Articles

Myocardial Imaging Agents: Synthesis, Characterization, and Evaluation of (Z)- and (Z,E)-18-[^{82}Br]Bromo-5-tellura-17-octadecenoic Acids[†,⊥]

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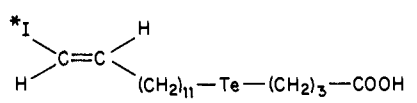
The effects of replacement of radioiodide with radiobromide on the biological properties of a model vinyl halide substituted tellurium fatty acid have been evaluated. The use of a facile radiobromination method involving the reaction of [^{82}Br]Br_2 with vinylmercuric bromide substrates has been investigated. Unexpectedly, both the *cis*- and *trans*-vinyl bromide products are formed as confirmed by chromatographic and spectral studies. With use of this technique, (*E*,*Z*)-1-[^{82}Br]bromo-13-iodo-1-tridecene was prepared and used as the substrate to prepare (*E*,*Z*)-18-[^{82}Br]bromo-5-tellura-17-octadecenoic acid (**13**-*E*,*Z*), which was evaluated in rats. Both [^{82}Br]-**13**-*E*,*Z* and [^{82}Br]-**13**-*Z*, prepared by an established procedure using *N*-chorosuccinimide–Br^- reaction with the *trans*-boronovinyl substrates, showed tissue distribution properties similar to those of (*E*)-18-[^{125}I]iodo-5-tellura-17-octadecenoic acid. These results demonstrate that replacement of I with Br and also the stereochemistry about the olefinic bond do not drastically affect heart uptake and retention.

The design and synthesis of various types of long-chain tellurium (Te) fatty acids which are retained (trapped) in the myocardium due to the unique properties of the Te heteroatom have been described.[1-11] In one group of radioiodinated Te fatty acids, several compounds were prepared having an 18-carbon chain length with radioiodide stabilized as a terminal vinyl iodide.[11] The analogue with Te in position 5, (*E*)-18-iodo-5-tellura-17-octadecenoic acid (1), showed the highest heart uptake (4.64% dose/g



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at 30 min) and heart:blood ratios (30:1 at 30 min), and excellent canine myocardial images have been obtained with use of iodine-123 and planar imaging techniques. As a result of the excellent biological properties exhibited by 1 and potential use of bromine radioisotopes as discussed below, the synthesis and tissue distribution of the corresponding brominated analogue are being studied. There are several attractive radionuclides of bromine for research and clinical studies.[12] Bromine-75 is a positron emitter with a half-life ($T_{1/2}$) of 101 min and decays with a high positron yield (76%). Bromine-76 ($T_{1/2}$ = 15.9 h) is also a positron emitter (yield 57%). Both these radionuclides are produced in medical cyclotrons, and there is widespread interest in their use for positron emission tomography (PET) studies. Bromine-82 (^{82}Br, $T_{1/2}$ = 35.7 h), although not useful for in vivo studies because of the high-energy γ photons (547 and 787 keV), is commercially available and has been used in the developmental studies reported here.

The availability of radiobrominated fatty acids that show high myocardial uptake and the low washout required for maximal reconstruction and extraction of quantitative data for PET studies is important for studies of myocardial metabolism and evaluation of the progression and management of acute infarction. Recent autoradiographic studies using hearts of hypertensive rats have demonstrated the heterogeneous distribution of radioiodinated fatty acids, such as 15-(*p*-[^{131}I]iodophenyl)-3-(*R*,*S*)-methylpentadecanoic acid, in regions of the myocardium having normal flow.[13] These important studies have demonstrated that some aspects of fatty acid delivery

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[⊥] Cis and *Z* and cis,trans and *Z*,*E* are used interchangeably.

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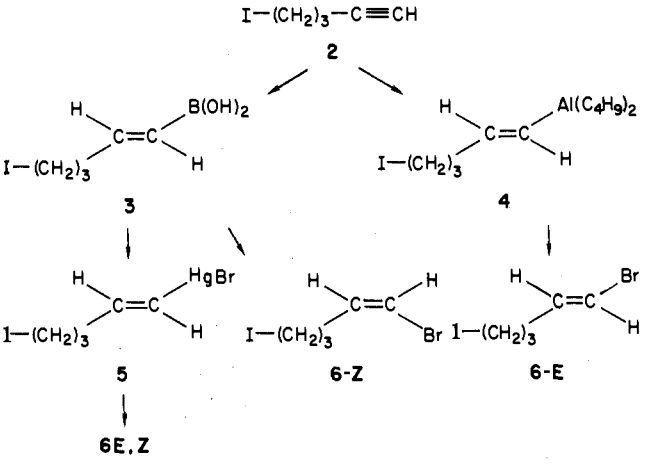
or metabolism can be uncoupled from blood flow. In addition, the use of radioiodinated tellurium (Te) fatty acids such as 15-(*p*-iodophenyl)-6-telluropentadecanoic acid to monitor the progression of acute ischemia after reflow following coronary artery occlusion in dogs has recently been demonstrated.[14] Both of these applications require minimal redistribution or "washout" of the radiotracer during the imaging period. These requirements are uniquely met by the properties of the Te fatty acids and indicate that positron emission tomography using bromine isotopes should be pursued to study these two important properties.

The bromine–carbon bond is generally stable in vivo and does not suffer the undesired dehalogenation observed with many alkyl iodide substituted agents. Stabilization of radiobromide as a vinyl bromide is thus not necessary to overcome radiobromide loss. It was the goal of the present studies, however, to evaluate the preparation of vinyl bromide agents for two reasons. First, from a structure–activity standpoint, such studies would allow a comparison of the tissue specificity of vinyl bromide substituted agents in comparison with the vinyl iodide analogues. These types of studies are important for a complete understanding of the factors affecting the biological properties of radiohalogenated agents. In addition, the preparation of vinyl bromides by the bromination/demercurybromination (bromodemercuration) reaction could offer a very simple alternative to other methods presently used for the preparation of radiobrominated agents.

The synthesis of (*E*)-(iodoalkyl)vinyl iodides by iododeboronation of the corresponding (*E*)-(iodoalkylvinyl)boronic acids using sodium iodide (NaI) and chloramine-T (C-T) has been reported.[11,15,16] Attempts to prepare the (*E*)-(iodoalkyl)vinyl bromides from the corresponding boronic acids using NaBr and C-T were unsuccessful, but the use of *N*-chlorosuccinimide (NCS) as the oxidizing agent provided the corresponding (*Z*)-vinyl bromides.[17] Reaction of (*E*)-vinylalanes (generated in situ from the corresponding alkynes) with Br_2 followed by acid hydrolysis proceeds with retention of stereochemistry and gives the (*E*)-vinyl bromides as the major product.[18] In a similar manner, reaction of Br_2 with (*E*)-vinyltrialkylsilanes with primary or secondary alkyl substitution proceeds with inversion of configuration.[19] The use of vinylmercuric halides for the preparation of vinyl halides is an alternative procedure. Treatment of the (*E*)-α,α'-bis[stilbene] with Br_2 in benzene has been reported to lead to formation of the corresponding (*E*)-bromostilbene with retention of the trans stereochemistry.[20] These literature reports of the reaction of bromine with substituted (*E*)-alkenylmercuric halides thus seem to indicate that the reactions proceed with retention of the stereochemistry about the double bond. With these facts in mind, the treatment of (*E*)-vinylmercuric bromides with radioactive bromine appeared to be a good alternative for the facile preparation of (*E*)-vinyl bromides. A variety of aromatic astatine compounds[21] and astatoimidazoles[22] have been prepared by using a similar approach via chloromercury intermediates.

Scheme I



Results and Discussion

Chemistry. For the synthesis of radiobrominated vinyl bromides, we have now studied the bromodemercuation of [(iodoalkyl)vinyl]mercury bromides prepared from the corresponding vinylboronic acids[23] (Scheme I). Our model studies involved transformations of (*E*)-(5-iodo-1-penten-1-yl)boronic acid (**3**) since this precursor was readily available in our laboratory.[10] Treatment of **3** with mercuric acetate readily formed (*E*)-(5-iodo-1-penten-1-yl)mercuric acetate, which was converted to the corresponding (*E*)-vinylmercuric bromide **5** by reaction with sodium bromide. Addition of 1 equiv of Br_2 to **5** in benzene at room temperature instantaneously provided 1-bromo-5-iodo-1-pentene (**6**) in 75% yield. The oily product exhibited one spot on thin-layer chromatographic analysis.

The proton nuclear magnetic resonance (NMR) analysis of the product **6**, however, indicated that reaction of **5** with Br_2 had led to the unexpected formation of a product apparently containing both the (*Z*)- and (*E*)-vinyl bromides. The *Z* isomer was synthesized from **3** with use of NaBr and NCS as described previously.[17] (*E*)-1-Bromo-5-iodo-1-pentene (**6-*E***) was synthesized by the addition of bromine to (*E*)-(5-iodo-1-penten-1-yl)diisobutylalane (**4**), which was generated in situ by the treatment of 5-iodo-1-pentyne (**2**) with diisobutylaluminum hydride.[18] The NMR of the crude product **6** demonstrated the presence of a downfield two-proton multiplet which was very similar to the multiplet pattern exhibited by a mixture of the **6-*Z*** and **6-*E*** isomers. In addition, the infrared (IR) spectrum of **6** was identical with the spectrum for the mixture of **6-*Z*** and **6-*E***. Gas–liquid chromatographic analysis of **6** confirmed the presence of two major peaks corresponding in retention times to **6-*Z*** (~60%) and **6-*E*** (~40%).

Carbon-13 nuclear magnetic resonance (^{13}C NMR) analysis of the *Z* isomer, **6-*Z***, which was prepared by established procedures, and the mixture of *Z* and *E* isomers

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Table I. Distribution of Radioactivity in Tissues of Female Fischer 344 Rats after Intravenous Administration of *cis*-18-[^{82}Br]Bromo-5-tellura-17-octadecenoic Acid (13-*Z*)[a]

tissue	mean (range) % injected dose/g of tissue			
	5 min	30 min	1 h	2 h
heart	2.77 (2.12–3.22)	2.51 (1.52–3.16)	3.01 (1.93–3.65)	2.56 (2.07–3.50)
blood	0.13 (0.12–0.15)	0.61 (0.46–0.90)	0.43 (0.37–0.48)	0.46 (0.41–0.52)
lungs	1.26 (1.21–1.34)	1.53 (1.34–1.64)	1.61 (1.29–2.08)	1.49 (1.43–1.55)
liver	7.33 (6.86–7.98)	6.13 (5.46–7.00)	5.47 (5.10–5.89)	5.00 (4.27–5.30)
kidney	1.62 (1.51–1.72)	1.49 (1.41–1.55)	1.53 (1.43–1.63)	1.34 (1.12–1.44)
thyroid	7.56 (6.26–9.31)	10.86 (9.04–15.08)	9.26 (7.99–11.08)	9.52 (8.79–10.55)
mean heart–blood	21:1	4:1	7:1	6:1

[a] These values represent the mean and range for five rats.

Table II. Distribution of Radioactivity in Tissues of Female Fischer 334 Rats after Intravenous Administration of 18-[^{82}Br]Bromo-5-tellura-17-octadecenoic Acid (13-*E,Z*)[a]

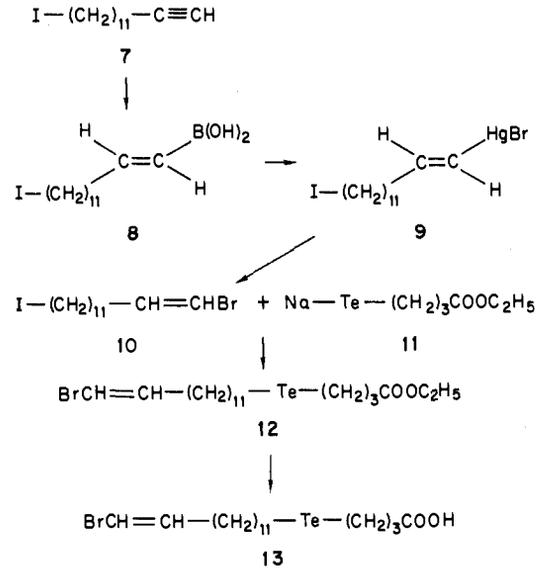
tissue	mean (range) % injected dose/g of tissue: tissue			
	5 min	30 min	1 h	1 d
heart	3.28 (2.82–4.09)	3.79 (3.36–4.27)	3.47 (3.34–3.63)	2.60 (1.95–3.23)
blood	0.18 (0.11–0.22)	0.34 (0.34–0.37)	0.39 (0.34–0.45)	0.88 (0.82–0.91)
lung	1.91 (1.20–2.38)	2.08 (1.95–2.19)	1.88 (1.59–2.56)	1.48 (1.37–1.78)
liver	6.87 (4.71–8.00)	6.79 (6.28–7.24)	6.04 (5.55–6.64)	3.15 (2.91–3.58)
kidney	2.31 (1.57–2.69)	2.15 (2.01–2.38)	2.11 (1.84–2.52)	1.07 (0.97–1.17)
mean heart–blood	18:1	11:1	9:1	3:1

[a] These values represent the mean and range for five rats.

(6-*E,Z*) further confirmed the presence of *Z* and *E* isomers in **6** prepared by treatment of the mercuric bromide **5** with Br_2. The four downfield lines observed in the spectrum of 6-*E,Z* corresponded to the expected relative positions of the lines of a mixture of *cis* and *trans*-vinyl bromides, by comparison to the published data for (*Z*)- and (*E*)-propenyl bromide.[24] In contrast, 6-*Z*, prepared by the bromodeboronation route, exhibited two lines in the expected positions for a *Z* isomer. These analyses have thus clearly shown that treatment of vinylmercuric bromides such as **5**, with Br_2 proceeds with the formation of both the (*Z*)- and (*E*)-vinyl bromide products. Single-crystal X-ray analysis of the (*E,Z*)-triphenyl(1-bromo-1-penten-5-yl)phosphonium iodide obtained as the condensation product of 6-*E,Z* and triphenylphosphine indicated 6-*E,Z* to be an approximate 60:40 cis:trans mixture.[25]

For the preparation of a model radiobrominated vinyl bromide substituted tellurium fatty acid, our attention focused on similar transformations of (*E*)-(13-iodo-1-tridecen-1-yl)boronic acid (**8**) prepared[11] from the corresponding alkyne **7**. This substrate was chosen since it could be incorporated into an analogue with tellurium in position 5 (Scheme II). The *E*- and *Z*-isomeric mixture of 1-bromo-13-iodo-1-tridecene (**10**) was similarly prepared by addition of bromine to (*E*)-(13-iodo-1-tridecen-1-yl)-mercuric bromide (**9**). Compound **9** was isolated as a low-melting solid by reaction of (*E*)-(13-iodo-1-tridecen-1-yl)boronic acid (**8**) with mercuric acetate followed by treatment with NaBr. Reaction of **9** with Br_2 then gave 10-*E,Z*. The cis isomer, (*Z*)-1-bromo-13-iodo-1-tridecene (10-*Z*), was prepared via the treatment of the corresponding boronic acid **8** with NaBr in the presence of NCS. Coupling of the iodotridecenyl bromide analogues 10-*Z* and 10-*E,Z* with sodium (ethoxycarbonyl)propyl telluride (**11**), generated in situ by sodium borohydride ($NaBH_4$) treatment of diethyl 5,6-ditelluradecane-1,10-dioate, provided crude ethyl (*Z*)-18-bromo-5-tellura-17-octadecenoate (12-*Z*) and ethyl (*E,Z*)-18-bromo-5-tellura-17-octadecenoate (12-*E,Z*), respectively. Purification using silica gel column chromatography provided pure 13-*Z* and 13-*E,Z*. Hydrolysis of 12-*Z* and 12-*E,Z* with NaOH in aqueous ethanol followed by acidification with HCl readily furnished the desired 18-bromo-5-tellura-17-octadecenoic acid products 13-*Z* and 13-*E,Z*. Following this sequence, the radiobrominated analogues [^{82}Br]-12-*Z* and [^{82}Br]-12-*E,Z*, were prepared by the same series of transformations. The [^{82}Br]-10-*Z* was prepared by Na^{82}Br–NCS treatment of **8** in overall 5% radiochemical yield with a specific activity (sp act.) of 128.8 mCi/mmol. Compound [^{82}Br]-10-*E,Z* was readily prepared by reaction of **9** with a mixture of $NH_4{}^{82}Br$ and Br_2. The reaction of $NH_4{}^{82}Br$ with **9** and incorporation of bromine-82 is almost instantaneous. The

Scheme II



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total time involved for this reaction including chromatographic purification is approximately 25 min. Although the exact ratio of *E* and *Z* isomers in the labeled compound could not be accurately determined, the quality of the labeled mixture by TLC analysis appeared to be the same as that of the corresponding unlabeled mixture. The radiochemical yield (bromine-82 incorporation) was 14% with a sp act. of 128.4 mCi/mmol. The low radiochemical incorporation could be attributed to the bromide (Br^-) form of bromine-82 used. In unlabeled reactions when bromine (Br_2) is used, the bromo compound is formed in high yields. Specific activities and overall yields of final products are reported in the Experimental Section.

Biological Studies. The distribution of radioactivity in tissues of female Fischer rats was determined after administration of the radiobrominated cis isomer 13-*Z* and the cis–trans mixture 13-*E,Z* (Tables I and II). Both 13-*Z* and 13-*E,Z* showed high heart uptake with prolonged retention. A comparison of the data (Table III) for radioiodinated 5-Te fatty acid analogue[11] 1 (*E* isomer) and the corresponding radiobrominated 5-Te fatty acid analogues 13-*Z* and 13-*E,Z* show heart uptake for these compounds in the order of 1 > 13-*E,Z* > 13-*Z*. These data may suggest higher heart uptake for the *E* isomer than for the *Z* isomer. The blood levels of 13-*Z* and 13-*E,Z* are similar but higher than for 1. The results suggest that the presence of the *Z* isomer might be responsible for the lower heart uptake of the *E,Z* mixture, and higher blood levels and lower heart–blood ratios as compared to those shown by 1.

Conclusion

The choice of the most efficient and reliable method for the preparation of radiohalogenated vinyl iodides or vinyl bromides depends upon the requirements of the individual investigator. These requirements include time, chemical and radiochemical yields, reliability, availability and stability of substrates and reagents, and stereochemical requirements of the product. For the preparation of vinyl bromide products where the *E,Z* product ratio is not important, we have found that the bromodemercuration method described in this paper represents a rapid, reliable method using stable substrates.

These studies have demonstrated the usefulness of a rapid, simple method for the preparation of radiobrominated cis,trans mixtures of vinyl bromide substituted radiopharmaceuticals via Br_2 treatment of *trans*-vinylmercuric bromide substrates. An *E,Z* mixture of a model ^{82}Br-labeled tellurium fatty acid appears to behave biologically very similarly to the *trans*-vinyl iodide analogue, suggesting that replacement of bromide for iodide and the stereochemistry of the vinyl halide are factors which do not significantly change the myocardial uptake and retention properties of these interesting agents. The techniques described in this report may be extended for the preparation of similar compounds labeled with ^{75}Br for positron emission tomographic studies.

An examination of the mechanism of this reaction and its scope for the application to the preparation of a variety of other radiopharmaceuticals are the goals of a more extensive study now in progress.

Experimental Section

The melting points (mp) were determined in capillary tubes with a Büchi SP apparatus and are uncorrected. Thin-layer chromatographic analyses (TLC) were performed with 250-μm-thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.). Spots on the TLC plates were detected by observation under short-wave UV light or exposure to iodine vapor. The low-resolution mass spectra (MS) were recorded at 70 eV with a Kratos MS 25 instrument. The NMR spectra were obtained at 60 MHz with a Varian 360 L instrument. The ^{13}C NMR spectra were obtained with a JEOL-FX90Q spectrometer. Samples (30–40 mg) were dissolved in the solvents indicated, and the resonances are reported downfield (δ) from the internal tetramethylsilane standard. The presence of exchangeable protons was confirmed by treatment with D_2O followed by reintegration of the NMR spectrum. The gas–liquid chromatographic analyses (GLC) were performed with a Perkin-Elmer Sigma 3 series instrument. Compounds were analyzed with a 6-ft-long ($^1/_4$ in. i.d.) column of 3% SE-30 stationary phase coated on 300-mesh Gas-Chrom Q. The column temperature was 100 °C with a helium flow rate of 40 mL/min. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Where analyses are indicated by only the symbols, the analytical results for the elements were within ±0.4% of the theoretical value.

Materials. All chemicals and solvents were analytical grade and were used without further purification. The ammonium [^{82}Br]bromide was purchased from New England Nuclear, Inc. (North Billierica, MA). The specific activity of $NH_4{}^{82}Br$ was adjusted with carrier Br_2 in benzene to 250 mCi/mmol prior to use.

Animal Tissue Distribution Studies. The distribution of radioactivity was determined in tissues of 10–12-week-old female Fischer 344 rats (170–200 g) after intravenous administration of ^{82}Br-labeled fatty acids 13-*Z* and 13-*E,Z*. The animals were allowed food and water ad libitum prior to and during the course of the experiment. The radiobrominated fatty acids were 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 0.22-μm Millipore filter and injected via a lateral tail vein into the ether-anesthetized animals. After the times indicated, the animals were killed by cervical fracture, and blood samples were obtained by cardiac puncture. The organs were then removed, rinsed with 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 thyroid glands were not weighed directly. The weight of the thyroid glands was calculated in the usual manner by multiplying the animal weight by 7.5 mg/100 g.[26]

Syntheses. General Comments. All reactions with the tellurium compounds 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 connected to an argon supply tube through an oil pressure release valve to maintain a slightly positive argon atmosphere. Tellurium fatty acids were sealed and stored under argon in a freezer.

(*E*)-(5-Iodo-1-penten-1-yl)mercuric Bromide (5). Mercuric acetate (636 mg, 2 mmol) was added to a stirred solution of (*E*)-(5-iodo-1-penten-1-yl)boronic acid[15] (3; 480 mg, 2 mmol) in tetrahydrofuran (THF, 2 mL). The homogeneous solution obtained was stirred for 10 min and poured to a vigorously stirred, cold (~0 °C) solution of NaBr (306 mg, 3 mmol) in water (10 mL). Addition of ethanol (10 mL) produced a crystalline white solid, which was collected by filtration, washed with water followed by ethanol, and dried to yield 700 mg (75%) of **5**. The sample was crystallized from boiling methanol to yield **5**: mp 63–64 °C; NMR ($CDCl_3$) δ 5.8–5.95 (m, 2, HC=CH), 3.05–3.3 (t, 2, J = 6 Hz, CH_2I), 1.7–2.5 (m, 4, CH_2CH_2). Anal. (C_5H_8BrIHg) C, H, Br, I, Hg.

(*E,Z*)-1-Bromo-5-iodo-1-pentene (6-*E,Z*). A solution of bromine (0.075 mL, 1.4 mmol) in benzene (1 mL) was added to a stirred solution of **5** (700 mg, 1.4 mmol) in benzene (15 mL). The reaction mixture became colorless immediately with precipitation of crystalline mercury salts, indicating an instantaneous reaction. After stirring for 10 min, the reaction mixture was extracted with petroleum ether (2 × 15 mL). The petroleum ether portion was washed with 5% aqueous sodium bisulfite (10 mL) followed by water and dried (Na_2SO_4). Evaporation of the pe-

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Table III. Comparison of the Heart Uptake and Heart–Blood Ratios of Racemic (*E,Z*)-18-[^{82}Br]Bromo-5-tellura-17-octadecenoic Acid with Values for (*E*)-[^{125}I]Iodo-5-tellura-17-octadecanoic Acid after Intravenous Administration to Female Fischer 344 Rats[a]

radiolabeled agent (radiolabel)	mean % dose/g values (mean heart–blood ratios)			
	5 min		60 min	
	heart	blood	heart	blood
(*E,Z*)-18-bromo-5-tellura-17-octadecenoic acid ([^{82}Br]-13-*E,Z*)	3.28 (18:1)	0.18	3.47 (9:1)	0.39
(*E*)-18-iodo-5-tellura-17-octadecenoic acid ([^{125}I]-1)	3.99 (37:1)	0.11	4.33 (23:1)	0.19

[a] Values for the (*E*)-18-iodo-5-tellura-17-octadecenoic acid are taken from ref 11.

troleum ether and silica gel column chromatography of the crude product using petroleum ether as the solvent gave 308 mg (80%) of the cis-trans mixture 6-*E,Z* (oil): NMR ($CDCl_3$) δ 5.9–6.4 (m, 2, CH=CHBr), 3.1–3.35 (t, 2, J = 6.5 Hz, CH_2I), 1.6–2.5 (m, 4, CH_2CH_2). Anal. (C_5H_8BrI) C, H, Br, I.

(*E*)-1-Bromo-5-iodo-1-pentene (6-*E*). The intermediate alane 4 was generated in situ by addition of a 1 M diisobutylaluminum hydride in hexane solution (5 mL) to precooled (0 °C) 5-iodo-1-pentyne[15,18] (**2**; 984 mg, 0.5 mL, 4.92 mmol) under argon atmosphere and heating the reaction solution at 50 ± 5 °C (bath temperature) for 1.5 h. A solution of bromine (0.27 mL) in THF (3 mL) was added at −50 °C and the solution then gradually warmed up to room temperature. The solution was adjusted to pH 5 by adding 1 N H_2SO_4 and diluted with water (20 mL). The crude product was extracted with petroleum ether and washed with a 5% aqueous solution of sodium metabisulfite followed by water. Silica gel column chromatography of the crude product and elution with petroleum ether provided 275 mg (20%) of pure 6-*E* as an oil: NMR ($CDCl_3$) δ 6.15 (m, 2, CH=CHBr), 3.2 (t, 2, J = 6 Hz, CH_2I), 1.7–2.3 (m, 4, CH_2CH_2). Anal. (C_5H_8BrI) C, H, Br, I.

(*E*)-(13-Iodo-1-tridecen-1-yl)mercury Bromide (9). Compound **9** was prepared from boronic acid[15] **8** as described for the synthesis of **5**: yield 48%; mp 91–92 °C; NMR ($CDCl_3$) δ 5.96 (m, 2, CH=CH), 3.1–3.36 (t, 2, J = 6 Hz, CH_2I), 1.1–2.2 (m, 20, 10 × CH_2). Anal. ($C_{13}H_{24}BrHgI$) C, H, Hg.

(*Z*)-1-Bromo-13-iodo-1-tridecene (10-*Z*). A solution of NaBr (52 mg, 0.5 mmol) in H_2O (1 mL) was added to a cold (0 °C) solution of **8** (180 mg, 0.5 mmol) in THF (2 mL) followed by addition of NCS (67 mg, 0.5 mmol). The reaction mixture was stirred in dark for 30 min and a clear solution was obtained. Water (20 mL) was added and the mixture treated with 5% aqueous sodium bisulfite (5 mL) to obtain a colorless solution, which was extracted with petroleum ether (2 × 15 mL). The petroleum ether portion was washed with water, dried (Na_2SO_4), and evaporated. The column chromatography was performed as described for 6-*E* to yield 48 mg (25%) of pure 10-*Z* as an oil: NMR ($CDCl_3$) δ 6.1–6.3 (m, 2, CH=CHBr), 3.2 (t, 2, J = 6 Hz, CH_2I), 1.1–2.3 (m, 20, 10 × CH_2). The compound was also characterized by comparison with 10-*E,Z* on TLC.

(*E,Z*)-1-Bromo-13-iodo-1-tridecene (10-*E,Z*). The bromotridecene derivative 10-*E,Z* was prepared as an oil from **9** (n = 11) the same way as described for 6-*E,Z* in 80% yield: NMR ($CDCl_3$) δ 5.8–6.3 (m, 2, CH=CHBr), 3.0–3.35 (t, 2, J = 6 Hz, CH_2I), 1.1–2.32 (m, 20, 10 × CH_2). Anal. ($C_{13}H_{24}BrI$) C, H.

Ethyl (*E,Z*)-18-Bromo-5-tellura-17-octadecenoate (12-*E,Z*). Diethyl 5,6-ditelluradecane-1,10-dioate[11] (243 mg, 0.5 mmol) was stirred in ethanol (10 mL). An argon-flushed ethanol–$NaBH_4$ suspension was added in portions until a vigorous reaction ensued with concomitant decolorization of the orange solution, indicating reduction of the bistelluride to **11**. An argon-purged solution of 10-*E,Z* (77 mg, 0.2 mmol) in ethanol (2 mL) was added and the mixture stirred at room temperature for 1 h. Water (50 mL) was added, and the mixture was extracted with ethyl ether (Et_2O, 2 × 50 mL). The combined ether portion was dried (Na_2SO_4) and evaporated and the residual oil applied to a column packed with silica gel (Sigma Sil B-200) slurried (70 mL) in petroleum ether. Elution with petroleum ether (200 mL) removed the unreacted 10-*E,Z*. Further elution with benzene gave the desired product as a colorless fraction followed by orange unreacted ditelluride. Evaporation of the colorless fraction provided 68 mg (68%) of 12-*E,Z* as an oil: NMR ($CDCl_3$) δ 6.0–6.25 (m, 2, CH=CHBr), 3.95–4.33 (q, 2, $COOC_2H_5$), 1.1–2.9 (other protons). Anal. ($C_{19}H_{35}BrO_2Te$) C, H.

(*E,Z*)-18-Bromo-5-tellura-17-octadecenoic Acid (13-*E,Z*). The ester 12-*E,Z* (50 mg, 0.1 mmol) was dissolved in ethanol (15 mL) and a solution of NaOH (1 N, 1.0 mL) was added. The mixture was refluxed in the dark under argon atmosphere for 1 h and then diluted with H_2O (50 mL). After cooling to room temperature, the mixture was extracted with Et_2O. The aqueous solution was adjusted to pH 1 by addition of 1 N HCl and further extracted with Et_2O (2 × 20 mL), which was washed with H_2O (20 mL) and dried (Na_2SO_4). Evaporation of ether under a stream of argon and trituration of the syrup with petroleum ether gave 39 mg (80%) of 13-*E,Z* as a low-melting solid: NMR ($CDCl_3$) δ 9.78 (br s, 1, COOH), 5.9–6.3 (m, 2, CH=CHBr), 1.2–2.8 (other protons). Anal. ($C_{17}H_{31}BrO_2Te$) C, H, Br, Te.

Ethyl (*Z*)-18-Bromo-5-tellura-17-octadecenoate (12-*Z*). Compound 12-*Z*, an oily product, was prepared from 10-*Z* exactly as described for 12-*E,Z* from 10-*E,Z* in comparable yields and identified by cochromatography with 10-*E,Z* on TLC (C_6H_6).

(*Z*)-18-Bromo-5-tellura-17-octadecenoic Acid (13-*Z*). The 13-*Z* isomer was obtained as a low-melting solid from the corresponding 12-*Z* ester exactly as described for 13-*E,Z* and identified by cochromatography on TLC (4% MeOH in C_6H_6).

Synthesis of Radiolabeled Compounds. (*E,Z*)-18-[^{82}Br]-Bromo-5-tellura-17-octadecenoic Acid ([^{82}Br]-13-*E,Z*). A Commercial sample of $NH_4{}^{82}Br$ (7.45 mCi) in 1 N NH_4OH (1.35 mL) was treated with 1 N HCl (1.35 mL) and bromine (0.002 mL) and added to a stirred solution of **9** (34 mg, 0.058 mmol) in benzene (C_6H_6, 1.5 mL) and MeOH (2 mL). An immediate disappearance of bromine color indicated instantaneous reaction. Although, in this particular case, the mixture was stirred for 15 min. The colorless reaction mixture was diluted with H_2O (20 mL) and extracted with petroleum ether (2 × 15 mL). The combined petroleum ether was washed with aqueous sodium metabisulfite (5%, 10 mL) followed by H_2O (15 mL) and dried (Na_2SO_4). The crude radiobrominated product was passed through a silica gel (Davison grade) column and the pure radiolabeled 10-*E,Z* was eluted with petroleum ether. Evaporation of petroleum ether using a stream of argon at 50–60 °C provided 1.0 mCi (14%) of pure [^{82}Br]-10-*E,Z*. The radioactive sample was dissolved in EtOH (1 mL) and added to a colorless solution of 11 obtained after $NaBH_4$ reduction of diethyl 5,6-ditelluradecane-1,10-dioate (150 mg, 0.24 mmol). Following the procedure described for 12-*E,Z*, the radiobrominated ester [^{82}Br]-12-*E,Z* was isolated by condensing [^{82}Br]-10-*E,Z* with **11** for 1 h. The hydrolysis of [^{82}Br]-12-*E,Z* as described for the corresponding unlabeled compound gave, after 1 h, 332-μCi (30% label incorporation, sp act. 128.4 mCi/mmol) of [^{82}Br]-13-*E,Z*. The radiobrominated compounds [^{82}Br]-12-*E,Z* (TLC, C_6H_6) and [^{82}Br]-13-*E,Z* (TLC, 4% MeOH in $CHCl_3$) cHCl_3) cochromatographed with the respective authentic samples. The overall radiochemical yield of this reaction was only 4.2%. The low radiochemical incorporation (14%) during bromination, probably due to the bromide (Br^-) form of Br-82 used, was responsible for overall poor yields.

(*Z*)-18-[^{82}Br]Bromo-5-tellura-17-octadecenoic Acid ([^{82}Br]-3-*Z*). A commercial sample of $NH_4{}^{82}Br$ (6.44 mCi) in 1 N NH_4OH (1.55 mL) was treated with 1 N HCl (1.55 mL) and added to a solution of boronic acid **8** (18 mg, 0.05 mmol) and NaBr (5.2 mg, 0.05 mmol) in 50% aqueous THF (2 mL) followed by the addition of NCS (6.7 mg, 0.05 mmol). The solution was stirred for 30 min in the dark and [^{82}Br]-10-*Z* was isolated as described for 10-*Z*. The radiobrominated 10-*Z* was condensed with 0.1 mmol of **11**. The radiobrominated 13-*Z* (293 μCi, 5% overall radiochemical yield, sp act. 128.8 mCi/mmol) was isolated exactly as described for [^{82}Br]-13-*E,Z* and characterized by cochromatography (TLC, 4% MeOH in $CHCl_3$) with authentic samples of 13-*Z* and 13-*E,Z*.

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Spiro[4.5] and Spiro[4.6] Carboxylic Acids: Cyclic Analogues of Valproic Acid. Synthesis and Anticonvulsant Evaluation[1]

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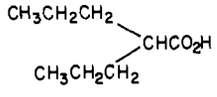
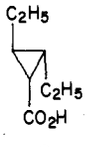
Spiro[4.5]decane-2-carboxylic acid (**12a**), spiro[4.5]decane-2,2-dicarboxylic acid (**11a**), spiro[4.6]undecane-2-carboxylic acid (**12b**), spiro[4.6]undecane-2,2-dicarboxylic acid (**11b**), and spiro[4.6]undecane-2-acetic acid (**13**) were synthesized by an improved method and evaluated for anticonvulsant activity. These analogues were synthesized to evaluate the role of the carboxylic acid group as an essential substituent in valproic acid (di-*n*-propylacetic acid, 1). Carbocyclic spiranes are known to resist metabolic alteration so that any activity elicited by these compounds would be due to the carboxylic acid function and not to any metabolic change. Spiro[4.6]undecane-2-carboxylic acid (**12b**) was the most active analogue tested and the pentylenetetrazol and picrotoxin evaluations of **12b** compared favorably to 1. However, **12b** failed to provide adequate protection against maximal electroshock seizures, bicuculline, or strychnine in mice. Possible reasons for these results are discussed.

Valproic acid (di-*n*-propylacetic acid, 1) was introduced into the United States in 1978 as an anticonvulsant specifically for the treatment of absence (petit mal) seizures.[2]



1

Metabolic alteration of 1 is a significant disadvantage, however.[3] A recent report[4] detailed the synthesis and anticonvulsant evaluation of rigid homologues of 1. This study showed that (±)-(*E*)-2,3-diethylcyclopropanecarboxylic acid (2) and dicyclopropylacetic acid (3) were as active as 1 against pentylenetetrazol-induced seizures in mice. We herein report our studies on spiro carboxylic acid analogues of 1 as potential anticonvulsants.



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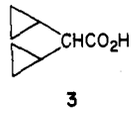
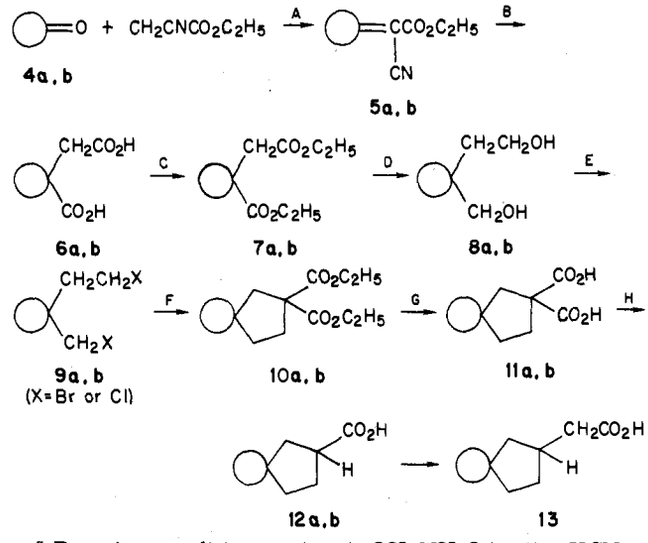


3

Chemistry. The target compounds were synthesized according to the procedure shown in Scheme I. This synthesis has been detailed in part previously.[5] Starting with the appropriate ketone (cyclohexanone or cycloheptanone, 4), ethyl cyanoacetate was reacted under Cope conditions[6] and the product, the cycloalkylidenecyanoacetic acid ester **5**, was then reacted with potassium cyanide in a hydroalcoholic solution. After the mixture stood at room temperature for 48 h, the solvents were evaporated, and the residue was treated with hydrochloric acid, refluxed overnight, and upon cooling, the 1-carboxy 1-acetic acid derivative **6** precipitated in nearly pure form.[7]

Scheme I[a]



[a] Reaction conditions: A = AcOH, NH_4OAc; B = KCN, HCl; C = EtOH, H_2SO_4; D = LAH or $NaAlH_2(O(CH_2)_2OCH_3)_2$; E = HBr, H_2SO_4, or $SOCl_2$; F = $CH_2(CO_2Et)_2$, NaOEt; G = KOH, EtOH, HCl; H = Δ; I = $SOCl_2$; CH_2N_2, Et_3N; $C_6H_5CO_2Ag$, Et_3N; NaOH, HCl. Series a = cyclohexanone; series b = cycloheptanone.

Esterification under standard conditions[8] produced the diethyl ester **7**. When **7** was reduced with lithium alu-

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