Quantitative Structure-Activity Relationships in the 2,4,5-Ring. Substituted Phenylisopropylamines

George M. Anderson III, Neal Castagnoli, Jr., and Peter A. Kollman

ABSTRACT

The potency of a series of 2,4,5-ring substituted phenylisopropylamines was examined using the rabbit hyperthermia assay. An excellent correlation (r=0.99) was found between the rabbit hyperthermic and human psychotomimetic potencies. In the hyperthermic model, the 4-X-substituted-2,5-dimethoxyphenylisopropylamines were found to be one to two orders of magnitude more potent than the 2-X- or 5-X-substituted positional isomers (X=-H,-CH₃,-SCH₃,-Br). Conformational perturbations induced by substituents ortho to the ethylamine side chain were studied with the PCIL0 and ab initio molecular orbital methods. The variations in the biological activities could not be rationalized in terms of the ability of the ortho substituents to stabilize conformations which mimic LSD. The electronic structures of the positional isomers were examined in the corresponding toluene analogues using the CNDO/2 method. A reasonable correlation (r=0.98) was found between the Highest Occupied Molecular Orbital (HOMO) energy and the ionization potentials reported from photoelectron spectroscopy studies. In the case of the positional isomers, the HOMO energies were ordered as follows: 4-X>5-X>2-X. However, the regression analysis of the relationship between these orbital energies and Log Biological Activity (B.A.) was not impressive. Examination of the partition coefficients (octanol/water) of the positional isomers indicated that the 4-X- and 5-X-substituted compounds have almost equivalent Log P's, but that the 2-X-substitute-4,5-dimethoxyphenylisopropylamines are unusually hydrophilic. The regression of Log H.P. to the HOMO energies resulted in a marginally significant relationship; addition of the Log P's resulted in no significant improvement. Qualitative models based on both regiospecific lipophilicity or electron densities and also metabolic conversion to reactive intermediates are presented.

INTRODUCTION

Structural manipulation of the aromatic moiety of amphetamine has provided numerous methoxy-substituted analogues and a variety of 4-substituted-2,5-dimethoxyphenylisopropylamines. Attempts to relate
the psychotomimetic potency of these compounds to physical properties have elaborated three "themes." The first approach is based on the basis of physical properties suggested by Karreman et al. (1959) and further elucidated by Snyder and Merrill (1965) and Kang and Green (1970) proposing that potency is related to the electron donor properties of the aromatic system. In the second scenario, addressed by Snyder (1970), Kang and Green (1970), Baker et al. (1973), and Nichols et al. (1978), the potency of various classes of agents having the arylethylamine structure is related to the ability of the side chain to assume conformations which mimic the potent psychotomimetic LSD. Finally, Barfknecht et al. (1975) and Nichols et al. (1978) have pointed to the correlation of activity with lipid solubility and implicated the importance of distribution effects in modulating the psychotomimetic potency of the ring substituted phenethylamines and phenylisopropylamines.

In the intact animal, psychotomimetic activity appears to be a complex function involving all of these variables. Since this is the case, it is difficult to draw conclusions about molecular events from the structure activity relations. We have attempted to simplify the structure activity relations by designing a novel series of "rearranged" phenylisopropylamines bearing substituents at the 2,4, and 5 positions:

The logic behind our approach is that positional isomers might be expected to be isolipophilic. We had therefore hoped to factor the electronic and conformational aspects of the activity equation from distribution considerations. With these expectations in mind, we began our theoretical investigation into the physical parameters of conformation and electronic structure using molecular orbital methods. Specifically, we have studied the side chain conformation of various ortho-substituted phenethylamines and attempted to relate this information to the biological activities of 2-X-substituted-4,5dimethoxyphenylisopropylamines. In parallel with this, we present rabbit hyperthermic potencies of these rearranged isomers and demonstrate a good correlation between these numbers and human psychotomimetic potencies. Next, we have analyzed the effects of substituents on the orbital energies and electron densities of the aromatic ring. We have evaluated the validity of the assumption that positional isomers are isolipophilic and have attempted to explain the deviations in the partition coefficients in terms of electronic effects. The data have also been interpreted in terms of how structural effects may influence the metabolic fate of these compounds. Finally, our studies have led us to propose potentially interesting analogues for further analysis.
Synthesis of the "rearranged" positional isomers was afforded by condensation of the appropriately substituted benzaldehydes with nitroethane followed by reduction of the phenylnitropene with lithium aluminum hydride. Details of the synthetic scheme will be described elsewhere.

The biological activities of compounds (1)-(14) were measured using the rabbit hyperthermia assay and the potencies are reported in Standard Rabbit Units (SRU) in which racemic DOM (5) is taken as the reference. Details of the assay have been reported by Jacob III et al. (1977).

The PCiLO semiempirical molecular orbital method (Diner et al. 1967) was used to study the conformational structure of the ethylamine side chain in a variety of ring substituted phenethylamines. Standard bond lengths and angles were used and parameters for the bromine atom were taken from the previous assignments of Kollman et al. (1973). Extensive applications of this method to problems of biological interest have been made by Pullman et al. (1973), who have demonstrated the reliability of the calculated conformational minima. Rotations were made about the T₁ and T₂ axes of the phenethylamine side chain in increments of 30°, and the energies of the localized Kekulé structures were averaged. The energy of several of the PCiLO minima were also calculated with the ab initio program Gaussian 70 (Hehre et al. 1974) using the STO-3G basis set.

The electronic structure of the variously substituted analogues was examined in the corresponding substituted toluenes using CNDO/2. The Highest Occupied Molecular Orbital energies were taken at the conformational minima with respect to 30° rotation of the methoxy substituents. Calculated HOMO energies have been shown by Domelsmith, et al. (1977) to correlate with ionization potentials measured by photoelectron spectroscopy. The technique is also appropriate for describing rotations about a bond with partial bond character as occurs with methoxy substituted benzenes.

The distribution characteristics of compounds (1)-(14) were modeled by partition coefficients (octanol/water). Substituent contributions to the overall molecular lipophilicity were derived from the measured Log P of the substituted phenylisopropylamine or from a study of model compounds. When partition coefficients were determined in solvents other than octanol, both the substituted and reference values were taken from the same solvent, converted into the Log P in octanol according to the equations of Leo et al. (1971), and subtracted to give the substituent π values.

RESULTS AND DISCUSSION

Rabbit Hyperthermia

The rabbit hyperthermia assay has been employed in the pharmacological evaluation of a series of LSD analogs (Cerletti 1959), substituted tryptamines (Brimblecombe 1967), and phenylisopropylamines (Aldous...
The applicability of this animal model to psychoactive agents can be measured in terms of the correlation between the animal and human potencies. The hyperthermic potencies of compounds (1)-(14) are summarized in Table 1; an excellent correlation exists between the hyperthermic and human potencies (n=8, r=0.99). As can be seen, the most potent compounds were the 4-X-substituted-2,5-dimethoxyphenylisopropylamines. In this series, substitution of the para-H with a -OCH₃, -SCH₃, -CH₃, and -Br group results in large increases in hyperthermic potency. Similar increases in activity are not achieved in the 5-X-substituted-2,4-dimethoxyphenylisopropylamines which all have

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Human Potency (MII)</th>
<th>Hyperthermic Potency (SBEU)</th>
<th>T.P. (ev)</th>
<th>HOMO Energy (a.u.)</th>
<th>Log P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) OCH₃</td>
<td>OCH₃</td>
<td>H</td>
<td>5</td>
<td>3</td>
<td>7.91</td>
<td>-0.410</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>(2) OCH₃</td>
<td>H</td>
<td>OCH₃</td>
<td>8</td>
<td>3</td>
<td>7.70</td>
<td>-0.409</td>
<td>1.72 1.88</td>
<td></td>
</tr>
<tr>
<td>(3) H</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>&lt;0.3</td>
<td>0.3</td>
<td>8.03</td>
<td>-0.419</td>
<td>1.20 1.06</td>
<td></td>
</tr>
<tr>
<td>(4) OCH₃</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>1</td>
<td>---</td>
<td>---</td>
<td>-0.403</td>
<td>2.24</td>
<td></td>
</tr>
<tr>
<td>(5) OCH₃</td>
<td>CH₃</td>
<td>OCH₃</td>
<td>80</td>
<td>100</td>
<td>7.62</td>
<td>-0.400</td>
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<td></td>
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<tr>
<td>(6) CH₃</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>0.5</td>
<td>---</td>
<td>---</td>
<td>-0.407</td>
<td>1.76</td>
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</tr>
<tr>
<td>(7) OCH₃</td>
<td>OCH₃</td>
<td>SCH₃</td>
<td>---</td>
<td>3</td>
<td>---</td>
<td>-0.409</td>
<td>2.17</td>
<td></td>
</tr>
<tr>
<td>(8) OCH₃</td>
<td>SCH₃</td>
<td>OCH₃</td>
<td>50</td>
<td>54</td>
<td>7.64</td>
<td>-0.405</td>
<td>2.17</td>
<td></td>
</tr>
<tr>
<td>(9) SCH₃</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>2</td>
<td>---</td>
<td>---</td>
<td>-0.412</td>
<td>1.81</td>
<td></td>
</tr>
<tr>
<td>(10) OCH₃</td>
<td>OCH₃</td>
<td>Br</td>
<td>4</td>
<td>2</td>
<td>---</td>
<td>-0.375</td>
<td>2.54</td>
<td></td>
</tr>
<tr>
<td>(11) OCH₃</td>
<td>Br</td>
<td>OCH₃</td>
<td>600</td>
<td>405</td>
<td>7.94</td>
<td>-0.375</td>
<td>2.54 2.58</td>
<td></td>
</tr>
<tr>
<td>(12) Br</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>3</td>
<td>---</td>
<td>---</td>
<td>-0.377</td>
<td>2.06</td>
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</tr>
<tr>
<td>(13) OCH₃</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>16</td>
<td>12</td>
<td>7.66</td>
<td>-0.397</td>
<td>1.10 1.74</td>
<td></td>
</tr>
<tr>
<td>(14) H</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>---</td>
<td>8.99</td>
<td>-0.473</td>
<td>1.63</td>
<td></td>
</tr>
</tbody>
</table>

Subscripts:

- a: Shulgin et al. (1969); b: Shulgin, (1978); c: Shulgin et al. (1976); d: Sepulveda et al. (1972); e: Shulgin et al. (1971); f: Aldous et al. (1974); g: Dimondsmith and Howk (1978); h: Barfknecht et al. (1975); i: Nichols, (1977); j: Assumed to be isolipophilic with compound (3).

1. Log P = Log Pₒ, 4-(OCH₃)₂-phenylisopropylamine + πCH₃ = 1.20 + 0.56.
2. Assumed to be isolipophilic with compound (6). Log P = Log Pₒ, 4-(OCH₃)₂-phenylisopropylamine + πSCH₃ = 1.20 + 0.61. Assumed to be isolipophilic with compound (11).

comparable potencies, except in the case of the methoxy analogue which clearly is more potent. In the 2-X-substituted-4,5-dimethoxy-phenylisopropylamines, replacement of the ortho-H with any group increases activity, but only the -OCH₃ analogue has any substantial potency.

**Analysis of Conformational Properties**

The hyperthermia results indicated that potent activity was generally associated with analogues bearing an ortho methoxy group. Since ortho substituents could be expected to influence the arylethylamine conformation, we have attempted to explain the inactivity of the ortho -H, -SCH₃, -CH₃ and -Br analogues in conformational terms. Historically, the psychotomimetic potency of the ring-substituted phenethylamines, phenylisopropylamines and tryptamines has been rationalized in terms of the ability of the ethylamine side chain to assume conformations which mimic certain aspects of the LSD structure. In the model proposed by Snyder et al. (1975), the crucial phenethylamine conformations are those which mimic the B and C ring of LSD. The “B Ring Mimic” was envisioned to arise from a gauche conformation (T₁=180°, T₂=0°) in which the side chain was planar with respect to the aromatic ring and the amine was folded back toward an ortho-H substituent. The C Ring of LSD was thought to be mimicked by a folded gauche conformation (T₁=0°, T₂=40°) in which the arylethylamine protons were involved in an intramolecular interaction with the electron density centered on the oxygen atom of an ortho methoxy substituent. Kang and Green (1970) have suggested that the LSD structure could be mimicked by an extended trans conformation (T₁=150°, T₂=170°) in which the phenethylamine portions both LSD and the ring substituted phenethylamines and phenylisopropylamines were directly superimposed. Baker et al. (1973) have analyzed the X-ray structure of LSD and 2,4,5-trimethoxyphenylisopropylamine (HCl salt) and have proposed a mimic conformation (T₁=40°, T₂=240°) in which the amine portions of the phenethylamines were superimposed with the N(6) of LSD and an ortho methoxy group was paired with the 9,10 double bond of LSD. Recently Nichols et al. (1978a) have proposed a mimic conformation which was similar to a trans conformation proposed by Kang and Green (1970), but the phenyl ring oriented differently with respect to the indole ring of LSD (T₁=150°, T₂=-120°). Nichols superimposed the N(6) and C(2) portions of the LSD structure on the amine and ortho methoxy groups of the ring substituted phenethyl and phenylisopropylamines.

Since these conformational theories were based on consideration of analogues bearing either hydrogen or methoxy substituents at the ortho position, it was of interest to reexamine the applicability of these conformational predictions for the novel series of 2-X-substituted-4,5-dimethoxyphenylisopropylamines studied by us. Thus, a PCIL60 conformational analysis of these analogues has been carried out and is summarized in table II.

There have been many theoretical studies of phenethylamine conformation using a variety of methods (Martin et al. 1975; Weintraub and Hopfinger 1973; Hall et al. 1975 and Pullman and Pullman 1975). These theoretical calculations have generally indicated that the side chain of these variously substituted phenethylamines was conformationally quite
unrestricted and that the trans conformation was slightly less favorable than the gauche. The location of the global and local minima for these compounds was similar to those obtained by us using PCILO.

Our PCILO calculations predict that in the gas phase or in an inert solvent, the folded gauche conformation \((T_1=90°, T_2=60°)\) was about 1 kcal/mole more stable than the extended trans conformation \((T_1=90°, T_2=180°)\). In the neutral phenethylamine, this can be rationalized by N-H...π attractions which preferentially favor the folded forms. In the protonated phenethylammonium, these attractions result in stabilization of the gauche forms relative to the trans conformations. The introduction of electron donating groups such as a methoxy group in the para position further increases the electron donating capacity of the aromatic ring and lowers the energy of the gauche conformers.

Comparison of the unsubstituted phenethylammonium with compounds substituted in the ortho position by a -OCH\(_3\), -OH, -SCH\(_3\) groups revealed that in these compounds, one of the gauche conformations \((T_1=120°, T_2=90°)\) was stabilized via N-H...OCH\(_3\), N-H...OH, N-H...SCH\(_3\) intramolecular attractions. In the orthomethoxyphenethylammonium molecule, PCILO found the global minimum to be the gauche conformation in which the ammonium hydrogen points to the oxygen electrons and predicted this conformation to be 6.5 kcal/mole more stable than the trans orientation. The intramolecular stabilization was considerably weaker in the orthothiomethyl case where the gauche conformation is energetically only 1.7 kcal/mole more favorable the trans. In the ortho -CH\(_3\) and -Br substituted phenethylammoniums, gauche conformation \((T_1=90°, T_2=-60°)\) in which the amine is folded toward the aromatic ring on the side opposite to the ortho substituent was found to be the global minimum and slightly more stable than the local trans minimum.

**Ab initio** calculation of the trans and gauche PCILO minima for phenethylammonium showed the gauche to be preferred over the trans form by 0.24 kcal/mole, in excellent agreement with the PCILO energies (0.30 kcal/mole). A similar comparison of the energies calculated by the **ab initio** and PCILO methods at the trans and gauche minima of orthomethoxyphenethylammonium found the gauche conformation to be more stable than the trans by 16.5 kcal/mole and 6.5 kcal/mole respectively.

The relevance of gas phase conformations in biological systems is indirect at best and calculations at all levels which have considered solvent effects have shown the trans conformations to be preferentially stabilized relative to the gauche (Weintraub and Hopfinger 1973; Pullman 1974). Determination of the T\(_2\) rotamer populations of phenethylamine (Ison et al. 1973), dopamine (Bustard and Egan 1971) and numerous poly-substituted phenylisopropylamines (Bailey et al. 1971) via NMR have shown almost equal populations of trans and gauche conformations in solution. X-ray structures have been reported for the salts of phenethylamine (Tsoucaris 1961), dopamine (Bergin and Carlstrom 1968), mescaline (Ernst and Cagle 1973), amphetamine (Bergin and Carlstrom 1971) and 2,4,5-trimethoxyphenethylamine (Baker et al. 1973). In each crystal structure, an extended trans conformation \((T_1=70-89°, T_2=171-175°)\) was found except for the 2,4,5-trimethoxy compound \((T_1=67°, T_2=50°)\).
A number of workers have proposed phenethylamine conformations which allow it to mimic LSD at a hypothetical hallucinogenic receptor. We have used our PGILQ calculations to evaluate the energy of these conformations and have attempted to rationalize the conformational effects of the ortho substituents in terms of these mimic structures. If the phenethylamine binds to the receptor 103 times weaker than LSD and has the same total intrinsic attraction at its LSD mimic conformation, one would expect that a reasonable upper bound for the conformational energy would be about 4 kcal/mole relative to the global minimum ($\Delta G = -2.3RT \log(10)^3$). If LSD has a greater intrinsic affinity for the receptor than the LSD mimic conformation of the analog, then the upper bound of the conformational energy must be correspondingly less to compensate for this.

Since our calculations employed fixed internal bond lengths and angles, the energy of conformations in which there are significant steric effects ($T_1$ between $-40^\circ$ and $40^\circ$ or between $140^\circ$ and $220^\circ$) is probably an overestimate of the true energy for these conformations. Table II lists the energies for the two LSD mimic conformations proposed by Snyder and the mimics proposed by Kang and Green (1970), Baker et al. (1973) and Nichols (1978).

It is clear that the Snyder conformations are impossibly high in energy but that the other three are energetically quite reasonable. However, comparison of the energies of the latter conformational mimics of the ortho-H and -OCH$_3$ analogues predicts that the ortho-OCH$_3$ phenethylammonium should bind correspondingly weaker than phenethylammonium, a prediction not supported by the biological activities. Further, no explanation for the low potency of the ortho substituted -SCH$_3$, -CH$_3$, and -Br analogues can be clearly defined in terms of LSD mimic conformations.

**Electron Donating Properties**

The apparent inability of conformational arguments to rationalize the variations in hyperthermic potency led us to a detailed investigation of the electronic structure of compounds (1) – (14). A very simple minded glance at the rearranged isomers might suggest that the electron donating properties of the aromatic rings would be very similar. However, CNDO/2 calculations as well as recent photoelectron spectroscopy measurements (Domelsmith and Houk 1978) have indicated to the contrary (see table I). On a qualitative level, these electronic differences are apparent from the resonance structures. For example, the dimethoxy benzenes, shown below, are accompanied by the number of resonance structures which place excess charge on the carbon atoms of the aromatic ring.
Table II. PCILO Conformational Analysis of a Series of Substituted Phenethylamines

<table>
<thead>
<tr>
<th>X=</th>
<th>Y=</th>
<th>Global Minimum(^a)</th>
<th>Local Minimum(^a)</th>
<th>S I(^c)</th>
<th>S II(^d)</th>
<th>Energy (kcal/mole)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-H</td>
<td>NH(_3)(+)</td>
<td>GI = G II</td>
<td>T (0.9)</td>
<td>253</td>
<td>480</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>-OCH(_3)</td>
<td>GI</td>
<td>G II (6.9)</td>
<td>260</td>
<td>278</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T (6.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-OH(^h)</td>
<td>GI</td>
<td>G II (7.6)</td>
<td>1705</td>
<td>474</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T (7.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G II (1.4)</td>
<td>10088</td>
<td>21.7</td>
<td>90.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T (0.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCH(_3)</td>
<td>GI</td>
<td>G II (0.9)</td>
<td>256</td>
<td>981</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T (1.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CH(_3)</td>
<td>GI</td>
<td>G I (1.1)</td>
<td>251</td>
<td>2117</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T (0.7)</td>
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</tr>
<tr>
<td></td>
<td>Br</td>
<td>GI</td>
<td>G I (0.3)</td>
<td>253</td>
<td>1061</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T (0.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) GI = gauche conformation with NH\(_3\)(+) group toward X (T\(_2\)>0); G II = gauche conformation with NH\(_3\)(+) group away from X (T\(_2\)>0); T = trans conformation.  
\(^b\) Energy above the conformational minimum.  
\(^c\) "B ring mimic" of Snyder (1970).  
\(^d\) "C ring mimic" of Snyder (1970).  
\(^e\) LSD mimic of Kang and Green (1973).  
\(^f\) LSD mimic of Baker et al. (1973).  
\(^g\) LSD mimic of Nichols (1978).  
\(^h\) OH pointed away from side chain.  
\(^i\) OH pointed toward side chain.
The trends seen in the $\pi$ densities are also reflected by the CNDO/2 calculated Mulliken population densities which account for both the $\sigma$ and $\pi$ electrons.

Calculation of the HOMO energies for compounds \(1\)-\(11\) (excluding the Br isomers which are suspect) has been made and a satisfactory correlation \((n=7, r=0.98)\) can be shown between these orbital energies and the ionization potentials determined by photoelectron spectroscopy in agreement with Koopmans Theorem. While the orbital energy differences between the various rearranged isomers were small, the CNDO/2 results indicated that the ionization potentials were ordered as follows: \(4-X<5-X<2-X\). However, the regression of these HOMO energies with the hyperthermic potencies \((\log \text{H.P.})\) was quite impoverished \((r=0.65)\) and barely significant at the 95% confidence level. The good correlations reported by others for the methoxy substituted phenylisopropylamines were not to be found among the rearranged isomers studied by us.

While quantitative electronic models seemed outside our grasp, a qualitative picture of drug-receptor inter-reaction did emerge:

Two pharmacophoric sites are postulated in the drug binding, the first involving the charged ammonium group and the second resulting from an electronic association between the receptor and the aryl-moiety. It is clear that good binding results from electron rich aromatic systems which have both large negative electrostatic potentials at the van der Waals radius \((=1.7\text{Å})\) and also favorable electrostatic potential gradients parallel to the aromatic plane as have been described by Weinstein et al. \((1976)\) for the 4,5,6, and 7-OH tryptamines. In general, addition of electron donating substituents such as a methoxy group was found to augment the $\pi$ electron density of the aromatic ring and presumably results in favorable electronic associations. The inplane electrostatic gradients were, however, quite sensitive to the position of the methoxy substituents. For example, in the
positional dimethoxy benzenes discussed previously, the resonance arguments predicted low π density at C₄ and high density at C₁ for the 2,4-dimethoxy substituted benzene, but little gradient was found in the 2,5- or 3,4-dimethoxy substituted benzenes. (The Mulliken populations are also consistent with this reasoning.) These gradients predict that analogues which are electron rich at the 3,4, and 5 positions and relatively electron poor at the 1,2, and 6 positions might be most potent at our diagrammatic receptor. While the unfavorable electrostatic gradient of the 2,4-dimethoxy orientation might be invoked to account for the low potency of the 5-X-substituted-2,4-dimethoxyphenylisopropylamines, apparently other arguments must be advanced to separate the very potent 4-X-substituted-2,5-dimethoxyphenylisopropylamines from the weakly potent 2-X-substituted-4,5-dimethoxyphenylisopropylamines.

Distribution Properties

If the molecular partition coefficient is assumed to be the linear sum of the component π substituent values, then the Log P’s of the mono-, di-, tri-, and tetramethoxy substituted phenylisopropylamines would be almost equivalent (±0.10). Were this actually the case, one would expect a rather poor correlation between the small differences in the distribution characteristics and the rather large variations in the biological activity of this class of phenylisopropylamines. Further, the various positional isomers would be isolipophilic and hence would be incorrectly predicted to be equiactive. These expectations have not been supported by experiment.

Barfknecht et al. (1975) have measured the partition coefficients of various methoxy substituted phenylisopropylamines and have shown conclusively that nonadditativity of π values was more the rule than the exception for these compounds. Some Precedent for these findings could be taken from the work of Leo et al. (1971) in which the π value of the central methoxy group in 1,2,3-trimethoxybenzene was derived to be -0.56 and much closer to the π value of an aliphatic methoxy group (-0.47) than an aromatic methoxy group (-0.02). It was postulated that unfavorable steric repulsions forced the central methoxy group out of the plane making the hybridization of the oxygen more "sp3" and hence resembling an aliphatic methoxy group.

Because of the nonadditive nature of these substituents, we have analyzed the π values of the various positional mono-, di-, and trimethoxy configurations in a number of model compounds and have summarized these results in table III. As can be seen, the positional monomethoxy isomers had almost equivalent π values (π=0.03 - 0.09) and were reasonably close to the traditional value of -0.02. Similar results were obtained for the 2,3-, 2,4-, and 2,5-dimethoxy orientations. However, in the case of the 3,4-dimethoxy grouping, a very large neighboring group interaction substantially lowered the π substituent value. In the trimethoxy arrangements, the 2,4,6- pattern appears to have a normal π value, whereas the 2,4,5-trimethoxy π value derived from Nichols et al. (1978) measurement resembles the 3,4-dimethoxy π value in that it is considerably more hydrophilic than expected. The 2,3,4- and 3,4,5-trimethoxy π values are very similar (π=0.20) and somewhat less lipophilic than expected.
Table III. Model System Study of the Positional Monomethoxy $\pi$ Substituent Values, and the Positional Di- and Trimethoxy $\pi$ Multisubstituent Values

<table>
<thead>
<tr>
<th>X = Monomethoxy</th>
<th>$\pi_{4-OCH_3}$</th>
<th>$\pi_{3-OCH_3}$</th>
<th>$\pi_{2-OCH_3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y = -COOH&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.09</td>
<td>0.15</td>
<td>---</td>
</tr>
<tr>
<td>-CH$_2$NO$_2$&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.06</td>
<td>0.09</td>
<td>0.33</td>
</tr>
<tr>
<td>-CH$_2$(CH$_2$)NO$_2$&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.34</td>
<td>-0.06</td>
<td>-0.07</td>
</tr>
<tr>
<td>-CH$_2$COOH&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.01</td>
<td>0.09</td>
<td>---</td>
</tr>
<tr>
<td>-OCH$_3$COOH&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.12</td>
<td>-0.03</td>
<td>-0.33</td>
</tr>
<tr>
<td>-OH&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.12</td>
<td>0.12</td>
<td>---</td>
</tr>
<tr>
<td>-NH$_2$&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.05</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>-CONH$_2$&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.22</td>
<td>0.30</td>
<td>0.23</td>
</tr>
<tr>
<td>-CH$_2$(CH$_3$)$_2$NH$_2$&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.14</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>-CH$_2$CH$(CH_3)_2$NH$_2$&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.15</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Average&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.03</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>(Stand. Dev.)</td>
<td>±0.19</td>
<td>±0.10</td>
<td>±0.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>X = Dimethoxy</th>
<th>$\pi_{2,3-(OCH_3)_2}$</th>
<th>$\pi_{2,4-(OCH_3)_2}$</th>
<th>$\pi_{2,3-(OCH_3)_2}$</th>
<th>$\pi_{3,4-(OCH_3)_2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y = -CH$_2$CH$_2$NO$_2$&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.13</td>
<td>0.23</td>
<td>-0.01</td>
<td>-0.86</td>
</tr>
<tr>
<td>-CH$_2$(CH$_3$)$_2$NH$_2$&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.11</td>
<td>-0.14</td>
<td>-0.19</td>
<td>-0.92</td>
</tr>
<tr>
<td>-CH$_2$CH$(CH_3)_2$NH$_2$&lt;sup&gt;c&lt;/sup&gt;</td>
<td>---</td>
<td>0.12</td>
<td>0.25</td>
<td>-0.43</td>
</tr>
<tr>
<td>-CH$_2$CH$(CH_3)_2$NH$_2$&lt;sup&gt;d&lt;/sup&gt;</td>
<td>---</td>
<td>---</td>
<td>0.07</td>
<td>-0.75</td>
</tr>
<tr>
<td>Average&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.01</td>
<td>0.07</td>
<td>0.03</td>
<td>-0.74</td>
</tr>
<tr>
<td>(Stand. Dev.)</td>
<td>±0.12</td>
<td>±0.15</td>
<td>±0.16</td>
<td>±0.19</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>X = Trimethoxy</th>
<th>$\pi_{2,3,4-(OCH_3)_3}$</th>
<th>$\pi_{2,4,5-(OCH_3)_3}$</th>
<th>$\pi_{2,4,6-(OCH_3)_3}$</th>
<th>$\pi_{3,4,5-(OCH_3)_3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y = -CH$_2$CH$(CH_3)_2$NH$_2$&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.27</td>
<td>(0.11)</td>
<td>-0.06</td>
<td>-0.34</td>
</tr>
<tr>
<td>-CH$_2$CH$(CH_3)_2$NH$_2$&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-0.12</td>
<td>-0.53</td>
<td>---</td>
<td>-0.12</td>
</tr>
<tr>
<td>Average&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.19</td>
<td>?</td>
<td>(-0.06)</td>
<td>-0.23</td>
</tr>
<tr>
<td>(Stand. Dev.)</td>
<td>±0.07</td>
<td>---</td>
<td>---</td>
<td>±0.11</td>
</tr>
</tbody>
</table>

These unusual results have prompted us to explore neighboring group effects in numerous other ortho oxygen substituted model compounds. The substituent \( \pi \) values along with the CNDO/2 calculated conformational minima of these groupings have been summarized in table IV. As can be seen from the table, the minimum energy conformation of both 2,3- and 3,4-dimethoxytoluene and also 3-methoxy-4-thiomethyltoluene was predicted by CNDO/2 to be nonplanar; however, in the latter two substitution patterns, a low-lying planar conformation was also found. In 3-methoxy-4-hydroxytoluene, a nonplanar orientation similar to the conformational minima of 3,4-dimethoxytoluene was computed to be slightly more stable than the planar form which differs from the dimethoxy case in that the hydrogen of the phenol is directed toward a methoxy group whose methyl substituent is pointed away. A planar global minima was found in 3,4-dihydroxytoluene whereas nonplanar conformations were favored in both 2,3,4- and 3,4,5-trimethoxytoluene. The variations in the lipid solubility of these groupings appear to be related to the solvation of the lone pair electrons of the methoxy groups by water. The hydrophilicity of the 3,4-dimethoxy grouping can be explained in one of two ways: 1) lone pair-lone pair repulsions in adjacent methoxy groups favor nonplanar conformations which are more strongly solvated than the planar structures, or 2) the planar orientation which exists as a low-lying local minima results in the buildup of electron density between the methoxy substituents, and this region provides a good site of solvation. It is difficult to rule out one of these explanations. Since both the 2,3- and 3,4-dimethoxytoluenes exist in nonplanar forms and yet only the latter has an abnormal \( \pi \) value, one might conclude that a specific solvation site is implicated. However, the differences between the \( \pi \) values in these two cases could also be explained by steric inhibition of solvation in the 2,3-dimethoxy compounds by the ortho substituent (such as an ethylamine side chain). Conversely, the methylenedioxy grouping, which is more lipophilic than the component substituents, is both planar and the specific solvation site is blocked by the methylene moiety. Similarly, 3-methoxy-4-hydroxy pattern is more lipophilic than expected due to intermolecular hydrogen bonding in the low-lying planar conformational minima.

In any case, it is clear that our initial assumption that the "rearranged" positional isomers were isolipophilic was in error. The adjacent methoxy group interaction makes the 4,5-dimethoxy-2-X-substituted analogues much more hydrophilic than the nearly isolipophilic 2,4-dimethoxy-5-Xand 2,5-dimethoxy-4-X-substituted compounds. Regression analysis showed a rather poor correlation between Log H.P. and HOMO energies; addition of the Log P resulted in no significant improvement. Scrutiny of the log-log plot showed a fairly straight line for the 2,5-dimethoxy-4-X-substituted compounds, but the H.P. of the other positional isomers was not correlated with Log P.

**Metabolism**

A potentially important consequence of the electronic and distribution properties of the "rearranged" isomers concerns their susceptibility to biotransformation in vivo. Investigation of the metabolic fate of DOM (5) (Zweig and Castagnoli 1977) had established the conversion of
Table IV. Model System Study of the $\pi$ Substituent Values and the CNDO/2 Calculated Conformational Structure of Various ortho-Oxygen Substituted Groups

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$R_4$</th>
<th>$\pi^{\text{add.}}$</th>
<th>$\pi^{\text{obs.}}$</th>
<th>$\pi^{\text{add.-obs.}}$</th>
<th>CNDO/2 Minima $^c$</th>
<th>Global</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>H</td>
<td>H</td>
<td>-0.04</td>
<td>0.01 (±0.12)</td>
<td>-0.05</td>
<td>NP$^d$</td>
<td>p$^o$(ΔE=78)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>-0.04</td>
<td>-0.74 (±0.19)</td>
<td>0.70</td>
<td>NP$^d$</td>
<td>p$^f$(ΔE=0.65)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>SCl$_3$</td>
<td>OCH$_3$</td>
<td>0.59</td>
<td>0.37 (±0.12)</td>
<td>0.22</td>
<td>NP$^d$</td>
<td>p$^d$(ΔE=1.06)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>OCH$_2$Cl$_3$</td>
<td>OCH$_3$</td>
<td>0.36</td>
<td>-0.65 (±0.17)</td>
<td>1.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>OCH$_3$</td>
<td>-0.69</td>
<td>-0.31 (±0.07)</td>
<td>-0.38</td>
<td>NP$^f$</td>
<td>p$^g$(ΔE=0.23)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>O--CH$_2$--O</td>
<td></td>
<td>-0.50</td>
<td>-0.02 (±0.03)</td>
<td>-0.48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>OH</td>
<td>-1.34</td>
<td>-1.42 (±0.10)</td>
<td>0.08</td>
<td>p$^h$</td>
<td>NP$^d$(ΔE=2.50)</td>
<td></td>
</tr>
<tr>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>H</td>
<td>-0.06</td>
<td>-0.19 (±0.07)</td>
<td>0.04</td>
<td>NP$^i$</td>
<td>p$^j$(ΔE=15.94)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>-0.06</td>
<td>-0.23 (±0.11)</td>
<td>0.17</td>
<td>NP$^k$</td>
<td>p$^m$(ΔE=0.02)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Substituent $\pi$ values taken from Hansch et al. (1973). $^b$Determined from measured Log P of model compounds. $^c$Energy in kcal/mole and $X$=Cl; NP=nonplanar, P=planar. $^d_{T_a}$=120°, $T_b$=180°(a-b). $^e_{T_a}$=0°, $T_b$=180°(a-b). $^f_{T_3}$=180°, $T_4$=90°. $^g_{T_a}$=180°, $T_b$=180°(a-b). $^h_{T_3}$=0°, $T_4$=0°. $^i_{T_1}$=225°, $T_2$=135°, $T_3$=180°. $^j_{T_1}$=90°, $T_2$=0°, $T_3$=180°. $^k_{T_1}$=135°, $T_3$=45°, $T_4$=180°. $^l_{T_2}$=0°, $T_3$=0°, $T_4$=180°.
this compound into the bis-O-demethylated metabolite (15), a close analogue of the selective noradrenergic toxin 6-hydroxydopamine (16). The chemical behavior of the hydroquinone (15) and 6-hydroxydopamine (16) is analogous in that both readily undergo spontaneous oxidation leading to electrophilic intermediates (Zweig and Castagnoli 1974) which in the case of 6-hydroxydopamine are likely to be responsible for the observed destruction of noradrenergic terminals (Malnifors and Thoenen 1971).

In this regard, the exceptional hyperthermic potency of phenylisopro-pylamines (5), (8), (11), and (13) (100, 54, 405, and 12 SRU respectively), all of which are 2,5-dimethoxy substituted, compared to the low hyperthermic potency of the positional isomers (4), (6), (7) and (12) (1, 0, 5, and 3 respectively), none of which are 2,5-dimethoxy substituted and are incapable of metabolic conversion to a para-hydroquinone, focused attention on the special structural features associated with the para-oxygen substitution pattern.

At the present time, no attempts have been made to determine if these substituent effects relate, in general, to the metabolic profiles of this class of compounds. Nonetheless, the potential association of psychotomimetic activity with the metabolic formation of 6-hydroxydopamine like intermediates from the potent para-oxygen substituted compounds studied here is intriguing. In vivo metabolic oxidation of psychotomimetic amines to electrophilic species capable of covalent interactions with brain enzymes responsible for the control of central amines could lead to biochemical lesions and account for the toxic CNS effects of these analogues.

Summary and Future Directions

The excellent correlation between rabbit hyperthermia and human psychotomimetic potencies for a variety of psychotomimetic agents strongly asserts the utility of this animal model in the pharmacological evaluation of this class of compounds. Consideration of the conformational, electronic, metabolic, and distribution properties of the "rearranged" isomers has led us to the conclusion that the psychotomimetic potencies cannot be related satisfactorily to overall molecular properties, such as Log P or the HOMO energies, but instead appears to be dependent upon the regiospecific properties such as in plane electrostatic gradients, local group lipophilicity, or metabolic conversion to reactive intermediates. While trends can be found in both the HOMO energies and Log P which do reflect the variations in psychotomimetic potency, the numerical formulation of the SAR using these variables results in
unimpressive regressions which have only marginal predictive capabili-
ties and contribute little to our understanding of these novel com-
ounds. Indeed, further analysis into the regiospecific properties
of the "rearranged" isomers and integration of these factors into a
QuaSAR equation constitute the direction of our researches. Towards
these ends, we have extended the analogue set by including both the
OCH₂CH₃ (17), (18), (19) and OH (20), (21), (22) substituted phenyl-
isopropylamines, In the OCH₂CH₃ analogues, the overall electronic
and distribution properties of these positional isomers are very nearly
equivalent and may provide insights into the potential relationships
between the inplane electrostatic gradient and psychotomimetic potency.

![Chemical structures](image)

The -OH substituted phenylisopropylamines provide an interesting exam-
ple of positional isomers which are probably much more lipophilic than
previously anticipated due to the intramolecular hydrogen bonding of
the adjacent OH...OCH₃ groups in compounds (20) and (21), and similarly
between the OH...NH₂ moieties in the 2-OH analogue (22). In these
examples, the involvement of regioolipophilicity and metabolic effects
will be investigated.

Clearly, the "rearranged" phenylisopropylamines represent a unique.
set of analogues whose SAR are quite different from the methoxy
substituted phenlisopropylamines or 2,5-dimethoxy-4-alkyphenyliso-
propylamines studied previously. Further research into these analogues
may well reveal the critical factors related to the molecular expres-
sion of the complex phenomenon of psychotomimesis.

"In the infancy of a science generalizations are rarely true beyond
narrow and too often undefined limits. Always the question, How?
punctures the bubble of theory, and the answer is to be sought in
analysis and ever more analysis."

K. S. Lashley, 1933

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