nephrine. A series of injections of procaine:epinephrine mixture are then injected and the results compared.

Procaine is aminobenzoyl-diethyl-amino-ethanol. A similar potentiation of pressor action of epinephrine has been obtained with phenylpropanolamine (2), with cocaine (methyl-benzoyl-ecgonine) (3) and with a number of other local anæsthetics of unrelated chemical structure (3). No particular chemical nucleus has been found essential in producing this pressor potentiation.

CONCLUSIONS.

1. By comparing the increases in blood pressure produced by a series of injections of procaine-epinephrine mixture with those produced by a previous series of injections of standard epinephrine it is possible to assay these mixtures by the method outlined in U. S. Pharmacopœia X for epinephrine. The results fall within the limits of experimental error.

2. A number of successive injections of solutions containing between one hundred parts and one thousand parts of procaine to one part of epinephrine potentiate the pressor response of epinephrine in the same solution and in standard epinephrine injected within a period of one hour. After that time the potentiating action seems to disappear.

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AMINO ALCOHOLS. 3.—THE POTENTIATION OF THE PRESSOR ACTION OF EPINEPHRINE BY ARYLPROPANOLAMINES.*

BY JAMES C. MUNCH AND WALTER H. HARTUNG.

The bioassay of ephedrine has been complicated by the findings (1, 5 and 6) that successive intravenous injections of the same quantity to dogs or cats give progressively smaller rises in blood pressure. To determine the pressor activity of ephedrine and its related homologues, Chen used the method first developed by Elliott (3) for the assay of epinephrine. Decerebrate cats are injected intravenously with varying doses of a standard solution of epinephrine, after which a single injection of ephedrine or related drug is given intravenously. The increase in blood pressure produced by this single injection is compared with the rises in the epinephrine series and the relative potency determined.

In the authors' investigations of amino alcohols (4) of the ephedrine and epinephrine type, we were interested in determining the effect of a single dose of ephedrine and its homologues upon the subsequent pressor effects of epinephrine itself. Experiments were conducted upon medium-sized dogs, anæsthetized with

* Scientific Section A. PH. A., Rapid City meeting, 1929.

morphine and chloretone. The use of atropine in some instances did not appear to influence the magnitude of blood-pressure changes. The series of injections of standard epinephrine usually ranged from five to fifty micrograms (0.005 to 0.050 mg.). The relative sensitivity of the test animals was determined from the dose of epinephrine which caused an increase of approximately thirty mm. Results were plotted and the quantity of epinephrine determined which would give a rise of thirty mm.

After the series of responses to graded doses of epinephrine had been obtained, a single injection of the product under investigation was made intravenously or orally. The effect of this single injection was recorded and will be reported in another paper of this series. At various intervals of time following this injection, the original doses of epinephrine were repeated. The results obtained in the second series have also been plotted and that quantity determined which would cause an increase of thirty mm. in blood pressure.

In the assay of epinephrine outlined in U. S. Pharmacopœia X, it is stated that various doses of epinephrine are to be given a dog until a rise in blood pressure between thirty and sixty mm. is produced. The increases in blood pressure obtained in this series fell rather close to thirty mm. in most instances. Accordingly, this particular value was selected as a matter of convenience.

The results obtained in this work are consolidated in Tables I and II. Ephedrine was administered as a solution of the sulphate, while the hydrochlorides of the other products were used. The doses are given in terms of the respective salts. Intravenous injections were made into the femoral vein. When oral administration was employed, all food was withheld from the dogs for twelve hours, although they were given drinking water *ad libitum*. The calculated quantity of the salt was dissolved in about 40 cc. of distilled water and injected from a record syringe

TABLE I.—EFFECT OF AMINO ALCOHOLS ON PRESSOR ACTION OF EPINEPHRINE. INTRAVENOUS ADMINISTRATION.

Product.	Chart no.	Dose, mg./Kg.	Mg. Epinephrine to Produce 30 Mm. Rise in B. P. Before.	After.	Ratio B/A.
Phenylethanolamine No. 133	154	1.0	9	9	1.00
Diphenylethanolamine No. 130	174	2.0	42	42	1.0
Ephedrine Sulphate	117	0.14	5	23	0.2
Ephedrine Sulphate	118	0.67	23	23	1.0
Ephedrine Sulphate	150	1.0	19	7	2.75
Phenylpropanolamine No. 63	136	0.75	20	14	1.4
Phenylpropanolamine No. 63	151	1.00	14	5	2.75
Phenylpropanolamine No. 63	152	1.00	11	4	2.75
Phenylpropanolamine No. 63	111	2.25	15	4	3.75
Phenylpropanolamine No. 63	166	2.50	28	15	1.75
p-Methylphenylpropanolamine No. 79	114	1.5	32	26	1.25
p-Methylphenylpropanolamine No. 79	112	3.0	6	3	2.0
p-Hydroxyphenylpropanolamine No. 148	135a	0.2	13	10	1.3
p-Hydroxyphenylpropanolamine No. 148	139	0.5	30	19	1.5
p-Hydroxyphenylpropanolamine No. 148	142	0.75	8	4	2.0
p-Hydroxyphenylpropanolamine No. 148	135	1.0	16	8	2.0
Phenylbutanolamine No. 64	172	1.0	38	38	1.0
Phenylbutanolamine No. 64	171	1.0	30	30	1.0
Phenylpentanolamine No. 167	170	1.0	19	25	0.75

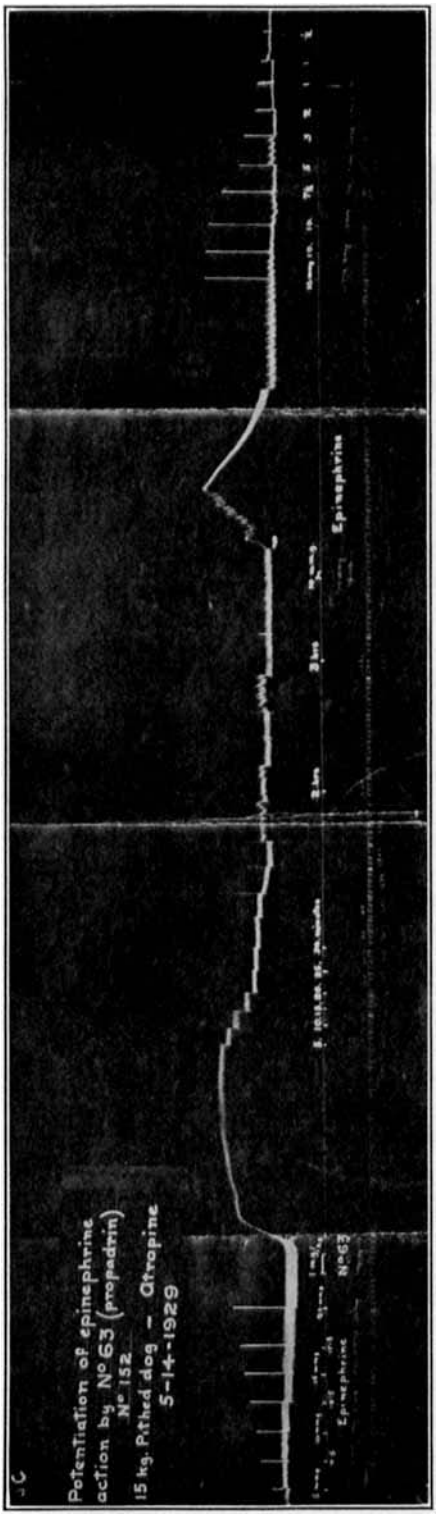


Fig. 1.—Potentiation of epinephrine action by No. 63. Pressor effect of 10 mmgm. epinephrine after intravenous injection of No. 63 is somewhat greater than the effect produced by 20 mmgm. before. Potentiation persisted in all epinephrine injections after No. 63.

through a rubber catheter which served as a stomach tube. Ten to twenty cc. of water were then used to wash the saline solution into the stomach.

The quantities of epinephrine in micrograms required to produce a rise of thirty mm. in blood pressure before and after the administration of the amino alcohols are recorded in the tables. To determine the effect of the drug upon the response to epinephrine, the quantity causing the desired effect before administration has been divided by the quantity causing the same effect after administration, and the quotient is given in the last column. A ratio of one indicates that the drug studied had no effect upon the pressor response to epinephrine; a ratio less than one that the pressor response was decreased; whereas a ratio greater than one, a potentiation of effect.

By inspection of the results of Table I, it is noted that an increase in the dose of any of these drugs intravenously causes an increase in ratio. There is a general trend of increase in potency with increase in dosage and there appears to be a stabilization at a ratio of about two. This would signify that the intravenous injection of epinephrine following that of any of the arylpropanolamines will produce a greater rise in blood pressure than will injections of the same quantity before their administration. The extent of increased action depends upon the dose employed but apparently tends to become twice as potent. Results obtained with ephedrine, phenylpropanolamine (No. 63) and its *para*-hydroxy derivative (No. 148) are in reasonable agreement.

The *para*-methyl derivative (No. 79) seemed to be somewhat less efficient in causing potentiation. No potentiation was noted following phenylethanolamine (No. 133), phenylbutanolamine (No. 64) nor diphenylethanolamine (No. 130) when given intravenously in doses of one mg. per Kg.

TABLE II.—EFFECT OF AMINO ALCOHOLS ON PRESSOR ACTION OF EPINEPHRINE. ORAL ADMINISTRATION.

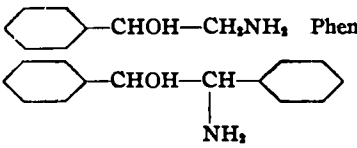
Product.	Chart no.	Dose, mg./Kg.	Mg. Epinephrine to Produce 30 Mm. Rise in B. P. Before.	After.	Ratio B/A.
Ephedrine Sulphate	127	10.0	32	37	0.9
Ephedrine Sulphate	163	12.5	40	34	1.25
No. 63	162	8.3	34	33	1.0
No. 63	161	12.5	7	13	0.67
No. 63	158	25.0	10	20	0.5
No. 63	162	25.0	11	9	1.25
No. 63	159	50.0	23	30	0.75
No. 63	168	75.0	42	42	1.0
No. 63	124	100.0	15	8	2.0
No. 63	167	100.0	32	40	0.75
No. 148	140	3.0	22	21	1.0
No. 148	141	10.0	3	3	1.0

Results of oral administration of some of these products are given in Table II. The results are more variable than those obtained with intravenous injections. It appears that potentiation of pressor action was not produced by the dose used. It is interesting to note that when quantities of phenylpropanolamine (No. 63) up to and including 75 mg. per Kg. orally failed to show any evidence of potentiation they also failed to show any definite evidence of increase in blood pressure. The injection of 100 mg. per Kg. orally causes a definite increase in the blood pressure of dogs and the results obtained suggest the possibility of some potentiation. The number of animals tested has been too small to warrant definite conclusions regarding the potentiating action of this oral dose. The conclusion seems warranted that the oral administration of these arylpropanolamines in the doses employed has not caused definite potentiation of the pressor effects of epinephrine.

After these experiments had been completed, a clinical report by Csepai and Doleschall (2) came to our attention. These authors report that the administration of ephedrine caused a subsequent injection of epinephrine to produce a greatly potentiated increase in blood pressure. The results obtained in our investigation suggest that this same potentiation may be produced by other arylpropanolamines. It has not been found following the intravenous injection of ethanol, butanol, pentanol nor diphenylethanol derivatives. It is shown by phenylpropanolamine, its *para*-methyl and *para*-hydroxy derivatives, as well as by the methylamino derivative (ephedrine).

The graphical formulae of the compounds studied are given below. From these results it is evident that the phenylpropanolamine skeleton (Group B) must be present to potentiate the action of epinephrine in this series of homologues. Substitution in the aromatic nucleus by OH or CH_3 in the *para*-position or CH_3 on the amino nitrogen does not appear to alter this potentiating action. Decreasing (Group A) or increasing (Group C) the length of the aliphatic side chain promptly eliminates this effect.

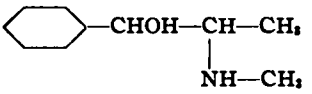
A. Ethanolamine Derivatives.



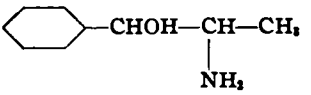
Phenylethanolamine

Diphenylethanolamine

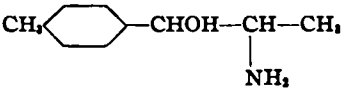
B. Propanolamine Derivatives.



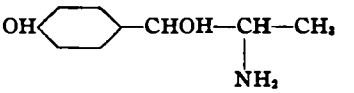
Phenylpropanolmethylamine (ephedrine)



Phenylpropanolamine

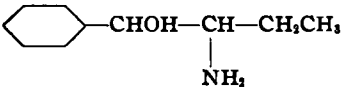


p-Methylphenylpropanolamine

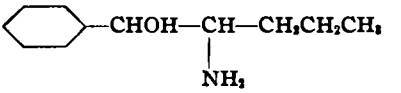


p-Hydroxyphenylpropanolamine

C. Higher Alkanolamine Derivatives.



Phenylbutanolamine



Phenylpentanolamine

CONCLUSIONS.

1. Phenylpropanolamine, its *para*-hydroxy and *para*-methyl derivatives and the methylamino derivative (ephedrine) given intravenously to dogs in doses of one to three mg. per Kg. potentiate the pressor action of epinephrine.

2. Homologous amino alcohols in which the aliphatic side chain is decreased or increased do not show this potentiation.

3. The degree of potentiation varies with the dose administered. Doses between one and three mg. per Kg. doubled the action of epinephrine.

4. Oral administration in doses which do not increase the blood pressure does not show any potentiating action.

5. Because of this potentiation, caution is necessary in the administration of epinephrine following these products.

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THE BELLIER TEST FOR SESAME OIL.*

BY E. FULLERTON COOK.

Is the Bellier test infallable, is it absolutely distinctive for Sesame Oil, how small a percentage of sesame oil in other oils will it detect, what conditions interfere with its application, can the principle responsible for the Bellier reaction be removed and can the original test be improved?

These are some of the obvious questions presenting themselves in the undertaking of this investigation.

Sesame oil is of much greater importance in Europe than in the United States as sesame seed is largely cultivated there, and the oil which it supplies is a valuable food and technical product while cotton seed oil and corn oil of the United States are practically unknown in Europe, except as a museum curiosity. Furthermore, the food laws in some European countries require the presence of a small percentage of sesame oil in all "Oleomargarine" as a ready means of identification, hence distinctive tests are of importance.

The Bellier reaction was first noted in the literature in 1899[1] and is now one of the several tests commonly used to identify or detect the presence of sesame oil.

The usual directions for the test are:

Over 1 volume (about 1 cc.) of colorless nitric acid (sp. gr. 1.4), in a test-tube, carefully overlay 1 volume of the oil to be tested, then add 1 volume of benzol, containing 1.5 per cent of resorcinol and shake once. The acid strata should become intensely green if sesame oil is present (which is the characteristic feature of the test) and the benzol-oil strata becomes violet. These colors quickly fade to dark red.

Considerable difficulty was experienced when using this technique in always obtaining the distinctive green color even when using the same acid and oil and, with even the most exact following of the technique, the test was at times uncertain in its results.

For this reason modifications were studied and the following is recommended as more simple, far more reliable and more sensitive.

MODIFIED BELLIER TEST (COOK).

Add 2 drops of the oil to 1 cc. of colorless nitric acid (sp. gr. 1.4) in a test-tube, agitate slightly, then add a small crystal of resorcin and again agitate. If sesame oil is present a green color should develop about the oil and extend into the acid. On adding benzol or chloroform practically all of the green color remains in the acid strata but fades within 3 to 5 minutes.

* Scientific Section, A. PH. A., Rapid City meeting, 1929.

[1] Experimental tests made in the Pharmaceutical Institute, University of Berne, Berne, Switzerland, under the direction of Prof. Alexander Tschirch.

Ann. chim. anal. appl., 4 (1899), 217–220; *Jahresb. Chem.* (1899), 1176; *Chem.-Ztg.* (1899), 263.