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The Synthesis and Pharmacological Actions of *Ortho*-Substituted Phenethylhydrazines

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Introduction

Substances related to amphetamine have been known for some time to cause inhibition of monoamine oxidase (MAO). It was found, in our laboratories, that *o*-methoxy-α-methylphenethylmethylamine hydrochloride* was a moderately good MAO inhibitor. Recently, α-methylphenethylhydrazine† (JB–516) was reported[1, 2] to be a very potent inhibitor of this enzyme. The present series of compounds, also related to amphetamine and containing various *ortho* substituents, was synthesized in the hope of obtaining more potent and more specific MAO inhibitory action.

The compounds prepared were screened against monoamine oxidase and 5-hydroxytryptophan decarboxylase both *in vitro* and *in vivo*. Effects of the compounds on spontaneous motor activity and hexobarbital sleeping time were also determined.

Chemical Synthesis

Intermediate *ortho*-substituted phenylacetones were prepared by the known[3] method of condensing a suitable benzaldehyde with nitroethane and submitting the product to reductive hydrolysis with iron and hydrochloric acid (Table I).

Most of the hydrazines in Table II were prepared by reaction of an *ortho*-substituted phenylacetone with hydrazine or a substituted hydrazine, followed by catalytic hydrogenation of the hydrazone. Special methods used to obtain certain compounds are described in the experimental section.

* Orthoxine Hydrochloride ® † Catron ®

Experimental*

Substituted phenylacetones (Table I). The preparation of 2-fluorophenylacetone is typical of the procedure used for these intermediates.

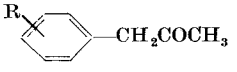
A mixture of *o*-fluorobenzaldehyde (100 g, 0·805 mole), toluene, (300 ml), *n*-butylamine (24 ml) and nitroethane (79·3 g, 1·06 mole) was heated under reflux until the calculated amount of water was collected in a Dean–Stark water trap (*ca.* 18 to 24 h). The cooled solution was mixed with water (875 ml), 100-mesh iron powder (326 g) and ferric chloride hexahydrate (3·3 g), and then stirred and warmed to 80°. The stirred mixture was treated with conc. HCl (292 ml) at such a rate that refluxing was maintained. (*Caution:* There is a variable induction period at the beginning of the addition before the exothermic reaction sets in.) After addition of the HCl, the mixture was stirred and refluxed for ½ h, then steam-distilled until a total of 8 l. of distillate was collected. The organic layer was separated and the aqueous layer was extracted with four 500-ml portions of benzene. The combined organic layers were washed twice with 1-l. portions of 3 per cent sodium bisulphite solution, then water, and dried over anhydrous magnesium sulphate. After evaporation of solvent, distillation gave 63·3 g (52 per cent) of a colourless oil, b.p. 47°/0·05 mm.

o-Methoxyphenylacetone was prepared by the published procedure.[3]

(o-*Methoxy-α-methylphenethyl*)-*hydrazine. Method A.* A solution of hydrazine hydrate (25 g, 0·5 mole) in methanol (75 ml) was added, at one time, to a boiling solution of *o*-methoxyphenylacetone (82 g, 0·5 mole) in methanol (150 ml). After the initial reaction subsided, the solution was heated under reflux for 1 h, then cooled, mixed with PtO_2 (1 g) and glacial acetic acid (35 g, 0·58 mole) and hydrogenated, starting at 50 lb/in² pressure. The calculated amount of hydrogen was absorbed in 3 h. After removal of catalyst, the solution was concentrated, made strongly alkaline with sodium hydroxide and extracted with three 100-ml portions of chloroform. The combined chloroform extracts were washed once with water, dried (Na_2SO_4 anhyd.) and evaporated. Distillation of the residue gave a crude base fraction which boiled

* All temperatures are uncorrected.

Table I. Intermediate phenylacetones



R	Formula	b.p., °C/mm	n_D^{25}	Yield, %	Analysis, % Calcd. C	Calcd. H	Calcd. Halogen	Found C	Found H	Found Halogen	m.p., °C 2,4-DNPH
o-F	C_9H_9FO	47/0·05	1·4974	52	71·04	5·96	12·49	71·29	6·11	12·79	129–133[a]
o-Cl[c]	C_9H_9ClO	81–85/0·35	1·5346	56	64·11	5·38	21·02	63·84	5·77	21·39	—
o,*o*′-Cl_2	$C_9H_8Cl_2O$	95–105/0·2	—	57	53·23	3·97	34·92	53·21	3·98	35·51	—
o,*p*-Cl_2	$C_9H_8Cl_2O$	70–89/0·6[b]	1·5530[b]	45	—	—	—	—	—	—	151[c]
o,*o*′-$(OCH_3)_2$	$C_{11}H_{14}O_3$	108–114/0·25	1·5280	47	68·02	7·27	—	67·86	7·17	—	[d]

[a] Recrystallized from isopropyl alcohol.
[b] Contained approximately 15% of unreacted 2,6-dichlorobenzaldehyde.
[c] Recrystallized from 95% ethanol.
[d] Semicarbazone: m.p. 196–197°, from 95% ethanol.
[e] R. T. Gilsdorf and F. F. Nord, *J. Amer. chem. Soc.*, **74**, 1837 (1952), reported b.p. 103–4°/6·0 mm for this compound.

at 85–105°/0·08 mm. The base was dissolved in anhydrous ether and treated with ethereal HCl to give the hydrochloride. Recrystallization from ethyl acetate gave 44·2 g of pure product, m.p. 108–110°.

The hydrobromide, prepared similarly, melted at 119–120° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{10}H_{16}N_2O \cdot HBr$: C, 45·99; H, 6·56; N, 10·73. Found: C, 46·09; H, 6·56; N, 10·77.

The phosphate, recrystallized from 95 per cent ethanol, melted at 135–145° (d.).

Anal. Calcd. for $C_{10}H_{16}N_2O \cdot H_3PO_4$: C, 43·16; H, 6·88; N, 10·07. Found: C, 43·01; H, 7·08; N, 10·13.

A maleate salt melted at 81–82° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{10}H_{16}N_2O \cdot C_4H_4O_4$: C, 56·74; H, 6·80; N, 9·46. Found: C, 56·92; H, 7·17; N, 9·68.

1-(o-Methoxy-α-methylphenethyl)-2-methylhydrazine. Method B. A 0·5 mole run, using methylhydrazine, was made as described in Method A. However, the intermediate hydrazone was distilled before hydrogenation to give 86·5 g (96 per cent), b.p. 99–101°/0·08 mm.; n_D^{26} 1·5457. The hydrazone was then dissolved in 95 per cent ethanol with a slight excess of acetic acid, mixed with PtO_2 and hydrogenated as in Method A.

1-Isopropyl-2-(o-methoxy-α-methylphenethyl)-hydrazine. Method C. A solution of (*o*-methoxy-α-methylphenethyl)-hydrazine hydrochloride (27·1 g, 0·1 mole) in water was rendered alkaline with NaOH and the base was extracted into chloroform. After evaporation of the chloroform, the base was mixed with methanol (100 ml) and acetone (6·3 g, 0·11 mole) and heated under reflux for 3 h. The cooled solution was mixed with glacial acetic acid (7·2 g, 0·12 mole) and PtO_2 (0·5 g) and hydrogenated, starting at 50 lb/in² pressure. Hydrogen absorption was complete in ½ h. The catalyst was removed and the product isolated as described in Method A.

1-(o-Methoxy-α-methylphenethyl)-1-methylhydrazine. Method D. A solution of *N*-[β-(*o*-methoxyphenyl)isopropyl] methylamine hydrochloride (43·2 g, 0·2 mole)[3] in water (170 ml) and 30 per cent sulphuric acid (51 g) was maintained at 5 to 10° and stirred during the addition of a solution of sodium nitrite (34 g, 0·5 mole)

in water (60 ml) over a 30 min period. After the addition, the mixture was stirred at 20° for 2 h, then extracted with two 250-ml portions of ether. The combined ether extracts were washed with 40 per cent potassium hydroxide solution (50 ml), dried (K_2CO_3 anhyd.) and evaporated on a steam bath. The residual crude *N*-nitroso intermediate was dissolved in anhydrous ether (300 ml) and added, over a 1 h period, to a stirred solution of lithium aluminium hydride (8·7 g, 0·23 mole) in anhydrous ether (500 ml). After the addition, the mixture was stirred and heated under reflux for 1 h, then decomposed by the careful addition of 2·2 g (0·25 mole) of ethyl acetate, then 45 g (2·5 moles) of water. The mixture was filtered, and the filtrate dried ($MgSO_4$ anhyd.), evaporated, and the residue distilled to give 15·6 g of crude base, b.p. 85–100°/0·07 mm. The base was dissolved in anhydrous ether and treated with ethereal HCl to give the hydrochloride, m.p. 141–142° after recrystallization from isopropyl alcohol.

1-(o-Methoxy-α-methylphenethyl)-1,2,2,-trimethylhydrazine. Method E. 1-(*o*-Methoxy-α-methylphenethyl)-2,2-dimethylhydrazine hydrochloride (compound 5, Table II) (4·9 g, 0·02 mole), was dissolved in a small amount of water, rendered alkaline with sodium hydroxide and extracted with chloroform. The combined chloroform extracts were washed once with water, then concentrated. The residual base was mixed with 37 per cent formaldehyde solution (3·6 g, 0·044 mole) and 98 per cent formic acid (4·6 g, 0·10 mole) and heated under reflux for 16 h. After cooling, the mixture was rendered alkaline with sodium hydroxide, extracted with chloroform, and the combined extracts were washed once with water and concentrated. The crude base was converted to its hydrochloride in the usual way to give 52 per cent of pure product, m.p. 99–101° after recrystallization from ethyl acetate.

3,4,5-Trimethoxyphenethylhydrazine. Method F. (*a*) *β-(3,4,5-Trimethoxyphenyl)-ethanol.* A Soxhlet apparatus containing 3,4,5-trimethoxyphenylacetic acid (45·2 g, 0·2 mole) was attached to a flask containing a solution of lithium aluminium hydride (11·2 g, 0·3 mole) in anhydrous ether (1·5 l). After 12 h, 32·6 g (0·144 mole) of acid had been extracted into the lithium aluminium hydride solution. The stirred solution was decomposed by the careful addition of ethyl acetate (35·2 g, 0·4 mole), then sufficient 10 per cent HCl to dissolve all solids. The ether layer was

separated, dried ($MgSO_4$ anhyd.) and evaporated. Distillation of the residue gave 10·2 g (33·5 per cent) of a somewhat impure, viscous product, b.p. 126–127°/0·06 mm; n_D^{25} 1·5382.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·60. Found: C, 61·07; H, 7·52.

A sample of the product was converted to its *p*-nitrobenzoate in 80 per cent yield by the method described by Shriner and Fuson.[4] The yellow product melted at 100–101° after recrystallization from methanol.

Anal. Calcd. for $C_{18}H_{19}NO_7$: C, 59·83; H, 5·30; N, 3·88. Found: C, 59·96; H, 5·39; N, 4·05.

Slotta and Müller[5] reported m.p. 100° for this *p*-nitrobenzoate obtained from crude β-(3,4,5-trimethoxyphenyl)-ethanol prepared by the action of nitrous acid on mescaline.

(*b*) *3,4,5-Trimethoxyphenethyl mesylate.* A solution of β-(3,4,5-trimethoxyphenyl)-ethanol (9·5 g, 0·045 mole) in pyridine (100 ml) was cooled in an ice bath and stirred during the addition of 6·2 g (0·054 mole; 20 per cent excess) of methanesulphonyl chloride over a 5-min period. After the addition, the mixture was stirred at room temperature for 1 h, then poured into 1·5 l. of ice water. Since no precipitate appeared, the mixture was extracted with four 250-ml portions of chloroform and the combined extracts were concentrated under reduced pressure. The residual solid was triturated with anhydrous ether, insoluble material was removed by filtration, and the filtrate refrigerated to give 1·6 g of white needles, m.p. 77·78°.

Anal. Calcd. for $C_{12}H_{18}O_6S$: C, 49·64; H, 6·25; S, 11·04. Found: C, 49·54; H, 6·00; S, 11·00.

(*c*) *3,4,5-Trimethoxyphenethylhydrazine hydrochloride.* A mixture of 3,4,5-trimethoxyphenethyl mesylate (1·0 g, 0·0034 mole) and anhydrous hydrazine (11 g, 0·34 mole) was heated on the steam bath for ½ h, then allowed to stand at room temperature overnight. After an additional 3 h of heating, the solution was cooled, dissolved in water (200 ml) and extracted with one 100-ml and three 50-ml portions of chloroform. The combined extracts were washed once with water and evaporated. The residual oil was dissolved in anhydrous ether, treated with ethereal HCl and the precipitated hydrochloride was recrystallized from ethyl acetate to give 0·5 g (55 per cent) of pure product, m.p. 96–98°.

Anal. Calcd. for $C_{11}H_{18}N_2O_3 \cdot HCl$: C, 50·29; H, 7·29; N, 10·67. Found: C, 50·08; H, 6·99; N, 10·43.

1,2-Bis(o-*methoxy-α-phenethyl*)-*hydrazine.* This substance was prepared by Method B except that the molar amount of hydrazine hydrate was reduced by one-half.

1-(o-*Methoxy-α-methylphenethyl*)-*semicarbazide Method G.* (*a*) o-*Methoxyphenylacetone semicarbazone.* A mixture of semicarbazide hydrochloride (41·5 g, 0·37 mole) and sodium acetate trihydrate (50·6 g, 0·37 mole) was ground in a mortar until syrupy. The mixture was triturated with methanol (250 ml), then filtered into a solution of *o*-methoxyphenylacetone (47 g, 0·29 mole). After standing at room temperature for 3 h and at 4° overnight, the precipitated solid was separated by filtration to give 57 g (90 per cent) of pure semicarbazone, m.p. 161–163°.

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59·71; H, 6·83; N, 18·99. Found: C, 59·95; H, 6·80; N, 18·83.

(*b*) *1*-(o-*Methoxy-α-methylphenethyl*)-*semicarbazide.* A mixture of *o*-methoxyphenylacetone semicarbazone (22·2 g, 0·1 mole), 95 per cent ethanol (500 ml), glacial acetic acid (12 g, 0·1 mole) and PtO_2 (1 g) was hydrogenated, starting at 50 lb/in^2 pressure. Hydrogen absorption was complete in 1 h. The catalyst was removed and the filtrate concentrated on the steam bath under an air-stream. The cooled residue was diluted with 100 ml of water, rendered alkaline with sodium hydroxide and the precipitated crude base was recrystallized from aqueous methanol to give 18·3 g (82 per cent) of product melting at 118–119°.

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 59·17; H, 7·68; N, 18·82. Found: C, 59·09; H, 7·06; N, 18·20.

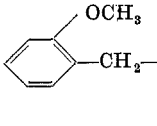
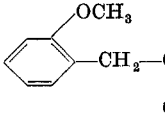
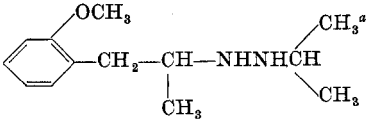
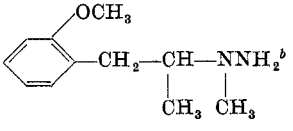
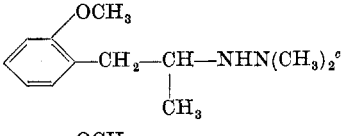
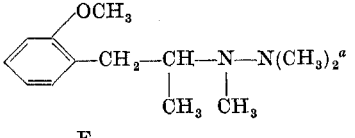
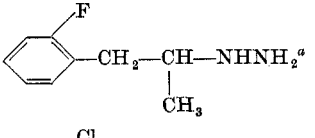
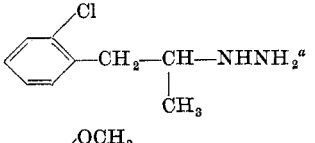
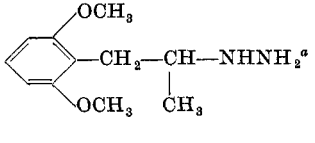
The *hydrochloride* was prepared by treating a solution of the base in ethanol with ethereal HCl and diluting the solution with anhydrous ether. After recrystallization from absolute ethanol–anhydrous ether, the salt melted at 188–189°.

Pharmacology

Methods

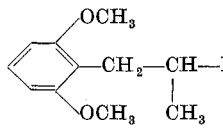
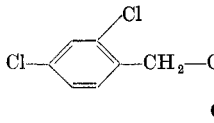
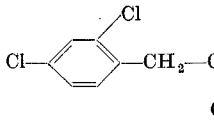
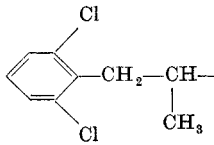
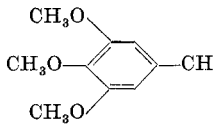
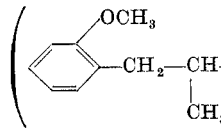
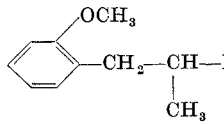
Inhibition of monoamine oxidase activity in vitro. Monoamine oxidase activity was determined by the method of Bhagvat *et al.*[6] using the Warburg apparatus. Vessels of about 15-ml capacity

Table II. Phenethylhydrazines

No.	Hydrochlorides	Formula	m.p., °C	Procedure	b.p. of base, °C/mm
1.		$C_{10}H_{17}ClN_2O$	108–110	A	85–104/0·08
2.		$C_{11}H_{19}ClN_2O$	107–109	B	91–99/0·07
3.		$C_{13}H_{23}ClN_2O$	111–113	C	74–78/0·05
4.		$C_{11}H_{19}ClN_2O$	141–142	D	85–100/0·07
5.		$C_{12}H_{21}ClN_2O$	154–155	B[f]	73–76/0·05
6.		$C_{13}H_{23}ClN_2O$	99–101	E	—
7.		$C_9H_{14}ClFN_2$	105–107	A	64–67/0·1
8.		$C_9H_{14}Cl_2N_2$	120–121	A	72–91/0·04
9.		$C_{11}H_{19}ClN_2O_2$	114–116	A	104–125/0·05

Analysis, %						Approx. LD_{50}, mg/kg i.p., mice	Monoamine oxidase inhibition (*in vitro*)		5-HTP inhibition (*in vitro*)	
Calcd.			Found				% Inhibition at 10^{-3}M	$[I]_{50}$	% Inhibition at 10^{-2}M	$[I]_{50}$
C	H	N	C	H	N					
55·42	7·91	12·93	55·31	8·21	12·99	100	100	3×10^{-6}	83	2×10^{-5}
57·25	8·30	12·14	57·57	8·04	11·88	200	31	—	82	—
60·33	8·96	10·83	60·24	8·60	10·36	200	62	—	74	2×10^{-3}
57·25	8·30	12·14	57·44	8·16	12·14	200	100	2×10^{-5}	100	1×10^{-5}
58·88	8·65	11·45	58·96	8·63	12·09	650	0	—	5	—
60·33	8·96	10·83	60·13	8·63	10·90	533	0	—	3	—
52·81	6·89	13·69	52·90	7·12	13·73	167	100	3×10^{-6}	not done	—
48·88	6·38	12·67	48·71	6·28	12·59	200	97	5×10^{-6}	100	3×10^{-5}
53·54	7·76	11·36	53·57	7·66	11·07	77	87	4×10^{-5}	100	3×10^{-5}

Table II—*continued*

No.	Hydrochlorides	Formula	m.p., °C	Procedure	b.p. of base, °C/mm
10.		$C_{13}H_{23}ClN_2O_2$	195–196	B[d, g]	94–98/0·06
11.		$C_9H_{13}Cl_3N_2$	125–150	A	93–115/0·05
12.		$C_{11}H_{17}Cl_3N_2$	135–136	A	72–91/0·03
13.		$C_9H_{13}Cl_3N_2$	130–133	A	93–118/0·0
14.		$C_{11}H_{19}ClN_2O_3$	96–98	F	—
15.		$C_{20}H_{29}ClN_2O_2$	129–131	B[h]	173–176/0·0
16.		$C_{11}H_{18}ClN_3O_2$	118–119	G	—

[a] Recrystallized from ethyl acetate. [b] Recrystallized from isopropyl alcohol. [c] Recrystallized from methyl ethyl ketone. [d] The hydrazone, obtained in 89% yield, boiled at 124–128°/0·06 mm. [e] Recrystallized from ethyl acetate–anhyd. ether. [f] The intermediate dimethylhydrazone boiled at 76–79°/0·05 mm; n_D^{23} 1·5250. [g] The intermediate dimethylhydrazone boiled at 124–128°/0·06 mm. [h] The intermediate azine boiled at 193–199°/0·1 mm; n_D^{26} 1·5734. [i] Recrystallized from absolute ethanol–anhydrous ether.

Analysis, %						Approx. LD_{50}, mg/kg i.p., mice	Monoamine oxidase inhibition (*in vitro*)		5-HTP inhibition (*in vitro*)	
Calcd.			Found				% Inhibition at 10^{-3}M	$[I]_{50}$	% Inhibition at 10^{-2}M	$[I]_{50}$
C	H	N	C	H	N					
56·82	8·44	10·20	57·13	8·48	10·88	167	0	—	9	—
42·29	5·13	10·96	41·82	5·06	10·58	300	95	5×10^{-6}	100	2×10^{-5}
46·58	6·04	9·88	46·72	6·14	9·90	200	0	—	0	—
42·29	5·13	10·96	42·48	5·44	11·15	not done	98	6×10^{-6}	not done	—
50·29	7·29	10·67	50·08	6·99	10·43	not done	100	3×10^{-5}	100	2×10^{-5}
65·83	8·01	7·68	65·71	7·93	7·39	233	0	—	63	—
50·86	6·98	16·18	50·73	6·59	16·30	533	0	—	11	—

with one side bulb were used. The source of enzyme was guinea pig liver which was homogenized in Na–K phosphate buffer pH 7·4, 0·25 M to give a 20 per cent suspension. Each vessel contained 1 ml of liver homogenate, 0·1 ml of M/15 NaCN solution, 0·5 ml of phosphate buffer and either 0·2 ml of water or 0·2 ml of a solution of the compound to be tested in a concentration of 10^{-2} M. The side bulb contained 0·2 ml of serotonin solution in a concentration of $6·2 \times 10^{-2}$ M. The centre well contained 0·1 ml of 0·002 N KOH solution and 0·1 ml of 0·02 N NaCN solution and a small piece of fluted Whatman No. 1 filter paper. The gas phase was air. After 10-min equilibration in the bath at 37°, the substrate was tipped into the main compartment, manometer readings were recorded at 10 min intervals for 1 h, oxygen consumption was calculated and percentage inhibition determined.

The values for monoamine inhibition at 10^{-3} M are the results of a screening procedure in which compounds were tested at this concentration in triplicate. When inhibitions significantly greater than 50 per cent at 10^{-3} M were found, a series of concentrations were tested and the molar concentration causing 50 per cent inhibition, or the $[I]_{50}$, determined graphically. A number of compounds tested were not completely soluble in the medium used. These were ground thoroughly and added as fine suspensions to the Warburg vessel. It is possible that the results for some slightly soluble compounds are unreliable. However, the $[I]_{50}$ values are probably reliable for the conditions of the experiment since a dose–response curve was obtainable. The results of the *in vitro* experiments are shown in Table II.

Inhibition of monoamine oxidase activity in vivo. To test for *in vivo* activity, the compounds were dissolved or suspended in water and given to rats by intraperitoneal or oral administration. At the time specified in the Table, the rats were decapitated, and the individual brains and livers removed, weighed and homogenized in buffer as described above. The brain homogenate contained 400 mg of tissue/ml, the liver 200 mg/ml. One millilitre of these homogenates was used in each vessel. The results of these experiments are shown in Table III.

Inhibition of 5-hydroxytryptophan decarboxylase activity in vitro. 5-Hydroxytryptophan decarboxylase activity was determined by the method of Clark *et al.*[7]

Table III. Monoamine oxidase activity *in vivo*[a]

Compound	Dose, mg/kg	Route of administration	Interval between dosing and decapitation, min	% Inhibition	
				liver	brain
Number 1	10	p.o.	60	94	100
	7	p.o.	60	98	98
	4	p.o.	60	75	48
	1	p.o.	60	24	0
	2	i.p.	60	68	32
			120	90	80
			180	90	90
	1	i.p.	60	55	17
			120	60	60
			180	58	58
	0·5	i.p.	60	30	27
			120	38	51
			180	32	51
Number 4	25	p.o.	60	100	85
			120	100	100
Number 8	25	p.o.	60	100	100
	25	p.o.	120	100	100
	1	i.p.	60	52	89
	0·1	i.p.	60	0	0
	0·5	i.p.	60	28	38
	0·5	i.p.	120	38	57
	0·5	i.p.	180	44	88
Number 9	25	p.o.	60	79	26
	25	p.o.	120	95	33
Number 11	25	p.o.	60	100	100
			120	100	100
	2	i.p.	60	100	0
	1	i.p.	60	42	0
Number 14	25	p.o.	60	100	86
			120	100	100

[a] Each pair of values represents one rat.

Potentiation of hexobarbital-induced sleep. The potentiating activity of the compounds was determined after intraperitoneal administration to six mice at each dose. Thirty min after the compound was given, hexobarbital was injected at 100 mg/kg i.p. The duration of sleep was determined using the loss of righting reflex as the criterion. The action of the compound is expressed as the percentage increase in sleeping time over the controls. The results are presented in Table IV.

Table IV. Effect on motor activity and sleeping time

Compound	% Decrease in motor activity		% Increase in sleeping time			
	Dose in % of LD_{50}		Dose in % of LD_{50}			
	40	20	20	10	5	2·5
1	38	26	248			
2	−4	6	222			
3	20	5	11			
4	67	59	490	177	182	93
5	94	50	650	> 700	> 415	392
6	26	19	> 700	248	218	148
7		17	739	220	210	
8	41	37	> 960	224	132	73
9	6	−9	50			
10	25	17	121			
11	62	18	1198	315	126	58
12	14	−1	180			
13	not done			not done		
14	not done			not done		
15	81	40	164			
16	not done		135			

Motor activity. The effect of compounds on motor activity was determined by the technique of Dews.[8] The compound was suspended in a 1 per cent solution of sodium carboxymethylcellulose and injected intraperitoneally into 6 male mice per dose. Thirty min after giving the compound, individual mice were put in an actophotometer. Motor activity for a 5-min period was

determined by using the number of breaks in the light beams as a criterion. The action of the compound is expressed as the percentage change in activity from the controls. The dose of chlorpromazine producing a 50 per cent decrease is about 3 mg/kg i.p. Results are presented in Tables IV and V.

Table V[a]. Effect on motor activity

Compound	% Decrease in motor activity				
	Dose in % of LD_{50}				
	10	5	2·5	1	0·1
1	25	19	16	3	0
4	46	10	10	0	0
5	23	21	13	0	20

[a] These representative compounds were tested at lower doses to demonstrate the lack of biphasic stimulation–depression in this series.

Discussion

From the data collected, it appears that the terminal nitrogen of the hydrazine group must be unsubstituted for good MAO inhibition. A single alkyl group on this nitrogen greatly reduced potency and the presence of two alkyl groups completely abolished inhibitory activity.

The various *ortho*substituents on the phenyl ring all gave comparable MAO inhibition and the presence of two *ortho*substituents did not give compounds superior to those with a single substituent.

In general, inhibition of monoamine oxidase was paralleled by inhibition of 5-hydroxytryptophan decarboxylase.

No obvious correlation of structure with effect on motor activity or sleep potentiation was seen.

Summary. A series of fifteen substituted phenethylhydrazines was prepared and tested for monoamine oxidase inhibition, 5-hydroxytryptophan decarboxylase inhibition, effect on spontaneous motor activity and sleep potentiation. Potent inhibition of the enzymes studied was observed with compounds having an unsubstituted terminal hydrazine nitrogen. Other activities showed no obvious correlation with structural features.

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