(−)-dibenzoyltartrate, 85663-21-4; (±)-**100**, 85663-55-4; (±)-**100**·2HCl, 80273-17-2; (±)-**101**, 85663-56-5; (±)-**101**·2HCl, 80273-18-3; (±)-**102**, 80273-19-4; (±)-**103**, 85663-57-6; (±)-**103**·2HCl, 80273-20-7; (±)-**104**, 85663-58-7; (±)-**104**·2HCl, 85663-07-6; (±)-**105**, 85663-59-8; (±)-**105**·2HCl, 85663-08-7; (±)-**106**, 85663-60-1; (±)-**106**·2HCl, 80273-26-3; (±)-**107**, 85663-61-2; (±)-**107**·2HCl, 80273-27-4; **108**, 62373-97-1; **109**, 52807-79-1; (±)-*cis*-V (X = 6-CF_3; Y = *p*-F; Z = H), 85663-12-3; (±)-*trans*-V (X = 6-CF_3; Y = *p*-F; Z = H), 85662-71-1; I (A = Br; X = 4-CF_3), 85118-34-9; I (A = Br; X = 4-Cl), 85663-10-1; (±)-*cis*-VIa, 80274-02-8; (±)-*trans*-VIa, 80274-59-5; dopamine, 51-61-6; 2-bromo-4-(trifluoromethyl)benzoic acid, 328-89-2; 4-(trifluoromethyl)anthranilic acid, 402-13-1; 2-bromo-4-(trifluoromethyl)benzoyl chloride, 85663-09-8; 2-bromo-4-(trifluoromethyl)benzaldehyde, 85118-24-7; ethyl cyanoacetate, 105-56-6; 2-bromo-4-chlorobenzaldehyde, 84459-33-6; 2-bromo-4-chlorobenzoic acid, 936-08-3; 1-bromo-4-fluorobenzene, 460-00-4; ethyl 3-[2-bromo-4-(trifluoromethyl)phenyl]-2-cyano-3-(4-fluorophenyl)propanoate, 85663-11-2; K-Selectride, 54575-49-4; 1-piperazineethanol, 103-76-4; piperazine, 110-85-0; phenethyl bromide, 103-63-9; cyclopropanecarbonyl chloride, 4023-34-1; propylene oxide, 75-56-9; methanesulfonyl chloride, 124-63-0; 1-(3-hydroxy-1-propyl)piperazine, 5317-32-8; 4-chloro-6-fluoro-1-(4-fluorophenyl)-1,2,3,4-tetrahydronaphthalene, 68351-24-6; 1-methylpiperazine, 109-01-3.

New Selenium-75 Labeled Radiopharmaceuticals: Selenonium Analogues of Dopamine[1]

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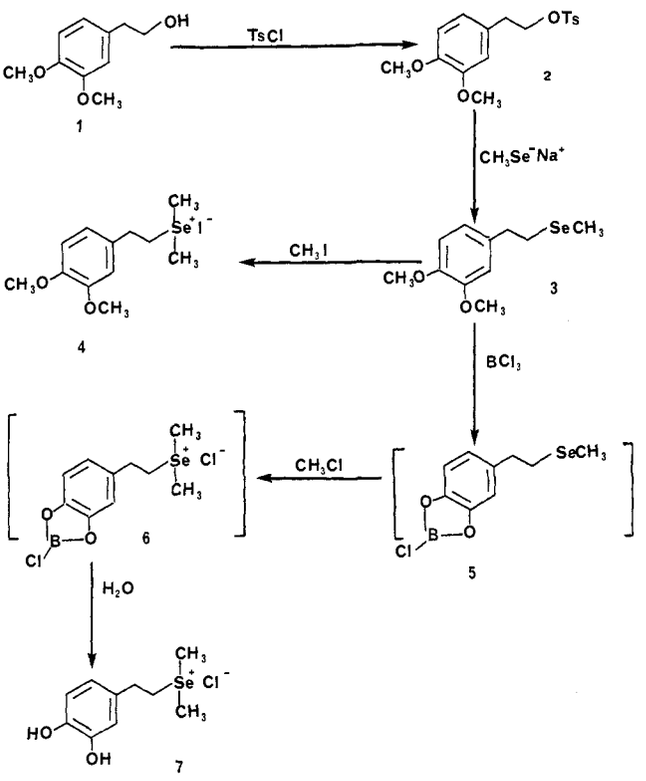
Selenium-75 labeled selenonium analogues of dopamine, [2-(3,4-dimethoxyphenyl)ethyl]dimethylselenonium iodide (**4**) and its dihydroxy analogue (**7**), were prepared by reducing [^{75}Se]selenious acid with sodium borohydride at pH 6.0 and reacting the NaSeH produced with 1-(3,4-dimethoxyphenyl)-2-(*p*-toluenesulfonyloxy)ethane. Tissue distribution studies in rats given the ^{75}Se-labeled selenonium agents intravenously demonstrated high initial heart uptake (2.38% dose/g at 5 min). Prolonged adrenal retention ($t_{1/2}$ = 10 h) and high adrenal to blood ratio of compound **4** (21/1 at 4 h after injection) were observed. The high uptake and adrenal to blood ratio suggest the potential use of compound **4** as a radiopharmaceutical for the adrenal gland.

The adrenal gland consists of two histologically and functionally distinct regions, the cortex and the medulla. Imaging the human adrenal cortex and its neoplasms has been possible for nearly a decade by using the radioiodinated cholesterol and ^{75}Se-labeled cholesterol analogues.[2-4] A comparable radiopharmaceutical is needed for imaging the adrenal medulla and its neoplasms, such as pheochromocytoma and neuroblastoma. Using guanidine derivatives, *m*-[^{123}I]iodo- and *m*-[^{131}I]iodobenzylguanidine, Wieland et al. were able to obtain scintiscans of the monkey adrenal medulla.[5] Recently, Hanson[6] has prepared another guanidine derivative, 1-carboxyimidine-4-phenylpiperazine, and demonstrated that its uptake by the adrenals was higher than that of radioiodobenzylguanidine.

It is well known that dopamine is synthesized and stored in the adrenal medulla.[7] Radiolabeled derivatives of dopamine have been proposed as potential adrenal medulla imaging agents.[8] In an attempt to develop such an agent, ^{11}C ($t_{1/2}$ = 20 min) was used as the radiolabel.[9] The short half-life of ^{11}C and the need for rapid synthesis were major drawbacks. There have been some attempts to use radiohalogen derivatives of dopamine as scanning agents for

Scheme I



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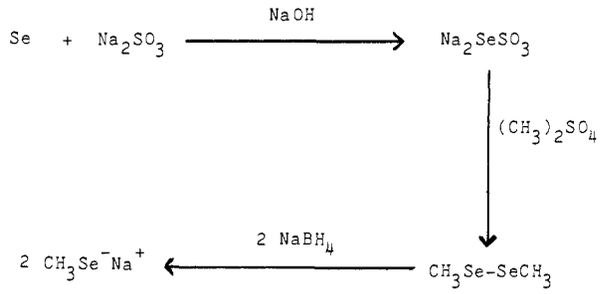
Scheme II



the adrenal medulla,[10] but they have met with limited success.

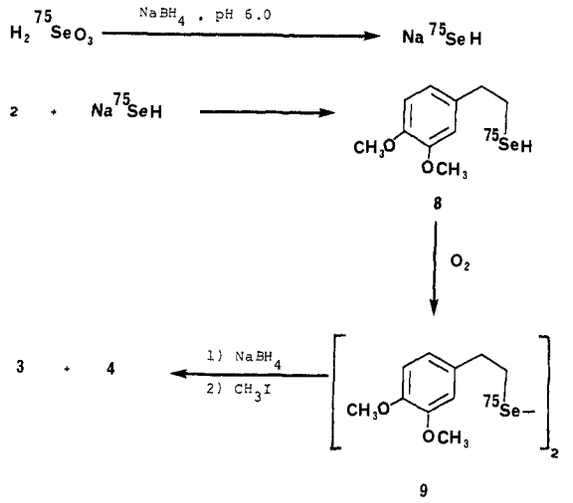
Although ^{75}Se may not be the ideal radionuclide for clinical use, it is of interest for the following reasons: (1) its long half-life (120 days) allows enough time for synthesis and handling, (2) it forms stable covalent bonds with carbon, (3) the organoselenium compounds are more stable in vivo than the corresponding halogenated derivatives, and (4) this radionuclide is quite useful for developmental studies to determine the feasibility of using the potentially more useful ^{73}Se ($t_{1/2}$ = 7 h, β^+).

Anderson et al[11] replaced the nitrogen atom of dopamine with the sulfonium functional group and found that the nitrogen atom is not essential for dopaminergic activity. Since sulfur and selenium are bioisosters, we were interested in determining if the nitrogen atom of dopamine could be replaced with a selenonium functional group and still localize in the adrenal gland. The objectives of the present investigation were to synthesize selenonium analogues of dopamine and to study the biodistribution of the ^{75}Se-labeled compounds in rats.

Chemistry. The synthesis of nonradioactive selenonium analogue **4** is outlined in Scheme I. Tosylation of 3,4-dimethoxyphenethyl alcohol (**1**) provided compound **2**. Sodium methylselenoate ($CH_3Se^-Na^+$), prepared by a modification (Scheme II) of the method described by Günther,[12] was used as a nucleophile to replace the tosyl group of compound **2** to give compound **3**. Methyl iodide treatment of compound **3** gave the selenonium salt **4**. Treatment of compound **3** with boron trichloride provided directly the selenonium salt **7**. On the basis of the known formation of alkyl halide from phenylalkyl ethers and boron trihalide,[13] as well as the formation of chloroboronates from the interaction of catechols with boron trihalide,[14] we have assigned structure **5** to the first intermediate. The methyl chloride generated would be expected to interact with the intermediate **5** to form the selenonium chloride intermediate **6**, which would be predicted to hydrolyze to compound **7**.[14] The NMR spectrum of compound **7** showed the absence of OCH_3 signals.

The synthesis of [^{75}Se]selenonium analogues is depicted in Scheme III. [^{75}Se]Selenious acid was reduced by sodium borohydride in phosphate buffer (pH 6.0, 0.5 M) to form $Na^{75}SeH$. The products of the reduction of selenious acid depend on the pH of the medium.[15] Sodium hydrogen selenide was used as a nucleophile to replace the

Scheme III



tosyl group of compound **2**, forming the selenol **8**, which upon exposure to air formed the diselenide **9**. The latter was separated from the nonreacted selenium by ether extraction. Reduction of the diselenide with sodium borohydride, followed by addition of methyl iodide, provided a mixture of compounds **3** and **4**. The two compounds were separated by ether extraction, since compound **4** is very soluble in water while compound **3** is very soluble in ether. Demethylation of compound **3** was accomplished with BCl_3. Compound **7** produced was purified by extracting the unreacted starting material with ether from an aqueous solution. The purity and the identity of the radioactive intermediates and final products were determined by TLC. Radioscans of the TLC plates showed >97% of the radioactivity coincident with the spot of the "cold" compounds. The aqueous solution of the selenoniums contained boric acid/sodium borate as a chemical impurity. Since boric acid/sodium borate is a relatively nontoxic material (LD_{50} = 5.14 g/kg in rats),[16] no attempt was made to remove it from the final products. For injection, the aqueous solution of the selenoniums was diluted with normal saline to give a final concentration of 5–6 μCi/0.2 mL.

Biological Distribution. The distribution of radioactivity in tissues of female Sprague–Dawley rats at 5, 15, 30, 60, 120, and 240 min after intravenous administeration of compound **4** and **7** is shown in Table I. The adrenal gland uptake reaches a maximum at 30 min for compound **4** and 15 min for compound **7**. The uptake of the selenonium analogues by the rat adrenal gland is comparable to values reported by Ice et al.[8] for [^{14}C]dopamine, i.e., 0.85% dose/g for [^{14}C]dopamine, 0.88% dose/g for salt **4**, and 0.83% for salt **7** at 30 min after intravenous injection. Also, the uptake of [^{11}C]dopamine in the dog adrenal medulla is reported as 0.094% dose/g.[9] Since our main interest is to evaluate compound **4** and **7** as adrenal medulla imaging agents, we compared the relative clearance of radioactivity by the adrenals to that of the kidneys as a function of time. Ideally, the radioactivity should remain constant in the adrenals and clear from the nearest interfering organs, the kidneys and the liver. As can be seen from Table II, the washout of radioactivity from the adrenal gland is very slow compared to that of the kidney and the liver. After 5 min the adrenal to kidney ratio was about 1/3, while after 4 h the ratio was about 4/1 for both compounds. The adrenal to liver ratio was about 1/3 for

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Table I. Tissue Distribution of ^{75}Se Activity at Various Intervals Following an Intravenous Injection of Compounds 4 and 7[a] in Rats

time, min	% dose/g ± SEM[b]						
	blood	adrenal	heart	liver	kidneys	lungs	brain
				Compound 4			
5	0.34 ± 0.03	0.86 ± 0.09	2.38 ± 0.37	2.48 ± 0.18	2.73 ± 0.19	1.44 ± 0.10	0.03
15	0.26 ± 0.01	0.88 ± 0.07	1.16 ± 0.10	1.93 ± 0.15	1.29 ± 0.06	0.97 ± 0.06	0.02
30	0.22 ± 0.01	0.94 ± 0.10	0.58 ± 0.05	1.75 ± 0.11	0.99 ± 0.05	0.75 ± 0.01	0.02
60	0.12 ± 0.01	0.71 ± 0.08	0.27 ± 0.02	0.62 ± 0.05	0.53 ± 0.09	0.38 ± 0.03	0.01
120	0.08 ± 0.00	0.74 ± 0.06	0.17 ± 0.02	0.29 ± 0.01	0.33 ± 0.04	0.19 ± 0.02	0.01
240	0.03 ± 0.00	0.64 ± 0.06	0.06 ± 0.00	0.18 ± 0.01	0.16 ± 0.01	0.07 ± 0.00	0.00
				Compound 7			
5	0.35 ± 0.03	0.78 ± 0.10	2.37 ± 0.38	1.86 ± 0.29	2.65 ± 0.08	1.25 ± 0.14	0.02
15	0.30 ± 0.02	0.87 ± 0.05	1.58 ± 0.14	2.00 ± 0.20	1.07 ± 0.08	1.14 ± 0.04	0.01
30	0.28 ± 0.03	0.86 ± 0.10	1.08 ± 0.25	2.73 ± 0.78	1.07 ± 0.16	0.83 ± 0.14	0.01
60	0.18 ± 0.02	0.87 ± 0.07	0.46 ± 0.12	0.80 ± 0.11	0.59 ± 0.09	0.58 ± 0.07	0.01
120	0.08 ± 0.01	0.73 ± 0.04	0.21 ± 0.01	0.32 ± 0.03	0.29 ± 0.02	0.20 ± 0.02	0.00
240	0.05 ± 0.00	0.59 ± 0.07	0.16 ± 0.01	0.23 ± 0.02	0.18 ± 0.01	0.09 ± 0.00	0.00

[a] Dose 5 μCi; other tissues studied and not listed were spleen, muscle, small intestine, and uterus. [b] The values represent the mean and standard error of the mean of five evaluations.

Table II. Tissue Radioactivity Ratios for Compounds 4 and 7 at Various Intervals After an Intravenous Injection in Rats

time, min:	5	15	30	60	120	240
			Compound 4			
adrenal/blood	2.53	3.39	4.27	5.92	9.25	21.33
adrenal/kidney	0.31	0.68	0.95	1.34	2.24	4.00
adrenal/liver	0.35	0.46	0.54	1.14	2.55	3.55
heart/blood	7.00	4.46	2.64	2.25	2.12	2.00
			Compound 7			
adrenal/blood	2.22	2.90	3.07	4.83	9.12	11.80
adrenal/kidney	0.29	0.81	0.81	1.47	2.52	3.28
adrenal/liver	0.42	0.43	0.31	1.04	2.28	2.56
heart/blood	6.77	5.27	3.86	2.55	2.62	3.20

both compounds after 5 min, while after 4 h the ratios were 3.6 and 2.6 for compound 4 and 7, respectively. Also, the clearance of the radioactivity from the adrenals was slower than that of the blood. From Table II, the adrenal/blood ratio was 2/1 at 5 min, while at 240 min the ratio increased to 21/1 and 12/1 for compound 4 and 7, respectively. In comparing the two selenoniums, it is preferable to use compound 4 as a radiopharmaceutical for the adrenal gland because it showed prolonged retention in the adrenals and there is one less step in the radioactive synthesis. Moreover, the dimethoxy analogues of catecholamines are more stable in vitro than the corresponding dihydroxy derivatives.

Tracer studies in animals with norepinephrine labeled with ^{3}H have shown its rapid localization in the heart.[17,18] This led some investigators to study radioiodinated dopaminergic compounds as heart imaging agents.[19] It was thus interesting to note initial high heart uptake of the two selenoniums (2.38% dose/g at 5 min). The heart/blood ratio was 7/1 at 5 min, but the washout of the activity from the heart was faster than that of the blood, and the ratio dropped to 2.6/1 and 3.9/1 within 30 min for compound 4 and 7, respectively. In comparing the rate of clearance of the radioactivity of the two compounds from the heart, we found that about 75% of the radioactivity of compound 4 and 54% of that of compound 7 in the heart at 5 min was washed out within 30 min postinjection. For that reason, compound 7 is considered to be a better scanning agent for the heart. The uptake by the myocardium may be due to the affinity of the compounds for dopaminergic receptors and/or the cationic nature of the compounds.[20] It has been shown that trimethyl[^{123m}Te]telluronium iodide concentrates in the heart with a heart/blood ratio of 5/1 after 10 min (Samy Sadek and Garo Basmadjian, unpublished data). A recent tracer study in rats with two phosphonium salts labeled with ^{3}H has shown high myocardial uptake of the radioactivity.[21] It was suggested that the myocardial localization is related to the high net negative resting potential existing in myocardial fibers.

In spite of the fact that the brain has an appreciable amount of dopaminergic receptors, its uptake was the lowest. This could be attributed to the exclusion of the hydrophilic selenoniums by the blood–brain barrier.

In conclusion, the high uptake and target tissue to blood ratios suggest the potential use of compound 4 for adrenal gland imaging and compound 7 for myocardial imaging. Efforts are being directed toward the study of the pharmacological activity of the two selenoniums and their specificity for dopaminergic receptors in the heart and adrenal medulla.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Selenium-75 was obtained as selenious acid in 1 N HCl from Oak Ridge National Laboratory (specific activity 308 mCi/mg of Se metal). All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover melting point apparatus. ^{1}H NMR spectra were determined on a Varian EM-360. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. NMR spectra of all compounds and intermediates were consistent with the assigned structures. Mass spectra were obtained with a CEC 110 double-focusing mass spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, IN. Analytical results for elements indicated were within ±0.4% of the theoretical values.

1-(3,4-Dimethoxyphenyl)-2-(*p*-toluenesulfonyloxy)ethane (2). 3,4-Dimethoxyphenethyl alcohol (7.5 g, 41.12 mmol) was dissolved in dry pyridine (60 mL) and chilled to 0 °C. *p*-Toluenesulfonyl chloride (15.3 g, 80.25 mmol) was dissolved in this solution and left in a refrigerator overnight. Needles of

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pyridine hydrochloride were formed, and the supernatant had a light brown color. The reaction mixture was poured on ice–water and stirred for a few minutes. The milky solution was extracted with ether. The organic layer was washed with dilute HCl to remove the pyridine. The ether was evaporated at room temperature. The residue was dissolved in methanol and left for crystallization to give a product yield of 9.0 g (65%), mp 49–50 °C.

1-(3,4-Dimethoxyphenyl)-2-(methylseleno)ethane (3). To dimethyl diselenide (2.23 g, 12 mmol) in THF, under nitrogen, sodium borohydride (1.9 g, 24 mmol) in ethanol was added dropwise until the solution decolorized. To this solution was added the tosyl derivative **2** (6.72 g, 20 mmol) in ethanol. After 30 min of stirring, water was added to the reaction mixture, and the mixture was extraced with chloroform. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated to leave 4 g (77%) of a pale yellow oil: NMR ($CDCl_3$) δ 6.73–6.83 (m, 3 H, ArH), 3.87 (s, 6 H, 2 OCH_3), 2.76–2.93 (m, 4 H, CH_2CH_2), 2.00 (s, 3 H, CH_3).

[2-(3,4-Dimethoxyphenyl)ethyl]dimethylselenonium Iodide (4). Methyl iodide (1.45 g, 10 mmol) was added to compound **3** (2.59 g, 10 mmol) and left at room temperature for 30 min. The yellow solid that formed was dissolved in absolute ethanol and left for crystallization. Yellow crystals (3 g, 75%) of the desired compound were obtained: mp 113–115 °C; NMR (D_2O) δ 6.95–7.05 (m, 3 H, ArH), 3.90 (s, 6 H, 2 OCH_3), 3.56–3.80 (t, 2 H, Ph-CH_2), 3.03–3.30 (t, 2 H, CH_2Se), 2.67 (s, 6 H, 2 CH_3); MS, *m/e* 260 (M for the cation – CH_3). Anal. ($C_{12}H_{18}O_2SeI$) C, H.

[2-(3,4-Dihydroxyphenyl)ethyl]dimethylselenonium Chloride (7). The selenide **3** (4 g, 16 mmol) was dissolved in CH_2Cl_2 and dried over anhydrous $MgSO_4$. The solution was filtered and transferred to a three-necked flask equipped with a condenser and dropping funnel. The system was placed under nitrogen and cooled to 0 °C. Boron trichloride (35 mL of 1 M solution in CH_2Cl_2, 35 mmol) was added. After the addition, the solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with methanol (50 mL), and the solvent was removed under vacuo to leave a white solid. Crystallization from methanol/acetone provided shiny crystals of compound **7** (3.5 g, 77%): mp 148–149 °C; NMR (D_2O) δ 6.85–7.02 (m, 3 H, ArH), 3.45–3.76 (t, 2 H, Ph-CH_2), 2.91–3.23 (t, 2 H, CH_2Se), 2.67 [s, 6 H, $Se(CH_3)$]; MS, *m/e* (M for cation – CH_3). Anal. ($C_{10}H_{15}O_2SeCl$) C, H.

Radioactive Synthesis. To selenious acid (1.29 mg, 10 μmol) in 0.1 mL of phosphate buffer (pH 6.0, 0.5 M), 3.5 mCi of $H_2{}^{75}SeO_3$ was added. The solution was stirred under argon, and sodium borohydride (1.14 mg, 30 μmol) in 0.1 mL water was added dropwise until a colorless solution was formed. To this solution, 0.2 mL of phosphate buffer (pH 6.0, 0.5 M) was added, followed by the addition of the tosyl derivative **2** (3.36 mg, 10 μmol) in 0.1 mL ethanol. Ethanol (0.5 mL) was added to the reaction mixture and stirred overnight. Then the mixture was extracted with ether, and the organic layer was left to evaporate at room temperature. The residue, diselenide **9** (3 mCi), in 0.2 mL of THF was transferred to a three-necked flask, and $NaBH_4$ (0.38 mg, 10 μmol) in 0.2 mL of 95% ethanol was added under argon, followed by the addition of CH_3I (2.9 mg, 20 μmol). After the solution was stirred for 15 min, 2 mL of water was added, and the solution was extraced with ether. The aqueous layer contained compound **4** (1.1 mCi), while the ether layer contained compound **3** (1.8 mCi). The ether layer was dried over anhydrous $MgSO_4$ and filtered, and the filtrate was evaporated to dryness by using a stream of nitrogen. The residue was dissolved in anhydrous CH_2Cl_2; to this solution, boron trichloride in CH_2Cl_2 was added under argon. After 5 h, excess BCl_3 was decomposed with methanol, and 0.5 mL of water was added. The solution was extracted with ether to remove the unreacted starting material. The aqueous layer contained 1.3 mCi of the desired salt **7**.

Tissue Distribution Studies. The tissue distribution of [^{75}Se]selenonium salts **4** and **7** was examined in female Sprague-Dawley rats (100–300 g). The rats were injected in a lateral tail vein with 0.2 mL of a saline solution containing 5–6 μCi of test compound. At different time periods after injection, groups of rats (five animals per group) were subjected to chloroform anesthesia and killed by cardioectomy. Samples of large organs (liver, lungs, small intestine, and muscle) were taken, and small organs (heart, kidneys, spleen, uterus, and adrenals) were taken intact, rinsed with saline, blotted dry, and weighed. The radioactivity in the samples was counted in a Beckman Automatic Gamma Counter (Model 9000), and the values were converted to percent of injected dose per gram of sample (% dose/g).

Registry No. 1, 7417-21-2; 2, 75010-39-8; 3, 85709-84-8; 3-^{75}Se, 85709-85-9; 4, 85709-86-0; 4-^{75}Se, 85709-87-1; 7, 85709-88-2; 7-^{75}Se, 85709-89-3; 9, 85709-90-6; TSCl, 98-59-9; $CH_3Se^-Na^+$, 37773-10-7; $H_2{}^{75}SeO_3$, 7783-00-8.

β_1-Selective Adrenoceptor Antagonists: Examples of the 2-[4-[3-(Substituted-amino)-2-hydroxypropoxy]phenyl]imidazole Class

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A series of 2-[4-[3-(substituted-amino)-2-hydroxypropoxy]phenyl]imidazoles is described. The compounds were investigated in vitro for β-adrenoceptor antagonism, and several examples were found to be selective for the β_1-adrenoceptor. The structure–activity relationship exhibited by this series of compounds is discussed. (*S*)-2-[*p*-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole [(*S*)-**13**] was over 100 times more selective than atenolol for the β_1-adrenergic receptor and has been selected for in-depth studies.

A substantial advance in the understanding of the adrenergic system occurred in 1948, when Ahlquist[1] proposed the existence of two discrete receptor types designated α and β. The introduction of pronethalol[2] and propranolol[3] reinforced this hypothesis and laid the foundation for the role of β-adrenoceptor antagonists in the management of various cardiovascular conditions, particularly angina pectoris, cardiac arrhythmias, and essential hypertension.[4] However, the use of such agents is occasionally associated with bronchospasms and Raynaud's phenomenon. An approach toward elimination of these side effects emerged with the discovery of practolol,[5] a cardioselective agent,

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