Effect of Tellurium Position on the Myocardial Uptake of Radioiodinated 18-Iodotellura-17-octadecenoic Acid Analogues

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The effect of tellurium (Te) position on myocardial specificity and retention of fatty acids in which radioiodide is stabilized as a *trans*-(*E*)-vinyl iodide has been evaluated in rats. Five analogues of 18-iodo-17-octadecenoic acid (ICH=CH–R–Te–R′–COOH) with Te at positions 5, 7, 9, 11, and 13 were prepared by coupling of a *trans*-diiodoalkene (ICH=CH–R–I) with the requisite sodium [(alkoxycarbonyl)alkyl]telluride substrate (NaTe–R′–COOR″; R″ = Me or Et), followed by basic hydrolysis. By varying R and R′, a series of analogues with a chain length of 18 carbon atoms was prepared. The telluride substrates were generated in situ by $NaBH_4$ reduction of the corresponding ditellurides, and the diiodoalkenes were prepared by sodium iodide–chloramine-T treatment of the corresponding vinylboronic acids [$(HO)_2$BCH=CH–R–I)]. The vinylboronic acids were prepared by treatment of the terminal acetylenes (HC≡C–R–I), synthesized from commercially available materials, with catecholborane. All new compounds were analyzed by TLC, NMR, MS, and elemental analyses. The ^{125}I analogues [(*E*)-^{125}ICH=CH–R–Te–R′–COOH] were prepared in the same manner and evaluated in rats (four per group). Heart uptake and retention were dependent upon the Te position. The analogue with Te at position 5 showed the most pronounced (5-min values) heart uptake (3.7–4.1 dose/g), myocardial retention, and heart/blood ratios (37:1) and is a candidate for radiolabeling with ^{123}I and further evaluation as a myocardial imaging agent.

Development of radiolabeled long-chain fatty acids for the evaluation of heart disease is of interest because of their potential use for measurement of myocardial fatty acid metabolism in relation to various disease states.[1,2] Because of the attractive physical properties of iodine-123 (159-keV γ photon, 13.2-h physical half-life) and the versatility of iodine chemistry, this radioisotope has been used to radiolabel a variety of fatty acids.[1,2] One approach involves the design of agents that are retained or "trapped" in the myocardium and exhibit only slow loss or "washout" from the heart muscle. Fatty acids containing the divalent tellurium (Te) heteroatom in the fatty acid chain show pronounced heart uptake in experimental animals and exhibit the unique property of slow myocardial washout.[1,3-5]

Tellurium can be readily incorporated while maintaining the linearity of the fatty acid molecule. The presence of the tellurium is a unique structural feature that results in the prolonged retention or "trapping" of the modified fatty acids in the myocardium by an unknown mechanism. A model agent, 9-telluraheptadecanoic acid (THDA, Chart I), is an isostere of oleic acid and has been studied most extensively.[3-5] Studies have shown that the *N*-chlorosuccinimide oxidation product of 9-THDA forms an insoluble material that is apparently a polymer.[6] A similar insoluble material may be the species that is irreversibly bound in the myocardial cells. The effects of chain length and Te position on the heart uptake of ^{123m}Te fatty acids in rats have also been investigated.[7] In the telluraheptadecanoic acid series, the 6-, 9-, and 10-telluraheptadecanoic acid analogues show optimal heart uptake and retention. In contrast, the 12- and 13-telluraheptadecanoic acid analogues, with Te close to the alkyl terminus, show lower heart uptake, more rapid myocardial washout, and high blood levels. These results demonstrate a dramatic relationship between heteroatom position and the biological properties of these agents.[7]

Radioiodinated tellurium fatty acids have also been investigated to take advantage of the attractive properties of ^{123}I. These "bifunctional" agents contain nonradioactive Te in the fatty acid chain, which results in prolonged myocardial retention, and the iodine radioisotope is used for imaging. The first radioiodinated agent, 17-[^{131}I]-iodo-9-telluraheptadecanoic acid, was prepared and evaluated in rats but showed significant in vivo deiodination,

Chart I. Structures of Radiolabeled Fatty Acids Developed for Applications in Nuclear Cardiology

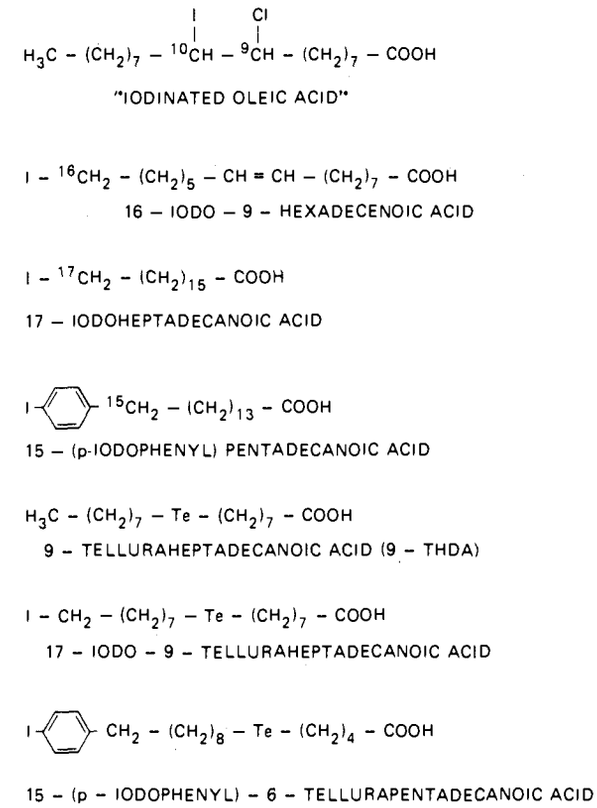

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Table I. Summary of Experimental Details for the Synthesis of the 18-Iodotellura-17-octadecenoic Acid Analogues 10a-d (Schemes I and II)

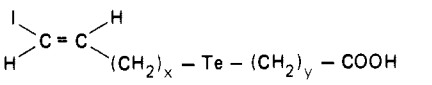
fatty acid	mp, °C	yield, %	diiodoalkene substrate (6)	ditelluride substrate (7)
10a	55-56	42	1,13-diiodo-12-tridecene	dimethyl 5,6-ditelluradecane-1,10-dioate
10b[a]	49-50	68	1,11-diiodo-10-undecene	dimethyl 7,8-ditelluratetradecane-1,14-dioate
10c	52-54	67	1,9-diiodo-8-nonene	dimethyl 9,10-ditelluraoctadecane-1,18-dioate
10d	gum	38	1,7-diiodo-6-heptene	dimethyl 11,12-ditelluradocosane-1,22-dioate
10e[a]	57-59	62	1,5-diiodo-4-pentene	dimethyl 13,14-ditellurahexacosane-1,26-dioate

[a] Data for these analogues are taken from ref 12 and are included here for comparison.

resulting in high blood levels of radioiodide and high thyroid uptake. These data indicated the necessity of chemical stabilization of the radioioidide to overcome iodide loss.[8] More recently, radioiodide has been successfully stabilized on 15-(*p*-iodophenyl)-6-telluraheptadecanoic acid (TPDA)[9] by attachment to the para-position of the phenyl ring. The synthetic method involved introduction of radioiodide by a triazene decomposition reaction. Both ^{125}I- and ^{131}I-labeled TPDA have been prepared and evaluated extensively in rats and exhibit the high heart uptake and prolonged retention described earlier for 9-THDA.[10,11] The low in vivo deiodination is exhibited by the persistent low blood and thyroid levels of radioiodide even 24 h after injection.

Fatty acids containing nonradioactive Te with radioiodide stabilized by attachment as a terminal vinyl iodide moiety have also been prepared.[12] The method developed for the preparation of this type of unique agent involved formation of 1-iodo-ω-enylboronic acids from the corresponding ω-iodo-1-acetylenes by treatment with catecholborane, followed by treatment with chloramine-T and NaI to give the 1,ω-diiodoalkenes. Coupling with a sodium alkyl tellurol then gave the alkyl ester of the iodovinyltellurium fatty acid, which was hydolyzed to the free acids. As an example, 18-[^{125}I]iodo-7-tellura-17-octadecenoic acid showed significant heart uptake in rats.[1,12] Low blood levels and marginal thyroid uptake demonstrate that introduction of the vinyl iodide moiety is an effective method of stabilizing the radioiodide in the Te fatty acid to overcome facile in vivo deiodination. An interesting observation in these studies was the effect of Te position on the biodistribution properties of the Te vinyl iodide fatty acids. The 18-[^{125}I]iodo-13-tellura-17-octadecenoic acid analogue, which has the same chain length but with Te in position 13, showed significantly reduced myocardial uptake and low heart/blood ratios.[1,12] The goals of the present investigation were to prepare additional analogues of 18-iodotellura-17-octadecenoic acid, with Te in the 5-, 9-, and 11-positions, and to investigate further the effects of Te position on myocardial uptake and retention properties of this important new class of myocardial imaging agents.

Chart II. Structures of 18-Iodotellura-17-octadecenoic Acid Analogues



NOTATION	ISOMER	X	Y
10a	5-TELLURA	11	3
10b	7-TELLURA	9	5
10c	9-TELLURA	7	7
10d	11-TELLURA	5	9
10e	13-TELLURA	3	11

Table II. Summary of Radiochemical Yields and Specific Activities of ^{125}I-Labeled 18-Iodotellura-17-octadecenoic Acid Analogues 10a-d (Chart II)

^{125}I-labeled fatty acid	Te position	sp act., mCi/mmol	radiochem yield, %
10a	5	125	27
10b[a]	7	20	21
10c	9	240	9
10d	11	182	32
10e[a]	13	20	55

[a] Data for these analogues are taken from ref 12 and are included here for comparison. [b] The radiochemical yields are calculated from the corresponding diiodoalkenes.

Results and Discussion

Chemistry. The three tellurium fatty acid analogues, 18-iodo-5-tellura-17-octadecenoic acid (**10a**), 18-iodo-9-tellura-17-octadecenoic acid (**10c**), and 18-iodo-11-tellura-17-octadecenoic acid (**10d**), were prepared as summarized in Scheme II. The route chosen for the preparation of the diiodoalkenes **6a–c**, involved transformation of the ω-hydroxyacetylenes **2a–c**, as summarized in Scheme I. The most direct route for preparation of the hydroxyacetylenes involved isomerization of commercially available 3-heptyn-1-ol (**1a**), 3-nonyn-1-ol (**1b**), and 2-tridecyn-1-ol (**1c**), using sodium 3-aminopropanamide, generated from sodamide treatment of 1,3-diaminopropane. Preparation of the *p*-toluenesulfonyl esters with *p*-toluenesulfonyl chloride–pyridine, followed by sodium iodide treatment, gave the iodoalkynes (**4a–c**) in 47–57% yield. Catecholborane treatment of **4a–c** in the usual manner[13] then gave the (iodoalkenyl)boronic acids (**5a–c**) in 76–85% yield. The boronic acids were smoothly converted to the diiodoalkenes **6a–c** by treatment with sodium iodide and chloramine-T.

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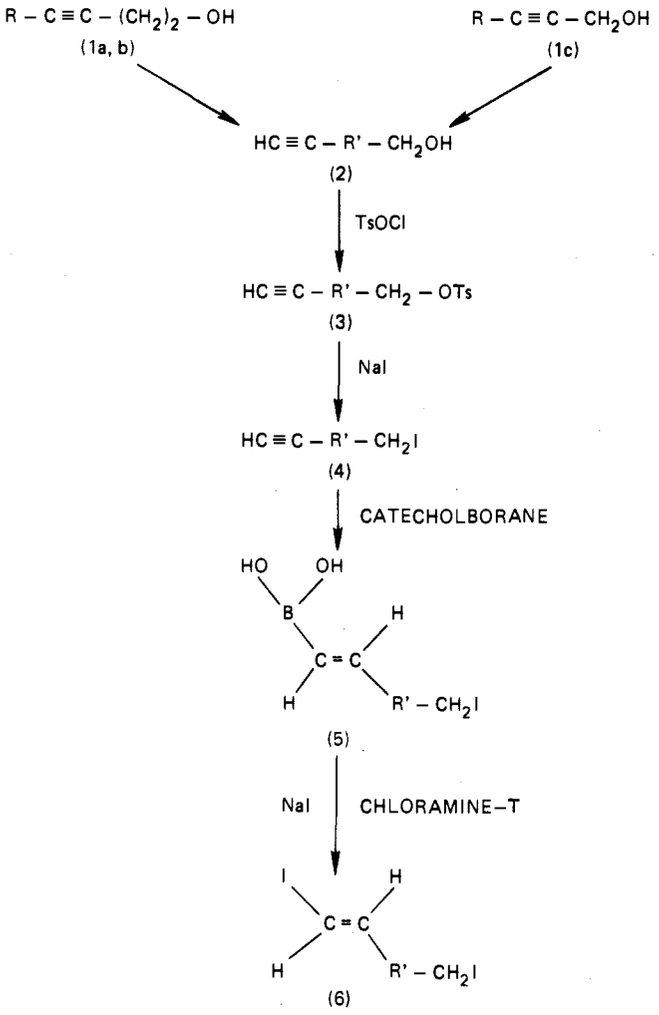
Table III. Distribution of Radioactivity in Tissues of Fischer 344 Female Rats Following Intravenous Administration of 18-[^{125}I]Iodo-5-tellura-17-octadecenoic Acid ([^{125}I]10a)[a]

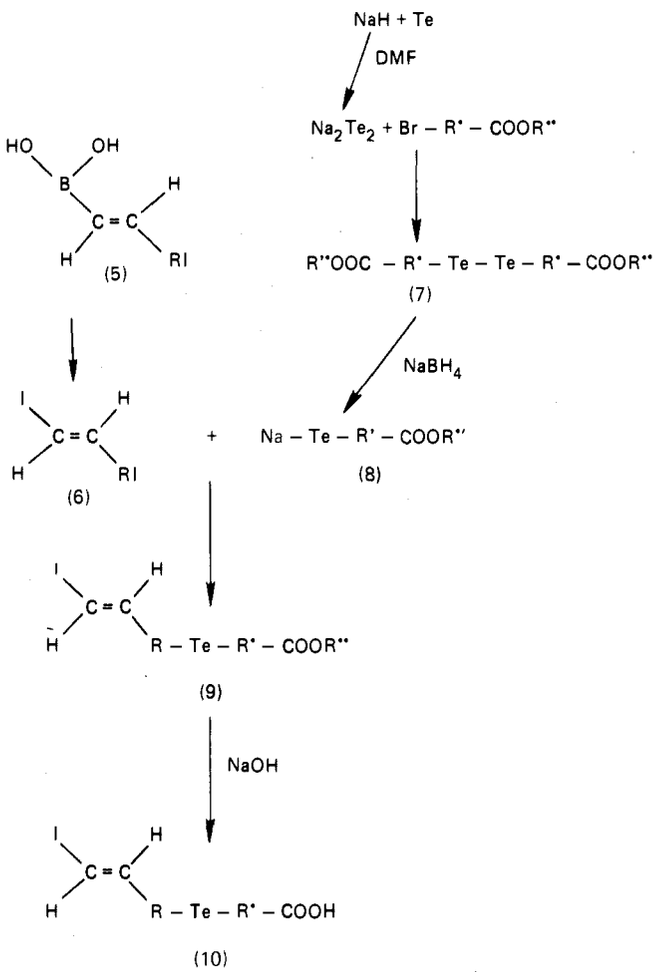
time after injection	mean % injected dose/g (range) in the following tissues					
	heart	blood	liver	lungs	kidney	thyroid
5 min	3.99 (2.13-5.43)	0.11 (0.10-0.12)	6.56 (5.12-8.74)	1.47 (1.02-2.15)	1.02 (0.78-1.37)	6.03 (5.04-7.53)
30 min	4.64 (3.91-5.91)	0.16 (0.13-0.17)	5.53 (4.92-6.53)	1.54 (0.97-1.98)	1.02 (0.96-1.06)	11.6 (8.9-17.1)
60 min	4.33 (3.52-5.65)	0.19 (0.19-0.19)	7.33 (6.33-8.20)	1.16 (0.97-1.39)	1.16 (0.98-1.24)	14.1 (13.3-14.8)
4 h	3.57 (2.64-4.78)	0.19 (0.15-0.25)	4.76 (3.46-6.47)	0.92 (0.84-1.06)	0.84 (0.69-1.10)	42.1 (24.8-62.2)
1 d	3.96 (3.88-4.04)	0.18 (0.17-0.19)	3.64 (3.07-4.20)	0.71 (0.67-0.74)	0.51 (0.42-0.60)	283 (263-303)

[a] Four rats were used for each time period. Each rat received ~4.8 μCi of the ^{125}I-labeled fatty acid (sp act. ~125 mCi/mmol) administered by injection in a lateral tail vein in 6% bovine albumin solution (0.5 mL).

Scheme I



Scheme II



The diiodoalkenes were then coupled with the requisite sodium (alkoxycarbonyl)alkyl telluride substrates (8; Scheme II), to provide the crude alkyl 18-iodotellura-17-octadecenoates (**10a,c,d**), which were purified by silicic acid column chromatography. The tellurides (8) were generated by in situ $NaBH_4$ reduction of the dialkyl ditelluraalkanedioates (7), which were prepared by alkylation of Na_2Te_2 with alkoxycarbonyl-ω-bromoalkanes. The esters (**10a,c,d**) were obtained in 50–70% yield after purification and converted to the 5-, 9-, and 11-tellura-18-iodo-17-octadecenoic acids (**10a,c,d**) by basic hydrolysis. The details of the preparation of these analogues are summarized in Table I.

The ^{125}I-labeled tellurium fatty acids **10a,c,d** were prepared in the same manner by Na^{125}I conversion of the (iodoalkenyl)boronic acids (5; Scheme I), followed by coupling with the telluride, purification of the alkyl ester, and hydrolysis with base. The ^{125}I-labeled fatty acids were obtained in 10–55% yield (Table II). The 5-, 9-, and 11-tellura analogues were evaluated in rats in the same manner described earlier for the 7- and 13-tellura agents. This series of five analogues, in which the total chain length was the same, allowed a detailed investigation of the effects of the Te position on the heart uptake and retention of this unique series of model compounds.

Biological Studies. The ^{125}I-labeled analogues were complexed with bovine serum albumin and injected intravenously into female Fischer rats. All three analogues (Tables III–V) showed rapid and pronounced heart uptake with high retention for the initial 4-h period of the study. The major difference detected was the degree of retention of radioactivity in the blood and the resulting heart/blood ratios. The data for the ^{125}I-labeled 5-, 9-, and 11-tellura analogues (**10a,c,d**) prepared in the present study are compared with data reported earlier[12] for the 7- and 13-tellura (**10b,e**) analogues in Table VI. A dramatic rela-

Table IV. Distribution of Radioactivity in Tissues of Fischer 344 Female Rats Following Intravenous Administration of 18-[^{125}I]Iodo-9-tellura-17-octadecenoic Acid ([^{125}I]10c)[a]

time after injection	mean % injected dose/g (range) in the following tissues					
	heart	blood	liver	lungs	kidney	thyroid
5 min	4.83 (4.02-6.25)	0.23 (0.20-0.24)	6.41 (4.79-7.54)	1.63 (1.52-1.76)	1.58 (1.35-1.73)	9.21 (8.56-10)
30 min	3.76 (3.11-4.28)	0.45 (0.34-0.61)	5.69 (4.26-6.42)	1.52 (1.31-1.60)	1.38 (1.20-1.55)	15.0 (12.7-18.1)
60 min	5.17 (4.47-5.66)	0.36 (0.34-0.38)	4.87 (4.53-5.53)	1.57 (1.07-2.10)	1.52 (1.37-1.64)	24.8 (21.9-30.4)
2 h	3.90 (3.56-4.26)	0.44 (0.41-0.45)	4.66 (4.33-5.14)	1.43 (1.19-1.64)	1.27 (1.12-1.38)	38.5 (24.5-56.4)
4 h	3.51 (2.72-3.99)	0.53 (0.51-0.56)	3.76 (2.97-4.58)	1.21 (1.16-1.45)	1.19 (1.18-1.21)	66.9 (57.5-87.9)
1 d	0.86 (0.70-1.04)	0.46 (0.38-0.51)	1.64 (1.40-2.22)	0.55 (0.50-0.57)	0.59 (0.54-0.64)	294 (199-405)
3 d	0.28 (0.27-0.29)	0.21 (0.20-0.21)	0.64 (0.62-0.68)	0.34 (0.32-0.37)	0.22 (0.21-0.23)	267 (227-394)

[a] Four rats were used for each time period. Each rat received ~8.8 μCi of the ^{125}I-labeled fatty acid (sp act. ~240 mCi/mmol) administered by injection in a lateral tail vein in 6% bovine albumin solution (0.5 mL).

Table V. Distribution of Radioactivity in Tissues of Fischer 344 Female Rats Following Intravenous Administration of 18-[^{125}I]Iodo-11-tellura-17-octadecenoic Acid ([^{125}I]10d)[a]

time after injection	mean % injected dose/g (range) in the following tissues					
	heart	blood	liver	lungs	kidney	thyroid
5 min	3.09 (2.68-3.60)	0.45 (0.41-0.55)	8.33 (5.46-10.30)	2.49 (1.96-2.89)	2.22 (2.05-2.49)	29 (26-35)
30 min	3.05 (2.65-3.95)	0.66 (0.62-0.69)	6.49 (5.61-8.10)	2.06 (1.81-2.20)	1.85 (1.71-2.12)	29 (24-33)
60 min	3.63 (3.02-4.38)	0.67 (0.62-0.74)	5.15 (4.19-7.20)	2.07 (1.59-2.78)	1.92 (1.66-2.07)	37 (32-44)
2 h	3.80 (2.47-6.89)	0.81 (0.79-0.84)	3.47 (2.96-4.24)	2.02 (1.22-3.40)	1.51 (1.26-1.71)	45 (32-55)
4 h	2.44 (1.78-3.26)	1.03 (0.91-1.11)	2.52 (2.11-2.98)	1.59 (1.48-1.73)	1.42 (1.18-1.69)	72 (70-75)
1 d	0.69 (0.65-0.72)	0.62 (0.56-0.65)	0.52 (0.46-0.56)	0.76 (0.67-0.84)	0.62 (0.54-0.67)	221 (178-259)
3 d	0.34 (0.26-0.44)	0.34 (0.19-0.26)	0.19 (0.13-0.24)	0.32 (0.26-0.43)	0.21 (0.19-0.24)	227 (202-344)

[a] Four rats were used for each time period. Each rat received ~4.3 μCi of the ^{125}I-labeled fatty acid (sp act. ~182 mCi/mmol) administered by injection in a lateral tail vein in 6% bovine albumin solution (0.5 mL).

Table VI. Comparison of the Heart Uptake (Percent Injected Dose/Gram) Values and Mean Heart/Tissue Ratios Determined After Intravenous Administration of ^{125}I-Labeled Analogues of 18-Iodotellura-17-octadecenoic Acid to Female Fischer Rats

^{125}I-labeled fatty acid	minutes after injection	heart uptake: % injected dose/g (range)	mean heart/tissue ratios[a]			
			blood	liver	lungs	kidneys
10a	5	3.99 (2.13-5.43)	37	0.60	2.7	3.9
	30	4.64 (3.91-5.91)	30	0.84	3.0	4.6
	60	4.33 (3.52-5.65)	23	0.59	3.7	3.7
	120	3.57 (2.64-4.78)	20	0.74	3.6	4.0
	240	3.96 (3.08-4.04)	18	0.75	3.9	4.3
10b[b]	5	3.47 (2.82-4.15)	13	0.56	2.7	3.3
	30	2.78 (1.47-3.45)	13	0.49	2.9	3.1
	60	2.96 (2.47-3.94)	13	0.55	2.9	3.1
	120	2.86 (2.71-2.96)	12	0.59	2.9	3.3
	240	2.37 (1.76-3.14)	8	0.54	2.8	3.1
10c	5	4.83 (4.02-6.25)	21	0.75	2.9	3.1
	30	3.76 (3.11-4.28)	8	0.66	2.5	3.7
	60	5.17 (4.47-5.66)	14	1.06	3.3	3.4
	120	3.90 (3.56-4.26)	9	0.84	2.7	3.1
	240	3.51 (2.72-3.99)	4	0.93	2.9	2.9
10d	5	3.09 (2.98-3.60)	7	0.37	1.2	1.4
	30	3.05 (2.65-3.95)	5	0.47	1.6	1.5
	60	3.63 (3.02-4.38)	5	0.70	1.8	1.0
	120	3.80 (2.47-6.89)	5	1.10	1.9	2.5
	240	2.44 (1.78-3.26)	2	0.97	1.5	1.7
10e[b]	5	1.46 (1.28-1.58)	8	0.17	1.6	1.5
	30	1.52 (1.23-1.65)	2.5	0.29	1.7	1.5
	60	1.81 (1.47-2.52)	2.6	0.41	1.6	1.6
	120	1.03 (0.89-1.17)	1.5	0.42	1.3	1.1
	240	0.76 (0.71-0.80)	1.2	0.39	1.1	1.9

[a] The mean heart/tissue values are calculated from the mean percent injected dose per gram of tissue values. [b] These values for the 7-tellura (10b) and 13-tellura (10e) analogues are taken from ref 12.

tionship is seen between heart uptake, myocardial retention, and heart/blood ratios and the position of the Te heteroatom.

Conclusion

The results of these studies have demonstrated the dramatic effect of the position of the tellurium heteroatom on the heart specificity of a series of five analogues of 18-[^{125}I]iodotellura-17-octadecenoic acid with Te in position 5, 7, 9, 11, or 13. The 5-tellura analogue shows the highest myocardial uptake. Although the mechanism on the molecular level for the effect of Te position on myocardial uptake has not yet been elucidated, our studies of the chemical oxidation of model Te fatty acids indicates that oxidation forms insoluble dihydroxy tellurium species.[6] It could be that these species are formed in vivo and that the position of the Te may effect the properties of similar oxidation products.

The structural features of this type of vinyl iodide–tellurium fatty acid have thus been optimized, and the

5-tellura analogue labeled with iodine-123 is a candidate for further preclinical testing. Since 18-[^{125}I]iodo-5-tellura-17-octadecenoic acid (**10a**) shows the highest heart uptake and optimal heart/blood ratios of the five analogues evaluated (Table III), studies are now directed at radiolabeling this agent with iodine-123 ($t_{1/2}$ = 13 h) for imaging studies in dogs.

Experimental Section

Materials. Dimethylformamide (DMF) was analytical grade and was stored over 4Å molecular sieves 24 h prior to use. The 10-bromodecanoic acid, 8-bromooctanoic acid, and ethyl 4-bromobutyrate were purchased from K&K Laboratories (Plainview, NY). The free acids were converted to the methyl esters with diazomethane. The sodium hydride (NaH) was obtained from Alfa Inorganics (Danvers, MA), and the 3-heptyn-1-ol, 3-nonyn-1-ol, and 2-tridecyn-1-ol substrates were purchased from Strem Chemicals, Inc. (Newburyport, MA).

All other solvents and chemicals were analytical grade and were used without further purification. The Na^{125}I was obtained from New England Nuclear Corp. (North Billerica, MD). The silicic acid (acidic grade, 60–200 mesh) used for column chromatography was obtained from Sigma Chemical Co. (St. Louis, MO). The thin-layer chromatographic analyses (TLC) were performed with 250-μm thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.) using the solvent systems indicated. The melting points were determined in capillary tubes on a Buchi SP apparatus and are uncorrected. The low-resolution mass spectra (MS) were recorded with a Kratos MS-25 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. Samples (30–40 mg) were dissolved in the solvents indicated, and the resonances are reported in parts per million (ppm) downfield (δ) from the internal tetramethylsilane standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Where analyses are indicate by only the symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical values.

Animal Tissue Distribution Experiments. The tissue distribution studies were performed on 10–12 week old female Fischer 344 rats (170–200 g). The animals were allowed food and water ad libitum prior to and during the course of experiments. 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 ether-anesthetized animals. After the time intervals indicated in Tables III–VI, the animals were killed by cervical fracture, and blood samples were obtained by cardiac puncture. The organs were then removed, rinsed with 0.9% saline solution, and blotted dry to remove residual blood. The organs were weighed and counted in a NaI autogamma counter (Packard Instruments). Samples of the injected radioactive solutions were also assayed as standards to calculate the percent injected dose per gram of tissue values. The weight of the thyroid glands was calulated in the usual manner by multiplying the animal weight by 7.5 mg/100 g.[14]

Synthesis. General Comments. All reactions involving the tellurium compounds were performed in an argon atmosphere under red lights in 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 maintained by an oil pressure-release valve. The boronic acids were prepared by the reaction of alkynes with catecholborane, followed by aqueous hydrolysis of the borole product as described previously.[12] The crystalline boronic acids were collected by filtration, washed with water and benzene to remove catechol, dried, and stored in the refrigerator (0 °C). The boronic acids were iodinated[12] in the dark with sodium iodide and chloramine-T in 50% aqueous THF. The iodinated product, the vinyl iodide, was extracted with petroleum ether and then washed with water and dried (Na_2SO_4). The petroleum ether was evaporated under vacuum, and the crude vinyl iodide was purified by column chromatography using silica gel and petroleum ether.

6-Heptyn-1-ol (2a). 1,3-Diaminopropane (120 mL) was added to sodamide (5.85 g, 150 mmol) under nitrogen atmosphere. The ammonia was evaporated under reduced pressure using an aspirator while warming the flask to 50 °C in a water bath. The 3-heptyn-1-ol (Ia; 5.6 g, 50 mmol) was then added to the sodium 3-aminopropanamide in 1,3-diaminopropane, and the mixture was warmed to 80 °C for 2 h. The thick reaction mixture was cooled and poured into ice–H_2O (500 g) and acidified with dilute HCl, and the product was extracted into Et_2O (500 mL). The ethereal extract was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude alcohol, which was distilled under reduced pressure to give 4.0 g (71%) of the pure product: bp 105 °C (20 mm); NMR ($CDCl_3$) δ 1.5 (br s, 6 H, alkane), 1.93 (t, 1 H, HC≡C, J = 2.5 Hz), 2.2 (m, 2 H, CH_2CH_2O), 2.63 (s, 1 H, OH), 3.6 (t, 2 H, J = 6 Hz, CH_2O).

6-Heptyn-1-yl *p*-Toluenesulfonate (3a). The 6-heptyn-1-ol (5.6 g, 50 mmol) was reacted with *p*-toluenesulfonyl chloride (19.05 g, 100 mmol) in pyridine to give 11.6 g (87%) of the tosylate: NMR ($CDCl_3$) δ 1.46 (br s, 6 H, alkane), 1.9 (t, 1 H, HC≡C, J = 2.5 Hz), 2.13 (m, 2 H, H_2CCH_2O), 2.43 (s, 3 H, Ar-CH_3), 4.0 (t, 2 H, J = 6 Hz, CH_2O), 7.56 (A_2 X_2, 4 H, Ar H).

1-Iodo-6-heptyne (4a). The 6-heptyn-1-yl *p*-toluenesulfonate (10.64 g, 40 mmol) was treated with NaI (37.5 g, 200 mmol) in 2-butanone to give 7.3 g (82%) of the iodide: NMR ($CDCl_3$) δ 1.53 (br s, 6 H, alkane), 1.93 (t, 1 H, HC≡C, J = 2.5 Hz), 2.2 (m, 2 H, CH_2CH_2I), 3.16 (t, 2 H, J = 6 Hz, CH_2I). Anal. ($C_7H_{11}I$) C, H.

(*E*)-(1-Iodo-6-hepten-1-yl)boronic Acid (5a). Treatment of 1-iodo-6-heptyne (4.45 g, 20 mmol) with catecholborane under a nitrogen atmosphere by the general procedure described in detail earlier[12] gave 4.1 g (76%) of the boronic acid: NMR (acetone-d_6) δ 1.33 (br s, 6 H, alkane), 1.96 (m, 2 H, CH_2CH_2I), 3.16 (t, 2 H, J = 7 Hz, CH_2I), 5.33 (d, 1 H, HC≡C*H*B, J = 18 Hz), 6.5 (m, 1 H, *H*C≡CHB), 6.46 (s, OH). Anal. ($C_7H_{14}O_2BI$) C, H.

(*E*)-1,7-Diiodo-6-heptene (6a). The (1-iodo-6-hepten-1-yl)-boronic acid (0.53 g, 2 mmol) was treated with NaI (2 mmol) in the presence of chloramine-T (0.91 g, 4 mmol) to yield 500 mg (71%) of the diiodide after purification: NMR ($CDCl_3$) δ 1.4 (br s, 4 H, alkane), 1.93 (m, 4 H, HC≡CHC*H*$_2$, CH_2CH_2I), 3.16 (t, 2 H, J = 6 Hz, CH_2I), 5.96 (d, 1 H, HC≡C*H*I, J = 15 Hz), 6.5 (m, 1 H, C*H*CHI). Anal. ($C_7H_{12}I_2$) C, H.

8-Nonyn-1-ol (2b). The 3-nonyn-1-ol (**1b**; 7.0 g, 50 mmol) was reacted with sodium 3-aminopropanamide (150 mmol), prepared as described for the preparation of 6-heptyn-1-ol in 1,3-diaminopropane, to yield 5.2 g (74%) of 8-nonyn-1-ol: bp 68–69 °C (0.5 mm); NMR ($CDCl_3$) δ 1.36 (br s, 10 H, alkane), 1.9 (t, 1 H, HC≡C, J = 2.5 Hz), 2.1 (m, 2 H, CH_2CH_2O), 2.4 (s, 1 H, OH), 3.53 (t, 2 H, J = 6 Hz, CH_2O).

8-Nonyn-1-yl *p*-Toluenesulfonate (3b). The 8-nonyn-1-ol (7.0 g, 50 mmol) was treated with *p*-toluenesulfonyl chloride (19.05 g, 100 mmol) in pyridine to give 13.3 g (90%) of the tosylate: NMR ($CDCl_3$) δ 1.30 (br s, 10 H, alkane), 1.9 (t, 1 H, HC≡C, J = 2.5 Hz), 2.08 (m, 2 H, H_2CCH_2O), 2.41 (s, 3 H, Ar-CH_3), 3.95 (t, 2 H, J = 6 Hz, CH_2O), 7.5 (A_2X_2, 4 H, Ar H).

1-Iodo-8-nonyne (4b). The 8-nonyn-1-yl *p*-toluenesulfonate (7.35 g, 25 mmol) was refluxed with NaI in 2-butanone to give, after purification, 5.3 g (85%) of the pure iodide (**4b**): NMR ($CDCl_3$) δ 1.36 (br s, 10 H, alkane), 1.9 (t, 1 H, HC≡C, J = 2.5 Hz), 2.08 (m, 2 H, CH_2CH_2I), 3.13 (t, 2 H, J = 6 Hz, CH_2I). Anal. ($C_9H_{15}I$) C, H.

(*E*)-(1-Iodo-8-nonen-1-yl)boronic Acid (5b). The 1-iodo-8-nonyne (10.0 g, 40 mmol) was treated with catecholborane (5.45 mL, 50 mmol) and worked up after aqueous hydrolysis in the usual manner to give 9.8 g (83%) of the boronic acid: NMR (acetone-d_6) δ 1.33 (br s, 10 H, alkane), 2.0 (m, 2 H, CH_2CH_2I), 3.23 (t, 2 H, J = 7 Hz, CH_2I), 5.33 (d, 1 H, HC≡C*H*B, J = 18 Hz), 6.43 (m, 1 H, *H*C=CHB), 6.5 (s, OH). Anal. ($C_9H_{18}O_2BI$) C, H.

(*E*)-1,9-Diiodo-8-nonenene (6b). The (1-iodo-8-nonen-1-yl)boronic acid (592 mg, 2 mmol) was treated with NaI (2 mmol) in the presence of chloramine-T (0.91 g, 4 mmol) to yield 610 mg

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(80%) of the diiodide: NMR ($CDCl_3$) δ 1.3 (br s, 8 H, alkane), 1.96 (m, 4 H, HC=CHCH_2, CH_2CH_2I), 3.13 (t, 2 H, J = 6 Hz, CH_2I), 5.93 (d, 1 H, HC=C*H*I, J = 15 Hz), 6.46 (m, 1 H, C*H*=CHI). Anal. ($C_9H_{16}I_2$) C, H.

12-Tridecyn-1-ol (2c). 1,3-Diaminopropane (120 mL) was added to sodamide (5.85 g, 150 mmol) under N_2 atmosphere and heated at 50 °C for 1 h under reduced pressure using a water pump. The 2-tridecyn-1-ol (**1c**; 9.8 g, 50 mmol) was added and then heated to 80 °C for 2 h. After cooling, the reaction mixture was poured into ice–H_2O and extracted with Et_2O (2 × 250 mL). The Et_2O extracts were washed with dilute HCl to remove 1,3-diaminopropane, and the solvent was concentrated to yield 12-tridecyn-1-ol: yield 6.9 g (70%); NMR ($CDCl_3$) δ 1.26 (br s, 18 H, alkane), 1.83 (t, 1 H, J = 6 Hz, C≡CH), 2.0 (m, 2 H, CH_2CH_2O), 3.53 (t, 2 H, J = 6 Hz, CH_2O).

12-Tridecyn-1-yl Toluenesulfonate (3c). 12-Tridecyn-1-ol (9.8 g, 50 mmol) was dissolved in pyridine (50 mL) and added to a cooled (0 °C) solution of *p*-toluenesulfonyl chloride (19.05 g, 100 mmol) in 200 mL of pyridine. The contents were stirred at 10 °C for 24 h. Water was then added, and the product was extracted into Et_2O (2 × 200 mL). The ether extracts were treated with dilute HCl (10%) and dried over anhydrous K_2CO_3–Na_2SO_4, and the solvent was removed under reduced pressure to give the crude ester, 14.5 g (83%), which was used directly for the next reaction without further purification: NMR ($CDCl_3$) δ 1.22 (br s, 16 H, alkane), 1.8 (m, 2 H, CH_2C≡C), 1.9 (t, 1 H, J = 6 Hz, C≡CH), 2.2 (m, 2 H, CH_2CH_2O), 2.4 (s, 3 H, Ar-CH_3), 3.96 (t, 2 H, J = 6 Hz, CH_2O), 7.5 (A_2X_2, 4 H, Ar H).

1-Iodo-12-tridecyne (4c). 12-Tridecyn-1-yl *p*-toluenesulfonate (3.5 g, 10 mmol), NaI (7.5 g, 50 mmol), and 2-butanone (100 mL) were heated under reflux for 18 h on a steam bath. The excess butanone was removed by distillation, the reaction mixture was filtered, and the precipitate was washed with petroleum ether (30–60 °C) to extract the product. The combined organic layers were washed with H_2O (100 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The pure product was isolated by chromatography using 90% petroleum ether/ethyl acetate as eluent to yield 2.5 g (80%) of **4c**: NMR ($CDCl_3$) δ 1.3 (br s, 18 H, alkane), 1.91 (t, 1 H, HC≡C, J = 2.5 Hz), 2.16 (m, 2 H, CH_2CH_2I), 3.2 (t, 2 H, J = 6 Hz, CH_2I). Anal. ($C_{13}H_{23}I$) C, H.

(*E*)-(1-Iodo-12-tridecen-1-yl)boronic Acid (5c). Catecholborane (1.64 mL, 15 mmol) was added slowly to 1-iodo-12-tridecyne (3.06 g, 10 mmol) under N_2. The mixture was heated to 55 °C and stirred for 6 h. The reaction mixture was then cooled to 0 °C, ice–H_2O (100 mL) was added, and the mixture was stirred overnight. The resulting white solid was filtered and washed successively with H_2O (300 mL) and petroleum ether (50 mL) to give the boronic acid: yield 3.0 g (85%); NMR (acetone-d_3) δ 1.3 (br s, 16 H, alkane), 1.9 (m, 4 H C=CCH_2, CH_2CH_2I), 3.26 (t, 2 H, J = 7 Hz, CH_2I), 5.36 (d, 1 H, HC=C*H*B, J = 18 Hz), 6.43 (m, 1 H *H*C=CHB), 6.5 (s, OH). Anal. ($C_{13}H_{26}O_2IB$) C, H.

(*E*)-1,13-Diiodo-12-tridecene (6c). The (1-iodo-12-tridecen-1-yl)boronic acid (0.7 g, 2 mmol) was dissolved in 8 mL of 50% aqueous THF. Aqueous NaI (2 mL of 1 M solution) was added, and the mixture was cooled to 0 °C. Chloramine-T (0.91 g, 4 mmol, in 8 mL of 50% aqueous THF) was added and stirred for 15 min. Water (25 mL) was then added, followed by petroleum ether (50 mL). The mixture was filtered, and the organic layer separated and concentrated to yield the crude diiodide. Further purification by preparative TLC on silica gel GF (2000 μm) using petroleum ether/ethyl acetate (80:20) as the solvent gave 0.65 g (75%) as an oil: NMR ($CDCl_3$) δ 1.26 (br s, 16 H, alkane), 1.95 (br m, 4 H, C=CCH_2, CH_2CH_2I), 3.18 (t, 2 H, J = 6 Hz, CH_2I), 5.95 (d, 1 H, HC=C*H*I), 6.51 (m, 1 H, *H*C=CHI). Anal. ($C_{13}H_{24}I_2$) C, H.

General Procedure A. Synthesis of Ditelluride Intermediates (7a–C). The dimethyl 11,12-ditelluradocosane-1,22-dioate (**7a**) was prepared (Scheme II) by methyl 10-bromodecanoate (**20**) alkylation of Na_2Te_2 as described below. In a similar manner, dimethyl 9,10-ditelluraoctadecane-1,18-dioate (**7b**) was prepared by alkylation of Na_2Te_2 with methyl 8-bromooctanoate and diethyl 5,6-ditelluradecane-1,10-dioate (**7c**) by alkylation of Na_2Te_2 with ethyl 4-bromobutyrate (Table I).

A suspension of dry and finely powdered Te metal (1.27 g, 10 mmol) and sodium hydride (60% oil dispersion, 0.44 g, 11 mmol) in anhydrous DMF (50 mL) was stirred at 70 ± 2 °C (bath temperature) under an argon atmosphere for 5 h. The purple disodium ditelluride (Na_2Te_2) solution was cooled to room temperature, and an argon-purged solution of the alkyl ω-bromoalkanoate substrate (11 mmol) in DMF (10 mL) was added (Scheme I). The resulting reaction mixture was stirred at room temperature for 1 h and poured into cold H_2O (100 mL). The solution was extracted several times with Et_2O, and the combined ether extracts were washed thoroughly with H_2O, dried (Na_2SO_4), and evaporated under vacuum. The dark orange, oily residue thus obtained was applied to a silica gel column slurried in petroleum ether. The column was eluted with petroleum ether/$CHCl_3$ (1:1, v/v), and aliquots of the fractions were analyzed by TLC (solvent C_6H_6). The appropriate orange-colored fractions were combined and evaporated under vacuum to provide the dialkyl ditelluraalkanedioate products **7a–c** as deep orange oils.

General Procedure B. Synthesis of Alkyl (*E*)-18-Iodotellura-17-octadecenoate Analogues (9a,c,d; Scheme II). The ditelluride (**7a**, **7b**, or **7c**; 1 mmol) was dissolved in EtOH (5 mLe and cooled in an ice bath (5 ± 5 °C). A suspension of $NaBH_4$ in EtOH was saturated with argon and added gradually in small portions to the stirred reaction mixture. Immediate reduction of the ditelluride with evolution of hydrogen occurred on warming of the reaction mixture to room temperature. Additional $NaBH_4$ was added with stirring until the reaction mixture became colorless. The diiodoalkene substrate (**6a**, **6b**, or **6c**; 0.9 mmol) was dissolved in EtOH (~5 mL), saturated with argon, and added to the reaction solution, which was stirred at room temperature for 1 h. Water (50 mL) was then added, and the mixture was extracted with Et_2O (2 × 50 mL). The combined ether portion was dried (Na_2SO_4) and evaporated under vacuum. The oily residue was applied to a silica gel (Sigma Sil B-200) column slurried in petroleum ether, and the column was washed with petroleum ether (200 mL). Further elution with C_6H_6 removed the product as a colorless fraction followed by the orange-colored unreacted ditelluride. The column fractions were monitored by TLC (solvent C_6H_6). The colorless fractions containing the product were combined and evaporated to provide the alkyl (*E*)-18-iodotellura-17-octadecenoate analogues as syrups in 38–68% yield (Table I). The fatty acid esters were stored under argon in sealed vials at 0 °C.

General Procedure C. Synthesis of (*E*)-18-Iodotellura-17-octadecenoic Acid Analogues (10a,c,d; Scheme II). The ester (**9a,c,d**; 0.5 mmol) was dissolved in EtOH (10 mL), and a solution of NaOH (1 N, 2 mL) was then added. The mixture was refluxed in the dark under argon atmosphere for 30 min, H_2O (50 mL) was then added, and the mixture was extracted with Et_2O (2 × 50 mL). The Et_2O portion was discarded, and the aqueous layer was adjusted to pH 1 with 1 N HCl and extracted with Et_2O (2 × 50 mL). The Et_2O portion was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated under argon to provide a residue (syrup). Trituration of the residue with petroleum ether yielded the product as a crystalline solid (**10a,c**) or oil (**10d**). The free acids were crystallized from petroleum ether and gave sharp melting points (Table I). The products also showed a major spot on TLC analysis (SiO_2-G; solvent, 4% MeOH/$CHCl_3$), and the NMR and MS data were consistent with the structures **10a,d**, similar to that described earlier for **10b,e**.[12] The acid products were stored under argon in sealed vials at <0 °C.

General Procedure D. Preparation of (*E*)-1-[^{125}I]Diiodo-1-alkene Substrates (6a–c). A solution of the [(*E*)-iodo-1-alken-1-yl]boronic acid substrate (**5a–e**; 0.1 mmol) in THF (0.5 mL) was cooled in an ice bath and shielded from light. Sodium [^{125}I]iodide was combined with carrier NaI (15 mg, 0.1 mmol) in H_2O (0.5 mL) and added to the reaction mixture. After the addition of a solution of chloramine-T (45 mg, 0.2 mmol) in 50% aqueous THF (1 mL), the mixture was stirred in the dark. After 0.5 h, the solution was diluted with H_2O (25 mL) and extracted with petroleum ether (2 × 15 mL). The petroleum ether portion was washed with aqueous sodium metabisulfite solution (5%, 20 mL), followed by H_2O (2 × 20 mL), and dried (Na_2SO_4). The petroleum ether was evaporated under argon at 35–40 °C to yield (65 ± 5%) of the radioiodinated diiodoalkene. The products were homogeneous by TLC (SiO_2 GF; solvent, petroleum ether) and were used without purification. The crude radioiodinated compound was purified by passing through a column (1.2 × 30 cm)

packed with a silica gel slurry (75 mL) in petroleum ether. The column was eluted with petroleum ether to provide pure (*E*)-1-[^{125}I]diiodo-1-alkene, which cochromatographed with respective cold authentic sample. Recovery of the ^{125}I after column chromatography was generally 90%.

General Procedure E. Synthesis of Alkyl (*E*)-18-[^{125}I]-Iodotellura-17-octadecenoate Analogues 10a,c,d (Scheme II). The dialkyl ditelluraalkanedioate substrate (**7a**, **7c**, or **7d**; 0.1 mmol) was dissolved in EtOH (5 mL, and the corresponding sodium tellurol (**8a**, **8c**, or **8d**) was generated by $NaBH_4$ reduction under argon atmosphere. The [^{125}I]diiodoalkene substrate (**6a**, **6b**, or **6c**), obtained as described in procedure D, was dissolved in EtOH (2 mL) and added to the reaction mixture. The solution was stirred for 1 h in the dark at room temperature under argon atmosphere, diluted with 0.9% saline solution (25 mL), and extracted with Et_2O (2 × 25 mL). The ether portion was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated under argon at ~70 °C. The residue (syrup) was dissolved in petroleum ether and applied to a column packed with a silica gel slurry (~65 mL) in petroleum ether. The column was eluted with petroleum ether (ca. 180 mL) to remove the unreacted [^{125}I]diiodoalkene. The column was then eluted with C_6H_6, and fractions (18 mL each) were collected. The fractions (generally 3 to 7) containing the product, (*E*)-18-[^{125}I]iodotellura-17-octadecenoate (compared with cold authentic sample on TLC, SiO_2 GF in benzene), were collected and evaporated to provide (60 ± 5%) of the alkyl (*E*)-18-[^{125}I]-iodotellura-17-octadecenoate.

General Procedure F. Preparation of (*E*)-18-[^{125}I]Iodotellura-17-octadecenoic Acid Analogues (10a,c,d). The hydrolysis was performed as described in general procedure C. The ^{125}I-labeled fatty acid ester (**9a**, **9c**, or **9d**) obtained from general procedure E was dissolved in EtOH (10 mL) and refluxed for 1 h with 1 N NaOH (1 mL). Following dilution with H_2O (~50 mL), the mixture was cooled to room temperature and extracted with Et_2O. The ether extract was discarded, and the aqueous portion was adjusted to pH 1 with 1 N HCl and extracted with ether (2 × 25 mL). The ether portion was washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of the ether portion under argon at ~40 °C provided the ^{125}I-labeled fatty acid **10a**, **10c**, or **10d**, which was stored under argon at <0 °C.

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Registry No. **1a**, 14916-79-1; **1b**, 31333-13-8; **1c**, 51887-25-3; **2a**, 63478-76-2; **2b**, 10160-28-8; **2c**, 18202-11-4; **3a**, 87462-63-3; **3b**, 87462-64-4; **3c**, 87462-65-5; **4a**, 87462-66-6; **4b**, 87462-67-7; **4c**, 87462-68-8; **5a**, 87462-69-9; **5b**, 87462-70-2; **5c**, 87462-71-3; **6a**, 87462-72-4; **6a** (^{125}I labeled), 87462-75-7; **6b**, 87462-73-5; **6b** (^{125}I labeled), 87462-76-8; **6c**, 87462-74-6; **6c** (^{125}I labeled), 87462-77-9; **7a**, 87462-78-0; **7b**, 81579-34-2; **7c**, 87462-79-1; **8a**, 87462-80-4; **8c**, 87462-81-5; **9a**, 87462-82-6; **9c**, 87462-83-7; **10a**, 87462-84-8; **10c**, 87462-85-9; **10d**, 87462-86-0; **10a** (^{125}I labeled), 87462-87-1; **10b** (^{125}I labeled), 87462-88-2; **10c** (^{125}I labeled), 87462-89-3.

Electronic Structures of Cephalosporins and Penicillins. 15. Inductive Effect of the 3-Position Side Chain in Cephalosporins

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Induction appears to be the primary means by which the side chain at position 3 of the cephem nucleus influences the chemical reactivity of the β-lactam ring. In vitro antibacterial activity data suggest that when the cephalosporin is in the active site of the target bacterial enzymes, the presence of a leaving group in the side chain can promote inhibition.

It has long been known that electron-withdrawing groups on the 3-position of cephalosporins enhance antibacterial activity.[1] Linear relationships between inductive σ_I constants for several 3-substituents and various other physicochemical properties that reflect the reactivity of the β-lactam ring toward nucleophiles have been discussed.[2-4] As indicated in Figure 1, a number of properties of, or related to, the β-lactam ring are now known to correlate with antibacterial activity of the compounds.[4-10] These include the theoretical transition-state energy (TSE), the net atomic charge on the β-lactam carbonyl oxygen [$Q(O_9)$], and the overlap population of the β-lactam carbonyl [$n(C_8{=}O_9)$] (all computed for model cephem structures), as well as experimental alkaline hydrolysis rates and carbon-13 chemical-shift differences for C_3 and C_4 measured for cephalosporins.[4,10,11]

Intuitively, it is reasonable that because of the intervening enamine system, the inductive effects of the 3-position side chain would have a very important, even dominant, influence on the β-lactam ring. However, without adequate data, it is difficult to conclude definitely that the effect of the substituent is *purely* inductive.[3,12]

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