Sulfur Analogues of Psychotomimetic Agents. Monothio Analogues of Mescaline and Isomescaline

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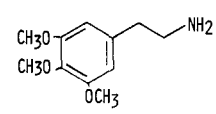
Two monothio analogues of mescaline and three monothio analogues of 2,3,4-trimethoxyphenethylamine (isomescaline) have been synthesized and characterized. Only the two mescaline analogues (3- and 4-thiomescaline) were found to be psychotomimetics in man, being 6 and 12 times more potent than mescaline, respectively. All five compounds can serve as substrates for bovine plasma monoamine oxidase in vitro, but no positive correlation is apparent between the extent of enzymatic degradation and human psychotomimetic potency.

Psychotomimetic agents, drugs which induce a transient altered state of consciousness, are of continuing interest to researchers and clinicians due to their potential utility in psychotherapy and their value in the study of the mechanisms of intellectual and sensory processes. Most psychotomimetics are either ring-substituted phenylalkylamines, of which mescaline (1) is the familiar example, or indolealkylamines, such as lysergic acid diethylamide (LSD). Structurally, these compounds bear a resemblance to the catecholamine and indoleamine neurotransmitters.

The few sulfur analogues that have been reported within this family of centrally active drugs have involved the insertion of sulfur in place of either an NH group, a vinyl unit, or an oxygen atom. This last substitution system, replacement of oxygen by sulfur, is particularly appealing to us because of the isovalent and near isosteric relationship between sulfur and oxygen. To our knowledge, the only analogues of the psychotomimetic drugs that have been reported with a sulfur atom in place of an oxygen atom are (1) the three monothio analogues of 2,4,5-trimethoxyphenylisopropylamine (TMA-2),[1] (2) the 4-thio analogue of 2,5-dimethoxy-4-ethoxyphenylisopropylamine (MEM) and its *n*-propyl counterpart;[2] (3) the 4-thio analogue of 4-hydroxy-*N*,*N*-dimethyltryptamine (Psilocin),[3] and (4) the 5-thio analogue of 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT).[4] Although mescaline is the simplest and the best studied of the phenethylamine psychotomimetics, there has been no report of studies of the several possible thio analogues.[5]

Mescaline is the principal active psychotomimetic component of the peyote cactus *Anhalonium lewinii* and is well known to be centrally effective in man in the dosage range of 300 to 500 mg.[6] The one possible positional isomer in which the adjacency of the three ring oxygens is maintained is 2,3,4-trimethoxyphenethylamine (isomescaline, "reciprocal" mescaline, **2**). The single report[7] on its central



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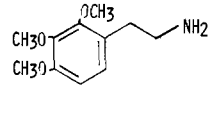

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activity indicates that it is apparently inactive in normal subjects, although it appears to exacerbate the clinical symptoms of schizophrenic patients. There are five monothio analogues of these two compounds possible: two for **1** and three for **2**. This report describes the syntheses of these five compounds and presents preliminary studies on their comparative pharmacology.

Chemistry. The five isomeric amines were synthesized according to the routes outlined in Schemes I–III. Vanillin (**3**) was the starting material for the synthesis of 3,4-dimethoxy-5-(methylthio)phenethylamine (**7**), the 3-thio analogue of mescaline. Thiocyanation, followed by acid-catalyzed cyclization, provided the known thiocarbonate **4**,[16] which was hydrolyzed and methylated to give aldehyde **5**. Knovenagal condensation of **5** with nitromethane yielded the nitrostyrene **6**. The structures of both aldehyde **5** and nitrostyrene **6** were confirmed by their NMR spectra, in which the resonances of the aromatic protons occurred as a pair of doublets, $J \simeq 2$ Hz, consistent with meta coupling. Reduction of the nitrostyrene with aluminum hydride in THF gave the desired amine **7**.

A somewhat novel route was used for the synthesis of the 4-thio analogue of mescaline, 3,5-dimethoxy-4-(methylthio)phenethylamine (**12**, Scheme II). Lithiation of resorcinol dimethyl ether (**8**) with butyllithium–tetramethylethylenediamine, followed by reaction of the resulting aryllithium reagent with dimethyl disulfide, provided the previously reported[17] thioether **9**. Bromination of **9** proceeded uniquely to give **10**, characterized by its

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(14) L. C. Clark, Jr., F. Benington, and R. D. Morin, *J. Med. Chem.*, 8, 353 (1965).
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(16) H. Fiedler, *Arch. Pharm. (Weinheim, Ger.)*, **297**, 226 (1964).
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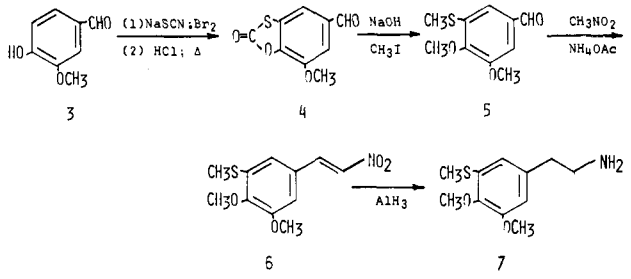
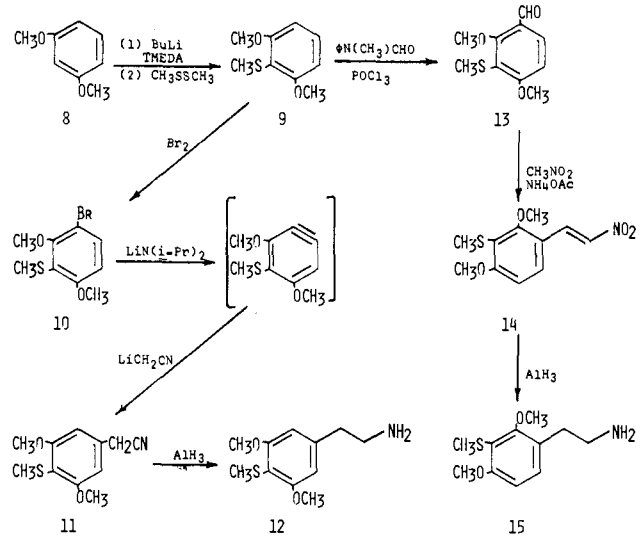
Scheme I. Synthesis of 3,4-Dimethoxy-5-(methylthio)phenethylamine (3-Thiomescaline)



Scheme II. Synthesis of 3,5-Dimethoxy-4-(methylthio)phenethylamine (4-Thiomescaline) and of 2,4-Dimethoxy-3-(methylthio)phenethylamine (3-Thioisomescaline)

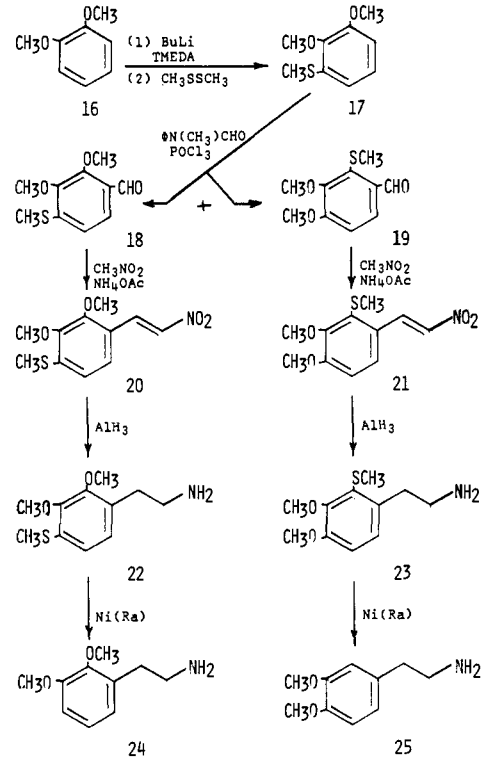


NMR spectrum in which the aromatic proton resonances were a pair of doublets, J = 8.9 Hz. Reaction of the aryl bromide **10** with the lithium salt of acetonitrile in the presence of lithium diisopropylamide provided substituted phenylacetonitrile **11**, presumably via a benzyne intermediate. It has been frequently observed that nucleophilic aromatic substitutions involving benzyne intermediates give rise to rearranged products, and in the case of 2-haloanisoles, the major product is generally a 3-substituted anisole resulting from "cine" substitution.[18] Reduction of nitrile **11** with aluminum hydride afforded the amine **12**. The aromatic proton resonances in the NMR spectra of both nitrile **11** and amine **12** were sharp singlets, which is consistent with two magnetically equivalent meta protons.

The synthesis of 2,4-dimethoxy-3-(methylthio)phenylethylamine (**15**, 3-thioisomescaline) was accomplished by Vilsmeir–Haack formylation of 2,6-dimethoxythioanisole (**9**) to give aldehyde **13**, conversion of **13** to nitrostyrene **14** by condensation with nitromethane, and reduction of **14** to amine **15** with aluminum hydride in the same manner as the analogous conversion of **5** to **7**. The structural assignment was confirmed by the NMR spectrum of the intermediate nitrostyrene **14**, which displayed a pair of doublets centered on δ 6.76 and 7.45 (J = 8.8 Hz), consistent with ortho-coupled aromatic protons.

The 2- and 4-thio analogues of isomescaline (**23** and **22**, respectively) were synthesized from 2,3-dimethoxythio-

Scheme III. Synthesis of 2,3-Dimethoxy-4-(methylthio)phenethylamine (4-Thioisomescaline) and of 3,4-Dimethoxy-2-(methylthio)phenethylamine (2-Thioisomescaline)



anisole (**17**, Scheme III). Formylation gave a mixture of aldehydes (**18** and **19**) in a ratio of approximately 1:2. The aldehyde mixture was converted to a mixture of nitrostyrenes **20** and **21**, which were separated on a small scale by column chromatography and isolated as crystalline solids. Using seed crystals so obtained, the nitrostyrene mixture was separated on a preparative scale by fractional crystallization from methanol. The NMR spectra of the two nitrostyrenes were consistent with the structures **20** and **21**. The major isomer was converted to the corresponding phenethylamine by aluminum hydride reduction. A small sample was desulfurized with Raney nickel, which yielded 3,4-dimethoxyphenethylamine (**25**),[14] thus establishing the identity of the parent amine as 2-thioisomescaline (**23**). In a similar fashion, the reduction product of the minor isomer was shown to be 4-thioisomescaline (**22**) by Raney disulfurization to 2,3-dimethoxyphenethylamine (**24**).[14]

Pharmacology. The five thio analogues of mescaline and isomescaline have been compared to one another and compared with their sulfur-free counterparts as substrates for bovine plasma monoamine oxidase (MAO) in vitro and as psychotropic agents in human subjects. Incubations with MAO were carried out in an attempt to correlate the relative ease of enzymatic degradation with the efficacy of these substances as psychotomimetic agents (Table I).

In human subjects, both **7** and **12**, the thio analogues of mescaline, produced a complex, psychologically disruptive syndrome of sensory synaesthesia and benign associative disinhibition with little physiological disturbance (pressor effects, anorexia, mydriasis) and no cognitive impairment. **12** was the longer lasting, with plateau effects especially rich in fantasy from ca. 1.5–8 h, followed by a rather rapid decline in intoxication. **7** lasted at its plateau to about the 6-h point following ingestion, followed by a somewhat slower recovery. With the latter, the early stage of the maximum effect was similar to the psychologically simpler

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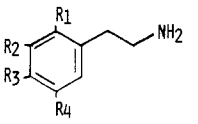
Table I



no.	R_1	R_2	R_3	R_4	MAO deamination, % without semicarbazide	MAO deamination, % with semicarbazide	human potency, MU[a]
1	H	OCH_3	OCH_3	OCH_3	21	1	1
2	OCH_3	OCH_3	OCH_3	H	55	4	<1[b]
7	H	SCH_3	OCH_3	OCH_3	60		6
12	H	OCH_3	SCH_3	OCH_3	56		12
15	OCH_3	SCH_3	OCH_3	H	31		<2
22	OCH_3	OCH_3	SCH_3	H	40		<2
23	SCH_3	OCH_3	OCH_3	H	78	10	<2
25	H	OCH_3	OCH_3	H	64	16	<1[c]

[a] Expressed as mescaline units, derived by dividing the effective dose of mescaline by the effective dose of the compound in question, both determined in man.[8] The "less than" sign indicates that no activity was observed at doses that would have shown the indicated MU values. [b] Value from the present study. Reference 7 reports no activity in normal subjects, but reports activity in schizophrenic patients. [c] Value from the literature.[10] Mild stimulation was observed at levels of 1500 mg.[11]

substances, MDA and MDMA,[9] but the latter half of this period consistently evolved into a more complex pattern of introspection and affective assertion. With neither **12** nor **7** were there indications of sleep disturbance or related sequelae. With **15**, **22**, and **23**, no threshold effects were observed at oral levels of 160 mg; with **2**, no threshold effects were observed even at oral levels of 400 mg. These results are shown in Table I.

Discussion

The identity of the group located in the 4 position of variously substituted phenethylamines and phenylisopropylamines has been consistently shown to exert a large influence on both the quantitative potency and the qualitative nature of the central effects expressed in man.[12] As the group is changed from hydrogen progressively to alkoxy, alkylthio, alkyl, and finally to halo, there is an increase in potency of almost two orders of magnitude. Homologation in those instances where this is possible (the alkoxy, alkylthio, and alkyl examples) has provided only modest quantitative change but, frequently, major qualitative differences. In the area of the psychotomimetic phenylisopropylamines, three examples are known allowing a direct comparison between an oxygenated compound and its sulfur analogue: the studies comparing the 4-methoxy, the 4-ethoxy, and the 4-*n*-propoxy-2,5-dimethoxyphenylisopropylamine with the three corresponding thio analogues. In all cases there is an increase in effectiveness with sulfur replacement of from 2- to 8-fold. Replacement of oxygen with sulfur in the other positions of the 2,4,5-trisubstituted phenylisopropylamine has led to a diminution or loss of potency. This generality now appears to be applicable to the phenethylamines as well, certainly in the case of mescaline. There is at least a 10-fold increase in effectiveness seen (see Table I) in a comparison of the activities of 4-thiomescaline (**12**) and mescaline (**1**).

It is apparent from Table I that the replacement of the 3-oxygen atom of mescaline with a sulfur atom also yields a compound more potent than mescaline itself. The two thio analogues **7** and **12** have a steric geometry nearly identical with that of mescaline, implying that the exactness of steric interaction with an appropriate receptor site is not of great importance in an explanation of potency.

The relationship between metabolic fate and psychotomimetic activity has been discussed in the literature, including the formation of potentially active metabolites.[13] Many ring-substituted phenethylamines have been shown to be readily deaminated by monoamine oxidase,[14] and the consistently greater potencies of the corresponding phenylisopropylamines ("amphetamines") has been accepted as being due to immunity from attack by these enzymes. The five thio compounds of this study, as well as mescaline, isomescaline, and 3,4-dimethoxyphenethylamine, were studied as substrates for bovine plasma MAO.[15] All compounds were effectively deaminated (see Table I), and most of the sulfur-containing compounds were better substrates than their oxygen counterparts. Other than this, there seems to be no simple correlation between the extent of enzymatic degradation and psychopharmacologic activity. Studies are currently in progress involving the synthesis and assay of a broader selection of analogues of known psychotomimetics, which should lead to a greater understanding of the pharmacologic consequences of exchanging an oxygen atom with sulfur.

Experimental Section

Melting points were determined on a Mel-temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Acculab-2 spectrometer. NMR spectra were recorded on either a Perkin-Elmer R-12B or a Varian FT-80 spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN, and were within 0.4% of the theoretical value.

5-Formyl-7-methoxy-2-oxo-1,3-benzoxathiole (4). The procedure of Fiedler[16] was modified as follows. A solution of bromine (16 g) in 40 mL of acetic acid was added dropwise over 15 min to an ice-cooled, stirred solution of sodium thiocyanate (20 g) and vanillin (**3**; 15 g) in 150 mL of acetic acid. Aqueous HCl (30 mL of 5%) and absolute ethanol (300 mL) were added. After stirring for 0.5 h, the mixture was heated to boiling. While still hot, the suspension was filtered, and the filtrate was diluted with an equal volume of H_2O, which precipitated the product as a flocculant yellow solid. The crude product, 12.5 g (mp 138–142 °C, 60%), was collected by filtration and used directly in the next step. Recrystallization from alcohol provided (with considerable loss) white product, mp 164 °C (sharp) (lit.[16] mp 163.5–164 °C).

3,4-Dimethoxy-5-(methylthio)benzaldehyde (5). A solution of 12 g (300 mmol) of sodium hydroxide in 100 mL of warm methanol was added to a suspension of 12.5 g (60 mmol) of crude thiocarbonate **4** in 100 mL of methanol containing 28.4 g (200 mmol) of methyl iodide. The mixture was heated under reflux for 1 h, after which most of the solvent was removed with a rotary evaporator. Me_2SO (100 mL) and methyl iodide (14.2 g, 100 mmol) were added, and the mixture was stirred for 1 h at ambient temperature. Additional NaOH (2.4 g) and methyl iodide (16 g)

were added, and the mixture was stirred for 2 h and then poured into 800 mL of H_2O. After acidification with HCl, the product was extracted with CH_2Cl_2 (3 × 75 mL). The combined extracts were washed first with 5% NaOH and then H_2O. Removal of solvent on a rotary evaporator, followed by a bulb to bulb distillation (Kugelrohr oven 110–130 °C) at 0.4 mmHg provided 0.9 g (7%) of colorless liquid which crystallized in the receiver: NMR ($CDCl_3$, Me_4Si) δ 2.47 (s, 3 H, SCH_3), 3.92 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 7.26 (br s, 2 H, ArH), 9.88 (s, 1 H, CHO). An analytical sample was recrystallized from ethanol, mp 57–58 °C. Anal. ($C_{10}H_{12}O_3S$) C, H.

3,4-Dimethoxy-5-(methylthio)-β-nitrostyrene (6). A solution of aldehyde **5** (0.9 g) in 100 mL of nitromethane was heated under reflux with 0.5 g of NH_4OAc as catalyst. After 4 h the excess nitromethane was removed using a rotary evaporator. The residue was taken up in 4 mL of hot methanol, and upon cooling the solution deposited yellow crystals (0.4 g, 37%): NMR ($CDCl_3$, Me_4Si) δ 2.44 (s, 3 H, SCH_3), 3.90 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.87 (d, J = 1.9 Hz, 1 H, A_2H), 6.91 (d, J = 1.9 Hz, 1 H, ArH), 7.52 (1 H, d, J = 13.6 Hz, vinylic CH), 7.95 (d, J = 13.6 Hz, vinylic CH). A small sample was recrystallized from ethanol, mp 119.5–120.5 °C. It should be noted than in one experiment in which reflux with nitromethane was carried out for 8 h, a poor yield of impure product was obtained. Anal. ($C_{11}H_{13}NO_4S$) C, H.

3,4-Dimethoxy-5-(methylthio)phenethylamine (7). A solution of aluminum hydride was prepared by the dropwise addition of 100% H_2SO_4 (1 mL) to a solution of 1.5 g of $LiAlH_4$ in 40 mL of THF, under N_2 with ice cooling. Nitrostyrene **5** (0.7 g) in 10 mL of THF was added dropwise to 25 mL of the ice-cooled, vigorously stirred, aluminum hydride solution. After the addition, the solution was heated under reflux for 5 min. The solution was then cooled, and excess hydride was destroyed by the careful addition of aqueous THF. NaOH (15% aqueous) was added dropwise until the gray, gelatinous precipitate of salts was transformed into a white granular solid. The mixture was filtered, the precipitate was washed with THF, and then the filtrate was combined with the washings and diluted 1:1 with ether. The amine was extracted from the filtrate with two 40-mL portions of dilute aqueous H_2SO_4, and the combined extracts were washed with ether. After having made the aqueous layer basic with NaOH, the product was extracted from the aqueous layer with methylene chloride (2 × 50 mL). Removal of solvent on the rotary evaporator, followed by a bulb to bulb distillation (124–130 °C) at 0.2 mmHg, gave 0.4 g of the free base as a colorless liquid. The hydrochloride salt was prepared by dissolving the free base in 8 mL of isopropyl alcohol, acidifying (against external damp pH paper) with concentrated HCl (6 drops), and diluting with 30 mL of anhydrous ether to crystallize the product. After filtration and air drying, a white crystalline solid was obtained (0.18 g), mp 167–168 °C. A second crop of white solid was obtained (0.11 g), mp 160–163 °C (total yield 40%) from the mother liquor with additional ether. Anal. ($C_{11}H_{18}ClNO_2S \cdot 1H_2O$) C, H, N.

2,6-Dimethoxythioanisole (9). In a 1-L flask with magnetic stirrer there were added, under nitrogen, 24.2 g of tetramethylethylenediamine (TMEDA, 210 mmol), 27.6 g of *m*-dimethoxybenzene (**8**, 200 mmol), and 400 mL of dry hexane. The solution was cooled to about 0 °C (with external ice) and there was added 125 mL of 2 M butyllithium in hexane. The reaction mixture became yellow and viscous, was brought to room temperature for a few minutes, cooled again, and treated with 18.8 g (200 mmol) of dimethyl disulfide. An exothermic reaction ensued, with the conversion of the yellow sludge to a loose white solid. This was stirred as the reaction mixture was allowed to return to room temperature. The reaction mixture was added to 2 L of water and acidified with dilute H_2SO_4. The resulting white solids were removed by filtration and recrystallized from about 50 mL of methanol, yielding **9** as white crystals (18.9 g): mp 81–82 °C (lit.[17] mp 80 °C). Extraction of the mother liquors yielded another 3.3 g for a total yield of 60% of theory.

3-Bromo-2,6-dimethoxythioanisole (10). A solution of 18.9 g of **9** (103 mmol) in 200 mL of CH_2Cl_2 was treated with 16 g of Br_2 in 75 mL of CH_2Cl_2. The color faded to pale yellow with the copious evolution of HBr. After solvent was removed in vacuo, the residual oil was distilled (118–121 °C at 0.25 mmHg) to yield 25.3 g of a highly refractive colorless oil (yield 93% of theory): NMR ($CDCl_3$, Me_4Si) δ 2.35 (s, 3 H, SCH_3), 3.85 (s, 6 H, OCH_3), 6.52 (d, J = 8.9 Hz, 1 H, ArH), 7.38 (d, J = 8.9 Hz, 1 H, ArH). The analytical sample was obtained in crystalline form, from hexane, mp 30–30.5 °C. Anal. ($C_9H_{11}BrO_2S$) C, H.

3,5-Dimethoxy-4-(methylthio)phenylacetonitrile (11). A solution of 19.3 g of diisopropylamine in 150 mL of THF was cooled, under nitrogen, with external methanol–cracked ice and stirred with a magnetic stirrer. There was added in sequence: 83 mL of 1.6 M butyllithium in hexane (132 mmol), 4.4 mL of acetonitrile (previously dried with molecular sieves), and 11.6 g of **10** (44 mmol). The initially colorless reaction mixture (with a slight precipitate) progressively developed a yellow, then orange, and finally a deep red-brown color. The external temperature was maintained at −10 °C for 20 min. The reaction mixture was poured (against N_2) into 1 L of water containing 10 mL of concentrated H_2SO_4, which largely dissipated the color. The reaction product was extracted with CH_2Cl_2 (3 × 100 mL), the extracts were pooled and washed with dilute acid and with saturated brine, and the solvent was removed in vacuo. The resulting oil (8.7 g) was separated by bulb to bulb distillation (0.1 mmHg) into two fractions, the first with bp 115–125 °C (3.8 g) and the second with bp 150–180 °C (1.8 g), both spontaneously crystallizing on standing. The higher boiling fraction was ground under cold methanol, filtered, and washed with cold methanol to yield 1.1 g (mp 95–96.5 °C; 11% of theory) of white crystals: NMR ($CDCl_3$; Me_4Si) δ 2.37 (s, 3 H, SCH_3), 3.78 (s, 2 H, CH_2), 3.94 [s, 6 H, $(OCH_3)_2$], 6.59 (s, 2 H, ArH). The IR spectrum showed a sharp nitrile band at 2250 cm^{-1} and no hydrogen functionality (mineral oil mull). The lower boiling fraction, crystals in an oily matrix, was separated by filtration and washed with methanol, and the isolate (0.9 g) was recrystallized from methanol (2 mL) to yield 0.5 g of a white crystalline solid (mp 60–63 °C, mmp with the phenylacetonitrile 60–91 °C) which has not been structurally identified. Anal. ($C_{11}H_{13}NO_2S$) C, H.

3,5-Dimethoxy-4-(methylthio)phenethylamine (12). To a suspension of 1.0 g of $LiAlH_4$ in 40 mL of THF at 0 °C under N_2 there was added dropwise 0.7 mL of 100% H_2SO_4 (made from concentrated H_2SO_4 and the appropriate amount of fuming H_2SO_4), followed by 1.2 g of **11**, also in THF. The reaction mixture was stirred at 0 °C for a few minutes and then for 1 h at room temperature and then finally heated to 40 °C for an additional 0.5 h. There was then added, in sequence, 1 mL of water (in 5 mL of THF), 3 mL of 15% NaOH, and 2 mL of water. The suspended solids were removed by filtration, the filter cake was washed with THF, and the combined filtrates were evaporated in vacuo. The residual oil was dissolved in 200 mL of CH_2Cl_2 and extracted with 3 × 100 mL of dilute H_2SO_4, and the extracts were pooled and washed with CH_2Cl_2. The aqueous fraction was made basic with 25% NaOH and extracted with CH_2Cl_2 (3 × 100 mL), the extracts were pooled, and the solvent was removed in vacuo. The colorless residue was distilled (122–132 °C at 0.05 mmHg) to give a viscous colorless oil, which was dissolved in a few milliliters of IPA, acidified with concentrated HCl added dropwise until acid as determined by external damp universal pH paper, and finally treated with 100 mL of ether. The product was removed by filtration, washed with ether, and air-dried to provide 0.95 g of glistening white crystals: mp 193–194 °C; yield 67%; NMR (D_2O, external Me_4Si) δ 2.20 (s, 3 H, SCH_3), 3.13 [m, 4 H, $(CH_2)_2$], 3.86 [s, 6 H, $(OCH_3)_2$], 6.64 (s, 2 H, ArH). Anal. ($C_{11}H_{18}ClNO_2S$) C, H.

2,4-Dimethoxy-3-(methylthio)benzaldehyde (13). A mixture of 2.8 g of *N*-methylformanilide and 3.1 g of $POCl_3$ was heated for 5 min on a steam bath (color, deep claret) and then treated with 3.0 g (16 mmol) of **9**. Heating was continued for 0.5 h, and the reaction mixture was added to 75 mL of water, stirred for several hours, and extracted with 3 × 75 mL of CH_2Cl_2. The extracts were pooled and evaporated in vacuo, and the partially crystalline residue was extracted with 3 × 20 mL of boiling hexane. Cooling the pooled hexane extracts yielded 1.5 g of off-white crystals, mp 67–69 °C, which were used for the subsequent reaction, as obtained. An analytical sample was obtained from 85% aqueous methanol, mp 67–68 °C: yield 43%. Anal. ($C_{10}H_{12}O_3S$) C, H.

2,4-Dimethoxy-3-(methylthio)-β-nitrostyrene (14). A solution of 1.3 g of **13** (6.1 mmol) in 60 mL of nitromethane was treated with 0.3 g of ammonium acetate and held at reflux for

3 h. The hot solution was decanted from a small amount of insoluble residue and the solvent was removed in vacuo. The resulting oil was dissolved in 10 mL of hot methanol, which on cooling yielded 0.9 g of pale yellow crystals: mp 130–133 °C; NMR ($CDCl_3$, Me_4Si) δ 2.41 (s, 3 H, SCH_3), 3.92 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 6.76 (d, J = 8.8 Hz, 1 H, ArH), 7.72 (d, J = 13.6 Hz, 1 H, vinylic CH), 8.14 (d, J = 13.7 Hz, 1 H, vinylic CH). An additional 0.2 g was obtained from the mother liquors, for a total yield of 71% of theory. An analytical sample was obtained from boiling methanol (10 g/g): lustrous yellow plates, mp 136–136.5 °C. Anal. ($C_{11}H_{13}NO_4S$) C, H.

2,4-Dimethoxy-3-(methylthio)phenethylamine (15). Nitrostyrene 14 (0.6 g) was reduced with aluminum hydride in a manner analogous to the reduction of 6. Bulb to bulb distillation (120–145 °C, 0.3 mmHg) provided 0.25 g of free base, which yielded 0.2 g (32%) of hydrochloride salt, mp 204–206 °C dec. Anal. ($C_{11}H_{18}ClNO_2S \cdot 0.5H_2O$) C, H, N.

2,3-Dimethoxythioanisole (17). Veratrole (16; 26.7 g, 200 mmol) was added over 5 min to a solution of n-butyllithium (150 mL of 1.6 M in hexane, 240 mmol) and petroleum ether (30–60 °C, 150 mL) with stirring and ice cooling, which resulted in the formation of a flocculant white precipitate. Ether (100 mL) and TMEDA (23.2 g, 200 mmol) were added. After the mixture was warmed to room temperature, dimethyl disulfide (20.7 g, 220 mmol) was added, portionwise, with stirring. The reaction was slightly exothermic. Stirring was continued for 30 min, after which the reaction was worked up by the addition of 10 mL of ethanol and 250 mL of 5% aqueous NaOH. The organic phase was separated and washed with 150 mL of 5% NaOH and then with two 100-mL portions of 5% HCl. Analysis by GC indicated an approximately 80:20 mixture of 17 and veratrole. (In one experiment, at this point the product was purified by bulb to bulb distillation, 72–80 °C, at 0.4 mmHg, giving an 86% yield of a product containing veratrole as a contaminant.) After stripping off the solvent, the product was distilled through a 6-cm Vigreaux column at 0.1 mmHg. Five fractions were taken. Fractions 4 and 5, boiling at 84–85 and 85–87 °C, respectively, were pure thioether 17. These fractions were combined to give 26.0 g (71% yield) of product. An analytical sample was obtained by cooling a concentrated methanol solution with dry ice, filtering, and washing with 0 °C methanol: white crystals; mp 36.5–37 °C. Anal. ($C_9H_{12}O_2S$) C, H, S. The picrate salt was obtained from a warmed ethanol solution in saturated picric acid, diluted with water, and cooled: orange crystals; mp 73–78 °C. Anal. ($C_{15}H_{15}N_3O_9S$) N.

Mixture of 2-(Methylthio)-3,4-dimethoxybenzaldehyde and 4-(Methylthio)-2,3-dimethoxybenzaldehyde (19 and 18). A mixture of 18 mL of $POCl_3$ and 25.0 mL of N-methylformanilide was allowed to stand at room temperature for 0.5 h and then treated with 17 (25.0 g). The mixture was heated on the steam bath for 2.5 h, added to 500 mL of water, and allowed to stir at ambient temperature for an additional 2 h. The product was extracted with 4 × 150 mL of CH_2Cl_2, the extracts were combined, and the solvent was removed in vacuo. The crude product, 17.9 g, was distilled through a 6-cm Vigreaux column. The fractions distilling below 125 °C (0.1 mmHg) were a mixture of thioether 17 and aldehydes 18 and 19, as indicated by GC analysis. The fraction distilling at 125–135 °C (11.9, 41%) was a mixture of aldehydes free of thioether 17.

A number of attempts were made to fractionate this mixture into its components with moderate success. Although neither fractional distillation (see above) or fractional hexane extraction of the undistilled product altered appreciably the ratio of aldehydes, it was found that fusion with p-anisidine (1.0 g of mixed aldehydes to 0.6 g of anisidine over open flame) yielded a solid anil (0.8 g) that on recrystallization from 10 mL of methanol yielded a pale yellow solid (0.45 g, mp 77–80 °C). Further recrystallization from boiling hexane yielded an analytical sample: pale cream colored; mp 80–81 °C. Anal. ($C_{17}H_{19}NO_3S$) N. Suspension of this anil in hot 3 N HCl (0.4 g in 5 mL) provided a mixture that at first darkened and then became colorless. Quenching in water, extraction with CH_2Cl_2, evaporation of the solvent, and distillation (bulb to bulb) of the residue gave a colorless oil that crystallized under cold hexane: white crystals; mp 23–24 °C. The conversion of a small amount of this "anil"-aldehyde to the corresponding nitrostyrene provided seed for aiding in the resolving of the mixture eventually obtained and established the anil to be composed of the reaction product of p-anisidine and the aldehyde with the longer retention time on GC (19). The aldehydes were employed as the mixture, as obtained, in the preparation of the subsequent nitrostyrenes.

2-(Methylthio)-3,4-dimethoxy-β-nitrostyrene (21). A mixture of aldehydes 18 and 19 (9 g) and 1.5 g of ammonium acetate in 50 mL of nitromethane was heated under reflux for 5 h, after which excess nitromethane was removed on the rotary evaporator. The crude product, 10.4 of dark orange oil, was taken up in 40 mL of warm methanol and allowed to evaporate at ambient temperature. The dark solid residue was recrystallized from 40 mL of methanol, and the crystals were collected by filtration and air dried, yielding 6.3 g of a yellow solid. This material was recrystallized a second time from boiling methanol (50 mL) to give 5.0 g (46%) of lemon yellow plates: mp 102–103.5 °C; NMR ($CDCl_3$, Me_4Si) δ 2.43 (s, 3 H, SCH_3), 3.91 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.93 (d, J = 8.9 Hz, 1 H, ArH), 7.37 (d, J = 8.9 Hz, 1 H, ArH), 7.51 (d, J = 13.5 Hz, 1 H, vinylic CH), 7.77 (d, J = 13.5 Hz, 1 H, vinylic CH). The aromatic doublet centered on δ 7.37 overlapped with the vinylic doublet centered on δ 7.51, resulting in a three-line pattern. An analytical sample was obtained from 2-propanol, mp 103–104 °C, and was a single spot by TLC (R_f 0.54, on silica gel, $CHCl_3$ solvent, visualization by UV absorption, see below). Anal. ($C_{11}H_{13}NO_4S$) C, H. The mother liquors from the initial recrystallization of crude product were employed in the isolation of the 4-(methylthio) isomer, q.v.

In the initial attempt to prepare the nitrostyrenes from the mixed aldehydes, a crystalline product was obtained spontaneously that although of consistent melting point (93–95 °C) and spectral character (IR), proved to be composed of two components by TLC. One component, with R_f 0.54, was the title compound 2-(methylthio)-3,4-dimethoxy-β-nitrostyrene, but the second component proved to be the sulfur-free counterpart 3,4-dimethoxy-β-nitrostyrene, with R_f 0.47 (silica gel, with $CHCl_3$). This mixed crystal could be recrystallized repeatedly from various solvents without variation in composition. It proved to be a 2:1 molecular complex of the two nitrostyrenes. Anal. ($C_{32}H_{37}N_3O_{12}S_2$) C, H, S. The 3,4-dimethoxy component came from the residual veratrole in the original 2,3-dimethoxythioanisole that was converted to the aldehyde 3,4-dimethoxybenzaldehyde and subsequently to the nitrostyrene as a continuing contaminant. It was never encountered in subsequent runs where the isolated 2,3-dimethoxythioanisole was rigidly purified from veratrole by careful distillation.

4-(Methylthio)-2,3-dimethoxy-β-nitrostyrene (20). Preparation of Seed. The mixed nitrostyrenes obtained from the mixed aldehydes (see above) gave, on TLC analysis (silica gel, $CHCl_3$), three UV-absorbing spots: the slowest component had an R_f of 0.47, which proved to be 3,4-dimethoxy-β-nitrostyrene (a result from veratrole contamination and not observed in subsequent synthetic runs); the second component had an R_f of 0.54, which was 21 (q.v.); and the third component had an R_f of 0.61. This fastest moving component was isolated by column chromatography of the nitrostyrene mixture (300 mg of crude nitrostyrenes, in $CHCl_3$) on a 36 mm diameter × 100 mm column packed with chromatographic silica gel and eluted with $CHCl_3$. The initial band was removed, the solvent was evaporated, and when the residue was scratched under methanol, it provided gold-colored crystalline seed, mp 71–73 °C, of 4-(methylthio)-2,3-dimethoxy-β-nitrostyrene (20), a single spot by TLC analysis. This seed was employed in the final isolation of the title compound.

Isolation. The mother liquors from the initial recrystallization of the crude mixture of nitrostyrenes (see above) was evaporated on a rotary evaporator. Seed crystals of the lower melting nitrostyrene isomer 20, isolated by chromatography as described above, were added to the viscous residue, promoting partial solidification. Trituration with a small amount of methanol gave a crystalline solid. This was recrystallized from 10 mL of methanol to give 1.9 g of orange solid. A second recrystallization (5 mL of methanol) gave 0.7 g (6%) of pumpkin-colored needles: mp 70–71 °C; NMR ($CDCl_3$, Me_4Si) δ 2.45 (s, 3 H, SCH_3) 3.88 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 6.87 (d, J = 8.4 Hz, 1 H, ArH), 7.22 (d, J = 8.3 Hz, 1 H, ArH), 7.75 (d, J = 13.6 Hz, 1 H, vinylic CH), 8.12 (d, J = 13.6 Hz, 1 H, vinylic CH). Anal. ($C_{11}H_{13}NO_4S$) C, H. The product provided a single spot by TLC.

Structural Assignment of Nitrostyrenes 20 and 21. A few milligrams of the yellow isomer (mp 102–103.5 °C) were reduced with AlH_3 as described for the reduction of nitrostyrene **6**. Sodium hydroxide (1 mL of 10%) and Raney nickel alloy (50 mg) were added to the crude product. The mixture was heated to a boil and then cooled to room temperature and acidified with HCl to dissolve all solids. About 0.1 mL of the clear solution was made basic with NaOH and extracted with 1 mL of ether. The ether layer was separated and evaporated to dryness, and the amine was converted to its heptafluorobutyryl (HFB) derivative by heating with heptafluorobutyric anhydride (50 μL) in 2 mL of toluene for 15 min at about 120 °C in a tightly capped culture tube in the presence of a few milligrams of anhydrous K_2CO_3. GC analysis on a 2 m SP2100 column at 170 °C revealed a peak with a retention time of 1.85 min and only traces of minor peaks. The retention times of the HFB derivatives of authentic 3,4-dimethoxyphenethylamine (**25**)[14] and 2,3-dimethoxyphenethylamine (**24**)[14] were 1.85 and 1.36 min, respectively.

A few milligrams of the orange, lower melting (70–71 °C) nitrostyrene was reduced with AlH_3 and disulfurized with Raney nickel to give a product which, after conversion to its HFB derivative, had a retention time of 1.35 min.

2,3-Dimethoxy-4-(methylthio)phenethylamine (22). The orange nitrostyrene, mp 70–71 °C (**20**), 0.9 g, was reduced with AlH_3 as described for the reduction of 14. The crude free base was distilled bulb to bulb at 100–115 °C (0.3 mmHg) to give 0.45 g of free base, which yielded 0.45 g (48%) of the hydrochloride salt, mp 212–213 °C. Anal. ($C_{11}H_{18}ClNO_2S \cdot H_2O$) C, H, N.

3,4-Dimethoxy-2-(methylthio)phenethylamine (23). The yellow nitrostyrene, mp 102–103.5 °C (**21**), 4.4 g, was reduced with AlH_3 to give, after distillation (100–115 °C, 0.3 mmHg) and conversion to the hydrochloride salt, 3.2 g (70%) of white crystalline solid (platelets), mp 183–184 °C. Anal. ($C_{11}H_{18}ClNO_2S \cdot 0.25H_2O$) C, H, N.

Incubations with MAO. Solutions of the amines (50 μM) in 0.1 M phosphate buffer (pH 7.4) were treated with 0.01 unit bovine plasma MAO (E.C. 1.4.3.4, Sigma) in a total volume of 200 μL. Incubations were carried out at 37 °C in 13 × 100 mm culture tubes. Duplicate incubations were carried out for each amine. After 1 h the incubations were stopped by the addition of 0.5 mL of 0.5 N NaOH. An appropriate internal standard (substrate, internal standard: **1**, **25**; **2**, **25**; **7**, **12**; **12**, **7**; **15**, **12**; **22**, **12**; **23**, **12**; **25**, **1**) was added, and the mixture was extracted with 2 mL of CH_2Cl_2. The organic layer was separated, dried over anhydrous K_2CO_3, treated with 10 μL of heptafluorobutyric anhydride, and heated at 60 °C for 10 min. The solvent was evaporated under a current of nitrogen, and the residue was reconstituted with 0.5 mL of ethyl acetate. GC analysis was carried out on a 2 m × 2 mm i.d. column packed with 3% OV-101 on 100–120 mesh Chromosorb W.-HP, with a column-oven temperature of 185 °C. Quantitation was achieved using peak height ratios, employing standards prepared in an identical fashion without enzyme present. Retention times for the heptafluorobutyryl derivatives were (amine, retention time in minutes): **1**, 2.00; **2**, 1.49; **7**, 3.01; **12**, 4.19; **15**, 3.55; **22**, 2.62; **23**, 2.68; **25**, 1.33.

Incubations of amines **1**, **2**, **23**, and **25** were carried out in the presence of semicarbazide (50 μM), since this compound has been shown to inhibit the deamination of mescaline but not tyramine.[14]

Psychopharmacologic Assays. Effective human levels of action were determined in normal healthy adult subjects (age range 32–65 years, all experienced with a broad spectrum of psychotropic drugs) employing spaced trials (about 1 week separation) of small increments of chemical (1.6:1), starting with 2 mg of the hydrochloride orally. With the establishment of threshold levels, complete studies at fully active levels were conducted with both **12** (9 subjects, 16 trials, dosage range 16–40 mg) and **7** (9 subjects, 13 trials, dosage range 60–100 mg). Seven subjects were common to trials with both compounds. The same protocol was used with **2**, **15**, **22**, and **23** (4, 5, 7, and 8 trials, respectively, at dosage maxima of 400, 240, 160, and 240 mg, respectively). No central disturbance of any kind was observed. See ref 11 for complementary findings with **2**.

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N-(Methanesulfonyl)-16-phenoxyprostaglandincarboxamides: Tissue-Selective, Uterine Stimulants†

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In an effort to develop tissue-selective prostaglandin analogues resistant to the metabolic inactivating pathways of the natural materials, hybrid compounds modified both at C-1 with a sulfonimide moiety and in the *n*-amylcarbinol side chain with substituted phenoxy groups were synthesized and evaluated in a variety of in vitro and in vivo models. Several of these analogues exhibited potent, tissue-selective, uterine stimulant activity, a finding subsequently confirmed in clinical studies with one member of this series, *N*-(methanesulfonyl)-16-phenoxy-ω-tetranor-PGE_2-carboxamide (CP-34089/ZK-57671, sulprostone).

Widespread clinical use of prostaglandins, both the natural materials and analogues, for a variety of obstetric and gynecological uses has been limited by a lack of tissue selectivity and metabolic stability. In an attempt to circumvent these shortcomings, we sought to design congeners resistant to metabolic inactivation (i.e., C_{15}-dehydrogenation and β-oxidation).[1] It was reasoned that, in so doing, analogues would be found that would also exhibit pharmacological selectivity. We initially focused our attention on carboxyl-terminus modified analogues, among which *N*-(methanesulfonyl)-PGE_2-carboxamide displayed selective uterine stimulant activity.[2] In parallel, we explored modifications of the *n*-amylcarbinol side chain, an

† Compounds were synthesized in the laboratories of Pfizer Inc. and jointly evaluated at Pfizer Inc. and Schering A.G., Berlin, Germany.

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