out evidence of methemoglobin. In none of the 3 dogs thus studied was there a significant change in cardiovascular response to tilting, epinephrine, or acetylcholine. In other animals repeated sublethal doses of pentaquine did not lead to postural hypotension until at least 2½ days of treatment had elapsed.

None of the 6 animals given daily doses of 3.75 mg per kg of pentaquine for 4½ days showed a significant postural hypotension. Treatment of this group of dogs was continued for 4 days longer at which time one of the 6 showed a fall in blood pressure on tilting. It would appear from this that maximal cardiovascular effects from a particular dose might ordinarily be expected by 5 days, if they are to occur at all.

Also characteristic of these cardiovascular actions of pentaquine was a persistence of effect beyond the period of therapy. In some animals postural hypotension was observed for at least 5 days after drug administration had been discontinued. These same phenomena of slow onset, and persistence of action have been observed in man.[1,2]

Discussion. A consideration of the results presented above permits the following provisional analysis: (a) Since epinephrine in pentaquine-treated animals produces at least as great a degree of hypertension as in controls, one must assume that the peripheral sympathetic end organs are intact, (b) since epinephrine produces as much bradycardia the so-called "vagus cut off" mechanism is intact, (c) since acetylcholine still produces a fall in blood pressure the peripheral end organs of the parasympathetic system are unaffected, (d) the inability of the pulse to speed up with a fall in blood pressure either as a result of tilting or acetylcholine suggests that reflexes necessary for maintaining arterial pressure have been altered. These findings therefore taken in conjunction with those of Moe and Seevers[4] suggest that the cardiovascular actions of 8-amino quinolines are produced by a functional impairment of the central sympathetic system.

Conclusions. The repeated administration of high doses of pentaquine produces an effect upon the cardiovascular system such that unanesthetized animals develop a striking postural hypotension. Pentaquine has no effect upon the response of animals to epinephrine, but blocks the tachycardia produced by acetylcholine. It is suggested that these effects are produced by an impairment of the central portion of the sympathetic nervous system.

[4] Moe, G. K., and Seevers, M. H., *Fed. Proc.*, 1946, **5**, 193.

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The Circulatory Action of a Number of Phenylpropylamine Derivatives.*

EDWIN J. FELLOWS.

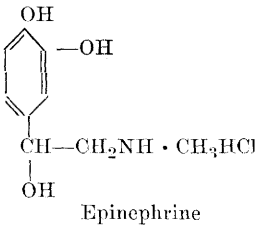
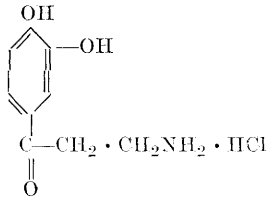
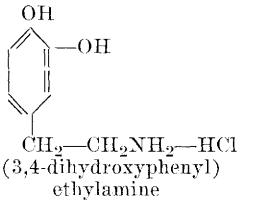
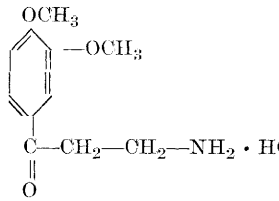
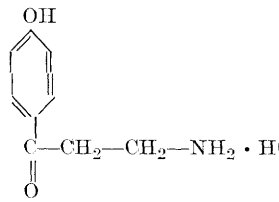
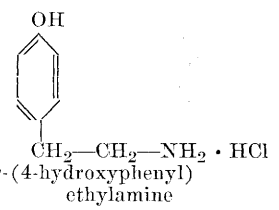
From the Department of Pharmacology, Temple University School of Medicine, Philadelphia, Penn.

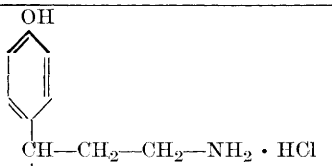
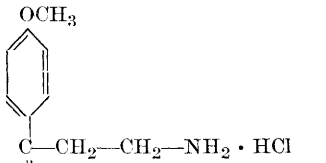
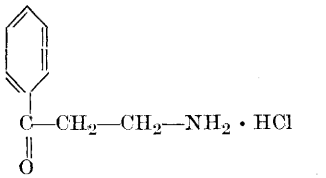
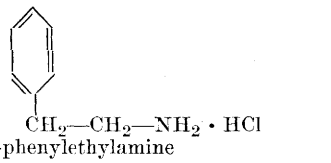
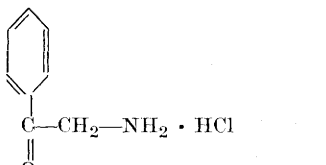
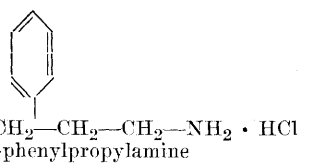
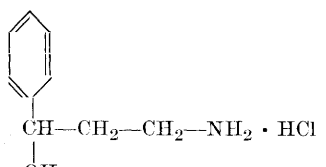
Barger and Dale[1] reported that phenethylamine presented the optimal basic chemical structure for sympathomimetic activity. This has been adequately confirmed by the synthesis and pharmacological examination of numerous modifications of the phenethylamine skeleton. A number of derivatives (Table I) in which an ethylamine side chain is separated from the benzene ring by either a keto or hydroxyl group have been made

* This investigation was supported in part by the Smith, Kline and French Laboratories Fellowship Fund.

[1] Barger, G., and Dale, H. H., *J. Physiol.*, 1910, **41**, 19.

TABLE I.
Comparative Pressor Activity.

Formula	Code	Dose ranges compared		Pressor equivalent (Epinephrine = 1)
		mg/kg	millimol/kg	
 Epinephrine	Epin.	0.0025 to 0.005	0.0000115 to 0.000023	1
 γ-(3,4-dihydroxyphenyl)-γ-Ketopropylamine	di-OH-K-Pr. (I)	0.5 to 1.0	0.0023 to 0.0045	1/100-1/200
 β-(3,4-dihydroxyphenyl) ethylamine	di-OH-Et. (II)	0.15 to 0.2	0.0008 to 0.0011	1/35-1/50
 γ-(3,4-dimethoxyphenyl)-γ-Ketopropylamine	di-me-K-Pr. (III)	10.0 to 12.5	0.040 to 0.051	<1/5000
 γ-(4-hydroxyphenyl)-γ-Ketopropylamine	OH-K-Pr. (IV)	1.5 to 3.0	0.0075 to 0.015	1/350-1/700
 β-(4-hydroxyphenyl) ethylamine	OH-Et. (V)	0.2 to 0.4	0.00115 to 0.0023	1/50-1/100

Formula	Code	Dose ranges compared		Pressor equivalent (Epinephrine = 1)
		mg/kg	millimol/kg	
 γ-(4-hydroxyphenyl)-γ-hydroxypropylamine	OH-Pr.-OH (VI)	1.5 to 3.0	0.0073 to 0.015	1/350-1/700
 γ-(4-methoxyphenyl)-γ-Ketopropylamine	Mc-K-Pr. (VII)	10.0 to 12.5	0.043 to 0.054	<1/5000
 γ-phenyl-γ-Ketopropylamine	K-Pr. (VIII)	2.5 to 5.0	0.0135 to 0.027	1/1200-1/2400
 β-phenylethylamine	Et. (IX)	0.15 to 0.3	0.00095 to 0.0019	1/100-1/200
 β-phenyl-β-Ketoethylamine	K-Et. (X)	0.4 to 1.0	0.00235 to 0.00587	1/200-1/500
 γ-phenylpropylamine	N-Pr. (XI)	2.0 to 4.0	0.0115 to 0.0233	1/1000-1/2000
 γ-phenyl-γ-hydroxypropylamine	Pr.-OH (XII)	4.0 to 8.0	0.0213 to 0.043	<1/4000

available† to us. It appeared desirable to evaluate these agents from the standpoint of their relationship to the pressor amine field. In the present experiments, atropinized dogs anesthetized with pentobarbital sodium received intravenous injections of small doses of epinephrine until a constant response was obtained. The animals then were standardized by injecting a wide range of doses of epinephrine. After standardization, a dose of one of the new compounds was injected intravenously, the response obtained compared with that of an equi-effective standard dose of epinephrine, and the epinephrine equivalent subsequently calculated. In other experiments the epinephrine equivalents of well-characterized phenethylamine‡ and phenylpropylamine‡ compounds were determined in the manner described for the new propylamine derivatives. In order to obviate the complicating factor of tachyphylaxis, only one dose of a compound was injected in a given animal in all of the present comparative pressor activity experiments.

Di-Substituted Phenyl Derivatives. The rise of blood pressure produced by 0.000023 millimol per kg of body weight§ (0.005 mg per kg of body weight§) of epinephrine (Fig. 1, A) was approximated in intensity by di-OH-K-Pr. (Fig. 1, B) in a dose range of 0.0023-0.0045 millimol (0.5-1.0 mg); however, duration of pressor action was more prolonged in the case of the propylamine derivative. Pressor activity comparable with the above doses of di-OH-K-Pr. and epinephrine was obtained following 0.0008-0.0011 millimol (0.15-0.2 mg) di-OH-Et (Fig. 1, C). Methylation of both hydroxyls of di-OH-K-Pr. results in a compound, di-me-K-Pr., which produced an initial depressor followed by a negligible pressor effect (Fig. 1, D).

Mono-Substituted Phenyl Derivatives. Pressor responses were obtained with 0.075-0.015 millimol (1.5-3.0 mg) of OH-k-Pr. (Fig. 2, A) which were comparable in intensity with those obtained following 0.00115 millimol (0.2 mg) of OH-Et. (Fig. 2, B); however, duration of pressor action following injection of the propylamine compound always was more prolonged than that obtained after the ethylamine derivative. A rise in blood pressure was caused by 0.0073-0.015 millimol (1.5-3.0 mg) OH-Pr.-OH (Fig. 2, C) which in intensity approximated that observed after the above doses of the propyl- and ethylamine compounds. Me-K-Pr. (Fig. 2, D) in doses of 0.054-0.043 millimol (12.5-10.0 mg) produced an initial depressor followed by a slight pressor effect.

Non-Substituted Phenyl Derivatives. The intensity of pressor action following 0.0135-0.027 millimol (2.5-5.0 mg) K-Pr. (Fig. 3, A) was of the same order as that obtained after 0.0019 millimol (0.3 mg) Et. (Fig. 3, B), as well as that observed on injection of 0.00587 millimol (1.0 mg) of K-Et. (Fig. 3, C) or after 0.01725 millimol (3.0 mg) of n-Pr. (Fig. 3, D). A negligible pressor effect was produced after 0.0216-0.043 millimol (4.0-8.0 mg) Pr.-OH (Fig. 3, E).

Discussion. From the standpoint of intensity of pressor action, di-hydroxy-γ-ketophenylpropylamine (I) was the most active of the new derivatives (Table I). Compound I exhibited 1/100-1/200 the pressor activity of epinephrine and 1/5 to 1/3 the activity of dihydroxy-phenethylamine (II) (Table I). Dimethoxy-γ-ketophenylpropylamine (III) evidenced less than 1/5000 the pressor activity of epinephrine (Table I). Hydroxy-γ-ketopropylamine (IV) was 1/8 as active as hydroxy-phenethylamine (II) and 1/350 to 1/700 as active as epinephrine (Table I). Hydroxy-phenyl-n-propanolamine (VI) manifested the same degree of pressor activity as that of its keto-analogue (Table I). Mono-

† Compounds I, III, IV, VI, VII, VIII, XII (Table I) were prepared and made available to us by the late Garfield Powell, Professor of Organic Chemistry, Columbia University. Compound VIII was prepared previously by Mannich, C., and Abdullah, S. M. (Ber. 68B: 113-20, 1935), but has not been investigated pharmacologically. All of the other above agents are new derivatives.

‡ We are indebted to Dr. Gordon A. Alles for samples of compounds II, V, IX, X, and XI (Table I).

§ Throughout the remainder of the text it is understood that all doses mentioned are per kilogram of body weight.

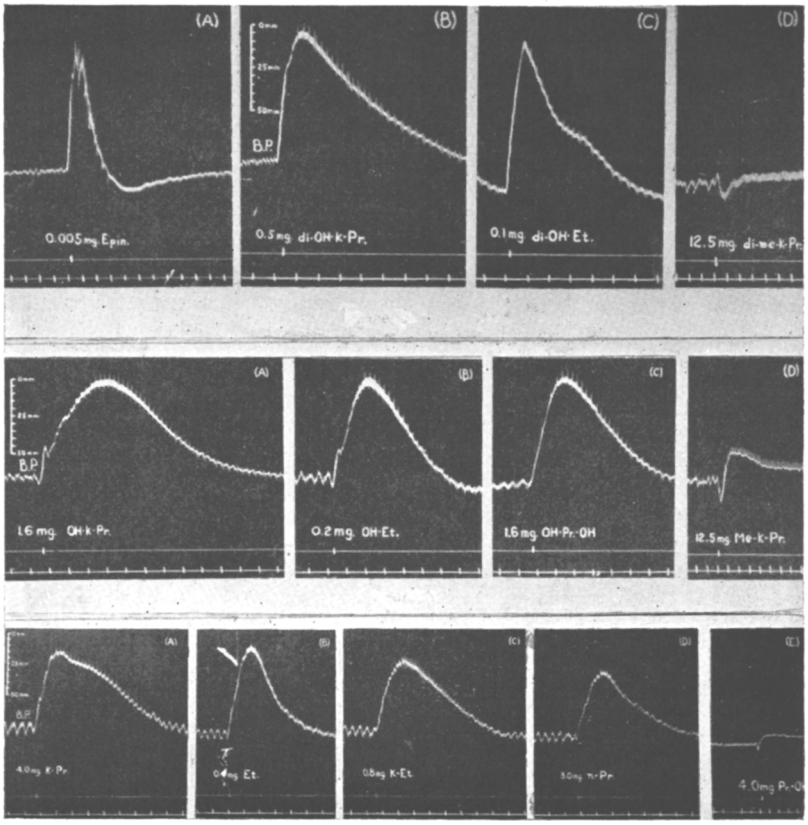


FIG. 1, top, FIG. 2, middle, FIG. 3, bottom. Atropinized (2.0 mg/kg) dogs anesthetized with pentobarbital sodium. B.P.—carotid blood pressure by mercury manometer. Upper lines indicate injection into a femoral vein. Lower lines indicate time in minutes. Doses are in mg per kilogram of body weight.

methoxy-γ-ketophenylpropylamine evidenced a low order of pressor effectiveness, being $<1/5000$ as active as epinephrine. γ-ketophenylpropylamine (VIII) possessed 1/16 the activity of phenethylamine (IX) and 1/1200 to 1/2400 the activity of epinephrine (Table I). The effectiveness of γ-ketophenylpropylamine (VIII) was slightly less than that of phenyl-n-propylamine (XI). Phenyl-n-propanolamine (XII) exhibited less than 1/4000 the pressor activity of epinephrine and was therefore much less active than its corresponding keto-derivative. The interrelationship between aryl and alkylamine substitution is, therefore, apparent because derivatives IV and VI were equi-active pressor agents.

Summary. The intravenous circulatory activity of the following phenylpropylamines was compared with that of corresponding phenethylamine derivatives and epinephrine in atropinized dogs anesthetized with pentobarbital sodium: γ-(3,4-dihydroxyphenyl)-γ-Ketopropylamine (I); γ-(4-hydroxyphenyl)-γ-Ketopropylamine (IV); γ-(4-hydroxyphenyl)-γ-hydroxypropylamine (VI); γ-phenyl-γ-ketopropylamine (VIII); γ-phenyl-γ-hydoxypropylamine (XII); γ-(4-methoxyphenyl)-γ-Ketopropylamine (VII); γ-(3,4-dimethoxyphenyl)-γ-Ketopropylamine (III). These derivatives all were found to exhibit some degree of pressor activity. The above listing is in the order of their decreasing pressor effectiveness. The most active compound (I) manifested 1/100-1/200 and the least active agent (III) possessed $<1/5000$ the activity of epinephrine.