Monomethylthio Analogues of 1-(2,4,5-Trimethoxyphenyl)-2-aminopropane


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Regiospecific syntheses of the three monomethylthio analogues of 1-(2,4,5-trimethoxyphenyl)-2-aminopropane are described. The three isomeric amines were evaluated for potential psychotomimetic potency using the rabbit hyperthermia assay. Enantiomeric compositions and time-concentration curves in rat brains were determined following intraperitoneal administration of each compound. The biological data are contrasted with the corresponding results obtained with the potent human psychotogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM).

Extensive structure-activity relationship studies among the ring-substituted 1-phenyl-2-aminopropanes have established that compounds bearing methoxy groups at the 2 and 5 positions and an alkyl, alkoxy, or halo substituent at the 4 position are potent psychotomimetic agents in man. This ring-substitution pattern also is found in the sympatholytic agent 6-hydroxydopamine (1). We and other workers have examined the metabolic fate of the well-known psychotomimetic agent 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (2, DOM). Our studies have established that bis-O-demethylation of DOM leads to the 6-hydroxydopamine analogue 3. As anticipated, this hydroquinone metabolite possesses 6-hydroxydopamine-like properties both in terms of its chemical behavior and its ability to cause neuronal damage in rat brains. In order to further evaluate the structural significance of the 2,5-dimethoxy substitution pattern with regard to psychopharmacological activity, we have synthesized the three methylthio analogues of 1-(2,4,5-trimethoxyphenyl)-2-aminopropane, compounds 6c, 9c, and 12c. The present paper describes the chemical characterization of these isomers together with a preliminary evaluation of their potential psychotomimetic activity as measured by the rabbit hyperthermia model.

In an effort to evaluate the influence of structure on the partitioning of these compounds into the central nervous system, we have determined the time-concentration curves of DOM and the methylthio analogues in rat brains following intraperitoneal administration. Finally, we have examined the enantiomeric composition of these compounds in rat brains since in those cases examined the R enantiomers of the one-ring psychotomimetic drugs have been shown to be the psychopharmacologically active isomers. Studies in our laboratory have shown that the in vivo and in vitro disappearance of DOM and the formation of DOM in vitro metabolites are under stereoschemical control.

Chemistry. The synthetic route to the three required methylthio analogues 6c, 9c, and 12c in each case started with the appropriately substituted dimethoxybenzene and involved two critical regiospecific aromatic substitution reactions (Scheme I). For example, 1,2-dimethoxybenzene (4) was converted to 3,4-dimethoxybenzenesulfonyl chloride (5a) by chlorosulfonation with chlorosulfonic acid. The product was further characterized by conversion to the corresponding sulfonamide 5b. Reduction of the sulfonyl chloride moiety with zinc and sulfuric acid provided the thiophenol derivative 5c which was readily methylated with methyl iodide to give 5d. Vilsmeier formylation of 5d gave 4,5-dimethoxy-2-methylthiobenzaldehyde (6a) in good yield. The expected 1,2,4,5-substitution pattern was confirmed by NMR spectroscopy.
which revealed two singlets in the aromatic region consistent with a para orientation of the aromatic protons. Condensation of 6a with nitroethane gave the 1-phenyl-2-nitropropene 6b, which was smoothly reduced with LiAlH4 to the desired 1-phenyl-2-aminopropane 6c. The two positional isomers 9c and 12c were prepared in an analogous manner (Scheme I), except that direct chlorosulfonation of 7 failed. The desired intermediate 8b was obtained by treatment of 7 with sulfuric acid followed by phosphorus oxychloride. The 4-methylthio isomer 12c has been previously prepared by a different procedure. 

### Pharmacology and Discussion

In a detailed paper by Aldous et al., 7 variously substituted 1-phenyl-2-aminopropanes were examined for their abilities to increase the rectal temperatures of trained rabbits. An exceptionally good correlation was observed between reported human psychotomimetic potency and the hyperthermia activity of the compounds examined. Recently, additional studies have confirmed the value of this animal model. Consequently, we determined the hyperthermia properties of the amines 6c, 9c, 12c, and DOM (2) according to this procedure.

The hyperthermia data are summarized in Table I, which includes the potencies of mescaline and LSD for comparison. The results clearly establish that only the 4-methylthio isomer 12c possesses significant hyperthermia activity. Compounds 6c and 9c, while somewhat more potent than mescaline, are approximately 1/50th as active as racemic DOM and 1/20th as active as 12c.

Table I. Hyperthermic Effects of the Three Isomeric Methylthio Compounds and of DOM in Rabbit

<table>
<thead>
<tr>
<th>Compd</th>
<th>Dose, µmol/kg</th>
<th>Period of peak effect, min</th>
<th>Mean max temp rise (method A)</th>
<th>Integration of time-temperature curve (0-300 min)</th>
<th>Approx dose for 1°C temp rise, µmol/kg</th>
<th>Potency rel to DOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6c</td>
<td>14.2</td>
<td>75-105</td>
<td>1.01 ± 0.13</td>
<td>0.545</td>
<td>~14</td>
<td>0.017</td>
</tr>
<tr>
<td>9c</td>
<td>7.1</td>
<td>105-135</td>
<td>1.03 ± 0.11</td>
<td>0.144</td>
<td>9.77</td>
<td>0.028</td>
</tr>
<tr>
<td>12c</td>
<td>10.6</td>
<td>135-165</td>
<td>1.09 ± 0.07</td>
<td>0.683</td>
<td>0.50</td>
<td>0.64</td>
</tr>
<tr>
<td>2 (DOM)</td>
<td>5.3</td>
<td>120-165</td>
<td>0.69 ± 0.07</td>
<td>0.451</td>
<td>0.07</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>195-225</td>
<td>2.31 ± 0.51</td>
<td>1.384</td>
<td>0.27</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.67</td>
<td>165-195</td>
<td>1.15 ± 0.22</td>
<td>0.751</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>120-135</td>
<td>0.60 ± 0.16</td>
<td>0.343</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>165-210</td>
<td>2.85 ± 0.35</td>
<td>1.651</td>
<td>0.27</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>195-225</td>
<td>1.98 ± 0.14</td>
<td>1.121</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>135-165</td>
<td>0.80 ± 0.11</td>
<td>0.489</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mescaline LSD 0.0006

*(From ref 7; normalized to DOM = 1.)*

Table II. Enantiomeric Ratios (R/S) of the Three Isomeric Methylthio Compounds and of DOM in Rat Brain Following Administration of the Racemates

<table>
<thead>
<tr>
<th>Compd</th>
<th>Amount injected, mg/kg</th>
<th>Enantiomeric ratio (R/S) at time t (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6c</td>
<td>30 (114.9 µmol/kg)</td>
<td>1.14 1.09 1.43</td>
</tr>
<tr>
<td>9c</td>
<td>30 (114.9 µmol/kg)</td>
<td>1.10 1.11 1.35</td>
</tr>
<tr>
<td>12c</td>
<td>30 (114.9 µmol/kg)</td>
<td>1.54 1.14 1.23 1.62</td>
</tr>
<tr>
<td>2</td>
<td>15 (61.2 µmol/kg)</td>
<td>0.95 1.06 1.46 1.55 1.34</td>
</tr>
</tbody>
</table>

### Figure 1

Time-concentration curves for the three isomeric methylthio compounds and DOM in rat brain. Each point represents an average obtained from at least three rats.

reached with the 4-methylthio derivative 12c than with the other two isomers. The time course of events appears to be approximately the same for all three methylthio compounds with peak brain concentrations being achieved between 30 and 60 min, slightly longer than observed for DOM.

At all times studied and with all four compounds (except for the 5-min observation with 2) it was observed that the R enantiomer was present in the brain at a higher concentration than was the S isomer. The ratio (R/S) observed for the three methylthio isomers was essentially constant at 1.10 at the time of maximum brain concentration (30 min following injection) and in general showed an increased enrichment in the R isomer (or a concomitant decrease in S isomer) at both earlier and later times, when the total concentration was lower.
The most striking fact to emerge from the above data is the clear-cut pharmacological distinction of the 4-methylthio compound 12c from the positional isomers 6c and 9c. It seems unlikely that the differences in biological properties could be due to lipophilicity differences, since these three isomeric compounds would be expected to have nearly identical partition coefficients. Furthermore, all three methylthio compounds should have nearly identical steric features, which would seem to argue against a sterically sensitive interaction of the parent compound with a receptor.

Our previous observation that DOM (2) is metabolically O-demethylated to the hydroquinone derivative 3 has led us to propose that the psychotomimetic properties of DOM may be mediated by this "6-hydroxydopamine-like" metabolite. Of the three methylthio analogues 6c, 9c, and 12c, only the 4-methylthio compound 12c has the potential for direct hydroquinone formation by O-demethylation. It is of interest therefore that compound 12c proved to be the most potent of the three isomers in the rabbit hyperthermia assay. The differences in brain concentrations of the methylthio isomers alone would probably not account for this difference in biological potency. Further studies on specifically substituted 1-phenyl-2-aminopropanes as well as studies concerning the formation of 6-hydroxydopamine-like metabolites are currently in progress.

Experimental Section

Chemistry. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained from mineral oil mulls using a Perkin-Elmer Model 337 spectrophotometer. NMR spectra were recorded on a Varian A-60 or Perkin-Elmer R-12B instrument. Chemical shifts are reported in parts per million relative to Me$_4$Si (CDCl$_3$) or DSS (D$_2$O). Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley, Calif. The syntheses and properties of the nitropropane 12b and amine 12c have been described previously.

3,4-Dimethoxybenzenesulfonyl Chloride (5a). The procedure was based on the method of Huntress and Carter. Sulfuric acid (50 g, 0.43 mol) was added portionwise, with stirring, to neat 1,3-dimethoxybenzene (4.27 g, 0.02 mol) over a 20-min period. The reaction was exothermic and HC1 was evolved. The viscous blue-green mixture was poured into 400 mL of crushed ice and after standing 1 h the mixture was extracted with methylene chloride (2 × 150 mL). The extract was concentrated in vacuo to give a colorless oil which solidified on standing. The yield of crude product was 37.1 g (79%): mp 63-66 °C (lit. mp 72-73 °C); NMR (CDCl$_3$) δ 4.00 (s, 3 H, OCH$_3$), 3.80 (s, 3 H, OCH$_3$), 4.02 (s, 3 H, OCH$_3$), 3.86 (s, 3 H, OCH$_3$), 3.80 (s, 3 H, OCH$_3$), 6.26-6.55 (m, 2 H, ArH), 7.90 (d, 1 H, J = 9 Hz, ArH). A small portion was converted to the amide 8b by heating with concentrated ammonium hydroxide. Recrystallization from ethanol provided white needles, mp 165.5-166.5 °C (lit. mp 166-167 °C).

2,5-Dimethoxythiophenol (10). This isomer was prepared as described for 10a, mp 109-112 °C; NMR (CDCl$_3$) δ 8.84 (s, 3 H, OCH$_3$), 4.02 (s, 3 H, OCH$_3$), 7.07 (d, 1 H, J = 9 Hz, ArH), 7.50 (d, 1 H, J = 2.5 Hz, ArH), 7.74 (d of d, 1 H, ArH).

The sulfonamide 5b was recrystallized from ethanol as colorless needles: mp 135-136 °C (lit. mp 135-136 °C).

2,5-Dimethoxybenzenesulfonyl Chloride (11a). This isomer was prepared from 10a as described for 5a, with the exception that the chlorosulfonation was carried out with methylene chloride as solvent. The yield of 11a was 42%: mp 109-112 °C; NMR (CDCl$_3$) δ 8.84 (s, 3 H, OCH$_3$), 4.02 (s, 3 H, OCH$_3$), 7.14-7.56 (m, 3 H, ArH).

The sulfonamide 11b, from ethanol, had mp 147.5-148.5 °C (lit. mp 150-152 °C).

2,5-Dimethoxybenzenesulfonyl Chloride (12a). The chlorosulfonic acid procedure described above for the sulfonation of the o- and p-dimethoxybenzenes 4 and 10, respectively, was not effective for the sulfonation of 7. The procedure employed was essentially that of Suter and Hansen. Concentrated sulfuric acid (29 g, 0.30 mol) was added to neat 1,3-dimethoxybenzene (7.27 g, 0.20 mol), with stirring, over a 15-min period. The mixture was stirred 1 h at ambient temperature and then poured slowly into 250 mL of saturated aqueous potassium carbonate. The resulting precipitate was collected by filtration and dried (air oven, 125 °C) to give 59.6 g of crude potassium 2,4-dimethoxybenzenesulfonate (8a). Phosphorus oxychloride (35 g, 0.10 mol) was added to the pulverized salt 8a (30 g) and the mixture was heated on a steam bath with occasional swirling (2 h). After cooling to room temperature the mixture was poured onto 300 mL of crushed ice, stirred until the ice had melted, and extracted with ether (2 × 150 mL). The combined extracts were washed with saturated aqueous NaCl (50 mL) and evaporated under reduced pressure to give 14.2 g (62% based on 7) of a white solid: mp 69-72 °C (lit. mp 70.5 °C); NMR (CDCl$_3$) δ 3.92 (s, 3 H, OCH$_3$), 4.05 (s, 3 H, OCH$_3$), 6.50-6.75 (m, 2 H, ArH), 7.90 (d, 1 H, J = 9 Hz, ArH). A small portion was converted to the amide 8c by heating with concentrated ammonium hydroxide. Recrystallization from ethanol provided white needles, mp 165.5-166.5 °C (lit. mp 166-167 °C).

2,5-Dimethoxythiophenol (11b). This isomer was prepared from 11c as described for 5c. It was obtained as a colorless liquid in 59% yield: bp 95-97 °C (0.6 mm); N$_2$O$_4$ 1.5829 (lit. bp 138-140 °C (14 mm); N$_2$O$_4$ 1.5848).

2,4-Dimethoxythiophenol (12b). To a nitrogen-flushed 250-mL flask was added 3,4-dimethoxythiophenol (5c, 10 g, 59 mmol), absolute ethanol (50 mL), and KOH (5 g, 65%, ~75 mmol) in 80 mL of ethanol. A reflux condenser was attached to the flask and 20 min after the addition of KOH the mixture was saturated with hydrogen sulfide. The ether was removed under reduced pressure and the residue distilled to provide 26.2 g (87%) of a colorless liquid: bp 86-88 °C (0.4 mm) (lit. bp 86-88 °C (0.4 mm)); NMR (CDCl$_3$) δ 5.34 (s, 1 H, SH), 3.71 (s, 3 H, OCH$_3$), 3.80 (s, 3 H, OCH$_3$), 6.26-6.55 (m, 2 H, ArH), 7.15 (d of d, 1 H, ArH). A small portion was converted to the amide 8b by heating with concentrated ammonium hydroxide. Recrystallization from ethanol provided white needles, mp 165.5-166.5 °C (lit. mp 166-167 °C).
over 5 min. The reaction was exothermic, and the color changed from orange to dark red. The mixture was heated on the steam bath for 20 min and then poured into 200 mL of water. After stirring 15 min the precipitated product was collected by filtration and recrystallized from ethanol (100 mL) to give 8.05 g (85% of off-white needles: mp 112-113 °C; NMR (CDCl₃) δ 2.56 (s, 3 H, SCH₂), 3.92 (s, 3 H, OCH₂), 3.98 (s, 3 H, OCH₃), 6.42 (s, 1 H, ArH), 7.40 (s, 1 H, ArH), 10.43 (s, 1 H, CHO). Anal. Calcd for C₂H₅NO₂S: C, 56.58; H, 5.58; N, 5.78.

2.4-Dimethoxy-5-methylthio benzaldehyde (9a). This isomer was prepared from 8e as described for 6a. Recrystallization from methanol provided a 96% yield of fine white crystals, mp 124.5-125.5 °C. This compound exhibits dimorphism. In one experiment, the product melted at 109-110 °C and displayed an infrared spectrum. NMR analysis as a methanol (691, 734, 819, and 994 cm⁻¹). These were lost and an infrared spectrum of the more stable higher melting form (894, 731, 839, and 897 cm⁻¹) was obtained following intense grinding prior to mull preparation or by recrystallization from a more concentrated methanolic solution: NMR (CDCl₃) δ 2.42 (s, 3 H, SCH₂), 3.95 (s, 3 H, OCH₂), 3.98 (s, 3 H, OCH₃), 6.47 (s, 1 H, ArH), 7.68 (s, 1 H, ArH), 10.32 (s, 1 H, CHO). Anal. Calcd for C₂H₅NO₂S: C, 56.58; H, 5.58; N, 5.78.

2.5-Dimethoxy-4-methylthio benzaldehyde (12a). This isomer was prepared in 53% yield from 11d as described for 6a. Off-white crystals from methanol were obtained: mp 97.5-98.5 °C. The melting point melting with an authentic sample (lit.: mp 98.5-99.5 °C). The melting point with an authentic sample (lit.: mp 96-96.5 °C) was 96-96.5 °C: NMR (CDCl₃) δ 2.49 (s, 3 H, SCH₂), 3.95 (s, 3 H, OCH₂), 6.76 (s, 1 H, ArH). Found: C, 53.39; H, 5.59; N, 5.19.

1-(4,5-Dimethoxy-2-methylthio)-2-nitropropene (6b). A mixture of aldehyde 6a (20.0 g, 9.4 mmol) and ammonium acetate (0.45 g) in 8 mL of nitroethane was heated on a steam bath for 4.5 h. Removal of the excess nitroethane in vacuo gave a red oil, which upon addition of methanol (5 mL) spontaneously crystallized. The crude product (mp 98-101 °C) was recrystallized from 25 mL of boiling methanol and provided a 1.85 g (75%) of bright orange crystals: mp 104-105 °C: NMR (CDCl₃) δ 2.87 (s, 3 H, SCH₂), 2.99 (d, 2 H, CH₂), 3.51-3.83 (m, 1 H, CHI, 3.99 (s, 3 H, OCH₂), 6.75 (s, 1 H, ArH), 10.42 (s, 1 H, CHO). Anal. Calcd for C₂H₇NO₂S: C, 55.51; H, 5.61; N, 5.20. Found: C, 53.39; H, 5.62; N, 5.19.

1-(2,4-Dimethoxy-5-methylthio)-2-nitropropene (9b). This isomer was prepared in 80% yield from 9a with nitroethane as described for 6b: mp 112-113 °C (ethanol); NMR (CDCl₃) δ 2.89 (s, 3 H, SCH₂), 3.93 (s, 3 H, OCH₂), 6.56 (s, 1 H, ArH), 7.30 (s, 1 H, ArH). Found: C, 53.45; H, 5.62; N, 5.21.

1-(4,5-Dimethoxy-2-methylthio)-1-(2,4-dimethoxy-5-methylthio)-2-aminopropane (6c). A mixture of aldehyde 6b (2.0 g, 9.4 mmol) and ammonium acetate (0.45 g) in 8 mL of nitroethane was heated on a steam bath for 4.5 h. Removal of the excess nitroethane in vacuo gave a red oil, which upon addition of methanol (5 mL) spontaneously crystallized. The crude product (mp 98-101 °C) was recrystallized from 25 mL of boiling methanol and provided a 1.85 g (75%) of bright orange crystals: mp 104-105 °C: NMR (CDCl₃) δ 2.42 (s, 3 H, SCH₂), 2.45 (s, 3 H, SCH₂), 3.97 (s, 3 H, OCH₂), 6.83 (s, 1 H, ArH), 7.02 (s, 1 H, ArH), 8.40 (br, s, 1 H, ArCH). Anal. Calcd for C₂H₇NO₂S: C, 53.51; H, 5.61; N, 5.20. Found: C, 53.45; H, 5.62; N, 5.21.

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References and Notes


Synthesis and Evaluation of α-Hydroxythiol Esters as Antitumor Agents and Glyoxalase I Inhibitors

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Synthesis of a series of α-hydroxythiol esters made available, for the first time, product-like molecules that were evaluated as inhibitors of the enzyme glyoxalase I and as potential antitumor agents. All the α-hydroxythiol esters tested were competitive inhibitors of the enzyme, albeit weak; however, the relative \([K_i]\) values suggested information about the active site. Antileukemic activity in L1210 lymphoid leukemia indicated no significant activity by these α-hydroxythiol esters.

The glyoxalase system, which consists of glyoxalase I [S-lactoylglutathione methylglyoxal lyase (isomerizing); E.C. 4.4.1.5], the coenzyme glutathione (GSH), and glyoxalase II (S-2-hydroxyacylglutathione hydrolase; E.C. 3.1.2.6), converts methylglyoxal (1) to lactic acid (4) (see Scheme I).

It has been suggested that the glyoxalase enzyme system, which is found widely distributed in cells of all forms of life,2,3 may be involved in the regulation of cell growth by maintaining a proper concentration of one of the substrate components methylglyoxal (1).4,5 The deficiency of this ketoaldehyde16 and the unusually high concentration of lactic acid2 in cancer cells imply that such cells, having lost the ability to maintain a proper concentration of methylglyoxal, continue to proliferate at an unchecked rate. Selective inhibition of glyoxalase I that may result in a buildup of methylglyoxal (1) again in these cells might provide an effective means of chemotherapy.

Numerous studies, testing this hypothesis, have been carried out using substrate-related molecules. The carcinostatic activity of α-ketoaldehydes, including methylglyoxal (1), is known6 but not effective since these agents are rapidly metabolized to the corresponding α-hydroxy acids by the glyoxalase enzyme system.4 S-Alkyl derivates and related compounds of the coenzyme glutathione (GSH) cause potent competitive inhibition of glyoxalase I4,6-11 and cytotoxic activity against L1210 leukemia and KB cells in tissue culture.12 However, the rapid degradation of S-substituted glutathione derivatives by gly-

\[
\begin{align*}
\text{Glyoxalase I} & \quad \text{Glyoxalase II} \\
\text{CH,CH-COH + GSH} & \quad \text{CH,CH-COH + GSH} \\
\text{CH,CH-COH + GSH} & \quad \text{CH,CH-COH + GSH}
\end{align*}
\]