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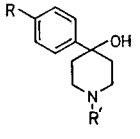
Some basic ketones with central nervous system depressant activity

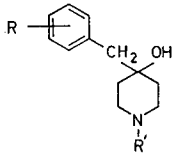
N. J. HARPER*, A. B. SIMMONDS, W. T. WAKAMA†, G. H. HALL‡ AND D. K. VALLANCE§

Some γ-(4-benzyl-4-hydroxypiperidino)-butyrophenones and related compounds have been prepared and screened for central nervous system depressant activity. One of the more active, γ-(4-*p*-chlorobenzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenone, was selected for further study and in experimental animals was found to have effects on the central nervous system similar to both those of chlorpromazine and of haloperidol.

RECENTLY, some structural modifications of analgesics of the prodine type were prepared in an attempt to produce compounds without analgesic effects but having other potentially useful central nervous system (CNS) depressant activity (Harper & Simmonds, 1959, 1964). Although the alcohols (I; R = F or CF_3, R′ = $[CH_2]_2$·Ph. II; R = *p*-Cl, *o*-Cl or *p*-F, R′ = $[CH_2]_2$·Ph) had significant activity when assessed by a hot-plate test, they did not have the characteristic mydriatic action of the narcotic analgesics. Some of these alcohols were also found to possess a protective effect against amphetamine toxicity in aggregated mice and to block a conditioned avoidance response in rats (unpublished observations).



(I)



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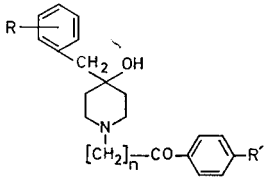
Janssen (1958) and Carrabateas & Grumbach (1962) showed that the introduction of a propiophenone group onto the basic nitrogen atom of analgesics of the pethidine and prodine types gave compounds with greatly increased morphine-like analgesic activity. Lengthening the chain of carbon atoms on the basic nitrogen atom to a butyrophenone group, however, gave compounds with marked activity in the hot-plate test which was not antagonised by nalorphine. The compounds were also without mydriatic activity (Janssen & Eddy, 1960). These observations led to the introduction of tranquillising compounds such as haloperidol, γ-(4-*p*-chlorophenyl-4-hydroxypiperidino)-*p*-fluorobutyrophenone hydrochloride (I; R = Cl, R′ = $[CH_2]_3$·CO·C_6H_4·F-*p*) (Janssen & others, 1959).

From the School of Pharmacy, Chelsea College of Science & Technology, London, S.W.3 and Smith Kline & French Laboratories Ltd., Welwyn Garden City, Herts.

Present addresses: * College of Advanced Technology, Birmingham. † University of Nigeria, Nsukka, Nigeria. ‡ The Tobacco Research Council Laboratories, Harrogate, Yorks. § The British Drug Houses Ltd., Godalming, Surrey.

It thus became of interest to prepare propiophenones and butyrophenones of Type II and to test these for their effects on the CNS. Preliminary investigation of the pharmacological actions of these propiophenones (III; $n = 2$; R = *p*-Cl; R′ = H or F) and butyrophenones (III; $n = 3$; R = *p*-Cl; R′ = H, Br, Cl, F, OMe or Me. R = *p*-F; R′ = F. R = 2,4-Cl_2; R′ = Cl or F. R = 3,4-Cl_2; R′ = Cl or F), together with some related compounds, is now reported. These studies resulted in the selection of γ-(4-*p*-chlorobenzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenone for further investigation.



(III)

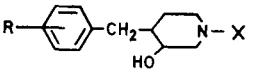
Chemistry

The compounds of type III ($n = 3$) were prepared by the addition of the appropriate Grignard reagent to 1-benzyl-4-oxopiperidine; catalytic debenzylation gave the secondary bases, which were reacted with the appropriate γ-chlorobutyrophenone by heating in toluene in the presence of sodium bicarbonate and a trace of potassium iodide. γ-(4-*p*-Chlorobenzyl-4-hydroxy-3-methylpiperidino)-*p*-fluorobutyrophenone was prepared in this way from 1-benzyl-3-methyl-4-oxopiperidine. Benzylmagnesium halides have been shown in some instances to give rise to the isomeric *o*-tolyl derivatives (Austin & Johnson, 1932). Such rearrangements did not occur in the present investigations and with compound III ($n = 3$; R = 3,4-Cl_2, R′ = F) oxidative degradation studies identified the structure of the Grignard addition product as 1-benzyl-4-(3,4-dichlorobenzyl)-4-hydroxypiperidine.

p-Fluoro-γ-[4-hydroxy-4-(pyrid-2-ylmethyl)piperidino]-butyrophenone was prepared from 1-benzyl-4-oxopiperidine and pyrid-2-ylmethyl-lithium (obtained by exchange from α-picoline and phenyl-lithium), followed by debenzylation and condensation with γ-chloro-*p*-fluorobutyrophenone.

β-(4-*p*-Chlorobenzyl-4-hydroxypiperidino)propiophenone was prepared by a Mannich base exchange reaction from 4-*p*-chlorobenzyl-4-hydroxypiperidine and the methiodide of dimethylaminoethyl phenyl ketone. The corresponding *p*-fluoropropiophenone was prepared by a Mannich reaction between 4-*p*-chlorobenzyl-4-hydroxypiperidine, paraformaldehyde and *p*-fluoroacetophenone. β-(4-*p*-Chlorobenzyl-4-hydroxypiperidino)-*p*-fluoro-α-methylpropiophenone was prepared in the same way by a Mannich reaction of 4-*p*-chlorobenzyl-4-hydroxypiperidine, paraformaldehyde and *p*-fluoropropiophenone.

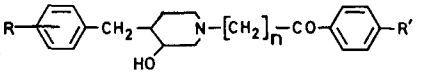
TABLE 1. 4-BENZYL-4-HYDROXYPIPERIDINES



R	X	M.p. °C	Found (%)				Formula	Required (%)			
			C	H	N	Equiv		C	H	N	Equiv
p-Cl	CH_2Ph	215	64·5	6·9	4·2	358	$C_{19}H_{22}ClNO{\cdot}HCl$	64·8	6·6	4·0	352
p-F	CH_2Ph	218	59·7	6·2	3·9	381	$C_{19}H_{22}FNO{\cdot}HBr$	60·0	6·1	3·7	380
O-Cl	CH_2Ph	219	65·2	6·3	4·1	360	$C_{19}H_{22}ClNO{\cdot}HCl$	64·8	6·6	4·0	352
†*p*-Cl	CH_2Ph	206	65·7	7·4	3·8	365	$C_{20}H_{24}ClNO{\cdot}HCl$	65·5	6·9	3·8	366
o,p-Cl_2	CH_2Ph	209	58·7	5·7	3·7	384	$C_{19}H_{21}ClNO{\cdot}HCl$	59·0	5·7	3·6	387
m,p-Cl_2	CH_2Ph	213	58·6	5·8	3·7	390	$C_{19}H_{21}ClNO{\cdot}HCl$	59·0	5·7	3·6	387
2-Pyr*	CH_2Ph	180	67·6	7·3	8·6	320	$C_{18}H_{22}N_2O{\cdot}HCl$	67·8	7·3	8·8	318
p-Cl	H	226	55·5	6·7	5·5	264	$C_{12}H_{16}ClNO{\cdot}HCl$	55·0	6·5	5·3	262
p-F	H	221	50·0	6·3	4·9	294	$C_{12}H_{16}FNO{\cdot}HBr$	49·7	5·9	4·8	290
†*p*-Cl	H	240	56·9	7·1	5·2	270	$C_{13}H_{18}ClNO{\cdot}HCl$	56·5	6·9	5·1	276
o,p-Cl_2	H	138	56·4	5·9	5·4	261	$C_{12}H_{15}Cl_2NO$	55·4	5·8	5·4	260
m,p-Cl_2	H	208	49·6	5·5	4·7	301	$C_{12}H_{15}Cl_2NO{\cdot}HCl$	48·6	5·4	4·7	297
2-Pyr*	H	164	56·8	7·3	12·4		$C_{11}H_{16}N_2O{\cdot}HCl$	57·8	7·4	12·3	

* Phenyl replaced by pyrid-2-yl group. † 3-Methylpiperidino derivative.

TABLE 2. γ-(4-BENZYL-4-HYDROXYPIPERIDINO)BUTYROPHENONES, PROPIOPHENONES AND RELATED COMPOUNDS



No.	R		R′	M.p. °C	Found (%)				Formula	Required (%)			
					C	H	N	Equiv		C	H	N	Equiv
1	*p*-Cl	3	H	192	65·1	6·7	3·4	408	$C_{22}H_{26}ClNO_2 \cdot HCl$	64·7	6·7	3·4	408
2	*p*-F	3	F	180	64·5	6·4	3·4	410	$C_{22}H_{25}F_2NO_2 \cdot HCl$	64·8	6·8	3·6	410
3	*p*-Cl	3	F	198	62·4	6·5	3·3	427	$C_{22}H_{25}ClFNO_2 \cdot HCl$	62·0	6·2	3·3	426
4†	*p*-Cl	3	F	205	62·3	6·5	3·4	437	$C_{23}H_{27}ClFNO_2 \cdot HCl$	62·7	6·4	3·2	440
5	*o,p*-Cl_2	3	F	191	57·4	5·6	3·1	461	$C_{22}H_{24}Cl_2FNO_2 \cdot HCl$	57·3	5·5	3·0	461
6	*m,p*-Cl_2	3	F	191	56·8	5·6	3·1	459	$C_{22}H_{24}Cl_2FNO_2 \cdot HCl$	57·4	5·5	3·0	461
7	2-Pyr*	3	F	171	64·1	6·5	7·4	388	$C_{21}H_{25}FN_2O_2 \cdot HCl$	64·1	6·7	7·2	394
8	*p*-Cl	3	Cl	188	60·4	5·9	3·3	444	$C_{22}H_{25}Cl_2NO_2 \cdot HCl$	59·7	5·9	3·2	443
9	*o,p*-Cl_2	3	Cl	191	54·6	5·7	3·0	474	$C_{22}H_{24}Cl_3NO_2 \cdot HCl$	55·4	5·3	2·9	477
10	*m,p*-Cl_2	3	Cl	147	54·9	5·0	3·1	479	$C_{22}H_{24}Cl_3NO_2 \cdot HCl$	55·4	5·3	2·9	477
11	*p*-Cl	3	Br	190	54·2	5·4	3·0	487	$C_{22}H_{25}BrClNO_2 \cdot HCl$	54·2	5·4	2·9	487
12	*p*-Cl	3	Me	218	65·8	6·9	3·5	421	$C_{23}H_{28}ClNO_2 \cdot HCl$	65·5	6·9	3·3	422
13	*p*-Cl	3	OMe	197	63·8	6·7	3·2	440	$C_{23}H_{28}ClNO_3 \cdot HCl$	63·0	6·7	3·2	438
14	*p*-Cl	3	Th‡	174	57·4	6·1	3·2	413	$C_{20}H_{24}ClNO_2S \cdot HCl$	58·0	6·1	3·4	414
15	*p*-Cl	2	H	206	64·0	6·2	3·4	393	$C_{21}H_{24}ClNO_2 \cdot HCl$	64·0	6·4	3·5	394
16	*p*-Cl	2	F	197	61·2	5·9	3·5	406	$C_{21}H_{23}ClFNO_2 \cdot HCl$	61·2	5·9	3·4	412
17	*p*-Cl	$CH_2 \cdot CHMe$	F	210	62·0	6·1	3·5	428	$C_{22}H_{25}ClFNO_2 \cdot HCl$	62·0	6·2	3·3	426

* Phenyl replaced by pyrid-2-yl group. † 3-Methylpiperidino derivative. ‡ Phenyl group replaced by thien-2-yl group.

EXPERIMENTAL

1-Benzyl-4-halogenobenzyl-4-hydroxypiperidines. An ethereal solution of 1-benzyl-4-oxopiperidine (0·25 mole) was added dropwise to a stirred solution of the halogenobenzyl magnesium chloride prepared from halogenobenzyl chloride (0·5 mole) and magnesium (0·55 mole). The mixture was stirred overnight and then poured onto crushed ice and acetic acid. The ethereal layer was washed with water and the combined acidic solutions were made alkaline with ammonium hydroxide solution. Extraction with ether gave an oil which on treatment with ethanolic hydrogen chloride gave 1-benzyl-4-halogenobenzyl-4-hydroxypiperidine (yield 50–60%) (Table 1).

4-Halogenobenzyl-4-hydroxypiperidines. A solution of 1-benzyl-4-halogenobenzyl-4-hydroxypiperidine (40 g) in ethanol (1 litre) was shaken with hydrogen in the presence of palladium on charcoal (10%, 10 g) at 40° until the theoretical amount of hydrogen had been absorbed. The mixture was filtered through kieselguhr and the filtrate concentrated under reduced pressure. Dilution with ether gave crystals of the debenzylated product in almost quantitative yield (Table 1).

γ-(4-Halogenobenzyl-4-hydroxypiperidino)butyrophenones. A mixture of 4-halogenobenzyl-4-hydroxypiperidine (0·5 mole), sodium hydrogen carbonate (0·8 mole), *γ-chlorobutyrophenone* (0·55 mole) and a trace of potassium iodide in toluene (500 ml) was heated under reflux for 3 days. The mixture was then filtered, the solids washed with ether, and the combined filtrates were made acid with hydrochloric acid. Evaporation of the solvents gave γ-(4-halogenobenzyl-4-hydroxypiperidino)butyrophenone hydrochloride. Compound 14 (Table 2) was similarly prepared from γ-chloro-2-butyrylthiophen.

β-(4-Halogenobenzyl-4-hydroxypiperidino)propiophenones. The appropriate secondary amine hydrochloride (1 mole), paraformaldehyde (3 mole), a few drops of hydrochloric acid, and *p*-fluoroacetophenone (for compound 16) or *p*-fluoropropiophenone (for compound 17) (1 mole) in isopropanol were heated together under reflux for 3 hr. Evaporation of the solvent gave the Mannich bases (compounds 16 and 17) as their hydrochlorides.

β-(4-p-Chlorobenzyl-4-hydroxypiperidino) propiophenone. Dry nitrogen was passed through a mixture of 4-*p*-chlorobenzyl-4-hydroxypiperidine (extracted from its hydrochloride, 5·2 g), sodium carbonate (1 g), 2-dimethylaminopropiophenone methiodide (7 g) and formdimethylamide (25 ml) until no more trimethylamine was evolved. The mixture was diluted with water (50 ml). Extraction with ether gave an oil which on treatment with ethanolic hydrogen chloride gave β-(4-*p*-chlorobenzyl-4-hydroxypiperidino)propiophenone hydrochloride.

All salts were recrystallised from ethanol except *p*-fluoro-γ-[4-hydroxy-4-(pyrid-2-ylmethyl)piperidino]butyrophenone hydrochloride which was recrystallised from isobutyl methyl ketone. Equivalent weights of the salts were determined by titration with 0·02N perchloric acid in acetic acid in the presence of mercuric acetate.

Pharmacology

METHODS

General. Male Schofield albino mice, 18–24 g but with a maximum weight range of 4 g in any one test, male Wistar albino rats, 130–150 g, male cats, 2–4 kg, and mongrel dogs of either sex, about 10 kg, were used. Unless otherwise stated, the compounds, dissolved or suspended in 5% acacia, were administered orally to groups of five animals, the dose volume being 25 ml/kg body weight. The compounds were initially studied at a dose corresponding to about 40% of the acute LD50, those effective in all animals then being re-examined at varying dose levels in parallel with a suitable reference compound. ED50 values were calculated using Kärber's (1931) method.

Acute toxicity. Approximate LD50 values were determined by inspection from the mortalities occurring within 7 days of oral or subcutaneous administration, two animals being used at each dose level.

Hot plate test (after Eddy & Leimbach, 1953). At 30, 60 and 90 min after giving the compounds by the subcutaneous route the mice were placed in turn on a hot plate at 55–56°. "Analgesia" was considered present if the animal failed to show any signs of discomfort (as judged by raising, shaking or licking of the hind paws) within 30 sec. The ED50 was estimated from the numbers of animals showing "analgesia" at one or more observation times.

Tail pinch test (after Bianchi & Franceschini, 1954). Only mice which, in a preliminary test, made repeated attempts within 15 sec to remove the rubber covered bulldog clip were used for the test. The clip was then applied for 30 sec to each mouse in turn at 30, 60 and 90 min after the subcutaneous administration of the compounds. "Analgesia" was considered present if no attempt was made to remove the clip. The ED50 was estimated from the numbers of animals showing "analgesia" at one or more observation times.

Nalorphine antagonism. Four groups of 10 mice were injected subcutaneously with γ-(4-*p*-chlorobenzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenone (5 mg/kg). The animals in three of the groups were injected at the same time with nalorphine at dose levels of 50, 100 and 200 mg/kg. 30 min later, the presence of analgesia was determined by the hot plate method as described above.

Prevention of maximal electroshock seizures (after Swinyard, Brown & Goodman, 1952). At 1, 2 and 3 hr after giving the compounds, an electroshock (25 mA, 50 cps AC for 0·2 sec, just sufficient to produce seizures characterised by tonic extension of fore and hind limbs in untreated animals) was applied to each mouse in turn via corneal electrodes. The ED50 was estimated from the numbers of animals in which the hind leg tonic extensor component of the normal seizure pattern was prevented at one or more observation times.

Prevention of maximal leptazol seizures (after Goodman, Grewal, Brown & Swinyard, 1953). Two hr after giving the test compounds, each mouse was injected intravenously with 0·2 ml/20 g body weight of a 0·6% aqueous solution of leptazol. This dose was just sufficient to

produce seizures characterised by tonic extension of fore and hind limbs in untreated mice. The ED50 was estimated from the numbers of animals in which the hind leg tonic extensor component of the normal seizure pattern was prevented.

Protection against tremorine-induced tremors (after Everett, 1956). The compounds were given to mice deprived of food for 18 hr previously. One hr later, an aqueous solution of tremorine (30 mg/25 ml/kg body weight) was injected intraperitoneally. This dose was shown to produce characteristic tremors in untreated mice. Each animal was observed for a period of 15 min after the tremorine injection and the ED50 was estimated from the numbers of animals without tremors.

Protection against amphetamine toxicity in aggregated mice (after Lasagna & McCann, 1957). The compounds were given to groups of 10 mice deprived of food for 18 hr previously. One hr later, the mice were injected subcutaneously with an aqueous solution of (±)-amphetamine sulphate, 20 mg/kg body weight. They were then placed in a constant temperature cabinet maintained at approximately 27°, food and water being provided. Most or all of a group of control animals injected with amphetamine sulphate alone and kept under similar conditions died within 24 hr. The number surviving in each treated group was recorded after 24 hr and the ED50 estimated.

Blockade of a conditioned avoidance response (after Cook & Weidley, 1957). Previously conditioned rats were given the compounds after being deprived of food for 18 hr. At 1, 2 and 3 hr after dosing, the animals were placed in the test chamber and subjected to the sound of the buzzer. Failure to climb the pole within 30 sec indicated blockade of the conditioned response. They were then subjected to the shock and buzzer together for 30 sec and if they then failed to climb the pole, the unconditioned response was also considered to be blocked. The ED50 for blockade of the conditioned response was estimated from the numbers of animals failing to respond at one or more observation times. The ED50 for blockade of the unconditioned response was estimated similarly.

Production of catalepsy. 2½ hr after giving the compounds, each rat was removed gently and quietly from its cage and placed with its feet on four corks spaced at suitable intervals. The ED50 was estimated from the numbers of animals considered cataleptic as evidence by failure to assume normal posture within 5 min.

Cardiovascular effects. The carotid blood pressure and contractions of the nictitating membrane were recorded in a cat anaesthetised with chloralose (80 mg/kg, intravenously) and in a dog anaesthetised with pentobarbitone sodium (30 mg/kg, intravenously). Responses were obtained to preganglionic stimulation of the vagus and cervical sympathetic nerves and to intravenous injection of adrenaline (both species) and noradrenaline (cat only), before and after the intravenous injection of varying amounts of γ-(4-*p*-chlorobenzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenone in aqueous solution.

Behavioural studies. Varying amounts of γ-(4-*p*-chlorobenzyl-4-

hydroxypiperidino)-*p*-fluorobutyrophenone were administered by mouth in gelatin capsules to male cats (two per dose) and by stomach tube in 5% acacia to dogs (one male and one female per dose). Changes in behaviour and condition of the animals were recorded on the day of the experiment and, where necessary, on subsequent days.

Results

Table 3 summarises the results of the investigations of the CNS depressant activity of the propiophenones (III; $n = 2$; R = *p*-Cl; R′ = H or F) and butyrophenones (III; $n = 3$; R = *p*-Cl; R′ = H, Br, Cl, F, OMe or Me. R = *p*-F; R′ = F. R = 2,4-Cl_2; R′ = Cl or F), together with some related compounds. The activities of the more potent γ-(4-benzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenones relative to those of suitable reference compounds are shown in Table 4. The results of certain additional investigations on a representative compound are described below.

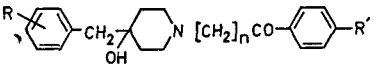
Nalorphine antagonism. The activity of γ-(4-*p*-chlorobenzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenone in the hot-plate test was not antagonised by nalorphine in doses up to 200 mg/kg.

Cardiovascular effects. γ-(4-*p*-Chlorobenzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenone, injected intravenously, has a blocking action on the sympathetic nervous system of both the cat and the dog at doses of 0·1 mg/kg and above. This is probably not due to ganglionic blockade for, although the responses to pre-ganglionic stimulation of the cervical sympathetic nerve were reduced, those to vagal stimulation were unaffected, even when the dose was increased to 1 mg/kg. As the pressor responses to injected adrenaline in the cat were inhibited at low and reversed at high doses, those to noradrenaline also being inhibited, it appears that the compound has α-adrenergic receptor blocking activity. The pressor responses to injected adrenaline were also inhibited in the dog.

Behavioural studies. γ-(4-*p*-Chlorobenzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenone in doses of 5–40 mg/kg caused ataxia in the cat, this being due to incoordination rather than hypotonia. The animals in general then adopted a crouching position with the fore-legs extended in front of the head, with the claws also fully extended. Three animals were seen to paw repeatedly at imaginary objects immediately in front of them, after which they backed away in an apprehensive manner. This suggested a possible hallucinogenic effect. Intermittent clonic seizures ensued at the highest dose, with tremors at lower doses. All animals subsequently recovered, usually within 24 hr.

Ataxia and tremors were also observed initially in the dog at 5 and 10 mg/kg, again with no evidence of muscle weakness. The animals subsequently assumed a position similar to that adopted by the cats, with head and body on the ground and the forelegs extended forwards on either side of the head. Complete prostration, but without loss of consciousness, ensued in the male given 10 mg/kg and this animal did not fully recover until 3–4 days after dosing. Only minimal effects were observed at 2·5 mg/kg.

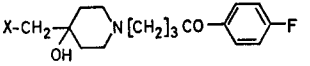
TABLE 3. CNS DEPRESSANT PROPERTIES OF γ-(4-BENZYL-4-HYDROXYPIPERIDINO)BUTYROPHENONES, PROPIOPHENONES AND RELATED COMPOUNDS



No.	R	n	R'	ED50, mg/kg								
				Block of conditioned avoidance response	Block of uncon-ditioned response	Protection against amphetamine toxicity	Prevention of tremorine-induced tremors	Hot-plate test	Prevention of maximal electroshock seizures	Prevention of maximal leptazol seizures	Production of catalepsy	Tail Pinch test
1	*p*-Cl	3	H	<100		<60	47	6·7				
2	*p*-F	3	F	4·6		0·35	1·3	3·0	Inactive	Inactive		
3	*p*-Cl	3	F	8·1, 3·1	28, 25	0·8	2·3, 2·5	1·5	Inactive	Inactive	9·2	2·2
4†	*p*-Cl	3	F	11		1·2	9·8	4·3	Inactive	Inactive		
5	2,4-Cl_2	3	F	6·2		3·5	31	6·2	Inactive	Inactive		
6	3,4-Cl_2	3	F	5·4		0·4	3·7	4·0	Inactive	8·5		
7	2-Pyr*	3	F	Inactive		4·0	13	18	Inactive			
8	*p*-Cl	3	Cl	56		Inactive	31	Inactive	Inactive	Inactive		
9	2,4-Cl_2	3	Cl	Inactive		Inactive	Inactive	Inactive	28	Inactive		
10	3,4-Cl_2	3	Cl	Inactive		<20	Inactive	Inactive	<27	Inactive		
11	*p*-Cl	3	Br	Inactive		Inactive	Inactive	Inactive	28	Inactive		
12	*p*-Cl	3	Me	Inactive		Inactive	Inactive	27	Inactive	Inactive		
13	*p*-Cl	3	OMe	Inactive		7·6	Inactive	Inactive	Inactive	Inactive		
14	*p*-Cl	3	Th‡	27		27	41	13	Inactive	Inactive		
15	*p*-Cl	2	H	Inactive		Inactive	Inactive	Inactive	45	53		
16	*p*-Cl	2	F	Inactive			Inactive	Inactive	20	Inactive		
17	*p*-Cl	CH_2·CH(Me)§	F			52						
Haloperidol				1·2	4·9	0·3	6·5	2·5				

† 3-Methylpiperidino derivative * Phenyl group replaced by pyrid-2-yl group ‡ Phenyl group replaced by thien-2-yl group § $[CH_2]n$ replaced by CH_2·CH(Me)

TABLE 4. COMPARISON OF γ-(4-BENZYL-4-HYDROXYPIPERIDINO)-*p*-FLUOROBUTYROPHENONES IN SOME CNS-DEPRESSANT TESTS



Compound No.	X	Relative activity: Block of conditioned avoidance response Chlorpromazine = 1·0	Block of unconditioned response Chlorpromazine = 1·0	Protection against amphetamine toxicity Chlorpromazine = 1·0	Prevention of tremorine -induced tremors Atropine = 1·0	Hot plate test Pethidine = 1·0	Tail pinch test Pethidine = 1·0	Production of catalepsy Chlorpromazine = 1·0
3	*p*-Cl.C_6H_4	1·3	0·8	2·5	3·6	10·0	4·0	1·7
5	2,4-Cl_2:C_6H_3	1·5		0·3	0·2	3·5		
6	3,4-Cl_2:C_6H_3	2·0		5·0	2·0	3·4		
4	*p*-F·C_6H_4	1·5		7·0	8·0	6·0		
7	pyrid-2-yl	Inactive		0·9	0·5	1·5		
Haloperidol ..	.. .. ..	*2·6	*5·0	16·0	*0·4	7·0		
Chlorpromazine	.. .. ..	—	—	—	2·4	13·0	—	—

* relative to Compound No. 3 = 1·0

Discussion

γ-(4-*p*-Chlorobenzyl-4-hydroxpiperidino)-*p*-fluorobutyrophenone shows effects on the CNS similar to both those of chlorpromazine and those of haloperidol. It is intermediate in activity between these compounds in protecting against amphetamine toxicity in aggregated mice and in blocking a conditioned avoidance response in rats. It appears, however, to have greater specificity with regard to the latter property in that the ratio of the ED50 for blockade of the unconditioned response to that for blockade of the conditioned response is greater than with chlorpromazine or haloperidol. It is also more active than either of these drugs in preventing tremors induced by tremorine and in the hot-plate test. Despite its high activity in the hot-plate test, and in the tail pinch test, it is probable that the compound is not a morphine-like analgesic since nalorphine does not antagonise its activity in the hot-plate test. Its resemblance to chlorpromazine has been further demonstrated by the production of catalepsy and by its action in blocking α-adrenergic receptors.

A high order of activity has also been shown for other members of the series, particularly the γ-(4-benzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenones listed in Table 2. It is evident that relatively small changes in activity result from variations in the substituent in the phenyl ring of the benzyl group. Introduction of a methyl group in position 3 of the piperidyl group of γ-(4-*p*-chlorobenzyl-4-hydroxypiperidino)-*p*-fluorobutyrophenone also had little effect on overall activity. The essential nature of the *p*-fluorobutyrophenone moiety is demonstrated by the marked reduction or complete loss of activity observed on replacing the F atom by a H, Cl or Br atom or by a Me or OMe group, on replacing the whole moiety by a 2-butyrylthiophen or a *p*-fluoroisobutyrophenone moiety, and on shortening the polymethylene chain.

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