by occluding the carotid arteries with 7-mm Mayfield aneurysm clips for 5 min. Interruption of the carotid blood flow was confirmed by observation of the blanching of radial arteries of the retina using an opthalmoscope. Following removal of the clips, the incision was closed and the animal was allowed to recover. In sham animals, the carotids were exposed, and each animal was maintained under anesthesia for 5 min. After complete recovery from surgery, animals were returned to home cages. Seven days after surgery, the gerbils were killed and their brains were prepared for histological evaluation. Left and right hemispheres were assessed separately for hippocampal damage by three independent investigators who were blind to the treatments. Damage was quantified by using a scoring system which has previously been reported.[14] Damage scores for each group were averaged to obtain the reported values. Comparisons were made by using the Student's t test with the significance level set at $p < 0.05$.

Binding of Indolylalkylamines at 5-HT$_2$ Serotonin Receptors: Examination of a Hydrophobic Binding Region

Richard A. Glennon,*,† Chandra Chaurasia,† and Milt Titeler‡

Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298-0581, and Department of Pharmacology, Albany Medical College, Albany, New York 12208.
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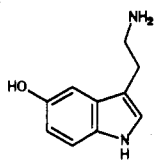
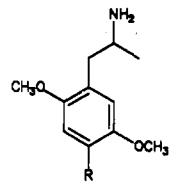
Taking advantage of a proposed hydrophobic region on 5-HT$_2$ receptors previously identified by radioligand-binding studies utilizing various phenylisopropylamine derivatives, we prepared and evaluated several N_1 - and/or C_7-alkyl-substituted derivatives of α-methyltryptamine in order to improve its affinity and selectivity. It was determined that substitution of an *n*-propyl or amyl group has similar effect on affinity regardless of location (i.e., N_1 or C_7). The low affinity of several N_1-alkylpyrroleethylamines suggests that the benzene portion of the α-methyltryptamines is necessary for significant affinity. Whereas tryptamine derivatives generally display little selectivity for the various populations of 5-HT receptors, N_1-*n*-propyl-5-methoxy-α-methyltryptamine (**3h**) binds with significant affinity (K_i = 12 nM) and selectivity at 5-HT$_2$ receptors relative to 5-HT$_{1A}$ (K_i = 7100 nM), 5-HT$_{1B}$ (K_i = 5000 nM), 5-HT$_{1C}$ (K_i = 120 nM), and 5-HT$_{1D}$ (K_i > 10000 nM) receptors. As a consequence, this is the most 5-HT$_2$-selective indolylalkylamine derivative reported to date.

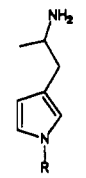
The 5-HT$_2$ population of serotonin (5-hydroxytryptamine; 5-HT) receptors is currently of clinical interest because of its potential role in cardiovascular function and possible involvement in various mental disorders such as schizophrenia, depression, hallucinations, and anxiety (see ref 1 for a review). To date, there are two major classes of 5-HT$_2$ agonists: indolylalkylamines, such as 5-HT (1)



1



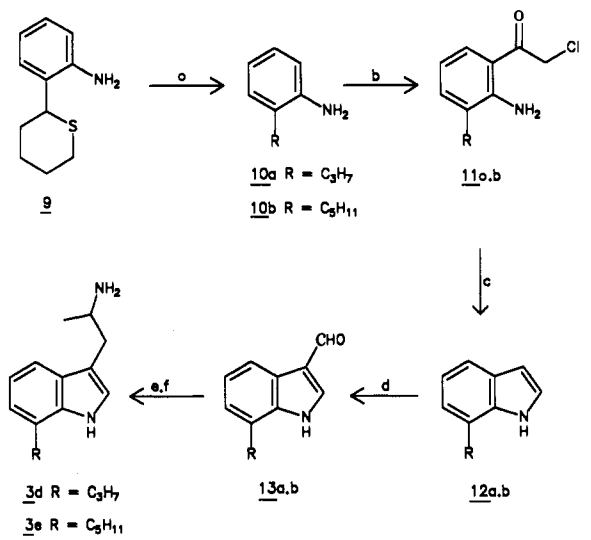
2



4a R = H
4b R = C_3H_7
4c R = C_5H_{11}

itself, and phenylisopropylamines, such as certain 4-substituted derivatives of 1-(2,5-dimethoxyphenyl)-2-aminopropane (2,5-DMA; **2**, R = H) (e.g. **2**, R = methyl, *n*-propyl, and bromo). In general, indolylalkylamines are nonselective agents that bind at multiple populations of 5-HT receptors.[2,3] The phenylisopropylamines, on the other hand, are considerably more selective and bind primarily at 5-HT$_2$ sites (with a significant, though lower, affinity for 5-HT$_{1C}$ sites);[4] however, certain of these agents may only be partial agonists.[5] The selectivity and affinity of the phenylisopropylamines for 5-HT$_2$ sites is related to the nature of the 4-position substituent; specifically, we have found that high affinity is associated with increased lipo-

Scheme I[a]



9 → 10a R = C_3H_7; 10b R = C_5H_{11} → 11a,b → 12a,b → 13a,b → 3d R = C_3H_7; 3e R = C_5H_{11}

[a] (a) Raney Ni; (b) $BCl_3/AlCl_3$, $ClCH_2CN$; (c) $NaBH_4$; (d) $POCl_3$/DMF; (e) $EtNO_2$; (f) $LiAlH_4$.

† Virginia Commonwealth University.
‡ Albany Medical College.

(1) Glennon, R. A. *Neurosci. Biobehav. Rev.* **1990**, *14*, 35.
(2) α-Methyl-5-HT has been claimed by some to be a 5-HT$_2$-selective agent. However, we have recently shown (Ismaiel, A. M.; Titeler, M.; Miller, K. M.; Smith, T. S.; Glennon, R. A. *J. Med. Chem.* **1990**, *33*, 755) that α-methyl-5-HT is not nearly as selective as previously suspected.
(3) Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1.
(4) Titeler, M.; Lyon, R. A.; Glennon, R. A. *Psychopharmacology* **1988**, *94*, 213.
(5) Glennon, R. A. *Neuropsychopharmacology*, in press.

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philicity of the 4-position substituent.[6,7] Furthermore, we have proposed the existence of a hydrophobic region on the receptor to account for the higher affinity of some of these agents.[7]

The purpose of the present investigation was 2-fold: (a) to further define the nature of the hydrophobic region associated with the 5-HT_2 receptors and (b) to take advantage of this site to possibly enhance the affinity, and hence, selectivity, of indolylalkylamine derivatives for 5-HT_2 receptors.

Chemistry

1-Propyl- and 1-amyl-α-methyltryptamine (**3b** and **3c**, respectively) were obtained by subjecting the appropriate N_1-alkylindole to Vilsmeier–Haack formylation, condensation of the resulting 3-carboxaldehyde with nitroethane to yield the corresponding nitropropene **7** and **8**, and subsequent reduction of the nitropropenes with $LiAlH_4$. The 7-propyl and 7-amyl derivatives **3d** and **3e** were prepared in a similar manner. The requisite 7-alkylindoles **12** were prepared by the SASK indole synthesis[8] from the appropriately substituted anilines **10** (Scheme I). Aniline **10b** was prepared from aniline according to the method of Gassman and Gruetzmacher[9] via thiopyran intermediate **9**.

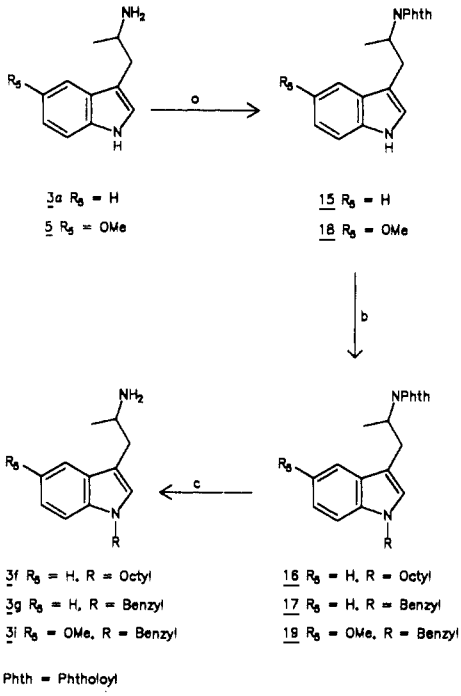
1-Octyl and 1-benzyl derivatives **3f** and **3g** were prepared by alkylation of terminal-amine phthaloyl-protected α-methyltryptamine (**15**) (Scheme II). Formation of the reactive indolyl anion of **15** by treatment with sodium hydride in DMF, followed by alkylation with either 1-bromooctane or benzyl bromide, afforded the phthaloyl-protected derivatives **16** and **17**, which were deprotected by treatment with hydrazine. The 1-benzyl-5-methoxy derivative **3i** was prepared in essentially the same manner from phthaloyl-protected 5-methoxy-α-methyltryptamine (i.e., **18**). This sequence was unsuccessful for the synthesis of **3h**. Consequently, **3h** was prepared from 5-methoxyindole-3-carboxaldehyde via condensation with nitroethane and reduction of the nitropropene with $LiAlH_4$.

Pyrrolealkylamines **4** were prepared from 2,5-dimethoxytetrahydrofuran-3-carboxaldehyde essentially according to the method of Hamdan and Wasley.[10]

Results and Discussion

In order to account for their similar pharmacological properties, there have been a number of suggestions over the years as to how the structures of the phenylisopropylamines might be related to those of the indolylalkylamines. This is also true with regard to how these agents might orient themselves at 5-HT receptors. Although these lines of reasoning have not, for the most part, been specifically applied to the interactions of these agents at 5-HT_2 receptors (i.e., most of these hypotheses were proposed prior to the discovery of multiple populations of 5-HT receptors), they should, nevertheless, be considered in as much as they might lend some insight as to the nature of this interaction. As originally described, the different modes of binding can be divided into two broad categories: (a) that in which the aromatic ring of the phenylisopropylamines mimics the benzene ring of the indolylalkylamines (e.g. ref 11) and (b) that in which it mimics the pyrrole portion of the indolylalkylamines.[12] The former mode of binding is the most parsimonious and accounts for the activity of ergoline derivatives which, from a structural perspective, possess both an indolylalkylamine and a phenylisopropylamine moiety in their structures. The possibility of the latter mode of binding was briefly entertained[12] but was later rejected;[13] to date there is no evidence for this second type of interaction at any of the 5-HT receptors. With particular reference to 5-HT_2 receptors, there is some support for the idea that the interaction of indolylalkylamines and phenylisopropylamines with the receptor is of the aromatic/benzene-ring type;[14] however, the alternative mode of binding has not been specifically ruled out.

Scheme II[a]

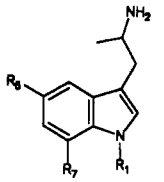


[a] (a) Phthalic anhydride; (b) NaH, RBr; (c) H_2NNH_2.

Because substitution at the 4-position of 2,5-DMA by a propyl (i.e., **2**, R = propyl) or amyl (i.e., **2**, R = amyl) group enhances affinity by 75- and 750-fold (i.e., K_i = 69 and 7 nM, respectively),[6] we reasoned that similar substitution at either the 1- or 7-position of an indolylalkylamine would allow us to determine which of the two possible modes of interaction was most likely. Thus, we prepared and examined the 1-propyl (**3b**) and 1-amyl (**3c**) derivatives of α-methyltryptamine (**3a**) for comparison with the corresponding 7-propyl and 7-amyl derivatives **3d** and **3e**. It might be noted that racemates were employed in each case because there is little difference in the affinities of optical isomers of α-methyltryptamine derivatives for 5-HT_2 receptors;[14] furthermore, the presence of an α-methyl group has little effect on 5-HT_2 affinity (e.g. compare compounds **5** and **6** in Table II). All four al-

(6) Seggel, M. R.; Lyon, R. A.; Titeler, M.; Roth, B. L.; Suba, E. A.; Glennon, R. A. *J. Med. Chem.* **1990**, *33*, 1032.
(7) Glennon, R. A.; Seggel, M. R. In Probing Bioactive Mechanisms; Magee, P. S., Henry, D. R., Block, J. H., Eds.; American Chemical Society Press: Washington, DC, 1989; pp 264–280.
(8) Sugasawa, T.; Asachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* **1979**, *44*, 578–586.
(9) Gassman, P. G.; Greutzmacher, G. D. *J. Am. Chem. Soc.* **1974**, *96*, 5489–5495.
(10) Hamdan, A.; Wasley, J. W. F. *Synth. Commun.* **1985**, *15*, 71–74.
(11) Kang, S.; Green, J. P. *Proc. Nat. Acad. Sci. U.S.* **1970**, *67*, 62.
(12) Nichols, D. E.; Pfister, W. R.; Yim, G. K. W.; Cosgrove, R. J. *Brain Res. Bull.* **1977**, *2*, 169.
(13) Nichols, D. E.; Weintraub, H. J. R.; Pfister, W. R.; Yim, G. K. W. In *QuaSAR Research Monograph 22*; Barnett, G., Trsic, M., Willette, R., Eds.; U.S. Government Printing Office: Washington, DC, 1978; pp 70–83.
(14) Lyon, R. A.; Titeler, M.; Seggel, M. R.; Glennon, R. A. *Eur. J. Pharmacol.* **1988**, *145*, 291.

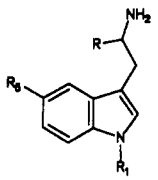
Table I. Binding Affinities at 5-HT$_2$ and 5-HT$_{1A}$ Serotonin Receptors



	R_1	R_5	R_7	K_i,[a] nM 5-HT$_2$	K_i,[a] nM 5-HT$_{1A}$
			Indolylalkylamines		
3a (α-MeT)	H	H	H	>10000[b]	530 (±125)
3b	propyl	H	H	1550 (±80)	715 (±25)
3c	amyl	H	H	100 (±10)	2400 (±700)
3d	H	H	propyl	1040 (±50)	1000 (±150)
3e	H	H	amyl	140 (±15)	6850 (±2000)
3h	propyl	5-OMe	H	635 (±120)	7100 (±1400)
3i	benzyl	5-OMe	H	250 (±15)	>10000
			Pyrrolealkylamines		
4a	H			>10000	>10000
4b	propyl			>10000	>10000
4c	amyl			5200 (±600)	7500 (±2000)

[a] K_i values (±SEM) for binding at [^{3}H]ketanserin-labeled 5-HT$_2$ and [^{3}H]-8-OH-DPAT-labeled 5-HT$_{1A}$ receptors. [b] SEM not determined where K_i > 10000 nM. For purpose of comparison, 2,5-DMA (**2**, R = H) binds at 5-HT$_2$ receptors with K_i = 5200 nM.[4]

Table II. A Comparison of the Binding of Selected Indolylalkylamine Derivatives at 5-HT$_2$ Sites Labeled by either [^{3}H]Ketanserin or [^{3}H]DOB



	R_1	R_5	R	K_i,[a] nM [^{3}H]KET	K_i,[a] nM [^{3}H]DOB	[^{3}H]KET/[^{3}H]DOB[b]
5	H	OMe	Me	345 (±30)	7 (±2)	49
6	H	OMe	H	302	5 (±1)	60
3f	octyl	H	Me	280 (±60)	78 (±15)	3.6
3g	benzyl	H	Me	160 (±35)	30 (±8)	5.3
3h	propyl	OMe	Me	635 (±120)	12 (±2)	53
3i	benzyl	OMe	Me	250 (±15)	15 (±6)	17

[a] Affinities (K_i values) followed by SEM. [b] K_i value at [^{3}H]-ketanserin-labeled receptors divided by the K_i value at [^{3}H]DOB-labeled 5-HT$_2$ receptors.

kyl-substituted derivatives were found to bind with higher affinity (Table I) than α-methyltryptamine (**3a**). Interestingly, the two propyl derivatives were of similar affinity (K_i = 1550 and 1040 nM for **3b** and **3d**, respectively). Similar results were obtained for the two amyl derivatives (K_i = 100 and 140 nM for **3c** and **3e**, respectively) (Table I). Furthermore, as with the difference in affinity between the propyl and amyl analogues of 2,5-DMA, there was an approximate 10-fold difference between the affinity of the propyl and amyl analogues in the indolylalkylamine series. Although these results shed little light on the mode of binding, they do support the contention that there exists a hydrophobic region on the receptors capable of accommodating these alkyl groups. In addition, they suggest that the hydrophobic region is wider than previously suspected in that it accommodates the alkyl groups regardless of whether they are at the indole 1- or 7-position. It should be noted that while this work was in progress, Marzoni et al.[15] reported that substitution of small alkyl groups (e.g. methyl, ethyl, isopropyl) at the N_1-position of several indole derivatives results in enhanced affinity for 5-HT$_2$ receptors.

As mentioned above, there is some support for an aromatic/benzene-ring type of interaction at 5-HT$_2$ receptors.[14] In order to eliminate the possibility of the aromatic/pyrrole-ring type of interaction, we prepared several pyrrolealkylamines (i.e., **4a–4c**) that may be viewed as indolylalkylamines in which the benzene ring is structurally dissected. If the dimethoxy-substituted aromatic ring of the phenylisopropylamines mimics the electron-rich pyrrole ring, analogues **4** would be expected to bind with high affinity. As shown in Table I, the pyrrole analogues display little affinity for 5-HT$_2$ receptors. Furthermore, the N_1-alkyl-substituted derivatives bind with significantly lower affinity than **2**, where R = n-propyl or amyl. These results support the aromatic/benzene-ring type of interaction proposed previously,[14] and further indicate that the benzene-ring portion of the indolylalkylamines contributes to binding. It is interesting to note, however, that the pyrrole analogue with the highest affinity for 5-HT$_2$ receptors is the N_1-amyl-substituted derivative **4c**.

In order to further delineate the hydrophobic region, we examined the octyl and benzyl derivaties of α-methyltryptamine (**3a**). In the 2,5-DMA (i.e., **2**) series, replacement of the 4-propyl group with a benzyl or *n*-octyl substituent results in an additional 10- and 20-fold increase in affinity (i.e., K_i values = 7 and 3 nM, respectively).[6] Because alkyl substitution of the indolylalkylamines produced nearly parallel effects regardless of whether the propyl or amyl substituent was at the N1- or C7-positions, we prepared N_1-octyl- and N_1-benzyl-α-methyltryptamine (**3f** and **3g**). Although both **3f** and **3g** were found to bind at 5-HT$_2$ receptors with appreciable affinity (Table II) and although the benzyl derivative displayed the anticipated 10-fold higher affinity than the corresponding propyl-substituted indolylalkylamine, the enhancement of affinity observed with the octyl derivative was only about 3-fold. Nevertheless, both **3f** and **3g** bind with an affinity greater than that of α-methyltryptamine (**3a**) itself.

Finally, because it is known that a 5-methoxy group enhances the affinity of indolylalkylamines for 5-HT$_2$ receptors, we prepared the 5-methoxy analogues of the N_1-propyl and N_1-benzyl derivatives **3b** and **3g** (i.e., **3h** and

(15) Marzoni, G.; Garbrecht, W. L.; Fludzinski, P. L.; Cohen, M. L. *J. Med. Chem.* **1987**, *30*, 1823.

3i, respectively). Surprisingly, the affinities of these agents were only $^1/_2$ that of their non-methoxy counterparts.

[^{3}H]Ketanserin labels both the high- and low-affinity states of 5-HT$_2$ receptors whereas [^{3}H]DOB labels only the high-affinity state;[16,17] thus, for an anticipated agonist, the use of [^{3}H]DOB as radioligand may give more meaningful information. For this reason, the affinities of **3f–3i** were determined for [^{3}H]DOB-labeled 5-HT$_2$ receptors and compared with the affinities of 5-methoxy-α-methyltryptamine (**5**) and its desmethyl derivative 5-methoxytryptamine (**6**) (Table II). Typically, agonists bind with about a 50-fold higher affinity at [^{3}H]DOB-labeled receptors relative to their affinity at [^{3}H]ketanserin-labeled receptors, whereas antagonists show little difference in affinity regardless of which radioligand is employed. Both 5-methoxy-α-methyltryptamine (**5**; K_i = 7 nM) and 5-methoxytryptamine (**6**; K_i = 5 nM) bind at tritiated DOB-labeled receptors with about a 50-fold higher affinity than they display for [^{3}H]ketanserin-labeled 5-HT$_2$ receptors. A similar result is noted for the 5-methoxy-1-propyl derivative **3h** (K_i = 12 nM), suggesting that it too is most likely an agonist. The results further suggest that the octyl and benzyl deriatives **3f** and **3g** may be antagonists or very weak partial agonists. However, as was the case when [^{3}H]ketanserin was used as radioligand, the affinity of **3h** is only $^1/_2$, and not greater than, that of 5-methoxy-α-methyltryptamine.

With regard to selectivity, indolylalkylamines are relatively nonselective.[2] Therefore, as an initial estimation of selectivity, all of the compounds in Table I were examined at 5-HT$_{1A}$ receptors. It is evident that 5-HT$_{1A}$ receptors do not tolerate the larger alkyl groups at either the N$_1$- or C$_7$-positions. To further characterize its selectivity, the 5-methoxy-1-propyl analogue **3h** was evaluated at other populations of 5-HT$_1$ sites. Although it binds with moderate affinity at 5-HT$_{1C}$ sites (K_i = 120 ± 35 nM, relative to 5-HT$_2$ K_i = 12 nM), it possesses a very low affinity for the other populations of sites: 5-HT$_{1A}$, K_i = 7100 ± 1400 nM (Table I); 5-HT$_{1B}$, K_i = 5000 ± 320 nM; 5-HT$_{1D}$, K_i > 10 000 nM. Thus, with the exception of only a 10-fold selectivity for 5-HT$_2$ vs 5-HT$_{1C}$ sites, compound **3h** possesses considerable selectivity for 5-HT$_2$ versus the other populations of 5-HT$_1$ sites and, as such, is the most 5-HT$_2$-selective indolylalkylamine reported to date.[2] Hartig has found that there is nearly an 80% homology between cloned 5-HT$_2$ and 5-HT$_{1C}$ receptors and has further suggested that these receptors be called 5-HT$_{2\alpha}$ and 5-HT$_{2\beta}$ receptors;[18] thus, it is not surprizing that **3h** binds at these two types of receptors with relatively little selectivity.

Coupled with our previous findings,[14] the results of the present study suggest that, with regard to their interaction at 5-HT$_2$ receptors, the phenylisopropylamines most likely mimic the benzene portion, and not the pyrrole portion, of the indolylalkylamines. Furthermore, substitution of alkyl groups at the N$_1$- and C$_7$-position of α-methyltryptamine enhances its affinity for 5-HT$_2$ receptors. However, incorporation of an N_1-*n*-propyl or N_1-benzyl group, though it leads to increased selectivity, does not seem to enhance the affinity of 5-methoxy-α-methyltryptamine for 5-HT$_2$ receptors. Apart from a different orientation at the receptors, we are currently unable to explain this phenomenon. Nevertheless, the N_1-*n*-propyl analogue of 5-methoxy-α-methyltryptamine (**3h**) binds with high affinity at, and is the first indolylalkylamine derivative to display significant selectivity for, 5-HT$_2$ receptors.

Experimental Section

Synthesis. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR and proton magnetic resonance spectra were obtained on a JEOL FX90Q FT-NMR spectrometer at 89.55 MHz. Chemical shift values are reported as parts per million (δ) relative to tetramethylsilane as an internal standard. Spectral data are consistent with assigned structures. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA, and found values are within 0.4% of the theoretical values. Davison Chemical grade 62 silica gel (60–200 mesh) was used for column chromatography. Flash chromatography was performed on silica gel (Merck, grade 60, 230–400 mesh, 60 Å). Chloroform and methylene chloride were dried by distillation from phosphorous pentoxide. Toluene was dried by distillation and stored over sodium metal; MeOH, DMF, and MeCN were dried by distillation and stored over 3- or 4-Å molecular sieves. THF was distilled from $LiAlH_4$.

(±)-1-(1-*n*-Propylindol-3-yl)-2-aminopropane Hydrochloride (3b). A solution of **7** (4.0 g, 15.9 mmol) in dry THF (80 mL) was added to a cooled (0–5 °C) slurry of $LiAlH_4$ (3.7 g, 100 mmol) in dry THF (70 mL). The reaction mixture was allowed to stir at 15–20 °C for 45 min under N_2 and then was cooled to 0–5 °C on an ice bath. Excess $LiAlH_4$ was decomposed by the dropwise addition of water (3.7 mL), 15% NaOH (3.7 mL), and water (11 mL) in succession. The inorganic solid was removed by filtration and washed with THF (3 × 50 mL), and the combined filtrates were dried ($MgSO_4$). Removal of solvent under reduced pressure gave a pale-yellow oil. Distillation of the oil [short path, bp 125–132 °C (0.2 mmHg)] afforded the target compound as its free base. The free base was dissolved in a minimal amount of anhydrous Et_2O and converted to its hydrochloride salt by the dropwise addition of an ethereal solution of hydrogen chloride gas until precipitation was complete. Recrystallization from acetonitrile afforded 0.3 g (8%) of **3b**: mp 147–150 °C. Anal. ($C_{14}H_{20}N_2$·HCl) C, H, N.

(±)-1-(1-*n*-Amylindol-3-yl)-2-aminopropane Maleate (3c). Nitropropene **8** was reduced with $LiAlH_4$ as described for **3b**. The resultant pale-yellow oil was distilled [short path, bp 150–160 °C (0.06 mmHg)] to afford compound **3c** as its free base. An ethereal solution of this amine was treated with a saturated ethereal solution of maleic acid, and recrystallization of the resulting crude maleate salt from MeCN afforded 3.5 g (30%) of **3c**: mp 151–153 °C. Anal. ($C_{16}H_{24}N_2$·$C_4H_4O_4$) C, H, N.

(±)-1-(7-*n*-Propylindol-3-yl)-2-aminopropane Hydrochloride (3d). Nitropropene **14a** was reduced with $LiAlH_4$ as described for **3b**. The resultant free base (yellow oil) was distilled [short path, bp 165–173 °C (0.5 mmHg)] and treated with hydrogen chloride gas to give the crude salt. Recrystallization from MeCN afforded 0.3 g (8%) of **3d**: mp 179–182 °C. Anal. ($C_{14}H_{20}N_2$·HCl) C, H, N.

(±)-1-(7-*n*-Amylindol-3-yl)-2-aminopropane Hydrochloride (3e). Compound **3e** was prepared by $LiAlH_4$ reduction of **14b** using the same procedure used in the preparation of **3d**. Distillation of the crude oil [short path, bp 185–193 °C (0.5 mmHg)] gave **3e** (free base) which was subsequently converted to its hydrochloride salt. Recrystallization from MeCN afforded 0.2 g (8%) of **3e**: mp 157–159 °C. Anal. ($C_{16}H_{24}N_2$·HCl) C, H, N.

(±)-1-(1-*n*-Octylindol-3-yl)-2-aminopropane Fumarate (3f). A solution of *N*-phthaloyl-1-indol-3-yl-2-aminopropane (**15**; 1.7 g, 5.6 mmol) in freshly distilled DMF (25 mL) was added to a suspension of NaH (0.3 g, 6.8 mmol, 60% oil dispersion, washed with 2 × 1 mL of dry toluene) in DMF (15 mL). The suspension was allowed to stir for 2 h at room temperature under N_2. 1-Bromooctane (3.3 g, 16.9 mmol) was added dropwise and the reaction mixture was heated at 45–52 °C (oil bath) for 22 h. Excess NaH was decomposed by the dropwise addition of MeOH (4 mL) at 0–5 °C. The solvents were removed under reduced pressure to give a yellow residue that was suspended in $CHCl_3$ (50 mL); the precipitated inorganic salt was removed by filtration and washed with $CHCl_3$ (2 × 10 mL), and the combined filtrates were concentrated under reduced pressure to give a yellow oil. The

(16) Titeler, M.; Herrick, K.; Lyon, R. A.; McKenney, J. D.; Glennon, R. A. *Eur. J. Pharmacol.* **1985**, *117*, 145.
(17) Lyon, R. A.; Davis, K. H.; Titeler, M. *Mol. Pharmacol.* **1987**, *31*, 194.
(18) Hartig, P. R. *Trends Pharmacol. Sci.* **1989**, *10*, 64.

crude product was purified by flash chromatograhy (silica gel, 2.5 × 40 cm, toluene) to afford 1.3 g (57%) of **16** as a pale-yellow oil. A mixture of **16** (1.1 g, 2.6 mmol), anhydrous hydrazine (0.8 mL, 26 mmol), and absolute EtOH (55 mL) was heated at reflux for 90 min. The white flocculent precipitate that formed during the reaction was removed by filtration and washed with EtOH (2 × 5 mL), and the combined filtrates were evaporated in vacuo to give a white, solid residue. The solid was suspended in $CHCl_3$ (40 mL) and washed with water (2 × 15 mL). The organic portion was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a pale-yellow oil which was purified by column chromatography (silica gel, 70 g, 1.3 × 40 cm, chloroform/methanol 9:1) to afford 0.4 g (51%) of **3f** as its free base. The amine (0.3 g) was converted to its fumarate salt and recrystallized from absolute EtOH/Et_2O to afford 0.25 g of **3f**: mp 144–147 °C. Anal. ($C_{19}H_{30}N_2 \cdot C_4H_4O_4$) C, H, N.

(±)-1-(1-Benzylindol-3-yl)-2-aminopropane Hydrochloride (3g). Compound **3g** was prepared by alkylation of **15** (0.6 g, 2 mmol) with benzyl bromide (1 g, 5.8 mmol) as described for **3f**. The pale-yellow oil was purified by flash chromatography (silica gel, 2.5 × 20 cm, CH_2Cl_2) to afford 0.7 g (89%) of **17** as a pale-yellow oil. A mixture of **17** (0.7 g, 1.8 mmol), anhydrous hydrazine (0.5 mL, 15.9 mmol), and absolute EtOH (15 mL) was heated at reflux for 90 min and the white, flocculent precipitate that formed was removed by filtration and washed with EtOH (2 × 3 mL); the combined filtrates were evaporated in vacuo to give a solid residue. The solid was suspended in $CHCl_3$ (30 mL) and washed with water (2 × 10 mL), and the organic portion was dried ($MgSO_4$). The solvent was removed under reduced pressure to give a pale-yellow oil which was purified by column chromatography (silica gel, 50 g, 2.5 × 80 cm, chloroform/methanol 9:1) to afford 0.3 g (58%) of **3g** as its free base. The hydrochloride salt was prepared and recrystallized from abolute EtOH to afford 0.13 g of **3g**: mp 188–189 °C (Note: this tryptamine derivative has been reported in the literature;[19] however, no physical or spectral data were provided for purposes of comparison). Anal. ($C_{18}H_{20}N_2 \cdot HCl$) C, H, N.

(±)-1-(5-Methoxy-*n*-propylindol-3-yl)-2-aminopropane Maleate (3h). 5-Methoxyindole (1 g, 6.8 mmol) was alkylated with 1-bromopropane (0.9 g, 7.7 mmol), by using the method described for **3f**, to afford 1.1 g (87%) of 5-methoxy-1-*n*-propylindole as a pale-yellow liquid after purification by flash chromatography (silica gel, 2 × 30 cm, toluene/hexane 7:3). Formylation of this indole was accomplished by using a Vilsmeier–Haack reaction: Freshly distilled phosphorus oxychloride (1.7 mL, 17.5 mmol) was added dropwise under N_2, to stirred, freshly distilled DMF (5 g, 65 mmol) cooled at 0 °C. The solution was allowed to stir for 30 min and a solution of 5-methoxy-1-*n*-propylindole (3 g, 15.9 mmol) in DMF (1.5 mL) was slowly added; during the addition, the temperature of the reaction mixture was kept at 10–15 °C with an ice bath. The reaction mixture was heated at 35–40 °C (oil bath) for 1 h, allowed to cool to room temperature, and then poured onto crushed ice with stirring. The resultant pale-yellow precipitate was suspended in water (100 mL) and the suspension was treated with 2 N NaOH to pH 6. The suspension was rapidly boiled for ca. 2 min, allowed to cool to room temperature, and then placed in a refrigerator (10 °C) for 10 h to yield a pale-yellow solid product. The crude product was collected by filtration, washed with water (50 mL), and purified by flash chromatograhy (silica gel, 2.5 × 30 cm, CH_2Cl_2) to afford 1.7 g (49‰) of the aldehyde as a colorless oil: IR (Nujol) 1662 (C=O), 1254 (COC) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.95 (s, 1 H, not exchangeable with D_2O, CHO) 7.90–6.82 (m, 4 H, ArH), 4.10 (t, J = 8 Hz, 2 H, CH_2), 3.90 (s, 3 H, OCH_3), 2.15–1.70 (m, 2 H, CH_2), 0.96 (t, 3 H, J = 8 Hz, CH_3).

A mixture of this aldehyde (1.8 g, 8.3 mmol), NH_4OAc (1.8 g, 8.3 mmol), and nitroethane (90 mL) was heated at reflux for 30 h. After being allowed to cool to room temperature, the solution was evaporated under reduced pressure, leaving a viscous yellow residue. The crude product was dissolved in $CHCl_3$ (100 mL) and washed successively with brine (2 × 40 mL) and water (2 × 40 mL), and the organic portion was dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow solid product which was purified by flash chromatography (silica gel, 2.5 × 30 cm, CH_2Cl_2) to afford 1.8 g (79%) of the corresponding nitropropene: mp 139–140 °C. A solution of the nitropropene (1.6 g, 5.8 mmol) in dry THF (15 mL) was reduced with $LiAlH_4$ (1.3 g, 34.6 mmol) as described for **3b** and the crude product was converted to its maleate salt. Recrystallization from 2-propanol/Et_2O afforded 0.2 g (10%) of **3h**: mp 157–158 °C. Anal. ($C_{15}H_{22}N_2O \cdot C_4H_4O_4$) C, H, N.

(±)-1-(5-Methoxy-1-benzylindol-3-yl)-2-aminopropane Maleate (3i). Compound **18** (0.6 g, 1.8 mmol) was alkylated with benzyl bromide (0.6 g, 3.5 mmol), as described for **3h**, to afford 0.3 g (35%) of phthaloyl-protected **3i** (i.e., **19**) as a pale-yellow solid after purification by flash chromatography (silica gel, 1.5 × 25 cm, CH_2Cl_2): mp 137–138 °C. Deprotection was accomplished with hydrazine, as with **17**, to give 0.8 g (58%) of **3i** as its free base. Treatment of an ethereal solution of this amine with a saturated ethereal solution of maleic acid afforded a crude maleate salt which was recrystallized from 2-propanol to afford 0.06 g of **3i**: mp 148–149 °C. Anal. ($C_{19}H_{22}N_2O \cdot C_4H_4O_4$) C, H, N.

(±)-1-(1-*n*-Propylpyrrol-3-yl)-2-aminopropane (4b). *n*-Propylamine (0.38 g, 6.3 mmol) and glacial HOAc (20 mL) were added in succession to stirred 2,5-dimethoxytetrahydrofuran-3-carboxaldehyde (1.1 g, 6.3 mmol) at 0–5 °C. The resultant solution was heated at reflux for 2.5 h, during which time the color of the reaction mixture gradually changed from yellow to dark brown. After allowing the reaction mixture to cool to room temperature, the solvents were evaporated under reduced pressure to leave a brown solid. The solid was suspended in water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic portions were dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 0.9 g of a brown oil which was distilled [Kugelrohr, bp 44–48 °C (0.45 mmHg)] to afford 0.5 g (59%) of 1-*n*-propylpyrrole-3-carboxaldehyde as a pale-yellow oil. A mixture of the aldehyde (5 g, 36.5 mmol), NH_4OAc (2.8 g, 36.5 mmol), and nitroethane (300 mL) was heated at reflux for 5 h. After allowing the reaction mixture to cool to room temperature, the solvent was evaporated under reduced pressure to give a yellow oil. The oil was dissolved in CH_2Cl_2 (125 mL) and washed successively with water (2 × 40 mL) and brine (2 × 40 mL), the organic portion was dried ($MgSO_4$), and the solvent was removed in vacuo to give a crude product. Purification using flash chromatography (silica gel, 2.5 × 40 cm, $CHCl_3$) afforded 6.2 g (88%) of 1-(1-*n*-propylpyrrol-3-yl)-2-nitropropene as a yellow oil. A solution of the nitropropene (6.7 g, 34.4 mmol) in dry THF (20 mL) was added dropwise to a slurry of $LiAlH_4$ (3.9 g, 104 mmol) in THF (150 mL) cooled to 0–5 °C. After the addition was complete, the reaction mixture was allowed to stir at room temperature for 1 h. Excess $LiAlH_4$ was decomposed by dropwise addition of water (4 mL), 15% NaOH (4 mL), and water (11 mL) at 0–5 °C. The inorganic solid was removed by filtration and washed with THF (2 × 20 mL), and the combined filtrates were dried ($MgSO_4$). The solvent was removed in vacuo to give a yellow oil. Distillation of the crude product [short path, 80–83 °C (0.65 mmHg)] gave **4b** as its free base. Further purification of the amine was carried out by converting it to its maleate salt and reprecipitating the free amine by treatment with 10% NaOH to pH ~11. The free base was extracted with ether (2 × 40 mL) and the combined organic portions were dried ($MgSO_4$). Removal of the solvent in vacuo gave 1.3 g (25%) of the free amine as a pale-yellow oil. The amine was dissolved in anhydrous Et_2O (5 mL) and the resulting solution was added dropwise to a saturated solution of oxalic acid in anhydrous Et_2O. The oxalate salt was recrystallized from 2-propanol to yield 1 g of **4b**: mp 161–163 °C. Anal. ($C_{10}H_{18}N_2 \cdot C_2H_2O_4$) C, H, N.

(±)-1-(1-*n*-Amylpyrrol-3-yl)-2-aminopropane Oxalate (4c). Compound **4c** was prepared from *n*-amylamine[9] (1.8 g, 21 mmole), via 1-*n*-amylpyrrole-3-carboxaldehyde [57% yield; Kugelrohr distillation, bp 50–54 °C (0.15 mmHg)] and 1-(1-*n*-amylpyrrol-3-yl)-2-nitropropene (97% yield; flash chromatography, silica gel, 2 × 40 cm, $CHCl_3$) in a manner that parallels the synthesis of **4b**. The crude amine was converted to its oxalate salt and the salt was washed with a large amount of Et_2O. The salt was converted to the free base by treatment with 10% NaOH to pH ~10; the amine was extracted with Et_2O (2 × 20 mL), and the combined

(19) Gorkin, V. Z.; Tat'yaneko, L. V.; Suvorov, N. N.; Neklyudov, A. D. *Biokhimiya* **1967**, *32*, 1036–1046.

ethereal portions were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 0.77 g of an oil. Further purification by distillation [Kugelrohr, bp 45–49 °C (0.12 mmHg)] gave 0.5 g (32%) of the desired free base of **4c**. A small portion of the amine (0.13 g) was converted to the oxalate salt which was recrystallized from 2-propanol/Et_2O to afford 0.19 g of **4c**: mp 105–106 °C. Anal. ($C_{12}H_{22}N_2 \cdot C_2H_2O_4$) C, H, N.

1-(1-*n*-Propylindol-3-yl)-2-nitropropene (7). Freshly distilled phosphorus oxychloride (3.2 mL, 33.4 mmol) was added in a dropwise manner under N_2 to stirred, freshly distilled DMF (9.5 g, 129.4 mmol) cooled at 0 °C. The resultant solution was allowed to stir for 30 min and then a solution of 1-*n*-propylindole[20] (4.7 g, 29.8 mmol) in DMF (3.3 g) was slowly added; during the addition, the temperature of the reaction mixture was maintained at 10–15 °C with an ice bath. The reaction mixture was heated at 35–42 °C for 1 h, allowed to cool to room temperature, and then poured onto crushed ice with stirring. The resultant pale-yellow precipitate was suspended in water (400 mL). The suspension was treated with 2 N NaOH to pH 6, rapidly boiled for ca. 2 min, allowed to cool to room temperature, and then placed in a refrigerator (10 °C) for 10 h. The resulting crystalline solid was collected by filtration and washed with water (50 mL) to give a pale-yellow product which was suspended in a saturated aqueous solution of $NaHSO_3$ (5 mL); the suspension was allowed to stir for 6 h and the resulting white bisulfite adduct was collected by filtration, washed with anhydrous Et_2O (2 × 50 mL), and suspended in $CHCl_3$ (30 mL). The suspension was cooled on an ice bath and an aqueous 5% solution of $NaHCO_3$ was added to pH 8. The organic phase was separated and the aqueous portion was extracted with $CHCl_3$ (3 × 30 mL). The combined $CHCl_3$ portions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to afford 4.2 g (75%) of 1-*n*-propylindole-3-carboxaldehyde as white crystals: mp 65–66.5 °C.

A stirred mixture of the aldehyde (3.7 g, 23.3 mmol), NH_4OAc (2.6 g, 33 mmol), and nitroethane (200 mL) was heated at reflux for 14 h. After allowing the solution to cool to room temperature, the resulting orange-yellow precipitate was collected by filtration, washed successively with brine (50 mL) and water (100 mL), and dried under vacuum to give 4.6 g (81%) of **7** as fine yellow crystals after recrystallization from MeOH: mp 95–97 °C. Anal. ($C_{14}H_{16}N_2O_2$) C, H, N.

1-(1-*n*-Amylindol-3-yl)-2-nitropropene (8). A solution of indole (10 g, 85.4 mmol) in freshly distilled DMF (5 mL) was added to a suspension of NaH (5.1 g, 50% oil dispersion, washed with 2 × 3 mL of dry toluene) in DMF (10 mL). After allowing the suspension to stir for 90 min under N_2, 1-bromopentane (14.7 g, 97.3 mmol) was added in a dropwise manner and the reaction mixture was heated at 50–55 °C (oil bath) for 36 h. Excess NaH was decomposed by the dropwise addition of methanol (4 mL) at 0–5 °C. The solvents were removed in vacuo to yield a yellow residue. The residue was suspended in $CHCl_3$ (30 mL), and the precipitated inorganic salt was removed by filtration and washed with $CHCl_3$ (2 × 10 mL). The combined filtrates were concentrated under vacuum to give a crude oily residue. Purification of the crude oil by flash chromatography (silica gel, 40 × 30 cm, toluene/hexane 3:1) afforded 12 g (75%) of 1-amylindole as an oil. Freshly distilled phosphorus oxychloride (6.2 mL, 65.6 mmol) was added dropwise under N_2 to stirred, freshly distilled DMF (18.8 g, 255.2 mmol) cooled to 0 °C. The solution was allowed to stir for 30 min and a solution of 1-amylindole (11 g, 58.7 mmol) in DMF (7 g) was slowly added; during the addition, the temperature of the reaction mixture was maintained at 10–15 °C with an ice bath. The resulting solution was heated at 35–42 °C for 1 h, allowed to cool to room temperature and then poured onto crushed ice with stirring. The resultant pale-yellow precipitate was suspended in water (400 mL) and treated with NaOH (2 N) to pH 6. The suspension was rapidly boiled for ca. 2 min, allowed to cool to room temperature, and then placed in a refrigerator (10 °C) for 10 h, affording an amorphous solid residue. The product was collected by filtration, washed with water (50 mL), and dried under vacuum to give a pale-yellow product which was purified by flash chromatography (30 × 40 cm, toluene/hexanes 2:3) to give 11.4 g (90%) of 1-amylindole-3-carboxaldehyde as an oil: IR (KBr) 1657 (C=O) cm^{-1}. The aldehyde (10.0 g, 46.5 mmol, used without further characterization) was allowed to react with nitroethane (400 mL), as described for the preparation of **7**, to give 9.3 g (74%) of **8** after recrystallization from MeOH: mp 63–64 °C. Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

7-*n*-Propylindole (12a). A solution of 2-*n*-propylaniline (**10a**; 2.0 g, 14.8 mmol) in dry toluene (40 mL) was added dropwise to a stirred solution of BCl_3 (1.0 M in CH_2Cl_2, 35 mL) at 0 °C under N_2. The resultant solution was allowed to stir for 5 min, and then chloroacetonitrile (6 mL, 93.3 mmol) and $AlCl_3$ (3.8 g, 28.6 mmol) were added in succession in small portions. The mixture was heated at reflux for 6 h and cooled on an ice bath, and HCl (2 N, 20 mL) was added. The suspension was warmed on an oil bath at 70–72 °C for 45 min. NaOH (2 N) was added slowly to the resultant hydrolyzed product to pH 6 with stirring; during the addition, the temperature was kept below 15 °C with an ice bath. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic portions were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure to give a viscous, brown residue which was triturated with hexanes (5 × 30 mL); the combined hexanes portion was evaporated under reduced pressure to give a yellow solid, mp 54–59 °C. The crude product was chromatographed on a silica gel column (70 g, 4 × 70 cm, toluene) to yield 1.8 g (59%) of compound **11a**: mp 60–61 °C.

$NaBH_4$ (5.1 g, 134.2 mmol) was slowly added to a stirred solution of **11a** (1.8 g, 8.5 mmol) in dioxane (56 mL) and water (5.6 mL) and the mixture was heated at reflux for 6 h. After being allowed to cool to room temperature, the reaction mixture was decanted, and the solvents were evaporated under reduced pressure to give an oily mass. Water (25 mL) was added to the oil and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give 2.7 g of a crude oil which was purified with a silica gel column (80 g, 4 × 70 cm, toluene). Evaporation of the eluent under reduced pressure yielded 0.8 g of a pale-yellow oil which was further purified by distillation [Kugelrohr, bp 45–52 °C (0.07 mmHg)] to afford 0.7 g (48%) of **12a**. Anal. ($C_{11}H_{13}N$) C, H, N.

7-*n*-Amylindole (12b). 2-Amino-3-*n*-amyl-α-chloroacetophenone (**11b**) was prepared from 2-*n*-amylaniline[9] (**10b**) in a manner analogous to that employed for the synthesis of **11a**. Purification of crude **11b** by column chromatography (silica gel, 70 g, 4 × 70 cm, toluene) afforded 1.8 g (57%) of a crystalline solid: mp 57–59 °C. IR (KBr) 3501 (NH_2), 1658 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (d, 1 H, J = 8.1 Hz, ArH), 7.21 (d, 1 H, J = 8.1 Hz, ArH), 6.63 (t, 1 H, J = 6.5 Hz, ArH), 4.71 (s, 2 H, CH_2), 2.48 (t, J = 6.5 Hz, 2 H, CH_2), 1.85–1.18 (m, 6 H, CH_2), 1.58 (s, 2 H, D_2O exchangeable, NH_2), 0.91 (t, 3 H, J = 6.5 Hz, CH_3).

This chloroacetophenone **11b** (0.8 g, 3.4 mmol) was allowed to react with $NaBH_4$ (2.0 g, 52.8 mmol), by using the same procedure described under the preparation of **12a**, to give an oily residue which was purified by column chromatography (silica gel, 40 g, 2.5 × 60 cm, toluene) to remove the unreacted starting material. The product was further purified by distillation [Kugelrohr, bp 50–60 °C (0.05 mmHg)] to afford 0.4 g (59%) of **12b** as a colorless oil. The spectral properties of indole **12b** were in agreement with those reported for this compound in the literature.[21]

7-*n*-Propylindole-3-carboxaldehyde (13a). Freshly distilled phoshporus oxychloride (0.6 mL, 6.1 mmol) was added in a dropwise manner under N_2 to stirred, freshly distilled DMF (1.7 g, 23.4 mmol) at 0 °C. The resultant solution was allowed to stir for 30 min and a solution of 7-*n*-propylindole (**12a**, 0.9 g, 5.4 mmol) in DMF (0.6 g, 8.2 mmol) was slowly added; during the addition, the temperature of the reaction mixture was kept at 10–15 °C with an ice bath. The mixture was heated at 35–42 °C for 1 h, cooled to room temperature, and then poured onto crushed ice with stirring. The pale-yellow precipitate was suspended in water (200 mL), NaOH (2 N) was added dropwise to pH 6, and the suspension was rapidly boiled for ca. 2 min. The resultant solution was allowed to cool to room temperature and was then placed in

(20) Cardillo, B.; Casnati, G.; Pochini, A.; Ricca, A. *Tetrahedron* **1967**, *23*, 3771–3783.

(21) Ito, Y.; Kobayashi, K.; Seko, N.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73–84.

a refrigerator (10 °C) for 14 h to afford a crystalline product. The crystals were collected by filtration and washed with water (50 mL) to give a pale-yellow product, mp 105–108 °C. The crude aldehyde was suspended in a saturated aqueous solution of $NaHSO_3$ (2 mL) and allowed to stir for 6 h. The resultant white bisulfite adduct was collected by filtration, washed with anhydrous Et_2O (2 × 20 mL), and suspended in $CHCl_3$ (10 mL). The suspension was cooled on an ice bath and an aqueous 5% solution of $NaHCO_3$ was added to pH 8. The organic product was separated and the aqueous portion was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ portions were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give 0.7 g, (71%) of **13a** as white crystals: mp 109–110.5 °C, which was used in the synthesis of **14a** without further characterization.

7-*n*-Amylindole-3-carboxaldehyde (13b). This compound was prepared via Vilsmeier–Haack formylation of **12b** following the method used for the synthesis of compound **13a**. Purification of the crude product by column chromatography (silica gel, 12 g, 1.2 × 25 cm, $CHCl_3/CH_3OH$ 9:1) gave 0.3 g (56%) of **13b**: mp 90–91 °C. Anal. ($C_{14}H_{17}NO$) C, H, N.

2-Nitro-1-(7-*n*-propylindol-3-yl)propene (14a). A stirred mixture of compound **13a** (0.44 g, 2.34 mmol), nitroethane (60 mL), and NH_4OAc (0.31 g, 4.0 mmol) was heated at reflux for 12 h. After allowing the reaction mixture to cool to room temperature, the solvent was removed under reduced pressure to give a viscous oil which was dissolved in CH_2Cl_2 (15 mL) and washed successively with brine (3 × 15 mL) and water (2 × 15 mL). The CH_2Cl_2 portion was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to obtain an orange-red solid (0.54 g, mp 142–145 °C). The crude compound was recrystallized from MeOH to yield 0.45 g (79%) of compound **14a** as orange-red needles: mp 151–153 °C. Anal. ($C_{14}H_{16}N_2O_2$) C, H, N.

2-Nitro-(7-*n*-amylindol-3-yl)propene (14b). A stirred mixture of 7-*n*-amylindole-3-carboxaldehyde (**13b**, 2.5 g, 11.4 mmol) was allowed to react with nitroethane (200 mL), by using the same conditions described for **14a**, to give a viscous residue. A solution of this material in CH_2Cl_2 (50 mL) was washed successively with brine (2 × 30 mL) and water (2 × 40 mL); the CH_2Cl_2 extract was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give 3.6 g of an orange solid residue, mp 117–125 °C. The solid was chromatographed on a silica gel column (160 g, 5 × 80 cm, CH_2Cl_2) to afford 2.3 g (74%) of **14b** as a orange-red solid: mp 135–137 °C. Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

(±)-*N*-Phthaloyl-1-indol-3-yl-2-aminopropane (15). A mixture of α-methyltryptamine (2 g, 11.5 mmol), phthalic anhydride (1.9 g, 12.8 mmol), triethylamine (1.3 g, 12.8 mmol), and toluene (25 mL) was heated at reflux for 6 h with continuous removal of water into a Dean–Stark tube. After being allowed to cool to room temperature, the reaction mixture was washed successively with 2 N NaOH (2 × 20 mL), water (2 × 20 mL), and 10% HCl (2 × 20 mL). The organic portion was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give a viscous yellow residue that solidified on standing at room temperature. Purification of the crude phthaloyl derivative by chromatography (silica gel, 20 × 40 cm, CH_2Cl_2) afforded 2.8 g (80%) of **15** as a pale-yellow solid: mp 103–106 °C; IR (KBr) 3374–3332 (NH), 1764, 1701 (C=O); ^1H NMR ($CDCl_3$) δ 7.92 (br s, 1 H, NH), 7.85–6.90 (m, 9 H, ArH), 4.92–4.50 (m, 1 H, CH), 3.65–3.19 (m, 2 H, CH_2), 1.55 (d, J = 6.8 Hz, 3 H, CH_3). The phthaloyl derivative **15** was used without further characterization.

(±)-*N*-Phthaloyl-1-(5-methoxyindol-3-yl)-2-aminopropane (18). A mixture of 1-(5-methoxyindol-3-yl)-2-aminopropane (0.8 g, 3.9 mmol), phthalic anhydride (0.7 g, 4.7 mmol), triethylamine (0.44 g, 4.3 mmol), and toluene (15 mL) was heated at reflux for 6 h with continuous removal of water with a Dean–Stark trap. After being allowed to cool to room temperature, the mixture was washed successively with 2 N NaOH (2 × 10 mL), water (2 × 10 mL), and 10% HCl (2 × 10 mL); the organic portion was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a pale-yellow solid. Purification of the crude product by flash chromatography (silica gel, 1 × 20 cm, CH_2Cl_2) gave 0.8 g (58%) of **18** as a pale-yellow solid: mp 122–123 °C; IR (KBr) 3409 (NH), 1764, 1708 (C=O); ^1H NMR ($CDCl_3$) δ 7.92 (br s, 1 H, NH), 7.95–6.58 (m, 8 H, ArH), 4.85–3.94 (m, 1 H, CH), 3.73 (s, 3 H, OCH_3), 3.53–2.92 (m, 2 H, CH_2), 1.95 (d, J = 6.8 Hz, 3 H, CH_3). The phthaloyl derivative **18** was used without further characterization.

Radioligand Binding Assays.[22] Previously frozen rat brains (Products for Neuroscience; Indianapolis, IN) or brains obtained by decapitation of male Sprauge–Dawley rats were dissected on ice for frontal cortex, hippocampus, and striatum. Fresh calf brains were dissected for caudate. The tissue was homogenized in ice-cold 50 mM Tris-HCl, 0.5 mM Na_2EDTA, 10 mM $MgSO_4$, at pH 7.4 (1:10 w/v) and centrifuged twice at 30000g for 10 min (with a resuspension between centrifugations). The final pellet was stored at −30 °C until used.

The 5-HT_2 receptor studies were performed with 5–10 mg of homogenized rat frontal cortex and 0.4 nM [^3H]ketanserin (76 Ci/mmol; New England Nuclear) or 0.4 nM [^3H]DOB (170 Ci/mmol; New England Nuclear) to label the receptors. Cinanserin (1.0 μM) was used to define nonspecific binding. The 5-HT_{1A} receptor affinity was assayed with [^3H]-8-OH-DPAT (127.9 Ci/mmol; New England Nuclear), 5 mg of rat hippocampal tissue, and 10 μM 8-OH-DPAT to define nonspecific binding. 5-HT_{1B} receptor affinity was assayed with [^3H]-5-HT (24.1 Ci/mmol; New England Nuclear), 5 mg of rat striatal homogenate, 100 nM 8-OH-DPAT to block 5-HT_{1A} receptors, and 10 μM 5-HT to define nonspecific binding. 5-HT_{1C} receptor affinity was assayed with 1.0 nM [^3H]mesulergine (75.8 Ci/mmol; Amersham), 20 nM spiperone to block 5-HT_2 receptors, 10 mg of homogenized rat frontal cortex, and 10 μM 5-HT to define nonspecific binding. The 5-HT_{1D} receptor affinity was assayed with 2.0 nM [^3H]-5-HT, 1 μM pindolol, 0.1 μM mesulergine (to block 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} receptors), and 10 mg of calf caudate; 5-HT (10 μM) was used to define nonspecific binding.

Eleven concentrations (10^{-10}–10^{-5}) of competing drug were prepared fresh prior to use. The assay buffer was identical with the tissue buffer described above except that it contained 10 μM pargyline and 0.1% ascorbate. Assay tubes were incubated for 15 min (for 5-HT_2, 5-HT_{1A}, and 5-HT_{1D} assays), 20 min (for 5-HT_{1B}), or 30 min (for 5-HT_{1C}) at 37 °C, filtered through glass-fiber filters (pre-soaked in 0.1% polyethyleneimine), and washed with 10 mL of ice-cold 50 mM Tris-HCl buffer. The filters were counted by liquid-scintillation spectrometry in 5 mL of aqueous counting scintillant following 6 h of equilibration. Protein determinations were performed by the method of Lowry et al.[23] with bovine serum albumin as the standard. The results of the competition experiments were subjected to nonlinear regression analysis using EBDA[24] to determine K_i values. Results represent a minimum of triplicate determinations, 8-OH-DPAT was purchased from Research Biochemicals Inc. (Natick, MA); 5-HT, pindolol, and spiperone were from Sigma (St. Louis, MO); and mesulergine was a gift from Sandoz Research Institute (East Hanover, NJ).

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Registry No. 1, 50-67-9; **3a**, 299-26-3; **3b**, 128600-42-0; **3b**·HCl, 128600-73-7; **3c**, 128600-43-1; **3c**·maleate, 128600-74-8; **3d**, 128600-44-2; **3d**·HCl, 128600-75-9; **3e**, 128600-45-3; **3e**·HCl, 14702-62-6; **3f**, 128600-46-4; **3f**·fumarate, 128600-76-0; **3g**, 10510-21-1; **3g**·HCl, 128600-77-1; **3h**, 128600-47-5; **3h**·maleate, 128600-78-2; **3i**, 128600-48-6; **3i**·maleate, 128600-79-3; **4a**, 128600-49-7; **4b**, 128600-50-0; **4c**, 128600-51-1; **4c**·oxalate, 128600-80-6; **5**, 85181-23-3; **6**, 608-07-1; **7**, 128600-52-2; **8**, 128600-53-3; **10a**, 1821-39-2; **10b**, 53334-33-1; **11a**, 128600-54-4; **11b**, 128600-55-5; **12a**, 128600-56-6; **12b**, 90901-48-7; **13a**, 128600-57-7; **13b**, 128600-58-8; **14a**, 128600-59-9; **14b**, 128600-60-2; **15**, 128600-61-3; **16**, 128600-63-5; **17**, 128600-64-6; **18**, 128600-62-4; **19**, 128600-65-7; benzyl bromide, 100-39-0; 1-bromopropane, 106-94-5; 5-methoxyindole, 1006-94-6; 5-methoxy-1-*n*-propylindole, 128600-66-8; 5-methoxy-1-*n*-propylindole-3-carboxaldehyde, 128600-67-9; 1-(5-methoxy-1-*n*-propylindol-3-yl)-2-nitropropene, 128600-68-0; *n*-propylamine, 107-10-8; 2,5-dimethoxytetra-

(22) Titeler, M.; Lyon, R. A.; Davis, K. H.; Glennon, R. A. *Biochem. Pharmacol.* **1987**, *36*, 3265.
(23) Lowry, O. H.; Rosebrough, N. J.; Farr, A. L.; Randall, R. J. *J. Biol. Chem.* **1951**, *193*, 265.
(24) Macpherson, G. A. *Comput. Prog. Biomed.* **1983**, *17*, 107.

hydrofuran-3-carboxaldehyde, 50634-05-4; 1-*n*-propylpyrrole-3-carboxaldehyde, 128600-69-1; 1-(1-*n*-propylpyrrol-3-yl)-2-nitropropene, 128600-70-4; *n*-amylamine, 110-58-7; 1-*n*-amylpyrrole-3-carboxaldehyde, 35250-63-6; 1-(1-*n*-amylpyrrol-3-yl)-2-nitropropene, 128600-71-5; 1-*n*-propylindole, 16885-94-2; 1-*n*-propylindole-3-carboxaldehyde, 119491-08-6; nitroethane, 79-24-3; indole, 120-72-9; 1-bromopentane, 110-53-2; 1-amylindole, 59529-21-4; 1-amylindole-3-carboxaldehyde, 128600-72-6; chloroacetonitrile, 107-14-2; phthalic anhydride, 85-44-9; 1-(5-methoxyindol-3-yl)-2-aminopropane, 85181-23-3.

Chemistry and Structure–Activity Relationships of C-17 Unsaturated 18-Cycloalkyl and Cycloalkenyl Analogues of Enisoprost. Identification of a Promising New Antiulcer Prostaglandin

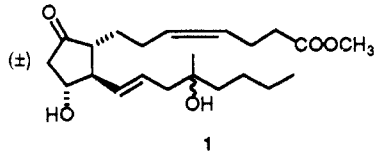
P. W. Collins,* A. F. Gasiecki, W. E. Perkins, G. W. Gullikson, R. G. Bianchi, S. W. Kramer, J. S. Ng, E. E. Yonan, L. Swenton, P. H. Jones, and R. F. Bauer

Gastrointestinal Diseases Research, Physical Methodology and Chemical Development Departments, G. D. Searle & Co., Skokie, Illinois 60077. *Received March 19, 1990*

A series of Δ^{17} unsaturated cycloalkyl and cycloalkenyl analogues of enisoprost was synthesized to investigate the effects of ω chain unsaturation on gastric antisecretory activity and diarrheogenic side effects. Of these, the 17*E*, 18-cyclopentenyl analogue **5d** displayed potent gastric antisecretory activity in dogs but very weak diarrheogenic properties in rats and is the most selective prostaglandin compound discovered in these laboratories. Structurally, **5d** contains both a conjugated diene and tertiary allylic alcohol in the ω chain, and these chemical features impart some interesting oxidative and acid-catalyzed epimerization and allylic rearrangement reactivities, respectively.

Introduction

In an earlier paper[1] we reported that incorporation of cycloalkyl groups at C-18 of enisoprost (**1**)[2] led to compounds **2a–e** with reduced gastric antisecretory activity in dogs, but with greater selectivity with respect to diarrheogenic side effects in rats. There was also an indication of increased duration of antisecretory activity with the 18-cyclobutyl analogue **2b**.



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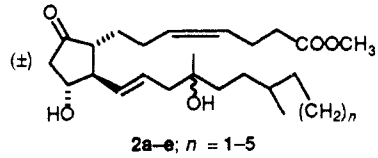

2a–e; n = 1–5

In the quest for more selective and longer acting analogues, we continued our investigation of this series and established several interrelated structure–activity relationships. As previously reported,[1] gastric antisecretory activity drops dramatically once a particular ring size is exceeded (cyclopentyl ≫ cyclohexyl). We next examined the effect of chain length between C-16 and the cycloalkyl moiety. Interestingly, there was an inverse relationship between ring size and chain length. Thus, as chain length increased, the maximally allowed ring size to maintain good gastric antisecretory activity decreased. Similarly, when an angular methyl group was placed on the ring juncture carbon, gastric antisecretory activity decreased more sharply as ring size increased. These findings prompted the establishment of a useful empirical rule that, for optimal gastric antisecretory activity, the total number of carbon atoms composing the ring and the chain linking the ring to C-16 should not exceed seven. Diarrheogenic activity in this expanded series of compounds generally paralleled the finding in the original work; that is, diarrheogenic activity was more sensitive than antisecretory activity to total ω chain size, again suggesting that the parietal cell receptor is more accommodative of larger chains than are the receptors responsible for the diarrheogenic response. Although none of the aforementioned compounds was superior to the initial cycloalkyl compounds, **2a–c**, we decided to continue this line of investigation by studying the effects of unsaturation both at C-17 and, where synthetically feasible, within the rings of **2a–d**. This report details the synthesis and structure–activity relationships of a series of Δ^{17} unsaturated cycloalkyl and cycloalkenyl analogues of enisoprost. The strategy of adding unsaturation eventually led to the discovery of a very promising compound, **5d** (Table I), which possesses the greatest separation of gastric antisecretory and diarrheogenic activities thus far observed in our research. The presence of a tertiary allylic alcohol and a conjugated diene in **5d** imparts some interesting chemical reactivities which also are described.

Chemistry

Synthesis. Compounds **5a–g** of Table I were prepared by standard cuprate addition of the respective racemic cuprate reagents (**4a–g**) to the racemic cyclopentenone **3**[3] followed by mild acid hydrolysis of protecting groups and chromatographic purification (Figure 1). In previous work, an aqueous acetic acid medium was employed to deprotect prostaglandin products, but in the present series a milder reagent, pyridinium *p*-toluenesulfonate (PPTS)[4] in aqueous acetone, was used to minimize formation of various

(1) Collins, P. W.; Gasiecki, A. F.; Perkins, W. E.; Gullikson, G. W.; Jones, P. H.; Bauer, R. F. *J. Med. Chem.* **1989**, *32*, 1004.
(2) Thomson, A. B. R.; McCullough, H. N.; Kirdeikis, P.; Zuk, L.; Simpson, I.; Cook, D. J.; Wildeman, R. A. *Aliment. Pharmacol. Therap.* **1988**, *2*, 325.
(3) Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *36*, 786.
(4) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

0022-2623/90/1833-2784$02.50/0