C-2 and C-9), 3.54 and 3.31 (singlets, NCH_3), 2.16 (singlet, CH_3COO). *Anal.* ($C_{13}H_{24}INO_2$) C, H, N.

Reduction of 3-Quinolinol (6) in THF.—3-Quinolinol (**6**) (10 g) was dissolved in THF (180 ml) and hydrogenated over Raney Ni (*W*-2,[9] 3.0 g) with an initial pressure of 215 kg/cm². It was heated to 150° during which time the pressure rose to 246 kg/cm² and these conditions were maintained for 24 hr. After cooling, the solution was filtered through Celite and the solvent was removed *in vacuo* leaving 10 g of oil. Glpc indicated nearly equal quantities of *trans*-decahydroquinoline, *trans*-decahydro-3(e)-quinolinol (**11**), *trans*-decahydro-3(a)-quinolinol (**10**), and *cis*-decahydro-3(e)-quinolinol (**9**). After standing, the oil solidified. A small amount of EtOAc was added, and the solid was removed by filtration and washed with EtOAc to give 8 g of a white solid, mp 130–136°. Several recrystallizations from MeOH–EtOAc gave 2 g of pure *trans*-decahydro-3(e)-quinolinol (**11**): mp 149–150°; methiodide mp 276°; ir ($CHCl_3$), 2.77, 3.05 broad, 3.35, 3.42, 3.51, 6.92 μ; nmr ($CDCl_3$), δ 3.65 (septet J_{aa} = 11 cps, J_{ae} = 5 cps, axial H at C-3), 3.21 (eight-line multiplet J_{gem} = 11 cps, J_{ae} = 5 cps, J_{ee} = 2 cps, equatorial H at C-2), 2.41 (triplet, $J_{gem,aa}$ = 11 cps, axial H at C-2). *Anal.* ($C_9H_{17}NO$) C, H, N.

The solids, recovered from the purification of *trans*-decahydro-3(e)-quinolinol (**11**) were chromatographed on silica gel (Brinkmann, 100 g) and eluted with MeOH. A small amount of the *trans*-equatorial alcohol **11** was eluted first. It was followed by *cis*-decahydro-3(e)-quinolinol (**9**) and *trans*-decahydro-3(a)-quinolinol (**10**). Recrystallization of *cis*-decahydro-3(e)-quinolinol (**9**) from MeOH–EtOAc gave 300 mg; mp 159–160°; ir ($CHCl_3$), 2.77, 3.0 broad, 3.35, 3.42, 3.51, 6.93 μ; nmr ($CDCl_3$), δ 3.85 (septet, J_{aa} = 9 cps, J_{ae} = 4 cps, axial H at C-3), 3.20 (eight-line multiplet, J_{gem} = 12 cps, J_{ae} = 4 cps, J_{ee} = 1.5 cps, equatorial H at C-2), 2.82 (H at C-10, $W_{1/2}$ = 9 cps), 2.49 (axial H at C-2, four-line multiplet, J_{gem} = 12 cps, J_{aa} = 9 cps). *Anal.* ($C_9H_{17}NO$) C, H, N.

Recrystallization of *trans*-decahydro-3(a)-quinolinol (**10**) from EtOAc gave 200 mg; mp 95–96.5°; ir ($CHCl_3$), 2.92, 3.34, 3.42, 3.51, 6.93 μ; nmr ($CDCl_3$), δ 3.86 ($W_{1/2}$ = 7 cps, equatorial H at C-3), 3.02 (six-line multiplet, J_{gem} = 13 cps, J_{ee} = 2 cps, equatorial H at C-2), 2.73 (four-line multiplet, J_{gem} = 13 cps, J_{ae} = 2 cps, axial H at C-2). *Anal.* ($C_9H_{17}NO$) C, H, N.

N-Methylation of *trans*-Decahydro-3(a)-quinolinol (10).—The amino alcohol **10** (1.3 g, 8.44 mmoles) was stirred with H_2CO (2.4 ml of 40% solution) in dry MeOH (40 ml) at 25° for 2 hr. $NaBH_4$ (1.2 g) was added portionwise at 10–20°. The solution was allowed to stir for 2 hr at 25°. Me_2CO was added dropwise until the excess $NaBH_4$ was decomposed. Ice was added and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* leaving N-methyl-*trans*-decahydro-3(a)-quinolinol (**7**) as a crystalline solid (1.39 g, 97%): mp 74–78°; nmr (C_6H_6), δ 3.80 ($W_{1/2}$ = 8 cps, equatorial H at C-3), 2.80 (six-line multiplet, J_{gem} = 12 cps, J_{ee} = 2 cps, equatorial H at C-2), 2.07 (singlet, NCH_3).

Acknowledgments.—We wish to thank Dr. E. J. Walaszek, Department of Pharmacology, University of Kansas, for the muscarinic assays and Dr. H. Higman, Department of Neurology, University of Pittsburgh, for the acetylcholinesterase studies and the nicotinic assay. The authors gratefully acknowledge support of this project by the National Institutes of Health Grant RG-9254 and GM-25,247.

Aroylalkylpyrrolidines. Central Nervous System Depressants

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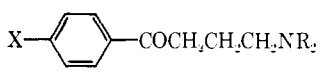
Received November 13, 1968

The title compounds were prepared by alkylating 3-substituted pyrrolidines with the ketal of γ-chlorobutyrophenones. Several compounds show CNS depressant activity comparable to chlorpromazine. Hypotensive effects were also observed in many of the compounds.

Our continued interest in drugs which affect the CNS has led us to explore in some detail the structural requirements for CNS depressant activity in the group of compounds generally classified as aminobutyrophenones.[1] This paper is the first of several which describe a series of chemical modifications beginning with the aminobutyrophenone I and leading to new structures with potent CNS activities.

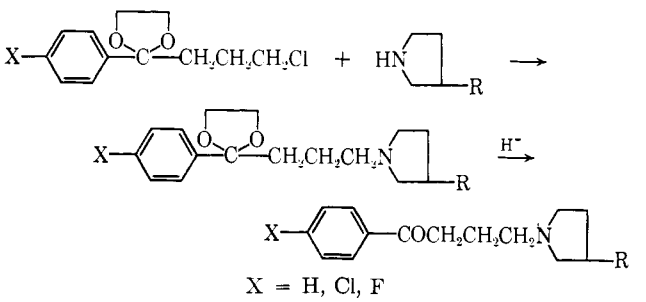


I

The work described in this paper deals primarily with variations on the amino portion of the molecule. More specifically, our interest in pyrrolidine chemistry led us to prepare a series of 3-substituted pyrrolidine analogs, most of which are structurally more rigid than the better studied piperidine derivatives. The compounds described herein include a group of 3-aryloxypyrrolidines (Table I), 3-acyloxypyrrolidines (Table II), and 3-anilinopyrrolidines (Table III) which are attached to the 4 position of a butyrophenone moiety.

Chemistry.—Most of the 3-aryloxy- and 3-anilinopyrrolidinylbutyrophenones reported herein (Tables I and III) were prepared by alkylating the appropriate pyrrolidine with a γ-chlorobutyrophenone (protected as the ethylene glycol ketal) followed by removal of the protecting group (Chart I). By the same reaction

CHART I



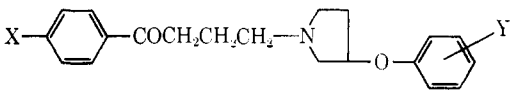
X = H, Cl, F

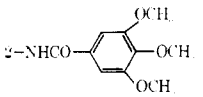
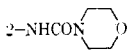
sequence 3-hydroxypyrrolidinyl analogs were prepared and converted by standard methods to the acyloxy and carbamoyloxy derivatives described in Table II.

Compounds reported in Table IV were prepared from

(1) (a) P. A. J. Janssen in "Medicinal Chemistry," M. Gordon, Ed., Academic Press, Inc., New York and London, 1967, p 199; (b) P. A. J. Janssen, P. Demoen, B. Hermans, P. Van Daele, K. H. L. Schellekens, C. Vander Eychen, and C. J. E. Nremegeers, *J. Med. Pharm. Chem.*, 1, 281 (1959).

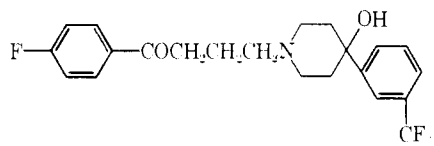
TABLE I



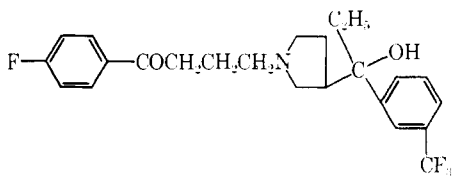
Compd	X	Y	Yield, %	Recrystn solvent[a]	Mp or bp (mm), °C[b]	Formula[c]	Fighting mouse assay ED_{50}, mg/kg ip, or no protected/ no. tested (mg/kg ip)
1	F	H	50	I	74–77	$C_{20}H_{22}FNO_2$	5.8
2	F	2-OCH_3	36	MIK	166–168	$C_{21}H_{25}ClFNO_3$[d]	1.6
3	F	3-OCH_3	73	Ip	118–122	$C_{25}H_{28}FNO_7$[e]	3/5 (20)
4	F	4-OCH_3	87	Ip	138.5–140.5	$C_{21}H_{25}ClFNO_3$[d]	3/5 (20
5	F	2-OC_2H_5	75	Ip	78–81	$C_{26}H_{30}FNO_7$[e]	0.7
6	F	2-OC_3H_7	63	Ip	90–92	$C_{27}H_{32}FNO_7$[e]	3/5 (20)
7	H	2-OCH_3	31		190 (0.01)	$C_{21}H_{25}NO_3$	7.2
8	Cl	2-OCH_3	59	Ip–Et	182–184	$C_{21}H_{25}ClNO_3$[d]	14.1
9	F	2-OCH_3, 4-$COCH_3$	27	IE	76–79	$C_{23}H_{26}FNO_4$	6.0
10	F	4-$COCH_3$	45	IE	83–84.5	$C_{22}H_{24}FNO_3$	5/5 (20) 0/5 (5)
11	F	2-CH_3	73	Ip	94–96	$C_{25}H_{28}FNO_6$[e]	2/5 (20)
12	F	2-$CONH_2$	67	M–W	91–94	$C_{21}H_{23}FNO_3$	11.7
13	F	3-CF_3	26	MIK–IE	127–130	$C_{21}H_{22}ClF_4NO_2$[d]	3/5 (20)
14	F	4-F	66	Ip–IE	165–167	$C_{20}H_{22}ClF_2NO_2$[d]	4.5
15	F	2-$NHCOCH_3$	20	E–W	109–115	$C_{22}H_{25}FN_2O_3 \cdot H_2O$	3/5 (20)
16	F		35	Ip–IE	162–164	$C_{32}H_{35}FN_2O_8$[f]	2/5 (20)
17	F		50	Ip–W	165–167	$C_{27}H_{31}FN_2O_8$[g,h]	0/5 (20)
CPZ[i]							2.5
TPL[j]							2.2
HPL[k]							3.6

[a] Solvent abbreviations: A, acetone; B, C_6H_6; D, DMF; E, EtOH; EA, EtOAc; Et, Et_2O; I, isooctane; IE, *i*-Pr_2O; Ip, *i*-PrOH; L, ligroin (60–110°); M, MeOH; MIK, MeCO-*i*-Bu; P, petroleum ether (30–60°); W, H_2O. [b] Melting points are uncorrected. [c] All compounds were analyzed for C, H, N. [d] HCl salt. [e] Maleate salt. [f] Hemifumarate salt. [g] Oxalate salt. [h] C analyzed 0.52% low. [i] Chlorpromazine. [j] Trifluperidol. [k] Haloperidol.

novel 3-pyrrolidinylmethanols and are structurally related to the potent tranquilizer trifluperidol. The general method for the preparation of the novel pyrrolidinylmethanols (Table IV) has been described.[2]



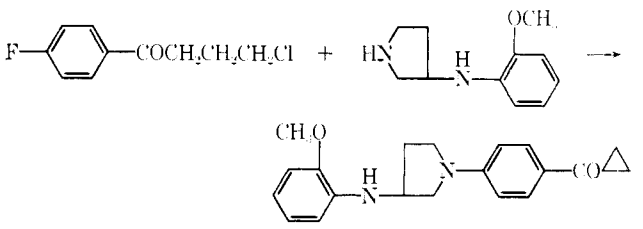
trifluperidol



36

Several miscellaneous but related compounds are included in Table V primarily to show interesting structure–activity correlations. The preparation of these compounds is described in the Experimental Section.

Early attempts to alkylate various amines with γ-chloro-*p*-fluorobutyrophenone (rather than the ketal thereof) using previously reported conditions[1b,3] often resulted in low yields. Further studies on the reaction showed that the low yields were, at least in part, the result of two competing side reactions, cyclopropane formation[4] and displacement of the fluorine atom from the aromatic ring by the amine.[5] In one case, using DMSO as solvent and K_2CO_3 as a proton acceptor, a 46% yield of abnormal product (II) was isolated. The structure of II was determined from its nmr spectrum



II

and confirmed by elemental analysis. Deactivation of the butyrophenone by ketal formation[6] eliminated both side reactions and increased the yields of alkylation product.

Most of the novel pyrrolidines used in the synthetic sequence (Chart I) were prepared by a nucleophilic displacement reaction on a 3-halo- or tosyloxypyrrolidine

(2) G. C. Helsley, J. A. Richman, C. D. Lunsford, H. Jenkins, R. P. Mays, W. H. Funderburk, and D. N. Johnson, *J. Med. Chem.*, 11, 472 (1968).

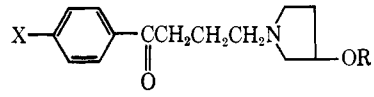
(3) A. F. Casy, A. H. Beckett, G. H. Hall, and D. K. Vallance, *ibid.*, 4, 535 (1961).

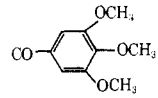
(4) W. J. Close, *J. Am. Chem. Soc.*, 79, 1455 (1957).

(5) H. Bader, A. R. Hansen, and F. J. McCarty [*J. Org. Chem.*, 31, 2315 (1966)] have recently explored the scope of this type of reaction.

(6) H. O. House and J. Warren Blaker, *ibid.*, 23, 334 (1958).

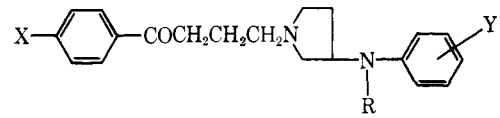
TABLE II



Compd	X	R	Yield, %	Recrystn solvent[a]	Mp, °C[b]	Formula	Fighting mouse assay ED_{50}, mg/kg ip, or no. protected/ no. tested at 20 mg/kg ip
18	H	H	22	Ip	140–142	$C_{14}H_{20}ClNO_2$[c]	0/5
19	F	H	51	IE	49–51	$C_{14}H_{18}FNO_2$	4.6
20	H	$CONHCH_3$	54	IE–I	82–85	$C_{16}H_{22}N_2O_3$	0/5
21	F	$CONHCH_3$	70	IE	78–80	$C_{16}H_{21}FN_2O_3$	2.9
22	H	$CONHC_6H_5$	94	B–I	122–124	$C_{21}H_{24}N_2O_3$	1/5
23	F	$CONHC_6H_5$	90	B–I	117–119	$C_{21}H_{23}FN_2O_3$	3/5
24	F	C_2H_5	77	Ip	151–155	$C_{18}H_{24}FNO_6$[d]	13.2
25	F	COC_2H_5	75	Ip	146–148	$C_{19}H_{24}FNO_7$[d]	13.5
26	F	$CONHC_6H_4CH_3$-*m*	95	Ip	146–148	$C_{24}H_{24}F_4N_2O_7$[d]	14.1
27	F		80	Ip	175–177	$C_{24}H_{29}ClFNO_6$[c]	3/5

[a] See footnote *a* of Table I for solvent abbreviations. [b] Melting points are uncorrected. [c] HCl salt. [d] Oxalate salt.

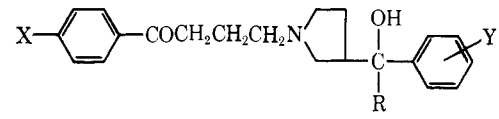
TABLE III



Compd	X	Y	R	Yield, %	Recrystn solvent[a]	Mp or bp (mm), °C[b]	Formula	Fighting mouse assay ED_{50}, mg/kg ip, or no. protected/ no. tested at 20 mg/kg ip
28	H	H	H	44	P	58–60	$C_{20}H_{24}N_2O$	1/3[c]
29	F	H	H	53			$C_{20}H_{23}FN_2O$[d]	1/5
30	H	H	COC_2H_5	78		230 (0.01)	$C_{23}H_{28}N_2O_2$	0/5
31	F	H	COC_2H_5	68			$C_{23}H_{27}FN_2O_2$[d,e]	0/5
32	F	2-OCH_3	H	25	A	120–123	$C_{21}H_{25}FN_2O_6$[f]	13

[a] See footnote *a* of Table I for solvent abbreviations. [b] Melting points are uncorrected. [c] Two animals died. [d] Compound was purified by chromatography on a Florisil column, eluted with C_6H_6–Me_2CO. [e] C analyzed 0.43% low. [f] Fumarate salt.

TABLE IV



Compd	X	Y	R	Yield, %	Recrystn solvent[a]	Mp or bp (mm), °C[b]	Formula	Fighting mouse assay No. protected/ no. tested at 20 mg/kg ip
33	H	H	CH_3	30		200–202 (0.05)	$C_{22}H_{27}NO_2$	0/5
34	F	H	C_2H_5	46			$C_{23}H_{28}FNO_2$[c]	2/5
35	F	4-CF_3	CH_3	22[d]	L	106–108	$C_{23}H_{26}F_3NO_2$	2/5
36	F	3-CH_3	C_2H_5	26[e]	MIK–IE	63–66	$C_{26}H_{29}F_4NO_6$[f]	2/5

[a] See footnote *a* of Table I for solvent abbreviations. [b] Melting points are uncorrected. [c] Compound was purified by chromatography on a Florisil column, eluted with C_6H_6–Me_2CO. [d] Prepared from an isomer mixture but only one product isomer was isolated (nmr). [e] Prepared from the α isomer. [f] Oxalate salt.

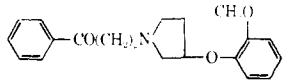
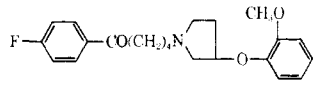
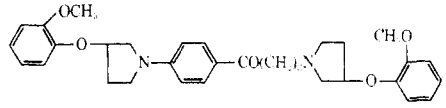
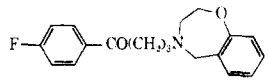
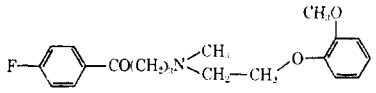
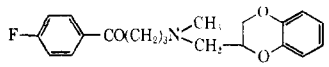
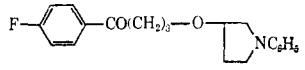
which was protected on the 1 position by a benzyl or acetyl group. Removal of the protecting group by reduction or hydrolysis, as appropriate, gave the desired intermediate (Chart II)[7] (Tables VI and VII).

Testing Procedures.—CNS depressant activity of the compounds listed in Tables I–V was evaluated by the isolation-induced aggressive behavior test described previously by DaVanzo.[8] Male albino mice were used. Following development of the behavior, normal mice were exposed to the isolated, aggressive animals. A

(7) Some of the pyrrolidine intermediates have been reported previously by W. J. Welstead, Jr., J. P. DaVanzo, G. C. Helsley, C. D. Lunsford, and C. R. Taylor, *J. Med. Chem.*, **10**, 1015 (1967).

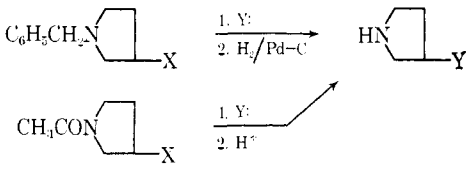
(8) J. DaVanzo, M. Daugherty, R. Ruckart, and L. Kang, *Psychopharmacologia*, **9**, 210 (1966).

TABLE V
MISCELLANEOUS COMPOUNDS

Compd	Structure	Yield, %	Recrystn solvent[a]	Mp, °C[b]	Formula	Fighting mouse assay ED_{50} mg/kg ip, or no protected/no tested at 20 mg/kg ip
37		70	Ip	116–119	$C_{24}H_{27}NO_7$[c]	0/5
38		58	Ip–Et	114–117	$C_{21}H_{27}ClFNO_3$[d]	10.9
39		60	M	109–112	$C_{32}H_{38}N_2O_5$	2/5
40		34	Ip	179–181	$C_{19}H_{21}ClFNO_2$[d]	0/5
41		50	Ip–IE	126–129	$C_{20}H_{23}ClFNO_3$[d,e]	3/5
42		54	Ip	159–160	$C_{20}H_{23}ClFNO_3$[d]	12.3
43		21	M	94.5–96.5	$C_{20}H_{22}FNO_2$	0/5

[a] See footnote *a* of Table I for solvent abbreviations. [b] Melting points are uncorrected. [c] Maleate salt. [d] HCl salt. [e] Parke, Davis and Co., Belgium Patent 668,124 (1965).

CHART II



X = *o*-Ts or Cl
Y = ArNH, ArO, or RO

well-directed attack on the normal animals was used as the end point of the test. Blockade of this attack was regarded as evidence of depressant action. Tests were conducted 60 min after drug administration.

Compounds were dissolved or suspended in physiological saline. With each compound, groups of five mice were tested initially at 20 mg/kg ip. In those cases where aggressive behavior was prevented in all animals, additional doses were tested to allow estimation of the effective dose 50 by the statistical method of Litchfield and Wilcoxon.[9]

Representative compounds from the series were studied in anesthetized dogs using the procedure described in the accompanying publication.[10] In addition, several compounds were investigated in conscious dogs in which hypertension developed following surgery which produced renal ischemia.[11] Comparisons reported herein were made at the 1-mg/kg iv dose level.

The acute toxicity of one compound, **2**, was investigated in the mouse, rat, and guinea pig. The oral route was used in each species and, in addition, the intraperitoneal and intravenous routes were employed in the rat.

Several additional tests including conditioned-avoidance, amphetamine antagonism, and others were carried out on the most active compounds in this series. Some of these results will be reported later.

Results and Discussion

It can be seen from the pharmacological results listed in Tables I–V that modest changes in the amino portion of the aminobutyrophenone structure (I) result in significant variations in the ability of these compounds to block aggressive behavior in fighting mice.

In the aryloxypyrrolidine series (Table I) the two most active compounds, **2** and **5**, show ED_{50}'s of 1.6 and 0.7 mg/kg, respectively, compared with 2.5 mg/kg for chlorpromazine and 3.6 mg/kg for haloperidol in the same test. Moving the methoxyl group around the ring (**3**, **4**), increasing the size of the alkoxy group to propoxy (**6**), or replacing the alkoxy group with other substituents generally reduced activity.

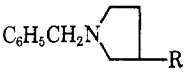
It is interesting that the simple pyrrolidinol (**19**) and its carbamate derivative (**21**), both of which contain no aromatic rings on the amino portion of the molecule, are among the most active compounds.

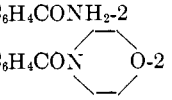
The results in Table IV show that the pyrrolidinemethanol derivatives (**33**–**36**) are not nearly as active as their piperidinol relative, trifluperidol, in this test.

Table V shows some additional structural modifications of the active compound **2** which include the valerophenone **38**, a benzoxazepine **40**, and two ring-opened

(9) J. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).
(10) R. L. Duncan, Jr., G. C. Helsley, W. J. Welstead, Jr., and B. V. Franko, *J. Med. Chem.*, **12**, 442 (1969).
(11) H. Goldblatt, J. Lynch, R. F. Hanzal, and W. M. Summerville, *J. Exp. Med.*, **59**, 347 (1934).

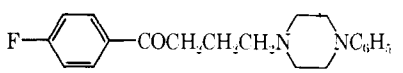
Table VI
Intermediate Pyrrolidines



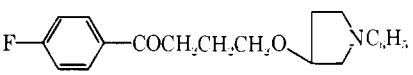
Compd	R	Yield, %	Recrystn solvent[a]	Mp or bp (mm), °C[b]	Formula
44	OC_6H_5	67	Ip–IE	120–123	$C_{21}H_{23}NO_5$[c]
45	$OC_6H_4OCH_3$-3	42	Ip–IE	138–139.5	$C_{22}H_{25}NO_6$[d]
46	$OC_6H_4OCH_3$-4	50	Ip–IE	131–133	$C_{22}H_{25}NO_6$[d]
47	$OC_6H_4OC_2H_5$-2	44	Ip	96–98	$C_{23}H_{27}NO_6$[d]
48	$OC_6H_4OC_3H_7$-2	45		170–174 (0.13)	$C_{20}H_{25}NO_2$[e]
49	$OC_6H_4CH_3$-2	55	Ip	114.5–116.5	$C_{22}H_{25}NO_5$[d]
50	$OC_6H_4CF_3$-3	29	Ip–IE	148.5–150.5	$C_{18}H_{19}ClF_3NO$[f]
51	OC_6H_4F-4	47	Ip–IE	147–148	$C_{17}H_{19}ClFNO$[f]
52	$OC_6H_4CONH_2$-2	42	EA–IE	120.5–122	$C_{18}H_{20}N_2O_2$
53		53		235–238 (0.1)	$C_{22}H_{26}N_2O_3$
54	$OC_6H_4NH_2$-2	34		180–185 (0.1)	$C_{17}H_{20}N_2O$
55	$OC_6H_4NHCOCH_3$-2	73	Ip	139–141	$C_{23}H_{26}N_2O_6$[d]
56	OC_2H_5	63	g	108.5–111.5	$C_{15}H_{21}NO_5$[h]
57	$-(CH_3)CC_6H_4CF_3$-p (OH)	55		145–147 (0.005)	$C_{20}H_{22}F_3NO$[i]
58	$-(C_2H_5)CC_6H_4CF_3$-m (OH)	67		138–140 (0.07)	$C_{21}H_{24}F_3NO$[i]

[a] See footnote *a* of Table I for solvent abbreviations. [b] Melting points are uncorrected. [c] Fumarate salt. [d] Maleate salt. [e] Characterized by nmr only. [f] HCl salt. [g] Precipitated from Et_2O. [h] Oxalate salt. [i] Isomer mixture.

analogs **4** and **42**. All of these compounds were less active than **2**. The oxygen analog **43** of the known butropipazone[1a] was inactive.



butropipazone



43

In all cases a *p*-fluoro substituent on the butyrophenone moiety increased the activity over that of the corresponding unsubstituted derivative. Similar observations have been noted by Janssen in related compounds.[1b]

Certain representative compounds were evaluated in the anesthetized dog for hypotensive effects. Of the compounds tested only **43** was essentially without effect; each of the other compounds lowered arterial blood pressure. The primary mechanism was apparently interference with α-adrenergic function. Compounds having the greatest effect on blood pressure (−40 to −50%) are **2**, **5**, **12**, **27**, and **32**; compounds with intermediate potency are **22**, **23**, **29**, **37**, and **38**. Compounds **10**, **26**, and **42** decreased arterial blood pressure by less less than 20%. Neither duration of the depressor effect nor α-adrenergic inhibitory potency paralleled the degree of hypotensive action. With regard to duration, **29** and **25** were the longest acting while **13** and **38** were among the shortest acting compounds. The most potent α-adrenergic blockers include **2**, **5**, **38**, and **42**, whereas **26**, **27**, and **37** are among the least effective.

Results obtained in studies of selected compounds in unanesthetized, renal hypertensive dogs provided confirming evidence of the hypotensive action in this series. The results in anesthetized and unanesthetized dogs were in agreement, not only with regard to the degree of hypotension produced, but also with regard to the duration of this effect.

In acute toxicity studies carried out on **2**, the predominant effect in three species by various routes of administration was related to impairment of CNS function. Following treatment at the higher dose levels, effects apparent upon gross observation included catatonia, occasional mild body tremors and/or mild clonic convulsions, loss of the righting reflex, flaccidity, and depressed respiration; also, ptosis and lacrimination were noted frequently. These effects were seen in the rat, for example, following intravenous doses of 12.5–15 mg/kg or oral doses of 100–371 mg/kg.

Based on these and other pharmacological tests, **2** has been selected for study in human subjects.

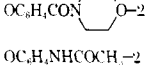
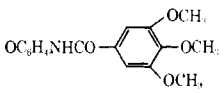
Experimental Section

The general procedures given below are representative for the preparation of the compounds described in Tables I–VII. Analyses, yields, and physical properties are recorded in the tables. Temperatures are uncorrected. Microanalyses were done by Micro-Tech Laboratories, Inc., Skokie, Ill., and Spang Microanalytical Laboratory, Ann Arbor, Mich. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

4-[3-(*o*-Ethoxyphenoxy)-1-pyrrolidinyl]-4′-fluorobutyrophenone Maleate (5).—This procedure generally gives the highest yields and cleanest products. A mixture of 10.4 g (0.05 mole) of 3-(2-ethoxyphenoxy)pyrrolidine, 13.4 g (0.055 mole) of γ-chloro-*p*-fluorobutyrophenone ethylene glycol ketal, and 15.2 g (0.11 mole) of K_2CO_3 in 100 ml of *n*-BuOH was allowed to reflux for 24 hr. After filtering and concentrating, the residual oil was dissolved in 50 ml of Et_2O and stirred with 100 ml of 3 *N* HCl for 1 hr. The aqueous layer was separated and made basic with 3 *N* NaOH, and the oily product was extracted into Et_2O. The Et_2O extract was dried ($MgSO_4$) and concentrated to an oil. The crude product was dissolved in C_6H_6 and chromatographed on a Florisil column, eluting with C_6H_6–Me_2CO. The purified product was converted to a crystalline maleate salt.

4-[3-(*o*-Methoxyphenoxy)-1-pyrrolidinyl]-4′-fluorobutyrophenone Hydrochloride (2).—A stirred mixture of 10 g (0.05 mole) of 3-(*o*-methoxyphenoxy)pyrrolidine, 9.5 g (0.05 mole) of γ-chloro-

TABLE VII
INTERMEDIATE PYRROLIDINES

Compd	R	Yield, %	Recrystn solvent[a]	Mp or bp (mm), °C[b]	Formula
59	OC_6H_5	82	Ip–IE	89–91	$C_{10}H_{14}ClNO$[c]
60	$OC_6H_3OCH_3$-3	91	Ip	110–112.5	$C_{11}H_{16}ClNO_2$[c]
61	$OC_6H_4OCH_3$-4	94	Ip	130.5–132.5	$C_{11}H_{16}ClNO_2$[c]
62	$OC_6H_4OC_2H_5$-2	93	Ip	70–73	$C_{16}H_{21}NO_6$[d]
63	$OC_6H_4OC_3H_7$-2	91	Ip–IE	72–75	$C_{17}H_{23}NO_6$[d]
64	$OC_6H_4CH_3$-2	95	Ip	94–97	$C_{15}H_{19}NO_5$[d]
65	$OC_6H_4CF_3$-3	74	Ip–IE	91–94	$C_{11}H_{13}ClF_3NO$[c]
66	OC_6H_4F-4	83	Ip	119–121	$C_{10}H_{13}ClFNO$[c]
67	$OC_6H_4CONH_2$-2	82	MIK–Ip	155–158	$C_{11}H_{13}ClN_2O_2$[c]
68		24	E	185 dec	$C_{17}H_{21}N_3O_4$[c]
69	$OC_6H_4NHCOCH_3$-2	31	E–W	162–165	$C_{16}H_{20}N_2O_6$[f]
70		27[g]	D	252–254	$C_{20}H_{25}ClN_2O_5$[c]
71	OC_2H_5	58	Ip	91–93	$C_8H_{15}NO_5$[h]
72	$OC_6H_3COCH_3$-4, OCH_3-2	7[i]	Ip	173–175	$C_{13}H_{18}ClNO_3$[c]
73	$-(CH_3)CC_6H_4CF_3$-*p*, OH	81		115–117 (0.005)[j]	$C_{13}H_{16}F_3NO$
74	$-(C_2H_5)CC_6H_4CF_3$-*m*, OH	75		103–105 (0.07)[k]	$C_{14}H_{18}F_3NO$

[a] See footnote *a* of Table I for solvent abbreviations. [b] Melting points are uncorrected. [c] HCl salt. [d] Maleate salt. [e] Oxamate salt. [f] Fumarate salt. [g] Over-all yield for acylation and debenzylation. [h] Oxalate salt. [i] Based on two-step reaction from 1-acetyl-3-pyrrolidinol. [j] Isomer mixture (nmr). [k] From the mixture a single isomer (*α*) was isolated: mp 101–104°, recrystallized from isooctane.

p-fluorobutyrophenone, and 20 g of $NaHCO_3$ in 100 ml of MeCO-*t*-Bu was allowed to reflux for 48 hr. The mixture was cooled and shaken with H_2O and the organic layer was dried ($MgSO_4$) and concentrated to an oil. The crude oil was converted to a crystalline HCl salt.

4-(3-Anilino-1-pyrrolidinyl)-4′-fluorobutyrophenone (28).—A mixture of 20 g (0.12 mole) of 3-anilinopyrrolidine, 22.2 g (0.11 mole) of γ-chloro-*p*-fluorobutyrophenone, and 20 g of K_2CO_3 in 200 ml of dry PhMe was refluxed under N_2 for 3 days. The reaction mixture was filtered and concentrated to an oil. The oil was dissolved in C_6H_6 and chromatographed on a Florisil column using C_6H_6–Me_2CO to elute. A sample was molecularly distilled for analysis.

4-[3-(*p*-Acetylphenoxy)-1-pyrrolidinyl]-4′-fluorobutyrophenone (10).—To a stirred suspension of 4.0 g (0.01 mole) of 4-(3-phenoxy-1-pyrrolidinyl)-4′-fluorobutyrophenone, 3.2 g (0.024 mole) of $AlCl_3$, and 60 ml of CS_2 was added a solution of 1.0 g (0.014 mole) of MeCOCl in 80 ml of CS_2. After the addition was complete, the mixture was stirred and heated at reflux for 1 hr, cooled, and poured onto a mixture of ice and 100 ml of concentrated HCl. The CS_2 layer was separated and the aqueous suspension was made basic with 6 *N* NaOH. The oil which separated was extracted into C_6H_6, dried ($MgSO_4$), and concentrated. The product crystallized on standing.

4-[4-(N-Methylcarbamoyloxy)-1-pyrrolidinyl]-4′-fluorobutyrophenone (21).—A solution of 10 g (0.04 mole) of 1-[3-(*p*-fluorobenzoyl)propyl]-3-pyrrolidinol and 4.55 g (0.08 mole) of MeNCO in 100 ml of dry C_6H_6 was allowed to reflux under N_2 for 12 hr. The solvent and excess MeNCO evaporated under reduced pressure and the resulting oil crystallized on standing.

4-(3-Propionyloxy-1-pyrrolidinyl)-4′-fluorobutyrophenone Oxalate (25).—A mixture of 9.9 g (0.04 mole) of 1-[3-(*p*-fluorobenzoyl)propyl]-3-pyrrolidinol and 15 g of K_2CO_3 in 100 ml of $CHCl_3$ was cooled and stirred while 4.15 g (0.04 mole) of EtCOCl was added dropwise. After 15 min, 100 ml of H_2O was added and stirring was continued another 30 min. The $CHCl_3$ layer was separated, dried ($MgSO_4$), and concentrated to an oil. The product was converted to a crystalline oxalate salt.

3-[3-(*o*-Methoxyphenoxy)-1-pyrrolidinyl]propiophenone Maleate (37).—A stirred mixture of 10.6 g (0.05 mole) of 2-benzoylethyldimethylamine hydrochloride, 10.1 g (0.05 mole) of 3-(*o*-methoxyphenoxy)pyrrolidine, and 10 g of K_2CO_3 in 75 ml of DMF was heated at 60° for 6 hr while N_2 was bubbled through the mixture. The mixture was poured into 200 ml of H_2O, and the insoluble product was extracted into C_6H_6. The C_6H_6 extracts were washed, dried ($MgSO_4$), and concentrated to an oil. The product was converted to a crystalline maleate salt.

5-[3-(*o*-Methoxyphenoxy)-1-pyrrolidinyl]-4′-fluorovalerophenone Hydrochloride (38).—A mixture of 10.8 g (0.056 mole) of 3-(*o*-methoxyphenoxy)pyrrolidine, 13.3 g (0.062 mole) of δ-chloro-*p*-fluorovalerophenone, and 16.1 g (0.12 mole) of K_2CO_3 in 100 ml of *n*-BuOH was allowed to reflux for 23 hr. The mixture was filtered, concentrated to an oil, and chromatographed on a Florisil column using C_6H_6–Me_2CO to elute. The pure product was converted to a crystalline HCl salt.

4-[3-(*o*-Methoxyphenoxy)-1-pyrrolidinyl]-4′-[3-(*o*-methoxyphenoxy)-1-pyrrolidinyl]butyrophenone (39).—A stirred mixture of 3 g (0.008 mole) of 4-[3-(*o*-methoxyphenoxy)-1-pyrrolidinyl]-4′-fluorobutyrophenone hydrochloride, 2 g (0.01 mole) of 3-(2-methoxyphenoxy)pyrrolidine, and 4 g of K_2CO_3 in 30 ml of DMSO was heated under N_2 at 145–150° for 4 hr. After cooling, the mixture was poured into H_2O and extracted (C_6H_6). The C_6H_6 extracts were washed (H_2O), dried ($MgSO_4$), and concentrated to an oil. The product crystallized from MeOH.

4-(N-Phenyl-3-pyrrolidinyloxy)-4′-fluorobutyrophenone (43).—A stirred suspension of 5.76 g (0.12 mole) of NaH (53% in mineral oil) in 100 ml of PhMe at 80° was treated dropwise with 16.3 g (0.1 mole) of 1-phenyl-3-pyrrolidinol, then the temperature was raised and the mixture was refluxed for 1 hr. To the refluxing mixture was added 26.9 g (0.11 mole) of γ-chloro-*p*-fluorobutyrophenone ethylene glycol ketal, and the mixture was refluxed for an additional 44 hr. After cooling, 100 ml of H_2O was slowly added to the reaction mixture and the PhMe layer was separated and concentrated to an oil. The oil was dissolved in 15 ml of Et_2O and stirred with 100 ml of 3 *N* HCl for 1 hr. The Et_2O layer was separated and the aqueous layer was made basic with 3 *N* NaOH. The product was extracted into C_6H_6 which was dried ($MgSO_4$) and concentrated to a solid. By triturating the solid with MeOH, the unreacted 1-phenyl-3-pyrrolidinol was separated from the product.

1-Benzyl-3-(*m*-methoxyphenoxy)pyrrolidine Maleate (45).—A mixture of 55 g (0.28 mole) of 1-benzyl-3-chloropyrrolidine, 35 g (0.28 mole) of *m*-methoxyphenol, and 41.5 g (0.3 mole) of K_2CO_3 in 200 ml of DMSO was stirred at 110–112° for 6 hr. After cooling, 100 ml of H_2O was added and the solution was extracted with Et_2O. The ethereal extracts were collected and extracted with 3 *N* HCl. The acid extracts were then made basic and the oily product was extracted into Et_2O. The ethereal extracts were dried ($MgSO_4$) and concentrated to an oil. After distillation, the product was converted to a crystalline maleate salt.

1-Benzyl-3-phenoxypyrrolidine Fumarate (44).—A solution of 317 g (1 mole) of 1-benzyl-3-pyrrolidinol tosylate and 116 g (1 mole) of $NaOC_6H_5$ in 1 l. of DMSO was heated with stirring to 65° whereupon the reaction became exothermic and cooling was necessary for several minutes. The temperature was maintained at 65° for 1 hr, then allowed to drop to room temperature while stirring overnight. The mixture was treated with 1 l. of H_2O followed by 1.5 moles of 50% NaOH. The resulting oil was taken up into Et_2O, and the basic products were then taken into 3 *N* HCl. The acidic extracts were treated with 50% NaOH, and the resulting free base was extracted into Et_2O. After drying ($MgSO_4$), the Et_2O extracts were concentrated to an oil and distilled. The product was converted to a crystalline fumarate salt.

***o*-(1-Benzyl-3-pyrrolidinyloxy)acetanilide Maleate (55).**—To a solution of 25 g (0.08 mole) of 3-(*o*-aminophenoxy)-1-benzylpyrrolidine in $CHCl_3$ was added 12.5 g (0.12 mole) of Ac_2O. The solution was refluxed 3 hr, washed with dilute NaOH, dried (Na_2SO_4), and concentrated. The resulting oil was converted to a crystalline maleate salt.

1-Benzyl-3-ethoxypyrrolidine Oxalate (56).—To a suspension of 28.6 g (1.2 moles) of NaH (53% in mineral oil) in 1 l. of dry PhMe was added, slowly, 177 g (1.0 mole) of 1-benzyl-3-pyrrolidinol. After the addition was complete, the mixture was stirred and heated at 90° for 16 hr. The mixture was cooled and 120 g (1.1 moles) of EtBr was added slowly. The temperature of the reaction mixture was gradually increased to 90° and heating was maintained for 4 hr. The mixture was cooled and treated with 1 l. of cold H_2O. The organic layer was separated and extracted with 6 *N* HCl. The acidic extracts were made basic with 6 *N* NaOH, and the oil which separated was taken up in C_6H_6. The C_6H_6 extracts were washed (H_2O), dried ($MgSO_4$), and concentrated to an oil. The oil was distilled and converted to a crystalline oxalate salt.

3-(*o*-Ethoxyphenoxy)pyrrolidine Maleate (62).—Raney Ni catalyst was added to a solution of 37.0 g (0.12 mole) of 1-benzyl-3-(*o*-ethoxyphenoxy)pyrrolidine in 200 ml of 95% EtOH and the mixture was shaken for 1.5 hr. After filtering, 10% Pd–C catalyst was added to the filtrate and the mixture was shaken on the Parr hydrogenator for 1.5 hr. The mixture was filtered and concentrated. The resulting oil was converted to a crystalline maleate salt.

1-Acetyl-3-pyrrolidinol.—To a solution of 301 g (3.5 moles) of 3-pyrrolidinol in 1 l. of CH_2Cl_2 was added over a period of 3 hr 377 g (3.7 moles) of Ac_2O. The solution was then heated at reflux for 16 hr. After the solvent was evaporated, the residual oil was distilled at reduced pressure and the fraction boiling at 129–130° (0.04 mm) was collected. The product which solidified on standing weighed 234 g (53%). *Anal.* ($C_6H_{11}NO_2$) C, H, N.

3-(*p*-Acetyl-*o*-methoxyphenoxy)pyrrolidine Hydrochloride.—To a stirred solution of 68 g (1.25 moles) of NaOMe in 1.2 l. of MeOH was added 208 g (1.25 moles) of acetovanillone and the resulting mixture was stirred for about 20 min. To the reaction flask was then added over a period of 2 hr 354 g (1.25 moles) of the tosylate ester of 1-acetyl-3-pyrrolidinol. The mixture was heated at reflux for 18 hr, cooled, and filtered and the solvent was evaporated. The residual oil was taken up in C_6H_6, washed (H_2O), and concentrated. The oil was dissolved in a mixture of 600 ml of concentrated HCl and 600 ml of MeOH and heated at reflux for 18 hr. Most of the solvent was evaporated at reduced pressure and the residue was extracted (Et_2O). The aqueous layer was made basic with 50% NaOH and the oil which separated was extracted into C_6H_6. The combined extracts were dried ($MgSO_4$) and concentrated, and the oily product was converted to a crystalline HCl salt.

***p*-[-(*o*-Methoxyanilino)-1-pyrrolidinyl]phenyl Cyclopropyl Ketone.**—A stirred mixture of 15 g (0.075 mole) of γ-chloro-*p*-fluorobutyrophenone, 14.4 g (0.075 mole) of 3-(*o*-methoxyanilino)-pyrrolidine, and 25 g of K_2CO_3 in 100 ml of DMSO was heated at 100° for 18 hr. The mixture was cooled and poured into H_2O and the resulting oil was extracted into C_6H_6. The C_6H_6 extracts were dried ($MgSO_4$) and concentrated to an oil. The impure oil was dissolved in C_6H_6 and chromatographed on a Florisil column using 5% Me_2CO–C_6H_6 to elute. From the column, 10 g (46%) of pure product was obtained which was recrystallized from C_6H_6–isooctane; mp 149–151°. The nmr spectrum was consistent with the proposed structure. *Anal.* ($C_{21}H_{23}NO_2$) C, H, N.

Acknowledgments.—The authors wish to express their appreciation to Dr. Stephen S. Cheung, Marvel Daugherty, Donald L. Gilbert, Marilyn Houff, William E. King, and Dana M. Sakalas for pharmacological technical assistance.