

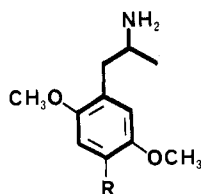
Behavioral and Serotonin Receptor Properties of 4-Substituted Derivatives of the Hallucinogen 1-(2,5-Dimethoxyphenyl)-2-aminopropane

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The serotonin (5-HT) receptor affinities and behavioral (discriminative stimulus) properties of a series of 4-substituted derivatives of 1-(2,5-dimethoxyphenyl)-2-aminopropane (2,5-DMA) were investigated. The substituents at the 4-position included H, OMe, OEt, Me, Et, F, Br, I, and NO₂. Substituent lipophilicities (π values) of these functionalities appear to have a minimal effect on either 5-HT receptor affinity or behavioral activity. Those derivatives previously found to be most potent in human studies possess significant affinity for 5-HT receptors. Furthermore, when rats trained to discriminate ($\pm$)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline were used, generalization was found to occur upon administration of the 4-substituted 2,5-DMA derivatives. Because a direct relationship exists between the ED₅₀ values obtained from these discrimination studies and human hallucinogenic potencies, the discriminative stimulus paradigm, with DOM as a training drug, appears to be a useful tool for comparing the quantitative and qualitative (DOM-like) effects produced by certain hallucinogenic agents.

In man, 1-(2,5-dimethoxyphenyl)-2-aminopropane (2,5-DMA, 1) is hallucinogenic.¹ Substitution at the 4-position



	R
1	H
2	OCH ₃
3	OC ₂ H ₅
4	CH ₃
5	C ₂ H ₅

of 2,5-DMA by a methoxy (2,4,5-TMA, 2), ethoxy (3), methyl (DOM, 4), or ethyl (DOET, 5) group increases the potency of the parent compound by two- to tenfold.¹ 4-Bromo (DOB, 7) and 4-iodo (DOI, 8) substitution result in an even further enhancement in activity, although there is some question as to whether these compounds produce behavioral effects similar to those of 1-4.¹ Examination of a series of 4-alkyl-substituted 2,5-DMA analogues, including the 4-*n*-propyl (DOPR), 4-*n*-butyl (DOBU), 4-*tert*-butyl (DOTB), and 4-amyl (DOAM) derivatives, in both human and animal studies, again reveals a dependence of activity on the nature of 4-position substituent.¹⁻⁴

How does this 4-substituent alter the potency of these agents? The presence of a substituent at this position apparently hinders the metabolism of 2,5-DMA;¹ however, this explanation does not adequately account for the observed range of activities within this series. That is, although metabolic studies have not been performed for all possible 4-substituted phenylisopropylamines, if the presence of such a substituent served merely to retard metabolism, a large range of activities might not be anticipated for these agents. It has been reported that the log *P* (octanol-water partition coefficient) of substituted phenylisopropylamines might be a significant determinant of hallucinogenic potency, in as much as it might be related to their distributional characteristics.⁵ However, recent studies reveal that activity cannot be accounted for by log

P alone and that log *P* consistently overestimates the potencies of agents with certain substitution patterns, while it underestimates the potencies of others.⁶ There is evidence that the substituent at the 4-position of various phenylisopropylamines might directly interact with receptors;^{7,8} to this extent, there appears to be a correspondence between serotonin (5-HT) receptor activation,⁷ as well as with human hallucinogenic potency,² and the lipophilic character of the 4-position substituent (as reflected by, for example, π values or substituent lipophilicities). An examination of a series of 13 phenylisopropylamine derivatives revealed a correlation ($r^2 = 0.81$) between their hallucinogenic potencies and the π values of their 4-position substituents (i.e., π_4).⁶ Although π_4 appears to be a significant indicator of hallucinogenic potency for 4-substituted phenylisopropylamines, Domelsmith et al.⁶ have commented that these agents can be divided into two basic categories, inactive (or relatively inactive) compounds that lack a lipophilic 4-substituent and several highly active compounds that possess such a substituent. Thus, it was of interest (a) to compare the 5-HT receptor affinities and behavioral properties of several derivatives of 2,5-DMA that vary only with respect to their 4-position substituent and (b) to determine if a relationship exists between the human hallucinogenic potency of these agents (where data are available) and either their 5-HT receptor affinity or their activity in a drug discrimination paradigm, in which animals are trained to detect either the presence or absence of DOM-like behavioral effects.

- (1) Shulgin, A. T. *Handb. Psychopharmacol.* 1978, 11, 243.
- (2) Shulgin, A. T.; Dyer, D. C. *J. Med. Chem.* 1975, 18, 1201.
- (3) (a) Morin, R. D.; Benington, F.; Mitchell, S. R.; Beaton, J. M.; Bradley, R. J.; Smythies, J. R. *Experientia* 1975, 31, 93. (b) Aldous, F. A. B.; Barrass, B. C.; Brewster, K.; Buxton, D. A.; Green, D. M.; Pinder, R. M.; Rich, P.; Skeels, M.; Tutt, K. J. *J. Med. Chem.* 1974, 17, 1100. (c) Kulkarni, A. S. *Biol. Psychiatry* 1973, 6, 177.
- (4) Geyer, M. A.; Petersen, L. R.; Rose, G. J.; Horwitz, D. D.; Light, R. K.; Adams, L. M.; Zook, J. A.; Hawkins, R. L.; Mandell, A. J. *J. Pharmacol. Exp. Ther.* 1978, 207, 837.
- (5) Barknecht, C. F.; Nichols, D. E.; Dunn, W. J. *J. Med. Chem.* 1975, 18, 208.
- (6) Domelsmith, L. N.; Eaton, T. A.; Houk, K. N.; Anderson, G. M.; Glennon, R. A.; Shulgin, A. T.; Castagnoli, N.; Kollman, P. A. *J. Med. Chem.* 1981, 24, 1414.
- (7) Nichols, D. E.; Shulgin, A. T.; Dyer, D. C. *Life Sci.* 1977, 21, 469.
- (8) Glennon, R. A.; Liebowitz, S. M.; Mack, E. C. *J. Med. Chem.* 1978, 21, 822.

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Chemistry. 2-Fluorohydroquinone, prepared by the Elbs persulfate oxidation of 2-fluorophenol as described by Feiring and Sheppard,⁹ was methylated (Me_2SO_4) to afford 2,5-dimethoxyfluorobenzene (**6c**). Formylation of **6c** to the aldehyde **6b** was accomplished with α, α -dichlorodimethyl ether under Friedel-Crafts conditions; evidence for formylation para to the fluoro group is derived from examination of the ^1H NMR spectrum of **6b**, which reveals two aromatic proton signals that appear as singlets and integrate for one proton each. The aldehyde **6b** was converted to the nitropropene **6a** and reduced to **6** by means of LiAlH_4 in ether. Coutts and Malicky have previously reported the synthesis of the iodo derivative **8** by subjecting 1-(2,5-dimethoxy-4-aminophenyl)-2-acylamino)propane to a Sandmeyer reaction, followed by hydrolysis.¹⁰ It was found that direct iodination of the *N*-acetyl derivative of 2,5-DMA (**1**) was possible if silver trifluoroacetate and I_2 were used; hydrolysis of the acetyl group afforded **8**. The nitro derivatives ($\pm$)-**9** and (*R*)-(-)-**9** were prepared by direct nitration of ($\pm$)-2,5-DMA (**1**) or its *R*(-) isomer. We have previously reported the synthesis of the positional isomer of ($\pm$)-DOB, i.e., **14**.¹¹

Results and Discussion

The serotonin (5-HT) receptor affinities (pA_2 values) of compounds **1**–**9** are shown in Table I; all compounds were found to interact in a competitive manner as determined by the slopes of their Schild plots. With respect to the behavioral (discriminative stimulus) study, generalization was found to occur between racemic DOM and compounds **1**–**9** (Table I). That is, all of the compounds in Table I are capable of producing behavioral (discriminative) effects in rats similar to those produced by the training dose of racemic DOM. Compounds in Table II do not result in stimulus generalization (i.e., they produce stimulus effects that apparently differ from those produced by racemic DOM). Response rates, under drug and nondrug (saline) conditions, were not significantly different, except where complete disruption of behavior (no responding) occurred.

Receptor Affinity Study. Of the six isomeric dimethoxyphenylisopropylamines, high 5-HT receptor affinity is associated with a 2,5-dimethoxy pattern. Variation of the 4-position substituent within the series of 2,5-DMA analogues appears to further modulate affinity, but it does so over a relatively narrow (less than tenfold) range. Previous attempts to determine the role of the 4-position substituent on biological activity have been limited to the study of alkyl-substituted derivatives² or have included a large group of compounds with widely varying substitution patterns,⁷ wherein the role of the 4-position substituent might have been masked. With respect to aromatic substituents, compounds **1**–**9** vary only at the 4-position. Examination of the pA_2 values for the nitro and iodo derivatives, **9** and **8**, respectively (whose 4-position substituents represent the extremes of the range of substituent-group π values¹² used in this study, i.e., $\pi_{\text{NO}_2} = -0.28$, $\pi_{\text{I}} = 1.12$), reveal less than a threefold difference in affinity, while the affinity of the fluoro derivative **6** ($\pi_{\text{F}} = 0.14$) is comparable to that of DOM ($\pi_{\text{Me}} = 0.56$) and DOET ($\pi_{\text{Et}} = 1.02$). These results suggest that the lipophilic nature of the 4-position substituent plays a minimal role in de-

termining 5-HT receptor affinity and support our previous suggestion to this effect.⁶ Nevertheless, such considerations cannot be completely ruled out because the effect of substituent lipophilicities may be overshadowed by the presence of a 2,5-dimethoxy pattern that, in itself, imparts substantial receptor affinity. The 4-position substituents differ not only in their lipophilic character but also with respect to, for example, their electronic and steric contribution. However, a detailed analysis of such effects is not warranted on the basis of the limited number of compounds examined and the narrow range of observed affinities.

Behavioral Studies. The discriminative stimulus paradigm is a useful tool for determining whether a group of agents is capable of producing similar behavioral effects (interoceptive cues) in animals.^{13,14} This paradigm is a very specific indicator of drug-induced similarities between challenge compounds as compared to a standard agent. In brief, rats, trained to discriminate the central effects of 1.0 mg/kg of racemic DOM from saline in a two-lever operant chamber,¹⁵ were challenged with agents **1**–**9**. Generalization ("transfer") is said to occur when a challenge compound results in the animals' responding >75–80% on the "DOM-appropriate" lever. That is, when generalization occurs, the animals apparently recognize the stimulus effects of a challenge drug as being similar to those of the training drug [i.e., in this case, 1.0 mg/kg of ($\pm$)-DOM]. As such, this procedure allows for both a qualitative and quantitative comparison within the series of agents under study. All of the compounds in Table I produce stimulus generalization when administered to the DOM-trained animals. Table I also shows that the *R*(-) isomers of DOB, DOI, and DON [(–)-**7** to (–)-**9**, respectively] are more active than their racemates. These results parallel our earlier findings that the *R*(-) isomers of 2,5-DMA, DOM, and DOET are several times more active than their *S*(+) enantiomers,²⁰ as well as the results of a study by Silverman and Ho, who have reported that (*R*)-(–)-DOM is more active than (*S*)-(+)-DOM when administered to ($\pm$)-DOM-trained animals.¹⁶

Correlations with Human Activity. We have previously suggested that the hallucinogenic potency of certain substituted phenylisopropylamines may be a consequence of, or related to, their affinity for 5-HT receptors.¹¹ Human hallucinogenic data exist for nine of the compounds in Table I [however, pA_2 data are only available for eight; (*R*)-(–)-DOB produces an agonistic response that precludes determination of a reliable pA_2 value¹⁷], and a relationship appears to exist between human potency and 5-HT receptor affinity (Figure 1). We have previously reported pA_2 values for six other phenylisopropylamines for which human data are available;^{11,18} these agents are also included in Figure 1. It might be noted that only compounds with pA_2 values greater than 6.0 have been included in Figure

(9) Feiring, A. E.; Sheppard, W. A. *J. Org. Chem.* **1975**, *40*, 2543.

(10) Coutts, R. T.; Malicky, J. L. *Can. J. Chem.* **1973**, *51*, 1402.

(11) Glennon, R. A.; Liebowitz, S. M.; Anderson, G. M. *J. Med. Chem.* **1980**, *23*, 294.

(12) Hansch, C.; Leo, A. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley-Interscience: New York, 1979.

(13) For reviews, see (a) Colpaert, F. C.; Rosecrans, J. A., Eds., "Stimulus Properties of Drugs: Ten Years of Progress"; Elsevier/North Holland Biomedical Press: Amsterdam, 1978. (b) Winter, J. C. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1974**, *33*, 1825. (c) Kuhn, D. M.; White, F. J.; Appel, J. B. in "Discriminative Stimulus Properties of Drugs"; Lal, H., Ed., Plenum Press: New York, 1977; p 137.

(14) Glennon, R. A.; Rosecrans, J. A. *Neurosci. Biobehav. Rev.* **1981**, *5*, 197.

(15) Young, R.; Glennon, R. A.; Rosecrans, J. A. *Commun. Psychopharmacol.* **1981**, *4*, 501.

(16) Silverman, P. B.; Ho, B. T. *Psychopharmacology* **1980**, *68*, 209.

(17) Glennon, R. A. *Life Sci.* **1979**, *24*, 1487.

(18) Glennon, R. A.; Doot, D. L.; Young, R. *Pharmacol. Biochem. Behav.* **1981**, *14*, 287.

Table I. Receptor Affinity and Behavioral Data

compd	R	pA ₂ ^a	slope ^b	N ^c	dose, mg/kg	N ^d	% DOM- appropriate responding (± SEM) ^a	ED ₅₀ ^f mg/kg	human hal- lucinogenic potency ^g
(±)-1	H	6.83						5.51 (3.98-7.63) ^h	50
(±)-2	OMe	6.81			3.0 3.5 4.0 5.0 5.5	6/6 5/5 5/5 5/6 6/6	20 (11.4) 59 (19.4) 70 (17.4) 81 (8.8) 90 (7.2)	3.59 (2.85-4.51)	20
(±)-3	OEt	6.78 (±0.21)	1.08 (±0.45)	4	2.0 5.0 8.0 9.0 10.0	5/5 5/5 5/5 4/5 1/5	2 (1.2) 16 (8.1) 68 (13.8) 85 (6.9) <i>i</i>	6.33 (4.34-9.22)	30
(±)-4	Me	7.13 (±0.13) ^j	0.92 (±0.12)	5				0.44 (0.29-0.68) ^h	2-5
(±)-5	Et	7.18			0.125 0.25 0.50	5/5 5/5 5/5	10 (4.0) 44 (17.7) 99 (0.8)	0.23 (0.14-0.39)	1.5-4
(±)-6	F	7.20 (±0.20)	0.93 (±0.29)	6	0.5 0.75 1.0 1.5 2.5 3.0	5/5 5/5 5/5 6/6 5/5 6/6	6 (3.8) 25 (19.0) 43 (8.4) 45 (10.0) 66 (10.5) 88 (5.5)	1.45 (0.95-2.20)	
(±)-7	Br	7.35			0.125 0.20 0.25 0.50	5/5 5/5 5/5 5/5	18 (12.0) 51 (14.0) 70 (8.0) 91 (5.6)	0.20 (0.13-0.32)	0.8-2.0
(-)-7	Br				0.10 0.15 0.20	5/5 5/5 5/5	47 (16.9) 79 (8.8) 91 (3.7)	0.10 (0.07-0.16)	0.4-1.0
(+)-7	Br	6.93			0.50 0.75 1.50	5/5 5/5 5/5	20 (13.0) 35 (21.6) 96 (2.9)	0.81 (0.55-1.20)	4-10
(±)-8	I	7.49 (±0.19)	1.13 (±0.33)	3	0.25 0.50 0.75 1.00	5/5 5/5 5/5 5/5	31 (14.6) 41 (13.8) 80 (19.9) 93 (2.4)	0.42 (0.25-0.71)	0.8-2.0
(-)-8	I	7.63 (±0.27)	1.01 (±0.19)	4	0.125 0.25 0.50 0.75	5/5 5/5 5/5 5/5	18 (10.4) 47 (19.8) 75 (19.8) 96 (3.8)	0.26 (0.15-0.44)	
(±)-9	NO ₂	7.07 (±0.47)	0.81 (±0.18)	3	0.5 1.0 1.5	5/5 4/5 5/5	32 (17.6) 55 (14.5) 87 (6.0)	0.76 (0.44-1.30)	
(-)-9	NO ₂	7.49 (±0.26)	0.93 (±0.14)	4	0.5 0.75 1.0	5/5 5/5 5/5	44 (10.2) 61 (18.2) 93 (6.5)	0.57 (0.38-0.85)	
saline (1 mL/kg)							5 (2.3)		

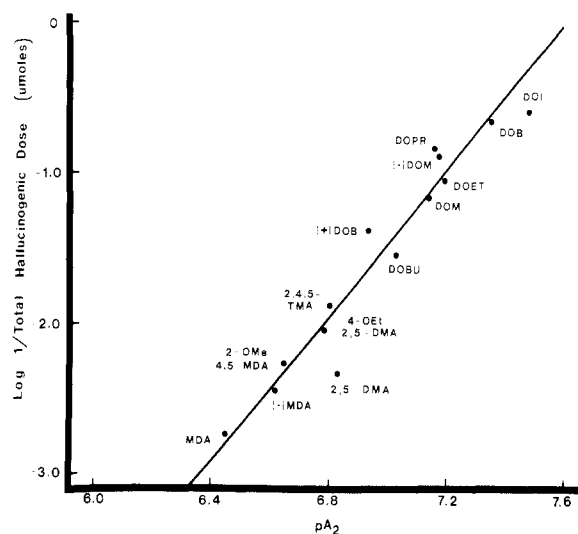
^a pA₂ value followed by standard deviation. Values for (±)-1, (±)-2, (±)-5, and 7 have been previously reported¹¹ and are included for comparative purposes. ^b Negative slope of Schild plot followed by standard deviation. ^c Number of pA₂ determinations, using four to six dose-response curves for 5-HT for each pA₂ determination. ^d Number of animals responding/number of animals tested. ^e Data obtained during 2.5-min extinction session. Response rates, except where disruption of behavior occurred, were not significantly different under drug of nondrug (saline) conditions. ^f ED₅₀ followed by 95% confidence limits. ^g Total dose in milligrams. ^h ED₅₀ for (±)-1 and (±)-4 have been previously reported.^{15,20} ⁱ Disruption of behavior at this dose; no responding. ^j Represents data from previously reported pA₂⁸ plus three new determinations.

Table II. Receptor Affinity and Behavioral Data for Several Miscellaneous Derivatives of 1-Phenyl-2-aminopropane

compd	R	dose, mg/kg	N ^a	% DOM-appropriate responding ($\pm$ SEM) ^b	pA ₂ ^c
(±)-10	H	1.0	5/5	2 (1.9)	5.27
		1.5	3/5	26 (8.4)	
		2.0	1/5	d	
		3.0	0/5	d	
(±)-11	2-OMe	2.0	5/5	2 (1.9)	5.54
		3.0	4/5	7 (4.7)	
		4.0	2/5	d	
(±)-12	3-OMe	2.0	5/5	8 (5.3)	5.93
		4.0	3/5	10 (2.3)	
		5.0	1/5	d	
(±)-13	4-OMe	0.5	5/5	13 (2.0)	5.15
		1.0	4/5	15 (1.8)	
		1.5	2/5	d	
(–)-13	4-OMe	0.5	5/5	18 (2.8)	5.38
		1.0	3/5	20 (4.6)	
		1.5	1/5	d	
(±)-14	2,5-(OMe) ₂ , 3-Br	1.0	5/5	2 (1.9)	5.27
		2.0	5/5	3 (2.1)	
		3.0	4/5	0	

^a Number of animals responding/number of animals tested. ^b Data obtained during 2.5-min extinction session. ^c pA₂ values from ref 11. ^d Disruption of behavior.

1 on the basis that the mechanism of action, and, indeed, the behavioral effects, of agents with lower affinities, such as the psychoactive PMA (13), might differ from those with higher affinities. In as much as phenylisopropylamines at the lower end of the affinity scale might be capable of producing behavioral effects that differ from those at the higher end (e.g., from those of DOM), several such derivatives were administered to the DOM-trained animals (Table II). Administration of racemic amphetamine (10) does not result in generalization at doses of 1.0 and 1.5 mg/kg, while doses of 2.0 and 3.0 mg/kg produce complete disruption of behavior (i.e., no responding). These results are consistent with those reported by Silverman and Ho,¹⁶ who found that generalization does not occur upon administration of (+)-amphetamine to DOM-trained rats. The 2-, 3-, and 4-methoxy derivatives (11–13, respectively), as well as the *R*(–) isomer of PMA [(–)-13], produce similar results, that is, no generalization at low doses and disruption of behavior at higher doses. The 3-positional isomer of DOB (i.e., 14) produces saline-like responding at all doses tested. Thus, these compounds do not produce DOM-like behavioral (discriminative) properties and should not be included in comparisons of activity and 5-HT receptor affinity. Two remaining compounds, which we have previously reported to possess 5-HT receptor affinities comparable to that of DOM (4), are DOTB (pA₂ = 7.22) and DOAM (pA₂ = 7.02).¹⁸ Complete DOM-stimulus generalization does not occur upon administration of either of these agents; thus, they too appear to produce an effect that differs from that produced by DOM and, as a consequence, are not included in Figure 1. Thus, for 14 phenylisopropylamines, there is excellent agreement¹⁹

**Figure 1.** Plot of human hallucinogenic potency vs. serotonin receptor affinity (pA₂). Total human hallucinogenic doses (in milligrams) are from Table I, except for (*R*)-(-)-DOM (1–2.5 mg), (±)-DOPR (2–5 mg), (±)-DOBU (10 mg), (±)-2-OMe-4,5-MDA (30–50 mg), (±)-MDA (100–125 mg), and (*R*)-(-)-MDA (40–70 mg);¹ where dose ranges are given, the arithmetic mean was used.

between activity and affinity. Those agents, which are most potent in man, possess the highest 5-HT receptor affinities. It must be emphasized, however, that the reverse of this statement does not necessarily apply; that is, based on the affinities of DOTB and DOAM, it cannot be concluded that all compounds with a significant 5-HT receptor affinity will necessarily produce DOM-like effects in animals and/or hallucinogenic effects in man.

Since the hallucinogenic response in man is a subjective phenomenon, the meaningfulness of a correlation between human dose and a particular biological property or physicochemical parameter, regardless of the statistical significance of the correlation, is still a matter for discussion. Nevertheless, the above relationship strongly supports the contention that the neurotransmitter serotonin plays a role in the mechanism of action of these hallucinogenic agents.

Is the discriminative stimulus paradigm a suitable model for studying these hallucinogenic agents? Generalization experiments, using this behavioral procedure, are based on the hypothesis that drugs that produce similar subjective effects in humans will have similar discriminative stimulus properties in animals.^{13c} Although the exact nature of the stimulus cues produced by these agents, as perceived by the animals, is unknown, this hypothesis has, nevertheless, received considerable support.¹³ With respect to this present study, Figure 2 is a plot of human hallucinogenic potency vs. activity (ED₅₀ value) in the discriminative stimulus paradigm for the nine compounds in Table I for which human data are available; also shown are five additional compounds for which we have already published ED₅₀ values.²⁰ Even though certain of these agents (e.g., DOI,¹ DOPR,² and DOBU²) have not been extensively investigated in man, there appears to be a good quantitative agreement between human hallucinogenic potency and generalization dose (ED₅₀ value) for those agents where

(19) Correlation equation: $\log 1/\text{total human hallucinogenic dose (micromoles)} = 2.33 (\pm 0.04) \text{ pA}_2 - 17.81 (\pm 1.90)$. $N = 14$, standard deviation = 0.21, r^2 (variance) = 0.92, $F = 141.1$, $p < 0.001$.

(20) Glennon, R. A.; Young, R.; Rosecrans, J. A. *Pharmacol. Biochem. Behav.* 1982, 1b, 553 and 559.

- (21) Correlation equation: $\log 1/\text{total human hallucinogenic dose (micromoles)} = 0.90 (\pm 0.01) \log 1/\text{ED}_{50} (\text{micromoles/kilogram}) - 0.93 (\pm 0.05)$. $N = 14$, standard deviation = 0.17, r^2 (variance) = 0.93, $F = 155.1$, $p < 0.001$.
- (22) Martin, W. R.; Sloan, J. W. in "Drug Addiction II"; Martin, W. R., Ed.; Springer-Verlag: Berlin, 1977; p 305.
- (23) Commissaris, R. L.; Semeyn, D. R.; Moore, K. E.; Rech, R. H. *Commun. Psychopharmacol.* **1981**, *4*, 393.

covered). Anal. ($C_9H_9FO_2$) C, H, F.

($\pm$)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane Hydrochloride [($\pm$)-8]. Compound (8a) was hydrolyzed in the manner described by Coutts and Malicky¹⁰ to give the title compound in 71% yield, mp 196 °C (lit.¹⁰ mp 198–200 °C) after two recrystallizations from EtOH–Et₂O.

($\pm$)-N-Acetyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (8a). To a stirred mixture of 4.42 g (0.02 mol) of silver trifluoroacetate²⁴ and ($\pm$)-N-acetyl-1-(2,5-dimethoxyphenyl)-2-aminopropane² (4.74 g, 0.02 mol) in CHCl₃ (5 mL) was added dropwise, over a 2-h period, a solution of I₂ (5.08 g, 0.02 mol) in CHCl₃ (65 mL). After the mixture was stirred for 18 h, the precipitated AgI was removed by filtration. The filtrate was washed with aqueous NaHSO₃ and H₂O and dried over anhydrous MgSO₄. Evaporation of the CHCl₃ yielded 5.5 g of a brown residue, which was recrystallized from boiling EtOH–H₂O to give 2.21 g of the title compound, mp 162–163 °C (lit.¹⁰ mp 165–166 °C).

(R)-(-)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane Hydrochloride [(-)-8]. By the same procedures for ($\pm$)-8, 13 g (0.056 mol) of (R)-(-)-1-(2,5-dimethoxyphenyl)-2-aminopropane hydrochloride²⁵ [$[\alpha]^{25}_D$ -18.7° (H₂O)] was converted to 10.7 g (81%) of the N-acetyl derivative, mp 106–107 °C; iodination with 11.5 g (0.045 mol) of I₂ and 10 g (0.045 mol) of silver trifluoroacetate in 150 mL of CHCl₃ gave 4.7 g (31%) of (R)-(+)-N-acetyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane: mp 184–185 °C; [$\alpha]^{23}_D$ +9.6° (MeOH). Hydrolysis with NaOH,¹⁰ followed by acidification, afforded 2.93 g (74%) of the title compound: mp 218–219 °C; [$\alpha]^{23}_D$ -12.0° (H₂O). Anal. ($C_{11}H_{17}ClINO_2$) N.

(R)-(-)-1-(2,5-Dimethoxy-4-nitrophenyl)-2-aminopropane Hydrochloride [(-)-9]. To an aqueous solution of 10 g (0.043 mol) of (R)-(-)-1-(2,5-dimethoxyphenyl)-2-aminopropane hydrochloride²⁵ was added an excess of 5 N NaOH. The liberated free base was taken up in C₆H₆–Et₂O, dried (anhydrous MgSO₄), and filtered. Removal of the solvents in vacuo yielded a colorless oil, which was dissolved in 40 mL of HOAc. This solution was added dropwise during 0.5 h to 43 mL of 50% HNO₃ (d 1.13), and the mixture was stirred and kept at 0–5 °C. The resulting clear solution was poured over ice, made alkaline with 50% NaOH, and extracted with C₆H₆–Et₂O. Evaporation of the solvent gave a residue, which was dissolved in dilute HCl, and this solution

was evaporated in vacuo to a nearly colorless solid residue. Recrystallization from EtOH–Et₂O gave 10.5 g (88%) of product: mp 231–232 °C dec; [$\alpha]^{23}_D$ -12.5° (H₂O). Anal. ($C_{11}H_{17}ClN_2O_4$) C, H, Cl, N. We prepared the racemic ($\pm$)-9 by direct nitration of ($\pm$)-1, using the above method, mp (HCl salt) 207–209 °C (lit.¹⁰ mp 203–204 °C).

Compounds ($\pm$)-1, ($\pm$)-2, ($\pm$)-4, ($\pm$)-5, and 7 were gifts from the NIDA, while ($\pm$)-3 was available from a previous study.

Affinity Assay. Male Sprague–Dawley rats (200–250 g) were used in this study. The fundus preparation employed was essentially that of Vane,²⁶ with the previously described modifications.^{8,11} Cumulative dose–response curves were obtained, after a 1-h equilibration period, for serotonin oxalate (7–10 increasing concentrations) both in the absence and in the presence of increasing concentrations of test compound. At least four to five dose–response curves were obtained for each pA₂ determination and at least triplicate pA₂ values were obtained (Table I). Certain compounds, notably ($\pm$)-4, (-)-8 and (-)-9, produced an agonistic response at the highest concentrations tested; when this occurred, the crest of this response was used as the new base line. The interaction of test compound with 5-HT receptors was assumed to be competitive when Schild plot slopes were between -0.8 and -1.2.

Behavioral Assay. The drug discrimination training procedure for these animals has been reported previously.¹⁵ Specifically, 30 male Sprague–Dawley rats were trained to discriminate racemic DOM (1.0 mg/kg) from saline in a two-lever operant task. In this procedure, the administration of saline or DOM, 15 min prior to a variable-interval, 15-s (VI-15 s) schedule of reinforcement, served as the discriminative cue for the correct (reinforced) lever. Occasional periods (2.5 min) of nonreinforcement were used to assess the degree of stimulus control exerted over behavior by saline and DOM and to evaluate the 4-substituted derivatives of 2,5-DMA. For those compounds where generalization (transfer, substitution) occurred, ED₅₀ values were determined from the dose–response data by the method of Litchfield and Wilcoxon.²⁷ (For a discussion of the use of the ED₅₀ value as it relates to classification of drugs on the basis of their discriminative stimulus characteristics in rats, see Barry.²⁸) These ED₅₀ values are the calculated doses at which the rats perform 50% appropriate drug-lever responding.

(26) Vane, J. R. *Br. J. Pharmacol.* 1957, 12, 344.

(27) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* 1949, 96, 99.

(28) Barry, H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1974, 33, 1814.

(29) Snyder, S. H.; Unger, S.; Blatchley, R.; Barfknecht, C. F. *Arch. Gen. Psychiatry* 1974, 31, 103.

(24) Janssen, D. E.; Wilson, C. V. In "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 547.

(25) Nichols, D. E.; Barfknecht, C. F.; Rusterholz, D. B.; Benington, F.; Morin, R. D. *J. Med. Chem.* 1973, 16, 480.

Potential Histamine H₂-Receptor Antagonists.¹ 4. Benzylhistamines

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As part of our studies aimed at designing histamine H₂-receptor antagonists, the effect on histaminergic activity of introducing benzyl substituents at various positions in the histamine molecule is described. New synthetic methods are reported for the novel 4-benzyl-, β -benzyl- and 4,N⁷-dibenzylhistamines and the reported 2-benzylhistamine. The novel N⁷-benzylhistamine was synthesized by the versatile route reported by us for the synthesis of N⁷-methylhistamine. These benzylhistamines, together with the reported N^α- and N^γ-benzylhistamines, were tested for agonist and antagonist activity at both H₁ and H₂ receptors. The results obtained indicate that introduction of a benzyl group into the histamine molecule causes a marked reduction in H₁- or H₂-agonist activity, and none of the compounds showed consistent antagonist activity. Evidently, the sterically demanding benzyl substituent is not easily accommodated in the agonist binding mode and is unable to locate a lipophilic receptor region for potential hydrophobic binding.

The discovery of the selective antagonist burimamide has permitted the characterization of histamine H₂ re-

ceptors and furnished a class of drugs with a completely novel pharmacological action.² Chemical modification of

(1) Paper 3: G. J. Durant, J. C. Emmett, C. R. Ganellin, A. M. Roe, and R. A. Slater, *J. Med. Chem.*, 19, 923 (1976).

(2) J. W. Black, W. A. M. Duncan, G. J. Durant, C. R. Ganellin, and M. E. Parsons, *Nature (London)*, 236, 385 (1972).