0.985 g (4.6 mmol) of 2,2-difluoroethyl trifluoromethanesulfonate, 0.76 g (9.0 mmol) of sodium bicarbonate, and 15 mL of ethanol. The reaction mixture was stirred and refluxed for 8 h. The reaction mixture was worked up as for **2b**, except that the mesylate salt of the product was crystallized from acetone and ether. In this manner, 1.07 g (62% yield) of product was obtained: mp 266–268 °C. Anal. ($C_{17}H_{25}F_2NO_4S$) C, H, F, N.

***N*-(2,2,2-Trifluoroethyl)normetazocine Methanesulfonate (2e).** In a 10-mL flask equipped with a reflux condenser and magnetic stirrer were placed 0.375 g (1.73 mmol) of normetazocine (**2a**), 0.40 g (1.73 mmol) of 2,2,2-trifluoroethyl trifluoromethanesulfonate, 0.29 g (3.45 mmol) of sodium bicarbonate, and 5 mL of ethanol. The reaction mixture was stirred and refluxed for 8 h and worked up as for **2b**, except that the mesylate salt of the product was crystallized from acetone. In this manner, 0.44 g (64% yield) of product was obtained: mp 276 °C (dec). Anal. ($C_{17}H_{24}F_3NO_4S$) C, H, F, N.

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Demethyl Analogues of Psychoactive Methoxyphenalkylamines: Synthesis and Serotonin Receptor Affinities

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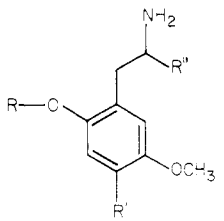
Mono-*O*-demethylation of several 2,5-dimethoxyphenalkylamines increases their affinity for the serotonin receptors of the isolated rat fundus preparation. In several instances, demethylation of methoxyphenalkylamines results in compounds which produce an antagonism which is not of a competitive nature. With respect to 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), demethylation of the 2-methoxy group alters affinity in a manner which parallels that observed upon demethylation of 5-methoxy-*N*,*N*-dimethyltryptamine. Using a discriminative stimulus paradigm, behavioral studies with rats reveal that the 2-hydroxy analogue, but not the 5-hydroxy analogue, of DOM produces effects (interoceptive cues) similar to those produced by 5-methoxy-*N*,*N*-dimethyltryptamine.

We have previously reported that certain substituted phenalkylamines (i.e., phenethylamine and phenylisopropylamine derivatives) possess an affinity for the serotonin (5-hydroxytryptamine, 5-HT) receptors of the isolated rat fundus preparation.[1,2] 2,5-Dimethoxy-substituted derivatives (e.g., 1, R = Me) possess the highest affinities; 4-methylation (e.g., 1, R = R′ = Me) further enhances affinity.



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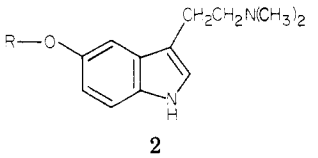

2

A number of attempts have been made to relate the structures of the psychoactive phenalkylamines to the structures of indolealkylamines by varying the orientation of the aromatic moiety and/or the conformation of the side chain.[3-5,8] Kang and Green have noted that the structure of LSD possesses both phenalkylamine and indolealkylamine molecular subfragments;[5] hence, this classical model requires the least manipulation, with respect to reorientation of the aromatic or side-chain functionalities, in order to visualize structural similarities. Though no presupposition is being made as to which is the most valid model, the classical model was used to generate a working hypothesis. 5-Methoxy-*N*,*N*-dimethyltryptamine (5-OMe-DMT; **2**, R = Me) possesses a rather high affinity for the 5-HT receptors of the rat fundus preparation. O-Demethylation of the methoxy group of 5-OMe-DMT to give bufotenine (**2**, R = H) results in a twofold increase in affinity (i.e., pA_2 values are 7.08 and 7.41, respectively). According to the classical model, the 5 position of the tryptamine analogues would correspond to the 2 position of the phenalkylamines. Thus, it was of interest to determine if the demethylation of 2-methoxyphenalkylamines would have an effect on affinity comparable to that seen upon demethylation of 5-OMe-DMT.

Chemistry. Synthesis of desired 2-hydroxy analogues **5d–f** began with the commercially available 2-hydroxy-5-

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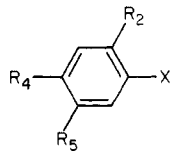
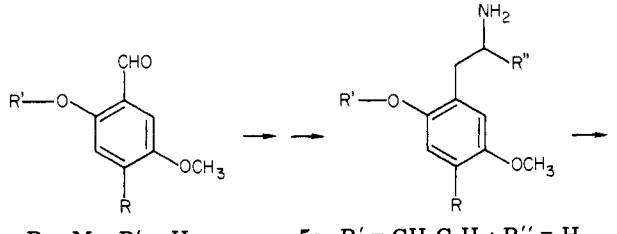
Table I. Properties of Hydroxyphenalkylamines and Their Intermediates



no.	R_2	R_4	R_5	R′	mp, °C	recrystn solv	% yield[a]	formula	anal.
					X^b = $-CH=C(NO_2)-R'$				
4b	$C_6H_5CH_2O$	H	OMe	Me	74-76[c]	EtOH	63	$C_{17}H_{17}NO_4$	C, H, N
4c	$C_6H_5CH_2O$	Me	OMe	Me	87-89	95% EtOH	92	$C_{18}H_{19}NO_4$	C, H, N
9a	$C_6H_5CH_2O$	OMe	H	Me	*d*		89	$C_{17}H_{17}NO_4$	C, H, N
10a	H	OMe	BzlO	Me	101-103	MeOH	74	$C_{17}H_{17}NO_4$	C, H, N
					X = $-CH_2CH(NH_2)-R'\cdot HCl$				
5b	$C_6H_5CH_2O$	H	OMe	Me	170-171[e]	95% EtOH	85	$C_{17}H_{21}NO_2\cdot HCl$	C, H, N
5c	$C_6H_5CH_2O$	Me	OMe	Me	194-196[f]	$MeOH/Et_2O$	76	$C_{18}H_{23}NO_2\cdot HCl$	
9b	$C_6H_5CH_2O$	OMe	H	Me	184-186[g]	$EtOH/Et_2O$	17	$C_{17}H_{21}NO_2\cdot HCl$	C, H, N
10b	H	OMe	BzlO	Me	177-179[h]	*n*-PrOH	96	$C_{17}H_{21}NO_2\cdot HCl$	
5d[i]	OH	H	OMe	H	131-132	EtOH/EtOAc	35	$C_9H_{13}NO_2\cdot HCl$	C, H, N
5e	OH	H	OMe	Me	170-171	EtOH/EtOAc	34	$C_{10}H_{15}NO_2\cdot HCl$	C, H, N
5f	OH	Me	OMe	Me	198-199.5[j]	$MeOH/Et_2O$	72	$C_{11}H_{17}NO_2\cdot HCl$	
8	H	OH	OMe	Me	259-260.5	$MeOH/Et_2O$	72	$C_{10}H_{15}NO_2\cdot HCl$	C, H, N
9	OH	OMe	H	Me	180-182	$EtOH/Et_2O$	86	$C_{10}H_{15}NO_2\cdot HCl$	C, H, N
10	H	OMe	OH	Me	157-159	$MeOH/Et_2O$	48	$C_{10}H_{15}NO_2\cdot HCl$	C, H, N
					X = $-CH_2CH(NMe_2)-R'\cdot HCl$				
6a	$C_6H_5CH_2O$	H	OMe	H	135-136	EtOAc	76	$C_{18}H_{23}NO_2\cdot HCl$	C, H, N
6b	$C_6H_5CH_2O$	H	OMe	Me	138-140	EtOAc	74	$C_{19}H_{25}NO_2\cdot HCl$	C, H, N
6c	OH	H	OMe	H	138-140	EtOH/EtOAc	39	$C_{11}H_{17}NO_2\cdot HCl$	C, H, N
6d	OH	H	OMe	Me	162-163	EtOH/EtOAc	23	$C_{12}H_{19}NO_2\cdot HCl$	C, H, N

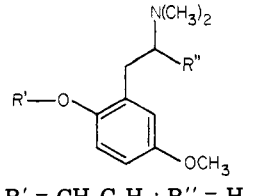
[a] Yields for **5b**, **6a**, **6b**, **9b**, and **10b** are for free bases; salts were prepared in nearly quantitative yield. [b] Precursor aldehydes for the following compounds have been previously reported: **4b**,[14] **9a**,[14] and **10a**.[15] [c] Lit.[8] mp 75.5-77 °C. [d] Purified by Kugelrohr distillation, bp 198 °C (0.55 mm). [e] Free base: bp 182-184 °C (0.5 mm). Lit.[8] mp 170-171.5 °C. [f] Lit.[8] mp 197.5-199 °C. [g] Free base: mp 104-106 °C. [h] Lit.[15] mp 175-177 °C. [i] The precursor benzyloxy compound has been previously reported.[16] [j] Lit.[8] mp 196-199 °C.

methoxybenzaldehyde or with 2,5-dimethoxy-4-methylbenzaldehyde. Using the method of Dean et al.,[6] the latter compound was demethylated with boron trichloride to afford 2-hydroxy-4-methyl-5-methoxybenzaldehyde (**3a**).



3a, R = Me; R′ = H
b, R = H; R′ = $CH_2C_6H_5$

5a, R′ = $CH_2C_6H_5$; R″ = H
b, R′ = $CH_2C_6H_5$; R″ = CH_3
c, R′ = $CH_2C_6H_5$; R″ = CH_3
d, R′ = H; R″ = H
e, R′ = H; R″ = CH_3
f, R′ = H; R″ = CH_3



6a, R′ = $CH_2C_6H_5$; R″ = H
b, R′ = $CH_2C_6H_5$; R″ = CH_3
c, R′ = H; R″ = H
d, R′ = H; R″ = CH_3

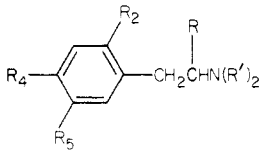
The 2-hydroxy compounds were alkylated with benzyl bromide to yield **3b** and **3c**. The aldehydes **3b** and **3c** were condensed with nitromethane and nitroethane to yield the nitroalkenes **4**, which could be reduced to the benzyloxy compounds **5a-c** with $LiAlH_4$. Hydrogenolysis of **5a-c** afforded the desired 2-hydroxy derivatives **5d-f** (see Table I). Using a similar reaction sequence, several related compounds (**8-10**) were synthesized for comparative purposes. Compounds **5a** and **5b** were subjected to Eschweiler-Clarke conditions to obtain the *N,N*-dimethyl derivatives **6a** and **6b**, which gave **6c** and **6d** after hydrogenolysis.

A preliminary account of this work has been reported;[7] however, this was predated by a paper by Zweig and Castagnoli,[8] who outlined the synthesis of **4b** and **5b** using nearly identical reactions with those reported here for these same two compounds.

Results and Discussion

The 5-HT receptor affinity data for the hydroxy compounds are reported in Table II. Affinity data for the corresponding methoxy analogues, if previously reported, are also shown in Table II (OMe pA_2). Antagonism by compounds **5d-f**, **6a**, **6d**, **8**, **10**, and **12** appears to be competitive as noted by the slopes of their Schild plots. Determination of receptor affinities via the pA_2 method requires that the observed antagonism be of a competitive nature (i.e., Schild plots must result in a negative slope approximating unity). Several of the 2-hydroxy analogues, for example, **9** and **11**, are not competitive antagonists; consequently, valid pA_2 values can not be obtained for

Table II. Serotonin Receptor Affinities



no.	R	R'	R_2	R_4	R_5	pA_2[a]	n[b]	slope[c]	OMe pA_2[d]
5d	H	H	OH	H	OMe	7.10 (±0.09)	3	0.93 (±0.31)	6.85
5e	Me	H	OH	H	OMe	7.00 (±0.08)	6	0.89 (±0.16)	6.83
5f	Me	H	OH	Me	OMe	7.44 (±0.29)	10	0.96 (±0.14)	7.12
5g	Me	H	OMe	Me	OH	7.91 (±0.21)	7	0.86 (±0.17)	7.12
6a	H	Me	$OCH_2C_6H_5$	H	OMe	5.44 (±0.16)	3	1.09 (±0.16)	6.52
6c	H	Me	OH	H	OMe	6.84 (±0.13)	2	0.76 (±0.14)	6.52
6d	Me	Me	OH	H	OMe	6.78 (±0.09)	3	0.92 (±0.21)	6.50
7	H	H	H	OH	OMe	*e*	6	0.48 (±0.13)	
8	Me	H	H	OH	OMe	5.19 (±0.19)	3	0.92 (±0.19)	5.45
9	Me	H	OH	OMe	H	*e*	5	0.46 (±0.08)	5.60
10	Me	H	H	OMe	OH	6.87 (±0.07)	5	0.88 (±0.17)	5.45
11	H	H	OH	H	H	*e*	2	0.54 (±0.10)	5.52
12	H	H	H	OH	H	5.07[f]	2	1.10 (±0.10)	5.10
13	H	H	OH	OH	OH	*g*	4		

[a] pA_2 values are followed by standard deviation. [b] Number of determinations. [c] Negative slope of Schild plot for *n* determinations. [d] pA_2 of corresponding methoxy compound.[2] [e] Valid pA_2 could not be obtained because negative slope of Schild plot was less than 0.6. [f] pA_2 previously reported. [g] Compound 13 results in discoloration (oxidation?) in the oxygenated muscle bath to give varying results. In one instance, a slope of 0.37 was obtained.

comparison with the pA_2 values of their corresponding methoxy counterparts. Hydroxy groups at positions other than the 2 position can also result in compounds which do not behave as competitive antagonists, e.g., **7**.

Demethylation of the 2-methoxy group of 2,5-dimethoxyphenethylamine, (±)-1-(2,5-dimethoxyphenyl)-2-aminopropane, and (±)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), to give **5d**, **5e**, and **5f**, respectively, results in a nearly twofold increase in affinity. Though the enhancement in affinity is slight, the trend is consistent; for example, the affinities of the *O*-demethyl analogues of the *N,N*-dimethyl derivatives of the first two compounds listed above (i.e., **6c** and **6d**) are also twice that of their *O*-methylated counterparts. It thus appears that O-demethylation of the 2-methoxy group, to give **5d–f**, **6c**, and **6d**, has the same effect on affinity as does O-demethylation of 5-OMe-DMT (**2**, R = Me) to give bufotenine (**2**, R = H).

Several related compounds were examined for comparative purposes. In both of the two cases examined, replacement of an R_5 OMe by an R_5 OH results in an increase in affinity (compounds **5g** and **10**). Nichols et al.[3e] have previously suggested that compounds such as DOM (**1**, R = R′ = R″ = Me) might interact with 5-HT receptors in such a manner that the 5-methoxy group, and not the 2-methoxy group, binds at the same site which accomodates the 5-OH group of 5-HT. Whereas demethylation of the 2-methoxy group of DOM (to give **5f**) has an effect on affinity which essentially parallels demethylation of the 5-methoxy group of 5-OMe-DMT (**2**, R = Me) and whereas demethylation of the 5-methoxy group of DOM (to give **5g**) results in a sixfold increase in affinity, it seems likely that the 2-methoxy group, and not the 5-methoxy group, of DOM interacts with the 5-HT receptors in the same manner as does the 5-methoxy group of 5-OMe-DMT.

In the phenethylamine series, there are two instances (compounds **7** and **11**) where demethylation of a methoxy group results in compounds which are not competitive antagonists. In compound **11** the hydroxyl group is at the 2 position; however, in compound **7**, the hydroxyl group is at the 4 position and the phenylisopropylamine counterpart of **7**, i.e., **8**, is clearly a competitive antagonist. These findings suggest that differences may exist in the manner in which hydroxyphenethylamines and hydroxyphenylisopropylamines interact with the 5-HT receptors.

O-Demethylation of the 2-methoxy group of (±)-1-(2,4-dimethoxyphenyl)-2-aminopropane, to give **9**, has an effect which does not parallel that observed with the corresponding O-demethylation of the 2,5-dimethoxy isomer. In addition, demethylation of a 4-methoxy group halves affintiy in one case (compound **8**), apparently has no effect on affinity in another instance (compound **12**), and in a third example results in antagonism which is not competitive (compound **7**). An assumption commonly made in binding studies is that all of the compounds are binding with the receptors in the same manner; this may not be the case with this series of compounds. In a study of the 5-HT receptor affinities of approximately 40 phenalkylamines, the 2,5-dimethoxy-substituted derivatives possessed more than ten times the affinity of most of the other compounds. Furthermore, the SAR with regard to methoxy substitution (with the general exception of 2,5-dimethoxy groups) was, for the most part, inconsistent and equivocal. It might be, then, that an unencumbered 2,5-dimethoxy pattern locks the spatial orientation of the ring with respect to the receptor site. In the absence of the 2,5-dimethoxy pattern, methoxylated or hydroxylated phenalkylamines might interact with the receptor in one or more different orientations.

In an additional series of studies, the behavioral activity of several of the hydroxy compounds was investigated and compared with that of 5-OMe-DMT using a discriminative stimulus assay. In such studies, challenge drugs can be administered to animals that are trained to recognize a training drug; if generalization occurs (i.e., if the animals perceive the challenge drug as being the training drug), it may be assumed that the challenge drug and training drug are producing similar behavioral effects. Rats were trained to detect 1.5 mg/kg of 5-OMe-DMT (training drug) from saline administration using a two-lever drug discrimination procedure.[9,10] Once the rats were able to learn to detect

(9) Glennon, R. A.; Rosecrans, J. A.; Young, R.; Gaines, J. *Life Sci.* **1979**, *14*, 993.
(10) Glennon, R. A.; Young, R.; Rosecrans, J. A.; Kallman, M. J. *Psychopharmacology* **1980**, *68*, 155.

the drug state, they were challenged with doses of 2,5-DMA (1; R = R'' = Me; R' = H), DOM (1; R = R' = R'' = Me), the *N,N*-dimethyl analogue of 2,5-DMA (2,5-DMDMA), and compounds **5e–g**. 2,5-DMA, DOM, **5e**, and **5f** were perceived to be like 5-OMe-DMT with the following respective ED_{50} values (followed by 95% confidence limits): 0.59,[10] 0.46,[10] 0.70 (0.34–1.06), and 2.46 (1.29–4.68) mg/kg. Thus, these compounds appear to be active and they produce behavioral effects similar to those of the training drug, 5-OMe-DMT. Interestingly, the hydroxy substituent of **5e** does not significantly alter potency when compared with 2,5-DMA, while it does reduce the potency of **5f** compared with that of DOM. Nevertheless, **5e** and **5f** do produce 5-OMe-DMT-like effects using the discriminative stimulus paradigm. On the other hand, generalization was not observed with either 2,5-DMDMA or with **5g**. The 2,5-DMDMA produced only partial generalization at doses of up to 8 mg/kg; maximal correct-drug lever responding was 62%. At doses between 0.25 and 1.0 mg/kg, **5g** produced saline-like responding (0–8% drug-lever); at doses of 2, 3, and 5 mg/kg, **5g** produced disruption. These data suggest that **5g** may be centrally active but that it does not have a spectrum of activity which parallels that of 5-OMe-DMT.

Comparing the two hydroxy analogues of DOM, i.e., **5f** and **5g**, affinity data and behavioral data lend some support to the classical model of phenalkylamine–5-HT receptor binding. By itself, these data are insufficient, however, to rule out any of the other theories. Furthermore, based on this and previous work (ref 2 and literature cited therein), it is entirely possible that there may be more than one mode of binding even within the phenalkylamine series.

Experimental Section

Proton magnetic resonance (NMR) spectra were recorded on a Perkin-Elmer R-24 high-resolution spectrometer using Me_4Si (DSS, for D_2O spectra) as an internal standard. 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., and determined values are within 0.4% of theoretical values. All melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected.

2-Hydroxy-4-methyl-5-methoxybenzaldehyde (3a). Approximately 25 g of BCl_3 (liquified at −78 °C prior to weighing) was added at one time to a stirred solution of 2,5-dimethoxy-4-methylbenzaldehyde[11] (23.6 g, 130 mmol) in CH_2Cl_2 (200 mL) under a N_2 atmosphere, at −78 °C. After the addition, the cooling bath was removed and the reaction flask was allowed to warm to room temperature. MeOH was added dropwise, until no further evolution of HCl. Water (200 mL) was added and stirring was continued for an additional 30 min. The CH_2Cl_2 portion was extracted five times with aqueous NaOH (5%, 100 mL); the combined NaOH solutions were acidified with 5% HCl and extracted four times with CH_2Cl_2 (100 mL). The CH_2Cl_2 solution was dried (Na_2SO_4) and evaporated to dryness under reduced pressure to yield the crude product. Recrystallization from ligroin yielded 14 g (65%) of **3a** as faint yellow crystals, mp 108–110 °C. Anal. ($C_9H_{10}O_3$) C, H.

2-(Benzyloxy)-4-methyl-5-methoxybenzaldehyde (3c). A solution of 2-hydroxy-4-methyl-5-methoxybenzaldehyde (**3a**; 0.75 g, 4.5 mmol), benzyl bromide (1.16 g, 6.8 mmol), and anhydrous K_2CO_3 (1.9 g, 13.5 mmol) in 95% EtOH (50 mL) was stirred at reflux for 16 h. The solvent was removed under reduced pressure and the residual mass was dissolved in Et_2O (150 mL). The Et_2O solution was washed twice with successive 50-mL portions of saturated NaCl solution, aqueous NaOH (5%), and H_2O; the Et_2O solution was dried ($MgSO_4$) and evaporated to dryness to yield the crude product. Recrystallization from EtOH gave 0.57 g (49%) of **3c** as pale-yellow crystals, mp 97–99 °C. Anal. ($C_{16}H_{16}O_3$) C, H.

1-[2-(Benzyloxy)-4-methyl-5-methoxyphenyl]-2-nitropropene (4c). A solution of **3c** (0.56 g, 2.2 mmol), $EtNO_2$ (1.5 g, 20 mmol), and NH_4OAc (0.17 g, 2.2 mmol) in benzene (20 mL) was heated at reflux for 14 h. The cooled solution was washed successively with saturated NaCl solution (2 × 25 mL) and H_2O (25 mL), dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Recrystallization of the crude product from 95% EtOH afforded 275 mg (40%) of **4c** as fine yellow needles, mp 87–89 °C. Anal. ($C_{18}H_{19}NO_4$) C, H, N. The yield of **4c** could be increased to 0.63 g (92%) by replacing the benzene with an equivalent amount of $EtNO_2$ as solvent.

Compounds **4b**, **9a**, and **10a** (Table I) were prepared in the same manner as **4c**, employing either $EtNO_2$ or $MeNO_2$ as solvent.

(±)-1-[2-(Benzyloxy)-4-methyl-5-methoxyphenyl]-2-aminopropane Hydrochloride (5c). A solution of **4c** (11.8 g, 37.7 mmol) in a mixture of THF (100 mL) and anhydrous Et_2O (150 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (3.0 g, 79.1 mmol) in Et_2O (50 mL) at 0 °C. The mixture was heated at reflux for 6 h; unreacted $LiAlH_4$ was decomposed by the addition of small portions of $Na_2SO_4 \cdot 10H_2O$ at 0 °C. The mixture was filtered, and the filtrate was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The crude oily product was distilled [Kugulrohr, 90–100 °C (0.375 mm)] and converted to the HCl salt. Recrystallization from MeOH/Et_2O gave 9.2 g (76%) of **5c** as white crystals, mp 194–196 °C (lit.[8] mp 197.5–199 °C). Compounds **5b**, **9b**, and **10b** (Table I) were prepared in the same manner as **5c**.

(±)-1-(2-Hydroxy-4-methyl-5-methoxyphenyl)-2-aminopropane Hydrochloride (5f). Compound **5c** (7.7 g, 24 mmol) was added to a suspension of 10% Pd/C (0.8 g) in absolute EtOH (100 mL). The solution was heated to 90 °C and then hydrogenated (50 psig) for 4 h. Filtration of the reaction mixture and evaporation of the filtrate under reduced pressure yielded 4 g (72%) of **5f** after recrystallization from an MeOH/Et_2O mixture, mp 198–199.5 °C (lit.[8] 196–198 °C). Compounds **5d**, **5e**, **6c**, **6d**, and **8–10** (Table I) were prepared in the same manner as **5f**.

***N,N*-Dimethyl-1-[2-(benzyloxy)-5-methoxyphenyl]-2-aminoethane Hydrochloride (6a).** A 40% formaldehyde solution (14 mL) was added to a stirred mixture of **5a** (12 g, 47 mmol) and formic acid (97%, 15 mL) at 10 °C. The reaction mixture was heated on an oil bath (95–100 °C) until CO_2 evolution was observed. At this time, heating was discontinued until evolution of CO_2 ceased. The mixture was heated at 95–100 °C for an additional 8 h, cooled to 0 °C, and acidified with 4 N HCl (32 mL). Solvent was removed under reduced pressure; the residual material was dissolved in H_2O (15 mL) and aqueous NaOH (18 N, 15 mL) was added. After extraction with benzene (3 × 25 mL), the combined extracts were dried (Na_2SO_4) and evaporated to dryness. Distillation afforded 10.1 g (76%) of the amine, bp 152 °C (0.14 mm). Dry HCl was bubbled thorugh an ether solution of the amine to yield **6a**, mp 135–136 °C, after recrystallization from EtOAc. Anal. ($C_{18}H_{23}NO_2 \cdot HCl$) C, H, N.

(±)-*N,N*-Dimethyl-1-[2-(benzyloxy)-5-methoxyphenyl]-2-aminopropane Hydrochloride (6b). Sodium cyanoborohydride (3.1 g, 43.9 mmol) was added to a solution of **5b** (as the free base; 8.3 g, 30.6 mmol) and aqueous formaldehyde (37%, 12.2 mL, 163 mmol) in CH_3CN (90 mL). After the initial exothermic reaction, the mixture was stirred for 15 min at room temperature; glacial acetic acid was added dropwise with stirring until the reaction mixture tested neutral on wet pH paper. The reaction was allowed to stir for an additional 2 h with intermittent addition of glacial acetic acid to maintain neutrality. The organic solvent was removed under reduced pressure; aqueous KOH solution (2 N, 120 mL) was added and then extracted with Et_2O (3 × 100 mL). The combined ether solutions were dried (K_2CO_3) and the solvent removed in vacuo to afford a yellow oil. Distillation gave 6.8 g (74%) of the desired amine, bp 145 °C (0.08 mm). The hydrochloride salt was prepared and recrystallized from EtOAc to yield **6b** as white plates, mp 138–140 °C. Alternatively, compound **6b** could be prepared in the same manner as **6a**, but only in 59% yield. Anal. ($C_{19}H_{25}NO_2 \cdot HCl$) C, H, N.

Receptor Affinity Assay. Male Sprague–Dawley rats weighing 200–300 g (Flow Laboratories, Dublin, VA) were used

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in this study. The rat stomach fundus preparation employed was essentially that of Vane,[12] with the previously described modifications.[1,2] Two strips were cut from the same tissue and were used in parallel 8-mL muscle baths. The relative sensitivity of the two strips was determined, after a 1-h equilibration period in Tyrodes solution at 37 °C, by the use of 5-HT oxalate doses giving submaximal contractions. Only one compound was tested per preparation. Dose–response curves were obtained for 5-HT, first in the absence of the agent in question and then in the presence of each of usually four different, increasing concentrations thereof. ED_{50} values for half-maximal contraction were determined, and apparent affinities were calculated as pA_2 values by the method of Arunlakshana and Schild.[13] Linear regression analysis gave not only the pA_2 values but also the slopes of the Schild plots.

Behavioral Pharmacology. The discriminative stimulus assay was performed in a manner identical with that which we have previously reported;[3,10] 5-methoxy-*N*,*N*-dimethyltryptamine hydrogen oxalate (1.5 mg/kg) was used as the training drug. Each dose of challenge drug was evaluated in three to six rats; the number and range of doses tested for each of the compounds are as follows: **5e**, three doses from 0.5 to 1.5 mg/kg; **5f**, six doses from 1.0 to 5.0 mg/kg; **5g**, six doses from 0.25 to 5.0 mg/kg; 2,5-DMDMA, five doses from 1.0 to 8.0 mg/kg. Generalization was considered to be greater than 70% responding on the 5-OMe-DMT lever, while partial generalization refers to 50–69% responding.

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Estrogen Receptor Based Imaging Agents. 1. Synthesis and Receptor Binding Affinity of Some Aromatic and D-Ring Halogenated Estrogens

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Steroidal and nonsteroidal estrogens substituted with halogens ortho to the phenolic hydroxyl group and in the D ring at C-16 have been prepared as potential estrogen receptor-based imaging agents for human breast tumors. Estrogens bearing an aromatic fluorine ortho to a phenolic hydroxyl group were prepared by the Schiemann reaction on the corresponding methyl esters; other ortho-halogenated estrogens were prepared by direct halogenation. Steroidal estrogens substituted at the 16α position were prepared by halogenation of estrone 3-acetate (17-enol acetate) followed by hydride reduction, and those substituted at the 16β position were prepared by epimerization prior to reduction. The binding affinity of these halogenated estrogens to the uterine estrogen receptor was measured relative to that of [^{3}H]estradiol by a competitive binding assay. All of the monosubstituted ortho-fluorinated estrogens show very high binding affinity for the receptor (64–250% that of estradiol). The monosubstituted and symmetrically disubstituted bromo- and iodohexestrols and 2- and 4-substituted estradiols have binding affinities considerably lower than those of the fluoro compounds, the 4-substituted estradiols having affinities greater than the corresponding 2-substituted isomers. Introduction of a halogen (Cl, Br, I) at the 16α position of 17β-estradiol results in compounds with receptor affinities comparable to that of 17β-estradiol itself; the 16β-epimers and the estrone derivatives are bound less well. Thus, provided that they can be labeled with suitable γ-emitting radioisotopes at sufficiently high specific activity, it appears that the A-ring fluoroestrogens and 16α-bromo- and 16α-iodoestradiol-17β are excellent candidates for receptor-based imaging of human breast tumors.

A sizeable fraction of human breast tumors contain significant levels of estrogen receptor,[1] and the measurement of the levels of these receptors by in vitro assays on surgical tumor samples has become an important diagnostic approach to determine the hormone responsiveness of the tumor, information that is essential for the selection of the most appropriate therapy for the breast cancer patient (hormonal therapy vs. chemotherapy or radiation).[2] There has been considerable interest in the development of γ-emitting estrogen analogues that might be concentrated in estrogen receptor-containing breast tumors and thus act as tumor imaging agents (see Discussion). In vivo radiopharmaceuticals of this kind could provide, noninvasively, valuable diagnostic information about both primary and metastatic breast tumors.

We have taken a systematic approach to the development of estrogen receptor based imaging agents, paying particular attention to the binding selectivity of these agents,[3a] that is, the affinity they show for the estrogen receptor relative to their binding affinity for nonreceptor sites. In this paper, we describe the synthesis of several

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