EPINEPHRINE AND RELATED COMPOUNDS: INFLUENCE OF STRUCTURE ON PHYSIOLOGICAL ACTIVITY

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"The real object of chemistry is not to make gold, but to prepare medicines."—PARACELSUS (1).

I. INTRODUCTION

The relationship between the structure and behavior of physiologically active compounds is still poorly understood. That there is such a relationship is well evidenced by the information available concerning individual series or homologs, as, e.g., the alcohols, amines, phenols, purines, barbituric acid derivatives, acridine dyes, chaulmoogric acid and its analogs and the piperazines, but the extent to which these various and varying groups may be interrelated still remains to be determined. Perhaps some day there will come another Mendeléeff, a man with a genius to appreciate existing knowledge, combined with a capacity to organize it into a second "periodic table," namely, a classification that will coördinate the physiological significance of the functional groups and at the same time preserve a regularity in structural sequence. The far-reaching consequences that will follow the formulation of such a "law" cannot be imagined, for it will serve as the course of illumination that will extend many times the horizon in a field of endeavor now shrouded in semidarkness. However, pending the attainment of such a coveted goal, the modern iatro-chemist must of necessity content himself with the limited view now possible.

One of the earliest, and possibly the best known, studies in

correlating chemical constitution and pharmacological behavior was made with compounds that produce a rise in blood pressure. The extent and nature of such studies immediately suggest themselves at the mere mention of such names as Abel, Barger and Dale, and Chen, or of compounds like tyramine, epinephrine and ephedrine.

Interest in these substances was aroused when Oliver and Schaefer in 1894 (2) and Scymonowicz independently in 1895 (3) found that extracts of the suprarenal glands, which are located above the kidneys and the importance of which was first observed by Addison in 1849, produced a rise in blood pressure when injected into the blood vessels of animals. This discovery aroused the interest of chemists, physiologists, and pharmacologists the world over and was the beginning of an intensive study of the gland and an effort to isolate its highly active principle. Progress was quickly made and a keen rivalry developed among the various workers. Among the pioneering investigators were Abel of this country and v. Fürth in Germany. The former was the most active and it was from his laboratory that most of the early information about the chemical nature of the active constituent of the glands came.

Abel and Crawford (4) separated the active hormone from the tissues in the form of a polybenzoyl derivative; this, when decomposed in an autoclave by means of hot dilute sulfuric acid, resulted in the formation of an active sulfate possessing all the characteristic activities of the glandular extracts to a very high degree (5, 6). From the analysis of the sulfate and other derivatives Abel concluded that the active principle was represented empirically by the formula $C_{17}H_{15}NO_4$ (7).

During the fall of 1900, while Abel was still at work on his processes, his laboratory was visited by Takamine, who became very much interested in the work and upon inquiry was informed that the process of isolation "could no doubt be improved and simplified." Takamine returned to his own laboratory, prepared concentrated extracts of the glands, and by the addition of ammonia (the base employed by Abel in precipitating his epinephrine) obtained burr-like clusters of crystals. These crystals were not,

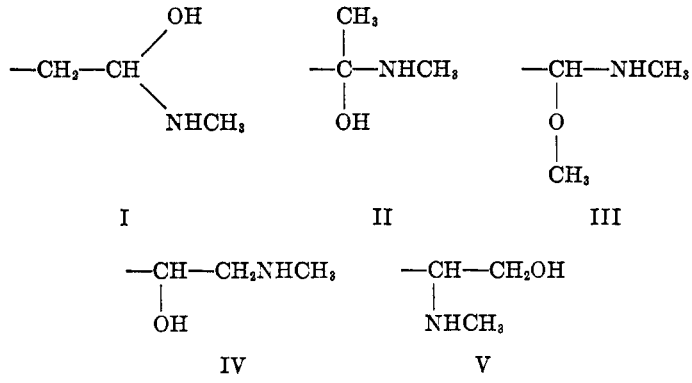
however, identical with those isolated by Abel. Takamine called his product adrenaline and gave it the formula $C_{10}H_{15}NO_3$ (8, 10). The product was crystalline epinephrine, but still not yet pure. It remained for Aldrich (11, 12) to show its true formula, which is $C_9H_{13}NO_3$. The error in Abel's product was, as Aldrich pointed out and Abel (13) had already demonstrated, that it contained a benzoyl radical, for "it is interesting to note . . . . that if we subtract a benzoyl residue from Abel's formula for epinephrine, $C_{17}H_{15}NO_4$, we obtain formula $C_{10}H_{10}NO_3$, which is not far removed from that of adrenalin" (14), and which agrees very well with the formula $C_{10}H_{15}NO_3$ proposed by Takamine. Abel suspected that this benzoyl group, which could not be hydrolyzed off, was attached to the amino nitrogen[1]—"an unusual circumstance in any event" (15).

The difficulties which confronted Abel are quite understandable. A trail blazer in science, attempting to isolate the active principle of an unusually active glandular extract, found that by a "benzoylation" process he could obtain, in a highly purified form, a substance that retained all the characteristic physiological activity of the extract itself, and to add to the difficulty the activity compared favorable with that of the pure principle; this substance actually was a monobenzoyl derivative of the product sought. What other secretion could undergo so drastic a modification as this without having its characteristic action destroyed or at least greatly changed? Such was the combination of circumstances which conspired against a pioneer. However, the scientific world today recognizes the value of Abel's contributions and he is now generally accorded the credit due him, namely, that of having isolated the first hormone.

[1] In the light of all that is now known it may not be out of place to suggest that this monobenzoyl derivative of epinephrine, which was obtained by Abel and his co-workers, is not the *N*-benzoyl derivative but rather that the benzoyl group entered the catechol nucleus, for acylation of the amino portion of compounds of this type tends to destroy their pressor activity and it is difficult to conceive, as Abel points out, how an *N*-benzoyl derivative could resist hydrolysis under the conditions employed. On the other hand, the entrance of the benzoyl group into the aromatic nucleus through an adaptation of the Fries rearrangement, would account for its nonremoval and probably would not interfere so greatly with its physiological activity. Such a reaction is quite common with phenols.

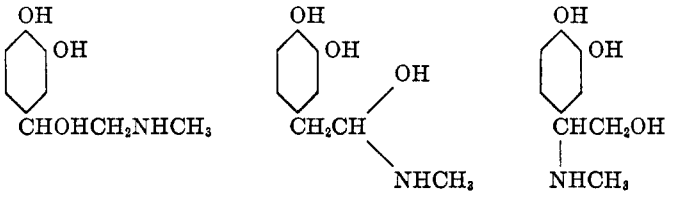
The principle has been given various names—epinephrine by Abel, suprarenine by v. Fürth (16), who isolated it through a ferric chloride complex, and adrenaline by Takamine. The term epinephrine has been adopted by the U. S. Pharmacopoeia. Rogoff (17) suggests that "it is preferable to employ the term 'epinephrine' as indicating the physiological secretion from the adrenal medulla, and to use 'adrenalin' when referring to the commercial product."

Once epinephrine was isolated, its formula was quickly established. Even before the existence of the hormone was suspected, a color reaction of the glandular extract led Krukenberg (18) to remark about its similarity to catechol, and Moore (19) believed that this color-producing body and the blood pressure raising principle were identical. Takamine, by fusing his adrenaline with alkali, obtained catechol and catechuic acid. v. Fürth (16, 20) added the observation that the molecule contained a methylamino group and proposed that it contained a catechol nucleus. Pauly, on the basis of his discovery that epinephrine contains an asymmetric carbon atom (21) and of other contributing considerations, suggested that the diphenolic nucleus was attached to one of the five theoretically possible side chains,



but considered groupings IV and V as most probable, since they would account for the formation of skatole or pyrrole derivatives which previous investigators had observed among the decomposition products. Jowett (22), with potassium permanganate, ob-

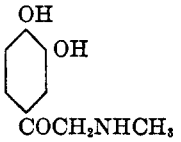
tained oxalic and formic acids and methylamine; after methylation and subsequent oxidation he obtained veratric acid and trimethylamine, proving thereby the presence of the complexes $C_6H_3(OH)_2C\equiv$ and $-NHCH_3$ in the original base. From these results he proposed the three possible formulas



VI VII VIII

and argued that formula VI was the most probable since a substance with formula VII should, after methylation and subsequent oxidation, give homoveratric acid, $(CH_3O)_2C_6H_3CH_2COOH$, and formula VIII does not so readily explain the formation of pyrrole derivatives.

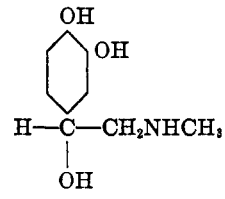
Stolz, convinced by the evidence of his predecessors that either VI or VIII of Jowett's formulas was correct, set out to synthesize VI. He prepared chloroacetylcatechol, $(HO)_2C_6H_3COCH_2Cl$ and condensed it with methylamine, thus obtaining methylaminoacetocatechol (IX).



IX

When he found that this ketone possessed qualitatively all the physiological activity of the hormone itself and that the reduction of the aminoketone gave a product that produced an even greater characteristic epinephrine activity, there could be no longer any doubt about the chemical identity of epinephrine (23, 24). The syntheses of related substances by Dakin (25) and by Friedmann (26) served to confirm these conclusions.

Hence, it is seen that epinephrine is a comparatively simple substance, being the levo form of (3,4-dihydroxyphenyl)—1-methylamino-2-ethanol (X).



Epinephrine

X

Probably no other compound has been so extensively used in physiological and chemical investigations as has this first-known hormone. A bibliography of epinephrine would form a large volume, as reference to the indices of any abstract journal will show. Some idea of the importance of this compound may be obtained from the graphic tabulation of the number of references in the indices of the annual volumes of Chemisches Zentralblatt (figure 1). From even a cursory survey of these numerous references one may readily see how important a substance it has become in therapeutics, diagnoses, and physiological experimentation and even as a chemical reagent.

Epinephrine is an extremely active substance, and has been found biologically to exert an effect on the isolated frog heart in dilutions as low as one part in five billion (27). The isolated frog heart, rendered hypodynamic by aconitine, was susceptible at even greater dilutions—one part per trillion (28, 29). The epinephrine content in the suprarenal glands averages, for healthy persons of middle age, about 4 mg. for each gram of dried gland (30). In the fresh glands of animals it varies from 150 mg. per thousand glands of the guinea pig to 2440 mg. per thousand glands of the horse (31). Barger has calculated that the glands of twenty million beeves are necessary for the isolation of a ton of the active principle (32). The average normal output of epinephrine from the glands as determined from 103 cats was 0.000226 $\pm$ 0.0000007 mg. per kilogram of body weight per minute; in 32 dogs the

figure was found to be 0.000227 ± 0.00000096 mg. per kilogram of body weight per minute (33). Since such small amounts of epinephrine are determined or estimated only with great difficulty, too much reliance cannot be placed on these figures.

The exact function of epinephrine does not appear to be completely or definitely determined, owing in part to the difficulty of removing all chromaffin tissue from experimental animals.

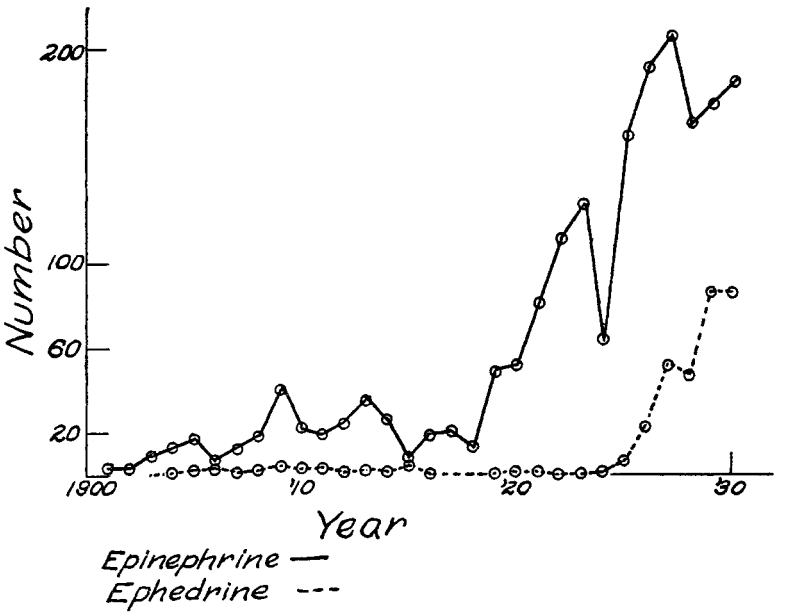


FIG. 1. REFERENCES TO EPINEPHRINE AND EPHEDRINE FOUND IN THE INDICES OF CHEMISCHES ZENTRALBLATT

Its therapeutic value is based in part on the effects its produces, viz.: its action on smooth muscle fibres, which affords relief in asthmatic spasms, hay fever, severe colds, and causes it to act as a constrictor on the arteriole muscles; its hyperglycemic effect, which causes the conversion of muscle and liver glycogen into glucose; and mydriasis, i.e., dilatation of the pupils. Recently the oxidation products of epinephrine have been shown to exert a peculiar catalytic effect on proteins (34, 35).

Sollman (36) states that "the striking actions of epinephrine invite the theory that it plays an important rôle as a hormone for maintaining the tone of the sympathetic system, particularly of the blood pressure; and that it is conceived in pathologic conditions of the sympathetic system." Guyer (37) has summed up the functions of epinephrine in the following words: "In the body it is of great importance in maintaining muscular tone; the proper amount keeps the blood vessels suitably contracted and blood pressure normal. . . . . Insufficiency of adrenaline . . . . results in lowered blood pressure, lack of muscular tone and the general loss of strength and 'nerve' which is characteristic of neurasthenia, 'shell-shock' and related ills. In general, adrenaline affects the same structures of the body that the sympathetic nervous system does; namely, the heart, blood vessels, kidneys and other viscera and the involuntary muscles. . . . . Injection of adrenaline into the blood tends to increase the quantity of sugar in the blood through release of the sugar from liver glycogen. It apparently counterbalances the action of insulin." Cannon (38, 39) has advanced a theory that any of the major emotions, such as pain, fear and anger, result in a large outpouring of epinephrine from the adrenal glands into the blood stream in order to mobilize the defense mechanisms of the individual. This theory has been extended in a most fascinating manner by Berman (40), and rather remarkable properties are ascribed to the "glands of combat and fight;" for instance, not only is courage determined by epinephrine secretion, but also neurasthenia, "the great American disease," may be directly traced to epinephrine insufficiency. Interesting and plausible as Berman's hypotheses may be, one must not forget that his book, which "adds somewhat to the gaiety but little to the sanity of the time," contains "speculations, unfounded or extremely doubtful generalizations . . . . so skillfully interwoven with the facts" that it must not be taken seriously (41). As for Cannon's original defense mechanism hypothesis, Rogoff (17) considers it based on very meagre and indirect evidence.

Since epinephrine is a phenol, it might, *a priori*, be expected to possess bacteriostatic or even bacteriocidal powers. Its "phenol

coefficient" seems not to have been determined and its germicidal value probably is not very large, for the natural product, obtained from tissues, must be sterilized before it can be used clinically (42). Sterilization is also necessary for its preservation. Nevertheless epinephrine has been found to have an antiseptic effect on the organisms in "brûlures" (43), and it appears to have some merit in neutralizing the effect of tetanus and diphtheria toxins (44, 45, 46, 47, 48, 49, 50, 51, 52). Derisi (52a) reports favorable results from oral administration of epinephrine in the treatment of infectious diseases such as grippe, typhoid, paratyphoid, diphtheria, scarlet fever and measles; however, he explains these favorable results on the supposition that these diseases have caused adrenal deficiencies.

Epinephrine is administered usually by injection subcutaneously, and rarely intravenously. Administration by way of the rectum produces no, or only very slight, effects (53). Given orally it has, as a rule, no influence on the blood pressure (54, 55, 56, 57), although some observers have recorded such effects. Such exceptions may, for the present, be regarded as unusual, for if the oral administration of epinephrine produced a characteristic effect on the blood pressure that fact should, from the hundreds of observations, be more obvious than is now the case. This oral inactivity is generally attributed to the inability of the easily modified epinephrine molecule to withstand the rather strenuous processes of absorption from the intestinal tract. This view, however, appears unwarranted, for while epinephrine may, *per os*, have no general effect on the blood pressure it does produce other systemic results. It will cause a rise in blood sugar (55, 60, 61, 62, 63) and in general will increase the basal metabolic rate (64), thus indicating that the theory of the rapid and complete destruction of the epinephrine in the alimentary tract will not explain the lack of action on the blood pressure, for it is sufficiently capable of producing some of the other characteristic epinephrine responses. Other considerations, which will be discussed later, show that this inactivity is attributable rather to a deficiency in minimum structural essentials that are necessary for oral activity.

While epinephrine is a very important secretion of the adrenal

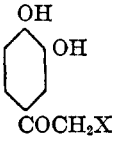
glands its real function in vital economy is as yet incompletely known. Addison's disease, which is always fatal, does not seem to be associated with a lack of epinephrine (65). In fact there is some question whether the hormone is really necessary in sustaining life (36, 66). Stewart, Rogoff and their co-workers report that the secretion of epinephrine is not indispensable to life and that they were able to suppress its secretion completely without causing any detectable harmful influence (67, 68, 69). However, the *complete* suppression of the functioning of the epinephrine-forming tissues has probably never been successfully accomplished (70), because epinephrine even in the smallest quantities is so very active (6). Whatever may ultimately be learned about the function of epinephrine in the economy of living tissues, it would appear that a substance so active must, from the very fact of its presence, play at least a very important if not an indispensable rôle.

Nor is epinephrine the only hormone of the glands. Extracts of the suprarenal cortex have been shown to be necessary to life. Popular interest was aroused in these extracts when Coffey and Humber (71, 71a, 71b) reported that they were able to cure carcinoma with them; Itama and McDonald (72), however, were unable to duplicate this work. Various extracts of the suprarenal cortex have, however, been used with much promise in the treatment of Addison's disease and in maintaining the normal health of adrenalectomized animals (73, 74, 75, 76, 77, 77a).

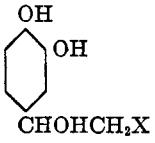
While the interest in epinephrine is usually associated with its presence and its function in the higher animals, it is found in structures other than the suprarenal glands. Abel and Macht (78) found that the venomous secretion of the Brazilian toad, the *Bufo agua*, used by the natives as an arrow poison, contained nearly 7 per cent epinephrine. While the death-dealing principle of the venom is a glucoside, *bufagin*, one can but wonder at the reason for the presence of the hormone, particularly in such high concentration. In 1916 Schimizu (79) reported the presence of an epinephrine-like body in "Senso" (Japanese) or "Ch'an Su" (Chinese), the dried venom of the Chinese toad. Jensen and Chen (80, 81) identified this substance as epinephrine and ob-

tained 350 mg. from 150 g. of Ch'an Su. It is not unlikely that the venom of all toads contains epinephrine, for Epstein and Gunn (79a) found an epinephrine-like substance also in the parotid secretion of the African toad, *Bufo regularis*. Collip (70) has demonstrated the presence of an epinephrine-like substance in the prostate gland of the bull.

Various methods for the synthetic preparation of epinephrine have been developed, most of them involving the reduction of adrenalone, the corresponding aminoketone. This desired intermediate ketone may be prepared by allowing halogenoacetylcatechol



to react with methylamine (23, 82); reduction of the resulting methylaminoketone, by appropriate methods, gives epinephrine (83, 84, 85). Several have tried condensing the methylamine directly with the halogenocarbinol (86, 87, 88),



but apparently were less successful in obtaining the desired product. An entirely new and more recent synthesis was made by Nagai (89), who reduced the condensation product from nitromethane and the diacetate of protocatechualdehyde with zinc and acetic acid in the presence of formaldehyde and obtained as the end product the desired epinephrine.

Much of the epinephrine used clinically is obtained from synthetic sources. The synthetic racemic substance is resolved into its levo and dextro components; the levo form is as effective as that obtained from natural sources and is accepted by the Pharmacopoeia. The dextro portion is racemized, by proper heating in a dilute acid solution, and the levo isomer again removed. In

this manner it is possible eventually to convert substantially all the synthetic product into acceptable *l*-epinephrine. However, the chief source of supply of epinephrine remains the suprarenal glands of beeves.

While the fame of epinephrine was steadily increasing, it was with considerable interest that the report of Abelous, Ribaut, Soulie and Toujan (90) in 1906 was received. They observed that extracts of putrified meat also contained a substance that produced a rise in blood pressure. Barger and Dale (91) identified the active ingredients as two definite compounds, isoamylamine and tyramine. Since both may be derived, by putrefactive processes, from the protein acids, leucine and tyrosine, respectively, these scientists were led to investigate first other bases of putrefactive origin and finally all substances structurally related to tyramine and epinephrine. Their results are reported in that classic which first showed what an intimate connection there is between the physiological activity of compounds possessing structural similarity (92).

Because all of the substances investigated caused a rise in the arterial blood pressure by constricting the muscular lining of the arterioles, Barger and Dale described them as "sympathomimetic," i.e., minicking sympathetic stimulants, a term which is now in the vocabulary of all physiologists and pharmacologists.

During the fourteen years following this work of Barger and Dale nothing of particular interest developed; known compounds were more intensively investigated and occasionally new ones without especial merit were introduced. Meanwhile epinephrine was becoming more firmly established.

In the autumn of 1923, at Peking Union Medical College, a decoction made from Ma Huang, a plant of the ephedra species, was injected into the vein of an anesthetized dog remaining alive at the end of the laboratory exercise (93). The curious student who made the experiment was Chen, and the results of that casual injection have been world-wide in their effect. Chen was quick to see that this substance, which had been used by the Chinese for over 5000 years as a sedative, diaphoretic and circulatory stimulant, produced an action on the blood pressure simulating that

of epinephrine. Further investigation of the active principle revealed its virtues and finally led to its introduction into modern medicine, where it has assumed an increasingly important rôle. The active principle of this old Chinese drug plant was isolated in 1885 by Nagai who gave it its name, ephedrine.[2]

Previous to 1923 the alkaloid had been investigated physiologically, but apparently in such doses that the toxic effects predominated. It had been found satisfactory as a mydriatic but never attained clinical prominence as such. It remained for Chen and his collaborators to discover its virtues. The extent to which Chen's observations have revived interest in this little-known alkaloid may be seen from figure 1 which gives a graphic summary of the number of references to ephedrine in the annual indices of Chemisches Zentralblatt. Since Chen and Schmidt (93), the modern sponsors of ephedrine, have recently written a monograph covering the history, chemistry, and drug action of this old Chinese alkaloid, it would be mere repetition to discuss it further here.

II. PHARMACOLOGICAL METHODS

It is beyond the province of this paper to discuss the methods of animal experimentation. These may be found described in any appropriate standard reference. But it should be emphasized that data obtained by biological means are not quantitative in the sense in which the analytical chemist understands the term (94), and that in evaluating the relative potencies of a series of physiologically active compounds many factors must be considered, of which the following deserve especial mention: (*a*) variation in individual animals; (*b*) variation in characteristic responses in different species of animals; (*c*) influence of experimental conditions and procedure; (*d*) significant differences in biochemical mechanisms through which individual reagents produce their effects.

[2] In the United States the pronunciation commonly heard is e-phĕ′-drine or, sometimes e-phē′-drine, with the accent on the second syllable. The name of the species from which the alkaloid is obtained is ĕph′-e-dra, and the American dictionaries give its active principle the pronunciation ĕph′-e-drine. See also NIELSON: Am. Druggist, Jan. 28, 1928, p. 90.

Even within a single species of animals there are very wide variations, and in some instances the animal may react in a manner that is qualitatively different. The results obtained from one animal may be indicative of a trend but they should never be accepted as the sole basis for a positive conclusion. The greater the number of animals used, the more reliable is the summation of findings.

Animals of different species do not necessarily give the same response. For example, a cold-blooded animal may react quite differently from a warm-blooded one; or a rabbit may be much less sensitive to a given compound than, say, a dog. The larger the variety of animals on which a drug has been tested the more certain one can be as to what may be expected of it. That this factor of species variation must always be considered is strikingly illustrated by Chen and Poth's observation that the mydriatic action of ephedrine is much more pronounced in Caucasians than in Chinese or Negroes (95), and by the fact that ephedrine mydriasis is much more effective in individuals with light irises than in those with dark irises (96).

Variations in experimental technique must always be considered, such as the type, size, age, sex, previous history, and the nature and depth of anesthesia of the experimental animal; the rate and method of administration of the chemical, namely, whether given orally, rectally, subcutaneously or intramuscularly; and the size of the dose. All these produce their own peculiar effects on the qualitative and quantitative nature of the physiological response. The adoption of a "standard" method or procedure for pharmacologists and physiologists would make all comparative results more reliable, but it might also keep hidden any peculiar drug action that another technique would reveal. For the purposes of comparison the different results of a single experimenter or author are the most reliable.

The biological mechanism through which a substance produces its effect cannot be ignored. Thus, epinephrine is distinctly "sympathicotropic," that is, it produces its effects by stimulating the sympathetic nervous system (97, 97a). On the other hand, while ephedrine may also stimulate the sympathetic system

according to some (98, 99), it is quite definitely "musculotropic," producing its effects by stimulating the muscles. Here, then, are two substances both of which affect the circulatory system but through quite different channels. Any real comparison must also consider such differences.

Keeping in mind, throughout the following pages, factors such as these, one can see that many apparent inconsistencies and contradictions are unavoidable in tracing the thread of relationship that weaves through a series of compounds having structural elements in common.

III. ALIPHATIC AMINES

The physiological effect of aliphatic amines may be exhibited in various ways (100, 101). Ammonia in small doses is a respiratory stimulant, but larger doses cause convulsions; it produces a rapid but very transitory depression of the blood pressure (102). As alkyl groups replace the hydrogen atoms of ammonia the stimulating action is diminished, becoming less as the size of the alkyl group increases; as the alkyl chain becomes longer, a depressant action on the heart and convulsions of spinal origin appear, the depressant action being perceptible even in isoamylamine.

The lower members of the series of aliphatic amines possess practically no pressor properties; in fact, they appear to be depressors rather than pressors (102, 103, 104, 105). While Barger and Dale did observe that large doses produced perceptible rises, they found that the record was complicated by volume effects (92). Abelous and Bardier credit trimethylamine with a "urohypertensive" action 1/200th as great as that of isoamylamine (106), an effect which Barger and Dale dismiss as negligible. Jackson, however, has obtained an excellent tracing which shows trimethylamine to be active as a pressor and also as capable of producing constriction of the bronchioles. A dose of 0.25 ml. (concentration not stated) given to a decerebrate dog produced a maximum rise in blood pressure of 63 mm. of mercury (107). Very recently Mercier (108) observed that the blood pressure of a chloralosed dog receiving 20 mg. per kilogram of trimethylamine (as hydrochloride) in the saphenous vein fell about 40 mm. of

mercury, and after about twenty seconds rose to 64 mm. above normal for a minute or longer.

Barger and Dale (92) examined the following twenty-one aliphatic amines: methylamine, ethylamine, propylamine, isopropylamine, isobutylamine, *n*-butylamine, isoamylamine, *n*-amylamine, *n*-hexylamine, *n*-heptylamine, *n*-octylamine, *n*-nonylamine, undecylamine, tridecylamine, cyclohexylamine, diethylamine, isoamylmethylamine, diisoamylamine, trimethylamine, tetraethylammonium iodide, pentamethylene diamine (cadaverine). They found that pressor activity began with *n*-butylamine; *n*-amylamine was much more active, while maximum activity of the whole series was observed in *n*-hexylamine, for *n*-heptylamine was slightly but distinctly less active, and octylamine even less active; pressor activity was still apparent in the higher homologs, even in tridecylamine; however, with the higher members increasingly greater toxic disturbances interfered with the purely sympathomimetic results. The normal chains were found more potent than the branched or isochains; thus isoamylamine, while several times more active than *n*-butylamine, was weaker than *n*-amylamine, and the effect of isobutylamine was doubtful.

Hanzlik (105) found that in atropinized dogs the butylamines caused a fall in blood pressure, and Trendelenburg (103) reported that isoamylamine did not always cause a rise in the blood pressure of rabbits.

Repeated doses of these amines produced, according to Barger and Dale, rapidly diminishing effects, that is, a second and equal dose did not produce the same response as was obtained from the first, and the response from the third dose was still less.

Introduction of an additional amino group into *n*-amylamine, giving cadaverine, converted it into a depressor, thus completely reversing the physiological effect. If the hexylamine was converted into a cyclic derivative, e.g., into cyclohexylamine, the physiological response was slower in appearing and was more prolonged, but otherwise resembled that obtained with the open chain compound (92).

The primary amines were more active, both as pressors and in their effect on the cat uterus, than were the secondary and

TABLE 1

Aliphatic amines

BASE	TOXICITY—M.L.D.*	PHYSIOLOGICAL ACTION
Methylamine	200–300 mg. per 100 g. of frog, subcutaneous (103) 300–400 mg. intravenous to rabbit not fatal (103) 2000 mg. subcutaneous to rabbit not fatal (103) 200–300 mg. of hydrochloride or sulfate subcutaneous to guinea pigs or rats (103)	Injection into mammals causes rapidly disappearing depression in blood pressure (103) 0.005–0.010 g./kg. intravenous to rabbits caused depression of 14 to 16 mm. Hg in blood pressure (110) Less depressant than ammonia (102)
Dimethylamine	0.6 g. of base (given as salt) fatal to rabbits (103) 4 g. orally to rabbits fatal (104)	Gives transitory depression in blood pressure (103) Less depressant than methylamine (102)
Trimethylamine	0.1–0.2 g. to frogs (103) 1 g./kg. to rabbits kills in 4 hrs. (103) 6 g. of base subcutaneous to rabbits (103) 0.15–0.20 g./kg. to frogs (104) 0.4 g./kg. intravenous to rabbits (104) 0.8 g./kg. subcutaneous to rabbits (104)	Action resembles methylamine and dimethylamine in rabbits 0.2 g./kg. intravenous gives fall in blood pressure for several minutes, then gives enormous rise (111) Less depressant than dimethylamine (102) 1/200th as great a pressor as isoamylamine (106) Good pressor (107) The hydrochloride injected intravenously gives preliminary fall followed by rise in blood pressure (108)
Ethylamine	0.35 g./kg. of hydrochloride intravenous to rabbits, no toxic symptoms (103) 2 g. of hydrochloride fatal to rabbit (103) 0.5 g. of hydrochloride fatal to rat (103)	Differs only quantitatively from methylamine (103)

* Minimum lethal dose.

TABLE 1—*Concluded*

BASE	TOXICITY—M.L.D.*	PHYSIOLOGICAL ACTION
Diethylamine	Less toxic than dimethylamine (103)	Inactive (103)
Propylamine		Inactive (103)
Isopropylamine		Inactive (103)
Dipropylamine	Ten times as toxic as diethylamine (103)	
n-Butylamine	0.60 ml. of 1 per cent solution subcutaneous to white rats (105)	In atropinized dogs cause fall in blood pressure
Di-*n*-Butylamine	0.47 ml. of 1 per cent solution subcutaneous to white rats (105)	Cause increase in cardiac volume and decrease in kidney volume
Tri-*n*-Butylamine	0.45 ml. of 1 per cent solution subcutaneous to white rats (105)	Smooth muscle stimulant (105)
Isoamylamine	150–200 mg. of hydrochloride per 100 g. of frog 250 mg./kg. not toxic to rabbits 1.5 g. of sulfate killed rat 1.8 g. of hydrochloride killed rabbit (103)	Does not always give blood pressure rise in rabbits (103)
Amylamine		More active pressor than isoamylamine (92)
n-Hexylamine		Most active of aliphatic amines (92)

tertiary amines (104). Methylisoamylamine was about half as active as isoamylamine (92).

Many of the aliphatic compounds, particularly those with a normal chain, may be found among various protein decomposition products (109).

In table 1 is given a summary of the information relative to the aliphatic amines.

The aliphatic aminoalcohols, that is, the amines with an alcoholic function added, are compounds of biochemical interest. Ethanolamine, $CH_2OH \cdot CH_2NH_2$, and ethanol-trimethylammonium hydroxide or choline, $CH_2OHCH_2N(CH_3)_3OH$, form constituent portions of the lecithins. Higher homologs have recently been prepared by Kanao (112). These, when converted into higher secondary bases, exhibit marked anesthetic properties. Thus, all of the following were found to be anesthetic.

$$(CH_3)_2CHCH_2\underset{\displaystyle NHCH_2C_6H_5}{\underset{|}{C}}HCHOHCH_3$$

$$(CH_3)_2CHCH_2CHOHCH(CH_3)NHCH_2C_6H_5$$

$$CH_2OHCH_2NHCH_2CH_2CH(CH_3)_2$$

$$(CH_3)_2CHCH_2\underset{\displaystyle C_6H_5}{\underset{|}{N}}CH_2CH_2OH$$

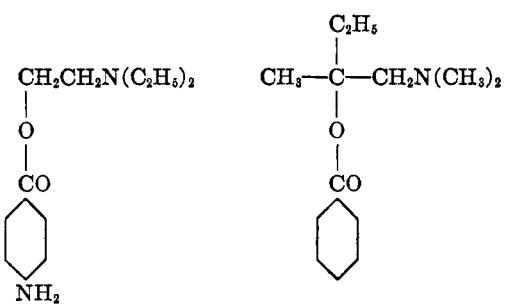
$$CH_2OHCH_2N(C_6H_5)_2$$

$$CH_3CHOHCH_2N(CH_2CH_2CH(CH_3)_2)_2$$

$$CH_3CHOHCH_2N(CH_2C_6H_5)_2$$

$$CH_3CHOHCH\underset{\displaystyle NHCH_2CH_2CH(CH_3)_2}{\underset{|}{C}}HCHOHCH_3$$

Other aliphatic aminoalcohols are of interest because their benzoic or substituted benzoic acid esters form anesthetics of the novocaine and stovaine type.

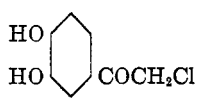


Novocaine Stovaine

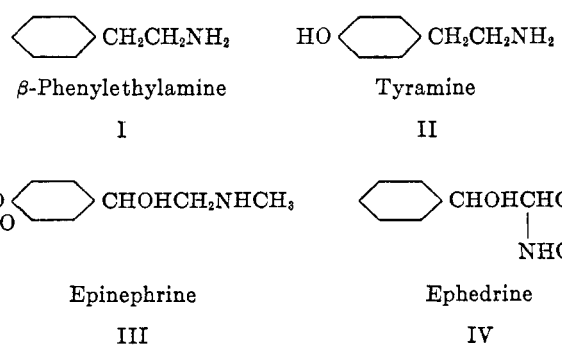
However, since ethanolamine does not have any marked effect on the blood pressure—higher homologs do not appear to have been investigated (25)—an extended discussion will not be given here.

IV. AROMATIC DERIVATIVES

While some of the fatty amines are capable of producing a hypertensive effect, the commoner and more effective compounds are aromatic derivatives. The presence of the aromatic nucleus is significant. Dakin (25), in his synthesis of epinephrine, found that catechol has the capacity to cause a rise in blood pressure, whereas ethanolmethylamine, $CH_2OHCH_2NHCH_3$, the side chain portion of epinephrine, has not. Tainter (113) also found catechol to have definite hypertensive properties. Even chloroacetyl catechol



is slightly active. Other dihydroxybenzenes, resorcinol and quinol, show no such effect; or, if one of the phenolic functions of catechol is covered, e.g., by acetylation, no action is obtained (114). Except for catechol the aromatic nucleus in itself is not sufficient to produce the desired physiological effect, but its presence is most important.



A comparison of the structure of the better known, natural pressors reveals the following facts:

The skeleton of β-phenylethylamine (I) is common to all.

I and II are primary bases, while III and IV are secondary bases.

III and IV have a secondary alcoholic hydroxyl group, which is lacking in I and II.

I, II and III are ethane derivatives, while IV is a derivative of propane.

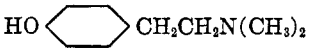
II and III are phenolic; II is a mono-para-phenolic and III is a di-meta-para-phenolic compound.

What is the significance of these differences? What are the differences in the physiological behavior of the substances? What is the change in the pharmacological action when still other modifications are introduced? In the following pages the effect of such structural modifications on the physiological activity will be considered.

V. VARIATION FROM THE β-PHENYLETHYLAMINE SKELETON

Why does Nature, in making her products, attach the aromatic nucleus to one carbon atom and the amino, or substituted amino, group to an adjacent carbon atom? What would be the effect if this characteristic arrangement should be disturbed? Barger and Dale (92) were the first to investigate this problem; they compared a series of compounds in which the relative positions of the phenyl and the amino portions varied. They found aniline to be without effect, benzylamine to be slightly active, α-phenylethylamine to be slightly more active and β-phenylethylamine to have maximum activity, while γ-phenylpropylamine was again much less active. From these results the authors concluded that the optimum constitution for sympathomimetic activity is that in which the phenyl group is attached to one carbon atom and the amino group to an adjacent carbon atom. Although these authors made no allowance for the successive introduction of an additional methylene group into the side chain, subsequent work has proved them substantially correct in concluding that "the optimum constitution of a fatty-aromatic amine for the production of sympathomimetic action is, therefore, that which is found in adrenaline itself, viz., a benzene ring with a side chain of two carbon atoms, of which the second bears the amino group."

From his examination of hordenine homologs



Hordenine

Heinz reported to v. Braun (115) that as the number of carbon atoms separating the amino group from the aromatic portion of the molecule was increased from two to three the pressor effect was completely reversed, i.e., the substance became a depressor; and as the length of the side chain was increased to four or five

TABLE 2

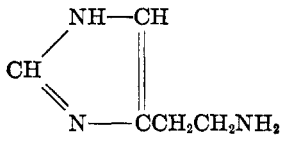
Phenylpropylamines (119)

AMINE	TOXICITY OF HYDROCHLORIDE		PRESSOR ACTIVITY OF HYDROCHLORIDE
	Rats—subcutaneous	Rabbits—intravenous	Dogs—intravenous
	mg./kg.	*mg./kg.*	
$C_6H_5CH_2CH_2NH_2$	450	60	1 mg./kg.—good rise which persisted for 20 minutes
$C_6H_5CH(NH_2)CH_2CH_3$	1000	50	1 mg./kg.—very slight rise
$C_6H_5CH_2CH(NH_2)CH_3$	25	25	1 mg./kg.—rise equal to that of $C_6H_5CH_2CH_2NH_2$; effect persisted longer
$C_6H_5CH_2CH_2CH_2NH_2$	100	50	1 mg./kg.—medium transitory rise
$C_6H_5CH(CH_3)CH_2NH_2$	500	50	Good pressor; also active on oral administration

carbon atoms the depressing effect became correspondingly greater. Pick (116, 117), working with the same series of compounds, did not observe this reversal, but he did find a weakening in the pressor effect. Hasama (118), comparing the effects produced by the two isomeric phenylethanolamines, $C_6H_5CH(NH_2)$-CH_2OH and $C_6H_5CHOHCH_2NH_2$, found the former inactive as a pressor, whereas the latter is a very potent pressor. Tainter (118a) observed that if the chain separating the amino group from the aromatic nucleus in 3,4-dihydroxyphenylethylamine, $(HO)_2C_6H_3CH_2CH_2NH_2$, was increased to three carbon atoms the pressor activity was diminished by two-thirds. Hartung and

Munch (119), wishing to obviate the criticism of the series studied by Barger and Dale, studied the pressor effects of four isomeric phenylpropylamines. The results, summarized in table 2, show convincingly that the optimum pressor activity is obtained when the phenyl and amino groups are attached to each of two adjacent carbon atoms.

It is of interest to note in this connection that if in histamine, which lowers the blood pressure, the length of the side chain is decreased to one carbon atom, or increased to four carbon atoms,



Histamine

the effect on the blood pressure is distinctly lessened (120). Thus it becomes evident that in the relative positions of the aromatic portion and the amino group of compounds of this type, nature cannot be improved upon.

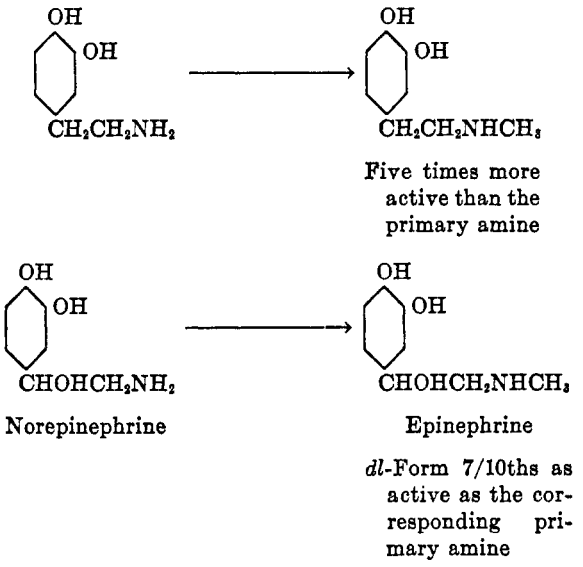
VI. MODIFICATIONS IN THE AMINO GROUP

Among the natural compounds belonging to the type under consideration will be found primary, secondary and tertiary bases. Tyramine is a primary base, while hordenine is the corresponding tertiary base; epinephrine is a secondary base, as is also ephedrine. Associated with ephedrine have been found in small amounts the corresponding primary and tertiary bases (121, 122, 123). Hence, the question naturally arises, what is the difference physiologically between the respective types of bases?

Barger and Dale (92) investigated this phase also in their classical studies. They reported that when β-phenylethylamine, tyramine and phenylethanolamine were converted into the corresponding secondary methylated bases there was no appreciable change in pressor potency. Perhaps the comparative determinations lacked the refinement necessary to reveal any differences that may exist, for subsequent observations by Chen, Wu and Henriksen (124) showed that methylation of phenylethanolamine,

that is, conversion into a secondary amine, decreases its activity very markedly.

In the case of 3,4-dihydroxyphenylethylamine, however, Barger and Dale found that methylation increased the activity fivefold. On the other hand, conversion of epinephrine into the corresponding primary amine—removal of the methyl—increased the activity by about 40 per cent (92, 125).



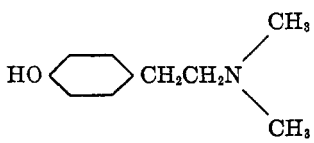
Perhaps this anomalous reversal may be attributed to the influence of the secondary alcoholic hydroxyl group in epinephrine. Recently Raymond-Hamet (126) reported another significant pharmacological difference between epinephrine and its corresponding "nor" or primary amino compound. While the pressor effect of epinephrine may be reversed with yohimbine, this drug does not affect the action of norepinephrine.

In the case of the nonphenolic compounds the trend appears more consistent. Chen, Wu and Henriksen, as already stated (124), found phenylethanolamine, $C_6H_5CHOHCH_2NH_2$, much more active than phenylethanolmethylamine, $C_6H_5CHOHCH_2NHCH_3$; the former is also the more toxic. However, in all the other compounds, the primary amine was found to be not only a

more potent pressor, but also much less toxic. *dl*-Phenylpropanolamine, $C_6H_5CHOHCH(NH_2)CH_3$, is about 20 per cent more active than is *dl*-ephedrine and the toxicity is approximately 15 per cent less. Hartung and Munch (127) found phenylpropanolamine to be as active as *l*-ephedrine and to produce in substantially every respect the characteristic responses of ephedrine; it is active after oral administration, given intravenously to dogs it produces a prolonged rise in blood pressure, and successive doses become less effective. Hasama (118) has published a tracing showing the effect of intravenous administration of phenylpropanolamine to a rabbit; the blood pressure curve showed a rise of comparatively short duration and in general resembled that obtained with phenylethanolamine. Such a result may be caused by an idiosyncracy of the test animal, or perhaps it is a characteristic response of the rabbit to this particular compound. Ehrhart (159) and Schaumann (160) report that in the ephedrine series and phenolic derivatives the primary bases are more strongly active than the corresponding methylamino compounds.

The effect of methylating isoamylamine has already been pointed out; the pressor activity is reduced by about one-half. It is of additional interest to note that the *N*-methylation of histamine reduces its blood pressure lowering capacity to about 1/200th that of histamine itself (120).

An introduction of a second methyl group works to further disadvantage. Hordenine,

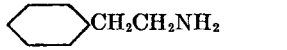
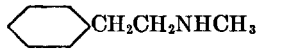
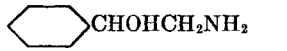
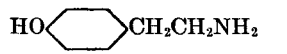
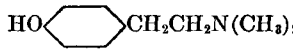


Hordenine

the tertiary base corresponding to tyramine, an alkaloid first isolated by Léger (128) from germinating barley and since identified by Späth (129) in cactus species under the name of anhalin, was studied by Camus (130) because of its value in combating diarrhea; it is still distinctly active as a pressor, but it has only 1/10th the activity of tyramine (32, 92).

TABLE 3

The effect of alkylating the amino group

BASE	TOXICITY—M.L.D.	ACTIVITY
(*A*) 	40–50 mg./kg. intravenous to rabbits (124)	1/350th as active as epinephrine (32) 0.00002 mole to 2.6 kg. of cat gave 64 mm. Hg (124)
		1/350th as active as epinephrine (32)
(*B*) 	80 mg./kg. intravenous to rabbits (124)	0.00002 mole to 2.63 kg. of pithed cat gave 58 mm. Hg (124) 1/350th as active as epinephrine (32)
	100 mg./kg. intravenous to rabbits (124)	0.00002 mole to 2.63 kg. of pithed cat gave 26 mm. Hg (124)
(*C*) 		1/150th as active as epinephrine (32)
		1/150th as active as epinephrine (32)
	300 mg./kg. intravenous to dogs and guinea pigs 250 mg./kg. intravenous to rabbits 2000 mg./kg. subcutaneous to guinea pigs 2000 mg./kg. oral to dogs (137)	1/700th as active as epinephrine (32) Nicotine-like action (134)

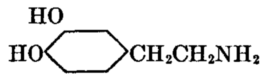
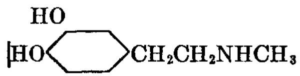
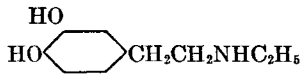
			Nicotine-like action (32)
			Less than 1/150th as active as epinephrine (32)
(*D*)			1/75th as active as epinephrine (32) 1/65th as active as epinephrine (118a)
			1/10th as active as epinephrine (32) 1/12th as active as epinephrine (138)
			1/43rd as active as epinephrine (32)
(*E*)	$C_6H_5CHOHCH(NH_2)CH_3$	175 mg./kg. of hydrochloride intraperitoneal to rats (127) 350 mg./kg. of hydrochloride subcutaneous to rats (137) 600 mg./kg. of hydrochloride subcutaneous to guinea pigs (137) 75 mg./kg. of hydrochloride intravenous to rabbits (137) 70 mg./kg. of hydrochloride intravenous to rabbits (124) 500 mg./kg. of hydrochloride intraperitoneal to dogs (127) 400–500 mg./kg. of sulfate subcutaneous to rabbits (139)	*dl*-Compound equals *l*-ephedrine (127) Same as ephedrine (139) *dl*-Compound 1/80th as strong as epinephrine (124) Strong mydriatic action (140)

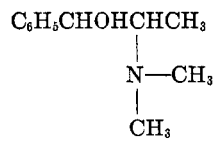
TABLE 3—*Concluded*

	BASE	TOXICITY—M.L.D.	ACTIVITY
(*E*)	$C_6H_5CHOHCHCH_3$* | $NHCH_3$	50 mg./kg. of hydrochloride intravenous to rabbits (127, 141) 350 mg./kg. of hydrochloride subcutaneous to guinea pigs (127) 320 mg./kg. of hydrochloride subcutaneous to rats (142) 400 mg./kg. of hydrochloride subcutaneous to guinea pigs (141) 320–400 mg./kg. of sulfate subcutaneous (140)	*dl*-Form 1/95th as potent as epinephrine to pithed cat .00001 mole of *l*-ephedrine gave 75 mm. Hg rise in 2.55 kg. of pithed cat (124)
	$C_6H_5CHOHCHCH_3$ | $N(CH_3)_2$		Much less active than ephedrine (124, 131) 0.00001 mole of *l*-isomer to 2.55 kg. of pithed cat gave rise of 10 mm. Hg (124)
	$C_6H_5CHOHCHCH_3$ | NHC_2H_5	50 mg./kg. intravenous to rabbits (124)	0.00002 mole gave rise of 59 mm. Hg in 2.8 kg. pithed cat
	$C_6H_5CHOHCHCH_3$ | NHC_3H_7	50 mg./kg. intravenous to rabbits (124)	Gave fall
	$C_6H_5CHOHCHCH_3$ | $NHCH(CH_3)_2$	40–50 mg./kg. intravenous to rabbits (124)	

$C_6H_5CHOHCH(NHC_4H_9)CH_3$	15 mg./kg. intravenous to rabbits	Gave fall
$C_6H_5CHOHCH(NHC_5H_{11})CH_3$	20 mg./kg. intravenous to rabbits (124)	Greater fall (124)
$C_6H_5CHOHCH(NHCH_2C_6H_5)CH_3$	20 mg./kg. intravenous to rabbits (124)	

* For complete table see Chen and Schmidt (140).

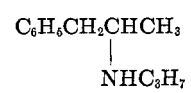
l-Methylephedrine,



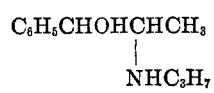
is much less active and appreciably more toxic than ephedrine and it has no longer a mydriatic action (124, 131). Still further methylation—conversion into quaternary ammonium compounds—completely eliminates all pressor activity and confers a nicotine-like action (32, 92, 132, 133). In fact, some of this nicotine-like behavior is present in hordenine even before it is converted into a quaternary ammonium derivative (134).

If the methylamino group is coupled with formaldehyde its physiological action becomes nil (134a).

The use of higher alkyl groups in the place of methyl is a step in the wrong direction. Ethylamine compounds are less desirable than the corresponding methyl derivatives, while propylamine analogs are still less active (92). Of the interesting series of ephedrine-like compounds prepared by Hyde, Browning and Adams (135) it was found (124) that as the alkyl attached to the amino group became larger the activity decreased, the depressant action on the heart became more pronounced, and the toxicity increased. Kanao (136) in a similar series found that if the alkyl group is sufficiently large the compound becomes an anesthetic. Thus $C_6H_5CHOHCH_2NHR$ is anesthetic when R = isobutyl or phenyl. $C_6H_5CHOHCH(CH_3)NHR$ is nonanesthetic when R = ethyl or propyl, but is anesthetic when R = allyl, butyl, isobutyl, isoamyl, benzyl, *p*-aminobenzyl, furfuryl or citral. He also found



to be anesthetic, whereas the corresponding aminoalcohol,



is nonanesthetic. This, again, would indicate some peculiar function that may be directly attributed to the alcoholic hydroxyl.

In table 3 will be found a summary of the available quantitative data on the various types of bases under consideration.

The preponderance of evidence thus far, with the very striking exception of 3,4-dihydroxyphenylethylamine, indicates that the primary bases are the most active in their effect on the blood pressure. Conversion into the corresponding secondary amine has a tendency to decrease the pressor activity; in the ephedrine series this becomes more pronounced as the alkyl group grows larger, and soon the sympathomimetic action disappears and a depressant action takes its place; if the alkyl group is allyl, butyl or greater the compound is anesthetic; the toxicity increases as the alkyl group becomes larger. The corresponding tertiary amines are very much less active, while conversion into the the quaternary ammonium derivatives removes all pressor activity and confers nicotine-like action.

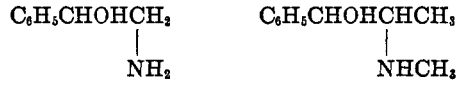
If the primary amines are the most active, why has nature given us secondary bases in ephedrine and epinephrine? Perhaps the activity that the pharmacologist and physiologist are measuring is not the sole indication of clinical desirability or therapeutic efficiency.

VII. INFLUENCE OF CHANGE IN THE LENGTH OF THE SIDE CHAIN

Epinephrine, extensively and variously used in the amelioration or treatment of various human afflictions, has one severe handicap, viz., that it is, as has already been pointed out, ineffective on the blood pressure, except when administered by injection. Hence, when Chen and Schmidt (143) showed that a substantially ephinephrine-like response could be obtained by the oral administration of ephedrine, this plant alkaloid was welcomed into the ranks of the therapeutic agents.

A structural difference between the hormone and the alkaloid that becomes apparent at once is the length of the side chain; the former is a derivative of ethane while the latter is derived from propane. That this is a most significant difference is revealed by the following observations.

Phenylethanolamine, which has been studied by the Council of Chemistry and Pharmacy of the American Medical Association (144, 145), possesses many of the pharmacological actions of ephedrine, except that its action is of much shorter duration; however, it is not active after oral administration. Phenylethanolamine differs from ephedrine by two methyl groups, one on the nitrogen and the other in the side chain.



Phenylethanolamine Ephedrine

In order to determine which of the two confers greater oral activity, Piness, Miller and Alles (146) studied two methyl derivatives of β-phenylethylamine; in one the methyl group was substituted on the nitrogen atom, $C_6H_5CH_2CH_2NHCH_3$, and in the other, in the side chain, $C_6H_5CH_2CH(NH_2)CH_3$. They found that the former compound was inactive, whereas the propylamino derivative was very active when taken by mouth; moreover, the duration of its action was very much extended. Chen and co-authors, from their study of ephedrine and its analogs, conclude that it is the third carbon atom in the side chain that confers oral activity. Hartung and Munch (119), from their results with four phenylpropylamines, found that oral activity was conferred when a methyl group was substituted on either carbon atom of the side chain in β-phenylethylamine, both phenyl-2-amino-1-propane and phenyl-1-amino-2-propane being active orally. (See table 2)

If increasing the side chain from two to three carbon atoms confers the desired activity after oral administration, what will further extension do? Strangely enough the whole pressor effect is so far reduced as to be practically negligible. Thus, Chen found phenylbutanolamine, prepared by Tiffeneau (124), to be slightly active in decerebrate cats, and Hartung, Munch, Deckert and Crossley (147) confirmed these findings on anesthetized dogs. On further lengthening of the side chain up to phenyloctanolamine no pressor activity is apparent, the most outstanding change in

physiological activity being a regular increase in toxicity when given intravenously. While the whole series has not yet been thoroughly investigated pharmacologically, phenylhexanolamine is the only member found thus far to exhibit an anomalous behavior; a dose of 10 mg. per kilogram to an anesthetized dog gave first a fall in pressure, which persisted for half an hour, after which the pressure gradually rose and finally went as high above normal as the fall had been below. Schaumann (161) found that if the side chain of epinephrine is increased to four carbon atoms,

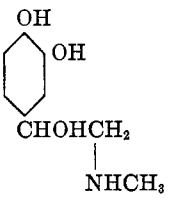
$$(HO)_2C_6H_3CHOHCHCH_2CH_3$$
$$\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad NHCH_3$$

the compound is no longer a pressor but has taken on a depressor action.

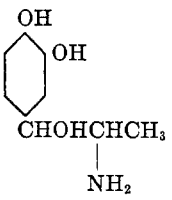
When phenylethanolamine is compared with the corresponding phenylpropanolamine, one other very marked difference in action appears. An intravenous injection of phenylethanolamine causes a rise in blood pressure that persists for several minutes and then returns to normal; a subsequent administration of the same dose produces an equal effect. Phenylpropanolamine or ephedrine, its *N*-methylated derivative, given either intravenously or orally, causes a rise in blood pressure that persists for two or more hours, and a subsequent dose produces a response of very much smaller magnitude.

Another significant difference between the two-carbon atom and three-carbon atom side chain derivatives is in their synergistic action, that is, the ability to potentiate the effect of epinephrine. Launoy and Nicolle (148) and Csepai and Doleschall (149) observed that when epinephrine was administered after ephedrine, its action was much greater than normally. The same phenomenon was observed independently by Munch and Hartung (150), and these authors reported that this ability to potentiate the pressor action of epinephrine is characteristic of the derivatives of phenylpropanolamine.

A most striking example of the physiological difference between the two- and three-carbon atom side chains is found in epinephrine and one of its isomers,"norhomoepinephrine."



Epinephrine



Norhomoepinephrine

The latter may be considered as epinephrine in which the *N*-methyl has been shifted to the side chain, giving the latter three carbon atoms. Except for the difference in potencies both produce, after intravenous administration, the same effect on the blood pressure; but, as has already been shown, epinephrine is without any accepted characteristic effect on the blood pressure after oral administration; nor homoepinephrine, on the other hand, was found to produce a very great and prolonged rise in the blood pressure when given by mouth to an anesthetized dog (151).

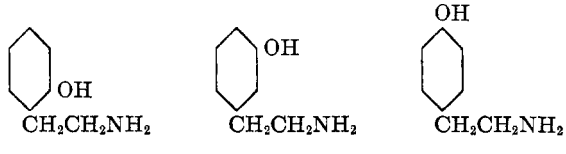
From all these considerations it is seen that ability to produce a rise in blood pressure is resident in compounds with two or three carbon atoms in the side chain; the ethane derivatives are effective after injection, while the propane derivatives produce an effect of longer duration and possess the added virtue of being potent after oral administration.

By what process is the living organism able to differentiate so readily and characteristically between certain members of an homologous series such as these phenylalkanolamines? The difference is probably more one of kind than of degree; the living tissue seems to be able to distinguish readily where by chemical methods the difference could be determined only with great difficulty. In view of these observations, can pharmacological response be a function only of purely chemical properties?

VIII. THE EFFECT OF HYDROXYL SUBSTITUTION IN THE AROMATIC NUCLEUS

Tyramine, hordenine and epinephrine are phenolic substances. It is well-known that the intensity of action of phenolic pressor substances is much greater than that of the corresponding non-phenolic compounds, but the complete rôle of the phenolic func-

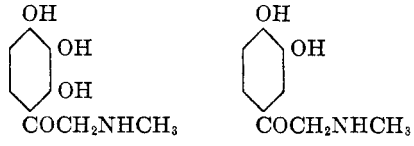
tion is not yet known. Barger and Dale (92) were the first to investigate the rôle of the phenolic hydroxyl group; they compared the three monohydroxy derivatives of β-phenylethylamine and observed that the ortho derivative (I) was no more active



Tyramine

I II III

than the phenylethylamine itself, whereas the meta (II) and para (III) compounds were equally active and about five times more potent than the parent amine. They found 2,3,4-tri-

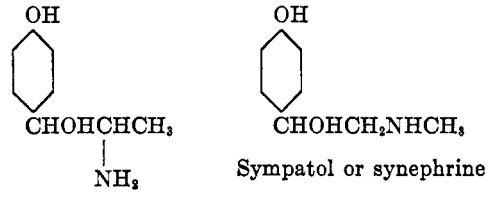


IV V

hydroxyphenyl methylaminomethyl ketone (IV) to be less active than 3,4-dihydroxyphenyl methylaminomethyl ketone (V), showing that the introduction of the third, or ortho, phenolic hydroxyl group decreases activity. Maximum activity was found in 3,4-dihydroxy derivatives, that is, in compounds which had a catechol nucleus. From these results Barger and Dale concluded that the meta and para hydroxyl groups are of equal influence, and that maximum activity results if both are present.

While Chen, Wu and Henriksen (124) did not work on phenolic compounds, they suggested, largely from the conclusions of Barger and Dale, that the presence of hydroxyl groups in the benzene ring confers "intensity of action" and ventured the prediction that *p*-hydroxyphenyl-1-amino-2-propanol (VI) might combine the desirable physiological properties of both epinephrine and ephedrine, namely, the intensity of response conferred by the para-hydroxyl, the minimum toxicity and greater activity of the pri-

mary amine, and the duration of action and oral activity conferred by the three-carbon atom side chain.



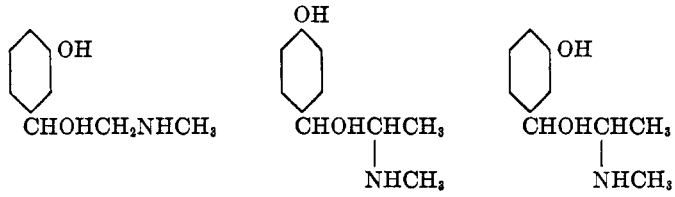
Sympatol or synephrine

VI VII

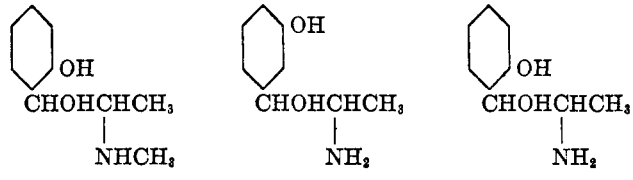
Meanwhile sympatol, or synephrine (VII), described as a stable "adrenaline-like" preparation, received considerable attention. Lasch (152) found it to be relatively nontoxic, with an action on the blood pressure resembling that of epinephrine although of somewhat longer duration and about 1/50th as strong. Hochrein and Keller (153) describe its action as being intermediate between that of epinephrine and ephedrine. Ehrisman (154) reported that he administered it orally to his patients with some evidence of success, and in 1930 the Council on Pharmacy and Chemistry of the American Medical Association (155) accepted synephrine for inclusion in "New and Non-Official Remedies" as a reagent in treating, either *orally* or hypodermically, attacks of hay fever, asthma, coughing, spasms of asthma and pertussis (whooping cough). Ehrisman (154) also reported that sympatol prolonged the effects of novocaine anesthesia two or three times. Tainter (156), in a comprehensive investigation of synephrine and its isomers, found the racemic form to be 1/116th as active a pressor as *l*-epinephrine. As for its oral activity, Stockton, Pace and Tainter (157) found that doses of 0.5–1.5 g. by mouth to patients did not give the desired effects but did induce nausea and vomiting. Nor did these authors find it to have any effect on procaine anesthesia. While the chemist must leave it to the physiologist to settle the question of the oral activity of this compound, nevertheless, from purely structural considerations which have already been discussed, one would expect it to be inactive when given by mouth.

Very recently other phenolic compounds have been prepared,

and a comparison of their pharmacological action will serve best to show the effect of the various phenolic substitutions. The monohydroxy compounds include *p*-sympatol (VII), *m*-sympatol (VIII) (158), the three monohydroxyephedrines (IX, X and XI) (159, 160, 161) and the three monohydroxyphenylpropanolamines (XI, XII and XIII) (151).



VIII IX X



XI XII XIII

All of the monohydroxyephedrines, when tested on the frog by the Laewen-Trendelenburg method, act like ephedrine itself and possess neither qualitatively or quantitatively the action of epinephrine. With ergotamine the meta compound (X) shows a reversal of effect on the circulation; the para compound is weakened but still active, while the action of the ortho isomer is probably augmented. In cocainized animals the ortho compound shows reversal, the para derivative is nearly inactive, whereas *m*-hydroxyephedrine shows not only definite potentiation but increased duration of action. These characteristic responses after ergotaminization and cocainization indicate that the ortho phenolic compound is most like ephedrine itself; that the meta derivative is least like ephedrine and that it has, in effect, begun to take on the properties ascribed to the catechol nucleus in epinephrine (113); and that the para isomer is somewhere intermediate between the two (161). None of the phenolic compounds exhibited tachyphylaxis, that is, second and third doses showed no

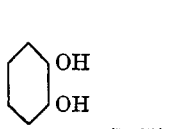
diminishing effects and they also differed from ephedrine and phenylpropanolamine in that larger doses always produced a rise in the blood pressure (151, 161).

The introduction of phenolic hydroxyl groups into phenylpropanolamine tends to cut down the duration of the pressor response. The ortho phenolic hydroxyl serves to increase the toxicity almost twofold and probably to decrease the pressor potency; the meta hydroxyl (XII) increases the activity about threefold and the toxicity by more than four times; the para phenolic function (VI) increases the activity and decreases the toxicity (151).

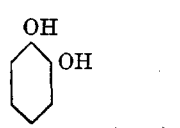
In modifying any circulatory effects the ortho phenols are least active, which is in agreement with the earlier findings of Barger and Dale (92). However, contrary to these pioneers the meta and para hydroxyl groups do not have equal or identical effects; *m*-hydroxyephedrine (X) is a stronger pressor than the para isomer (IX) (159, 160, 161); *m*-hydroxyphenylpropanolamine (XII) is at least twice as strong as *p*-hydroxyphenylpropanolamine (VI) (151); and Kuschinsky (158) has found that *m*-sympatol (VIII) is five times as active as is *l*-*p*-sympatol (VII). Hence, it is evident that most of the intensifying effect of epinephrine is conferred by the meta phenolic hydroxyl.

The simultaneous substitution of two hydroxyl groups in the aromatic nucleus gives a series of which epinephrine is a member. One may readily see what combinations are possible.

No record was found of a β-phenylethylamine derivative with the two hydroxyl groups in the ortho- and meta-positions. However, Tiffeneau (162) did find that 2,3-dihydroxybenzylamine (XIV) was more effective in increasing the rate and strength of



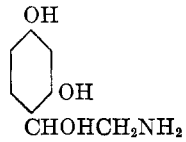
XIV



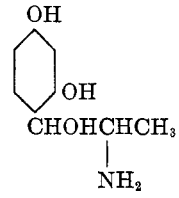
XV

the beat of the isolated rabbit heart, but that 3,4-dihydroxybenzylamine (XV) produced a stronger vasoconstriction and a greater rise in blood pressure.

References to but two 2,4-dihydroxy derivatives were found. Boruttau (163) found that 2,4-dihydroxyphenylethanolamine (XVI)



XVI

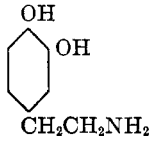


XVII

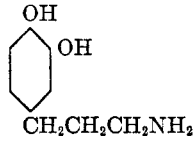
had but little effect on the circulation, even in large doses. 2,4-Dihydroxyphenylpropanolamine (not analytically pure) was equally inactive, and at larger doses gave a depression of the blood pressure (151).

The 3,4-dihydroxy compounds are the best known. The compounds belonging to this class are considered by Tainter (113) as true sympathicotropic reagents, compounds which produce their effect through the sympathetic nervous system. The known catechol derivatives of this type other than epinephrine are discussed below.

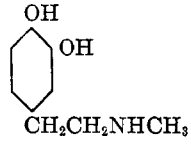
3,4-Dihydroxyphenylethylamine (XVIII) is 1/75th to 1/65th as active as epinephrine (32, 118a).



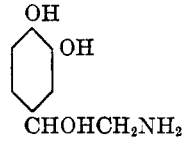
XVIII



XIX



XX

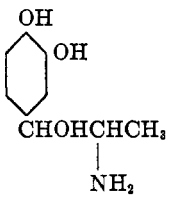


XXI

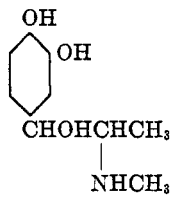
3,4-Dihydroxyphenylpropylamine (XIX) is, as one might expect from the fact that three carbon atoms separate the amino group and the nucleus, appreciably weaker, that is, it is about one-third as active as the ethylamine homolog (118a). 3,4-Dihydroxyphenylethylmethylamine (XX) may be obtained from papaverine or laudanosine (164, 165) and under the name of epinine it is used as an epinephrine substitute; it is about 1/12th as active as *l*-epinephrine (138).

3,4-Dihydroxyphenylethanolamine (XXI), also known as arternol, is described as giving substantially all the characteristic epinephrine reactions. However, being a primary amine, it is more active; Barger (92) and Schultz (125) found it to be about 10/7ths more active and Tiffeneau (166) found it to be twice as active as epinephrine. Raymond-Hamet (167) observed that if this compound is injected first and followed by epinephrine the latter is the weaker, but if the epinephrine is given first, then it is the stronger. This author also observed that a yohimbinized animal giving a reversal of action to epinephrine still gives a positive response to the same dose of 3,4-dihydroxyphenylethanolamine (XXI). Tainter (167a) found that *dl*-3,4-dihydroxyphenylethanolamine has 80 per cent of the activity of *l*-epinephrine as a circulatory stimulant in cats and that it possesses a therapeutic margin (ratio of toxic dose to effective dose) three times as great.

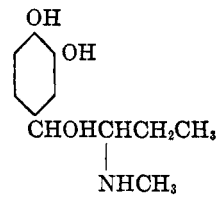
3,4-Dihydroxyphenylpropanolamine (XXII), an isomer of



XXII



XXIII



XXIV

epinephrine, has been known for some time. It was first prepared in the following way. α-Phthalimidopropionyl chloride was condensed, by means of the Friedel-Crafts reaction, with the dimethyl ether of catechol (168); the resulting ketone was treated with hydrochloric acid, under proper conditions, to yield 3,4-dihydroxyphenyl α-aminoethyl ketone, which after reduction gave the desired aminoalcohol. A simpler synthesis recently developed consists of the catalytic reduction of 3,4-dihydroxyphenyl α-oximinoethyl ketone (151). Kanao (172) prepared the compound with the two phenolic hydroxyl groups acetylated. The hydrochloride is very hygroscopic and can be dried only with the greatest difficulty. Resolution with *d*-tartaric acid (169)

gave a levo compound two to three times more potent than the racemic mixture.

Tiffeneau (170) found the l-isomer to be thirty times as active as the *d*-compound and from 60 to 75 per cent as active as *l*-epinephrine (171). However, since this compound possesses two asymmetric carbon atoms it is, like ephedrine, theoretically capable of existing in four optically active and two racemic forms; these have not as yet been reported. Bierry, Rathery and Leving (173) found norhomoepinephrine to have hyperglycemic actions resembling those of epinephrine itself. Working with the racemic compound as synthesized, Hartung and Munch (151) found that when it was injected intravenously into rabbits, its toxicity was less than 1/100th as great as that of epinephrine and that qualitatively it is indistinguishable from epinephrine in its effect on the circulatory system; however, it possesses a weaker action, being about 1/12th as potent as *l*-epinephrine. Schaumann (160) reports it to be 1/6th to 1/3rd as active as *l*-epinephrine. Since this compound produces the characteristic epinephrine responses and structurally contains the three-carbon atom side chain, it is of particular interest to note that it produces a rise in the blood pressure when given orally. A dog receiving a dose of 100 mg. per kilogram by mouth showed an effect within fifteen seconds and after ninety seconds the blood pressure rose so high that the animal died from cardiac failure. A second animal receiving 1 mg. per kilogram gave, within a minute, evidence of a blood pressure rise, reached a maximum effect in 25 to 30 minutes and the pressure remained at an elevated level for at least two and one-half hours. Two subsequent oral doses both produced rises (151).

Here is an excellent illustration of the fact that the effect produced by substituting groups in a physiologically active molecule is not necessarily additive, or cumulative, but that their effects may be reciprocally modifying. It has already been shown that in compounds like ephedrine and phenylpropanolamine the duration of action and oral activity are conferred by the third carbon atom in the aliphatic side chain, and that the second and third doses of the same agent produce a much decreased rise in blood pressure. When the meta or para phenolic function was introduced there was a marked diminution in the duration of action,

and second and third doses showed no diminishing effect; simultaneous introduction of the meta and para hydroxyl groups completely neutralizes this duration but apparently has left the oral potency unimpaired.

3,4-Dihydroxyephedrine (XXIII) also gives many of the characteristic epinephrine reactions. Being a secondary amine it is weaker and more toxic than the corresponding primary amine; smaller doses give a fall and larger doses a rise in blood pressure. The substance is definitely sympathicotropic (161).

3,4-Dihydroxyphenyl-1-methylamino-2-butanol-1 (XXIV), containing four carbon atoms in the side chain, is not only weaker than its lower homolog (XXIII), but shows a depressing effect on the blood pressure (161).

While the effect of phenolic substitution on the circulation is readily measured and clearly apparent, it is not improbable that such substitution also modifies the mechanism through which the physiological reaction is produced. Thus, epinephrine is generally accepted as being "sympathicotropic," for all the evidence indicates that its physiological effects are the result of stimulation of the sympathetic system. This sympathicotropic action is ascribed by Tainter (113) to the catechol nucleus, for he found that the pressor effects of the various optical isomers of adrenaline, epinine, adrenalone and even catechol itself were augmented by cocainization and reversed by ergotaminization. Ephedrine, on the other hand, behaves quite differently; ergotamine produces no reversal (174), large doses act directly on the para-sympathetic system (175), and in cocainized animals the effect of ephedrine may be absent or greatly reduced (97, 99). Whether these and other phenomena are to be interpreted as indicative of a purely musculotropic action (99), a predominantly sympathicotropic action (98), or a possible combination of the two is a question to be answered by those better qualified than the chemist. In any event there is an abundance of evidence to indicate that ephedrine is quite different in its mode of action from epinephrine (118a, 176, 177, 178), and perhaps one may not unreasonably expect that in some way there is, as Schaumann suggests (161), a gradual change from a distinctly ephedrine-like reaction to an epinephrine-like reaction as the substitution of a single phenolic

hydroxyl group is shifted from ortho to para to meta, the simultaneous introduction of both the meta and para hydroxyls conferring sympathicotropic reaction. In any event, all of the compounds which structurally bridge the gap between epinephrine and ephedrine are now available, and further study of their pharmacological properties will continue to throw more light on the physiological variation as one gradually proceeds from one compound to another.

Another difference between the nonphenolic and phenolic compounds, a difference not so well established is in the glycemic action. The decided hyperglycemic action of epinephrine has been considered one of its most characteristic physiological properties since Blum (179) first observed that suprarenal extracts given subcutaneously produced glycosuria. Its isomer, norhomoepinephrine, possesses a similar definite hyperglycemic action (173). Synephrine injected subcutaneously into rabbits also produces a great rise in the blood sugar (152, 180). While ephedrine is reported to have a hyperglycemic effect, it is so only in doses much larger, about 20 mg. per kilogram or more, than are necessary to influence the blood pressure (181, 182, 183); in fact, Nitzescu (184) suggested that the hyperglycemic action of ephedrine is a result of induced increased epinephrine secretion. If ephedrine is administered intravenously during full digestion smaller doses, 0.5 to 3 mg. per kilogram, are reported to be hyperglycemic (184). Others have found the hyperglycemic action to be comparatively low or even insignificant (185, 186).

Hence it is seen that the phenolic hydroxyl groups, especially those in the meta and para positions, contribute very specifically to the potency of the molecule and probably also modify very materially the mechanism of the physiological response.

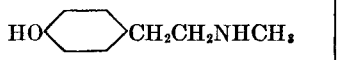
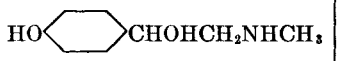
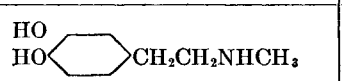
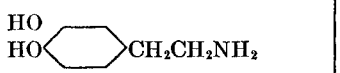
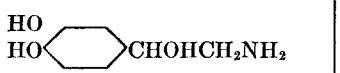
IX. THE EFFECT OF HYDROXYL IN THE SIDE CHAIN

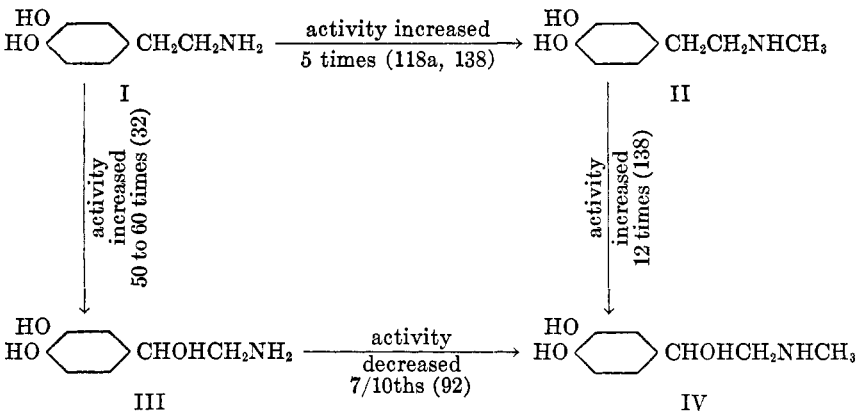
The significance of the alcoholic hydroxyl group in epinephrine and ephedrine does not appear to be completely defined. We have already seen that when 3,4-dihydroxyphenylethylamine (I) is methylated the pressor activity is increased fivefold, whereas the *N*-methylation of 3,4-dihydroxyphenylethylamine (III) decreases the activity in the ratio of 7:10 (92).

TABLE 4

Effect of alcoholic hydroxyl group in side chain

	AMINE	TOXICITY—M.L.D.	PHYSIOLOGICAL ACTIVITY
(*A*)	$C_6H_5CH_2CH_2NH_2$	450 mg./kg. of hydrochloride subcutaneous to rats (119) 60 mg./kg. of hydrochloride intravenous to rabbits (119) 40–50 mg./kg. of hydrochloride intravenous to rabbits (124) 200–250 mg./kg. of hydrochloride subcutaneous to guinea pigs (187)	1 mg./kg. to dog gave good rise that persisted 20 min. (119) Doses larger than 1 mg./kg. to rabbits produced fall (118)
	$C_6H_5CHOHCH_2NH_2$	80 mg./kg. of hydrochloride intravenous to rabbits (124) 90 mg./kg. of hydrochloride intravenous to rabbits (147) 1000 mg./kg. of hydrochloride subcutaneous to guinea pigs (147, 187) 30 mg./kg. of hydrochloride intravenous to rabbits (187)	Pressor activity equals that of ephedrine (187) 0.2 cc. of *M*/40 solution to decerebrate cat produced rise in blood pressure of 58 mm. Hg (124) 0.5–1.2 mg. intravenous to rabbits, cats and dogs caused rise in blood pressure of 10 to 280 per cent (188)
(*B*)	$C_6H_5CH_2CH(NH_2)CH_3$	25 mg./kg. of hydrochloride intravenous to rabbits (119) 25 mg./kg. of hydrochloride subcutaneous to rats (119)	1 mg./kg. gave rise equal to that of $C_6H_5CH_2CH_2NH_2$; effect persisted longer (119)
	$C_6H_5CHOHCH(NH_2)CH_3$	75–90 mg./kg. of hydrochloride intravenous to rabbits (119)	Equals ephedrine (119)

(*C*)			1/70th as active as *dl*-epinephrine (32)
		50 mg./kg. of hydrochloride intravenous to rabbits (152) 500 mg./kg. of hydrochloride subcutaneous to rats (152)	1/58th as active as *dl*-epinephrine (189) 0.2 cc. of *M*/20 solution to decerebrate cat produced rise of 45 mm. Hg (124)
(*D*)			1/12th as active as *l*-epinephrine (188)
			Activity of epinephrine previously given
(*E*)			1/50th as active as corresponding aminoalcohol derivative (32a) 1/65th as active as epinephrine (118a)
			50 times more active than simple amine (32)



This reversal of effect is obviously caused by the presence of the alcoholic function. It is also seen that the introduction of an alcoholic group increases tremendously the pressor potency, fifty or more times in the primary amine and twelve times in the secondary amine. These data serve as an excellent example that the compounded effect of the simultaneous introduction of two substituents into a physiologically active molecule may be reciprocally modifying; one cannot always rely on a summation of their individual effects.

Another outstanding difference between epinephrine and its desoxy compound, epinine (II), is the fact that the average duration of blood pressure rise for epinine is about twice as long as for *l*-epinephrine (138). There is insufficient evidence as yet to know whether the introduction of the alcoholic group generally increases the pressor potency (124).

Comparing β-phenylethylamine with the corresponding amino-alcohol, phenylethanolamine, Hasama (118) found the following:

$C_6H_5CH_2CH_2NH_2$	$C_6H_5CHOHCH_2NH_2$
1. Small doses give blood pressure rise. Doses larger than 1 mg. per kilogram cause depression.	1. Always produces rise.
2. No parallelism between dose and degree of response.	2. Degree of rise parallels the dose.
3. Minimum effective dose is 0.05 mg. per kilogram intravenous to rabbits.	3. Minimum effective dose is 0.1 mg. per kilogram.
4. Blood pressure curve rises gradually and falls sharply.	4. Blood pressure curve rises sharply and falls sharply.

Comparing the curves obtained from β-phenylethylamine and tyramine with those obtained with the corresponding alcohols it is seen that the presence of the hydroxyl group in the side chain makes the compound reach its maximum effect in much shorter time.

In the propane series Hartung and Munch (119) found that the introduction of the alcoholic group on the carbon atom adjacent to the aromatic nucleus in phenyl-1-amino-2-propane, that is, going from $C_6H_5CH_2CH(NH_2)CH_3$ to $C_6H_5CHOHCH(NH_2)CH_3$, decreased the toxicity from 25 mg. per kilogram to 350 mg. per kilogram subcutaneously injected into rats, and from 25 mg. per kilogram to 75 mg. per kilogram intravenously administered to rabbits, a decrease from three- to sixteen-fold, depending on the method of determination. The effect on the relative pressor potency has not yet been determined.

The mydriatic effect of these compounds may, in part, be ascribed to the alcoholic group, for compounds without this group are not mydriatic (124).

The results thus far available on the rôle of the hydroxyl group in the side chain are given in table 4.

A study of this table indicates that in general the alcoholic hydroxyl attached to the carbon bearing the aromatic group serves to detoxicate, at least in part, and to augment the pressor activity. Whether it also affects the mode of action has not been determined, nor is there any evidence to indicate what may be expected if the hydroxyl group is shifted to other positions in the side chain.

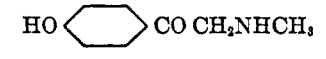
X. AMINOKETONES

If the secondary alcoholic group in the aminoalcohols, is oxidized, the corresponding ketonic derivative is obtained. While numerous ketones of this type are known, relatively few of them have been studied pharmacodynamically. The ketone corresponding to epinephrine, adrenalone, was the first known (23) and this was found to possess an action qualitatively like that of epinephrine. It has been introduced as a clinical reagent under the name of "stryphnon," but apparently is not being widely used as an epinephrine substitute. In its action it is much weaker;

Barger and Dale (32, 92) found it less than 1/20th as active as *dl*-epinephrine. Others have found the ratio to vary from 1:200 to 1:300 for adrenalone and *l*-epinephrine (190, 191). Tainter (138) was unable to establish a definite figure, since this ratio varied from 1:100 to 1:200. However, the duration of the pressure rise was approximately three times that obtained with *l*-epinephrine.

If the *N*-methyl is removed from adrenalone the activity is increased somewhat—quite as might be expected. If, however, it is replaced by an ethyl group the activity is increased by more than half, whereas substitution by a propyl radical decreases activity to about 1/5th (32, 92). In the light of the general effects of alkylating the amino nitrogen it looks as if the ethyl homolog of adrenalone is overrated. Should the value it now has be substantiated by future findings, it will be an excellent example of the reversal of a trend.

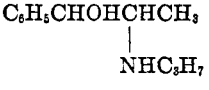
Barger and Dale also examined other ketones. Their effects were not extensively investigated but in general their activity was markedly less than that of the corresponding alcoholic derivatives.



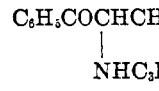
"Synephrine ketone"

A ketone that does deserve more than passing notice is that corresponding to synephrine (sympatol). Tainter and Seidenfeld (189) found this compound to behave quite differently from the corresponding aminoalcohol. The first injection usually gave a predominantly pressor response, although the curve was irregular because of the coincident depression. The second dose always produced a fall in blood pressure. This depression was induced by the large dose required, 10 to 20 mg. per kilogram intravenously, to produce a rise in blood pressure.

Chen, Wu and Henriksen (124) studied the action of phenylpropanolpropylamine,



and its corresponding ketone,



and found both to cause a fall in blood pressure. In the latter compound this effect is to be attributed perhaps more to the influence of the large alkyl group substituted on the amino group than to the ketonic structure.

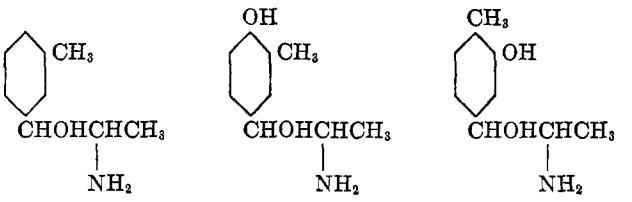
While our knowledge of pharmacodynamic relationships between the aminoketones and the corresponding aminoalcohols leaves much to be desired, all the evidence now available shows that the ketones are much less active and results with them are less capable of being reproduced.

XI. OTHER SUBSTITUTIONS IN THE AROMATIC NUCLEUS

The compounds thus far considered have been phenyl or hydroxyphenyl derivatives. Recently compounds with other substituents in the aromatic nucleus have been studied with very interesting results.

Hartung and Munch (127, 147) found that a methyl group substituted in the para position of phenylpropanolamine, namely a new isomer of ephedrine, decreases the activity to about 3/5ths and increases the toxicity about threefold. In an analogous manner the introduction of a methyl group into the para position of phenylbutanolamine very greatly increases its lethal effect. The greater toxicity of the *p*-tolyl derivatives as compared to the corresponding phenyl compounds is further shown by the work of de Burnaga Sanchez (192), who found *p*-methylephedrine to be about 20 per cent more toxic than ephedrine, and at the same time less active. A methyl group substituted in the meta position of phenylpropanolamine (I) seems to increase the toxicity as much as does a methyl group in the para position and probably also decreases the pressor activity (192a).

The introduction of a methyl group into phenolic derivatives of phenylpropanolamines produced unexpected results. The 3-methyl-4-hydroxy derivative (II)



I II III

is about twice as active and almost four times as toxic as phenylpropanolamine; that is, it possesses the increased activity conferred by the phenolic hydroxyl and the toxicity of the *m*-methyl group. Its isomer, 3-hydroxy-4-methylphenylpropanolamine (III), while equally as active was very much less toxic, less toxic in fact than phenylpropanolamine itself, which is contrary to anticipation, since the substitution of either the *p*-methyl or the *m*-hydroxyl alone increases the toxicity severalfold. It is most unexpected that their simultaneous introduction should counteract mutually their individual toxic effects (151).

Several compounds with other alkyl substitutions in the phenyl nucleus have been prepared. Manske and Johnson (192b) synthesized *p*-ethylphenylpropanolethylamine,

$$C_2H_5 \cdot C_6H_4CHOHCH(NHC_2H_5)\,CH_3$$

and 2,5-dimethylphenylpropanolethylamine,

$$2,5\text{-}(CH_3)_2\,C_6H_3CHOHCH(NHC_2H_5)\,CH_3$$

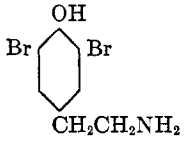
but they gave no indication of the physiological activity of these compounds. Ehrhart (159), however, stated that the *p*-ethyl and *p*-butyl derivatives of ephedrine are strongly toxic and exhibit no circulatory effects.

Results thus far would seem to indicate that alkyl substitution in the aromatic nucleus of ephedrine compounds produces effects analogous to similar substitution on the amino nitrogen.

Barger (32) prepared a series of para substituted β-phenylethylamines in which the substituent groups were —COOH, —$COOC_2H_5$, —NO_2, —NH_2 and Cl. The pressor activity of these compounds was determined by Tainter (118a). The *p*-COOH derivative was practically inactive, but its ethyl ester

was distinctly active, about 1/900th as active as epinephrine. The *p*-NO_2 compound gave first a small transitory depression which was followed by a marked rise that lasted for about five minutes; it is 1/823rd as strong as epinephrine. *p*-Chlorophenylethylamine is 1/368th as active as epinephrine and about half as active as tyramine. This would indicate that the effect of the chlorine in the aromatic nucleus compares favorably with that of a phenolic hydroxyl. All of these compounds are desensitized by cocaine and, hence, are characterized as pseudosympathicotropic.

Among other compounds of this general type which have been prepared are dichlorotyramine (V), dibromotyramine (IV) (193) and diiodotyramine (VI); the action of the latter compound has been found similar to that of the thyroid (194); a piperonal (VII) and methoxypiperonal derivative (VIII), a veratrol compound (IX) and the methyl ether of tyramine (X) (195, 208a); 2,4-dinitrophenylethylamine (XI) (196), β-phenyl-β-chloroethylamine (XII) (197), phenyl-1-chloro-1-amino-2-propane (119) and the methylene ether of epinephrine (XIV) (198).



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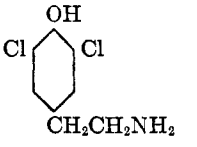

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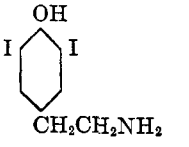

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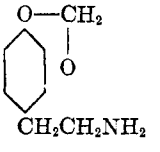
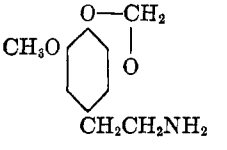
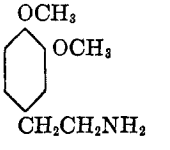


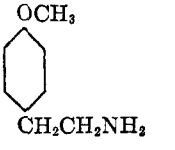
VII



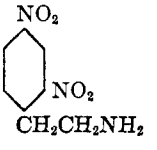
VIII



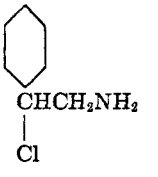
IX



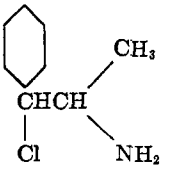
X



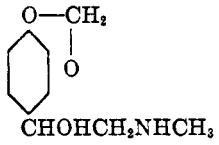
XI



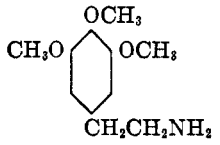
XII



XIII

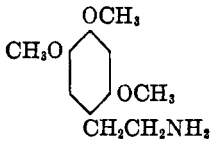


XIV



Mescaline

XV



XVI

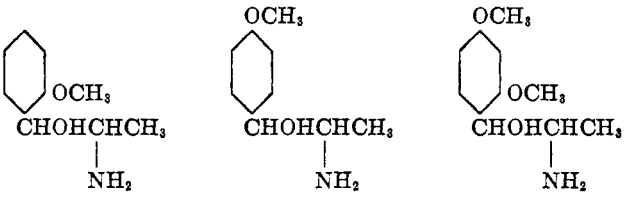
However, except for XIII, which is an active pressor (199), no reference was found as to their activity.

Another β-phenylethylamine substance that is of unusual interest is its 3,4,5-trimethoxyderivative (XV), known also as mescaline. Its relationship to the pressor compounds depends on its structure rather than on its physiological behavior. It is a natural product and is one of the six alkaloids found by Heffter (200) in the "button" of *Anhalonium Lewinii*, a cactus species, also known as mescaline; its structure was established by Späth (129). It is responsible, chiefly, for the color visions and religious fervor induced by "peyote" (201, 202), the ceremonial object of a growing religious cult among the Indians of Northern Mexico and Southwestern United States (203, 204, 205). Mescaline has been used with indifferent success in the treatment of psychopathic disturbances (206). Dixon, in examining the effect on the blood pressure (202), found that 0.05 g. of mescaline injected into the veins of a cat gave a fall; after seven and one-half minutes there was a sudden rise to normal and a minute later a sudden rise above normal. Raymond-Hamet (206a) reported mescaline as being practically without any effect on the blood pressure.

Jansen found that if one *m*-methoxyl group in mescaline is shifted to the ortho position (XVI) the stupefying effect is not lost, but the exalted feelings, pleasant color visions and general euphoria are no longer produced (207). For a more comprehensive treatise of the physiological and psychic results obtained with mescaline, the reader is referred to the monograph by Kurt Beringer on "der Mezkalinrausch" (208).

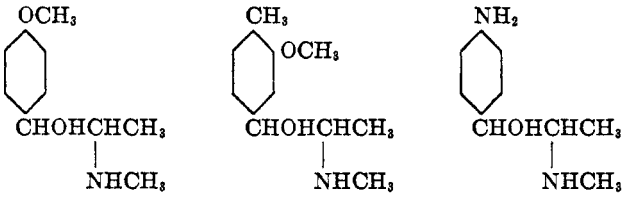
In the arylpropanolamine series several methoxy compounds are known. Hartung, Munch, Miller and Crossley (151) pre-

pared three methoxy substituted derivatives of phenylpropanolamine, and found that the orthoderivative (XVII) was as active but more than twice as toxic as phenylpropanolamine; the intro-



XVII XVIII XIX

duction of the *p*-methoxy group into phenylpropanolamine (XVIII) increased the toxicity twofold and reduced the pressor activity to about one-half; 2,4-dimethoxyphenylpropanolamine (XIX) was about as active but more than three times as toxic as phenylpropanolamine. Koller (208b) found *p*-methoxyephedrine to act like ephedrine but to be weaker in action, and that *m*-methoxy-*p*-hydroxyephedrine (XXI), when injected into rabbits, produced an indefinite effect on the circulation and a definite slowing of the respiration.



XX XXI XXII

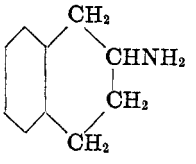
Very recently the synthesis of *p*-aminoephedrine (XXII) was announced (208c). This compound, introduced as "ephetonal," is described as being 1/3rd to 1/2 as toxic as ephedrine; it is said to exhibit typical ephedrine-like action on the sympathetic system, but unlike ephedrine it does not exhibit tachyphylaxis nor do large doses produce a depression in the blood pressure (208d).

From the evidence thus far available it appears that the phenyl group in the skeleton of pressor substances may undergo considerable modification before the circulatory effect is eliminated.

XII. OTHER COMPOUNDS

In addition to the substances thus far discussed, there are various individual compounds which deserve mention because of their general structural relationship to the series.

β-Tetrahydronaphthylamine (I)

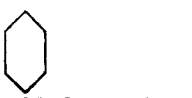


I

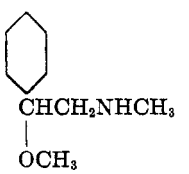
may be considered as a derivative of β-phenylethylamine, of γ-phenylpropylamine or of cyclohexylamine (32). This compound, when administered as the hydrochloride intravenously to a dog or rabbit in doses varying from 10 to 70 mg. per kilogram of body weight, produced curare effect, increase in temperature, and a strong rise in the peripheral blood pressure (209).

N-methylation gave a product that exerted a more marked effect on the blood pressure but decreased the duration effect. A second methyl group on the nitrogen reduced the stimulating effects very markedly and decreased the toxicity, but did not destroy the mydriatic activity. Conversion into the quaternary ammonium salt gave a molecule that exhibited a curare-like action, caused increase in blood pressure and dilated the pupils, but produced no effect in the body temperature (210). The effect of methylation in β-tetrahydronaphthylamine is quite different from that in other pressor compounds.

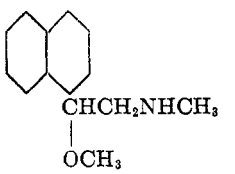
The activity of β-naphthylethylamine derivatives was investigated by Madinaveitia (211, 212). By comparing the activity of β-phenylethylmethylamine (II) with the methylether of phenylethanolmethylamine (III)



II

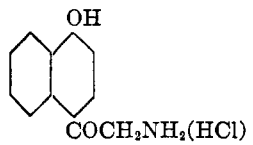


III

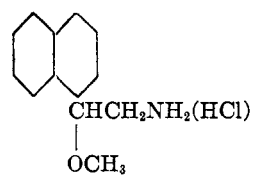


IV

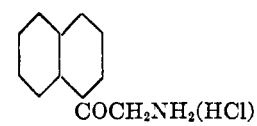
he observed that the introduction of the methoxyl group into the side chain did not change the sympathomimetic activity; but if the α-naphthyl nucleus (IV) was substituted for the phenyl, the activity was increased about forty times. Having found the naphthyl compound so active, Madinaveitia compared the activity of four other derivatives (V to VIII).



V

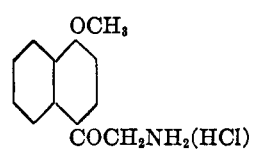


VI



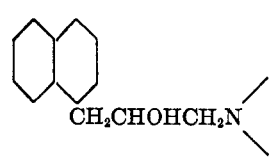
VII

and found that introduction of the hydroxyl group para to the side chain (V) greatly increased the activity and that etherification of the phenolic hydroxyl (VIII) greatly reduced the intensity; the ketone is much less active than the methyl ether of the corresponding alcohol, for 3 mg. of VI produced the same effect as was obtained from 20 mg. of VII.



VIII

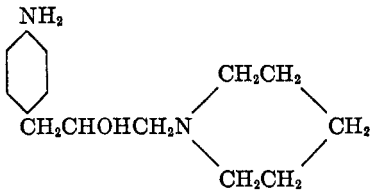
Another group of naphthylaminoalcohols was prepared by Fourneau, Tréfouel and Tréfouel (213), which has the general structure



and in which the naphthyl nucleus or the amino group, or both contained substitutes. The aim of these scientists was to determine, if possible, whether the naphthalene nucleus might not be

substituted for the quinoline portion in compounds that possess antimalarial action.

In the search for compounds simpler than plasmochin, Fourneau and Brydowna (214) also prepared *p*-aminophenyl-1-piperidino-3-propanol-2 (IX) but found it ineffective against malaria in birds.

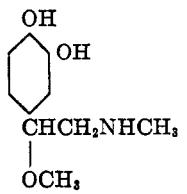


IX

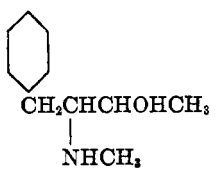
The sympathomimetic action of Fourneau's compounds appears not to have been determined, and from structural considerations alone one would expect them to possess little or no such action.

Since the appearance of ephedrine in a major rôle as a clinical reagent, various attempts have been made to synthesize a substance of different structure which would retain all the desired actions and not have the undesirable ones. The results of modifications in the side chain, in the amino group, and of the introduction of a para alkyl group have already been discussed. There are, however, other modifications, less easily classified, which must also be considered.

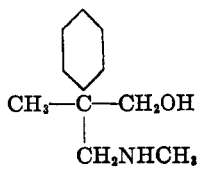
Dulière (215), prepared various ethers of ephedrine, and found that as the alkyl group attached to the alcoholic hydroxyl became larger, the toxicity increased and the characteristic ephedrine reaction became less pronounced. Some of the corresponding



X



XI

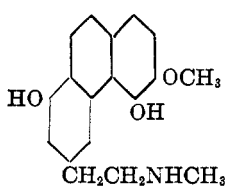


XII

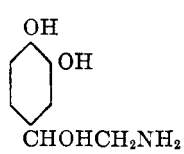
ethers of epinephrine, that is, through the alcoholic hydroxyl, have been prepared by Funk and Freedman (216). It was found (217) that the methyl ether (X) possessed a weaker hyperglycemic action than epinephrine, and that the ethyl ether was still less active.

Fourneau and Barrelet (218) prepared phenyl-4-methylamino-3-butanol-2 (XI) and found it to be much weaker than ephedrine, showing again the effect of going beyond the three-carbon atom side chain. On the other hand, phenyl-2-methyl-2-methylamino-3-propanol-1 (XII), which has a methyl substituted side chain of three carbon atoms, was found to be quite active (219). A dog receiving a dose of 0.2 mg. per kilogram gave a rise of 40 mm. of mercury in the arterial pressure and the effect persisted for some time; larger doses (5 mg. per kilogram) produced only a feeble rise.

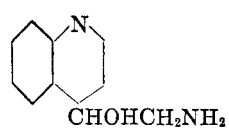
It has already been pointed out that the aromatic portion of the molecule may be a substituted phenyl or even a naphthyl group, although each structural modification does affect in some way the physiological response produced. Apparently the aromatic nucleus need not always be strictly hydrocarbon in nature. Hildebrandt reports that thebenine (XIII) (220) has a general reaction toward rabbits like that of 3,4-dihydroxyphenylethanolamine (XIV), and he credits this to the influence of the "Verbindungskette."



XIII



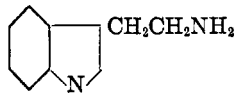
XIV



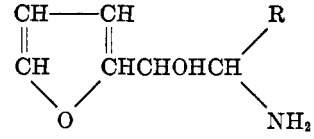
XV

Kaufmann (221) found quinolinylethanolamine (XV) to act on the blood pressure as does phenylethanolamine. Hasegawa (222), found β-indolethylamine (XVI) to dilate the pupil markedly and that large doses given intravenously gave an initial rise followed by a fall in blood pressure. Seki (222a), working with the α-methyl derivative of β-indolethylamine, found that it produced a rise in blood pressure by vasoconstric-

tion, and that it contracted the uterus and stimulated intestinal movements.

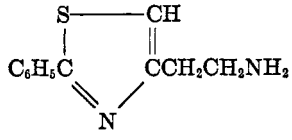


XVI

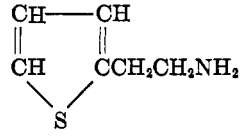


XVII

Kanao found the furylamino alcohols (XVII) to possess a mydriatic action, the intensity of which became less as the length of the side chain increased (223). Windaus and Dalmer (223a) found furethylamine to produce only a short-lived fall in blood pressure and that its tetrahydroderivative was without any effect. Hinegardner and Johnson (224) have prepared "thiazole bridges" of epinephrine- and tyramine-like bodies (XVIII)



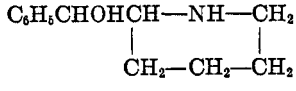
XVIII



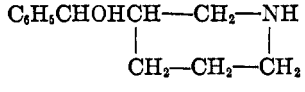
XIX

and report that these compounds possess pharmacological interest. Tainter (118a) found thienylethylamine (XIX) to be about as active as the phenyl analog.

Recently Crook and McElvain (225) prepared some phenylpiperidylcarbinols (XX and XXI)



XX



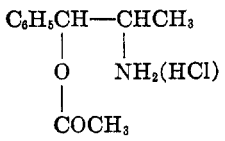
XXI

which may be considered as analogs of ephedrine, and which are reported to have weak ephedrine-like action.

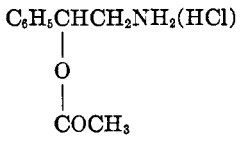
From a survey of all the compounds considered it would seem that examination of various modifications in the aromatic nucleus promises more positive results than do the changes in the side chain or the amino group.

While the etherification of the alcoholic hydroxyl has been found to affect somewhat adversely the activity of the molecule,

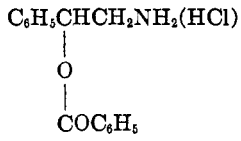
the influence of esterification has been determined only in part. Kester and Munch (226) found that the acetic ester of phenylpropanolamine (XXII)



XXII



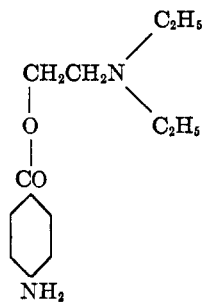
XXIII



XXIV

was practically devoid of pressor activity. Wolfheim (197) prepared the acetic acid and benzoic acid esters of phenylethanolamine (XXIII and XXIV), but gave no pharmacological data concerning them.

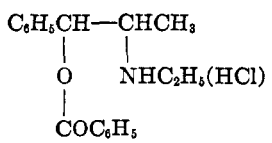
The benzoic ester (XXIV) should be of particular interest because of its structural similarity to anesthetics of the procaine type (XV)



Procaine

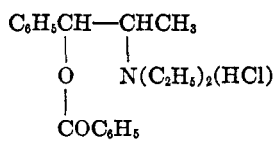
XXV

Would it continue to act as a pressor and at the same time take on anesthetic properties? If so, this would be the first synthetic anesthetic-pressor. Kubota (227) examined higher homologs, the allocains (XXVI and XXVII)



XXVI

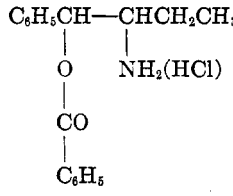
Allocain S (soluble)



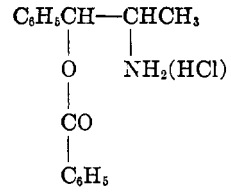
XXVII

Allocain A (insoluble)

and found them to be very strong as anesthetics, while in the circulatory system, they produced first a fall in the blood pressure and then a rise. Recently Tiffeneau (228) described the benzoic ester of phenylbutanolamine (XXVIII)



XXVIII



XXIX

as an anesthetic approaching cocaine in potency. Now, if generalizations are of any value to the research worker one may reasonably argue that while Kubota's allocaines (XXVI and XXVII), with alkyl substitution on the nitrogen that decreases the potency of the pressor portion of the molecule, and Tiffeneau's compound, the ester of a substance which by itself possesses a structure that weakens the activity, may be very potent anesthetics, they would probably not possess, at the same time, marked pressor powers, unless esterification should serve to intensify them. On the other hand, phenylethanolamine and phenylpropanolamine are highly active, and if esterification decreases the pressor activity, their benzoic esters (XXIV and XXIX) should *a priori* preserve this potency to a maximum, if at all. To determine this experimentally Hartung, Munch and Kester (229) investigated the ester of phenylpropanolamine (XXIX) and found that a dog receiving an intravenous dose of 10 mg. per kilogram gave a maximum rise in blood pressure of 26 mm. of mercury, and that the rise continued for more than three hours. When tested on the rabbit's eye it produced an anesthetic effect several times greater than that of novocaine. This is, so far as these authors are aware, the first compound with a demonstrated simultaneous pressor and anesthetic action. There is every reason to believe that Wolfheim's ester (XXIV) should act in a similar manner.

XIII. OPTICAL ISOMERISM

Up to this point emphasis has been placed on molecular modifications involving the introduction, elimination, or shift in the point of attachment of an element or organic radical. In addition to such changes there is another of a quite different nature that has its own mysterious influence on physiological reactivity, and which is very germane to the whole subject under discussion, namely, optical isomerism. Optical phenomena, ever since their discovery by Pasteur, have been very fascinating to the chemist, particularly their influence on the pharmacological reaction.

It was early noticed that natural epinephrine was levorotatory (21) and that the synthetic, i.e., racemic, compound was very much less active. Its resolution into the optically active components gave a levo form with an activity equal to that of the natural product. Cushny (230) found that natural epinephrine was twice as strong as the synthetic, optically inactive compound. Abderhalden and Müller (231) found the levo form fifteen times more active than the dextro form; Cushny (232) found the ratio to be 1:12. Others have checked it and found the ratio of *l*:*dl*:*d* to be 1:1/2:1/12 to 1/40 (113, 191, 233, 234, 235, 236, 237). Ishiwara (84) reported that by the Trendelenburg method there is practically no difference between the activity of the racemic and the optically active forms. Richaud is quoted by Bierry, Rathery and Leving (173) as saying that the difference in the hypertensive power of *l*- and *dl*-epinephrine disappears as the magnitude of the dose increases, that is, doses of 0.04 to 0.05 mg. produce sensibly the same effects.

The levo isomer is not only more active but it is also more toxic than *d*-epinephrine—from six to twenty times, depending on the method of determination (191, 232). Mice, pretreated with *d*-epinephrine, develop a tolerance for ten or more times the normal lethal dose toward the *l*-variety (238, 239), but such immunity is only temporary (240). It has even been reported (241) that the intravenous injection of *d*-epinephrine to cats and dogs would render them nonresponsive to larger doses of *l*-epinephrine.

Tainter (113), working with anesthetized cats, found the ratio

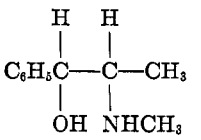
of activity for the *l*: *dl*: *d* isomers to be 1: 1/2: 1/30. In addition Tainter pointed out that the three isomers have their own characteristic effects in the duration of the pressor response. By employing doses which produced moderate and approximately equal elevation of the blood pressure, he observed that the rise following *l*-epinephrine lasted for an average of 1.5 minutes, while from the racemic mixture the average was 2.5 minutes, but the *d*-epinephrine gave a much longer rise, an average of 4.7 minutes. Tainter believes that this longer effect "would be favorable to the practical use of the dextro compound, since the extremely evanescent action of *l*-epinephrine has always been a drawback"; he also feels that this difference indicates "somewhat of the selectivity of the pressor responses,—a selective difference in protoplasmic reaction, which apparently was conditioned on a difference in configuration of the drug-molecule."

The Pharmacopoeia recognizes only *l*-epinephrine. Whether or not correspondingly larger doses of the racemic mixture, or even of the *d*-isomer, should not be of equal therapeutic merit apparently has never been determined.

From the laboratory of Tainter and Seidenfeld has come another valuable contribution to our knowledge of the influence of optical isomerism on physiological reaction. These investigators (189) found the ratio of activity for the synephrine isomers to vary in the following manner: *l*: *dl*: *d* = 1: 1/2: 1/60. Here also the *d*-synephrine gave a longer duration of blood pressure rise, a median of three minutes as compared to two minutes for both the *l*- and *dl*-compounds. When the effect of the three synephrine isomers was studied on perfused rabbit ears, unexpected results were obtained. Doses of 0.5 to 2.0 mg. of *l*-synephrine caused prompt vasoconstriction; the *d*-isomer even up to 10 mg. usually had no effect or caused dilatation; the racemic substances in doses ranging from 1 to 50 mg. never did produce constriction. Since the racemic mixture contains equal parts of the two optically active components it appears that the *d*-isomer is not only inactive but is also able to suppress the rather powerful vasoconstrictor action of the *l*-isomer. This is indeed an unusual example of antagonism.

The levorotatory isomer of the hypertensive amines has usually been found to be the most active. Thus *l*-norhomoepinephrine is two or three times as active as the racemic mixture and thirty times as active as the *d*-compound (169, 171). Of all the synthetic ephedrine analogs which have been resolved, the levorotatory form has always been found to be the most active (208b, 218). Of the pseudoephedrines, however, the *d*-form is the more active.

Ephedrine exists in the form of known optical isomers, but since it contains two asymmetric carbons



there are possible six isomers, four optically active and two racemic mixtures, namely *d*- and *l*-ephedrine and *d*- and *l*-pseudoephedrine and the respective racemic mixtures.

The constants for the six isomers are given in table 5.

TABLE 5

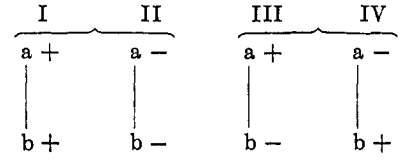
The isomers of ephedrine

ISOMER	MEETING POINT OF THE HYDROCHLORIDE	ROTATION OF HYDROCHLORIDE	
	°C.		
l-Ephedrine	214–216	$[d]_D^{25} = -35°$ (124)	$[M]_D^{20} = -72°$ (242)
d-Ephedrine	213	$[d]_D^{20} = +35°$	$[M]_D^{20} = +72°$
dl-Ephedrine	187	— —	— —
l-ψ-Ephedrine	178–179	$[d]_D^{25} = -62.5°$	$[M]_D^{20} = -125°$
d-ψ-Ephedrine	180.5	$[d]_D^{25} = +62.5°$	$[M]_D^{20} = +125°$
dl-ψ-Ephedrine	163	— —	— —

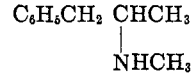
In nature the alkaloid is found as *l*-ephedrine, *d*-pseudoephedrine, or as a mixture of the two (243). Ernst Schmidt (244) early demonstrated the geometric isomerism between the two products from the ease with which they were interconvertible.

Gadamer (245) believed that such isomerization was caused by an "Umklappen," a shift of the hydroxyl group, but Emde (246) maintained that the methylamino group was equally susceptible of being shifted. Rabe (247) proved that the isomerism was not a question of position in a chain but of space about an asymmetric carbon atom. Emde (248), in his recent exhaustive examination of the steric phenomena of the ephedrine isomers, established their spatial structures.

Designating the two asymmetric carbon atoms as "a" and "b," the optical possibilities become

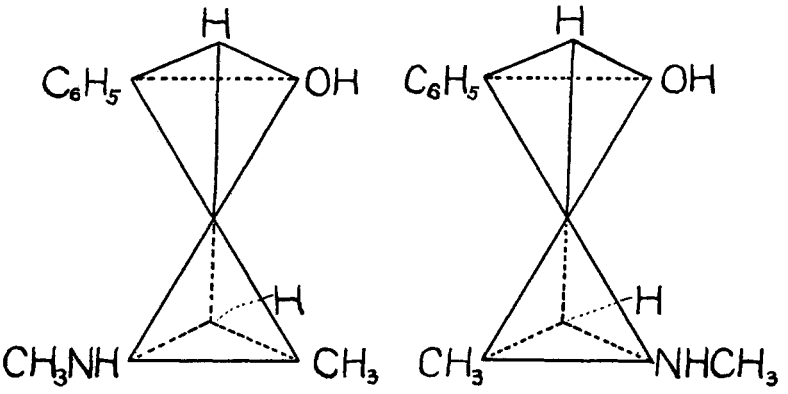


and mixtures of the two pairs are then the racemic compounds. Arrangements I and II have the largest rotations, and these are therefore the dextro and the levo forms of pseudoephedrine (see table 5); III and IV depend on whether the rotation of "a" alone is greater or less than that of "b." From a study of phenyl-1-methylamino-2-propane or desoxyephedrine,



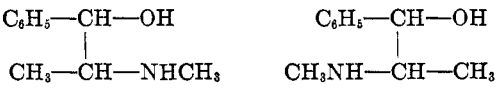
having for $[M]_D^{20}$ a value of $+33°$, Emde found the rotation of "a" greater than that for "b"; hence IV represents natural *l*-ephedrine and III represents the synthetic *d*-isomer.

From the fact that natural water-free ephedrine is an oil, which in the presence of water crystallizes as a monohydrate melting at 39–40°, and the fact that *d*-pseudoephedrine, melting at 118° does not, and probably cannot, take up water because of a betaine-like structure through the secondary alcoholic hydroxyl group, Emde believes that in the former the hydroxyl and methylamino groups the *trans* and in the *d*-pseudoephedrine they are *cis*. Therefore, are geometric configuration for the natural ephedrines may be given as follows:



Natural *d*-ψ-ephedrine Natural *l*-ephedrine

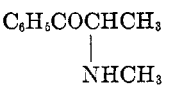
and for the racemic forms



syn-form Pseudoephedrine *anti*-form Ephedrine

The synthetic ephedrine is racemic and may contain mixtures of the two forms. Späth and Göhring (249) were the first to isolate the six isomers from a synthetic mixture.

Synthetic ephedrine is usually prepared by reducing catalytically the corresponding aminoketone



In the commercial preparation of "ephetonin," nickel deposited on pumice or asbestos is used as catalyst. Catalytic reduction methods lead to the formation, predominantly if not purely, of racemic ephedrine (250, 251, 252), whereas reduction with sodium or sodium amalgam results in the formation largely, if not exclusively, of the pseudo ephedrine (253, 254, 255).

Physiologically, ephedrine is more active than pseudoephedrine. *l*-Ephedrine is more active than the *d*-ephedrine, while the racemic mixture possesses an activity intermediate between the two.

Kreitmar's (256) observation that the differences between *l*-ephedrine and *dl*-ephedrine (ephetonin) are very slight has not been confirmed by other investigators. Of the isomers of pseudoephedrine, the order of decreasing activity is from *d* to *dl* to *l*. It is interesting to note that here the levo isomer is less active than the dextro compound.

In view of the fact that the pharmacological properties of the various ephedrine isomers have been extensively reviewed and investigated by Chen, Wu and Henriksen (124) and Chen and Schmidt (93), it will suffice here to give in table 6 a summary based on the results of these authors.

TABLE 6

Pharmacological activity of ephedrine isomers

ISOMER	M.L.D. INTRAVENOUS TO RABBITS	PER CENT (AVERAGE) INCREASE IN BLOOD PRESSURE AFTER INJECTION OF 2 MG. INTO PITHED CAT WEIGHING ABOUT 2.5 KG.	RATIO OF ACTIVITY TO *l*-ψ-EPHEDRINE
l-ψ-	80	8	1:1
dl-ψ-	70	28	1:4
d-ψ-	75	37	1:6.8
d-	80	68.5	1:11.9
dl-	60	211	1:26.5
l-	60	280	1:35.1

In examining the effects of the oral administration of the various isomers in doses of 50 mg. to men, Chen, Wu and Henriksen found all to produce a rise in the systolic blood pressure, except *d*-ephedrine and *l*-pseudoephedrine. Since these two, in the light of the previous discussion, should be interconvertible by the mere "Umklappen" of the alcoholic hydroxyl, the question might logically be raised: Is such oral activity conditioned by the position in the molecule of the hydroxyl group?

That the spatial arrangement within the molecule has tremendous influence on its physiological activity is demonstrated by the ponderously abundant evidence. But the reasons for such wide and characteristic differences still remain to be determined.

XIV. SUMMARY

The general effect of the influence of structure on the pharmacological reactivity of epinephrine and similar compounds cannot be expressed in a few words. Perhaps a summary (see figure 2) with graphic formulas will serve much better. Since β-phenylethylamine possesses the minimum skeleton for optimum activity it becomes an excellent starting compound. The vectors indicate

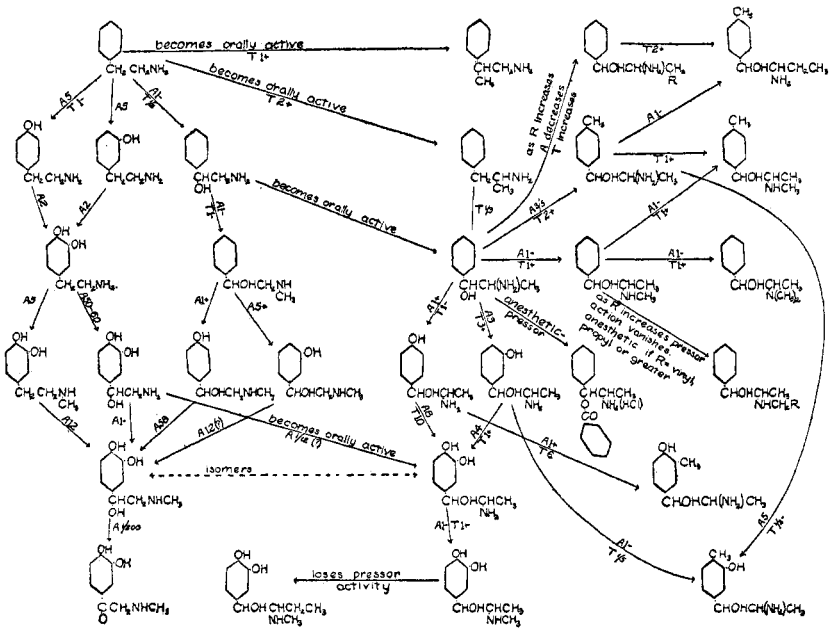
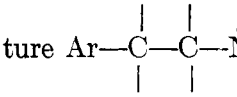


FIG. 2. INFLUENCE OF STRUCTURE ON THE PHARMACOLOGICAL REACTIVITY OF EPINEPHRINE AND SIMILAR COMPOUNDS

the derivatives obtained by single, successive substitutions. The number above the arrow, preceded by the letter "A" indicates the approximate change (when multiplied) in the pressor activity resulting from the substitution; in a similar manner the letter "T" followed by a number indicates the approximate change in toxicity.

Anyone who examines this summary, even though a casual observer, must be impressed with the sensitivity of the organism to what might be considered relatively minor modifications. Take, for instance, the effect of methyl substitution in phenylpropanolamine. There are indicated three such derivatives and what a difference there is in their respective physiological responses! If the chemist will consider, in addition, the mystifying difference between optical isomers, well may he envy the analytical capacity of living tissue. Whether the "protoplasmic reaction" is a resultant of physical forces or a consequence of chemical interplay has not been determined.

An examination of the approximations indicated in the summary will reveal certain general effects. Thus it is seen that:

1. Pressor activity is found in compounds possessing the structure  as a minimum.

2. If the side chain is increased to three carbon atoms pressor activity is retained and oral activity is conferred. There is also a tendency for these compounds to produce their effect over a longer period.

3. If the side chain is increased beyond three carbon atoms the favorable action on the circulation is lost. The toxicity of the compound increases as the side chain becomes longer.

4. The alcoholic hydroxyl group in the side chain apparently serves to detoxicate the phenylalkanolamines, and in the catechol derivatives it also increases the pressor activity.

5. Modification of the amino group affects adversely the favorable action, serving to decrease the activity and increase the toxicity, these effects being roughly a function of the size of the substituted groups.

6. The aromatic portion of the molecule need not necessarily be a phenyl or a substituted phenyl group. Various naphthalene and heterocyclic derivatives also possess pressor activity.

7. Substitutions in the phenyl nucleus modify the circulatory effect, but apparently no substitution will—with a possible excep-

tion of simultaneous 2,4-dihydroxy substitution or substitution of a large alkyl group—completely eliminate this physiological action. The evidence thus far indicates that meta and para phenolic hydroxyl groups and a para chlorine atom increase the activity, while methyl groups influence the activity adversely.

However, not all of the conclusions are of equal validity; the reason for including those which are also doubtful is that the evidence now available indicates such trends. That there should be some legitimate doubt about some of these must necessarily follow from any attempt to compare and correlate the none too abundant data in a realm where there are so many unavoidable variables as there are in biological experimentation. Coupled with this, one not infrequently finds that an author generalizes on the basis of results which warrant only limited conclusions. Also at times the personality of the experimenter influences the interpretation of his results; he selects his result as supporting a conclusion drawn up in advance, when his complete results do not warrant such a procedure. Hence, for the present, a completely satisfactory and reliable correlation, much as it may be desired, is still impossible.

It is hoped not only that the future research on the pharmacodynamics of compounds such as these will yield more experimental data but that their significance may be properly interpreted. And it remains for the chemist, with the invaluable coöperation of his colleagues from the biological and physical sciences, to determine the operating mechanism which predetermines the nature or type of characteristic responses obtained from the respective reagents. Such studies appear especially worthwhile because of the added light they will throw on the general problem of the dependence of physiological behavior upon the structure of compounds. If this knowledge is ever to become available in its larger aspects it can be so only after the accumulation of more pertinent and reliable information. For it must not be forgotten that the advantage Mendeléeff enjoyed over Döbereiner and Newland lay perhaps not so much in his greater genius as in the additional knowledge at his disposal.

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