SCIENTIFIC SECTION

A COMPARATIVE PHARMACOLOGICAL STUDY OF SOME RELATED EPHEDRINE COMPOUNDS.*

BY EDWARD E. SWANSON.[1]

The extensive investigations of the pharmacological action and subsequent therapeutic applications of *l*-ephedrine isolated from Ma Huang by Chen and Schmidt (1), (2) have led to the isolation and synthesis of related alkaloids of ephedrine. Various synthetic compounds related to ephedrine in structure were prepared, and partially studied pharmacologically by Curtis (3), Manske and Johnson (4), Branchli and Cloetta (5), Hyde, Browning and Adams (6), Duliere (7), (8), (9) and (10), Tiffeneau, Levy and Boyer (11), Kanao (12), Tiffeneau (13), Tiffeneau, Levy and Boyer (14) and Koller (15). More recently, Chen, Chang-Keng Wu and Erle Hendriksen (16) have reported an extensive study of ephedrine related compounds. These authors have made a comparative pharmacological study, particularly, the relationship between the pharmacological action and the chemical constitution and configuration of the optical isomers of ephedrine and related compounds.

Our investigation consists of a pharmacological comparison of 8 new ephedrine derivatives and one compound not of the ephedrine type but of the oxyindan structure.

The compounds listed in Table I have been partially reported by Johnson and Manske (17) and Manske and Johnson (4). We are much indebted to Doctor R. H. F. Manske of Yale University for compounds Nos. 2, 3, 4 and 9 and to Professor McIlvaine, Department of Chemistry of the University of Wisconsin, for Nos. 5, 6, 7 and 8.

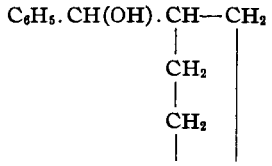
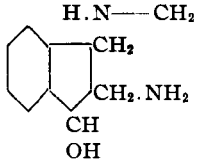
TABLE I.

No. of Drug.	Compound.	Melting Point of Hydrochloride.	Optical Activity of Hydrochloride.
1	L-natural $C_6H_5.CH(OH).CH(CH_3).NHC\ H_3.HCl$	215–216°	$x_D^{20} = -32.5$
2	$C_2H_5.C_6H_5.CH(OH).CH(CH_3).NH.C_2H_5.HCl$	208°	Racemic
3	$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C_6H_3.CH(OH).CH(CH_3).NH.C_2H_5.HCl$	221°	Racemic
4	$C_6H_5.CH(OH).CH(CH_3).NH.CH_2CH_2.C_6H_5.HCl$	207–208°	Racemic
5	$C_6H_5.CH(OH).CH(HN{-}CH_2{-}CH_2).HCl$	200-202°	Racemic
6	$C_6H_5.CH(OH).CH(H.N{-}CH_2{-}CH_2).HCl$ Stereoisomeric to No. 5	161–173°	Racemic
7	$C_6H_5.CH(OH).CH{-}CH_2$ $CH_2\ CH_2.HCl$ $H.N{-}CH_2$	190–192°	Racemic

* Scientific Section, A. PH. A., Toronto meeting, 1932.

[1] From the Lilly Research Laboratories, Indianapolis, Indiana.

TABLE I.—*Continued.*

No. of Drug.	Compound.	Melting Point of Hydrochloride.	Optical Activity of Hydrochloride.
8	 .HCl	191–193°	Racemic
9	 2-Amino-2-oxyindan	....	Racemic

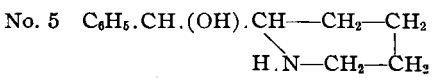
Chen, Chang-Keng Wu and Erle Hendriksen (16) reported a number of compounds as derivatives of β-phenylethylamine having the general formula

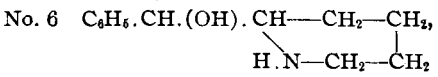
$$C_6H_5.CHH'.CHR.NR'R''$$

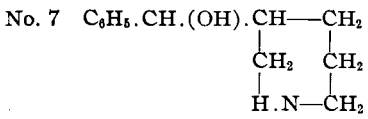
where H′ may be OH or H, and R, R′ and R″ may be H or an alkyl radical, respectively. In this study all the compounds except No. 9 are derivatives of ephedrine.

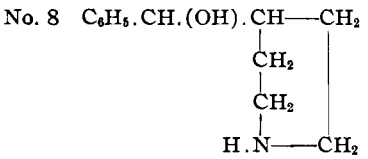
$$\begin{matrix} H' \\ H'' \end{matrix}\!\!\rangle C_4H_5.CH.(OH).CHR.NR'R''$$

where H′ and H″ may be a methyl (CH_3) or ethyl (C_2H_5) group as in compounds Nos. 2 and 3, and where R″ may be an ethyl or a phenylethyl group as in compounds Nos. 2, 3 and 4, respectively. Nos. 5, 6, 7 and 8 which are of the piperidine type on the B—C—atom from the N—atom structurally are:

No. 5 

No. 6  Stereoisomeric to No. 5

No. 7 

No. 8 

The hydrochlorides of these compounds yield clear solutions in distilled water. Only No. 3 is less soluble than the others.

A review of the literature shows that no pharmacological data have been reported on these compounds.

The comparative pharmacological properties of these compounds were determined by their mydriatic action in cats, the action on isolated uteri and intestinal strips of guinea pigs and rabbits, the blood pressure action on pithed cats, the

action on the frog's perfused heart, the astringent properties on the nasal mucous membrane of cats, the toxicity on rabbits, and their action on the bronchiole movements of the lungs of pithed dogs and isolated perfused lungs of cats. The methods of recording the movements of the bronchioles have been reported by Jackson (18), (19) and (20) on intact pithed dogs and the isolated perfused lungs by Sollmann and Von Oettingen (21). More recently Swanson (22) and Swanson and Webster (23) have studied the bronchodilator action of epinephrine, ephedrine and pseudo-ephedrine.

A. ACTION ON SMOOTH MUSCLE ORGANS.

The mydriatic action of each compound was tested in the cat's eye. It was found as shown in Table II that by local application of a 5 per cent solution or $\frac{M}{4}$ solution of natural *l*-ephedrine hydrochloride a satisfactory reaction is produced when the pupil of the treated eye is just perceptibly wider than that of the untreated eye. Munch (24), Munch and Gittenger (25) and Swanson, Thompson and Rose (26) have reported the threshold value or the dilatation of the pupil of the treated eye as just perceptibly wider than that of the untreated eye. These authors found that a $\frac{M}{4}$ solution of natural *l*-ephedrine hydrochloride gave this threshold value. Table II shows that the related ephedrine compounds do not produce a dilation of the eye (threshold dose) with $\frac{M}{4}$ solutions equal to that of a $\frac{M}{4}$ solution of ephedrine.

TABLE II.

Number of Compound.	Mydriasis 5 Per Cent (Cats).	Inhibition of Isolated Intestine (Rabbits).	Contraction of Uterus (Isolated). Guinea pigs.	Contraction of Uterus (Isolated). Rabbits.	Nasal Mucous Membrane Volume (Turbinates).	Blood Pressure in Cats by Intravenous Injection.	Toxicity per Kg. Rabbits (Intravenous).	Bronchioles. Intact pithed dogs, Jackson's method.	Bronchioles. Isolated lungs, Sollmann's and Von Oettingen's.
1	+++++	+	+	+	+	+	60 mg.	+	+
2	−	+	+	+	+	+	35 mg.	+	+
3	−	+	+	+	+	+	45 mg.	−	−
4	−	+	+	+	+	+	15 mg.	−	−
5	−	+	+	+	+	+	60 mg.	+	+
6	−	+	+	+	+	+	Not enough material	+	+
7	−	+	+	+	+	Lowered blood pressure	Not enough material	+	+
8	−	+	+	+	+	+	130 mg.	+	+
9	−	+?	+	+	?	+	Not enough material	−	−

Chen, Chang-Keng Wu and Erle Hendriksen (16) reported the mydriatic action of ephedrine and related compounds on albino rabbits' eyes. This same method was applied to cats. In Table II each plus mark under "Mydriasis" designates an increase of 0.5 mm. of the transverse diameter of the pupil. As pointed out by Chen, Chang-Keng Wu and Erle Hendriksen (16), the OH group on the B—C—atom from the N—atom is essential for the mydriatic action. Alkyl groups (methyl or ethyl) on the B—C—atom and that on the N—atom, or vice versa, the mydriasis remains. The extension or lengthening of these side chains makes this specific action disappear. The formation of tertiary amine abolishes

this action as in methyl ephedrine (16). Alkyl groups (methyl or ethyl) in the benzene ring as in compounds Nos. 2 and 3 also seem to abolish the mydriatic action. Chen (16) also found that the substitution of a β-hydroxyethyl group for the methyl group on the N—atom decreases the mydriatic action. The piperidine derivatives, Nos. 5, 6, 7 and 8, and the oxyindan compound, No. 9, have no mydriatic action in the above dilutions.

The effects of ephedrine upon isolated muscle of the intestinal tract are inconstant (27). In these experiments, however, the action of these compounds (except compound No. 9) with 0.2 cc. to 0.5 cc. of $\frac{M}{20}$ solution on the rabbits' isolated intestines (2 isolated intestinal strips for each compound) immersed in Locke-Ringer solution at body temperature shows constant inhibition of intestinal movements. Compound No. 9 shows no effects either inhibition or stimulation. Compound No. 4 shows more marked inhibition than the others. This may be due to the benzylethyl group which is known to have a depressant effect as well as local anesthetic properties. The local anesthetic properties of compound No. 4 were compared with cocaine, procaine and neothesin. This will be discussed later.

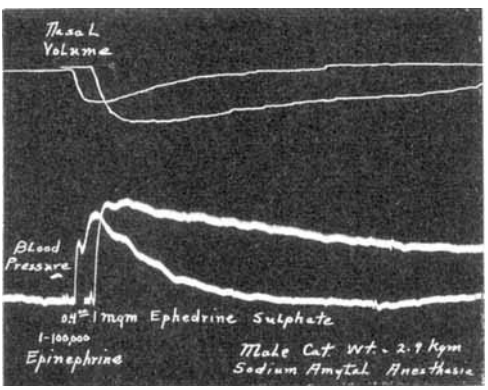


Fig. 1.—Represents an anesthetized male cat (sodium amytal), blood pressure and nasal volume recorded, injections of epinephrine and ephedrine were given. This is the method used to show the action of all these compounds on the nasal mucosa.

The effects of these compounds on the isolated uterine muscle immersed in Locke-Ringer solution at body temperature show a marked stimulation and increase of tone of the uterus. Compound No. 4 shows less stimulation than the others. Here again the benzylethyl group seems to show depression.

B. ACTION ON CIRCULATION.

The effect of these compounds on the blood pressure of pithed cats is probably the most important test of determining the comparative value of these compounds. The technique reported by Chen (28) was used in these experiments. The results are given in Table II. A plus sign under "Blood Pressure in Animals" indicates a rise. In performing the test, 0.1 cc. of a $\frac{M}{20}$ solution, or its equivalent, was injected intravenously. Fifty-eight cats of approximately the same weight (2 to 2.2 Kg.) were used. Comparisons were in all cases made equimolecularly. Compound No. 1 being natural *l*-ephedrine shows the well-known characteristic increase in blood pressure and duration of increase in blood pressure as shown in Fig. 1. Primary amines are more effective on blood pressure than secondary amines (ephedrine) and in turn tertiary amines are less active than the secondary (16). The extension or lengthening of the side chain on N—atom decreases the pressor value

as in compound No. 4 and also the piperidines, as in compounds Nos. 5, 6 and 8. The piperidine derivative No. 7 produces a fall in blood pressure. An ethyl or two methyl groups in the benzene ring, as in compounds Nos. 2 and 3, show no improvement in pressor action. The oxyindan compound No. 9 shows very little pressor action.

C. ACTION ON FROG'S HEART BY PERFUSION.

A comparison of the action on the frog's heart by perfusion was made by the method of Howell and Cooke (29), recently elaborated and extensively used by Sollmann and Barlow (30) and Chen, Chang-Keng Wu and Erle Hendriksen (16). Concentrations of $1:10^3$ were used. The compounds were, therefore, compared gram for gram, although molecular concentrations can be calculated from the perfusing solutions. At least three hearts were perfused with each compound. The results are summarized in Table III.

TABLE III.—THE PERFUSION OF THESE COMPOUNDS ON THE FROG'S HEART.

Compound Number.	Decrease in amplitude.	Effect of $1:10^3$ Solution. Decrease in rate per minute.		Disturbance in rhythm.
1	Moderate	−11	−13	None
2	Moderate	−14	−18	None
3	Marked	−22	..	None
4	Marked	−30	..	Block developed
5	Marked	−18	−24	Alternate rhythm
6	Marked	−22	..	None
7	Marked	−23	..	Alternate rhythm
8	Slight	− 4	−14	None
9	Slight	− 9	−11	None

According to the disturbance of the cardiac rhythm and decrease in rate per minute with dilutions of $1:10^3$, an interesting relationship may be observed by examining the results. An ethyl radical in place of the methyl radical on the N—atom does not materially change the action on the perfused heart nor does an ethyl radical in the benzene ring produce a change. However, two methyl radicals in the benzene ring produce a depression. A benzyl ethyl radical, as in compound No. 4 in place of the methyl radical on the N—atom, also produces a depression which is even more marked than with No. 3. A hydroxyethyl group in place of the methyl group on the N—atom shows less depression (16). Compounds Nos. 5, 6, 7 and 8 of the piperidine (phenyl piperidyl carbinyl) structure produce slightly more depression on the perfused heart than ephedrine, but less than Nos. 3 and 4. As shown in Table III, No. 8 of the piperidine group shows the least depression. Compound No. 9 shows no marked change on the perfused heart.

D. ACTION ON NASAL VOLUME OF CATS.

The action of these compounds on the nasal passage was determined by recording the nasal volume shrinkage of cats by an oncometer. This oncometer or plethysmograph has been described by Jackson (31). Our observations were considered only as qualitative, although the extent and duration of contraction could be recorded. As shown in Table II, all of the compounds cause shrinkage of the nasal passage or increase nasal volume. Figure 1 shows the type of curve

recorded by the nasal oncometer. No attempt was made to classify these compounds according to their chemical structure by their astringent action on the nasal mucosa.

E. TOXICITY IN RABBITS.

Rabbits of a pure breed (Chinchilla) were selected for the determination of the M. L. D. of each compound. Solutions of 10 per cent were made for intravenous injection with all compounds. The results are shown in Table IV. The toxicity of compounds Nos. 6, 7 and 9 was not determined because of insufficient material. Compounds Nos. 2, 3 and 4 show greater toxicity than ephedrine. Thus an extension or lengthening of side chain, or ethyl and methyl groups in the benzene ring increases toxicity. Compounds Nos. 5 and 8 of the piperidine group show considerable variation. The lethal dose of No. 5 is 60 mg. per Kg. and No. 8 is 130 mg. per Kg. Nos. 6 and 7 were not determined because of lack of material.

TABLE IV.—TOXICITY IN RABBITS (CHINCHILLA) BY INTRAVENOUS INJECTION OF COMPOUNDS.

Compound Number.	Concentration of Solution Per Cent.	Rabbit Number.	Sex.	Body Weight Kg.	Quantity Injected Mg. per Kg.	Result.	M. L. D. Mg. per Kg.
		1	M	2.420	40	Survived	
		2	M	2.515	50	Survived	
1	10	3	F	2.350	60	Survived	60
		4	M	2.535	60	Died	
		5	F	2.380	60	Died	
		40	M	2.865	10	Survived	
		41	F	2.753	20	Survived	
2	10	42	F	2.685	30	Survived	40
		43	M	2.635	40	Died	
		44	M	2.500	50	Died	
		45	M	2.245	30	Survived	
		46	M	2.295	30	Survived	
3	10	47	F	2.327	40	Survived	40–50
		48	M	2.320	40	Died	
		49	F	2.280	50	Died	
		55	F	2.080	5	Survived	
		56	M	2.231	10	Survived	
4	10	57	M	1.820	10	Survived	15
		58	M	2.080	15	Died	
		59	F	2.105	20	Died	
		66	F	2.100	50	Survived	
		67	M	1.655	50	Died	
5	10	68	M	2.065	50	Survived	60
		69	F	1.945	60	Died	
		70	M	1.870	60	Died	
		71	M	1.765	70	Died	
6 Insufficient material							
7 Insufficient material							
		72	M	2.335	60	Survived	
		73	M	2.085	70	Survived	
8	10	74	F	2.175	90	Survived	130
		75	F	1.960	110	Survived	
		76	F	1.855	120	Survived	
		77	M	2.025	130	Died	
9 Insufficient material							

F. LOCAL ANESTHETIC PROPERTIES OF COMPOUND NO. 4.

Compound No. 4 has a benzyl ethyl group in place of the methyl group on the N—atom. Read (32) reported local anesthetic properties with benzylephedrine Rose (33), Coles and Rose (34) and Rose, Coles and Thompson (35) have reported a comparative study of cocaine, procaine and neothesin. C. L. Rose has kindly included compound No. 4 in this study for local anesthetic properties. As shown in Table V and Table VI by various tests No. 4 has local anesthetic properties on the cornea of rabbit's eye and by the infiltration method in guinea pigs equal to and more effective than cocaine or procaine.

TABLE V.—COMPOUND NO. 4
DURATION OF ANESTHESIA.

Product.	Number of Rabbits.	Cornea (Minutes).	Number of Guinea Pigs.	Infiltration Method (Minutes).
No. 4	3	61	3	117
Cocaine	3	35	3	31
Procaine	.	..	3	24
Neothesin	3	34	3	44

TABLE VI.—COMPOUND NO. 4
TOXICITY.

Product.	Number of Rats Intravenous.	Mg. per Kg.	Number of Mice Subcutaneous.	Mg. per Kg.
No. 4	30	18	41	100
Cocaine	25	18	35	200
Procaine	20	50	25	900
Neothesin	20	20	30	800

In mice, No. 4 is twice as toxic as cocaine and nine times that of procaine. For local anesthetic use, this compound is too toxic.

G. ACTION ON THE LUNGS.

As previously stated this study includes the action of these compounds on the bronchioles of pithed dogs and on the perfused isolated lungs of cats. In pithed dogs by Jackson's method (18), (19) and (20), and elaborated by Swanson (22) and (23) the drugs, ergotoxine, epinephrine and ephedrine and derivatives, were injected in consistent amounts in all experiments. As shown in Fig. 2, the dog weighed 8 Kg. After pithing and attaching blood pressure manometer and bronchiole recorder, 1 mg. per Kg. of ergotoxine, 0.001 mg. per Kg. of epinephrine, and 1 mg. per Kg. of compound No. 4 were injected. By this technique none of the compounds failed to show dilatation of bronchioles equal to ephedrine. In Table II, the results are summarized. The same technique of consistent dosage was used in testing these drugs in the perfused isolated lung. Compound No. 3 shows no effect on either the bronchioles of pithed dogs or isolated perfused lungs of cats. No action is observed with compound No. 9. Compound No. 4 shows no effect on the dog but gives some dilatation in the isolated lungs of cats. Thus an extension or lengthening of the side chain weakens the bronchodilator action. Alkyl groups in the benzene ring weaken them still more. The piperidine group is less active than ephedrine and the oxyindan compound, No 9, shows no effects in doses equal to ephedrine.

COMMENT.

Chen, Wu and Hendriksen (16) have shown that the presence of a methyl or ethyl group on the B—C—atom, or the N—atom, weakens the activity of the compound as compared with β-phenylethylamine, the ethyl being less active than the methyl derivative. A methyl or ethyl on the B—C—atom renders that compound a prolongation of action and loss of pressor response upon repeated intravenous injections in animals. The increase in the number of C—atoms in the

side chain on the B—C—atom, or the N—atom, is accompanied by an increasing depressant action on the heart, decrease in pressor value and increase in toxicity in rabbits. Chen, Wu and Hendriksen (16) showed that the presence of a third alkyl group on the N—atom (a tertiary amine) further weakens the physiological effects.

Our results confirm the findings of Chen, Wu and Hendriksen (16) in regard to the secondary amines (ephedrine and derivatives) and in addition show that the presence of a methyl, 2 methyls or an ethyl group in the benzene ring also weakens the pressor value, bronchodilator action and increases the toxicity in rabbits. The presence of a piperidine group which is isomeric but structurally

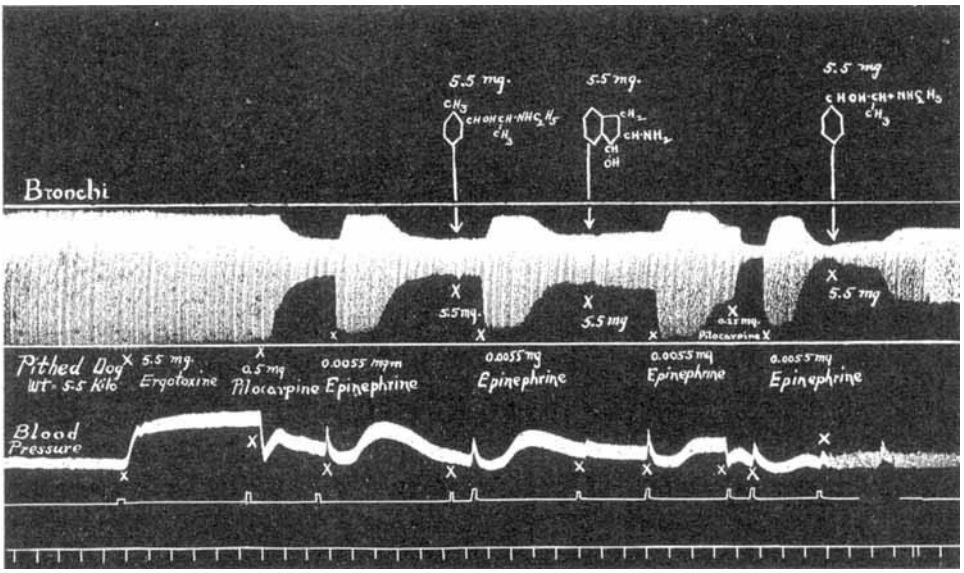


Fig. 2.—Represents a pithed dog, weight 5.5 Kg., artificial aspiration 28 per minute, blood pressure and bronchiole movement recorded. Ergotoxine injected 1 mg. per Kg. intravenously; pilocarpine 0.5 mg.; epinephrine 0.001 mg. per Kg.; compound No. 3 1 mg. per Kg.; epinephrine 0.001 mg. per Kg.; compound No. 9 1 mg. per Kg.; epinephrine 0.001 mg. per Kg.; pilocarpine 0.25 mg.; epinephrine 0.001 mg. per Kg., and finally ephedrine 1 mg. per Kg. Compounds Nos. 3 and 9 showed no dilatation of bronchioles in the above doses; whereas ephedrine did.

different on the B—C—atom appears to weaken the compound. An interesting observation of the piperidine group is the depressor action of No. 7; whereas the others give slight pressor action. No. 8 is approximately one-half as toxic as No. 5.

The oxyindan compound apparently shows only pressor action comparable to epinephrine. Its action on the bronchioles is negative.

CONCLUSIONS.

1. A series of eight new compounds was studied.

2. With increase in the number of C—atoms in R," the mydriatic and pressor actions are reduced, the cardiac depressant action is increased, the bronchodilator action is decreased and the toxicity rises.

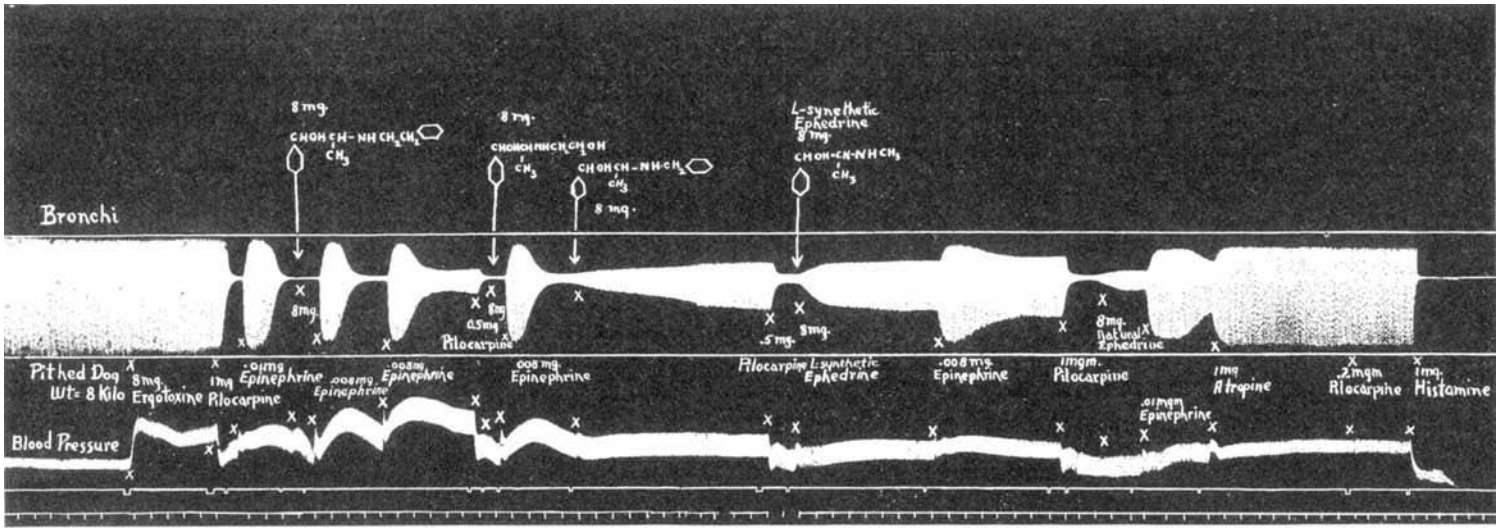


Fig. 3.—Represents a pithed dog, weight 8 Kg., artificial aspiration, blood pressure and bronchiole movement recorded. Dog ergotamized with 1 mg. per Kg.; injected 1 mg. pilocarpine; 0.001 mg. per Kg. epinephrine; 1 mg. per Kg. compound No. 4 (no effect on bronchioles); two doses 0.001 mg. per Kg. epinephrine; 0.5 mg. pilocarpine; 0.001 mg. per Kg. epinephrine; 0.5 mg. pilocarpine; 1 mg. per Kg. of synthetic *l*-ephedrine (district dilatation of bronchioles); 0.001 mg. per Kg. of epinephrine; 1 mg. of pilocarpine; 1 mg. per Kg. ephedrine; 0.001 mg. epinephrine; 1 mg. atropine; 2 mg. pilocarpine; and finally 1 mg. histamine.

3. Practically all of the ephedrine-like compounds inhibit the isolated rabbit's intestine, stimulate the isolated guinea pig's uterus and contract the nasal mucosa of cats.

4. Alkyl groups in the benzene ring decrease the mydriatic and pressor actions, increase cardiac depressant action, decrease the bronchodilator effects and increase toxicity.

5. The piperidine group on the B—C—atom reduces the mydriatic and pressor effects. In one case, it produces depressor action and variable results on the perfused heart of frogs and in the toxicity of rabbits. All show bronchodilator action but distinctly less than ephedrine.

6. The oxyindan compound, No. 9, in doses equivalent to ephedrine has no effect on smooth muscles, low pressor action and produces no marked change in the perfused heart.

The writer is much indebted to Doctor K. K. Chen for his many kind suggestions and criticisms during this work.

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