mixture was allowed to stand overnight at room temperature, treated with MeOH, neutralized with 60% KOH, and extracted with Et_2O (5 × 200 ml). The combined Et_2O extracts were washed (H_2O), dried ($MgSO_4$), and evaporated to give 1.5 g of the piperidyl ketone **30a**. The crude ketone was dissolved in 100 ml of THF and added to a freshly prepared CH_3MgI solution (0.1 mol) in 20 min. The mixture was stirred for 3 hr. After the excess Grignard reagent was consumed by H_2O, the Et_2O layer was separated. The aqueous phase was extracted with Et_2O (4 × 100 ml). The combined Et_2O solution was washed (H_2O), dried ($MgSO_4$), and evaporated to afford 1.2 g of 1-[3,6-bis(trifluoromethyl)-9-phenanthryl]-1-(4-piperidyl)ethanol (**29c**) as white crystals, mp 251–254°. Compound **29c** was also prepared in 88% yield by catalytic hydrogenation (in PtO_2) of **29f**. Treatment of 4.2 g of **29c** with 100 ml of Ac_2O for 30 min gave 4.1 g (90% yield) of the acetamide **29d** as white crystals, mp 218–220°.

A solution of 1 g of **29d** in 20 ml of DMF was treated with 0.5 g of NaH in mineral oil and 3 ml of EtI. The mixture was stirred at room temperature for 24 hr and then diluted with H_2O (300 ml). The ether **29e** was isolated by Et_2O extraction and then chromatographed over silica gel to separate the unreacted starting material. There was obtained 0.6 g of **29e**, which slowly solidified on standing. This was refluxed overnight with a mixture of 20 ml of EtOH and 20 ml of 60% aqueous KOH. The mixture was diluted with H_2O (300 ml) and extracted with Et_2O (3 × 100 ml). The combined Et_2O extracts were washed (H_2O), dried ($MgSO_4$), and evaporated. The residue was dissolved in 1 ml of EtOH saturated with HCl. Upon addition of Et_2O, the solid product precipitated. It was collected by filtration and recrystallized from MeOH–Et_2O to give 0.4 g of the HCl salt of **28**, mp 195–198°. *Anal.* ($C_{25}H_{25}F_6NO$·HCl) C, H, N.

Acknowledgment. This investigation was supported by Contract No. DA-49-193-MD-2049 with the U. S. Army Medical Research and Development Command. This paper is Contribution No. 1226 from the Army Research Program on Malaria. The authors wish to thank Dr. Richard E. Strube of WRAIR for his advice, encouragement, and interest. Thanks are also due to Mrs. Margaret L. Rounds, Mr. John R. Gravatt, and Mr. George Vaughn for their analytical and instrumental measurements.

References

(1) A. Marxer, *Chimia*, **21**, 592 (1967).
(2) A. Marxer, *Helv. Chim. Acta*, **52**, 262 (1969).
(3) A. Marxer, British Patent 1,133,302 (1968); U. S. Patent 3,488,356 (1970) [*Chem. Abstr.*, **70**, 68187s (1969)].
(4) W. Peters, *Ann. Trop. Med. Parasitol.*, **64**, 189 (1970).
(5) C. C. Cheng, *J. Pharm. Sci.*, **60**, 1596 (1971).
(6) P.-L. Chien, D. J. McCaustland, W. H. Burton, and C. C. Cheng, *J. Med. Chem.*, **15**, 28 (1972).
(7) P.-L. Chien and C. C. Cheng, *J. Med. Chem.*, **16**, 1093 (1973).
(8) C. J. Ohnmacht, A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, 14, 926 (1971).
(9) L. F. Fieser and V. Desreux, *J. Amer. Chem. Soc.*, **60**, 2255 (1938).

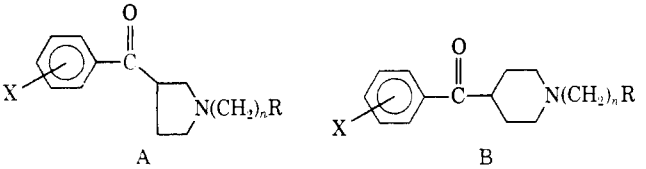
Synthesis of Some *N*-Carboxylic Acid Derivatives of 3-Phenoxypyrrolidines, 4-Phenoxypiperidines, and 3-Phenoxynortropanes with Muscle Relaxant and Anticonvulsant Activities

Robert F. Boswell, Jr.,* Grover C. Helsley, Robert L. Duncan, Jr., William H. Funderburk, and David N. Johnson

Research Laboratories, A. H. Robins Company, Inc., Richmond, Virginia 23220. *Received April 1, 1974*

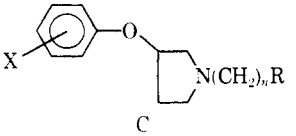
The title compounds were prepared by reacting the intermediate phenoxypyrrolidines, phenoxypiperidines, and phenoxynortropanes with cyanogen bromide, an isocyanate, a carbamoyl chloride, or phosgene and methylamine. Several of the intermediate ethers were prepared by a novel reaction in which an aromatic fluorine is displaced with a heterocyclic alkoxide ion. Anticonvulsant or muscle relaxant activities were observed for several of these compounds.

Previous reports from these laboratories described the preparation and CNS depressant activity of some *N*-alkyl derivatives of 3-benzoylpyrrolidines (A),[1] 4-benzoylpiperidines (B),[1] and 3-phenoxypyrrolidines (C).[2] *N*-Carboxylic



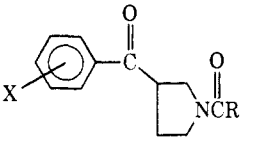
A

B

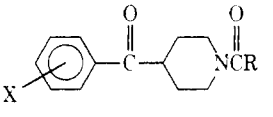


C

acid derivatives of the 3-benzoylpyrrolidines (D) and 4-benzoylpiperidines (E) were prepared in a study of structural modification and found to possess anticonvulsant and muscle relaxant activities.[3] As an extension of this work we have prepared *N*-carboxylic acid derivatives of 3-phenoxypyrrolidines (F), 4-phenoxypiperidines (G), and 3-phenoxynortropanes (H).

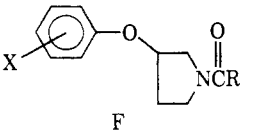


D

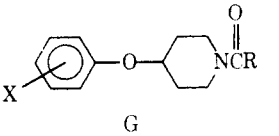


E

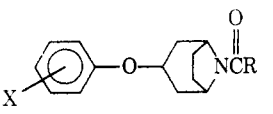
The *N*-carboxylic acid derivatives were prepared from the appropriate 3-phenoxypyrrolidine, 4-phenoxypiperidine, or 3-phenoxynortropane intermediate by reaction with nitrourea, an isocyanate, disubstituted carbamoyl chloride, or by treating the *N*-benzyl intermediates with cyanogen bromide (followed by hydrolysis) or phosgene



F

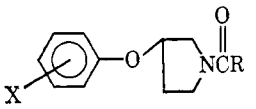


G



H

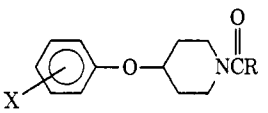
Table I



No.	X	R	Yield, %	Method	Recrystn solvent[a]	Mp or bp (mm),[b] °C	Formula
1	H	$NHCH_3$	81	E	I-B	122.5-123.5	$C_{12}H_{16}N_2O_2$
2	3-Cl	NH_2	14	D_1	B-EA	160-163	$C_{11}H_{13}ClN_2O_2$
3	3-Cl	$NHCH_3$	78 (59.5)	E (C)	I-B	112-113	$C_{12}H_{15}ClN_2O_2$
4	4-Cl	NH_2	23	D_1	EA	172-175	$C_{11}H_{13}ClN_2O_2$
5	4-Br	NH_2	12	D_1	B-EA	167-169	$C_{11}H_{13}BrN_2O_2$
6	4-F	NH_2	62	G	EA-IE	166-167	$C_{11}H_{13}FN_2O_2$
7	4-F	$N(CH_3)_2$	47	H		120-124 (0.04)	$C_{13}H_{17}FN_2O_2$
8	3-CF_3	NH_2	44	G	IE-EA	145-147	$C_{12}H_{13}F_3N_2O_2$
9	3-CF_3	$NHCH_3$	66	E	IE-B	102-103.5	$C_{13}H_{15}F_3N_2O_2$
10	3-CF_3	$N(CH_3)_2$	31	H		123-125 (0.08)	$C_{14}H_{17}F_3N_2O_2$
11	3-CF_3	NHC_2H_5	42	E	IE-I	77-79	$C_{14}H_{17}F_3N_2O_2$
12	3-CF_3	NHC_6H_5	70	E	B-I	150-152	$C_{18}H_{17}F_3N_2O_2$
13	2-OCH_3	NH_2	57	G	EA-IP	145-147	$C_{12}H_{16}N_2O_3$
14	2-OCH_3	NHC_6H_4-4-OCH_3	78	E	B-I	118-119.5	$C_{19}H_{22}N_2O_4$
15	2-OCH_3	$NHCH_3$	71	E	IE-B	156-158	$C_{13}H_{18}N_2O_3$
16	2-OCH_3	$N(C_6H_5)_2$	73	H		*c*	$C_{24}H_{24}N_2O_3$
17	2-OCH_3, 4-$COCH_3$	NH_2	26	G	EA-IE	154-156	$C_{14}H_{18}N_2O_4$
18	2-OCH_3, 4-$COCH_3$	$NHCH_3$	35	E	B	168-170	$C_{15}H_{20}N_2O_4$
19	2-OC_2H_5	NH_2	8	G	IE	116-119	$C_{13}H_{18}N_2O_3$
20	3,5-$(CH_3)_2$	NH_2	41	G	EA	166-168	$C_{13}H_{18}N_2O_2$
21	3,5-$(CH_3)_2$	$NHCH_3$	52	E	EA	166-169	$C_{14}H_{20}N_2O_2$
22	3-OCH_3	NH_2	51	G	IP	182-184	$C_{12}H_{16}N_2O_3$
23	4-OCH_3	NH_2	51	G	IP	161-163	$C_{12}H_{16}N_2O_3$

[a]The following solvent abbreviations are used in all tables: B = benzene; E = ethanol; EA = ethyl acetate; Et = diethyl ether; I = isooctane; IP = isopropyl alcohol; IE = isopropyl ether. [b]All melting point and boiling point temperatures in all tables are uncorrected. [c]Analytical sample molecularly distilled.

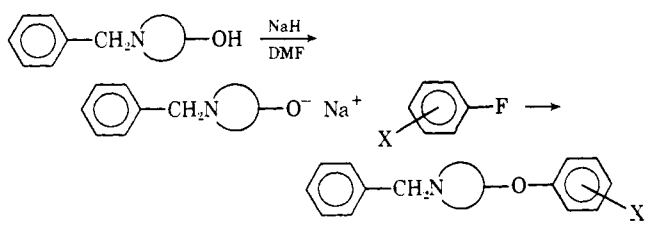
Table II



No.	X	R	Yield, %	Method	Recrystn solvent	Mp or bp (mm), °C	Formula
24	H	$NHCH_3$	91	E	I-B	95-96	$C_{13}H_{18}N_2O_2$
25	2-OCH_3	NH_2	37	I	EA	104-106	$C_{13}H_{18}N_2O_3$
26	3-CF_3	NH_2	36	G	EA-IE	148-150	$C_{13}H_{15}F_3N_2O_2$
27	3-CF_3	$NHCH_3$	67	E	IE-I	100-101	$C_{14}H_{17}F_3N_2O_2$
28	3-CF_3	$N(CH_3)_2$	54	H		121-124 (0.04)	$C_{15}H_{19}F_3N_2O_2$
29	3-CF_3	NHC_4H_9	65	E			$C_{17}H_{23}F_3N_2O_2$
30	3-CF_3	NHC_2H_5	66	E	I-B	78-79	$C_{15}H_{19}F_3N_2O_2$
31	3-CF_3	NHC_6H_5	69	E	I-B	146.5-147.5	$C_{19}H_{29}F_3N_2O_2$
32	3-CF_3	NHC_6H_4-3-Cl	82	E	I-B	115-116	$C_{19}H_{18}ClF_3N_2O_2$
33	4-CF_3	NH_2	56	G	B-I	176-178	$C_{13}H_{15}F_3N_2O_2$
34	4-CF_3	$NHCH_3$	81	E	I-B	139-141	$C_{14}H_{17}F_3N_2O_2$
35	4-CF_3	$N(CH_3)_2$	53	H		142-145 (0.05)	$C_{15}H_{19}F_3N_2O_2$

(followed by reaction with an amine). Details are given in Tables I-III and in the Experimental Section.

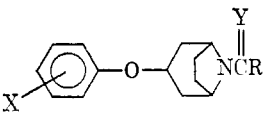
Most of the intermediates were prepared by nucleophilic displacement of a halogen or tosylate from 1-benzyl-3-bromo-, chloro-, or -tosylpyrrolidine or 1-benzyl-4-bromo-, chloro-, or -tosylpiperidine with a phenoxide ion.[2,4] The 8-benzyl-3-phenoxynortropanes[5] and several of the 1-benzyl-3-phenoxypyrrolidines and 1-benzyl-4-phenoxypiperidines were prepared in reasonable yields by treating the sodium salt of 1-benzyl-3-pyrrolidinol, 1-benzyl-4-piperidinol, or 8-benzyl-3α- (or β-) nortropanol in DMF with fluorobenzene or a substituted fluorobenzene at 60-70°.



X = H, Cl, F, Br, CF_3

The resulting ethers are thought to be formed by direct nucleophilic displacement of an aromatic fluorine by the alkoxide ion. Positional isomers of substituents on the aromatic ring resulting from benzyne formation have not been detected. There was no evidence of chlorine or bromine displacement. The surprising ease with which the nonactivated fluorobenzene undergoes nucleophilic displacement by an alkoxide ion under the conditions described suggests great synthetic utility.

Table III

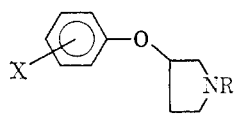
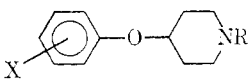


α or β

No.	X	α or β	Y	R	Yield, %	Method	Recrystn solvent	Mp or bp (mm), °C	Formula
36	3-CF_3	α	O	NH_2	62	G	I–B	106–109	$C_{15}H_{17}F_3N_2O_2$[a]
37	3-CF_3	β	O	NH_2	55	G	IE–EA	149–152	$C_{15}H_{17}F_3N_2O_2$
38	3-CF_3	α	O	$NHCH_3$	57	E	I–B	155–157.5	$C_{16}H_{19}F_3N_2O_2$
39	3-CF_3	β	O	$NHCH_3$	77	E	I–B	158–159	$C_{16}H_{19}F_3N_2O_2$
40	3-CF_3	β	O	$N(CH_3)_2$	59	H		146–148 (0.05)	$C_{17}H_{21}F_3N_2O_2$
41	3-CF_3	β	S	$NHCH_3$	80	J	I–IE	133–135.5	$C_{16}H_{19}F_3N_2O_2$
42	4-CF_3	α	O	NH_2	56	G	IE–EA	173–175	$C_{15}H_{17}F_3N_2O_2$
43	4-CF_3	α	O	NHC_2H_5	71	E	IE	140–142	$C_{17}H_{21}F_3N_2O_2$

[a] C analyzed 0.43% high.

Table IV

No.	X	R	Yield, %	Method	Recrystn solvent	Mp or bp (mm), °C	Formula[a]
							
44	3-Cl	$CH_2C_6H_5$	55 (91)	B (A)	IP–IE	123–124	$C_{17}H_{18}Cl_2NO_2$
45	3-Cl	H	21	D	IP–IE	95–97[b]	$C_{10}H_{13}Cl_2NO_2$
46	4-Cl	$CH_2C_6H_5$	59	B	IP–IE	158–159[c]	$C_{17}H_{19}Cl_2NO_2$
47	4-Cl	H	7	D	IP	135–138	$C_{12}H_{14}ClNO_5$[d]
48	4-Br	$CH_2C_6H_5$	45	B	IP–IE	156–158[e]	$C_{17}H_{19}BrClNO$
49	4-Br	H	12	D		144–145	$C_{10}H_{13}BrClNO$
50	2-OCH_3, 4-$COCH_3$	H	7	B	IP	173–175	$C_{13}H_{18}ClNO_3$
51	3,5-$(CH_3)_2$	$CH_2C_6H_5$	24	B	IP–IE	158–160.5[f]	$C_{19}H_{24}ClNO$
52	3,5-$(CH_3)_2$	H	86	F		133–135[g]	$C_{12}H_{18}ClNO$
							
53	H	$CH_2C_6H_5$	31	A	IE–IP	207–209	$C_{18}H_{22}ClNO$
54	H	H	22 (84)	B (F)	Not characterized[h]		$C_{11}H_{15}NO$[i]
55	4-Br	$CH_2C_6H_5$	64	A	E–Et	215–217	$C_{18}H_{21}BrClNO$
56	2-OCH_3	H	10	B, D		109–111 (0.07)	$C_{12}H_{17}NO_2$[j]
57	3-CF_3	$CH_2C_6H_5$	58	A	IE–IP	192–194	$C_{19}H_{21}ClF_3NO$
58	3-CF_3	H	3 (94)	K (F)	IP	196–198	$C_{12}H_{15}ClF_3NO$
59	4-CF_3	$CH_2C_6H_5$	94	A	IE–IP	255–257	$C_{19}H_{12}ClF_3NO$[k]
60	4-CF_3	H	78	F		43–47[j]	$C_{12}H_{14}F_3NO$[j]

[a] All are HCl salts unless otherwise indicated. [b] Bp (free base) 101–103° (0.07). [c] Bp (free base) 140–145° (0.04). [d] Oxalate salt. [e] Bp (free base) 170–175° (0.07). [f] Bp (free base) 145–148° (0.05). [g] Bp (free base) 93–95° (0.05). [h] Nmr and uv spectra are consistent with structure. [i] Free base. [j] Bp (free base) 74–76° (0.05).

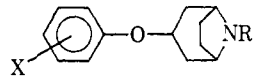
Several of the intermediate 3-phenoxypyrrolidines and their *N*-benzyl derivatives have been reported previously by some of us.[2,4] Chemical data for the intermediates not previously reported are given in Tables IV and V. Representative synthetic procedures are given in the Experimental Section.

Pharmacology. Compounds were tested for anticonvulsant activity in adult, female mice (ICR strain) using the methods of Swinyard, *et al.*,[6] as modified by Helsley, *et al.*[3] Prior to challenge by maximal electroshock or by pentylenetetrazole administration, behavioral effects in the animals were recorded. Most compounds which produced loss of righting in subtoxic doses were further evaluated for central muscle relaxant properties in acutely prepared cats.

For these studies, the patellar reflex (monosynaptic) was elicited every 2 sec by means of a solenoid which pulled on an exposed patellar tendon with the resulting contraction recorded on a Grass polygraph. In the contralateral hind leg, the flexor reflex (polysynaptic) was obtained by electrical stimulation (100 Hz, 0.5–2 V intensity, 2 msec pulse width and 80 msec duration) of the central end of the sectioned tibial nerve, and the contraction of the tibial muscle was recorded on a second channel of the polygraph. In addition, carotid-arterial blood pressure was monitored. To eliminate supraspinal influences, the spinal cord was severed at C_1 and artificial ventilation instituted. Test compounds, dissolved in distilled water or polyethylene glycol-300, were administered slowly into a cephalic vein.

Although acute LD_{50}'s were not determined, most compounds were not lethal in mice in doses up to 200 mg/kg ip. Only compound **30** appeared very toxic, with an approximate LD_{50} of 42 mg/kg ip. No muscle relaxant or an-

Table V



No.	X	α or β	R	Yield, %	Method	Recrystn solvent	Mp or bp (mm), °C	Formula
61	3-CF_3	α	$CH_2C_6H_5$	68	A	IP-E	204–206[a]	$C_{23}H_{24}F_3NO_3$[b]
62	3-CF_3	α	H	92	F	IP-IE	227–230.5	$C_{14}H_{17}ClF_3NO$[c]
63	3-CF_3	β	$CH_2C_6H_5$	66	A	IP-IE	148–150[d]	$C_{23}H_{24}F_3NO_3$[b]
64	3-CF_3	β	H	80	F	IP-IE	218–220	$C_{14}H_{17}ClF_3NO$[c]
65	4-CF_3	α	$CH_2C_6H_5$	71	A	IP-IE	235–238	$C_{21}H_{23}ClF_3NO$[c]
66	4-CF_3	α	H	84	F	IP	283–285	$C_{14}H_{17}ClF_3NO$[c]

[a] Bp (free base) 153–156° (0.05). [b] Oxalate salt. [c] HCl salt. [d] Bp (free base) 156–158° (0.10).

ticonvulsant properties were seen for this compound in lower doses.

Pharmacological test results are summarized in Tables VI–VIII and compared with data for reference compounds (also in Table VIII). Several compounds (**3**, **9**, **21**, **26**, **27**, and **35**) showed pronounced muscle relaxant activity in the range of mephenesin as determined by suppression of the flexor reflex. Unlike mephenesin, however, compound **3** did not appear selective, in that a dose-dependent reduction in patellar reflex activity was also recorded. None of the substituted phenoxynortropanes appeared to possess muscle relaxant properties except compound **40**, while several phenoxypyrrolidine and phenoxypiperidine derivatives were active.

While none of the test compounds appeared superior to diphenylhydantoin in suppressing electroshock-induced convulsions, several (**33–39**, **42**, and **43**) had protective ED_{50}'s against pentylenetetrazole lower than that of ethosuximide. With but three exceptions (**33–35**), all compounds in this latter class contained the substituted phenoxynortropane moiety.

Subsequent studies[7] with compound **3** indicated that polysynaptic pathways in the spinal cord were selectively suppressed with doses as low as 10 mg/kg iv. This was ascertained by investigations of segmental action potentials in spinal cats. For these experiments, the lumbrosacral region of the spinal cord was exposed by laminectomy and a dorsal and ventral root on the same side of one segment, usually L_7 or S_1, were sectioned.

Stimulation of the dorsal root (0.1 Hz, 1 msec pulse width and 0.2–2 V intensity) produced an initial monosynaptic spike followed by a series of slower, lower amplitude polysynaptic action potentials. Compound **3**, at 10 or 20 mg/kg iv, suppressed polysynaptic spike activity while having no effect on the monosynaptic spike, or producing a transient increase of up to 40% in the amplitude of the monosynaptic action potential.

The suppression of the patellar reflex by compound **3** was apparently due to peripheral blockade at, or beyond, the neuromuscular junction. This was realized using an *in situ* peroneal nerve–tibial muscle preparation. In these experiments, compound **3** produced a dose-dependent decrease in the amplitude of the muscle contraction in response to stimulation of the peroneal nerve.

Experimental Section

The procedures given below are representative for the preparation of the compounds listed in Tables I–VI. Yields and physical properties are recorded in the tables. Temperatures are uncorrected. Melting points were taken in a Thomas-Hoover capillary apparatus. All compounds were analyzed for C, H, and N and were within ±0.4% of the theoretical values except where noted.

Procedure A.[5] **1-Benzyl-3-(*m*-chlorophenoxy)pyrrolidine (44).** To a stirring suspension of 11.2 g (0.25 mol) of a 57% mineral oil dispersion of NaH in 200 ml of dry DMF was added a solution of 30.6 g (0.17 mol) of 1-benzyl-3-pyrrolidinol in 50 ml of dry DMF at a rate so as to maintain the temperature of the reaction mixture at *ca.* 32–35° and to maintain a steady evolution of H_2. After the addition was complete, the mixture was heated at about 50° until evolution of H_2 ceased. To the reaction mixture 27.6 g (0.213 mol) of *m*-fluorochlorobenzene was added at a rate so as to maintain a temperature of 50–60°. After the addition was complete the reaction mixture was stirred at 60–70° for 3 hr and then at 35° for an additional 12 hr. The mixture was cooled and a large excess of H_2O was added. The mixture was extracted with C_6H_6, the combined extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue was dissolved in C_6H_6 and extracted with 6 *N* HCl. The hydrochloride separated from solution. The oily hydrochloride and the acid layer were combined and basified with NaOH solution. The aqueous mixture was extracted with C_6H_6, the combined extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue weighed 44.7 g (91% yield). This product was considered pure enough to carry on to the next step (C_1).

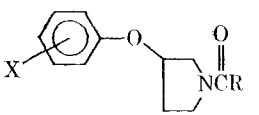
Procedure B. 1-Benzyl-3-(*m*-chlorophenoxy)pyrrolidine (44). A stirred mixture of 302 g (1.55 mol) of 1-benzyl-3-chloropyrrolidine, 200 g (1.55 mol) of *m*-chlorophenol, 84 g (1.55 mol) of $NaOCH_3$, and 1 l. of DMF was heated at 110–113° for 16 hr, cooled, and treated with 1 l. of H_2O. The oil which separated was extracted with C_6H_6 and the combined extracts were washed successively with 10% NaOH solution and H_2O. After the solvent was evaporated the residual oil was distilled at reduced pressure, yielding 232 g (55% yield) of product boiling at 152–155° (0.07 mm).

Procedure C_1. 1-Chlorocarbonyl-3-(*m*-chlorophenoxy)pyrrolidine. Into a 500-ml three-necked flask containing 200 ml of C_6H_6 was bubbled 36.2 g (3.66 mol) of $COCl_2$. Under anhydrous conditions 84.1 g (0.294 mol) of 1-benzyl-3-(*m*-chlorophenoxy)pyrrolidine was added over a period of 1–2 hr. The temperature of the reaction was maintained between 20 and 25° using an ice bath. After the addition was completed the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue, a dark brown oil, weighed 93.7 g and the nmr showed the presence of about 0.5 equiv of benzyl chloride. The crude product was triturated with petroleum ether (bp 30–60°) and the petroleum ether decanted away from the insoluble oily carbamoyl chloride. The residual oil obtained weighed 75.4 g and the nmr indicated 0.25 equiv of benzyl chloride. The yield was theoretical.

Procedure C_2. 3-(*m*-Chlorophenoxy)-1-(*N*-methylcarbamoyl)pyrrolidine (3). A mixture of 60 ml of THF and 40 ml of a 40% solution of CH_3NH_2 in H_2O was stirred and cooled to −5 to 0°. To the stirring mixture was added 49.3 g (0.143 mol) of 1-chlorocarbonyl-3-(*m*-chlorophenoxy)pyrrolidine at a rate so as to maintain the temperature at 0°. When the addition was completed, the reaction mixture was allowed to come to room temperature while stirring overnight. About 200 ml of H_2O was added to the reaction mixture and after stirring for 0.5 hr the reaction mixture was filtered. The solid residue was triturated in 40 ml of *i*-Pr_2O, filtered, and dried to give 30.7 g (89.5% yield) of crude product. The crude product was dissolved in 120 ml of $CHCl_3$ and washed through 10 g of Florisil in a fritted glass funnel under vacuum in 40-ml portions to remove an impurity. The collected $CHCl_3$ solution was evaporated and the solid residue triturated in *i*-Pr_2O, collected by filtration, and dried to give 21.6 g (59.5% yield) of off-white solid product.

Procedure D_1. 1-Carbamoyl-3-(*m*-chlorophenoxy)pyrrolidine (2). Over a period of 4 hr 204 g (0.70 mol) of 1-benzyl-3-(*m*-chloro-

Table VI. Pharmacological Data



	Anticonvulsant						Muscle relaxant activity					
	Electroshock			Pentylenetetrazole			Loss of righting (LRR)			Spinal cat		
No.	Dose, mg/kg ip	% protected	ED_{50} (95% conf limits), mg/kg ip	Dose, mg/kg ip	% protected	ED_{50} (95% conf limits), mg/kg ip	Dose, mg/kg ip	% LRR	ED_{50} (95% conf limits), mg/kg ip	Dose, mg/kg iv	% decrease flexor	% decrease patellar
1			50 (36.4–68.5)	100	0		100	0				
				150	100		150	100				
							200	Lethal in 40%				
2			66 (37.2–98.8)			111 (82.3–150)			134 (96.1–194.5)			
3			54 (30.0–97.2)			88 (49.1–150)			113 (82.2–165.0)	5	60	10
										10	100	25
										20	100	40
4			35 (23.2–53.2)	67	0		67	0				
				100	67		100	20				
5			55 (37.8–83.3)	45	0		45	0				
				67	60		67	0				
							100	Lethal in 60%				
6			46 (35.1–60.3)	67	30		67	0				
				100	45		100	25				
							150	Lethal in 30%				
7			150 (62.8–360.1)	67	20		67	0				
				100	20		100	0				
				150	60		150	0				
8			35 (22.9–53.0)			89 (66.3–121)			136 (101.0–182.5)	10	0	0
9			80 (47.1–135.7)	100	0		50	0		5	90	40
				200	80		100	30		10	90	0
							200	100		20	90	0
10			47 (24.1–89.5)	100	0		100	10		5	30	0
				200	80		200	100				
11	50	40		100	0		50	0		10	40	36
	100	80		200	40		100	80				
							200	100				
12	50	0		100	0		100	0		25	0	0
	100	20		200	20		200	0				
13			109 (60.0–197.3)	100	20		50	0				
				200	40		100	10				
							200	40				
14	50	20		100	0		50	0				
	100	20					100	0				
15	100	60		100	0		100	0				
	200	100		200	0		200	0				
16	50	60		100	20		50	0		10[a]	0	0
	100	100					100	0				
							200	Lethal in 60%				

17	50	20			100	0	50	0											0	
	100	20			200	20	100	0											0	
							200	0											0	
18			112 (74.7–168.0)		100	0	50	0												
							100	0												
							200	0												
								Lethal in 20%												
19	50	0			100	0	50	0											0	
	100	20			200	0	100	0												
							200	20												
20	100	20			100	0	100	10												
					200	40	200	80												
21	50	0			100	20	50	0											20	
	100	20			200	0	100	10											0	
							200	60												
22	50	0			100	0	50	0												
	100	20			200	0	100	0												
							200	0												
23	50	0			100	0	50	0												
	100	0			200	40	100	0												
							200	0												

[a]Spinal cord not severed. Animal anesthetized with α-chloralose.

phenoxy)pyrrolidine was added to a stirred solution of 89 g (0.85 mol) of cyanogen bromide in 600 ml of $CHCl_3$. After the addition was complete, the mixture was heated at reflux 1 hr and the solvent then evaporated at reduced pressure. The residual oil was treated with 1.2 l. of 3 *N* HCl and heated at reflux for 16 hr. The mixture was then cooled and basified with 25% NaOH solution. The oil which separated was extracted with C_6H_6 and the combined extracts were washed with H_2O. The crystalline product which formed on standing was collected by filtration. The filtrate was used in procedure D_2.

Procedure D_2. 3-(*m*-Chlorophenoxy)pyrrolidine (45). The filtrate (C_6H_6 solution) from procedure D_1 was treated with 400 ml of concentrated HCl and heated at reflux for 64 hr, cooled, and basified with 50% NaOH solution. The oil which separated was extracted with C_6H_6 and the combined extracts were washed with H_2O. After drying ($MgSO_4$), the solvent was evaporated and the residual oil distilled at reduced pressure.

Procedure E. 3-(*m*-Chlorophenoxy)-1-methylcarbamoylpyrrolidine (3). A solution of 2.3 g (0.04 mol) of methyl isocyanate in 15 ml of C_6H_6 was added dropwise to a stirring solution of 7.9 (0.04 mol) of 3-(*m*-chlorophenoxy)pyrrolidine in 60 ml of dry C_6H_6. After the addition was complete, the reaction mixture was stirred at room temperature for 2 hr. The solvent was evaporated and the residue which crystallized on cooling was recrystallized from a C_6H_6–isooctane mixture.

Procedure F. 4-(*p*-Trifluoromethylphenoxy)piperidine (60). A solution of 46.0 g (0.138 mol) of 1-benzyl-4-(*p*-trifluoromethylphenoxy)piperidine in 250 ml of 95% EtOH was treated with about 6 g of 10% palladium-on-charcoal catalyst and was shaken with H_2 at 60° in the Parr reduction apparatus until 1 equiv of H_2 was absorbed. The suspension was then cooled and filtered and the solvent evaporated at reduced pressure. The residual oil was distilled at reduced pressure.

Procedure G. 4-(4-Trifluoromethylphenoxy)-1-piperidinecarboxamide (33). A stirred mixture of 7.4 g (0.03 mol) of 4-(*p*-trifluoromethylphenoxy)piperidine, 4.2 g (0.04 mol) of nitrourea, and 70 ml of 95% EtOH was heated gently until the evolution of gas ceased (about 20 min) and then heated at reflux for 15 min. The mixture was cooled and treated with 300 ml of H_2O. The crystalline product which formed on standing was collected by filtration and recrystallized.

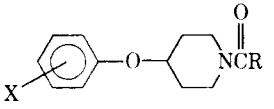
Procedure H. *N,N*-Dimethyl-4-(*p*-trifluoromethylphenoxy)-1-piperidinecarboxamide (35). A solution of 5.0 g (0.020 mol) of 4-(*p*-trifluoromethylphenoxy)piperidine in 50 ml of $CHCl_3$ was added to a solution of 10 g of K_2CO_3 in 50 ml of H_2O. The stirred mixture was then treated with 4.4 g (0.040 mol) of dimethylcarbamoyl chloride in 30 ml of $CHCl_3$ and stirring continued for 16 hr. The $CHCl_3$ layer was separated, washed with H_2O, and dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. The residual oil was distilled at reduced pressure.

Procedure I. 4-(*o*-Methoxyphenoxy)-1-carbamoylpiperidine (25). A solution of 4.1 g (0.020 mol) of 4-(o-methoxyphenoxy)piperidine in 20 ml of 1.0 *N* HCl was treated with 1.6 g (0.020 mol) of potassium cyanate in 5 ml of H_2O. The mixture was stirred for 16 hr at room temperature and then extracted with C_6H_6. The combined C_6H_6 extracts were washed with H_2O and dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. The residue crystallized on standing and was recrystallized.

Procedure J. *N*-Methyl-3β-(*m*-trifluoromethylphenoxy)-8-nortropanethiocarboxamide (41). A solution of 1.5 g (0.02 mol) of methyl isocyanate in 25 ml of dry C_6H_6 was added slowly to a stirring solution of 5.4 g (0.02 mol) of 3β-(*m*-trifluoromethylphenoxy)nortropane in 50 ml of dry C_6H_6 at room temperature. The reaction mixture was then stirred for 1 hr at room temperature and heated at reflux for an additional hour, and the solvent was evaporated at reduced pressure. The residual oil crystallized on trituration with isooctane.

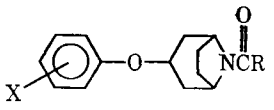
Procedure K. 4-(*m*-Trifluoromethylphenoxy)piperidine (58). A mixture of 340 g (1.2 mol) of 1-acetyl-4-benzenesulfonatopiperidine, 194 g (1.2 mol) of *m*-trifluoromethylphenol, 65 g (1.2 mol) of sodium methoxide, and 1 l. of absolute EtOH was heated at reflux for 16 hr, cooled, filtered, and concentrated at reduced pressure to give 200 g of crude 1-acetyl-4-(*m*-trifluoromethylphenoxy)-piperidine. This was treated with 800 ml of 6 *N* HCl and 300 ml of EtOH and heated at reflux for 12 hr. The reaction mixture was cooled and extracted with Et_2O. The aqueous layer was neutralized with 50% NaOH solution and the oil which separated extracted with C_6H_6. The combined extracts were washed (H_2O), dried ($MgSO_4$), and concentrated at reduced pressure. The residual oil was distilled at reduced pressure and the fraction boiling at 70–74° (0.5 mm) was collected. The light oil weighed 11.0 g.

Table VII. Pharmacological Data



	Anticonvulsant						Muscle relaxant activity					
	Electroshock			Pentylenetetrazole			Loss of righting (LRR)			Spinal cat		
No.	Dose, mg/kg ip	% protected	ED_{50} (95% conf limits), mg/kg ip	Dose, mg/kg ip	% protected	ED_{50} (95% conf limits), mg/kg ip	Dose, mg/kg ip	% LRR	ED_{50} (95% conf limits), mg/kg ip	Dose, mg/kg iv	% decrease flexor	% decrease patellar
24	50	0		100	20		50	0				
	100	0		200	100		100	0				
							200	60				
25	50	20		100	0		50	0				
	100	0		200	0		100	0				
							200	0				
26			69 (47.6–101.0)			88 (55.4–137.3)			109 (72.7–164.1)	10	45	0
27			29 (15.6–52.8)			97 (63.4–148.0)			71 (49.6–100.1)	10	40	0
28			47 (34.0–65.3)			89 (62.1–120.1)			138 (109.1–173.6)	25	30	0
29	50	0		100	40		50	0				
	100	40		200	60		100	0				
							200	0				
30	22	20		22	0		15	0				
	33	40					22	0				
							33	0				
							50	Lethal in 60%				
31	50	0		100	0		50	0				
	100	40		200	40		100	0				
							200	0				
32	50	0		100	20		50	0				
	100	20		200	0		100	0				
							200	0				
33			32 (20.4–51.1)			37 (18.5–77.9)	45	0				
							67	0				
							100	60				
34			36 (21.0–62.0)			20 (10.5–38.0)	20	0				
							30	0				
							45	20				
35			28 (19.3–40.6)			64 (44.4–92.2)	67	0		20	50	0
							100	20				
							200	100				

Table VIII. Pharmacological Data



	Anticonvulsant						Muscle relaxant activity					
	Electroshock			Pentylenetetrazole			Loss of righting (LRR)			Spinal cat		
No.	Dose, mg/kg ip	% protected	ED_{50} (95% conf limits), mg/kg ip	Dose, mg/kg ip	% protected	ED_{50} (95% conf limits), mg/kg ip	Dose, mg/kg ip	% LRR	ED_{50} (95% conf limits), mg/kg ip	Dose, mg/kg iv	% decrease flexor	% decrease patellar
36			23 (16.3-33.8)			47 (32.4-68.1)	35	0				
							53	0				
							119	0				
37			29 (19.8-42.3)			47 (36.1-80.9)	35	0				
							53	0				
							119	20				
38			43 (29.8-60.8)			53 (34.6-82.1)			94 (78.3-113)			
39			28 (18.7-42.0)			72 (54.4-88.0)	50	0				
							100	35				
							200	100				
40			34 (24.2-47.6)	100	40		50	0				
				200	80		100	0				
							200	0				
41			74 (42.3-129.5)	119	0		53	0				
				179	0		119	0				
							179	0				
42			15 (8.8-23.9)			33 (22.0-49.5)	35	0				
							53	0				
							119	0				
43			36 (25.7-50.4)			34 (23.1-48.6)	35	0				
							53	0				
							119	80				
Diphenylhydantoin			5 (3.1-8.4)									
Ethosuximide						88 (46.1-166.8)						
Mephenesin			172 (132.3-223.9)			244 (154.3-386.1)			142 (105.4-191.6)	10	43	0
										25	75	0

References

(1) R. L. Duncan, Jr., G. C. Helsley, W. J. Welstead, Jr., J. P. DaVanzo, W. H. Funderburk, and C. D. Lunsford, *J. Med. Chem.*, **13**, 1 (1970).
(2) W. J. Welstead, Jr., G. C. Helsley, R. L. Duncan, Jr., A. D. Cale, Jr., C. R. Taylor, J. P. DaVanzo, B. V. Franko, and C. D. Lunsford, *J. Med. Chem.*, **12**, 435 (1969).
(3) G. C. Helsley, R. L. Duncan, Jr., W. H. Funderburk, and D. N. Johnson, *J. Med. Chem.*, **12**, 1098 (1969).
(4) W. J. Welstead, Jr., J. P. DaVanzo, G. C. Helsley, C. D. Lunsford, and C. R. Taylor, Jr., *J. Med. Chem.*, **10**, 1015 (1967).
(5) G. C. Helsley and R. F. Boswell, Jr., U. S. Patent 3,657,253 (1972).
(6) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).
(7) D. N. Johnson, W. H. Funderburk, A. E. Hakala, and J. W. Ward, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **31**, 535 (1972).

Notes

Antihypertensive Activity of 1-Dimethylphosphinylmethyl-4-arylpiperazines

Edward J. Glamkowski,* Joseph Strupczewski, Erhard Wolf,

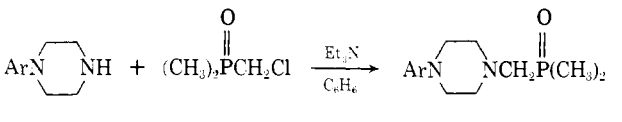
Chemical Research Department

and David L. Woodward

Department of Pharmacology, Hoechst-Roussel Pharmaceuticals, Inc., Somerville, New Jersey 08876. *Received March 6, 1974*

1-Alkyl-4-phenylpiperazines have been shown to possess potent antihypertensive activity.[1] Our interest in phosphorus-containing molecules with pharmacological activity[2] has prompted the preparation of a series of arylpiperazines bearing an *N*-dimethylphosphinylmethyl moiety [$-CH_2P(O)(CH_3)_2$] as potential antihypertensive agents.

The compounds were synthesized by the alkylation reaction shown below.

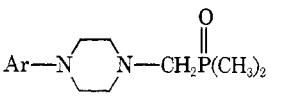


The structures and the physical and antihypertensive data for these novel 1-dimethylphosphinylmethyl-4-arylpiperazines are recorded in Table I.

Pharmacological Results. The compounds of Table I were initially screened for antihypertensive activity using spontaneous hypertensive rats (SHR) by a standard indirect tail-cuff method.[3] In a standard 3-day test, systolic blood pressure readings were made at 0 time (control) on days 1 and 3, and at 2 hr after administration of the compound on days 1 and 3. Dosing was orally at 100 mg/kg at 0 hr 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.[4] A value of −15 mm or more is considered significant.

From Table I it will be seen that compounds where Ar = phenyl or substituted phenyl are active. Inserting a heteroatom in the Ar ring (2-pyridyl, compound 8) or separating the Ar group from the piperazine ring by a methylene bridge ($C_6H_5CH_2$, compound **9**) abolished activity. Compounds **1**, **4**, and **7** showed especially marked reductions in blood pressure in the SHR screen and were there-

Table I



Compd	Ar	Yield, %[a]	Mp, °C	Recrystn solvent[b]	Formula[c]	Antihypertensive act. (Δ mm)[d] Day 1	Day 3
1	C_6H_5	79	149–151	A	$C_{13}H_{21}N_2OP$	−25	−43
2	$2\text{-}ClC_6H_4$	88	222–223 dec	B	$C_{13}H_{20}ClN_2OP \cdot HCl$	−12	−16
3	$3\text{-}ClC_6H_4$	34	108–110	C	$C_{13}H_{20}ClN_2OP$	±	±
4	$4\text{-}ClC_6H_4$	55	184–187	B	$C_{13}H_{20}ClN_2OP$	−10	−54
5	$2\text{-}CH_3C_6H_4$	77	114–117	D	$C_{14}H_{23}N_2OP$	−20	−14
6	$4\text{-}CH_3COC_6H_4$	82	170–172	A	$C_{15}H_{23}N_2O_2P$	±	±
7	$3\text{-}CF_3C_6H_4$	74	217–218 dec	E	$C_{14}H_{20}F_3N_2OP \cdot 2HCl$	−87	−66
8	$2\text{-}C_5H_4N$	61	116–120	A	$C_{12}H_{20}N_3OP$	−6	+1
9	$C_6H_5CH_2$	34	110–113	C	$C_{14}H_{23}N_2OP$	−2	+3

[a] Isolated yield of crude solid, fairly pure by melting point and tlc. [b] A = acetone, B = EtOH, C = cyclohexane, D = A + hexane, E = MeOH + Et_2O. [c] All compounds were analyzed for C, H, and N within ±0.4% of the theoretical values. [d] The experimental procedures are described in the text; ± indicates marginal or transient activity.