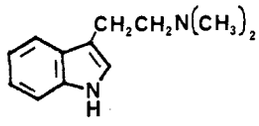
Synthesis and Evaluation of a Novel Series of *N,N*-Dimethylisotryptamines

Richard A. Glennon,*† John M. Jacyno,† R. Young,† J. D. McKenney,† and David Nelson‡

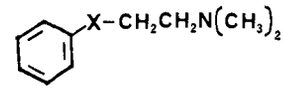
Department of Pharmaceutical Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298, and Department of Pharmacology, School of Pharmacy, University of Arizona, Tucson, Arizona 85721. *Received March 21, 1983*

A novel series of *N,N*-dimethylisotryptamine (isoDMT) derivatives, i.e., derivatives of 1-[2-(dimethylamino)ethyl]indole, was prepared and found to be isosteric with their corresponding *N,N*-dimethyltryptamine (DMT) counterparts with respect to serotonin receptor (rat fundus) affinity. Whereas the isoDMT derivatives possessed a greater affinity than did their corresponding DMT derivatives, they were relatively ineffective in displacing [^{3}H]-5-HT binding from rat brain (cortex) homogenates. In a drug discrimination paradigm, using rats as subjects, 6-OMe-isoDMT produced effects similar to those of 5-OMe-DMT. Attempts to antagonize the discriminative stimulus effects of the hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) using two of the isoDMT derivatives proved unsuccessful.

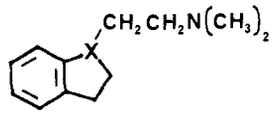
Various indolylalkylamine and phenylalkylamine hallucinogens possess a high affinity for the serotonin (5-HT) receptors of the isolated rat fundus preparation and result in DOM-stimulus generalization in tests of discriminative control of behavior in animals.[1-3] In the course of our studies, various molecular modifications of these agents have been examined (a) in order to determine what structural features are required for receptor affinity and/or behavioral activity and (b) in an attempt to identify compounds that might serve as hallucinogen antagonists. We have found, for example, that removal of the five-membered ring of the hallucinogenic agent *N,N*-dimethyltryptamine (DMT, **1**), to afford **2**, decreases receptor affinity and abolishes behavioral activity but that replacement of the benzylic carbon atom of **2** with a nitrogen atom (i.e., **3**) or conversion of **2** to a somewhat more conformationally constrained molecule (i.e., **5**) both result in an enhancement of affinity.[4] Thus, it was of interest to prepare **6**, the nitrogen counterpart of **5**, as well as several related unsaturated derivatives of **6**, i.e., *N,N*-dimethylisotryptamines, **7**. These compounds were studied with respect to their (a) 5-HT receptor affinities, (b) ability to displace tritiated 5-HT binding in rat brain homogenates, and (c) discriminative stimulus properties using animals trained to discriminate DOM (1 mg/kg) from saline.



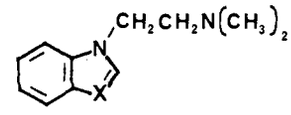
1



2 X = CH_2
3 X = NH
4 X = NEt



5 X = CH
6 X = N



7 X = CH
9 X = N

Chemistry. The synthesis of the 1-[2-(dimethylamino)ethyl]indole (i.e., *N,N*-dimethylisotryptamine, isoDMT) derivatives **7** (Table I) was quite straightforward and simply involved alkylation of the appropriately substituted indolyl anion (generated by the action of NaH on the indole in hexamethylphosphoramide) with 2-(dimethylamino)ethyl chloride (liberated beforehand by treatment of the hydrochloride salt with 40% aqueous NaOH). This same approach was used to prepare **8** and **9** from DMT (**1**) and benzimidazole, respectively.

Results and Discussion

5-HT Receptor Affinity Studies. 5-HT receptor affinities were determined by using the isolated rat fundus preparation of Vane.[5] With the exception of compounds **7f** and **8**, all compounds (Table II) were found to interact in a competitive manner; i.e., the negative slopes of their Schild plots approximated unity. The slopes generated by **7f** were not indicative of a competitive interaction. Successive cummulative dose–response curves to 5-HT in the presence of increasing concentrations of **8** resulted in steadily decreasing maximal responses, again suggestive of an interaction that was other than competitive in nature.

The indoline derivative **6** possessed ten times the receptor affinity of its corresponding 2,3-dihydrotryptamine (i.e., 2,3-H_2-DMT; $pA_2 = 5.68$[4]). This same relationship was evident when the affinity of isoDMT (**7a**) was compared with that of DMT (**1**; $pA_2 = 6.00$[6]). Opening of the five-membered ring of **6** resulted in a compound, **4**, that produced erratic responding of the fundus preparation; this effect is reminiscent of that reported for **3**.[4]

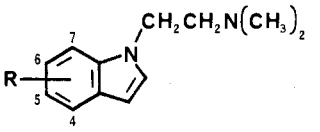
The question now arises as to the relative orientation of the receptor interaction. In other words, does the indole nucleus of **7** interact as does the indole ring in the dialkyltryptamine series (in which case the terminal amines of both series are probably not interacting at the same site) or do the dimethylisotryptamine derivatives possess an isosteric relationship with the dialkyltryptamines? Several lines of evidence support the latter possibility. First, compound **8** does not interact with the 5-HT receptors in a competitive manner. Second, variation of the substituents in the dimethylisotryptamine series has an effect on affinity, which supports an isosteric relationship. For example, 5-OMe-DMT (**10**) possesses greater than ten times the affinity of 6-OMe-DMT,[6] while 6-OMe-isoDMT (**7b**) possesses approximately ten times the affinity of 5-OMe-isoDMT (**7c**). Furthermore, of the 4-, 5-, 6-, and 7-methyl derivatives of DMT, only the 6-methyl derivative does not interact with the 5-HT receptors in a competitive manner;[1,6-8] in the isoDMT series, it is the 5-methyl de-

† Virginia Commonwealth University.
‡ University of Arizona.

(1) Glennon, R. A.; Rosecrans, J.A. *Neurosci. Biobehav. Rev.* **1981**, *5*, 197.
(2) Glennon, R. A.; Young, R.; Benington, F.; Morin, R. D. *J. Med. Chem.* **1982**, *25*, 1163.
(3) Glennon, R. A.; Rosecrans, J. A.; Young, R. in "Drug Discrimmination: Applications in CNS Pharmacology", Colpaert, F. C.; Slangen, J. L., Eds.; Elsevier Biomedical Press: Amsterdam, 1982; p 69.
(4) Glennon, R. A.; Jacyno, J. M.; Salley, J. J. *J. Med. Chem.* **1982**, *25*, 68.
(5) Vane, J. R. *Br. J. Pharmacol.* **1957**, *12*, 344.
(6) Glennon, R. A.; Gessner, P. K. *J. Med. Chem.* **1979**, *22*, 428.

0022-2623/84/1827-0041$01.50/0

Table I. Properties of *N,N*-Dimethylisotryptamine Derivatives



no.	compd	R_7	R_6	R_5	R_4	emp formula[a]	mp, °C	recrystn solvent	yield,[b] %
7a	isoDMT	H	H	H	H	$C_{12}H_{16}N_2 \cdot (COOH)_2$	167-168	MeOH	80
7b	6-OMe-isoDMT	H	OMe	H	H	$C_{13}H_{18}N_2O \cdot (COOH)_2$	166-167	abs EtOH	65
7c	5-OMe-isoDMT	H	H	OMe	H	$C_{13}H_{18}N_2O \cdot (COOH)_2$	179-180	MeOH	95
7d	7-Me-isoDMT	Me	H	H	H	$C_{13}H_{18}N_2 \cdot (COOH)_2$	199-202	abs EtOH	73
7e	6-Me-isoDMT	H	Me	H	H	$C_{13}H_{18}N_2 \cdot (COOH)_2$	195-197	MeOH	56
7f	5-Me-isoDMT	H	H	Me	H	$C_{13}H_{18}N_2 \cdot (COOH)_2$	169-171	MeOH	59
7g	4-Me-isoDMT	H	H	H	Me	$C_{13}H_{18}N_2 \cdot (COOH)_2$	183-185	MeOH	84

[a] Results of elemental analyses for C, H, and N were within 0.4% of theory. [b] Yield of free base prior to conversion to hydrogen oxalate salt.

Table II. Serotonin-Receptor Affinity and Brain-Binding Data for *N,N*-Dimethylisotryptamines and Related Compounds

	serotonin-receptor affinity (rat fundus)			inhibn of specific [^{3}H]-5-HT binding (rat cortex)[h]	
compd	pA_2[a]	slope[b]	N[c]	IC_{50},[i] nM	N[j]
isoDMT (7a)	6.98 (±0.14)	1.13 (0.23)	4	3 260 (±560)	4
6-OMe-isoDMT (7b)	7.68 (±0.22)	0.88 (±0.20)	7	775 (±116)	4
5-OMe-isoDMT (7c)	6.87 (±0.20)	0.90 (±0.19)	4	4 290 (±1180)	3
7-Me-isoDMT (7d)	7.32 (±0.13)	0.96 (±0.10)	3		
6-Me-isoDMT (7e)	6.86 (±0.15)	0.98 (±0.04)	3		
5-Me-isoDMT (7f)		0.63; 0.60			
4-Me-isoDMT (7g)	7.14 (±0.16)	1.04 (±0.06)	3		
3	6.02[d,e]				
4	6.27 (±0.75)[e]	0.77 (±0.23)	5		
6	6.57 (±0.13)	1.08 (±0.49)	3		
8	*f*			>20 000	3
9	6.86 (±0.20)	0.94 (±0.10)	4		
5-OMe-DMT (10)	7.08[g]			71 (±20)	4

[a] pA_2 values are followed by standard deviation. [b] Negative slope of Schild plot, followed by standard deviation for N determinations. [c] Number of pA_2 determinations; each pA_2 value was obtained from five to six cummulative dose-response curves to 5-HT. [d] pA_2 value has been previously reported;[4] data included for comparative purposes. [e] Responses produced by this compound were erratic. [f] Cummulative dose-response curves could not be obtained for this compound; see text for explanation. [g] pA_2 value previously reported.[6] [h] Control values for the displacement of [^{3}H]-5-HT by unlabeled 5-HT, i.e., IC_{50} = 3-4 nM, were consistent with previously reported values.[10] Single determinations for 4-OMe-DMT and 6-OMe-DMT gave IC_{50} values of 220 and 630 nM, respectively. [i] IC_{50} values are plus or minus SEM. [j] Number of determinations.

rivative **7f** that does not interact competitively. Thus, the dimethylisotryptamines apear to be isosteric with the dimethyltryptamines and, furthermore, possess a somewhat greater 5-HT receptor affinity than their corresponding DMT counterparts.

Brain-Binding Studies. Tritiated 5-HT labels distinct populations of rat brain serotonin sites;[9-11] displacement of [^{3}H]-5-HT binding to rat brain membranes can serve as a rough measure of the affinity of various compounds for these high-affinity, central 5-HT sites. Certain tryptamine derivatives are relatively effective in displacing [^{3}H]-5-HT;[11] therefore, binding data were obtained for compounds **7a–c** and **8**, and these were compared with that for 5-OMe-DMT (**10**). None of the dimethylisotryptamines displayed significant activity, with the exception of 6-OMe-isoDMT (**7b**), which was one-tenth as active as 5-OMe-DMT (**10**) but at least five times more effective than **7c** (Table II).

Behavioral Studies. Using a two-lever drug discrimination paradigm, stimulus generalization can occur between two agents that presumably produce similar effects. That is, animals, trained to discriminate a particular dose of training drug, will respond to a challenge drug in a similar manner ("stimulus generalization") if the challenge drug is recognized as producing effects similar to those of the training drug. Agents that produce similar behavioral and subjective effects in man often generalize to one another in tests of discriminative control of responding in animals. Using rats trained to discriminate 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline, DOM-stimulus generalization occurs upon administration of the tryptamine derivative 5-OMe-DMT (**10**);[3] stimulus generalization also occurs between these two agents when 5-OMe-DMT (**10**) is used as the training drug.[3] Doses of isoDMT (**7a**), as well as its 6-methoxy (**7b**) and 5-methoxy (**7c**) derivatives, and the benzimidazole analogue **9** were administered to groups of rats trained to discriminate 1.0 mg/kg of DOM from saline administration (Table III). While the DOM stimulus generalized to 6-

(7) Glennon, R. A.; Schubert, E.; Jacyno, J. M.; Rosecrans, J. A. *J. Med. Chem.* **1980**, *23*, 1222.
(8) A pA_2 value has not been previously reported for 4,*N*,*N*-trimethyltryptamine (4-Me-DMT) but was determined, during the course of this study, to be 6.85 (±0.26); Schild slope = 0.93 (±0.21), n = 4.
(9) Peroutka, S. J.; Snyder, S. H. *Mol. Pharmacol.* **1979**, *16*, 687.
(10) Nelson, D. L.; Pedigo, N. W.; Yamamura, H. I. *J. Physiol. (Paris)* **1981**, *77*, 369.
(11) Leysen, J. E.; Tollenaere, J. P. *Annu. Rep. Med. Chem.* **1982**, *17*, 1.

Table III. Discriminative Stimulus Effects of Several *N,N*-Dimethylisotryptamine Derivatives[a]

compd	dose, mg/kg	N[b]	% DOM appropriate responding (±SEM)[c]	response rate[d]
isoDMT (7a)	6.0	5/5	7 (5.1)	12.0 (1.8)
	10.0	5/5	9 (5.6)	12.4 (2.0)
	12.5	4/5	10 (4.4)	12.5 (1.0)
	13.5	3/5	14 (3.5)	11.8 (1.3)
	15.0	2/5	*g*	
6-OMe-isoDMT (7b)[e]	1.0	5/5	6 (4.1)	15.2 (1.8)
	3.0	6/6	12 (6.9)	13.5 (1.8)
	7.0	5/5	56 (19.9)	14.8 (2.1)
	8.0	5/5	76 (12.8)	15.4 (2.6)
	9.0	4/5	86 (8.1)	15.0 (4.4)
	10.0	3/5	97 (2.7)	10.0 (3.5)
5-OMe-isoDMT (7c)	3.0	5/5	4 (3.1)	14.4 (1.2)
	6.0	5/5	9 (6.1)	14.4 (3.0)
	8.0	5/5	2 (1.6)	14.6 (1.6)
	12.0	5/5	6 (2.8)	13.2 (2.0)
	16.0	5/5	2 (1.2)	13.4 (2.8)
	20.0	1/5	*g*	
9	7.0	5/5	0	12.6 (1.1)
	12.0	5/5	0	15.2 (3.1)
DOM	1.0	5/5	95 (3.0)	14.0 (1.6)
DOM (1 mg/kg) +[f]				
saline (1.0 mL/kg)		5/5	95 (2.1)	15.2 (2.1)
7b (1.0 mg/kg)		5/5	94 (3.8)	12.8 (1.5)
7b (3.0 mg/kg)		5/5	97 (1.1)	13.1 (3.2)
DOM (1 mg/kg) +[f]				
saline (1.0 mL/kg)		5/5	97 (2.5)	12.8 (1.4)
7c (3.0 mg/kg)		5/5	96 (3.9)	12.2 (2.7)
7c (12.0 mg/kg)		1/5	*g*	

[a] Rats were trained to discriminate 1.0 mg/kg of DOM from saline. [b] Number of animals responding/number of animals receiving that particular dose of drug. [c] Responses made on the DOM-appropriate lever as a percent of total responses; data were collected during the 2.5-min extinction session. [d] Mean responses per minute during the extinction session. [e] ED_{50} = 7.11 mg/kg (95% confidence limit = 6.15–8.23 mg/kg). [f] Effect of DOM after pretreatment of the animals with either saline or doses of 7b and 7c. [g] Disruption of behavior (i.e., no responding).

OMe-isoDMT (**7b**) in a dose-related manner (ED_{50} = 7.11 mg/kg), both isoDMT (**7a**) and 5-OMe-isoDMT (**7c**) produced saline-like effects at lower doses and complete disruption of behavior (i.e., no responding) at 15.0 and 20.0 mg/kg, respectively. The benzimidazole analogue **9** was inactive at 7.0 and 12.0 mg/kg. Administration of DMT (**1**) and 5-OMeDMT (**10**) (to this same group of animals) resulted in DOM-stimulus generalization (ED_{50} values = 5.80 and 1.22 mg/kg, respectively[3]), while administration of 6-OMe-DMT produced saline-like responding at doses of up to 10 mg/kg.[3] As in the 5-HT receptor affinity and brain-binding assays, 6-OMe-isoDMT (**7b**) was more active than 5-OMe isoDMT (**7c**); nevertheless, **7b** was only one-sixth as active as 5-OMe-DMT (**10**). Additional comparisons were made between **7b** and **10** by examining their time course of effects in the DOM-trained animals. Using doses of 10 and 3 mg/kg for **7b** and **10**, respectively (i.e., doses that resulted in complete DOM-stimulus generalization) and by varying the presession injection interval by 15-min increments, it was found (Figure 1) that 6-OMe-isoDMT (**7b**) and 5-OMe-DMT (**10**) possessed a relatively short but identical duration of action.

In a third study, attempts were made to antagonize the effects of 1 mg/kg of DOM in DOM-trained rats by pretreating groups of animals with nondisruptive doses of 5-OMe-isoDMT (**7c**) or low doses of 6-OMe-isoDMT (**7b**). As shown in Table III, no antagonistic effects were evident. Administration of DOM in combination with 6-OMe-isoDMT (**7b**; 1.0 and 3.0 mg/kg) or with 5-OMe-isoDMT (**7c**; 3.0 mg) gave results that did not differ from administration of DOM plus saline; 12 mg/kg of **7c** in combination with DOM resulted in disruption of behavior.

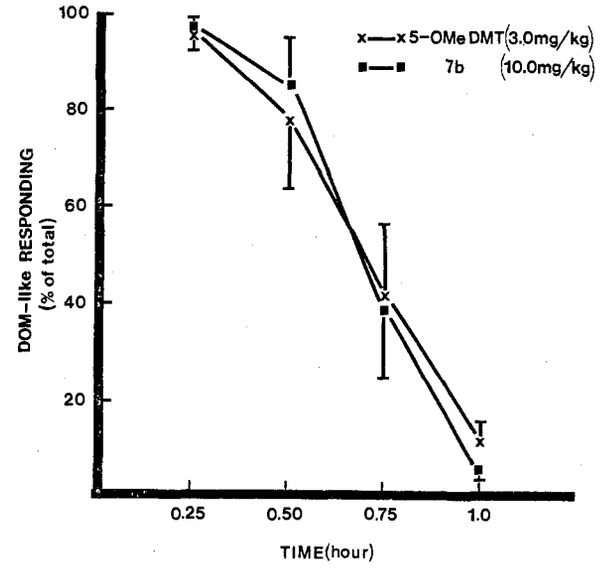


Figure 1. Results of time-course study showing similar duration of action for 5-OMe-DMT (**10**) and 6-OMe-isoDMT (**7b**).

Conclusion

The indole nitrogen atom and C_3 atom of a series of *N,N*-dimethyltryptamies can be interchanged to afford a novel series of isosteric *N,N*-dimethylisotryptamines. A comparison of 5-HT receptor affinity data revealed that the relative affinities within the series of isoDMT derivatives roughly paralleled those of their DMT counterparts, although the former possess a greater affinity than do the latter. On the other hand, the dimethylisotryptamine derivatives **7a–c** were not as potent as 5-OMe-DMT (**10**) in displacing [^{3}H]-5-HT from rat brain homogenates.

When a drug discrimination paradigm was used, which is a drug detection procedure, 6-OMe-isoDMT (**7b**), like 5-OMe DMT (**10**), was found to produce stimulus effects similar to those produced by the training drug DOM.

Compound **7b**, however, was only one-sixth as active as 5-OMe-DMT, although 6-OMe-isoDMT (**7b**) and 5-OMe-DMT (**10**) demonstrated a similar time course of effects. We have previously reported that various hallucinogenic indolylalkylamines and phenylalkylamines possess a high affinity for the 5-HT receptors of the isolated rat fundus preparation but that significant receptor affinity is not, by itself, a sufficient condition for behavioral potency. This seems also to be the case with the *N,N*-dimethylisotryptamines; although they possess a higher receptor affinity than their dimethyltryptamine counterparts, they do not appear to possess comparably greater behavioral potency. As such, it would seem that such compounds might serve as potential hallucinogen antagonists; however, studies with **7b** and **7c** revealed that they were unable to effectively attenuate the discriminative stimulus effects of the hallucinogen DOM.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Perkin-Elmer R-24 spectrometer, and chemical shifts are reported relative to tetramethylsilane. Infrared and mass spectra were obtained with a Perkin-Elmer 257 spectrophotometer and a Finnigan 4000 series GC/MS, respectively. Spectral data were in accord with the assigned structures. Melting points were determined on a Thomas-Hover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA, and values are within 0.4% of theoretical. The synthesis of compound **4** has been reported.[12]

1-[2-(Dimethylamino)ethyl]indoline Hydrogen Oxalate (6). Anhydrous K_2CO_3 (2.8 g) and 2-(dimethylamino)ethyl chloride hydrochloride (1.5 g, 0.01 mol) were added to a stirred soluton of indoline (1.2 g, 0.01 mol) in absolute EtOH (40 mL). The stirred mixture was heated at reflux for 3 h, cooled to room temperature, and diluted with water (100 mL). After extraction with Et_2O (3 × 100 mL), the combined Et_2O extracts were washed with water (100 mL) and dried ($MgSO_4$). The solvent was removed by evaporation in vacuo, and the crude brown product was purified by column chromatography (40 g silica gel, with 50:1 ethyl acetate/triethylamine as eluent). Pooling and evaporating similar (TLC) fractions gave 0.7 g of a yellow oil, which was characterized by infrared and ^{1}H NMR spectroscopy. The remaining product was converted to the hydrogen oxalate salt, mp 153–154 °C after recrystallization from absolute EtOH. Anal. ($C_{12}H_{18}N_2 \cdot C_2H_2O_4$) C, H, N.

5-Methoxy-1-[2-(dimethylamino)ethyl]indole Hydrogen Oxalate (5-OMe-isoDMT; 7c). 5-Methoxyindole (4.4 g, 0.03 mol) in dry HMPA (25 mL) was added dropwise to a stirred, chilled (0 °C) suspension of NaH (1.5 g of a 50% oil dispersion washed with dry benzene) in HMPA (20 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 2 h, a KOH-dried benzene solution of 2-(dimethylamino)ethyl chloride (from 8.6 g of the hydrochloride treated with 40% aqueous NaOH and extracted with 2 × 10 mL portions of benzene) was added, and stirring was continued at room temperature overnight. The reaction mixture was poured into saturated NH_4Cl solution (450 mL), and the aqueous mixture was extracted with Et_2O (4 × 100 mL). The Et_2O extracts were combined, washed with water (5 × 100 mL), and dried ($MgSO_4$). Removal of the solvent by evaporation in vacuo gave 6.2 g (65%) of product as a yellow oil, which was homogeneous by TLC. Without further purification, this free base was converted to the hydrogen oxalate salt: mp 179–180 °C after recrystallization from MeOH; ^{1}H NMR (free base/$CDCl_3$) δ 2.7 (t, 2 H), 3.8 (s, 3 H), 4.2 (t, 2 H), 6.4 (d, 1 H), 6.7–7.4 (m, 4 H). Anal. ($C_{13}H_{19}N_2O \cdot C_2H_2O_4$) C, H, N.

The compounds in Table I were prepared in the same manner as **7c**, starting with the appropriately substituted indole.

1,3-Bis[2-(dimethylamino)ethyl]indole Dihydrogen Oxalate (8). Compound **8**, as the free base, was prepared in 32% yield from *N,N*-dimethyltryptamine (**1**), employing the same procedure used for the synthesis of **7c**, and was converted to the hydrogen oxalate salt, mp 199–201 °C after recrystallization from MeOH. Anal. ($C_{16}H_{25}N_3 \cdot 2C_2H_2O_4$) C, H, N.

1-[2-(Dimethylamino)ethyl]benzimidazole Dihydrogen Oxalate (9). The free base of **9** was prepared in approximately 80% yield by subjecting benzimidazole to the reaction conditions outlined for the synthesis of **7c**. This crude product could be neither crystallized nor converted to a salt. Approximately 3 g of crude material in a minimal amount of acetone was added dropwise to a stirred solution of picric acid (15 g of damp acid) in 350 mL of absolute EtOH. The yellow precipitate that formed was collected by filtration, washed well with absolute EtOH, and air-dried; the picrate decomposed without melting at about 230 °C. The free base was liberated by adsorbing a portion of the picrate onto an alumina column and eluting with $CHCl_3$. The eluate was evaporated to dryness, and the residue was taken up in a minimal amount of MeOH. Dropwise addition of this solution to a methanolic solution of oxalic acid gave an oxalate salt, which was washed with 1-propanol to afford the product as ivory-colored flakes, mp 204–205 °C. Anal. ($C_{11}H_{15}N_3 \cdot 2C_2H_2O_4$) C, H, N.

4,*N*,*N*-Trimethyltryptamine Hydrogen Oxalate. Oxalyl chloride (2.9 g, 0.02 mol) was added dropwise to a stirred suspension of 4-methylindole[13] (2.6 g, 0.02 mol) in 25 mL of H_2O at 5 °C. After the addition was complete, the reaction mixture was stirred for an additional hour, and the crude orange product was collected by filtration and washed well with Et_2O. This product was added to a solution of dimethylamine (40%, 10 mL) in 15 mL of H_2O and was stirred overnight. The white precipitate was collected by filtraton and washed well with Et_2O to yield 1.3 g of the glyoxamide. A solution of this glyoxamide (1.0 g, 4 mmol) in freshly distilled dioxane (25 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.0 g) in dioxane (25 mL) at 0 °C. The reaction mixture was heated at reflux for 3 h, cooled to 0 °C, and quenched by the successive dropwise addition of H_2O (1 mL), aqueous NaOH (15%, 1 mL), and H_2O (3 mL). The mixture was filtered, and the filtrate was evaporated to dryness in vacuo to yield 720 mg (82%) of colorless oil, which crystallized upon standing, mp 95–97 °C. The product was characterized as its hydrogen oxalate salt, mp 169–171 °C after recrystallization from MeOH. Anal. ($C_{13}H_{18}N_2 \cdot C_2H_2O_4$) C, H, N.

Receptor Affinity Studies. The method employed has been previously described in detail.[2] In brief, male Sprague-Dawley rats (200–300 g) were used, and the fundus preparation employed was that of Vane.[5] Dose–response curves were obtained, after an initial 1-h equilibration period, for 5-HT (9 to 11 increasing concentrations) both in the absence and presence of 4 to 5 increasing concentrations of test compound. Apparent affinities were calculated as pA_2 values by the method of Arunlakshana and Schild.[14] The interaction was assumed to be competitive when the slopes of these pA_2 plots (Schild plots) were between −0.80 and −1.20.

Binding Studies. Male Sprague–Dawley rats (150–200 g) were sacrificed by decapitation, and the brains were rapidly removed and placed on ice. The cortex dorsal to the rhinal sulcus was dissected. Tissue from six to ten rats was pooled and homogenized in at least 40 vol of Tris-HCl buffer (0.05 M, pH 7.4) by using a Brinkman Polytron (setting 5 for 20 s). This homogenate was centrifuged at 48000*g* for 10 min; the pellet was resuspended, and the process was repeated three more times. Between the second and third washes, the tissue homogenate was incubated at 37 °C for 10 min. The final pellet was resuspended in 50 vol of Tris buffer for use in the binding assay. Binding of [^{3}H]-5-HT (26.2 Ci/mmol) was measured as previously described by Nelson et al.[15] Tissue homogenate (0.5 mL) and various concentrations of [^{3}H]-5-HT and test compound were added to glass tubes containing modified Tris-HCl buffer to yield a final volume of 2 mL having the following composition: 10 μM pargyline, 4 mM $CaCl_2$, and 50 mM Tris, pH 7.4, at 37 °C. Incubation (7 min at 37 °C) was terminated by vacuum filtration through Whatman GF/B filters, followed by three 5-mL washes with cold buffer. Radioactivity was extracted overnight in 6 mL of scintillation liquid

(12) Bach, F. L.; Brabander, H. J.; Kushner, S. *J. Am. Chem. Soc.* **1957**, *79*, 2221.
(13) Batcho, A. D.; Leimgruber, W. U.S. Patent 3732245, 1973.
(14) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 28.
(15) Nelson, D. L.; Herbet, A.; Bourgoin, S.; Glowinski, J.; Hamon, M. *Mol. Pharmacol.* **1978**, *14*, 983.

(3 L of toluene, 16 g of Omnifluor, and 1 L of Triton X-100) and measured by liquid scintillation spectrometry (50% efficiency). Specific [^{3}H]-5-HT binding was defined as the difference between binding in the absence and presence of 1 μM metergoline.

Behavioral Assay. The drug discrimination training procedure for these animals has been reported previously.[16] Briefly, 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-15s) schedule of reinforcement served as the cue for the correct (reinforced) lever. Occasional periods (2.5 min) of nonreinforcement (extinction) were used to assess the degree of stimulus control exerted by saline and DOM over behavior and to evaluate the isoDMT derivatives. For those compounds where generalization (transfer, substitution) occurred, ED_{50} values were determined from the dose–response data by the method of Finney.[17] These ED_{50} values are the calculated doses at which the rats perform 50% appropriate drug-lever responding.

Time-course studies investigated the effects of increasing the time interval between the injection of doses of **7b** (10 mg/kg) and **10** (3 mg/kg) which produced stimulus generalization and the beginning of a test (extinction) session. Presession injection intervals were varied up to 1 h.

During antagonism tests, doses of **7b** (1 and 3 mg/kg), **7c** (3 and 12 mg/kg), or saline were injected just prior to the administration of the training dose of DOM (1.0 mg/kg). A subsequent 15-min time interval elapsed before the animals were exposed to the 2.5-min nonreinforced test session. Drugs were administered by intraperitoneal injection.

Acknowledgment. This work was supported in part by a grant from the A. D. Williams fund.

Registry No. 1, 61-50-7; 3, 6711-46-2; 4, 27692-91-7; 6 (free base), 87482-07-3; 6 oxalate, 87482-08-4; 7a (free base), 87482-09-5; 7a oxalate, 87482-10-8; 7b (free base), 87482-11-9; 7b oxalate, 87482-12-0; 7c (free base), 87482-13-1; 7c oxalate, 87482-14-2; 7d (free base), 87482-15-3; 7d oxalate, 87482-16-4; 7e (free base), 87482-17-5; 7e oxalate, 87482-18-6; 7f (free base), 87482-19-7; 7f oxalate, 87482-20-0; 7g (free base), 87482-21-1; 7g oxalate, 87482-22-2; 8 (free base), 87482-23-3; 8 oxalate, 87482-24-4; 9 (free base), 87482-25-5; 9 oxalate, 87482-26-6; 10, 1019-45-0; 2-(dimethylamino)ethyl chloride hydrochloride, 4584-46-7; indoline, 496-15-1; 5-methoxyindole, 1006-94-6; 2-(dimethylamino)ethyl chloride, 107-99-3; benzimidazole, 51-17-2; 4-methylindole, 16096-32-5; oxalyl chloride, 79-37-8; 4,*N*,*N*-trimethyl-α,β-dioxo-1*H*-indole-3-ethanamine, 87482-28-8; 4,*N*,*N*-trimethyltryptamine, 28289-23-8; 4,*N*,*N*-trimethyltryptamine hydrogen oxalate, 87482-27-7; serotonin, 50-67-9.

(16) Young, R.; Glennon, R. A.; Rosecrans, J. A. *Commun. Psychopharmacol.* **1981**, *4*, 501.
(17) Finney, D. J. "Probit Analysis"; Cambridge University Press: London, 1952.

8-Hydroxy-2-(alkylamino)tetralins and Related Compounds as Central 5-Hydroxytryptamine Receptor Agonists

Lars-Erik Arvidsson,*[†] Uli Hacksell,[†] Anette M. Johansson,[†] J. Lars G. Nilsson,[†] Per Lindberg,[‡] Domingo Sanchez,[‡] Håkan Wikström,[‡] Kjell Svensson,[§] Stephan Hjorth,[§] and Arvid Carlsson[§]

Department of Organic Pharmaceutical Chemistry, Biomedical Center, University of Uppsala, S-751 23 Uppsala, Organic Chemistry Unit, Department of Pharmacology, University of Gothenburg, and Department of Pharmacology, University of Gothenburg, S-400 33 Göteborg, Sweden. *Received March 24, 1983*

A series of 2-(alkylamino)tetralins related to 8-hydroxy-2-(di-*n*-propylamino)tetralin (**21**) were prepared and tested as dopamine (DA) and 5-hydroxytryptamine (5-HT) receptor agonists. Several of the compounds were potent 5-HT agonists devoid of DA-mimetic effects. *N*-Ethyl or N-propyl substitution of 8-hydroxy-2-aminotetralin gave the most potent agonists. It was shown that the most potent compound, (+)-**21**, has the 2*R* configuration. 5,8-Dimethoxy-2-(di-*n*-propylamino)tetralin (**31**) was found to be a weak DA agonist devoid of 5-HT activity. The corresponding indan derivative, 4,7-dimethoxy-2-(di-*n*-propylamino)indan (**39**), has been reported to be active on both DA and 5-HT receptors. The 5-HT-stimulating properties of compounds **21** and **39** as compared to the incapability of compound **31** to activate the 5-HT receptor is tentatively explained by the assumed mode of binding of the compounds to the 5-HT receptor.

The tricyclic antidepressants have become the most widely used drugs in the treatment of endogenous depressions. The therapeutic effects have previously been attributed to their capability of inhibiting the uptake of the monoamines noradrenaline (NA)[1] and 5-hydroxytryptamine (5-HT).[2] This mechanism of action is presently challenged,[3] but it is likely that 5-HT mechanisms are involved. A disadvantage with the use of the tricyclic antidepressants is that there is a latency period of 1–3 weeks before the appearance of clinical improvement. In order to surmount this problem, drugs that act by a different mechanism than the tricyclic antidepressants would be needed. One of the possibilities would be the use of selective 5-HT agonists.[4]

Presently known 5-HT agonists, like *d*-LSD, 5-methoxy-*N*,*N*-dimethyltryptamine, and 1-(2,5-dimethoxy-4-methylphenyl)-2-propylamine (**37**, DOM), have the dis-

[†] University of Uppsala.
[‡] University of Gothenburg, Organic Chemistry Unit, Department of Pharmacology.
[§] University of Gothenburg, Department of Pharmacology.

(1) Glowinski, J.; Axelrod, J. *Nature (London)* **1964**, *204*, 1318. Iversen, L. L. *J. Pharm. Pharmacol.* **1965**, *17*, 62. Carlsson, A.; Fuxe, K.; Hamberger, B.; Lindqvist, M. *Acta Physiol. Scand.* **1966**, *67*, 481.
(2) Ross, S. B.; Renyi, A. L. *Eur. J. Phamacol.* **1969**, *7*, 270. Carlsson, A.; Corrodi, H.; Fuxe, K.; Hökfelt, T. *Ibid.* **1969**, *5*, 357. Carlsson, A.; Jonason, J.; Lindqvist, M. *J. Pharm. Pharmacol.* **1969**, *21*, 769.
(3) Ögren, S. O.; Fuxe, K.; Agnati, L. F.; Gustafsson, J. Å.; Jonsson, G.; Holm, A. C. *J. Neural Transm.* **1979**, *46*, 85; Savage, D. D.; Mendels, J.; Frazer, A. *J. Pharmacol. Exp. Ther.* **1980**, *212*, 259. Peroutka, S. J.; Synder, S. H. *Ibid.* **1980**, *215*, 582. Aghajanian, G. K. In "Neuroreceptors: Basic and Clinical Aspects"; Usdin, E.; Bunney, W. E.; Davis, J. M., Eds.; Wiley: Chichester, 1981; p 27.
(4) Green, A. R.; Grahame-Smith, D. G. *Nature (London)* **1976**, *260*, 487.

0022-2623/84/1827-0045$01.50/0