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Aroylpiperidines and Pyrrolidines. A New Class of Potent Central Nervous System Depressants

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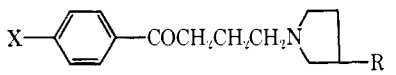
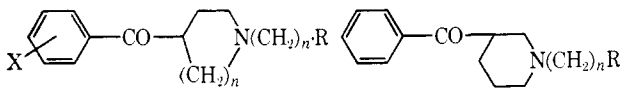
The 3- and 4-benzoylpiperidines and 3-benzoylpyrrolidines were prepared by the reaction of 1-acetylisonipecotoyl or 1-acetylnipecotoyl chloride with a substituted aromatic compound under Friedel–Crafts conditions or by treatment of the cyanopiperidines and pyrrolidines with an arylmagnesium halide. Alkylation gave the 1-substituted compounds which were evaluated as CNS depressants. The 1-substituted 4-(*p*-fluorobenzoyl)-piperidines were the most active compounds, several of which were more potent than chlorpromazine, triperidol, or haloperidol in the fighting mouse assay.

The investigation of the structural requirements for CNS depressant activity of aminobutyrophenones (I) reported earlier[1,2] led to the preparation of 1-substituted 4-aroylpiperidines (II), 3-aroylpyrrolidines (III), and 3-aroylpiperidines (IV) as potentially active compounds. The initial compound (**16**) in this series was prepared due to its structural similarity to V which is a CNS depressant comparable to chlorpromazine.[1]

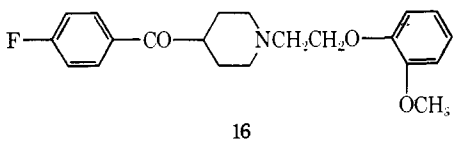


I

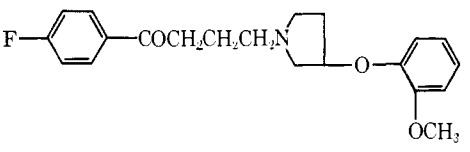


II, $n = 2$
III, $n = 1$

IV



16



V

The pharmacological activity of **16** indicated that a more detailed study of the structure–activity relationship was justified.

Chemistry.—The 4-benzoylpiperidines were prepared as outlined in Chart I. The N-acetylisonipecotic acid was treated with thionyl chloride and the resulting acid chloride reacted with benzene, fluorobenzene, or anisole under Friedel–Crafts conditions. Acid hydrolysis of the protecting acetyl group gave the 4-benzoylpiperidines in high yield. The 3-benzoylpiperidine was prepared from nipecotic acid by the same reaction sequence.

The 4-(*m*-trifluoromethyl)benzoylpiperidine (**7**, Table I) was prepared by dehydration of 1-acetylisonipecotamide to the nitrile, and reaction of the nitrile with *m*-trifluoromethylphenyl magnesium bromide followed by acid hydrolysis (Chart II).

The 3-benzoylpyrrolidines were prepared by converting the 1-benzyl-3-benzoylpyrrolidines[3] to the N-cyano compound by the Von Braun cyanogen bromide reaction[4] followed by acid hydrolysis (Chart III).

An alternate method was used to obtain 3-benzoylpyrrolidine as outlined in Chart IV. A transamination of the β-(N,N-dimethylamino)propiophenone with aziridine produced the N-substituted aziridine. The aziridine ring was opened with ethyl chloroformate[5] and the resulting carbamate was closed with sodium hydride to 3-benzoyl-1-carbethoxypyrrolidine. Acid hydrolysis produced the secondary amine in good over-all yield.

The tertiary amines reported in Tables II and III were prepared in general by alkylation of the corresponding aroylpiperidines and aroylpyrrolidines with various alkyl halides. Compound **24**, which is described in the Experimental Section, was prepared from 3-(N,N-dimethylamino)propiophenone by displacement of dimethylamine with 4-(*p*-fluorobenzoyl)piperidine.

In Chart V a sequence of reactions also used to prepare compound **16** in low yield is outlined. Ethanolamine was successively alkylated with γ-chloro-*p*-fluorobutyrophenone and 2-(*o*-methoxyphenoxy)ethyl bromide. Following acid hydrolysis of the ketal and

(1) 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).

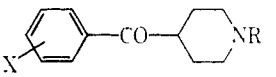
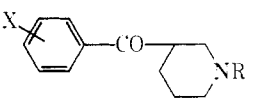
(2) R. L. Duncan, Jr., G. C. Helsley, W. J. Welstead, Jr., and B. V. Franko, *ibid.*, **12**, 442 (1969).

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

(4) H. A. Hageman, *Org. Reactions*, **7**, 198 (1953).

(5) H. Bestian, *Ann. Chem.*, **566**, 210 (1950).

TABLE I

Compd	X	R	Yield, %[c]	Recrystn solvent[a]	Mp, °C[b]	Formula[c]
						
1	4-F	$COCH_3$	80	I–IE	75–78	$C_{14}H_{16}FNO_2$
2	4-F	H	69	I	222–224	$C_{12}H_{14}ClFNO$[d]
3	H	$COCH_3$	62	B–IE	83–85	$C_{14}H_{17}NO_2$
4	H	H	74	I	223–225	$C_{12}H_{16}ClNO$[d]
5	4-OCH_3	$COCH_3$	56	I	115.5–117.5	$C_{15}H_{19}NO$
6	4-OCH_3	H	84	I	254–256	$C_{13}H_{18}ClNO_2$[d]
7	3-CF_3	H	9	I–IE	196–198	$C_{13}H_{15}ClF_3NO$[d]
						
8	H	H	16	I	193–195	$C_{12}H_{16}ClNO$[d]

[a] Solvent abbreviations: B, C_6H_6; E, EtOH; Et, Et_2O; I, *i*-PrOH; IE, *i*-Pr_2O; L, ligroin (60–110°); M, MeOH; MEK, EtMeCO; PE, petroleum ether (30–60°); O, isooctane; W, H_2O. [b] Melting points are uncorrected. [c] All compounds were analyzed for C, H, N. [d] HCl salt.

CHART I

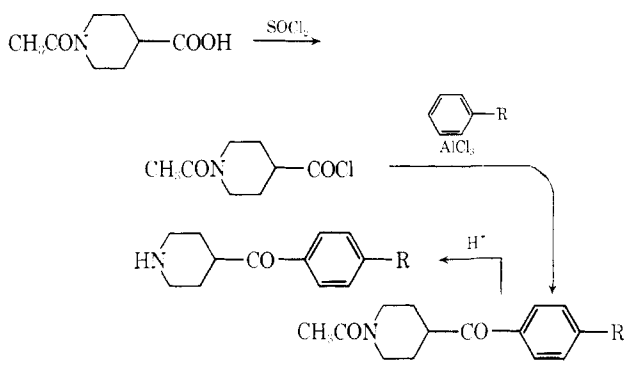


CHART II

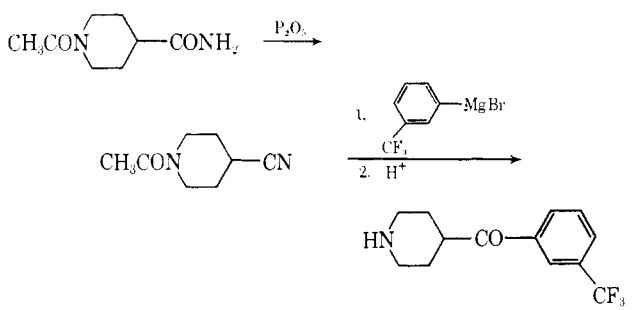


CHART III

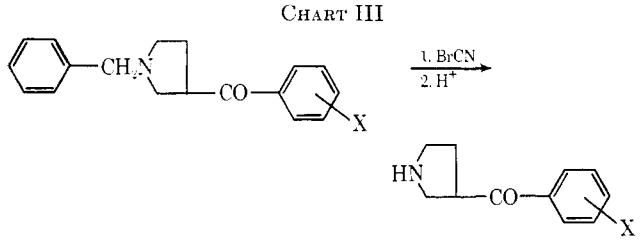


CHART IV

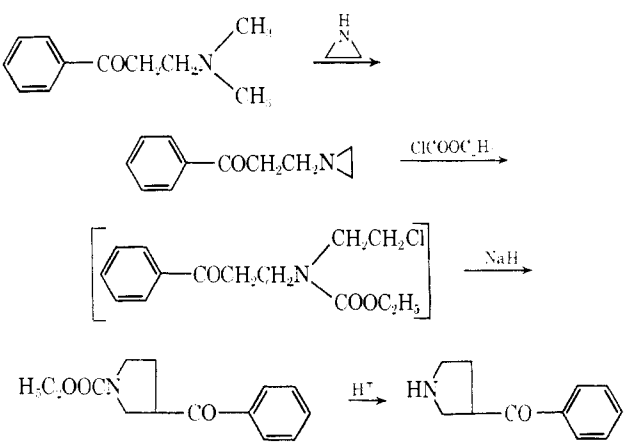
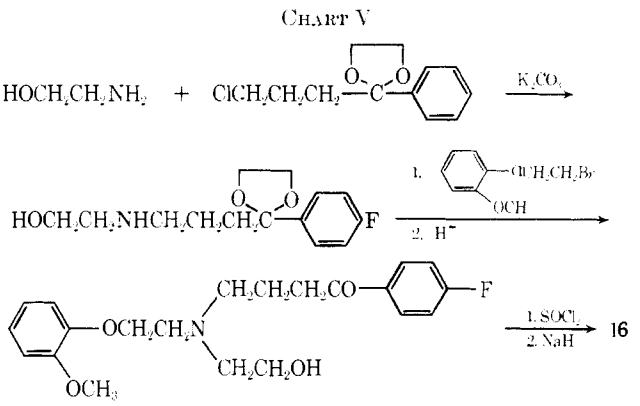


CHART V



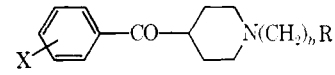
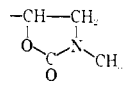
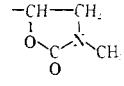
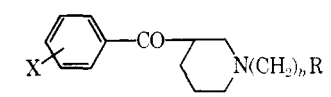
reaction with thionyl chloride, the chloroethylamine was obtained. Sodium hydride was then used to effect the ring closure.

Pharmacological Studies.—The isolation-induced aggressive behavior test[6] was used as a primary screen to determine tranquilizing activity of the compounds listed in Tables II and III. Male albino mice were used. Following development of the behavior, normal mice were exposed to the isolated, aggressive animals. A 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 tranquilizing 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 10 or 20 mg/kg ip. In most cases where aggressive behavior was prevented in all animals, additional doses were used to allow estima-

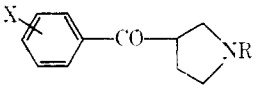
(6) J. DaVanzo, M. Daugherty, R. Ruckart, and L. Kang, *Psychopharmacologia*, **9**, 210 (1966).

Table II

Compd	X	n	R	Yield, %	Recrystn[a] solvent	Mp, °C[b]	Formula[c]	Fighting mouse assay: mg/kg ip	Fighting mouse assay: No. protected/no. tested	ED_{50} (confid limits), mg/kg
										
9	4-F	2	OC_6H_3-2-OCH_3-4-$COCH_3$	44	IE	133–136	$C_{23}H_{26}FNO_4$			6.0 (5.0–7.3)
10	4-F	3	OC_6H_3-2-OCH_3-4-$COCH_3$	27	I	210–212	$C_{24}H_{29}ClFNO_4$[d]			0.88 (0.62–1.2)
11	H	3	OC_6H_3-2-OCH_3-4-$COCH_3$	66	I	201–203.5	$C_{24}H_{30}ClNO_4$[d]			6.1 (3.2–11.6)
12	4-OCH_3	3	OC_6H_3-2-OCH_3-4-$COCH_3$	50	I	178.5–180.5	$C_{50}H_{66}Cl_2N_2O_{11}$[e]	10	2/5	
13	3-CF_3	3	OC_6H_3-2-OCH_3-4-$COCH_3$	47		190–195	$C_{25}H_{29}ClF_3NO_4$[d]	10	0/5	
14	4-F	4	OC_6H_3-2-OCH_3-4-$COCH_3$	89	I–IE	160–163	$C_{25}H_{31}ClFNO_4$[d]			1.02 (0.58–1.8)
15	4-F	5	OC_6H_3-2-OCH_3-4-$COCH_3$	37	I	94–98	$C_{26}H_{32}FNO_4$			3.4 (2.2–5.1)
16	4-F	2	OC_6H_4-2-OCH_3	90	I	154–157	$C_{25}H_{28}FNO_7$[f]			7.5 (3.1–18.0)
17	4-F	3	OC_6H_4-2-OCH_3	89	I	170–173	$C_{22}H_{27}ClFNO_3$[d]	20	4/5	
18	4-F	2	OC_6H_4-2-OC_2H_5	55	I	198.5–200.5	$C_{22}H_{27}ClFNO_3$[d]	20	4/5	
19	4-F	3	OC_6H_4-4-$COCH_3$	67	I	191–194	$C_{23}H_{27}ClFNO_3$[d]			7.1 (3.9–12.8)
20	H	3	OC_6H_4-4-$COCH_3$	51	I	192–194	$C_{23}H_{28}ClNO_3$[d]	20	0/5	
21	4-F	3	COC_6H_4-4-F	74	I–M	255–257	$C_{22}H_{24}ClF_2NO_2$[d]			0.57 (0.32–1.0)
22	H	3	COC_6H_4-4-F	59	I–E	230–233	$C_{22}H_{25}ClFNO_2$	20	4/5	
23	4-OCH_3	3	COC_6H_4-4-F	88	I–M	233.5–235	$C_{23}H_{27}ClFNO_3$[d]			2.35 (1.3–4.1)
24	4-F	2	COC_6H_5	30	B	137–139	$C_{21}H_{22}FNO_2$	10	3/5	
25	4-F	3	OC_6H_4-4-F	57	I	186–188.5	$C_{21}H_{24}ClF_2NO_2$[d]	20	4/5	
26	4-F	3	OC_6H_5	58	I	196–198	$C_{42}H_{52}Cl_2F_2N_2O_5$[e]			4.25 (2.5–7.3)
27	H	3	OC_6H_4-4-F	24	I	185–187	$C_{21}H_{25}ClFNO_2$[d]	20	2/5	
28	4-F	2	OC_2H_5	41	I–Et	174–175	$C_{18}H_{24}FNO_6$[g]	10	0/5	
29	4-F	2	OH	60	I	171–174	$C_{14}H_{19}ClFNO_2$[d]	20	1/5	
30	4-F	3	OH	48.5	PE	105–110	$C_{15}H_{20}FNO_2$	10	0/5	
31	4-F	2	$OCONH_2$	12	I	154–156	$C_{15}H_{19}FN_2O_3$	20	4/5	
32	4-F	2	$OCONHCH_3$	30	IE	93–94.5	$C_{16}H_{21}FN_2O_3$			3.0 (1.3–6.9)
33	4-F	3	$OCONHCH_3$	49.5	IE	90–91.5	$C_{17}H_{23}FN_2O_3$			1.7 (1.5–4.1)
34	4-F	3	$OCONHC_6H_5$	34	IE	90–93.5	$C_{22}H_{25}FN_2O_3$	20	1/5	
35	4-F	1		40.5	I–IE	115–118	$C_{17}H_{21}FN_2O_3$			5.0 (3.2–7.8)
36	4-F	2		25	E	105–110	$C_{18}H_{23}FN_2O_3$			5.4 (3.9–8.6)
37	4-F	2	C_6H_5	95	I	254–257	$C_{20}H_{23}ClFNO$[d]			7.0 (5.0–9.8)
38	4-F	3	$N(CH_3)_2$	32	I–M	278–280 dec	$C_{34}H_{56}Cl_4F_2N_4O_3$[h]	20	2/5	
39	4-F	2	$OCOC_2H_5$	57	I	154–157	$C_{17}H_{23}ClFNO_3$[d]			
40	4-F	2	$OCOC_6H_4$-4-Cl	70	I	121–124	$C_{21}H_{21}ClFNO_3$	20	1/5	
41	4-F	2	$OCOCH_2OC_6H_5$	30	I	75–78	$C_{22}H_{24}FNO_4$			
42	H	1	$CHOHCH_2OH$	54	O–B	91–96	$C_{13}H_{21}NO_3$	10	0/5	
43	4-OCH_3	1	$CHOHCH_2OH$	89	I	149–153	$C_{16}H_{24}ClNO_4$[d]	20	0/5	
44	4-F	0	$C_6H_4COC_6H_4$-4-F	20	B–O	207–209	$C_{25}H_{21}F_2NO_2$	10	0/5	
										
45	H	3	OC_6H_3-2-OCH_3-4-$COCH_3$	41	I	105–108	$C_{26}H_{31}NO_8$[g]	20	0/5	
46	H	3	COC_6H_4-4-F	44	I	206–208 dec	$C_{22}H_{25}ClFNO_2$[d]	20	2/5	
Chlorpromazine										2.5 (1.5–4.6)
Triperidol										2.2 (1.4–3.5)
Haloperidol										3.6 (2.5–5.1)

[a] See footnote *a* of Table I for solvent abbreviations. [b] Melting points are uncorrected. [c] All compounds were analyzed for C, H, N. [d] Hydrochloride salt. [e] HCl hemihydrate. [f] Maleate salt. [g] Oxalate salt. [h] Dihydrochloride hemihydrate.

TABLE III



Compd	X	R	Yield, %	Recrystn. solvent[a]	Mp, °C[b]	Formula[c]	Fighting mouse assay: mg/kg ip	Fighting mouse assay: No. protected/no. tested	ED_{50}, (Confid limits), mg/kg
47	4-F	$(CH_2)_3OC_6H_3$-2-OCH_3-4-$COCH_3$	61	I	100–103	$C_{23}H_{28}FNO_5$[d]	20	3/5	
48	H	$(CH_2)_3OC_6H_3$-2-OCH_3-4-$COCH_3$	26	I	114–119	$C_{25}H_{29}NO_8$[d]	20	1/5	
49	H	$(CH_2)_2OC_6H_3$-2-OCH_3-4-$COCH_3$	56	I	129–132	$C_{24}H_{27}NO_8$[d]	20	0/5	
50	4-F	$(CH_2)_3COC_6H_4$-4-F	21			$C_{21}H_{21}F_2NO_2$[e]			6.9 (3.1–15.2)
51	4-F	$(CH_2)_2OC_2H_5$	19	I–Et	141–142	$C_{17}H_{22}FNO_6$[d]	20	1/5	
52	4-F	$CH_2C_6H_5$	41	I–IE	163–165	$C_{28}H_{19}ClFNO$[f]			
53	4-F	H	46	I	120–124	$C_{13}H_{14}FNO_5$[d]			
54	H	$CH_2C_6H_5$	53	W	116–118.5	$C_{18}H_{22}ClNO_2$[g]			
55	H	H	53	I–Et	59–61	$C_{11}H_{16}ClNO_2$[g]			
56	3-CF_3	$CH_2C_6H_5$	37	MEK	158–160.5	$C_{19}H_{19}ClF_3NO$[f]	20	1/5	
57	3-CF_3	H	7	I	86–87	$C_{14}H_{14}F_3NO_2$[d]			

[a] See footnote *a* of Table I for solvent abbreviations. [b] Melting points are uncorrected. [c] All compounds were analyzed for C, H, N. [d] Oxalate salt. [e] Oil purified by column chromatography on Florisil, eluted with C_6H_6–Me_2CO. [f] HCl salt. [g] HCl hydrate.

tion of the ED_{50} by the statistical method of Litchfield and Wilcoxon.[7]

The most active compounds in this test were **10**, **14**, **21**, and **33** having ED_{50}'s of 0.9, 1.0, 0.6, and 1.7 mg/kg, respectively, compared with 2.5 mg/kg for chlorpromazine and 2.2 mg/kg for triperidol. All of these new compounds are 1-substituted 4-(*p*-fluorobenzoyl)piperidines.

In all cases studied the *p*-fluorobenzoyl compounds were more active than the corresponding unsubstituted derivatives.

The 4-aroylpiperidines (**11**, **21**, **22**) were generally more potent than the 3-aroylpiperidines (**45**, **46**) or 3-aroylpyrrolidines (**48**, **50**) having the same 1 substituent.

In the active 1-aroyloxyalkyl series of compounds the effects of chain length and aromatic substituents were investigated. Increasing the chain length from three (**10**) to four carbon atoms (**14**) produced a negligible reduction in the activity, but a further increase to five (**15**) or a decrease to a two-carbon chain (**9**) decreased potency. The removal of the 2-methoxy (**19**) and/or the 4-acetyl groups (**17**, **26**) produced a decrease in activity. The 1-carbamoyloxyalkyl compounds (**31**–**33**) were active and retained activity even in a cyclic arrangement (**35** and **36**).

Two of the most active compounds (**10** and **21**) were more thoroughly investigated. To record electrical activity of the brain, cats were prepared under ether anesthesia. For cortical potentials, stainless steel screws were placed in appropriate areas of the calvarium and used as electrodes. In studies of subcortical structures pairs of stainless steel wires (0.01 in.), insulated except at the tips, were placed stereotaxically in various subcortical centers and used as recording or stimulating electrodes. The trachea was cannulated to facilitate artificial ventilation and a femoral vein was cannulated for injection of drugs. The animals were immobilized with gallamine triethiodide and, after sufficient time was allowed for recovery from ether, electrical potentials were recorded with a Type T Offner electroencephalograph. Animals with chronically implanted electrodes were also used. The electrodes were attached to a miniature tube socket which was fixed to the exposed skull with dental cement. To record potentials a tube adaptor with wires leading to the recorder was plugged into the socket. These methods have previously been described in detail.[8]

Both compounds (**10** and **21**) produced generalized slowing of cortical waves which became more pronounced following the administration of 0.5, 1, and 3 mg/kg iv. Fast activity interrupted the slow activity after an additional 5 mg/kg and convulsions occurred after a total dose of 19.5 mg/kg of each compound. Qualitatively these actions are similar to those produced by chlorpromazine although this drug does not produce convulsions until 50 mg/kg or more has been given intravenously to cats.

Like chlorpromazine, doses of 1 and 3 mg/kg decreased responses to stimulation of the reticular activating system but unlike chlorpromazine which does not abolish this response, both compounds abolished this effect after total doses of 10 mg/kg. These compounds produce a diphasic response in thalamic recruitment similar to that produced with chlorpromazine. Low doses, up to 5 mg/kg, of both compounds improved the pattern of thalamic recruitment and higher doses distorted the pattern.

The effects of **10** and **21** on hippocampal after-discharge were not the same. Like chlorpromazine, **10** prolonged hippocampal after-discharge and spread of the discharges to the cortex occurred after a total dose of 4.5 mg/kg. This response was abolished after relatively low doses of **21** (this is similar to the effect of barbiturates or meprobamate).

Both compounds differed from chlorpromazine in antagonism of cortical after-discharge. Low doses of chlorpromazine had a tendency to prolong cortical after-discharge while the present experimental compounds had no effect on the response until 4.5 mg/kg

(7) J. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

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had been given. This dose shortened after-discharge and additional amounts of 5 mg/kg abolished the evoked potentials.

Electrodes placed in the amygdala did not provide evidence that convulsions produced with either **10** or **21** originated in this area as they apparently do when chlorpromazine is used as the convulsant agent. Rather, convulsions appeared to occur in all areas examined simultaneously.

Two cats with chronically implanted cortical electrodes were studied. They were able to move about in their cage as the potentials were recorded. A dose of 1 mg/kg of **10** or **21** was given by intraperitoneal injection daily for 5 days. The effects seen with these drugs were ataxia, sedation, and slight relaxation of nictitating membranes. The EEG activity was slowed and the amplitude increased. Compound **21** produced transient catatonia on days 2, 4, and 5 of treatment. Compound **21** appeared to produce a more pronounced effect on behavior and cortical EEG than did **10** in comparable doses. These drugs produced no apparent tolerance and following **21** the effects appeared to become more pronounced after daily treatment. Qualitatively these effects are similar to those produced by chlorpromazine although the latter drug is much less potent.

Compound **10** or **21** was administered to two cats with implanted stimulating electrodes in the perifornical region of the hypothalamus using doses of **1** and 2 mg/kg ip. Both compounds raised the threshold for hissing which was used as the end point. This is unlike the effect of chlorpromazine which lessens the hissing threshold, but it is similar to the action of trifluoperazine.

Both compounds (**10**, **21**) suppressed the toxic effect of amphetamine in aggregated mice[9] having ED_{50}'s of 0.25 and 0.21 mg/kg, respectively, compared with 0.094 mg/kg for haloperidol.

The LD_{50}'s for **10** and **21** in mice (120 hr) were 62 mg/kg iv, 145 mg/kg oral, and 50 mg/kg iv, 135 mg/kg oral, respectively.

Experimental Section

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

1-Acetylisonipecotic Acid.—A solution of 51.6 g (0.4 mole) of isonipecotic acid in 200 ml of $(CH_3CO)_2O$ was refluxed for 2 hr and allowed to stir at room temperature for 16 hr. The solution was concentrated and the residue which remained was triturated in Et_2O. The solid was collected by filtration and weighed 48.2 g (70%). The white product was recrystallized from *i*-PrOH–*i*-Pr_2O and melted at 180–182°. *Anal.* ($C_8H_{13}NO_3$) C, H, N.

1-Acetyl-4-(*p*-fluorobenzyl)piperidine (1).—To 400 ml of $SOCl_2$ was added 65.4 g (0.38 mole) of 1-acetylisonipecotic acid, which dissolved. The acid chloride precipitated from solution and 1 l. of petroleum ether (30–60°) was added. The mixture was filtered and the solid residue was washed several times with petroleum ether. The solid was dried and weighed 70 g (97%). The ir spectrum showed complete conversion from acid to acid chloride. The 70 g (0.37 mole) of 1-acetylisonipecotoyl chloride was slowly added to a stirring mixture of 93.0 g (0.7 mole) of $AlCl_3$ in 150 ml of fluorobenzene. After the addition was complete, the mixture was refluxed for 1 hr. The mixture was poured onto ice and the two resulting layers were separated. The aqueous layer was extracted twice with $CHCl_3$ and the extracts were added to the fluorobenzene which was separated previously. The organic solution was dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure and the residue was a crystalline white solid.

4-(*p*-Fluorobenzoyl)piperidine Hydrochloride (**2**).—A solution of 70.6 g (0.27 mole) of 1-acetyl-4-(*p*-fluorobenzyl)piperidine in 200 ml of 6 *N* HCl was refluxed for 2 hr. The cooled solution was extracted twice with Et_2O. The aqueous solution was made basic (NaOH) and then extracted with C_6H_6. The C_6H_6 extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure, and the residual oil was converted to the HCl salt.

1-Acetyl-4-cyanopiperidine.—A mixture of 204 g (1.2 mole) of 1-acetylisonipecotamide and 300 g (2.1 moles) of P_2O_5 was heated until the two solids melted and formed a brown glasslike solid. The solid was dissolved in a minimum of H_2O, and the solution was made basic (NaOH). The oily nitrile which separated was extracted into $CHCl_3$. The extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated under vacuum, and the residual oil was distilled. A yellow oil which weighed 98.8 g (55%) was obtained at 153–155° (0.05 mm). The liquid crystallized upon standing and melted at 49–53°. *Anal.* ($C_8H_{12}N_2O$) C, H, N.

4-(*m*-Trifluoromethylbenzoyl)piperidine Hydrochloride (**7**).—A solution of 102.5 g (0.45 mole) of *m*-bromobenzotrifluoride in 25 ml of Et_2O was added dropwise to a stirring mixture of 11.5 g (0.47 g-atom) of Mg in 300 ml of anhydrous Et_2O to maintain a moderate reflux. The dark mixture was stirred for 1 hr. A solution of 60.0 g (0.43 mole) of 1-acetyl-4-cyanopiperidine in 100 ml of THF was added slowly, and then the mixture was allowed to stir for 16 hr. An excess of NH_4Cl solution was added and the mixture was heated on a steam bath for 3 hr. The cooled mixture was extracted with C_6H_6 and the collected extracts were dried (Na_2SO_4) and concentrated under vacuum. The residue was dissolved in 200 ml of EtOH and the solution was made basic (NaOH). The mixture was refluxed for 3 hr and cooled, and the basic solution was extracted with C_6H_6. The C_6H_6 extracts were dried ($NaSO_4$) and concentrated under vacuum and the residual oil was converted to the HCl salt.

1-[3-(*p*-Acetyl-*o*-methoxyphenoxy)propyl]-4-(*p*-fluorobenzoyl)-piperidine Hydrochloride (**10**).—A mixture of 9.3 g (0.045 mole) of 4-(*p*-fluorobenzoyl)piperidine, 14.0 g (0.049 mole) of 3-(*p*-acetyl-*o*-methoxyphenoxy)propyl bromide, and 16.6 g (0.12 mole) of anhydrous K_2CO_3 in 150 ml of 1-BuOH was allowed to reflux for 1.5 hr. The mixture was filtered and the filtrate was concentrated. The oily residue was dissolved in C_6H_6 and the solution was extracted with 3 *N* HCl. The aqueous acidic layer was made basic (NaOH) and extracted with Et_2O. The collected ethereal extracts were dried (Na_2SO_4) and concentrated. The oily residue was converted to the HCl salt.

4-Benzoyl-1-[3-(*p*-fluorobenzoyl)propyl]piperidine Hydrochloride (**22**).—A stirred mixture of 7.0 g (0.037 mole) of 4-benzoylpiperidine, 9.8 g (0.040 mole) of γ-chloro-*p*-fluorobutyrophenone ethylene glycol ketal, 20.0 g (0.145 mole) of anhydrous K_2CO_3, and 100 ml of 1-BuOH was heated at reflux for 16 hr. The mixture was filtered and the filtrate was concentrated under vacuum. The residual oil was stirred with 100 ml of 3 *N* HCl and 100 ml of EtOH for 1 hr. The mixture was made basic (NaOH) and extracted with C_6H_6. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was converted to the HCl salt.

1-(2-Carbamoyloxyethyl)-4-(*p*-fluorobenzoyl)piperidine (**31**).—A mixture of 4.0 g (0.016 mole) of 4-(*p*-fluorobenzoyl)-1-(2-hydroxyethyl)piperidine and 6.0 g (0.09 mole) of sodium cyanate in 25 ml of CF_3COOH[10] was allowed to stir at room temperature for 18 hr. After the addition of 25 ml of H_2O, the mixture was made basic and extracted with C_6H_6. The combined extracts were dried (Na_2SO_4) and concentrated under vacuum. The solid residue which remained was repeatedly recrystallized.

4-(*p*-Fluorobenzoyl)-1-[2-(N-methylcarbamoyloxy)ethyl]piperidine (**32**).—To a solution of 3.0 g (0.012 mole) of 4-(*p*-fluorobenzoyl)-1-(2-hydroxyethyl)piperidine in 30 ml of dry C_6H_6 was added 0.69 g (0.012 mole) of methyl isocyanate. The solution was stirred under N_2 at room temperature for 1 hr. The solution was concentrated under vacuum and the residue was crystallized.

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4-(*p*-Fluorobenzoyl)-1-(2-propionyloxyethyl)piperidine Hydrochloride (39).—To a stirring solution of 7.5 g (0.03 mole) of 4-(*p*-fluorobenzoyl)-1-(2-hydroxyethyl)piperidine in 100 ml of $CHCl_3$ was added dropwise 4.6 g (0.035 mole) of $(CH_3CH_2CO)_2O$. The mixture was allowed to stir at reflux for 3 hr and then concentrated under vacuum. The residue which remained was converted to the HCl salt.

1-[2-(*p*-Chlorobenzoyloxy)ethyl]-4-(*p*-fluorobenzoyl)piperidine (40).—A solution of 3.5 g (0.02 mole) of *p*-chlorobenzoyl chloride in 10 ml of $CHCl_3$ was slowly added to a stirring mixture of 4.25 g (0.04 mole) of Na_2CO_3 and 5.0 g (0.02 mole) of 4-(*p*-fluorobenzoyl)-1-(2-hydroxyethyl)piperidine in 100 ml of $CHCl_3$. The mixture was allowed to stir at room temperature for 18 hr. After adding 50 ml of H_2O, the layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined extracts were dried (Na_2SO_4) and concentrated. The residue which remained crystallized.

1-(2-Benzoylethyl)-4-(*p*-fluorobenzoyl)piperidine (24).—A mixture of 12.8 g (0.06 mole) of 3-(*N*,*N*-dimethylamino)propiophenone, 12.6 g (0.06 mole) of 4-(*p*-fluorobenzoyl)piperidine and 12.0 g (0.11 mole) of anhydrous Na_2CO_3 in 100 ml of dry DMF was stirred at 50–60° for 32 hr. During this time N_2 was bubbled vigorously through the mixture. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was repeatedly recrystallized to give a white crystalline solid.

4-Fluoro-4′-[4-(*p*-fluorobenzoyl)-1-piperidinyl]benzophenone (44).—A mixture of 11.0 g (0.05 mole) of 4,4′-difluorobenzophenone, 12.0 g (0.05 mole) of 4-(*p*-fluorobenzoyl)piperidine hydrochloride, and 30 g of Na_2CO_3 in 100 ml of DMSO was heated at 110° for 4 hr. The mixture was cooled and poured into H_2O and the resulting solid was triturated several times with 200-ml portions of C_6H_6. The C_6H_6 was separated and concentrated and the residue crystallized.

1-Benzyl-3-(*p*-fluorobenzoyl)pyrrolidine Hydrochloride (52).—In a 3-l. flask equipped with a reflux condenser, mechanical stirrer, and addition funnel were placed 42.5 g (1.76 g-atoms) of Mg turnings, 300 ml of dry Et_2O, and a crystal of I_2. After several milliliters of a solution of 308 g (1.76 moles) of *p*-fluorobromobenzene in 400 ml of dry Et_2O was added, the reaction started and the remainder of the solution was added at a rate which maintained refluxing. When the addition was complete, the mixture was refluxed for 30 min. To the stirred Grignard solution was then added 164 g (0.88 mole) of 1-benzyl-3-cyanopyrrolidine in 100 ml of dry Et_2O at a rate which maintained gentle refluxing. The mixture was stirred for 1 hr at ambient temperature, cooled, and treated with a solution of 94 g (1.8 moles) of NH_4Cl in 500 ml of H_2O. The resulting suspension was stirred and heated on a steam bath for 16 hr, cooled, and treated with 500 g of 50% NaOH to ensure hydrolysis of the imine. Toluene was added to the flask and the mixture was heated for 1 hr on a steam bath. The suspension was filtered and the cake was washed with toluene. The combined toluene extracts were dried ($MgSO_4$) and concentrated. The residual oil was distilled and then converted to the HCl salt.

3-(*p*-Fluorobenzoyl)pyrrolidine Oxalate (53).—A mixture of 50.0 g (0.226 mole) of 1-carbamoyl-3-(*p*-fluorobenzoyl)pyrrolidine[11] [prepared from 1-benzyl-3-(*p*-fluorobenzoyl)pyrrolidine[3] by the Von Braun reaction[4]] in 400 ml of concentrated HCl was heated at reflux for 3 days, cooled, and made basic with 50% NaOH. The oil which separated was extracted with C_6H_6, and the combined extracts were washed (H_2O), dried ($MgSO_4$), and concentrated. The residual oil was converted to the oxalate salt.

1-(2-Ethoxyethyl)-3-(*p*-fluorobenzoyl)pyrrolidine Oxalate (51).—The procedure described above for compound **52** was used and 1-(2-ethoxyethyl)-3-cyanopyrrolidine was added to *p*-fluorophenyl magnesium bromide. The oily tertiary amine which was obtained was converted to the oxalate salt.

2-[3-(*N*-2-Hydroxyethylamino)propyl]-2-(*p*-fluorophenyl)-dioxolane.—To 129 g (2.1 moles) of aminoethanol at 100–110° was added, dropwise, 85 g (0.35 mole) of 2-(3-chloropropyl-2-(*p*-fluorophenyl)dioxolane. After addition (~3 hr) the temperature was raised to 120° and stirring was continued for an additional 2 hr. The mixture was cooled and made basic with 3 *N* NaOH and the product was extracted into C_6H_6. After drying ($MgSO_4$), the C_6H_6 extract was concentrated to an oil, the major portion of which distilled at 148–150° (0.09 mm); yield 76.5 g (80%). The low-melting solid could be recrystallized from *i*-Pr_2O, mp 70–71°. *Anal.* ($C_{14}H_{20}FNO_3$) C, H, N.

p-Fluoro-γ-[N-2-hydroxyethyl-N-2-(*o*-methoxyphenoxy)ethyl]-aminobutyrophenone.—A stirred mixture of 33 g (0.12 mole) of 2-[3-(*N*-2-hydroxyethylamino)propyl]-2-(*p*-fluorophenyl)dioxolane, 30 g (0.13 mole) of 2-(*o*-methoxyphenoxy)ethyl bromide, 33 g of K_2CO_3, and 200 ml of 1-BuOH was refluxed overnight. The mixture was cooled, filtered, and stripped to an oil. The oily ketal was added to 200 ml of 3 *N* HCl and heated on a steam bath with stirring for 30 min. The mixture was cooled, triturated with Et_2O, then converted to the free base with 3 *N* NaOH. The crude base was taken up into $CHCl_3$, dried ($MgSO_4$), and evaporated to an oil which solidified on standing. Recrystallization from *i*-Pr_2O gave 35.2 g (78%) of product which melted at 67–73°. The analytical sample melted at 70–72°. *Anal.* ($C_{21}H_{26}FNO_4$) C, H, N.

p-Fluoro-γ-[N-2-chloroethyl-N-2-(*o*-methoxyphenoxy)ethyl]-aminobutyrophenone.—A solution of 21 g (0.055 mole) of *p*-fluoro-γ-[N-2-hydroxyethyl-N-2-(*o*-methoxyphenoxy)ethyl]aminobutyrophenone in 50 ml of $CHCl_3$ was acidified with dry HCl gas and treated with 11.9 g (0.1 mole) of $SOCl_2$. The mixture was refluxed for 4 hr, cooled, and poured into H_2O and the $CHCl_3$ layer was separated, dried ($MgSO_4$), and concentrated to an oil (2.5 g). The oil was dissolved in hot methyl isobutyl ketone and the insoluble material was filtered off. After cooling 3 g (12%) of product was isolated which melted at 162–164°. *Anal.* ($C_{21}H_{25}Cl_2FNO_3$) C, H, N.

1-[2-(*o*-Methoxyphenoxy)ethyl]-4-(*p*-fluorobenzoyl)piperidine.—A small sample (0.3 g) of *p*-fluoro-γ-[N-2-chloroethyl-N-2-(*o*-methoxyphenoxyethyl]aminobutyrophenone in a test tube was dissolved in 2 ml of dry DMF and treated with 0.1 g of 50% NaH in mineral oil. The mixture was warmed on a steam bath for 5 min, cooled, treated with H_2O, and extracted with C_6H_6. The C_6H_6 extract was washed with H_2O, dried ($MgSO_4$), and chromatographed on 10 g of 60–100 mesh Florisil. Elution with C_6H_6 containing increasing amounts of Me_2CO gave 0.05 g of pure product. The product had nmr and ir spectra which were identical with those of **16** prepared by the procedure outlined for compound **10**.

3-Benzoyl-1-carbethoxypyrrolidine.—A mixture of 0.2 mole of β-dimethylaminopropiophenone (from 42.8 g of HCl salt) in 200 ml of DMF was treated with 50 g (1.2 moles) of aziridine and allowed to stand for 4 hr while a slow stream of N_2 was passed through the mixture. The mixture was poured into H_2O and the product was extracted into 200 ml of C_6H_6. The C_6H_6 extract was washed several times (H_2O) and dried ($MgSO_4$). (An aliquot of the C_6H_6 solution was concentrated to an oil which was molecularly distilled. A satisfactory analysis could not be obtained.)

The dried C_6H_6 extract containing β-aziridinylpropiophenone was cooled to 20° and treated dropwise with ethyl chlorocarbonate. After 18 g (0.17 mole) had been added, tlc showed no starting material remained.

The C_6H_6 solution was then treated with 4.8 g (0.02 mole) of NaH and refluxed for 6 hr. No H_2 evolution was noted. About half of the C_6H_6 was boiled off and 50 ml of DMF was added. A vigorous evolution of H_2 took place. After refluxing 30 min the mixture was cooled and poured into H_2O. The C_6H_6 layer was separated, dried ($MgSO_4$), and concentrated to an oil. The crude product (35 g) was chromatographed in two batches on 400 g of 60–100 mesh Florisil, using C_6H_6–Me_2CO to elute. The purified oil was molecularly distilled for analysis. (25 g, 50% over-all yield). *Anal.* ($C_{14}H_{17}NO_3$) C, H, N.

3-Benzoylpyrrolidine.—A suspension of 10 g (0.04 mole) of 3-benzoyl-1-carbethoxypyrroldine in 50 ml of 6 *N* HCl was refluxed for 3 hr. No hydrolysis was noted by tlc. The mixture was then treated with 25 ml of EtOH and 25 ml of 12 *N* HCl and refluxing was continued for 18 hr. After cooling, the mixture was extracted with Et_2O and concentrated to an oil which crystallized from hot Me_2CO; yield 5 g (63%). The nmr and ir spectra of the free base were identical with those of compound **55** which was prepared by the method described for **53**.

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