# 6-Substituted 1,3,4,5-Tetrahydrobenz[cd]indol-4-amines: Potent Serotonin Agonists

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A series of 6-substituted tricyclic ergoline partial structures has been synthesized and found to possess very strong serotonin agonist activity. A methoxy group at the 6-position greatly enhances activity, but at the expense of compound stability. Substituting the 6-position with protophyllic groups that are also electron-withdrawing in character enhances both activity and stability.

The ABC tricyclic partial ergoline 1 was synthesized first by Stoll and Petrzilka<sup>1</sup> and then by Harris and Uhle.<sup>2</sup> More recently the synthesis of both 1 and 2 was reported by Bach et al.<sup>3</sup> of our laboratories. In this latter paper it was also reported that 1 and 2 exhibited substantial dopaminergic character. In addition to this published observation, it was also noted that these compounds displayed significant affinity for serotonin receptors. Perceiving that 1 and 2 are in fact rigid analogues of tryptamine, we reasoned that a similar structure bearing a hydroxyl group or some comparable protophilic<sup>4</sup> group at position 6 (e.g., 3-5) would be a closer analogue of serotonin. Because of the greatly restricted mobility of the amine moiety imposed by the tricyclic structure, one might anticipate an enhancement of specificity for certain serotonin receptor subtypes. It was one or more of the above considerations that led ourselves as well as groups at Troponwerke (Glaser et al.<sup>5</sup>) and at SK&F (Kruse and Meyer<sup>6</sup>) to decide independently to undertake the synthesis of compounds 4 and 5.

6-Methoxy Analogues 4 and 5. Our first synthesis of 4 and 5 followed the general scheme used by Bach et al.<sup>3</sup> to make 1 and 2 (see Scheme I). Benzyl 5-methoxyindole-3-propionate (6) was prepared by using our previously reported procedure.<sup>7</sup> Reduction with  $NaCNBH_3/$ HOAc followed by N-benzoylation and hydrogenolysis afforded 9, which was readily cyclized by using PPA. As in the previously cited prototype, carbonyl transposition was effected by reduction, dehydration, epoxidation, and ZnI<sub>2</sub>-promoted epoxide rearrangement. Oximination and hydrogenation of 14 produced two readily separable diastereomeric amines, 16 and 17, assignment of the relative stereochemistry of which was based on their NMR spectra. Either of these primary amines could be bisalkylated, debenzoylated, and oxidized to give 4 and 5. Unlike the literature prototype, this final step could not be achieved with MnO<sub>2</sub>. The indoline oxidation procedure of Kikugawa<sup>8</sup> ultimately afforded 4 and 5 in what proved to be the only low-yield step of this synthesis.

6-Carboxamido Analogues 24 and 25. From preliminary pharmacological evaluation of 4 and 5 (see below), it was immediately evident that these compounds are potent serotonin agonists. Equally evident was the fact that both are extremely sensitive to acid. Salts of each

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- (2) Harris, L. S.; Uhle, F. C. J. Pharmacol. Exp. Ther. 1960, 128, 358.
- (3) Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. J. Med. Chem. 1980, 23, 481.
- (4) The term "protophilic" is used herein to denote the capability of forming a hydrogen-bonding interaction with a suitability disposed receptor proton.
- (5) Glaser, T.; Junge, B.; Traber, J.; Allen, G. German Patent DE 3346573 A1, 1985; Chem. Abstr. 1985, 103, 178166s.
- (6) Kruse, L. I.; Meyer, M. D. J. Org. Chem. 1984, 49, 4761.
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- (8) Kikugawa, Y.; Kawase, M. Chem. Lett. 1981, 445.



 $^a$  (a) NaCNBH<sub>3</sub>/HOAc; (b) BzCl/pyr; (c) H<sub>2</sub>/Pd on C; (d) PPA, 80 °C; (e) NaBH<sub>4</sub>/EtOH; (f) Amberlyst-15, 110 °C; (g) m-ClPhCO<sub>3</sub>H/CHCl<sub>3</sub>; (h) ZnI<sub>2</sub>/C<sub>6</sub>H<sub>6</sub>; (i) NH<sub>2</sub>OH; (j) H<sub>2</sub>/Ni; (k) Et-CHO/HOAc/NaCNBH<sub>3</sub>; (l) H<sup>+</sup>/H<sub>2</sub>O; (m) Me<sub>2</sub>S/NCS, -78 °C; (n) Et<sub>3</sub>N.





could be prepared, but they invariably decomposed rapidly in solution or when exposed to heat or moist air. By comparison, salts of the previously known compounds 1 and 2 were only moderately sensitive, and amines 18-23, the indoline precursors to 4 and 5, were also reasonably stable to acid. We therefore postulated that the sensitivity



# Figure 1.

of 4 and 5 is the result of the C-N bond at position 4 being weakened by a transannular effect exerted by the very electron-rich methoxyindole moiety (Scheme II). Loss of secondary amine following protonation would produce the cation 27. The positively charged carbon atom at position 4 of this cation is in a proximity to the indole  $\pi$ -system that should permit interaction with that orbital at both position 2a and position 5a, thus creating an exceptional homobenzylic-type stabilization. The cation might then attract a nucleophile or eject a proton.<sup>9</sup> This assumption leads to the prediction that replacing the methoxy group with some alternative protophilic group that tends to withdraw electrons should suppress acid sensitivity.

It has been suggested that high electron density in the indole ring is essential to the affinity of serotonin to its receptors.<sup>6,10</sup> This generalization fails to distinguish between cases in which the electron density reducing feature is remote from the protophilic group at the indole's 5position and those in which these two groups are one and the same. In the former cases, one can easily recognize that the electron density of the aromatic system could directly influence the protophilic character of a substituent such as a hydroxy or alkoxy group at the 5-position. In the latter case, however, electron density is no longer a significant factor in the contribution of the 5-substituent toward receptor affinity. In point of fact, it has been claimed that replacing the hydroxyl group of serotonin with carboxamide functions results in a series of compounds with pharmacological properties that are consistent with a retention of serotonin receptor affinity.<sup>11</sup>

In order to apply the general synthetic scheme described above to the synthesis of the carboxamide-substituted analogues 24 and 25, some significant modifications were required. Limitations in the scope of the intramolecular acylation used to form 10 precluded starting with indole-5-carboxamide or, for that matter, with 5-bromoindole. For this reason the decision was made to introduce a bromo group onto the appropriate position following the intramolecular acylation and to replace this halogen with a carboxamide at the end of the synthesis. The prospect of reductive debromination forced us to set aside the oxime reduction used above in favor of a simple reductive amination. The three-step sequence to introduce the tertiary

Scheme III



° (a) NaBH<sub>4</sub>/EtOH; (b) Br<sub>2</sub>/HOAc; (c) Cl<sub>3</sub>CCH<sub>2</sub>OCOCl/pyr; (d) 220 °C; (e) PrNH<sub>2</sub>/HOAc/NaCNBH<sub>3</sub>/MeCN; (f) (EtCO)<sub>2</sub>O/pyr; (g) BH<sub>3</sub>/THF; (h) Zn/HOAc; (i) MnO<sub>2</sub>/C<sub>6</sub>H<sub>14</sub>; (j) CuCN, 200 °C; (k) PPA, 85 °C.

amino group at the 4-position was found to be more efficient than a direct amination with a secondary amine, but it necessitated protecting the 1-position again, this time as a carbamate. This modified plan is shown in Scheme III.

The debenzoylated "Kornfeld-Woodward ketone" 28<sup>12</sup> was reduced to the alcohol 29, which proved to be the substrate of choice for bromination of the 6-position. Advantage was taken of the fact that protection of the 1-position of 29 with trichloroethyl chloroformate also gave a carbonate moiety at the 5-position. Thermolysis of this carbonate afforded the olefin 32, which was converted to the ketone 33 as before. Reductive amination of 33 with NaCNBH<sub>3</sub> and PrNH<sub>2</sub> gave the amine 34 as a mixture of diastereomers. Acylation with propionic anhydride and then reduction with BH<sub>3</sub>/THF produced the tertiary amines 35 and 36, which could be separated easily. As before, the relative stereochemistry was based on NMR spectra. Cleavage of the carbamate with Zn/HOAc and oxidation of the resulting indoline gave the indole 37. Note that in this case oxidation of 35 could be achieved with  $MnO_2$  in a yield that was quite good. The bromo group

<sup>(9)</sup> No effort has been made to isolate and characterize the artifacts from the decomposition of 4, 5, or 37; however, in each case we have noted a prominant decomposition product, which rapidly air oxidizes to an intensely colored intermediate (violet in the case of 4 and 5, green in the case of 37) and subsequently to a black, intractable material. These properties are consistent with elimination followed by oxidation to a fully unsaturated benz[cd]indole, which in turn decomposes.

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<sup>(11)</sup> Feniuk, W.; Humphrey, P. P. A.; Watts, A. D. Br. J. Pharmacol. 1984, 82, 209P.

<sup>(12)</sup> Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Woodward, R. B. J. Am. Chem. Soc. 1956, 78, 3087.



compound	x	R			in vivo <sup>b</sup>	
			in vitro <sup>a</sup>		5HIAA in	serum
			[ <sup>3</sup> H]-5HT: IC <sub>50</sub> , nM	[ <sup>3</sup> H]SPIP: IC <sub>50</sub> , nM	hypothalamus, % of control	corticosterone, $\mu/100 \text{ mL}$
control					$100 \pm 4$	$5 \pm 1$
2	Н	n-Pr	$141 \pm 38 (3)$	$723 \pm 63 (3)$		
4	OMe	n-Pr	$36 \pm 12 (3)$	$1179 \pm 63 (5)$	$58 \pm 2*$	$48 \pm 2^*$
5	OMe	Me	$96 \pm 34 (2)$	$1756 \pm 373$ (2)	$65 \pm 3*$	$41 \pm 4^*$
37	Br	n-Pr	$241 \pm 83$ (4)	$15444 \pm 3675$ (4)	$77 \pm 5*$	$13 \pm 2^*$
38	CN	n-Pr	90	390	$90 \pm 3$	$47 \pm 4^*$
24	CONH <sub>2</sub>	<i>n</i> -Pr	$83 \pm 26$ (6)	$4817 \pm 843$ (6)	61 ± 1*	$49 \pm 2^*$
25	CONH <sub>2</sub>	Me	390	5440	<b>99 ±</b> 3	9 ± 1*

<sup>a</sup>Number of replicates is found in parentheses. <sup>b</sup>Compounds were injected at 0.3 mg/kg sc 1 h before rats were killed.

of 37 was displaced with methoxide in the presence of CuI, giving a very good yield of 24. Thus Scheme III represents a more efficient synthesis of this compound than does Scheme I.

Displacement of the bromo group of 37 with cyanide ion was considerably more difficult than with methoxide. Nevertheless, by heating 37 with CuCN in *N*-methyl-2pyrrolidone for a minimal period it was possible to realize good yields of 38. The cyano group of 38 proved refractory to most conventional methods of hydration. Fortunately, PPA converted 38 to the desired final product very cleanly. That 24 possessed the desired stability to acid was readily confirmed, and its pharmacologic properties (see below) actually exceeded our expectations.

Application of Scheme III to the synthesis of the N,Ndimethyl analogue 25 led to an unexpected complication. Reductive amination of 33 with MeNH<sub>2</sub> and NaCNBH<sub>3</sub> followed by formylation with N-formylimidazole gave the anticipated mixture of diastereomeric amides 39 (see Scheme IV), but when these intermediates were taken on as in Scheme III to the dimethylamino analogue of 37, it was found that the cyanide displacement reaction with CuCN gave virtually no tractable products. Apparently the relatively unhindered dimethylamino group permits such a strong complexation with copper that the metal is able to cause decomposition in a manner not unlike that proposed for the salts of 4 and 5.

To avoid this complication the order of the steps was altered; that is, reduction of the formamido group was deferred until after the displacement with cyanide. Thus the (trichloroethoxy)carbonyl group was removed from the amides 39 with Zn/HOAc to give the easily separated amides 40 and 41. Each of these was then oxidized with  $MnO_2$ . Treatment of the indolic amide 42 with CuCN in N-methyl-2-pyrrolidone gave a particularly clean conversion to the nitrile 43, which lends support to the abovementioned conclusions regarding the sensitivity of the corresponding amines. Careful reduction of 43 with BH<sub>3</sub>/Me<sub>2</sub>S gave a good yield of the amine 44, and hydration with PPA proceeded well to afford the desired dimethylamino analogue 25. The key to the success of the variation of steps leading to 25 is the great facility of the reduction of the formamido group with borane. Ironically, when an attempt was made to apply this same variation to the synthesis of 24, reduction of the analogous propionamide with  $BH_3/Me_2S$  could not be carried out



<sup>a</sup> Conditions: (a)  $MeNH_2/HOAc/NaCNBH_3/MeCN$ ; (b) *N*-formylimidazole; (c) Zn/HOAc; (d)  $MnO_2/CH_2Cl_2$ ; (e) CuCN/200 °C; (f)  $BH_3:Me_2S/THF$ ; (g) PPA/85 °C.

without substantial reduction of the cyano group as well.

**Pharmacology.** The various serotonin analogues reported herein were evaluated for their ability to inhibit binding of tritiated serotonin to the serotonin-1 (5HT-1) receptor (method of Bennett and Snyder<sup>13</sup>) and of tritiated spiperone to the 5HT-2 receptor (method of Peroutka and Snyder<sup>14</sup>) in rat brain frontal cortex membranes. Eleven concentrations of test compound were used in duplicate between 0.1 and 10 000 nM. IC<sub>50</sub> values were defined as the amount that reduced specific binding of the radioactive ligand by 50%, and they were determined by using the ALLFIT curve-fitting program of Munson and Rodbard.<sup>15</sup> The resulting IC<sub>50</sub> values (shown in Table I) provide an indication of the relative affinities of the compounds for 5HT-1 and 5HT-2 receptors, respectively.

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<sup>(14)</sup> Peroutka, S. J.; Snyder, S. H. Mol. Pharmacol. 1979, 16, 687.

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A comparison of the  $IC_{50}$ 's found for the compound (1) previously prepared by Bach<sup>1</sup> and others<sup>2,3</sup> with values found for the newer compounds reveals that substituting the 6-position leads to a general enhancement of affinity for the 5HT-1 receptor and a loss of affinity for the 5HT-2 receptor. Not surprisingly our initial target compounds (4 and 5) with a 6-methoxy group exhibited the highest 5HT-1 affinity in this series. Replacing the N-propyl groups with N-methyl groups (5 and 25 vs 4 and 24) causes a decrease in affinity, a result consistent with the trend reported for the well-studied 8-substituted 2-aminotetralins.<sup>16</sup> The 6-carboxamido compounds (24 and 25) do not appear to bind to 5HT-1 receptors quite as well as the 6-methoxy compounds in this in vitro setting.

Serotonin agonist activity in vivo was determined by the ability of the compounds to decrease brain serotonin turnover<sup>17</sup> and to increase serum corticosterone concentration<sup>18</sup> in male Wistar rats. The concentration of 5hydroxyindoleacetic acid in whole brain was measured by liquid chromatography with electrochemical detection<sup>19</sup> as an index of serotonin turnover. Serum corticosterone concentration was measured spectrofluorometrically by the method of Solem and Brinck-Johnsen.<sup>20</sup>

A comparison of the in vivo serotonergic activity of the various analogues reveals that the relative order of potency in this assay roughly parallels that seen in the in vitro assay. Four of six 6-substituted compounds decreased 5HIAA concentration significantly. The 6-(aminocarbonyl)-N,N-dimethyl compound (25) had the lowest affinity among these compounds for the 5HT-1 binding site in vitro; it did not affect 5HIAA concentration in the hypothalamus and caused the least change in serum corticosterone concentration. The N,N-dipropyl compounds with a 6-aminocarbonyl (24) or 6-methoxy (4) substituent caused the largest changes in hypothalamic 5HIAA and serum corticosterone concentrations in vivo.

#### **Experimental Section**

All reactions were carried out under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover melting point apparatus and are not corrected. Sonications were conducted with a Branson Model B-12 ultrasonic cleaning tank. Although only selected spectral data are provided herein, all new compounds exhibited IR, UV, and NMR spectra consistent with the reported structures. IR spectra were determined with a Nicolet 10-MX spectrometer. UV spectra were run on a Cary 219 spectrophotometer. Mass spectra were determined with a CEC 21-110 electron-impact mass spectrometer. NMR spectra were run on a Varian T-60, a JEOL FX-90Q, a Bruker WM-270, a GE QE-300, or a Bruker WH-360 NMR spectrometer. All new compounds were subjected to elemental analysis, and unless otherwise indicated, results were within  $\pm 0.4\%$  of theoretical values.

Benzyl 2,3-Dihydro-1-benzoyl-5-methoxy-1H-indole-3**propanoate** (8). A solution of 26.0 g (84 mmol) of benzyl 5-methoxy-1*H*-indole-3-propanoate (6)<sup>7</sup> in 500 mL of HOAc was cooled as 26 g (0.41 mol) of NaCNBH<sub>3</sub> were added. The resulting reaction mixture was stirred at room temperature for 3.5 h and was then poured into 2 L of cold  $H_2O$ . The aqueous mixture was extracted with several portions of CH<sub>2</sub>Cl<sub>2</sub>. These extracts were combined, washed with aqueous  $NaHCO_3$ , and then dried over

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 $Na_2SO_4$ . Removal of the solvent in vacuo yielded 25.5 g of the crude indoline (7). This material, a viscous oil, was dissolved in 200 mL of CHCl<sub>3</sub>. While the mixture was being cooled with ice, 8 mL (0.10 mol) of pyridine was added followed by 11.5 mL (0.10 mol) of benzoyl chloride. The ice bath was removed, and the acylation mixture was stirred for 1 h. It was then washed once with H<sub>2</sub>O, twice with aqueous NaHCO<sub>3</sub>, and finally with aqueous NaCl. The  $CHCl_3$  solution was dried over  $Na_2SO_4$ , and the solvent was removed in vacuo. The crude product was dissolved in EtOAc and passed over a short Florisil column. Evaporating the EtOAc and allowing the residue to stand overnight afforded crystalline product. Recrystallization from toluene/hexane gave 30.2 g (87% yield) of 8: mp 102-103 °C; NMR (60 MHz, CDCl<sub>3</sub>) δ 2.0 (mult, 2 H, α-CH<sub>2</sub>), 2.4 (mult, 2 H, β-CH<sub>2</sub>), 3.3 (mult, 1 H, 3-H), 3.7 (mult, 1 H,  $2\beta$ -H), 3.8 (s, 3 H, OCH<sub>3</sub>), 4.2 (qt, 1 H,  $2\alpha$ -H), 5.1 (s, 2 H, PhCH<sub>2</sub>), 6.7 (mult, 1 H, 7-H), 6.8 (br s, 1 H, 4-H), 7.4 (mult, 1 H, 8-H), 7.4 (s, 5 H, Ph), 7.5 (s, 5 H, PhCO). Anal. (C<sub>26</sub>H<sub>25</sub>NO<sub>4</sub>) C. H. N.

Journal of Medicinal Chemistry, 1988, Vol. 31, No. 9 1749

2,3-Dihydro-1-benzoyl-5-methoxy-1H-indole-3-propanoic Acid (9). A solution of 17.0 g (41 mmol) of the benzyl ester 8 in 125 mL of warm THF was diluted with 125 mL of EtOH. It was then hydrogenated at 40 psi over 1 g of 10% Pd/C. After the solvents were filtered and evaporated, the product was recrystallized from EtOH. The recrystallized 9, mp 169-170 °C, weighed 12.5 g (94% yield): NMR (60 MHz, Me<sub>2</sub>SO- $d_6$ )  $\delta$  1.8 (mult, 2 H, α-CH<sub>2</sub>), 2.3 (mult, 2 H, β-CH<sub>2</sub>), 3.4 (mult, 1 H, 3-H), 3.7 (mult, 1 H,  $2\beta$ -H), 3.8 (s, 3 H, OCH<sub>3</sub>), 4.2 (qt, 1 H,  $2\alpha$ -H), 6.8 (mult, 1 H, 7-H), 6.9 (br s, 1 H, 4-H), 7.6 (s, 5 H, Ph), 7.6 (mult, 1 H, 8-H). Anal. (C<sub>19</sub>H<sub>19</sub>NO<sub>4</sub>) C, H, N.

1,2,2a,3-Tetrahydro-1-benzoyl-5-methoxybenz[*cd* ]indol-5(4H)-one (10). Over a 10-min period, 19.0 g (58 mmol) of the acid 9 was added to 350 g of polyphosphoric acid that was mechanically stirred and had been preheated in an oil bath maintained at 80-85 °C. After another 90 min, the mixture was cooled and then carefully treated with ice chips until the complex was destroyed. Further dilution with water precipitated the crude 10. This material was dissolved in  $CH_2Cl_2$  and was washed with NaHCO<sub>3</sub> solution. The  $CH_2Cl_2$  was dried over  $Na_2SO_4$  and then evaporated. Recrystallization of the residue from toluene afforded 15.0 g (84% yield) of 10: mp 152-153 °C; IR (KBr) v<sub>max</sub> 1634, 1672 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{max}$  236 nm ( $\epsilon$  14 400), 251 (13 400), 273 sh (8100), 353 (3100); NMR (270 MHz, Me<sub>2</sub>SO-d<sub>6</sub>) δ 1.81 (quint, 1 H,  $3\beta$ -H), 2.18 (br d, 1 H,  $3\alpha$ -H), 2.53 (mult, 2 H, 4-CH<sub>2</sub>), 3.33 (mult, 1 H,  $2\beta$ -H), 3.61 (mult, 1 H,  $2\alpha$ -H), 3.80 (s, 3 H, OCH<sub>3</sub>), 4.14 (mult, 1 H, 2α-H), 6.97 (mult, 1 H, 7-H), 7.59 (mult, 5 H, Ph), 8.11 (mult, 1 H, 8-H). Anal. (C<sub>19</sub>H<sub>17</sub>NO<sub>3</sub>) C, H, N.

1,2,2a,3,4,5-Hexahydro-1-benzoyl-5-methoxybenz[cd]indol-5-ol (11). A suspension of 29.9 g (97 mmol) of the ketone 10 in 350 mL of EtOH was treated gradually with a solution of 5.5 g (145 mmol) of NaBH<sub>4</sub> in 150 mL of EtOH. Compound 10 slowly dissolved, producing a pale green solution. After the mixture was stirred for 4 h, the bulk of the EtOH was evaporated under vacuum. The residual material was taken up in 400 mL of H<sub>2</sub>O. The pH of this mixture was adjusted to 7 by adding 3 N HCl. The precipitated product was extracted into  $CH_2Cl_2$ . After being dried  $(Na_2SO_4)$ , the  $CH_2Cl_2$  was evaporated leaving a nearly quantitative yield of 11, which crystallized upon trituration with toluene. This material had a broad melting range (133-160 °C), as expected for a mixture of epimers, but the elemental analysis and spectra established its purity: IR (CHCl<sub>3</sub>)  $\nu_{\rm max}$  1632 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\rm max}$  273 nm ( $\epsilon$  7900), 302 sh (6000). Anal. (C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub>) C, H, N.

1,2,2a,3-Tetrahydro-1-benzoyl-5-methoxybenz[cd]indole (12). A mixture of 30.1 g (97 mmol) of the alcohol 11 and 4.0 g of Amberlyst-15 resin in 350 mL of toluene was refluxed in a flask fitted with a Dean-Stark trap. Removal of H<sub>2</sub>O was complete within 3 h. The catalyst was removed by filtration, and the toluene was removed under vacuum. Trituration of the residue with hexane gave crystalline 12 weighing 27.2 g (96% yield), mp 125-126 °C. For analysis and spectral characterization, a sample was recrystallized from toluene/hexane: mp 126-127 °C; IR (CHCl<sub>3</sub>)  $\nu_{\rm max}$  1631 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\rm max}$  236 nm ( $\epsilon$  13 300), 320 sh (3500). Anal.  $(C_{19}H_{17}NO_2)$  C, H, N.

1,2,2a,3,4,5-Hexahydro-1-benzoyl-5-methoxy-4,5-epoxybenz[cd]indole (13). After a solution of 27.2 g (93 mmol) of the olefinic compound 12 in 1 L of CHCl<sub>3</sub> was cooled to 0-5 °C, 21.8

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g (107 mmol) of 3-chloroperoxybenzoic acid (85% pure) was added. Stirring at <5 °C was continued for 5 h. The mixture was then washed twice with 1 N NaOH, twice with NaHSO<sub>3</sub> solution, and once again with 1 N NaOH. Evaporation of the CHCl<sub>3</sub> gave an oil, which crystallized when triturated with toluene. After recrystallization from toluene the yield of 13 was 24.5 g (86%), mp 174–175 °C. The question as to whether the 13 so obtained is a single epimer or a mixture of epimers has not been pursued because it has no bearing on the rearrangement that follows: IR (CHCl<sub>3</sub>)  $\nu_{max}$  1634 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{max}$  273 nm ( $\epsilon$  10700), 300 sh (7700). Anal. (C<sub>19</sub>H<sub>17</sub>NO<sub>3</sub>) C, H, N.

1,2,2a,3-Tetrahydro-1-benzoyl-5-methoxybenz[cd]indol-4(5H)-one (14). A suspension of 5.0 g of  $ZnI_2$  in 650 mL of benzene was dried by distillation of 50 mL of the solvent. The temperature was allowed to drop to about 50 °C, and 24.5 g (80 mmol) of the epoxide(s) 13 were added in small portions over a period of 15 min. The temperature rose to near reflux during this addition. Following the addition, the temperature was maintained at reflux for 1 h. After cooling, the solution was washed with NaCl solution and was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent and recrystallization from EtOAc afforded 21.3 g (87% yield) of 14: mp 188-189 °C; IR (CHCl<sub>3</sub>) v<sub>max</sub> 1636, 1717 cm<sup>-1</sup>; NMR (270 MHz, CDCl<sub>3</sub>) δ 2.34 (qt, 1 H, 3β-H), 2.90 (br d, 1 H, 3α-H), 3.31 (d, 1 H, 5β-H), 3.66 (d, 1 H, 5α-H), 3.8 (mult. 2 H,  $2a\alpha$ -H and  $2\beta$ -H), 3.80 (s, 3 H, OCH<sub>3</sub>), 4.33 (mult, 1 H,  $2\alpha$ -H), 6.75 (mult, 1 H, 7-H), 7.54 (mult, 5 H, Ph), 7.96 (mult, 1 H, 8-H). Anal. (C<sub>19</sub>H<sub>17</sub>NO<sub>3</sub>) C, H, N.

1,2,2a,3-Tetrahydro-1-benzoyl-5-methoxybenz[*cd*]indol-4(5*H*)-one Oxime (15). A solution of 10.0 g (33 mmol) of the ketone 14, 10 g of hydroxylamine hydrochloride, 50 mL of pyridine, and 250 mL of EtOH was boiled for 15 min. The hot solution was diluted with 500 mL of hot H<sub>2</sub>O. Upon cooling, 10.5 g (99% yield) of crystalline 15 separated: mp 193 °C; IR (CHCl<sub>3</sub>)  $\nu_{max}$ 1634 cm<sup>-1</sup> (both C=O's); MS, *m/e* 322. Anal. (C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

 $(2a\alpha, 4\alpha)$ -1,2,2a,3,4,5-Hexahydro-1-benzoyl-5-methoxybenz[cd]indol-4-amine (16) and (2aa,4b)-1,2,2a,3,4,5-Hexahydro-1-benzoyl-5-methoxybenz[cd]indol-4-amine (17). A hydrogenation of 10.5 g (33 mmol) of the oxime 15 was carried out in ethanolic ammonia at 100 °C and 750 psi with 10 g of Raney Ni catalyst. At the end of 10 h the hydrogenation was stopped. The catalyst was filtered off, and the solvents were evaporated. The crude product was dissolved in 0.5 N HCl. This solution was washed with CH<sub>2</sub>Cl<sub>2</sub>. It was then basified with 1 M NaOH, and the product was extracted into CHCl<sub>3</sub>. Evaporation of this extract gave the crude mixture of epimeric amines as a viscous oil. When this mixture was dissolved in toluene, the majority of one of the amines crystallized. Careful addition of hexane to the mother liquor completed this separation. The crystallization epimer 16 (Tentative assignment based on NMR spectra-particularly those of 19, 21, and 23; see below.), mp 140-144 °C, weighed 4.17 g (41% yield): IR (CHCl<sub>3</sub>)  $\nu_{max}$  1631 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{max}$  275 nm ( $\epsilon$ 11 500), 300 sh (9000); MS, m/e 308. Anal. (C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>) C, H, Ν

Evaporation of the mother liquor gave epimer 17, a viscous oil weighing 4.41 g (43% yield). This epimer showed a slightly higher  $R_f$  than did 16 on silica gel TLC (10% EtOAc/90% toluene). Its UV extinctions and elemental analysis indicate that it was slightly impure as isolated. It was used without further purification: IR (CHCl<sub>3</sub>)  $\nu_{max}$  1630 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{max}$  274 nm ( $\epsilon$  10400), 300 sh (8100); MS, m/e 308. Anal. (C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>) Calcd: C, 74.00; H, 6.54; N, 9.08. Found: C, 72.73; H, 6.27; N, 8.19.

 $(2a\alpha,4\alpha)$ -1,2,2a,3,4,5-Hexahydro-1-benzoyl-5-methoxy-N,-N-dipropylbenz[cd]indol-4-amine (18). When a suspension of 1.36 g (4.42 mmol) of the primary amine 16 in 12.5 mL of MeCN was treated with 1.9 mL (26 mmol) of propionaldehyde, the solid immediately dissolved. To this solution was added 0.45 g (7.2 mmol) of NaCNBH<sub>3</sub> followed by enough HOAc to lower the pH to 7 (as measured by moist Hydrion pH paper). The reaction mixture was stirred for 3 h while occasionally a drop of HOAc was added. At the end of this time frothing had ceased, and TLC indicated that no 16 remained. The mixture was poured into 2 N NaOH and extracted with ether. The product was extracted from the ether solution with 1 N HCl. This aqueous solution was washed twice with ether and then basified with 2 N NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. Evaporation of the solvent after drying over  $Na_2SO_4$  afforded 1.07 g (63% yield) of 18 as a viscous oil, showing only one spot by TLC. Treatment of a sample of this material with ethereal HCl produced a salt that analyzed correctly for H, N, and Cl but was 2% low in C. This product was spectrally identical with the material from the PrI alkylation procedure given below, and it could be converted to 19 in comparable yield.

Alternatively, a solution of 16 in MeCN could be treated with a large excess of PrI in the presence of  $K_2CO_3$  to provide 18 in a slightly higher yield (68–75%). The HCl salt of this product gave a good analysis. Unfortunately this reaction is extremely slow. Monopropyl compound was still present after 14 days: IR (CHCl<sub>3</sub>)  $\nu_{max}$  1636 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{max}$  274 nm ( $\epsilon$  10 800), 300 sh (8400); MS, m/e 392. Anal. (C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>·HCl) C, H, N, Cl.

 $(2a\alpha,4\alpha)$ -1,2,2a,3,4,5-Hexahydro-5-methoxy-N,N-dipropylbenz[cd]indol-4-amine (19). A solution of 1.39 g (3.54 mmol) of 18 in 20 mL of 6 N HCl was refluxed under nitrogen for 3 h. After cooling, the solution was basified with 5 N NaOH and then extracted with  $CH_2Cl_2$ . The extract was dried ( $Na_2SO_4$ ) and evaporated. The crude 19 was purified either by chromatography over Florisil with 2% MeOH in EtOAc or by being taken up in pentane and filtering off the insoluble byproducts. Crystallization from isooctane then gave 0.80 g (78% yield) of 19: mp 73-74 °C; IR (CHCl<sub>3</sub>) v<sub>max</sub> 3380 cm<sup>-1</sup>; NMR (270 MHz, CDCl<sub>3</sub>)  $\delta 0.89$  (t, 6 H, CCl<sub>3</sub>), 1.39 (qt, J = 12, 12, and 12 Hz, 1 H,  $3\beta$ -H), 1.48 (sextet, 4 H,  $CH_2Me$ ), 2.16 (br d, J = 12 Hz, 1 H,  $3\alpha$ -H), 2.47 (mult, 5 H, CH<sub>2</sub>Et and 5 $\beta$ -H), 2.83 (qt, J = 6 and 16 Hz, 1 H, 5a-H), 3.14 (mult, 3 H, 2a-H, 2B-H, and NH), 3.48 (br s, 1 H, 2aα-H), 3.62 (mult, 1 H, 4α-H), 3.77 (s, 3 H, OCH<sub>3</sub>), 6.46 (qt, 2 H, 7-H and 8-H). Anal. (C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O) C, H, N.

 $(2a\alpha,4\beta)$ -1,2,2a,3,4,5-Hexahydro-1-benzoyl-5-methoxy-N,-N-dipropylbenz[*cd*]indol-4-amine (20). Reductive alkylation of 17 according to the procedure described above for the preparation of 18 gave an identical yield (63%) of 20. As before, the HCl salt so obtained analyzed slightly low (i.e., 1.2%) in C. Also as before, analytically pure product was obtainable in good yield by alkylation with PrI: IR (CHCl<sub>3</sub>)  $\nu_{max}$  1631 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{max}$  274 nm ( $\epsilon$  10500), 300 sh (7200); MS, *m/e* 392. Anal. (C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>·HCl) C, H, N, Cl.

(2aα,4β)-1,2,2a,3,4,5-Hexahydro-5-methoxy-N,N-dipropylbenz[*cd*]indol-4-amine (21). Hydrolysis of 20 as described above for the preparation of 19 produced 21 in 52% yield: mp 75–78 °C (from isooctane); IR (CHCl<sub>3</sub>)  $\nu_{max}$  3380 cm<sup>-1</sup>; NMR (270 MHz, CDCl<sub>3</sub>) δ 0.87 (t, 6 H, CCH<sub>3</sub>), 1.45 (mult, 5 H, CH<sub>2</sub>Me and 3α-H), 2.20 (sextet, J = 6, 7, and 14 Hz, 1 H, 3β-H), 2.49 (mult, 5 H, CH<sub>2</sub>Et and 5α-H), 2.91 (qt, J = 4 and 14 Hz, 1 H, 5β-H), 3.12 (mult, 2 H, 2α-H and 2β-H), 3.26 (mult, 1 H, 2aα-h), 3.64 (mult, 1 H, 4β-H), 3.77 (s, 3 H, OCH<sub>3</sub>), 6.48 (qt, 2 H, 7-H and 8-H). Anal. (C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O) C, H, N.

1,3,4,5-Tetrahydro-5-methoxy-N,N-dipropylbenz[cd]indol-4-amine (4). From 19: A suspension of 0.14 g (1.05 mmol) of NCS in toluene at 0 °C was treated with 0.20 mL (2.72 mmol) of Me<sub>2</sub>S. After 15 min the temperature was lowered to -78 °C with dry ice/acetone, and a solution of 0.25 g (0.87 mmol) of 19 in 1 mL of toluene was added. After another hour at -78 °C, a solution of 5 mmol of NaOEt in 3 mL of EtOH was added. The mixture was stirred at room temperature for 2 h. It was then poured into cold H<sub>2</sub>O and extracted with toluene. The toluene was evaporated, and the residue was chromatographed over 5 g of silica gel with 5% EtOAc in toluene. The product from the column was an amber oil weighing 50 mg (20% yield).

From 21: Oxidation of 0.93 g of 21 was carried out according to the above procedure with the exception that the treatment with NaOEt was replaced by an addition of 2 equiv of  $Et_3N$ . The yield of 4 after chromatography was 0.44 g (42%).

From 37 (see below): A solution of 12 mmol of NaOMe in 3 mL of MeOH was added to 10 mL of N<sub>2</sub>-sparged DMF followed by 0.30 g (1.6 mmol) of CuI. To this suspension was added 0.20 g (0.60 mmol) of 37. The mixture was heated at 130 °C for 5 h. It was then cooled and filtered. The filtrate was diluted with cold H<sub>2</sub>O and extracted with ether. The extracts were washed with NaCl solution and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the ether the product was chromatographed as above. The yield of 4 was 137 mg (80%). In all cases the product was an oil, which crystallized upon standing or seeding. It could be recrystallized from isooctane: mp 87–89 °C; UV (EtOH)  $\lambda_{max}$  278 nm ( $\epsilon$  5200), 301 (4700), 311 sh (3500); MS, m/e 286 and 186 (M – 100, loss of Pr<sub>2</sub>N); NMR of HCl salt (270 MHz, CDCl<sub>3</sub>)  $\delta$  1.02 (mult, 6 H, CCH<sub>3</sub>), 1.99 (mult, 4 H, CH<sub>2</sub>Me), 3.04 (t, J = 14 and 14 Hz, 1 H,  $3\alpha$ -H), 3.17 (mult, 5 H, CH<sub>2</sub>Et and  $5\alpha$ -H), 3.47 (br d, J = 14, 1 H,  $3\beta$ -H), 3.77 (br d, J = 14 Hz,  $5\beta$ -H), 3.80 (mult, 1 H,  $4\beta$ -H), 3.89 (s, 3 H, OCH<sub>3</sub>), 6.85 (d, 1 H, 8-H), 6.94 (s, 1 H, 2-H), 7.19 (d, 1 H, 7-H), 8.18 (s, 1 H, NH), 12.14 (br s, 1 H, HCl). Anal. (C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O) C, H, N.

 $(2a\alpha,4\beta)$ -1,2,2a,3,4,5-Hexahydro-1-benzoyl-5-methoxy-N,-N-dimethylbenz[cd]indol-4-amine (22). To a solution of 2.41 g (7.8 mmol) of 17 in 25 mL of MeCN was added 3.2 mL of formalin solution (37%) and 0.78 g (12.4 mmol) of NaCNBH<sub>3</sub>. Enough HOAc was then added to lower the pH to 7 (according to moist Hydrion pH paper). The mixture was stirred for 2 h. It was then poured into 2 N NaOH and extracted with ether. The product was extracted from the ether solution with 1 N HCl. This aqueous solution was basified with 2 N NaOH and extracted with  $CH_2Cl_2$ . The solvent was evaporated from the extract, and the residue was chromatographed over Florisil with 2% MeOH in EtOAc. The product from the column was converted to an HCl salt with ethereal HCl. The yield of this salt was 1.99 g (68%): IR (CHCl<sub>3</sub>)  $\nu_{max}$  1637 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$  274 nm ( $\epsilon$  12000), 300 sh (9300); MS, m/e 335. Anal. (C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>·HCl) C, H, N, Cl.

 $(2a\alpha,4\beta)$ -1,2,2a,3,4,5-Hexahydro-5-methoxy-N,N-dimethylbenz[*cd*]indol-4-amine (23). A solution of 1.90 g (5.09 mmol) of the HCl salt of 22 in 20 mL of 3 M H<sub>2</sub>SO<sub>4</sub> was refluxed under N<sub>2</sub> for 3 h. It was cooled, extracted twice with ether, basified with 5 N NaOH, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The solvent was removed from this extract, and the crude product was chromatographed over a short Florisil column with 5% MeOH in EtOAc. The purified 23 was an amber oil weighing 1.06 g (90% yield): IR (CHCl<sub>3</sub>)  $\nu_{max}$  3380 cm<sup>-1</sup>; NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$  1.48 (sextet,  $J = 4, 12, \text{ and } 14 \text{ Hz}, 1 \text{ H}, 3\alpha$ -H), 2.29 (mult, 1 H, 3 $\beta$ -H), 2.38 (s, 3 H, NCH<sub>3</sub>), 2.42 (s, 3 H, NCH<sub>3</sub>), 2.50 (mult, 1 H, 5 $\alpha$ -H), 2.82 (qt, J = 6 and 16 Hz, 1 H, 5 $\beta$ -H), 3.10 (mult, 2 H, 2 $\alpha$ -H and 2 $\beta$ -H), 3.30 (mult, 1 H, 2a $\alpha$ -H), 3.49 (br s, 1 H, NH), 3.71 (mult, 1 H,  $4\beta$ -H), 3.78 (s, 3 H, OCH<sub>3</sub>), 6.48 (qt, 2 H, 7-H and 8-H). Anal. (C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O) C, H, N.

1,3,4,5-Tetrahydro-5-methoxy-N,N-dimethylbenz[cd]indol-4-amine (5). Oxidation of 23 was carried out according to the procedure described for the conversion of 19 to 4. The crude product was chromatographed over Florisil with 2% MeOH in EtOAc. The product from the column was an oil, which crystallized on standing. The yield of 5, mp 133–136 °C, was 14%: UV (EtOH)  $\lambda_{max}$  277 nm ( $\epsilon$  4600), 300 (4150), 311 sh (3100); MS m/e 230; NMR of HCl salt (270 MHz, CDCl<sub>3</sub>)  $\delta$  2.86 (d, 3 H, NCH<sub>3</sub>), 2.97 (d, 3 H, NCH<sub>3</sub>), 3.04 (qt, J = 11 and 14 Hz, 1 H,  $3\alpha$ -H), 3.18 (qt, J = 14 and 14 Hz, 1 H,  $5\alpha$ -H), 3.51 (br d, J =14 Hz, 1 H,  $3\beta$ -H), 3.67 (br d, J = 14 Hz, 1 H,  $5\beta$ -H), 3.80 (mult, 1 H,  $4\beta$ -H), 3.90 (s, 3 H, OCH<sub>3</sub>), 6.87 (d, 1 H, 8-H), 6.96 (s, 1 H, 2-H), 7.19 (d, 1 H, 7-H), 8.00 (s, 1 H, NH), 12.79 (br s, 1 H, HCl). Anal. (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O) C, H, N.

1,2,2a,3,4,5-Hexahydrobenz[cd]indol-5-ol (29). A portionwise addition of 1.63 g (42.9 mmol) of NaBH<sub>4</sub> was made to a mixture of 5.00 g (28.6 mmol) of 2810 and 100 mL of EtOH. After 4 h of stirring, the bulk of the EtOH was removed under vacuum. The residual slurry was taken up in  $H_2O$  and treated with 3 N HCl until acidic. This solution was then treated with 2 N NaOH to precipitate the product. After being collected, washed with H<sub>2</sub>O, and dried; 29 weighed 4.72 g (93% yield). This crude product was a mixture of epimeric alcohols but was reasonably pure. The crude product from larger runs was recrystallized from MeOH to give the major epimer in 70% yield, mp 205 °C: NMR (300 MHz, Me<sub>2</sub>SO- $d_6$ )  $\delta$  1.46 (quint, 1 H, 3 $\beta$ -H), 1.57 (quint, 1 H, 4 $\alpha$ -H), 2.03 (mult, 1 H,  $3\alpha$ -H), 2.15 (mult, 1 H,  $4\beta$ -H), 2.88 (mult, 1 H, 2β-H), 2.97 (mult, 1 H, 2α-H), 3.47 (t, 1 H, 2aα-H), 4.59 (qt, 1 H, 5β-H), 5.08 (d, 1 H, NH), 5.31 (s, 1 H, OH), 6.32 (d, 1 H, 8-H), 6.63 (d, 1 H, 6-H), 6.87 (d, 1 H, 7-H). Anal. (C<sub>11</sub>H<sub>13</sub>NO) C, H, Ν

1,2,2a,3,4,5-Hexahydro-6-bromobenz[cd]indol-5-ol (30). A solution of 35.0 g (0.20 mol) of crude 29 in 1 L of HOAc was treated with a solution of 32 g (0.20 mol) of  $Br_2$  in 150 mL of HOAc. The bulk of the HOAc was removed under vacuum. The residue was diluted with  $H_2O$  and basified with 5 N NaOH. The crude product mixture contained 29, 30, and considerable dibromo product (very sparingly soluble in MeOH). Recrystallization from MeOH af-

forded 24.1 g (47% yield) of reasonably pure **30**, still a mixture of epimers. Elemental analysis proved slightly high in Br and low in C, indicating the presence of a trace of dibromo product: IR (CHCl<sub>3</sub>)  $\nu_{\rm max}$  3410, 3570 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{\rm max}$  211 nm ( $\epsilon$  25 400), 254 (8500), 304 (2300); MS m/e 253 (<sup>79</sup>Br), 255 (<sup>81</sup>Br). Anal. (C<sub>11</sub>H<sub>12</sub>BrNO) Calcd: C, 51.99; H, 4.76; N, 5.51; Br, 31.44. Found: C, 49.04; H, 4.52; N, 4.92; Br, 31.88.

1,2,2a,3,4,5-Hexahydro-6-bromo-1-[(2,2,2-trichloroethoxy)carbonyl]-5-[[(2,2,2-trichloroethoxy)carbonyl]oxy]benz[cd]indole (31). A solution of 24.0 g (94.5 mmol) of 30 in 100 mL of pyridine was cooled in ice as 31 mL (225 mmol) of 2,2,2-trichloroethyl chloroformate was added over a 20-min period. An addition of 1 g of 4-(dimethylamino)pyridine was made, and the solution was stirred at room temperature for 5 h. The solution was then poured into 1 L of cold  $H_2O$ . This two-phase mixture was stirred until the organic layer solidified. The aqueous supernatant was extracted with CH<sub>2</sub>Cl<sub>2</sub>. This extract was combined with a CH<sub>2</sub>Cl<sub>2</sub> solution of the solid material and was then washed with 1 N HCl. After the mixture was dried over  $Na_2SO_4$ , the  $CH_2Cl_2$  was evaporated, leaving an oil that slowly solidified. The still oily product was broken up under hexane, the hexane was decanted, and the solid was washed with fresh hexane. Evaporation of the hexane solutions left an oil, which also slowly solidified when warmed under a vacuum. After being washed again with hexane, this solid was combined with the main crop. After further drying (50 °C at 4 mm of pressure), the total yield of 31 was 54.9 g (96%). This crude product, still a mixture of epimers, gave a good analysis. It melted over a broad range and decomposed above 205 °C: IR (CHCl<sub>3</sub>)  $\nu_{max}$  1718, 1758 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$  251 nm ( $\epsilon$  40 000), 316 (3510). Anal. (C<sub>17</sub>H<sub>14</sub>BrCl<sub>6</sub>NO<sub>5</sub>) C, H, N, Br, Cl.

1,2,2a,3-Tetrahydro-6-bromo-1-[(2,2,2-trichloroethoxy)carbonyl]benz[cd]indole (32). Thermolysis of 31 was carried out on 10-g portions, each portion being heated under N<sub>2</sub> for 20 min in an oil bath preheated to 210 °C. Most of the residual trichloroethanol was removed by warming in vacuo. The crude product was then chromatographed over silica gel with toluene. The product from the column crystallized upon trituration with hexane. Yields from these runs were typically 70–75%: mp 115–117 °C; IR (CHCl<sub>3</sub>)  $\nu_{max}$  1717 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$  213 nm ( $\epsilon$  19000), 255 (10 000), 291 (2100). Anal. (C<sub>14</sub>H<sub>11</sub>BrCl<sub>3</sub>NO<sub>2</sub>) C, H, N, Br, Cl.

1,2,2a,3-Tetrahydro-6-bromo-1-[(2,2,2-trichloroethoxy)carbonyl]benz[cd]indol-4(5H)-one (33). A solution of 10 g (24.3 mmol) of 32 in 500 mL of CHCl<sub>3</sub> was cooled to 0-5 °C and then was treated with 6.0 g (30 mmol) of 3-chloroperoxybenzoic acid (85%). The reaction mixture was maintained at <5 °C for 15 h. It was then worked up as described above for 13. The crude epoxidation product was recrystallized from toluene/hexane (1:3) to give, in two crops, 9.22 g (89% yield) of analytically pure material. Of this material, 9.0 g (21.1 mmol) was rearranged to 33 with  $ZnI_2$  as described above for 14. The crude product was chromatographed over silica gel with 2.5% EtOAc in toluene and then crystallized from toluene/hexane. The purified 33, mp 177-178 °C, weighed 5.60 g (62% yield): IR (CHCl<sub>3</sub>) v<sub>max</sub> 1718 cm<sup>-1</sup> (both C=O's); UV (EtOH)  $\lambda_{max}$  212 nm ( $\epsilon$  26000), 256 (17000); NMR (90 MHz, CDCl<sub>3</sub>)  $\delta$  2.35 (qt, 1 H, 3 $\beta$ -H), 3.04 (qt, 1 H,  $3\alpha$ -H), 3.52 (d, 1 H,  $5\beta$ -H), 3.63 (d, 1 H,  $5\alpha$ -H), 3.79 (mult, 2 H,  $2a\alpha$ -H and  $2\beta$ -H), 4.54 (mult, 1 H,  $2\alpha$ -H), 4.84 (br s, 2 H, CH<sub>2</sub>CCl<sub>3</sub>), 7.40 (br s, 2 H, 7-H and 8-H). Anal. (C<sub>14</sub>H<sub>11</sub>BrCl<sub>3</sub>NO<sub>3</sub>) C, H, N.

1,2,2a,3,4,5-Hexahydro-6-bromo-1-[(2,2,2-trichloroethoxy)carbonyl]-N,N-dipropylbenz[cd]indol-4-amine (34). A mixture of 11.8 g (27.6 mmol) of 33, 23.9 mL (291 mmol) of PrNH<sub>2</sub>, and 4.13 mL (72 mmol) of HOAc in 250 mL of MeCN was stirred under N<sub>2</sub> for 90 min. An addition of 4.72 g (75 mmol) of NaC-NBH<sub>3</sub> was made followed by 11.8 mL (210 mmol) of HOAc and 1 g of 3-Å molecular sieves. At 2-h intervals, two additional 5.9-mL (100-mmol) portions of HOAc were introduced. After a total of 7.5 h, the red solution was decanted from the sieves, and the bulk of the MeCN was removed under vacuum. The red oil that remained was added to cold 2 N NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. This extract was washed with H<sub>2</sub>O and then with NaCI solution. After the extract was dried over Na<sub>2</sub>SO<sub>4</sub>, the solvent was evaporated, leaving crude secondary amine as a red oil. This intermediate was acylated directly by dissolving in 75 mL of pyridine, cooling with ice, and treating with 14 mL (109 mmol) of propionic anhydride. The acylation mixture was allowed to stand overnight. Most of the pyridine was removed under vacuum, and the residue was taken up in 25 mL of CH<sub>2</sub>Cl<sub>2</sub>. The excess anhydride was destroyed by stirring this solution with saturated Na<sub>2</sub>CO<sub>3</sub> solution for a few hours. The resulting mixture was treated with CH<sub>2</sub>Cl<sub>2</sub> containing 5% i-PrOH. The organic layer was separated and washed successively with 0.5 N NaOH, 1 N HCl, and NaCl solution. After the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, the solvents were evaporated. the crude amide that remained was reduced by dissolving in 40 mL of THF and adding over 15 min to 60 mL of 1 M BH<sub>3</sub>/THF maintained at 0 °C. The solution was refluxed for 90 min. It was then cooled, and the excess hydride was destroyed by carefully adding 10 mL of MeOH. The solvents were again removed in vacuo, and the residual material was dissolved in 20 mL of DMSO containing 5%  $H_2O$ . This solution was heated on a steam bath for 15 min,<sup>21</sup> cooled, diluted with NaHCO<sub>3</sub> solution, and extracted with CH2Cl2 containing 5% i-PrOH. After the mixture was washed with NaCl solution and dried over  $Na_2SO_4$ , the  $CH_2Cl_2$  was evaporated. The crude 34 was chromatographed over 100 g of silica gel with EtOAc. Recrystallization of the product from the column from isooctane gave, in three crops, a total of 12.3 g (87% overall yield) of 34. While analytically pure, the product had a melting range (97-105 °C) and a complex NMR spectrum that supported the expectation that it was a mixture of epimers: IR (CHCl<sub>3</sub>)  $\nu_{max}$  1716 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$  212 nm  $(\epsilon 30400), 253(19000), 284(2400).$  Anal.  $(C_{20}H_{26}BrCl_3N_2O_2) C$ , H, N, Br, Cl.

(2aα,4α)-1,2,2a,3,4,5-Hexahydro-6-bromo-N,N-dipropylbenz[cd]indol-4-amine (35) and  $(2a\alpha, 4\beta)$ -1,2,2a,3,4,5-Hexahydro-6-bromo-N,N-dipropylbenz[cd]indol-4-amine (36). A solution of 11.75 g (22.9 mmol) of 34 in 350 mL of HOAc and 40 mL of H<sub>2</sub>O was stirred with 37.5 g of Zn dust for 3 h. The unreacted Zn was filtered off, and most of the HOAc was removed from the filtrate under vacuum. The oil that remained was taken up in CH<sub>2</sub>Cl<sub>2</sub> and carefully treated with NaHCO<sub>3</sub> to remove the last of the HOAc. The Zn salts that separated during this process were removed by filtration though Celite. The organic layer was separated from the two-phase filtrate, and the aqueous layer was extracted with fresh CH2Cl2. The combined extracts were washed with NaCl solution and dried over  $Na_2SO_4$ . The crude product left after evaporation of the CH2Cl2 was chromatographed over Florisil with EtOAc. The product from the column was recrystallized from isooctane to give 3.90 g of analytically pure material, mp 60-62 °C. A comparison of the NMR spectrum of this material with those of 19, 21, and 23 revealed that it was in fact a 1:1 mixture of 35 and 36. Evaporation of the mother liquors afforded 3.74 g of an oil, which, though less pure, was also a mixture of 35 and 36: IR (CHCl<sub>3</sub>)  $\nu_{max}$  3400 cm<sup>-1</sup>; UV 210 nm ( $\epsilon$  29 000), 251 (9300), 295 (2200); MS, m/e 336 (<sup>79</sup>Br), 338 (<sup>81</sup>Br). Anal. (C<sub>17</sub>-H<sub>25</sub>BrN<sub>2</sub>) C, H, N, Br.

1,3,4,5-Tetrahydro-6-bromo-N,N-dipropylbenz[cd]indol-4-amine (37). A solution of 2.00 g of the mixture of 35 and 36 in 100 mL of hexane was sonicated (50–55 kHz) in the presence of 8.0 g of MnO<sub>2</sub> for 90 min. The oxidant was removed by filtration through Celite, and the solvent was evaporated. The crude 37 was combined with the product from a similar 1.90-g run (11.6 mmol in all) and chromatographed over 100 g of silica gel with 10% EtOAc in toluene. Crystallization of the product from isooctane gave 2.17 g (56% yield) of 37: mp 75–76 °C; IR (CHCl<sub>3</sub>)  $\nu_{max}$  3480 cm<sup>-1</sup>; MS, m/e 334 (<sup>79</sup>Br), 336 (<sup>81</sup>Br); NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$  0.92 (t, 6 H, CCH<sub>3</sub>), 1.49 (sextet, 4 H, CH<sub>2</sub>Me), 2.57 (t, 4 H, CH<sub>2</sub>Et), 2.75 (t, 1 H, 3 $\alpha$ -H), 2.79 (t, 1 H, 5 $\alpha$ -H), 2.96 (qt, 1 H, 3 $\beta$ -H), 3.13 (qt, 1 H, 5 $\beta$ -H), 3.24 (mult, 1 H, 4 $\beta$ -H), 6.85 (s, 1 H, 2-H), 7.01 (d, 1 H, 8-H), 7.24 (d, 1 H, 7-H), 7.87 (s, 1 H, NH). Anal. (C<sub>17</sub>H<sub>23</sub>BrN<sub>2</sub>) C, H, N, Br.

1,3,4,5-Tetrahydro-4-(dipropylamino)benz[cd]indole-6carbonitrile (38). A mixture of 1.00 g (2.99 mmol) of 37 and 0.70 g (7.82 mmol) of dried CuCN in 10 mL of N<sub>2</sub>-sparged Nmethyl-2-pyrrolidone was heated under N<sub>2</sub> for exactly 1 h in an oil bath preheated to 200 °C. The cooled reaction mixture was then poured into a mixture of ice and CH<sub>2</sub>Cl<sub>2</sub>. The precipitated Cu salts were removed by filtration though Celite. The aqueous layer of the filtrate was extracted with fresh CH<sub>2</sub>Cl<sub>2</sub>. The combined CH<sub>2</sub>Cl<sub>2</sub> solutions were then washed with dilute NH<sub>4</sub>OH and with NaCl solution. After the mixture was dried over Na<sub>2</sub>SO<sub>4</sub>, the CH<sub>2</sub>Cl<sub>2</sub> was evaporated, and the residue was warmed at 50 °C and 0.05 mm of pressure to remove the *N*-methyl-2-pyrrolidone. The crude product was chromatographed over 10 g of silica gel with 10% EtOAc in toluene and then crystallized from hexane containing a small amount of toluene. The crystalline **38** weighed 0.51 g (61% yield): mp 133–134 °C; IR (CHCl<sub>3</sub>)  $\nu_{max}$  2219, 3474 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{max}$  204 nm ( $\epsilon$  20500), 241 (54500), 282 (4700); MS, *m/e* 281. Anal. (C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>) C, H, N.

1,3,4,5-Tetrahydro-4-(dipropylamino)benz[cd]indole-6carboxamide (24). To 30 g of polyphosphoric acid (PPA) mechanically stirred and heated in an oil bath maintained at 85 °C was added 1.50 g (5.34 mmol) of 38. After 5 h the mixture was cooled, and the PPA was carefully decomposed with ice chips. The resulting solution was further diluted with cold water, basified with 2 N NaOH, and extracted with  $CH_2Cl_2$ . The  $CH_2Cl_2$  was evaporated, and the crude 24 was chromatographed over 30 g of Florisil with 10% MeOH in EtOAc. Trituration of the product from the column with hot toluene gave reasonably pure 24. Recrystallization from EtOAc/toluene (1:2) provided 1.08 g (68% yield) of product, mp 163-164 °C, which analyzed correctly after block drying at 120 °C but which tended to retain solvated EtOAc. A purer sample, mp 165-166 °C, could be obtained by redissolving the product in CH<sub>2</sub>Cl<sub>2</sub> containing 2% MeOH, adding toluene, seeding, and slowly evaporating the CH<sub>2</sub>Cl<sub>2</sub> and MeOH under vacuum: IR (CHCl<sub>3</sub>) v<sub>max</sub> 1661, 3410, 3477, 3530 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$  242 nm ( $\epsilon$  34 500), 284 (5500); MS, m/e 299, 199 (loss of Pr<sub>2</sub>N); NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$  0.91 (t, 6 H, CCH<sub>3</sub>), 1.48 (sextet,  $\overline{4}$  H,  $CH_2Me$ ), 2.57 (t, 4 H,  $CH_2Et$ ), 2.80 (t, 1 H,  $3\alpha$ -H), 2.98 (qt, 1 H,  $3\beta$ -H), 3.02 (t, 1 H,  $5\alpha$ -H), 3.22 (mult, 1 H,  $4\beta$ -H), 3.54 (qt, 1 H, 5β-H), 5.72 (br s, 2 H, NH<sub>2</sub>), 6.90 (s, 1 H, 2-H), 7.15 (d, 1 H, 8-H), 7.45 (d, 1 H, 7-H), 8.04 (s, 1 H, NH). Anal.  $(C_{18}H_{25}N_3O)$  C, H,

N-[1,2,2a,3,4,5-Hexahydro-6-bromo-1-[(2,2,2-trichloroethoxy)carbonyl]-4-benz[cd]indolyl]-N-methylformamide (39). A cold solution of 4.4 g (140 mmol) of MeNH<sub>2</sub> in 100 mL of MeCN was treated with 1.9 mL (33 mmol) of HOAc followed by 1.5 g (24 mmol) of NaCNBH<sub>3</sub>, 7.3 g (17 mmol) of 33, and 2 g of 3-Å molecular sieves. After 2 h, 6.2 mL (108 mmol) of HOAc was added; at 2-h intervals, two successive additions of 1.3 mL of HOAc were made. After a total of 8 h, the reaction mixture was decanted from the sieves and then poured into cold 2 N NaOH and extracted with  $CH_2Cl_2$ . The solvent was removed from this extract under vacuum, and the residue was partioned between Et<sub>2</sub>O and 1 N HCl. The aqueous layer was basified with 1 N NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. After this layer was washed with NaCl solution and dried over Na<sub>2</sub>SO<sub>4</sub>, the CH<sub>2</sub>Cl<sub>2</sub> was evaporated from the extract leaving 6.4 g of crude secondary amine that was reasonably clean by NMR. This crude amine was formylated by dissolving in 25 mL of THF and adding to a solution of Nformylimidazole. This N-formylimidazole solution had previously been prepared in situ by combining a solution of 5.0 g (31 mmol) of 1,1'-carbonyldiimidazole in 75 mL of THF with a solution of 1.5 g of 98% HCOOH (32 mmol) in 25 mL of THF and stirring for 1 h. After 3 h the THF was removed from the formylation mixture under vacuum. The residue was stirred overnight with a two-phase mixture of  $CH_2Cl_2$  and  $NaHCO_3$ . The aqueous layer was extracted with fresh CH<sub>2</sub>Cl<sub>2</sub>. The combined CH<sub>2</sub>Cl<sub>2</sub> solutions were washed with 1 N HCl and with NaCl solution and then dried over  $Na_2SO_4$ . Removal of the solvent gave the expected mixture of epimeric formamides (39) as a viscous oil. Clean by NMR, this material was taken directly on to 40 and 41.

N-[(2a $\alpha$ ,4 $\alpha$ )-1,2,2a,3,4,5-Hexahydro-6-bromo-4-benz[cd]indoly1]-N-methylformamide (40) and N-[(2a $\alpha$ ,4 $\beta$ )-1,2,2a,3,4,5-Hexahydro-6-bromo-4-benz[cd]indoly1]-Nmethylformamide (41). The crude 39 was treated with Zn and HOAc as described above for the preparation of 35 and 36. The resulting crude product was a viscous oil weighing 4.28 g. When this material was taken up in toluene, one of the epimers (40, based on NMR) began to crystallize. After chilling, 2.15 g (43% yield based on 33) of 40 was collected: mp 177-179 °C; IR (CHCl<sub>3</sub>)  $\nu_{max}$  1667, 3400 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$  209 nm ( $\epsilon$  33000), 254 (9400), 295 (1900); MS, m/e 294 (<sup>79</sup>Br), 296 (<sup>81</sup>Br), 235 and 237 (loss of

<sup>(21)</sup> This use of wet DMSO to cleave the borane/amine complex will be discussed more fully in a separate publication.

# 1,3,4,5-Tetrahydrobenz[cd]indol-4-amines

MeNHCHO). Anal. (C<sub>13</sub>H<sub>15</sub>BrN<sub>2</sub>O) C, H, N, Br.

Evaporation of the mother liquor and chromatography of the residual oil over silica gel with EtOAc afforded 1.22 g (24% yield based on **33**) of the noncrystalline epimer **41** (assignment based on NMR): IR (CHCl<sub>3</sub>)  $\nu_{max}$  1664, 3400 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$  210 nm ( $\epsilon$  32 000), 255 (9100), 298 (2000); MS, m/e 294 (<sup>79</sup>Br), 296 (<sup>81</sup>Br), 235 and 237 (loss of MeNHCHO). Anal. (C<sub>13</sub>H<sub>15</sub>BrN<sub>2</sub>O) C, H, N, Br.

N-[1,3,4,5-Tetrahydro-6-bromo-4-benz[cd]indolyl]-N-methylformamide (42). A solution of 2.00 g (6.78 mmol) of 40 in 100 mL of CH<sub>2</sub>Cl<sub>2</sub> was sonicated (50–55 kHz) in the presence of 8.0 g of MnO<sub>2</sub> for 3 h. Removal of the oxidant by filtration through Celite and evaporation of the solvent gave 1.63 g of crude 42. Similar treatment of 1.15 g (3.90 mmol) of 41 afforded another 1.02 g of crude 42. These combined products were chromatographed over 50 g of silica gel by applying the products to the column with a minimal amount of EtOAc containing 5% MeOH and then eluting with EtOAc. Recrystallization of the chromatographed product from EtOAc provided 2.17 g (69% yield) of pure 42: mp 204–205 °C; IR (KBr)  $\nu_{max}$  1648 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$  227 nm ( $\epsilon$  38000), 288 (5700); MS, m/e 292 (<sup>79</sup>Br), 294 (<sup>81</sup>Br), 233 and 235 (loss of MeNHCHO). Anal. (C<sub>13</sub>H<sub>13</sub>BrN<sub>2</sub>O) C, H, Br, N.

N-[1,3,4,5-Tetrahydro-6-cyano-4-benz[cd]indoly1]-N-methylformamide (43). A mixture of 2.15 g (7.32 mmol) of 42 and 1.71 g (19.1 mmol) of dried CuCN in 20 mL of N<sub>2</sub>-sparged N-methyl-2-pyrrolidone was heated under N<sub>2</sub> at 200 °C for 4 h. The workup of the reaction was similar to that described for the preparation of 38 except that *i*-PrOH was added to the CH<sub>2</sub>Cl<sub>2</sub> to help dissolve the product. When triturated with toluene, the crude product crystallized. It was purified by digesting in hot EtOAc, chilling, and collecting. The yield of 43 was 0.57 g (58%): mp 203-205 °C; IR (KBr)  $\nu_{max}$  1650, 2213; UV (EtOH)  $\lambda_{max}$  205 nm ( $\epsilon$  25 000), 241 (58 000), 282 (5200); MS m/e 239, 180 (loss of MeNHCHO). Anal. (C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O) C, H, N.

1,3,4,5-Tetrahydro-4-(dimethylamino)benz[cd]indole-6carbonitrile (44). An ice-cooled mixture of 1.40 g (5.86 mmol) of 43 and 50 mL of THF was treated with 5.9 mL (11.8 mmol) of 2 M BH<sub>3</sub>/Me<sub>2</sub>S in THF. After the mixture was stirred at room temperature for 2.5 h, the excess hydride was destroyed by careful addition of 5 mL of MeOH. The solvents were evaporated under vacuum, and the residual oil was taken up in 20 mL of DMSO. A slurry of 1 g of NaHCO<sub>3</sub> and 3 mL of H<sub>2</sub>O was added to the solution, and it was heated on a steam bath for 10 min. After cooling, the solution was diluted with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> containing 5% *i*-PrOH. From this solution the product was extracted into 1 N HCl and then recovered from this acid extract by being treated with 1 N NaOH and reextracting with fresh CH<sub>2</sub>Cl<sub>2</sub> containing *i*-PrOH. Evaporation of these solvents after drying over Na<sub>2</sub>SO<sub>4</sub> afforded 0.97 g of crude 44, which was further purified by partially dissolving in hot EtOAc, adding toluene, and cooling. The purified 44 weighed 0.90 g (68% yield): mp 196–198 °C; IR (CHCl<sub>3</sub>)  $\nu_{max}$  2219, 3474 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$ 205 nm ( $\epsilon$  20000), 239 (51 000), 282 (4800); MS, m/e 225. Anal. (C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>) C, H, N.

1,3,4,5-Tetrahydro-4-(dimethylamino)benz[*cd*]indole-6carboxamide (25). A mechanically stirred stirred mixture of 0.90 g (4.00 mmol) of 44 and 20 g of PPA was heated at 85 °C for 6 h. After cooling, the mixture was carefully treated with cold H<sub>2</sub>O. The resulting aqueous solution was basified with 5 M NaOH, and the precipitated product was collected. The crude product was chromatographed over 14 g of Florisil with 10% MeOH in EtOAc. The product from the column was digested briefly in hot EtOAc, chilled, and collected. It weighed 0.43 g (44% yield): mp >230 °C dec; IR (KBr)  $\nu_{max}$  1655 cm<sup>-1</sup>; UV (EtOH)  $\lambda_{max}$  242 nm ( $\epsilon$ 36000), 282 (5500); MS, m/e 243, 199 (loss of Me<sub>2</sub>N); NMR (300 MHz, Me<sub>2</sub>SO-d<sub>6</sub>)  $\delta$  2.34 (s, 6 H, NCH<sub>3</sub>), 2.70 (qt, 1 H, 3 $\alpha$ -H), 2.84 (mult, 1 H, 4 $\beta$ -H), 2.95 (br d, 1 H, 3 $\beta$ -H), 3.01 (qt, 1 H, 5 $\alpha$ -H), 3.34 (s, 2 H, NH<sub>2</sub>), 3.43 (br d, 1 H, 5 $\beta$ -H), 7.01 (s, 1 H, 2-H), 7.09 (d, 1 H, 8-H), 7.30 (d, 1 H, 7-H), 10.77 (s, 1 H, NH). Anal. (C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>O) C, H, N.

Acknowledgment. We wish to thank Dr. D. E. Dorman and T. K. Elzey for their assistance in interpreting some of the NMR spectra and Harold D. Snoddy for the in vivo experiments in rats.

**Registry No.** 2, 69380-15-0; 4, 98770-53-7; 5, 92622-93-0; 6, 76834-79-2; 7, 100561-44-2; 8, 100561-45-3; 9, 2813-36-7; 10, 100561-46-4; cis-11, 114943-07-6; trans-11, 114943-21-4; 12, 114943-08-7; 13, 100561-49-7; 14, 114943-09-8; 15, 114943-10-1; 16, 114943-11-2; 17, 114943-12-3; 18, 114943-13-4; 18.HCl, 114943-41-8; 19, 114943-14-5; 20, 114943-15-6; 20-HCl, 114943-42-9; 21, 114943-16-7; 22, 114943-17-8; 22-HCl, 114943-06-5; 23, 114943-18-9; 24, 114943-19-0; 25, 114943-20-3; 28, 100561-34-0; cis-29, 114943-22-5; trans-29, 114943-26-5; cis-30, 114943-22-5; trans-29, 114943-24-7; trans-31, 114943-26-9; cis-34, 114943-25-8; 32 (epoxide), 100561-66-8; 33, 114943-26-9; cis-34, 114943-27-0; trans-34, 114943-31-6; cis-39, 114943-32-7; trans-39, 114943-30-5; 38, 114943-33-6; cis-31, 114943-32-7; 40, 114943-33-8; 41, 114943-34-9; 42, 114943-35-0; 43, 114943-36-1; 44, 114943-37-2.