

Selenium and Tellurium as Carbon Substitutes

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INTRODUCTION

Although a large number of ^{75}Se -labeled radiopharmaceuticals have been prepared over the last three decades, the majority of these agents are analogues of the corresponding sulfur compounds. A variety of selenium analogues of naturally occurring sulfur amino acids have been prepared as potential pancreatic imaging agents (1). The preparation of such agents has generally been pursued since there are no gamma emitting radionuclides of sulfur and the properties of many compounds are not altered when the sulfur heteroatom is replaced with selenium.

The present discussion is limited to a description of radiopharmaceuticals in which radionuclides of selenium or tellurium substitute for carbon. A relatively small number of selenium compounds of this type have been prepared and only recently have the tellurium agents been described in the literature. There is considerable flexibility in the design and development of such unique compounds. Since very few of these agents have been prepared and tested their biological properties cannot be predicted. The present review is not meant to be exhaustive in scope, but, rather to offer a comprehensive discussion of the structure-activity information that has been reported in the literature for radiopharmaceuticals in which selenium and tellurium have been inserted between carbon-carbon bonds.

Although preparation of such compounds can often present rather challenging chemical problems, a discussion of the synthetic details and physical properties of these unique compounds is also beyond the scope of this review. Special emphasis has been placed on comparing the tissue distribution, excretion, metabolism and other biological properties of a variety of ^{75}Se - and ^{123m}Te -labeled radiopharmaceuticals. Although only limited metabolic studies have been reported in the literature, an understanding of the metabolism of these unique compounds is of interest not only to the biochemist, but information obtained from a detailed analysis of the metabolism of these compounds can potentially be useful in the design of new and useful agents.

Organo selenium and tellurium compounds are named by the rules established by the International Union on Pure and Applied Chemistry (2). Although the terms seleno or telluro are generally used to indicate the substitution of the heteroatom for a $-\text{CH}_2-$ moiety in heterocyclic compounds, this nomenclature is also very useful for naming selenium or tellurium analogs of well known aliphatic compounds, such as long-chain fatty acids. In situations where the selenium or tellurium compound is not an analogue of a known compound, the substitutive nomenclature must be used, i.e., alkyltelluroalkane or alkylselenoalkane.

USEFUL RADIONUCLIDES OF SELENIUM AND TELLURIUM

The radionuclidic properties and production routes for the three useful radionuclides of selenium and tellurium are summarized in Table I. Despite the relatively unattractive properties of ^{75}Se , there is still considerable interest in the preparation of ^{75}Se radiopharmaceuticals. The interest in such agents undoubtedly results from the considerable versatility available for the introduction of selenium into organic compounds. Selenium-75 is also inexpensive and can be produced in quite high yields by neutron irradiation of enriched ^{74}Se . In some instances, ^{75}Se agents are quite useful for developmental studies to determine the feasibility of using the corresponding ^{73}Se -labeled radiopharmaceuticals for positron emission tomographic studies. Selenium-73 is one of the longer lived positron emitting radionuclides ($t_{1/2} = 7.2$ hours), indicating that ^{73}Se -labeled agents can be distributed over long distances. Only a limited number of radiopharmaceuticals have been labeled with ^{73}Se and this is probably a result of the limited availability of this radionuclide. In addition, the production yields of ^{73}Se on most cyclotrons by the particle reactions outlined in Table I are evidently not significantly high to warrant more extensive studies. It is conceivable that ^{73}Se -labeled agents would be of more widespread interest if greater quantities of this radionuclide were readily available.

Tellurium-123 m is the only useful radionuclide of tellurium for labeling radiopharmaceuticals and decays by isomeric transition with the emission of a single gamma photon with an energy of 159 keV in high abundance (84%). This is within the optimal energy region for efficient detection by sodium iodide crystal detectors and is the primary reason why several investigators have studied the synthesis and biological properties of ^{123m}Te -labeled tissue imaging agents. The long physical half-life (119 days) and radiation dose contributions from the conversion electrons are two factors which contribute significantly to the absorbed radiation dose values. In several instances, however, ^{123m}Te -labeled agents exhibit rapid biological elimination and unique tissue distribution properties which result in much lower absorbed radiation dose values than would be suspected *a priori* from an analysis of the decay scheme of this radionuclide. Tellurium-123 m is reactor produced by neutron irradiation of enriched ^{122}Te . Unfortunately, the thermal neutron production cross section (~ 1 barn) is considerably less than the neutron capture (burn-up) cross section (7000 barns) for the ^{123m}Te product, resulting in production yields much lower (1-2 mCi/mg) than calculated if ^{123m}Te burn-up did not occur (37 mCi/mg) (3). Radiopharmaceuticals with maximal specific activities of about 250 mCi/mmol can be prepared from reactor produced ^{123m}Te . Specific activities in this range are quite useful for many applications such as steroids for adrenal imaging,

fatty acids for myocardial applications and amino acids for pancreatic imaging. Although ^{123m}Te can also be produced "carrier-free" by the $^{123}\text{Sb}(p,n)^{123m}\text{Te}$ reaction, production yields appear too low to indicate that production of large amounts of ^{123m}Te would be feasible by this method (4).

METHODS FOR THE INTRODUCTION OF SELENIUM AND TELLURIUM INTO
COMPOUNDS OF BIOLOGICAL INTEREST

Although a detailed discussion of the synthetic methodologies available for the introduction of selenium and tellurium into organic compounds is far beyond the scope of this review, a brief description of the general approaches that have been used to prepare ^{75}Se - and $^{123\text{m}}\text{Te}$ -labeled agents in which the heteroatom substitutes for carbon is appropriate. The introduction of unusual electronic properties and drastic steric features to tissue-specific agents is undesirable. For these reasons S, Se and Te are generally introduced into organic molecules in the divalent state. The organic chemistry of sulfur, selenium and tellurium is in some respects quite similar, although there are many notable exceptions and any general comparison of the reactivity and stability of organic compounds containing these heteroatoms would be very difficult. The tendency for oxidation from the 2- oxidation state to the metal increases quite dramatically in the series S, Se and Te, and the deposition of large amounts of tellurium metal from reaction mixtures is a common problem encountered during the synthesis of many organic tellurium compounds (10). Nonetheless, with a combination of prudent synthetic design and careful manipulation of reaction mixtures, a large variety of compounds of biological interest containing tellurium can be

prepared in acceptable yields. Several excellent texts describing the extensive organic chemistry of selenium are available (11, 12). Interest in the chemistry of organic tellurium compounds has increased dramatically over the last decade and one comprehensive book has been published (10). In addition, reviews of the literature of organic tellurium chemistry are published regularly in the "Journal of Organometallic Chemistry" (13).

The feasibility of performing micro-scale reactions is an additional important requirement for the preparation of selenium and tellurium radiopharmaceuticals. All of the agents described in this review were prepared by the nucleophilic displacement of suitable leaving groups from substrates using selenols and tellurols. Most of the agents that have been prepared have two different groups attached to the heteroatom and the preparation of these compounds resembles simple unsymmetrical selenide or telluride syntheses. These synthetic routes begin with dissolution of metallic Se or Te (M) with a suitable reducing agent to yield the diselenide or ditelluride anions ($M \rightarrow M_2^-$). Reduction of Se or Te with sodium metal in liquid ammonia followed by alkylation with an alkyl halide is one common route ($M_2^- + RX \rightarrow R_2M_2$). Several new methods are now available for this transformation and include reduction with sodium metal in ethylenediamine or sodium hydride in dimethylformamide (R. A. Grigsby and K. J. Irgolic, personal communication). Following reduction of the

dialkyl diselenide or ditelluride ($R_2M_2 \rightarrow R-M^-$), the resulting anions are strong nucleophiles that can be used to displace various leaving groups from substrate molecules ($R-M^- + R^1X \rightarrow R^1-M-R$). The metal can also be solubilized in water or alcohol solution with sodium borohydride, with subsequent conversion to the ditelluride ($M \rightarrow H-M^- \rightarrow R-M-H \rightarrow R_2M_2$) or alkylation directly in two steps to the unsymmetrical product ($M \rightarrow H-M^- \rightarrow H-M-R \rightarrow R^1-M-R$) (14). The symmetrical selenides or tellurides such as 2-selena- or 2-tellura-A-nor-5 α -androstan-17 β -ol (XVI and XVII) are much more easily prepared than the unsymmetrical agents since alkali metal salts of Se^- and Te^- are prepared by reaction of the Se or Te metal with excess reducing agents, and the stoichiometric balance between the two reactants need not be controlled.

ADRENAL IMAGING AGENTS

As a result of the superior adrenal imaging properties of radioiodinated 6β -(iodomethyl)-19-nor-cholest-5(10)-en- 3β -ol compared with 19-iodocholesterol (15), the preparation of a variety of ^{75}Se -labeled 6β -(alkylseleno)methyl- and (arylseleno)methyl-steroids have been reported (16, 17). These agents were readily prepared from 6β -(iodomethyl)-19-nor-cholest-5(10)-en- 3β -ol by nucleophilic substitution with alkyl- or arylselenols. The first member of this series of compounds reported was ^{75}Se - 6β -(benzylseleno)methyl-19-nor-cholest-5(10)-en- 3β -ol (Id) (16). In a systematic study of the influence of 6β -(alkylseleno)methyl and 6β -(arylseleno)methyl substituents on the adrenal uptake of a series of ^{75}Se -labeled steroids, the compounds illustrated in Figure I were prepared and tested in rats (17). Of these agents, ^{75}Se - 6β -(methylseleno)methyl-19-nor-cholest-5(10)-en- 3β -ol (Ia) showed the highest adrenal uptake (14.4% kg dose/g at six days). The adrenal uptake decreased as the size of the alkyl substituent increased in the order (Ia) > (Ib) > (Ic) > (Id) > (Ie). The 6β -(cyclohexylseleno)methyl-19-nor-cholest-5(10)-en- 3β -ol analog (Ie) showed the lowest adrenal uptake of the steroids studied (3.6% kg dose/g). Selenium-75 labeled 6β -(methylseleno)methyl-19-nor-cholest-5(10)-en- 3β -ol (Ia) is presently marketed in Europe as ScintidrenTM, and appears to be a useful agent for the diagnosis of a variety

of types of adrenal disease (18, 19).

Other ^{75}Se -labeled steroids have also been prepared and tested as adrenal imaging agents (Figure II). The preparation of one such agent involved attachment of the methylseleno moiety to the C-19 angular methyl group of cholesterol, presumably because of the ready availability of the 19-iodocholesterol substrate (20, 21). The uptake of ^{75}Se -labeled 19-(methylseleno)-cholesterol (II) was greater in female rats than the uptake reported for ^{131}I -19-iodocholesterol. This agent also showed high adrenal uptake in rabbits and radioactivity was found to concentrate primarily in the adrenal medullary tissue of dogs, which was an unexpected and interesting finding (21). The levels of radioactivity in blood and liver tissue of experimental animals were higher than those observed with other agents such as ^{131}I -19-iodocholesterol, however, clinical trials with ^{75}Se (II) have not been reported. Extensive *in vitro* and *in vivo* studies with ^{75}Se (Ia) and (II) have been recently reported in an effort to determine the biological fate of these unique steroids (22). The seleno steroids did not appear to be hydroxylated by the rat liver 7α -hydroxylase system under conditions where ^{14}C cholesterol was converted to 7α -cholesterol to an extent of 12.5%. The ability of the rat serum lecithin:cholesterol acyltransferase enzyme to esterify the seleno steroids was also investigated. While ^{75}Se -19-(methylseleno)-cholesterol (II) was esterified to about 50% of the

level detected for ^{14}C -cholesterol, ^{75}Se -6 β -(methylseleno)methyl-19-nor-cholest-5(10)-en-3 β -ol (Ia) was esterified at a rate much slower than that observed for (II). An unexpected observation was the greater rate of esterification of (Ia) compared to (II) by the rat adrenal microsomal acyltransferase system. The ability of these two steroids to serve as substrates for the bovine adrenal cortex sidechain cleavage enzyme was also studied. While significant levels of pregnenolone analogues were formed from ^{75}Se (Ia), the ^{75}Se 19-(methylseleno) agent (II) did not yield any detectable sidechain cleavage products.

At Oak Ridge National Laboratory we have investigated the synthesis of ^{123m}Te -labeled steroids for adrenal imaging applications. We have pursued introduction of the tellurium into the steroid sidechain since the many degrees of freedom suggested that the heteroatom could be easily accommodated in this region of the molecule. This approach was also attractive since a large variety of bile acids were commercially available and could be readily converted to steroids brominated in the sidechain which could serve as substrates for reaction with sodium alkyl telluroils. We initially prepared 23-(isopropyltelluroil)-24-nor-5 α -cholan-3 β -ol (IV; Figure III), an analogue of 5 α -cholestan-3 β -ol, by coupling sodium isopropyl telluroil with 3 β -acetoxy-23-bromo-24-nor-5 α -cholane. Tellurium- 123m -labeled (IV) is the first reported tissue-specific agent labeled with this radionuclide (23, 24) and

showed pronounced adrenal uptake after administration to rats (Figure IV). In female rats the adrenal glands accumulated 4.5% of the injected radioactivity one day after administration of ^{123m}Te (IV) and the adrenal:liver ratio increased from 42:1 after one day to 100:1 after three days. Representative high-quality images of rat adrenals are illustrated in Figure V, and the adrenal glands of rabbits have also been imaged with this new agent (Figure VI).

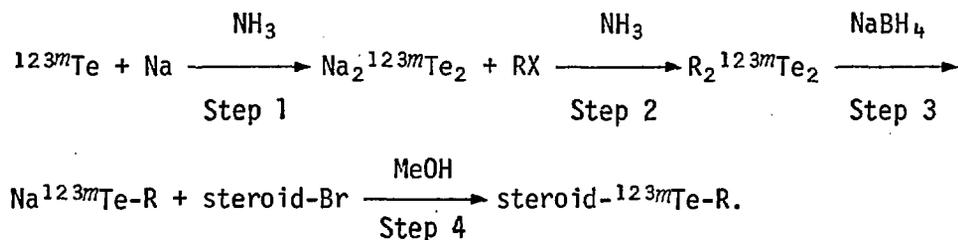
Lipid extracts from the adrenals and ovaries of female rats injected with ^{123m}Te (IV) were analyzed by silicic acid column chromatography to determine if the pronounced accumulation of radioactivity in these organs was accompanied by metabolic transformation of the injected agent. Several radioactive components were detected by chromatographic analysis of these tissue extracts (Figure VII) which suggests that ^{123m}Te (IV) is metabolized in rat tissues. In addition to non-polar radioactive material initially eluted from the columns in benzene, several more polar products were eluted with increasing proportions of ether in benzene. Radioactivity eluted with 10% ether in benzene chromatographs with the expected mobility of the (IV) which may indicate that a significant portion of the administered agent was not metabolized by the adrenals. It seems probable that the non-polar products may represent esterified material since it is well established that cholesterol is esterified with long-chain fatty acids by

adrenal tissue. Although identification of the other more polar radioactive components has not been pursued, they may represent hydroxylated products since an additional metabolic fate of cholesterol in adrenal tissue involves the conversion to more polar products by oxidative modifications of both the nucleus and sidechain. In addition to the analysis of the radioactive lipids from adrenals and ovaries, we have examined the lipid extracts from the lungs and liver tissues from both male and female rats. Only non-polar radioactive components were detected in the lung extracts whereas the livers contained only polar radioactive components which were eluted from the silicic acid columns with methanol. Although the various tissues were always manipulated in the same manner, the column profiles observed upon chromatographic analysis of lipid extracts were consistently the same for each type of tissue. For these reasons, we feel that the radioactive components represent true metabolites of ^{123m}Te (IV) and are not artifacts that accumulate during manipulation of the tissues. Identification of the metabolites formed from the ^{123m}Te (IV) will depend upon the results of *in vitro* incubations. Under these conditions the appropriate controls and cofactor requirements can be studied.

Organotellurium compounds of biological interest had not been described prior to our recent studies with (IV), and detailed toxicity tests with such compounds have therefore not yet

been reported. We have not detected any toxicity in rats for periods up to 5-6 weeks following administration of 1-2 mg of the ^{123m}Te (IV) (specific activity 30-40 mCi/mmol). These levels are 40-50 fold higher on a kilogram basis than the amounts that would be expected to be required for human adrenal imaging. An extrapolation of the rat tissue distribution data suggests that the adrenal accumulation of radioactivity ($\sim 4\%$ of injected dose) would be adequate for human adrenal visualization.

The general synthetic strategy developed for introduction of ^{123m}Te into the sidechain of (IV) is adaptable for the preparation of a wide variety of ^{123m}Te -labeled steroids. As a result of our interests in obtaining structural information that could potentially be used to design a ^{123m}Te -labeled steroid that would exhibit maximal adrenal uptake at an early time interval after administration, we have also investigated the tissue distribution in rats of a series of ^{123m}Te -labeled steroids that contain structural modifications of both the nucleus and sidechain (25, 26). The general synthetic scheme used for the preparation of the ^{123m}Te -labeled steroids involved the following transformations:



This general procedure was adapted for the preparation of a variety of compounds by using the appropriate alkyl halide in Step 2 and the requisite brominated steroid in Step 4. The various structural modifications which were chosen involved both the sidechain and nuclear regions of the steroid framework (Figure III). A summary of the ^{123m}Te -labeled steroids which we have prepared and a brief description of their unique structural features are summarized in Table II. The results of tissue distribution studies in rats (Table II) clearly illustrate that a combination of structural features are required for significant adrenal uptake of steroids labeled in the sidechain with ^{123m}Te . Pronounced adrenal uptake was detected with both ^{123m}Te (IV) and (VII), indicating that the C-5 nuclear double bond does not destroy adrenal specificity. These results also illustrate that minor sidechain modifications do not destroy the adrenal uptake, since (VII) contains an additional carbon in the sidechain (C-24). An equatorial C-3 hydroxyl group appears to be required for maximal adrenal uptake since only moderate levels of radioactivity were detected in the adrenal glands of female rats after administration of the 3β -methoxy derivative of VII, ^{123m}Te -(VIII). It was noted in these studies, however, that the levels of radioactivity in the adrenals did not change from one to seven days after injection of ^{123m}Te -(VII). The analogue with the long C-17 sidechain, ^{123m}Te -(VI), has the same nuclear structure

as (IV). The importance of the sidechain structure in determining the adrenal uptake of steroids labeled in the sidechain with ^{123m}Te is vividly illustrated by the low adrenal uptake of radioactivity after injection of ^{123m}Te (VI), although the radioactive contents of the adrenal glands did increase steadily to a moderate level after seven days. The importance of sidechain structure is further illustrated by the low levels of radioactivity detected in adrenal glands after injection of ^{123m}Te (IX), the analogue with a short sidechain. Since this analogue has the same nuclear structure as (VIII), the very low adrenal uptake observed even after seven days can be attributed to the short sidechain. The importance of the A/B ring stereochemistry is clearly evidenced by the low adrenal uptake of ^{123m}Te (V), an analogue of (IV) having a *cis* A/B ring juncture. The adrenal:liver ratios are particularly convenient indices of the potential usefulness of the ^{123m}Te -labeled analogs for adrenal imaging, and these values are compared for various ^{123m}Te -labeled steroids in Figure VIII.

The results of our studies indicate that the structural features required for maximal adrenal uptake in rats of steroids labeled in the sidechain with ^{123m}Te include a planar *trans* ring structure, an equatorial C-3 hydroxyl group and a 17β -sidechain of moderate length. These results closely parallel structure-distribution patterns that have been established for radioiodinated steroids which indicate that while considerable structural

variation can be tolerated for rings A and B, the structure of the 17β -sidechain is considerably important in determining adrenal specificity (27).

Since ^{123m}Te (IV) and (VII) showed pronounced adrenal uptake in our rat tissue distribution studies, several additional studies were performed to investigate the biological properties of these new agents in more detail. Examination of the radioactive contents of the excretory products from rats administered these agents indicated a major difference in the rate of excretion of radioactivity. While radioactivity was detected primarily in the feces from animals injected with either agent, the rate of excretion of radioactivity following administration of ^{123m}Te (VII) was slower than that observed after injection with ^{123m}Te (IV). Approximately 50 percent of the administered radioactivity was excreted from rats injected with ^{123m}Te (IV) within five days. In contrast, only 41 per cent of the injected activity was detected in the excretory products of rats seven days after injection of ^{123m}Te (VII).

As a result of our interest in the potential use of ^{73}Se -labeled steroids for the tomographic imaging of adrenal glands, we have also prepared ^{75}Se -24-(isopropylseleno)-chol-5-en-3 β -ol (III, Figure II), the selenium analogue of (VII), by reaction of ^{75}Se -sodium isopropyl selenol with 3 β -acetoxy-24-bromo-chol-5-ene. Tissue distribution studies in female rats demonstrated pronounced adrenal uptake after injection of ^{75}Se (III). The tissue distribution and excretory properties of ^{75}Se (III) and ^{123m}Te (VII) were very similar, indicating that substitution of tellurium with selenium in the C-25 position of the steroid sidechain has little effect on the biological properties of these compounds. The adrenal:tissue ratios determined one day after administration of these two agents are compared in Table III. The radioactive contents of the urine and feces from female rats administered ^{123m}Te (VII) and ^{75}Se (III) were also monitored and indicated a close similarity in the excretion properties of the two compounds. Approximately 41 percent of the administered activity was excreted

from animals injected with ^{123m}Te (VII) after seven days, primarily in the feces, as would be the expected excretory route for a neutral steroid. The majority of the excreted radioactivity was also found in the feces from animals administered ^{75}Se (III), and about 38% of the injected activity was excreted in the same time interval.

The use of ^{73}Se -labeled steroids for tomographic visualization of adrenal masses could represent a unique and potentially powerful tool for the diagnosis of adrenal disease. Extensive tissue distribution studies with ^{75}Se (III) have recently been performed in female rats at a variety of time intervals from 1 hour to 2 weeks. The adrenal:blood (17:1) and adrenal:liver (7:1) ratios are sufficiently high within six hours after administration to indicate that adrenal visualization by positron emission tomography should be possible with ^{73}Se (III). In addition to the moderate adrenal:tissue ratios, the absolute uptake of radioactivity in the female rat adrenal glands is quite high (1.6% injected dose). Although the adrenal:tissue ratios are probably not sufficiently high after six hours for adrenal visualization by single photon techniques, emission tomographic imaging of the adrenal should be possible with ^{73}Se (III). Liver uptake should not present as serious a problem as is encountered in conventional single-photon techniques since only coincident events are detected during emission tomography and higher background levels can be tolerated.

The chemical synthesis and purification of ^{75}Se (III) can be easily completed within a 4-hour period, indicating that the ^{73}Se -labeled agent could be available in considerably less than one half-life after end of bombardment (E.O.B.) of the cyclotron target. By extrapolation of the rat tissue distribution data to humans, an approximation of the levels of radioactivity that would be expected in the adrenals can be achieved. If adrenal visualization were not attempted until six hours after administration of this agent (2 half-lives E.O.B.), sufficient radioactivity would be retained (50% of the injected dose) to indicate that the expected 1.6% adrenal uptake would be sufficient for adrenal visualization. Thus, administration of 10 mCi of ^{73}Se (III) would be expected to result in the accumulation of about 80 μCi of the radioactive label in the adrenal glands after 6 hours.

Using tissue distribution and excretory data from female rat studies we have recently estimated the radiation dose values to human organs from ^{123m}Tc (IV), ^{123m}Tc (VII) and the ^{75}Se analog of (IV) (28). These values are compared in Table V with similar estimates for ^{75}Se (Ia ScintidenTM), and ^{131}I -6 β -(iodomethyl)-19-nor-cholest-5(10)-en-3 β -ol (NP-59). The latter two compounds are presently the agents of choice for the diagnosis of adrenal disease by nuclear medicine procedures (15, 18, 19). The ^{123m}Tc (VII) agent results in a considerably higher radiation dose to the

adrenals and ovaries than calculated for ^{123m}Te (IV). This is primarily due to the much slower rate of excretion, as has been discussed earlier. The absorbed radiation dose to the adrenal glands from ^{123m}Te (IV) is comparable to estimates for ^{75}Se (II) and ^{75}Se (Ia), although the ovarian dose from ^{123m}Te (IV) is less than estimated for the other two agents. The relatively low calculated absorbed radiation dose values to the adrenals and ovaries from the ^{75}Se -labeled analog of (IV) were unexpected, but are consistent with a comparison of the decay properties of ^{123m}Te and ^{75}Se . The actual radiation dose values for the ^{123m}Te and ^{75}Se -labeled agents may in fact be much lower than has been estimated since the radiation dose values calculated for ^{131}I -NP-59 using human tissue biopsy samples are considerably lower than the calculated values (29).

The absence of any observed chemical toxicity, the estimation of radiation dose values within acceptable limits and the excellent imaging properties of ^{123m}Te suggest that ^{123m}Te -labeled (IV) may represent an attractive new agent for adrenal imaging in humans. Our studies also indicate that ^{75}Se (III) may be an attractive agent for clinical use and suggest that use of ^{73}Se (III) for positron emission tomography of adrenals may be possible.

BILE ACID ANALOGUES

The preparation of bile acid analogues labeled in the side-chain with ^{75}Se have also been reported (30). These new agents are potentially useful to monitor biliary and hepatic function (Figure IX). Several of these agents are analogues of natural bile acids which are excreted in human bile (Compounds XIa, XIb and XIII). In addition, ^{75}Se analogues of unnatural bile acids were also synthesized in which the C-17 sidechain was lengthened, presumably to increase the lipophilicity of this region of the molecule (Compounds X, XIb, XII, XIII). Biological evaluation of these compounds involved analysis of bile fistula fractions obtained from rats following oral administration of mixtures of the individual ^{75}Se bile acids and ^{14}C cholic acid (31). Differences in the $^{14}\text{C}:^{75}\text{Se}$ ratios of the administered mixtures compared to the recovered bile fractions were used as a convenient index to compare the rates of absorption and excretion of the ^{75}Se test compounds with the ^{14}C cholic acid. The ^{75}Se bile acids that most closely resemble ^{14}C cholic acid in the rat included 22-selena cholic acid (XIIIa), and the taurine conjugates of (XIIIa) and of 23-selena-25-homocholeic acid (XIIIb). These agents may be useful for the clinical detection of impairment in the resorption and excretion of bile acids in man since external counting techniques could be used to quantitate regional radio-

activity with time. The availability of such a technique would be significantly more attractive than the tedious method presently used to determine the ^{14}C content of exhaled breath after administration of ^{14}C -labeled bile acid conjugates. There was a two to three-fold greater rate of absorption and excretion of ^{14}C cholic acid compared with that observed for 23-selena-25-homodesoxycholic acid (XII) and the glycine conjugate of 22-selena cholic acid. The $^{14}\text{C}:^{75}\text{Se}$ ratio of bile obtained after administration of a mixture of ^{14}C cholic acid and 23-selena- 3α , 7α -chenodesoxycholic acid (XIa) was increased greater than forty-fold over that of the original mixture, indicating that (XIa) is a particularly poor bile acid analogue in the rat.

Earlier studies had reported the isolation of radioactive material which behaved chromatographically like amino acid conjugates of bile acids after administration of ^{75}Se -19-(methyl-selena) cholesterol (30). This crude material also served as a substrate for the cholyglycine hydrolase enzyme. These combined results suggested that the ^{75}Se -labeled cholesterol analogue (II) may have been converted to a bile acid conjugate after administration to rabbits. Studies similar to those described above were performed by administration of a mixture of the crude ^{75}Se -labeled bile acid conjugate sample and ^{14}C -cholic acid to rats (31). The results of these studies indicated that the ^{75}Se -bile acid fraction was absorbed and excreted about 70% less

efficiently than cholic acid. The identity of the components in the crude bile acid fraction from rabbits obtained after administration of ^{75}Se (Ia) has not been reported. Biological studies with the ^{123m}Te -labeled bile acid analogue (XIV) have not been reported.

LONG CHAIN FATTY ACIDS

The energy requirements of the normal myocardium are primarily supplied by the oxidation of long-chain fatty acids (32). Since the fatty acids are concentrated from the plasma, fatty acid analogues radiolabeled with gamma-emitting radio-nuclides are attractive agents for myocardial imaging. If the radiolabeled fatty acids do not contain structural modifications which interfere with the uptake of these agents by the myocardium, the use of modified fatty acids can be an effective means of concentrating sufficient levels of radioactivity within the heart for imaging by external counting techniques. A variety of ^{123m}Te and ^{75}Se -labeled long-chain fatty acids have been investigated as myocardial imaging agents. Although the preparation of ^{123m}Te -16-(methyltelluro)-9-hexadecenoic (17-tellura-9-octadecenoic acid) has been described (33, 34), no biological data have been reported for this agent. In view of the well documented instability of many methyltelluro-substituted organic compounds (10), this telluro fatty acid would be expected to be exceptionally unstable.

More recently, we have described the synthesis and biological properties of the tellurium isostere of oleic acid, 9-tellura-heptadecanoic acid (35). This unusual fatty acid is easily prepared by basic hydrolysis of the methyl ester formed by coupling

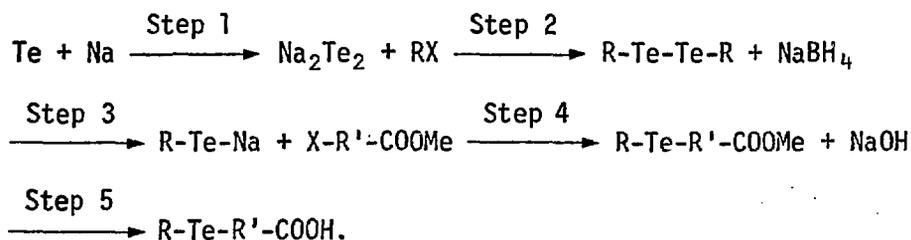
of sodium octyl tellurol with methyl-8-bromooctanoate. The 9-telluraheptadecanoic acid was chosen as an attractive candidate to investigate the potential use of ^{123m}Te -labeled fatty acids for myocardial imaging because of the established isosteric similarity between tellurium and the $-\text{CH}=\text{CH}-$ moiety (36). In classical pharmacological terminology, "isosteres" are compounds that have similar electron arrangements, or in a broader sense, exhibit similar pharmacological or biological activity. The replacement of selected olefinic linkages in molecules of biological interest with ^{123m}Te therefore appeared to be an attractive strategy for the preparation of new radiopharmaceuticals. The feasibility of this approach was strengthened by the reported potent androgenic activity of the tellurium and selenium isosteres of olefinic androgens (37, 38). The preparation and testing of these compounds is described later in this report.

Tellurium- 123m 9-telluraheptadecanoic acid (denoted as $^{123m}\text{Te}-\text{C}_{18}-\Delta^9$) exhibited pronounced heart uptake after administration to rats (Figure X). Since it is crucially important to establish that the radioactivity is present primarily within the myocardium and not in the blood pooled within the cardiac chambers, the rat hearts were excised from the animals while beating and the blood removed from the chambers by thorough perfusion with physiological saline solution in all of our studies. The high heart:blood ratios determined in the tissue distribution studies suggested

that differentiation between myocardial uptake and blood pooled within the cardiac chambers would be possible using $^{123m}\text{Te-C}_{18}-\Delta^9$ agent. Rat hearts are clearly delineated with a rectilinear scanner after administration of this agent (Figure XI) and rabbit hearts can also be imaged (Figure XII). The distribution of radioactivity in rat tissues showed a striking similarity with tissue distribution data reported in the literature for ^{14}C -oleic acid (39). These results suggested that replacement of olefinic linkages with ^{123m}Te or ^{75}Se may be a new approach for the preparation of a variety of radiopharmaceuticals. In addition, the radioactive contents of the rat hearts remained high for at least one hour after injection. This unexpected and important observation can be contrasted to the rapid "wash-out" of radioactivity from the heart observed after administration of ^{11}C -palmitic acid (40) or radioiodinated fatty acids (41). The identification of structural features which would lead to an increase in the residence time of radiolabeled fatty acids in the heart could be of considerable importance since greater counting statistics could be obtained. In addition, less radioactivity would be injected which would lead to smaller absorbed radiation dose.

A variety of ^{123m}Te -labeled fatty acids were prepared and tested in rats to systematically determine the structural features required for the heart uptake of these unusual compounds. We investigated the effects of both total chain length and the

position of the tellurium heteroatom in the fatty acid alkyl chain. These agents were prepared by the general procedure summarized below. By choosing the appropriate alkyl halide in Step 2 and the requisite ω -bromo acid methyl ester substrate in Step 4, a large variety of compounds can be easily prepared.



The results of tissue distribution studies with the various ^{123m}Te -labeled fatty acids are summarized in Table V. To determine if the presence of ^{123m}Te heteroatom in the C-9 position of the $\text{C}_{18}\text{-}\Delta^9$ isostere was the primary structural feature responsible for the remarkable heart uptake of this agent, the $^{123m}\text{Te}\text{-C}_{18}\text{-}\Delta^6$ analogue was also prepared and administered to rats. This analogue also showed high heart uptake as did the $^{123m}\text{Te}\text{-C}_{18}\text{-}\Delta^{11}$ isostere illustrating that the high heart uptake observed with the $^{123m}\text{Te}\text{-C}_{18}\text{-}\Delta^9$ analogue does not result from the isosteric similarity between this agent and oleic acid. To investigate in more detail the effect of total chain length, several additional ^{123m}Te fatty acids were prepared. Only moderate levels of radioactivity were detected in rat hearts after injection of the ^{123m}Te -labeled $\text{C}_{14}\text{-}\Delta^6$ (42) and $\text{C}_{14}\text{-}\Delta^9$ isosteres. These results suggested that

the total chain length, and not the position of the tellurium heteroatom, was a major factor affecting heart uptake of these unusual agents. The ^{123m}Te -labeled isostere of palmitoleic (9-hexadecanoic) acid, 9-tellurahexadecanoic acid ($\text{C}_{16}-\Delta^9$), also showed pronounced heart uptake (35) as well as the much longer chain acid with the tellurium in the C_{17} position ($\text{C}_{22}-\Delta^9,17$) (42).

These combined results demonstrate a striking relationship between heart uptake and the structure of the telluro fatty acids. The position of the ^{123m}Te in the alkyl chain appears to have little effect on the heart uptake of these agents. The effects of total chain length on the heart uptake of these fatty acids are consistent with the well-established structure-activity relationships described in the literature for the heart uptake observed of simple alkanolic acids (43). Although the radionuclidic properties of ^{75}Se are not as attractive as those exhibited by ^{123m}Te , the anticipated greater stability of the seleno fatty acids coupled with the potential use of ^{73}Se -labeled fatty acids for tomographic imaging of the myocardium stimulated our interest in preparing and testing a variety of ^{75}Se -labeled fatty acids. Since extensive tissue distribution, excretion and imaging studies were conducted with the $^{123m}\text{Te}-\text{C}_{18}-\Delta^9$ agent, we chose to prepare ^{75}Se -labeled 9-selenaheptadecanoic acid ($^{75}\text{Se}-\text{C}_{18}-\Delta^9$) as the initial member of this potentially useful class of compounds (44). The ^{75}Se -labeled fatty acids are prepared in a manner similar to that described for

the ^{123m}Te -labeled agents, and involve the coupling of ^{75}Se -sodium alkyl selenols with ω -bromo acid methyl ester substrates. As we expected, the seleno fatty acids are considerably more stable than the corresponding tellurium analogs. The selenium compounds are crystalline solids that can be stored indefinitely. The results of tissue distribution studies in rats indicated significant heart uptake of radioactivity after administration of $^{75}\text{Se-C}_{18}-\Delta^9$. The concentration of radioactivity in the heart tissue, however, was not as pronounced as that found following injection of $^{123m}\text{Te-C}_{18}-\Delta^9$ acid (Figure XI). This result was unexpected in light of the greater chemical stability of the ^{75}Se -labeled fatty acid.

We have also examined the effects of both total chain length and the position of the selenium heteroatom by determining the tissue distribution in rats of a series of structurally modified ^{75}Se -labeled fatty acids. These compounds were synthesized by the same general procedure described earlier for the preparation of ^{123m}Te -labeled fatty acids and involved reaction of various ^{75}Se -sodium alkyl selenols with terminally brominated acid methyl ester substrates. The results of tissue distribution studies (Table VI) demonstrate that total chain-length dramatically affects heart uptake of the ^{75}Se -labeled fatty acids. The $^{75}\text{Se-C}_{18}-\Delta^{13}$ and $^{75}\text{Se-C}_{14}-\Delta^9$ isosteres showed only moderate heart uptake, similar to that described for $^{75}\text{Se-9-selenaheptadecanoic acid (C}_{18}-\Delta^9)$. The

longer-chain $^{75}\text{Se-C}_{22}-\Delta^{13}$ and $\text{C}_{25}-\Delta^9$ isosteres, however, showed pronounced heart uptake, although not as significant as that found for several ^{123m}Te -labeled fatty acids (Table V). A comparison of the data for the ^{123m}Te agents (Table V) and the ^{75}Se agents (Table VI) demonstrates that the heart uptake of members from both series of compounds is affected by total chain-length and that the position of either heteroatom appears to have little effect. The requirement for a longer chain-length in the selenium series before substantial heart uptake is observed presently cannot be explained. The greater heart uptake of radioactivity observed after administration of the $^{123m}\text{Te-C}_{18}-\Delta^9$ agent compared with the ^{75}Se -labeled analog was unexpected.

This differential uptake was substantiated by a double labeling study in which a mixture of the two agents was administered to female rats. To avoid any potential variations in tissue distribution that could possibly result from differences in specific activities, the two fatty acids were prepared with similar specific activities. The $^{123m}\text{Te-C}_{18}-\Delta^9$ agent had a specific activity of 24 mCi/mmole and $^{75}\text{Se-C}_{18}-\Delta^9$ agent was prepared with a specific activity of 27 mCi/mmole. The $^{123m}\text{Te}:^{75}\text{Se}$ ratio of a mixture of the two acids in 6% bovine serum albumin solution was 0.74:1 after filtration through a 0.22 micron Millipore filter. Female rats were injected intravenously with 0.5 ml of this solution containing 4.35 μCi of the ^{123m}Te -labeled fatty acid and

5.85 μCi of the ^{75}Se -labeled fatty acid. After 30 minutes the animals were sacrificed, the organs removed and the ^{123m}Te and ^{75}Se contents of the various tissues determined. These results are summarized in Table VII and agree well with similar tissue distribution results determined earlier in experiments with the individual fatty acids. The $^{123m}\text{Te}:^{75}\text{Se}$ ratios were also calculated for each tissue and clearly indicate a selective uptake of the ^{123m}Te -labeled fatty acid by the heart compared with the other tissues. In fact, the $^{123m}\text{Te}:^{75}\text{Se}$ ratio of the heart was nearly two-fold greater than the blood ratio, which closely parallels the ratio calculated from the results of studies with the individual agents. These results also illustrate that all of the tissues examined retained considerably higher levels of ^{123m}Te than ^{75}Se since the $^{123m}\text{Te}:^{75}\text{Se}$ ratios for the tissues were significantly greater than the 0.74 ratio of the injected mixture. The results of excretion studies are discussed below and did indicate that radioactivity was retained considerably longer in rats administered the $^{123m}\text{Te}-\text{C}_{18}-\Delta^9$ compared with the $^{75}\text{Se}-\text{C}_{18}-\Delta^9$ -analogue. The elimination kinetics are considerably slower than that observed with the analogous ^{75}Se -labeled agent and explain the greater tissue retention of ^{123m}Te observed in the dual labeling study (Table VII).

We have not yet determined why the $^{123m}\text{Te}-\text{C}_{18}-\Delta^9$ agent results in substantially greater levels of radioactivity in rat

hearts than has been observed after administration of the ^{75}Se analogue. Although contributions from differences in bond lengths, bond angles and other physical properties cannot be eliminated, it would appear unlikely that these factors would adequately explain the pronounced and reproducible difference in the heart uptake of the ^{123m}Te and ^{75}Se analogues. In our estimation it is more likely that the tellurium fatty acid undergoes chemical modification and there is convincing evidence that supports this possibility. Although the physical properties of the unlabeled tellurium fatty acids are consistent with the proposed structures, these compounds are prepared in larger amounts (>1 mmol) and are not as susceptible to the potential oxidative transformations that are encountered with the small amounts (<1 μmol) of radiolabeled agents used for the biological studies. Thin-layer chromatographic analysis of dilute solutions of the radiolabeled fatty acids have demonstrated the accumulation of polar products and this may provide a clue as to the identity of these product(s). Investigations are presently in progress in an attempt to identify these products. The possibility of heart uptake of decomposition products which no longer resemble long-chain fatty acids seems improbable since reproducible differences in the effects of chain-length on the uptake of radioactivity in rat hearts after injection of the various ^{123m}Te fatty acids have been observed.

In addition to the differences in tissue distribution, we have also observed striking differences in both the rate and also the route of excretion of radioactivity from rats administered $^{123m}\text{Te}-\text{C}_{18}-\Delta^9$ and $^{75}\text{Se}-\text{C}_{18}-\Delta^9$ isosteres of oleic acid. Analysis of the urine and feces over a seven-day period indicated that radioactivity was excreted considerably more rapidly from rats administered the ^{75}Se agent. Within the first 24-hour period after injection, nearly 50% of the administered radioactivity was excreted from these animals, primarily in the urine. In contrast, nearly equal levels of radioactivity were detected in both the urine and feces from rats administered the ^{123m}Te agent. In addition, after 5 days only 50% of the injected radioactivity was excreted, indicating a longer biological half-life than observed with the ^{75}Se agent. Major differences in the thin-layer radiochromatographic profiles of radioactive lipid extracts from the hearts of rats injected with the two agents have also been observed. Folch extracts from rats injected with the ^{75}Se agent contained radioactive components which co-chromatographed with both diolein and triolein standards, suggesting that the ^{75}Se -labeled fatty acid is incorporated into glycerides by the rat heart. Lipid extracts from the hearts of rats injected with the ^{123m}Te agent contained only very polar radioactive material.

Using tissue distribution and excretion data from rats, the radiation dose estimates to humans have been calculated (45) for

^{123m}Te -9-telluraheptadecanoic acid ($^{123m}\text{Te-C}_{18}-\Delta^9$) and ^{75}Se -9-selenaheptadecanoic acid ($^{75}\text{Se-C}_{18}-\Delta^9$). The results of our calculations (Table VIII) indicate that the liver receives the highest dose from both agents. The radiation dose estimates are well within acceptable limits, however, since the estimated dose from ^{201}Tl -thallous chloride is very similar. We have also projected the radiation dose values for the $^{73}\text{Se-C}_{18}-\Delta^9$ agent because of our interest in the potential use of this agent or similar selenium fatty acids for positron emission tomography. The estimated radiation dose to the kidneys is only 0.76 rads/mCi, although considerably greater levels of radioactivity would probably have to be used to obtain the high count rate required for positron emission tomography. We are presently investigating the relative distribution of radioactivity in the normal and infarcted myocardial tissue of laboratory animals with experimental infarctions after administration of the $^{123m}\text{Te-C}_{18}-\Delta^9$ agent and several other ^{123m}Te and ^{75}Se -labeled long-chain fatty acids. The potential clinical usefulness of these agents will depend on the demonstration that they can be used to delineate myocardial infarctions and access ischemic conditions in these model systems.

MISCELLANEOUS AGENTS

The identification of the potent myotrophic and androgenic activity of heterocyclic androgen analogues containing selenium or tellurium in the A ring (36, 37) prompted several investigators to examine the synthesis and biological properties of the ^{75}Se and $^{123\text{m}}\text{Te}$ -labeled compounds. If such agents showed high uptake in the ventral prostate, they could potentially be used for prostatic imaging. There are presently no nuclear medicine imaging procedures routinely available for the diagnosis of prostatic disease.

The preparation and testing of the selenium and tellurium heterocyclic steroids by Wolf and co-workers (36, 37) was stimulated by their observation that androgen analogues which lack a C-3 substituent and contain sp^2 hybridized carbon atoms in the A ring, such as 5α -androst-2-en-17 β -ol (XV, Figure XIV), exhibit significant androgenic activity (46). In addition, ^{14}C -labeled 17α -methyl- 5α -androst-2-en-17 β -ol binds tightly to minced rabbit ventral prostate preparations (47). These results clearly indicated that an oxygenated C-3 substituent is not required for androgenic activity.

As described in the earlier section of this review on the properties of ^{75}Se and $^{123\text{m}}\text{Te}$ fatty acids, the bivalent S, Se and

Te atoms are isosteric with the -CH=CH- moiety. Isosteres of 5 α -androst-2-en-17 β -ol (XV) were therefore prepared by Wolf and co-workers by fabrication of the A-nor ring of heterocyclic steroids in which the sulfur, selenium or tellurium heteroatom replaced the Δ^2 -double bond (36, 37). Weights of the ventral prostate, seminal vesicles and the levator ani muscle all increased significantly compared with castrated controls after administration of 2-thia-A-nor-5 α -androstan-17 β -ol (XVI), 2-selena-A-nor-5 α -androstan-17 β -ol (XVII) and 2-tellura-A-nor-5 α -androstan-17 β -ol (XVIII, Figure XIII). These results clearly indicate that the potent androgenic and myotrophic activity of 5 α -androst-2-en-17 β -ol (XV) is maintained when the olefinic linkage is replaced with the S, Se, or Te heteroatoms.

In an *in vitro* assay system, using minced rat prostate tissue, (XVII) produced a significant decrease in nuclear binding of 5 α -dihydrotestosterone (48). Gel permeation analysis of a dialyzed rat prostate preparation combined with ⁷⁵Se-(XVII) resulted in a chromatographic profile that closely resembled that obtained in a similar experiment employing ³H-5 α -dihydrotestosterone. These results suggest that both (XVII) and 5 α -dihydrotestosterone bind to the same receptor protein present in rat prostate dialysate. Tissue distribution studies in rats with ⁷⁵Se-(XVII) demonstrated uptake in a variety of tissues. Although pronounced uptake of

radioactivity in the prostate was not observed in these studies, the concentration of radioactivity in the ventral prostate did remain constant for at least one hour, during which time the radioactive contents of the other tissues decreased significantly. The relatively low specific activity (3 Ci/mmol) was undoubtedly the major factor why preferential uptake of ^{75}Se -(XVII) was not observed in the rat ventral prostate. Preparation of very high specific activity material should be feasible, however, since (XVII) is prepared by coupling of sodium selenide (Na_2Se) with 17β -acetoxy-1,4-dibromo-1,4-seco-2,3-bisnor-5 α -androstane, a reaction which can be conducted on an extremely small scale. Since a large excess of reducing agent can be used to generate the monoselenide dianion from metallic selenium, careful control of the ratio of the reducing species to Se is not important. More importantly, the preparation and testing of ^{73}Se -(XVII) should be pursued because of the potential use of this agent for the tomographic imaging of the ventral prostate. The synthesis of ^{123m}Te -2-tellura-A-nor-5 α -androstan-17 β -ol (XVIII) has also been reported (49). Although this agent is easily prepared by generation of Na_2Te in the same manner as described above, the low specific activity of ^{123m}Te (maximum of 250 mCi/mmol) preclude the potential use of this agent for prostatic imaging. In addition, tissue distribution studies in rats have failed to demonstrate the prostatic uptake of this agent (F. F. Knapp and

D. V. Woo, unpublished experiments).

Recently, the pronounced brain uptake in rats of ^{75}Se -labeled di- β -(morpholinoethyl)-selenide (MOSE) and di- β -piperidinoethyl)-selenide (PIPSE) (Figure XIV) have been reported (50). These neutral compounds are lipid soluble at normal blood pH and freely diffuse into cells. In regions of low intracellular pH, the tertiary amine nitrogens of the morpholine or piperidine ring systems are apparently protonated, rendering the resultant charged species unable to diffuse out of the cell. This is an effective mechanism for cellular trapping of the ^{75}Se -labeled agents. Both MOSE and PIPSE show high brain uptake in rats within 2 minutes after injection. Single photon tomographic images of a rhesus monkey brain have been obtained after administration of ^{75}Se -MOSE and the anatomical distribution of this agent was noted to closely resemble images obtained with both ^{18}F -2-fluorodeoxyglucose and ^{13}N -ammonia (50). These results indicate that MOSE and PIPSE or related compounds are attractive agents for cerebral perfusion studies. The relatively simple structure of these two agents would suggest that preparation and testing of the ^{73}Se and $^{123\text{m}}\text{Te}$ -labeled analogues would be possible.

SUMMARY

This review has summarized structure-activity studies with ^{75}Se - and ^{123m}Te -labeled radiopharmaceuticals in which the selenium or tellurium heteroatom has been inserted between carbon-carbon bonds. The agents that have been investigated in most detail include steroids for adrenal imaging and long-chain fatty acids, and a variety of other unique agents have also been studied. Because of the great versatility of the organic chemistry of selenium and tellurium, there is continuing interest in the preparation of radiopharmaceuticals labeled with ^{75}Se , ^{73}Se and ^{123m}Te . There are two important factors which will determine the extent of future interest in such agents. These include the necessity of a decrease in the cost of highly enriched ^{122}Te to make the reactor production of ^{123m}Te cost effective. In addition, the potential preparation of large amounts of ^{73}Se should stimulate the development of ^{73}Se -labeled radiopharmaceuticals.

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Table I. Useful Radionuclides of Selenium and Tellurium

Radionuclide	Gamma Emissions	Physical Half-Life	Production Method	Reference
^{75}Se	121 keV (17%) 136 keV (57%) 265 keV (60%)	120.4 days	$^{74}\text{Se}(n,\gamma)^{75}\text{Se}$ $^{75}\text{As}(p,n)^{75}\text{Se}$	5,6 5,6 5-9 5-8 6 6
^{73}Se	511 keV (131%; β^+) 360 keV (97%)	7.2 hours	$^{70}\text{Ge}(\alpha,n)^{73}\text{Se}$ $^{72}\text{Ge}(\alpha,3n)^{73}\text{Se}$ $^{72}\text{Ge}(^3\text{He},2n)^{73}\text{Se}$ $^{73}\text{Ge}(^3\text{He},3n)^{73}\text{Se}$ $^{75}\text{As}(p,3n)^{73}\text{Se}$ $^{75}\text{As}(d,4n)^{73}\text{Se}$	5,6 5,6 5-9 5-8 6 6
^{123m}Te	159 keV (84%)	119.9 days	$^{122}\text{Te}(n,\gamma)^{123m}\text{Te}$ $^{122}\text{Sb}(p,n)^{123m}\text{Te}$	

Table II. Adrenal Uptake (% Injected Dose) of Structurally Modified ^{123m}Te Steroids One Day after Administration to Female Rats

Steroid	Unique Structural Feature	Adrenal Uptake \pm Range
23-(Isopropyltelluro)-24-nor-5 α -cholan-3 β -ol (IV) (24-Tellura-5 α -cholestan-3 β -ol)	Saturated Nucleus; All <i>trans</i> Ring Structure	4.02 (3.73 - 4.35)
23-(Isopropyltelluro)-24-nor-5 α -cholan-3 β -ol (V)	<i>Cis</i> A/B Ring Junction	0.44 (0.43 - 0.45)
23-(Octyltelluro)-24-nor-5 α -cholan-3 β -ol (VI)	Long, Hydrophobic Sidechain	0.59 (0.56 - 0.64)
24-(Isopropyltelluro)-chol-5-en-3 β -ol (VII)	Nuclear Double Bond	4.41 (4.28 - 4.59)
3 β -Methoxy-24-(Isopropyltelluro)-chol-5-ene (VIII)	C-3 Hydrophobic Substituent	1.38 (1.34 - 1.41)
17 β -[(Isopropyltelluro)methyl]-androst-5-en- 3 β -ol (IX)	Short C-17 Sidechain	0.13 (0.12 - 0.14)

*Mean values for three rats.

Table III. Comparison of the Adrenal/Tissue Ratios One Day after Administration of ^{75}Se -24-(Isopropylseleno)-chol-5-en-3 β -ol (III, 24-ISC) and ^{123m}Te -24-(Isopropyltelluro)-chol-5-en-3 β -ol (VII, 24-ITC) to Female Rats

Tissue	^{123m}Te -24-ITC	^{75}Se -24-ISC
Blood	54.8	67.3
Liver	27.1	27.1
Ovaries	4.9	9.0
Lung	18.7	10.9
Kidneys	56.2	30.0
Spleen	14.0	19.2
Pancreas	122.8	46.4

*The ratios are calculated from the % dose/g of tissue data for three rats.

Table IV. Comparison of the Estimated Radiation Dose Values (rads/mCi) of
 ^{75}Se - and ^{123m}Te -Labeled Adrenal Imaging Agents with ^{131}I -6 β -
 (Iodomethyl)-19-nor-cholest-5(10)-en-3 β -ol

Adrenal Imaging Agent	Adrenals	Ovaries
^{123m}Te -23-(Isopropyltelluro)-24-nor-5 α -cholan-3 β -ol (IV)	98	8
^{123m}Te -24-(Isopropyltelluro)-chol-5-en-3 β -ol (VII)	210	13
^{75}Se -24-(Isopropylseleno)-chol-5-en-3 β -ol (III)	25	2
^{75}Se -19-(Methylseleno)-cholest-5-en-3 β -ol (II)	61	10
^{75}Se -6 β -(Methylseleno)methyl-19-norcholest-5(10)-en-3 β -ol (Ia) (Scintidren TM)	93	14
^{131}I -6 β -Iodomethyl-19-norcholest-5(10)-en-3 β -ol	151	7

Table V. Comparison of the Absolute Heart Uptake (% Injected Dose) Values and Heart:Tissue Ratios 5 Minutes after Administration of ^{123m}Te Fatty Acids to Female Rats

Fatty Acid	Isosteric Notation	Heart Uptake	Heart Blood	Heart Liver	Heart Lung
9-Telluraheptadecanoic Acid	$\text{C}_{18}-\Delta^9$	2.1	15.7	0.53	4.2
6-Telluraheptadecanoic Acid	$\text{C}_{18}-\Delta^6$	1.9	17.9	0.66	3.5
11-Telluraheptadecanoic Acid	$\text{C}_{18}-\Delta^{11}$	2.0	29.2	0.34	4.9
6-Telluratridecenoic Acid	$\text{C}_{14}-\Delta^6$	0.5	1.5	0.24	1.5
9-Telluratridecenoic Acid	$\text{C}_{14}-\Delta^9$	0.9	5.4	0.13	0.9
9-Tellurapentadecanoic Acid	$\text{C}_{16}-\Delta^9$	2.3	9.2	0.46	3.4
17-Tellura-9-heneicosenic Acid	$\text{C}_{22}-\Delta^{9,17}$	1.7	11.4	0.54	2.2

*The % dose values for the heart are the mean values for three rats. The ratios are mean values for three rats calculated from the % dose/g tissue data.

Table VI. Comparison of the Absolute Heart Uptake (% Injected Dose) Values and Heart:Tissue Ratios 5 Minutes after Administration of ^{75}Se Fatty Acids to Female Rats

Fatty Acid	Isosteric Notation	Heart Uptake	$\frac{\text{Heart}}{\text{Blood}}$	$\frac{\text{Heart}}{\text{Liver}}$	$\frac{\text{Heart}}{\text{Lung}}$
9-Selenaheptadecanoic Acid	$\text{C}_{18}-\Delta^9$	0.87	5.4	0.15	1.5
9-Selenatridecanoic Acid	$\text{C}_{14}-\Delta^9$	0.63	1.9	0.37	1.4
13-Selenaheptadecanoic Acid	$\text{C}_{18}-\Delta^{13}$	0.45	3.3	0.12	0.7
13-Selenaheneicosonic Acid	$\text{C}_{22}-\Delta^{13}$	1.5	9.9	0.42	2.6
9-Selenapentacosonic Acid	$\text{C}_{25}-\Delta^9$	1.9	7.3	0.38	4.8

*The % dose values for the heart are the mean values for three rats. The ratios are mean values for three rats calculated from the % dose/g tissue data.

Table VII. Distribution of Radioactivity in Female Rat Tissues and $^{123m}\text{Te}/^{75}\text{Se}$
 Tissue Ratios 30 Minutes after Administration of a Mixture of the
 $^{123m}\text{Te-C}_{18}\text{-}\Delta^9$ and $^{75}\text{Se-C}_{18}\text{-}\Delta^9$ Agents

Tissue	Mean percent dose/g		$^{123m}\text{Te}:^{75}\text{Se}$
	^{123m}Te	^{75}Se	
Heart	5.6 (3.3)	1.8 (1.9)	3.11
Blood	0.5 (0.5)	0.3 (0.5)	1.66
Liver	6.0 (12.1)	6.3 (7.9)	0.95
Kidneys	1.8 (1.9)	1.6 (1.7)	1.13
Lungs	1.6 (1.1)	1.3 (1.6)	1.23
Spleen	0.6 (0.5)	0.4 (0.3)	1.50
Pancreas	1.2 (0.7)	0.7 (0.9)	1.71
Small Intestine	0.8 (0.9)	0.4 (0.7)	2.00
Large Intestine	0.08 (0.09)	0.05 (0.11)	1.60
Brain	0.1 (0.1)	0.1 (0.2)	1.00

*Mean values for three animals. The numbers in parentheses are the values obtained in control experiments in which the agents were administered separately.

Table VIII. Comparison of the Estimated Radiation Dose Values (Rads/mCi) of ^{123m}Te -9-telluraheptadecanoic Acid ($^{123m}\text{Te-C}_{18}-\Delta^9$), ^{75}Se - and ^{73}Se -9-selenaheptadecanoic Acids ($^{75}\text{Se-C}_{18}-\Delta^9$ and $^{73}\text{Se-C}_{18}-\Delta^9$) with ^{201}Tl -Thallous Chloride

	$^{123m}\text{Te-C}_{18}-\Delta^9$	$^{75}\text{Se-C}_{18}-\Delta^9$	$^{73}\text{Se-C}_{18}-\Delta^9$	$^{201}\text{TlCl}$
Total Body	1.5	0.49	0.19	...
Heart Wall	2.0	0.61	0.31	0.17-1.3
Kidneys	5.0	1.3	0.58	0.39-3.8
Liver	2.1	1.12	0.84	0.15-0.62

FIGURE LEGENDS

Figure I. Chemical structures of 19-nor steroids substituted at C-6 with various axial alkylselenomethyl and arylselenomethyl groups.

Figure II. Chemical structures of 19-(methylseleno)-cholest-5-en-3 β -ol (II) and 23-(isopropylseleno)-24-nor-5 α -cholan-3 β -ol (III).

Figure III. Structures of telluro steroid analogues.

Figure IV. Distribution of radioactivity in female rat tissues after administration of ^{123m}Te -23-(Isopropyltelluro)-24-nor-5 α -cholan-3 β -ol (IV). (From ref. 24. Reproduced with permission from the editor of the Journal of Nuclear Medicine).

Figure V. Posterior rectilinear scan of a female rat 2 days after administration of 50 μCi of ^{123m}Te -23-(Isopropyltelluro)-24-nor-5 α -cholan-3 β -ol (IV). (From ref. 24. Reproduced with permission from the editor of the Journal of Nuclear Medicine).

Figure VI. Anterior gamma camera image (500K counts) of a female rabbit obtained 7 days after administration of 200 μCi of $^{123\text{m}}\text{Te}$ -24-(Isopropyltelluro)-24-nor-5 α -cholan-3 β -ol (IV).

Figure VII. Silicic acid column chromatographic profiles of Folch extracts from the adrenals and ovaries of female rats obtained 2 days after administration of $^{123\text{m}}\text{Te}$ -23-(Isopropyltelluro)-24-nor-5 α -cholan-3 β -ol (IV). (From ref. 24. Reproduced with permission from the editor of the Journal of Nuclear Medicine).

Figure VIII. Adrenal/liver ratios for the $^{123\text{m}}\text{Te}$ steroid analogues calculated from the % dose/g data at 1, 3 and 7 days after administration. (From ref. 26. Reproduced with permission from the editor of the Journal of Nuclear Medicine).

Figure IX. Chemical structures of selenium and tellurium bile acid analogues.

Figure X. Distribution of radioactivity in the heart, blood and liver of female rats after administration of $^{123\text{m}}\text{Te}$ -9-telluraheptadecanoic acid ($^{123\text{m}}\text{Te}$ -C₁₈- Δ^9).

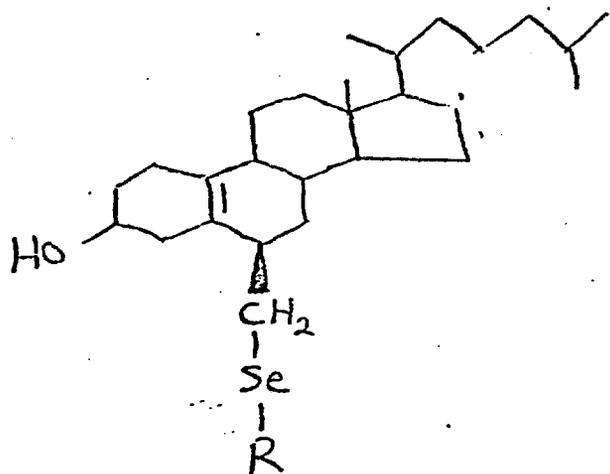
Figure XIII. Distribution of radioactivity in the heart, blood and liver of female rats after administration of ^{75}Se -9-selenaheptadecanoic acid (^{75}Se -C₁₈- Δ^9).

Figure XII. Anterior gamma camera image (500K counts) of the thoracic region of a male rabbit obtained 50 minutes after administration of 117 μCi of $^{123\text{m}}\text{Te}$ -9-telluraheptadecanoic acid ($^{123\text{m}}\text{Te}-\text{C}_{18}-\Delta^9$).

Figure XI. Posterior rectilinear scan of the thoracic region of a female rat 30 minutes after administration of 50 μCi of $^{123\text{m}}\text{Te}$ -9-telluraheptadecanoic acid ($^{123\text{m}}\text{Te}-\text{C}_{18}-\Delta^9$).

Figure XIV. Chemical structures of androgen analogues.

Figure XV. Chemical structures of symmetrically substituted piperidinoethyl and morpholinoethyl selenides.

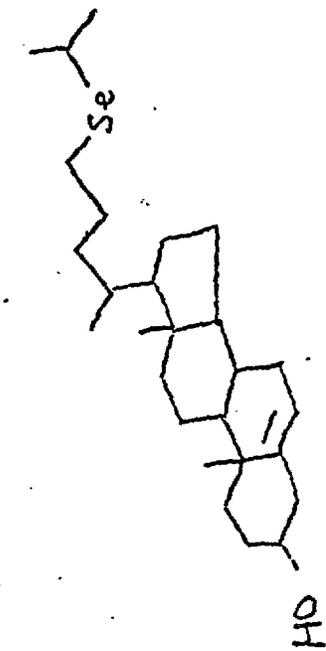


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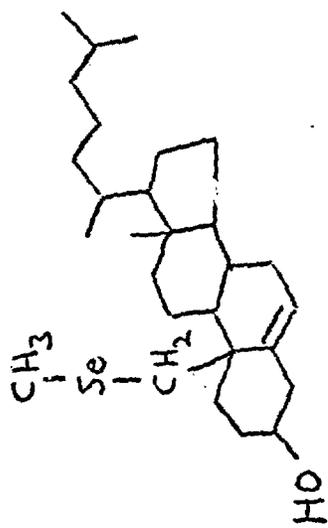
- R
- a $-\text{CH}_3$
 - b $-(\text{CH}_2)_3-\text{CH}_3$
 - c 
 - d $-\text{CH}_2-$ 
 - e 

Figure I

Figure II



III



II

Figure II

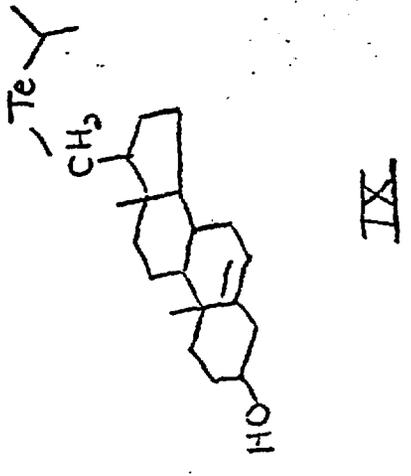
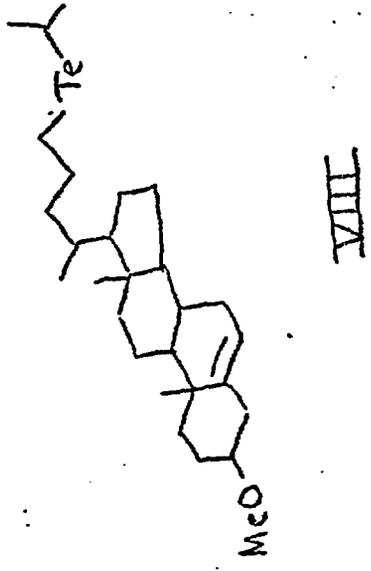
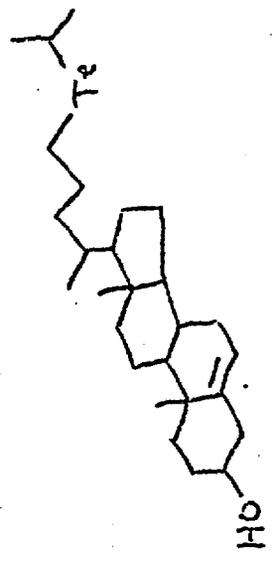
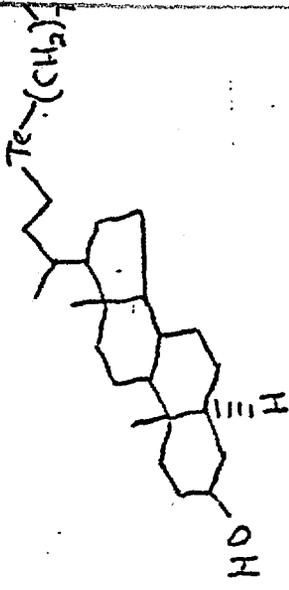
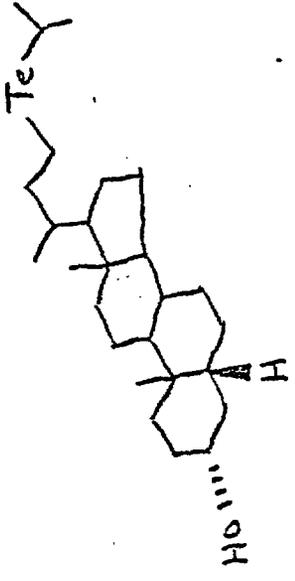
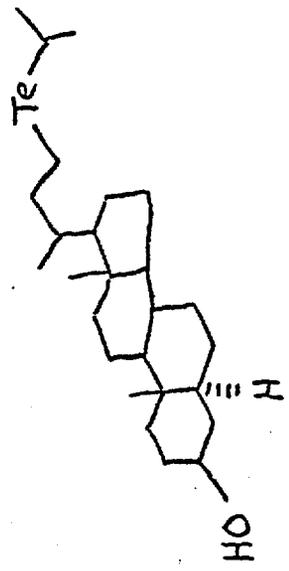


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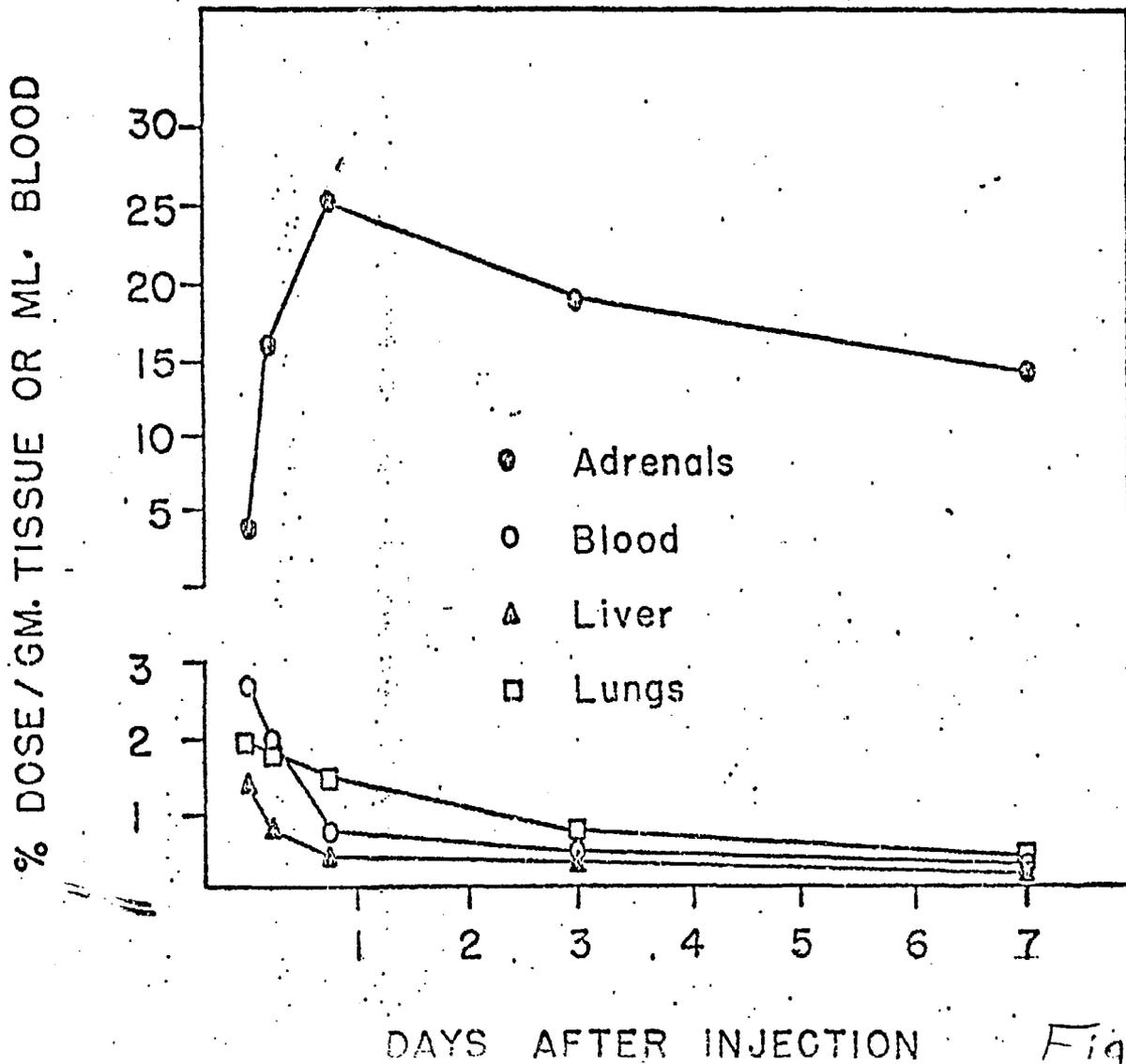


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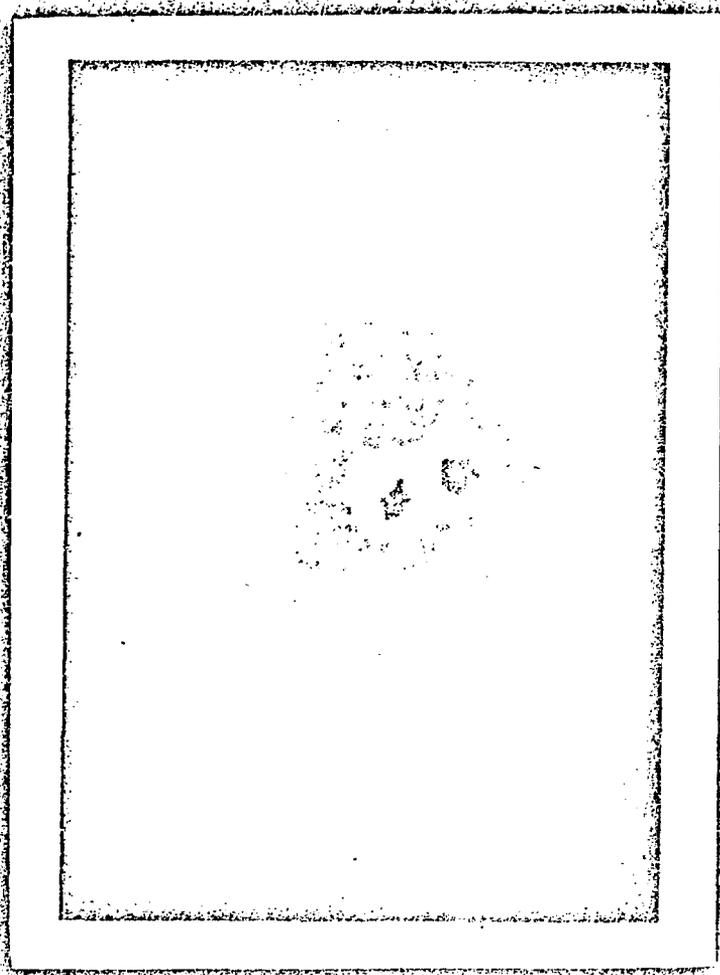


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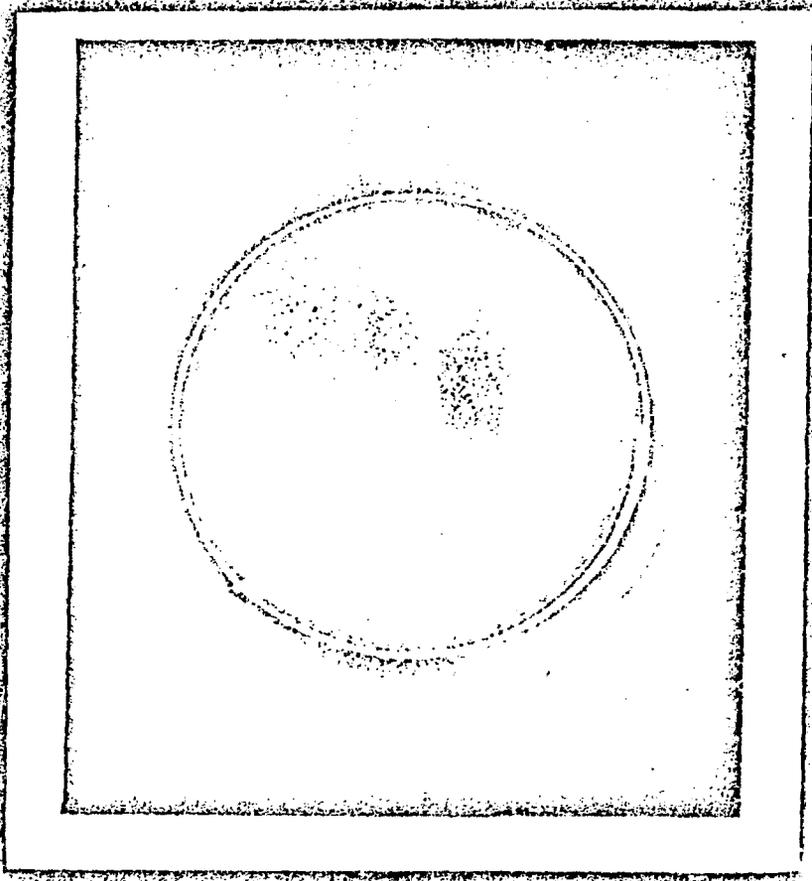


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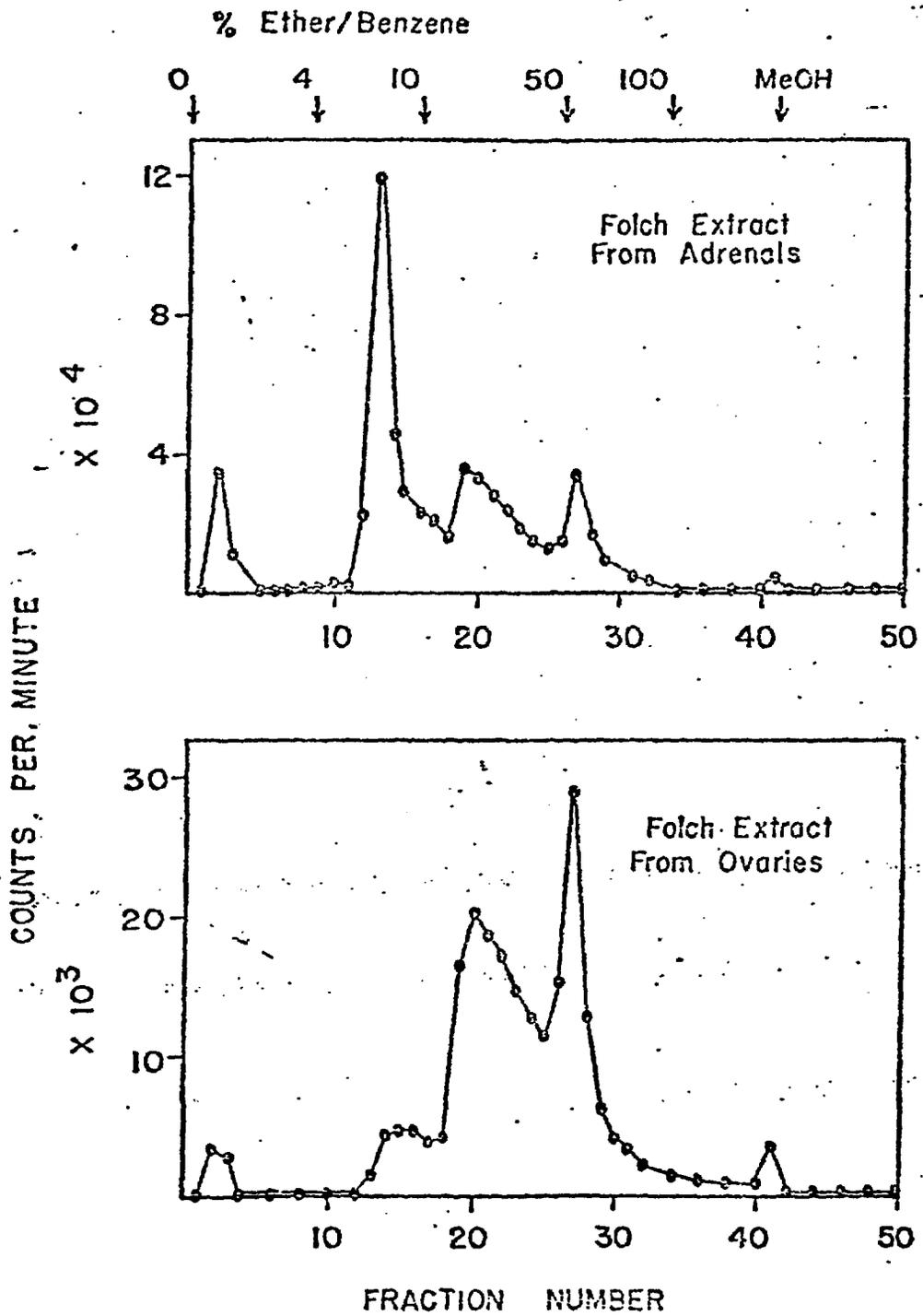


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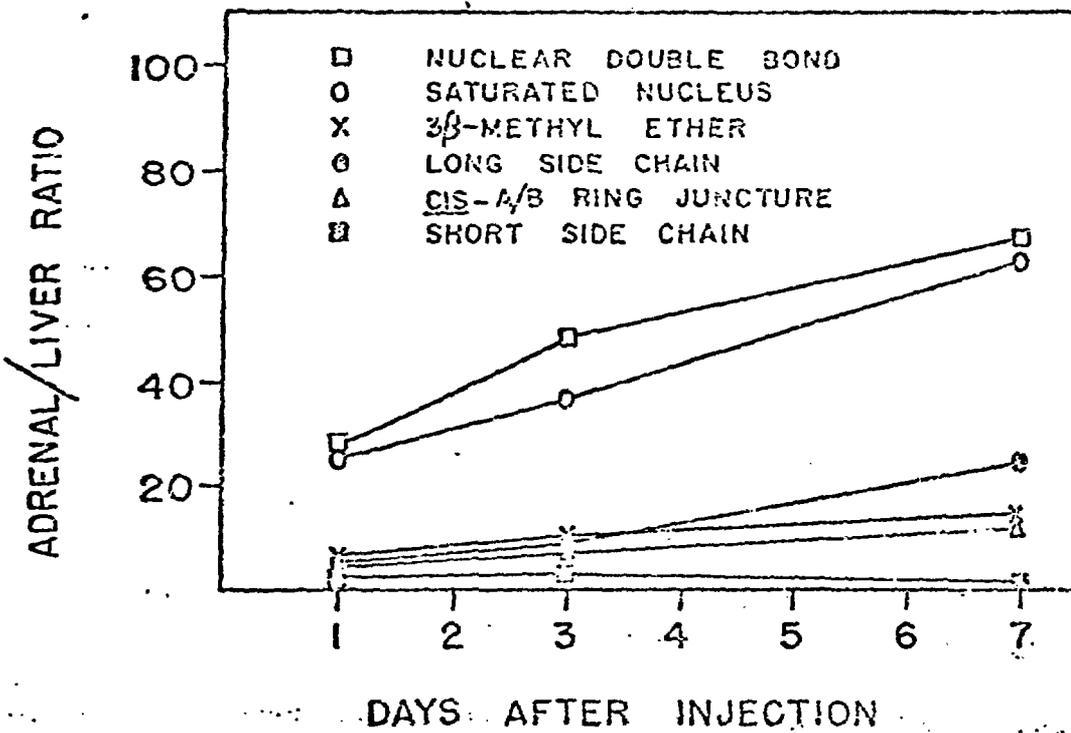
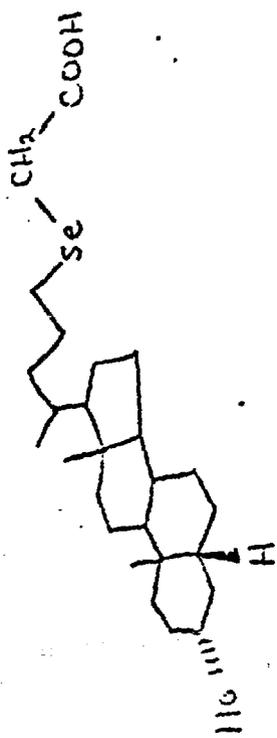
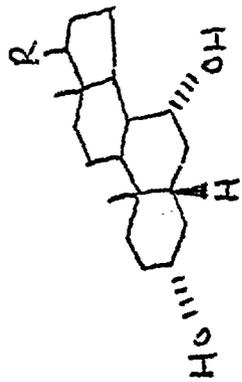


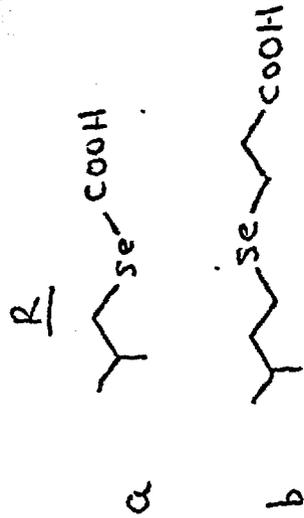
Figure VIII



V

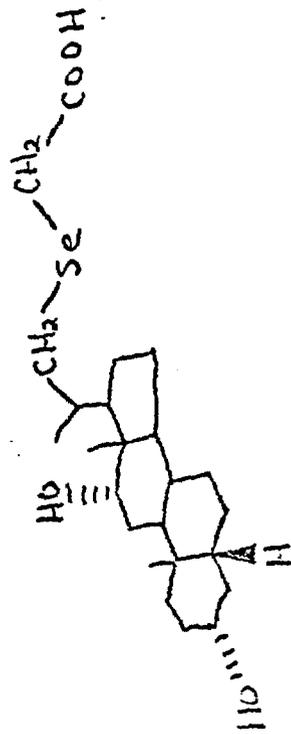


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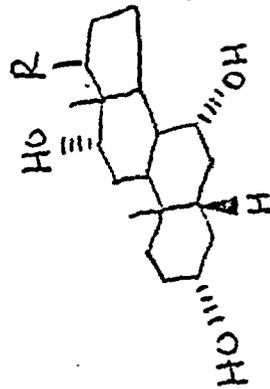


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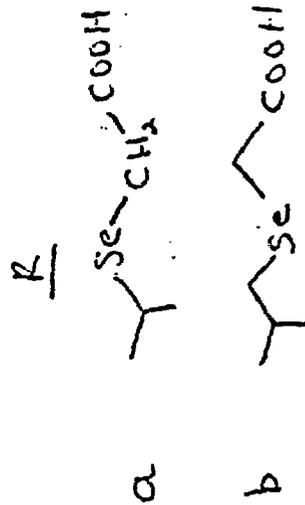
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VIII

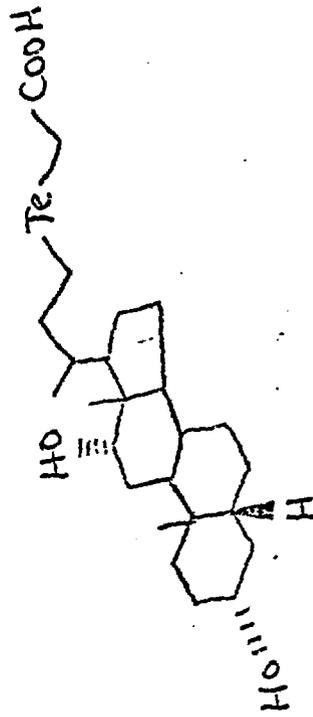


IX



a

b



XI

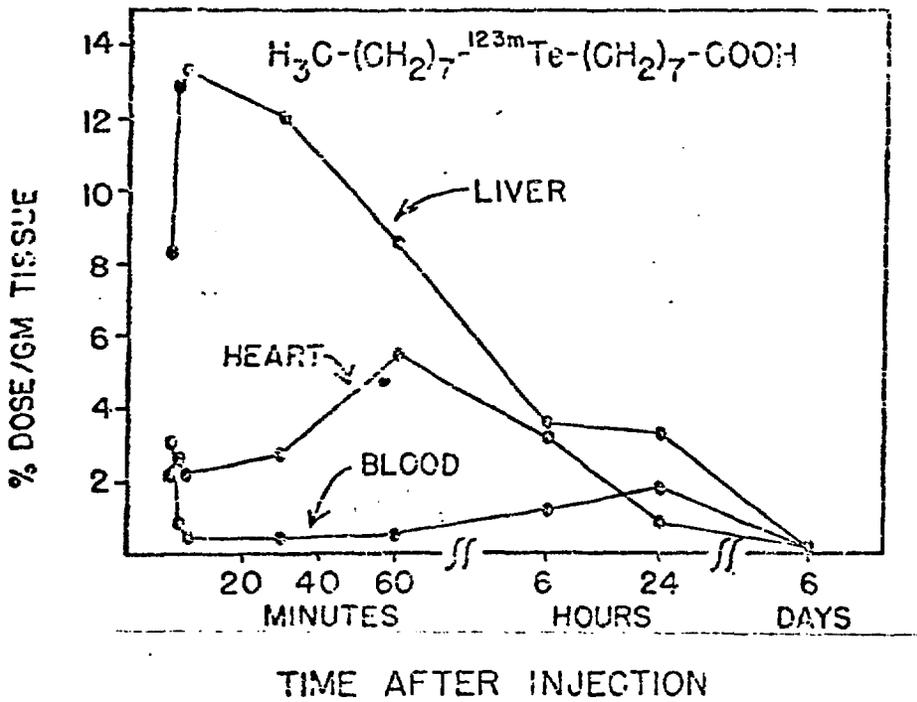
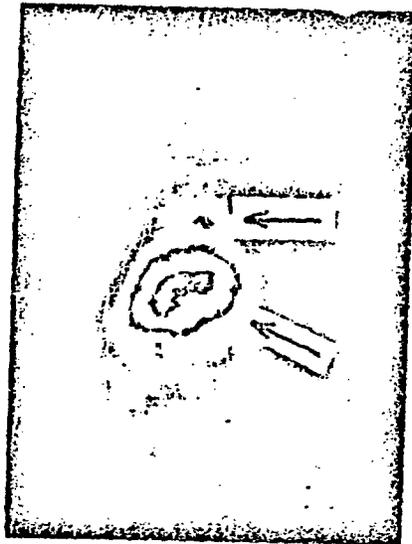


Figure X

Left



Right

Heart

Liver Mass

Figure XI

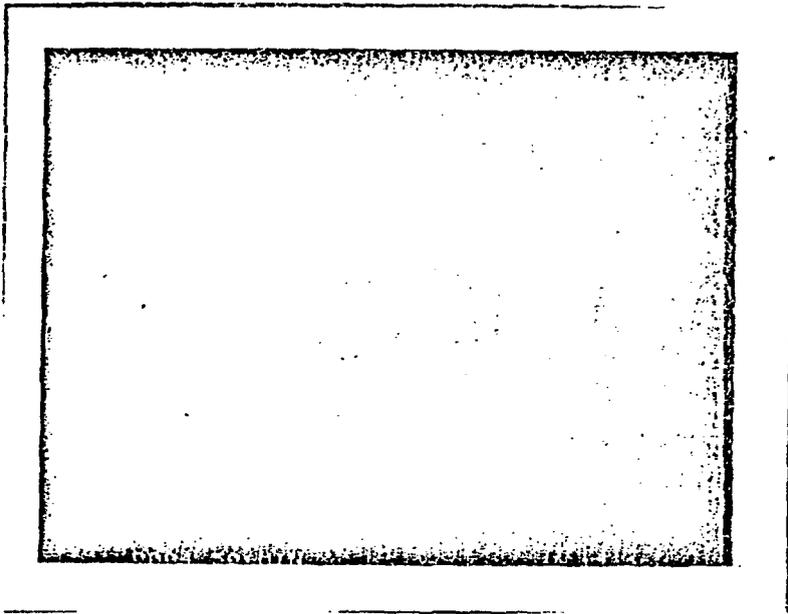


Figure XII

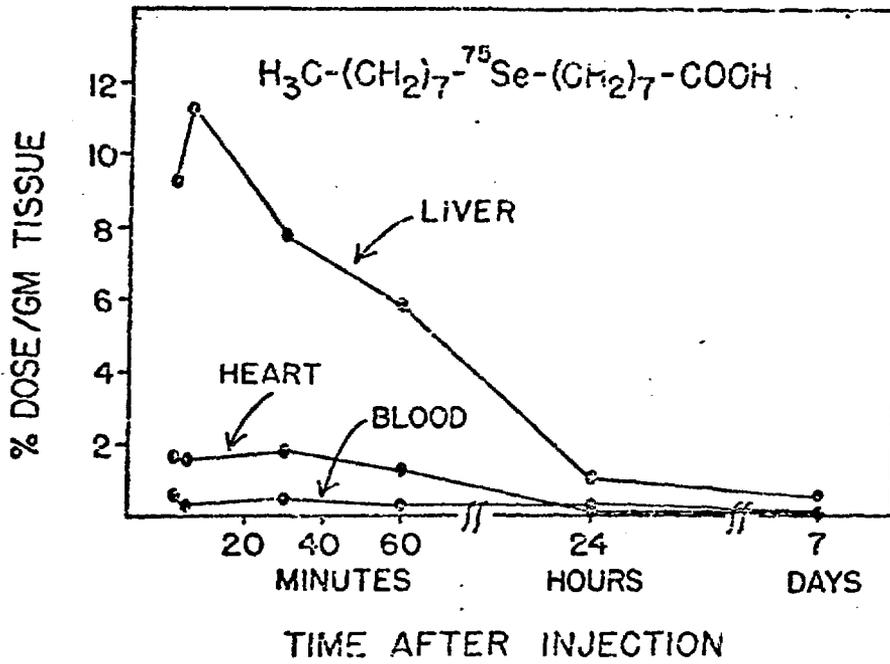
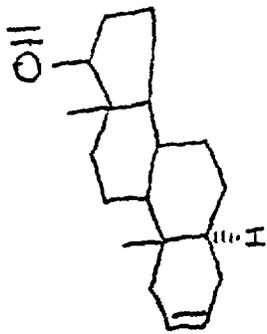
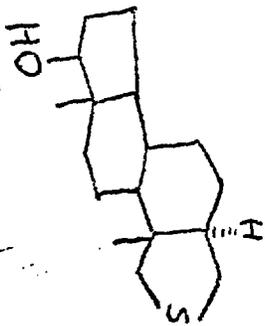


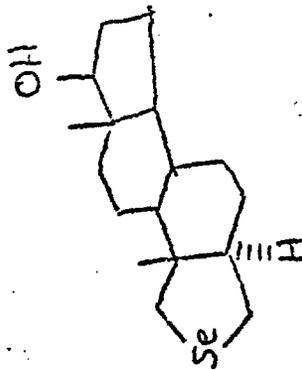
Figure XIII



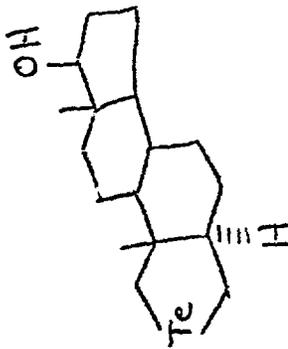
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XVI

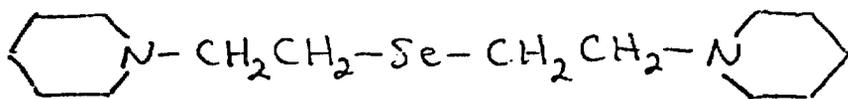


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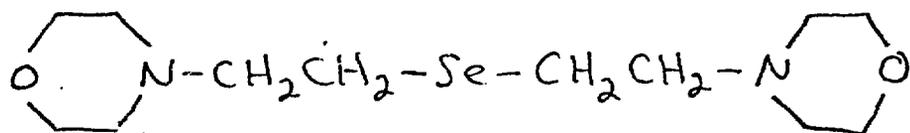


XVIII

Figure XIV



Di- β -(piperidinoethyl)-selenide (PIPSE)



Di- β -(morpholinoethyl)-selenide (MOSE)

Figure XV