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Synthesis and Biological Evaluation of 17-[^{131}I]Iodo-9-telluraheptadecanoic Acid, a Potential Myocardial Imaging Agent

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A method has been developed for the preparation of terminal halogenated tellurium fatty acids (X-R-Te-R'-COOH). The synthesis and physical properties of 17-bromo- and 17-iodo-9-telluraheptadecanoic acid (17-iodo-9-THDA) are described. The radiohalogenated agents are of interest as a result of their expected pronounced and prolonged heart uptake and potential use for evaluation of regional myocardial fatty acid metabolism. Evaluation in rats indicates that the myocardial uptake of 17-[^{131}I]iodo-9-telluraheptadecanoic acid (17-[^{131}I]iodo-9-THDA) is accompanied by significant in vivo deiodination. A comparison of the heart uptake and deiodination of 17-[^{131}I]iodo-9-THDA and 16-[^{131}I]iodopalmitic acid has demonstrated a close similarity in blood levels of radioactivity and thyroid uptake of radioiodide after administration of these agents to rats. These data suggest that the mechanism of deiodination of terminal radioiodinated alkanoic acids primarily results from direct cleavage of the carbon–iodine bond and not from loss of radioiodine from the final catabolite.

Long-chain free fatty acids are the principal energy source for the normal myocardium. A variety of modified long-chain fatty acid analogues labeled with γ-emitting radionuclides have been prepared and evaluated as myocardial imaging agents. Terminal ^{123}I-labeled long-chain fatty acids, such as 16-[^{123}I]iodohexadecenoic acid[1] and 17-[^{123}I]iodoheptadecanoic acid,[2] have been developed for the purpose of delineating areas of infarcted and ischemic tissue and measuring myocardial fatty acid metabolism.[3-5] The significant in vivo deiodination of these agents, however, results in a rapid washout of radioactivity from the heart and pronounced accumulation of the radiolabel in the thyroid and blood. Significant levels of radioactivity in the blood interfere with the measurement of the myocardial fatty acid uptake unless methods are employed to correct for blood levels of free radioiodide.[5,6] As a result of the problem of facile deiodination, the widespread clinical application of these agents may therefore be limited. The formation of significant levels of free radioiodide has been postulated to result from the rapid metabolism of the radioiodinated fatty acid with subsequent loss of the radiolabel from the final metabolic product or by direct nonenzymatic or enzymatic cleavage of the carbon–halogen bond.[6] The actual mechanism of dehalogenation has not yet been determined and probably results from a combination of these two processes.

Recently, a new class of agents has been developed by Machulla et al. in which radiohalogens have been chemically stabilized on the fatty acids by introduction on a terminal phenyl moiety.[7] The terminal substituted, para-radiohalogenated phenyl fatty acids, such as *p*-[^{82}Br]bromo- and *p*-[^{131}I]iodophenylpentadecanoic acid, were chosen as model compounds because of the availability of the 15-phenylpentadecanoic acid substrate and the established chemical stability of the radiohalogen bound to the aromatic system. In addition, the classic β-oxidation experiments of Knoop[8] and Dakin[9] had demonstrated that terminal phenyl-substituted long-chain fatty acids were readily metabolized by mammalian systems. Tissue distribution studies in mice with the *p*-[^{82}Br]bromo- and *p*-[^{131}I]iodophenylpentadecanoic acids have shown, however, that although the radiolabel does not suffer facile in vivo deiodination, the radioactivity exhibits a relatively rapid myocardial washout. With *p*-[^{82}Br]bromophenylpentadecanoic acid, greater than 75% of the radioactivity in the heart at 5 min was washed out 25 min after injection.[7] These results are similar to those observed in mice with 17-[^{125}I]iodoheptadecanoic acid in which 75% of the early maximum accumulation of radioactivity in the heart was lost 10 min after injection.[2]

The incorporation of ^{123m}Te and ^{75}Se into long-chain fatty acids was first reported by Knapp et al.[10] Tellurium and selenium could be readily incorporated while maintaining the linearity of the fatty acid molecule and were envisioned as unique structural features that could possibly inhibit catabolism of the molecule and result in prolonged retention or "trapping" of the modified fatty acids in the myocardium. The results of tissue distribution studies with several ^{75}Se- and ^{123m}Te-labeled fatty acids have demonstrated that significant levels of radioactivity are retained in the heart after intravenous administration of

(1) Robinson, G. D. *Int. J. Appl. Radiat. Isot.* **1977**, *28*, 149.
(2) Machulla, H. J.; Stocklin, G.; Kupfernagel, W.; et al. *J. Nucl. Med.* **1978**, *19*, 298.
(3) Poe, N. D.; Robinson, G. D.; Graham, L. S.; et al. *J. Nucl. Med.* **1976**, *17*, 1077.
(4) Poe, N. D.; Robinson, G. D.; Zielinski, F. W.; et al. *Radiology* **1977**, *124*, 419.
(5) Freundlieb, W.; Hock, A.; Vyska, K.; et al. *J. Nucl. Med.* **1980**, *21*, 1043.
(6) Feinendegen, L. E.; Vyska, K.; Freundlieb, W.; et al. *Eur. J. Nucl. Med.* **1981**, *6*, 191.
(7) Machulla, H. J.; Marsmann, M.; Dutschka, K.; et al. *Radiochem. Radioanal. Lett.* **1980**, *42*, 243.
(8) Knoop, F. "Der Abbau aromatischer Fettsauren im Tierkorper", Freiburg, 1904.
(9) Dakin, H. D. *J. Biol. Chem.* **1909**, *6*, 221.
(10) Knapp, F. F., Jr.; Ambrose, K. R.; Callahan, A. P.; et al. "Radiopharmaceuticals II"; Society of Nuclear Medicine: New York, 1979; pp 101–108.

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these agents.[10-12] ^{123m}Te-labeled 9-telluraheptadecanoic acid (9-THDA) shows pronounced and prolonged myocardial uptake in rats[10,11] and has been investigated extensively in dogs[12,13] as a potential myocardial imaging agent. More recently, tissue distribution and autoradiographic analyses by Knapp et al. have indicated that the alkyl R portion of 9-THDA [R–Te$(CH_2)_7$COOH, where R = $H_3C(CH_2)_6(^{14}CH_2)$] is retained in the myocardium 1 h after administration.[14] These results suggest that ω-radiohalogenated fatty acids containing stable tellurium may demonstrate similar rapid and prolonged retention in the myocardium and, therefore, represent attractive new agents that could be useful for the measurement of regional myocardial fatty acid metabolism.

The goals of the present investigation were to develop a method for the synthesis of terminal iodinated tellurium fatty acids and to evaluate the distribution properties of the radioiodinated compounds in rats. We specifically wished to prepare 17-[^{131}I]iodo-9-telluraheptadecanoic acid (17-[^{131}I]iodo-9-THDA) as a model agent. This new compound is the analogue of 9-telluraheptadecanoic acid (9-THDA), which has been evaluated extensively in laboratory animals.[10-13]

Results and Discussion

The two routes initially explored for introduction of terminal halogens into model tellurium fatty acids are shown in Schemes I and II. Methyl 18-hydroxy-7-telluraoctadecanoate (**5**) was prepared as a model substrate for functionalization of the terminal hydroxyl group with a suitable leaving group (Y = tosyl, mesyl, or trifyl) that could be readily displaced with bromide or iodide (F. F. Knapp, Jr., M. M. Goodman, and D. R. Elmaleh, unpublished experiments). Formation of the *p*-toluenesulfonate or methanesulfonate derivatives (**6**) of methyl 18-hydroxy-7-telluraoctadecanoate (**5**) by the usual route was not possible because of the competing reaction involving addition of the acyl chlorides to the tellurium heteroatom to form the telluronium species ($R_3Te^+X^-$). Attempts to form the trifluoroacetate derivative by treatment of the hydroxyl intermediate with trifluoroacetic acid anhydride did not proceed smoothly.

An alternative route (Scheme II) involved fabrication of the vinylic tellurium fatty acid that was envisioned as a candidate for reaction with diborane, followed by subsequent treatment with iodine monochloride to form the terminal iodide.[15] Although the methyl 11-tellura-16-heptadecenoate substrate (**11**) could be readily prepared, attempted synthesis of the desired product (**13**) by the treatment of **11** with diborane and then iodine monochloride gave an intractable product (F. F. Knapp, Jr., and G. W. Kabalka, unpublished experiments), presumably as a result of formation of a telluronium species ($R_2XTe^+X^-$).

The general method for synthesis of tellurium fatty acids involves initial fabrication of the methyl ester (**18**), followed by purification by absorption column chromatography.[10] The final step involves hydrolysis of the methyl ester to the free acid (**19**) (Scheme III). Our initial synthetic approach for the preparation of 17-iodo-9-telluraheptadecanoic acid (**26**) involved fabrication of the corresponding terminal iodinated fatty acid methyl ester (**25**), followed by hydrolysis to the free acid as outlined in Scheme IV. In this route, compound **25** was prepared by coupling sodium (methyloctanoyl)tellurol (**22**) with 1,8-dibromooctane (**23**), followed by halogen exchange (Finkelstein reaction) with sodium iodide in refluxing acetone. Although this route worked well for the preparation of methyl 17-iodo-9-telluraheptadecanoate (**25**), our attempts to transform compound **25** to the corresponding free fatty acid by either basic or acidic hydrolysis resulted in loss of iodide. Because of the lability of the halogenated tellurium fatty acid methyl ester to usual hydrolytic conditions, preparation of the halogenated free acids necessitated the development of an alternative synthetic route.

The successful synthesis of the terminal brominated and iodinated free tellurium fatty acids involved a modification of the classical unsymmetrical telluride synthesis (Scheme III). This route (Scheme V) involves a reversal of the order

Scheme I

$$Na_2Te_2 + HO(CH_2)_{11}Br \rightarrow \underset{1}{HO(CH_2)_{11}Te—Te(CH_2)_{11}OH} + NaBH_4 \rightarrow \underset{2}{HO(CH_2)_{11}Te—Na} + Br(CH_2)_5COOMe \rightarrow \underset{3}{HO(CH_2)_{11}Te(CH_2)_5COOMe} \rightarrow \underset{4}{Y—O(CH_2)_{11}Te(CH_2)_5COOMe} + X^- \rightarrow \underset{5}{X—(CH_2)_{11}Te(CH_2)_5COOMe} \rightarrow \underset{6}{}$$

Scheme II

$$Na_2Te_2 + Br(CH_2)_3CH=CH_2 \rightarrow \underset{7}{H_2C=CH(CH_2)_3Te—Te(CH_2)_3CH=CH_2} + NaBH_4 \rightarrow \underset{8}{H_2C=CH(CH_2)_3Te—Na} + Br(CH_2)_9COOMe \rightarrow \underset{9}{H_2C=CH(CH_2)_3Te(CH_2)_9COOMe} + B_2H_6 \rightarrow \underset{11}{B[H_2C(CH_2)_4Te(CH_2)_9COOMe]_3} + ICl \rightarrow \underset{12}{I(CH_2)_5Te(CH_2)_9COOMe} \rightarrow \underset{13}{}$$

Scheme III

$$Na_2Te_2 + \underset{14}{RX} \rightarrow \underset{15}{R—Te—Te—R} + NaBH_4 \rightarrow \underset{16}{R—Te—Na} + X—R'—\underset{17}{COOMe} \rightarrow \underset{18}{R—Te—R'—COOMe} + NaOH \rightarrow \underset{19}{R—Te—R'—COOH}$$

Scheme IV

$$Na_2Te_2 + Br(CH_2)_7COOMe \rightarrow \underset{20}{MeOOC(CH_2)_7Te—Te(CH_2)_7COOMe} + NaBH_4 \rightarrow \underset{21}{Na—Te(CH_2)_7COOMe} + Br(CH_2)_8Br \rightarrow \underset{22}{} \underset{23}{} Br(CH_2)_8Te(CH_2)_7COOMe + NaI \rightarrow \underset{24}{I(CH_2)_8Te(CH_2)_7COOMe} + NaOH \rightarrow \underset{25}{I(CH_2)_8Te(CH_2)_7COOH} \rightarrow \underset{26}{}$$

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(15) Kabalka, G. W.; Gooch III, E. E. *J. Org. Chem.* **1981**, *45*, 3578.

Scheme V

$$\underset{}{\mathrm{MeOOC(CH_2)_7Te{-}Te(CH_2)_7COOMe}} + \mathrm{NaOH} \rightarrow$$
$$\underset{\mathbf{21}}{\mathrm{NaOOC(CH_2)_7Te{-}Te(CH_2)_7COONa}} + \mathrm{NaBH_4} \rightarrow$$
$$\underset{\mathbf{27}}{\mathrm{Na{-}Te(CH_2)_7COONa}} + \underset{\mathbf{23}}{\mathrm{Br(CH_2)_8Br}} \rightarrow$$
$$\underset{\mathbf{29}}{\mathrm{Br(CH_2)_8Te(CH_2)_7COOH}} + \mathrm{NaI} \rightarrow$$
$$\underset{\mathbf{26}}{\mathrm{I(CH_2)_8Te(CH_2)_7COOH}}$$

of substrate addition traditionally used for the synthesis of unsymmetrical "functionalized" Te compounds and was necessitated by the reactivity of 1,8-dibromooctane (**23**). In this approach, the "functionalized" bis(methyloctanoyl)ditelluride (**21**) was prepared by the classical method involving treatment of disodium ditelluride with methyl 8-bromooctanoate. Following basic hydrolysis, compound **21** was reduced in situ with sodium tetrahydridoborate ($NaBH_4$) in the presence of excess 1,8-dibromooctane (**23**). The excess 1,8-dibromooctane was required to minimize formation of the undesired $HOOC(CH_2)_7Te(CH_2)_8Te(CH_2)_7COOH$ species and was conveniently removed from compound **29** by trituration of the crystallized material with cold petroleum ether. Treatment of compound **29** with sodium iodide in refluxing acetone gave, after crystallization, 17-iodo-9-telluraheptadecanoic acid (**26**) in 70% yield. The new iodinated tellurium fatty acid (**26**) was characterized by thin-layer chromatography, low-resolution mass spectrometry, and proton nuclear magnetic resonance spectroscopy. This assignment was confirmed by the preparation of compound **26** by a convergent route by the coupling of intermediate **28** with 1,8-diiodooctane. The products obtained from both synthetic routes possessed identical physical and spectral properties.

Although the formation of a cyclic telluronium species of the general $R_3Te^+X^-$ could possibly occur by intramolecular cyclization of the terminally halogenated compounds **24–26**, the expected downfield resonances for the methylene protons adjacent to the Te heteroatom in the NMR spectra of these compounds were not observed. In addition, the resonance for the methylene protons adjacent to the terminal halogens was located at the expected position. The entropic impediment introduced by the eight-carbon chain and the subsequent formation of a nine-membered ring are two factors which do not favor formation of the cyclic telluronium product. We have observed formation of a selenonium species by intramolecular cyclization of a shorter chain selenium compound, phenyl 4-bromobutyl selenide (N. Dereu, K. J. Irgolic, and F. F. Knapp, Jr., unpublished experiments).

The radioiodinated Te fatty acid, 17-[^{131}I]iodo-9-telluraheptadecanoic acid (17-[^{131}I]iodo-9-THDA), was prepared by Na–^{131}I treatment of 17-bromo-9-telluraheptadecanoic acid (**29**) as described for the preparation of unlabeled **26**. The radioiodinated product exhibited a single radioactive component upon thin-layer radiochromatographic analysis (SiO_2) and cochromatographed with the unlabeled standard **26**.

The distribution of radioactivity in tissues of female Fischer rats at 2, 10, 30, and 60 min, 2, 6, and 24 h, and 4 and 7 days after intravenous administration of 17-[^{131}I]iodo-9-telluraheptadecanoic acid (17-[^{131}I]iodo-9-THDA) is shown in Table I. The level of accumulation of radioactivity in the myocardium after injection of 17-[^{131}I]iodo-9-telluraheptadecanoic acid is not as high as observed with 9-[^{123m}Te]THDA but greater than with 16-[^{131}I]iodohexadecanoic acid (Figure 1). The myocardial

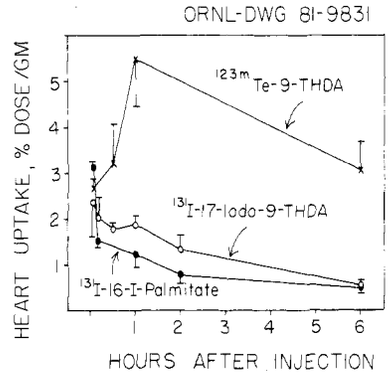

Figure 1. Comparison of the heart uptake (percent injected dose/g) of radioactivity at various time intervals over a 6-h period after intravenous administration of 9-[^{123m}Te]telluraheptadecanoic acid (^{123m}Te-9-THDA), 17-[^{131}I]iodo-9-telluraheptadecanoic acid (^{131}I-17-iodo-9-THDA), and 16-[^{131}I]iodopalmitic acid (^{131}I-16-I-Palmitate) to female Fischer rats. The mean and range values for four rats are shown for each time point.

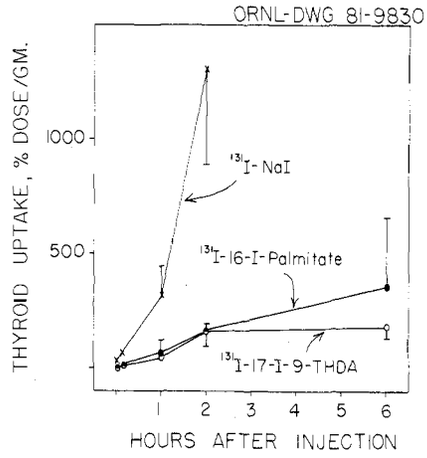

Figure 2. Comparison of the thyroid uptake of I-131 after 5, 10, 60 min and 6 h after intravenous administration of 17-[^{131}I]-iodo-9-telluraheptadecanoic acid (^{131}I-17-I-9-THDA), 16-[^{131}I]-iodopalmitic acid (^{131}I-16-I-Palmitate), and sodium [^{131}I]iodide (^{131}I-NaI) to female Fischer rats. The mean and range values for four rats are shown for each time point.

uptake for 17-[^{131}I]iodo-9-THDA reaches a maximum at 2 min and remains constant to 60 min. The liver and lungs, which are organs that might interfere with myocardial imaging, exhibited an elimination of 67 and 47%, respectively, at 60 min compared with their uptake at 2 min. After 60 min, the heart to liver ratio was 1.6:1 and the heart to lung ratio was 2.2:1. The heart to blood ratio reached a maximum of 3:1 at 60 min. The accumulation of activity in the thyroid (percent injected dose per gram) showed a rapid and pronounced accumulation, from 6.3% at 2 min to 166% at 2 h. The magnitude and kinetics of iodine loss from the 17-[^{131}I]iodo-9-THDA was further assessed by a comparison of the tissue uptake values with tissue distribution data from female Fischer rats after administration of 16-[^{131}I]iodohexadecanoic acid and Na–^{131}I (Figure 2). The thyroid uptake of radioiodide following administration of the radioiodinated fatty acids was very similar.

Although the 17-[^{131}I]iodo-9-THDA showed prolonged myocardial retention in rats, the absolute uptake was not as high as that observed with 9-[^{123m}Te]THDA (Figure 1). The tissue distribution of 17-iodo-9-[^{123m}Te]telluraheptadecanoic acid was also assessed in rats (Table II). The similarity of the magnitude of myocardial uptake of radioactivity from 17-[^{131}I]iodo-9-THDA and 17-iodo-9-[^{123m}Te]THDA suggests that significant deiodination does

Table I. Distribution of Radioactivity in Tissues of Fischer 344 Female Rats Following Intravenous Administration of 17-[^{131}I]Iodo-9-telluraheptadecanoic Acid[a]

time after injection	mean percent injected dose/gram (range)						
	heart	blood	lungs	liver	kidneys	thyroid	brain
2 min	2.39 (1.56–3.21)	1.28 (1.13–1.40)	1.40 (1.18–1.51)	3.71 (3.17–4.00)	1.36 (1.22–1.46)	6.27 (3.35–9.51)	0.17 (0.13–0.20)
10 min	2.01 (1.39–2.49)	0.88 (0.81–0.93)	1.11 (1.03–1.24)	3.23 (2.97–3.44)	1.14 (1.00–1.36)	12.1 (5.8–17.3)	0.11 (0.10–0.12)
30 min	1.78 (1.75–1.84)	0.72 (0.65–0.81)	0.85 (0.81–0.88)	1.75 (1.66–1.80)	0.80 (0.77–0.86)	41.9 (31.9–49.9)	0.06 (0.06–0.06)
60 min	1.86 (1.54–2.09)	0.64 (0.56–0.75)	0.75 (0.62–0.87)	1.16 (0.92–1.32)	0.68 (0.60–0.79)	74.7 (38.3–122.7)	0.05 (0.04–0.05)
2 h	1.33 (1.15–1.61)	0.61 (0.57–0.68)	0.68 (0.64–0.69)	1.02 (0.57–1.22)	0.54 (0.52–0.56)	166 (93–238)	0.04 (0.04–0.04)
6 h	0.57 (0.51–0.63)	0.44 (0.39–0.47)	0.48 (0.42–0.52)	0.51 (0.47–0.62)	0.36 (0.35–0.38)	184 (131–212)	0.03 (0.25–0.04)
24 h	0.11 (0.09–0.12)	0.08 (0.07–0.07)	0.18 (0.18–0.19)	0.13 (0.11–0.13)	0.08 (0.08–0.08)	475 (306–786)	0.03 (0.01–0.05)
4 days	0.04 (0.02–0.05)	0.02 (0.02–0.02)	0.06 (0.05–0.07)	0.02 (0.02–0.03)	0.03 (0.02–0.03)	226 (182–299)	<0.007
7 days	0.016 (0.014–0.017)	0.009 (0.008–0.010)	0.031 (0.022–0.038)	0.014 (0.013–0.016)	0.016 (0.012–0.018)	203 (163–258)	<0.002

[a] Four rats were used at each time period. Other tissues that were analyzed include the spleen and large and small intestines. Each rat received ~3 μCi of the ^{131}I-labeled fatty acid (sp act. ~20 mCi/mmol) administered by injection in a lateral tail vein in 6% bovine serum albumin solution (0.5 mL).

not precede myocardial uptake. In addition, these results indicate that the presence of the terminal iodide must be responsible for the decreased myocardial uptake in comparison with 9-THDA. The extensive iodide loss from 17-[^{131}I]iodo-9-THDA is very similar to that observed in rats with 16-[^{131}I]iodohexadecanoic acid (Figure 1). Therefore, the myocardial uptake of 17-[^{131}I]iodo-9-THDA cannot be accurately measured unless corrections are employed for the presence of the free radioiodide in the blood. Nevertheless, these results provide insight to several important questions regarding the mechanism of deiodination of radioiodinated terminal iodoalkyl-substituted long-chain fatty acids.

The much slower thyroid accumulation of radioactivity following injection of the two radioiodinated fatty acids in comparison to the Na–^{131}I control study (Figure 2) indicates that loss of radioiodide from the fatty acids is not an initial rapid reaction. The deiodination observed with 16-[^{131}I]iodohexadecanoic acid could result from direct cleavage of the carbon–iodine bond, loss of iodide from the labile β position of the expected β-iodoacetylcoenzyme A final catabolite, or from a combination of these two processes. Loss of iodide from β-iodoacetylcoenzyme A formed from degradation of 17-iodo-9-THDA would not occur, since β-oxidation would not be expected to proceed beyond the tellurium heteroatom. The results of these studies strongly suggest that deiodination of the terminal iodinated alkanoic acids, such as 16-iodohexadecanoic acid and 17-iodoheptadecanoic acid, primarily results from direct cleavage of the carbon–iodine bond rather than iodide loss from the final degradation product. Until now, the relative contribution of iodide loss from these two processes has been only speculative.[2,14]

Conclusion

A new route has been developed for the synthesis of terminal radiohalogenated tellurium fatty acids. A model agent, 17-[^{131}I]iodo-9-THDA, shows significant myocardial uptake but also suffers extensive in vivo deiodination in rats.

Studies now in progress include an evaluation of radiobrominated tellurium fatty acids, such as 17-[^{82}Br]-bromo-9-THDA, because of the expected greater stability of the carbon–bromine bond. In addition, the ^{75}Br- and ^{77}Br-labeled analogues may be useful for evaluation of myocardial fatty acid metabolism by positron emission tomography. An additional goal is chemical stabilization of the iodine on the tellurium fatty acid molecule. Two approaches that are being pursued are the fabrication of model Te fatty acids containing terminal vinyl iodide and *p*-iodophenyl substituents.

Experimental Section

The melting points were determined in capillary tubes using a Buchi SP apparatus and are uncorrected. Thin-layer chromatographic analyses were performed using 250-μm thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.). The infrared spectra (IR) were recorded on a Beckman 18-A spectrophotometer with NaCl plates or KBr pellets. The low-resolution mass spectra (MS) were recorded using the Oak Ridge National Laboratory low-resolution instrument under the following conditions: ionizing energy, 70 eV; accelerating potential, 8000 V; trap current, 100 μA; probe temperature, 200–300 °C. The proton nuclear magnetic resonance spectra (NMR) were obtained at 60 MHz with a Varian 360-L instrument or at 190 MHz with a Nicolet high-resolution instrument. Samples (30–40 mg) were dissolved in deuteriochloroform, and the resonances are reported downfield (δ) from the internal tetramethylsilane standard.

Materials. Tellurium metal was purchased from Alpha Inorganics and was ground to a fine 45-μm powder before use. Dimethylformamide (DMF) was analytical grade and was stored

Table II. Distribution of Radioactivity in Tissues of Fischer 344 Female Rats Following Intravenous Administration of 17-Iodo-9-[^{123m}Te]telluraheptadecanoic Acid[a]

time after injection	mean percent injected dose/gram (range)				
	heart	blood	lungs	liver	kidneys
5 min	1.38 (1.07-1.60)	0.13 (0.10-0.17)	0.67 (0.62-0.71)	3.33 (3.01-3.89)	1.17 (1.05-1.25)
30 min	2.24 (1.49-3.22)	0.36 (0.32-0.38)	0.62 (0.57-0.67)	2.11 (1.92-2.40)	1.05 (0.98-1.14)
60 min	1.58 (1.18-1.74)	0.25 (0.23-0.27)	0.56 (0.51-0.62)	1.65 (1.47-1.82)	0.99 (0.94-1.09)

[a] Four rats were used at each time period. Other tissues that were analyzed include the spleen, brain, and large and small intestines. Each rat received ~2.5 μCi of the ^{123m}Te-labeled fatty acid (sp act. ~16 mCi/mmol) administered by injection in a lateral tail vein in 6% bovine serum albumin solution.

over 4A molecular sieves 24 h prior to use. All other chemicals and solvents were analytical grade and were used without further purification. The sodium [^{131}I]iodide (4.87 mCi) was purchased from New England Nuclear, Inc. (North Billerica, MA). The specific activity of the no carrier added radioiodide was adjusted to 48.7 mCi/mmol prior to use.

Animal Tissue Distribution Experiments. The distribution of radioactivity was determined in tissues of 10–12 week old female Fischer 344 rats (170–200 g) after intravenous administration of the labeled fatty acid. The animals were allowed food and water ad libitum prior to and during the course of the experiment. The radioiodinated fatty acid was dissolved in 0.5 mL of absolute ethanol and added dropwise to a stirred solution of 6% bovine serum albumin at 40 °C. The final ethanol concentration was 10%. The solution was filtered through a 22-μM Millipore filter and injected via a lateral tail vein into the ether-anesthetized animals. The animals were anesthetized with CO_2 and killed by cervical fracture, and the organs were excised, rinsed, and blotted to remove adhering blood. The organs were then placed in tared vials. The vials were weighed, the radioactive contents were determined in a multichannel Ge(Li) analyzer, and the percent injected dose per gram of tissue values were then calculated.

Syntheses. General Comments. All reactions were performed in an argon atmosphere under red lights in dry, three-necked flasks. The reaction vessel was fitted with a rubber septum and an argon-purged addition funnel for the introduction of reactants and was equipped with a magnetic stirrer. Condensers were protected with a $CaCl_2$ drying tube, and a slight positive argon atmosphere was maintaned by an oil pressure-release valve.

Bis(methyloctanoyl) Ditelluride (21). Tellurium metal (1.27 g, 10 mmol), sodium hydride (0.44 g, 11 mmol), and dry dimethylformamide (DMF, 50 mL) were stirred at 70 °C under an argon atmosphere for 3 h. The purple sodium ditelluride solution was cooled to room temperature, and a mixture of methyl 8-bromooctanoate (2.6 g, 11 mmol) in 10 mL of argon-purged dry DMF was added. The resulting mixture was stirred at room temperature for 60 min, cooled, poured into water (100 mL), and extracted several times with Et_2O. The combined orange-colored Et_2O extracts were washed thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the Et_2O was removed in vacuo to give a dark orange oil. The crude ditelluride was dissolved in C_6H_6 (3 mL) and applied to a silicic acid column (basic grade) slurried in $CHCl_3$. The column was eluted with $CHCl_3$, and fractions (100 mL) 6–10 were combined to give bis(methyloctanoyl) ditelluride (1.92 g, 68%) as a dark orange oil. Analysis by TLC (SiO_2-GF) in $CHCl_3$ (R_f 0.56) indicated the presence of a single component: IR (NaCl) 2960, 2915 (CH), 1750 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.38 (s, 14 H, CH_2), 1.64 (m, 6 H, CH_2), 2.33 (t, J = 3 Hz, 4 H, CH_2C=O), 3.15 (t, J = 4 Hz, 4 H, CH_2Te), 3.70 (s, 6 H, OCH_3); MS, m/z 444 (M^+ [^{130}Te], 3), 256 (M^+ [^{130}Te]$TeC_7H_{14}COOCH_3OCH_3$, 8), 157 (79). Anal. ($C_{18}H_{34}O_4Te_2$) C, H, Te.

Methyl 17-Bromo-9-telluraheptadecanoate (24). The ditelluride **21** (284 mg, 0.5 mmol), $NaBH_4$ (40 mg, 1 mmol), and 10 mL of absolute EtOH were stirred under an argon atmosphere at room temperature. After 15 min the vigorous evolution of hydrogen ceased, and a colorless solution of sodium (methyloctanoyl)tellurol (**22**) was obtained. The resulting solution was transferred with the aid of a syringe to an argon-purged dropping funnel and added dropwise over 30 min to solution of 1,8-dibromooctane (1.09 g, 4 mmol) in 50 mL of absolute EtOH. The solution was stirred under argon at room temperature for 3 h, poured into 100 mL of H_2O, and extracted several times with Et_2O. The combined Et_2O extracts were washed thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude product was dissolved in C_6H_6 (2 mL) and applied to a silicic acid column (acidic grade) slurried in petroleum ether (30–60 °C). Fractions (20 mL in volume) were eluted with petroleum ether (1–20) and C_6H_6 (21–30). Fractions 24–25 were combined to give methyl 17-bromo-9-telluraheptadecanoate (315 mg, 64%) as a colorless oil: IR (NaCl) 2930, 2860 (CH), 1790 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 18 H, CH_2), 1.76 (m, 6 H, CH_2), 2.35 (t, J = 3 Hz, 2 H, CH_2C=O), δ 2.65 (t, J = 4 Hz, 4 H, CH_2Te), 3.50 (t, J = 4 Hz, 2 H, CH_2Br), 3.65 (s, 3 H, OCH_3); MS, m/z 480 (M^+ [^{130}Te and ^{81}Br], 20), 399 (M^+ - Br, 78), 256 ($M^+ - C_8H_{16}BrOCH_3$, 20). Anal. ($C_{17}H_{33}O_2BrTe$) C, H.

Methyl 18-Iodo-9-telluraheptadecanoate (25). A mixture of **24** (200 mg, 0.43 mmol) and NaI (635 mg, 5 mmol) was refluxed for 4 h in 10 mL of acetone. The mixture was cooled to room temperature, poured into 50 mL of H_2O, and extracted several times with Et_2O. The combined Et_2O extracts were washed once with 50 mL of 10% sodium bisulfite and then thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the Et_2O was concentrated in vacuo to afford a colorless oil. The crude product was dissolved in C_6H_6 (2 mL) and applied to a silicic acid column (acid grade) slurried in C_6H_6. The column was eluted with C_6H_6, and fractions 24–25 (20 mL in volume) were combined to give **25** (167 mg, 73%) as a colorless oil. Analysis by TLC (SiO_2-GF) in C_6H_6 (R_f 0.44) indicated the presence of a single component: NMR ($CDCl_3$) δ 1.35 (s, 18 H, CH_2), 1.75 (m, 6 H, CH_2), 2.35 (t, J = 3 Hz, 2 H, CH_2C=O), 2.65 (t, J = 4 Hz, 4 H, CH_2Te), 3.10 (t, J = 3 Hz, 2 H, CH_2I), 3.65 (s, 3 H, OCH_3); MS, m/z 526 (M^+ [^{130}Te], 5), 399 (M^+ - I, 90), 256 ($M^+ - C_8H_{16}I - OCH_3$, 30). Anal. ($C_{17}H_{33}O_2ITe$) C, H.

17-Bromo-9-telluraheptadecanoic Acid (29). The orange-colored ditelluride **21** (284 mg, 0.5 mmol) was added to 20 mL of EtOH containing 4 mL of 1 N NaOH and gently refluxed for 1 h. After the mixture was cooled to room temperature, a solution of 1,8-dibromooctane (1.09 g, 4 mmol) in 46 mL of an EtOH–THF mixture (1:1) was added. Sodium tetrahydridoborate (148 mg, 4 mmol) was added in small portions to the reaction vessel, and a positive argon pressure was maintained throughout the reaction. The resulting mixture was stirred at room temperature for 3 h. The colorless solution was poured into 100 mL of H_2O and extracted several times with hexane. The aqueous layer was cooled to 0 °C and was acidified to pH 3 by careful addition of 10% H_2SO_4. The resulting mixture was extracted several times with Et_2O, the combined Et_2O extracts were washed thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the Et_2O was reduced in vacuo to afford a white solid. The crude product was crystallized from petroleum ether (30–60 °C) to give (270 mg, 29%) of **29**: mp 46–47 °C; analysis by TLC (SiO_2-GF) in MeOH–$CHCl_3$ (8:92) indicated the presence of a single component (R_f 0.5); NMR δ 1.30 (s, 18 H, CH_2), 1.65 (m, 6 H, CH_2), 2.30 (t, J = 3 Hz, 2 H, CH_2C=O), 2.50 (t, J = 4 Hz, 4 H, CH_2Te), 3.50 (t, J = 4 Hz, 2 H, CH_2Br); MS, m/z 466 (M^+ [^{130}Te and ^{81}Br], 385 (M^+ - Br, 74), 256 ($M^+ - C_8H_{16}Br$ - OH, 30). Anal. ($C_{16}H_{31}O_2BrTe$) C, H.

17-Iodo-9-telluraheptadecanoic Acid (26). Method A. A mixture of **29** (232 mg, 0.50 mmol) and NaI (635 mg, 5 mmol) were reacted as described above for **25**. The crude product was crystallized from petroleum ether (30–60 °C) to afford 163 mg (60%) of **26**: mp 60–62 °C; analysis by TLC (SiO_2-GF) in MeOH–$CHCl_3$ (8:92) indicated the presence of a single component (R_f 0.50); IR (NaCl) 2920, 2850 (CH), 1690 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 18 H, CH_2), 1.60 (m, 6 H, CH_2), 2.25 (t, J = 3 Hz, 2 H, CH_2C=O), 2.50 (t, J = 4 Hz, 4 H, CH_2Te), 3.10 (t, J = 3 Hz, 2 H, CH_2I); MS, m/z 512 (M^+ [^{130}Te], 20), 384 (M^+ - HI,

32), 256 ($M^+ - C_8H_{16}I - OH$, 10). Anal. ($C_{16}H_{31}O_2ITe$) C, H. Method B

The ditelluride **21** (2.84 mg, 0.5 mmol) and 1,8-diiodooctane (1.5 g, 4 mmol) were allowed to react according to the procedure for **29**. The crude product was crystallized from petroleum ether (30–60 °C) to afford 71 mg (20%) of **26**, mp 60–62 °C.

17-[^{131}I]Iodo-9-telluraheptadecanoic Acid. Sodium [^{131}I]-iodide (4.87 mCi, 15 mg, 0.1 mmol) and **29** (46 mg, 0.1 mmol) were refluxed in 15 mL of acetone as described for **25**. The dried ether extracts were concentrated by a stream of argon to give ^{131}I-labeled **26** (1.52 mCi, 30%). The radiochemical and chemical purity were confirmed by TLC (SiO_2-GF) in MeOH–$CHCl_3$ (8:92), R_f 0.50.

Bis(methoxyoctanoyl) [^{123m}Te]Ditelluride (21). Tellurium-123m metal (4.5 mCi, 63 mg, 0.5 mmol), sodium hydride (22 mg, 0.55 mmol), and methyl 9-bromooctanoate (130 mg, 0.55 mmol) were allowed to react as described for **21**. The $CHCl_3$ fractions were concentrated by a stream of argon to give ^{123m}Te-labeled **21** (400 μCi, 9%). The radiochemical and chemical purity were confirmed by TLC (SiO_2-GF) in $CHCl_3$ (R_f 0.56).

17-Iodo-9-[^{123m}Te]telluraheptadecanoic Acid. A mixture of ^{123m}Te-labeled **21** (400 μCi, 13 mg, 0.025 mmol) and 1,8-diiodooctane (1.0 g, 3.33 mmol) were allowed to react according to the procedure for **29**. The dried ether extracts were concentrated by a stream of argon to give ^{123m}Te-labeled **26** (165 μCi, 41%). The radiochemical and chemical purity were confirmed by TLC (SiO_2-GF) in MeOH–$CHCl_3$ (8:92), R_f 0.50.

16-[^{131}I]Iodohexadecanoic Acid.[16] Sodium [^{131}I]iodide (3.5 mCi, 15 mg, 0.1 mmol) and 18-bromohexadecanoic acid (35 mg, 0.1 mmol) were refluxed in 15 mL of acetone according to the procedure for **25**. The dried ether extracts were concentrated by a stream of argon to give 16-[^{131}I]iodohexadecanoic acid (2.46 mCi, 70%). The chemical and radiochemical purity were confirmed by TLC (SiO_2-GF) in MeOH–$CHCl_3$ (8:92), R_f (0.50).

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Potential Organ- or Tumor-Imaging Agents. 22. Acyl-Labeled Cholesterol Esters[1]

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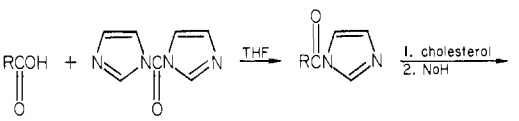
A series of cholesteryl phenylalkanoic esters was synthesized in which the acyl moiety served as the carrier for radioiodine. Tissue distribution studies in rats revealed that several of these radioiodinated esters selectively accumulated in steroid-secreting tissues, such as the adrenal cortex and ovary. Furthermore, this selective uptake was shown to correlate with the stability of these esters to in vivo hydrolysis. An unexpected finding was the unusually high propensity of some of these esters to localize in the ovary and thus afford a possible approach to ovarian imaging agents.

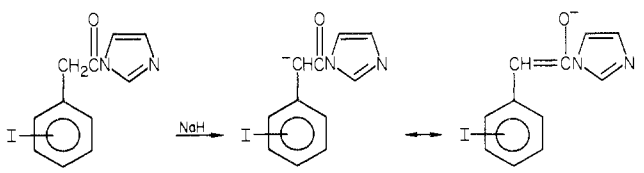
Cholesterol is the essential precursor for the biosynthesis of the steroid hormones. In the steroid-secreting endocrine glands, such as the adrenals and gonads, the three major sources of cholesterol are (1) the circulation, (2) intracellularly stored cholesterol ester, and (3) intracellular de novo synthesis from acetate (Figure 1). Moreover, recent studies have demonstrated that under normal circumstances lipoprotein-carried cholesterol derived from the plasma represents the major substrate for steroidogenesis in the adrenal[2,3] and ovaries.[4,5]

Radioiodinated derivatives of cholesterol[6-8] have been widely used as imaging agents for the diagnosis of a variety of human adrenal disorders.[9] Animal studies have revealed that 19-radioiodinated cholesterol rapidly becomes associated with plasma lipoproteins following intravenous

Scheme I. Synthesis of Cholesteryl Iodophenylalkanoates



Scheme II. Action of NaH on Iodophenylacetates



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