

Effect of Changes of the Hydrogen-Ion Concentration.—In these experiments 10-cc. samples of the two solutions containing 0.5 cc. phenol red solution were adjusted to different p_H by the addition of small quantities of $N/10$ hydrochloric acid or $N/10$ sodium hydroxide.

SUMMARY.

A method is described, which allows the preparation of pure dibismuthyl monosodium citrate, with a good yield.

The preparation obtained with this method is identical with the compound obtained with the modified Fabrègue method.

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AMINOALCOHOLS VI—A STUDY OF THE ACTION OF PHENYLPROPANOLAMINE UPON THE BLOOD SUGAR OF RABBITS.*

BY JOHN C. KRANTZ, JR., AND WALTER H. HARTUNG.

INTRODUCTION.

It was established years ago by Blum (1) that injections of a solution of epinephrine caused hyperglycemia and often glycosuria. For some time it was considered that the elevation of the blood-sugar level was caused by increased glycogenolysis in the liver (2). Recent investigations by Cori (3) using more refined analytical methods indicate that the importance of the liver in the hyperglycemia is only secondary and further that the factor of primary importance in producing the accumulation of sugar in the blood is the decreased utilization of the sugar in the peripheral tissues.

Since the introduction of ephedrine into clinical medicine by the classical investigations of Chen and Schmidt (4), Wilson (5) at the suggestion of Chen studied the effect of this compound related to epinephrine upon the blood sugar of dogs and rabbits and observed a definite hyperglycemia. This action is claimed by Nagel (6) to be characteristic of the sympathomimetic amines.

Out of these Research Laboratories has come a series of synthetic arylalkanolamines (7) which because of their analogy to and homology with ephedrine were examined as to their effect on blood sugar in rabbits. Since phenylpropanolamine, a primary amine, has a pharmacological action much like that of ephedrine (Chen 8), a secondary amine, and because of its possible therapeutic interest, the effect of this compound was examined more extensively than the others.

METHOD OF STUDY.

Rabbits were starved twenty-four hours prior to the administration of the drug. The blood-sugar determinations were made by the method of Shaffer and Hart-

*Scientific Section, A. P. H. A., Baltimore meeting, 1930.

mann (9). The maximum rise or fall of blood was found to occur in practically all instances within 30 to 70 minutes after the intravenous injections.

The therapeutic doses of phenylpropanolamine hydrochloride which were found to influence the blood-sugar level of rabbits when administered intravenously were from 20 to 30 mg. per kilo. Studies were also made of the influence on blood sugar when this compound were administered subcutaneously and orally.

RESULTS.

Table I records the changes in the blood-sugar level of rabbits after intravenous injections of phenylpropanolamine hydrochloride.

TABLE I.—CHANGES IN THE BLOOD SUGAR OF RABBITS CAUSED BY INTRAVENOUS INJECTIONS OF PHENYLPROPANOLAMINE HYDROCHLORIDE.

Wt. of rabbit, Kg.	Dose, mg./Kg.	Fasting blood sugar, mg. per 100 cc.	Blood sugar 30 min. after injection.	Blood sugar 70 min. after injection.
2.3	30	120	106	103
1.7	40	101	137	127
1.7	40	104	122	98
3.0	40	98	116	106
1.8	40	109	151	146
2.0	40	116	124	132
1.7	20	95	101	82
2.0	30	104	95	95
1.5	30	104	140	124
1.6	30	98	89	87
2.2	20	104	82	87
3.5	20	106	92	89
3.2	30	111	101	95
2.1	30	92	101	101
3.0	20	92	76	104
3.2	20	101	82	89
2.0	25	92	114	114
2.0	25	106	116	89
1.3	25	95	106	116
1.9	25	116	119	114
1.9	25	98	104	89
1.9	25	114	119	109
1.9	25	106	114	119
1.2	30	116	132	109
1.2	30	122	127	114
1.2	30	127	116	114
1.8	25	116	151	124
2.1	25	106	132	106
2.1	25	98	106	111
1.8	25	119	116	104
1.8	25	109	119	109
1.8	25	124	114	101

The results tabulated in Table I indicate that the injection of 20 to 30 mg. of phenylpropanolamine hydrochloride influences the blood-sugar level of rabbits. The influence is not marked and may be either hypo or hyperglycemic.

Chart I shows the frequency of occurrence and the degrees of hyper and hypoglycemia produced by these injections.

With intravenous injections of ephedrine sulphate in rabbits' dose 20 to 30 mg. per kilo Wilson (5) found variable but definite hyperglycemic action. Thus in two rabbits with doses of 30 mg. per kilo he obtained significant rises in blood sugar of 92 and 65 mg. Repeating the experiment of Wilson on three rabbits using the same time intervals as were employed (in the experiments) with phenylpropanolamine hydrochloride definite hyperglycemic activity was observed in only one of the three rabbits as shown in Table II.

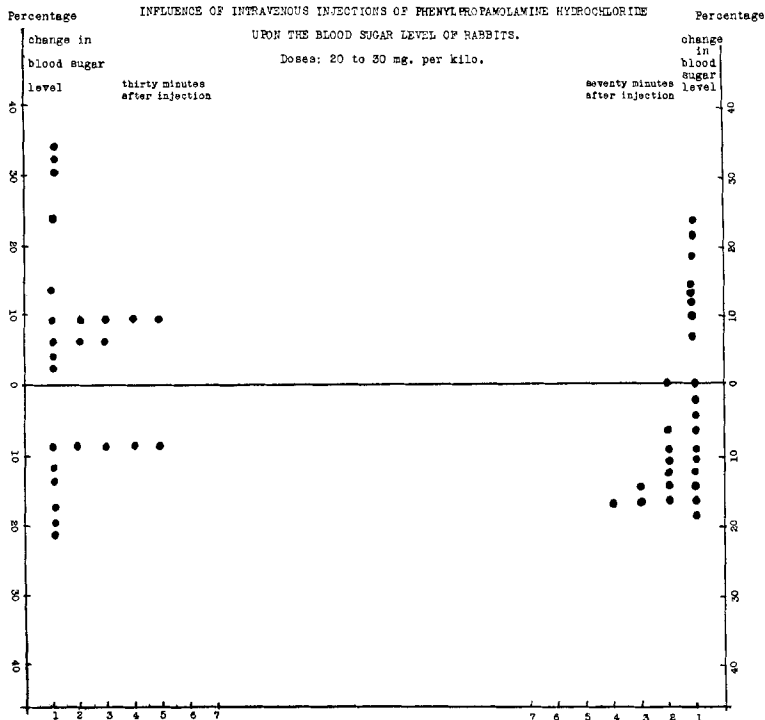


Chart I.

TABLE II.—THE ACTION OF INTRAVENOUS INJECTIONS OF EPHEDRINE SULPHATE UPON THE BLOOD-SUGAR LEVEL OF RABBITS.

Wt. in kilo.	Dose per kilo mg.	Fasting blood sugar of rabbit, mg. per 100 cc.	Blood sugar 30 min. after injection.	Blood sugar 70 min. after injection.
1.6	25	106	109	104
1.3	25	92	106	95
1.7	25	116	143	122

TABLE III.—THE ACTION OF SUBCUTANEOUS INJECTIONS OF PHENYLPROPANOLAMINE HYDROCHLORIDE UPON THE BLOOD-SUGAR LEVEL OF RABBITS.

Wt. in kilo.	Dose, mg./Kg.	Fasting blood sugar of rabbits, mg. per 100 cc.	Blood sugar 1 hr. after injection.	Blood sugar 2 hrs. after injection.
2.4	100	104	119	119
1.8	100	106	98	101
2.8	100	109	101	101
2.1	100	132	114	111

Further experiments were conducted with phenylpropanolamine hydrochloride upon rabbits studying its influence upon the blood-sugar level when administered subcutaneously and orally.

The results of these experiments are shown in Tables III and IV.

TABLE IV.—THE ACTION OF PHENYLPROPANOLAMINE HYDROCHLORIDE UPON THE BLOOD SUGAR OF RABBITS ADMINISTERED ORALLY.

Wt. in kilo.	Dose, mg./Kg.	Fasting blood sugar of rabbit, mg. per 100 cc.	Blood sugar 1 hr. after dose.	Blood sugar 25 hrs. after dose.
2.6	200	87	111	89
2.1	200	71	76	79
2.8	200	82	89	79
1.8	200	84	74	76
2.4	200	82	87	92

The action of certain compounds homologous to phenylpropanolamine were studied by intravenous injections. The results of these experiments are recorded in Table V.

TABLE V.—THE ACTION OF INTRAVENOUS INJECTIONS OF CERTAIN HOMOLOGS OF PHENYLPROPANOLAMINE UPON THE BLOOD SUGAR OF RABBITS.

A.				
Phenylbutanolamine Hydrochloride.				
Wt. in kilo.	Dose, mg./Kg.	Fasting blood sugar of rabbit, mg. per 100 cc.	Blood sugar 30 min. after injection.	Blood sugar 70 min. after injection.
1.9	25	100	113	94
2.3	25	85	100	117
B.				
Phenylhexanolamine Hydrochloride.				
1.7	25	98	Died	...
3.0	20	82	124	146
C.				
<i>p</i> -Tolyl Propanolamine Hydrochloride.				
2.3	20	109	180	220
3.2	20	76	84	111

DISCUSSION OF RESULTS.

The frequency chart showing the influence of intravenous injections of phenylpropanolamine hydrochloride upon blood sugar shows the following trends: Thirty minutes after injection, the tendency of activity is toward a mild hyperglycemia in most instances, approximately 60 per cent, resulting in a rise of about 10 mg. per 100 cc. of blood. Seventy minutes after injection, the tendency of the blood sugar level is to fall below the fasting level, most of these determinations indicate a fall of about 18 mg. When administered subcutaneously (100 mg. per kilo) or orally (200 mg. per kilo) the drug is without appreciable effect upon the blood-sugar level of rabbits. The marked hyperglycemic action of ephedrine sulphate reported by Wilson (5) was not observed in the three rabbits used; the hyperglycemia was practically negligible in two cases, but in no instance was there a fall below the normal blood sugar as occurred in some cases with phenylpropanolamine hydrochloride.

The injections of phenylbutanolamine hydrochloride and phenylhexanolamine hydrochloride seem to indicate that their actions are hyperglycemic. The introduction of the methyl into the aromatic nucleus, as in *p*-tolylpropanolamine hydrochloride, produces marked hyperglycemic activity when injected intravenously. These results indicate that possibly an interesting relationship between hyperglycemic activity and homology might be revealed by a more comprehensive study of the compounds of this series, and such a study will be undertaken in these laboratories.

SUMMARY.

1. The action of phenylpropanolamine hydrochloride upon the blood sugar level of rabbits has been studied intravenously, subcutaneously and orally.

2. The action of certain homologs of phenylpropanolamine has been studied intravenously.

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RESEARCH LABORATORIES,
SHARP & DOHME.

PHYTOCHEMICAL NOTES.***

NO. 105. MONARDA PUNCTATA, L.†

BY A. A. HARWOOD.

For the purpose of supplementing earlier chemical work on this species, it seemed desirable to subject the several parts of the plant to a preliminary chemical examination. More particularly did it seem important to acquire some understanding of the inorganic constituents because of the possible relation these may have to the thymol-carvacrol isomerism of the two species *M. punctata* and *M. fistulosa*.

The Root.—Two moisture determinations yielded 4.0 p. c. and 4.5 p. c., respectively, in the air-dried material when determined by the xylene method. The same material yielded the following amounts of ash in two determinations.

	I.	II.
Water-soluble ash	0.96 p. c.	1.03 p. c.
Water-insoluble ash	6.67 " "	4.71 " "
Total ash	7.63 " "	5.74 " "

* Part of a thesis submitted for the degree of Doctor of Philosophy, University of Wisconsin.

** From the laboratory of Edward Kremers.

† See also THIS JOURNAL, 18 (1929), 228; 19 (1930), 1171.