Evaluation of Certain Hypotensive Agents VI

Tetramethylpiperidine Derivatives

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The hypotensive activity of a series of 2,2,6,6-tetramethylpiperidine derivatives was investigated in anesthetized rats and dogs. The piperidine compounds were derivatives of pempidine (1,2,2,6,6-pentamethylpiperidine), an orally effective potent ganglionic blocking compound. *N*-Amino-*N*-[β-(2,2,6,6-tetramethylpiperidino-)-ethyl]-guanidine sulfate (EX 4510) appeared to be slightly more active than pempidine. All of the active hypotensive compounds in this series which were tested against pressor challengers in anesthetized dogs potentiated the epinephrine and angiotensin II pressor responses and depressed or blocked the bilateral carotid occlusion pressor response. Preliminary data suggest that the active compounds, like pempidine, are ganglionic blockers.

INVESTIGATORS (1-3) HAVE REPORTED that pempidine (1,2,2,6,6,-pentamethylpiperidine) is a long acting, orally effective ganglionic blocking compound. Smirk and Hodge (4) discussed the hypotensive activity of several compounds chemically related to pempidine and concluded that 2,2,6,6,-tetramethylpiperidine hydrochloride was slightly more potent than pempidine and was the most potent compound in this particular series. All of the related compounds appeared to be ganglionic blocking agents and produced side effects in hypertensive patients characteristic of this class of compounds. Several other investigators (5, 6) have also reported that pempidine is an orally effective ganglionic blocking compound in humans.

Twenty-six compounds,[1] chemically related to pempidine,[2] have been synthesized by Biel and his coworkers (7) and evaluated for hypotensive activity in rats and dogs (see Table I). This present report concerns the hypotensive activity of this series of compounds and pempidine.

EXPERIMENTAL

Hypotensive Activity in Normotensive Rats.—The compounds were evaluated for their hypotensive activity in anesthetized normotensive Wistar rats using the method described by Bickerton, *et al.* (8). Fresh aqueous solutions of the compounds were administered intravenously *via* a femoral vein and the blood pressure obtained by direct cannulation of a carotid artery and recorded on a slowly moving smoked kymograph. Blood pressure recordings were measured 10 minutes after administration of the compound. Compounds producing effects of less than 10 minutes' duration were classified as inactive.

Hypotensive Activity in Normotensive Dogs.—Certain of the compounds were further evaluated in anesthetized normotensive dogs. Mongrel dogs were anesthetized with pentobarbital sodium, 35 mg./Kg., i.v., and the blood pressure recorded from a femoral artery onto a Grass polygraph utilizing a Statham pressure transducer. The effects of the compounds on the pressor responses to 10-second bilateral carotid occlusion; epinephrine, 1 to 2 mcg./Kg., i.v.; and synthetic angiotensin II,[3] 1 mcg./Kg., i.v., were also investigated. In several preparations 1 to 2 mcg./Kg. levarterenol was also administered intravenously.

RESULTS

Hypotensive Activity in Normotensive Rats.—The hypotensive activity of the compounds studied in this current investigation is summarized in Table II. All of the compounds except EX 4608, EX 4493, EX 4399, and EX 4890 produced some degree of hypotensive activity. The most active compounds were pempidine; EX 4510, *N*-amino-*N*-[β-2,2,6,6-tetramethylpiperidino)-ethyl]-guanidine sulfate; EX 4602, 2,2,6,6-tetramethylpiperidine succinate, EX 4454, di-(2,2,6,6-tetramethylpiperidine) dihydrogenethylenediamine tetraacetate; EX 10020, *N*-methylamino-2,2,6,6-tetramethylpiperidine tartrate monohydrate; EX 10041, 4-nitrato-2,2,6,6-tetramethylpiperidine maleate; EX 4690, 2,2,6,6-tetramethyl piperidine salicylate; and EX 4707, 1,2,2,7,7-pentamethyl - 4 - (β -chloroethyl) -homo -piperazine dihydrochloride.

EX 4510 appeared to be slightly more active than pempidine, whereas EX 4602 appeared to be approximately equal in hypotensive action to pempidine. EX 4608, α-(2,6-dimethylphenoxy)-β-(2′,2′,6′,6′-tetramethylpiperidino)-ethane hydrochloride produced marked pressor effects in the anesthetized rat, and EX 4453, *N*-β-chloroethyl-2,2,6,6-tetramethylpiperidine hydrochloride, produced stimulatory effects.

Hypotensive Activity in Normotensive Dogs.—The effects of the compounds in anesthetized dogs are summarized in Table III. EX 4510 was also the most active compound when investigated in

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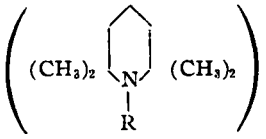
[1] Experimental compounds supplied by Lakeside Laboratories, Milwaukee, Wis.

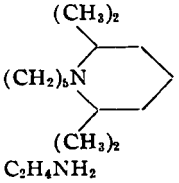
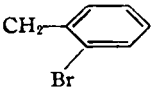
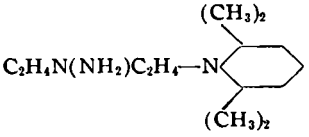
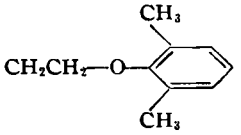
[2] Pempidine kindly supplied by May and Baker, Ltd., Dagenham, Essex, England.

[3] Kindly supplied as Hypertensin by Ciba Pharmaceutical Products, Inc., Summit, N. J.

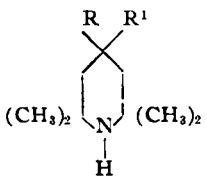
TABLE I.—CHEMICAL STRUCTURES OF COMPOUNDS INVESTIGATED

Group I



Compd.	R	X	R¹
Pempidine	CH_3	1	Bitartrate
EX 4392	$CH_2COOC_2H_5$	1	Maleate
EX 4399	CH_2COOH	1	
EX 4431	H	1	$(CSNHCH_2CO_2H)_2$
EX 4450	CH_2CH_2OH	1	Maleate
EX 4453	CH_2CH_2Cl	1	HCl
EX 4454	H	2	Ethylenediamine tetraacetate
EX 4458		1	2HBr
EX 4464	$C_2H_4NH_2$	1	2 HCl
EX 4469	$C_2H_4SCCH_3$ (O)	1	HCl
EX 4489	$C_2H_4NHCNH_2$ (NH)	2	H_2SO_4
EX 4493		1	HCl
EX 4510	$C_2H_4N(NH_2)C(=NH)NH_2$	2	H_2SO_4
EX 4513		2	3 HCl
EX 4531	$C_2H_4NH\ NH_2$	1	2 HCl
EX 4602	H	1	Succinate
EX 4608		1	HCl
EX 4690	H	1	Salicylate
EX 10020	$NHCH_3$	1	Tartrate monohydrate

Group II



·R²

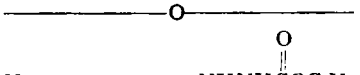
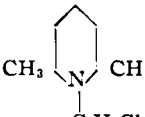
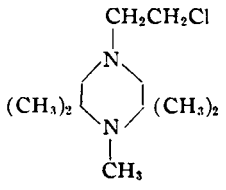
EX 4451			Maleate
EX 4601	H	$NHNHCOC_2H_5$ (O)	2 HCl
EX 4611	H	OH	HCl

TABLE I.—(*continued*)

Compd.	R	X	R¹
EX 4890	H	$NHNH_2$	Dimaleate
EX 10041	H	ONO_2	Maleate
		Group III	
EX 4634			·HCl
EX 4707			·2 HCl

anesthetized dogs. EX 4608, a compound which produced hypertensive effects in rats, failed to alter the blood pressure of an anesthetized dog. EX 4489, a compound which was lethal in rats in doses over 2.5 mg./Kg. was also lethal at the 20 mg./Kg. dosage in anesthetized dogs. In general, there was good correlation between the data obtained in anesthetized rats and that obtained in the anesthetized dog. All of the active pempidine derivatives produced responses characteristic of ganglionic blocking agents in that they potentiated the epinephrine pressor response, depressed or blocked the pressor response induced by bilateral carotid occlusion, and potentiated the anglotensin II and levarterenol pressor responses. The preliminary data obtained in this study suggest that the active compounds, like pempidine, produced their hypotensive effects through blockade of autonomic ganglia.

DISCUSSION

The following structure-activity relationship of the compounds reported in this communication was obtained utilizing the data found in Table II. The replacement of the methyl group in the number 1 position by an *N*-amino-*N*-ethylguanidine group (EX 4510) appeared to enhance the hypotensive activity of the piperidine structure, whereas replacement by a hydrogen group (EX 4602) produced a compound which was approximately equally potent to pempi-

TABLE II.—EVALUATION OF CERTAIN HYPOTENSIVE COMPOUNDS ON THE BLOOD PRESSURE OF NORMOTENSIVE RATS

Compd. No.	Dose, mg./Kg.	Animals, No.	Drop in b.p. % ±S.D.	Mean Time to Return to Predrug Levels, min. ±S.D.	Rating and Comments
Pempidine	5.0	8	36.7 ± 11.3	250 +	++++
EX 4392	10.0	5	35 ± 7	13 (2–34)	+
EX 4399	80.0	7	...	...	Inactive
EX 4431	20.0	6	26 ± 9	203 ± 78	++++
EX 4450	10.0	8	48 ± 16	77 ± 52.4	++
EX 4451	25.0	4	44 ± 6	104 ± 61.2	+++
EX 4453	40.0	5	11 to 53	...	Analeptic, convulsions
EX 4454	5.0	6	39 ± 5.7	184 ± 93	++++
EX 4458	10.0	6	35 ± 18	113 ± 58	+++
EX 4464	40.0	2	44.5	70.5	++
EX 4469	15.0	6	36 ± 12.8	59 ± 29	++
EX 4489	2.5	2	46.5	21	+
EX 4493	40.0	9	...	...	Primary pressor effect
EX 4510	5.0	6	44.5 ± 8.0	350+	++++
EX 4513	5.0	2	0	0	0
EX 4513	40.0	2	0	0	0
EX 4531	10.0	8	30.4 ± 7.2	53 ± 29	++
EX 4601	40.0	6	36.5 ± 5.9	84 ± 8	+++
EX 4602	5.0	6	39.2 ± 5.7	250+	++++
EX 4608	20.0	10	...	...	Pressor
EX 4611	25.0	10	43 ± 10	69 ± 30	++
EX 4634	40.0	9	28 to 43	10 to 36	+
EX 4690	10.0	8	42 ± 5	287 ± 9	++++
EX 4707	5.0	6	51.8 ± 7	141 ± 45	++++
EX 4890	40.0	6	...	...	Inactive
EX 10020	25.0	6	36 ± 9	354 ± 144	++++
EX 10041	25.0	6	42 ± 26	237 ± 22	++++

TABLE III.—EFFECTS OF EXPERIMENTAL COMPOUNDS ON THE BLOOD PRESSURE AND SEVERAL PRESSOR RESPONSES IN THE ANESTHETIZED[a] DOG

Compd. No.	Dose, mg./Kg.	Dogs, No.	% Drop in b.p.	Time to Return to Predrug Levels, min.	% Control Responses			
					BCO[b]	Epi[c]	Ang[d]	L-art[e]
Pempidine	5	1	51	720+	17	171	132	...
EX 4392	10	1	0	0	...	...	...	...
EX 4431	5	1	41	155+	0	114	156	...
EX 4451	2.5	1	68	190+	0	294	289	...
EX 4451	10	2	47	150+	57	215	117	...
EX 4458	10	1	50	200+	0	206	214	...
EX 4469	10	1	29	200+	34	190	120	...
EX 4489	20	1	Lethal	...	...	...	...	...
EX 4493	10	1	69	80	100	191	90	...
EX 4510	5	2	46	720+	24	150	139	...
EX 4513	10	2	8	9	...	...	...	...
EX 4531	10	2	44	415	23	172	136	...
EX 4601	20	2	28	170	31	251	177	...
EX 4602	5	1	32	600	25	174	192	...
EX 4608	5	1	0	0	84	75	100	...
EX 4611	20	2	35	233+	8	174	161	174
EX 4634	30	1	53	86	0	131	100	...
EX 4690	10	1	33	114+	0	285	261	173
EX 4707	2.5	1	27	100	55	132	117	162
EX 4707	5	1	34	93	21	273	137	184
EX 4890	10	1	26	105	72	91	114	...
EX 10020	15	1	43	160+	0	168	178	...
EX 10041	20	1	58	163+	0	211	90	176

[a] Anesthetic, pentobarbital sodium, 35 mg./Kg., i.v. [b] BCO = 10-second bilateral carotid occlusion. [c] Epi = epinephrine [d] Ang = synthetic angiotensin II. [e] L-art = levarterenol.

dine. The ethylhydrazine substitution in the 1 position (EX 4531) greatly reduced activity. Carbethoxyhydrazine substitution in the 4 position of 2,2,6,6-tetramethylpiperidine (EX 4601) markedly reduced hypotensive activity. β-Chloroethyl substitution at the 1 position (EX 4453) produced analeptic effects, while pressor activity was produced by ethylphenoxy (EX 4608) or *o*-bromobenzyl (EX 4493) substitution at the 1 position.

Smirk and Hodge (4) have reported that the *N*-methylamino substitution at the 1 position in place of a methyl group did not alter hypotensive activity in humans. In this current study, the *N*-methylamino substituted compound (EX 10020) was found to be approximately one-fifth as potent as pempidine on a dose-dose relationship. Although the 2,2,6,6-tetramethylpiperidine structure (EX 4602, EX 4690, and EX 4431) was highly active, it did not appear to be more potent than the parent pempidine structure when administered intravenously to rats.

SUMMARY

The hypotensive activity of a series of tetramethylpiperidine derivatives, chemically related to pempidine, was investigated.

N - Amino - *N* - [β - (2,2,6,6 - tetramethylpiperidino)-ethyl]-guanidine sulfate (EX 4510) appeared to be a slightly more active hypotensive compound than pempidine. The data reported in this current study suggest that the active compounds, like pempidine, produced their hypotensive effects through blockade of autonomic ganglia.

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