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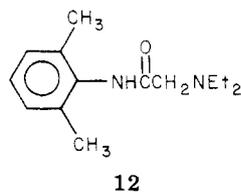
Oxindole-3-spiropyrrolidines and -piperidines. Synthesis and Local Anesthetic Activity

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The synthesis and local anesthetic properties of five 1-dealkyloxindole-3-spiropyrrolidines and six 1-dealkyloxindole-3-spiropiperidines are described. The compounds studied include members of all five possible positional isomers of the two classes of spirooxindoles; all showed local anesthetic activity by the rat sciatic nerve block method. The coincidence of the least variability in the relative positions of basic nitrogen, amide carbonyl, and aromatic ring (compounds 1 and 6) with lowest normalized toxicity is noteworthy.

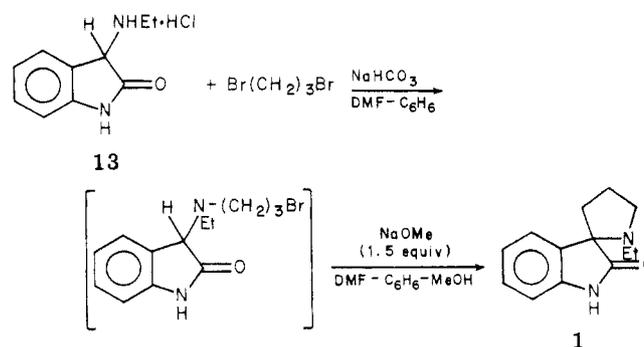
In our continuing search for novel local anesthetics,¹ we have synthesized and tested a number of oxindole-3-spiropyrrolidines and -piperidines (1-11). These compounds incorporate the principal structural moieties of the local anesthetic and antiarrhythmic drug lidocaine (12)—viz. an aromatic nucleus, an amide linkage, and a basic amino group—in a nearly rigid framework. Since both N-methylation and N-ethylation of the amide function in lidocaine congeners have been shown to result in decreased activity and increased toxicity,^{2a} we have limited this study to the 1-dealkyloxindoles.



The efficacy of lidocaine has led to the preparation of many different series of *N*-aminoacylanilines,^{2b-e} and there is a recognized need for local anesthetics with well-defined stereochemistry³ for use in the study of the concept of receptor(s) involved in blockage of nerve impulses. Conformational and other stereochemical effects on local anesthetic activity have been the subject of several recent studies,^{4a} some partially rigid local anesthetics have been synthesized,^{4b,c} and a highly rigid molecule, tetrodotoxin, has been found to have high local anesthetic potency.⁵ Nevertheless, we are aware of no attempts at molecular modification involving preparation of all possible positional isomers of a rigid local anesthetic.

The spirooxindoles discussed in this paper represent all possible isomeric types in the two classes of compounds being studied. The structural rigidity of each member is such that conformational variations in the spatial orien-

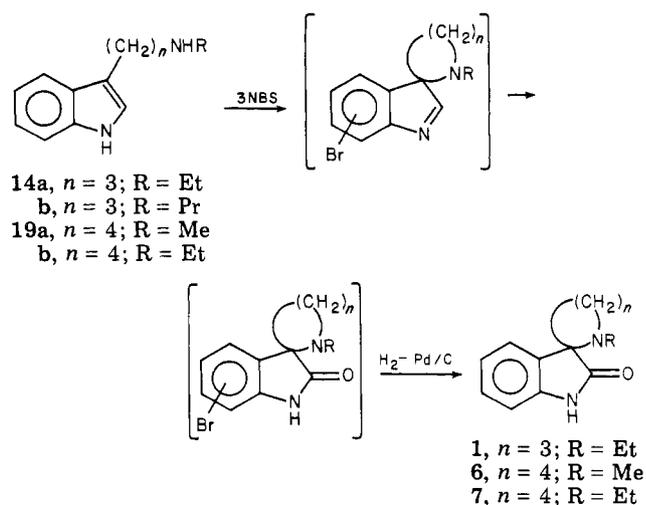
Scheme I



tation of component functional groups—known to be of considerable magnitude in flexible drug molecules⁶—are restricted within a narrow range. In isomers where the basic nitrogen is located next to the spiro carbon, the activity-controlling distance between the basic nitrogen, the amide carbonyl, and the aromatic ring^{2c} becomes completely fixed.

Although designed as lidocaine congeners, however, the resemblance of the title compounds to lidocaine is only superficial, and a closer examination shows that they possess unique structural features which set them apart from all known classes of local anesthetics. Significant differences can be discerned in the stereochemistry of lidocaine and our compounds. Thus, the spirooxindoles all have the *cis*-amide configuration while the *trans* configuration has been deduced for the protonated form of lidocaine^{7a} which is supposed to be the active form of this drug.⁸ Another difference is seen in the coplanarity of the amide carbonyl group with respect to the aromatic moiety; steric hindrance precludes such a conformation in the lidocaine molecule.^{7a,c} Finally, unlike in the case of

Scheme II



other amide- or ester-type local anesthetics, hydrolysis will not necessarily result in effective deactivation of our compounds; the resulting amino acid may conceivably regenerate the drug molecule by facile intramolecular ring closure.^{9a}

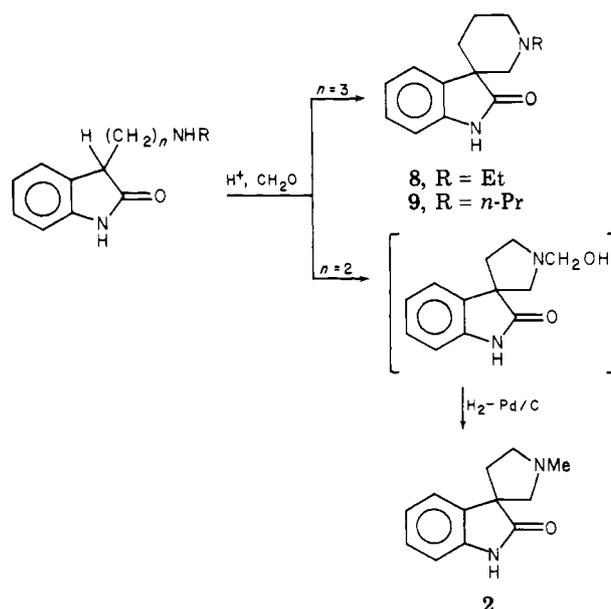
Chemistry. 2-Indolinone-3-spiro-2'-(*N*-ethylpyrrolidine) (1) was prepared via two independent routes (Schemes I and II). Scheme I involves a two-step alkylation of 3-(*N*-ethylamino)oxindole (13) by 1,3-dibromopropane. The preparation of 13 was accomplished via catalytic hydrogenation in the presence of PtO_2 catalyst of a solution of 3-(ethylimino)oxindole^{9b} in glacial acetic acid.

The second method for the preparation of 1 is an adaptation of the procedure used by Witkop et al. in the synthesis of 5-bromodioxindole-3-propionic acid lactone.¹⁰ Scheme II is depicted in analogy to the mechanism given for the lactone formation, but no effort has been made to isolate the intermediate indolenine. Since similar oxidations of *N*-acetyltryptamines using smaller proportion of oxidants have led to tricyclic pyrrolo[2,3-*b*]indoles via ring closure at the 2 position,^{11,12} an alternate pathway involving initial formation of tetrahydro- α -carbolines cannot be precluded. The intermediate 3-[3'-(ethylaminopropyl)]indole (14) was prepared from 3-indolepropionic acid via the amide by lithium aluminum hydride reduction. The products obtained via Schemes I and II were identical; a mixture melting point determination showed no depression.

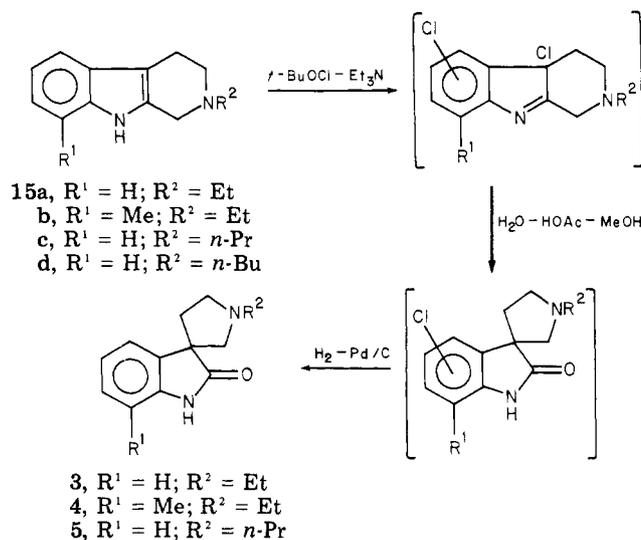
The (1-dealkyloxindole)-3-spiro-3'-(1'-alkylpyrrolidines) are closely related to the oxindole alkaloids.^{13,14} However, although Ghosal and Banerjee believe to have spectrophotometric evidence of the formation of 5-methoxy-2-indolinone-3-spiro-3'-(*N*-methylpyrrolidine) when they reacted 5-methoxy-3-(methylaminoethyl)indole with formaldehyde,¹⁵ the two examples presented in this paper seem to be the only reported synthesis of the simple members of this class of compounds.

2-Indolinone-3-spiro-3'-(*N*-methylpyrrolidine) (2) was prepared in poor yield via a Mannich reaction followed by catalytic hydrogenation of the intermediate *N*-methylol compound (Scheme III). The problems encountered in working out an analogous procedure have been related previously,^{9a} and it is of interest to note that, in contrast, a similar attempt is reported to yield 1-hydroxymethyl-2-indolinone-3-spiro-3'-pyrrolidine.¹⁶ The poor yield may be due to competing reactions involving the addition of formaldehyde to the 1 position of the oxindole¹⁶ and/or to decomposition of the product during distillation, since oxindoles are known to easily form 3,3-dimethylene-

Scheme III



Scheme IV



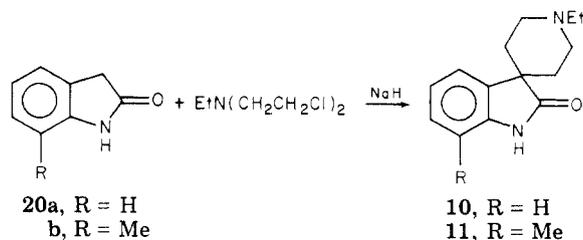
oxindoles upon heating.¹⁷ The product was identified by its characteristic uv, NMR,^{9a} and mass spectra^{18,19} and by comparison of these spectra with those of the *N*-ethyl homologue 3 which was synthesized via an independent route (vide infra).

2-Indolinone-3-spiro-3'-(*N*-ethylpyrrolidine) (3) was prepared in fair yield via an oxidative rearrangement of 2-ethyl-1,2,3,4-tetrahydro- β -carboline (15a) by adopting the procedure of Zinnes and Shavel²⁰ (Scheme IV). This type of rearrangement has been well documented.^{21,22} We have modified the procedure by the addition of a hydrogenation step to ensure the removal of any Cl which might have been introduced into the phenyl radical.²³ The same method was used in the synthesis of 7-methyl-2-indolinone-3-spiro-3'-(*N*-ethylpyrrolidine) (4) and of 2-indolinone-3-spiro-3'-(*N*-*n*-propylpyrrolidine) (5).

The 2-alkyltetrahydro- β -carbolines (15) were prepared from the appropriate 3-(alkylaminoethyl)indoles (16) and formaldehyde in glacial acetic acid via a Pictet-Spengler reaction.²⁴ The precursors 16 were made from the indole by the method of Speeter and Anthony.^{25,26}

2-Indolinone-3-spiro-2'-(*N*-methylpiperidine) (6) and 2-indolinone-3-spiro-2'-(*N*-ethylpiperidine) (7) were pre-

Scheme V



pared in poor yields from the appropriate 3-[4'-(alkylamino)butyl]indole (19) by application of reaction conditions analogous to those employed in the oxidative synthesis of the pyrrolidine analogues (Scheme II).²⁷

The precursors 19a and 19b were prepared in a manner analogous to the previously depicted synthesis of the homologous 3-[3'-(ethylamino)propyl]indole.

2-Indolinone-3-spiro-3'-(*N*-ethylpiperidine) (8) and 2-indolinone-3-spiro-3'-(*N*-propylpiperidine) (9) were prepared by a two-step synthesis from 14a and 14b, respectively. The first step involves an oxidative rearrangement of the appropriate indole to the corresponding oxindole by a procedure reported for a similar transformation by Hinman and Bauman.²⁸ The crude reaction product was subsequently ring closed via a Mannich reaction in the manner reported for the preparation of 2-indolinone-3-spiro-2'-piperolidine^{9a} (Scheme III).

1-Alkyl-2-indolinone-3-spiro-4'-(*N*-alkylpiperidines) have been prepared via direct alkylation of 1-alkyloxindoles with a nitrogen mustard in 1952.²⁹ The available literature on the alkylation of 1-dealkyloxindole^{30,31} does not seem to preclude the possibility of utilizing a similar approach for the synthesis of the analogous 1-dealkylspirooxindoles. However, the latter class of compounds has not been reported and the remark has been made that its preparation would present considerable problems.³² We now report the synthesis of two 2-indolinone-3-spiro-4'-(*N*-alkylpiperidines), i.e., 10 and 11, by direct alkylation (Scheme V). The yields, however, were low and no efforts have been made to optimize.

All structures have been found to be consistent with the elemental analysis and spectral data. Ultraviolet spectra of compounds 1-3, 6, 9, and 10, which represent the five different types of spirooxindoles, show the characteristic^{9a,33} absorption maxima between 248 and 252 nm (ϵ 7250-9000) and inflection between 270 and 285 nm (ϵ 1000-2250). The carbonyl absorption maxima in the infrared spectra occur between 1689 and 1718 cm^{-1} . The proton magnetic resonance spectra exhibit a very broad one-proton singlet in the δ 8.85-10.02 region (oxindole NH) which disappeared upon admixture of 1 drop of D_2O .

Mass spectral data are of particular importance in the elucidation of oxindole structures.¹⁸ In common with other amino lactams, formation of the major part of the important fragment ions seems to be triggered by the amino rather than by the lactam function.³⁴ The formation of the main fragments can thus be readily rationalized in analogy to the fragmentation of pyrrolidines and piperidines.^{35,36} In contrast to the mass spectra of the simple pyrrolidines and piperidines, however, the spirooxindole spectra do not exhibit strong $M - 1$ peaks. This is consistent with the presence of structural features which facilitate α -cleavage of C-C bonds.

Local Anesthetic Results. The local anesthetic activity was determined by the rat sciatic nerve block method as previously described.^{1b} Lidocaine was used as the standard. Results of these experiments are summarized in Table I. Toxicity data are recorded in Table II.

Table I. Local Anesthetic Activity. Rat Sciatic Nerve Block Method

Compound ^a	% as base	pH	Onset, min	Freq. quency	Duration, ^b min, mean \pm SD
1	1.0	5.1	6	10/10	83 \pm 26
1	2.0	5.1	5	9/10	107 \pm 22
Lidocaine (Lid.)	2.0	6.8	2	10/10	165 \pm 18
2	1.0	6.1	11	9/10	56 \pm 7
2	2.0	6.0	6	10/10	83 \pm 14
Lid.	2.0	6.6	2	10/10	172 \pm 9
3	1.0	6.0	4	5/5	67 \pm 9
3	2.0	6.0	3	5/5	85 \pm 4
Lid.	2.0	6.5	1	5/5	176 \pm 15
4-HCl	1.0	4.9	3	4/5	93 \pm 29
4-HCl	2.0	5.0	2	5/5	125 \pm 29 ^c
Lid.	2.0	5.4	1	5/5	149 \pm 12
5-HCl	1.0	5.3	3	5/5	66 \pm 13
5-HCl	2.0	5.4	2	5/5	78 \pm 16
Lid.	2.0	6.0	1	5/5	180 \pm 27
6	1.0	4.6	5	5/5	81 \pm 6
6	2.0	4.6	3	5/5	97 \pm 26
Lid.	2.0	4.5	1	5/5	175 \pm 29
9-H ₂ SO ₄	1.0	4.4	6	5/5	75 \pm 9
9-H ₂ SO ₄	2.0	4.3	4	5/5	95 \pm 6
Lid.	2.0	5.7	1	5/5	194 \pm 37
10	1.0	5.9	6	5/5	86 \pm 11
10	2.0	6.0	5	5/5	120 \pm 11
Lid.	2.0	6.6	1	5/5	152 \pm 13
11	1.0	4.8	3	5/5	131 \pm 44
11	2.0	4.9	3	5/5	227 ^d
Lid.	2.0	5.8	2	5/5	198 \pm 61
11 ^e	1.0	5.8	3	7/7	108 \pm 8
11 ^e	2.0	5.8	3	7/7	166 ^f
Lid. ^e	2.0	6.1	1	7/7	141 \pm 13

^a All solutions contained 1:100 000 epinephrine unless otherwise noted. ^b Since the duration of action of lidocaine varied in different runs, the value for lidocaine in each run is reported. ^c One animal died within 30 min. ^d Two animals "blocked" for 1 day and two died within 25 min. ^e Without epinephrine. ^f Mean of two animals; 5/7 died within 40 min.

Table II. Toxicity

Compound	pH	LD ₅₀ , mg/kg ^a	Norm toxicity ^b
Lidocaine	5.1	27 (20-41)	1.0
1	5.3	119 (105-135)	0.23
2		^c	
3	6.2	38 (30-55)	0.71
4	6.0	23 (19-28)	1.2
5	5.9	25 (22-30)	1.1
6	5.0	97 (86-112)	0.28
9	4.5	41 (34-199)	0.66
10	5.3	53 (46-60)	0.51
11	5.3	21 (16-33)	1.3

^a Intravenous in mice with 95% Fieller confidence limits. ^b Normalized toxicity in comparison to toxicity of lidocaine. ^c Not determined because of insufficient compound.

The structure-activity relationship results obtained in this work regarding methyl substitution on the aromatic ring parallel findings previously made for lidocaine analogues.³⁷

Among the spiro-pyrrolidines, the greatest activity resides in compound 4 which has a 7-methyl group and where the basic nitrogen is furthest removed from the spiro carbon. Compounds without the 7-methyl and possessing the 3'-pyrrolidine substituent are less active than 4. These compounds have similar activity even though the N-substituent changes progressively from methyl to ethyl to propyl. The indolinone with a 2'-pyrrolidine substituent

exhibited a longer duration than the isomeric 3'-pyrrolidine indolinone 3.

The compound showing the longest duration among the spiropiperidines also had a 7-methyl substituent in addition to a 4'-piperidine ring. The durations of anesthesia at 2% of the related 7-demethyl compound 10 approximate those seen with 2% lidocaine, but with longer onset times.³⁸ If the size of the *N*-alkyl substituent plays an insignificant role as was seen in the five-membered ring compounds, then it is not surprising that the indolinone with a 2'-(*N*-methylpiperidine) ring 6 is somewhat more active than the compound with a 3'-(*N*-propylpiperidine) ring 9.

Comparison of structure with acute toxicity showed an increase in toxicity with 7-methyl substitution. Indolinones with either a 2'-pyrrolidine or 2'-piperidine substituent (compounds 1 and 6) had the lowest iv toxicities. Apparently, an increase in size of the *N*-alkyl function also produces an increase in toxicity (compare 3 and 5).

Discussion

No definite conclusion about the stereochemical requirements of possible local anesthetic receptors can be drawn from the data presented in this paper; different types of pharmacological testing are necessary for such purpose.^{39a} However, the well-defined stereochemistry and the presence of an asymmetric spiro carbon^{39b} in these spirooxindoles should be of interest to workers engaged in studies of the local anesthetic receptor.

The coincidence of the least variability in the relative positions of the three pharmacophoric moieties, basic nitrogen, amide carbonyl, and aromatic ring (i.e., compounds 1 and 6), with lowest normalized toxicity is intriguing, particularly since it does not seem to be accompanied by a proportional decrease in activity. This suggests potential application in areas where the toxicity of lidocaine has been shown to be undesirably high, e.g., as antiarrhythmic drugs. Some studies along these lines are in progress in our laboratories.⁴⁰

Experimental Section

Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. All compounds analyzed within $\pm 0.4\%$ of theory. NMR spectra were obtained using a Varian A-60A spectrometer; uv spectra were recorded on a Beckman DK-2A; ir spectra were taken on a Beckman IR-8; and mass spectra were measured using a RMU-7 double-focusing mass spectrometer by Hitachi Perkin-Elmer. Melting points in capillary tubes were taken on a Thomas-Hoover apparatus, and others were taken on a Fisher-Johns apparatus; they are not corrected. TLC was performed on Eastman silica gel chromatogram sheets with fluorescent indicator.

2-Indolinone-3-spiro-2'-(*N*-ethylpyrrolidine) (1, Scheme I). To a water-cooled, dry suspension of NaHCO₃ (4.20 g, 0.050 mol) in a mixture of C₆H₆ (55 ml) and DMF (13 ml) was added, with stirring under N₂, 1,3-dibromopropane (5.05 g, 0.025 mol), followed by 3-(ethylamino)oxindole hydrochloride (13, 5.32 g, 0.025 mol). After stirring for 40 h at room temperature, the mixture was refluxed for 5 h, cooled in a water bath, and poured rapidly, under N₂, into a stirred solution of NaOMe (2 g) in MeOH (300 ml), which had been previously refluxed 0.5 h under N₂. The dark-pink suspension was stirred under N₂ at room temperature overnight, refluxed for 7 h, air cooled, acidified to pH 5 by the addition of HOAc (50 ml), and stirred overnight at room temperature. After removal of the volatile solvents on the rotary evaporator, the residue was covered with CH₂Cl₂ (50 ml) and H₂O (75 ml) and basified to pH 8 by the addition of solid Na₂CO₃. Workup of the CH₂Cl₂ extract yielded a thick pinkish liquid distillate (2.80 g, 55%), bp 154–164° (0.3–0.4 mmHg), which solidified spontaneously. Recrystallization from isopropyl ether-hexane (charcoal) afforded colorless crystals of 1: mp 142–144°; ir (KBr) 1695 cm⁻¹ (C=O); uv (MeOH) max 249 nm

(ϵ 6489), 272 sh (1432); NMR (CDCl₃) δ 0.95 (t, 3, CH₃), 1.82–2.67 (m, 6, all CH₂ except NCH₂), 3.02–3.47 (m, 2, ring NCH₂), 6.74–7.42 (m, 4, ArH), 9.15 ppm (br s, 1, ArNHCO); mass spectrum (70 eV) *m/e* (rel intensity) 261 (51), 201 (1), 188 (41), 187 (100), 173 (42), 159 (10), 145 (18), 130 (16), 117 (10). Anal. (C₁₃H₁₆N₂O) C, H, N.

2-Indolinone-3-spiro-2'-(*N*-ethylpyrrolidine) (1, Scheme II). A solution of NBS (21.4 g, 0.12 mol) in MeCN (200 ml) was added dropwise within 0.5 h, in a N₂ atmosphere, to a stirred, ice-cooled solution of 3-[3'-(ethylamino)propyl]indole (14, 8.08 g, 0.040 mol) in a mixture of MeCN (210 ml) and 2.0 M NaOAc buffer (480 ml, pH 3.8). After 0.25 h, the ice bath was removed and the mixture was stirred for an additional 2.75 h. A solution of 0.4 M ammonium formate buffer (160 ml, pH 3.8) was added, followed after 0.25 h by a suspension of KHCO₃ (100 g) in H₂O (200 ml) until the aqueous phase was basic to litmus. The mixture was then saturated with solid NaCl and extracted repeatedly with Et₂O. The Et₂O extract was evaporated, the residue was dissolved in 250 ml of 50% aqueous HOAc, and the resulting solution was hydrogenated (Parr, 2.8 g of 10% Pd/C) overnight. The filtered solution was evaporated, basified with NaHCO₃, and extracted with CHCl₃. The CHCl₃ extract, washed with warm H₂O, dried (MgSO₄), and evaporated, afforded 5.55 g of a dark-colored oil from which 1 (2.18 g, 25.2%) was isolated via dry-column chromatography (Woelm silica gel, EtOAc). Recrystallization gave a product, mp 145–146° (C₆H₆-hexane, charcoal), which showed ir and NMR spectra identical with those of 1 prepared via Scheme I. A mixture melting point showed no depression.

2-Indolinone-3-spiro-3'-(*N*-methylpyrrolidine) (2, Scheme III). A solution of 3-(2'-aminoethyl)oxindole hydrochloride (17c, 8.0 g, 0.038 mol) in HOAc (10 ml) and 37% CH₂O (6.1 ml, 0.075 mol) was added to a solution of NaOAc·3H₂O (5.12 g, 0.038 mol) in HOAc (30 ml) under N₂.^{9a} This reaction mixture was stirred under N₂ at room temperature for 48 h, refluxed for 1 h, diluted with MeOH (50 ml), and hydrogenated for 1 h at 50 psi of H₂ (Parr, 4.8 g of 10% Pd/C). After addition of more 37% CH₂O (6.1 ml, 0.075 mol), the mixture was hydrogenated for another 1 h and the catalyst filtered off. The solution was then basified under ice cooling by the addition of concentrated NaOH solution and extracted with CHCl₃. The dried (MgSO₄) CHCl₃ extract taken to dryness yielded a yellow powdery glass, which melted at 80–90° accompanied by much gas evolution. Vacuum distillation of this glass afforded 0.87 g of a very viscous yellow liquid [bp 166–174° (0.5 mmHg)] which solidified spontaneously. Recrystallization first from ligroine (bp 60–80°)-Et₂O (charcoal) and subsequently from hexane (charcoal) yielded 2 as near-colorless crystals: mp 123.5–124.5°; ir (KBr) 1695 cm⁻¹ (C=O); uv (MeOH) max 250 nm (ϵ 7718), 272 sh (1573); NMR (CDCl₃) δ 1.80–3.33 (m, 9, aliphatic H, including a CCH₂N s at 2.90 and an NCH₃ s at 2.47), 6.82–7.57 (m, 4, ArH), 9.58 ppm (br s, 1, ArNHCO); mass spectrum (70 eV) *m/e* (rel intensity) 202 (62), 185 (7), 174 (2), 159 (10), 145 (26), 130 (20), 117 (10), 57 (100). Anal. (C₁₂H₁₄N₂O) C, H, N.

2-Indolinone-3-spiro-3'-(*N*-ethylpyrrolidine) (3, Scheme IV). This experiment is based on a procedure of Zinnes and Shavel.²⁰ To minimize decomposition of *t*-BuOCl reagent, all operations prior to its removal from the reaction mixture were conducted under N₂ in the dark. A solution of *t*-BuOCl (3.24 g, 0.030 mol) in CH₂Cl₂ (6 ml) was added dropwise with stirring over a period of 15 min to a cooled (–40°) solution of 2-ethyl-1,2,3,4-tetrahydro- β -carboline (15a, 3.0 g, 0.015 mol) and Et₃N (3 ml) in CH₂Cl₂ (100 ml). The mixture was allowed to warm to –20° in 1 h, kept at this temperature for 1.5 h, and then treated with H₂O (100 ml). The CH₂Cl₂ layer was separated, washed with H₂O, dried (MgSO₄), and taken to dryness. To the residue were added consecutively MeOH (60 ml), H₂O (30 ml), and HOAc (0.3 ml). The resulting mixture was refluxed for 45 min, evaporated, mixed with H₂O (60 ml), acidified to pH 4 by the addition of dilute HCl, and filtered. The filtrate was basified with concentrated NH₄OH and extracted with CHCl₃. The dried (MgSO₄) CHCl₃ extract yielded 3.0 g of a brown-colored liquid residue which was dissolved in absolute EtOH (120 ml) and hydrogenated for 4.15 h (Parr, at 54 psi of H₂) in the presence of Et₃N (10 ml) and 5% Pd/C (10 g). The hydrogenated mixture showed a characteristic oxindole uv spectrum^{9a,33} and was evaporated to give a semisolid residue which was suspended in H₂O (25 ml). The suspension was ex-

tracted repeatedly with CHCl_3 at successively higher pH (pH 7–11, by addition of 1 N NaOH) and the combined dried (MgSO_4) CHCl_3 extract was evaporated to yield a yellow thick oily residue. Vacuum distillation of this oil afforded 1.41 g (43%) of product as a clear yellow, very viscous glass, 161–166° (0.40 mmHg), which crystallized after trituration with hexane. Recrystallization (hexane) afforded colorless crystals of **3**: mp 83.5–85°; ir (KBr) 1689 cm^{-1} (C=O); NMR (CDCl_3) δ 1.15 (t, 3, CH_3), 1.72–3.52 (m, 8, CH_2 , including a CCH_2N s at 2.92), 6.78–7.62 (m, 4, ArH), 9.42 ppm (br s, 1, ArNHCO); uv (MeOH) max 252 nm (ϵ 5066), 274 sh (1043); mass spectrum (70 eV) m/e (rel intensity) 216 (52), 201 (15), 199 (7), 187 (3), 172 (4), 159 (9), 145 (21), 130 (17), 117 (8), 71 (100). Anal. ($\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$) C, H, N.

7-Methyl-2-indolinone-3-spiro-3'-(N-ethylpyrrolidine) (4, Scheme IV). The synthesis of this compound from 2-ethyl-8-methyl-1,2,3,4-tetrahydro- β -carboline (**15b**, 6.4 g, 0.030 mol) and t -BuOCl (9.78 g, 0.090 mol) was conducted similar to the preparation of **3**, with the following modifications. After completion of the oxidation, the reaction mixture was treated with saturated aqueous NaCl solution and the separated CH_2Cl_2 layer washed with the same. After the acid-catalyzed rearrangement step, the filtrate was adjusted to pH 8 by the addition of solid Na_2CO_3 prior to extraction with CHCl_3 . The residue obtained after evaporation of the hydrogenated mixture was dissolved in CHCl_3 and the resulting CHCl_3 solution washed with two portions of 20% aqueous KHCO_3 solution, dried (MgSO_4), and evaporated on the rotary evaporator. The dark liquid residue was converted into the HCl salt. Recrystallization from absolute EtOH (charcoal) afforded 5.23 g (65%) of the HCl salt of **4**: mp 265–266° (sealed tube, decomposition); ir (KBr) 1715 cm^{-1} (C=O); NMR (D_2O) δ 1.45 (t, 3, CH_2CH_3), 2.12–4.03 (m, 11, CH_2 , including a CCH_2CH_2 t at 2.40, a CCH_2N s at 3.67, an ArCH_3 s at 2.25), 7.07–7.48 ppm (m, 3, ArH); mass spectrum (70 eV) m/e (rel intensity) 230 (62), 215 (16), 213 (9), 201 (5), 186 (4), 173 (11), 159 (31), 144 (12), 130 (12), 115 (7), 71 (100). Anal. ($\text{C}_{14}\text{H}_{19}\text{ClN}_2\text{O}$) C, H, N.

2-Indolinone-3-spiro-3'-(N-propylpyrrolidine) (5, Scheme IV). This compound was prepared as described for **4** from 2-propyl-1,2,3,4-tetrahydro- β -carboline (**15c**). The crude product (2.5 g, 73%) showed only one spot on TLC (C_6H_6 –EtOAc, 4:1) and was converted into the HCl salt (1.71 g, 43%): colorless crystals; mp 256–259° (absolute EtOH–Et₂O) (closed capillary, decomposition with gas evolution); ir (KBr) 1706 cm^{-1} (C=O); NMR (D_2O) δ 1.03 (t, 3, CH_3), 1.43–3.95 (m, 10, CH_2 , including a CCH_2CH_2 t at 2.39, a CCH_2N s at 3.66), 6.83–7.48 ppm (m, 4, ArH); mass spectrum (70 eV) m/e (rel intensity) 230 (31), 213 (3), 201 (100), 187 (2), 172 (13), 158 (7), 145 (13), 130 (16), 117 (9), 85 (27), 84 (68). Anal. ($\text{C}_{14}\text{H}_{19}\text{ClN}_2\text{O}$) C, H, N.

2-Indolinone-3-spiro-2'-(N-methylpiperidine) (6, Scheme II). This compound was prepared from 8.08 g (0.040 mol) of 3-[4'-(N-methylamino)butyl]indole (**19a**) and 21.4 g (0.12 mol) of NBS in a manner essentially similar to the preparation of **3**. The crude reaction product was purified by dry-column chromatography (Woelm silica gel, EtOAc) and yielded 3.05 g of a solid which showed mainly one component on TLC (C_6H_6 –EtOAc, 4:1). Recrystallization (C_6H_6 –hexane) gave 1.74 g (20.1%) of colorless crystals, mp 172–174°. A second recrystallization (C_6H_6) raised the melting point to 173–174°: ir (KBr) 1698 cm^{-1} (C=O); uv (MeOH) max 248 nm (ϵ 7051), 272 sh (1568); NMR (CHCl_3) δ 1.48–3.55 (m, 11, CH_2 , including an NCH_3 s at 2.07), 6.78–7.57 (m, 4, ArH), 9.44 ppm (br s, 1, ArNHCO); mass spectrum (70 eV) m/e (rel intensity) 216 (69), 201 (3), 188 (59), 187 (100), 173 (24), 172 (21), 159 (15), 144 (14), 130 (16), 117 (14), 70 (20), 42 (37). Anal. ($\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$) C, H, N.

2-Indolinone-3-spiro-2'-(N-ethylpiperidine) (7, Scheme II). 3-[4'-(N-Ethylamino)butyl]indole (**19b**, 5.41 g, 0.025 mol) and NBS (8.9 g, 0.050 mol), reacted in the manner described for the preparation of **6**, resulted in 1.43 g of oil. Workup via dry-column chromatography (Woelm silica gel, EtOAc) and conversion of the purified product into its perchlorate salt gave 69 mg of colorless crystals: mp 255–258° (absolute EtOH–Et₂O); ir (KBr) 1718 cm^{-1} (C=O); NMR (CHCl_3) δ 0.93 (t, 3, CH_3), 1.20–3.53 (m, 10, CH_2 , including an NCH_2 q at 2.25), 6.71–7.58 (m, 4, ArH), 9.84 ppm (br s, 1, ArNHCO); mass spectrum of free base obtained from the perchlorate (70 eV) m/e (rel intensity) 230 (56), 229 (3), 202 (34), 201 (100), 187 (35), 186 (30), 173 (16), 159 (7), 144 (11), 130 (13), 118 (9), 117 (11). Anal. ($\text{C}_{14}\text{H}_{19}\text{ClN}_2\text{O}_5$) C, H, N.

2-Indolinone-3-spiro-3'-(N-ethylpiperidine) (8). A solution of 3-[3'-(ethylamino)propyl]indole (**14a**, 4.14 g, 0.0205 mol) in 95% t -BuOH (130 ml) was treated with 70% aqueous HClO_4 until acidic to congo red indicator. NBS (3.65 g, 0.0205 mol) was added to the solution at room temperature under N_2 over a period of 20 min, and the mixture was left stirring for 1 h before it was taken to dryness on the rotary evaporator. The residue was dissolved in water, basified with solid Na_2CO_3 , and extracted with CHCl_3 . Evaporation of the dried (MgSO_4) CHCl_3 extract gave 3.3 g of a yellow oil which exhibited an oxindole uv spectrum.^{9a,33} The solution of this oil in 25 ml of glacial HOAc was left at room temperature overnight in order to rearrange any aniline-type compound present into the desired oxindole.^{9a} The next day 37% CH_2O (1.225 ml, 0.0151 mol) was added and the mixture was kept under N_2 at room temperature for 66 h followed by 2 h of reflux. The residue obtained after solvent removal was dissolved in H_2O , basified with NaHCO_3 , and extracted with CHCl_3 . The dried (MgSO_4) CHCl_3 solution yielded after distillation 1.07 g of an oil [bp 170–200° (0.05 mmHg)] from which **8** was obtained via dry-column chromatography (Woelm silica gel, EtOAc). The analytical sample was obtained as its perchlorate salt (128 mg): mp 247–250° (absolute EtOH); ir (KBr) 1689 cm^{-1} ; NMR (CDCl_3) δ 1.01 (t, 3, CH_3), 1.44–3.26 (m, 10, CH_2), 6.75–8.03 (m, 4, ArH), 9.48 ppm (br s, 1, ArNHCO); mass spectrum of free base obtained via the perchlorate (70 eV) m/e (rel intensity) 230 (42), 215 (13), 201 (4), 173 (15), 159 (3), 158 (3), 145 (27), 130 (9), 117 (20), 90 (13), 85 (21), 72 (100), 57 (37). Anal. ($\text{C}_{14}\text{H}_{19}\text{ClN}_2\text{O}_5$) C, H, N.

2-Indolinone-3-spiro-3'-(N-propylpiperidine) (9). 3-[3'-(N-n-Propylamino)propyl]indole (**14b**, 8.64 g, 0.04 mol) was converted into the perchlorate salt and then oxidized with NBS (14.24 g, 0.08 mol) in t -BuOH as described in the preparation of **8**. The residue obtained after evaporation of the t -BuOH was dissolved in 300 ml of 50% aqueous HOAc and hydrogenated overnight (Parr, 2.8 g of 10% Pd/C). After removal of the catalyst, the solution was evaporated on the rotary evaporator and the residue dissolved in H_2O . The aqueous solution was basified with Na_2CO_3 and extracted with CHCl_3 in a continuous liquid–liquid extractor for 48 h. Evaporation of the dried (MgSO_4) CHCl_3 extract gave a residue which was dissolved by boiling with absolute EtOH. Succinimide [4.64 g, mp 126–127° (lit. mp 125–126°)] separated out upon cooling and was filtered off; EtOH was evaporated off and the residue (13.2 g) so obtained was dissolved in acetic acid and allowed to react with 37% CH_2O (3.3 g, 0.044 mol) in essentially the same manner as described for **8** to give 9.0 g of material which after dry-column chromatography (Woelm silica gel, EtOAc) yielded **9** (4.86 g, 49.8%) as a yellow oil showing only one spot on TLC (C_6H_6 –EtOAc, 4:1). Neutralization of a solution of this oil in ether with concentrated H_2SO_4 resulted in the bisulfate salt of **9**: mp 145–146° (absolute EtOH–Et₂O); uv (MeOH) max 250 nm (ϵ 6650), 268 sh (1469); NMR (CDCl_3) δ 0.63–3.18 (m, 15, spiran H, including a CH_2CH_3 t at 0.83), 6.70–7.85 (m, 4, ArH), 9.44 ppm (br s, 1, ArNHCO). Anal. ($\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$) C, H, N. The perchlorate salt of **9** was also prepared: mp 240–242° (95% EtOH); ir (KBr) 1689 cm^{-1} (C=O); mass spectrum of the base obtained from the bisulfate (70 eV) m/e (rel intensity) 244 (34), 227 (2), 215 (100), 201 (2), 186 (6), 173 (11), 172 (12), 158 (6), 145 (22), 130 (11), 117 (21), 98 (8), 90 (11), 86 (76), 84 (18), 70 (22), 57 (13). Anal. ($\text{C}_{15}\text{H}_{21}\text{ClN}_2\text{O}_5$) C, H, N.

2-Indolinone-3-spiro-4'-(N-ethylpiperidine) (10, Scheme V). A solution of oxindole (13.32 g, 0.10 mol) in THF (200 ml) was added dropwise, with stirring under N_2 , to a suspension of NaH (14.4 g of 50% NaH, washed with hexane and THF, 0.30 mol) in 300 ml of THF. As soon as the gas evolution ceased (± 0.5 h), bis(2-chloroethyl)ethylammonium chloride (20.66 g, 0.10 mol)⁴¹ was added portionwise to the well-stirred mixture. (Caution: avoid contact and inhalation of the mustard gas!) When after 1 h the gas evolution was seen to be slowing the mixture was heated to reflux for 3 h, then cooled to room temperature, and treated with an additional quantity of a suspension of NaH (4.8 g of 50% NaH, 0.10 mol) in THF (100 ml). The mixture was refluxed overnight, cooled in an ice bath, and treated with 75 ml of saturated aqueous NH_4Cl to decompose excess NaH. It was then basified by the addition of 100 ml of saturated aqueous NaHCO_3 and saturated with NaCl. The THF layer was separated from the salt slurry and combined with subsequent THF extracts

(4 × 100 ml). Workup and distillation [bp 175–185° (0.6 mmHg), 2.5 g] followed by recrystallization afforded **10** (1.28 g, 5.6%): mp 121.5–123° (hexane, charcoal); ir (film) 1695 cm⁻¹ (C=O); uv (MeOH) max 248 nm (ϵ 8609), 272 sh (1974); NMR (CDCl₃) δ 1.19 (t, 3, CH₃), 1.70–2.28 (m, 4, CCH₂), 2.42–3.30 (m, 6, NCH₂), 6.90–7.62 (m, 4, ArH), 9.60 ppm (br s, 1, ArNHCO); mass spectrum (70 eV) m/e (rel intensity) 230 (50), 215 (17), 202 (3), 173 (5), 159 (5), 146 (6), 144 (6), 130 (7), 103 (11), 85 (100), 84 (31), 70 (17), 57 (31), 56 (17). Anal. (C₁₄H₁₈N₂O) C, H, N.

7-Methyl-2-indolinone-3-spiro-4'-(N-ethylpiperidine) (**11**, Scheme V). This compound was prepared in the same manner as **10** from 7-methyloxindole (14.7 g, 0.10 mol), NaH (21.6 g of 50% NaH, 0.45 mol), and bis(2-chloroethyl)ethylammonium chloride (20.66 g, 0.10 mol).⁴¹ The crude product (8.3 g), collected by distillation at 175–190° (0.08–0.10 mmHg), solidified spontaneously and was recrystallized from benzene (charcoal) to yield **11** (5.2 g, 21.3%): mp 162–163°; ir (KBr) 1695 cm⁻¹ (C=O); NMR (CDCl₃) δ 1.16 (t, 3, CH₂CH₃), 1.77–3.22 (m, 13, CH₂, including an ArCH₃ s at 2.31), 6.72–7.37 (m, 3, ArH), 9.82 ppm (br s, 1, ArNHCO); mass spectrum (70 eV) m/e (rel intensity) 244 (26), 229 (9), 216 (3), 201 (1), 187 (5), 173 (6), 160 (10), 158 (9), 144 (13), 142 (13), 130 (22), 115 (10), 103 (6), 85 (100), 84 (38), 70 (20), 57 (45), 56 (40). Anal. (C₁₅H₂₀N₂O) C, H, N.

3-(Ethylamino)oxindole Hydrochloride (**13**). *N*-Ethylisatinimine (17.21 g, 0.10 mol), prepared according to Haslinger^{9b} and used without purification, was partially dissolved in 150 ml of ice-cooled glacial HOAc and hydrogenated at room temperature for 10 min (Parr, 47 psi of H₂, 0.5 g of PtO₂). The mixture was diluted with absolute EtOH (100 ml) and treated with concentrated HCl (20 ml) before filtration. The filtrate was taken to dryness on a rotary evaporator by repeated evaporation after addition of anhydrous EtOH to the residue. Practically colorless crystals of **13** (15.2 g, 71%) were obtained and were purified by washing with anhydrous Et₂O, followed by recrystallization from MeOH: mp 190–210° dec; ir (KBr) 1733 cm⁻¹ (C=O). Anal. (C₁₀H₁₃N₂OCl) C, H, N. The free base could not be isolated (cf. aminoindole⁴²); when the imine was treated with NaBH₄ in *i*-PrOH, an indigo-colored powder resulted.

3-[3'-(Alkylamino)propyl]indoles (**14a,b**). These compounds were prepared via LiAlH₄ reduction of the appropriate *N*-alkyl-3-(3'-indolyl)propionamides which were readily synthesized by the ethoxyformic anhydride coupling method⁴³ from 3-(3'-indolyl)propanoic acid and the alkylamine. Thus anhydride coupling of 3-(3'-indolyl)propanoic acid (25.0 g, 0.132 mol) and EtNH₂ (11.8 g, 0.264 mol) resulted in a practically quantitative yield of *N*-ethyl-3-(3'-indolyl)propionamide (29 g): colorless needles; mp 80.5–82° (C₆H₆-hexane); ir (film) 1629 cm⁻¹ (C=O); NMR (CDCl₃) δ 0.92 (t, 3, CH₃), 2.27–3.42 (m, 6, CH₂CH₂C:ONCH₂), 5.72 (br s, 1, O=CNH), 6.74–7.70 (m, 5, heteroatom H), 8.62 ppm (br s, 1, indole NH). The crude amide (29 g, 0.132 mol) was reduced with LiAlH₄ (20.0 g, 0.528 mol) in THF (400 ml) by overnight refluxing to furnish 3-[3'-(ethylamino)propyl]indole (**14a**, 18.4 g, 69%): mp 110–111.5° (Et₂O); ir (KBr) 1621 cm⁻¹ (indole C=C); NMR δ 0.93–1.42 (m including t at 1.08, 4, aliphatic NH and CH₃), 1.60–2.43 (m, 2, CCH₂C), 2.43–3.13 (m, 6, indolyl CH₂ and CH₂NCH₂), 8.55 ppm (br s, 1, indole NH). Anal. (C₁₃H₁₈N₂) C, H, N. Similarly, reduction of crude *N*-propyl-3-(3'-indolyl)propionamide yielded 3-[3'-(*n*-propylamino)propyl]indole (**14b**, 22 g, 77%): mp 105–106° (C₆H₆); ir (KBr) 1621 cm⁻¹ (indole C=C); NMR (CDCl₃) δ 0.86 (t, 3, CH₃), 1.18–2.35 (m, 5, CCH₂C, CH₂Me, aliphatic NH), 2.35–3.03 (m, 6, indolyl CH₂ and CH₂NCH₂), 6.95–7.90 (m, 5, heteroatom H), 8.61 ppm (br s, 1, indole NH). Anal. (C₁₄H₂₀N₂) C, H, N.

2-Alkyl-1,2,3,4-tetrahydro- β -carbolines (**15a-d**). These compounds were synthesized from the appropriate 3-[2'-(alkylamino)ethyl]indole **16** and CH₂O in glacial HOAc by a Pictet-Spengler reaction. Thus CH₂O (4.25 ml of a 40% aqueous solution, 0.057 mol) was mixed under N₂ with *N*-ethyl-7-methyltryptamine (**16c**, 11.5 g, 0.057 mol) in glacial HOAc (60 ml). After 20 h of stirring at room temperature, the mixture was refluxed for 2 h and taken to dryness in vacuo. The residue was treated with H₂O (50 ml) and CHCl₃ (50 ml) and then basified by the addition of 2 N NaOH. The CHCl₃ layer was separated and the aqueous layer was reextracted with three 50-ml portions of CHCl₃. The combined CHCl₃ solution was extracted with three 60-ml portions of 10% aqueous H₂SO₄. The acidic aqueous phase was

cooled in an ice bath, basified with concentrated aqueous NaOH, and extracted with four 75-ml portions of Et₂O. The dried (MgSO₄) Et₂O extract was evaporated to dryness and the residue was recrystallized from C₆H₆ to yield 2-ethyl-8-methyl-1,2,3,4-tetrahydro- β -carboline (**15b**, 6.7 g, 55%): mp 135–136° (C₆H₆); ir (KBr) 1629 cm⁻¹ (indole C=C); NMR (CDCl₃) δ 1.18 (t, 3, CH₃), 2.40 (s, 3, aromatic CH₃), 2.31–2.75 (m, 2, NCH₂Me), 2.82 (s, 4, H_{3,4}), 3.62 (s, 2, H₁), 6.78–7.38 (m, 3, H_{5,6,7}), 7.57 ppm (br s, 1, NH). Anal. (C₁₄H₁₈N₂) C, H, N. Similarly prepared were 2-ethyl-1,2,3,4-tetrahydro- β -carboline (**15a**, 4.14 g, 56%) [mp 153–155° (CH₂Cl₂) (closed capillary, decomposition with gas evolution); lit.⁴⁴ 153–154° (aqueous EtOH)]; ir (KBr) 1629 cm⁻¹ (indole C=C); NMR (CDCl₃) δ 1.14 (t, 3, CH₃), 2.23–2.75 (m, 2, NCH₂Me), 2.82 (s, 4, H_{3,4}), 3.46 (s, 2, H₁), 6.88–7.73 (m, 4, H_{5,6,7,8}), 8.18 ppm (br s, 1, NH). Anal. (C₁₃H₁₆N₂) C, H, N]. 2-*n*-propyl-1,2,3,4-tetrahydro- β -carboline (**15c**, 4.5 g, 43%) [mp 137–138° (CH₂Cl₂); lit.⁴⁴ 136.5–137.5° (aqueous EtOH)]; ir (KBr) 1629 cm⁻¹ (indole C=C); NMR (CDCl₃) δ 0.92 (t, 3, CH₃), 1.18–1.90 (m, 2, CH₂Me), 2.20–2.67 (m, 2, NCH₂Et), 2.81 (s, 4, H_{3,4}), 3.48 (s, 2, H₁), 6.90–7.55 (m, 4, H_{5,6,7,8}), 7.95 ppm (br s, 1, NH)], and 2-*n*-butyl-1,2,3,4-tetrahydro- β -carboline (**15d**, 2.5 g, 12%) [mp 113–114° (CH₂Cl₂); NMR (CHCl₃) δ 0.77–1.85 (m, 7, CH₂CH₂CH₃), 2.28–2.70 (m, 2, NCH₂Pr), 2.80 (s, 4, H_{3,4}), 3.47 (s, 2, H₁), 6.87–7.55 (m, 4, H_{5,6,7,8}), 7.94 ppm (br s, 1, NH). Anal. (C₁₅H₂₀N₂) C, H, N].

3-[2'-(Alkylamino)ethyl]indoles (**16a-d**). These compounds and the precursors **17** and **18** were prepared by the method of Speeter and Anthony.²⁵ Thus LiAlH₄ reduction of **17c** (27.3 g, 0.1185 mol) in THF resulted in a 50% yield of 7-methyl-3-[2'-(ethylamino)ethyl]indole (**16c**, 12 g): mp 75–76° (ligroine bp 63–75°); NMR (CDCl₃) δ 1.06 (t, 3, CH₃), 0.91–1.33 (br s, 1, CONH), 2.42 (s, 3, ArCH₃), 2.32–3.15 (m, 6, CH₂CH₂NCH₂), 6.72–7.57 (m, 4, heteroatom H), 8.18 (br s, 1, indole NH). Anal. (C₁₃H₁₈N₂) C, H, N. Analogous procedures were used for the preparation of the known 3-[2'-(ethylamino)ethyl]indole (**16a**),⁴⁵ 3-[2'-(*n*-propylamino)ethyl]indole (**16b**),^{45,46} and 3-[2'-(*n*-butylamino)ethyl]indole (**16d**).⁴⁶

***N*-Ethyl(7-methylindole)-3-glyoxylylamide** (**17c**). Reaction of crude (7-methylindole)-3-glyoxylyl chloride (**18c**, 31.5 g, 0.142 mol) and EtNH₂ (6.4 g, 0.142 mol) afforded **17c** (25.9 g, 84%): mp 219–220° (95% EtOH); NMR consistent with structure. Anal. (C₁₃H₁₄N₂O₂) C, H, N. The precursor **18c** (32.5 g) was obtained from 7-methylindole and oxalyl chloride. Recrystallization furnished crystals: mp 176–177° (CHCl₃, decomposition); NMR consistent with structure. No satisfactory elemental analysis could be obtained and the product was used as is in the next step. Analogous procedures were used in the preparation of the known *N*-ethylindole-3-glyoxylylamide (**17a**)^{45b} and *N*-(*n*-propyl)-indole-3-glyoxylylamide (**17b**).²⁵

3-[4'-(*N*-Alkylamino)butyl]indoles (**19a,b**). These compounds were prepared in a manner analogous to the procedure described for **14a** and **14b**. Thus overnight reflux of *N*-methyl-4-(3'-indolyl)butylamide (prepared via the ethoxyformic anhydride method⁴³ and used without further purification) (11.2 g, 0.045 mol) in THF with a fourfold molar ratio of LiAlH₄ furnished 3-[4'-(*N*-methylamino)butyl]indole (**19a**): mp 75–76° (hexane); NMR (CDCl₃) δ 8.54 (br s, 1, indole NH), 6.87–7.80 (m, 5, heteroatom H), 2.16–3.03 [m including s at 2.43, 7, CH₂NCH₃ and C(3) H₂], 0.57–2.08 (m including br s at 1.23, 5, CCH₂CH₂C and aliphatic NH). Anal. (C₁₃H₁₈N₂) C, H, N. Analogously prepared was 3-[4'-(*N*-ethylamino)butyl]indole (**19b**, 20.7 g, 78%): mp 73–74° (ligroine bp 63–75°); NMR (CDCl₃) δ 9.28 (br s, 1, indole NH), 6.90–7.88 (m, 5, heteroatom H), 2.43–3.15 [m, 6, NCH₂ and C(3) H₂], 1.33–2.22 (m, 4, CCH₂CH₂C), 0.45–1.33 (m including t at 1.10, 4, aliphatic NH and CH₃). Anal. (C₁₄H₂₀N₂) C, H, N.

7-Methyl-2-indolinone (**20b**). Oxindoles were prepared from isatins by catalytic reduction.⁴⁷ Thus a mixture of 7-methylisatin (6.44 g, 0.04 mol), glacial HOAc (192 ml), HClO₄ (6.8 ml of 70% aqueous solution), H₂O (1.2 ml), and 10% Pd/C (600 mg) was hydrogenated at 60° (Parr, 60 psi of H₂) for 1 h. Workup afforded **20b** (2.5 g, 42%), mp 208–209° (C₆H₆) (lit.⁴⁸ 203–204°).

Similarly prepared was **4,7-dimethyl-2-indolinone** (2.7 g, 21%), mp 204.5° (95% EtOH). Anal. (C₁₀H₁₁NO) C, H, N.

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