(E)-4-Bromo-1-phenyl-1-butene (20a). Prepared from **18a** by the same procedure used for **19a** to give 58% of a colorless oil, bp 76–82 °C (0.08 mm) [lit.[26] bp 144–145 °C (10 mm)].

(E)-4-Bromo-1-[3-(trifluoromethyl)phenyl]-1-butene (20b). Compound **20b** was prepared from **18b** by the same procedure used for **20a** to give 49% of a clear yellow liquid, bp 65–67 °C (0.07 mm). Anal. ($C_{11}H_{10}BrF_3$) C, H.

Pharmacology. The isolated perfused rabbit ear artery preparation described by Steinsland et al.[8] was used in these studies. In brief, male rabbits (2–4 kg) were sacrificed by a blow to the head, and a 2–4 cm portion of the central ear artery was disected free at the base of the ear, cannulated at both ends, and mounted in a perfusion chamber immersed in a bath maintained at 37 °C. Perfusion flow was delivered at a constant rate (2 mL/min) from a polystaltic pump. Changes in the intraluminal flow pressure were measured with a Statham P23AA pressure transducer and recorded on a physiograph equipped with strip recorder. Both the intraluminal and extraluminal perfusion fluid was oxygenated in Krebs bicarbonate solution. All test compounds were introduced into the extraluminal flow of perfusate following an initial 2-h equilibration period. The periarterial sympathetic nerves were excited by a field stimulation produced by rectangular pulses of 1-ms duration and a supramaximal voltage (80–90 V), delivered from a Grass Model S-8 stimulator, and applied through platinum electrodes mounted at the top and bottom of the perfusion chamber. The dissociation contants (K_B values) were calculated using the formula K_B = antagonist concentration/(dose ratio −1), where the dose ratio represents the concentration of dopamine required to produce 50% inhibition of the constrictor response to nerve stimulation in the presence of antagonist divided by the dopamine concentration required to produce the same degree of inhibition with no antagonist present.

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Synthesis and Pharmacological Evaluation of Sulfonium Analogues of Dopamine: Nonclassical Dopamine Agonists

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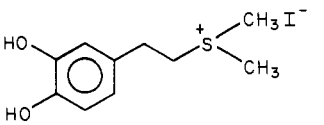
In order to test whether the nitrogen/ammonium moiety in the dopamine molecule is required for dopaminergic activity, we have synthesized two sulfonium analogues of dopamine and tested them for biological activity in an in vivo and in an in vitro system. These analogues have provided a means of investigating (1) the ability of the sulfonium function to serve as a bioisostere for the dopamine amino group and (2) whether charged molecules have the ability to bind to dopamine receptors. Both sulfonium analogues, **1** and **2**, as well as dopamine, when injected directly into the striatum of rats, previously lesioned unilaterally with 6-hydroxydopamine (6-OHDA), produced circling behavior. The potency of the sulfonium analogues was approximately one-tenth that of dopamine. The effects of all three compounds on circling were inhibited by the dopamine antagonist haloperidol. In addition, both sulfonium analogues inhibited the high affinity binding of radiolabeled dopamine to a crude membrane fraction prepared from the striatum. This study suggests that the nitrogen atom found in the dopamine molecule is not essential for dopaminergic activity, since the nitrogen can be replaced by a sulfonium functional group for this activity.

In the late 1950's Blaschko[1] suggested that dopamine, well known as a precursor of norepinephrine and epinephrine, might have a physiological role of its own. Since that time, dopamine has been shown to be a neurotransmitter present in mammalian brain and periphery, and a large amount of research on the chemistry, physiology, and pharmacology of this substance has been reported. Abnormal dopaminergic transmission has been implicated in a wide variety of diseases, including Parkinson's disease, mental disorders, Huntington's disease, tardive dyskinesia, and neuroendocrine disorders associated with prolactin control.[2]

The structural requirements for compounds producing dopaminergic activity have been the subject of considerable study.[3-6] A variety of studies have been directed toward understanding the conformational and configurational requirements for dopamine receptors. Among the ligands showing dopaminergic activity, the structural requirements for nitrogen substitution do not seem highly stringent, since primary, secondary, and tertiary amines have shown dopaminergic activity.

The present study is directed toward a better understanding of what the basic structural requirements are for dopaminergic activity. We were interested in knowing if the nitrogen atom of dopamine could be replaced with other heteroatoms and still retain dopamine agonist activity. The synthesis and preliminary biological investigations including dopamine binding and behavioral studies of the two sulfonium analogues of dopamine, **1** and **2**, represent our initial effort in this area.



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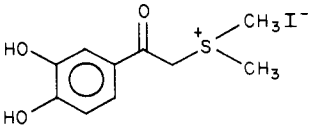

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Chemistry. The synthesis of sulfonium analogue **1** is outline in Scheme I. Following esterification of piperonylic acid, the resulting ester was treated with the lithium salt of dimethyl sulfoxide to give keto sulfide **4**. Reduction of

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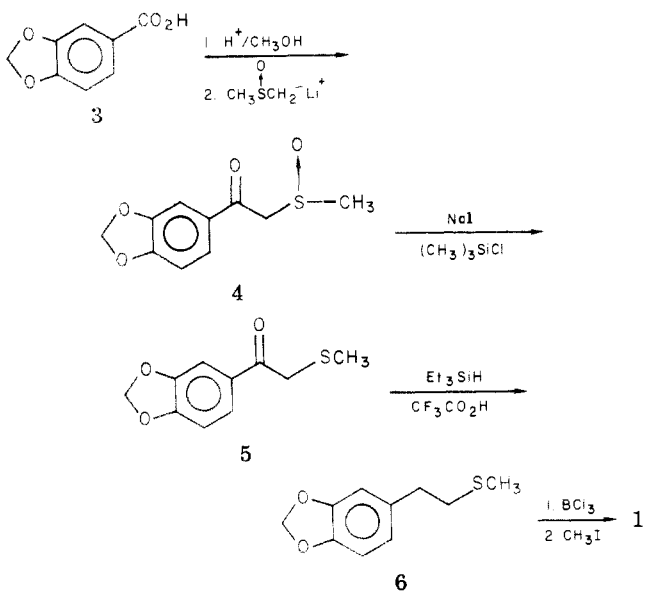
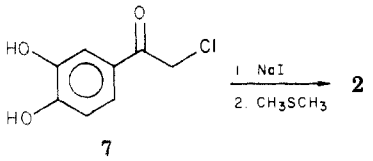
Scheme I



Scheme II



the sulfoxide with trimethylchlorosilane and sodium iodide according to the procedure of Olah[7] provided the sulfide **5** in 89% yield. Reduction of the keto sulfide with triethylsilane in trifluroacetic acid gave the sulfide **6**, which upon treatment with boron trichloride, followed by methyl iodide, gave the desired sulfonium salt **1**. The preparation of compound **2** is illustrated in Scheme II. Treatment of α-chloro-3,4-dihydroxyacetophenone (**7**) with NaI in acetone, followed by dimethyl sulfide, gave sulfonium salt **2**.

Inhibition of [^{3}H]Dopamine Binding by the Sulfonium Analogues of Dopamine. A crude membrane fraction was prepared from striatum of rat brain as described under Experimental Section. The specific binding of dopamine to this membrane fraction was determined by measuring the displacement of radiolabeled dopamine (2 nM) by unlabled dopamine (1×10^{-8} to 1×10^{-5} M). The displacement of [^{3}H]DA was maximal at a concentration of 1 μM and produced a 32% inhibition of the total binding (Figure 1). The amount of radioactivity displaced by 1 μM dopamine was defined as specific binding. The concentration of unlabeled dopamine required to reduce specific binding of tritiated dopamine by 50% was 2.9×10^{-8} M. The two analogues **1** and **2** also caused inhibition of the specific binding of [^{3}H]dopamine at low concentrations. However, the maximal degree of inhibition of total [^{3}H]dopamine binding by these two agents, **1** and **2**, was 19 and 29% only (Figure 1). The concentration of **2** required to inhibit specific binding by 50% was 3.7×10^{-7} M, while that of **1** was 4.4×10^{-7} M. In contrast, the sulfur-containing compound, trimethylsulfonium iodide, caused only 9% inhibition of the [^{3}H]DA binding to striatal membranes, even at very high concentrations (3 to 30 μM).

In order to determine if the two dopamine analogues and trimethylsulfonium iodide were binding to the same site as the unlabeled dopamine, experiments were designed to observe the effect of adding a high concentration of these compounds to a 1×10^{-6} M concentration of unlabeled dopamine. The results of the additive experiments are presented in Table I. Addition of the two analogues to 1 μM concentration of unlabeled dopamine did not cause any further inhibition of [^{3}H]DA binding, while trimethylsulfonium iodide caused further displacement of [^{3}H]DA binding.

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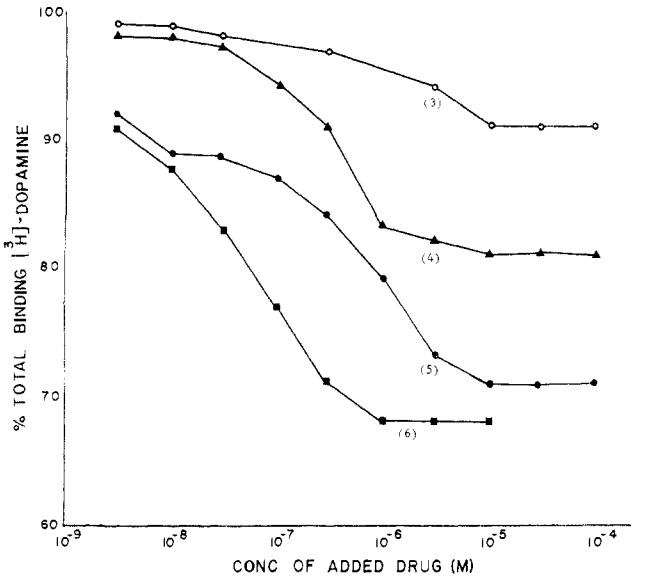

Figure 1. Inhibition of [^{3}H]dopamine binding by dopamine analogues. Increasing concentrations of drug were added to tubes containing 2 nM [^{3}H]dopamine and the crude membrane preparation of striatal tissue. The numbers in parentheses indicate the number of experiments, and each experiment represents duplicate or triplicate estimations. For all values, the SEM was less than 12% of the mean values. Dopamine (■–■), sulfonium analogues 1 (▲–▲) and 2 (●–●), and trimethylsulfonium iodide (○–○).

Table I. Additive Effect of Sulfonium Salts on the Maximal Binding Produced by Unlabeled Dopamine[a]

drug added	concn of added drug, μM	% total binding
dopamine (alone)	1	72 ± 2.4
dopamine + 1	3	72 ± 1.8
	10	72 ± 2
	30	72 ± 1.6
dopamine + 2	3	72 ± 1.2
	10	72 ± 2.1
	30	72 ± 1.8
dopamine + trimethylsulfonium iodide	3	68 ± 0.8
	10	63 ± 1.0
	30	63 ± 1.1

[a] Rat striatal tissue was assayed with 2 nM [^{3}H]dopamine and high concentrations of either the analogues or trimethylsulfonium iodide were added along with dopamine (1 μM). The results are expressed as the mean plus or minus SEM of three experiments, each experiment done in duplicate.

Circling Behavioral Studies. In order to determine whether the dopamine analogues exert a functional effect, dopamine and the dopamine analogues were injected into the caudate nucleus of rats with 6-hydroxydopamine-induced lesions in the substantia nigra. All of the drugs produced a dose-related circling in a direction contralateral to the injection site. The onset of turning was observed within 5 min, and the peak effect was observed within 45 to 90 min after injection (Figure 2). The circling behavior induced by dopamine or the analogues continued for a period of 2 h.

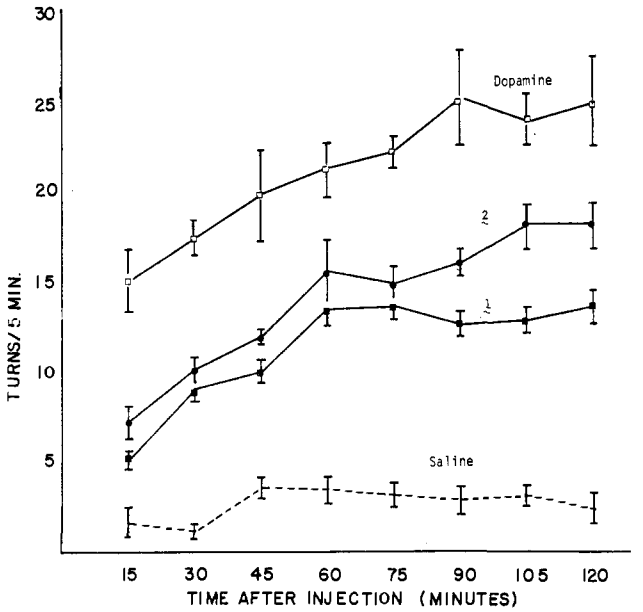

Figure 2. Time course of circling produced by dopamine and the dopamine analogues in rats lesioned unilaterally in the substantia nigra with 6-hydroxydopamine. Dopamine (10 nm), the dopamine analogues 1 and **2** (30 nm), or saline was injected directly into one striatum on the same side as the 6-OHDA-induced lesion. After the injection, the rats were placed in a round-bottom flask, and the number of complete contralateral turns was recorded at 5-min intervals for 2 h. Each point represents the mean plus or minus SEM of five to six experiments. Dopamine (□–□), sulfonium analogue **2** (●–●), sulfonium analogue 1 (■–■), and saline (---).

In order to determine if the circling produced by these agents could be blocked by a dopamine receptor blocking agent, haloperidol (0.08 mg/kg) or vehicle (1% lactic acid) was given (ip) 45 min after intrastriatal injection of dopamine or the analogues (Figure 3). The vehicle used for haloperidol caused a transient decrease in circling behavior immediately after injection, which returned to the preinjection level within 30 min (Figure 3). Haloperidol produced a long-lasting inhibition of the circling behavior induced by either dopamine or the dopamine analogues (Figure 3).

Discussion

The binding of [^{3}H]DA to rat striatal membranes has been developed as a method for studying dopamine receptors. As observed in earlier studies,[8,9] the nonspecific binding of dopamine is very high in this system and represents about 65–70% of total binding, and two binding sites have been reported for [^{3}H]DA in rat striatum.[8] However, the binding of [^{3}H]DA to the high-affinity site is saturable. In addition, the affinity of [^{3}H]DA for the high-affinity site, as well as the drug specificity of this site, is similar to that found in preparations from calf caudate nucleus where there is less nonspecific binding.[8] Thus, the properties of the high-affinity binding of [^{3}H]DA are consistent with the concept that [^{3}H]DA is binding to a receptor for dopamine.

If the sulfur analogues, 1 and 2, of dopamine possess agonist activity, then they should inhibit the binding of [^{3}H]dopamine to striatal membranes. Our results show that both analogues of dopamine, as well as unlabeled

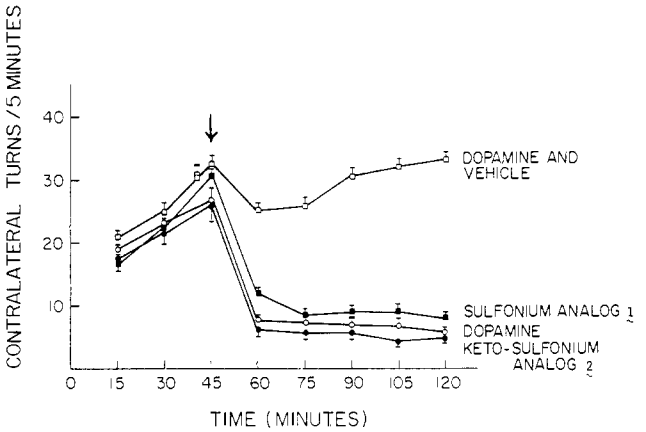

Figure 3. Antagonism by haloperidol of the circling behavior produced by dopamine and the analogues. The contralateral turning produced by intrastriatal injection of DA (10 nm) and the analogues 1 and **2** (30 nm) in rats with unilateral lesion induced by 6-OHDA is presented. Haloperidol (0.08 mg/kg) or vehicle alone was given ip 45 min after the injection of the test compounds (↓). Each graph represents the result of three to five experiments. Dopamine plus haloperidol vehicle alone (□–□), sulfonium analogue 1 plus haloperidol (■–■), sulfonium analogue **2** plus haloperidol (●–●), and dopamine plus haloperidol (○–○).

dopamine, produce a concentration-dependent decrease in [^{3}H]dopamine binding. However, the maximal inhibition of [^{3}H]dopamine binding by the two analogues was less than that of unlabeled dopamine (Figure 1). The results of the additivity experiments (Table I) shows that the combination of the analogues and unlabeled DA (1 μM) at concentrations that maximally inhibit [^{3}H]dopamine binding did not inhibit [^{3}H]dopamine binding further than that produced by unlabeled dopamine alone. This suggests that the analogues of dopamine and unlabeled dopamine are displacing [^{3}H]dopamine from the same high-affinity dopamine binding sites in the striatum. At present we have no explanation of why the maximal inhibition of [^{3}H]dopamine binding by the dopamine analgues is less than that of dopamine. It is possible that the permanent positive charge on the analogues prevents them from gaining access to receptors located deep in the striatal membranes. Alternatively, since recent evidence has suggested that there may be multiple dopamine binding sites, it is possible that the dopamine analogues do not bind to all the sites.[12] Figure 1 shows that the IC_{50} of both dopamine analogues for the inhibition of specific [^{3}H]-dopamine binding is greater than that of dopamine, suggesting that these compounds have a lower affinity for the dopamine binding sites.

To compare the effects of these analogues with dopamine on motor function, the ability of these compounds to produce circling behavior was studied in rats lesioned unilaterally in the substantia nigra with 6-hydroxydopamine.[10] Dopamine and the analogues were injected directly into one striatum ipsilateral to the 6-hydroxydopamine-induced lesion, since these drugs when administered systemically would probably not cross the blood–brain barrier. Previous studies[8,11] have shown that rats with a substantia nigral lesion are very sensitive to the effects produced by the direct injection of dopamine into the striatum on the lesioned side.

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(9) H. L. Komiskey, J. F. Bossart, D. D. Miller, and P. N. Patil, *Proc. Natl. Acad. Sci. U.S.A.*, **75**, 2641 (1978).
(10) P. E. Setler, M. Malesky, J. McDevitt, and K. Turner, *Life Sci.*, **23**, 1277 (1978).
(11) B. Costall and R. J. Naylor, in "Cocaine and Other Stimulants", Eds. E. H. Ellirwood, Jr., and M. Marlyne Kilbey, Eds., 1976, p 47.

Table II. Contralateral Rotation Produced by Intrastriatal Injection of Catecholamines in Rats with Unilateral 6-Hydroxydopamine-Induced Lesions of the Substantia Nigra[a]

test compd	dose, nmol	max rate of rotn, turns/5 min
dopamine	1	8.25 ± 0.6
	3	19.5 ± 1.04
	10	39.75 ± 2.25
1	10	11.25 ± 1.49
	30	20.75 ± 1.31
	90	31.75 ± 2.78
2	10	8.4 ± 1.07
	30	25.33 ± 1.3
	90	38.83 ± 4.36
ascorbic acid & saline	2 μL	4.5 ± 1.23

[a] Rats were injected with tranylcypromine (1 mg/kp ip). Three hours later, the test compounds were injected into the striatum on the same side as the lesion. After the injection they were placed in the hemispherical glass chambers and circling was recorded for 2 h. The results are expressed as the mean maximum rate of rotation in 5 min plus or minus SEM.

The two analogues caused contralateral turning in lesioned rats in a similar manner to dopamine. The turning elicited by the analogues was dose dependent, but higher doses of the analogs are required to produce maximum rates of rotation equivalent to that of dopamine (Table II). This suggests that these analogues have a lower affinity or intrinsic activity for dopamine receptors. However, we cannot exclude the possibility that the lower rates of circling produced by the analogues may in part be related to the inability of these permanently charged molecules to distribute to sites reached by dopamine. The contralateral circling produced by the analogues, as well as dopamine, was blocked by the systemic administration of low doses of haloperidol. This observation supports the hypothesis that the behavioral effects of the analogues are mediated through the activation of dopamine receptors.

Since the sulfonium analogues 1 and 2 are permanently charged, they apparently interact with the dopamine receptors as charged species. With dopamine and related coumpounds a fundamental question remains:[4,13-16] is the molecular species of dopamine and related compounds when interacting with dopamine receptors? Armstrong and Barlow[13] suggested that the active form of apomorphine at dopamine receptors was the uncharged phenolic amine. Goldberg and co-workers[17] have drawn hypothetical structures of dopamine and related molecules interacting with dopamine receptors in the uncharged phenolic amine form. Others have indicated that the lone pair on the teritary nitrogen of apomorphine is required for ligand-receptor interaction.[18] Cassady and co-worker[15] have indicated that the nitrogen at the 6 position in ergoline derivatives should be basic or uncharged for dopaminergic activity in inhibiting the release of prolactin, while Iversen and colleagues[16] have also indicated *N,N,N*-trimethyldopamine has very low activity on dopamine-sensitive adenyl cyclase. Topographical methods[19-21] have been postulated for dopamine receptors utilizing either agonist or antagonist molecules. Humber and co-workers[20,21] have suggested that it is the uncharged form of butaclamol which interacts with the dopamine receptor, since the drug has a pK_a of 5.9 and would exist primarily in the deprotonated form at physiological pH. However, dopamine would exist to a large extent in the protonated form at physiological pH[4] and, thus, it is difficult to use primary, secondary, or tertiary amine agonists or antagonists to indicate what molecular species is interacting with the dopamine receptor. Also, dopamine agonists and antagonists are possibly not binding to the same binding site. From our studies it appears that charged molecules are capable of binding to the dopamine receptor and eliciting a dopamine agonist response. Further studies would appear to be warranted in attempts to determine the molecular species preferred at the dopamine receptors and the spectrum of dopaminergic activity of sulfonium analogues of dopamine.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Spectral data were obtained using a Beckman 4230 infrared spectrophotometer and a Varian A-60A NMR (60 MHz) or on a 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. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Analytical results for elements indicated were within ±0.4% of the theoretical values.

3′,4′-(Methylenedioxy)-2-(methylsulfinyl)acetophenone (4). Into a 250-mL flask equipped with a reflux condenser was placed piperonylic acid (10.0 g, 0.06 mol), methanol (45 mL), and concentrated sulfuric acid (1.4 mL). The mixture was then refluxed for 12 h. After cooling, the solution was neutralized with 5% sodium bicarbonate solution, extracted with CH_2Cl_2 (3 × 50 mL), washed with H_2O (2 × 75 mL), and dried over $MgSO_4$. Solvent evaporation yielded a light yellow oil which crystallized upon standing. The solid was recrystallized from ether/hexane to give 9.7 g (90%) of methyl 3,4-(methylenedioxy)benzoate: mp 48–50 °C;[22] IR (KBr) 1700 (C=O) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 7.64 (d of d, J = 8.5 and 1.8 Hz, 1 H, Ar H), 7.46 (d, J = 1.8 Hz, 1 H, Ar H), 6.82 (d, J = 8.5 Hz, 1 H, Ar H), 6.01 (s, 2 H, CH_2), 3.83 (s, 3 H, CH_3).

Into a 250-mL flask equipped with mechanical stirrer, condenser, and dropping funnel was added 30 mL of Me_2SO and 100 mL of dry THF. The system was placed under argon and cooled to 0 °C. Next, 42 mL (45.5 mmol, 2.5 equiv) of a solution of 1.09 M methyllithium in ether was transferred to the dropping funnel via syringe. While maintaining vigorous stirring, the methyllithium was added dropwise. During this time a white slurry of the lithium salt of dimethyl sulfoxide formed. After the addition was complete, 3.3 g (18.2 mmol) of methyl piperonylate in 10 mL of THF was added as rapidly as possible. The slurry was allowed to stir in the cold for 2 h, followed by quenching with a few milliliters of methanol. Solvent was removed in vacuo, and the residue was poured into a saturated ammonium chloride solution. The product was extracted with CH_2Cl_2 (4 × 50 mL), washed with H_2O (3 × 75 mL) and saturated salt solution, and dried over Na_2SO_4. Removal of solvent afforded a white solid, which was recrystallized from Et_2O/CH_2Cl_2 to give a product yield of 3.9 g (94%): mp 107–108 °C; IR (KBr) 1040 (S→O) cm^{-1}; NMR

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(22) E. Mosettig and A. Burger, *J. Am. Chem. Soc.*, **52**, 2988 (1930).

($CDCl_3$, 90 MHz) δ 7.59 (d of d, J = 8.1 and 2.7 Hz, 1 H, Ar H), 7.45 (d, J = 2.7 Hz, 1 H, Ar H), 6.91 (d, J = 8.1 Hz, 1 H, Ar H), 6.08 (s, 2 H, CH_2), 4.40 (d, J_{gem} = −14 Hz, 1 H, 0.5 CH_2), 4.23 (d, J_{gem} = −14 Hz, 1 H, 0.5 CH_2), 2.73 (s, 3 H, CH_3). Anal. ($C_{10}H_{10}O_4S$) C, H, S.

3′,4′-(Methylenedioxy)-2-(methylthio)acetophenone (5). To a 100-mL flask equipped with condenser and dropping funnel were added 4 (1.0 g, 4.4 mmol) and sodium iodide (2.0 g, 13.2 mmol) dissolved in 20 mL of acetonitrile. The system was then placed under argon and cooled to 0 °C. A solution of trimethylchlorosilane (0.7 g, 6.6 mmol) in acetonitrile was then added dropwise. The reaction was then allowed to warm to room temperature and stir for 3 h. The mixture was then taken up into ether and washed with 10% aqueous sodium thiosulfate (2 × 50 mL). The aqueous phase was then extracted with Et_2O (2 × 75 mL). The combined organic phases were washed with a saturated salt solution and dried over N_2SO_4. Solvent removal afforded a pale yellow oil which crystallized upon standing. The solid was recrystallized from hexane/ether to give a product yield of 0.82 g (89%): mp 43–44 °C; IR (KBr), 1670 (C=O) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 7.59 (d of d, J = 8.1 and 2.7 Hz, 1 H, Ar H), 7.45 (d, J = 2.7 Hz, 1 H, Ar H), 6.94 (d, J = 8.1 Hz, 1 H, Ar H), 6.04 (s, 2 H, OCH_2O), 3.69 (s, 2 H, CH_2S), 2.13 (s, 3 H, CH_3). Anal. ($C_{10}H_{10}O_3S$) C, H, S.

1-[3,4-(Methylenedioxy)phenyl]-2-(methylthio)ethane (6). Carbonyl reduction of the β-ketosulfide was accomplished by dissolving 5 (1.0 g, 4.7 mmol) in 15 mL of trifluoroacetic acid, followed by treatment with 2 mL (1.36 g, 2.5 equiv) of triethylsilane. The mixture was allowed to stir at room temperature, under argon, for 3 h. The solution was then taken up into methylene chloride and washed with 10% sodium hydroxide until neutral. The aqueous phase was then extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were dried over sodium sulfate. Removal of solvent in vacuo afforded a yellow oil, which was chromatographed on silica gel with CH_2Cl_2, for removal of silicon byproducts, to yield 0.73 g (80%) of a light brown oil: NMR ($CDCl_3$, 90 MHz) δ 6.81–6.56 (m, 3 H, Ar H), 5.91 (s, 2 H, OCH_2O), 2.89–2.61 (m, 4 H, CH_2CH_2), 2.02 (s, 3 H, CH_3). Anal. ($C_{10}H_{12}O_2S$) C, H.

[2-(3,4-Dihydroxyphenyl)ethyl]dimethylsulfonium Iodide (1). To a solution of 6 (500 mg, 2.5 mmol) in CH_2Cl_2, cooled to 0 °C, was added 5.1 mL of a solution of boron trichloride in CH_2Cl_2 (1 M) via syringe. After addition was complete, the solution was allowed to warm to room temperature and stir for 4 h under argon. The reaction was then quenched with CH_3OH (6 mL) and solvent was removed in vacuo. To the unpurified oil was added an excess of methyl iodide and the mixture was stored for 24 h at 0 °C. The sulfonium salt, 1, formed as a yellow solid, which was recrystallized from Et_2O/CH_3OH to give 652 mg (80%) of a white solid: mp 112–114 °C; (KBr) 3390–3380 (OH) cm^{-1}; NMR (Me_2SO-d_6, 90 MHz) δ 8.90 (br s, 2 H, OH), 6.67–6.50 (m, 3 H, Ar H), 3.58–3.28 (m, 4 H, CH_2CH_2), 2.89 (s, 6 H, 2 × CH_3). Anal. ($C_{10}H_{15}O_2SI$) C, H, S.

[2-(3,4-Dihydroxyphenyl)-2-oxoethyl]dimethylsulfonium Iodide (2). To 5 g of the chloro ketone 7 (0.026 mol) in 250 mL of acetone was added 4.5 g of NaI (0.03 mol) and the mixture was refluxed for 5 h. The mixture was allowed to sit at room temperature overnight. The solid, NaCl, was removed by filtration and dimethyl sulfide (1.67, 0.027 mol) was added to the acetone solution. The solution was allowed to stir at room temperature overnight. The resulting solid was collected by filtration and the solid (3.3 g, 37%) was washed with ether and acetone. The solid was recrystallized from $EtOH/Et_2O$ to give a white crystaline solid: mp 135 °C; NMR (Me_2SO-d_6, 60 MHz) δ 7.25–7.58 (m, 2 H, Ar H), 6.87 (d, J = 8 Hz, 1 H, Ar H), 5.48 (br s, 2 H, CH_2), 3.05 (s, 6 H, 2 × CH_3). Anal. ($C_{10}H_{13}SO_3I$) C, H, S.

Dopamine Receptor Binding Studies. Male Sprague–Dawley rats were prepared for the dopamine binding assay essentially as described by Burt et al.[8] and Kosmiskey et al.[9] The corpora striata were homogenized in 40 vol of cold 50 mM Tris buffer (pH 7.7) at 25 °C, with a Brinkman Polytron PT-10 (setting 6.5 s). The homogenate was centrifuged twice at 50000g for 10 min with rehomogenization (setting 6 s) of the intermediate pellet in fresh buffer. The final pellet was homogenized in 90 vol of cold 50 mM Tris/0.1% ascorbic acid/10 mM pargyline/120 mM NaCl/5 mM KCl/2 mM $CaCl_2$, to give a final pH of 7.1. This homogenate was placed in a 37 °C bath for 5 min and then returned to ice. Incubations (10 min 37 °C) were carried out in a final volume of 2 mL, consisting of 2 nM [^{3}H]dopamine (15.4 Ci/mmol, New England Nuclear), which was added in 100 μL of 0.1% ascorbic acid, 1.8 mL of tissue suspension, annd 100 μL of various concentrations of drugs dissolved in 0.1% ascorbic acid. Incubations were terminated by rapid filtration under vacuum through Whatman GF/B filters with two 5-mL rinses of cold buffer. The filters were placed in scintillation vials containing 10 mL of thrift solve liquid scintillation cocktail (Kew Scientific). The vials were mechanically shaken for 60 min to remove [^{3}H]-dopamine from the filters and thereby minimize self-absorption of tritium. The radioactivity of each sample was determined using a Beckman liquid scintillation spectrometer (Model LS 345). Quench was monitored by an automatic external standard. Counting efficiencies were between 35 and 40%.

Behavioral Studies. The effects of dopamine and the analogues of dopamine were studied in vivo by the direct injection of dopamine into the caudate nucleus on the same side as a unilateral 6-hydroxydopamine-induced lesion of the substantia nigra. Rats were anesthesized with chloral hydrate, 400 mg/kg ip. 6-Hydroxydopamine (8 μg) was injected stereotaxically in a volume of 4 μL into the right substantia nigra using coordinates A 2.4, V 2.4, and L 1.8.[23] A cannula was then implanted into these lesioned rats in the caudate nucleus ipsilateral to the injected substantia nigra. The cannula was aimed at coordinates A 8.2, L 2.5, and V 0.0. Ten days after surgery the animals were tested for circling responses to apomorphine (1 mg/kg sc). Only those lesioned rats which responded to apomorphine with contralateral turning were selected for testing of drugs. The implanted cannula usually remained patent for 2–3 months, and the animals were used repeatedly with a minimum of 3 drug-free days between tests.

Test compounds were infused in a total volume of 2.0 μL at a rate of 1.0 μL/min through an injection cannula inserted into and projecting 1 mm below the implanted caudate cannula. The needle was kept in position for 1 min after the injection. Three hours before the administration of the test compounds, 1 mg/kg of tranylcypromine, ip, was given to inhibit monoamine oxidase.

The rats were kept in a 22-L hemispherical glass chamber for 30 min to allow them to adapt to the test surroundings. The test compounds were then injected into the caudate nucleus. Complete turns (360°) were counted every 5 min at 15-min intervals for a period of 2 h. In some of the animals, haloperidol was injected ip after the circling effect was well established. Control animals received an intracaudate injection of the appropriate vehicle.

Test compounds were dissolved in saline–ascorbic acid and vehicle or distilled water. Apomorphine was dissolved with the addition of 0.1% sodium metabisulfite and haloperidol with the addition of 1% lactic acid.

Histology. Rats were killed at the end of the experiments after the injections of Methylene blue, and the position of the cannula tip was verified.

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