The P-388 leukemia assay was performed according to standard protocol.

**Toxicity Tests.** Toxicity tests of the perchlorate ion in mice were carried out by the procedure described above. Mice were also checked visually daily for any change in their appearance.

**Melting Curve.** Thermal denaturation studies were carried out with a Beckman DU-8 spectrophotometer. The temperatures of the thermal denaturation experiments were obtained with a programmed temperature of 0.7 °C per minute. Calf thymus DNA, 5-nitrobenzothiazolo[3,2-a]quinolinium salt (4b), and fargaronine (1a) were dissolved in SHE buffer (2 mM HEPES, 10 μM EDTA, 0.4 mM NaCl adjusted to pH 7.0 with NaOH). For determination of thermal denaturation profiles, the final concentration of DNA was identical in the presence or absence of the test drug in all experiments.

**Acknowledgment.** The authors are indebted to Dr. José A. Carrasco Canales for performing the antimicrobial assay, to Diana Valdejui Román for her expert technical assistance, and to Dr. Carmen Mercado for the use of the Beckman DU-8 spectrophotometer. We also gratefully acknowledge the National Science Foundation (CHE-79-1462) for funds used to purchase the JEOL FX-90Q NMR spectrometer. Part of this work was supported by Biomedical Research Support Grant RR-08102-09.

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### Structure–Activity Relationships for Hallucinogenic N,N-Dialkyltryptamines: Photoelectron Spectra and Serotonin Receptor Affinities of Methylthio and Methylenedioxy Derivatives

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Serotonin receptor affinity and photoelectron spectral data were obtained on a number of substituted N,N-dialkyltryptamines. Evidence is presented that electron-donating substituents in the 5-position lead to enhanced behavioral disruption activity and serotonin receptor affinity as compared to unsubstituted N,N-dimethyltryptamine and analogues studied in the 4- or 6-position. Some correlation was found between ionization potentials and behavioral activity, which may have implications concerning the mechanism of receptor binding.

In a recent communication, we described the relative behavioral activities of a series of ring-substituted N,N-dialkyltryptamines, as well as the effectiveness of these compounds in displacing tritiated serotonin (5-HT) and lysergic acid diethylamide (LSD) from 5-HT binding sites. Because photoelectron spectroscopic (PES) properties and rat fundus 5-HT receptor affinities (pA2 values) have been previously used to study various hallucinogenic agents, we have undertaken an examination of those properties for five novel substituted N,N-dimethyltryptamines (1-5).

**Photoelectron Spectroscopy.** Figure 1 shows the PES of compounds 1 through 5. The vertical ionization potentials (IP, in eV) taken from these spectra appear in Table I. Each distinct IP, can be assigned to an ionization event from a particular molecular orbital, φ. The changes in IP's, which, by sign convention, are lowered as φ is raised, indicate the influence of the substituents upon the corresponding molecular orbital of N,N-dimethyltryptamine, DMT (7). Assignments were made in accordance with the methodology of Domelsmith et al. and in these experiments.

**Ionization Potentials.** From the relative coefficient magnitudes and symmetry properties of the wave function of indole, it is possible to make some predictions regarding substituent effects in this series of compounds. Generally, electron-donating substituents lower aromatic IP's most when attached at a site where the electron density in φ at the substitution site is large. The high-lying filled orbitals of the indole nucleus, shown in Figure 2, are useful in interpreting the spectra obtained here. Thus, substituent effects in the series of 5,6-positionally substituted N,N-dialkyltryptamines were considered in the following discussion.

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5. These were obtained by ab initio STO-3G calculations on indole.

(6) These were obtained by ab initio STO-3G calculations on indole.
N,N-Dimethyltryptamine and Derivatives, amine nitrogen lone pair.
electrons.

associated with oxygen lone pair.

should have an opposite effect, lowering IP2 but having

tation at position 4 in the indole nucleus can be expected
to lower IP1 and IP3 substantially but have little effect on
IP2 because $\phi_1$ and $\phi_3$, but not $\phi_2$, have large coefficients
at the 4-position. An electron-donor group at position 5
should have an opposite effect, lowering IP3 but having

Table I. Vertical Ionization Potentials ($\pm 0.06$ eV) of
N,N-Dimethyltryptamine and Derivatives, 1–5

<table>
<thead>
<tr>
<th>ring no.</th>
<th>substit</th>
<th>$\pi_1$</th>
<th>$\pi_2$</th>
<th>$\pi_4$</th>
<th>$n_N$</th>
<th>$n_O$</th>
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</thead>
<tbody>
<tr>
<td>7</td>
<td>H</td>
<td>7.57</td>
<td>8.22</td>
<td>9.54</td>
<td>~8</td>
<td></td>
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<tr>
<td>1</td>
<td>4,5-OCH$_3$O</td>
<td>7.25</td>
<td>8.25</td>
<td>9.25</td>
<td>~8.0</td>
<td>10.13</td>
</tr>
<tr>
<td>2</td>
<td>4,5-OCH$_2$O</td>
<td>7.48</td>
<td>~7.5</td>
<td>9.31</td>
<td>~8.0</td>
<td>9.84</td>
</tr>
<tr>
<td>3</td>
<td>4-SMe</td>
<td>7.43</td>
<td>8.12</td>
<td>8.25</td>
<td>8.99</td>
<td>~8</td>
</tr>
<tr>
<td>4</td>
<td>5-SMe</td>
<td>7.68</td>
<td>8.23</td>
<td>~8.5</td>
<td>9.75</td>
<td>~8.1</td>
</tr>
<tr>
<td>5</td>
<td>6-SMe</td>
<td>7.52</td>
<td>~8.1</td>
<td>8.39</td>
<td>9.58</td>
<td>~8</td>
</tr>
</tbody>
</table>

$^a$ $\pi_i$ = vertical ionization potentials associated with $\pi$ electrons.
$^b$ $n_N$ = ionization potential associated with amine nitrogen lone pair.
$^c$ $n_O$ = ionization potential associated with oxygen lone pair.

Table II. Ionization Potentials

<table>
<thead>
<tr>
<th>no.</th>
<th>IP$_1$</th>
<th>IP$_{av}$ $^a$</th>
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<tr>
<td>2</td>
<td>7.46</td>
<td>7.5</td>
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<tr>
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<td>7.75</td>
</tr>
<tr>
<td>4</td>
<td>7.68</td>
<td>7.95</td>
</tr>
</tbody>
</table>

$^a$ (IP$_1$ + IP$_3$)/2.

Figure 1. Photoelectron spectra (PES) of experimental compounds 1–5. Ionization potentials (IP) are taken as positions of band maxima.

Figure 2. High-lying $\pi$ orbitals (STO-3G) of indole.

l小小 influence on IP$_1$ and IP$_3$. Substitution at position 6 would result in a large decrease in IP$_2$, a modest decrease in IP$_4$, and negligible effects IP$_2$ and IP$_4$. In the instance of the 4,5-methylenedioxy compound 1, a lowering of both IP$_1$ and IP$_2$ would be anticipated, while in the 5,6-congener 2, IP$_2$ and IP$_4$ should be most affected.

These predictions were more or less realized. In particular, the methylthio compounds have increasing IPs in the order: 3 < 5 < 4, the same as the decreasing order of coefficient sizes in the HOMO at the site of the substituent. Ionization potentials from subordinate orbitals $\phi_1$ and $\phi_4$ were frequently obscured in a poorly resolved envelope. Two very interesting spectra were obtained from 1 and 2, both of which are methylenedioxy compounds. Compound 2 showed a relatively large decrease of ~0.7 eV in IP$_2$, accompanied by a 0.11 eV decrease in IP$_3$, as predicted by the coefficients of $\phi_1$ and $\phi_2$. The 1,2-benzodioxole ring is necessarily planar, and such a conformational constraint forces the p orbitals of oxygen into maximal overlap with the $\pi$ system of this molecule. Compound 1 has an IP$_2$ that is 0.32 eV lower than the first IP of DMT and slightly below IP$_1$ of LSD.

The IP$_1$ of 4 is slightly higher than that of DMT, while IP$_2$ is essentially unchanged. A resonable explanation for these data is that the 5-CH$_3$S group is rotated out of plane of the aromatic $\pi$ system causing it to be an inductively electron-withdrawing group and a relatively poor $\pi$ donor. A similar out of plane rotation has been demonstrated for thianisole and related compounds. As described in our work on polysubstituted amphetamines, the broadness of the spectrum of 4 may be indicative of the nonplanarity of the thiomethoxy group.

With respect to behavioral activity, a mechanistic model dominated by the HOMO of the compound interacting with the LUMO of the receptor would be expected if IP$_1$ correlated with activity; no such correlation exists between IP$_1$ and the activity of compounds 1–5 as reported by Klinc et al. Nevertheless, the IP$_1$ of 4 is similar to that of 5-OH-DMT (6), i.e., 7.61, and, in fact, the discriminative properties of 4 and 6 in rats are, indeed, quite similar. Furthermore, IP$_{av}$ values, where contributions from the

two highest-lying molecular orbitals are taken into account, and IP, both correctly identify the 5-methylthio derivative 4 as being the most active agent in the series of 1–5.

**5-HT Receptor Affinity and Activity.** The ability of 5-HT to produce contractions of the isolated rat fundus is antagonized by certain other ligands for this 5-HT site; thus, the diminution of such contractions is a useful measure of ligand affinity when the interaction is of a competitive nature (i.e., when the negative slope of the Schid plot approximates infinity). It has been reported that those indolealkylamine hallucinogens that are most potent in man possess relatively high 5-HT receptor affinities (pA₂ values), although it cannot be assumed that all compounds possessing high affinities are necessarily hallucinogenic.

Table III lists the 5-HT receptor affinities for 1–5, along with those of four previously reported reference compounds. The interaction of these agents with the 5-HT receptors was found to be of a competitive nature as noted by the slope of their Schid plots (Table III). With respect to indolealkylamines, pA₂ values are sensitive to the presence and location of certain substituent groups. For example, Glennon and co-workers have found that 5-methoxylation of various indolealkylamines resulted in a 10 to 20-fold increase in affinity and that the affinity for a series of methoxylated derivatives of DMT increases in the order 6-OMe > 4-OMe > 5-OMe. This same trend is observed for the methylthio derivatives 3–5. The affinity of the 5-methylthio derivative 4 is similar to, and that of the 4-methylthio derivative 3 is about one-seventh, that of 5-OMe-DMT (6). Interestingly, in tests of discriminative stimulus control of behavior, the activity of 5-OMe-DMT was found to be similar to that of 4 and approximately seven times that of 3. With respect to the methylenedioxy derivatives 1 and 2, it appears that incorporation of a second oxygenated substituent at either the 4- or 6-position reduces the affinity of the resultant compound below that of 5-OMe-DMT (6).

The data presented herein, taken together with the results of our previous studies, support the importance of the role played by electron-donating substituents (e.g., OMe, SMe) at the 5-position of monosubstituted indolealkylamines. Of the five compounds evaluated, 5-(methylthio)-N,N-dimethyltryptamine possesses the highest ionization potential, is the most active with respect to 5-HT receptor affinity and behavioral activity (as evaluated with Bovet–Gatti profiles), is more active than its 4-methylthio counterpart as a discriminative stimulus in rats, and is the most effective in displacing both triitated 5-HT and LSD binding to brain homogenates.

### Experimental Section

The preparation of compounds 1–5 has been described previously. Both reference tryptamines were obtained from Dr. A. Manian of NIMH.

**Photoelectron Spectroscopy (PES).** Compounds were analyzed (as the free bases) at a constant temperature between 65 and 112 °C, with a Perkin-Elmer PS-18 photoelectron spectrometer equipped with a He(I) source. Xenon and argon were used as internal calibrants. Resolution was approximately 50 meV.

### Acknowledgment

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