Piperidylalkylindoles. 1. Hypotensive Activity of 3-[2-(Phenoxypiperidyl)ethyl]indoles

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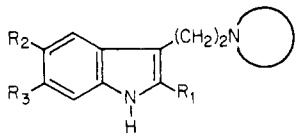
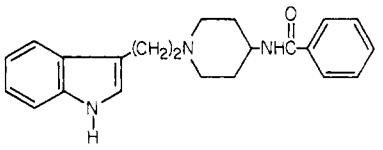
A series of 3-[2-(phenoxypiperidyl)ethyl]indoles was synthesized and evaluated for hypotensive activity in the spontaneous hypertensive rat. Maximum hypotensive activity appeared when the phenoxy substituent was para substituted and occupied the 4 position of the piperidine ring.

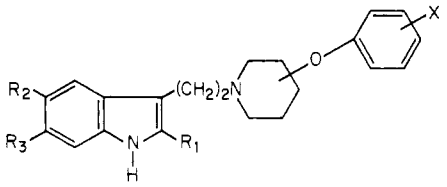
Compounds incorporating a tryptamine unit have consistently shown interesting biological activity.[1] Of singular interest are structures of type I, where the



I



II



III

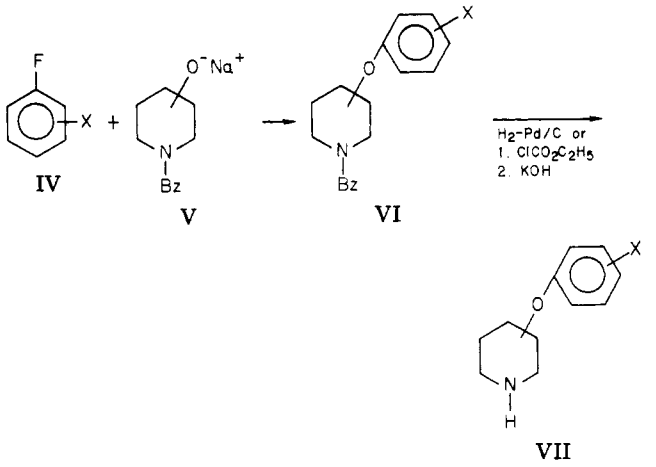
side-chain nitrogen of a tryptamine has become part of a peripheral ring. Compounds of this type, as a rule, have shown potent CNS activity.[2-4] The discovery by Archibald[5] of the sustained hypotensive properties of benzamidopiperidylethylindoles, and in particular of indoramin (II), has revealed a new potential therapeutic use for this structural type.

To examine other functional variants which might impart hypotensive activity to the piperidylalkylindoles, we synthesized a series of phenoxypiperidylethylindoles III and evaluated these for hypotensive activity.

Chemistry. The route to the phenoxypiperidines is illustrated in Scheme I. The compounds were prepared as described by Helsley.[6] Accordingly, nucleophilic displacement of fluorine from an aryl fluoride IV by a sodium 1-benzylpiperidinoxide V afforded a 1-benzylphenoxypiperidine VI. Subsequent debenzylation to the phenoxypiperidine VII was accomplished by catalytic hydrogenation (method A) or by reaction of the benzylpiperidine with ethyl chloroformate, followed by hydrolysis of the intermediate carbamate[7] (method B). The novel phenoxypiperidines are illustrated in Tables I and II.

The synthesis of the phenoxypiperidylethylindoles is illustrated in Scheme II. Reaction of a phenoxypiperidine VII with an indole-3-glyoxyloyl chloride VIII gave an indole-3-glyoxamide IX. Reduction of the glyoxamides to the phenoxypiperidylethylindoles III was accomplished by $LiAlH_4$[8] (method C) or by BH_3 in THF[9] (method D). Alternatively, two compounds (**33** and **39**) were synthesized

Scheme I



IV V VI VII

Bz = benzyl

by alkylation of a phenoxypiperidine with 3-(2-bromoethyl)indole (X) (method E). The novel indole-3-glyoxamides and the phenoxypiperidylethylindoles are illustrated in Tables III and IV.

Pharmacology. The compounds in Table IV were screened for antihypertensive activity using spontaneous hypertensive rats (SHR) by the indirect tail-cuff method.[10] In a standard 3-day test, systolic blood pressure readings were made at 0 time (control) on days 1 and 3 and at 2 h after administration of the compound on days 1 and 3. Dosing was orally at 100 mg/kg at 0 h on days 1, 2, and 3 on groups of six animals per test. Activity was determined by comparison of the treatment blood pressure values with the 0 time (control) blood pressure readings. Comparisons were made using the paired t test method for evaluation of statistical significance.[11]

From Table IV it can be seen that maximum hypotensive activity was achieved when the phenoxy moiety occupied the 4 position on the piperidine ring and possessed a para substituent (**29**, **31**, and **34**). Substitution of a methyl at the 2 position of the indole ring (**35**) led to apparently increased activity as well as increased toxicity at the screening dose. When a methoxy (**36**) or benzyloxy (**37**) group was present at the 5 position of the indole ring, activity declined. Combining some of the structural features of **35** and **36** with an additional 6-methoxy substituent on the indole ring gave the tetrasubstituted indole **38**. This compound possessed good activity and no apparent toxicity. A significant decrease in activity resulted when the phenoxy substituent was moved to the 3 position of the piperidine ring (**39**). It is of interest to note that a similar decline in hypotensive activity was realized in the benzamidopiperidylethylindoles when the benzamido moiety was moved to the 3 position from the 4

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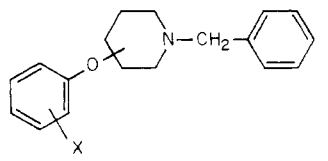
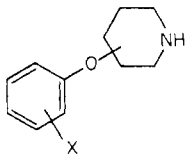
Table I. 1-Benzylphenoxypiperidines



No.	X	Position of phenoxy	Rxn conditions: Temp, °C	Rxn conditions: Time, h	% yield	Bp, °C[a] (mm)	Recrystn solvent[b]	Mp, °C[a]	Formula	Analyses[c]
1	2-CH_3	4	95-100	63	52	161-163 (0.1)	I	71-73	$C_{19}H_{23}NO$	C, H, N
2	3-CH_3	4	95-100	63	59	159-163 (0.05)	A-C	216-218	$C_{19}H_{23}NO\cdot HCl$	C, H, N
3	4-CH_3	4	95-100	44	27	178 (0.02)	B-C	224-226	$C_{19}H_{23}NO\cdot HCl$	C, H, N, Cl
4	4-CH_3	3	95-100	87	45	163 (0.2)	A	151-153	$C_{19}H_{23}NO\cdot(CO_2H)_2$	C, H, N
5	3-Cl	4	65-70	16	70		A-C	215-217	$C_{18}H_{20}ClNO\cdot HCl$	C, H, N
6	4-Cl	4	65-70	16	67		B	208-211	$C_{18}H_{20}ClNO\cdot HCl$	C, H, N
7	4-F	4	75-80	48	42		A-C	198-200	$C_{18}H_{20}FNO\cdot HCl$	C, H, N

[a] Uncorrected. [b] A = EtOH, B = *i*-PrOH, C = Et_2O, D = H_2O, E = MeOH, F = EtOAc, G = MeCN, H = cyclohexane, I = petroleum ether (bp 30-60 °C). [c] Elements shown, unless otherwise indicated, analyzed correctly to ±0.4% of calculated values.

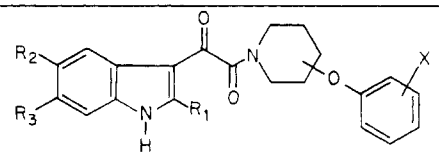
Table II. Phenoxypiperidines



No.	X	Position of phenoxy	% yield	Method	Recrystn solvent[b]	Mp, °C[a]	Formula	Analyses[c]
8	2-CH_3	4	32	A	A-C	205-207	$C_{12}H_{17}NO\cdot HCl$	C, H, N
9	3-CH_3	4	89	A	A-C	193-195	$C_{12}H_{17}NO\cdot HCl$	C, H, N
10	4-CH_3	4	66	A	A-C	209-210	$C_{12}H_{17}NO\cdot HCl$	C, H, N, Cl
11	4-CH_3	3	68	A	A-C	179-180	$C_{12}H_{17}NO\cdot HCl$	C, H, N
12	3-Cl	4	79	B	A	202-204	$C_{11}H_{14}ClNO\cdot HCl$	C, H, N

[a] Uncorrected. [b] See footnote *b*, Table I. [c] Elements shown, unless otherwise indicated, analyzed correctly to ±0.4% of calculated values.

Table III. 1-(Indol-3-ylglyoxyloyl)-4-phenoxypiperidines



No.	R_1	R_2	R_3	X	Position of phenoxy	% yield	Recrystn solvent[b]	Mp, °C[a]	Formula	Analyses[c]
13	H	H	H	H	4	43	A	205-207	$C_{21}H_{20}N_2O_3$	C, H, N
14	H	H	H	2-CH_3	4	72	A-D	171-173	$C_{22}H_{22}N_2O_3$	C, H, N
15	H	H	H	3-CH_3	4	71	F-H	199-200	$C_{22}H_{22}N_2O_3$	C, H, N
16	H	H	H	4-CH_3	4	94	E	209-211	$C_{22}H_{22}N_2O_3$	C, H, N
17	H	H	H	3-Cl	4	64	E-D	145-147	$C_{21}H_{19}ClN_2O_3$	C, H, N
18	H	H	H	4-Cl	4	98	A-D	199-200	$C_{21}H_{19}ClN_2O_3$	C, H, N
19	H	H	H	4-CF_3	4	96	A-D	200-202	$C_{22}H_{19}F_3N_2O_3$	C, H, N
20	H	H	H	4-F	4	75	A-D	205-207	$C_{21}H_{19}FN_2O_3$	C, H, N
21	CH_3	H	H	4-F	4	66	A-D	213-215	$C_{22}H_{21}FN_2O_3$	C, H, N
22	H	OCH_3	H	4-F	4	92	A-D	176-178	$C_{22}H_{21}FN_2O_4$	C, H, N
23	H	OCH_2Ph	H	4-F	4	66	A-D	148-150	$C_{28}H_{25}FN_2O_4$	C, H, N, F
24	CH_3	OCH_3	OCH_3	4-CF_3	4	98	E-D	211-213	$C_{25}H_{25}F_3N_2O_5$	C, H, N
25	H	H	H	4-CH_3	3	49	A-D	196-198	$C_{22}H_{22}N_2O_3$	C, H, N

[a] Uncorrected. [b] See footnote *b*, Table I. [c] Elements shown, unless otherwise indicated, analyzed correctly to ±0.4% of calculated values.

position of the piperidine ring.[5]

The glyoxyamides illustrated in Table III were devoid of any significant hypotensive activity.

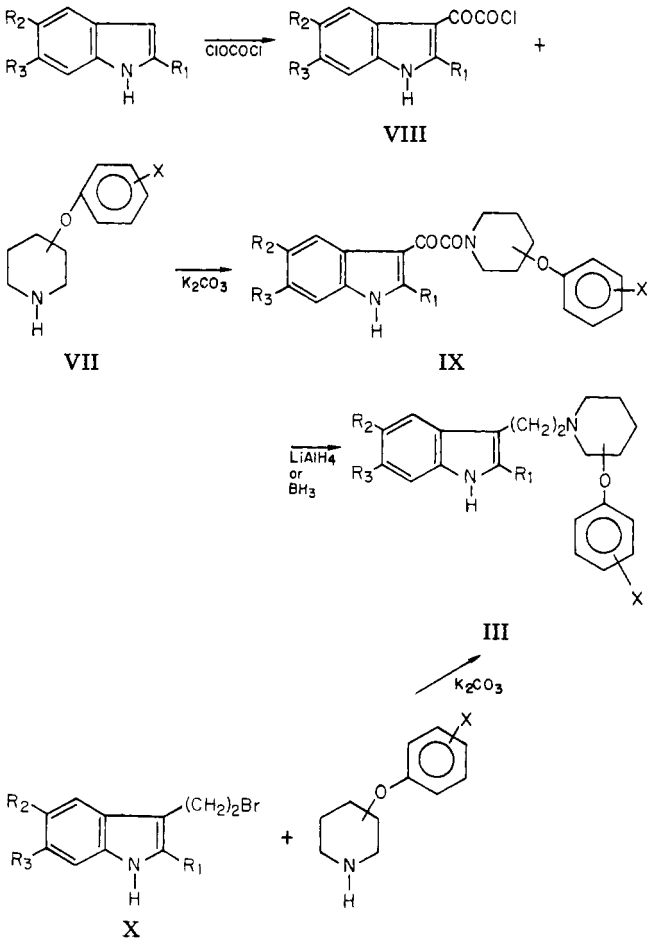
Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. The structures of all compounds are supported by their IR (Perkin-Elmer 457) and ^1H NMR (JEOL C60HL).

Piperidines not recorded in Tables I and II are described in ref 5, except for 4-(4-fluorophenoxy)piperidine.[12]

1-Benzyl-4-(3-tolyloxy)piperidine Hydrochloride (2). To a stirred suspension of a 50% oil dispersion of NaH (16.0 g, 0.32 mol) in 400 mL of dry DMF at 65–70 °C was added, dropwise, a solution of 1-benzyl-4-piperidinol (42.0 g, 0.22 mol) in 110 mL of DMF. When the evolution of H_2 had ceased, a solution of 3-fluorotoluene (48.0 g, 0.44 mol) in 150 mL of DMF was added,

Scheme II



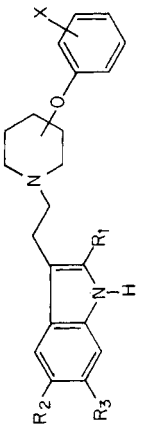
and the reaction was stirred at 95–100 °C for 63 h. The reaction was cooled and poured into H_2O, and the mixture was extracted with C_6H_6. The C_6H_6 extract was washed with H_2O and dried (Na_2SO_4), and the solvent was evaporated to give a brown oil. The oil was fractionally distilled, and the compound was characterized as a hydrochloride salt.

Method A. 4-(3-Tolyloxy)piperidine Hydrochloride (9). A solution of 1-benzyl-4-(3-tolyloxy)piperidine (16.6 g, 0.059 mol) in 105 mL of 95% EtOH was hydrogenated over 2.5 g of 10% palladium-on-charcoal catalyst at ca. 50 °C until the theoretical amount of H_2 was absorbed. The suspension was cooled and filtered, and the solvent was evaporated to give a colorless oil. The oil was dissolved in anhydrous Et_2O and a solution of Et_2O–HCl added to precipitate a white hydrochloride salt, 12.0 g (89%).

1-Benzyl-4-(3-chlorophenoxy)piperidine Hydrochloride (5). To a stirred suspension of a 50% oil dispersion of NaH (8.7 g, 0.18 mol) in 225 mL of anhydrous DMF at 65–70 °C was added, dropwise, a solution of 1-benzyl-4-piperidinol (21.6 g, 0.11 mol) in 75 mL of DMF. When the evolution of H_2 had ceased a solution of 3-chlorofluorobenzene (19.6 g, 0.15 mol) in 75 mL of DMF was added, and the reaction was stirred at 65–70 °C for 16 h. The reaction was cooled to ambient temperature and poured into H_2O, and the mixture was extracted with C_6H_6. The C_6H_6 extract was washed with H_2O and dried (Na_2SO_4), and the solvent was evaporated to give a yellow oil. The oil was dissolved in 200 mL of anhydrous Et_2O, and 200 mL of a saturated Et_2O–HCl solution was slowly added to precipitate a yellow hydrochloride salt, 35.7 g; recrystallization from EtOH afforded 25.9 g (70%) of white crystals.

Method B. 4-(3-Chlorophenoxy)piperidine Hydrochloride (12). 1-Benzyl-4-(3-chlorophenoxy)piperidine hydrochloride (21.5 g, 0.064 mol) was converted to the free base by dissolving it in 200 mL of $CHCl_3$ and stirring vigorously with 3 N NaOH. The layers were separated, the aqueous layer was reextracted with $CHCl_3$, the organic extracts were combined and dried (Na_2SO_4), and the solvent was evaporated to give the free base as a yellow

Table IV. 3-[2-(4-Phenoxypiperidyl)ethyl]indoles



No.	R_1	R_2	R_3	X	Position of phenoxy	% yield	Method	Recrystn solvent[g]	Mp, °C[a]	Formula	Analyses[b]	Antihypertensive act. (Δ, mm)[c] Day 1	Day 3
26	H	H	H	H	4	68	C	A–D	123–125	$C_{21}H_{24}N_2O$	C, H, N	−10	−31
27	H	H	H	2-CH_3	4	57	C	B–D	88–90	$C_{22}H_{26}N_2O$	C, H, N	−7	−8[f]
28	H	H	H	3-CH_3	4	68	C	G	145–146	$C_{22}H_{26}N_2O$	C, H, N	−3	−14[f]
29	H	H	H	4-CH_3	4	60	C	A–D	115–117	$C_{22}H_{26}N_2O$	C, H, N	−48	−57
30	H	H	H	3-Cl	4	30	D	A–D	121–123	$C_{21}H_{23}ClN_2O$	C, H, N, Cl	−11.2	−8[f]
31	H	H	H	4-Cl	4	27	D	A–D	132–133	$C_{21}H_{23}ClN_2O$	C, H, N, Cl	−47	−54
32	H	H	H	4-CF_3	4	48	C	H	130–132	$C_{22}H_{23}F_3N_2O$	C, H, N	−24	*d*
33	H	H	H	4-Br	4	13	E	G	132–134	$C_{21}H_{23}BrN_2O$	C, H, N, Br	−24	−59
34	H	H	H	4-F	4	42	C	A–D	109–111	$C_{21}H_{23}FN_2O$	C, H, N	−49	−55
35	CH_3	H	H	4-F	4	49	C	A–D	97–99	$C_{22}H_{25}FN_2O$	C, H, N, F	−56	*d*
36	H	OCH_3	H	4-F	4	54	C	A	132–134	$C_{22}H_{25}FN_2O_2$	C, H, N, F	−18	−6[f]
37	H	OCH_2Ph	H	4-F	4	53	C	A	135–137	$C_{28}H_{29}FN_2O_2$	C, H, N	−2	−16
38	CH_3	OCH_3	OCH_3	4-CF_3	4	53	C	A–D	139–141	$C_{25}H_{29}F_3N_2O_3$	C, H, N, F	−24	−58
39	H	H	H	4-CH_3	3	16	E	A	134–136	$C_{22}H_{26}N_2O\cdot(CO_2H)_2$	C, H, N	−12	−12[f]
Indoramin hydrochloride (II)												−63	−79[e]

[a] Uncorrected. [b] Elements shown, unless otherwise indicated, analyzed correctly to ±0.4% of calculated values. [c] The experimental details are described in the text. [d] No data due to toxicity. [e] At 50 mg/kg po. [f] Not statistically significant. [g] See footnote *b*, Table I.

oil. The oil was dissolved in 220 mL of C_6H_6, 12 mL of ethyl chloroformate was added, and the solution was refluxed for 18 h. Evaporation of the solvent afforded the *N*-ethoxycarbonylpiperidine as an uncrystallizable oil (characterized by IR and NMR). The oil was stirred and refluxed under N_2 for 12 h in a mixture of EtOH–45% aqueous KOH (210:130 mL). Most of the EtOH was evaporated and the resultant aqueous mixture was extracted with Et_2O. The Et_2O extract was washed with 3 N HCl, and the acid wash was made basic with aqueous NaOH. The basic mixture was extracted with C_6H_6, the C_6H_6 extract was washed with H_2O and dried (Na_2SO_4), and the solvent was evaporated to give a colorless oil. The oil was dissolved in anhydrous Et_2O and an Et_2O–HCl solution was slowly added to precipitate the hydrochloride salt, 13.2 g. Recrystallization of the salt from EtOH yielded (with concentration of the mother liquor) 12.2 g (79%) of the product as white flakes.

1-(Indol-3-ylglyoxyloyl)-4-(3-tolyloxy)piperidine (15). To a vigorously stirring mixture of K_2CO_3 (10.1 g in 45 mL of H_2O) and 4-(3-tolyloxy)piperidine hydrochloride (9.5 g, 0.043 mol, in 45 mL of $CHCl_3$) was added, portionwise, indole-3-glyoxyloyl chloride (8.3 g, 0.04 mol). After stirring for 16 h no precipitate was visible; the $CHCl_3$ layer was separated and evaporated to a yellow oil. The oil was triturated with Et_2O, and 13.7 g of a white solid formed. Recrystallization from EtOAc–C_6H_{12} afforded 10.8 g (71%) of white product.

Method C. 3-[2-[4-(3-Tolyloxy)piperidyl]ethyl]indole (28). To a stirring mixture of $LiAlH_4$ (4.8 g, 0.13 mol) in 140 mL of dry THF, under N_2, was added, dropwise, a solution of 1-(indol-3-ylglyoxyloyl)-4-(3-tolyloxy)piperidine (10.0 g, 0.028 mol) in 200 mL of THF. The mixture was stirred and refluxed for 3 h and cooled in an ice bath, and H_2O was added dropwise. The mixture was filtered, the inorganic salts were washed thoroughly with THF, and the THF was evaporated to give 8.3 g of white solid. Recrystallization from MeCN gave 6.4 g (68%) of the product as colorless needles.

Method D. 3-[2-[4-(3-Chlorophenoxy)piperidyl]ethyl]indole (30). To a stirred suspension, under N_2, of 1-(indol-3-ylglyoxyloyl)-4-(3-chlorophenoxy)piperidine (5.3 g, 0.014 mol) in 100 mL of dry THF was added, dropwise, 49 mL (0.049 mol) of 1 M BH_3 in THF. The solution was stirred at ambient temperature for 13 h; the solvent was then evaporated to leave a solid borane complex. The complex was refluxed in 100 mL of MeOH containing a few drops of AcOH for 1 h; then the solvent was evaporated to give a yellow oil. The oil was evacuated at ca. 3 mm for 72 h, and the resultant gum, 5.2 g, was recrystallized from MeCN, followed by EtOH–H_2O, to afford 1.5 g (30%) of white product.

Method E. 3-[2-[4-(4-Bromophenoxy)piperidyl]ethyl]indole (33). A mixture of 4-(4-bromophenoxy)piperidine hydrochloride (8.1 g, 0.028 mol), K_2CO_3 (12.6 g, 0.09 mol), and 60 mL of *i*-PrOH was stirred and refluxed for 1 h; then 3-(2-bromoethyl)indole[13] (6.5 g, 0.03 mol) was added in 15 mL of *i*-PrOH. The mixture was stirred and refluxed for 22 h, then the reaction was filtered hot and cooled, and Et_2O was added to precipitate some unreacted piperidine. The mixture was filtered, and the filtrate was evaporated to a yellow oil. The oil crystallized after 3 weeks, and the resultant soft solid was triturated with benzene and collected. The yellow crystals, 2.2 g, were recrystallized from MeCN to give 1.5 g (13%) of slightly yellow cubes of the product.

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