Amesergide and Structurally Related Nor-*D*-ergolines: $5HT_2$ Receptor Interactions in the Rat

Michael J. Martinelli,* William Bloomquist, Barry C. Peterson, and Marlene L. Cohen*

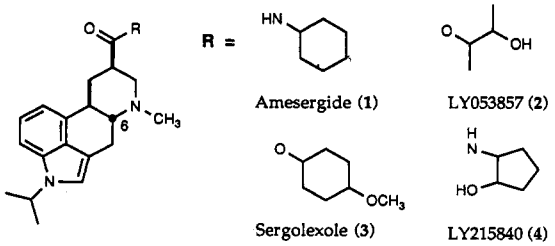
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

Received March 22, 1993

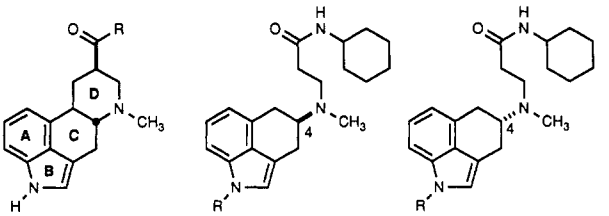
A series of tricyclic (nor-D) partial ergolines were synthesized *via* a highly convergent enantiospecific strategy, ultimately arising from a racemic tricyclic ketone. Michael addition to an acrylamide, followed by reductive methylation, afforded the key intermediate. Selective deprotection and oxidation provided the tricyclic ergoline. Vascular $5HT_2$ receptor interactions for the partial ergolines were dramatically reduced compared to the parent ergoline, amesergide, as determined *in vivo* by activation of a pressor response or blockade of 5HT-induced pressor responses in pithed rats. The desisopropyl tricyclic ergolines possessed some modest pressor activity that was unlikely to be related to $5HT_2$ receptor activation since these compounds did not inhibit the pressor response to serotonin. In contrast, the isopropyl tricyclic ergolines exhibited no agonist activity, but inhibited the pressor response to serotonin at 1 mg/kg iv. The ergoline amesergide inhibited the pressor response to serotonin in doses of 0.01–0.1 mg/kg iv. The homochiral isopropyl tricyclic ergoline was more potent as a $5HT_2$ receptor antagonist than the epimeric (unnatural stereochemistry) analogue. Thus, the isopropyl moiety on the indole nitrogen is important for vascular $5HT_2$ receptor affinity in the rat. Most importantly, these data suggest that conformational rigidity of the ergoline D-ring is required for optimal $5HT_2$ receptor interactions in the rat.

Introduction

Amesergide (LY237733, 1), a potent ergoline amide $5HT_2$ receptor antagonist,[1] was developed as a result of a program which previously identified the potent ergoline esters LY53857 (2)[2] and sergolexole (LY281067, 3),[3a,b] and more recently the ergoline amide LY215840 (4),[3c] as $5HT_2$ receptor antagonists. Although an extensive structure–activity relationship existed for the ergoline esters[3b] and amides[1] at vascular $5HT_2$ receptors, to date there has been no exploration of the importance of the intact ergoline D-ring structure to vascular $5HT_2$ receptor blockade. The synthetic challenge of preparing partial structures of the ergoline D-ring system *de novo* has hindered this research thus far. Since the stereochemistry of the D-ring amino stereogenic center is fixed in dihydrolysergic acid, the critical precursor to LY53857, sergolexole, and amersergide, preparation of tricyclic compounds, devoid of the D-ring, would permit an examination of the effect of stereochemical modification of the N-6 position on the interaction with vascular $5HT_2$ receptors. Furthermore, previous studies with ergoline esters and amides emphasized the importance of isopropyl substitution on the indole nitrogen in conferring potent antagonist affinity at rat vascular $5HT_2$ receptors. Removal of the isopropyl moiety of amesergide results in **5**, an *in vivo* metabolite of amesergide.[3d] Preparation of tricyclic partial ergoline structures can be used to further probe the importance of the isopropyl substitution to antagonist potencies in yet another series.



To accomplish these goals, we describe methods for the syntheses of the tricyclic partial ergolines **6–9** analogous to amesergide and have utilized these compounds to probe (1) the importance of the D-ring to vascular $5HT_2$ receptor interactions, (2) the importance of the stereochemistry in the 4-position relative to $5HT_2$ receptor interactions, and (3) the importance of the isopropyl moiety on the indole nitrogen to vascular $5HT_2$ receptor interactions for the partial and full ergoline structures.



5, R = HN-C_6H_{13}
10, R = OH (Δ-9,10)

6, R = *i*-Pr
8, R = H

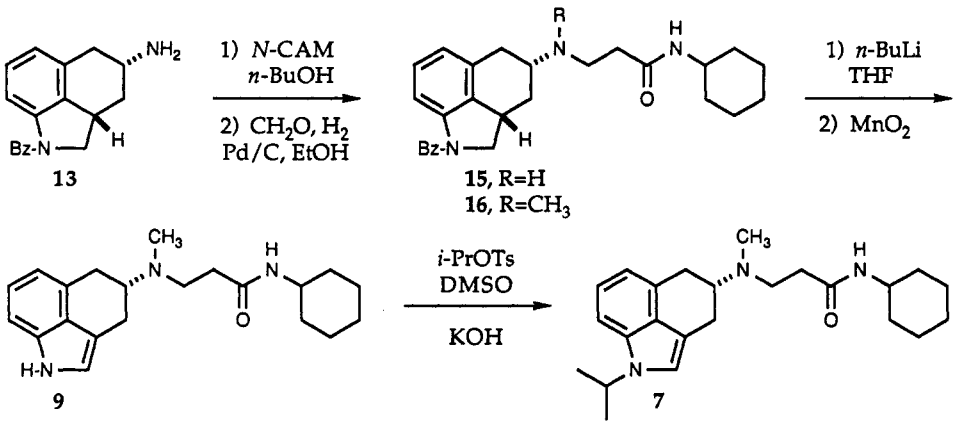
7, R = *i*-Pr
9, R = H

Chemistry

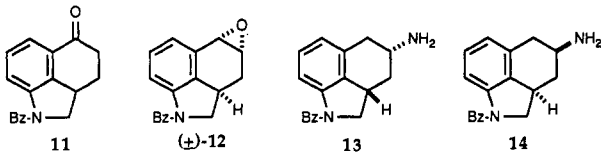
Earlier synthetic studies on the ergot alkaloids resulted in the landmark total synthesis of lysergic acid (**10**). The chemistry allowed access to a number of congeners with an interesting structure–activity relationship that has continued for nearly four decades.[6] Several other syntheses of the ergot alkaloids have appeared.[7] The Kornfeld–Woodward synthesis of lysergic acid utilized the intermediacy of ketone **11**, which was a logical starting point for the current syntheses of the requisite partial ergolines **6–9**. The ketone transposition from C-5 to C-4 has been well established,[8] which, followed by reductive amination, has provided a diastereomeric mixture of C-4 amines. The reductive amination process introduced a second stereogenic center (C-2_a and C-4), and hence diastereomers were formed. The stereochemistry at C-4 could therefore not be determined until C-2_a was removed through oxidation of the indoline to the indole. Alternatively, amination of β-tetralones followed by B-ring

0022-2623/93/1836-2671$04.00/0

Scheme I



annulation has also been reported, although this approach was somewhat lengthy.[4] Despite these elegant approaches, we sought an alternative method which could provide a high level of stereocontrol at C-4. Utilization of enantiomerically enriched intermediates would ultimately afford products that would enable an assessment of the stereochemical significance of C-4 and the $5HT_2$ receptor interactions.



The synthesis of opically pure primary amines **13** and **14** from Kornfeld's ketone **11** was previously described.[9] This synthesis relied upon a highly diastereoselective epoxidation method to afford epoxide **12**.[10] The racemic epoxide **12** was then converted to the amines **13** and **14** via a covalent resolution. The optically pure primary amine **13** was then reacted with *N*-cyclohexylacrylamide (*N*-CAM) in *n*-BuOH at reflux to afford the Michael addition product **15** (Scheme I). *N*-Methylation was accomplished with aqueous formaldehyde in the presence of 10% Pd/C under a hydrogen atmosphere producing amide **16**. Selective deprotection of the *N*-benzoyl group in the presence of the cyclohexylamide moiety was then required. Thus, amide **16** was treated with 2 equiv of *n*-BuLi at −78 °C to cleave the N^1-benzoyl moiety. The first equivalent of *n*-BuLi deprotonates the N^4H, thereby protecting the amide, while the second *n*-BuLi equivalent undergoes nucleophilic attack at the benzoyl carbonyl. Workup then affords the deprotected product. Oxidation of the intermediate indoline was accomplished by dehydrogenation with MnO_2 in CH_2Cl_2 to yield indole **9**. Isopropylation of the indole nitrogen occurred under conditions previously described to give **7**.[11] Both compounds **7** and **9** were isolated as the tartrate salts. The enantiomeric amine **14** was subjected to the identical scheme for preparation of the complementary series **6** and **8**.

Results and Discussion

The parent ergoline amesergide (**1**) possessed no agonist activity as it did not increase mean arterial pressure after intravenous administration to pithed rats (data not shown). Serotonin produced a marked increase in mean arterial pressure (Figure 1), an increase mediated by activation of vascular $5HT_2$ receptors.[12] Both tricyclic compounds **8** and **9**, lacking substitution on the indole nitrogen, modestly increased mean arterial pressure in pithed rats (Figure 1), but were considerably less potent than serotonin. Since a similar increase in arterial pressure occurred with both isomers, this effect was independent of the stereochemistry at the N-4 position. In contrast to the small but significant increase in mean arterial pressure seen with the tricyclic compounds lacking substitution on the indole nitrogen, compounds **6** and **7** which possessed an isopropyl moiety on the indole nitrogen did not increase mean arterial pressure (Figure 1), analogous to the lack of $5HT_2$ receptor agonist activity seen with amesergide. Furthermore, the desisopropyl derivative of amesergide, **5**, also did not increase mean arterial pressure in pithed rats after its intravenous administration in marked contrast to the desisopropyl tricyclic compounds (Figure 1).

Since serotonin and compounds **8** and **9** increased mean arterial pressure, we evaluated the duration of effective activity of these partial agonists, using equivalently effective doses. Both desisopropyl tricyclic compounds, administered intravenously, produced a relatively long lasting increase in mean arterial pressure whereas the response to intravenous administration of serotonin was rather transient at an equivalently effective dose of serotonin (Figure 2). Thus, the desisopropyl tricylic

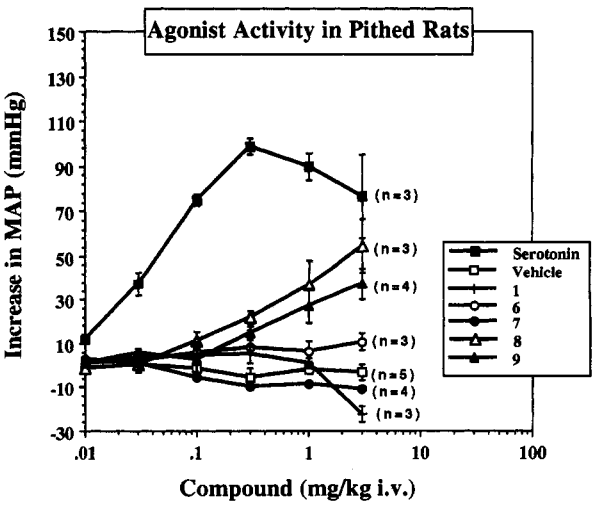


Figure 1. Effect of amesergide (**1**) and the four tricyclic partial ergoline derivatives (**6–9**) on mean arterial pressure (MAP). Compounds were administered intravenously to pithed normotensive rats. Points are mean values, and vertical bars represent the standard error of the mean for the number of animals indicated in parentheses.

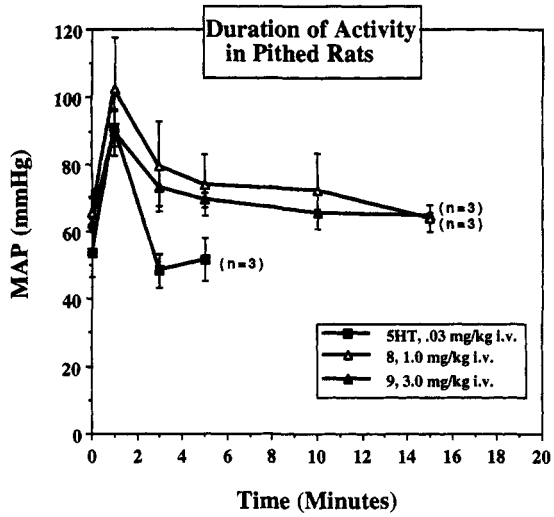


Figure 2. Effects of serotonin and the desisopropyl tricyclic ergoline derivatives (8, 9) on mean arterial pressure as a function of time after the intravenous administration of equivalently effective doses to pithed normotensive rats. Points are mean values, and vertical bars represent the standard error of the mean for the number of animals indicated in parentheses.

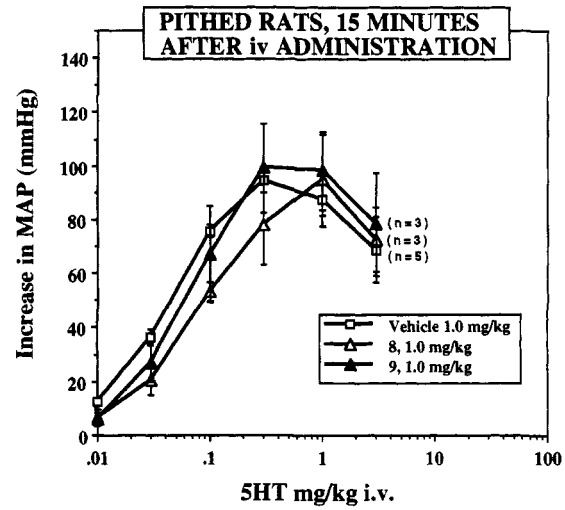


Figure 3. Ability of the desisopropyl tricyclic ergolines (8, 9) to inhibit the pressor response to increasing doses of serotonin. Serotonin was given 15 min after the intravenous administration of the tricyclic partial ergolines to pithed normotensive rats. Points are mean values, and vertical bars represent the standard error of the mean for the number of animals indicated in parentheses.

compounds produced an increase in mean arterial pressure that persisted longer than the increase seen after serotonin. These data are consistent with the possibility that the tricyclic compounds are not metabolized as rapidly as serotonin or with the possibility that these agents are increasing mean arterial pressure via a different receptor or at a different *in vivo* site than the locus of action for serotonin.

To examine whether the partial agonist effects of the desisopropyl tricyclic compounds resulted from interaction with vascular 5HT$_2$ receptors, we next examined their ability to inhibit the more potent and efficacious pressor response to serotonin. However, neither compound 8 nor 9 (1 mg/kg iv) significantly inhibited the pressor response to serotonin administered 15 min after the tricyclic compound. Since these compounds lack the ability to inhibit the response to the stronger agonist, serotonin (Figure 3), a response known to be mediated via activation of vascular 5HT$_2$ receptors, it is unlikely that compound 8 or 9 is interacting with vascular 5HT$_2$ receptors at the doses studied. Thus, the modest pressor response to these compounds most likely resulted from non-5HT$_2$ receptor mediated events.

We then explored the ability of the isopropyl-substituted tricyclics to inhibit the pressor response to serotonin relative to amesergide. Given intravenously, amesergide (0.01–0.1 mg/kg iv) markedly and potently inhibited the increase in mean arterial pressure to serotonin in pithed rats (Figure 4). In contrast, compound 6 (1.0 mg/kg iv) produced only modest inhibition of the pressor response to serotonin (Figure 5). However, compound 7 markedly inhibited the pressor response to serotonin albeit considerably weaker than the inhibitory effect of amesergide (Figure 5 vs Figure 4). Thus, the isopropyl-substituted tricyclic compound with stereochemistry comparable to amesergide retained weak antagonist activity at vascular 5HT$_2$ receptors. However, the opposite stereochemistry resulted in reduced activity, either agonist or antagonist, at vascular 5HT$_2$ receptors.

Comparison of the results for amesergide (1) and congeners 2–4 with the *D*-nor partial ergolines 6–9 revealed the importance of the D-ring pharmacophore. Opening

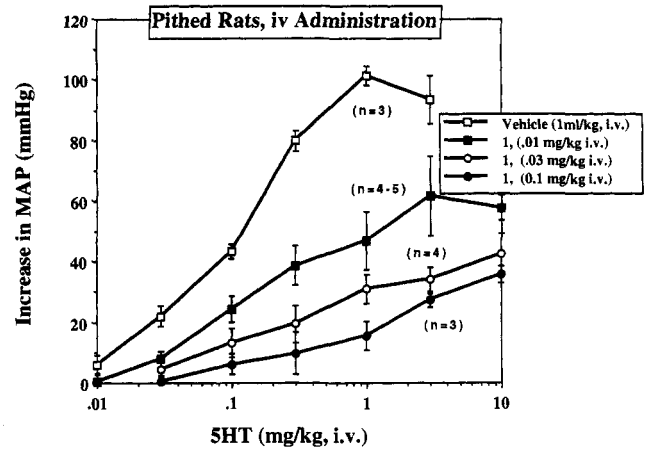


Figure 4. Inhibition by amesergide (1) of the pressor response to serotonin. Serotonin was adminstered 15 min after intravenous injection of amesergide to pithed normotensive rats. Points are mean values, and vertical bars represent the standard error of the mean for the number of animals indicated in parentheses.

the D-ring to impart higher conformational mobility dramatically reduced 5HT$_2$ receptor interactions relative to the intact ergoline structures. This large reduction in activity was independent of the amine stereochemistry and the indole nitrogen substitution. Apparently, there is an optimal fixed distance between the amide moiety and the indole ring necessary for 5HT$_2$ receptor interactions. Simple MM2 calculations of the tricyclic partial ergolines have shown the preferred side chain conformation to be in a linear direction with nearly an opposite vector to that in the intact ergoline structures, as opposed to the fixed orientation found in the ergolines. Thus, the intact D-ring appears to provide the side chain conformation critical for optimal binding to 5HT$_2$ vascular receptors.

Furthermore, activity of the tricyclic partial ergolines 6–9 at the rat vascular 5HT$_2$ receptor was markedly enhanced by the presence of an indole N-*i*-Pr moiety. This effect has been previously established for the ergot alkaloids[13] as well as the indole series.[14] In fact, removal of the *i*-Pr moiety from the partial ergolines eliminated

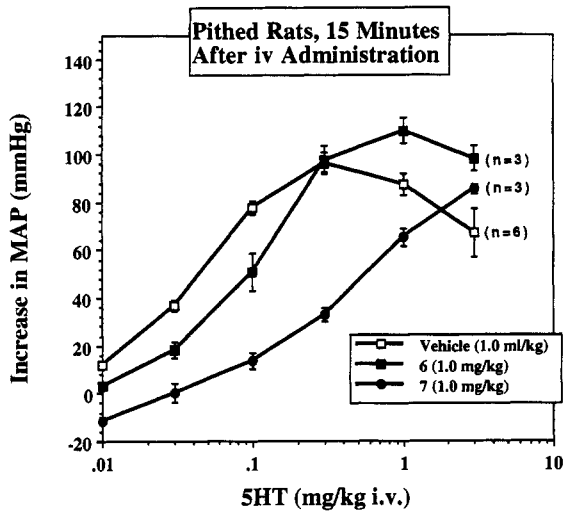


Figure 5. Ability of the isopropyl tricyclic ergolines (**6**, **7**) to inhibit the pressor response to serotonin. Serotonin was administered 15 min after the intravenous dosing of the tricyclic partial ergolines to pithed normotensive rats. Points are mean values, and vertical bars represent the standard error of the mean for the number of animals indicated in parentheses.

all measurable affinity at the vascular $5HT_2$ receptor based on the *in vivo* estimate of activity as agonists or antagonists. The stereochemistry at N-4 was determined to be optimal with the natural configuration, consistent with existing 5HT models.[15] The compound with the highest relative activity at the $5HT_2$ receptor in this study was therefore the partial ergoline **7**, possessing the natural configuration at N-4 and an *i*-Pr moiety at N-1. Most importantly, however, was the observation that the conformational rigidity imposed by the intact ergoline D-ring is an absolute requirement for optimal $5HT_2$ receptor interactions.

Experimental Section

General Experimental Procedures. Melting points were determined on a hot-stage microscope and are uncorrected. All experiments were conducted under an atmosphere of nitrogen, unless otherwise noted, and monitored by thin-layer chromatography using Merck F254 silica gel plates. All solvents and reagents were used as obtained. Compounds **12** and **13** were prepared according to ref 10. ^1H and ^{13}C NMR spectra were obtained on either a GE QE-300 or a Bruker ACP-300 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Microanalyses were conducted by the Physical Chemistry Department of Lilly Research Laboratories. The experimental procedures used for the preparation of compounds **7** and **9** were applied to the syntheses of compounds **6** and **8**, respectively, and are therefore given only once.

1-Benzoyl-4-[[2-(cyclohexylcarbamoyl)ethyl]amino]-1,2,-2a,3,4,5-hexahydrobenz[*cd*]indole (15). Primary amine **13** (1.0 g, 4.3 mmol) was dissolved in *n*-BuOH (15 mL) to which was then added *N*-cyclohexylacrylamide (661 mg, 4.3 mmol). The reaction mixture was stirred at reflux for 72 h, cooled to room temperature, and concentrated to dryness. The product was purified by column chromatography (SiO_2, 5% CH_3OH/CH_2Cl_2) to afford 1.44 g, 92.6% yield. ^1H NMR ($CDCl_3$) δ: 1.14 (m, 3H), 1.31 (m, 3H), 1.63 (m, 3H), 1.87 (m, 3H), 2.36 (m, 2H), 2.46 (m, 2H), 3.00 (m, 2H), 3.31 (m, 3H), 3.65 (m, 1H), 3.73 (m, 1H), 4.35 (m, 1H), 6.79 (m, 1H), 7.19–7.61 (m, 9H). Anal. ($C_{27}H_{33}N_3O_2$) C, H, N.

1-Benzoyl-4-[[2-(cyclohexylcarbamoyl)ethyl]methylamino]-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (16). The secondary amine **15** (1.44 g, 3.3 mmol) was dissolved in absolute EtOH (30 mL) to which was then added 10% Pd/C (900 mg) and 37% aqueous formaldehyde solution (1.25 mL, 16.7 mmol). The reaction mixture was degassed and stirred at room temperature under an atmosphere of H_2 gas. Upon complete methylation, the catalyst was removed by filtration and the filtrate concentrated to dryness. The product was purified by column chromatography (SiO_2, 5% CH_3OH/CH_2Cl_2) to afford 1.46 g, 96% yield. ^1H NMR ($CDCl_3$) δ: 1.81 (m, 3H), 1.37 (m, 2H), 1.52 (m, 1H), 1.67 (m, 4H), 1.89 (m, 2H), 2.42 (s, 3H), 2.46 (m, 2H), 2.79 (m, 1H), 2.90 (m, 2H), 3.37 (m, 2H), 3.69 (m, 1H), 3.76 (m, 1H), 4.35 (m, 1H), 6.82 (m, 1H), 7.22–7.59 (m, 7H). Anal. ($C_{28}H_{35}N_3O_2$) C, H, N.

4-[[2-(Cyclohexylcarbamoyl)ethyl]methylamino]-1,3,4,5-tetrahydrobenz[*cd*]indole (9). Benzamide **16** (582 mg, 1.31 mmol) was dissolved in THF (20 mL) and cooled to −78 °C. A solution of *n*-BuLi (1.6 M in hexanes, 1.6 mL, 2.6 mmol) was then added dropwise with continued stirring at −78 °C for another 1 h. Another aliquot of *n*-BuLi (0.80 mL, 1.3 mmol) was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was then partitioned between 1 N HCl (20 mL) and Et_2O (20 mL). The organic layer was extracted with additional 1 N HCl (20 mL) and the aqueous layer rinsed with Et_2O (3 × 20 mL). The pH of the aqueous layer was adjusted to 10 with 5 N NaOH and extracted with CH_2Cl_2 (3 × 10 mL). Following dessication with Na_2SO_4, the volatiles were removed and the concentrate was used directly in the next step without further purification. ^1H NMR ($CDCl_3$) δ: 1.19 (m, 4H), 1.42 (m, 3H), 1.67 (m, 2H), 1.90 (m, 2H), 2.21 (m, 2H), 2.34 (s, 3H), 2.37 (m, 2H), 2.68–2.84 (m, 4H), 3.16 (m, 3H), 3.75 (m, 3H), 6.51 (m, 2H), 6.98 (m, 1H), 8.20 (m, 1H). Oxidation to the indole was then accomplished as follows. The crude indoline from above was dissolved in CH_2Cl_2 (20 mL) and treated with activated brown MnO_2 (1.09 g). The reaction mixture was stirred at ambient temperature for 24 h, whereupon the insolubles were removed by filtration and the filtrate concentrated to dryness. The product was purified by column chromatography (SiO_2, 8% CH_3OH/CH_2Cl_2) to afford 280 mg, 68% yield. ^1H NMR ($CDCl_3$) δ: 1.09–1.44 (m, 5H), 1.71 (m, 3H), 1.93 (m, 2H), 2.38 (m, 2H), 2.44 (s, 3H), 2.90 (m, 2H), 3.05 (m, 4H), 3.30 (m, 1H), 3.78 (m, 1H), 6.85 (m, 2H), 7.15 (m, 2H), 8.10 (m, 1H), 8.35 (m, 1H). Anal. ($C_{21}H_{29}N_3O$) C, H, N.

4-[[2-(Cyclohexylcarbamoyl)ethyl]methylamino]-1-isopropyl-1,3,4,5-tetrahydrobenz[*cd*]indole (7). Indole **9** (140 mg, 0.412 mmol) was dissolved in DMSO (3.0 mL) and treated with powdered KOH (150 mg, 2.27 mmol) at ambient temperature. *i*-PrOTs (133 mg, 0.619 mmol) in DMSO (1.0 mL) was then added dropwise over 1 h with stirring. The reaction mixture was stirred for an additional 2 h and then poured onto crushed ice (10 mL) and extracted with EtOAc (3 × 10 mL). The combined extract was rinsed with brine (10 mL), dried over Na_2SO_4, and concentrated. The product was purified by column chromatography (SiO_2, 8% CH_3OH/CH_2Cl_2) to afford 122 mg, 78% yield. ^1H NMR ($CDCl_3$) δ: 1.18 (m, 3H), 1.37 (m, 3H), 1.51 (d, 6H, J = 7.0 Hz), 1.69 (m, 3H), 1.92 (m, 2H), 2.39 (m, 2H), 2.44 (s, 3H), 2.91–3.18 (m, 6H), 3.31 (m, 1H), 3.79 (m, 1H), 4.62 (hep, 1H, J = 7.0 Hz), 6.81 (m, 1H), 6.92 (br s, 1H), 7.14 (m, 2H), 8.37 (br d, 1H). Anal. ($C_{24}H_{35}N_3O$) C, H, N.

4-[[2-(Cyclohexylcarbamoyl)ethyl]methylamino]-1,3,4,5-tetrahydrobenz[*cd*]indole (8). Indole **8** was prepared by the method used for compound **9** except with the antipodal primary amine **14**. ^1H NMR ($CDCl_3$) δ: same as **9**. Anal. ($C_{21}H_{29}N_3O$) C, H, N.

4-[[2-(Cyclohexylcarbamoyl)ethyl]methylamino]-1-isopropyl-1,3,4,5-tetrahydrobenz[*cd*]indole (6). Isopropylation was accomplished using the method described for **7**. ^1H NMR ($CDCl_3$) δ: same as **7**. Anal. ($C_{24}H_{35}N_3O$) C, H, N.

Pressor Responses in Pithed Rats. 5-HT and the tricyclic compounds were evaluated in pithed Wistar normotensive rats (Charles River, Inc., Portage, MI, 240–374 g) because serotonergic responses in the pithed preparation are primarily direct vascular effects. Rats were anesthetized with Metofane (methoxyflurane), pithed, and ventilated with room air[2,12] *via* tracheal cannulae. The carotid artery and femoral vein were cannulated, and blood pressure was measured *via* a P23XL pressure transducer connected to the carotid arterial cannula. Drugs were injected into the right femoral vein. An equilibrium period of 15 min was observed before control measurements or iv administration of drugs or vehicle. To study blockade of the pressor response to serotonin, increasing iv doses of 5-HT were injected 15 min after iv administration of $5\text{-}HT_2$ receptor antagonist or vehicle. Compounds were dissolved in either physiological saline or in

EtOH and HCl brought up to volume with saline, depending upon solubility. Vehicles were tested as appropriate for each compound with no significant differences in response to 5HT; therefore, vehicle data were pooled for graphic representation.

Supplementary Material Available: Characterization data (elemental analyses, high-resolution mass spectral data, and HPLC chromatograms) for all compounds (6 pages). Ordering information is given on any current masthead page.

References

(1) Misner, J. W.; Garbrecht, W. L.; Marzoni, G.; Whitten, K. R.; Cohen, M. L. (8β)-6-Methylergoline Amide Derivatives as Serotonin Antagonists: N^1-Substituent Effects on Vascular 5HT$_2$ Receptor Activity. *J. Med. Chem.* **1990**, *33*, 652–656.

(2) Cohen, M. L.; Kurz, K. D.; Mason, N. R.; Fuller, R. W.; Marzoni, G. P.; Garbrecht, W. L. Pharmacological Activity of the Isomers of LY53857, Potent and Selective 5HT$_2$ Receptor Antagonists. *J. Pharmacol. Exp. Ther.* **1985**, *235*, 319–323.

(3) (a) Cohen, M. L.; Parli, C. J.; Fuller, R. W. 5HT$_2$ Receptor Antagonist Activity of the Acid Metabolite (1-*iso*-Propyldihydrolysergic Acid) of the Ergoline Ester, Sergolexole (LY281067). *J. Pharmacol. Exp. Ther.* **1989**, *251*, 1006–1011. (b) Garbrecht, W. L.; Marzoni, G.; Whitten, K. R.; Cohen, M. L. (8β)-Ergoline-8-carboxylic Acid Cycloalkyl Esters as Serotonin Antagonists: Structure-Activity Study. *J. Med. Chem.* **1988**, *31*, 444–448. (c) Cohen, M. L.; Robertson, D. W.; Bloomquist, W. E.; Wilson, H. C. LY215840, A Potent 5-Hydroxytryptamine (5-HT)$_2$ Receptor Antagonist, Blocks Vascular and Platelet 5-HT$_2$ Receptors and Delays Occlusion in a Rabbit Model of Thrombosis. *J. Pharmacol. Exp. Ther.* **1992**, *261*, 202–261. (d) Foreman, M. M.; Fuller, R. W.; Nelson, D. L.; Calligaro, D. O.; Kurz, K. D.; Misner, J. W.; Garbrecht, W. L.; Parli, C. J. Preclinical Studies on LY237733, A Potent and Selective Serotonergic Antagonist. *J. Pharmacol. Exp. Ther.* **1991**, *260*, 51–57.

(4) Flaugh, M. E.; Mullen, D. L.; Fuller, R. W.; Mason, N. R. 6-Substituted 1,3,4,5-Tetrahydrobenz[*cd*]indol-4-amines: Potent Serotonin Agonists. *J. Med. Chem.* **1988**, *31*, 1746–1753.

(5) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, J. M.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. The Total Synthesis of Lysergic Acid. *J. Am. Chem. Soc.* **1956**, *78*, 3087–3114.

(6) Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. Bicyclic and Tricyclic Ergoline Partial Structures. Rigid 3-(2-Aminoethyl)-pyrroles and 3- and 4-(2-Aminoethyl)pyrazoles as Dopamine Agonists. *J. Med. Chem.* **1980**, *23*, 481–491.

(7) Ninomiya, I.; Kiguchi, T. Ergot Alkaloids. In *The Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 38, pp 1–156.

(8) Nichols, D. E.; Robinson, J. M.; Li, G. S.; Cassady, J. M.; Floss, H. G. An Improved Synthesis of 1-Benzoyl-4-keto-1,2,2a,3,4,5-Hexahydrobenz[*cd*]indole. *Org. Prep. Proc. Int.* **1977**, *9*, 277–280.

(9) Martinelli, M. J.; Leanna, M. R.; Varie, D. L.; Peterson, B. C.; Kress, T. J.; Wepsiec, J. P.; Khau, V. V. The Synthesis of (+)- and (−)-1-Benzoyl-1,2,2a,3,4,5-Hexahydrobenz[*cd*]indol-4-amine, and Preparation of LY228729. *Tetrahedron Lett.* **1990**, *31*, 7579–7582.

(10) Leanna, M. R.; Martinelli, M. J.; Varie, D. L.; Kress, T. J. Diastereoselectivity in Ergoline Synthesis: A Face Selective Epoxidation *Tetrahedron Lett.* **1989**, *30*, 3935–3938.

(11) Marzoni, G.; Garbrecht, W. L. N^1-Alkylation of Dihydrolysergic Acid. *Synthesis* **1987**, 651–653.

(12) Cohen, M. L.; Fuller, R. W.; Kurz, K. D. LY53857, A Selective and Potent 5HT$_2$ Receptor Antagonist, Does Not Lower Blood Pressure in the Spontaneously Hypertensive Rat. *J. Pharmacol. Exp. Ther.* **1983**, *227*, 327–332.

(13) Marzoni, G.; Garbrecht, W. L.; Fludzinski, P.; Cohen, M. L. 6-Methylergoline-8-carboxylic Acid Esters as Serotonin Antagonists: N^1-Substituent Effects on 5HT$_2$ Receptor Affinity. *J. Med. Chem.* **1987**, *30*, 1823–1826.

(14) Fludzinski, P.; Wittenauer, L. A.; Schenck, K. W.; Cohen, M. L. 2,3-Dialkyl(dimethylamino)indoles: Interaction with 5HT$_1$, 5HT$_2$, and Rat Stomach Fundal Serotonin Receptors. *J. Med. Chem.* **1986**, *29*, 2415–2418.

(15) Moon, M. W.; Morris, J. K.; Heier, R. F.; Chidester, C. G.; Hoffmann, W. E.; Piercey, M. F.; Althaus, J. S.; Von Voigtlander, P. F.; Evans, D. L.; Figur, L. M.; Lahti, R. A. Dopaminergic and Serotonergic Activities of Imidazoquinolinones and Related Compounds. *J. Med. Chem.* **1992**, *35*, 1076–1092.