controlled by the muscle length. More exact methods of recording length and oxygen consumption simultaneously will be devised to improve the accuracy of the curve showing this relationship. This curve should also be very useful in determining other theoretical energy calculations involved in muscle physiology.

Conclusions. Ryanodine causes a high oxygen consumption in muscles which do not shorten. In those muscles that shorten the oxygen consumption falls off as the muscle shortens. The length of the muscle seems to regulate the oxygen consumption of the Ryanodine-treated muscle. Complete cutting off of the extra metabolism due to Ryanodine occurs at 30% of the rest length.

We are indebted to Dr. Roeder and to Merck and Co. for supplying us with the purified Ryanodine powder.

We wish to thank Dr. Robert W. Ramsey for his helpful advice and interest in this problem. We are also indebted to him for making many of the microscopic observations on the structure of the muscle at the conclusion of the experiments.

Received August 11, 1950. P.S.E.B.M., 1950, v75.

Pharmacology of Para-substituted Derivatives of Diphenhydramine. (18112)

GRAHAM CHEN, CHARLES R. ENSOR, AND ISABEL G. CLARKE

From the Research Laboratories, Parke, Davis & Co., Detroit, Mich.

Among a number of the derivatives of 2-benzhydryloxy-N-N-dimethylethylamine (diphenhydramine), tested for their antihistaminic activity, the para-substituted compounds were found of special interest from the standpoint of the relationship between chemical constitution and pharmacological action. In this report, a comparison of the pharmacological properties will be made of the para-alkyl-, para-methoxy- and the para-halogen-derivatives of 2-benzhydryloxy-N, N-dimethylethylamine with a view of appraising their therapeutic applicability.

Materials and methods. The following compounds,* p-methyl, p-ethyl, p-n-propyl, p-methoxy, p-fluoro, p-chloro, p-bromo and p-iodo benzhydryloxy-N, N-dimethylethylamine as their hydrochlorides, have been investigated. They are white crystalline compounds, freely soluble in water.

The antihistamine potency of a compound was determined: (a) by protection against the lethal toxicity of histamine aerosol in guinea pigs, and (b) by suppression of the histamine-induced contraction of an isolated intestinal strip with procedures as previously described(1,2). Similar technics were employed for estimating anticholinergic and myotropic spasmolytic activities. Acetyl-beta-methylcholine chloride (methacholine) was used to produce a fatal cholinergic bronchospasm to guinea pigs(3). At least 48 animals, 12 per group for each dose, were used to determine a 50% protective dose of the drug.

Acute toxicity was determined in mice by intraperitoneal injection. The LD_{50} and average standard error were calculated from the mortalities, obtained with 5 doses of the drug in groups of 20 animals each, by the method of Miller and Tainter(4).

The potentiation of epinephrine by and the atropine-like action of these compounds on blood pressure were investigated in dogs under pentobarbital anesthesia with standard procedures.

Results and discussion. As the data in

* Kindly made available to us by Drs. R. W. Fleming and G. Rieveschl, Chemical Division Research Laboratories, Parke, Davis and Co.

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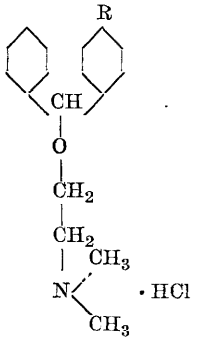
TABLE I. Efficacy of p-Substituted Diphenhydramine Derivatives in Preventing Fatal Histamine-induced and Mecholyl-induced Bronchoconstriction in Guinea Pigs; and Acute Toxicity in Mice.

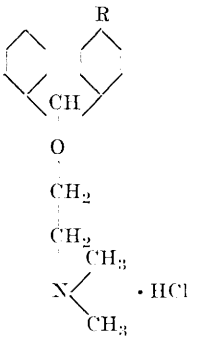
Compound	Antihistamine: mg/kg P.D. 50 ± S.E. (I.P.)	Antihistamine: Activity ratio*	Toxicity: mg/kg L.D. 50 ± S.E. (I.P.)	Toxicity: Ratio	Therapeutic index‡: Activity ratio / Toxicity ratio	Anti-cholinergic mg/kg (P.D. 50, I.P.)
						0.058 (Atropine)
R = H†		1	56 ± 2.2	1	1	25.0
R = CH_3 (R = H)	0.73 ± 0.14§ (2.08 ± 0.44)	2.85 ± 0.82 S.E.	150 ± 2.0	.37	7.7	Ineffective at 50
R = C_2H_5		2	117 ± 4.0	.48	4.2	Ineffective at 50
R = n-C_3H_7		1	67 ± 1.6	.84	1.2	
R = CH_3O		1	148 ± 2.4	.38	2.6	Ineffective at 50
R = F		3	57 ± 2.0	.98	3.1	"
R = Cl		1	79 ± 2.7	.71	1.4	"
R = Br (R = H)	1.25 ± 0.20‖ (2.70 ± 0.67)	2.16 ± 0.64 S.E.	108 ± 2.5	.50	4.3	"
R = I		3	92 ± 3.3	.61	4.9	"

* The activity of each compound was determined simultaneously with that of diphenhydramine with the same stock of guinea pigs.
† Diphenhydramine.
‡ Assuming that the toxicity in guinea pigs is directly proportional to that in mice.
§ 7 experiments.
‖ 3 experiments.

Table I indicate, para-substitution with a halogen or an alkyl group results either in an enhancement of antihistamine activity, a decrease in toxicity or both. The anticholinergic action, on the other hand, is greatly diminished by the substitution. In the alkyl-substituted compounds, the methyl group is the most effective giving a therapeutic index seven times that of the parent substance by an increase in activity and a decrease in toxicity. The lengthening of the alkyl chain decreases the therapeutic efficacy. In the halogen series, with the exception of fluorine, the therapeutic index increases with the atomic weight. By substitution with fluorine, the antihistamine activity is increased, while the toxicity remains about the same. The para-methoxy derivative of diphenhydramine is equal to the parent compound in activity but only half as toxic.

The *in vitro* results in Table II, obtained with the isolated ileal strip, are generally in agreement with those from histamine aerosol and from mecholyl aerosol in guinea pigs. The myotropic spasmolytic effect of the para-substituted compounds, as determined by suppression of $BaCl_2$-induced contraction of the gut, is approximately of the same magnitude

TABLE II. Concentrations of p-Substituted Diphenhydramine Derivatives Which Inhibit the Spasmogenic Effects of Histamine, Acetylcholine, and Barium Chloride on Isolated Guinea Pig Ileum.

Compound	Histamine activity* ratio		Acetylcholine activity* ratio		Barium chloride activity* ratio	
						
R = H	.0058 γ/cc†	1	.350 γ/cc†	1	2.55 γ/cc†	1
R = CH_3	.0028 "	2.07	2.175 "	0.16	2.56 "	1.04
R = H	.0066 "	1	.125 "	1	1.51 "	1
R = C_2H_5	.0082 "	0.80	2.500 "	0.05	1.40 "	1.08
R = H	.0138 "	1	.0122 "	1	1.47 "	1
R = n-C_3H_7	.0338 "	0.41	.738 "	0.17	0.99 "	1.49
R = H	.0072 "	1	.0995 "	1	1.47 "	1
R = CH_3O	.0107 "	0.76	1.8965 "	0.05	1.79 "	0.82
R = H	.0131 "	1	.0955 "	1	0.25 "	1
R = F	.0073 "	1.79	.1966 "	0.48	0.38 "	0.66
R = H	.0218 "	1	.0547 "	1	3.95 "	1
R = Cl	.0140 "	1.56	.1986 "	0.27	2.30 "	1.70
R = H	.0101 "	1	.0775 "	1	0.97 "	1
R = Br	.0074 "	1.36	.3150 "	0.24	1.09 "	0.89
R = H	.0127 "	1	.1277 "	1	4.06 "	1
R = I	.0088 "	1.45	.8210 "	0.16	2.38 "	1.62

* The activities of diphenhydramine and the derivative being compared on the same intestinal strip.

† Concentration that inhibits 50% of the maximal contractions by the spasmogenic agent, each value representing an average of 2 determinations on different strips.

as that of diphenhydramine.

The modification of antihistamine potency and toxicity of parasubstitution has been reported for tripelennamine(5). In tripelennamine, para-substitution with a methoxy group (Neoantergan) increases the antihistaminic activity with no change in toxicity. The para-bromobenzyl derivative is less toxic but not more active than the parent compound. On the other hand, the antihistaminic activity is somewhat lowered by para-substitution with a methyl group, and activity is almost lost in the ethyl analog. In contrast, an increase of antihistaminic activity results by adding a halogen, methyl or an ethyl radical at the para-position of diphenhydramine.

Like diphenhydramine, the para-substituted derivatives produced a slight rise in blood pressure in the dog with small intravenous doses and an immediate transient fall following large doses. They potentiate the vasopressor effect of epinephrine and antagonize the vasodepressor effect of acetylcholine. Their atropine-like action, however, is much less than that of diphenhydramine.

The manifestations of acute toxicity in mice of these p-substituted compounds are qualitatively similar to those of diphenhydramine, *viz.*, excitement followed by depression.

The therapeutic efficacy of the para-methyl

5. Viand, P., Produits pharmac. France 2/2, 53-64, 1947.

and para-bromo derivatives of diphenhydramine has been appraised clinically. The collective data indicate that their antihistaminic activity is comparable to that of diphenhydramine. The incidence of drowsiness and atropine-like effects is low with the para-methyl derivative(6,7); it is insignificant with the para-bromo compound(8).

Summary. The antihistaminic, anticholinergic and musculotropic spasmolytic properties of the para-halogen, para-methoxy and some para-alkyl derivatives of 2-benzhydryloxydimethylethyl amine have been investigated. Para-substitution with methyl, ethyl and halogen atom results in an enhancement of antihistaminic activity, a decrease in acute toxicity, or both. It lowers the atropine-like action but does not produce a significant change in musculotropic spasmolytic activity.

Received August 25, 1950. P.S.E.B.M., 1950, v75.

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Hypoadrenalism: Steroidal Mediation of Sodium Action on Blood Pressure; Modification of Antiarthritic Response to Cortisone.* (18113)

GEORGE A. PERERA AND CHARLES RAGAN

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Edward Daniels Faulkner Arthritis Clinic, Presbyterian Hospital, New York.

Considerable evidence has accumulated that both the sodium ion and the adrenal cortex are concerned to some extent with the maintenance of blood pressure levels in hypertensive patients(1-3). Although the rigid restriction of salt masks the pressor response of hypertensives to desoxycorticosterone(4), this type of observation does not establish the fact that alterations in sodium metabolism modify the arterial tension through an adrenal mechanism. It has been noted that the adrenals of rats on a reduced sodium intake may be smaller and different in color(5), temporarily depleted of ascorbic acid(6), and may show secretory changes(7) and (in nephritic animals) subcapsular hyperplasia (8). Furthermore, excessive salt, or liberal amounts in animals receiving desoxycorticosterone, has resulted in progressive structural and functional atrophy of the glomerular zone of the adrenal cortex(9,10). Finally, chromatographic patterns of urinary steroid excretion may be influenced by the salt intake(11).

In order to investigate further the possibility that sodium influences the blood pressure through steroidal action, studies were

* This study was supported in part by a research grant from the National Heart Institute, U.S.P.H S., and was aided through the generosity of the Albert and Mary Lasker Foundation, the Albert H. and Jessie D. Wiggin Foundation, and the Masonic Foundation for Medical Research and Human Welfare.

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