nation of morphine in dosage forms and has the advantage of greater specificity as compared to direct U.V. measurements.

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Evaluation and Mechanisms of Action of Several Experimental Hypotensive Agents

By WILLIAM J. HUDAK†, WILLIAM J. KINNARD, Jr., and JOSEPH P. BUCKLEY

The hypotensive activity of [1-methyl-3-(2'5'6'-trimethyl-1'-cyclohexenyl)propyl] [3-morpholinopropyl] dimethyl ammonium bromide methobromide (RO 2-7832), (+) - 6 - methyl - 9 - diethylaminomethyl - 10 - hydroxy - 1,2,3,3a,5,6,6a,7,11b,11c-decahydro-4H-dibenzo [de,g] quinoline dihydrobromide (RO 2-9618), and 8,8'-bis(2-dimethylaminoethoxy)-6,6'-bithiachroman-4,4'-dione dihydrochloride (RO 2-9811) were investigated in anesthetized rats and dogs. Central and peripheral hypotensive activities were studied utilizing dog cross circulation preparations; and included trimethidinium methosulfate and beta-dimethyl-aminoethyl-N-methylpipecolinate dimethobromide (JB-591) as well as the previously mentioned compounds. RO 2-7832 and trimethidinium appeared to act as potent ganglionic blockers. The hypotensive activity of RO 2-9618 was due to both ganglionic blockade and mild adrenolytic activity. JB-591 was the only compound that demonstrated any central hypotensive activity.

ALTHOUGH the etiology of essential hypertension is still not fully understood, many investigators agree that the reduction in arterial blood pressure is beneficial to the hypertensive patient and will, in many instances, prolong life (1–4). Even though there are many hypotensive compounds available, there is still a need for safer therapeutic agents possessing a minimum of side effects, thereby permitting the patient to lead a useful, productive life. The mechanism of action of the compound should be understood so that the drugs can be intelligently used by the physician in the control of hypertensive cardiovascular disease. This present report is mainly concerned with the evaluation of the hypotensive activity of RO 2-7832,[1] RO 2-9618,[1] and RO 2-9811[1] (Fig. 1), and the mechansim of action of these compounds, and trimethidinium[2] (5) and JB-591[3] (6–8).

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[1] Kindly supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.
[2] Kindly supplied as WY-1395 (Ostensin) by Wyeth Laboratories, Philadelphia, Pa.
[3] Kindly supplied by Lakeside Laboratories, Inc., Milwaukee, Wis., (beta-dimethylaminoethyl-N-methylpipecolinate dimethobromide).

EXPERIMENTAL

Hypotensive Activity in Rats.—The RO compounds were screened and evaluated in anesthetized Wistar rats (urethan, 1.25 Gm./Kg., i.p.) utilizing the method described in a previous paper (9). Direct blood pressure was recorded via the left common carotid artery onto a slowly moving kymograph. The compounds were dissolved prior to use in distilled water and administered via a femoral vein. Hexamethonium, 5 mg./Kg., was utilized as a control compound in this phase of the study.

The oral activity of the three RO compounds was investigated in: (*a*) anesthetized normotensive albino rats, (*b*) unanesthetized normotensive rats, and (*c*) unanesthetized hypertensive rats.

The animals in (*a*) were fasted for 24 hours prior to their use. They were anesthetized with urethan, 1.25 Gm./Kg., i.p., and prepared for direct blood pressure recording. The proximal end of the trachea was cannulated with polyethylene tubing (2 mm. o.d. and 1.5 mm. i.d.). Fresh solutions of the compounds were administered via gastric intubation utilizing a Davol No. 8 French rubber catheter, and each dose was diluted with distilled water to a volume of 2 ml.

The blood pressures of unanesthetized normotensive rats (*b*) were obtained utilizing the photoelectric tensometer (10). Albino Wistar rats were trained for a period of one week prior to the initiation of the study. The animals were fasted for 24 hours, after which fresh solutions of the compounds were administered via gastric intubation as previously described. Blood pressures were obtained periodically prior to and after drug administration.

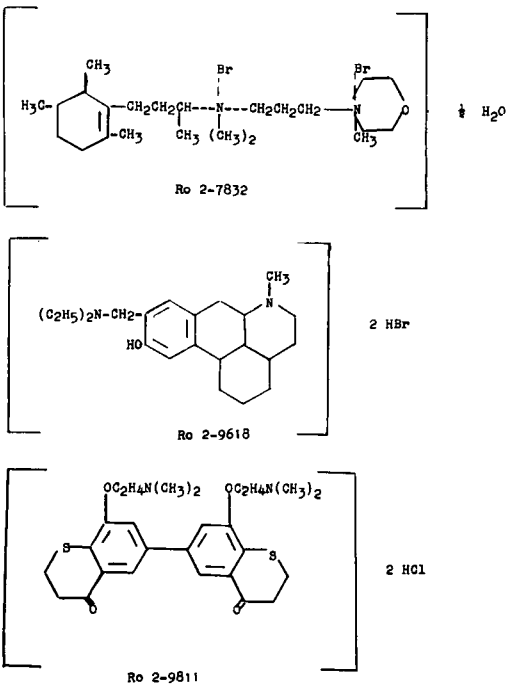


Fig. 1.—Structures of the compounds evaluated for hypotensive activity.

Hypertensive rats (*c*) were prepared by applying a figure-of-eight ligature to the right decapsulated kidney and removing the contralateral kidney 1 week later. After an additional 4-week period, the rats received 6.25 mg. of desoxycorticosterone trimethylacetate,[4] intramuscularly, and 0.9% saline drinking solution once weekly. Of 48 rats, 40 developed arterial pressures in excess of 180 mm. Hg 8 weeks after the initial operation. Fresh solutions of the compounds were administered orally to rats fasted for 24 hours and the blood pressures determined, utilizing the photoelectric tensometer, prior to and periodically after administering the compounds.

Ganglionic Blocking Activity.—Adult cats of both sexes were anesthetized with an intraperitoneal injection of pentobarbital sodium, 35 mg./Kg. Blood pressure was recorded from the right femoral artery via a mercury manometer. The preganglionic segment of the cervical sympathetic nerve was stimulated with a submaximal stimulus (determined for each animal) using a Harvard stimulator at a frequency of 60 impulses per second for 10 seconds, and the effect on the nictitating membrane recorded. Three such stimuli were applied at 5-minute intervals and the average response determined. The submaximal stimulus was also determined for the postganglionic fiber. The responses obtained after injection of the test compound were reported as per cent of the mean response. The antagonism of the experimental compounds to the hypertensive activity of 1,1-dimethyl-4-phenyl-piperazinium iodide (DMPP) (11–13) were also studied in the same preparations. The mean pressor response to several 10 mcg./Kg. intravenous injections of DMPP prior to administering the experimental compounds was obtained, and the degree of inhibition of the pressor response after administration of the compounds was calculated in terms of per cent of the mean control response. The effects of the compounds in antagonizing the pressor response obtained by bilateral carotid occlusion were also determined in a similar manner.

Hypotensive Activity in Dogs.—The hypotensive activities of the compounds were studied in unanesthetized normotensive dogs. A permanent catheter (Bardic 10) was inserted into a femoral artery permitting direct recording of the blood pressure onto a slowly moving kymograph by way of a mercury manometer (14). Each animal received a particular compound via the oral or intravenous routes to determine the approximate degree of oral absorption. The dogs were starved 24 hours prior to oral administration, and the oral dose equivalent to 10 times the i.v. dose was administered in capsule form. A minimum of two days elapsed prior to administering the compounds via the intravenous route. Approximately one week after receiving the last dose of the compound, the animal was anesthetized with pentobarbital sodium, 35 mg./Kg., i.v., and the blood pressure recorded via the femoral catheter onto a slowly moving kymograph. The trachea was cannulated and the common carotid arteries isolated in the usual manner. The vagi were isolated, doubly ligated, and the nerves sectioned between the ligatures. The following tests were utilized at 5-minute intervals: (*a*) the stimulation of the central vagal stump (35 volts at a frequency of 60 per second for 10 seconds); (*b*) stimulation of the caudal vagal stump utilizing the same stimuli as described above; (*c*) bilateral carotid occlusion for 10 seconds; (*d*) DMPP (10 mcg./Kg.) i.v.; (*e*) epinephrine (1 ml. of 1:100,000) i.v.; (*f*) histamine base (2.5 mcg./Kg.) i.v. The mean per cents of two responses prior to medication were utilized as controls and the degree of augmentation or inhibition was calculated in terms of the per cent of this mean control response.

Dog Cross Circulation Studies.—The following procedure was utilized to produce a vascularly isolated, neurally intact head preparation: The recipient dog was anesthetized with pentobarbital sodium, 35 mg./Kg., i.v., and the blood pressure recorded via the right femoral artery by way of a mercury manometer onto a slowly moving kymograph. The trachea was cannulated and both common carotid arteries and jugular veins isolated. The internal jugular veins were doubly ligated and sectioned. A circumferential incision was then made around the midneck and the skin retracted. All the neck musculature from C-2 to C-5 was separated and removed using electrocautery. A dorsal laminectomy was performed between C-2 and C-3 or C-3 and C-4 to expose the underlying cord. The cord was gently retracted and a soft rubber sponge (0.75 cm. × 4.0 cm. × 0.25 cm.), through which a length of 21-gauge steel wire had been passed, was inserted between the spinal cord and dorsal surface of the centrum. The wire was looped around the central portion of the spinal column and guided into the intervertebral space and passed between the two common carotid arteries. The wire was then tightened with a Shifrin wire tightener

[4] Generously supplied as Percorten by Ciba Pharmaceutical Products, Inc., Summit, N. J.

to occlude the venous sinuses and vertebral arteries and the tightener left in place. The dog was placed ventral side up and artificial respiration administered. The left rib cage was exposed and the pleural cavity opened between the third and fourth ribs, utilizing a chest spreader. Loose ligatures were placed around the innominate and left subclavian arteries and superior vena cava (caudal to the entry of the vertebral veins). The donor dog (approximately 25% larger than the recipient) was anesthetized and the blood pressure recorded via the right femoral artery. The donor was heparinized with 2,000 to 4,000 units of heparin intravenously, and 50 mg. of pyribenzamine was administered subcutaneously to prevent possible anaphylactic reactions. Anastomosis between the recipient's two common carotid arteries and two external jugular veins with the corresponding left vessels of the donor was accomplished, and the ligatures around the innominate and left subclavian arteries and superior vena cava tightened securely (see Fig. 2). After both donor and recipient blood pressures had stabilized, 0.25 ml. of Lugol's solution (U.S.P.) was injected into the tubing supplying the blood to the head of the recipient. Approximately 15 minutes later, 10 μc. of iodine^{131} (radio-iodinated serum albumin, human, Squibb) was administered intra-arterially into the head of the recipient. Circulatory leakage between the head and body of the recipient animal was determined at 5, 15, 30, 60 minutes, and then at hourly intervals after administration of radioactive iodine, using the procedure described in a previous paper (15). The mean leakage in 19 experiments, at the end of 3 hours, was 3.1%. The compounds were administered via the arterial inflow to the recipient's head.

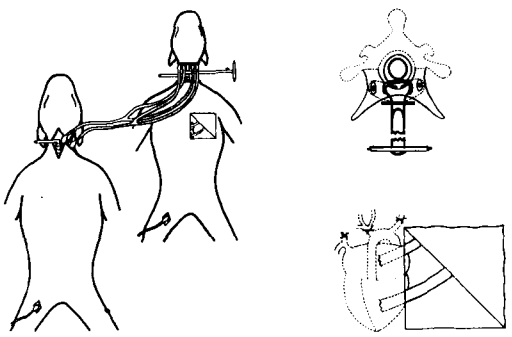


Fig. 2.—Diagrammatic illustration of the cross circulation technique used.

RESULTS

Hypotensive Activity in Rats.—The hypotensive activity of the RO compounds, administered intravenously, is summarized in Table I. RO 2-7832 appeared to be the most active hypotensive compound investigated as 1 mg./Kg., i.v., produced marked hypotensive effects persisting for over 4 hours. The compound was also very active when administered orally to anesthetized normotensive rats. RO 2-7832, in doses ranging between 1 and 20 mg./Kg., produced drops in blood pressure between 40 and 55%, the onset of action occurring between 15 and 31 minutes, and the hypotensive effects persisting for approximately 8 hours after the onset of action. RO 2-7832 was also the most active compound when administered orally to unanesthetized normotensive albino rats. The onset of action usually occurred within 60 minutes, and the duration of action was usually over 8 hours. A decrease in oral and nasal secretions and marked pupil dilatation were observed with the onset of the hypotensive effects. RO 2-7832 was administered to 10 hypertensive rats. Doses of 20 mg./Kg. produced a mean drop in blood pressure of 26% and the maximum hypotensive effect occurred approximately 100 minutes after the administration of the compound (see Tables II and III). The average duration of action was in excess of 354 minutes; however, the blood pressures of four of the rats had not returned to predrug levels after 8 hours. Dryness of the mouth and marked pupil dilatation were observed with the onset of drug action.

Ganglionic Blocking Activity.—The ganglionic blocking activity and the effect on bilateral carotid occlusion pressor response of the RO compounds on normotensive cats are summarized in Table IV. RO 2-7832 elicited powerful ganglionic blockade and almost completely blocked the pressor response to DMPP. Moderate ganglionic blocking activity was produced by RO 2-9618, and RO 2-9811 had little effect on ganglionic transmission. All of the compounds inhibited the pressor response to bilateral carotid occlusion with RO 2-7832 demonstrating the least activity in inhibiting this pressor reaction.

Hypotensive Activity in Dogs.—The effects of the RO compounds on the blood pressure of unanesthetized normotensive dogs are summarized in Table V. RO 2-7832 appeared to be the most active compound when administered either intravenously or orally. The compound produced almost complete relaxation of the nictitating membrane, dryness of the eyes and mouth, mydriasis, and loss of pupillary reflex. The effects of the RO compounds on the blood pressure of anesthetized normotensive dogs and the physiological responses to electrical stimulation of the central vagal stump and caudal vagal stump, bilateral carotid occlusion, DMPP, epinephrine, and histamine are summarized in Table VI. The pressor response to central vagal stump stimulation was completely inhibited in one instance by 2 mg./Kg. of RO 2-7832. RO 2-9811 had no apparent effects upon this physiological response. The depressor response to stimulation of the caudal vagal stump was completely blocked by RO 2-7832 in one dog, and a pressor response was obtained in another. The other compounds decreased the depressor response. The pressor response produced by bilateral carotid occlusion was completely inhibited by RO 2-7832, RO 2-9618 had little or no effect, and RO 2-9811 inhibited this response by 40 and 68%. The pressor response to DMPP, i.v., was blocked by RO 2-7832 and augmented by RO 2-9811 and RO 2-9618. The pressor response to exogenous epinephrine was enhanced by RO 2-7832 and RO 2-9811 and slightly diminished by RO 2-9618.

Cross Circulation Studies.—The effects of the compounds on the dog cross circulation preparations are summarized in Table VII. JB-591 was the only compound which appeared to produce a centrally mediated hypotensive effect (Fig. 3). Marked de-

TABLE I.—EVALUATION OF CERTAIN EXPERIMENTAL COMPOUNDS ON THE BLOOD PRESSURE OF NORMOTENSIVE RATS[a]

Compound	Dose, mg./Kg.	No. of Rats	Drop in Blood Pressure, % ± S.D.	Mean Time to Return to Original Level, min. ± S.D.	Rating[b]
RO 2-7832	1.0	6	44.8 ± 4.1	264 ± 35.9	++++
RO 2-9811	10.0	5	35.2 ± 7.8	52 ± 24.1	++
RO 2-9618	25.0	6	46.0 ± 5.9	6 ± 2.8	+
Hexamethonium	5.0	8	46.5 ± 17.9	30 ± 15.2	+

[a] Administered intravenously, rats anesthetized with urethan, 1.25 Gm./Kg., i.p. [b] Rating +, 0–40 min. duration; ++, 41–80 min.; +++, 81–120 min.; ++++, 121+ min.

TABLE II.—EFFECTS OF 20 MG./KG., RO 2-7832, *Per Os*, ON THE BLOOD PRESSURE OF UNANESTHETIZED HYPERTENSIVE RAT PREPARATIONS[a]

Weight, Gm.	245	215	208	241	281	176	135	138	147	148
Time, min.	Blood Pressure, mm. Hg									
0	204	232	236	214	196	198	198	204	204	218
15	...	215	230	188	214	168	178	212	...	212
30	136	...	202	170	178	164	180	182	188	230
60	140	164	...	...	...	...	...	...	156	182
65	...	...	198	162	164	174	154	176	...	...
90	...	...	182	158	166	...	...	...	...	194
120	152	182	176	162	...	...	...	...	164	...
125	...	...	...	...	178	178	172	170	...	...
160	...	186	194	184	188	...	...	...	...	172
180	152	...	...	...	...	192	...	...	144	...
185	...	...	...	188	192	...	196	184	...	...
240	166	220	210	212	206	208	194	192	120	148
300	192	220	214	204	200	204	202	190	144	192
360	222	214	214	210	192	...	...	...	146	160
420	206	214	210	...	...	...	...	...	142	166
480	206	218	210	...	...	...	...	...	146	158
Maximum % drop	33.3	29.3	25.4	26.1	16.3	17.1	22.2	16.6	41.1	32.1
Mean maximum % drop	26.0 ± 8.2									

[a] S.D. = $\sqrt{\frac{\epsilon(x-\bar{x})^2}{n-1}}$.

TABLE III.—SUMMARIZATION OF THE EFFECTS OF CERTAIN HYPOTENSIVE COMPOUNDS (*Per Os*) ON THE BLOOD PRESSURE OF UNANESTHETIZED HYPERTENSIVE RAT PREPARATIONS

Compound	No. of Rats	Dose, mg./Kg.	Mean Onset of Hypotensive Activity, min.	Mean Time of Maximum Hypotensive Activity, min.	Mean Maximum % Drop	Mean Duration of Action, min.
RO 2-7832	10	20	21	106.5	26.0	354+
RO 2-9811	6	50	20	65.3	23.4	247
RO 2-9618	6	50	15	47.5	20.9	230

TABLE IV.—SUMMARIZATION OF THE GANGLIONIC BLOCKING ACTIVITY AND THE EFFECT ON THE BILATERAL CAROTID OCCLUSION PRESSOR RESPONSE OF CERTAIN HYPOTENSIVE AGENTS ON NORMOTENSIVE CATS

Compound	Animal No.	Dose, mg./Kg.	Drop in Blood Pressure, %	Duration,[a] min.	Sympathetic Ganglionic Blockade, %	DMPP Blockade, %	Bilateral Carotid Occlusion Blockade, %
RO 2-7832	1	0.5	77.4	55	100	100	30.7
	2	0.5	61.6	168	100	75	0.0
	3	0.5	68.2	297	100	85.7	84.2
RO 2-9811	1	5.0	53.4	30	0	0	69.6
	2	5.0	50.5	98	12.6	0	75.0
	3	5.0	55.3	96	0	23.5	53.5
RO 2-9618	1	15.0	60.0	57	32.8	0	86.0
	2	15.0	60.0	83	15.8	43.2	73.3
	3	15.0	62.5	61	32.0	0	53.3

[a] Experiments terminated, all blood pressures below original levels.

TABLE V.—EFFECT OF THE EXPERIMENTAL COMPOUNDS, *Per Os* AND *I.V.*, ON THE BLOOD PRESSURE OF UNANESTHETIZED NORMOTENSIVE DOGS

Dog No.	Weight, Kg.	Sex	Compound	Dose, mg./Kg.	Original Blood Pressure, mm. Hg	Onset of Drug Action, min.	Time of Maximum Drop, min.	Maximum Drop, mm. Hg	Maximum % Drop	Time to Return to Original Level, min.
1	7.04	F	RO 2-7832	20 (*per os*)	122	8	38	52	42.6	746[a]
	6.61	F	RO 2-7832	2 (*i.v.*)	120	immediate	3	40	33.3	396[b]
2	12.0	F	RO 2-7832	20 (*per os*)	146	15	22	16	10.9	276
	12.0	F	RO 2-7832	2 (*i.v.*)	156	immediate	2	50	32.0	190[c]
3	7.55	F	RO 2-9811	50 (*per os*)	100	.....	..	0	0	..[d]
	7.30	F	RO 2-9811	5 (*i.v.*)	100	immediate	1	60	60	75
4	7.55	F	RO 2-9811	50 (*per os*)	96	64	73	16	16.6	50
	7.48	F	RO 2-9811	5 (*i.v.*)	100	immediate	1	60	60	53
5	7.6	M	RO 2-9618	150 (*per os*)	130	26	84	50	38.4	114
	6.55	M	RO 2-9618	15 (*i.v.*)	124	immediate	2	56	45.1	92
6	7.0	M	RO 2-9618	150 (*per os*)	104	15	22	34	32.6	64
	7.5	M	RO 2-9618	15 (*i.v.*)	108	.....	..	..	..	126[e]

[a] Experiment terminated, blood pressure 40 mm. Hg from original level. [b] Experiment terminated, blood pressure 52 mm. Hg from original level. [c] Experiment terminated, blood pressure 34 mm. Hg from original level. [d] No effect in 266 minutes. [e] No effect in 126 minutes.

TABLE VI.—CARDIOVASCULAR ACTION OF THE EXPERIMENTAL COMPOUNDS ON NORMOTENSIVE ANESTHETIZED DOGS

						Per Cent Response of Control Value					
Dog No.	Weight, Kg.	Sex	Compound	Dose, mg./ Kg.	Original Blood Pressure	% Drop	Central Vagal Stump Stimulation	Caudal Vagal Stump Stimulation	Bilateral Carotid Occlusion	DMPP	Epinephrine	Histamine Base
1	6.4	F	RO 2-7832	2	110	45	0	[a]	0	0	317	132
2	11.0	F	RO 2-7832	2	192	43	122	0	0	0	545	95
3	6.78	F	RO 2-9811	5	130	45	100	38	68	126	153	79
4	7.2	F	RO 2-9811	5	150	46	92	21	40	228	143	72
5	6.8	M	RO 2-9618	15	146	41	78	44	84	138	88	97
6	7.3	M	RO 2-9618	15	106	42	280	69	100	103	88	100

[a] Pressor response obtained.

pressor responses were produced in all of the recipient animals by JB-591. In most instances, the maximum hypotensive effect occurred more rapidly in the donor than in the recipient. All of the compounds produced marked hypotensive effects in the donor animals. Neither hexamethonium chloride nor trimethidinium (Fig. 4) produced any effect upon the recipient's blood pressure and it would appear that these compounds induce hypotensive effects purely through their peripheral ganglionic blocking activity.

DISCUSSION

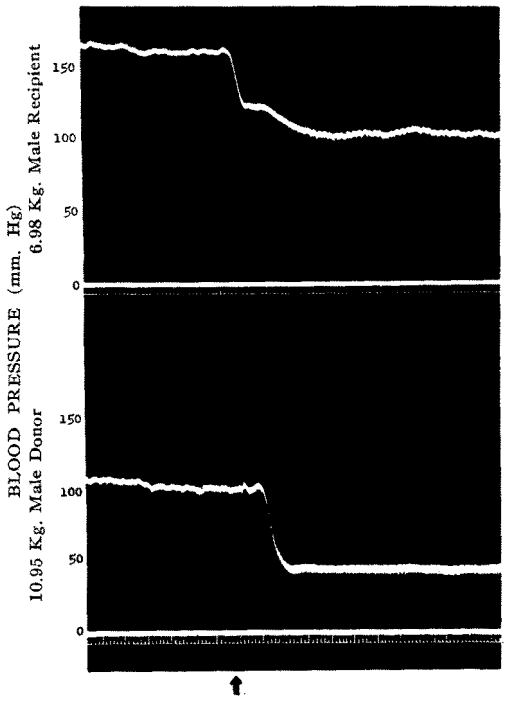
RO 2-7832 appeared to be the most potent of the RO compounds investigated. It produced marked hypotensive effects for prolonged periods of time in normotensive anesthetized rats, dogs, and cats. The cats appeared to be especially sensitive to this compound as minute doses produced marked hypotensive responses. The depressor response, produced by 10 times the intravenous dose of RO 2-7832 administered orally to unanesthetized normotensive and hypertensive rats, was approximately 50% that produced by intravenous administration to anesthetized rats. The depressor response produced by the compound following oral or intravenous administration to unanesthetized dogs was also markedly reduced in contrast to the response in anesthetized animals. This would indicate that the anesthesia had an augmentory action on the hypotensive activity of RO 2-7832. The following physiological responses indicate that RO 2-7832 is a ganglionic blocking agent: (*a*) complete inhibition of the pressor response of DMPP; (*b*) inhibition of the contraction of cat nictitating membrane to preganglionic stimulation of the superior cervical sympathetic nerve (nictitating membrane responded to stimulation of the postganglionic fiber); (*c*) inhibition of the depressor response produced by bilaterial carotid occlusion· (*d*) inhibition of the depressor response produced by caudal vagal stump stimulation; (*e*) marked enhancement of the pressor response to exogenous epinephrine. The compound did not exhibit any evidence of central hypotensive activity (Fig. 5).

Although RO 2-9618 was the least effective of the compounds investigated in the anesthetized rat evaluation studies, it appeared to be one of the most effective compounds when administered via the oral route; however, the duration of action was extremely short. The compound augmented the response produced by DMPP in the dog and suppressed the depressor response produced by stimulation of the caudal vagal stump in the dog. It also partially blocked the pressor response produced by DMPP and contraction of the nictitating membrane to preganglionic stimulation in the cat. Slight adrenergic blocking activity was also indicated by the partial suppression of the pressor response to exogenous epinephrine, and it appears that the hypotensive activity of RO 2-9618 is due to ganglionic blockade and a mild adrenergic blocking action.

TABLE VII.—EFFECT OF THE EXPERIMENTAL COMPOUNDS ON THE DOG CROSS CIRCULATION PREPARATIONS

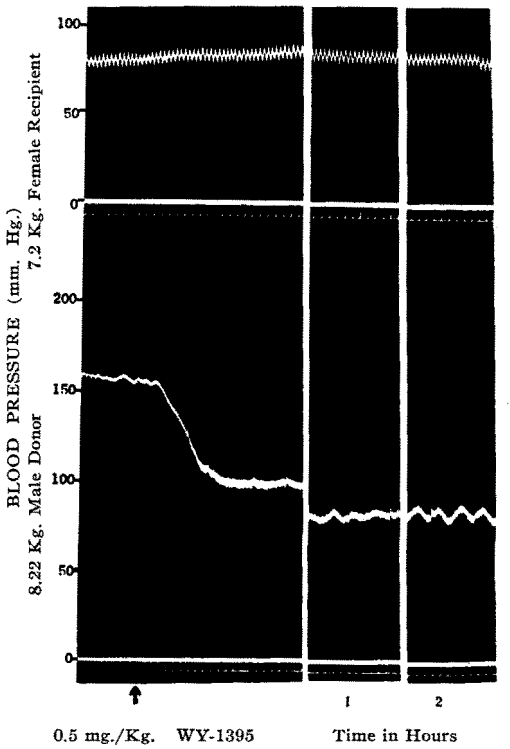
Expt. No.	Compound	Dose,[a] mg./Kg.	Donor Weight, Kg.	Donor Sex	Donor Original Blood Pressure, mm. Hg	Donor Maximum Drop, mm. Hg	Donor Maximum % Drop	Recipient Weight, Kg.	Recipient Sex	Recipient Original Blood Pressure, mm. Hg	Maximum Effect, mm. Hg	Maximum % Effect
1	RO 2-7832	2	10.02	M	112	52	46.4	8.03	F	86	+6	+6.9
2	RO 2-7832	2	11.12	M	134	74	55.2	6.67	F	82	no effect	...
3	RO 2-7832	5	10.72	M	160	118	74.0	7.25	F	78	+10	+13.5
4	RO 2-7832	5	7.86	F	70	30	42.8	7.06	F	74	no effect	...
5	RO 2-7832	5	8.20	M	80	46	57.5	8.99	F	72	−30	−41.7
6	RO 2-9811	5	7.00	F	102	68	66.7	6.69	F	124	+236	+190.0
7	RO 2-9811	5	7.42	F	120	46	38.3	6.48	F	88	no effect	...
8	RO 2-9618	15	7.44	F	114	88	78.2	6.68	M	82	no effect	...
9	RO 2-9618	15	10.39	M	80	50	62.5	7.24	M	126	+10	+7.9
10	JB-591	10	10.35	F	160	90	56.3	7.38	F	80	−50	−62.5
11	JB-591	10	10.95	M	100	58	58.0	6.98	M	158	−100	−63.3
12	JB-591	10	9.95	F	104	60	57.7	6.73	F	100	−54	−54.0
13	JB-591	10	10.20	M	104	42	40.4	6.54	F	114	−38	−33.3
14	Hexameth.[b]	3	6.70	M	88	42	47.7	6.01	F	70	no effect	...
15	Hexameth.	3	6.84	M	86	44	51.2	6.66	F	96	no effect	...
16	WY-1395	0.5	7.85	M	138	92	66.7	6.96	F	72	no effect	...
17	WY-1395	0.5	8.22	M	156	102	65.4	7.26	M	80	no effect	...
18	WY-1395	0.5	10.60	M	108	50	53.7	6.00[c]	F	74	no effect	...
19	WY-1395	0.5	13.70	F	80	40	50.0	6.90[c]	F	76	+10	+13.0

[a] Calculated on donor's weight. [b] Hexamethonium chloride. [c] Bilateral denervation of the carotid sinus-body areas.



10 mg./Kg. JB-591 IA-Recipient

Fig. 3.—The effects of JB-591, 10 mg./Kg., via the recipient carotid inflow, on the peripheral arterial pressures of the recipient and donor dogs.



0.5 mg./Kg. WY-1395 Time in Hours

Fig. 4.—The effects of trimethidinium (WY-1395), 0.5 mg./Kg., via the recipient carotid inflow, on the peripheral arterial pressures of the recipient and donor dogs.

RO 2-9811 produced mild hypotensive effects when administered intravenously and orally to dogs. It also produced a marked depression of respiration. The pressor response caused by bilateral carotid occlusion was inhibited approximately 50%, suggesting possible reflex or ganglionic blocking activity; however, the compound had relatively little effect on ganglionic transmission. It appears that RO 2-9811 may possibly lower blood pressure through some reflex mechanism.

Although trimethidinium has been suggested to have a dual mechanism of action (ganglionic

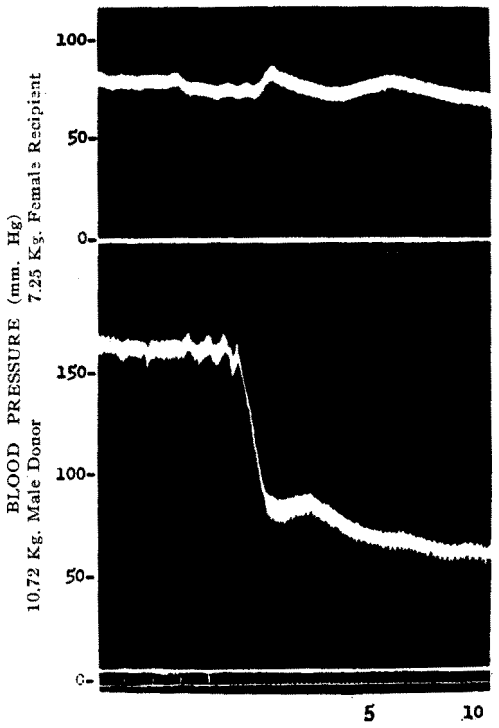


Fig. 5.—The effects of RO 2-7832, 5.0 mg./Kg., via the recipient carotid inflow, on the peripheral arterial pressures of the recipient and donor dogs.

blockade and some form of central depression) (16), the cross circulation studies indicated that the compound does not possess any central hypotensive activity. Since both trimethidinium and hexamethonium have been reported to be potent ganglioplegic agents, it would appear that the hypotensive effects produced by both trimethidinium and hexamethonium are essentially due to their ganglionic blocking activity.

JB-591 was the only compound to demonstrate a centrally mediated hypotensive response. Previous papers have shown the compound to possess ganglionic blocking properties, and it appears that the compound has a dual mechanism of action, namely ganglionic blockade and a central hypotensive action. Clinical studies have shown this compound to possess some tranquilizing action which would further strengthen the possibility of the compound possessing a centrally mediated hypotensive property.

SUMMARY

1. Three new compounds were evaluated for their hypotensive activity in anesthetized normotensive rats.

2. [1 - Methyl - 3 - (2′,5′,6′ - trimethyl - 1′-cyclohexenyl) propyl] [3-morpholinopropyl] dimethyl ammonium bromide methobromide (RO 2-7832) was the most potent hypotensive compound investigated.

3. Central hypotensive activities were studied utilizing dog cross circulation preparations.

4. Trimethidinium and hexamethonium did not elicit central hypotensive responses and apparently act through peripheral ganglionic blockade.

5. JB-591 (β-dimethyl-aminoethyl-N-methyl-pipecolinate dimethobromide) was the only compound to produce a centrally mediated hypotensive response and apparently lowers blood pressure through both ganglionic blockade and some central depressor mechanism.

6. The hypotensive activity of RO 2-7832 was produced predominantly by ganglionic blockade.

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