acetonitrile-H_2O (2:1) mixture.

Preparation of No-Carrier-Added ^{99m}Tc Complexes of BPA-BAT. The no-carrier-added ^{99m}Tc-BPA-BAT was prepared by a ligand-exchange reaction. A solution of ^{99m}Tc-glucoheptonate (1-10 mCi, 0.1-1 mL), prepared by adding a desired amount of sodium [^{99m}Tc]pertechnetate into a freeze-dried kit (1 mg of glucoheptonate + 0.25 mg of stannous chloride), and 1 mg of ligand was heated at 100 °C for 30 min. The product was extracted with chloroform (3 × 2 mL), and the combined extracts were dried over anhydrous sodium sulfate. The solution was then condensed with a stream of air and redissolved in saline (radiochemical yield >80%). No decomposition of the ^{99m}Tc complex was observed on standing at room temperature for 18 h. For separating the syn and the anti isomers, the racemic mixture was injected into HPLC and appropriate fractions were collected (Table I). After condensing, reextraction with ethyl acetate (3 × 1 mL), and condensing with a stream of nitrogen, the products were redissolved in saline (total radiochemical yield >50%, radiochemical and isomeric purity >98%).

Partition Coefficients. The partition coefficient was measured by mixing the ^{99m}Tc-BAT compound with 3 g each of 1-octanol and buffer (pH 7.0 or 7.4, 0.1 M phosphate) in a test tube. This test tube was vortexed for 3 min at room temperature and then centrifuged for 5 min. Two weighed samples (0.5 g each) from the 1-octanol and buffer layers were counted in a well counter. The partition coefficient was determined by calculating the ratio of counts per minute/gram of octanol to that of buffer. Samples from the octanol layer were repartitioned until consistent partition coefficient values were obtained. The measurement was repeated three times.

Animal Distribution Studies. Male Sprague-Dawley rats (200-300 g) were injected intravenously (femural vein under ether anesthesia) with 0.2 mL of a saline solution containing the ^{99m}Tc-BAT complex (0.5-20 μCi). At selected intervals following the injection, blood samples (1 mL each) were collected by cardiac puncture, and the rats were sacrificed immediately thereafter by cardiectomy. The organs of interest were subsequently excised, weighed, and counted in a dual-channel automatic gamma counter (Beckman 5500). The % dose/organ values were determined by comparison of the tissue radioactivity with suitable dilutents of the injected dose. The % dose/gram values were computed from the % dose/organ values and the corresponding mean organ weights (mean organ weights: heart, 0.85 g; brain, 1.65 g; blood, 18 g; liver, 9 g; Kidneys, 1.9 g; lungs, 1.6 g). Finally, the brain:blood ratio was calculated from the corresponding % dose/gram values.

X-ray Crystallography. Crystal Data. ^{99}Tc-BPA-BAT (syn): $TcS_2ON_4C_{22}H_{37}$, dark brown, crystallized from 2:1 MeCN-water, monoclinic-b, $P2_1/n$ (no. 14), a = 15.241 (5) Å, b = 15.658 (7) Å, c = 11.385 (3) Å, β = 109.91 (2)°, from 24 reflections, T = -70 °C, V = 2554.6 Å^3, Z = 4, FW = 536.69, D_{calcd} = 1.395 g/cm^3, μ(Mo) = 7.26 cm^{-1}.

^{99}Tc-BPA-BAT (anti): $TcS_2ON_4C_{22}H_{37}$, red, block, -0.30 × 0.40 × 0.35 mm, crystallized from acetonitrile-water, monoclinic-b, $P2_1/c$ (no. 14), a = 12.243 (7) Å, b = 11.022 (2) Å, c = 19.180 (5) Å, β = 102.19 (3)°, from 20 reflections, T = -70 °C, V = 2529.8 Å^3, Z = 4, FW = 537.70, D_{calcd} = 1.411 g/cm^3, μ(Mo) = 7.33 cm^{-1}.

Data Collection and Treatment. For the syn isomer: Enraf-Nonius CAD4 diffractometer, graphite monochromator, Mo Kα radiation, 6607 data collected, 2.6° < 2θ <55.0°, maximum hkl = 19,20,14, data octants = +++, -++, -+-, ω scan method, scan width = 1.20-1.80° ω, scan speed = 1.80-20.10°/min, typical half-height peak width = 0.35° ω, two standards collected 30 times, adjusted for a 10% decrease in intensity, 1098 omitted, 10.2% variation in azimuthal scan, corrected for absorption (DIFABS), range of transmission factors = 0.77-1.05, 176 duplicates, 1.8% R-merge, 2077 unique reflections with $I > 3.0\sigma(I)$.

For the anti isomer: Enraf-Nonius CAD4 diffractometer, graphite monochromator, Mo Kα radiation, 6607 data collected, 2.2° < 2θ <55.0°, maximum hkl = 19,20,14, data octants = +++, -++, σ scan method, scan width = 1.80-2.00° ω, scan speed = 2.20-4.00°/min, typical half-height peak width = 0.28° ω, two standards collected 30 times, 7.3% variation in azimuthal scan, corrected for absorption (DIFABS), range of transmission factors = 0.77-1.05, 174 duplicates, 3.1% R-merge, 3360 unique reflections with $I \geq 3.0\sigma(I)$.

Solution and Refinement. For the syn isomer: The structure was solved by automated Patterson analysis (PHASE). The hydrogen atom on N1 was obtained from a difference map and refined. All other hydrogen atoms were idealized with C-H = 0.95 Å refinement by full-matrix least squares on F. Scattering factors include anomalous terms for Tc, S, weights $\alpha[\sigma^2(I) + 0.0009I^2]^{-1/2}$, 275 parameters, refined anisotropic, all non-hydrogen atoms; isotropic, H; fixed atoms, H; final R = 0.027, R_w = 0.028, error of fit = 1.11, max Δ/σ = 0.58 largest residual density = 0.26 e/Å^3, near S2. For the anti isomer: The structure was solved by automated Patterson analysis (PHASE). The hydrogen atom on N1 was obtained from a difference map and refined. All other hydrogen atoms were idealized with C-H = 0.95 Å refinement by full-matrix least squares on F. Scattering factors include anomalous terms for Tc, S, weights $\alpha [\sigma^2(I) + 0.0009I^2]^{-1/2}$, 271 parameters, refined anisotropic, all non-hydrogen atoms; isotropic, H; fixed atoms, H; final R = 0.035, R_w = 0.038, error of fit = 1.56, max Δ/σ = 0.04, largest residual density = 0.58 e/Å^3, near Tc.

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Registry No. syn-^{99}Tc BPA-BAT, 117708-18-6; anti-^{99}Tc BPA-BAT, 117652-30-9; Sn, 7440-31-5; glucoheptonate, 23351-51-1.

A Novel Class of "GABAergic" Agents: 1-Aryl-3-(aminoalkylidene)oxindoles

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Antagonism of mercaptopropionic acid (MPA) induced convulsions, reflecting a GABAergic mechanism, was observed in a series of 1-aryl-3-(aminoalkylidene)oxindoles. Optimal MPA antagonism was associated with 3-halo, 3-alkyl, and/or 4-alkoxy substituents in the pendant aryl ring and with (dimethylamino)methylene, 1-(dimethylamino)-ethylidene and *N*-methyl-2-pyrrolidinylidene side chains. The precise mechanism of action of these agents is unclear at this time; however, they are not GABA mimics and they do not affect GABA levels. Like other GABAergic agents, these compounds are potent enhancers of benzodiazepine binding and they antagonize cyclic GMP elevations induced by isoniazid. Compounds from this series may therefore have potential therapeutic utility as anticonvulsants or anxiolytics.

Safe GABAergic agents have been attractive targets for drug research in recent years because GABA serves as an important inhibitory neurotransmitter in the central nervous system and GABAergic agents have potential utility in the therapy of epilepsy, Huntington's chorea, schizophrenia, tardive dyskinesia, depression, and spas-

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ticity.[1] The discovery of a link between benzodiazepine and GABA receptors also suggests that GABAergics may exert anxiolytic activity.[2] Known GABAergics, operating via several proposed mechanisms, include GABA mimics (compounds that bind to GABA receptors, such as muscimol and THIP[3]), GABA-B receptor selective agonists (e.g., baclofen[4]), prodrugs for GABA (such as progabide[1b,c]), agents that enhance GABA binding (e.g. tracazolate[5]), agents that enhance synaptic GABA levels by interfering with GABA reuptake (e.g. nipecotic acid[6]), and agents that elevate neuronal GABA content by blocking GABA metabolism (i.e., GABA transaminase inhibitors such as valproic acid, γ-acetylenic- and γ-vinyl-GABA).[7,8] Many of these agents have drawbacks such as high toxicity, undesirable side effects, or low potency.[9a]

In our search for GABAergic agents, we prepared compounds **1** and **2** as remote analogues of a weak GABA receptor binding lead. It was fortunate that we prepared the 3-chlorophenyl compound **2** for reasons of synthetic accessibility, because it, in contrast to the hydrogen-substituted analogue **1**, was active in our secondary screen for GABAergics: compound **2** was found to antagonize convulsions in mice induced by 3-mercaptopropionic acid (MPA). MPA is a glutamate decarboxylase inhibitor and activator of GABA transaminase; it induces convulsions in mice that are antagonized by GABAergic agents.[9b]

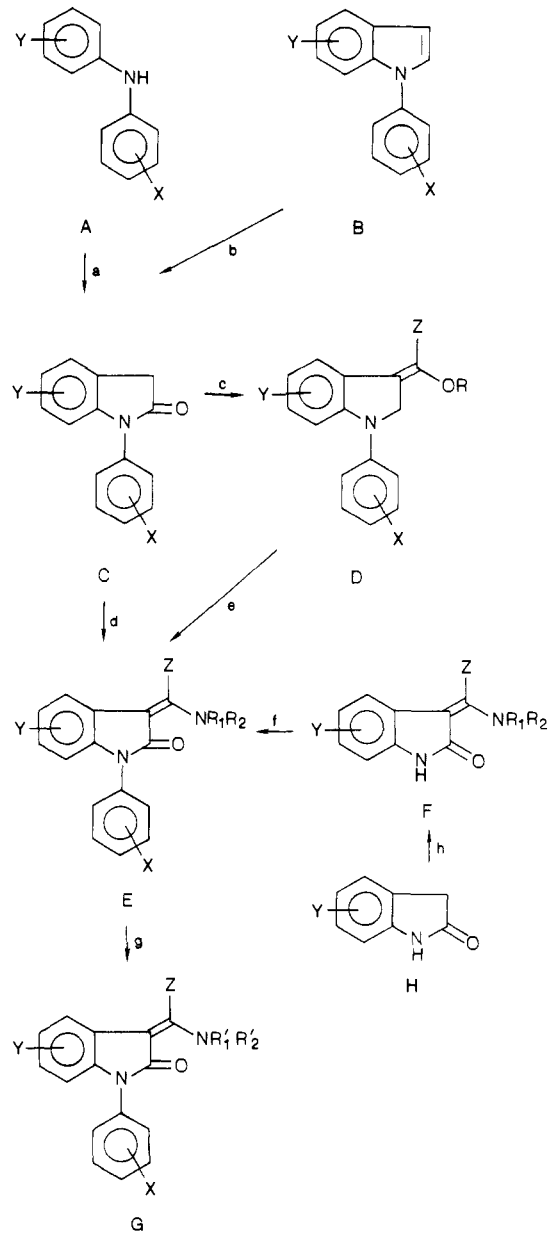
The activity of **2** in the MPA screen suggested a GABAergic mode of action, although **2** did not bind to the GABA receptor ($IC_{50} > 10^{-5}$ M) and it had no apparent effect on GABA levels. Like other GABAergic compounds, however, it antagonized cyclic GMP elevations in rat cerebellum induced by another glutamate decarboxylase inhibitor, isoniazid, and it enhanced the binding of [^{3}H]-flunitrazepam in vivo.[9c] This interesting profile prompted us to investigate more fully the structure–activity relationships in this class of compounds.

Chemistry

The 1-aryl-3-(aminoalkylidene)oxindoles E and G were accessible by a variety of routes, which are summarized in Scheme I. Our initial synthesis involved the preparation of 1-aryloxindoles C via the method of Stollé et al.[10] Thus, condensation of the commercially available diphenylamines A with chloroacetyl chloride in refluxing benzene or toluene gave an essentially quantitative yield of the α-chloroacetanilides, which could then be cyclized by heating in $AlCl_3$ to a melt at 180–200 °C for 10–15 min (pathway a). In the case of 3-chlorodiphenylamine, we obtained by this process all three possible isomers of C (**86**, X = 3-Cl, Y = H, 40%; **87**, X = H, Y = 6-Cl, 7%; **88**, X = H, Y = 4-Cl, 5%), which were readily separated by silica gel chromatography. A more attractive and general route to 1-aryloxindoles, which avoided the formation of positional isomers, involved the preparation of arylindoles B by a modified Ullmann reaction of indole with substituted aryl iodides or bromides in the presence of cuprous bromide and sodium carbonate in refluxing *N*-methyl-2-pyrrolidinone and subsequent conversion with *N*-chlorosuccinimide and H_3PO_4/acetic acid[11] to C. Several attempts to prepare C by a one-step condensation of substituted anilines with *o*-chlorophenylacetic acid catalyzed by copper oxide[12] gave very poor results in our hands.

Treatment of the 1-aryloxindoles C with dimethylformamide or dimethylacetamide acetals in refluxing $CHCl_3$ for 1–6 h gave excellent yields of compounds E with Z = H or CH_3 (pathway d). Use of 1 equiv of the acetal was found

Scheme I



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to be optimal, since excess acetal resulted in poorer yields and the formation of byproducts. The compounds in which the α substituent formed a ring with one of the N substituents (e.g., the pyrrolidinylidene derivatives) were accessible by reaction of the aryloxindoles C with either lactam acetals or with a Vilsmeir–Haack complex formed from the lactam and $POCl_3$ (pathway d). In the latter case, preparation of the Vilsmeier complex with $POCl_3$ at 0 °C, followed by treatment with an oxindole in a suitable solvent, gave after several hours at 50–80 °C the desired compounds E, along with varying amounts of 2-chloroindoles as byproducts. The Vilsmeier complex method was also successful with *N*-methylformanilide to give **49**, and to a lesser extent with *N*,*N*-dimethylbenzamide to give **60**. The compounds in Table IV with R = H (**72**, **77**, and **78**) were prepared by heating the 1-aryloxindole C with an excess of the *O*-methyl lactim in toluene[13] (pathway d). The congeners of E with varying amine components were available in most cases by treating E ($NR_1R_2 = NMe_2$) with an excess (2–5 equiv) of the desired amine either neat or in ethanol solution (pathway g). In some instances, this displacement of the dimethylamino group could not be effected even under more forceful conditions (i.e., refluxing ethanolic solution), but compounds such as **40**, **46**, and **61** were accessible via the intermediate hydroxy- or alkoxyalkylidenes D (pathway c, e) according to the methods of Winn and Kyncl.[14]

We also prepared a large number of 1-aryl-3-(aminoalkylidene)oxindoles by converting oxindoles H to 3-(aminoalkylidene)oxindoles F (pathway h), followed by an Ullmann arylation step (pathway f). While this provided an efficient route to achieve variability in the pendant aryl ring, the yields to step f were good only when Z = H. Thus, oxindole, or substituted oxindoles (prepared from reduction of substituted isatins or oxidation of substituted indoles), were converted with dimethylformamide or dimethylacetamide acetals in refluxing $CHCl_3$ to the 3-(aminoalkylidene)oxindoles, (i.e., Z = H or CH_3, **99–105**, Table V). These intermediates were allowed to react with NaH in dry DMF to give the insoluble sodium salts, which were then treated with a variety of substituted aryl bromides or iodides in the presence of Cu_2Br_2 at elevated temperatures for 24–72 h to give the compounds E (**3**, **4**, **6–36**) in yields ranging up to 72%. Although the ethylidene homologues such as **52** could also be prepared in this manner, yields were often extremely poor (8% for **52**), possibly due to competitive deprotonation of the α-methyl group; pathways a,d or b,d were clearly preferable for the preparation of the ethylidene compounds. Similarly, some pyrrolidinylidene oxindoles F (e.g., **106** and **107**) were prepared by condensation of substituted oxindoles with lactam acetals (pathway h), and subsequent Ullmann arylation (pathway f) gave compounds E (**64–68**, **79–81**). Again, the yields in this arylation step were generally poor, but adequate to obtain test samples.

Pharmacology

Antagonism of MPA-Induced Convulsions.[15] Charles River male mice, Swiss CD strain, 17–21 g, were fasted for 18 h prior to testing. Compounds were administered subcutaneously at 100 mg/kg in a vehicle consisting of 5% ethanol, 5% emulphor 620, and 90% saline. Vehicle alone served as a control treatment. If active, the compound was further evaluated at lower points on a 0.5 × $\log_{10}$ dosage scale to determine an ED_{50} value. Solution concentrations were varied at different doses to provide a constant injection volume of 10 mL/kg. Groups of five mice were treated with each test compound and 1 h later with MPA, 32 mg/kg, intraperitoneally. The animals were then observed continuously for 10 min. In untreated mice this MPA challenge caused clonic convulsions within 4 min of treatment. Protection against MPA convulsions in a given mouse was said to occur if no convulsions occurred during the 10-min test period.

Enhancement of [^{3}H]Flunitrazepam Binding in Vivo. [^{3}H]Flunitrazepam ([^{3}H]FNP) binding to mouse brain was measured as described previously[9c,16] by the method of Chang and Snyder.[17] Groups of five mice were injected intraperitoneally with 320 μmol/kg of the test compound or vehicle 1 h prior to an intravenous injection of 200 μCi/kg [^{3}H]FNP. Twenty minutes after the [^{3}H]FNP injection, the mice were sacrificed by cervical dislocation, and the brains were removed and immediately frozen. Each brain was weighed quickly and homogenized in 40 volumes (w/v) ice-cold 50 mM Tris-HCl pH 7.7 buffer using a Brinkmann Polytron. Triplicate 1.0-mL samples were filtered through Whatman GF/B glass fiber filters under vacuum and washed with two 5-mL aliquots of the ice-cold buffer. The bound [^{3}H]FNP was measured by adding the filters to vials containing 10 mL of Aquasol-2 and counting the radioactivity. Bound [^{3}H]FNP for drug-treated mice was calculated as percentage of bound [^{3}H]FNP for vehicle-treated mice.

Antagonism of Cyclic GMP Accumulation after Isoniazid. Experiments to determine the effect of drugs on cyclic GMP accumulation after isoniazid were conducted as described by Koe and Lebel.[18] Sprague-Dawley CD male rats received ip drug or vehicle 90 min before administration of isoniazid, 450 mg/kg sc (n = 7). Thirty minutes later the rats were killed by focused microwave irradiation of the brain. The cerebellum was dissected and assayed for cyclic GMP by radioimmunoassay.

Results and Discussion

The SAR results are summarized in Tables I–IV, and key oxindoles are compared with reference compounds in Table VI. Analogues of **2** with modification of substituents in the pendant phenyl ring and in the aromatic portion of the oxindole ring are listed in Table I. The 3-chloro derivative **2** was clearly more potent in antagonizing MPA than were the 2- or 4-chloro congeners **3** and **4**. Replacement of chlorine by fluorine, methyl, or ethyl gave MPA-active agents **5**, **7**, and **10**; **7** was again more potent than the 4-methyl congener **9**, although the 2-methyl congener **8** had surprisingly good MPA activity. Both the 3- or 4-methoxy derivatives (**13** and **14**) were weakly MPA active. Replacement of the chlorine in **2** with CF_3 gave good MPA activity, but substitution by a variety of other electron-withdrawing substituents led to inactive compounds (**17–20**). Potency enhancement was observed by combining the 4-methoxy group with a 3-chloro, 3-fluoro, or 3-methyl substituent (**26**, **27**, **29**) but surprisingly not by combining the 3- and 4-methoxy groups (**31**). Addition of chlorine in any of the positions of the oxindole nucleus of **2** led to inactive compounds (**32–36**).

The influence of substituting the dimethylamino group of **2** with other amines is shown in Table II. The MPA

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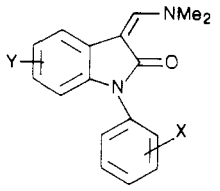
Table I. 3-[(Dimethylamino)methylene]oxindoles



no.	X	Y	method	yield, %	mp, °C	recrystal solvent[a]	formula[b]	MPA antagonism,[c] ED_{50}	[^{3}H]FNP bound,[d] % control ± S.E.	isoniazid antagonism,[e] ED_{50}
1	H	H	D1	47	135–9[f]	Et_2O	$C_{17}H_{16}N_2O$	>100	150 ± 6	
2	3-Cl	H	D1	87	116–8	Et_2O	$C_{17}H_{15}ClN_2O$	26.1	138 ± 6	1–3.2
3	2-Cl	H	G	12	169–71	Et_2O·P	$C_{17}H_{15}ClN_2O$	>100	131 ± 6	3.2–10
4	4-Cl	H	G	10	176.5–9	Et_2O	$C_{17}H_{15}ClN_2O \cdot {}^1/_4H_2O$	>100	117 ± 4	
5	3-F	H	D1	40	87–88.5	Et_2O·PE	$C_{17}H_{15}FN_2O \cdot {}^1/_4H_2O$	39.9	191 ± 11	
6	3-Br	H	G	24	118–21	Et_2O	$C_{17}H_{15}BrN_2O$	>100		
7	3-CH_3	H	G	38	105–8	Et_2O·P	$C_{18}H_{18}N_2O$	14.1	184 ± 12[g]	
8	2-CH_3	H	G	10	105–7		$C_{18}H_{18}N_2O$	18		
9	4-CH_3	H	G	23	135–7	PhH·PE	$C_{18}H_{18}N_2O$	56		
10	3-Et	H	G[h]	39	112–4	Et_2O·P	$C_{19}H_{20}N_2O$	14.1		
11	3-Ph	H	G	34	131–3	Et_2O	$C_{23}H_{20}N_2O$	>100		
12	3-OH	H	G	83	200–3	CH_2Cl_2·H	$C_{17}H_{16}N_2O_2$	>100		
13	3-OCH_3	H	G	42	106–8.5	Et_2O	$C_{18}H_{18}N_2O_2$	27.9	217 ± 9	<10
14	4-OCH_3	H	G	20	136–8	Et_2O·P	$C_{18}H_{18}N_2O_2$	48.2	153 ± 11	
15	3-OEt	H	G	17	99–102[h]	Tol·PE	$C_{19}H_{20}N_2O_2$	27.9		
16	3-CF_3	H	G	21	103–6	Et_2O·P	$C_{18}H_{15}F_3N_2O$	22.2	131 ± 4	
17	3-NO_2	H	G	51	113–6	EA·H	$C_{17}H_{15}N_3O_3$	>100	171 ± 7	
18	3-CHO	H	G	18	120–2	Et_2O	$C_{18}H_{16}N_2O_2$	>100		
19	3-CN	H	G	22	140–3	EA·H	$C_{18}H_{15}N_3O$	>100	192 ± 9	
20	3-$CONMe_2$	H	G	24	180.5–3	Tol·PE	$C_{20}H_{21}N_3O_2 \cdot {}^1/_4H_2O$	>100		
21	4-NMe_2	H	G	32	192–5	EA	$C_{19}H_{21}N_3O$	>100		
22	4-SCH_3	H	G	32	144–7	EA·P	$C_{18}H_{18}N_2OS$	56		
23	2,5-Cl_2	H	G	19	161–3	Et_2O	$C_{17}H_{14}Cl_2N_2O$	>100	147 ± 4	~10
24	3,4-Cl_2	H	G	28	149–51	Et_2O	$C_{17}H_{14}Cl_2N_2O$	>100	144 ± 5	0.1–0.3
25	3,5-Cl_2	H	G	72	147–9.5		$C_{17}H_{14}Cl_2N_2O$	>100	153 ± 6	
26	3-Cl, 4-OCH_3	H	G[i]	38	148–51	PhH·P	$C_{18}H_{17}ClN_2O_2$	7.2	244 ± 4	
27	3-F, 4-OCH_3	H	G	10	113–4	Et_2O·P	$C_{18}H_{17}FN_2O_2$	6.6	194 ± 8	
28	2-OCH_3, 5-Cl	H	G	27	161–3	Et_2O·PhH	$C_{18}H_{17}ClN_2O_2$	>100	149 ± 11	
29	3-CH_3, 4-OCH_3	H	G[j]	18	172–4	PhH·PE	$C_{19}H_{20}N_2O_2$	9.1		
30	3-Cl, 4-OMe, 5-Me	H	G[k]	33	147–50	Et_2O·P	$C_{19}H_{19}ClN_2O_2$	15.3		
31	3,4-$(OMe)_2$	H	G	6	164–7	Et_2O	$C_{19}H_{20}N_2O_3$	>100	138 ± 6	<10
32	3-Cl	4-Cl	G	5	169–70	$CHCl_3$·Et_2O	$C_{17}H_{14}Cl_2N_2O$	>100		
33	3-Cl	5-Cl	G	24	165–8		$C_{17}H_{14}Cl_2N_2O$	>100		
34	3-Cl	6-Cl	G	2	128–30	CH	$C_{17}H_{14}Cl_2N_2O$	>100		
35	3-Cl	7-Cl	G	31	172–5	MeOH·Et_2O	$C_{17}H_{14}Cl_2N_2O$	>100	169 ± 2	
36	3-Cl	5-OMe	G	9	128–30	MeOH·Et_2O	$C_{18}H_{17}ClN_2O_2$	>100		
37	H	6-Cl	D1	18	148–51	PhH·P	$C_{17}H_{15}ClN_2O$	>100		

[a] Recrystallization solvents: P (pentane); PE (petroleum ether), PhH (benzene); H (hexane), Tol (toluene), EA (ethyl acetate), IPE (isopropyl ether), CH (cyclohexane). [b] Analysis for C, H, and N was within ±0.4% of the theoretical values. [c] ED_{50}, mg/kg sc. [d] Compounds were administered at 320 μmol/kg ip, 60 min before [^{3}H]FNP, μCi/kg iv, and 80 min before killing, unless otherwise noted. $P < 0.05$ or less vs contemporary controls for all entries except as indicated by NS (nonsignificant). [e] ED_{50}, mg/kg ip, for antagonism of isoniazid induced elevation of cyclic GMP in mouse brain. [f] Belgian Patent 849, 626; mp 130–2 °C. [g] At 178 μmol/kg, ip. [h] Prepared from 3-ethyliodobenzene (Horner, L.; Subramanian, P. *Ann. Chem.* **1968**, *714*, 91; bp 51–52 °C (0.05 mmHg)). [i] Prepared from 2-chloro-4-iodoanisole (Matheson, D.; McCombie, H. *J. Chem. Soc.* **1931**, 1103; mp 83 °C). [j] Prepared from 4-bromo-2-methylanisole (Nasipuri, D.; Roy, D. N. *Chem. Abstr.* **1960**, *59*, 8803f; mp 68 °C). [k] Prepared from 4-bromo-2-chloro-6-methylanisole (bp 122–124 °C (0.9 mmHg)) which was prepared in 81% by methylating 4-bromo-6-chloro-o-cresol (Aldrich) with dimethyl sulfate in acetone.

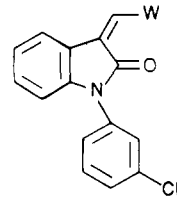
activity of **2** was shared only by the primary amine analogue **39** and by the diethylamino analogue **40**. The inactivity of the monomethyl amine derivative **38** was especially surprising. In this regard it is interesting to note that all alkylideneoxindoles of this series are mixtures of rapidly equilibrating *Z* and *E* isomers as measured by NMR.[19] In derivatives with a proton on nitrogen, such as **38** and **39**, the *Z* isomer predominates in solvents such as chloroform by stabilization via a hydrogen bond to the oxindole carbonyl. However, a preferred *Z* configuration cannot explain the inactivity of **38**, because a similar preference is shown by the MPA active analogue **39**.

The compounds with the α-substituted side chain listed in Table III were prepared in an effort to decrease, by steric hindrance, the hydrolysis of the aminoalkylideneoxindoles to the corresponding (biologically inactive) 3-acyloxindoles observed in acidic media. For instance, compound **2** was hydrolyzed under acidic conditions (50% methanol–water, pH 2) with a half-life of 35 min.[20] To our surprise, while the introduction of the α-methyl group doubled the potency with some (e.g. **51** vs **2**, **54** vs **26**) but not all (e.g. **52** vs **7**, **55** vs **27**, **57** vs **39**) compounds, it decreased dramatically the acid stability, contrary to our expectations. For example, **51** was hydrolyzed at pH 2 in

(19) We are grateful to Dr. E. B. Whipple of Pfizer Central Research for these NMR determinations.

(20) We are grateful to Dr. T. A. Hagen of Pfizer Central Research for these stability studies.

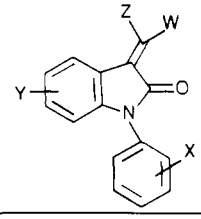
Table II. Amino Variations at the 3-Position



no.	W	method	yield, %	mp, °C	recrystal solvent[a]	formula[b]	MPA antagonism,[c] ED_{50}	[^{3}H]FNP bound,[d] % control ± S.E.	isoniazid antagonism,[e] ED_{50}
2	NMe_2	D1	87	116–8	Et_2O	$C_{17}H_{15}ClN_2O$	26.1	138 ± 6	1–3.2
38	NHMe	F2	73	151.5–3	EtOH	$C_{16}H_{13}ClN_2O$	>100	119 ± 3	
39	NH_2	F2	93	141–3	Et_2O	$C_{15}H_{11}ClN_2O \cdot {}^1/_4H_2O$	22.1	134 ± 4	
40	NEt_2	F1	59	74–5.5	Et_2O·P	$C_{19}H_{19}ClN_2O$	18		
41	NHPr	F2	88	144–6	*f*	$C_{18}H_{17}ClN_2O$	>56		
42	NPr_2	F2	54	68–71	Et_2O	$C_{21}H_{23}ClN_2O$	>100		
43	pyrrolidino	F2	78	108–12	Et_2O	$C_{19}H_{17}ClN_2O$	>100		
44	piperidino	F2	62	153–5	EA·H	$C_{20}H_{19}ClN_2O$	>56	131 ± 5	
45	morpholino	F2	80	130–2.5	Et_2O·P	$C_{19}H_{17}ClN_2O_2$	>100	121 ± 3	
46	imidazo	F1	11	164–6	Tol	$C_{18}H_{12}ClN_3O$	>100	139 ± 8	
47	$NHCH_2Ph$	F2	90	97–9	EtOH	$C_{22}H_{17}ClN_2O$	>100		
48	$N(Me)CH_2Ph$	F2	3	118–20	EA·H	$C_{23}H_{19}ClN_2O \cdot {}^1/_2H_2O$	>100	135 ± 5	
49	N(Me)Ph	E	19	127–9	Et_2O·P	$C_{22}H_{17}ClN_2O$	>100	133 ± 6	
50	OEt	C	17	132–4	EA·H	$C_{17}H_{14}ClNO_2$	>100		

[a] See note *a*, in Table I. [b] See note *b*, in Table I. [c] See note *c*, in Table I. [d] See note *d*, in Table I. [e] See note *e*, in Table I. [f] Precipitated from reaction.

Table III. Branched 3-(Aminoalkylidene)oxindoles



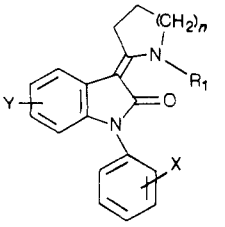
no.	X	Y	W	Z	method	yield, %	mp, °C	recrystal solvent[a]	formula[b]	MPA antagonism,[c] ED_{50}	[^{3}H]FNP bound,[d] % control ± S.E.	isoniazid antagonism,[e] ED_{50}
2	3-Cl	H	NMe_2	H	D1	87	116–8	Et_2O	$C_{17}H_{15}ClN_2O$	26.1	138 ± 6	1–3.2
51	3-Cl	H	NMe_2	Me	D1	36	113–6	Et_2O	$C_{18}H_{17}ClN_2O$	13.3	136 ± 8[f]	1
52	3-Me	H	NMe_2	Me	G	8	96–9	PE	$C_{19}H_{20}N_2O$	17.8		
53	4-OMe	H	NMe_2	Me	D1	66	176–7.5	Et_2O	$C_{19}H_{20}N_2O_2$	>100		
54	3-Cl, 4-OMe	H	NMe_2	Me	D1	74	138–41	Et_2O	$C_{19}H_{19}ClN_2O_2$	2.8		
55	3-F, 4-OMe	H	NMe_2	Me	D1	48	187–9	Et_2O	$C_{19}H_{19}FN_2O_2$	>100	157 ± 9[g]	
56	H	6-Cl	NMe_2	Me	D1	5	118–21	Et_2O·PE	$C_{18}H_{17}ClN_2O$	35.9		
57	3-Cl	H	NH_2	Me	F2	70	200–2	EtOH	$C_{16}H_{13}ClN_2O$	>100	103 ± 5[NS]	
58	H	6-Cl	NH_2	Me	F2	29	170–2.5	EtOH	$C_{16}H_{13}ClN_2O$	>56		
59	H	6-Cl	pyrrolidino	Me	F2	28	128–31	Et_2O·P	$C_{20}H_{19}ClN_2O$	>56	213 ± 9	
60	3-Cl	H	NMe_2	Ph	E	4	124–6	Et_2O·P	$C_{23}H_{19}ClN_2O \cdot H_2O$	>100		
61	3-Cl	H	NH_2	CF_3	F1	84	197–200	*h*	$C_{16}H_{10}ClF_3N_2O \cdot {}^3/_2H_2O$	>56		

[a] See note *a*, in Table I. [b] See note *b*, in Table I. [c] See note *c*, in Table I. [d] See note *d*, in Table I. [e] See note *e*, in Table I. [f] At 178 μmol/kg ip. [g] At 100 μmol/kg ip. [h] Precipitated from reaction.

50% methanol–water with a half-life of only 2 min.[20] Therefore, the observed potency increase must be due to enhanced intrinsic activity, but the relative acid instability made these derivatives less attractive for further development. The inactivity of **55** against MPA convulsions was surprising but can probably by explained by poor absorption after sc administration; **55** showed an ED_{50} of 32–100 mg/kg after oral administration. The inactivity of **57** was probably due to extreme insolubility of the compound in vehicle, leading to poor absorption.

An interesting class of compounds was ultimately obtained by forming a ring between the nitrogen and the α position of the side chain. Excellent MPA activity was found in the *N*-methylpyrrolidinylidene compounds **66**, **69**, and **70** (Table IV). Of these, **66** appeared to be particularly interesting since it did not exhibit the twitches and myoclonic jerks seen with **69** and **70** at higher doses. At low pH compound **66** was converted to the ring-opened 3-(4-aminobutanoyl)oxindole, which can readily recyclize to **66**, thereby resulting in greatly enhanced overall acid stability for **66** relative to **51** or **2**. Another interesting compound in this table was **63**. This direct analogue of **2** surprisingly had no MPA activity when administered sc. However, **63** was equipotent to **66** when given intraperitoneally (ED_{50} ~ 3.2 mg/kg) in the MPA test, and it was also quite potent after ip administration in reducing the isoniazid-induced cyclic GMP elevation and in enhancing [^{3}H]FNP binding. Therefore, absorption after sc administration may be inadequate for certain members of this series, and the SAR results in the standard MPA test reflect a combination of

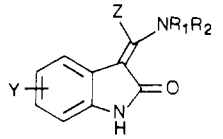
Table IV. Cyclic Derivatives



no.	X	Y	n	R_1	method	yield, %	mp, °C	recrystal solvent[a]	formula[b]	MPA antagonism,[c] ED_{50}	[^{3}H]FNP bound,[d] % control ± S.E.	isoniazid antagonism,[c] ED_{50}
62	H	H	1	Me	D1	50	165–7.5	CH_2Cl_2·IPE	$C_{19}H_{18}N_2O$	>100	143 ± 7	
63	3-Cl	H	1	Me	E	86	139–41	CH_2Cl_2·IPE	$C_{19}H_{17}ClN_2O$	>100	192 ± 19	1–3.2
64	4-Cl	H	1	Me	G	48	174–6		$C_{19}H_{17}ClN_2O$	>56	127 ± 9	
65	3-OMe	H	1	Me	G	20	127–9	$CHCl_3$·Et_2O	$C_{20}H_{20}N_2O_2$	32–100	214 ± 9	
66	4-OMe	H	1	Me	D1	58	129–31	CH_2Cl_2·IPE	$C_{20}H_{20}N_2O_2$	3.2–5.6	211 ± 7	0.3–7
67	3-CN	H	1	Me	G	16	172–4	$CHCl_3$·Et_2O	$C_{20}H_{17}N_3O$	>100	121 ± 6	
68	3-$CONMe_2$	H	1	Me	G	17	170–2	$CHCl_3$·Et_2O	$C_{22}H_{23}N_3O_2$·$^1/_4H_2O$	>100	164 ± 15	
69	3-Cl, 4-OMe	H	1	Me	E	42	126–7.5	Et_2O	$C_{20}H_{19}ClN_2O_2$	3.6	220 ± 7[f]	
70	3-F, 4-OMe	H	1	Me	E	12	68–71	Et_2O·P	$C_{20}H_{19}FN_2O_2$	5.6	225 ± 12[f]	
71	3-Cl	H	2	Me	E	7	162–5	EA·PE	$C_{20}H_{19}ClN_2O$	>100	135 ± 2	
72	3-Cl	H	3	H	D2	44	158–61	EA·H	$C_{20}H_{19}ClN_2O$	>100	138 ± 9	
73	3-Cl	H	1	Et	E	38	105–7	EA·H	$C_{20}H_{19}ClN_2O$	>100	164 ± 6	
74	3-Cl	H	1	Ph	E	33	128–30	Et_2O	$C_{24}H_{19}ClN_2O$	>100	125 ± 5	
75	3-Cl	H	1	CH_2-Ph	E	53	72–5	Et_2O·P	$C_{25}H_{21}ClN_2O$	>100	149 ± 9[f]	
76	3-Cl	H	1	CH_2-Ph-Cl_p	G	29	115–7	Et_2O	$C_{25}H_{20}Cl_2N_2O$·$^1/_2H_2O$	>100	131 ± 4	
77	3-F, 4-OMe	H	1	H	D2	38	169–71	EA	$C_{19}H_{17}FN_2O_2$	~56		
78	H	H	3	H	D2	46	144–6	PhH·PE	$C_{20}H_{20}N_2O$	>100		
79	H	4-Cl	1	Me	E	20	78–80	Et_2O·H	$C_{19}H_{17}ClN_2O$	>100	190 ± 7	
80	H	6-Cl	1	Me	E	12	177–9	Et_2O	$C_{19}H_{17}ClN_2O$	>100	158 ± 8	
81	3-Cl	6-Cl	1	Me	G	43	103–6	Et_2O·CH	$C_{19}H_{16}Cl_2N_2O$	>100	189 ± 10	

[a] See note *a*, in Table I. [b] See note *b*, in Table I. [c] See note *c*, in Table I. [d] See note *d*, in Table I. [e] See note *e*, in Table I. [f] At 100 μmol/kg ip.

Table V. 3-(1-Aminoalkylidene)oxindoles



no.	Y	Z	R_1	R_2	method	yield, %	mp, °C	formula[a]
99	H	H	CH_3	CH_3	D1	94	193–6[b]	$C_{12}H_{12}N_2O$
100	H	CH_3	CH_3	CH_3	D1	87	204–7	$C_{12}H_{14}N_2O$
101	4-Cl	H	CH_3	CH_3	D1[c]	82	220–3	$C_{11}H_{11}ClN_2O$·$^1/_8H_2O$
102	5-Cl	H	CH_3	CH_3	D1[d]	67	204–6	$C_{11}H_{11}ClN_2O$
103	6-Cl	H	CH_3	CH_3	D1	100	224–6	$C_{11}H_{11}ClN_2O$·$^1/_4H_2O$[e]
104	7-Cl	H	CH_3	CH_3	D1[f]	70	230–2	$C_{11}H_{11}ClN_2O$
105	5-OCH_3	H	CH_3	CH_3	D1[f]	66	222–5	$C_{12}H_{14}N_2O_2$·$^1/_2H_2O$
106	H	-$(CH_2)_3$-		CH_3	D1	47	269–72[g]	$C_{13}H_{14}N_2O$
107	6-Cl	-$(CH_2)_3$-		CH_3	D1	50	227–9	$C_{13}H_{13}ClN_2O$[h]

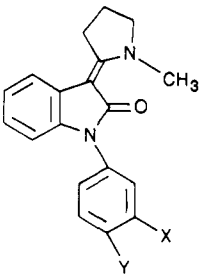
[a] See note *b*, in Table I. [b] Reference 30. [c] Prepared according to the method of Koelsch, C. F. *J. Am. Chem. Soc.* 1944, *66*, 2019. [d] From 5-chlorooxindole (Aldrich Chem. Co.). [e] *m/e*: 224, 222. [f] U.S. 3,882,236, from the oxindoles via the isatins. [g] Chandramohan, M. R. *Ind. J. Chem.* 1974, *12*, 940; mp 267–8 °C. [h] *m/e*: 250, 248.

varying intrinsic activity and varying bioavailability.

Conclusion

These results suggest that many members of this oxindole series exert GABAergic activity. All the oxindoles of this series which were tested significantly enhance [^{3}H]FNP binding in vivo, with the exception of the extremely insoluble compound **57**. Such activity has been reported for GABA agonists and GABAergic agents, e.g. progabide[16] and tracazolate,[5,9c] but not to the degree observed with the best members in this oxindole series (potency rank order: **69** > **66** > **63** > tracazolate > progabide). Antagonism of isoniazid parallels enhancement of [^{3}H]FNP binding in this series within the subset of compounds for which both tests were run. It is not clear whether isoniazid activity is an expression of GABAergic activity or secondary to a benzodiazepine-like effect, especially since benzodiazepines (e.g., diazepam) and tracazolate are also active in this test (Table VI). MPA activity in this series does not always parallel [^{3}H]FNP binding activity or isoniazid activity, probably reflecting poor bioavailability for certain compounds after sc dosing, as we have shown in the case of **63**, which gave good MPA activity after ip administration. Nevertheless, several compounds, such as **66**, **69**, and **70** showed an excellent combination of intrinsic activity, as measured by [^{3}H]FNP binding, and of MPA antagonism after sc administration. Whether or not the GABAergic activity of these oxindoles is related to binding at the

Table VI. Biological Activity of Key Oxindoles and of Reference Compounds



	X	Y
63	Cl	H
66	H	OCH_3
69	Cl	OCH_3

	mouse LD_{50},[a] mg/kg		MPA antagonism,[b] ED_{50}, mg/kg		[^{3}H]FNP bound,[c] % control ± S.E. at the following dose (μmol/kg ip):						isoniazid antagonism,[d] ED_{50},
no.	sc	ip	sc	ip	1000	320	100	32	10	3.2	mg/kg ip
63	>1000	>320	>100	~3.2		192 ± 19	132 ± 7	105 ± 4^{NS}	105 ± 4^{NS}		1–3.2
66	>1000	>320	3.2–5.6	~3.2		211 ± 7	192 ± 9	125 ± 4	103 ± 3^{NS}	105 ± 6^{NS}	0.3–1
69	≥320	32–100	3.6				220 ± 7	159 ± 5	128 ± 8	115 ± 9^{NS}	
muscimol	4.2	3.2–10	0.7					124 ± 6[e]			1.5
progabide	>1000	~1000	>100		178 ± 15	93 ± 3^{NS}	89 ± 8^{NS}				<32
Na valproate	>1000	>1000	212		128 ± 6[f]						
tracazolate		>1000	>100			127 ± 7					~3
diazepam	500	320–1000	0.7				7 ± 0.3		39 ± 2	66 ± 2	<0.9

[a] Mice were observed for 7 days after drug administration. [b] See note *c*, in Table I. [c] See note *d*, in Table I; compounds were administered at the dose level indicated. [d] See note *e*, in Table I. [e] Sc. [f] 15 min.

barbiturate site of the putative barbiturate–benzodiazepine–GABA postsynaptic receptor complex[21] should provide the basis of further efforts with this novel series.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer, while mass spectra were obtained on a Hitachi-Perkin Elmer RMU-6E mass spectrometer for low resolution and an A.E.I. MS-30 for high resolution. ^{1}H NMR spectra were recorded on Varian A-60 or T-60 or Bruker WM-250 spectrometers, using Me_4Si as an internal standard. Microanalyses were performed by the Pfizer Analytical Department and agree within ±0.4% of calculated values, unless noted otherwise.

Method A. Preparation of *N*-Aryloxindoles C from Diphenylamines. 1. 2-Chloro-*N*,*N*-diphenylacetamide (82). A solution of 84.6 g of diphenylamine (0.5 mol) and 80 mL of chloroacetyl chloride (1.0 mol) in 500 mL of toluene was refluxed for 1.5–2.0 h under N_2, cooled, and concentrated in vacuo. The residue was recrystallized from EtOH to give 103 g (84%) of **82** as tan crystals, mp 113–116 °C (lit.[22] mp 114–117 °C). Similarly, 3-chlorodiphenylamine (Aldrich) gave the 3′-chloro analogue **83** (95%, mp 94–96.5 °C, aqueous EtOH) and 3-fluorodiphenylamine[23] gave the 3′-fluoro analogue **84** (88%, mp 115–117 °C, aqueous EtOH).

2. 1-Phenyloxindole (85). A mixture of 32.5 g of **82** (0.132 mol) and 41 g of $AlCl_3$ (0.307 mol) was mixed while being heated in an open beaker until an internal temperature of 180–190 °C was attained (*Note*: copious evolution of HCl) and then heated an additional 10 min. The molten mass was allowed to cool to approximately 70 °C and then was treated with crushed ice and 100 mL of 1 N HCl. The crude product that solidified was filtered, washed well with H_2O, and air-dried. Recrystallization from absolute EtOH gave **85** as light golden colored crystals, 22.5 g (81.5%), mp 117–119 °C (lit.[10] mp 116–118 °C). By analogy, the following 1-phenyloxindoles were prepared: 3′-chloro (**86**, 40%, mp 104–107 °C); 4-chloro (**87**, 5% mp 87–90 °C); 6-chloro (**88**, 7% mp 113–115 °C); 3′-fluoro (**89**, 28% , mp 94–96 °C); and 6-fluoro (**90**, 9%, mp 63–67 °C).[24]

Alternatively, the diphenylamine could be combined with oxalyl chloride (1.12 equiv) in CH_2Cl_2 and then cyclized to the isatin with $AlCl_3$ (3.1 equiv) in CH_2Cl_2. Using a modified Wolff–Kishner reduction (isatin, 85% KOH, 64% hydrazine hydrate and diethylene glycol at 160 °C for 16–18 h followed by acidification with concentrated HCl and extraction into CH_2Cl_2), the isatin could be reduced to the 1-aryloxindole. In this manner, 40 g of *N*,*N*-bis(4-fluorophenyl)amine was converted to 47.6 g (94.3%) of 5-fluoro-1-(4-fluorophenyl)isatin, mp 185–188 °C. Anal. ($C_{14}H_7F_2NO_2$) C, H, N. Reduction of 9.6 g (0.037 mol) of the isatin with 10 mL of hydrazine hydrate and 6 g of KOH in 100 mL of diethylene glycol gave, after recrystallization from *i*-PrOH, 7.0 g (77%) of **91**, as tan crystals, mp 138–140 °C. Anal. ($C_{14}H_9F_2NO$) C, H, N.

Method B. Preparation of *N*-Aryloxindoles C from *N*-Arylindoles. 1. *N*-Arylindoles: 1-(3-Chloro-4-methoxyphenyl)indole (95). A mixture of 14 g of indole (0.12 mol), 34.0 g of 2-chloro-4-iodoanisole[25] (**109**, 0.127 mol), 18 g of anhydrous K_2CO_3 (0.13 mol), and 1.0 g of cuprous bromide (0.004 mol) in 200 mL of dry *N*-methyl-2-pyrrolidinone (NMP) was heated at 200 °C for 24 h under N_2. The mixture was then cooled, poured over 300 mL of ice/H_2O, and extracted with EtOAc. The organic extracts were washed with H_2O and saturated NaCl and dried over $MgSO_4$. Concentration in vacuo gave a crude oil, which was chromatographed on 230–400-mesh silica gel (7.5 × 24 cm), eluting with 1:1 hexane/CH_2Cl_2 to give the product (**95**) as a colorless oil, 5.3 g (17%); ms, *m*/*e* 259, 257 (P^+).

A more polar component, 5.0 g of viscous oil, was identified as 1-(3-chloro-4-hydroxyphenyl)indole by ms [*m*/*e* 245, 243 (P^+)] and NMR spectra in $CDCl_3$ (bs, approximately 1 H, δ 5.6).

Similarly 4-bromo-2-fluoroanisole[26] gave 1-3-fluoro-4-methoxyphenyl)indole (**96**, 35%, mp 65–67 °C); 3-chloro-1-iodobenzene gave 1-(3-chlorophenyl)indole (**97**, 64%, bp 133–138 °C (0.1

(21) (a) Skolnick, P.; Paul, S. M. *Annu. Rep. Med. Chem.* **1981**, *16*, 21. (b) Wong, D. T.; Threlkeld, P. G.; Bymaster, F. P.; Squires, R. F. *Life Sci.* **1984**, *34*, 853.
(22) Verderame, M. *J. Pharm. Sci.* **1961**, *50*, 312.
(23) Prepared by the method of Leonard, N. J.; Sutton, L. E. *J. Am. Chem. Soc.* **1948**, *70*, 1564; bp 130–135 °C (2.2 mmHg).
(24) Isomer mixtures were separated by flash chromatography (230–400-mesh silica gel), eluting with hexane/ethyl acetate (95:5).
(25) See note i in Table I.
(26) Schieman, G. *J. Prakt. Chem.* **1935**, *143*, 18.

mmHg)); and 4-iodoanisole gave 1-(4-methoxyphenyl)indole (**98**, 59%, mp 52–54 °C).

2. Oxidation of *N*-Arylindoles B to *N*-Aryloxindoles C: 1-(3-Chloro-4-methoxyphenyl)oxindole (94). To 0.93 g of the indole from part B.1 (3.6 mmol) in 25 mL of CH_2Cl_2 was added 0.492 g of *N*-chlorosuccinimide (98%, 3.6 mmol) at 25 °C under N_2 with good stirring. After 1 h, the light orange solution was concentrated in vacuo, and the residue was redissolved in 15 mL of glacial acetic acid and warmed to approximately 70 °C. In one portion, 3.9 mL of 85% H_3PO_4 was added, and the temperature was increased to reflux for an additional 2 h. After cooling, the mixture was poured over 200 mL of ice/H_2O, the pH was adjusted to 7.0 with saturated $NaHCO_3$ (*Caution*: foams vigorously), and the resulting mixture was extraced 2× with 200 mL of EtOAc. The combined organic extracts were washed with H_2O, saturated NaCl, dried ($MgSO_4$), and concentrated in vacuo to a yellow semisolid. Chromatography (230–400-mesh silica gel, 4.5 × 15 cm), eluting with EtOAc/hexane (2:3), gave the title product as a yellow solid, 0.71 g (72%), mp 165–167 °C. Anal. ($C_{15}H_{12}ClNO_2$) C, H, N. Similarly, oxidation of **96** gave 1-(3-fluoro-4-methoxyphenyl)oxindole (**92**, 51%, mp 133–136 °C), while **98** gave 1-(4-methoxyphenyl)oxindole (**93**, 90%, mp 121–123 °C[27]).

Method C. Preparation of (Hydroxy(or alkoxy)alkylidene)oxindoles D. 1. 3-(Hydroxymethylene)-1-phenyloxindole. Potassium *tert*-butoxide (1.63 g, 14.5 mmol) and 5 mL of EtOH were heated to 80 °C. 1-Phenyloxindole (2.09 g, 10 mmol) was added, followed immediately by ethyl formate (1.09 mL, 13.5 mmol), and the mixture was heated another 5 min at 80 °C and allowed to cool to 25 °C. Crushed ice and H_2O (50 mL) were added, the mixture was acidified with 3 N HCl to pH 3, and the crude product was filtered and washed with water. Recrystallization from MeOH gave pure product, 2.2 g (93%), mp 197–199 °C (lit.[28] mp 202–204 °C).

2. 1-(3-Chlorophenyl)-3-(ethoxymethylene)oxindole (50). A mixture of 1-(3-chlorophenyl)oxindole (**86**, 2.4 g, 0.01 mol) and triethyl orthoformate (8.3 mL, 0.05 mol) was heated at 140–160 °C for 18 h. Another 20 mL of orthoformate was added, and the mixture was heated another 2 h, cooled to 25 °C, diluted with Et_2O, and washed with H_2O and saturated NaCl. After drying ($MgSO_4$), the filtrate was concentrated in vacuo. The oily residue was triturated with pentane and the resultant solids (4.2 g) chromatographed on silica gel (7.5 × 15 cm), eluting with 4:1 hexane/EtOAc. Product **50** was isolated in 17% yield, mp 132–134 °C. Anal. ($C_{17}H_{14}ClNO_2$) C, H, N.

Method D. Preparation of (Aminoalkylidene)oxindoles E. 1. From C-3 Unsubstituted Oxindoles and Acetals: 1-(3-Chlorophenyl)-3-(*N*-methylpyrrolidinylidene)oxindole (63). A solution of 5.0 g (20.5 mmol) of **86** in 50 mL of $CHCl_3$ was treated with 1.2 equiv of 2,2-diethoxy-1-methylpyrrolidine[29] under N_2 and refluxed for 3 h. After cooling, the solution was washed with saturated $NaHCO_3$ and saturated NaCl and dried ($MgSO_4$). After treatment with decolorizing charcoal and filtration through Celite, the filtrate was concentrated in vacuo to a tan solid. Recrystallization from CH_2Cl_2/IPE gave **63** as a tan crystalline solid, 5.72 g (86%), mp 139–141 °C. Anal. ($C_{19}H_{17}ClN_2O$) C, H, N.

2. From C-3 Unsubstituted Oxindoles and Lactims: 1-Phenyl-3-(perhydroazepin-2-ylidene)oxindole (78). A mixture of 1.047 g (5 mmol) of **85** and 1.45 mL (10 mmol) of 2-methoxy-1-aza-1-cycloheptene (Aldrich Chemical Co.) in 10 mL of toluene was refluxed for 18 h, cooled, diluted with Et_2O, and washed with H_2O, 1 N HCl, and saturated NaCl and dried ($MgSO_4$). After decolorizing and filtering through Celite, the product was isolated as a pale orange solid. Recrystallization from benzene/petroleum ether gave **78** as white needles, 0.703 g (46%), mp 144–146 °C dec. Anal. ($C_{20}H_{20}N_2O$) C, H, N.

Method E. Preparation of (Aminoalkylidene)oxindoles E from Oxindoles and Vilsmeier–Haack Complexes. 1. 1-(3-Chlorophenyl)-3-(*N*-benzylpyrrolidin-2-ylidene)oxindole (75). With ice-bath cooling, under N_2, 1.58 mL (9.85 mmol) of *N*-benzyl-2-pyrrolidinone and 0.55 mL (5.9 mmol) of $POCl_3$ in 5 mL of toluene were stirred for 30 min. To this were added 1.2 g (4.92 mmol) of **86** and 3 mL of toluene; the mixture was allowed to warm to 25 °C for 30 min and then heated at 70–75 °C for 18 h until TLC in CH_2Cl_2 showed a new more polar spot. After cooling and dilution with CH_2Cl_2, the mixture was washed with saturated $NaHCO_3$, H_2O, and saturated NaCl and dried ($MgSO_4$). The oil obtained on concentration was chromatographed on 230–400-mesh silica gel (4.5 × 15 cm), eluting with CH_2Cl_2 to give the product as a yellow oil, which was crystallized from Et_2O/pentane to give **75** as a pale yellow solid, 1.04 g (53%), mp 72–75 °C. Anal. ($C_{25}H_{21}ClN_2O$) C, H, N.

Method F. Preparation of (Aminoalkylidene)oxindoles G by Amine Displacements. 1. Reaction of Amines with (Hydroxy (or alkoxy)alkylidene)oxindoles: 1-(3-Chlorophenyl)-3-[(diethylamino)methylene]oxindole (40). A solution of 0.15 g (0.5 mmol) of oxindole **50** (from Method C.2) in 30 mL of EtOH was treated with 5 mL (48 mmol) of diethylamine and stirred at 25 °C for 24 h to give, after removal of the solvent, the crude amine. This was redissolved in EtOAc, washed with H_2O, and saturated NaCl, dried ($MgSO_4$), decolorized with charcoal, and concentrated in vacuo. The oil was triturated with Et_2O and pentane with dry ice cooling to produce **40** as a pale yellow crystalline solid, 96 mg (59%), mp 74–75.5 °C. Anal. ($C_{19}H_{19}ClN_2O$) C, H, N.

2. Reaction of Amines with (Aminoalkylidene)oxindoles: 1-(3-Chlorophenyl)-3-(1-pyrrolidinylmethylene)oxindole (43). A solution of 0.30 g (1 mmol) of **2** in 10 mL of absolute EtOH was treated with 0.42 mL (5 mmol) of pyrrolidine in 10 mL of absolute EtOH and stirred at 25 °C for up to 24 h. Progress of the reaction could be followed by TLC (EtOAc/hexane), and, upon completion, the solvent was removed in vacuo and the product recrystallized from Et_2O to give **43** as a white solid, 0.253 g (78%), mp 108–112 °C. Anal. ($C_{19}H_{17}ClN_2O$) C, H, N.

Method G. Ullmann Reaction of 3-[(Dimethylamino)methylene]oxindoles with Aryl Halides. 1-(3,5-Dichlorophenyl)-3-[(dimethylamino)methylene]oxindole (25). Under N_2, in dry glassware, 0.96 g (0.02 mol, 50% oil dispersion) of NaH was washed with pentane, suspended in 70 mL of dry DMF, and treated with 3.765 g (0.02 mol) of 3-(dimethylaminomethylene)oxindole,[30] **99**. After 1 h at 25 °C, no further H_2 evolution was noted, and the suspension of the precipitated sodium salt was treated with 10.92 g (0.04 mol) of 3,5-dichloroiodobenzene (99%, Fairfield Chemical Company) in 20 mL of DMF, followed by 5.74 g (0.02 mol) of cuprous bromide. The darkly colored solution was heated at 100 °C for 24 h, after which TLC (EtOAc) showed the reaction to be essentially completed. After cooling to 25 °C, the mixture was poured over 300 mL of ice/H_2O, stirred with 300 mL of Et_2O for 30 min, and filtered through Celite, washing with acetone. The combined Et_2O and acetone filtrates were washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo to a tan solid, 10.8 g. This crude product was chromatographed on 1 kg of silica gel, eluting with CH_2Cl_2 and then EtOAc, to obtain the pure product **25** as a yellow solid, 4.8 g (72%) mp 147–149.5 °C; ms, *m/e* 335, 333. Anal. ($C_{17}H_{14}Cl_2N_2O$) C, H, N.

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(27) Ref. 10, mp 118–122 °C (aq. EtOH).
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