Tellurium-123m-Labeled 23-(Isopropyl Telluro)-24-Nor-5α-Cholan-3β-ol: A New Potential Adrenal Imaging Agent

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Tellurium-123m-labeled 23-(isopropyl telluro)-24-nor-5α-cholan-3β-ol (24-telluracholestanol, or 23-ITC) has been prepared as a potential adrenal-imaging agent. The new agent was synthesized by the coupling of 3β-acetoxy-23-bromo-24-nor-5α-cholan with Te-123m-labeled sodium isopropyl tellurol. Tissue distribution experiments in both male and female rats indicate a high adrenal concentration of radioactivity following administration of this agent. In female rats the adrenal glands accumulated 4.5% of the injected radioactivity only 1 day after administration of Te-123m-23-ITC. The adrenal-to-liver ratio was 42 after 1 day, and this increased to 100 after 3 days. Chromatographic analyses of lipid extracts from adrenal, ovary, liver, and lungs suggest that this agent is metabolized by these tissues. Examination of the rats' excretory products has indicated that approximately 50% of the administered radioactivity is excreted in the feces within 5 days after injection of Te-123m-23-ITC. Moreover, the adrenals and ovaries of rats have been clearly imaged with this agent, both with a rectilinear scanner and with an RC type of proportional-counter camera.

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The accumulation of intravenously administered C-14-cholest-5-en-3β-ol (cholesterol) in the adrenal glands of mice was demonstrated several years ago by Apelgren and coworkers (*1*). Their results suggested that steroids, labeled with gamma-emitting radionuclides, might also concentrate in adrenal glands, and that such agents could be used for adrenal imaging. The effectiveness of radiolabeled steroids for the diagnosis of adrenal disorders is now well documented. Successful clinical applications have been reported using I-131 19-iodocholest-5-en-3β-ol for the diagnosis of Cushing's syndrome (*2,3*), adrenal adenoma (*4,5*), adrenal remnants after "total" adrenalectomy (*4–6*), and aldosterone-secreting adrenal tumors (*7–10*). In addition, this agent has been used to detect metastatic adrenal carcinoma (*11*) and also for visualization of the gallbladder (*12*).

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Several groups have reported the formation of 6β-(iodomethyl)-19-nor-cholest-5(10)-en-3β-ol by homoallylic rearrangement of 19-iodocholest-5-en-3β-ol (*13–16*). It is particularly interesting that the I-131-labeled rearrangement product (I-131 NP-59) concentrates more rapidly in the adrenal glands of rats, and also results in higher adrenal-to-tissue ratios than I-131 19-iodocholest-5-en-3β-ol (*17–19*). More recently, a new route has been developed for the synthesis of 6β-(iodomethyl)-19-nor-cholest-5(10)-en-3β-ol and 6β-(bromomethyl)-19-nor-cholest-5(10)-en-3β-ol (*20*). The synthesis and tissue distribution studies of the Br-82-labeled compound have also been reported, and these results suggest that this compound would not be a good adrenal-seeker (*21*). Continued interest in preparing steroids labeled with other gamma emitters has resulted in the synthesis of 19-(methyl[^{75}Se]seleno)-cholest-5-en-3β-ol, which has been found to concentrate in the adrenal medulla of rats, rabbits, and dogs (*22*).

The use of I-131-labeled agents can result in high radiation doses to patients as a result of the beta emissions of this nuclide (major β at 610 keV), and the ra-

dioiodinated agents are also often unstable in vivo. Such disadvantages suggest that the routine clinical use of I-131-labeled adrenal agents may be impractical. The use of Se-75-labeled agents would overcome the problems resulting from the short shelf-life, high beta dose, and in vivo instability of the I-131-labeled agents. The Se-75 nuclide decays with the emission of two high-energy photons (280 and 265 keV), however, which result in inefficient collimation and poor-quality images. The use of a Te-123m-labeled agent would overcome several of the disadvantages of Se-75. Tellurium succeeds selenium in the chalcogen series (Group IVa) and can be covalently attached to organic molecules. The Te-123m nuclide ($T_{1/2}$ = 120 days) decays by isomeric transition with the emission of a single gamma photon (84% abundance) having an energy of 159 keV. The superior radionuclidic properties of Te-123m suggest that this nuclide would present an attractive candidate for use in nuclear medicine. Although the use of agents labeled with Te-123m has been suggested (*23*), there are no reports in the literature of attempts to synthesize a Te-123m-labeled diagnostic agent. In this paper we describe the radiochemical synthesis and purification of 23-(isopropyl[^{123m}Te]telluro)-24-nor-5α-cholan-3β-ol. Good adrenal uptake of this agent has been demonstrated in rats, and excellent images of the adrenals and ovaries of rats have also been obtained.

MATERIALS AND METHODS

General. The Te-123m was produced by the ^{122}Te(n,γ)^{123m}Te* reaction by irradiation of Te-122 for 14 days in the Oak Ridge High Flux Isotope Reactor (2×10^{15} neutrons/cm^2 × sec). Radioactive samples were counted using a Ge(Li) detector and multichannel analyzer or with a liquid-scintillation counter using a set of matched polycrystalline sodium iodide wells. The latter system detected the 159-keV gamma of Te-123m with an efficiency of 39%. Thin-layer radiochromatographic analyses were performed using 250-μ-thick layers of silica gel G-PF-254 coated on glass plates.† After development in chloroform, sections of the plates were scraped into vials for radioactive determinations. These TLC analyses were performed in the dark to minimize photochemically-induced decomposition of the telluro steroid. Column chromatographic analyses were performed using 60- to 200-mesh silicic acid.

Production and purification of Te-123m. Reactor irradiation of metallic tellurium results in the formation of a molten target mass that solidifies hard when cooled. To optimize the formation of sodium ditelluride (Na_2Te_2) by reaction of metallic sodium and tellurium in liquid ammonia, it is important that the tellurium be introduced into the reaction system as a fine powder. In order to determine accurately the specific activity of the Te-123m, and also to prepare the product as a fine powder suitable for sodium reduction, the target is dissolved in *aqua regia* and aliquots are taken for counting. The solution is then taken to incipient dryness, dissolved in concentrated hydrochloric acid, and taken to dryness again. The acid treatment is repeated again and the resulting solid is then dissolved in 200 ml of water. After the addition of NaBr (5 g), the solution is boiled for 30 min, cooled, and sulfur dioxide is then passed through the solution (two bubbles per sec) for 2 hr. The tellurium metal precipitates as very fine particles, which are recovered by centrifugation. The powder is washed three times with water, then dried in an oven at 140°C. A number of targets have been processed by this method and the recovery of Te-123m has been consistently greater than 90%.

Preparation of 23-(isopropyl[^{123m}Te]telluro)-24-nor-5α-cholan-3β-ol (4). The microscale synthesis of the Te-123-labeled steroid (Fig. 1) involved reaction of sodium isopropyl[^{123m}Te]tellurol with 3β-acetoxy-23-bromo-24-nor-5α-cholane. The method is easily adaptable to the 200–500 μmole scale. In a typical preparation, reactor-produced Te-123m (22 mg, 25.8 mCi) was combined with carrier tellurium (45-μ powder) to yield a sample with specific activity 25.8 mCi/millimol. Approximately 25 ml of liquid ammonia was then condensed into the reaction vessel containing the tellurium powder. The reaction vessel had been flushed previously with argon gas and was connected to a small trap such that a slight argon pressure could be maintained during the reaction. Freshly cut pieces of metallic sodium (23 mg, 1 millimol) were added to the rapidly stirred slurry. The solution was stirred for 2 hr, progressing through the typical color change: yellow → green → blue → red. Isopropyl iodide (174 mg, 1 millimol) was then added by means of a Hamilton syringe inserted through a rubber septum. The initial deep-red color of the solution slowly turned to a yellow-amber hue concomitant with the appearance of colloidal tellurium. After 1 hr of stirring, the ammonia was allowed to evaporate under a stream of argon, yielding a residue consisting of an orange gum containing metallic tellurium. The residue was extracted with several small portions of benzene (15 ml total volume) and the orange-colored extracts combined and washed well with water. The benzene solution was diluted with methanol to 25 ml in a volumetric flask, and aliquots were taken for counting. The benzene-extracted material showed 10.7 mCi of radioactivity, indicating a 42% yield of diisopropyl[^{123m}Te]ditelluride (**1**). This solution was combined with 25 ml of methanol and the mixture stirred vigorously under an argon atmosphere. Small portions of sodium borohydride were then added until a colorless solution was obtained, which indicated complete reduction of the ditelluride (**1**) to sodium isopropyl[^{123m}Te]tellurol (**2**). Gentle warming of the ditelluride solution was sometimes required to initiate the vigorous

reductive process. Approximately 80 mg (2 millimols) of sodium hydroxide were added to the colorless solution and the mixture then refluxed. The 3β-acetoxy-23-bromo-24-nor-5α-cholane (**3**, 112 mg, 250 μmole) was then added as a slurry in a small volume of benzene, and the mixture was refluxed for 1 hr. At this time thin-layer chromatographic analysis of an aliquot indicated the reaction to be complete. The solution was poured into water, and the organic layer washed several times with water. The yellow-colored benzene solution was applied to a silicic acid column slurried in benzene. Fractions (25 ml) were collected by elution with increasing concentrations of ethyl ether in benzene. Aliquots (100 μl) of each fraction were taken for counting.

Animal studies. Fischer 344 rats were used for these investigations, groups of three or four animals being tested at each time point. The animals were 6–10 wk old, the males weighing 225–300 g, the females 160–180 g. Food and water were allowed ad libitum before injection and throughout the duration of the experiment. The benzene solution of the Te-123m-labeled steroid was taken to dryness under argon and the solid dissolved in ethanol. This solution was filtered through a Millipore filter directly into a sterile vile containing 1% Polysorbate 80 in 0.9% saline. The final ethanol concentration of this solution was 10%. The steroid solution (1 ml, 6–14 μCi) was injected through a lateral tail vein into anesthetized rats. At selected times the rats were killed by decapitation under ether anesthetization. Blood was drained from the carcass into a beaker containing a small amount of sodium citrate solution. The organs were carefully removed, rinsed with 0.9% saline solution and blotted dry before weighing. The tissue distribution data were analyzed through a multifactorial analysis-of-variance program. Subsequent mean % dose/g values for individual tissues were further accessed for statistical significance ($P < 0.05$) by a Newman-Keuls test.

Isolation and analysis of Te-123m-labeled lipids extracted from rat tissues. Male and female rats were injected with 23-(isopropyl[^{123m}Te]telluro)-24-nor-5α-cholan-3β-ol (100–300 μCi) as described earlier. After 3 days the animals were killed and the adrenals, livers, lungs, and ovaries were removed. The tissues were homogenized in 45 ml of a chloroform-methanol mixture (2:1; Folch medium) at 5000 rpm for 30 sec. The homogenates were filtered through cheesecloth, and after the addition of an equal volume of water the two phases were allowed to separate. Aliquots of the lower organic phase and the upper aqueous phase were counted. The organic layers, containing more than 85% of the extracted radioactivity, were evaporated to dryness in vacuo. Each resulting residue was dissolved in a small volume of chloroform and applied to a silicic acid column (60–200 mesh, 2 × 30 cm). Fractions (25 ml) were collected by elution with increasing volumes of ether in benzene. The columns were finally washed with methanol to remove any very polar material.

Rectilinear scans and camera images. The animals were anesthetized by intraperitoneal injection of a sodium pentobarbital solution (30–50 mg/kg) and scans were obtained using a rectilinear scanner equipped with a 63-hole gold collimator. The focal distance was 3 in., and the animals were scanned at 0.25 in/sec. The camera images were obtained with a RC-type proportional-counter camera with a gas-filled detector (xenon).

RESULTS AND DISCUSSION

The present investigation was initiated to develop a radiochemical synthesis of 23-(isopropyl[^{123m}Te]telluro)-24-nor-5α-cholan-3β-ol (Te-123m 23-ITC) and to determine the potential of this new compound as an adrenal-imaging agent. The high reactor burn-up cross section resulted in the production of Te-123m with much lower specific activity than had been calculated (*25*). Consequently the specific activity of the Te-123m-labeled steroid product was 26 mCi/millimol. During the isolation of Te-123m 23-ITC by column chromatography, a nonpolar component was initially eluted from the column with benzene (fractions 5–9) and corresponded in mobility to diisopropyl ditelluride. A second radioactive component was eluted with 5% ether in benzene (fractions 28–42) and chromatographed with the expected mobility of 23-ITC. Aliquots of the combined fractions containing Te-123m 23-ITC were analyzed by thin-layer radiochromatography. The radioactive samples were combined with unlabeled 23-ITC as carrier to minimize the formation of the oxidized polar products that often result from exposure of small amounts of the telluro steroids on the chromatogram to atmospheric oxygen. The results of these analyses with two solvent systems indicated the presence of only one major radioactive component, which co-chromatographed with the unlabeled standard. The purified product contained

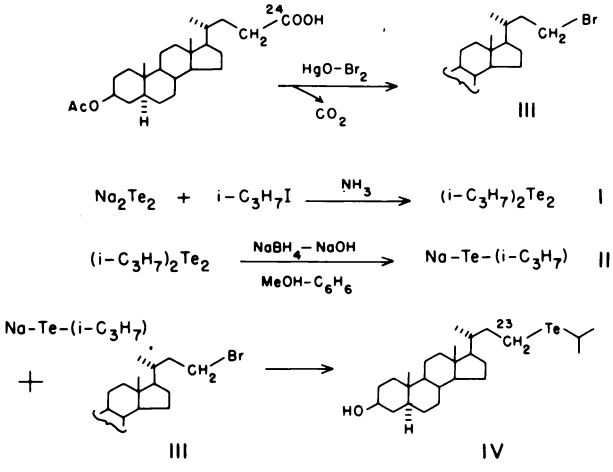

FIG. 1. Synthesis of 23-(isopropyl[^{123m}Te]telluro)-24-nor-5α-cholan-3β-ol (**4**).

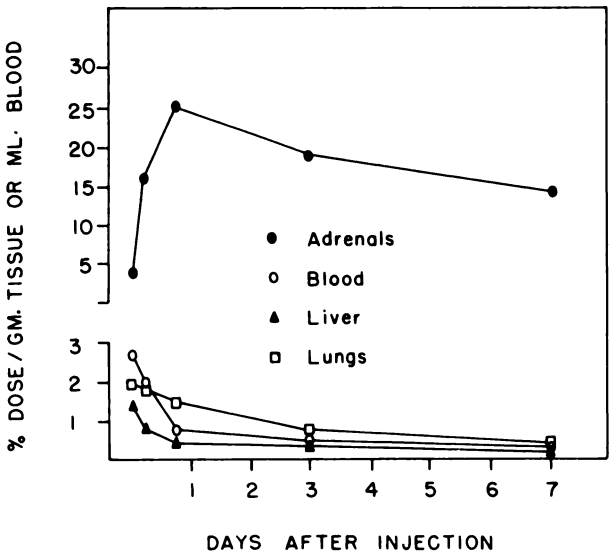

FIG. 2. Tissue distribution (of injected activity per g of tissue) in male rats at various times following i.v. administration of compound **4**.

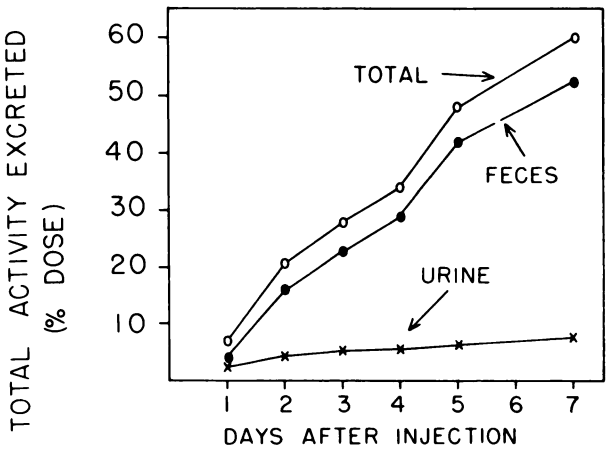

FIG. 3. Radioactive contents of urine and feces from male rats following i.v. administration of compound **4**.

3.58 mCi of radioactivity, indicating that the Te-123m 23-ITC was obtained in 20% overall yield. The coupling of 3β-acetoxy-23-bromo-cholane-24-nor-5α and sodium isopropyl[^{123m}Te]tellurol (Fig. 1) proceeded in 47% yield. The Te-123m 23-ITC has been stored in benzene solution at 4°C in the dark for several weeks, with only slight loss of radiochemical integrity. Although the factors affecting stability have not yet been studied in detail, silicic acid column chromatographic analysis of a sample of Te-123m 23-ITC (**4**) stored for 10 wk as described above indicated that 86% of the radioactivity co-chromatographed with authentic 23-ITC.

The distribution of radioactivity in the tissues of male rats was determined at time intervals varying from 1 hr to 21 days following i.v. administration of Te-123m 23-ITC. Figure 2 shows the % dose/g in selected tissues for postinjection periods from 6 hr to 7 days, illustrating the relative changes in the distribution of radioactivity with time. The maximal concentration of radioactivity in the adrenal glands was reached at 1 to 2 days after injection of Te-123m 23-ITC. The adrenal-to-liver ratio was 25 after 1 day, and increased to 65 after 7 days. A similar increase was detected in the adrenal-to-lung and adrenal-to-spleen ratios, whereas the adrenal-to-blood and adrenal-to-kidney ratios did not increase substantially over the 7-day period. The radioactive contents of urine and feces from male rats were also monitored over a 7-day period following injection of Te-123m 23-ITC (Fig. 3). These data indicate that approximately half of the administered radioactivity was excreted, primarily in the feces, within 5 days. The distribution of radioactivity was also determined in female rats at periods of 1, 3, and 7 days after administration of the Te-123m 23-ITC (Table 1). Although the radioactive content of the adrenals, and the resulting adrenal-to-tissue ratios, were

TABLE 1. DISTRIBUTION OF RADIOACTIVITY IN FEMALE RAT TISSUES FOLLOWING I.V. INJECTION OF 23-(ISOPROPYL[^{123m}Te]TELLURO)-24 NOR-5α-CHOLAN-3β-OL

Tissue	Mean % dose/g (range)		
	1 day after dose	3 days after dose	7 days after dose
Blood	0.95 (0.82–1.09)	0.49 (0.43–0.55)	0.34 (0.32–0.37)
Liver	1.62 (1.46–1.80)	0.72 (0.67–0.76)	0.41 (0.36–0.48)
Spleen	2.08 (1.85–2.32)	0.62 (0.55–0.68)	0.34 (0.29–0.40)
Pancreas	0.45 (0.42–0.49)	0.39 (0.34–0.44)	0.27 (0.25–0.32)
Stomach	0.15 (0.13–0.15)	0.12 (0.09–0.14)	0.07 (0.04–0.18)
Small intestine	0.83 (0.81–0.86)	0.39 (0.35–0.41)	0.16 (0.12–0.24)
Large intestine	1.13 (1.00–1.22)	0.41 (0.35–0.46)	0.19 (0.10–0.36)
Adrenals	67.98 (61.34–78.75)	71.74 (68.18–75.93)	34.76 (32.99–37.79)
Kidneys	1.24 (1.14–1.32)	1.23 (1.19–1.27)	0.94 (0.89–0.99)
Ovaries	12.12 (11.73–13.95)	7.44 (6.53–8.86)	4.51 (3.26–6.07)
Heart	0.75 (0.71–0.77)	0.45 (0.43–0.48)	0.18 (0.15–0.20)
Lungs	2.16 (1.82–2.33)	1.09 (1.08–1.11)	0.41 (0.36–0.45)
Thyroid	1.85 (1.78–1.89)	1.64 (1.20–2.19)	0.67 (0.56–0.77)
Brain	0.09 (0.08–0.10)	0.09 (0.09–0.10)	0.09 (0.08–0.10)

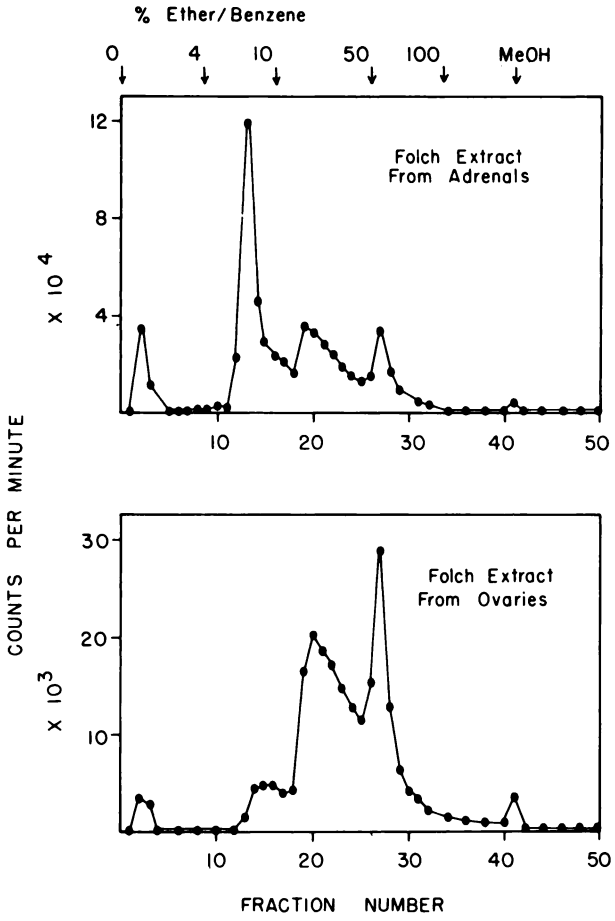

FIG. 4. Silicic acid column chromatographic profiles of Folch extracts from adrenals and ovaries of female rats, at 3 days after i.v. administration of compound **4**.

both higher than the values obtained with males, these data are qualitatively similar to the male data. In the female rats the adrenal-to-tissue ratios were high at 1 day and increased steadily during the 7-day period. The concentration of radioactivity in the ovaries was also high, suggesting that this telluro steroid may mimic cholesterol, since the ovaries concentrate neutral steroids from the blood as potential substrates for estrogen biosynthesis.

Experiments were conducted to determine whether the Te-123m 23-ITC was metabolized by the adrenals and other tissues in rats. Chromatographic analysis of the Folch extracts from the adrenal glands of male rats administered Te-123m 23-ITC indicated the presence of several metabolites. An initial radioactive peak, eluted with benzene, chromatographed with the expected mobility of steryl esters. In addition, at least three other major radioactive peaks were detected. Two of these contained material of intermediate polarity and were eluted with 10% and 50% ether in benzene. Additional radioactivity was also eluted in the methanol wash. The liver extracts contained predominately highly polar radioactive components that were eluted from similar columns with methanol. Chromatographic analysis of the lung extract indicated only the presence of very nonpolar radioactive material that was eluted from the column in the benzene fractions. The chromatographic profiles for both the adrenal and ovarian extracts from female rats indicated the presence of several labeled components and were qualitatively very similar to profiles obtained with male adrenal extracts (Fig. 4). The adrenal extract from the female rat contained a nonpolar

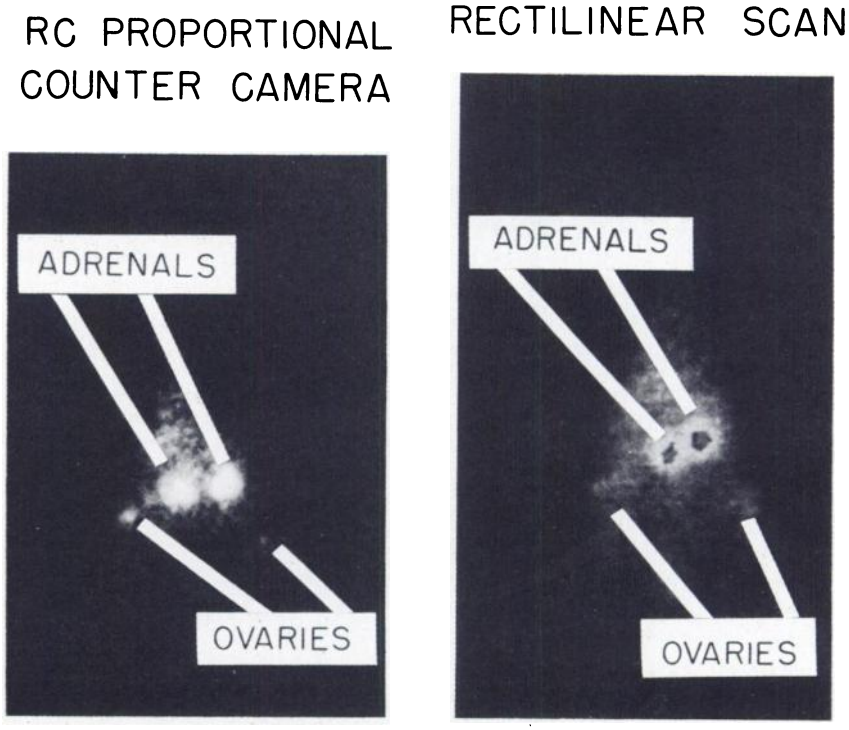

FIG. 5. RC proportional-counter camera image, and rectilinear scan, of female rat 1 day after administration of 100 μCi of compound **4**.

radioactive component, and also contained significant radioactivity chromatographing in the region of 23-ITC, which may indicate that a significant portion of the administered agent was not metabolized by the adrenals in this experiment. The profile obtained from this animal also indicated the presence of several polar components.

Cholesterol is metabolized in the adrenal by esterification with long-chain fatty acids and by conversion to more polar products by oxidative modifications of both the nucleus and side chain. If 23-ITC were metabolized in a similar manner, one would expect the formation of nonpolar radioactive components representing some ester species. We have no evidence to indicate that the Te-123m-labeled material eluted with benzene is an ester, or whether it contains the intact administered steroid. Such nonpolar radioactive components are always observed, however, upon chromatographic analysis of adrenal extracts. The column profiles observed upon chromatographic analysis of lipids extracted from these tissues were consistently the same for each type of tissue. For these reasons, we feel that the radioactive components represent true metabolites of Te-123m 23-ITC and are not artifacts that accumulated during tissue manipulation. Identification of the metabolites formed from the Te-123m-labeled steroid will depend upon the results of future studies, which include in vitro incubations. Under these conditions the appropriate controls and cofactor requirements can be studied.

The adrenal glands of male rats have been clearly imaged 1 day after administration of Te-123m 23-ITC. Following the injection of this agent, both the adrenals and ovaries of female rats have also been imaged with both a rectilinear scanner and an RC-type proportional-counter camera. Representative images are shown in Fig. 5. The concentration of radioactivity in these organs was confirmed by laparotomy. An extrapolation of the rat-tissue distribution data indicates that the adrenal accumulation of radioactivity (~4% of injected dose) would be adequate for human adrenal visualization. Organotellurium compounds of biological interest had not been described before our recent studies with telluro steroids, so detailed toxicity tests of such compounds have not yet been reported. We have not observed any toxicity in rats for periods up to 8–10 wk following administration of 1–2 mg of the Te-123m-labeled 23-ITC (specific activity 30–40 mCi/millimol). On a per-kilogram basis, these levels are 40 to 50 times the amounts that one would expect to require for human adrenal imaging.

TABLE 2. TISSUE DISTRIBUTION RESULTS, EXPRESSED AS PERCENTAGE OF DOSE TO THE WHOLE ORGAN, AFTER ADMINISTRATION OF 23-(ISOPROPYL[^{123m}Te]-TELLURO)-24-NOR-5α-CHOLAN-3β-OL (23-ITC) TO FEMALE RATS. THE VALUES ARE COMPARED WITH SIMILAR DATA REPORTED FOR NP-59 IN MALE RATS (*24*)

		% Dose to whole organs		
Organ	Agent	1 day	3 days	7 days
Adrenals	23-ITC	4.5	3.9	2.3
	NP-59	1.6	2.6	2.6
Liver	23-ITC	9.9	4.3	2.5
	NP-59	1.4	0.90	0.31
Blood	23-ITC	0.94	0.48	0.33
	NP-59	14.4	7.9	2.7
Ovaries	23-ITC	1.6	0.76	0.58
	NP-59	—	—	—

In Table 2 the percentage injected dose values for Te-123m 23-ITC to the whole organs of rats are compared with similar data reported for NP-59 (*24*). For the 23-ITC the adrenal uptake of radioactivity is considerably greater and the blood levels are substantially less. In contrast, liver uptake of NP-59 is less than that observed for 23-ITC. We have also compared the adrenal-to-tissue ratios for 23-ITC with values reported for NP-59 in three separate studies (Table 3). The ratios for liver, blood, lung, and ovaries are similar for the two agents at 1 day after administration, whereas the ratios are considerably greater with NP-59 after longer periods. The adrenal-to-tissue ratios vary considerably between the separate studies with NP-59, however, indicating that an accurate comparison of these two agents would

TABLE 3. ADRENAL-TO-TISSUE RATIOS CALCULATED FROM THE % DOSE/g TISSUE DISTRIBUTION DATA DETERMINED FOR Te-123m 23-ITC IN FEMALE RATS, COMPARED WITH SIMILAR DATA REPORTED FOR NP-59 (*18,19,24*)

	1 day				3 days				7 days			
		NP-59				NP-59				NP-59		
Tissue	23-ITC	(*18*)	(*19*)	(*24*)	23-ITC	(*18*)	(*19*)	(*24*)	23-ITC	(*18*)	(*19*)	(*24*)
Liver	42	30	86	52	100	118	296	336	82	482	1,094	653
Blood	72	56	166	90	149	225	652	5,720	101	204	495	14,037
Lung	32	26	48	—	66	68	126	—	85	883	2,971	—
Ovaries	5.4	—	—	3.1	9.8	—	—	4.8	8.1	—	—	6.5

be possible only under carefully controlled experimental conditions.

We have recently calculated the expected radiation doses to human organs by an extrapolation of the rat-tissue distribution data described in the present investigations (*25*). The results of these calculations indicated the following radiation dose values per mCi of injected labeled 23-ITC: adrenals 98 rad; ovaries 8 rad; total body 0.10 rad. Values reported for NP-59 (*19*) are 151 rad/mCi to the adrenals and 7.3 rad/mCi to the ovaries.

Our studies represent the development of a tissue-specific agent labeled with Te-123m. The absence of any observed chemical toxicity of 23-ITC in rats, and the similarity between the estimated radiation dose values for NP-59 and this agent, suggest that Te-123m 23-ITC is an attractive candidate that should be considered for preliminary adrenal-imaging studies in humans.

FOOTNOTES

* Tellurium-122, isotopically enriched to 94.71%, Oak Ridge National Laboratory, Oak Ridge, TN ($24/mg).

† Analtech, Inc., Newark, DE.

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