pigs (200–400 g, both sexes) were suspended in 10-mL organ baths containing oxygenated (95% O_2, 5% CO_2) warm (37 °C) Krebs solution. For the bioassays with the dog carotid artery, EDTA (59.5 μM) and indomethacin (2.8 μM) were added to the Krebs' solution, and the preparation was contracted with noradrenaline (4.4×10^{-6} M) in order to enable the measurement of the relaxant effect of substance P.[28]

The tissues were stretched with 0.5 g (vein and ileum strips) and with 2 g (carotid artery strips), and the changes of tension were recorded isometrically with Grass (FT .03C) force transducers connected to a Grass polygraph (Model 7D). Concentration–response curves to SP and its analogues were measured by consecutive additions of drug solutions (0.05–0.1 ml) to the bath fluid after an initial equilibration period of 60 min for the ileum and the vein and 120 min for the carotid artery. The arteries were contracted (1.0-g tension) with noradrenaline and cumulative dose–response curves were measured for SP and its analogues.

For more details concerning some of the pharmacological preparations, the reader is referred to recent publications.[26,28]

Acknowledgment. We thank Drs. Nabil Seidah and Claude Lazure (Institut de Recherche Clinique de Montréal) for some of the amino acid analyses and Jean-Marc Lalonde and Martin Boussougou for the technical assistance in this project. We acknowledge the secretarial work of Cécile Pépin. This work was supported by research grants from the Medical Research Council of Canada, the Quebec Heart Foundation, and the Kidney Foundation of Canada.

(27) H. P. Rang, *Br. J. Pharmacol.*, **22**, 356 (1964).
(28) R. Couture, P. Gaudreau, S. St-Pierre, and D. Regoli, *Can. J. Physiol. Pharmacol.*, **58**, 1234 (1980).
(29) J. Bergmann, M. Bienert, H. Niedrich, B. Mehlis, and P. Oehme, *Experientia*, **30**, 401 (1974).
(30) R. W. Bury and M. L. Mashford, *J. Med. Chem.*, **19**, 854 (1976).
(31) R. E. Chipkin, J. M. Stewart, V. E. Sweeney, K. Harris, and R. Williams, *Arch. Int. Pharmacodyn.*, **240**, 193 (1979).
(32) J. Leban, G. Rackur, I. Yamaguchi, K. Folkers, V. Björkroth, S. Rosell, N. Yanaihara, and C. Yanaihara, *Acta Chem. Scand., Ser. B*, **B33**, 664 (1979).
(33) J. W. Growcott and N. N. Petter, *J. Pharm. Pharmacol.*, **32**, 376 (1980).

2,3-Dihydro and Carbocyclic Analogues of Tryptamines: Interaction with Serotonin Receptors

Richard A. Glennon,* John M. Jacyno, and John J. Salley, Jr.

Department of Pharmaceutical Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298. *Received July 20, 1981*

Several dihydro and carbocyclic analogues of tryptamine were evaluated in order to determine the role of the heterocyclic portion of the indole nucleus on the interaction of indolealkylamines with the serotonin receptors of the rat fundus. Reduction of the C_2–C_3 double bond or replacement of the indole nitrogen with an sp^3-hybridized carbon atom results in a 50% decrease in receptor affinity. Complete removal of the five-membered ring of *N,N*-dimethyltryptamine reduces affinity by an order of magnitude. It appears that an intact indole nucleus, though not entirely necessary, results in an optimal receptor interaction for the indolealkylamines examined.

Recent reports from this laboratory have outlined our findings with respect to the affinity of indolealkylamines for the serotonin (5-hydroxytryptamine, 5-HT) receptors of the rat fundus preparation.[1,2] Not only have structure–activity relationship been formulated,[2] but the interaction has been demonstrated to be a stereoselective event.[3] Phenylalkylamines also interact with these 5-HT receptors, and certain phenyl-substituted derivatives possess an affinity greater than that of some indolealkylamines.[1,4] Thus, it appears that the presence of a heterocyclic ring is not an essential feature for these drug–5-HT receptor interactions. The aim of this present study was to examine the influence of molecular modification in the heterocyclic portion of the indole nucleus and thereby determine the extent to which this portion of the ring system contributes to indolealkylamine–5-HT receptor interactions.

Chemistry. 2,3-Dihydro-*N',N'*-dimethyltryptamine (**3a**) was synthesized by reduction of 3-indole-*N',N'*-dimethylglyoxamide with BH_3·THF, essentially according to the method of Littell and Allen.[5] The 5-methoxy derivative **3b** was prepared by an adaptation of the above method; the 5-methoxy glyoxamide was reduced to the indole analogue with BH_3·THF, and further reduction to the indoline was effected in situ by the addition of CF_3COOH, after the method of Maryanoff and McComsey.[6] The tetrahydroquinoline derivatives **9** and **10** were prepared by acyloxyborohydride reduction of the corresponding aminoquinoline by the method of Gribble and Heald.[7]

Results and Discussion

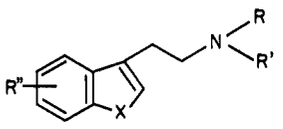
The apparent 5-HT receptor affinity of the compounds in Table I are reported as pA_2 values. Using the equation $pA_x = -\log K_2 - \log (x - 1)$, where x is the dose ratio, pA_2 is equivalent to $-\log K_2$.[20] Thus, when $\log (x - 1)$ is plotted against pA_x, a straight line results with a slope of $-n$. This line intersects the pA_x axis at a point corresponding to pA_2, and the interaction is assumed to be competitive when $-n$ is approximately 1.[20]

Based on the slopes of their Schild plots, compounds **1a–d**, **2a**, **3a,b**, **4a–d**, and **5–8** interact with the 5-HT receptors of the rat fundus in a competitive manner. Comparing the affinity (pA_2) of *N',N'*-dimethyltryptamine (DMT, **1c**) or its 5-methoxy derivative (5-OMe-DMT, **1d**) with that of the corresponding 2,3-dihydro derivatives **3a** and **3b**, respectively, reveals that reduction of the "pyrrolic" or 2,3 bond halves affinity. We have previously reported that replacement of the indole nitrogen atom of DMT with an sp^3-hybridized carbon atom (i.e., comparing **1c** with **2a**) results in a 2-fold decrease in affinity;[2] the

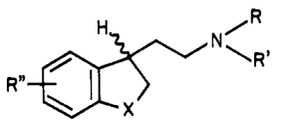
(1) Glennon, R. A.; Liebowitz, S. M.; Mack, E. C. *J. Med. Chem.* **1978**, *21*, 822.
(2) Glennon, R. A.; Gessner, P. K. *J. Med. Chem.* **1979**, *22*, 428.
(3) Glennon, R. A. *Life Sci.* **1979**, *24*, 1487.
(4) Glennon, R. A.; Liebowitz, S. M.; Anderson, G. M. *J. Med. Chem.* **1980**, *23*, 294.
(5) Littell, R.; Allen, G. R. *J. Org. Chem.* **1973**, *38*, 1504.
(6) Maryanoff, B. E.; McComsey, D. F. *J. Org. Chem.* **1978**, *43*, 2733.
(7) Gribble, G. W.; Heald, P. W. *Synthesis* **1975**, 650.

0022-2623/82/1825-0068$01.25/0

Table I. Serotonin Receptor Affinities of Tryptamine and Related Analogues



1, X = NH
2, X = CH_2



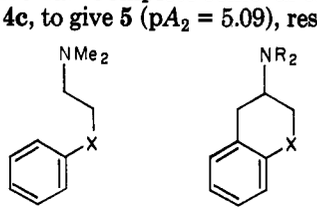
3, X = NH
4, X = CH_2

compd	R	R′	R″	pA_2 [a]	slope [b]	N [c]
1a	H	H	H	6.27 [d]		
1b	H	Me	H	5.97 (±0.08)	0.92 (±0.06)	3
1c	Me	Me	H	6.00 [d]		
1d	Me	Me	5-OMe	7.08 [d]		
2a	Me	Me	H	5.68 [d]		
(±)-3a	Me	Me	H	5.68 (±0.09)	0.94 (±0.14)	5
(±)-3b	Me	Me	5-OMe	6.74 (±0.15)	0.95 (±0.14)	3
(±)-4a	H	H	H	5.60 (±0.19)	1.15 (±0.20)	3
(±)-4b	H	Me	H	5.37 (±0.23)	0.82 (±0.22)	7
(±)-4c	Me	Me	H	5.34 (±0.18)	1.11 (±0.27)	4
(+)-4d	H	Me	H	5.66 (±0.46)	1.05 (±0.11)	11
(−)-4e	H	Me	H	e	0.68 (±0.20)	7
5				5.09 (±0.21)	1.03 (±0.28)	3
6				5.32 (±0.16)	0.97 (±0.25)	5
7				6.02 (±0.18)	1.31 (±0.63)	5
8				5.61 (±0.44)	1.02 (±0.27)	7
9				e	0.55 (±0.20)	4
10				e	0.53; 0.58	2

[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 dose–response curves to 5-HT. [d] pA_2 values for 1a, 1c, 1d, and 2a have been previously reported[2] and are reproduced here for comparative purposes. [e] Unable to determine valid pA_2 value due to slope of Schild plot.

2-fold difference in affinity between 2,3-H_2-DMT (**3a**) and the indane derivative **4c** parallels this earlier finding. Replacement of the indole nitrogen atom by carbon and reduction of the 2,3 bond both decrease pA_2 by a factor of approximately 0.3 log unit. It may be anticipated that making both changes in the same molecule at the same time would decrease pA_2 by about 0.6 log unit; comparing the affinities of **1a–c** with those of **4a–c**, respectively, shows this to be the case. Although we have, so far, been unable to resolve **3a** and **3b**, compound **4b** was resolved to yield the dextro and levo isomers **4d** and **4e**, respectively; **4d** possesses twice the affinity of its racemate while **4e** apparently interacts with the 5-HT receptors in a manner which is not competitive.

Demethylation of the terminal amine group, in both the indolealkylamine series as well as the phenylalkylamine series, results in a doubling of affinity;[2,4] this same effect is observed for the demethylation of **1b** to **1a** and either **4b** or **4c** to give **4a**. Complete removal of the five-membered ring of **4c**, to give **5** (pA_2 = 5.09), results in a further



5, X = CH_2
6, X = C=O
7, X = NH

8, X = CH_2; R = H
9, X = NH; R = H
10, X = NH; R = Me

decrease in affinity. Incorporation of a keto group at the benzylic position of **5**, to yield **6**, enhances affinity via either an electronic or conformation-limiting effect, whereas incorporation of a nitrogen atom into the side chain, to give **7**, enhances affinity approximately 10-fold. The conformationally restricted analogue of the primary amine derivative of **5** (i.e., 2-aminotetralin, **8**) possesses a pA_2 of 5.61, while incorporation of a nitrogen atom into the ring of **8** (i.e., **9**), as well as N,N-dimethylation of **9** (i.e., **10**), results in compounds which do not interact with the 5-HT receptors in a competitive manner.

The results reported here support our previous finding[4] that an intact heterocyclic ring is not an essential feature in order for aralkylamines to interact with the 5-HT receptors of the fundus preparation. Nevertheless, an optimal interaction is associated with the presence of the heterocyclic portion of the indole nucleus. Replacement of the indole nitrogen with a carbon atom reduces affinity, as does reduction of the 2,3 bond. Reduction of this bond not only alters the electronic nature of the system but also creates an asymmetric center. Resolution of one of the indolines would be expected to provide useful information. Nevertheless, the affinity of the dextro isomer of **4b** (i.e., **4d**) is twice that of its racemate and is essentially equivalent to the affinity of the indene analogue **2a**.

Removal of the five-membered ring of **4c** (i.e., **5**) reduces affinity. It has been previously demonstrated that 2-aminotetralin (**8**) interacts with 5-HT receptors.[8,9] In the rat fundus preparation, the affinity of **8** is identical with that of the indane **4a** but is several fold greater than that of the ring-open analogue **5**. This may be explained on the basis of the conformational restraint offered by the saturated six-membered ring of **8** and, to a lesser extent, by the five-membered ring of **4a**, as opposed to the more freely rotating side chain of **5** (which might require a higher-energy conformation for receptor interaction). Introduction of a carbonyl group, as in **6**, increases affinity in a manner which parallels the increase observed upon introduction of a double bond to the five-membered rings of **3a**, **3b**, and **4c** (to give **1c**, **1d**, and **2a**, respectively). Affinity enhancement may be more a result of the steric (i.e., effect on conformation) rather than electronic nature of the carbonyl group. On the other hand, replacement of the benzylic carbon of **5** with a nitrogen atom, whose effect should be more electronic than steric, results in a compound (i.e., **7**) with ten times the affinity of **5**. However, the high Schild plot slope obtained for **7** suggests that the nature of the receptor interaction may be different than that for **5** or **6**. Furthermore, **9** and **10**, which may be looked upon as rigid analogues of **7** or as nitrogen analogues of **8**, do not interact with the 5-HT receptors in a competitive manner.

In summary, the intact indole nucleus results in an optimal indolealkylamine–5-HT receptor interaction; however, agents which lack the intact heteroaromatic moiety, such as certain phenylalkylamine derivatives[4] and, for example, **3b**, still possess a considerable affinity for the 5-HT receptors of the fundus preparation. Finally, although an electronic role for the presence of the "2,3 double bond" can not be ruled out, the biological consequences of its presence or absence can be accounted for on stereochemical grounds.

Experimental Section

Proton magnetic resonance (NMR) spectra were recorded on a Perkin-Elmer R-24 spectrometer using Me_4Si as an internal standard. Infrared spectra were obtained on a Beckmann Acculab 8 spectrophotometer, and mass spectra were obtained on a Finnigan 4000 Series GC/MS data system. Melting points were determined on a Thomas-Hoover melting point apparatus (unless

(8) Gaddum, J. H. *Ann. N.Y. Acad. Sci.* **1957**, *66*, 643.
(9) Cheng, H. C.; Long, J. P.; Nichols, D. E.; Barfknecht, C. F.; Rusterholz, D. B. *Arch. Int. Pharmacodyn.* **1974**, *208*, 264.

otherwise noted) and are uncorrected. Optical rotations were determined using a Perkin-Elmer 141 polarimeter. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA, and determined values are within 0.4% of theoretical values.

N'-Methyltryptamine Hydrogen Oxalate (1b). N'-Methyltryptamine was prepared via ethyl N-[2-(3'-indolyl)-ethyl]carbamate according to the general method of Horner and Skinner.[17] The crude carbamate intermediate was reduced without purification to yield an oil [Kugelrohr, 60–80 °C (0.25 mm)]. A portion of this free base was converted to the oxalate salt in ethanolic solution; recrystallization from MeOH yielded **1b** as colorless, felted needles, mp 179–180 °C (lit.[18] mp 178–180 °C). Because **1b** has not been previously analyzed, and in order to determine stoichiometry, the product was submitted for microanalysis. Anal. ($C_{11}H_{14}N_2 \cdot C_2H_2O_4$) C, H, N.

(±)-2,3-Dihydro-N',N'-dimethyltryptamine (3a). Borane in THF (1 M, 90 mL) was added dropwise to a stirred soolution of 3-indole-N',N'-dimethylglyoxamide[10] (4.3 g, 20 mmol) in THF (350 mL) at room temperature. When the addition was complete, the mixture was stirred at room temperature for 45 min, then warmed to gentle reflux; heating at reflux was continued for 2.5 h. The reaction mixture was then chilled on an ice bath and hydrolyzed by the dropwise addition of, first, excess wet ether, followed by water (20 mL). Concentrated hydrochloric acid (ca. 10 drops) was added, and stirring was continued at room temperature for another 50 h. The mixture was made strongly basic (pH 14) by the addition of 20% aqueous NaOH and was diluted by the addition of ether (100 mL). The aqueous phase was extracted with ether (100 mL) and the combined ethereal fractions were washed with brine and dried (K_2CO_3). Evaporation of the solvent in vacuo yielded an oil (4.6 g).[11] The oil was suspended in 6 M HCl (25 mL), and the solution was gently heated until gas evolution commenced. When frothing had subsided, the mixture was heated at reflux for 1.5 h. After chilling on an ice bath and basification to pH 14 by the addition of solid NaOH, the resulting mixture was extracted with ether (3 × 10 mL), and the combined ether portions were washed with brine (10 mL), dried (K_2CO_3), and evaporated under reduced pressure to give 3.4 g (91%) of an oil. A portion of the crude product was distilled [Kugelrohr, 50–60 °C (0.1 mm)] to afford **3a** as a colorless oil: IR (film) 1605 (s), 1490 (s), 1460 (s), 1250 (s), 1040 (s), 750 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.25 (s, 6 H), 1.5–4.0 (m, 8 H), 6.5–7.3 (m, 4 H); mass spectrum, m/e 190 (M^+). The oxalate salt was prepared in methanolic solution, giving colorless crystals, mp 145–147 °C after recrystallization from MeOH. Anal. ($C_{12}H_{18}N_2 \cdot 2C_2O_4H_2 \cdot 1MeOH$) C, H, N.

(±)-5-Methoxy-2,3-dihydro-N',N'-dimethyltryptamine (3b). 5-Methoxy-3-indole-N',N'-dimethylglyoxamide[12] (1.23 g, 5 mmol) was suspended in dry THF (250 mL); the stirred suspension was gently warmed. When most of the glyoxamide had dissolved, 1 M BH_3·THF (25 mL) was added dropwise. The reaction mixture was heated at reflux for 2.25 h and chilled on an ice bath, and trifluoroacetic acid (15 mL) was added dropwise with stirring over a 45-min period. After an additional 1 h of stirring at 0 °C, the reaction was worked up by the dropwise addition of water (10 mL), followed by evaporation of solvent under reduced pressure, to give a semisolid residue. The residue and 6 M HCl (20 mL) were heated at reflux until solution was effected (no effervescence was observed). The solution was chilled (ice bath) and strongly basified to pH 14 by the addition of solid NaOH. Ether (100 mL) was added and the phases were separated; the aqueous phase was extracted twice with ether (50 mL). The combined ethereal fractions were dried (K_2CO_3) and evaporated under reduced pressure to give an oil (1.3 g). A portion of the product was distilled [Kugelrohr, 60–100 °C (0.1 mm)] to yield a fluorescent oil which darkened rapidly upon exposure to air/light: IR (film) 3360 (s), 1500 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.5–4.0 (complex, 8 H), 2.2 (s, 6 H), 3.7 (s, 3 H), 6.65 (apparent d, J = 10 Hz, 3 H). The free base was converted to a colorless, crystalline oxalate salt, mp 178–179 °C, after recrystallization from MeOH. Anal. ($C_{13}H_{20}N_2O \cdot 2C_2O_4H_2$) C, H, N.

Resolution of 1-[(N-Methylamino)ethyl]indane (4b). Treatment of the free base of racemic **4b**[13] with d-(+)-tartaric acid in methanol afforded a salt (**4d**), which, after six recrystallizations from MeOH, had a constant melting point (mp 143–145 °C; Fisher-Johns melting point apparatus) and optical rotation, $[\alpha]^{29}_D$ +6.9° (water). Treatment of the residue, obtained after evaporation and neutralization of the combined mother liquors from the above resolution, with l-(−)-tartaric acid yielded a crystalline salt from MeOH/Et_2O. Two additional recrystallizations from 2-propanol gave a material, **4e**, with constant melting point (mp 143–145 °C; Fisher-Johns) and optical rotation $[\alpha]^{29}_D$ −10.9° (water). Microanalysis of this tartrate reveals a 1:1 stoichiometry. Anal. ($C_{12}H_{17}N \cdot C_4H_6O_6$) C, H, N.

(±)-3-Amino-1,2,3,4-tetrahydroquinoline (9). Sodium cyanoborohydride (1.83 g, 29 mmol) was added portionwise, over a 5-min period, to a stirred solution of 3-aminoquinoline (1.0 g, 6.9 mmol) in glacial HOAc (20 mL) at 0 °C. The brown reaction mixture was stirred at room temperature for 2 h, at 50–55 °C (oil bath temperature) for 1.5 h, and at room temperature overnight and was then poured into water (50 mL). The solution was basified to pH 11 by the addition of 50% aqueous NaOH and was extracted twice with CH_2Cl_2 (75 mL). The combined CH_2Cl_2 portion was washed with water (2 × 50 mL), dried (Na_2SO_4/$MgSO_4$), and evaporated under reduced pressure to give a brown oil. Kugelrohr distillation [53–56 °C (0.2 mm)] gave 0.67 g (66%) of a colorless oil; the hydrochloride salt was prepared and recrystallized from an EtOH/Et_2O mixture to give **9**·2HCl as white plates, mp 258–260 °C (lit.[14] mp 250 °C).

(±)-3-(Dimethylamino)-1,2,3,4-tetrahydroquinoline (10). Compound **10** was prepared from **10a**, using the same procedure employed for the synthesis of **9**, in 44% yield after distillation, bp 90–95 °C (0.15 mm) [lit.[15] bp 108–110 °C (1.5 mm)]. A hydrochloride salt was prepared but decomposed on exposure to air; the oxalate salt (mp 113–115 °C), however, was stable.

3-(Dimethylamino)quinoline (10a). A mixture of 3-aminoquinoline (2.0 g, 14 mmol), 90% formic acid (3.58 g, 70 mmol), and 37% formaldehyde (3.41 g, 42 mmol) was heated on an oil bath (90 °C) for 4 h. The dark mixture was poured into 10% HCl (15 mL), neutralized with 20% aqueous NaOH, and was extracted twice with $CHCl_3$ (75 mL). The combined $CHCl_3$ fractions were dried (Na_2SO_4/$MgSO_4$) and evaporated under reduced pressure to afford a crude yellow product. Distillation, bp 95–100 °C (0.04 mm), gave 1.3 g (54%) of a clear yellow oil which crystallized upon standng, mp 55–57 °C (lit.[16] mp 61 °C).

Receptor Affinity Assay. Male Sprague–Dawley rats weighing 200–300 g (Flow Laboratories, Dublin, VA) were used. The rat stomach fundus preparation employed was essentially that of Vane,[19] with the previously described modifications.[1] Dose–response curves were obtained, after a 1-h equilibration period, for 5-HT oxalate (9–11 increasing concentrations) both in the absence and presence of four to five increasing concentrations of test compound. We have previously described the methodology in greater detail.[1,4] Apparent affinities were calculated as pA_2 values by the method of Arunlakshana and Schild.[20] Linear-regression analysis gave not only pA_2 values but also the slope of the Schild plots.

Acknowledgment. This work was supported in part by U.S. Public Health Service Grant DA-01642. We thank Ms. D. Leming Doot for obtaining the pA_2 values, and we are indebted to Dr. J. Data for his generous gifts of compounds **4a–c**.

(10) Speeter, M. E. U.S. Patent 2825734, 1958; *Chem. Abstr.* **1958**, *52*, 12923.
(11) The spectroscopic and chromatographic properties of this material indicated that the foregoing hydrolysis conditions had been too mild to effect cleavage of the amine–borane adduct.
(12) Julia, M.; Manoury, P. *Bull. Soc. Chim. Fr.* **1965**, 1411.
(13) Data, J. B.; Taylor, M. L.; Forcione, M. *J. Pharm. Sci.* **1974**, *63*, 848.
(14) Chiavarelli, S.; Marini-Bettol, G. B. *Gazz. Chim. Ital.* **1952**, *82*, 86; *Chem. Abstr.* **1953**, *47*, 6944.
(15) Kusuda, F.; Matsuo, Y.; Takewaki, N. Japanese Patent 13741, 1966; *Chem. Abstr.* **1966**, *65*, 20107.
(16) Berlot, J.; Renault, J. *Bull. Soc. Chim. Fr.* **1973**, 3175.
(17) Horner, J. K.; Skinner, W. A. *Can. J. Chem.* **1966**, *44*, 315.
(18) Stauffer, R. *Helv. Chim. Acta* **1966**, *49*, 1199.
(19) Vane, J. R. *Br. J. Pharmacol.* **1957**, *12*, 344.
(20) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.