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Chemistry and Pharmacology of CNS Depressants Related to 4-(4-Hydroxy-4-phenylpiperidino)butyrophenone

Part I—Synthesis and screening data in mice

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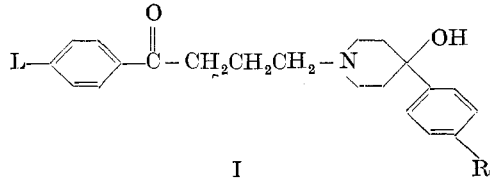
Introduction

Our chemical and pharmacological experimental programme[8,9] in the field of substituted piperidines led to the discovery that 4-(4-hydroxy-4-phenylpiperidino)butyrophenone (I: L = R = H) was a powerful CNS depressant in various species. This unexpected result led us to investigate the CNS depressant properties of a new series of over 500 related basic ketones. The relevant



I

chemical and pharmacological results obtained with these compounds will be presented and discussed in this series of papers.

The purpose of this paper is to describe a convenient method of synthesis and some physicochemical properties, as well as some relevant CNS depressant properties in mice of a selected group of 8 typical compounds of structure I (L = H or F; R = H, F, Cl or

CH_3) (Table I). Further details will be presented in subsequent papers.

Table I. Physical properties

Structure		M.p. in °C		pK′a*	U.V. spectrum maximum of absorption				Solubility in water mg/100 ml†	
					mμ		$\epsilon.10^{-3}$			
L	R	base	HCl		base	HCl	base	HCl	base	HCl
H	H	129·4–130·6	182·0–184·0	8·4	242	245	12	13	2·8	1,800
H	F	117·4–118·6	188·0–190·0	8·5	245	246	13	13	1·5	1,000
H	Cl	128·2–130·2	216·5–218·0	8·2	245	245	13	14	0·7	400
H	CH_3	101·0–102·5	179·6–181·5	—	245	245	13	13	—	900
F	H	135·6–136·2	204·5–205·5	8·5	247	247	13	13	2·6	900
F	F	120·0–121·0	201·0–203·5	8·3	247	247	12	12	2·4	1,300
F	Cl	148·0–149·4	226·0–227·5	8·3	247	247	12	12	1·4	300
F	CH_3	118·0–119·5	212·0–213·0	8·3	247	248	—	14	1·6	—

* Method described by Beckett[1].

† Aqueous suspension shaken for 4 h and allowed to stand at room temperature for 12 h at 20° ± 2°; the concentration in filtrate determined using ultraviolet spectrophotometry.

Chemistry

Compounds I were readily obtained by condensation in an apolar solvent, such as toluene, of 4-chloro- or 4-chloro-4′-fluorobutyrophenone with an appropriately substituted 4-phenylpiperidin-4-ol. The 4-chlorobutyrophenones were prepared by a Friedel–Craft reaction using 4-chlorobutyryl chloride and benzene or fluorobenzene,[2] whereas 4-phenylpiperidin-4-ol and its 4′-fluoro-, 4′-chloro- and 4′-methyl-derivatives were obtained in 3 steps from α-methylstyrene or its 4-fluoro-, 4-chloro- and 4-methyl-derivatives using a modification of the method described by Schmidle and Mansfield.[12–15] The appropriate α-methylstyrene was condensed with formaldehyde and ammonium chloride to give a 6-methyl-6-phenyltetrahydro-1,3-oxazine which was converted with excess acid to the corresponding 4-phenyl-1,2,3,6-tetrahydropyridine. Addition of hydrobromic acid gave the 4-bromo-4-phenylpiperidine hydrobromide which hydrolyses easily in water to yield the desired 4-phenylpiperidin-4-ol.

Experimental

4-Chlorobutyrophenone.[2] A solution of 4-chlorobutyrylchloride (71 g) in benzene (70 ml) was added with stirring and cooling to a suspension of aluminium chloride (71 g) in benzene (350 ml). Stirring was continued for 30 min at room temperature after the addition was complete and the reaction mixture poured into water containing ice. The benzene layer was separated, dried and filtered, the filtrate concentrated *in vacuo* and the residue distilled to yield 4-chlorobutyrophenone, (80 per cent) b.p. 134–137° (5 mm), n_D^{20} 1·541. *Anal.* Calcd. for $C_{10}H_{11}ClO$: Cl, 19·4 per cent. Found: Cl, 19·2 per cent.

4-Chloro-4′-fluorobutyrophenone. This was similarly obtained from fluorobenzene in 80–95 per cent yield as a colourless oil, b.p. 136–142° (6 mm), n_D^{20} 1·523. *Anal.* Calcd. for $C_{10}H_{10}ClFO$ Cl, 17·7; F, 9·5. Found: Cl, 17·4; F, 9·3.

4-Phenyl-1,2,3,6-tetrahydropyridine. A mixture of ammonium chloride (856 g) and 36 per cent formaldehyde (3,000 ml) was stirred and heated to about 60°. α-Methylstyrene (944 g) was slowly added with cooling to maintain this temperature. After the addition was complete, the mixture was stirred at room temperature until the temperature of the reaction mixture fell to 40°. Methanol (2,000 ml) was then added and stirring continued for 20 h. After removal of the methanol *in vacuo*, the residue was diluted with concentrated hydrochloric acid (3,000 ml). The mixture was heated with stirring at 100°, cooled, diluted with water (2,000 ml), made alkaline with sodium hydroxide (15 N) and extracted with benzene. The dried extract (K_2CO_3) was filtered and distilled *in vacuo* to yield 4-phenyl-1,2,3,6-tetrahydropyridine (46–50 per cent) as an oil, b.p. 97–112° (1 mm), n_D^{25} 1·586. Hydrochloride: m.p. 199–202°. *Anal.* Calcd. for $C_{11}H_{13}N$: equiv., 159. Found: equiv., 160. Ultraviolet spectrum: $\lambda_{max} = 248$ mμ (ε 11,700). The following compounds were prepared similarly: *4′-fluoro-4-phenyl-1,2,3,6-tetrahydropyridine:* b.p. 139–141° (4 mm). *Anal.* Calcd. for $C_{11}H_{12}FN$: equiv., 177. Found: equiv., 184. Ultraviolet spectrum: $\lambda_{max} = 245·5$ mμ (ε 10,100). *4′-chloro-4-phenyl-1,2,3,6-tetrahydropyridine:* b.p. 167–170° (8 mm). *Anal.* Calcd. for $C_{11}H_{12}ClN$: equiv., 194. Found: equiv., 197. Ultraviolet spectrum: $\lambda_{max} = 254·5$ mμ (ε 14,100). *4′-methyl-4-phenyl-1,2,3,6-tetrahydropyridine:* b.p. 162–170° (10 mm). *Anal.*

Calcd. for $C_{12}H_{15}N$: equiv., 173. Found: equiv., 176. Ultraviolet spectrum: $\lambda_{max} = 251$ mμ (ϵ 11,300).

4-Bromo-4-phenylpiperidine hydrobromide. Anhydrous hydrogen bromide gas was passed, at 10 to 20°, for 7 h through a stirred solution of 4-phenyl-1,2,3,6-tetrahydropyridine (160 g) in acetic acid (500 ml). After 16 h at room temperature the acetic acid and excess hydrogen bromide were removed *in vacuo* at 40° bath temperature. The residue was treated with ether and the cooled solution filtered to give crude 4-bromo-4-phenylpiperidine hydrobromide (65–70 per cent yield). Recrystallization from acetone–*iso*propanol gave the pure product, m.p. 209·5–210·5°. *Anal.* Calcd. for $C_{11}H_{14}BrN.HBr$: Br, 49·8; equiv., 321. Found: Br, 49·7; equiv., 320. The following compounds were prepared similarly: *4-bromo-4′-fluoro-4-phenylpiperidine hydrobromide:* m.p. 143–144°. *Anal.* Calcd. for $C_{11}H_{13}BrFN.HBr$: Br, 47; equiv., 339. Found: Br, 46·1; equiv., 333; *4-bromo-4′-chloro-4-phenylpiperidine hydrobromide:* m.p. 213–215°. *Anal.* Calcd. for $C_{11}H_{13}BrClN.HBr$: Br, 45·0; equiv., 356. Found: Br, 45·0; equiv., 354; *4-bromo-4′-methyl-4-phenylpiperidine hydrobromide:* m.p. 190–192°. *Anal.* Calcd. for $C_{12}H_{16}BrN.HBr$: Br, 47·7; equiv., 335. Found: Br, 48·2; equiv., 332.

4-Phenylpiperidin-4-ol. A solution of 4-bromo-4-phenylpiperidine hydrobromide (160 g) in water (3,000 ml) was treated with excess 20 per cent sodium hydroxide solution. The resulting precipitate was filtered, washed with water and recrystallized from toluene to give 4-phenylpiperidin-4-ol (78 per cent); m.p. 159–160°. *Anal.* Calcd. for $C_{11}H_{15}NO$: equiv., 177. Found: equiv., 177. Ultraviolet spectrum: $\lambda_{max} = 260$ mμ (ϵ 225). The following compounds were prepared similarly: *4′-fluoro-4-phenylpiperidin-4-ol:* m.p. 116·4–117·6°. *Anal.* Calcd. for $C_{11}H_{14}FNO$: equiv., 195. Found: equiv., 197. Ultraviolet spectrum: $\lambda_{max} = 266$ mμ (ϵ 815); *4′-chloro-4-phenylpiperidin-4-ol:* m.p. 134·4–136°. *Anal.* Calcd. for $C_{11}H_{14}ClNO$: equiv., 212. Found: equiv., 210. Ultraviolet spectrum: λ_{max} 269·5 mμ (ϵ 460); *4′-methyl-4-phenylpiperidin-4-ol:* m.p. 136–137°. *Anal.* Calcd. for $C_{12}H_{17}NO$: equiv., 191. Found: equiv., 193. Ultraviolet spectrum: λ_{max} 265·5 mμ (ϵ 295).

4-(4-Hydroxy-4-phenylpiperidino)butyrophenone. A mixture of 4-chlorobutyrophenone (8·7 g), 4-phenylpiperidin-4-ol (14·2 g)

and potassium iodide (0·1 g) in toluene (150 ml) was heated in a closed reaction vessel at 100–110°. The solid residue, obtained by filtration of the cooled reaction mixture, was washed with water and ether, and the ether layer added to the filtrate of the original reaction mixture. The dried (K_2CO_3) combined solutions were then filtered and concentrated to a quarter of their volume, cooled and the precipate filtered and recrystallized from di*iso*propyl ether to yield 4-(4-*hydroxy*-4-*phenylpiperidino*)*butyrophenone*, (70 per cent) m.p. 129·4–130·6°. *Anal.* Calcd. for $C_{21}H_{25}NO_2$: C, 78·0; H, 7·8; N, 4·3; equiv., 323. Found: C, 78·1; H, 7·8; N, 4·3; equiv., 324. Ultraviolet spectrum: $\lambda_{max} = 246$ mμ (ϵ 12,600). *Hydrochloride:* m.p. 182·0–184·0°. Calcd. for $C_{21}H_{25}NO_2$.HCl: Cl^- 9·9; equiv., 360. Found: Cl^- 9·8; equiv., 360. Prepared similarly were: *4-(4-hydroxy-4′-fluoro-4-phenylpiperidino)butyrophenone*, m.p. 117·4–118·6°. *Anal.* Calcd. for $C_{21}H_{24}FNO_2$: C, 73·9; H, 7·1; N, 4·1; equiv., 341. Found: C, 73·8; H, 7·1; N, 4·0; equiv., 342. Ultraviolet spectrum: $\lambda_{max} = 245$ mμ (ϵ 13,300). *Hydrochloride:* m.p. 188·0–190·0. *Anal.* Calcd. for $C_{21}H_{24}FNO_2$.HCl: Cl^-, 9·4; equiv., 378. Found: Cl^-, 9·3; equiv., 384; *4-(4-hydroxy-4′-chloro-4-phenylpiperidino)butyrophenone:* m.p. 128·2–130·2°. *Anal.* Calcd. for $C_{21}H_{24}ClNO_2$: C, 70·5; H, 6·8; N, 3·9; equiv., 358. Found: C, 70·4; H, 6·7; N, 3·9; equiv., 358. Ultraviolet spectrum: $\lambda_{max} = 245·5$ mμ (ϵ 13,400). *Hydrochloride:* m.p. 216·5–218·0°. *Anal.* Calcd. for $C_{21}H_{24}ClNO_2$·HCl: Cl^-, 9·0; equiv., 394. Found: Cl^- 9·0; equiv., 397; *4-(4-hydroxy-4′-methyl-4-phenylpiperidino)butyrophenone:* m.p. 101·0–102·5°. *Anal.* Calcd. for $C_{22}H_{27}NO_2$: C, 78·3; H, 8·1; N, 4·2; equiv., 337. Found: C, 78·2; H, 8·1; N, 4·2; equiv., 339. Ultraviolet spectrum: $\lambda_{max} = 245$ mμ (ϵ 13,000). *Hydrochloride:* m.p. 179·6–181·5°. *Anal.* Calcd. for $C_{22}H_{27}NO_2$.HCl: Cl^-, 9·5; equiv., 374. Found: Cl^-, 9·4; equiv., 380; *4-(4-hydroxy-4-phenylpiperidino)-4′-fluorobutyrophenone:* m.p. 135·6–136·2°. *Anal.* Calcd. for $C_{21}H_{24}FNO_2$: C, 73·9; H, 7·1; N, 4·1; equiv. 341. Found: C, 73·7; H, 7·1; N, 4·1; equiv., 338. Ultraviolet spectrum: $\lambda_{max} = 246·5$ mμ (ϵ 12,500). *Hydrochloride:* m.p. 204·5–205·5°. *Anal.* Calcd. for $C_{21}H_{24}FNO_2$.HCl: Cl^-, 9·4; equiv., 378. Found: Cl^-, 9·3; equiv., 381; *4-(4-hydroxy-4′-fluoro-4-phenylpiperidino)-4′-fluorobutyrophenone:* m.p. 120·0–121·0°. *Anal.* Calcd. for $C_{21}H_{23}F_2NO_2$: C, 70·2; H, 6·5; N, 3·9;

equiv., 359. Found: C, 70·1; H, 6·5; N, 4·0; equiv., 361. Ultraviolet spectrum: $\lambda_{max} = 247$ mμ (ϵ 12,400). *Hydrochloride:* m.p. 201·0–203·5°. *Anal.* Calcd. for $C_{21}H_{23}F_2NO_2$.HCl: Cl^- 9·0; equiv., 396. Found: Cl^-, 9·0; equiv., 394; *4-(4-hydroxy-4'-chloro-4-phenylpiperidino)-4'-fluorobutyrophenone:* m.p. 148·0–149·4°. *Anal.* Calcd. for $C_{21}H_{23}ClFNO_2$: C, 67; H, 6·2; N, 3·7; equiv., 376. Found: C, 67·1; H, 6·2; N, 3·8; equiv., 376. Ultraviolet spectrum: $\lambda_{max} = 247$ mμ (ϵ 11,900). *Hydrochloride:* m.p. 226·0–227·5°. *Anal.* Calcd. for $C_{21}H_{23}ClFNO_2$.HCl: Cl^-, 8·6; equiv., 412. Found: Cl^-, 8·4; equiv., 417. *4-(4-hydroxy-4'-methyl-4-phenylpiperidino)-4'-fluorobutyrophenone:* m.p. 118·0–119·5°. *Anal.* Calcd. for $C_{22}H_{26}FNO_2$: C, 74·3; H, 7·4; N, 3·95; equiv., 355. Found: C, 74·2; H, 7·4; N, 3·9; equiv., 350. Ultraviolet spectrum: $\lambda_{max} = 246·5$ mμ (ϵ 12,200). *Hydrochloride:* m.p. 212·0–213·0°. *Anal.* Calcd. for $C_{22}H_{26}FNO_2$.HCl: Cl^-, 9·1; equiv., 392. Found: Cl^-, 9·1; equiv., 385. Ultraviolet spectrum: $\lambda_{max} = 247·5$ mμ (ϵ 13,500).

Melting points were determined with a Hershberg apparatus. Ultraviolet spectra were measured with a ratio recording Beckman DK–2 instrument, a solvent mixture of 90 ml *iso*propanol and 10 ml HCl 0·1 N being used.

Pharmacology

Methods

All pharmacological results to be described were obtained in adult white mice of both sexes. The substances under investigation were administered in aqueous solution by subcutaneous injection (10 ml per kg body weight). The 5 screening methods adopted were chosen for the following reasons:

(1) In view of the desirability to obtain quantitative data on a large number of new compounds, preference was given to relatively simple methods.

(2) Experimental evidence showed these 5 methods to be reproducible within this laboratory. All results to be described were systematically duplicated on a blind basis with an interval of about one month and the more important compounds were retested several times in various seasons over a period of up to 4

years. Very few statistically significant (P 0·05) differences were found between successively obtained data.

(3) All CNS depressants investigated in this laboratory are active in at least one of the 5 screening tests used. Qualitatively different results, allowing for gross classification of a new compound, are obtained in this series of tests with various types of known CNS depressants such as morphine-like narcotics, hypnotics, neuroleptics (e.g. certain phenothiazine derivatives), sedatives with atropine-like activity (e.g. benactyzine, scopolamine, promethazine), muscular relaxants (e.g. meprobamate), antihistaminics (e.g. hydroxyzine), etc.

(4) The effects of administration were measured at several intervals after dosage in order to obtain data on peak effect and duration of action and to minimize the risk of 'missing' significant activity.

Tests

The pharmacological tests are described below:

The results were statistically evaluated using the graphical method of Litchfield and Wilcoxon,[10] and expressed using the following symbols: ED50: median effective dose (mg/kg); L.L. and U.L.: lower and upper fiducial (confidence) limits (P = 0·05); S: slope; f_s: factor for computing confidence limits (P = 0·05).

(A) *Inhibition of righting reflex in mice.* Groups of 10 female white mice (24 ± 5 g) were injected subcutaneously with a given dose of the substance under investigation. At constant intervals after dosage ($\frac{1}{4}$, $\frac{1}{2}$, 1, 2, 3, 4 and 5 h) each animal was placed gently on its back on an undulated surface made of white iron and kept at constant temperature (30°). Loss of righting reflex is said to have occurred if the mouse remains on its back for more than 30 sec. Such a 'positive' response did not occur after injection of solvent in a series of over 300 mice. A geometric series of doses (80, 40, 20 – mg/kg) was investigated using one or more groups of 10 mice per dose. The median effective dose (HED50 in mg/kg subcutaneously) inducing loss of righting reflex at one or more timed intervals after injection was calculated.

(B) *Potentiation of the hypnotic effect of pentobarbital in mice.* Loss of righting reflex, as defined above, did not occur after intravenous injection of 10 mg/kg pentobarbital in a series of 300

untreated white mice. Loss of righting reflex, however, may occur after this dose of pentobarbital in animals pre-treated with a suitable dose of certain compounds not inducing loss of righting reflex when given alone. Such compounds are said to potentiate the hypnotic effect of pentobarbital in mice.

A geometric series of doses (40, 20, 10 – mg/kg subcutaneously) was given to groups of 10 mice and 30 min thereafter the same animals were treated with 10 mg/kg pentobarbital intravenously. The righting reflex of each animal was measured as described above at the following intervals: 15 min after subcutaneous injection, immediately after intravenous injection of pentobarbital, and ½, 1½, 2½ and 3½ h thereafter. The median effective doses (PED50 in mg/kg) were calculated.

(C) *Pentobarbital potentiation ratio (PPR).* The ratio (HED50: PED50) is defined as the pentobarbital potentiation ratio (PPR).

(D) *'Hot plate' method and mydriatic activity.* The influence of subcutaneous doses (40, 20, 10 – mg/kg) of the substances under investigation on the typical reflex behaviour of mice dropped on a 'hot plate' at 55° was investigated using a previously described method.[6,7] The median effective doses are symbolized as AED50 (mg/kg). Mydriatic activity was studied in the same animals using the method described in previous publications,[6,7] and the results are expressed in MED50-values (mg/kg).

(E) *Influence on induced coordinated activity (rotating rod).* Male and female albino mice (22 ± 5 g) were used. The untreated animals were placed on a horizontal wooden rotating rod (32 mm diam; 5 rev/min) at 30 min intervals. Animals remaining in equilibrium on the rod during 3 or more min in 2 successive trials are selected and divided in groups of five. Each group was then injected subcutaneously (40, 20, 10 – mg/kg) and placed on the rotating rod ½, 1, 1½, 2 and 2½ h after dosage. The induced coordinated activity of an animal, failing more than once to remain on the rod for 3 min in 5 trials at the time intervals indicated, is said to be significantly affected (positive effect). Using this all-or-none criterion of effectiveness, median effective doses (RED 50 in mg/kg) were calculated. In a control series of 1,000 mice, observed over a period of about one year, only 28 positive effects occurred.

Results

The results tabulated in Tables II, III and IV were obtained with the 8 selected compounds of structure I as well as with a series of 20 known CNS depressants, including 9 derivatives of phenothiazine, 4 narcotics, 2 hypnotics, 3 parasympatholytics, meprobamate and hydroxyzine. These 20 compounds are included for comparison and were selected at random on a rather arbitrary basis.

The 8 compounds of structure I obviously have similar pharmacological properties in this series of tests. Significant quantitative differences do, however, occur.

(1) Compounds I potentiate pentobarbital-hypnosis at very low dose levels (0·23–1·4 μ mol/kg), the 4 fluoro-derivatives (L = F) being 2·3 to 3·3 times more active than the 4 unsubstituted

Table II. Pharmacological screening data in mice (subcutaneous injection)

Structure I		ED50		Fiducial limits of ED50 (P = 0·05)		Slope and slope function		Number of mice used
L	R	Test*	mg/kg	L.L.†	U.L.†	S†	f_s†	
H	H	H	6·2	4·1	9·4	3·1	1·5	120
		P	0·50	0·30	0·83	4·1	2·3	80
		A	2·2	1·5	3·3	2·8	1·5	90
		R	3·6	2·2	5·7	2·1	1·7	40
		M	inact.	—	—	—	—	—
H	F	H	20	13	31	3·1	2·0	70
		P	0·42	0·29	0·61	2·4	1·4	120
		A	3·4	2·6	4·5	1·9	1·2	85
		R	5·1	4·0	6·6	2·1	1·2	100
		M	inact.	—	—	—	—	—
H	Cl	H	11	7·1	17	3·5	1·9	100
		P	0·26	0·18	0·36	2·6	1·4	100
		A	2·2	1·6	2·9	2·3	1·3	125
		R	5·0	3·0	8·5	3·8	2·2	80
		M	inact.	—	—	—	—	—
H	CH_3	H	13	9·0	19	2·3	1·5	80
		P	0·20	0·13	0·31	3·5	1·7	120
		A	2·1	1·6	2·6	1·7	1·2	70
		R	8·8	6·0	13	1·9	1·4	50
		M	inact.	—	—	—	—	—

Table II—*continued*

Structure I		ED50		Fiducial limits of ED50 (P = 0·05)		Slope and slope function		Number of mice used
L	R	Test*	mg/kg	L.L.†	U.L.†	S†	f_s†	
F	H	H	2·0	1·3	3·2	5·2	2·4	90
		P	0·20	0·14	0·29	2·4	1·6	80
		A	1·1	0·77	1·4	1·7	1·2	75
		R	1·4	0·95	2·1	1·6	1·4	30
		M	inact.	—	—	—	—	—
F	F	H	1·5	1·1	2·1	2·1	1·3	120
		P	0·13	0·09	0·18	2·2	1·5	80
		A	0·84	0·66	1·1	1·7	1·1	95
		R	1·2	0·74	2·0	1·8	1·5	50
		M	inact.	—	—	—	—	—
F	Cl‡	H	4·4	3·5	5·6	2·6	1·4	160
		P	0·10	0·08	0·13	2·3	1·3	190
		A	0·53	0·43	0·66	2·6	1·2	270
		R	0·40	0·28	0·57	3·9	1·5	175
		M	inact.	—	—	—	—	—
F	CH_3	H	6·0	4·2	8·6	2·7	1·5	100
		P	0·09	0·06	0·15	4·4	1·9	120
		A	0·80	0·62	1·0	1·8	1·2	110
		R	1·4	0·65	3·0	8·5	4·5	60
		M	inact.	—	—	—	—	—
Acetopromazine		H	1·0	0·76	1·4	2·0	1·2	110
		P	0·30	0·21	0·43	2·7	1·5	100
		A	1·0	0·73	1·4	2·1	1·3	95
		R	0·50	0·29	0·86	2·4	2·0	40
		M	inact.	—	—	—	—	—
Atropine		M	0·10	0·08	0·11	1·4	1·1	130
Benactyzine		H	67	54	82	1·3	1·1	30
		P	50	38	64	1·3	1·2	30
		A	> 40	—	—	—	—	30
		R	54	37	80	1·9	1·4	40
		M	1·1	0·74	1·6	1·9	1·4	70
Chlorpromazine		H	2·7	2·2	3·3	2·0	1·2	250
		P	0·52	0·38	0·72	4·4	1·6	240
		A	2·2	1·9	2·6	2·4	1·1	265
		R	2·3	1·3	4·0	3·0	2·4	40
		M	inact.	—	—	—	—	—
Dextromoramide		H	2·0	1·2	3·2	2·2	1·4	70
		P	0·78	0·53	1·2	1·6	1·4	30
		A	0·53	0·47	0·61	2·2	1·1	485
		R	4·4	2·5	7·7	2·5	1·8	50
		M	0·82	0·75	0·90	1·8	1·1	490

Table II—*continued*

Structure I		ED50		Fiducial limits of ED50 (P = 0·05)		Slope and slope function		Number of mice used
L	R	Test*	mg/kg	L.L.†	U.L.†	S†	f_s†	
Hydroxyzine		H	>160	—	—	—	—	30
		P	⩾40§	—	—	—	—	40
		A	98	74	129	1·9	1·4	60
		R	~160	—	—	—	—	40
		M	inact.	—	—	—	—	—
Mepazine		H	162	99	266	1·8	1·7	40
		P	52	38	71	1·9	1·5	50
		A	50	44	58	1·4	1·2	50
		R	74	46	118	2·6	1·9	40
		M	inact.	—	—	—	—	—
Meprobamate		H	⩾160	—	—	—	—	30
		P	96	63	147	1·6	1·5	30
		A	>80	—	—	—	—	30
		R	~160	—	—	—	—	40
		M	inact.	—	—	—	—	—
Methadone		H	16	11	24	1·9	1·7	40
		P	3·1	2·2	4·3	1·5	1·2	40
		A	4·6	4·2	5·0	1·8	1·1	575
		R	14	7·7	24	2·5	2·0	40
		M	5·2	4·9	5·5	1·5	1·03	575
Morphine		H	45	29	68	2·3	2·0	30
		P	6·1	3·1	12	4·6	2·6	50
		A	10·5	9·9	11	1·8	1·1	1,005
		R	22	15	33	2·2	1·6	40
		M	15	14	16	2·1	1·1	870
Pentobarbital		H	28	22	34	1·5	1·2	30
		P	18	11	29	2·1	1·7	40
		A	37	27	50	1·4	1·2	30
		R	37	29	46	1·4	1·1	80
		M	inact.	—	—	—	—	—
Perphenazine		H	5·0	3·7	6·8	2·3	1·3	100
		P	0·50	0·34	0·73	2·4	1·6	80
		A	1·3	0·97	1·6	2·5	1·3	130
		R	0·46	0·30	0·69	3·9	0·7	120
		M	inact.	—	—	—	—	—
Pethidine		H	⩾160	(toxic)	—	—	—	30
		P	15	9·3	24	2·1	1·6	40
		A	22	20	25	1·9	1·1	655
		R	52	35	78	1·9	1·7	30
		M	24	22	25	1·5	1·0	655

Table II—*continued*

Structure I		ED50		Fiducial limits of ED50 (P=0·05)		Slope and slope function		Number of mice used
L	R	Test*	mg/kg	L.L.†	U.L.†	S†	f_s†	
Phenobarbital		H	48	35	66	2·5	1·4	90
		P	22	8·8	56	11·3	8·0	60
		A	67	55	82	1·4	1·2	40
		R	⩾80	—	—	—	—	50
		M	inact.	—	—	—	—	—
Prochlorperazine		H	14	11	19	2·0	1·3	80
		P	1·1	0·71	1·5	3·5	1·8	100
		A	3·7	2·8	4·9	2·3	1·3	110
		R	2·2	1·4	3·6	2·6	1·5	60
		M	inact.	—	—	—	—	—
Promazine		H	15	11	21	2·0	1·4	80
		P	2·4	1·7	3·3	2·6	1·6	80
		A	5·8	3·3	10	3·0	1·7	80
		R	4·7	3·5	6·3	2·2	1·4	80
		M	inact.	—	—	—	—	—
Promethazine		H	⩾160	—	—	—	—	70
		P	6·0	3·1	12	4·6	2·3	70
		A	13	11	16	2·4	1·3	210
		R	31	21	45	1·9	1·4	40
		M	7·6	6·4	9·0	2·0	1·2	210
Scopolamine		H	>80	—	—	—	—	20
		P	>80	—	—	—	—	30
		A	>80	—	—	—	—	20
		R	>160	—	—	—	—	20
		M	0·024	0·016	0·036	1·8	1·3	75
Thiopropazate		H	5·5	4·0	7·4	2·4	1·3	120
		P	0·53	0·38	0·73	2·1	1·4	80
		A	1·5	1·2	1·9	1·9	1·1	120
		R	0·95	0·63	1·4	3·8	1·9	100
		M	inact.	—	—	—	—	—
Trifluprom azine		H	2·2	1·6	3·1	1·7	1·2	110
		P	0·47	0·31	0·69	2·5	1·7	80
		A	1·0	0·77	1·4	1·6	1·2	90
		R	1·0	0·61	1·6	2·2	1·6	50
		M	inact.	—	—	—	—	—

* H: inhibition of righting reflex
P: potentiation of pentobarbital
A: hot plate method
R: rotating rod
M: mydriatic activity

† For definition see page 287.

‡ Serial number R 1625 (generic name: haloperidol) was selected for clinical trial. The first results, obtained in psychiatric patients, were described by Divry *et al.*[3, 4] and Paquay *et al.*[11].

§ Log dose *vs* probit effect curve not linear.

compounds (L = H) from which they are derived. *Para*-substitution with F, Cl or CH_3 in the phenyl ring attached to the piperidine nucleus also increases potency by 50, 100 and 150 per cent respectively.

Table III. Pentobarbital potentiation ratio (PPR)

Structure I		PPR	Limits of PPR (P = 0·05)		Slope ratio and function	
L	R		L.L.*	U.L.*	S*	f_s*
H	H	12	6·5	24	1·3	2·5
H	F	48	27	84	1·3	2·1
H	Cl	43	25	75	1·3	2·0
H	CH_3	65	37	115	1·5	1·9
F	H	10	5·4	18	2·1	2·7
F	F	12	7·3	19	1·0	1·6
F	Cl	42	30	60	1·2	1·5
F	CH_3	65	36	115	1·6	2·1
Promethazine		⩾26	—	—	—	—
Prochlorperazine		14	8·0	22	1·8	1·9
Pethidine		⩾11	—	—	—	—
Thiopropazate		10	6·6	16	1·1	1·5
Perphenazine		10	6·2	16	1·0	1·7
Morphine		7·3	3·3	16	2·0	3·2
Promazine		6·6	4·2	10	1·3	1·7
Methadone		5·2	3·1	6·7	1·3	1·7
Chlorpromazine		~5	—	—	—	—
Acetopromazine		3·4	2·1	5·4	1·4	1·6
Mepazine		3·1	1·7	5·6	1·1	1·9
Dextromoramide		2·6	1·4	4·7	1·4	1·6
Phenobarbital		2·2	0·81	5·7	4·6	8
Pentobarbital		1·5	0·91	2·6	1·5	1·7
Meprobamate		⩾1	—	—	—	—
Hydroxyzine		⩾1	—	—	—	—

* For definition see page 287.

(2) At about 5 times higher dose levels (AED50 = 1·4 to 8·9 μ mol/kg; AED50 : PED50 ≅ 5), all compounds of structure I were found to inhibit the typical reflexes of mice in the hot plate test.

Table IV. Pharmacological screening data (ED50-values) expressed in μmol per kg body weight

Substances	Molecular weight	Test ED50-values H	P	A	R	M *
I: L = H; R = H	360	17	1·4	6·1	10	inact.
H F	378	53	1·1	8·9	13	,,
H Cl	358	31	0·72	6·1	14	,,
H CH_3	374	35	0·53	5·6	21	,,
F H	378	5·3	0·53	2·9	3·7	,,
F F	396	3·8	0·33	2·1	3·0	,,
F Cl	376	11	0·27	1·4	1·1	,,
F CH_3	392	15	0·23	2·1	3·6	,,
Phenothiazines:						
Acetopromazine maleate	443	2·2	0·67	2·2	1·1	inact.
Chlorpromazine HCl	355	7·6	1·4	6·2	6·4	,,
Mepazine HCl	347	467	150	144	213	,,
Perphenazine 2HCl	477	10	1·0	2·7	0·96	,,
Prochlorperazine 2HCl	447	31	2·5	8·3	4·9	,,
Promazine HCl	321	47	7·5	18	15	,,
Promethazine HCl	321	⩾500	19	41	97	24
Thiopropazate 2HCl	519	11	1·0	2·9	1·8	inact.
Triflupromazine HCl	389	5·6	1·2	2·6	2·6	,,
Hypnotics:						
Pentobarbital sodium	248	110	70	145	145	inact.
Phenobarbital sodium	254	189	87	260	⩾320	,,
Atropine-like compounds:						
Atropine$\frac{1}{2}$ H_2SO_4	347			⩾230		0·29
Benactyzine HCl	364	184	137	>110	148	3·0
Scopolamine HBr.$3H_2O$	438	>180	>180	⩾180	>365	0·055
Narcotics:						
Dextromoramide	393	5·1	2·0	1·3	11	2·1
DL-methadone HCl	346	46	9·0	13	40	15
Morphine HCl.$3H_2O$	376	120	16	28	59	40
Pethidine HCl	284	⩾565	53	77	183	85
Others:						
Hydroxyzine 2HCl	448	>350	⩾90	220	~355	inact.
Meprobamate	218	⩾735	440	>365	~735	inact.

* For definitions see page 292.

Again, *para*-fluoro substitution in I (L = F) produced 4 substances 2 to 4 times more active than the 4 unsubstituted parent compounds. *Para*-F-, Cl- or CH_3-substitution in the second phenyl

ring (R = F, Cl, CH_3) has negligible influence on AED50, but greatly increases duration of action in the order: $Cl > CH_3 > F > H$ (unpublished results). Peak effects are observed between $\frac{1}{2}$ and 2 h after subcutaneous injection. It should be noted that the activity of these compounds in the hot plate and other tests is not antagonized by nalorphine (unpublished results).

(3) At slightly higher dose levels (RED50 = 1·1 to 21 μ mol/kg) the 8 compounds of type I were found to inhibit induced co-ordinated activity of mice placed on a rotating rod. Once again fluoro substitution in I (L = F) increased potency 2·7 to 13 times in the 4 pairs of compounds studied. On the other hand, RED50 values are hardly influenced, but duration of action is significantly increased ($Cl > CH_3 > F > H$) by substitution (R) in the other phenyl ring.

(4) At relatively high but still atoxic dose levels (HED50 = 3·8 to 53 μ mol/kg) the compounds I produce 'behavioural' loss of righting in mice. As in the other 3 tests, fluoro substitution in L (L = F) increases activity 2·3 to 14 times whereas F, Cl or CH_3 substitution in R (R = F, Cl, CH_3) leads to a small but significant decrease of activity in 5 out of 6 examples (Fig. 1). Duration of action was increased in the same order as described above: $Cl > CH_3 > F > H$.

(5) The 8 compounds of type I are devoid of mydriatic activity in mice at the relatively high but atoxic dose level of 40 mg/kg subcutaneously.

Based on the experimental evidence presented in this paper, the group of 8 compounds of structure I may be considered as a pharmacological entity and distinguished as follows from several known types or classes of CNS depressants:

(1) Unlike scopolamine, benactyzine and morphine-like analgesics, they are devoid of mydriatic activity in mice.[5] Furthermore, the Straub phenomenon and morphine-like excitement is not observed in this species after administration of compounds of type I.

(2) Unlike pheno- and pento-barbital but similar to the phenothiazines, compounds I are active in the hot plate and rotating rod experiments at dose levels (AED50 and RED50) much lower than those required to produce loss of righting reflex (HED50).

(3) Meprobamate and hydroxyzine are active only at very high dose levels in these tests. They are nearly devoid of pentobarbital potentiating activity as defined above.

(4) In this series of tests, however, the properties of compounds I are qualitatively similar to those of chlorpromazine and other active phenothiazines, such as acetopromazine, trifluprom azine,

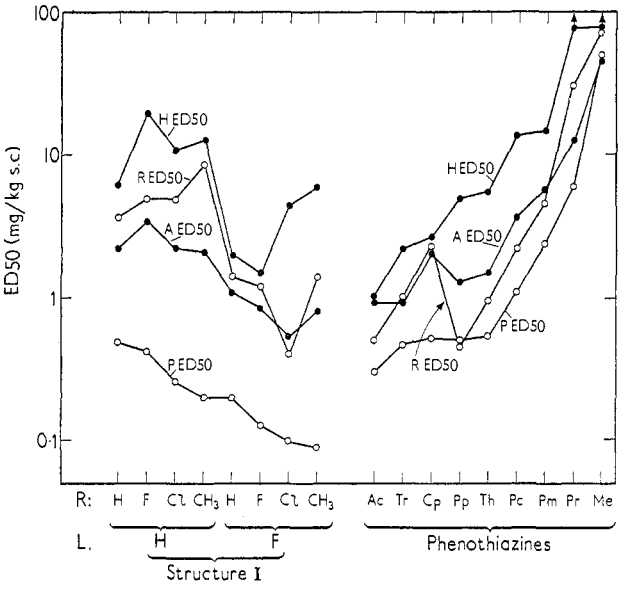


Fig. 1. Pharmacological activities of compounds of structure I and some phenothiazines.

Ac = Acetopromazine; Tr = Trifluprom azine; Cp = Chlorpromazine; Pp = Perphenazine; Th = Thiopropazate; Pc = Prochlorperazine; Pm = Promazine; Pr = Promethazine; Me = Mepazine.

perphenazine, thiopropazate, prochlorperazine and promazine. Mepazine has a very low potency and promethazine is an atropine-like mydriatic. With both compounds of type I, and the more active phenothiazines, typical sedation is observed at low dose levels. With increasing dosage, spontaneous and induced motor activity is progressively depressed until loss of righting reflex occurs. Most compounds of structure I, however, are several times more active as potentiators of pentobarbital hypnosis than the most active phenothiazine tested.

The order of magnitude of the respective ED50-values is as follows:

compound I: $HED50 > RED50 > AED50 \gg PED50$
phenothiazines: $HED50 > AED50 \geqslant RED50 > PED50$

Further evidence is obviously required to characterize the activity of the new compounds in detail. Such evidence will be presented in subsequent papers of this series.

Summary. Some pharmacological properties in mice of a series of 8 compounds related to 4-(4-hydroxy-4-phenylpiperidino)butyrophenone are described. These substances possess potent CNS depressant effects in low doses. A suitable method of synthesis is outlined.

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