The P-388 leukemia assay was performed according to standard protocol.[21]

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 denaturations were obtained with a programmed temperature of 0.7 °C per minute. Calf thymus DNA, 3-nitrobenzothiazolo[3,2-*a*]quinolinium salt (**4b**), and fagaronine (**1a**) were dissolved in SHE buffer (2 μM Hepes, 10 μM EDTA, 0.4 μM 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.

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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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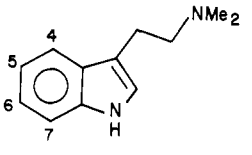
Serotonin receptor affinity and photelectron spectral data were obtained on a number of substituted *N,N*-dimethyltryptamines. Evidence is presented that electron-donating substituents in the 5-position lead to enhanced behavioral disruption activity and serotonin receptor affinity as compared to unsubstituted *N,N*-dimethyltryptamine and analogues substituted 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,[1a] 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 sepctral (PES) properties and rat fundus 5-HT receptor affinities (pA_2 values) have been previously used to study various hallucinogenic agents,[1b] 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[2] (IP, in eV) taken from these spectra appear in Table I. Each distinct IP_i can be assigned to an ionization event from a particular molecular orbital, ϕ_i. The changes in IP_is, which, by sign convention, are lowered as ϕ_i is raised, indicate the influence of the substitutents upon the corresponding molecular orbital of *N,N*-dimethyltryptamine, DMT (**7**). Assignments were made in accordance with the methodology of Domelsmith et al.[2,4,5] in these experiments.

Ionization Potentials. From the relative coefficient magnitudes and symmetry properties of the wave function of indole,[2] it is possible to make some predictions regarding substituent effects in this series of compounds. Generally,



R

1	4,5-<O,O
2	5,6-<O,O
3	4-CH_3S-
4	5-CH_3S-
5	6-CH_3S-
6	5-CH_3O-
7	H

electron-donating substituents lower aromatic IPs 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.[6] Thus, substitu-

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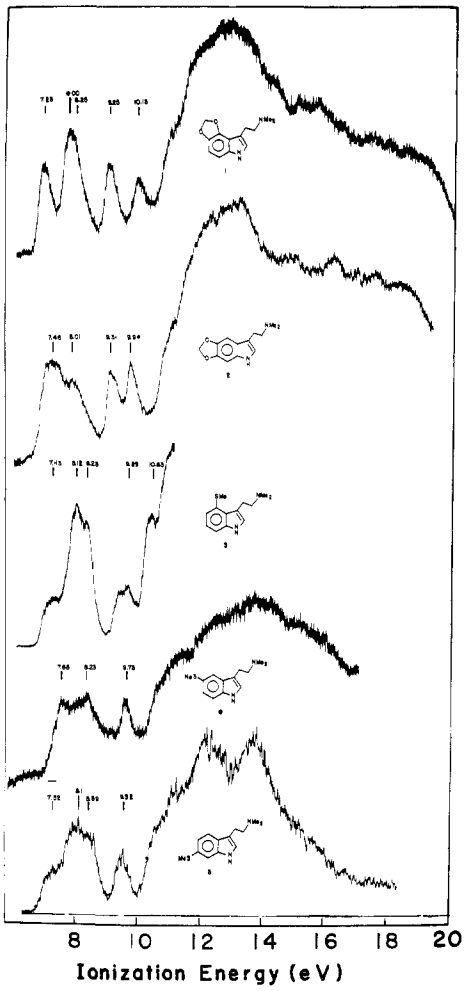

Figure 1. Photoelectron spectra (PES) of experimental compounds 1–5. Ionization potentials (IP) are taken as positions of band maxima.

Table I. Vertical Ionization Potentials (±0.06 eV) of *N,N*-Dimethyltryptamine and Derivatives, 1-5

no.	ring substit	π_1[a]	π_2	π_3	π_4	n_N[b]	n_O[c]
7	H	7.57	8.22	9.54		~8	
1	4,5-OCH_2O	7.25	8.25	9.25		~8.0	10.13
2	4,6-OCH_2O	7.46	~7.5	9.31		~8.0	9.94
3	4-SMe	7.43	8.12	8.25	9.89	~8	
4	5-SMe	7.68	8.23	~8.5	9.75	~8.1	
5	6-SMe	7.52	~8.1	8.39	9.58	~8	

[a] π_i = vertical ionization potentials associated with π 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

no.	IP_1	IP_{av}[a]
2	7.46	7.5
3	7.43	7.8
5	7.52	7.8
1	7.25	7.75
4	7.68	7.95

[a] $(IP_1 + IP_2)/2$.

tion at position 4 in the indole nucleus can be expected to lower IP_1 and IP_3 substantially but have little effect on IP_2 because ϕ_1 and ϕ_3, but not ϕ_2, have large coefficients at the 4-position. An electron-donor group at position 5 should have an opposite effect, lowereing IP_2 but having

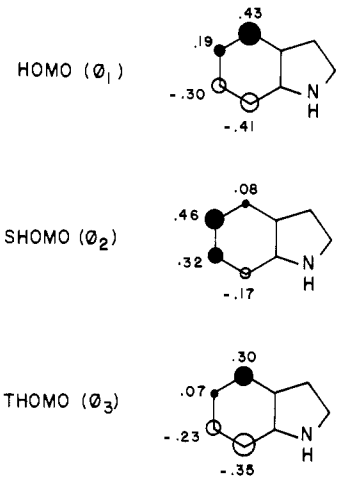

Figure 2. High-lying π orbitals (STO-3G) of indole.

little influence on IP_1 and IP_3. Substitution at position 6 would result in a large decrease in IP_4, a modest decrease in IP_1, and negligible effects IP_2 and IP_3. 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 ϕ_3 and ϕ_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_1, as predicted by the coefficients of ϕ_1 and ϕ_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 π system of this molecule. Compound 1 has an IP_1 that is 0.32 eV lower than the first IP of DMT and slightly below IP_1 of LSD.[2]

The IP 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_3S group is rotated out of plane of the aromatic π system causing it to be an inductively electron-withdrawing group and a relatively poor π donor. A similar out of plane rotation has been demonstrated for thianisole and related compounds.[7-10] As described in our work on polysubstituted amphetamines,[10] 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 Kline et al.[1a] Nevertheless, the IP_1 of 4 is similar to that of 5-OMe-DMT (6), i.e., 7.61,[2] and, in fact, the discriminative properties of 4 and 6 in rats are, indeed, quite similar.[11] Furthermore, IP_{av} values,[2] where contributions from the

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Table III. 5-HT Receptor Affinity Data

no.	compd	pA_2 [a]	M [b]	N [c]
3	4-SMe-DMT	6.21 (±0.18)	0.90 (±0.13)	3 [d] (15)
4	5-SMe-DMT	6.84 (±0.07)	1.03 (±0.06)	3 [d] (14)
5	6-SMe-DMT	5.92 (±0.14)	0.96 (±0.06)	2 [e] (10)
1	4,5-MDO-DMT	6.40 (±0.15)	1.02 (±0.08)	2 [e] (10)
2	5,6-MDO-DMT	5.99 (±0.07)	0.92 (±0.06)	2 [e] (10)
8	4-OMe-DMT	6.17 [f]		
6	5-OMe-DMT	7.08 [f]		
9	6-OMe-DMT	5.77 [f]		
7	DMT	6.00 [f]		

[a] pA_2 followed by standard deviation. [b] Negative slope of Schild plot . [c] Number of determinations, followed by number of dose-response curves. [d] Run twice as free base + equiv HCl; then run once as HCl salt. [e] Run as free base + equiv HCl. [f] Value previously reported;[12,13] included for comparative purposes.

two highest-lying molecular orbitals are taken into account, and IP_1 both correctly identify the 5-methylthio derivative **4** as being the most active agent[1a] 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 Schild plot approximates unity).[12,13] It has been reported that those indolealkylamine hallucinogens that are most potent in man possess relatively high 5-HT receptor affinities (pA_2 values), although it cannot be assumed that all compounds possessing high affinities are necessarily hallucinogenic.[14] 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 Schild plots (Table III). With respect to indolealkylamines, pA_2 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.[12-14] 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**.[11] 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[1a] (as evaluated with Bovet–Gatti profiles), is more active than its 4-methylthio counterpart as a discrimative stimulus in rats,[11] and is the most effective in displacing both tritiated 5-HT and LSD binding to brain homogenates.[1a]

Experimental Section

The preparation of compounds **1–5** has been described previously.[1a] 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.

5-HT Receptor Affinity (pA_2).[12,13] Sprague–Dawley rats of either sex weighing 200–250 g were used. The rat stomach fundus preparation was a modification of the Vane procedure; two strips were cut from the same tissue and used in parallel 8-mL muscle baths. After a 1-h equilibration period, the relative sensitivity of the two strips was determined by the use of 5-HT doses giving submaximal contractions. Only one compound was tested per preparation, the second strip served as control.

Cumulative dose–response curves to 5-HT were first obtained in the absence of any competing ligand. An experimental compound and 5-HT were then allowed to compete for the available sites, and dose–response curves for 5-HT were obtained under the competitive conditions. Several concentrations of each experimental compound were individually examined. These data gave the relative potency of each compound in inhibiting the 5-HT-induced contraction of the fundus muscle; the ED_{50} of 5-HT in each curve gave the apparent affinities (pA_2) for each experimental compound.

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