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Biomedical Radioisotope Program Progress Report for Quarter Ending March 31, 1977

J. K. Poggenburg

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HEALTH AND SAFETY RESEARCH DIVISION

BIOMEDICAL RADIOISOTOPE PROGRAM
PROGRESS REPORT FOR QUARTER ENDING MARCH 31, 1977

Work sponsored by
ERDA Division of Biomedical and
Environmental Research

J. K. Poggenburg *js*

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ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

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Previous reports in this series:

ORNL/TM-5809

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BIOMEDICAL RADIOISOTOPE PROGRAM
PROGRESS REPORT FOR QUARTER ENDING MARCH 31, 1977

SUMMARY

Progress is reported for the applications of ^{11}C , $^{195\text{m}}\text{Pt}$, and $^{123\text{m}}\text{Te}$. Of note in this report period is the presentation of images of rat adrenals with a $^{123\text{m}}\text{Te}$ -labeled steroid and an investigation of steroid structural parameters which affect adrenal concentration. Two new $^{195\text{m}}\text{Pt}$ -labeled compounds have been prepared for evaluation as chemotherapeutic agents.

CARBON-11

T. A. Butler

Two production runs were made this quarter to study the chemical synthesis of ^{11}C -DL-tryptophan for use in the ORAU-ORNL preclinical studies. Carbon-11-labeled compound preparation and clinical testing were limited due to a series of malfunctions of the cyclotron which made it inoperable during most of this period.

Equipment was ordered to provide for the synthesis and purification of ^{11}C -labeled glucose. The process involves the photosynthetic conversion of $^{11}\text{CO}_2$ in light-starved Swiss chard leaves, extraction of ^{11}C -glucose with ethanol and purification by ion exchange.

Design studies are in progress to examine the feasibility of using a flat plate window target for B_2O_3 to produce ^{11}CO - $^{11}\text{CO}_2$. A target of this design would allow the full dimensions of the proton beam to impinge on the B_2O_3 with the potential of increasing the yield of ^{11}C .

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CARBON-11 IONIZATION-EXCHANGE LABELING

D. V. Woo

Construction of the apparatus described in the last report has continued during this quarter. The cylindrical ionization chamber is constructed of borosilicate glass that can be separated into two sections which are connected by a high-vacuum ground-glass tapered joint with a Viton O-ring. One section contains two feed-through rods of Kovar which support a thoria-coated tungsten filament across the ends to serve as the electron source. This ionizing filament resembles those used in mass spectrometers. The other section contains a removable stainless steel cylinder supported by two copper rings which position the cylinder concentrically within the glass chamber.

High-vacuum borosilicate glass-teflon valves have been obtained and will be connected to the chamber with high-vacuum ground glass ball joints. These valves will control admission of the CO gas and the vacuum into the chamber. A mercury diffusion pump with freeze trap will be used to evacuate the chamber to approximately 10^{-7} torr. This is the estimated vacuum necessary prior to addition of the gases.

The electromagnets for collimating the electron beam have been constructed in four separate sections, to facilitate assembly and removal from the chamber, and have a total rating of approximately 400 gauss. Each section has its own power supply to permit focusing of the beam and adjustments for deviations in magnet geometry and alignment. Appropriate power supplies have been obtained to adjust the electron energy in the unipotential region of the stainless steel cylinder between the filament and collecting plate.

Plans for the next quarter call for assembling the apparatus and checking out individual components for reliability and safety.

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PLATINUM-195m

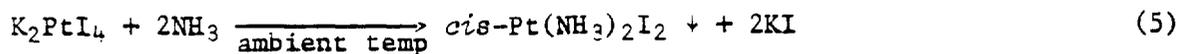
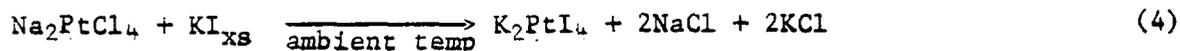
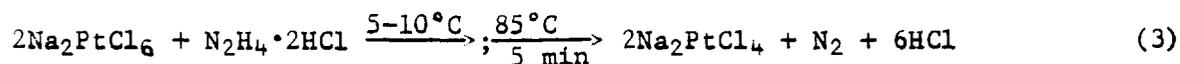
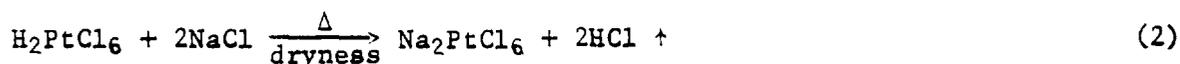
J. D. Hoeschele and T. A. Butler

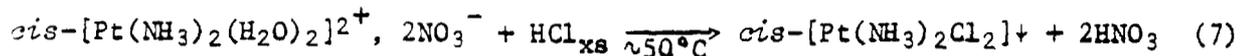
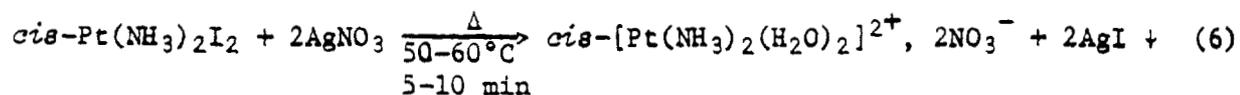
As part of the continuing medical cooperative program to study antitumor compounds, five shipments of ^{195}mPt -hexachloroplatinic acid were made to the University of Southern California, one shipment of ^{195}mPt -labeled *cis*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ to George Washington University Medical Center, one shipment of ^{195}mPt -labeled $[\text{Pt}(\textit{trans}\text{-}\ell\text{-DAC})\text{sulfate}]$ to Wadley Institutes of Molecular Medicine (WIMM), and one shipment of ^{195}mPt -labeled $[\text{Pt}(\textit{trans}\text{-}\ell\text{-DAC})\text{malonate}]$ to Mary Hitchcock Memorial Hospital. In addition, each of the latter three ^{195}mPt -labeled compounds was supplied to the ORNL Biology Division for DNA binding studies.

Efforts to optimize the microscale radioisotopic synthesis of ^{195}mPt -labeled *cis*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ (^{195}mPt -DDP) are continuing. This optimization, which will be completed in the next quarter, is important in view of the ever-increasing interest in ^{195}mPt -DDP and the direct applicability of some of the synthetic steps to planned syntheses.

Microscale Synthesis of *cis*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ (0.1 mmole)

The present microsynthetic scheme for ^{195}mPt -DDP is illustrated below by equations (1) to (7):





The above synthesis scheme appears little changed from that reported in the previous report (ORNL/TM-5809) but the following modifications have already increased the yields to greater than 50% with achievement of 60-80% as the ultimate goal:

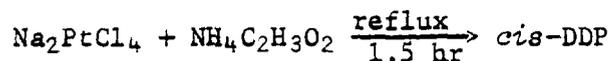
- Step 2. Addition of NaCl followed by evaporation to dryness to the thermally stable salt, Na_2PtCl_6 , rather than to the less stable H_2PtCl_6 residues, leads to (1) more reliable spectrophotometric assays for platinum, and (2) minimal carry-over (occlusion) of HCl to Steps 4 and 5. The second consideration is important since too high an HCl concentration would prevent NH_3 from reacting completely and could retard or limit the extent of K_2PtI_4 formation because of high Cl^- concentration.
- Step 3. The reduction of Pt(IV) \rightarrow Pt(II) proceeds equally as rapidly and smoothly (no Pt^0 metal formation) with Na_2PtCl_6 as with H_2PtCl_6 . K_2PtCl_6 is no longer being used as the Pt(IV) starting material for this step. By means of a micro combination pH electrode, the pH of the reduced solution is adjusted to ~ 6 .
- Step 4. Studies using stable Pt(II) have established that the use of excess KI, rather than the stoichiometric amount, greatly increases the rate of formation and stability (lifetime) of K_2PtI_4 without sacrificing yields. (In fact, some enhancement of yields occurs.) A mole ratio of I/Pt = 6.0, instead of 4.0 for stoichiometric conditions, appears satisfactory. The use of NH_4I instead of KI appears promising since the ammonolysis step (5) would, in effect, be moderated by the $\text{NH}_4^+/\text{NH}_3$ buffer system. Relatively high overall yields were obtained for a single preliminary synthesis employing NH_4I .

An important parameter in optimizing and/or reducing the scale of synthesis is the concentration of platinum, especially at Step 4. It is highly desirable to maintain as high a Pt(II) concentration as possible and, optimally, above 0.1 M. At concentrations much below this level, rates become slower and causes of loss through competing side reactions increase. The concentration of Pt(II) can be maximized (a) by dissolving the Na₂PtCl₆ residue in a minimum volume of H₂O after Step 2, and (b) by concentration by evaporation using an air stream during the elevated temperature (85°C) phase of Step 3.

Syntheses to date have been carried out on a 0.1 mmole scale; however, a 0.05 mmole (50 μmole) scale is feasible.

Work during the next quarter will focus on:

- (1) Quantitating the extent of reduction of Pt(IV) → Pt(II).
- (2) Completing the remaining parametric studies outlined in the previous report.
- (3) Establishing the chemical purity of the product by spectroscopic and chromatographic techniques.
- (4) Examining an alternative mode of synthesis via the following reaction scheme:



Microscale Syntheses of ¹⁹⁵mPt-[Pt(DAC)X₂]

X₂ = sulfate and malonate (C₃H₂O₄²⁻); DAC = *trans*-1,2-diaminocyclohexane

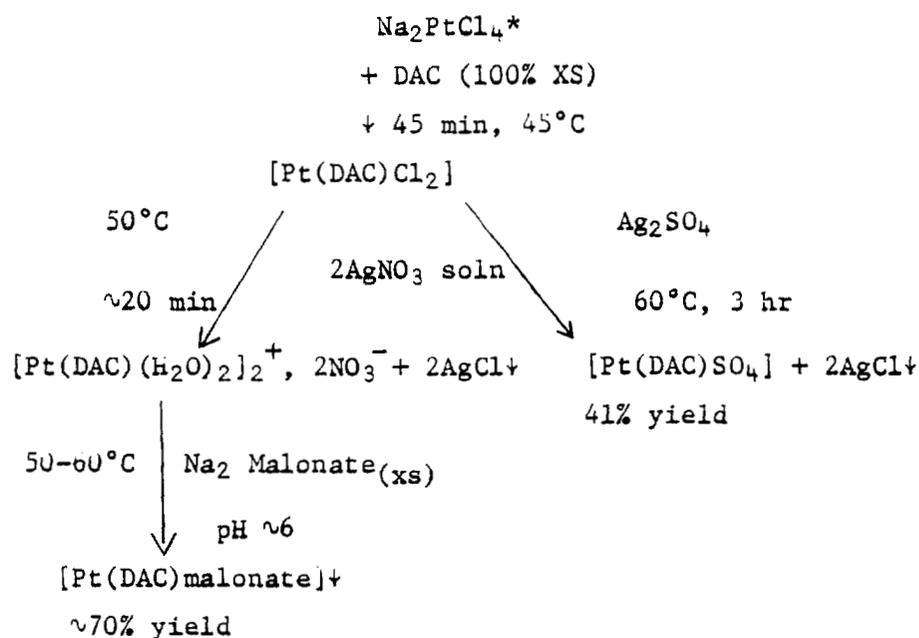
Microscale syntheses (0.1 mmole) of two closely related potential second generation antitumor Pt(II) drugs were developed in conjunction with Medical Cooperative Programs established with the Wadley Institutes of Molecular Medicine (Dallas, TX) and the Mary Hitchcock Memorial Hospital (Hanover, NH).

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These ^{195}mPt -labeled compounds are being used for uptake distribution studies in rats, and in the case of the malonate analog, for eventual combinational therapy (with radiation) *vs* a brain tumor model system in the rat. Both compounds have been entered into Phase I clinical studies at WIMM.

Methods of synthesis of these compounds are almost identical as outlined below:

Synthesis of $[\text{Pt}(\text{DAC})\text{X}_2]$



*Prepared as in Steps (1-3) for ^{195}mPt -DDP.

Distribution Studies

In general, organ distribution studies will be carried out for each new ^{195}mPt -labeled compound synthesized in order to ascertain whether a unique tissue distribution exists which might suggest therapeutic and/or diagnostic applications. These limited studies might also provide a basis of comparing different preparations of the same compound at a later date.

A comparison of the distribution of [Pt(*trans*- ℓ -DAC) malonate] and [Pt(*trans*- ℓ -DAC) sulfate] in the rat (Fisher 344) after \sim 24 hr is shown in Table 1.

General comments are as follows:

- (1) The data for the malonate were particularly valuable to E. Douple (Mary Hitchcock Memorial Hospital) in planning his initial experiments, i.e., in terms of the amount of activity to be injected to determine uptake in the brain. Reported levels of platinum uptake in the brain (>1%), as determined by atomic absorption spectroscopy, are significantly higher than those obtained here and by Douple by radiochemical methods.
- (2) The relative order of uptake (% dose/g tissue) for the malonate is kidney > spleen > pancreas > liver > lung > s. intestine > heart >> brain, while that for the sulfate analog is kidney > blood > spleen > liver > lung > s. intestine > pancreas > heart > testes > brain.
Noteworthy is the relatively higher uptake by the pancreas for the malonate compared to the sulfate.
- (3) The relatively high blood level (1% dose/ml) remains constant, according to the Wadley group, from 20 min to 7 days post-injection.

PHOSPHORUS-33

D. V. Woo and A. F. Rupp

Construction of the inert atmosphere glove box has been completed. The system is now being tested for leaks, and operational procedures are being developed to comply with safety and quality assurance requirements.

A microscale *in situ* process has been developed for synthesis of high-specific activity ^{33}P -labeled cyclophosphamide. Reactions on a scale of one millimole have been conducted. The reaction scheme involves generation of the bis-(2-chloroethyl)-phosphoramidate dichloride in dichloromethane followed by the careful addition of 3-amino-1-propanol and triethylamine. The reaction between bis-(2-chloroethyl)phosphoramidate dichloride and 3-amino-1-propanol releases HCl, and consequently, addition of the 3-amino-1-propanol must be done in the presence of triethylamine base in order to

Table 1. Distribution Studies: Pt(*trans*- λ -DAC)X₂ in the Rat
(21-24 Hours)

Experimental Details	X ₂ = Malonate		X ₂ = Sulfate	
	nanomoles/ g tissue	% dose/ g tissue	nanomoles/ g tissue	% dose/g tissue (WIMM*)
Dose: Chemical Activity	1.84 mg/kg 12.85 μ Ci/animal		5.83 mg/kg 371 μ Ci/animal	
Medium	Saturated solution (2.5 ml)		\sim 0.347 ml of 3.55 mg/ml	
Route of injection	i.p.		i.v.	
Sacrifice (post-injection)	21 hr		24	
Animal	Fisher 344, 320 g		Fisher 344, 211 g	
Distribution Data	nanomoles/ g tissue	% dose/ g tissue	nanomoles/ g tissue	% dose/g tissue (WIMM*)
<u>Organ</u>				μ g Pt/ g tissue
Brain			0.441	0.0145 (0.022)
Cerebrum	\sim 3.7 x 10 ⁻⁵	2.57 x 10 ⁻³		0.0861
Cerebellum	<6.1 x 10 ⁻⁵	<4.3 x 10 ⁻³		
Medulla	<6.1 x 10 ⁻⁵	<4.3 x 10 ⁻³		
heart	0.595	0.0416	5.74	0.189 (0.096)
S. Intestine	0.795	0.0556	4.84	0.159 (9.161)
Kidney	4.26	0.298	47.5	1.56 (1.07)
Liver	0.987	0.0690	13.02	0.428 (0.375)
Lung	0.911	0.0637	10.4	0.340 (0.279)
Pancreas	1.69	0.118	3.29	0.108 (0.098)
Testes	-	-	1.43	0.047 (0.068)
Spleen	2.07	0.147	28.2	0.927 (0.557)
Blood	-	-	29.0	0.953 (0.96)

* Results obtained by the Wadley Institutes of Molecular Medicine using identical ^{195m}Pt-[Pt(DAC)SO₄] solution (Sprague-Dawley Rat, 180 g, i.v. \sim 200 μ Ci).

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prevent acid hydrolysis of the phosphorus-nitrogen bond and regeneration of the bis-(2-chloroethyl) amine hydrochloride. The crude cyclophosphamide product is recovered from the reaction mixture by evaporation of the solvent, addition of dioxane to precipitate the salts, filtration of the salts, and concentration of the mixture for purification by column chromatography on a silica gel column. The column is eluted with a solvent gradient of decreasing proportions of benzene:acetone. The elution order of products is: unreacted bis-(2-chloroethyl)-phosphoramid dichloride, bis-(2-chloroethyl)amine hydrochloride, and finally cyclophosphamide. Any triethylamine salts which remain on the column are removed with methanol. Experimental yields have not yet been determined. This will be accomplished with ^{32}P - or ^{33}P -labeled POCl_3 .

Earlier problems associated with the purification of the bis-(2-chloroethyl)-phosphoramid dichloride have been solved using the same column and solvent system. The isolation and purification of this intermediate is not necessary, however, during the synthesis of cyclophosphamide. It is only necessary when it is required as a starting material for other phosphorus compounds with alkylating functions.

Present apparatus and techniques developed for the synthesis of ^{33}P -labeled phosphorus oxychloride (POCl_3) from phosphorus pentachloride (PCl_5) and phosphorus pentoxide (P_2O_5) have been tested with variable results. Several factors influence the reaction conditions and subsequent yields for this solid-solid interaction. Uneven coating of P_2O_5 on the small glass fritted disk in the reactor gives variable yields due to areas in which PCl_5 can pass through without reaction. Size, volume, and geometry of the reactor also appear to affect yields. Sublimation of PCl_5 to achieve effective interaction with P_2O_5 depends upon the rate of argon flow and PCl_5 entering the reactor, as well as upon maintaining the correct temperature to distill off the POCl_3 free of P_2O_5 and PCl_5 . An alternative procedure has therefore been devised for the reaction of PCl_5 with P_2O_5 . This procedure involves sublimation of PCl_5 directly into an inert carrier solvent (carbon tetrachloride, chloroform, or benzene) containing P_2O_5 with constant stirring.

The preliminary experiments in which PCl_5 and P_2O_5 were reacted in benzene at room temperature to produce POCl_3 appear promising. Removal of the POCl_3 -solvent mixture from unreacted excess P_2O_5 was accomplished by simple distillation of the mixture into a receiving vessel. The solvent should have no effect during the synthesis of cyclophosphamide; therefore, the POCl_3 -solvent mixture can be used directly, or, if need be, the solvent can be separated by fractional distillation.

Plans for the next quarter will include refinement of the cyclophosphamide synthesis, further evaluation and optimization of the two methods for POCl_3 production, synthesis of ^{32}P - and/or ^{33}P -labeled POCl_3 for determining yields, and synthesis of high-specific-activity cyclophosphamide for radiolytic decomposition studies.

TELLURIUM-123m

F. F. Knapp and K. R. Ambrose

We have demonstrated the accumulation of $^{123\text{m}}\text{Te}$ -labeled 3β -hydroxy-24-nor-23-(isopropyl tellura)-5 α -cholane in the adrenal glands of male rats following intravenous administration of the labeled compound. More recently, the adrenal glands of both male and female rats have been clearly visualized with both a rectilinear scanner and a camera equipped with an RC-type proportional counter. The latter studies have been performed in conjunction with the Medical Instrumentation Group of the Health and Safety Research Division and the Basic Measurement Science Group of the Instrument and Controls Division, respectively. The ovaries of female rats were also distinctly imaged with this agent. An image of a female rat two days after administration of the labeled compound is illustrated in Fig. 1a. This image was obtained with an RC-proportional counter camera with a xenon gas detector. This method detects the low energy K_α and K_β x rays emitted by the $^{123\text{m}}\text{Te}$ nuclide. Figure 1b is a rectilinear scan obtained on the same animal. The latter system detects both x rays and the higher energy photons. The image shown was obtained from data collected for the 159-kev gamma photon.

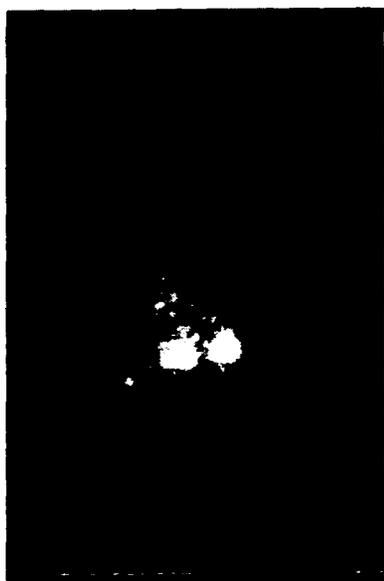


Fig. 1a.

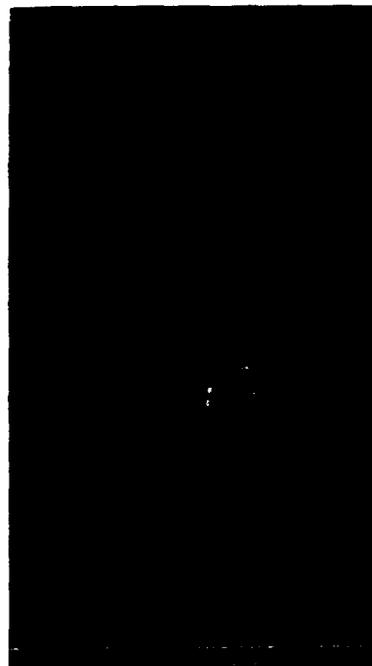


Fig. 1b.

Fig. 1. Posterior views of a female rat two days after the administration of 100 μ Ci of ^{123}mTe -labeled 3 β -hydroxy-24-nor-23-(isopropyl tellura)-5 α -cholane. The image shown in Fig. 1a was obtained with an RC-type proportional counter camera with a xenon gas detector. The same rat was imaged (Fig. 1b) with a rectilinear scanner equipped with a high resolution gold collimator. In both images the two centrally located Hot (bright) spots are the adrenal glands and the two smaller peripherally located hot spots are the ovaries.

Tissue distribution studies of intravenously injected $^{123\text{m}}\text{Te}$ - 3β -hydroxy-24-nor-23 (isopropyl tellura)- 5α -cholane conducted in both male and female Fisher strain rats showed a higher steroid concentration in the adrenals of female rats as compared to males. For example, the adrenal/blood ratios one day after injection were 68 for females and 44 for males. By the seventh day the adrenal/blood ratios were 100 for females and 53 for males.

Distribution studies designed to look at intervals shorter than one day, and also up to three weeks, showed that in male rats the peak concentration of the $^{123\text{m}}\text{Te}$ -labeled steroid in the adrenals is reached by 18-24 hr and then slowly declines over the next three weeks (approximately 10% of maximal concentration remaining at three weeks). Attempts to determine the relative radioactivity in the medulla and cortex of the adrenals were hampered by the small size of rat adrenals. These studies will be done in rabbits.

The combined results of the tissue distribution and scanning studies indicate that $^{123\text{m}}\text{Te}$ - 3β -hydroxy-24-nor-23-(isopropyl tellura)- 5α -cholane may be useful as an agent for the detector of various adrenal disorders and may also aid in the detection of ovarian tumors and cysts.

The adrenal glands of female rabbits have also been clearly imaged four days after administration of the $^{123\text{m}}\text{Te}$ -labeled steroid using both the rectilinear scanner and a gamma camera. The latter studies were performed in conjunction with the ORAU medical facilities. Neither of the two female rabbits treated with this agent showed ovarian concentration of radioactivity. Without any exceptions the ovaries of female rats have concentrated radioactivity after the injection of this material. It is possible that ovarian uptake is a function of the estrus cycle, which in rabbits is dependent upon coitus.

The adrenal glands and livers of male rats were excised two days after the administration of $^{123\text{m}}\text{Te}$ - 3β -hydroxy-24-nor-23-(isopropyl tellura)- 5α -cholane. The tissues were Folch extracted and the lipid-soluble portions

subjected to silicic acid chromatography. The liver extract contained predominantly very polar radioactive components which were eluted from the column in the methanol wash. In contrast, the adrenal extracts contained a number of labeled components. One major component was very non-polar and was eluted from the column with the expected mobility of steryl esters. An expected metabolic fate of neutral monohydroxy steroids concentrated in the adrenal gland would be esterification with long-chain fatty acids. The adrenal extract also contained two other major components of moderate polarity which may represent nuclear modifications of the administered compound. These results were reproduced in a separate experiment performed in the same manner. The fact that the tissues were manipulated in the same manner and the radioactive column profiles of the adrenal and liver extracts were consistently different suggests that the radioactive components detected upon silicic acid chromatographic analyses must represent true metabolites of the administered compound. From a biochemical vantage point these results raise several interesting questions, since it is known that the saturated steroid cholesterol is not metabolized by rat adrenal homogenates.

The general scheme that was developed for the introduction of ^{123m}Te into the steroid sidechain is efficient and easily adaptable for the preparation of a wide variety of steroids. These methods are thus uniquely suited for an investigation of the effect of steroid structure on the ability of the adrenal to concentrate such substances. Several structural modifications of the steroid nucleus and sidechain were envisioned which could give a general indication of the structural parameters which determine uptake of steroids by the adrenals. The structural modifications that were investigated include the following: (1) the stereochemistry of the A/B ring juncture, (2) the presence of a hydrophobic C-3 substituent, (3) the effect of the Δ^5 -nuclear double bond, and (4) the presence of a large alkyl tellurium substituent in the sidechain. The syntheses of representative steroids exemplifying these structural variations are discussed below with results of biological studies with the ^{123m}Te -labeled steroids.

- (1) During the initial stages of our investigations directed towards the preparation of steroids labeled in the sidechain with ^{123m}Te , 3 α -acetoxy-5 β -cholanic acid was chosen as a model substrate to determine the efficacy of the Hünsdiecker degradation to prepare the corresponding 24-nor bromide. This technique resulted in a 32% yield of the 3 α -acetoxy-24-bromo-5 β -cholane which was then coupled with sodium isopropyl tellurol in the usual manner to give 3 α -hydroxy-24-nor-23-(isopropyl tellura)-5 β -cholane. The ^{123m}Te -labeled compound was prepared in the same manner. Tissue distributions of the labeled steroid in female rats indicated only minimal adrenal uptake. These results were further substantiated by rectilinear scans of both male and female rats following administration of the labeled analog. The adrenal glands of these rats could not be visualized during the period of up to two weeks after injection. These results indicate that the stereochemistry of the A/B ring juncture is an important structural feature affecting adrenal uptake of such compounds.
- (2) and (3) The Hünsdiecker-type degradation was not applicable for the decarboxylation-halogenation of bile acids containing a nuclear double bond. For this reason an alternative procedure was used for the synthesis of the requisite halogenated sidechain intermediate. Methyl-3 β -methoxy-chol-5-en-24-oate was prepared from the methyl ester of the parent compound by reaction with trimethyl orthoformate and perchloric acid. Reduction with methoxy ethoxy sodium aluminum hydride gave 3 β -methoxy-24-hydroxy-chol-5-ene which was converted to 3 β -methoxy-24-bromo-chol-5-ene by reaction with the intermediate species generated by the reaction of carbon tetrabromide and triphenyl phosphine. The 24-bromide was coupled with sodium isopropyl tellurol in the usual manner to yield the 3 β -methoxy-24-(isopropyl tellura)-chol-5-ene. Tissue distribution experiments with the ^{123m}Te -labeled compound in female rats indicated an adrenal concentration (% dose/g) lower than that obtained with ^{123m}Te -3 β -hydroxy-24-nor-23-(isopropyl tellura)-5 α -cholane (24 and 65, respectively). In addition, the concentration in other tissues was high, resulting in only moderate adrenal/tissue ratios (e.g., 5:1 adrenal/liver).

These data were corroborated by the rectilinear scans of a rat for periods up to a week after injection with labeled compound. After fifteen days, however, the adrenals and ovaries of a female rat were clearly imaged. These results indicate that certain structural features of the steroid not only determine adrenal uptake but also dictate the rates at which steroids are taken up and cleared by other tissues.

To study the effect of the Δ^5 -nuclear double bond the 3 β -methoxy-24-bromo-chol-5-ene was converted to 3 β -acetoxy-24-bromo-chol-5-ene by reaction with anhydrous ferric chloride in a mixture of acetic anhydride-ethyl acetate. The acetate was then coupled with sodium isopropyl tellurol in the usual manner to yield 3 β -hydroxy-24-(isopropyl tellura)-chol-5-ene. Although the tissue distribution experiments with the ^{123}mTe -labeled compound have not yet been initiated, rectilinear scans of both male and female rats following administration of this agent have indicated a very rapid adrenal-specific uptake of this material. These preliminary results suggest that this analog is even more efficient for early visualization of adrenals than ^{123}mTe -3 β -hydroxy-24-nor-23-(isopropyl tellura)-5 α -cholane.

- (4) To investigate the effect of enlarging the alkyl tellura sidechain substituent, sodium octyl tellurol was prepared by the general procedure described earlier and coupled with 3 β -acetoxy-24-nor-23-bromo-5 α -cholane to give 3 β -hydroxy-24-nor-23-(octyl tellura)-5 α -cholane. This interesting analog was fully characterized by the usual methods and the ^{123}mTe -labeled compound was then prepared. Although tissue distributions of this analog have not been initiated, rectilinear scans of both male and female rats injected with this material have given discouraging results. Even ten days after injection only minimal adrenal uptake could be detected. These results indicate that the steroid sidechain also plays an important role in determining adrenal uptake.

During the next quarter the factors that affect ovarian uptake of ^{123m}Te -3 β -hydroxy-24-nor-23-(isopropyl tellura)-5 α -cholane and 3 β -hydroxy-24-(isopropyl tellura)-chol-5-ene will be investigated. In addition, biological studies of the new compounds described in this report will be completed. These include *in vitro* incubations of the above two steroids with rat adrenal homogenates. The results of the latter experiments will be compared to those discussed earlier for the adrenal extracts obtained following *in vivo* administration. In addition, both the *in vivo* and *in vitro* experiments will be performed to determine the metabolic fate of the above two ^{123m}Te -labeled steroids in ovarian tissue.

MISCELLANEOUS

Nine shipments of ^{43}K were made this quarter. Three shipments to the University of Mississippi were used for radioisotope imaging in heart disease studies in comparison with ^{201}Tl . Three shipments to Brookhaven National Laboratory were used in their studies of exchangeable electrolytes in human subjects. One shipment was made to National Institute for Environmental Health for study of alkali metal ion perfusion in the inner ear of guinea pigs to relate uptake in the endolymph as a function of noise and disease factors. One shipment was made to the City College of New York for imaging studies, and one shipment was made to Argonne National Laboratory for use in chemical studies.

One shipment of high-specific activity ^{64}Cu was sent to ORAU for tumor localization studies. This positron emitter has potential usefulness with their new Emission Computed Axial Tomographic (ECAT) scanner.

J. D. Hoeschele attended a meeting at the University of Vermont Regional Cancer Center concerning the prospective use of Pt(II) compounds in treating brain tumors (chemotherapy plus radiation therapy). He also presented seminars at both the East Tennessee Section of the American Chemical Society and at ORAU concerning "Platinum Antitumor Complexes in Cancer Chemotherapy." J. K. Poggenburg presented a seminar on "Medical Applications of Radioisotopes" at Union University, Jackson, TN.

Visitors this period include Dr. Jack Coupal, Radiopharmacist at the V. A. Hospital, Lexington, KY, and Mr. Richard Yanzey, a student in the School of Pharmacy, University of Kentucky, who spent a day learning techniques for the synthesis of ^{195}mPt -DDP.

PUBLICATIONS

Reports

J. K. Poggenburg, *Biomedical Radioisotope Program Progress Report for Quarter Ending December 31, 1976*, ORNL/TM-5809, Oak Ridge National Laboratory (February 1977).

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