THE CHEMISTRY OF NITROGEN AS DISCLOSED IN THE CONSTITUTION OF THE ALKALOIDS.*

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To the compounds of carbon chemistry has devoted its main strength ever since this science reached maturity of purpose. In the work among organic compounds science has made its nearest approaches to an actual acquaintance with the molecule as a chemical center, and from these advances every branch of chemical art receives full benefit.

Carbon was the first to gain attention as the member giving specific character to organic compounds (1).† Hydrogen entered into the definition of organic chemistry (2) at a later period. At present, hydrocarbons are represented to be the parent forms of chemical families, with carbon as the member for fixed position and hydrogen as the member for exchange. Upon these two elements, and upon their relations in the molecule, investigation has fixed its steadfast eyes in the will to divine the ways of chemical action.

Nitrogen comes next in turn as an organic element of importance. Hitherto, for the most part, organic nitrogen has been regarded only as a member peculiar to certain categories of carbon compounds. The name of nitrogen has not entered into any definition of general or commanding interest. Nevertheless, *the carbonaceous compounds of nitrogen* have already so appeared as to shed a good light upon chemical structure. It is hardly too much to say that in the study of these compounds lies before us the very organic chemistry of organic chemistry.

Through the inorganic world and its majestic round of supplies for the sustenance of living bodies, nitrogen has been noted as a unique element. The physiological availability of the free nitrogen of the air, long found a divided question, was well discussed in the last annual address before this section. The artificial conversion of atmospheric nitrogen into ammonia, an old attempt, is constantly urged at the hands of invention by new demands from the great chemical industries. The service of nitrogen in the ex-

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†List of references at end of the address.

plosives, fairly well under control in the use of projectile agents, is still in the need of improvements for safety and for rate of action. The element assumes strangely diverse relations: it presents to us an enigma in physiology: it leads in our estimates of the agricultural value of plant foods: it stands in its indifference as an obstruction in the way of great chemical manufactures; it keeps the post of a trusted agent for projectile force in arts of war and of peace: it mocks us with its abundant presence in an inapproachable virgin state; the same element that holds the structure of the aniline dyes and governs the constitution of the vegetable alkaloids. The character of nitrogen challenges mechanical skill.

The chemistry of nature instructs the chemistry of art. Molecular syntheses wrought out in the vegetable kingdom, sometimes too complex for analysis, often too difficult to reproduce, always claim our study; and the reasons so far shadowed forth are more than enough to justify the attempt here entered upon to trace back the path of attainment, and take the bearings of our progress in the chemistry of nitrogen as disclosed in the structure of the alkaloids.

The history and the present state of the constitution of the vegetable alkaloids, and other nitrogenous bases, may be outlined in the following order:

(1) The conception of the type of ammonia in the formation of nitrogenous bases. The light of this theory has enabled great numbers of artificial compounds to be produced, but for the most part it has failed to reveal the structure of the vegetable alkaloids.

(2) The study of the aromatic type of structure in closed chains of six positions of carbon, conjoined with the ammonia type in side chains. Great numbers of new bases of amido-benzenoid constitution have been produced while the benzenoid type has been found in but few of the vegetable alkaloids.

(3) The demonstration of the pyridine and quinoline aromatic groups, holding nitrogen in position within the closed chain in the constitution of numerous vegetable alkaloids. Already artificial production of both new and natural alkaloids follows up the discovery of the pyridine type of formation.

(4) The researches upon azo and diazo benzenoid bases, in which nitrogen is linked to nitrogen in an open side chain of benzenoid

molecules. Color substances in abundance have been made upon these types, and a late announcement implies that the diazo structure takes part among animal decomposition products.

I. Nitrogenous Bases as Derivatives of Ammonia.

It was remarked by Justus Liebig in 1830 (3), that the capacity for saturation of acids, possessed by the plant bases, was in proportion to the number of equivalents of nitrogen they contained. As early as 1837 Berzelius (4), reasoning on the results of Regnault and Liebig, advanced the doctrine that the vegetable bases were conjugated compounds of ammonia—binary combinations in which the entire molecule of ammonia was united with a group or compound radical containing carbon—represented by H_3 N X. The saturating power of the alkaloid was stated to be the same as that of the contained ammonia. Liebig departed from the doctrine of Berzelius to this extent, that he held the organic bases to be binary combinations, not of entire ammonia, but of amidogen, so that they were represented by H_2NY. Liebig's view looked toward but did not reach the idea of substitution for the hydrogen in ammonia.* The doctrine of Berzelius as a whole, "by no means met with general approbation, but" to use the words of Hofmann, "it was retained and carried out by Berzelius with the perseverance and ratiocination peculiar to that great chemist."

At the time of these studies, vegetable alkoloids had been known in the chemical world for about twenty years. The chief bases of opium, cinchona, strychnos, veratrum, aconite, and the solanaceous plants had been obtained. The first distinct announcement of a plant base was that of morphine by Sertürner in 1805, but this did not gain attention until Sertürner's fuller report in 1817 (5). In 1803, however, Derosne (6) had obtained a "crystallizable opium salt" by two methods, one of which must have given him morphine, and the other, narcotine. In 1844, about fifty vegetable alkoloids were enumerated, including some whose indentity has not been established (7).

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* In 1840 (*loc. cit.*) he made a remarkable prediction of the nature of the amines, obtained by Wurtz and by Hofmann ten years afterward. "If," said Liebig, "we were able to replace by amidogen the oxides of methyl and ethyl, and of two basal radicals, we should without the slightest doubt obtain a series of compounds exhibiting a deportment similar in every respect to that of ammonia. Thus a compound of the formula C_2H_5 H_2N would be endowed with the properties of a base."

The disadvantage incurred in investigation of organic bases under the Binary Theories of Berzelius and Liebig is shown by the difficulty described by A. W. Hofmann (8) in London, as late as 1849. "Vainly have I hoped in the course of my investigation on this subject," he says in conclusion of a paper on certain organic compounds of ammonia, "to cause aniline to split up into ammonia and the conjunct C_6H_4."[†] The introduction of the Theory of Substitution and the Theory of Types by Dumas and Laurent (9) prepared the way soon after 1840 for the production of derivatives from ammonia.

The first representatives, methylamine and ethylamine, were obtained by Adolph C. Wurtz, in February, 1849, (10) — through the action of potash upon the cyanic ethers.[‡] The year before he had made report (11) on the same reaction, with the surmise that he had obtained a derivative either of a urea or of an ether,[§] but after obtaining methylamine as a caustic volatile alkali, he was emphatic in declaring it an ammonia. "I have succeeded, in fact," he said, "in converting ammonia into a true organic compound, by adding to it the elements of the hydrocarbon CH_2."[‖] Wurtz at first christened the new products "methylamid" and "ethylamid." Mr. T. Sterry Hunt, then writing in *Silliman's Journal* (12), proposed the names of "methylamine," "ethylamine," etc., as "more consonant with the nomenclature of the alkaloids." The names "methyliak," "butyriak," etc., were offered by Dumas; and the names "methammine," "ethammine," etc., by Gerhardt (13). In his communication of August, 1849, Wurtz adopts the terms "methylamine," etc., and about this time he presents rational formulæ, on the ammonia type, for a good number of artificial bases, aniline, toluidine, and picoline, for nicotine, and conine, and claims formulæ for several oxygenated bases.

Dr. Hofmann had been engaged in investigation "on the volatile organic bases," communicated in 1849 and 1850 and already

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[†] Original, $C_{12}H_4$.

[‡] That is, the methyl and ethyl isocyanates. Also by action of potash on the isocyanurates and ureas.

[§] "Either a urea in which one equivalent of water is replaced by one of ether, or methyl ether in which the molecule of oxygen (weight 8) is replaced by a molecule of amidogen, NH_2." The latter view corresponds to that in the prediction of Liebig already quoted.

[‖] "Ammonia," said Wurtz, "should decidedly be regarded as the most simple and most powerful of the organic bases; and it would be for all chemists the type of that numerous class of bodies, did it not differ in one undoubtedly important character, but to which," he concludes, "an exaggerated value has been attributed. Ammonia contains no carbon."

referred to (8), and he welcomed "the splendid investigation of M. Wurtz" with unstinted enthusiasm. He now adopted the theory of substitution for the hydrogen of ammonia, and with remarkable celerity he verified the theory by replacing the second and the third atoms of hydrogen by organic radicals. Beyond this he substituted the fourth hydrogen atom of ammonium salts, explained the formation of "white precipitate" and other metallic derivatives, and set forth the likeness of oxygenated alkaloids to the compounds of ammonium. For the greater number of his results he employed the simple reaction which bears his name, the reaction between iodides or bromides of radicals and the ammonia or lower derivatives of ammonia. His masterly reports of 1850 and 1851 fill seventy-eight pages of the Philosophical Transactions (14), concluding with an extensive classification of new substances, and with ambitious expectations of finding the constitution of important vegetable bases. This reaction, used by Hofmann for the introduction of "alkyls" or alcohol radicals into ammonia, producing successively primary, secondary and tertiary amines and then alkyl ammonium salts, is a reaction now in constânt use upon alkaloids in the course of investigations. By this reaction, for example, morphine is convertible into methyl-morphine, which is codeine, and an homologous ethyl-morphine is readily obtained (15). Brucine is dimethoxy-strychnine ; a methyl-strychnine and an ethyl-strychnine are produced (16); and these artificial products are under trial as to their physiological effects. Quinine is a methoxy-cinchonine. Cocaine is readily formed by the introduction of methyl into benzoyl-ecgonine, and the corresponding ethyl, propyl, and butyl products are now under physiological trial (17). It is of great practical interest that homologous alkaloids, prepared by successive substitutions of methyl through Hofmann's reaction, are found to exhibit a gradation of physiological intensity quite in correspondence with the graded intensity of the homologous alcohols of the paraffin series.

Whatever we have gained by modern theories of other types of structure it still remains true that the nitrogenous bases represent the type ammonia. Whatever other types govern the constitution of alkaloids in general, they carry central atoms of nitrogen, whose valence and whose chemical activities are typified by the nitrogen of this simple volatile alkali. Nevertheless, the type ammonia represents only the "ammonia rest," a small part of the molecule of a natural fixed alkaloid. Unable to reach a clew to the constitution of the larger part, and therefore without data as to the relations and valences held by nitrogen, chemists were not able to assign rational formulæ to the oxygenated alkaloids of plants in general until within the past ten or fifteen years, during which time light has been obtained upon typical structures of the carbon and hydrogen of these bases.

II. Nitrogenous Bases represented by Aniline.

Phenylamine or amidobenzene is the type, in its simplest form, of compounds made by the substitution of an aromatic radical in ammonia. Obtained by distillation from indigo in 1826, from coal-tar in 1834, and from benzene by reduction of the nitro-derivative in 1841, it was at once recognized by Wurtz and by Hofmann, in 1850, as a primary amine. Its aromatic constitution, with that of benzene itself, came to light in the closed chain theory of Kekulé in 1865 (18). The aniline color industry, instituted by the inventions of Perkin in 1856, could not have reached its great and beneficent development without the impulses due to the knowledge, first, of the ammonia type in the linking of nitrogen, and second, of the closed chain of six positions of carbon.* On the other hand, the resources of pure organic chemistry could not have reached the wide extent they have attained without the patient and efficient investigation of the industrial chemists engaged in the work of the world.

While the aromatic type of structure has furnished artificial nitrogenous bases for innumerable dyestuffs, the inquiry whether any considerable number of the alkaloids of plants were aromatic compounds or not was for years a perplexing question. Large numbers of vegetable alkaloids yield simple aromatic products when decomposed. For example, atropine and its related alkaloids, when heated or forcibly oxidized, yield benzoic and salicylic aldehydes and related bodies. At the same time, research has failed to find rational formulæ for alkaloids wherein nitrogen was attached, as it is in aniline, to a benzenoid group—a closed chain

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* In use of the chemical term position the author will be understood to refer, not to arrangement in space, but to the order of union of atoms with each other.

of six carbon positions. It was not until the discovery of the pyridine and quinoline type in the alkaloids—a type of aromatic structure holding five positions of carbon and one of nitrogen within the closed chain—nitrogen in a position central to the molecule—that it could be understood in what way the natural alkoloids, yielding aromatic decomposition products, were themselves of aromatic composition.

Before taking up the consideration of the pyridine type of basis, it may be said that the complete benzenoid group, so extensively found in vegetable acids, has been very little found in vegetable bases. In narcotine and narceine, the benzenoid group is found with four hydrogen atoms replaced, but not at all replaced by nitrogen. The nitrogen of the compound is not directly linked to the complete benzenoid group.

III. The Pyridine Type in the Vegetable Alkaloids.

The aromatic constitution of pyridine and quinoline was apprehended in 1870 (19). In this constitution, pyridine differs from benzene only in the substitution of one trivalent N, for the trivalent group CH; and quinoline differs from naphthalene only in the substitution, in the same way, of one N for one CH. As constituted in closed chains of six positions, pyridine and quinoline are aromatic compounds, but of a type radically different from that of complete benzenoid bodies conjugated with nitrogen, like aniline or azobenzene. The pyridine molecule, C_5H_5N, violates the first condition of benzenoid compounds, namely, that the six primary positions of the molecule, C_6H_6, are all equal to each other. Here we have *nitrogen interlinked in the closed chain* in the position of central influence. The great numbers of compounds which have been found in nature and formed by art, upon the pyridine type, during the last sixteen years, give evidence that this type is an essential effect of *the chemism of nitrogen* as much as the benzene type is an effect of the chemism of carbon. The fact that only one atom of nitrogen is found to enter the closed chain of six positions renders it not unlikely that the nitrogen atom is directly united to more than two atoms of carbon in the ring. That the nitrogen is united to three atoms, Riedel and others (20) sometime since concluded on experimental grounds.

That the vegetable alkaloids containing oxygen are *tertiary* amines, or ammonium compounds, so that they do not contain hydrogen directly united to their nitrogen—and so that all the hydrogen of the typical ammonia is replaced—was announced by Hofmann, in 1851, and has always been assented to. With this view, the theory of the pyridine type quite accords. Pyridine and quinoline are actually tertiary amines, and their derivatives retain the exclusion of hydrogen from the first three valences of nitrogen, those which represent hydrogen of ammonia.

In their isomerisms and in their deportment, pyridine and quinoline resemble benzene and naphthalene, their simpler aromatic types. By the facility of substitution of methyl and other radicals for their hydrogen, they yield homologous series; by oxidation of the alcohol radicals, carboxylic acids are obtained; and by reduction of the acids, the original compounds are restored. In a very important quality, however, pyridine differs from benzene in deportment, that the former gives much more stable addition products with hydrogen than can be obtained from the latter. Two, four, or six atoms of hydrogen are united. Hexahydro-pyridine is the alkaloid piperidine. Piperidine in union with piperic acid constitutes the piperine of black pepper, the latter being, therefore, a saponifiable alkaloid. The pyridine from which is derived tropine, the central group in solanaceous alkaloids, is tetrahydrated, and the typical quinoline in the cinchona alkaloids is tetrahydrated. The stability of these addition products renders possible the great complexity of natural derivatives of pyridine. And in this capacity for larger combinations we have proof, again, that *the chemism of nitrogen* introduces distinct character into the pyridine derivatives.

Pyridine was obtained from bone oil in 1850 (21), from coal tar in 1855 (22), by synthesis from an azo compound in 1865 (23), and may be prepared from various alkaloids by distilling them with alkali. A pungent liquid, miscible with water, boiling at 116.7° C., its appearance scarcely commends its claim to be the chemical protoplasm of the alkaloids of plants. Quinoline was obtained from quinine and from strychnine in distilling with alkali by Gerhardt, in 1842 (24), from the latter distillates of coal tar as finally confirmed by Hoogewerff in 1883, from bone oil, along with pyridine, and by synthesis in several ways, best from nitro-benzene with aniline and glycerine as done by Skraup in 1881. As a liquid it corresponds in appearance as it does in composition to pyridine, being heavier and less volatile. It is easily oxidized to pyridine dicarbonic acid, as naphthalene is to phthalic acid,—as by the cutting away of one of a pair of joined hexagons. When manufactured from cinchoninequinoline it is accompanied by lepidine*, as prepared from nitrobenzene it is liable to retain the latter as an impurity. It is in demand for color manufacture and for introduction to medicinal uses. Pyridine is still prepared from bone oil, but should much demand arise for it more favorable sources would doubtless be found.

About eight years ago the researches of many chemists reached the discovery of the pyridine type of constitution in several groups of the vegetable alkaloids. In some instances, as in the chief cinchona alkaloids, results have established a rational aromatic formula for the entire base as it exists in nature. In other instances, the pyridine type has been revealed, not at first in the natural alkaloid as a whole, but in an alkaloid previously found to lie within the alkaloid of nature, and obtained therefrom by reactions fairly denoted as those of saponification. And before bringing up examples of the pyridine and quinoline types of constitution, it is necessary to summarize the principal saponifiable alkaloids with the products into which they split up.

The saponification of alkaloids, as accomplished in the last thirty years, corresponds, in its delightful simplification of complex compounds, to the saponification of fats achieved over fifty years ago,—with this striking difference, that the chief or representative product of the saponification of an alkaloid is another alkaloid while the more elaborate product of the saponification of a fat is usually an acid. Indeed, in case of an alkaloid, its saponification may be defined as the removal of an acid or other radical, by replacing it with hydrogen. And the saponification of alkaloids does not fulfill the accepted definition of chemical saponification, in that its resulting base in most cases does not appear in classification as an alcohol, nor is the subject of the decomposition classed

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*For the manufacture of cyanine, the lepidine is necessary, pure quinoline not yielding this blue coloring matter in treatment with amyl iodide and alkalies (HOOGEWERFF and VAN DORP, 1882).

as an ester. The saponification of alkaloids is instituted by action of an alkali then left in union with the resulting acid, or by an acid then left in union with the obtained new alkaloid, or by digestion with only water, which of course is always taken up. The following are representative instances of the saponifications of alkaloids:

Atropine with *water* yields *tropine* and *tropic acid* (25).

$C_{17}H_{23}NO_3+H_2O=C_8H_{15}NO+C_9H_{10}O_3$

Aconitine with *water* yields *aconine* and *benzoic acid* (26).

$C_{33}H_{43}NO_{12}+H_2O=C_{26}H_{39}NO_{11}+C_7H_6O_2$

Cocaine with *water* yields *bedzoyl-ecgonine* and *methyl alcohol.*

$C_{17}H_{21}NO_4+H_2O=C_{16}+_{19}NO_4+CH_4O$ (27).

Benzoyl-ecgonine with *water* yields *ecgonine* and *benzoic acid.*

$C_{16}H_{19}NO_4+H_2O=C_9H_{15}NO_3+C_7H_6O_2$

Narcotine with *water* yields *hydrocotarnine* and *meconine* (28).

$C_{22}H_{23}NO_7+H_2O=C_{12}H_{15}NO_3+C_{10}H_{10}O_5$

Ceradine with *water* yields *cevine* and *methylcrotonic acid* (29).

$C_{32}H_{49}NO_9+H_2O=C_{27}H_{43}NO_8+C_5H_8O_2$

Veratrine with *water* yields *verine* and *veratric acid* (29).

$C_{37}H_{53}NO_{11}+H_2O=C_{28}H_{45}NO_8+C_9H_{10}O_4$

Piperine with *water* yields *piperidine* and *piperic acid* (30).

$C_{17}H_{19}NO_3+H_2O=C_5H_{11}N_9+C_{12}H_{10}O_4$

Each reaction of saponification here cited is limited to the single step taken in the appropriation of one molecule of water.* In the case of cocaine, a second saponification directly follows the first, and treatment may yield together the products of both reactions.

After Chevreul effected the saponification of ordinary fats, it was a long time before the reverse change was obtained in the synthesis of fats from fatty acids and glycerine. But not so long an interval interposed between the analytic and the synthetic results represented by the saponification of some of the alkaloids. The construction of atropine by union of its saponification products was brought about by Ladenburg in 1879 (31). The like synthesis of cocaine was obtained by Skraup, and by W. Merck, in 1885 (32).

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*According to Wright, japaconitine, with three molecules of water, yields two molecules each of japaconine and benzoic acid.

The liability of alkaloids to saponification is a property that closely concerns the treatment they receive in manufacture and in pharmacy, and gives explanation of numerous perplexities in practical operations. These very perplexities have sometimes been assumed to show that results promised by theory fail to appear in practice,—a failure that finds remedy in this case, as in many others, by a more liberal use of just the theoretical knowledge complained of. At all events, the operations of pharmacy have been the source of unnumbered contributions to the pure chemistry of the alkaloids, and this indebtedness of science pays honor to faithful investigations, represented in a rich and extensive body of pharmaceutical literature.

Returning to our inquiry into the discovery of the pyridine type of aromatic composition in the alkaloids, we find the last three years to have been a period of great attainment. It may be placed first that tropine, the common base of the entire atropine group of alkaloids, the midriatic alkaloids of the solanaceæ, is itself a derivative of pyridine. This was experimentally established in 1884 and 1885, by Ladenburg (33), Hofmann, Hantzsch, and Könings. In 1882 Ladenburg had termed tropine "a nitrogenous alcohol of which the tropines are the ethereal derivatives." But after a succession of reports on the nature of tropine, beginning in 1881, Ladenburg has presented evidence, fully confirmed by others just named, that tropine is directly derived from pyridine. Starting with tetrahydro-pyridine, the introduction of an ethylene-hydroxyl and a methyl, in place of two atoms of hydrogen, forms tropine: $C_5H_7\ (C_2H_4OH)\ N\ (CH_3)$.

Piperdine, the decomposition product of the alkaloid of black pepper, was shown by Hofmann, in 1879 (34), and by Ladenburg and Roth in 1884, to be a hexahydro-pyridine, Nicotine, the volatile alkaloid of tobacco, is a dihydro-dipyridine, as claimed in 1880 by Wischnegradsky (35). Conine, early classed as a secondary amine, is ascertained to be a propyl-piperidine (36).

The alkaloids of cinchona barks, though counting over twenty-five in number, are certainly represented in their constitution by cinchonine, of which quinine is the oxymethyl derivative.

In 1881, Wischnegradsky deduced from his results that cinchonine contains both a quinoline and a pyridine group, but accumulating proofs since render it strongly probable, if not certain, that cinchonine is a quite simple di-quinoline derivative (37). Starting with quinoline, then tetrahydrated, two molecules unite by dropping a hydrogen from each, when oxymethyl is made to replace one hydrogen for cinchonine, or two hydrogens for quinine.*

This is by no means an account of the pyridine type as known in all the alkaloids. Strychnine and brucine are the subjects of especial activity and it is clear that they are pyridine compounds, as are also the alkaloids of opium.

The evidence seems to be, at present, very strong, that, in general terms, the vegetable alkaloids are hydrogenized pyridine derivatives. Under the belief that any useful understanding of the structure of these bodies must be based upon a full experimental acquaintance with the pyridine and quinoline series, there is great activity in the study of the typical compounds. For some time, now, researches have been undertaken to find the positions of groups introduced into these bodies (38). On the success of these studies of chemical position, the chemistry of the natural alkaloids will in the future necessarily depend. Until the isomerisms due to position are under control, there can be no distinction established between, for example, numbers of compounds, each having the same constituent groups represented in the present formula for quinine, or in that for atropine. Also the present acquaintance with plant bases, accumulated in the progress of analytical chemistry, has still to be advanced, as a foundation for studies of chemical structure.

General methods of synthesis of pyridine derivatives have been sought at many hands. The reaction of Hofmann, beginning with alkyl iodide addition products, on subsequent exposure to a high temperature in sealed tubes, results in the substitution of radicals in pyridine compounds. The production of the hydrogen addition compounds, as piperidine, is effected only by the strongest of reducing agents, such as metallic sodium applied in alcholic solution (39). This affords another illustration, that the most violent reducing agencies of the laboratory are required to accomplish changes constantly carried on by the silent forces of plants.

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*$C_9H_{10}N.C_9H_9N.(O.CH_3)$, cinchonine.

$C_9H_{10}N.C_9H_8N.(O.CH_3)_2$, quinine.

At the present time, there appears a degree of encouragement, that the synthetic manufacturer of the alkaloids, hitherto obtained from plants, will sometime become realized as an industry. Not from the chance efforts of ignorant dreamers, nor from any premature short cuts of special attempt, but, if at all, from the well-earned progress of the science of the world will these results be accomplished.

A large amount of well directed chemical investigation in the service of manufacturing interests is devoted to reasonable questions of new production of alkaloids—including the conversion of those more abundant into those more valuable. Artificial alkaloids of a composition allied to natural ones are being constantly put upon trial as respects their usefulness in medicine and the arts. The periodicals of pharmacy and medicine are thickly strewn with records of the physiological power of new alkaloids, especially of quinoline derivatives of many forms, "Kairines E. to Q.," "thallines," and "antipyrines," ethyl morphine, and methyl and ethyl strychnine. It should not surprise us, if, at any time, artificial alkaloids should assume a commercial importance rivalling that of articles already brought into general use, such as carbolic and salicylic acids.

IV. New Azo and Diazo Bases.

It was said that the nitrogen of organic bases in general, whether of the pyridine type or otherwise, still conforms to the type of ammonia, preserving the valence and the character so well known in ammoniacal compounds. To this statement perhaps an exception should be made, as it does not apply to the diazo compounds. However, the diazo compounds are not distinctly bases, but act both as bases and as acids. The azo compounds, acting alone, are scarcely bases at all, but in conjugation as azo-amido compounds they unite with acids to form salts, and such salts owe much of their character to their azo-nitrogen. The nitrogen of the class of azo and diazo compounds in general is nitrogen acting in a way intermediate between that of the basal nitrogen of the ammonia type and acidulous nitrogen of organic nitro-acids. And so far as they represent bases, the diazo and azo types of structure must be taken into account in a survey of the base-forming activities of nitrogen.

The diazo compounds were produced (40) shortly before the date of Kekulé's lucid theory of aromatic chemistry ; the azo compounds were obtained (41) much earlier, but both classes of substances were seen through definite rational formulæ after 1865 (42). The diazo group contains two atoms of nitrogen so interlinked that the group serves, with a valence of only two, to connect the benzene group on one side with an acid or metallic radical on the other side. Diazo compounds are very frail, readily breaking up with explosive violence, due to the liberation of free nitrogen. The azo compounds, less instable, have the same bivalent group of two nitrogen atoms, here interposed between two benzene rings. Whatever be the truth as to the valences of nitrogen in the diazo group it is impossible to avoid thinking that the two atoms are united to each other by two units of valence of each : $(-N{=}N-)$. This structure, at all events, is wholly unlike that of the ammonia type, but bears some resemblance to that of isocyanogen.

Almost innumerable color compounds of the azo and diazo formation have been manufactured from coal tar materials, but not until now (to the writer's knowledge) has the azo type been discovered in immediate relation to natural organic products.

This year Dr. V. C. Vaughn, from further work upon the albuminoid decomposition product tyrotoxicon (43), has announced the identity of this body with diazobenzene (44), and says, "We think it highly probable that diazobenzene or some closely allied substance will be found in all those foods, which from putrefactive changes produce nausea, etc." The same author gives his conviction that diazobenzene, and possibly allied bodies, are " transition products of putrefaction."

The study of albuminoid constitution has scarcely been entered upon as yet with advantage, and the relations of albuminoid nitrogen may yet add new chapters of the highest interest in the history of this element. It has been deemed highly probable on certain experimental data, that albuminous substances, like alkaloids, are built up through the transition of the pyridine compounds. On evidence just cited it may appear that the same bodies are broken down through the transition of the diazo compounds. Whatever may be in reserve for future chemistry, to come from the study of the proteids of food, its importance is sure to belong, in greater part, to the chemistry of nitrogen.

In the brief and inadequate review now concluded, an early mention was made of those first two steps that counted so much then for progress, the making of methylamine by Wurtz, and the proof of primary and secondary amines by Hofmann. Of these workers, the one died only three years ago, and the other is living as an active promoter of science. The advances made in the lifetime of these men bring a deep sense of gratitude to the heart of every chemist. We pay honor to them for the good works they in their days have done, and we have been grateful, with them, for the rich and beneficient fruits they in their lives have seen.

Literature.

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