and then carefully balanced in order to secure results that are of value. It is important to note that the same factors which impart commercial value to flour are in a general way in harmony with those which impart nutritive value. The flours which make the best bread are those which are well milled and are free from fibrous offals, and these are the flours which give the low ash content. They are also mediumly rich in proteids, which impart desirable physical properties and insure a loaf of the highest value. The best commercial grades of flour are of mediumly fine granulation in contradistinction to graham and whole wheat flours. Fine granulation insures more complete digestion and absorption of the nutrients of the flour by the body.[1]

[FROM THE DEPARTMENT OF EXPERIMENTAL MEDICINE, PARKE, DAVIS & CO., DETROIT, MICH.]

ADRENALIN, THE ACTIVE PRINCIPLE OF THE SUPRARENAL GLANDS.*

BY T. B. ALDRICH.

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THE OBJECT of this paper is to take up the chemical side of adrenalin, the active principle of the suprarenal glands, but, before doing so, I will review very briefly this subject up until the time when adrenalin was discovered.

Addison[1]† (1855) was the first to recognize the great importance of the suprarenal glands in the animal economy, particularly in their relation to the disease since called "Addison's Disease."

Vulpian[2] (1856) observed that the expressed juice of these glands, obtained from various animals, gave certain characteristic color reactions, not given by any other glands in the body; for example, ferric chloride gave a green color, while iodine gave a pink or rose-red color.

Virchow[3] (1857) substantiated Vulpian's observations, but added nothing new of importance.

Vulpian and Cloez[4] (1857), Arnold[5] (1866), and Holm[6] (1867), attempted the isolation of the active principle, but were unsuccessful.

[1] Office of Experiment Stations, U. S. Dept. of Agriculture, Bulls. 101 and 126.

* Read before the Section of Physiology, at the Buffalo Meeting of the American Chemical Society, June 23, 1905.

† The numbers refer to the literature at the end of the article.

Krukenberg[7] (1885) called attention to the similarity of the color reactions of the extract and those of pyrocatechol. He endeavored to isolate the active principle according to Arnold's method. A body was obtained and analyzed, but no formula was proposed.

Brunner[8] (1892) confirmed Krukenberg's work, in reference to the similarity of the color reaction of pyrocatechol and the active principle.

Oliver and Schafer[9] (1894) made the important discovery that the extract produced a rise in blood-pressure when injected intravenously.

Moore[10] (1895) found that the reducing property and the ability to raise the blood-pressure went hand in hand, and concluded that the physiologically active body is identical with the reducing body which gives the green color reaction with ferric chloride.

Frankel[11] (1896) isolated a syrup-like body which he considered a pure substance. He called it "sphygmogenin," but no chemical criteria are given of its purity. It was not even shown to possess a constant composition, and no attempt was made to establish an empirical formula for it. Frankel held the active principle to be a nitrogenous pyrocatechol derivative.

Mühlmann[12] (1896) considered the active principle to be pyrocatechol.

Moore[13] (1897) held that Frankel was wrong in assuming the active principle to be a derivative of pyrocatechol, and argued rather that it was a derivative of pyridine, but of this he was not certain.

Abel and Crawford[14] (1897) showed that what they called the active principle may be precipitated from aqueous extracts of the gland with benzoyl chloride and sodium hydroxide, and that this benzoyl product may be decomposed with hot, dilute sulphuric acid. This so-called active principle was obtained in the form of a sulphate of a tarry consistency which possessed physiological activity and which gave the color and other specific reactions of the suprarenal extract.

In two subsequent papers by Abel (1898)[15], (1899)[16], the following statements among others were made in reference to the so-called active principle which he now named "epinephrin."

Epinephrin is a basic substance thrown out of its solution in acid

by ammonia in the form of an amorphous flocculent compound, which rapidly loses its power to raise the blood-pressure. It gives reactions with a number of alkaloidal reagents, the color reactions of Vulpian, reduces silver nitrate and in all other ways agrees with Vulpian's chromogen. After saponifying the benzoyl product, the liberated base may be precipitated as a picrate, and from this picrate other salts formed possessing considerable activity. $C_{17}H_{15}O_4N$ is the formula ascribed to the base. Later I will discuss the various formulas proposed by Abel from time to time for the active principle.

v. Fürth (1897)[17], (1898)[18], (1900)[19], from the analyses of an impure acetyl product, assumed the constituent which raises the blood-pressure to be either tetrahydrodioxypyridine, $C_5H_9O_2N$, or dihydrodioxypyridine, $C_5H_7O_2N$. As v. Fürth has lately abandoned this theory, no more need be said in reference to this claim. A contribution of value, however, was the isolation of what he concluded to be the active principle in the form of a physiologically active, though impure, iron compound. In the analysis of the same, he assumes by comparison with the commercial preparation, adrenalin, that those fractions of his iron compound which shows the highest percentage of carbon most nearly represent the true composition of the substance which raises the blood-pressure. To this body v. Fürth gave the name "suprarenin," claiming that it was different from epinephrin, and even going so far as to state that epinephrin itself has no connection with the active principle, but is a very different substance slightly contaminated with the true blood-pressure-raising constituent.

Up until 1900 the active principle of the suprarenal gland, as such, had not been isolated, although derivatives and salts of what they presumed to be the same, were claimed by both Abel and v. Fürth, but these compounds were no doubt either impure derivatives or products formed from a modified form of the active substance. For example, Abel assumed that his autoclave product, after saponification, was the active principle, but this later was found to be wrong, being really a monobenzoyl derivative of a modified form of the real active principle.

It was not until January, 1901, that the active principle was isolated by Takamine who gave a preliminary paper[20] before the New York Section of the Society of Chemical Industry, entitled "Adrenalin, the Active Principle of the Suprarenal Gland," and,

who in November of the same year published a more detailed article[21] on the same subject in the *American Journal of Pharmacy*. In August of 1901 the writer[22] succeeded also by a method differing slightly from that of Takamine's in isolating a body, which was shown to be identical with adrenalin. Later Aldrich[23] showed by reduction tests, and blood-pressure-raising experiments, that adrenalin is identical with the blood-pressure-raising and reducing body as found in the gland and is therefore the active principle of the same. Before the decomposition products, and the empirical and structural formulas of the active principle could be determined, it was necessary to obtain it in a fairly pure condition. To-day, however, we can make the statement that this elusive body, which baffled the efforts of a number of able investigators, has been isolated in a pure form, in comparatively large amounts, that it is an article of commerce (both as such and in solution), and that several investigators even claim to have produced the same, or bodies having the same physiological properties, synthetically.

I would like to add here that, although the investigations on this subject extend over such a long period of time, by far the greater number and the most important contributions have been made during the past few years. From 1855-1895 we find ten articles, some of which are very short, while from 1895-1905, one-fourth the time, we have upwards of thirty, dealing mainly with the isolation and chemistry of the active principle of these glands. The incentive for the increased interest in this field was no doubt in part due to the discovery of Oliver and Schafer that the extract of the gland, when injected intravenously, caused a rise of blood-pressure, and also in a very great degree to the very important discovery of Dr. Bates, of New York, that the very dilute extract possessed marked haemostatic properties. Considerable interest was also aroused in determining the empirical formula of adrenalin, its decomposition products and eventually its synthesis.

Having reviewed briefly the history of the isolation of the active principle of the suprarenal gland up to 1901, we are now brought to a discussion of the chemical side of adrenalin, but before taking up this subject, I will state briefly one method of isolation and some of the chemical and physical properties of the substance.

The glands are finely disintegrated and steeped in slightly acidulated water for a few hours at a temperature of about 70° C.

with frequent agitation. The temperature is then raised to about 95° so as to coagulate a portion of the proteid. The insoluble portion is now pressed and separated from the extract which contains most of the adrenalin, cooled and separated from the fat. This extract is now evaporated to a small volume and four or five times its volume of alcohol added, whereby more inert matter is separated. The alcoholic solution is then evaporated, preferably in a vacuum, and to this residual liquid, alkali is added, preferably ammonia until the solution is distinctly alkaline. The yellowish brown precipitate, which forms very quickly if the solution is sufficiently concentrated, is crude adrenalin which may be purified in various ways.

When pure, adrenalin is a very light yellowish micro-crystalline body, crystallizing in various forms according to the condition of the solution, etc., from which it is obtained. I have observed burrs of needles, tomato-like forms, wheat-sheaf forms (similar to tyrosine), boat-shaped forms and others. When dry it is perfectly stable. Adrenalin is a basic body, forming salts which are difficult to isolate. It is very slightly soluble in both cold and hot water, quite insoluble in the organic solvents, and gives all the characteristic color reactions of the suprarenal extract, as described by Vulpian, except in an intensified manner. Its solution reduces Fehling's solution by boiling, silver solution and gold chloride solution in the cold, etc., and does not give in general the so-called alkaloidal reactions. Furthermore, adrenalin is very susceptible to oxidation, the presence of alkalies favoring this process.

THE EMPIRICAL FORMULA OF ADRENALIN.

In one of my earlier articles[22] the results of some combustion analyses of adrenalin, prepared according to two different methods (Takamine's, Aldrich's), were given, showing that the active principles obtained by these two methods are identical. Furthermore, the empirical formula $C_9H_{13}O_3N$ was proposed as the most probable formula for adrenalin, the analytical data obtained from these combustions agreeing more closely with this formula than with any other expression that could be deduced.

Somewhat later, Takamine[21] gave $C_{10}H_{15}O_3N$ as the *probable* empirical formula of adrenalin, this being calculated from five combustion analyses of the base. In addition to these two

formulas no less than four formulas for the active principle have been proposed by Abel from time to time. These are as follows:

(1) $C_{17}H_{15}O_4N$, formerly supposed to be the formula of the active principle, called by Abel, epinephrin, later, however, proven to be a monobenzoyl derivative of a modified form of the active principle.

(2) $C_{10}H_{11}O_3N$, the formula resulting by subtracting the benzoyl residue, C_6H_5CO, from $C_{17}H_{15}O_4N$ and replacing the hydrogen. This is designated as reduced epinephrin, plain epinephrin, free epinephrin, alkaloidal epinephrin, etc.

(3) $C_{10}H_{13}O_3N$ represents the same as the preceding formula $C_{10}H_{11}O_3N$, 2 hydrogen atoms being added in order to have it agree with the analytical data of certain salts and also with the formula $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$.

(4) $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$, epinephrin hydrate, the formula derived from the analysis of the active principle prepared according to the ammonia method. This compound is adrenalin pure and simple. The analytical data, however, for some inexplicable reason, according to Abel, do not agree with $C_9H_{13}O_3N$.

We have then the following empirical formulas for the active principle of the suprarenal gland:

Takamine.	Abel.	Aldrich.
$C_{10}H_{15}O_3N$	(1) $C_{17}H_{15}O_4N$	$C_9H_{13}O_3N$
	(2) $C_{10}H_{11}O_3N$	
	(3) $C_{10}H_{13}O_3N$	
	(4) $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$	

and the question arises, which, if any, of these formulas represents the true composition of the active principle?

The only support for the formula $C_{10}H_{15}O_3N$, proposed by Takamine, is found in his own analytical data, and these data do not agree with the above formula, as seen by the following: Average: C, 59.38; H, 7.84; N, 7.88. Calculated for $C_{10}H_{15}O_3N$: C, 60.91; H, 7.61; N, 7.11. The difference in carbon (1.5 per cent.) and nitrogen (0.7 per cent.) naturally condemns this formula.

Relative to the four formulas proposed by Abel during the past few years, only two ($C_{10}H_{13}O_3N$ and $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$) deserve any attention whatever; the other two ($C_{17}H_{15}O_4N$ and $C_{10}H_{11}O_3N$) having both been abandoned by Abel himself, while Pauly and

others have shown conclusively that the formula $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$ should also be abandoned.

Abel considered $C_{17}H_{15}O_4N$ to be the correct empirical formula for the active principle of the suprarenal gland until a time (1901) when he endeavored to account for certain differences between von Fürth's so-called "suprarenin," and "epinephrin." At this time he stated that: "The saponification of the benzoyl derivative of epinephrin may not have been a complete one, one benzoyl having been retained, etc., equals monobenzoyl epinephrin." This was only surmised by Abel and it was not until the appearance of my first paper[22] where the following statement is found: "If we subtract a benzoyl residue from Abel's formula for 'epinephrin,' $C_{17}H_{15}O_4N$, we obtain a formula, $C_{10}H_{11}O_3N$, which is not very far removed from that of adrenalin, $C_9H_{13}O_3N$, etc., etc.," that Abel finally became positively assured that his "epinephrin," so-called, is really a monobenzoyl derivative of the modified active principle.

After Takamine's and Aldrich's method of obtaining the true active principle from the glands became known, Abel, using practically the same method (with slight modifications), prepared adrenalin, and, after the purification of the same, and making analyses, concluded that the active substance is represented not by the formulas $C_9H_{13}O_3N$ or $C_{10}H_{15}O_3N$ but by the empirical formula $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$ (epinephrin hydrate). By dissolving epinephrin hydrate in *concentrated* sulphuric acid a sulphate was obtained, the analysis of which led to the formula $(C_{10}H_{13}O_3N)_2.H_2SO_4$. Accordingly, the formula $C_{10}H_{11}O_3N$ was changed to $C_{10}H_{13}O_3N$ to bring it into conformity with this. We have then, according to Abel, $C_{10}H_{13}O_3N$ for the formula of reduced epinephrin, and $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$ for the formula of epinephrin hydrate (adrenalin). Pauly having shown by his own, as well as by Abel's, investigations that there is no such compound as epinephrin hydrate, we really have but one of Abel's formulas in the discussion, *viz.*, $C_{10}H_{13}O_3N$.

The ground for assuming *even this* formula is based for the most part on the analyses of derivatives of the original so-called reduced epinephrin, these derivatives being of questionable purity. In fact some were thrown out in an amorphous condition, no doubt mixed with other substances. Furthermore, *no one* has, as yet, to

my knowledge, confirmed Abel's analytical results relative to so-called epinephrin hydrate or reduced epinephrin.

Since the analytical data given in my first paper did not agree very closely (as far as carbon is concerned) with the formula $C_9H_{13}O_3N$, my advocacy of this formula at that time was made with some reservation, knowing that my results were open to criticism; still my analytical data would not allow me to accept a formula with higher or lower carbon content. Facts which will be cited below, however, leave now no doubt of the correctness of this formula and also of my previous statements. I found later that this deficiency in carbon (about 1.0 per cent.) lay in the fact that the substance was incompletely burned. However, by burning the adrenalin with powdered copper oxide, the results were found to compare favorably with the formula $C_9H_{13}O_3N$.

Below are given the results of some combustion analyses and nitrogen determinations where the adrenalin employed was purified strictly according to the oxalate method as advocated by Abel and where it was mixed with copper oxide.

(1) 0.1663 gram substance gave 0.3611 gram CO_2 and 0.1080 gram H_2O.
(2) 0.2782 gram substance gave 0.6016 gram CO_2 and 0.1833 gram H_2O.
(3) 0.1618 gram substance gave 0.3534 gram CO_2 and 0.1092 gram H_2O.
(4) 0.2177 gram substance gave 0.4727 gram CO_2 and 0.1465 gram H_2O.
(5) 0.2393 gram substance gave 0.5184 gram CO_2 and 0.1630 gram H_2O.
(1) 0.29415 gram substance gave 20.8 cc. N at 25° and 736 mm.
(2) 0.2665 gram substance gave 18.4 cc. N at 22° and 744 mm.
(3) 0.2403 gram substance gave 16.6 cc. N at 22° and 745 mm.
(4) 0.4765 gram substance gave 32.6 cc. N at 22° and 745 mm.

	Calculated for.	Found.					Average.
	$C_9H_{13}O_3N$.	I	II	III	IV	V	
C.....	59.01	59.17	58.97	59.51	59.21	59.08	59.19
H.....	7.10	7.21	7.29	7.47	7.43	7.56	7.39
N.....	7.65	7.63	7.65	7.66	7.59	...	7.63

The formula of adrenalin, $C_9H_{13}O_3N$ (mol. wt. 183), not only finds confirmation in the analyses given above, but also in the titrations given below where the average of seven titrations gives a molecular weight of 183.7. The formulas $C_{10}H_{15}O_3N$ (Takamine), $C_{10}H_{13}O_3N$ and $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$ (Abel), are not to be considered in this connection, since their molecular weights are much above that actually obtained, $C_{10}H_{15}O_3N$ requiring 197, $C_{10}H_{13}O_3N$ 195, and $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$ 204.

(1) 0.3519 gram adrenalin requires 19.1 cc. N/10 H_2SO_4 to form neutral salt 183.7.

(2) 0.41495 gram adrenalin requires 22.5 cc. N/10 H_2SO_4 to form neutral salt 184.0.

(3) 0.3253 gram adrenalin requires 17.7 cc. N/10 H_2SO_4 to form neutral salt 183.3.

(4) 0.4258 gram adrenalin requires 23.3 cc. N/10 H_2SO_4 to form neutral salt 182.6.

(5) 0.2951 gram adrenalin requires 16.2 cc. N/10 H_2SO_4 to form neutral salt 182.7.

(6) 0.3568 gram adrenalin requires 19.3 cc. N/10 H_2SO_4 to form neutral salt 184.9.

(7) 0.3285 gram adrenalin requires 17.8 cc. N/10 H_2SO_4 to form neutral salt 184.3.

Average, 183.7.

My formula, $C_9H_{13}O_3N$, does not rely solely on the above for confirmation as it has during the past few years been verified through analyses by a number of investigators among whom may be mentioned v. Fürth,[25] Pauly,[26] Jowett[27] and others.[28,29] Furthermore, v. Fürth and others by molecular weight determinations have excluded the possibility of doubling the formula $C_9H_{13}O_3N$.

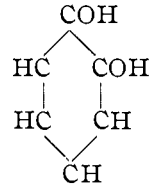
From all the foregoing it would seem that we are warranted in assuming $C_9H_{13}O_3N$ to be the correct empirical formula of adrenalin, the active principle of the suprarenal gland.

STRUCTURAL FORMULAS.

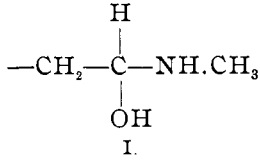
Before the active principle of the suprarenal glands had been isolated in a pure form, certain facts were observed relative to certain reactions and decomposition products, but those observed facts were of doubtful value for the reason that it was not certain whether the observed products came from the active principle or from some body or bodies with which it was associated.

As early as 1885 Krukenberg expressed his belief that the substance which gives the green color with ferric chloride is pyrocatechol, and from this time on the belief that pyrocatechol or some derivative of it is present in the glands gained a firm hold. In 1895 Moore came to the conclusion that the pyrocatechol-like body and the blood-pressure-raising body are identical. In 1901 Takamine obtained from the pure active principle, by fusing with potassium hydroxide, crystals that possessed the physical and chemical properties of pyrocatechol and protocatechuic acid.

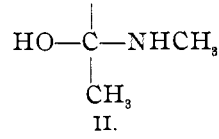
Later v. Fürth confirmed Takamine's observations and also demonstrated with others that adrenalin contains a methylamine group and also probably three hydroxyl groups, one of which is situated outside of the ring nucleus. From his own experiments and observations v. Fürth proposed the cyclic complex



as the basis of the adrenalin molecule and Pauly,* discovering that adrenalin contains an asymmetric carbon atom, accepted the foregoing, and suggested the following five possible formulas for the side-chain in the adrenalin molecule:



I.



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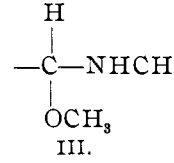
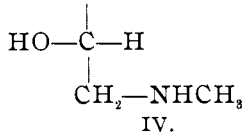
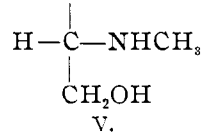


III.

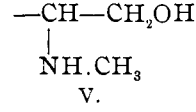


IV.



V.

Of these five possible structural side-chains, Pauly considers IV and V to be the most probable, since they explain the formation of several decomposition-products the most satisfactorily, but V is given the preference:

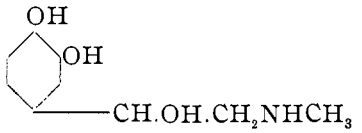


V.

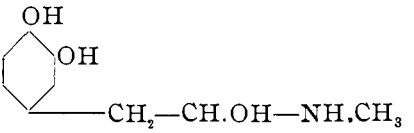
Jowett[27] confirmed the formula $C_9H_{13}O_3N$, first proposed by Aldrich, by the analysis of carefully prepared material and by molecular weight determinations. He also obtained by fusion with potassium hydroxide what he supposed to be protocatechuic acid, although he was not certain whether the presence of this

* *Ber.*, **36**, 2944 (1903).

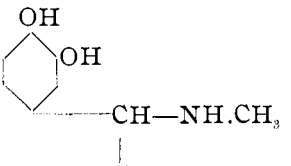
complex in the original substance could be correctly deduced from its formation. Oxalic acid, formic acid, and methylamine were also obtained by oxidation with permanganate. By thorough methylation and subsequent oxidation with permanganate, trimethylamine and veratric acid were obtained, thus proving the existence of the complexes $C_6H_3(OH)_2$—C and $NH.CH_3$ in the original base. He deduces from his results the following possible constitutional formulas for adrenalin:



I.



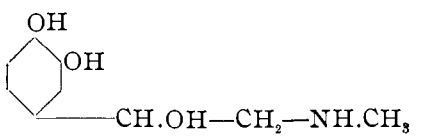
II.



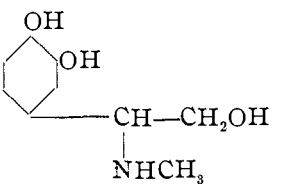
III.

Jowett considers I to be the most probable, for after methylation and subsequent oxidation of II* we would expect to obtain homoveratric acid, $C_6H_3(OCH_3)_2CH_2COOH$, whereas veratric acid, $C_6H_3(OCH_3)_2COOH$, was actually obtained. The objection to III is that it would not so readily explain the formation of pyrrol or skatol derivatives. I will add here, however, that Pauly in a later paper states that III can explain the formation of pyrrol as well as I, and that skatol should not be considered in this connection as it was not obtained from adrenalin but from benzoylepinephrin.

We have then from what has been cited the two following structural formulas for adrenalin:



I.

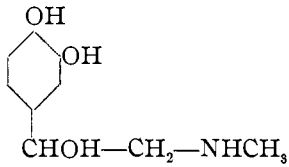


II.

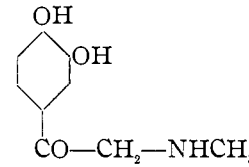
* Jowett's argument for Formula I is not entirely convincing, for II would no doubt also yield veratric acid, since it would be difficult to stop at the homoveratric stage.

As to which is the correct formula, we are unable to state positively at the present time. Evidence has been and is accumulating, however, in favor of I, still there is some evidence in favor of II.

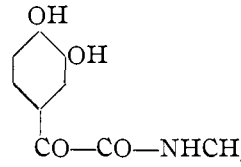
E. Friedmann* endeavored to establish the constitution of adrenalin in another manner. By oxidizing tribenzolsulphoadrenalin (described by v. Fürth), he obtained a body (adrenalon) having the same carbon content, but having no asymmetric carbon atom. It has the character of a ketone. By further oxidation, there was obtained another oxidation product (peradrenalon) with the same amount of carbon. It is to be considered a substituted acid amide. From these results it is concluded that the formula of adrenalin is represented by I, as advocated by Jowett.



I, adrenalin.

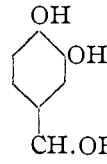


II, adrenalon.



III, peradrenalon.

Friedmann also endeavored to support the above by preparing II, adrenalon, synthetically and then forming the tribenzolsulpho body from the same. This tribenzolsulpho body is not to be distinguished from the first oxidation product obtained from tribenzolsulphoadrenalin; neither is its oxidation product different from the peradrenalon product obtained from adrenalin.

Assuming 

to be the correct constitutional formula for adrenalin, a number of investigators have endeavored, by

* *Beiträge zur chemischen Physiologie u. Pathologie*, **6**, 92, September, 1904.

starting with pyrocatechol, to prepare adrenalin synthetically, and, although their endeavors have not been entirely successful, still bodies have been obtained that have at least the qualitative physiological properties of adrenalin as well as some of the physical and chemical properties. Among those who have prepared such bodies may be mentioned Roser[31], who claims to have produced synthetic adrenalin or at least a substance acting like adrenalin. This body, methylaminorthodioxyacetophenon, was described by H. Meyer at the International Congress of Physiologists at Brussels. Qualitatively it exhibited an effect exactly like that of adrenalin, not only as far as the peripheral vaso-constricting action following intravenous injection is concerned, but also as to the action on the smooth muscular fiber and the causation of diabetes. It was further found that a series of homologous compounds (aminoketones, ethylaminoketones, etc.) exert a similar action.

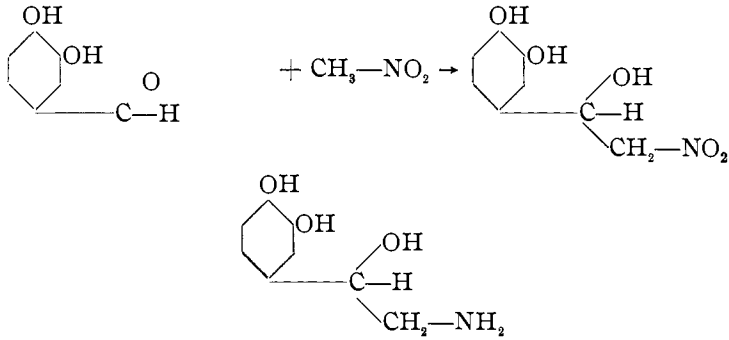
E. Friedmann[30] prepared methylaminoacetopyrocatechol (adrenalon) and found that it possessed marked physiological properties in raising the blood-pressure.

F. Stolz,[32] having convinced himself by experiment that the formula of Aldrich, $C_9H_{13}O_3N$, for adrenalin was correct, and that its degradation products were essentially as given by others, accepted the structural formulas advocated by Pauly and Jowett. Stolz prepared substances having properties similar to those of adrenalin, such as methylaminoacetopyrocatechol, which, when reduced, approached adrenalin still more closely, ethylaminoacetopyrocatechol, and aminoacetopyrocatechol. Exact identity could not be established, however.

Dakin[33] has contributed the latest article on this subject, "The Physiological Action of Synthetic Substances Allied to Adrenalin." The basic body, which was obtained from methylaminoacetopyrocatechol by reduction, differs somewhat from the native product. The salts of this base, however, show all the chemical reactions of adrenalin. Furthermore, the physiological activity of the new substance is about the same as adrenalin. This base is no doubt the same as that obtained by Stolz,* where he states: "By reduction of the alkylaminoacetopyrocatechol a compound is formed whose physiological activity approaches more closely that of adrenalin."

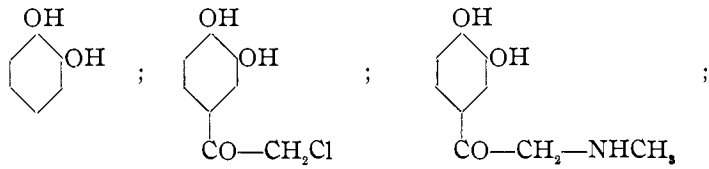
* *Ber.*, **37**, 4149.

A further attempt was made by Dakin to prepare synthetically from protocatechuic aldehyde, bodies similar to adrenalin. This was accomplished by condensing protocatechuic aldehyde with nitromethane without the elimination of water and then reducing the nitro group. The changes are represented as follows:

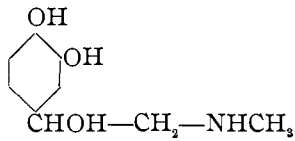


This base was found to be also physiologically active.

The original material in making all of the synthetic bodies cited above, excepting the last, is pyrocatechol from which successively chloracetopyrocatechol, methylaminoacetopyrocatechol and the reduction product of the latter are formed. The successive bodies are indicated by the following formulas:



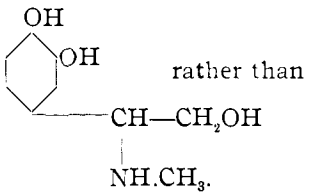
Pyrocatechol. Chloracetopyrocatechol. Methylaminoacetopyrocatechol.



Adrenalin (?)

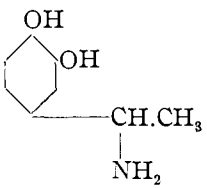
All the synthetic work thus far published, relative to adrenalin, is along the lines indicated above, and it has all been more or less anticipated by S. Dzierzgovsky,[34] who not only prepared chloracetopyrocatechol but dimethylaminoacetopyrocatechol and other similar bodies.

In closing, I wish to say that for some time past (since July, 1904) I have been occupied with some bodies which have been built up along the lines of the formula

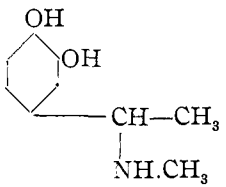


rather than

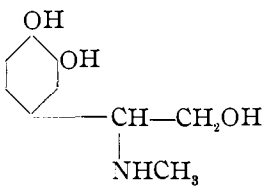
Qualitatively, these bodies act in solution very similarly to adrenalin, when injected intravenously. No doubt they are represented by the formulas:



and



Work along this line is being carried out at the present time, and I am in hopes soon to be able to report more specifically relative to the same, also to have carried the work far enough so as to obtain the body represented by the formula:



RÉSUMÉ

(1) Adrenalin is the native active principle of the suprarenal gland, this being shown conclusively by reduction tests and blood-pressure tests, in which a definite amount of extract was taken, divided into two equal parts and the reducing power and blood-pressure-raising power of one portion, compared with that of the adrenalin obtained from the other portion. These were found to be practically the same after making due allowance for the small amount of adrenalin that it is difficult to precipitate from the extract.

(2) From the evidence at hand none of the following formulas proposed by different authors, (Takamine) $C_{10}H_{15}O_3N$, (Abel) $C_{17}H_{15}O_4N$, $C_{10}H_{11}O_3N$, $C_{10}H_{13}O_3N$ and $C_{10}H_{13}O_3N.\frac{1}{2}H_2O$, can be accepted as representing the true composition of adrenalin.

(3) $C_9H_{13}O_3N$, the formula first proposed by Aldrich for adrenalin, represents without doubt the true composition of this body, this being shown not only by Aldrich's later analyses but also by the confirmatory analyses of v. Fürth, Pauly, Jowett, Abderholden and Bergell and Bertrand.

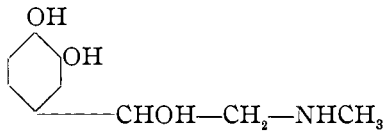
(4) The formula $C_9H_{13}O_3N$ finds also confirmation in the titration experiments cited, where the average of seven determinations gives a molecular weight of 183.7 ($C_9H_{13}O_3N$, 183).

(5) Molecular weight determinations of adrenalin and its derivatives by *physical methods* also confirm the formula $C_9H_{13}O_3N$.

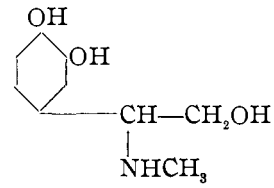
(6) Adrenalin contains undoubtedly a pyrocatechol complex, an asymmetric carbon atom, three hydroxyl groups, one being in the side-chain and a methylimide group (N—CH_3).

(7) Thorough methylation of adrenalin and subsequent oxidation gives veratric acid and trimethylamine.

(8) One of the two following formulas proposed by Pauly represents possibly the structure of the adrenalin molecule:



I.



II.

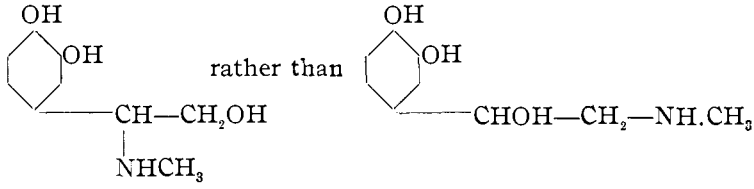
(9) It is not positively decided as yet which of the above formulas is the correct one. Preponderance of opinion seems, however, to favor I.

(10) Assuming I to be the correct formula, a number of bodies have been prepared from pyrocatechol, through chloracetopyrocatechol, by treatment with ammonia, alkylamines and other basic bodies, some of which qualitatively seem to be similar to adrenalin as regards their physiological effects.

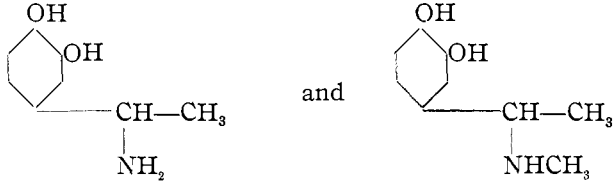
(11) Dakin has apparently obtained a body by reducing methylaminoacetopyrocatechol, whose salts show all the reactions

of natural adrenalin, but certain differences appear to exist between the free bases. The physiological activity is about the same as adrenalin.

(12) Bodies have been prepared in solution, that have been built up along the lines of the formula:

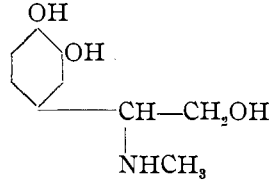


Qualitatively, these are similar to adrenalin, when injected intravenously. They are probably represented by the formulas:



respectively.

There is hope of obtaining the body represented by the following formula:



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[29] Bertrand: *C. R.*, **139**, 502 (1904).
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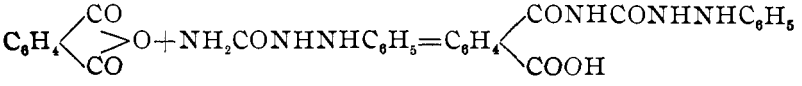
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN.]

THE ACTION OF PHENYLSEMICARBAZIDE AND SEMICARBAZIDE HYDROCHLORIDE ON PHTHALIC ANHYDRIDE.

BY FREDERICK L. DUNLAP.

Received July 3, 1905.

WHEN phenylsemicarbazide and phthalic anhydride are heated together to 140-145°, they combine to form phthalic acid monophenylsemicarbazide as follows:



This acid decomposes on heating, carbon dioxide and small quantities of ammonia being at first evolved. As the decomposition proceeds, the amount of carbon dioxide formed gradually