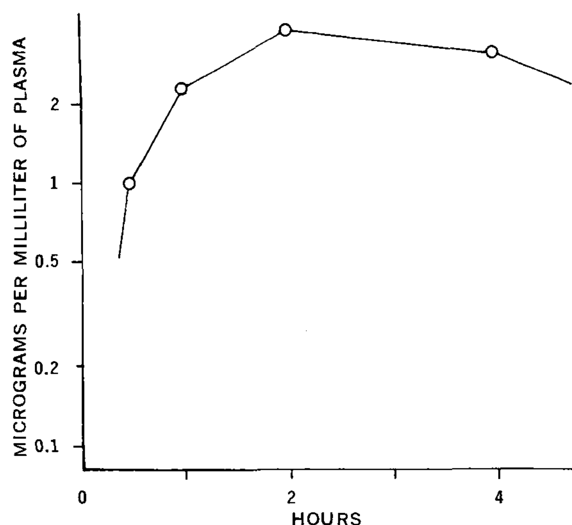

Figure 3—*Plasma concentrations of I in human subject following an oral dose of 3 g of I/m² in tablets.*

slow absorption through the GI mucosa. When given orally, I was slowly absorbed in all experiments, although an aqueous solution was used in rats and rabbits. The bioavailability of I is being studied.

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Synthesis of 2-(*N*-Arylcarboxamide)-3-substituted Ethoxyindoles and Their Monoamine Oxidase Inhibitory and Anticonvulsant Activities

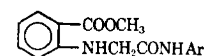
A. K. GUPTA *, C. DWIVEDI ‡, T. K. GUPTA *, SURENDRA S. PARMAR *ˣ, and RAYMOND D. HARBISON ‡

Abstract ☐ 2-(*N*-Arylcarboxamide)-3-substituted ethoxyindoles were synthesized by the reaction of 2-(*N*-arylcarboxamide)-3-hydroxyindoles, which were obtained by the cyclization of 2-carbomethoxyphenylglycine-substituted anilides. These 2-(*N*-arylcarboxamide)-3-substituted ethoxyindoles were evaluated for their *in vitro* monoamine oxidase inhibitory ability and *in vivo* monoamine oxidase inhibitory property as evidenced by reserpine reversal response. Their anticonvulsant activity also was determined against pentylenetetrazol-induced seizures. No definite correlation could be observed between chemical structure and biological activity.

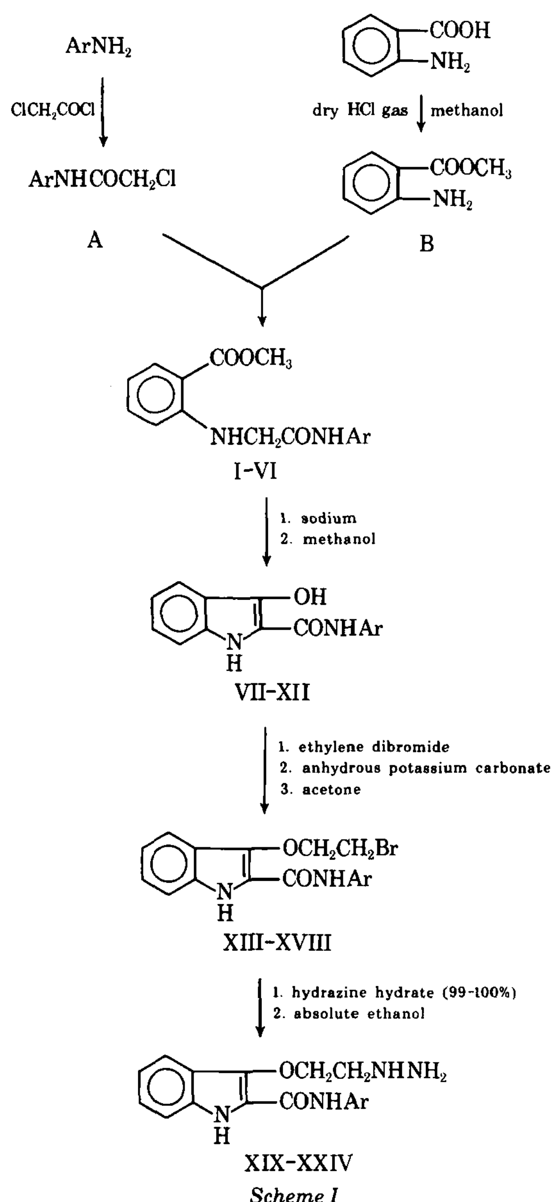
Keyphrases ☐ 2-(*N*-Arylcarboxamide)-3-substituted ethoxyindoles—synthesis, monoamine oxidase inhibitory and anticonvulsant activities ☐ Monoamine oxidase inhibitory activity—synthesis and screening of 2-(*N*-arylcarboxamide)-3-substituted ethoxyindoles, rat brain homogenate ☐ Anticonvulsant activity—synthesis and screening of 2-(*N*-arylcarboxamide)-3-substituted ethoxyindoles, mice

Identification of serotonin in the brain as a possible central neurohumoral agent (1) and the widespread occurrence of the indole nucleus among both naturally occurring and synthetic psychoactive compounds (2) stimulated an investigation of indole analogs with potent central nervous system (CNS) activity. In addition, clinical efficacy of 3-(2-aminobutyl)indole for the treatment of some types of depression (3) and the ability of indole derivatives to inhibit rat brain and rat liver monoamine oxidase (4, 5) and to protect against pentylenetetrazol-induced seizures (6, 7) prompted the synthesis of some 2-(*N*-arylcarboxamide)-3-substituted ethoxyindoles and their evaluation for CNS effects.

Table I—2-Carbomethoxyphenylglycine-substituted Anilides



Compound	Ar	Melting Point	Yield, %	Molecular Formula	Analysis, % Calc.	Found
I	α-$C_{10}H_7$	165°	62	$C_{20}H_{18}N_2O_2$	C 75.47 H 5.66 N 8.81	75.22 5.51 8.53
II	β-$C_{10}H_7$	171°	65	$C_{20}H_{18}N_2O_2$	C 75.47 H 5.66 N 8.81	75.32 5.54 9.17
III	2-$OC_2H_5C_6H_4$	128°	62	$C_{18}H_{20}N_2O_3$	C 69.23 H 6.41 N 8.97	69.01 6.31 9.22
IV	4-$OC_2H_5C_6H_4$	138°	70	$C_{18}H_{20}N_2O_3$	C 69.23 H 6.41 N 8.97	69.51 6.23 8.69
V	2,4-$(CH_3)_2C_6H_3$	155°	60	$C_{18}H_{20}N_2O_2$	C 72.97 H 6.76 N 9.46	74.13 6.68 9.17
VI	3,4-$(CH_3)_2C_6H_3$	140°	67	$C_{18}H_{20}N_2O_2$	C 72.97 H 6.76 N 9.46	72.69 6.67 9.73



Scheme I

In the present investigation, these indole derivatives were tested for their *in vitro* monoamine oxidase inhibitory property using kynuramine as a substrate and for their *in vivo* monoamine oxidase inhibitory property as evidenced by the reserpine reversal tests. Their anticonvulsant activity against pentylenetetrazol-induced seizures was also determined so that it could be correlated with their monoamine oxidase inhibitory property. These 2-(*N*-arylcarboxamide)-3-substituted ethoxyindoles were synthesized following the steps outlined in Scheme I.

EXPERIMENTAL

Chemistry—Arylamines, on treatment with chloroacetyl chloride, gave *N*-chloroacetyl derivatives (B) which, on reaction with methyl anthranilate (A), gave 2-carbomethoxyphenylglycine-substituted anilides (I–VI). These anilides were cyclized in the presence of sodium and methanol to the corresponding 2-(*N*-arylcarboxamide)-3-hydroxyindoles (VII–XII). These 3-hydroxyindoles were refluxed with ethylene dibromide in the presence of anhydrous potassium carbonate in acetone. This reaction gave 2-(*N*-arylcarboxamide)-3α-bromoethoxyindoles (XIII–XVIII) which, on treatment with hydrazine hydrate, yielded 2-(*N*-arylcarboxamide)- 3α-hydrazinoethoxyindoles (XIX–XXIV).

Analyses for carbon, hydrogen, and nitrogen were performed; melting points were taken in open capillary tubes.

***N*-Chloroacetyl Arylamines (A)**—A mixture of suitable arylamine (0.1 mole) and chloroacetyl chloride (0.11 mole) in dry benzene was refluxed on a steam bath for 4–5 hr. On cooling, the solid mass which separated was filtered, washed with water, dried, and recrystallized (8).

Methyl Anthranilate (B)—Anthranilic acid (0.20 mole) was introduced into absolute ethanol (100 ml) saturated with dry hydrogen chloride gas. The contents were refluxed for 2 hr, and the hot solution was poured into an excess of water. The pH of this solution was adjusted to 7.0 with sodium carbonate solution, and the solution was extracted with ether. The ether extract was dried, and removal of ether yielded methyl anthranilate, mp 23° (9).

2-Carbomethoxyphenylglycine-substituted Anilides (I–VI)—*N*-Chloroacetyl arylamine (0.03 mole) and methyl anthranilate (0.12 mole) were mixed and heated on a steam bath under anhydrous conditions. After 10 hr, 100 ml of dry benzene was added and the separated methyl anthranilate hydrochloride was removed by filtration. Benzene was removed by distillation from the filtrate. The residue was further heated for 8 hr, and the formed hydrochloride was again removed by filtration. The clear benzene solution was washed with 10% H_2SO_4, 10% Na_2CO_3, and water to re-

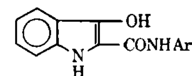


Table II—2-(*N*-Arylcarboxamide)-3-hydroxyindoles

Compound	Ar	Melting Point	Yield, %	Molecular Formula	Analysis, % Calc.	Found
VII	α-$C_{10}H_7$	235°	62	$C_{19}H_{14}N_2O_2$	C 75.50	75.73
					H 4.63	4.50
					N 9.27	9.03
VIII	β-$C_{10}H_7$	220°	65	$C_{19}H_{14}N_2O_2$	C 75.50	75.28
					H 4.63	4.70
					N 9.27	9.48
IX	2-$OC_2H_5C_6H_4$	153°	54	$C_{17}H_{16}N_2O_3$	C 68.92	68.68
					H 5.41	5.31
					N 9.46	9.65
X	4-$OC_2H_5C_6H_4$	210°	67	$C_{17}H_{16}N_2O_3$	C 68.92	68.73
					H 5.41	5.32
					N 9.46	9.73
XI	2,4-$(CH_3)_2C_6H_3$	204°	60	$C_{17}H_{16}N_2O_2$	C 72.86	72.62
					H 5.71	5.51
					N 10.00	10.29
XII	3,4-$(CH_3)_2C_6H_3$	225°	58	$C_{17}H_{16}N_2O_2$	C 72.86	73.13
					H 5.71	5.58
					N 10.00	9.72

move excess methyl anthranilate and dried. Excess benzene was removed by distillation; solid anilide, which separated on cooling, was collected by filtration, dried, and recrystallized. Crystals were characterized by their sharp melting points and elemental analyses (Table I).

2-(*N*-Arylcarboxamide)-3-hydroxyindoles (VII–XII)—To a solution of 2-carbomethoxyphenylglycine-substituted anilides (I–VI) (0.015 mole) in 15 ml of dry benzene with a few drops of methanol was added dry sodium (0.017 g-atom). This reaction mixture was refluxed on a steam bath for 2 hr under anhydrous conditions. The reaction mixture was allowed to cool, dry ether was added, and the residue was filtered and dissolved in cold water. The resulting solution was acidified with cold hydrochloric acid (50%), and the separated solid was filtered, dried, and recrystallized from suitable solvents. These crystals were characterized by their sharp melting points and elemental analyses (Table II).

2-(*N*-Arylcarboxamide)-3α-bromoethoxyindoles (XIII–XVIII)—To a solution of 0.011 mole of 2-(*N*-arylcarboxamide)-3-

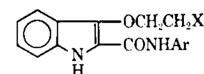


Table III—2-(*N*-Arylcarboxamide)-3-substituted Ethoxyindoles

Compound	Ar	X	Melting Point	Yield, %	Molecular Formula	Analysis, % Calc.	Found
XIII	α-$C_{10}H_7$	Br	100°	50	$C_{21}H_{17}BrN_2O_2$	C 61.61	61.42
						H 4.15	3.94
						N 6.85	7.11
XIV	β-$C_{10}H_7$	Br	113°	53	$C_{21}H_{17}BrN_2O_2$	C 61.61	61.87
						H 4.15	4.30
						N 6.85	6.58
XV	2-$C_2H_5C_6H_4$	Br	95°	48	$C_{19}H_{19}BrN_2O_3$	C 56.58	56.74
						H 4.71	4.61
						N 6.95	6.73
XVI	4-$C_2H_5C_6H_4$	Br	106°	55	$C_{19}H_{19}BrN_2O_3$	C 56.58	56.82
						H 4.71	4.64
						N 6.95	6.69
XVII	2,4-$(CH_3)_2C_6H_3$	Br	105°	50	$C_{19}H_{19}BrN_2O_2$	C 58.91	59.21
						H 4.91	4.79
						N 7.24	7.10
XVIII	3,4-$(CH_3)_2C_6H_3$	Br	138°	55	$C_{19}H_{19}BrN_2O_2$	C 58.91	58.63
						H 4.91	4.73
						N 7.24	7.51
XIX	α-$C_{10}H_7$	$NHNH_2$	125°	57	$C_{21}H_{20}N_4O_2$	C 70.00	70.28
						H 5.56	5.46
						N 15.56	15.31
XX	β-$C_{10}H_7$	$NHNH_2$	230°	69	$C_{21}H_{20}N_4O_2$	C 70.00	69.73
						H 5.56	5.66
						N 15.56	15.72
XXI	2-$C_2H_5C_6H_4$	$NHNH_2$	100°	45	$C_{19}H_{22}N_4O_3$	C 64.41	64.71
						H 6.22	6.13
						N 15.82	15.58
XXII	4-$C_2H_5C_6H_4$	$NHNH_2$	135°	58	$C_{19}H_{22}N_4O_3$	C 64.41	64.28
						H 6.22	6.08
						N 15.82	16.13
XXIII	2,4-$(CH_3)_2C_6H_3$	$NHNH_2$	145°	53	$C_{19}H_{22}N_4O_2$	C 67.45	67.73
						H 6.51	6.41
						N 16.57	16.33
XXIV	3,4-$(CH_3)_2C_6H_3$	$NHNH_2$	168°	55	$C_{19}H_{22}N_4O_2$	C 67.45	67.27
						H 6.51	6.38
						N 16.57	16.81

Table IV—Biological Activities of 2-(*N*-Arylcarboxamide)-3-substituted Ethoxyindoles[a]

Compound[b]	Approximate LD_{50}, mg/kg	Anticonvulsant Activity[c] Protection, %	24-hr Mortality, %	Monoamine Oxidase Inhibition[d]
XIII	>1000	10	60	33.33 ± 1.04
XIV	>1000	0	80	45.24 ± 0.92
XV	>1000	20	80	23.81 ± 0.68
XVI	>1000	30	70	38.09 ± 0.62
XVII	>1000	20	80	28.57 ± 0.95
XVIII	>1000	20	80	33.34 ± 0.58
XIX	>1000	10	70	76.19 ± 1.21
XX	>1000	20	70	21.43 ± 1.10
XXI	1000	0	100	28.57 ± 0.82
XXII	1000	20	70	30.95 ± 0.77
XXIII	>1000	0	100	26.19 ± 0.58
XXIV	>1000	0	100	33.28 ± 0.49

[a] No reserpine reversal response was noted. [b] Compound numbers as given in Table III. [c] Compounds were administered at a dose of 100 mg/kg ip. [d] All values represent the mean with standard error calculated from three separate experiments done in duplicate. All compounds were dissolved in propylene glycol. An equivalent amount of propylene glycol was added to control tubes. Final concentrations of compounds and kynuramine were 2×10^{-4} and 1×10^{-4} *M*, respectively.

hydroxyindoles (VII–XII) in dry acetone was added 0.011 mole of ethylene dibromide and 0.011 mole of anhydrous potassium carbonate. This reaction mixture was refluxed on a steam bath for 15–20 hr. The reaction mixture was filtered, and excess acetone was removed by distillation. The crude product, which separated on cooling, was filtered, dried, and recrystallized from suitable solvents. These compounds were characterized by their sharp melting points and elemental analyses (Table III).

2-(*N*-Arylcarboxamide)-3α-hydrazinoethoxyindoles (XIX–XXIV)—A mixture of 0.004 mole of 2-(*N*-arylcarboxamide)-3α-bromoethoxyindole and 99–100% hydrazine hydrate (0.004 mole) in absolute ethanol was refluxed on a steam bath for 12–15 hr. Excess ethanol was removed by distillation. The crude product, which separated on cooling, was filtered, dried, and recrystallized from suitable solvents. These compounds were characterized by their sharp melting points and elemental analyses (Table III).

Determination of *In Vitro* Monoamine Oxidase Activity—Monoamine oxidase activity of rat brain homogenates, using kynuramine as the substrate, was determined by the spectrophotofluorometric method described by Dwivedi *et al.* (10). The 4-hydroxyquinoline formed during oxidative deamination of kynuramine was measured fluorometrically[1], using activating light of 315 nm and measuring fluorescence at the maximum of 380 nm. The percent inhibition was calculated from the decrease observed in absorbance.

Determination of *In Vivo* Monoamine Oxidase Inhibition by Reserpine Reversal Test—Male healthy mice, 20–25 g, were divided into groups of five and kept in separate cages. A group of five mice was used for each compound. The compounds were administered in a 5% suspension of gum acacia in a dosage of 200 mg/kg ip. Reserpine was administered (5 mg/kg ip) 4 hr after the administration of the compounds.

In the control group of mice, reserpine produced sedation, ptosis, and miosis; in animals pretreated with phenelzine and pargyline, known monoamine oxidase inhibitors, reserpine administration caused excitation, piloerection, mydriasis, and increased motor activity. Animals treated with test compounds were observed for these effects.

Determination of Anticonvulsant Activity—Groups of 10 male mice, 20–25 g, were used. Aqueous suspensions (5% gum acacia) of the test compounds were injected intraperitoneally at a dosage of 100 mg/kg. Pentylenetetrazol (80 mg/kg sc) was administered 4 hr after administration of the test compounds. Animals were observed 60 min for occurrence of seizures (10). The number of animals protected in each group was recorded and the percent protection was calculated. Mortality was recorded 24 hr after pentylenetetrazol treatment.

Determination of Approximate LD_{50}—The approximate LD_{50} was determined by the method of Verma *et al.* (11). All compounds were suspended in 5% aqueous gum acacia and administered intraperitoneally.

[1] Aminco Bowman spectrophotofluorometer.

RESULTS AND DISCUSSION

2-(*N*-Arylcarboxamide)-3-substituted ethoxyindoles inhibit brain monoamine oxidase activity (Table IV). All indole derivatives tested were found to inhibit rat brain monoamine oxidase at a concentration of 2×10^{-4} *M*. The various aryl substituents linked to a carboxamide moiety at position 2 of the indole nucleus have no significant effect on the degree of inhibition, except 2-(*N*-α-naphthylcarboxamide)-3α-hydrazinoethoxyindole (XIX) which produces a relatively higher degree of inhibition. The presence of α-bromoethoxy (XIII–XVIII) and α-hydrazinoethoxy (XIX–XXIV) groups at position 3 of the indole nucleus also had no significant effect on the degree of inhibition.

In vivo monoamine oxidase inhibitory activity of these compounds, as evidenced by the reserpine reversal test, is recorded in Table IV. These indole derivatives (XIII–XXIV) failed to produce a reserpine reversal response as observed with phenelzine and pargyline. These observations revealed that these compounds were inactive in producing *in vivo* monoamine oxidase inhibition.

The anticonvulsant activity of the indole derivatives ranged from 10 to 30% (Table IV). Compounds XIV, XXI, XXIII, and XXIV were completely devoid of anticonvulsant activity. These compounds also had lower protective ability against pentylenetetrazol-induced death. All indole derivatives had an approximate LD_{50} of either 1000 or >1000 mg/kg (Table IV). These data demonstrate the relatively low toxicity of these indole derivatives. No structure–activity relationships were noted.

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PHARMACEUTICAL ANALYSIS

GLC Trace Analysis of Dextromethorphan and Bromhexine Salts in Pharmaceutical Preparations

J. L. FABREGAS and A. MARGALET [x]

Abstract □ GLC proved to be particularly well suited for trace analysis of dextromethorphan and bromhexine salts in different pharmaceutical preparations, using diphenhydramine as the internal standard.

Keyphrases □ Dextromethorphan salts—GLC analysis in pharmaceutical preparations □ Bromhexine salts—GLC analysis in pharmaceutical preparations □ GLC—analysis, dextromethorphan and bromhexine salts in pharmaceutical preparations

Due to its bronchial mucolytic action, bromhexine has been incorporated in pharmaceutical preparations, especially since the preparation of *N*-(2-amino-3,5-dibromobenzyl)-*N*-cyclohexylmethylamine hydrochloride (1). Other studies reported its pharmacology (2), antitussive (3) and bronchosecretolytic activities (4), and metabolism (5, 6).

However, analytical procedures have been inadequate to determine bromhexine and dextromethorphan quantitatively in a pharmaceutical mixture, because of their similar solubilities, analogous UV absorptions (7, 8), and similar colorimetric reactions (9). Methods utilizing GLC analysis of dextromethorphan have been reported (10). None of these methods has been used for the quantitative determination of bromhexine. Under the conditions described here, GLC was particularly well suited for the analysis of dextromethorphan and bromhexine in pharmaceutical formulations containing antibiotics and essential oils.

Table I—Determination of Bromhexine and Dextromethorphan in Pharmaceutical Formulations

Formulation	Label Claim, mg	Range Found, mg	*SD*, mg	*CV*, %
Syrup				
Bromhexine	1.80	1.770–1.801	0.033	1.83
Dextromethorphan	2.90	2.904–2.940	0.037	1.28
Granulation				
Bromhexine	1.80	1.770–1.800	0.033	1.83
Dextromethorphan	2.90	2.860–2.901	0.042	1.45

EXPERIMENTAL

Chromatographic Conditions—A gas chromatograph[1] equipped with a −0.2–1.0-mv recorder[2] was used. A 1.5-m × 0.3-cm (5-ft × 0.125-in.) stainless steel column packed with 3% SE-30 (silicone rubber) on 100–120-mesh Varaport 30 was used. The column temperature was 180°, and the detector and injection port temperatures were 255 and 200°, respectively. The nitrogen carrier gas flow rate was 30 ml/min at 37 psi. A flame-ionization detector was used with a hydrogen flow rate of 30 ml/min and an air flow rate of 300 ml/min. The optimal working attenuation was 8×10^{-10} amp/mv.

Reagents—Carbon tetrachloride and chloroform[3], spectroscopic grade, were used.

Internal Standard—After a number of trials with other materials (codeine, ephedrine, chlorpromazine, and papaverine), diphenhydramine was chosen as the internal standard because of its commercial availability as a pure reagent[4] and its adequate separation from the other compounds, resulting in a symmetrical peak of low retention time (≃2.5 min).

For the internal standard solution, 30 mg of diphenhydramine hydrochloride was extracted with carbon tetrachloride, in alkaline media, following the procedure described for the sample preparation. The combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness, and the residue was dissolved and diluted to 100 ml with carbon tetrachloride.

Preparation of Samples—An accurately weighed sample, containing dextromethorphan and bromhexine salts equivalent to

[1] Varian Aerograph 1740, Walnut Creek, Calif.
[2] Electronik 15, Honeywell, Inc., Philadelphia, Pa.
[3] Merck.
[4] Benadryl hydrochloride, Parke-Davis & Co., Detroit, Mich.