quantum yield in the presence of transfer. ϕ_D^0 was measured with the corresponding [Phe^4]enkephalin analogues. In the computation of R_0, a value of $^2/_3$ was used for κ^2 on the basis of arguments which have recently been outlined in detail.[14] For the Tyr-Trp donor-acceptor pair a value of $J_{AD} = 4.8 \times 10^{-16}$ M^{-1} cm^6 was adopted from the literature,[40] while in the case of the Tyr-(OMe)-Trp pair a performed computation based on the corrected fluorescence emission spectrum of [Tyr(OMe)^1,Met^5]enkephalin and the absorption spectrum of tryptophan resulted in a value of 9.1×10^{-16} M^{-1} cm^6 for the overlap integral.

(40) J. Eisinger, B. Feuer, and A. A. Lamola, *Biochemistry*, 8, 3908 (1969).

Acknowledgment. This work was supported by an operating grant of the Medical Research Council of Canada (MA-5655). The excellent technical assistance of U. G. Goehlert, T. M. D. Nguyen, and C. Lemieux is gratefully acknowledged.

Serotonin Receptor Affinities of Psychoactive Phenalkylamine Analogues

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Employing a rat fundus model, the serotonin (5-HT) receptor affinities of 45 phenalkylamine analogues were determined. Phenethylamine and phenylisopropylamine possess relatively low receptor affinities; in general, mono-, di-, and trimethoxylation enhance affinity. Of the disubstituted compounds, methoxyl groups at the 2 and 5 positions are optimal for imparting a high affinity. 4-Methylation, 4-ethylation and 4-bromination also enhance receptor affinity, while N,N-dimethylation of the terminal amine decreases affinity. α-Methylation of phenethylamines has little effect on affinity when racemates are examined. Introduction of a benzylic keto group can either increase or decrease affinity, depending upon the presence of other aromatic substituents. The most behaviorally active compounds were found to possess the highest 5-HT receptor affinities, while less active compounds were found to possess lower affinities.

The involvement of serotonergic systems may play a role in the mechanism of action of various hallucinogenic/psychotomimetic agents such as LSD and derivatives of tryptamine and phenalkylamine. Suggestions to this effect are supported by microiontophoretic studies, brain homogenate binding assays, and various biochemical investigations; much of this evidence has been reviewed by Brimblecombe and Pinder[1] and, more recently, by Freedman.[2] Other neurotransmitter systems, e.g., dopaminergic, might also be involved, to varying degrees, in the mechanism of action of these agents;[3,4] however, there is a need to investigate the serotonergic component of these mechanisms in greater detail. Vane initially reported that several phenethylamine and phenylisopropylamine analogues interact in an agonistic manner with 5-HT receptors of the rat stomach fundus preparation and other investigators have since examined the agonistic effects of a number of such compounds using a variety of isolated tissue preparations.[5] In a recent publication from this laboratory, we reported that the more potent hallucinogenic tryptamine and phenalkylamine analogues possess a relatively high affinity for the 5-HT receptors of the isolated rat fundus preparation while the less behaviorally active derivatives possess a lower affinity.[6] In a subsequent publication, we reported the results of a more extensive SAR investigation of a series of tryptamine analogues.[7] We now delineate the results of a detailed examination of the 5-HT receptor affinities of a series of phenalkylamine analogues.

Chemistry. While biological data have been previously reported for the 2,4-dimethoxy compound **16**, no melting point or microanalytical data could be found in the literature. Compound **16** was prepared by the catalytic hydrogenation of the 2-aminopropiophenone **43** to a diastereomeric mixture of 2-aminopropanols **43a**; continued reduction of the latter in the presence of $HClO_4$ gave the desired product. Alternatively, condensation of 2,4-dimethoxybenzaldehyde (**16a**) with $EtNO_2$ afforded the nitropropene **16b**, which could be reduced to **16** with $LiAlH_4$.

Elbs persulfate oxidation of 2-hydroxy-3-methoxybenzaldehyde, followed by methylation of the resultant hydroquinone, gave 2,3,5-trimethoxybenzaldehyde. The aldehyde was condensed with $EtNO_2$ and the nitropropene reduced with $LiAlH_4$ to yield the desired 2,3,5-trimethoxy compound **28**.

Compound **33** was prepared in a manner similar to that reported by Shulgin,[8] i.e., $LiAlH_4$ reduction of 1-(3,4,5-trimethoxyphenyl)-2-nitropropene (**33a**). However, in an initial attempt to prepare **33a**, a benzene solution of 3,4,5-trimethoxybenzaldehyde was allowed to react with $EtNO_2$ and NH_4OAc under refluxing conditions; in addition to **33a**, a white crystalline product, **33b**, was isolated. Compound **33b** was assigned the following structure based on NMR, ^{13}C NMR, and mass spectra. Additional support for the presence of an imino group is derived from the acid-catalyzed hydrolysis of **33b** to the parent 3,4,5-trimethoxybenzaldehyde and the corresponding amine **33c**. It is speculated that the desired nitropropene **33a** was formed and then underwent Michael attack to yield **33b**. A survey of the literature reveals that a similar reaction

(1) R. W. Brimblecombe and R. M. Pinder, "Hallucinogenic Agents", Wright-Scientechnica, 1975.
(2) D. X. Freedman and A. E. Halaris in " Psychopharmacology: A Generation of Progress", M. A. Lipton, A. Dimascio, and K. F. Killam, Eds., Raven Press, New York, 1978, pp 347-359.
(3) P. M. Whitaker and P. Seeman, *J. Pharm. Pharmacol.*, **29**, 506 (1977).
(4) P. C. Waldmeier and L. Maitre, *Psychopharmacology*, **52**, 137 (1977).
(5) J. R. Vane in "Adrenergic Mechanisms", J. R. Vane, G. E. W. Wolstenholme, and M. O'Connor, Eds., Little, Brown and Co., Boston, 1960, pp 356-372.
(6) R. A. Glennon, S. M. Liebowitz, and E. C. Mack, *J. Med. Chem.*, **21**, 822 (1978).
(7) R. A. Glennon and P. K. Gessner, *J. Med. Chem.*, **22**, 428 (1979).
(8) A. T. Shulgin, *J. Med. Chem.*, **9**, 445 (1966).

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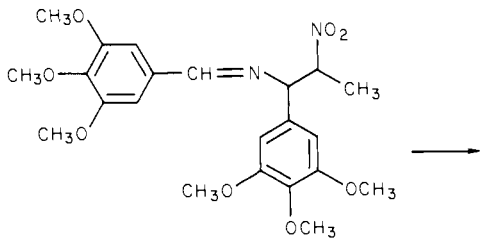
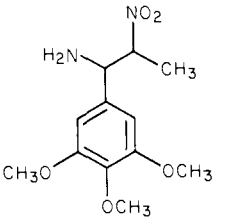


33b



33c

on a closely related compound has been reported once before.[9]

The positional isomer of DOM (37), i.e., 35, was also prepared from the appropriate aldehyde, via the nitropropene intermediate **35g**. The aldehyde itself was synthesized by catalytic reduction of 2,6-bis(hydroxymethyl)-4-methoxyphenol (**35a**) to the hydroxymethyl analogue **35b**, followed by methylation and oxidation of the resultant benzyl alcohol, **35d**, with pyridinium chlorochromate. Crude **35b** and **35d** were prepared according to literature procedures;[10] however, heating the crude **35b** in a sublimation apparatus, to remove as much 2,6-dimethyl-1-hydroxy-4-methoxybenzene (**35c**) as possible, slightly enhances yield (from 45.5 to 60%) and improves the isolation procedure of **35d**. Even with this, not all of the **35c** was removed, as evidenced by isolation of 1,4-dimethoxy-2,6-dimethylbenzene (**35e**) after the methylation step. Compound **36**, a positional isomer of DOB (**39**), was obtained from the nitropropene **36c**. Reduction of **36c** with $LiAlH_4$ gave a mixture of the desired product **36** and an equal amount of the dehalogenated product **18**, as determined by GC/MS. Use of AlH_3 in place of $LiAlH_4$ obviates this problem.

Most of the remaining compounds have been previously reported; these were either prepared via literature procedures or were, in several instances, obtained from the National Institute on Drug Abuse.

Results and Discussion

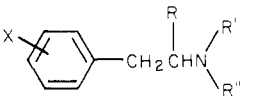
Serotonin (5-hydroxytryptamine, 5-HT) receptor affinity data were obtained by treating compounds **1–45** as partial agonists, i.e., as mixed agonist–antagonists. These data are reported as apparent pA_2 values in Tables I and II. Antagonism appears to be competitive (except for compound **44**), as noted by parallel dose–response curves in the absence and in the presence of increasing concentrations of compound; in addition, Schild plots result in negative slopes approximating unity.

In general, there does not appear to be any simple and straightforward SAR which would explain the affinities of all the compounds examined. In some instances, trends can be observed, while in others the results are confounding. For example, terminal amine methylation, 4-methylation, and α-methylation have a predictable effect on affinity. As we have previously reported, N,N-dimethylation of the terminal amine group halves affinity;[6] for the one compound examined (comparing **32** with **34**), N-methylation also halves affinity. 4-Methylation of the aromatic nucleus, on the other hand, doubles affinity. This is observed for the methylation of phenethylamine (**1**) itself and for the methylation of the 2,5-dimethoxy compound **18** to give **14** and **37**, respectively. Replacement of the 4-methyl group of this latter compound with an ethyl group, to give DOEt (**38**), has no additional effect on affinity. When racemates are examined, α-methylation has no apparent effect on affinity.[11] In eight of the nine cases examined, the phenethylamine analogue has an affinity similar to its phenylisopropylamine counterpart; compare the affinities of the following pairs of compounds: **1, 2; 5, 6; 7, 8; 9, 10; 17, 18; 19, 20; 22, 23; 32, 33**. In one case, α-methylation of the methylenedioxy compound **24** results in a slightly enhanced affinity. With respect to the affinity of individual isomers of the α-methylated derivatives, the (*R*)-(−) enantiomers of DOB (**39**), DOM (**37**), and MDA (**25**) constitute the eutomeric series.[11] There is, however, very little difference between the affinity of the individual isomers of compounds whose racemates possess relatively low affinities; for example, compare **3** with **4** and **11** with **12**. With few exceptions, mono-, di-, and trimethoxylation of phenethylamine and phenylisopropylamine result in an increased 5-HT receptor affinity. In considering monomethoxy compounds, both 2- and 3-methoxylation enhance affinity, while 4-methoxylation has no significant effect. With respect to dimethoxy compounds, the pA_2 values usually fall within the 5.4 to 5.6 range with two exceptions; the affinity of the 2,6-dimethoxy analogue **21** is somewhat lower and the affinity of the 2,5-dimethoxy analogues **17** and **18** are an order of magnitude greater than those of the other dimethoxy compounds. Other than **17** and **18**, all of the dimethoxy compounds possess a lower affinity than the 3-methoxy analogues **7** and **8**. It should be borne in mind, although there is no evidence to support this suggestion, that the 3-methoxy derivatives may interact with the 5-HT receptors either as the 3-methoxy compound, as their rotamer, the 5-methoxy compound, or perhaps as both.

The manner in which these methoxy substituents alter affinity is complex and does not readily lend itself to SAR interpretation; this is quite apparent when the trimethoxy analogues are scrutinized. For example, introduction of a 4-methoxy group to either the 2,5-dimethoxy compound, **18**, or the 3,5-dimethoxy compound, **26**, to give **29** and **33**, respectively, has very little effect on affinity as does 4-methoxylation of phenylisopropylamine itself. However, 4-methoxylation of **15** to give the 2,3,4-trimethoxy compound **27** decreases affinity, while, in contrast, 4-methoxylation of the 2,6-dimethoxy compound **21**, to give **31**, results in a respectable increase in affinity. It may not be the actual position of the methoxy groups, i.e., orientation about the periphery of the ring, which is important but rather the subtle effects these substituents may have on the overall electronic constitution of the aromatic nucleus. Recent studies of various methoxy-substituted aromatics have demonstrated the complexity inherent in the physical properties of these seemingly simple molecules. For example, of the three isomeric dimethoxybenzenes, the methoxy groups in both the para- and meta-substituted compounds are planar; by contrast, the preferred orientation in *o*-dimethoxybenzene is nonplanar.[12] These conformational preferences result in numerous differences

(9) A. T. Shulgin, *Experientia*, 19, 127 (1963).
(10) D. E. Nichols, C. F. Barfnecht, J. P. Long, R. T. Standridge, H. G. Howell, R. A. Partyka, and D. C. Dyer, *J. Med. Chem.*, 17, 161 (1974).
(11) R. A. Glennon, *Life Sci.*, 24, 1487 (1979).
(12) G. M. Anderson, P. A. Kollman, L. N. Domelsmith, and K. N. Houk, *J. Am. Chem. Soc.*, 101, 2344 (1979).

Table I. 5-HT Receptor Affinities of Phenalkylamines[a]



no.		X	R	R'	R''	pA_2[b]	n[h]
1[c]		H	H	H	H	5.26 (±0.03)	2
2	(±)	H	CH_3	H	H	5.27 (±0.14)	2
3	(*R*)-(−)	H	CH_3	H	H	5.16 (±0.02)	3
4	(*S*)-(+)	H	CH_3	H	H	5.35 (±0.17)	5
5[c]		2-OMe	H	H	H	5.52 (±0.15)	3
6	(±)	2-OMe	CH_3	H	H	5.54 (±0.04)	2
7[d]		3-OMe	H	H	H	5.89 (±0.09)	3
8	(±)	3-OMe	CH_3	H	H	5.93 (±0.07)	3
9[c]		4-OMe	H	H	H	5.10 (±0.18)	3
10[e]	(±)	4-OMe	CH_3	H	H	5.15 (±0.04)	5
11[d]	(*R*)-(−)	4-OMe	CH_3	H	H	5.38 (±0.06)	2
12[d]	(*S*)-(+)	4-OMe	CH_3	H	H	5.16 (±0.10)	3
13[f]		4-OH	H	H	H	5.07 (±0.11)	3
14[c]		4-Me	H	H	H	5.51 (±0.11)	2
15[d]	(±)	2,3-$(OMe)_2$	CH_3	H	H	5.54 (±0.17)	3
16	(±)	2,4-$(OMe)_2$	CH_3	H	H	5.60 (±0.08)	4
17[g]		2,5-$(OMe)_2$	H	H	H	6.85 (±0.19)	3
18[g]	(±)	2,5-$(OMe)_2$	CH_3	H	H	6.83 (±0.09)	4
19[g]		2,5-$(OMe)_2$	H	CH_3	CH_3	6.52 (±0.19)	3
20[g]	(±)	2,5-$(OMe)_2$	CH_3	CH_3	CH_3	6.50 (±0.08)	2
21	(±)	2,6-$(OMe)_2$	CH_3	H	H	5.09 (±0.30)	3
22		3,4-$(OMe)_2$	H	H	H	5.36 (±0.04)	4
23[d]	(±)	3,4-$(OMe)_2$	CH_3	H	H	5.45 (±0.16)	3
24[d]		3-OCH_2O-4	H	H	H	6.10 (±0.16)	3
25[g]	(±)	3-OCH_2O-4	CH_3	H	H	6.45 (±0.04)	2
26[d]	(±)	3,5-$(OMe)_2$	CH_3	H	H	5.56 (±0.08)	2
27[d]	(±)	2,3,4-$(OMe)_3$	CH_3	H	H	5.07 (±0.12)	2
28	(±)	2,3,5-$(OMe)_3$	CH_3	H	H	5.38 (±0.05)	2
29[g]	(±)	2,4,5-$(OMe)_3$	CH_3	H	H	6.81 (±0.08)	2
30[d]	(±)	2-OMe, 4-OCH_2O-5	CH_3	H	H	6.65 (±0.12)	2
31[d]	(±)	2,4,6-$(OMe)_3$	CH_3	H	H	6.28 (±0.06)	2
32[g]		3,4,5-$(OMe)_3$	H	H	H	5.65 (±0.10)	4
33[d]	(±)	3,4,5-$(OMe)_3$	CH_3	H	H	5.60 (±0.22)	4
34		3,4,5-$(OMe)_3$	H	H	CH_3	5.28 (±0.19)	4
35	(±)	2,5-$(OMe)_2$, 3-Me	CH_3	H	H	5.33 (±0.06)	2
36	(±)	2,5-$(OMe)_2$, 3-Br	CH_3	H	H	5.27 (±0.03)	2
37[g]	(±)	2,5-$(OMe)_2$, 4-Me	CH_3	H	H	7.12 (±0.07)	2
38[e]	(±)	2,5-$(OMe)_2$, 4-Et	CH_3	H	H	7.18 (±0.09)	2
39[g]	(±)	2,5-$(OMe)_2$, 4-Br	CH_3	H	H	7.35 (±0.08)	2

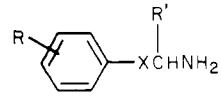
[a] 5-HT, pD_2 = 7.46 (±0.28), *n* = 146. [b] pA_2 value followed by standard deviation. [c] HCl salt prepared from freshly distilled, commercially available amine: 1, mp 217–219 °C, lit. (ref 30) 218–219 °C; 5, mp 141–142 °C, lit. (ref 31) 140–141 °C; 9, mp 211–213 °C, lit. (ref 32) 210 °C; 14, mp 217–218 °C, lit. (ref 33) 218–219 °C. [d] Prepared following literature procedure: 7 (ref 34), 11 (ref 35), 12 (ref 35), 15 (ref 36), 23 (ref 36), 24 (ref 37), 26 (ref 36), 27 (ref 8), 30 (ref 38), 31 (ref 8), 33 (ref 8). [e] Compound obtained from NIDA. [f] Tyramine was prepared by refluxing 9 in concentrated HCl, mp 268–270 °C, lit. (ref 39) 269 °C. [g] pA_2 value reported in previous paper (ref 6). [h] Number of determinations.

in the properties of compounds bearing these substituents. For example, the octanol/water partition coefficients of the three isomeric dimethoxyphenylisopropylamine derivatives **16**, **18**, and **23** dramatically illustrate this point; the water solubility of **23** is about five times greater than that of its two isomers due to enhanced solvation of the localized oxygen lone-pair electrons.[12] Such conformational differences can also affect gas-phase π ionization potentials and π electron charge distribution in the aromatic nucleus.[12] Thus, it may be the nonplanarity of the methoxy groups of 3,4-DMA (**23**) which accounts for the lower affinity of this molecule as compared with MDA (**25**), which possesses a more planar methylenedioxy group and a tenfold greater affinity. Although the similarity in affinity between **29** and **30** is more difficult to explain, conformational effects are also evidenced in the more highly substituted derivatives such as DOM (**37**) as compared with its positional isomer **35**, where the 4-methyl group has been moved to the 3 position. The preferred conformation of the 2-methoxy group in **35** is clearly nonplanar due to the large steric repulsion provided on the one side by the 3-methyl substituent and on the other by the isopropylamine side chain. However, in **37** the 2-methoxy substituent can comfortably maintain a planar conformation with the methoxy methyl group directed away from the side chain. Hence, in **35**, but not in **37**, the physical properties should be altered in a fashion similar to that seen in **23**. Consequently, the affinity of **35** is more than 60 times less than the affinity of **37**. This same effect is observed regardless of the nature of the 3-position substituent; compare the affinities of **28** and **36** with those of their 4-substituted isomers 2,4,5-TMA (**29**) and DOB (**39**).

However, one must be aware that electronic interactions between the receptor and its substrate may be of sufficient magnitude to overcome the torsional barriers to rotation of the methoxy groups. The remarkable flexibility, with regard to the methoxy-substitution pattern of these agents, may result from this phenomenon.

Substitution of a keto or hydroxy group at the benzylic position of the phenalkylamines leads to an interesting series of compounds. Serotonin receptor affinity data for several of these compounds are reported in Table II; two of these derivatives, cathinone [(*S*)-(−)-α-aminopropiophenone, **41**] and cathine [(+)-1-phenyl-2-aminopropanol

Table II. 5-HT Receptor Affinities of Related Phenalkylamine Analogues



	X	R	R'	pA_2[a]	n[f]
40[b] (±)	C=O	H	CH_3	5.55 (±0.29)	5
41[c] (S)-(−)	C=O	H	CH_3	5.52 (±0.38)	4
42[b] (±)	C=O	4-OMe	CH_3	5.65 (±0.07)	3
43[b] (±)	C=O	2,4-$(OMe)_2$	CH_3	4.95 (±0.09)	3
44[c] (+)	CHOH	H	CH_3	*d*	3
45[e]	CH_2CH_2	H	H	4.93 (±0.09)	3

[a] pA_2 value followed by standard deviation. [b] Gift from Dr. J. D. Smith, MCV/VCU. [c] Gift from United Nations Narcotics Laboratory via Dr. E. May. [d] Unable to determine pA_2 value; see text for explanation. [e] HCl salt prepared from freshly distilled, commercially available amine; mp 214–216 °C, lit. (ref 40) 218 °C. [f] Number of determinations. Compounds 40 and 41 produce an agonistic response, at the higher concentrations tested, which may have an effect on the actual pA_2 value.

or "(+)-norpseudoephedrine", **44**], are constituents of the intoxicant khat.[13] Introduction of a keto group at the benzylic carbon of amphetamine (**2**) serves to double affinity when racemates are compared; however, the same effect is observed for the (*S*)-(−) isomer **41**, as compared to (*S*)-(+)-amphetamine (**4**). The presence of a methoxy group at the 2 position of the aromatic ring appears to have a detrimental effect upon the affinity of **43**. [Although diastereomeric mixtures were employed, this 2-methoxy group also reduces the affinity of the corresponding 2-amino-1-propanols. For example, the pA_2 values for 1-(4-methoxyphenyl)-2-aminopropanol, 5.22 ± 0.12, n = 3, and 1-(4-methylphenyl)-2-aminopropanol, 5.40 ± 0.18, n = 4, do not differ substantially from those of **10** and **14**, while the pA_2 value for 1-(2,4-dimethoxyphenyl-2-aminopropanol (**43a**), 4.90 ± 0.10, n = 3, is considerably lower than the pA_2 of the corresponding 2,4-dimethoxyphenylisopropylamine (**16**).] Perhaps the 2-methoxy substituent interferes with a side-chain conformation which is optimal for a 5-HT receptor interaction.

Compound **44** has an adverse effect on the muscle preparation, which precludes the determination of a reliable pA_2 value. The responsiveness of the fundus strips to 5-HT decreased as the concentration of **44** was increased. The antagonism produced by **44** may be of a noncompetitive nature or else **44** is having an effect on the fundus preparation other than its direct effect on the 5-HT receptors. This problem is being further studied.

A question which now emerges is whether or not a relationship exists between the 5-HT receptor affinity of the compounds investigated and their psychotomimetic activity in man. Within a given series of compounds a direct relationship of this sort may not exist because the in vitro fundus assay ignores such features as lipid solubility, relative rate of metabolism, distribution, etc., which might be of paramount interest in vivo. Because the primary impact of an α-methyl group may be to hinder the rate of metabolism of the phenalkylamines,[14] phenethylamines being on the average at least 2–10 times less active than their corresponding phenylisopropylamine counterparts in human studies,[15] the following discussion will be limited only to analogues of the latter series. Phenylisopropylamines with pA_2 values greater than 7.0 usually display their psychotomimetic effect[16] at total doses well below 10 mg: DOB (**39**), DOEt (**38**), and DOM (**37**). Compounds with pA_2 values between 6.0 and 7.0 usually possess activity in the 10–100-mg range: 2,4,5-TMA (**29**), 2,5-DMA (**18**), MMDA-2 (**30**), 2,4,6-TMA (**31**), MDA (**25**); compounds with pA_2 values below 6.0 are usually less active: 3,4,5-TMA (**33**) and 3,4-DMA (**23**).

The activity of PMA (**10**) and amphetamine (**2**) in humans is not consistent with the above generalization; both possess pA_2 values of less than 6.0, yet both are relatively active. Amphetamine produces behavioral effects in both human and nonhuman species which are qualitatively dissimilar to those produced by certain other members of the phenylisopropylamine series, such as DOM (**37**), and is not usually considered to be hallucinogenic.[17] PMA (**10**) has been reported to possess a pharmacological profile quite similar to that of amphetamine.[18,19] Previous investigations (for example, see ref 19–21) have concluded that methoxylated phenylisopropylamines can produce effects which are both amphetamine-like and LSD-like; the phenylisopropylamines may represent a series of compounds, then, whose activity varies on an "amphetamine-like" to "serotonergic" continuum. The results of this present investigation support these previous studies and suggest, from an affinity standpoint, that compounds such as DOB (**39**), DOEt (**38**), and DOM (**37**) may be nearer to the serotonergic extreme of this continuum (i.e., have more of a serotonergic component), while PMA (**10**) is representative of the other extreme.

With respect to the affinity of phenalkylamine analogues for the 5-HT receptors of the isolated rat fundus preparation, the results may be summarized as follows: (a) phenethylamine and phenylisopropylamine possess relatively low affinities; (b) extension of the side chain of phenethylamine by one methylene group, to give the phenylpropylamine **45**, further decreases affinity; (c) mono-, di-, and trimethoxylation generally enhance affinity; (d) of the disubstituted compounds, a 2,5-dimethoxy pattern appears to be optimal; (e) substitution of a methyl, ethyl, or bromo group at the 4 position enhances affinity; (f) a benzylic keto group can either increase or decrease affinity, depending upon the presence of other ring substituents; (g) N,N-dimethylation of phenalkylamines reduces affinity; (h) the presence of an α-methyl group (comparing phenethylamines with phenylisopropylamines) has little effect on affinity when racemates are examined; (i) when optically active phenylisopropylamines are ex-

(13) "The Botany and Chemistry of Khat", United Nations Document MNAR/3, 1979.
(14) A. T. Shulgin in "The Psychopharmacology of Hallucinogens", R. C. Stillman and R. E. Willette, Eds., Pergamon Press, New York, 1978, p 74.
(15) V. Braun, G. Braun, P. Jacob, D. E. Nichols, and A. T. Shulgin in "Quantitative Structure Activity Relationships of Analgesics, Narcotic Antagonists, and Hallucinogens", G. Barnett, M. Trsic, and R. E. Willette, Eds., U.S. Government Printing Office, Washington, D.C., 1978, p 27.
(16) A. T. Shulgin, *Handb. Psychopharmacol.*, **2**, 243 (1978).
(17) P. Brawley and J. C. Duffield, *Pharmacol. Rev.*, **24**, 31 (1972); J. C. Winter, *Psychopharmocology*, **44**, 29 (1975); H. A. Tilson, T. G. Baker, and J. A. Gylys, *ibid.*, **44**, 225 (1975); P. B. Silverman and B. T. Ho in "Stimulus Properties of Drugs: Ten Years of Progress", F. C. Colpaert and J. A. Rosecrans, Eds., Elsevier/North Holland Biomedical Press, Amsterdam, 1978, p 189.
(18) R. A. Harris, D. Snell, and H. H. Loh, *J. Pharmacol. Exp. Ther.*, **204**, 103 (1978).
(19) W. R. Martin, D. B. Vaupel, J. W. Sloan, J. A. Bell, M. Nozaki, and L. D. Bright in ref 14, p 118.
(20) F. A. B. Aldous, B. C. Barrass, K. Brewster, D. A. Buxton, D. M. Green, R. M. Pinder, P. Rich, M. Skeels, and K. J. Tutt, *J. Med. Chem.*, **17**, 1100 (1974).
(21) H. H. Loh and L. F. Tseng in ref 14, p 13.

amined, the *R* isomers usually possess a higher affinity than the *S* isomer; however, for those analogues whose racemates possess a low affinity, the eudismic ratio is very small.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were recorded on a Perkin-Elmer R-24 high-resolution spectrometer, and chemical shifts are reported relative to tetramethylsilane. Infrared spectra were obtained on a Perkin-Elmer 257 spectrophotometer, and mass spectra were determined using a Finnigan 4000-series GC/MS data system. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA, and determined values are within 0.4% of theoretical values. All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Unless otherwise stated all final products, listed in Tables I and II, are HCl salts.

(±)-1-(2,4-Dimethoxyphenyl)-2-aminopropane Hydrochloride (16). A solution of **43**·HCl (0.49 g, 2 mmol) in absolute EtOH (50 mL) was shaken with Pd/C (10%, 0.1 g) under an atmosphere of H_2 (45 psig) until 1 equiv of H_2 was taken up. The reaction mixture was filtered, and the solvent was removed under reduced pressure to afford the crude product; recrystallization from EtOH/Et_2O gave 0.37 g (76%) of **43a** as white crystals, mp 235–236 °C (lit.[22] mp 219 °C). Anal. ($C_{11}H_{17}NO_3$·HCl) C, H, N.

A mixture of **43a** (0.31 g, 1.25 mmol), Pd/$BaSO_4$ (5%, 0.03 g), $HClO_4$ (70%, 0.1 mL), and glacial HOAc (50 mL) was heated to 85 °C and then hydrogenated at 50 psig at room temperature for 18.5 h. The solvent was removed under reduced pressure and the residue was dissolved in 25 mL of H_2O. The aqueous solution was basified and extracted with Et_2O (2 × 10 mL); the Et_2O solution was dried ($MgSO_4$) and treated with HCl gas to give crude **16**, mp 140–143 °C. Recrystallization from EtOH afforded 0.05 g (17%) of **16**, mp 150–152 °C. Anal. ($C_{11}H_{17}NO_2$·HCl) C, H, N.

Compound **16** was also prepared by reacting 2,4-dimethoxybenzaldehyde with $EtNO_2$, followed by reduction of the resulting nitropropene **16b** (mp 76–78 °C) with $LiAlH_4$. Though **16** has been previously prepared in this manner,[23] no melting point or microanalytical data can be found in the literature.

(±)-1-(2,3,5-Trimethoxyphenyl)-2-aminopropane (28). A solution of 2,3,5-trimethoxybenzaldehyde[24] (1.1 g, 5.6 mmol), NH_4OAc (0.5 g), and $EtNO_2$ (100 mL) was refluxed for 5 h. The solvent was removed under reduced pressure and the product was recrystallized from MeOH/EtOH to yield 0.9 g (64%) of 1-(2,3,5-trimethoxyphenyl)-2-nitropropene as bright yellow crystals, mp 85–86 °C (lit.[8] mp 88 °C). The nitropropene (0.8 g) was then reduced with $LiAlH_4$ and converted to the HCl salt in a manner similar to that used by Shulgin.[8]

***N*-[1-(3,4,5-Trimethoxyphenyl)-2-nitropropyl]-3,4,5-trimethoxybenzaldimine (33b).** A solution of 3,4,5-trimethoxybenzaldehyde (5.0 g, 25.5 mmol), ammonium acetate (2.0 g, 25.9 mmol), and nitroethane (17.2 g, 229 mmol) in benzene (125 mL) was refluxed overnight. The yellow solution was washed with brine (3 × 50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was crystallized by trituration with MeOH (15 mL) and ligroin (30 mL). Recrystallization from MeOH yielded 0.8 g (15% based on starting aldehyde) of white crystals: mp 138–140 °C; NMR ($CDCl_3$) δ 1.45 (d, 3 H, CH_3), 3.9 (s, 18 H, OCH_3), 4.5 (d, 1 H, CH), 4.7 (m, 1 H, CH), 6.75 (s, 2 H, Ar H), 7.05 (s, 2 H, Ar H), 8.2 (s, 1 H, =CH); MS (70 eV) *m/e* (relative intensity) 448 (17), 374 (100). Anal. ($C_{22}H_{28}N_2O_8$) C, H, N. The recrystallized mother liquor was removed in vacuo, yielding 4.1 g of a yellow oil which solidified upon standing. This was identified as 1-(3,4,5-trimethoxyphenyl)-2-nitropropene (**33a**).

1-(3,4,5-Trimethoxyphenyl)-1-amino-2-nitropropane Hydrochloride (33c). A solution of **33b** (0.24 g, 0.53 mmol) in MeOH (10 mL) and aqueous HCl (5%, 5 mL) was heated at reflux for 18 h. When the solution cooled, MeOH was removed under reduced pressure and the remaining aqueous mixture was extracted with Et_2O (3 × 25 mL); the combined Et_2O solution was dried ($MgSO_4$) and evaporated to dryness to yield 100 mg (96%) of 3,4,5-trimethoxybenzaldehyde (mp 71–73 °C). The aqueous portion was evaporated to dryness to yield crude **33c**; recrystallization from an MeOH–Et_2O mixture afforded 157 mg (96%) of **33c** as a fine white powder, mp 194–196 °C dec. Anal. ($C_{12}H_{18}N_2O_5$·HCl) C, H, N.

(±)-1-(2,5-Dimethoxy-3-methylphenyl)-2-aminopropane (35). A solution of **35g** (3 g, 12.6 mmol) in anhydrous Et_2O (100 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1 g, 25.3 mmol) in Et_2O (25 mL) at 0 °C. After the solution was heated at reflux for 6 h, Na_2SO_4·$10H_2O$ was added in small portions, at 0 °C, until no further evolution of H_2 occurred. The solvent was evaporated under reduced pressure and the residual oil was distilled to give 1.1 g (42%) of **35** as a colorless liquid, bp 115–118 °C (0.3 mm). The oxalate salt was prepared by adding an anhydrous Et_2O solution of the amine to a saturated solution of oxalic acid in Et_2O: mp 231–233 °C after recrystallization from MeOH; NMR (free base, $CDCl_3$) δ 1.1 (d, 3 H, CH_3), 1.5 (d, 2 H, NH_2), 2.25 (s, 3 H, Ar CH_3), 2.7 (m, 3 H, CH, CH_2), 3.7 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 6.6 (s, 2 H, Ar H); MS (70 eV) *m/e* (relative intensity) 209 (5), 166 (100). Anal. [$(C_{12}H_{19}NO_2)_2$·$(COOH)_2$] C, H, N.

2,5-Dimethoxy-3-methylbenzyl Alcohol (35d). 2-Hydroxy-3-methyl-5-methoxybenzyl alcohol (**35b**) was prepared by catalytic reduction of 15 g of 2,6-bis(hydroxymethyl)-4-methoxyphenol (**35a**) as previously reported.[10] Workup differed in that the crude brown residue (13 g) was heated in a sublimation apparatus (0.1 mm, bath temperature 80–100 °C) to yield approximately 3.5 g of a sublimed product as long white needles (mp 71 °C). This product was identified (NMR, mass spectrum) as being 2,6-dimethyl-1-hydroxy-4-methoxybenzene (**34c**) (lit.[25] mp 77 °C). The residual dark brown mass of crude **35b** was used without further purification. An acetone solution of this residue was methylated with MeI as reported by Nichols et al.[10] In addition to obtaining 5 g of the desired product **35b** [bp 93–96 °C (0.1 mm), lit.[10] 94–96 °C (0.1 mm)] in approximately 60% yield (based on **35a** and recovered byproducts), 2 g of a lower boiling fraction [bp 52–57 °C (0.09 mm)] was also isolated and characterized (NMR, mass spectrum) as 1,4-dimethoxy-2,6-dimethylbenzene (**35e**), lit.[26] bp 103 °C (10 mm).

2,5-Dimethoxy-3-methylbenzaldehyde (35f). A solution of **35d** (4 g, 22 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a stirred solution of freshly prepared pyridinium chlorochromate (7 g, 33 mmol) in CH_2Cl_2 (250 mL) at room temperature. After anhydrous Et_2O (100 mL) was added, stirring was continued for an additional 15 min. The solvent was decanted and filtered through a thick pad of Florisil (100–200 mesh) to yield a pale-yellow solution. (In a separate experiment, the use of 30–60-mesh Florisil resulted in a brown solution from which no crystalline product was isolated.) Solvent was removed under reduced pressure to yield 3.8 g (96%) of **35f** as white crystals after recrystallization from hexane, mp 42–44 °C, lit.[10] mp 42.5–43 °C.

1-(2,5-Dimethoxy-3-methylphenyl)-2-nitropropene (35g). A solution of **35f** (5 g, 27.7 mmol), NH_4OAc (2.1 g, 27.7 mmol), and $EtNO_2$ (100 mL) was refluxed for 5 h. Solvent was removed under reduced pressure; the crude product was dissolved in Et_2O (75 mL), washed with saturated NaCl solution (3 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Recrystallization of the product from MeOH gave 5.5 g (84%) of **35g** as bright-yellow needles, mp 92–93 °C. Anal. ($C_{12}H_{15}NO_4$) C, H, N.

(±)-1-(2,5-Dimethoxy-3-bromophenyl)-2-aminopropane (36). A solution of AlH_3 in THF was prepared by the dropwise addition of a solution of 0.1 mL (0.188 g, 1.92 mmol) of 100% H_2SO_4 in 10 mL of THF to a stirred suspension of $LiAlH_4$ (0.15 g, 3.84 mmol) in THF (75 mL) at 0 °C under an atmosphere of N_2. Without removing the precipitated Li_2SO_4, a solution of **36c** (400 mg, 1.32 mmol) in THF (50 mL) was added over a 30-min period. After the solution was stirred at room temperature for

(22) W. H. Hartung, J. C. Munch, E. Miller, and F. Crossley, *J. Am. Chem. Soc.*, **53**, 4149 (1931).
(23) K. Bailey, A. W. By, K. C. Graham, and D. Verner, *Can. J. Chem.*, **49**, 3143 (1971).
(24) J. R. Merchant, R. M. Naik, and A. J. Mountwalla, *J. Chem. Soc.*, 4142 (1957).
(25) W. Reeve and A. Sadle, *J. Am. Chem. Soc.*, **72**, 3252 (1950).
(26) A. A. R. Sayigh, H. Ulrich, and M. Green, *J. Chem. Soc.*, 3482 (1964).

an additional hour, the excess hydride was decomposed by the addition of small chips of ice, followed by 10% NaOH solution until a white precipitate resulted. The mixture was filtered under suction, and the filter cake was washed several times with THF. The solvent was evaporated under reduced pressure and the residual oil was distilled [Kugelrohr, 80–90 °C (0.14 mm)] to give **36** as a colorless liquid. The oxalate salt was prepared by adding an anhydrous Et_2O solution of the amine to a saturated solution of oxalic acid in Et_2O: mp 232–234 °C after recrystallization from MeOH; NMR (D_2O) δ 1.3 (d, 3 H, $-CH_3$), 2.95 (m, 3 H, CH_2, CH), 3.85 (s, 6 H, $-OCH_3$), 6.95 (s, 1 H, Ar H), 7.30 (s, 1 H, Ar H); MS (70 eV) *m/e* (relative intensity) 276 (46), 274 (48), 77 (100). Anal. $[(C_{11}H_{16}NO_2Br)_2 \cdot (COOH)_2]$ C, H, N.

2,5-Dimethoxy-3-bromobenzaldehyde (36b). Methylation of 2-hydroxy-3-bromo-5-methoxybenzaldehyde (**36a**)[27] was achieved only with great difficulty according to the following procedure: A solution of 4 g of NaOH in 70 mL of MeOH was added dropwise to a stirred refluxing solution of **36a** (7 g, 30 mmol) and MeI (50 mL) in 150 mL of a 50:50 mixture of MeOH/EtOH with the formation of an insoluble precipitate of the phenoxide salt. Refluxing was continued for 2 days, after which time 50 mL of MeI was added dropwise. Following 2 more days of additional heating, a solution of 8 g of NaOH in MeOH (150 mL) was added dropwise to the reaction mixture. After 2 more days of heating at reflux, the addition of MeI, followed by NaOH described above, was repeated. Subsequently, the reaction was terminated, solvent was removed under vacuum, H_2O (200 mL) was added, and the pH was adjusted to 12 by the addition of 4 N NaOH. The aqueous reaction mixture was then extracted twice with CH_2Cl_2 (100 mL). The combined organic extracts were then extracted with 100 mL of 2 N NaOH. The solvent was evaporated, resulting in an oily material to which 100 mL of MeOH was added. Again the solvent was removed by slow evaporation under vacuum, yielding a crude crystalline product (5.6 g). Recrystallization from MeOH gave 5.2 g (67%) of **36b** as white needles, mp 64–65 °C, lit.[27] mp 63 °C.

1-(2,5-Dimethoxy-3-bromophenyl)-2-nitropropene (36c). Compound **36c** was prepared in 87% yield in a manner similar to that used for **35g**. Recrystallization of the product from absolute EtOH gave **36c** as yellow needles, mp 79–80 °C. Anal. ($C_{11}H_{12}NO_4Br$) C, H, N.

Affinity Assay Studies. Sprague–Dawley rats (Flow Labs; Dublin, VA) of either sex, weighing 200–250 g, were used. The rat stomach fundus preparation employed was essentially that of Vane[28] with the previously described modifications.[6] Two strips were cut from the same tissue and used in parallel 8-mL muscle baths. The relative sensitivity of the two strips was determined, after a 1-h equilibration period, by the use of 5-HT doses giving submaximal contractions. Only one compound was tested per preparation, the second strip serving as control.

The ability or potency of each agent to inhibit the contractile response of 5-HT was determined by obtaining cumulative dose–response curves to 5-HT (at 7–9 concentrations of 5-HT ranging from approximately 1 nm to 10 μm), first in the absence of the agent in question and then in the presence of increasing concentrations thereof. Compounds **1–45** were examined a minimum of twice at each of usually four different concentrations. The ED_{50} of 5-HT was determined for each of the curves and the apparent affinities were calculated as pA_2 values by the method of Arunlakshana and Schild.[29] In addition, Schild plots were subjected to linear-regression analysis in order to determine slopes (which usually ranged from −0.8 to −1.2, with the exception of compound **44**). At high enough concentrations, certain compounds produced an agonistic response; all attempts were made to avoid such high concentrations.

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(27) L. Rubenstein, *J. Chem. Soc.*, **127**, 1998 (1925).
(28) J. R. Vane, *Br. J. Pharmacol.*, **14**, 87 (1959).
(29) O. Arunlakshana and H. O. Schild, *Br. J. Pharmacol.*, **14**, 48 (1959).
(30) T. B. Johnson and H. H. Guest, *Am. Chem. J.*, **42**, 346 (1909).
(31) J. B. Shoesmith and R. J. Conner, *J. Chem. Soc.*, 2232 (1927).
(32) K. H. Slotta and H. Heller, *Chem. Ber.*, **63B**, 3029 (1930).
(33) K. Ciesielski, *Chem. Zentralbl.*, 1793 (1907).
(34) J. S. Buck, *J. Am. Chem. Soc.*, **54**, 3661 (1932).
(35) D. E. Nichols, C. F. Barfnecht, D. B. Rusterholz, F. Benington, and R. D. Morin, *J. Med. Chem.*, **16**, 480 (1973).
(36) B. T. Ho, W. M. McIsaac, R. An, W. Tansey, K. E. Walker, L. F. Englert, and M. B. Noel, *J. Med. Chem.*, **13**, 26 (1970).
(37) F. Benington, R. D. Morin, L. C. Clark, Jr., and R. P. Fox, *J. Org. Chem.*, **23**, 1979 (1958).
(38) A. T. Shulgin, *Experientia*, **20**, 336 (1964).
(39) J. S. Buck, *J. Am. Chem. Soc.*, **55**, 3388 (1933).
(40) J. Tafel, *Chem. Ber.*, **22**, 1854 (1889).