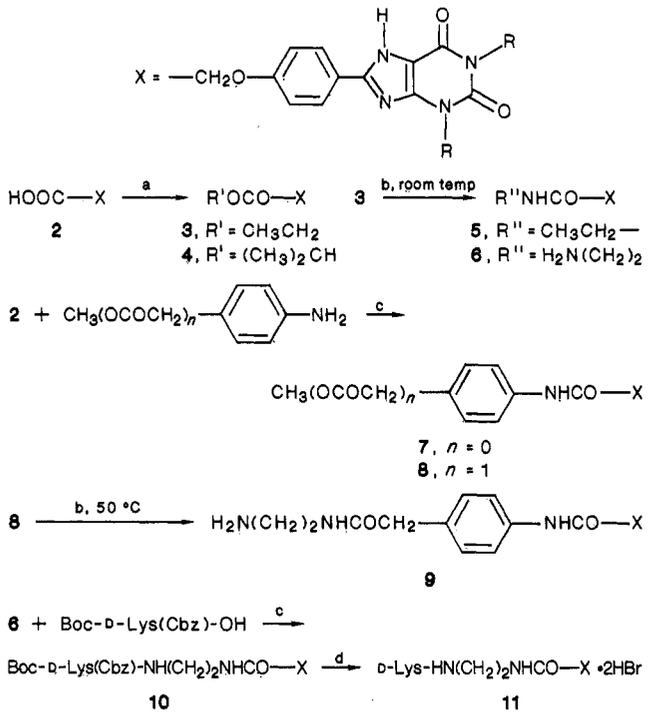

Figure 1. Synthesis of xanthine derivatives. Reagents: (a) EtOH/HCl,[7] 50 °C (**3**) or R'OH/DMAP/EDAC (**4**); (b) 70% ethylamine, aqueous (**5**) or ethylenediamine, neat[6] (**6**, **9**); (c) DCC/HOBt; (d) HBr/HOAc. R = Me, Et, or *n*-Pr, corresponding to compound suffixes **a**, **b**, and **c**, respectively.

suspended in a solution of 4-(dimethylamino)pyridine (7 mg) and 2-propanol (0.1 mL) in dimethylformamide (1 mL) and the mixture treated with 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (24 mg, 110 μmol). After several minutes a solution formed, followed by precipitation. After 2 h, water (3 mL) was added, and the white solid was collected, washed with water, and dried, giving 15.8 mg of compound **4**; CIMS (NH_3), m/e 401 $(M + 1)^+$.

8-[4-[[[[(2-Aminoethyl)amino]carbonyl]methyl]oxy]-phenyl]-1,3-diethylxanthine (6b). Compound **3b** (70 mg, 0.18 mmol) was dissolved in ethylenediamine (2 mL) with stirring. The solvent was evaporated under a stream of nitrogen. The oily residue was triturated with methanol and ether to give compound **6b** (67 mg, 92% yield) as a solid; CIMS (NH_3), m/e 401 $(M + 1)^+$.

Alternately, the carboxylic acid **2b** was preactivated with 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate in dimethylformamide, and this mixture was added slowly to a solution of 1 equiv of ethylenediamine. The product, **6b**, was isolated by thin-layer chromatography ($CHCl_3$/MeOH/HOAc, 10:10:1, on silica gel plates) in 44% yield (determined by UV).

8-[4-[[[[4-(Carboxymethyl)anilino]carbonyl]methyl]-oxy]phenyl]-1,3-diethylxanthine Methyl Ester (8b). Compound **2b** (80.8 mg, 0.23 mmol), methyl (*p*-aminophenyl)acetate hydrochloride (55 mg, 0.27 mmol), HOBt (31 mg, 0.23 mmol), and finally 1-ethyl-3-[3-(dimethylamino)propyl)carbodiimide hydrochloride (98 mg, 0.46 mmol) were combined with stirring in 8 mL of dimethylformamide. Diisopropylethylamine (39 μL, 0.23 mmol) was added, and the mixture was stirred overnight. Water was added, and the product (60 mg) was collected, washed with water, and dried; CIMS (NH_3), m/e 506 $(M + 1)^+$.

8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-diethylxanthine 2-(D-Lysylamino)ethylamide Dihydrobromide (11b). Compound **6b** (50 mg, 0.13 mmol) was suspended in 2 mL of dimethylformamide and treated with N^{α}-Boc-N^{ϵ}-Cbz-D-lysine (95 mg, 0.25 mmol), HOBt (17 mg, 0.13 mmol), and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (54 mg, 0.25 mmol). The mixture was stirred overnight. Aqueous workup, as above, followed by recrystallization from ethyl acetate/hexanes provided 75 mg of compound **10b**. The protecting groups were removed with 30% HBr/acetic acid (2 mL), giving compound **11b** (72 mg). An analytical sample was prepared by recrystallization from methanol/ether.

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Registry No. **1a**, 961-45-5; **1b**, 75922-48-4; **1c**, 85872-53-3; **2a**, 96865-82-6; **2b**, 104576-44-5; **2c**, 96865-83-7; **3a**, 104576-45-6; **3b**, 104576-46-7; **3c**, 96865-87-1; **4b**, 104576-47-8; **5b**, 104576-48-9; **6a**, 104576-49-0; **6b**, 104598-39-2; **6c**, 96865-92-8; **7a**, 96865-84-8; **7b**, 104576-50-3; **8a**, 104576-51-4; **8b**, 104576-52-5; **9a**, 104576-53-6; **9b**, 104576-54-7; **10b**, 104576-55-8; **10c**, 102255-74-3; **11b**, 104576-56-9; **11c**, 104576-57-0; 2-PrOH, 67-63-0; $H_2NCH_2CH_2NH_2$, 107-15-3; 4-$H_2NC_6H_4CH_2CO_2Me$·HCl, 83528-16-9; N^{α}-Boc-N^{ϵ}-Cbz-D-lysine, 55878-47-2; 4-$MeC_6H_4NH_2$, 106-49-0.

Dopamine Agonists: Effects of Charged and Uncharged Analogues of Dopamine

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Dopamine, at physiological pH, may exist as either an uncharged amine or a charged ammonium species. In order to gain insight as to which species is better suited for interaction with the dopamine receptor, we have synthesized dopamine analogues in which the nitrogen atom is replaced with a neutral methyl sulfide, a neutral methyl selenide, a charged dimethylsulfonium iodide, and a charged dimethylselenonium iodide. These analogues were tested for their ability to inhibit the K^+-stimulated release of [^{3}H]acetylcholine from striatal slices. At 30 μM concentration, the charged sulfonium and selenonium salts possessed significant agonist activity while the corresponding neutral species were inactive, suggesting that a charged species is optimal for dopamine agonist activity. In addition, the methyl sulfide was converted into the corresponding sulfoxide and sulfone; however, neither of these oxidation products possessed significant activity as dopaminergic agonists.

An extensive number of structure–activity relationship studies have been carried out with dopamine agonists and antagonists.[1] Previous work in our laboratory has shown that the sulfonium analogue **4** has direct dopamine agonist

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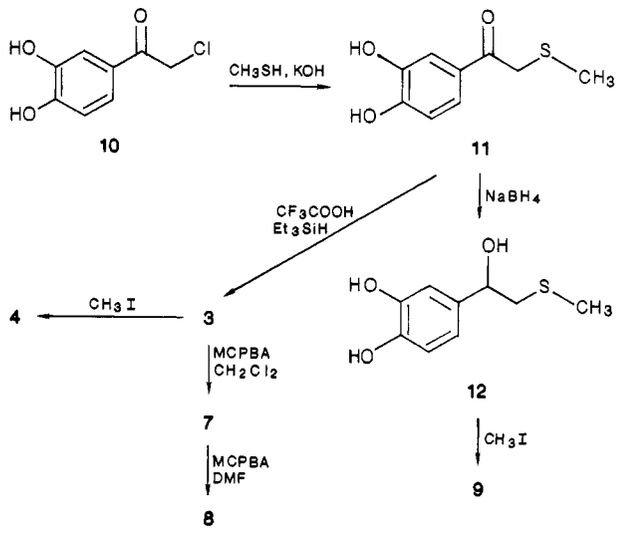
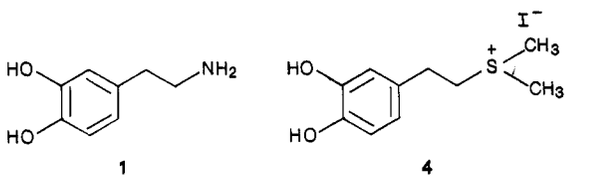
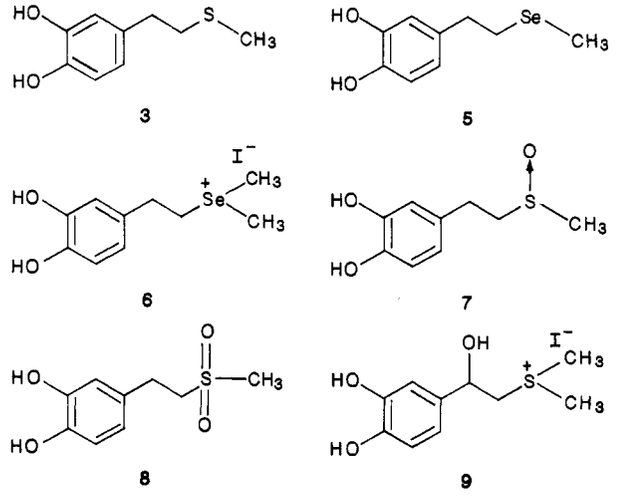
Scheme I



activity, indicating that the nitrogen atom of dopamine 1 is not required for the activation of dopaminergic receptors.[2] However, structural modifications of 4 have not

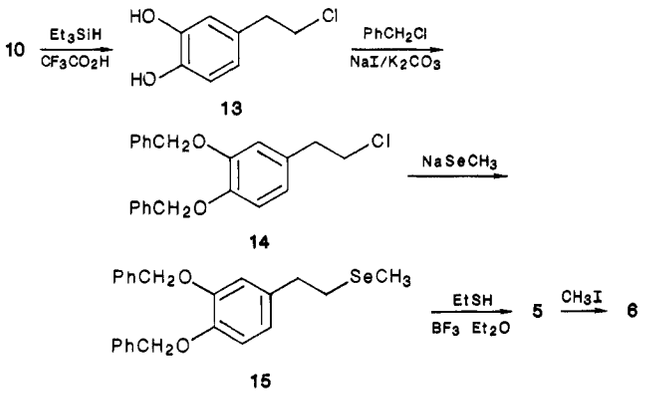


provided the same changes in the pattern of dopamine activity as has been observed with dopamine.[3] Our studies have been directed toward gaining a better understanding of the structural requirements for dopamine agonists. The present study is directed specifically at investigating the need of a positively charged functional group for dopamine agonist activity. The syntheses of a selected set of positively charged and uncharged dopamine analogues **3–9** are presented. The dopaminergic agonist actions of these



analogues along with those of amphetamine, apomorphine, and norepinephrine were evaluated with an in vitro model, the potassium-induced release of [^{3}H]acetylcholine from mouse striatal slices.[2-5] Dopamine agonists have been shown to inhibit the stimulation of [^{3}H]acetylcholine release from these slices, and this method has proven to be a very useful method of assaying drugs for D-2 dopaminergic activity.

Scheme II



Chemistry

The synthesis of the sulfur analogues of dopamine is outlined in Scheme I. Treatment of commercially available 2-chloro-3′,4′-dihydroxyacetophenone (**10**) with methanethiol and potassium hydroxide generated keto sulfide **11**, which upon reaction with lithium aluminum hydride yielded a mixture of hydroxy sulfide **12** and the fully reduced sulfide **3**. Substitution of lithium aluminum hydride with sodium borohydride provided solely **12**. This compound, upon treatment with methyl iodide, led to formation of the desired hydroxy sulfonium iodide **9**. Reduction of **11** with a mixture of trifluoroacetic acid and triethylsilane provided sulfide **3**, which was converted into the known sulfonium salt **4**[2] with methyl iodide. We have previously synthesized **3** as a nonisolated intermediate;[2] however, in the present paper, we describe a new pathway that allows for the isolation and characterization of this intermediate. Treatment of sulfide **3** with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 under appropriate conditions led to a high yield of sulfoxide **7**, which precipitated out of the reaction mixture. Dissolution of the sulfoxide in DMF followed by addition of 1 equiv of MCPBA provided the desired sulfone **8**.

The synthesis of the selenium analogues of dopamine is indicated in Scheme II. Trifluoroacetic acid/triethylsilane reduction of **10** provided the chloro catechol **13**. Treatment of **13** with sodium methaneselenoate (generated in situ from dimethyl diselenide and sodium borohydride) produced an inseparable mixture of starting material and selenide **5**. In order to achieve selenide purification, the chloro catechol **13** was first converted into the bis(benzyloxy) chloride **14**, which upon treatment with sodium methaneselenoate provided pure crystalline bis(benzyloxy) selenide **15** in good yield after chromatography. The remaining task at hand was debenzylation of **15** to provide the desired catechol selenide **5**. Common debenzylation procedures include catalytic hydrogenolysis[6] and hydrochloric acid in refluxing ethanol.[7] Hydrogenolysis, under conditions similar to those previously employed in our laboratory to remove bis(benzyloxy) groups,[8] proved

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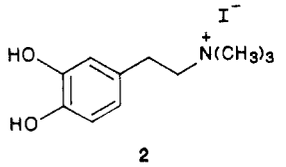
Table I. Effects of Drugs on K^+-Evoked Release of [^{3}H]Acetylcholine

compound	concn, μM	% of control (±SEM) normal	% of control (±SEM) dopamine depleted
1	0.3 μM	97 ± 5	
	1.0 μM	70 ± 4	
	3.0 μM	57 ± 5	
	10.0 μM	41 ± 5	44 ± 3
	30.0 μM	40 ± 4	
2	30.0 μM	52 ± 9	53 ± 5
3	30.0 μM	82 ± 10	100 ± 7
	1000.0 μM		100.0
4	30.0 μM	50 ± 1	61 ± 1
5	30.0 μM	95 ± 5	
6	30.0 μM	57 ± 7	47 ± 10
7	30.0 μM	101 ± 5	
8	30.0 μM	122 ± 13	
9	30.0 μM	113 ± 8	
	60.0 μM	76 ± 8	
norepinephrine	30.0 μM	101 ± 14	
	60.0 μM	85 ± 8	
apomorphine	0.1 μM	60 ± 3	56 ± 3
N-methylapomorphine	1.0 μM	59 ± 7	

to be ineffective, presumably due to poisoning of the catalyst. Treatment of **15** with concentrated hydrochloric acid in refluxing ethanol was complicated by formation of polar side products. Indeed, literature precedent exists for selenonium ion formation during the deprotection of a protected catechol selenide.[9] In view of these inadequacies, an alternative mild debenzylation method was sought. A literature search revealed a report by Fuji and co-workers,[10] who have successfully debenzylated various aromatic and aliphatic benzyl ethers with a boron trifluoride/ethanethiol system. We anticipated that this methodology could be applied to our catechol debenzylation with the additional advantage of a lack of reactivity between the selenide and the benzyl ethyl sulfide product formed during the reaction. Indeed, treatment of **15** with boron trifluoride etherate in ethanethiol led to the formation of catechol selenide **5** in reasonable yield. Treatment of **5** with methyl iodide led to formation of selenonium iodide **6**. The NMR spectrum of **6** was similar to that reported for the known chloride salt of this molecule.[9]

Pharmacology

As shown previously,[2] the dimethylsulfonium analogue **4** of dopamine, at 30 μM, inhibited the K^+-induced release of [^{3}H]acetylcholine, and this inhibition was only slightly antagonized by dopamine depletion with reserpine and α-methyl-*p*-tyrosine (Table I). It has been reported[11] that the *N*-trimethyl quaternary derivative **2** of dopamine is inactive as a dopamine agonist in stimulating cyclic AMP formation in rat striatal tissue. However, **2** inhibited the



2

K^+-stimulated [^{3}H]acetylcholine release as shown in Table I. This action of **2** was not due to the release of dopamine since this compound showed similar activity in dopamine-depleted slices. The dimethylselenonium analogue **6** also inhibited release of [^{3}H]acetylcholine, similar to the dimethylsulfonium analogue **4**. Again, this analogue showed direct dopaminergic agonist activity since the effects were also produced in dopamine-depleted slices. In contrast, the monomethyl sulfur analogue **3** of dopamine produced only a small inhibition (18%) of stimulated [^{3}H]acetylcholine release. This effect is due to the indirect action of this drug since it was completely antagonized in dopamine-depleted slices. At 30 μM, the monomethyl selenide **5** did not shown any dopamine agonist activity. The sulfoxide **7** and the sulfone **8** derivatives of dopamine, which do not carry a net charge, were ineffective in inhibiting the stimulated release of [^{3}H]acetylcholine at a concentration of 30 μM.

The β-hydroxylated derivative of the dimethylsulfonium analogue **9** of dopamine (i.e., the norepinephrine analogue) produced no significant change in stimulated [^{3}H]acetylcholine release at a concentration of 30 μM and produced a small decrease at 60 μM. Similar effects were noted with norepinephrine. Table I also shows that the quaternary ammonium derivative of apomorphine (*N*-methylapomorphine) had agonist activity at 1 μM.[12]

Discussion

One of the important portions of most dopaminergic agonists is a nitrogen atom. We have addressed the question of whether this atom is required, and our studies show that such an atom is not a prerequisite for producing dopaminergic agonist activity, since the charged sulfonium analogue **4** produces direct dopamine agonist activity.[2] Since dopamine and other catecholamines exist with a nitrogen atom as a charged ammonium form in equilibrium with an uncharged amine at physiological pH, a basic question arises as to which of these molecular species is important for binding and activation of the dopamine receptor.[13] It has been reported by some researchers that an uncharged nitrogen is required for agonist activity,[16-19] while others report that it is the charged ammonium functional group that is prerequisite for binding and activation of dopamine receptors.[14-15] Although the permanently charged quaternary dopamine analogue **2** has been reported to be inactive in stimulating dopamine-sensitive adenylate cyclase, a D_1-dopamine system, it possessed direct dopamine agonist activity in the K^+-induced release of acetylcholine, a D_2-dopamine receptor model system. This is the first instance of a quaternary derivative of dopamine displaying dopaminergic agonist effects.[19] We have also shown that permanently charged analogues, sulfonium analogue **4** and selenonium analogue **6**, are active in this D_2-dopamine receptor system along with the quaternary salt of apomorphine. In contrast, at the same concentration (30.0 μM), the uncharged sulfide

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3 and selenide 5 were inactive at inhibition of the K^+-induced release of acetylcholine. Also, as shown in the table, the sulfide 3 at a very high concentration (1000 μM) did not show agonist activity in the dopamine-depleted tissue. We also investigated the various oxidation states of the sulfur atom via sulfoxide 7 and sulfone 8, and neither of these agents showed direct dopamine agonist activity. These observations suggest that a positive charge is optimal for binding and activation of D_2-dopamine receptors.

In another examination, we studied the effect of the addition of a hydroxyl group to dopamine, using norepinephrine, and found significant reduction in dopamine agonist activity. Only at 60 μM did norepinephrine show dopamine agonist activity. We then examined the effect of the addition of a hydroxy group to the sulfonium dopamine analogue 4 to give rise to 9, and this latter compound was significantly less active than the parent 4 as shown in Table I. Thus, the relative order of activity of 4 and 9 is in agreement with that observed with norepinephrine and dopamine on dopamine receptors.

Our results indicate that changes in the nitrogen atom of dopamine can profoundly affect the D_2-dopamine receptor activity. These observations indicate that for optimum dopamine activity in a series, e.g., sulfide/sulfonium, selenide/selenonium, the charged species is preferred. Clearly, additional experiments are indicated to probe the molecular species requirements for D_1- and D_2-dopamine agonists and antagonist activity.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus or a Fisher-Johns melting point stage apparatus. Spectral data were obtained with a Beckman 4230 infrared spectrophotometer and Bruker HX-90E NMR spectrometer (90 MHz) in pulse mode. Mass spectra were obtained with a Du Pont Model 21-491 double-focusing mass spectrometer or at The Ohio State University Chemical Instrument Center, by use of a Kratos-MS 30 mass spectrometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Analytical results for elements indicated were within ±0.4% of the theoretical values.

3′,4′-Dihydroxy-2-(methylthio)acetophenone (11). Methanethiol (0.4 mol) obtained as a liquid by condensing in a dry ice/acetone bath was added to a KOH/CH_3OH solution (0.4 mol of KOH in 100 mL of CH_3OH) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, and 2-chloro-3′,4′-dihydroxyacetophenone (18.66 g, 0.1 mol) was added to the solution. KCl precipitated immediately. The mixture was stirred at room temperature for 2 h, and cold 10% HCl was added to acidify the solution. The reaction mixture was extracted with EtOAc. The solvent was removed under reduced pressure (a Clorox trap was used between the aspirator and the rotavap to prevent mercaptan escape). The yellow solid obtained was recrystallized from CH_2Cl_2 to give 15.3 g (77%) of a tan solid 11: mp 107–108 °C; ^1H NMR ($CDCl_3$) δ 7.66 (d, 1 H, $J_{2,6}$ = 1.9 Hz, Ar H), 7.52 (dd, 1 H, $J_{5,6}$ = 8.6 Hz, Ar H), 6.94 (d, 1 H, Ar H), 5.87 (s, 2 H, OH), 3.72 (s, 2 H, $COCH_2$), 2.15 (s, 3 H, SCH_3). Anal. ($C_9H_{10}O_3S$) C, H, S.

1-(3,4-Dihydroxyphenyl)-2-(methylthio)ethanol (12). 3′,4′-Dihydroxy-2-(methylthio)acetophenone (11; 1.0 g, 5 mmol) was dissolved in 50 mL of warm water (75 °C). The solution was cooled down to room temperature, and $NaBH_4$ (1.02 g, 27 mmol) was added slowly and stirred overnight at room temperature. The reaction mixture was extracted with EtOAc, and the combined EtOAc solution was dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a yellow solid, which was recrystallized from CH_2Cl_2 to give 12 as a white solid (0.91 g, 90%): mp 110–111 °C; ^1H NMR (CD_3OD) δ 6.81 (brs, 1 H, Ar H), 6.70 (brs, 2 H, ArH), 4.58 (m, 1 H, Ar CH), 2.7 (m, 2 H, CH_2), 2.00 (s, 3 H, SCH_3). Anal. ($C_9H_{12}O_3S$) C, H, S.

[2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl]dimethylsulfonium Iodide (9). The methyl sulfide 12 (200 mg, 1 mmol) was dissolved in a minimum amount of CH_3CN at room temperature, and excess CH_3I (31.3 mmol, 2 mL) was added to the solution. The reaction mixture was kept in a freezer overnight to give 342 mg of white solid 9 (quantitative yield): mp 140 °C; ^1H NMR (Me_2SO-d_6) δ 8.97, 8.96 (2 s, Ar OH), 6.78 (brs, 1 H, Ar H), 6.69 (brs, 2 H, Ar H), 6.12 (d, 1 H, $J_{H,OH}$ = 3.8 Hz, OH), 4.91–4.87 (m, 1 H, CHOH), 3.40 (m, 2 H, CH_2), 2.90 (s, 6 H, $S(CH_3)_2$). Anal. ($C_{10}H_{15}O_3SI$) C, H, S.

1-(3,4-Dihydroxyphenyl)-2-(methylthio)ethane (3). Acetophenone 11 (396 mg, 2.0 mM) was dissolved in 7 mL of CF_3COOH, and Et_3SiH (2.0 mL, 12.6 mmol in 10 mL of CH_2Cl_2) was added dropwise to the solution under argon. The reaction mixture was stirred at room temperature for 7 h, and then 25 mL of H_2O was added. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic solutions were washed with water (3 × 20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. The volatile silicon mixture was removed by vacuum at 70 °C (1 mmHg). The desired product was purified by silica gel flash column chromatography with EtOAc/petroleum ether (1:1) to give a pale yellow oil, yield 72%. A small sample was distilled for analysis: bp 186 °C (1.3 mm); ^1H NMR ($CDCl_3$) δ 6.6–6.8 (m, 3 H, Ar H), 2.6–2.8 (m, 4 H, Ar CH_2CH_2S), 2.11 (s, 3 H, CH_3). Anal. ($C_9H_{12}O_2S$) C, H, S.

2-(Methylsulfinyl)-1-(3,4-dihydroxyphenyl)ethane (7). The sulfide 3 (184 mg, 1 mmol) was dissolved in 25 mL of CH_2Cl_2 and cooled to 0 °C. *m*-Chloroperbenzoic acid (173 mg, 1 mmol) in 5 mL of CH_2Cl_2 was added dropwise. The sulfoxide began to precipitate out of the solution immediately. The reaction mixture was stirred and kept at 0 °C for 3 h. The sulfoxide was collected by filtration and washed with CH_2Cl_2, to give 191 mg of white solid 7 (95%): mp 158–159 °C; ^1H NMR (Me_2SO-d_6) δ 8.74 (brs, 2 H, OH), 6.70–6.42 (m, 3 H, Ar H), 3.32–2.79 (m, 4 H, CH_2CH_2), 2.54 (s, 3 H, CH_3). Anal. ($C_9H_{12}O_3S$) C, H, S.

2-(Methylsulfonyl)-1-(3,4-dihydroxyphenyl)ethane (8). The sulfoxide 7 (100 mg, 0.5 mmol) was dissolved in 15 mL of DMF. To this mixture was added dropwise 86 mg of *m*-chloroperbenzoic acid (0.5 mmol) in 5 mL of DMF at room temperature. The reaction mixture was stirred at room temperature overnight, and then the solvent was removed by vacuum at 80 °C (1 mmHg). The solid residue was washed with ether and CH_2Cl_2 to give 97 mg of gray solid (90%): mp 152–153 °C; ^1H NMR (Me_2SO-d_6) δ 8.7 (s, 2 H, OH), 6.70–6.45 (m, 3 H, Ar H), 3.38–3.21 (m, 2 H, CH_2SO_2), 2.92 (s, 3 H, CH_3), 2.92–2.71 (m, 2 H, $ArCH_2$). Anal. ($C_9H_{12}O_4S$) C, H, S.

1-Chloro-2-(3,4-dihydroxyphenyl)ethane (13). 2-Chloro-3′,4′-dihydroxyacetophenone (10; 9 g, 48 mmol) was suspended in trifluoroacetic acid (60 mL). Triethylsilane (28 mL, 0.18 mol) was added dropwise with stirring, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then poured into ice water (200 mL) and extracted with methylene chloride (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to leave a white solid, which was washed with petroleum ether and filtered, providing chloride 13, yield 7.18 g (86%): mp 99–101 °C; IR (KBr) 3300 cm^{-1} (br, OH); ^1H NMR ($CDCl_3$) δ 6.69–7.00 (m, 3 H, Ar H), 5.06, 4.96 (2 s, 2 H, OH), 3.75 (t, 2 H, CH_2Cl), 3.04 (t, 2 H, Ar CH_2). Anal. ($C_8H_9O_2Cl$) C, H.

1-Chloro-2-[3,4-bis(benzyloxy)phenyl]ethane (14). The catechol chloride 13 (3 g, 17 mmol), potassium carbonate (5 g), sodium iodide (300 mg), and benzyl chloride (5.35 g, 42 mmol) were suspended in acetone and heated to reflux for a period of 15 h. Water (75 mL) was added, and the mixture was extracted with ether (3 × 75 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated to an oil, which was purified by flash chromatography (ethyl acetate/hexane, 5:95) to provide 14 as a colorless semisolid, yield 3.5 g (57%). An analytical sample was prepared by crystallization from methanol/ethanol and filtration in the cold: mp 28 °C; IR (neat) 1595 cm^{-1} (aromatic); ^1H NMR (acetone)-d_6 δ 7.29–7.51 (m, 10 H, Ar H), 6.7–7.1 (m, 3 H, Ar H), 5.1 (2 s, 4 H, OCH_2Ar), 3.73 (t, 2 H, CH_2Cl), 2.96 (t, 2 H, Ar CH_2). Anal. ($C_{22}H_{21}O_2Cl$) C, H.

1-[3,4-Bis(benzyloxy)phenyl]-2-(methylseleno)ethane (15). Under an argon atmosphere, dimethyl diselenide (1.52 g, 8 mmol) was dissolved in tetrahydrofuran (15 mL), and sodium borohydride (856 mg, 22.5 mmol) in ethanol (15 mL) was added dropwise at such a rate that hydrogen evolution was not too vigorous. To the decolorized solution was added dropwise a solution of bis(benzyloxy) chloride 14 (1.98 g, 5.6 mmol) in 16 mL of a 25% etha-

nol/methanol solution. After addition was complete, the mixture was refluxed under argon for 12 h. After cooling, water (50 mL) was added, and the mixture was extracted with chloroform (3 × 60 mL). The combined organic layers were washed two times with water, dried ($MgSO_4$), and evaporated to an oil, which was purified by flash chromatography (ethyl acetate/hexane, 1:9). Selenide **15** was obtained as a colorless oil, which crystallized upon storage in a freezer, yield 2.14 g (92%). An analytical sample was prepared by recrystallization from hexane/ethyl acetate: mp 41–42 °C; ^1H NMR ($CDCl_3$) δ 7.29–7.47 (m, 10 H, Ar H), 6.68–6.93 (m, 3 H, Ar H), 5.1 (2 s, 4 H, OCH_2 Ar), 2.59–2.95 (m, 4 H, Ar CH_2CH_2Se) 1.95 (s, 3 H, $SeCH_3$). Anal. ($C_{23}H_{24}O_2Se$) C, H.

1-(3,4-Dihydroxyphenyl)-2-(methylseleno)ethane (5). Bis(benzyloxy) selenide **15** (822 mg, 2 mmol) was dissolved in ethanethiol (20 mL), and boron trifluoride etherate (4.5 g, 32 mmol) was added. The reaction mixture was stirred for 1 h at room temperature and then poured into water (50 mL). The mixture was extracted with chloroform (3 × 50 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to an oil, which was purified by flash chromatography (hexane/ethyl acetate, 2:1). Catechol selenide **5** was obtained as a colorless, somewhat unstable oil, yield 300 mg (65%). A solid sample may be obtained by thorough vacuum drying and freezer storage for several days: mp 36–37 °C; ^1H NMR ($CDCl_3$) δ 6.56–6.84 (m, 3 H, Ar H), 2.60–2.93 (m, 4 H, Ar CH_2CH_2Se), 1.98 (s, 3 H, $SeCH_3$). Anal. ($C_9H_{12}O_2Se$) C, H.

[2-(3,4-Dihydroxyphenyl)ethyl]dimethylselenonium Iodide (6). Selenide **5** (60 mg, 0.26 mmol) was dissolved in 2 mL of acetonitrile, and 2 mL (31.3 mmol) of methyl iodide was added. The mixture was set in a freezer for 75 h, resulting in the formation of a white solid. Removal of supernatant liquid by pipet, followed by drying, yielded 60 mg (62%) of a white solid **6**: mp 106–108 °C; ^1H NMR (D_2O) δ 6.58–6.82 (m, 3 H, Ar H), 3.42 (t, 2 H, J = 7.2 Hz, CH_2Se), 2.93 (t, 2 H, Ar CH_2), 2.44 (s, 6 H, $Se(CH_3)_2$). Anal. ($C_{10}H_{15}O_2ISe$) C, H, Se.

Inhibition of the K^+-Induced Release of [^{3}H]Acetylcholine from Striatal Slices. Striatal tissue rostral to the anterior commissures was dissected and then cut into 0.5 mm × 0.5 mm sections by using a McIlwain tissue chopper. The tissue was dispersed in Krebs–Ringer bicarbonate medium containing ascorbic acid, 0.6 mM, Na_2EDTA, 0.03 mM, and glucose, 11 mM. The medium was bubbled with a 95% O_2/5% CO_2 mixture. The slices were incubated for 20 min with 0.1 M [^{3}H]choline ([*methyl*-^{3}H]choline chloride, 15 Ci/mmol purchased from Amersham International Ltd. (Amersham, U. K.)). After being rinsed, the slices were transferred to a superfusion system and were superfused at a constant rate of 0.5 mL/min. At 35 min after the onset of the superfusion, the superfusate was collected every 5 min. At 55 min, transmitter release was stimulated by superfusion with medium containing 12.5 mM K^+ for 10 min (two fractions). The increase in the potassium concentration was compensated for by an equimolar decrease in the sodium concentration of the medium. The test drugs were added to the medium 10 min before the addition of high K^+ and were also present in the high-K^+ medium. At the end of the superfusion, the radioactivity remaining in the tissue slices was extracted by homogenizing the tissue in 0.4 N perchloric acid. The radioactivity in the superfusate samples and the tissue extracts was determined by liquid scintillation counting.

The outflow of tritium in the superfusate medium during each 5-min interval is expressed as a fraction of the total tritium content of the tissue at the beginning of each interval (fractional release). This was calculated by correcting the tissue content of each fraction for the radioactivity lost to the medium. The K^+-induced stimulation of tritium release is the mean of the fractional release obtained during the two 5-min periods that high K^+ was present in the medium above the base line of spontaneous outflow. Spontaneous outflow is the mean fractional release of tritium obtained in the two 5-min intervals preceding the addition of the high-K^+ medium. The effects of the test drugs on the release of tritium were always compared to that determined when the test drugs were not added to the medium.

Since several previous studies have demonstrated that radioactive acetylcholine formed from radioactive choline is released from brain slices by K^+ depolarization, the tritium released by the high-K^+ medium was not chemically characterized in these experiments. In those studies, physostigmine was added to the medium to inhibit the metabolism of acetylcholine. However, the inhibition of acetylcholine metabolism results in a high extracellular concentration of acetylcholine, which has been shown to inhibit the depolarization-induced release of acetylcholine by the process of feedback inhibition. In the present study, physostigmine was omitted from the medium. Under our conditions, the K^+-induced release of tritium was completely dependent on the presence of calcium ions in the superfusion medium (data not shown).

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