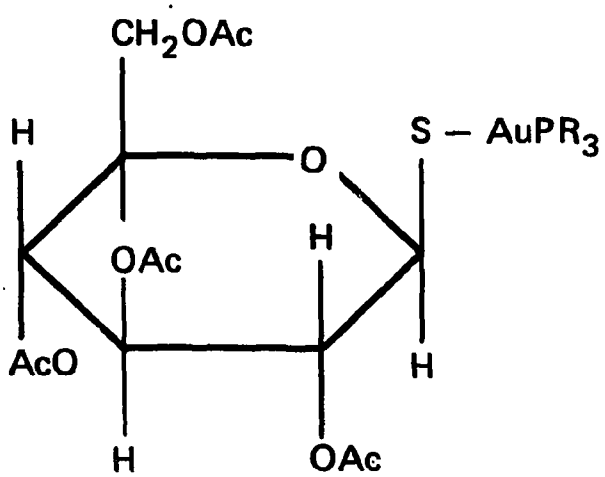

$$R = CH_3,\ C_2H_5,\ i-C_3H_7,\ n-C_4H_9,\ C_6H_5$$

Fig. 3. Structures of (β-D-thioglucosetetraacetate) trialkylphosphinegold (I) complexes R_3PAu(β-D-TGTA).

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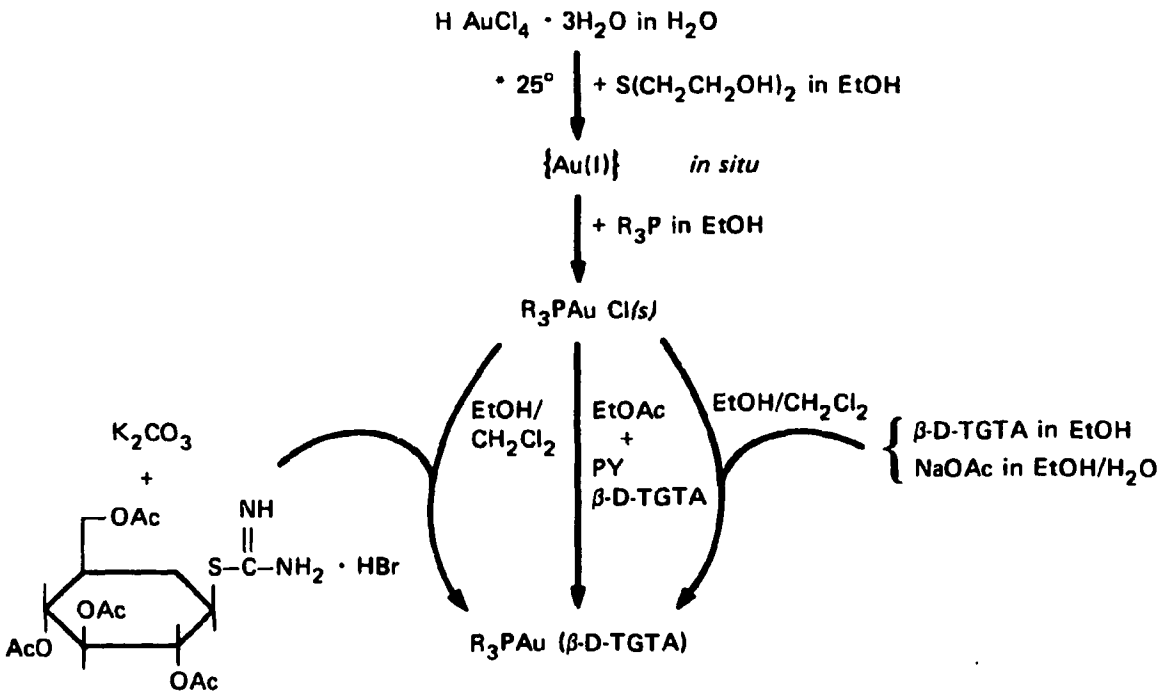

Fig. 4. General reaction scheme for the synthesis of $R_3PAu(\beta$-D-TGTA) complexes.

synthesized by the method of Sutton et al. involving reaction of the appropriate R_3P reagents with the soluble Au(I) intermediate formed by thioglycol reduction of $HAuCl_4$.[1] The R_3PAuCl species were purified by recrystallization from either ethanol or acetone. Each complex showed a single spot, visualized with I_2 vapor, when analyzed by thin-layer chromatography (TLC) using SiO_2-G plates developed with toluene: chloroform:methanol (6:3:1). Using this solvent system, the ethyl analog (R=Et) is more polar (R_f 0.57) than the phenyl (R=ϕ) analog (R_f 0.75).

The $R_3PAu(\beta$-D-TGTA) complexes are prepared by coupling the thiolate anion of β-D-TGTA with the R_3PAu-Cl intermediates. Three approaches were investigated for the formation of the β-D-TGTA thiolate anion. Generation of the thiolate anion by *in situ* basic hydrolysis of the thiuronium salt of β-D-TGTA was not pursued because

of the unavailability of the requisite glucosetetraacetate-S-thiourea derivative. An alternative strategy involved formation of the β-D-TGTA thiolate anion by K_2CO_3 or NaOAc neutralization of the weakly acidic thiol in an organic-aqueous biphasic system. The yields using the latter approach were low (~30%), presumably as a result of the limited solubility of the β-D-TGTA in the biphasic system. A new technique using pyridine as the base to generate the thiolate anion of β-D-TGTA in ethyl acetate (EtOAc) has been developed. This approach should be of general applicability for the preparation of a wide variety of R_3PAu-(β-D-TGTA) complexes and has been used to prepare Et_3PAu(β-TGTA) in consistently high yields (>75%). The R_3PAu(β-TGTA) complexes were also purified by crystallization from acetone (R=ϕ) or ethanol (R=Et) and were homogeneous upon TLC analysis using the solvent system described above (R=Et, R_f 0.61; R=ϕ, R_f 0.43).

The high extinction coefficients of the ultraviolet absorption maxima observed in the spectra of R_3PAu(β-TGTA) complexes can be used to determine accurately the purity and concentration of solutions of these complexes. As an example, the intense 231 and 266 nm absorptions exhibited by the Et_3PAu(β-TGTA) analog (Table 2) observe Beer's Law for concentrations >1 mg/ml.

Table 2. Spectral properties of [Et_3PAu(β-D-TGTA)] in EtOH (95%) at 25°C

Wavelength, nm	Molar absorptivity, E, cm^{-1} M^{-1}	
	Reference standard	Prepared sample
231	4.39×10^3	4.41×10^3
266	5.04×10^2	5.37×10^2
Ratio of $\frac{E, 231}{E, 266}$	8.7	8.2

REFERENCE

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PLATINUM ANTITUMOR AGENTS

J. D. Hoeschele and T. A. Butler

Development of a microscale synthesis of ^{195m}Pt-labeled *cis*-dichloro-*trans*-dihydroxy-*bis*-(isopropylamine)-platinum (IV) (^{195m}Pt-CHIP) has continued (Scheme I, A = isopropylamine). Emphasis has focused on the direct purification of CHIP by preparative thin-layer chromatography (TLC) of the crude product obtained from 30% H_2O_2 treatment of the partially pure *cis*-dichlorodiisopropylamineplatinum (II) (CIP) precursor. In addition, CHIP was also prepared from highly purified CIP to determine if the minor impurities accompanying CHIP synthesized from the impure precursor were formed during the H_2O_2 oxidation of CIP.

$$Pt^{\circ} \xrightarrow[NaCl,\ heat]{aqua\ regia} Na_2PtCl_4 \xrightarrow{KI} K_2PtI_4 \xrightarrow{A} cis\text{-}PtA_2I_2 \xrightarrow[HCl]{AgNO_3}$$

$$\underset{(\text{"CIP"})}{cis\text{-}PtA_2Cl_2} \xrightarrow{H_2O_2(30\%)} \underset{(\text{"CHIP"})}{cis\text{-}trans\text{-}[PtA_2(OH)_2Cl_2]}$$

Scheme I

The results of preparative TLC studies have demonstrated that CHIP (R_f 0.42) can be successfully purified on silica gel G plates using an ethyl acetate:acetone:0.1 *N* HCl (45:45:10) solvent mixture. The characteristic yellow-colored band of CHIP is easily visualized and can be recovered from the silica gel G by leaching the scrapped band with

water. Subsequent analytical TLC analysis of CHIP recovered by preparative TLC of a mixture containing several minor components demonstrated only a single component. Furthermore, analysis of ^{195m}Pt-CHIP purified in the same manner by preparative TLC revealed a single radioactive component that co-chromatographed with an unlabeled CHIP standard. The studies have demonstrated that CHIP can be readily purified by preparative TLC.

Two approaches have been investigated to purify the CIP precusor. Because purification of CIP by crystallization from N,N-dimethylacetamide has been only partially successful (ORNL/TM-7482), a second approach was pursued. Since addition of isopropylamine to the Na_2PtCl_4 intermediate is a crucial step during formation of CIP, several alterations of the conditions of this reaction were investigated. The purity of ^{195m}Pt-CIP has been increased by removal of excess HCl at ambient temperature *in vacuo* using a flash evaporator. In earlier preparations (ORNL/TM-7482), the HCl was removed using a hot plate after addition of H_2O. The lower yields of CIP under the latter conditions presumably resulted from the formation of unknown Pt(IV) species by hydrolysis of the $PtCl_6^{-2}$ anion. A second alteration of the reaction conditions that has increased yields of CIP involves introduction of the *i*-$PrNH_2$ as a gas, rather than as a liquid to a stirred solution of K_2PtI_4. In this manner, transiently high local concentrations of *i*-$PrNH_2$ are avoided. Earlier preparations of ^{195m}Pt-CHIP using impure ^{195m}Pt-CIP were only ~70% pure and contained radiolabeled impurity of unknown composition that remained at the origin during TLC analysis that represented 26% of the mixture. Levels of this impurity have been reduced substantially in ^{195m}Pt-CHIP samples prepared using purer ^{195m}Pt-CIP synthesized using the improvements outlined above.

Other reaction conditions which are being explored that may affect the purity of CIP include using purified K_2PtCl_4 rather than unpurified Na_2PtCl_4, which is presently generated *in situ*. The K_2PtCl_4 can be isolated and then crystallized following KCl treatment of the Na_2PtCl_4 intermediate. In addition, reducing the concentrations of Pt(II) may minimize side reactions during formation of *cis*-PtA_2I_2.

RADIONUCLIDES FOR MEDICAL COOPERATIVE PROGRAMS

F. F. Knapp, Jr., T. A. Butler, and J. D. Hoeschele

Carbon-11

Several ^{11}C-labeled amino acids were supplied for the Medical Cooperative Program with the Oak Ridge Associated Universities (ORAU) to study the application of these agents for tumor localization, pancreas imaging and brain scanning in human patients. Eight batches of ^{11}C-DL-tryptophan and ^{11}C-DL-valine were synthesized and used for brain uptake studies at ORAU using the emission computerized transaxial tomographic instrument. Seven products of ^{11}C-DL-leucine, ^{11}C-DL-tryptophan, and ^{11}C-DL-valine were prepared to develop further the methods for separation of the D and L optical isomers. The successful synthesis of ^{11}C-DL-leucine was the first time this compound has been prepared in our facilities. One experimental preparation of ^{11}C-DL-valine was made in which no nonradioactive carbon compound was added during the synthesis. The radiochemical yield of this "carrier free" product was about 50% of the previous syntheses in which carrier carbon was added. It will now be possible to vary the specific activity of ^{11}C-labeled amino acids over a wide range.

Platinum-195*m*

Five shipments of ^{195m}Pt-labeled *cis*-dichlorodiammineplatinum(II) were made to participants in the Medical Cooperative Program to study the pharmacokinetic properties of this antitumor agent and for potential application to monitor effective therapeutic levels. Three shipments were made to the University of Southern California (Dr. W. Wolf) and one shipment each to the University of Arizona (Dr. Jack Hall) and the University of California at Los Angeles (Dr. L. C. Ford).

Selenium-75 and Tellurium-123*m*

Radiolabeled selenium and tellurium fatty acids were supplied to collaborators in the Medical Cooperative Program for study as potential myocardial imaging agents. The Nuclear Medicine Division of Massachusetts General Hospital (Dr. Strauss) was supplied with ^{75}Se-13-selenaheneicosonic acid, ^{123m}Te-methyl-9-telluraheptadecanoate, and methyl-10-[^{14}C]-9-telluraheptadecanoate; the Medical Products Division, Union Carbide Corporation (Dr. Poggenburg) was supplied with ^{75}Se-13-selenaheneicosonic acid and ^{123m}Te-methyl-9-telluraheptadecanoate; Oak Ridge Associated Universities (Dr. Hayes) was supplied with ^{75}Se-13-selenaheneicosonic acid. Two new collaborative members of this Medical Cooperative Program, Johns Hopkins Medical Institutions (Dr. Wagner) and Mallinkrodt, Inc. (Dr. Wolfangel), were each supplied with ^{75}Se-13-selenaheneicosonic acid.

Copper-64

One shipment of ^{64}Cu solution was supplied under the Medical Cooperative Program to Oak Ridge Associated Universities (Dr. Hayes) for use as a tracer in the development of a process to separate the D and L optical isomers of ^{11}C-labeled amino acids.

OTHER NUCLEAR MEDICINE TECHNOLOGY GROUP ACTIVITIES

F. F. Knapp, Jr. and J. D. Hoeschele attended the 180th Annual Meeting of the American Chemical Society which was held in Las Vegas, Nevada, on August 25-29, 1980. On September 1-5, F. F. Knapp, Jr. participated in the International Symposium on Medical Radionuclide Imaging, sponsored by the International Atomic Energy Agency, held in Heidelberg, Federal Republic of Germany.

PAPERS AND PUBLICATIONS

Papers

F. F. Knapp, Jr., T. A. Butler, K. R. Ambrose, A. P. Callahan, J. A. Roberts, L. A. Ferren, R. A. Grigsby and K. J. Irgolic, "New Myocardial Imaging Agents—The Influence of Chain Length on the Heart Uptake of ^{75}Se-Labeled Fatty Acids," Symposium on Practical Applications of Nuclear and Radiochemistry, Annual Meeting of the American Chemical Society, Las Vegas, Nevada, August 25-29, 1980.

F. F. Knapp, Jr., "Tin-117*m*-Labeled Radiopharmaceuticals: Effects of Structural Modifications on the Adrenal Uptake of Steroids Labeled in the Sidechain with ^{117m}Sn," International Symposium on Medical Radionuclide Imaging, Heidelberg, Federal Republic of Germany, September 1-5, 1980.

J. D. Hoeschele, M. W. Williams, J. E. Turner, K. B. Jacobsen, and N. T. Christie, "Analysis of Softness Parameters as Potential Numerical Indices of Acute Metal Ion Toxicity," Annual Meeting of the American Chemical Society, Las Vegas, Nevada, September 1-5, 1980.

Reports

F. F. Knapp, Jr., *Nuclear Medicine Technology Progress Report for Quarter Ending June 30, 1980*, ORNL/TM-7482.