VEGETABLE ALKALOIDS

AND THE

METHODS OF THEIR SEPARATION.

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Historical and Introductory.—The alkaloids are among the most important of all the substances of the materia medica, either from a pharmaceutical or from a therapeutical aspect, for it is to their presence that a very large number, and, in many instances, the most valuable, of the natural organic drugs owe their remedial activity. That many plants possessed a highly poisonous action, and that this action when moderated might be utilized in the treatment of disease, has been known from time immemorial; but that the activity of the plant was in the majority of cases confined, and in a highly concentrated form, to a separable alkaloidal constituent of the plant, was not anticipated until shortly after the beginning of the present century, when Sertürner, Derosne and Seguin, working each apart from the other, shared the honour of preparing in a tolerably pure state the main active principle of opium, and to which the name of morphium (Gr. μορφή, *form*,—on account of its crystalline form) was given by Sertürner. Sertürner was an apothecary of Hamelin, and Derosne an apothecary of Paris. It was the former who first clearly recognized the basic or alkaline qualities of the newly found active principle; but, although he observed in his first communication, published in 1806, that the morphium possessed an alkaline reaction, yet it was not until eleven years later, in his classic work, 'Ueber das Morphium, eine neue salzfähige Grundlage, und das

Mekonsäure, als Hauptbestandtheile des Opiums," that he could write with perfect confidence as to the morphium possessing the character of a base. For his further examination of it had shown that in addition to possessing a well-marked alkaline reaction it was capable of uniting with acids to form salts. He even hazarded the opinion that in many respects it was closely related to ammonia, an opinion the correctness of which has since been amply verified, not only for morphia but for all other alkaloids.

The discovery of morphia, and the observation that it possessed the action of opium in a highly concentrated form, most naturally suggested to the minds of chemists and physicians the probability of other vegetable drugs besides opium containing an alkaloidal principle, to whose presence the activity of the drug was to be ascribed. The better known of the toxic and medicinal plants were accordingly, one after another, submitted to chemical analysis, and not without much persevering and ingenious labour were their active principles brought to light. The discovery of strychnine, brucine, quinine and cinchonine by Pelletier and his associate Caventou, of narcotine and codeine by Robiquet, of veratrine by Meissner, of caffeine by Runge, of coniine by Giesecke, of atropine by Mein, of nicotine by Reimann and Posselt, and of aconitine and hyoscyamine by Geiger and Hesse, and of several other less important alkaloids, followed in rapid succession within the sixteen years subsequent to the publication of Sertürner's completed work. Since then, almost every year has furnished its quota of separated alkaloids until at the present day their number is beyond being readily computed, and the chemistry of the alkaloids now claims for itself almost a special department in the broad and ever extending domain of organic chemistry. But, numerous as are the alkaloids which have already been separated and the plants that have been analysed for their presence, there yet remain many plants of considerable toxic activity, and presumably of some medicinal value, whose active principles have not yet been determined. Travellers and explorers, but more particularly our colonists, are bringing year after year such plants to our knowledge. And not only in newly discovered drugs is there much room for future chemical research, but even in the very drugs which have been longest known and are most used the labours of the chemist in his search for their active principles have not yet been brought to a close. For earlier investigators have sometimes failed to separate the principles in a perfectly pure state, or in certain cases to recognize that the product obtained was a mixture of various alkaloids, necessitating the separation of the one alkaloid from the other; and in other cases the drug is so rich in alkaloids, as, for example, opium, that chemists are by no means certain, when now and again we hear of the discovery of an additional alkaloid, that all the alkaloids which the drug actually contains have as yet been recognized and separated. It is not by any means Utopian to expect that the time is not far distant when our present organic materia medica, in so far as it consists of substances of highly complex and of very variable and in some instances of unknown composition, will give place to bodies with constant characters and a definite chemical constitution, the nature and extent of whose activity is to be relied upon with the greatest exactitude. We all of us can do a little to help towards the attainment of this most desirable end; and it is because I think that all of you, as chemists, would find it both pleasurable and profitable to be engaged in so laudable a work, that I have chosen in quite a general manner to place before you, for the instruction more particularly of the younger members of your Society, an outline of the processes most commonly employed for the separation of these basic bodies which are destined to occupy a very important position in a pure organic materia medica such as I speak of. This instruction might have been unnecessary, were a description of such methods to be obtained from any of our ordinary text-books, or from other readily accessible works; indeed they are in great part to be met with only in original and separate memoirs.

The method used for the separation of each alkaloid, it is true, is fully stated in most works on materia medica; but the operations required in the one case differ so widely in appearance from those required in the next, that, in the event of your meditating the separation of an unknown alkaloid you are quite at a loss which of the various methods to adopt; and the probability is, even did you select one of the methods given, that it is so specially adapted for the particular alkaloid which it is designed to separate that it may absolutely fail when applied to the drug you are investigating. And here lies the difficulty in the task I have assigned to myself. For to provide you with a method, or methods, absolutely comprehensive in application, is, and probably always will be, practically an impossibility. Some alkaloids are so erratic in their chemical deportment that specially devised methods are necessary for their separation. I have not, however, permitted this consideration to deter me from presenting to you the principles which in all cases should guide us, and from detailing a few of the methods of most general application, in the search for an unknown alkaloid.

CHARACTERS OF ALKALOIDS.—In order that we may clearly understand these general principles and the methods based on them, it is necessary that we first consider the characters of the alkaloids. They are all of them nitrogenous organic bases; and, although the name "alkaloid" is usually applied only to such bases obtainable from plants, yet they do not differ materially from other nitrogenous organic bases which have been artificially prepared in large number during recent years, as ethylamine, aniline, pyridine and picoline; nor from the similarly constituted bodies which are met with in animals, as choline and kreatine, and the recently discovered bases of dead bodies, the so-called ptomaines. Until lately, one distinction between the artificial bases and the natural bases or alkaloids was, that the latter, in addition to possessing a more powerful and more subtle physiological action, were incapable of being prepared artificially. This distinction has failed us since Hugo Schiff, in 1870, prepared coniine synthetically from butylaldehyde, and Schmiedeberg and Harnack, six years later, obtained muscarine by the oxidation of hydroxylentrimethylammonium (neurine), and Ladenburg has all but accomplished the synthesis of atropine. The alkaloids are not, therefore, to be chemically distinguished from other nitrogenous organic bases, although the exact constitution or intra-molecular arrangement is known for only a very few of them. Much work has been done in order to determine the constitution of alkaloids, and the conclusions arrived at all agree in this, that the alkaloids are to be regarded as substitution or other products of ammonia. For our present purpose it is unnecessary to consider more fully their constitution, except to remind you of the elementary fact that, whilst the alkaloids, as a rule, contain oxygen in addition to carbon, hydrogen and nitrogen, yet a very few of them are non-oxygenated. With the exception of the latter, which are few in number, and the more volatile of which are coniine, nicotine, sparteine, and the recently discovered piturine, all the known alkaloids are solid and, unless under special circumstances, non-volatile bodies. The oxygen-free alkaloids are, on the other hand, volatile liquids, a character, which by enabling us to adopt the method of distillation, renders their separation a matter of easy accomplishment. The solid alkaloids are generally colour-less, odourless, bitter to the taste, and, in most cases, crystallizable.

Solvents.—A knowledge of their relation to solvents is of the greatest importance in their separation. With a few exceptions (colchicine, curarine), they are either insoluble or difficultly soluble in water. In alcohol they are almost without exception, and, in most cases, tolerably freely, soluble. Ether is for many alkaloids the most active solvent we possess, but there are others which it hardly at all acts on (cinchonine, morphine, strychnine). Amylic alcohol is a very general and very capable solvent, and so also are chloroform, benzol, acetic ether and petroleum ether, although there are a very few alkaloids which are not acted on by these solvents. In fatty oils they are soluble only to a very small extent, but with the help of oleic acid they can be mixed in nearly every proportion with oils, a fact of pharmaceutical value. The solutions of the alkaloids in the various menstrua have generally a strong alkaline reaction, but in certain cases (*e. g.*, colchicine, narcotine), the reaction is extremely feeble.

Chemical relations.—Besides the action of solvents on the alkaloids, it is not of less importance, before we proceed to undertake the separation of an alkaloid, to know something of the chemical relations of the alkaloids, and more particularly of their behaviour towards acids. They comport themselves very like ammonia in most of their combinations with acids—for being bases they readily unite with acids to form salts—but, unlike ammonia, do not, as a rule, form salts with carbonic acid. If an alkaline carbonate be added to a solution of the salt of an alkaloid, the alkaloid is liberated, and carbonic acid evolved. This fact is of importance, because it enables us, when we so desire it, to set free the alkaloids by means of an alkaline carbonate, instead of employing the alkali itself, which, as in the case of atropia, may decompose the liberated base.

The salts formed with the mineral acids, as with sulphuric, hydrochloric, and nitric acids, and with the more simple of the organic acids, as acetic, tartaric, citric, oxalic, and malic acids, are highly crystalline, and are, as a rule, freely soluble in water, and still more soluble in alcohol. On the contrary, in ether, acetic ether, chloroform, amyl alcohol, benzol, and petroleum ether, they are, for the most part, completely, or almost completely, insoluble. In those cases where the alkaloid *e. g.*, quinine) unites with the acid in more than one proportion, the salt containing the highest proportion of acid is, as a rule, much the most soluble. Ammonia and the alkaline bases and the alkaline earths liberate the alkaloid from its combinations with acids, and the alkaloid, if insoluble in water, is precipitated; but this precipitation may be prevented if excess of the alkali be used, as several of the alkaloids (*e. g.*, morphine) are soluble in excess of alkali, whilst all of them, with only one or two exceptions, are soluble in excess of ammonia.

It is of great service in the separation of the alkaloids that they practically, without exception, form insoluble salts with tannic acid, picric acid, the double iodide of potassium and mercury, the double iodide of potassium and cadmium, the double iodide of potassium and bismuth, iodine dissolved in iodide of potassium or in alcohol, phospho-molybdic acid, metawolframic acid, phospho-wolframic acid, and with a mixture of chloride of antimony and phosphoric acid. Further, with the double cyanide of potassium and platinum, with the chlorides of gold, platinum, iridium, palladium, and mercury, and with nitro-prusside of sodium, nearly all the alkaloids form more or less insoluble salts.

Decomposition.—It is important also to remember that the alkaloids are not, as a rule, very stable bodies, so that when exposed in solution to the sunlight many of them undergo gradual decomposition. Similar and other decompositions of alkaloids are more readily effected if a solution of an alkaloid is boiled for some time or is kept for too long a period at a high temperature, as is apt to occur whilst evaporating the various extracts in the processes sometimes employed for the separation of the alkaloid. Decomposition is still more liable to occur if the alkaloid be heated along with dilute mineral acids, as with hydrochloric acid; and in some instances the decomposition results in the formation of a new alkaloid more or less different in its properties and action from the original alkaloid. Solanidine is such a decomposition product of solanine, ecgonine of cocaine, tropine of atropine or hyoscyamine. In the presence of nitric acid decomposition usually occurs to a still greater extent, resulting often in the formation of reddish resinoid substances. The oxidizing action of nitric acid may exhibit itself in the production of well-characterized oxidation bodies, as cinchonic acid from cinchonine, and nicotic acid from nicotine.

Similarly, if a solution of an alkaloid be heated for some time in the presence of an alkali, the alkaloid is apt to undergo decomposition, forming in many cases methyl-, dimethyl- and trimethylamine, and bases belonging to the pyridine and chinoline series. A few alkaloids, as atropine, are very readily decomposed in contact with alkalies even without the application of heat, so that in the course of their separation the use of free alkali, and, especially, prolonged contact of the alkaloid with the alkali, is as far as possible to be avoided.

SEPARATION OF ALKALOIDS.—Without being intelligently acquainted with these various physical and chemical qualities of alkaloids it is impossible that any one can competently undertake their separation. And it is based almost entirely upon the qualities I have briefly sketched, especially upon the relation of the alkaloids to solvents and precipitants, that the various methods for the separation of alkaloids have been devised.

Assuming that we are all more or less familiar with these characters of alkaloids, let us proceed to inquire in as plain and as practical a manner as is consistent with accuracy how we are to set about the separation of an unknown alkaloid. A plant is brought to us with reputed toxic powers, and we are desirous of isolating the alkaloid to which we suppose that the activity of the plant is due. We are not at once to assume that because the plant possesses a considerable degree of activity that its active principle is necessarily an alkaloid. It may belong to that important class of active principles, whose exact chemical constitution and position, with the exception of the glucosides, is so little understood that they are known by the very negative name of "neutral" principles. These bodies behave in relation to the various solvents I have already enumerated much in the same manner as alkaloids, and are often thus to be obtained by such methods employed for the separation of alkaloids as do not involve the use of precipitants. The activity of the plant may reside in a resin, as is the case with several plants possessing a cathartic action (*e.g.*, podophyllum), in a volatile oil (as in copaifera), or in a fixed oil (as in ricinus), or in some other constituent of the plant possessing no alkaloidal characters whatever. It is almost impossible to predict from the nature of the action of the plant whether its activity is dependent on the presence of an alkaloid or upon some other of the constituents. But as a rough guide in the expectation of the presence of one or other kind of active principle, it may be remembered that all poisonous plants which primarily act on the nervous system, producing tetanus, paralysis, or narcotism, generally possess alkaloids as their active principles. On the other hand, if the action of the plant is primarily on the muscular system, as, for example, the large class of plants possessing the action of digitalis, then expect to find a neutral principle. It is a rule without exception that all pure simple bitter tonic plants possess as their active ingredient, likewise, a neutral principle. Further, if the action of the plant be cathartic, emetic, or purely astringent, then again there is probably no alkaloid present, but merely a neutral principle, or, perhaps, a resin.

If, from a consideration of these and other points, we become tolerably assured of the presence of an alkaloid, we can the more confidently proceed to lay down our plans for its separation. It is always advisable, before beginning what may prove a long and tedious analysis of some imperfectly known plant, to ensure, by the administration of a small quantity of it to one of the lower animals—afrog, a rabbit, a cat, or a dog—that the specimen of the plant or drug about to be examined really possesses the action ascribed to it. There is another reason why it is desirable to make one, and, it may be, several such preliminary experiments, and it is, that we render ourselves familiar with the nature of the action of the plant, and therefore with that of the alkaloid we desire to separate; and, accordingly, by making a similar experiment with our successive extracts, solutions or precipitates, we are enabled readily to ascertain in which of them the alkaloid is present. This form of physiological testing is most conveniently made with frogs, and best by subcutaneous injection; but, unfortunately, under the Vivisection Act we are not permitted to practise even so small an operation as a subcutaneous injection without a licence from the Home Office, which is not always easily obtainable.

Preliminary Extraction.—This experiment having been made, and having selected for that purpose the portion of the plant (seed, bark, root, etc.) which we believe, or may have proved, to contain the active principle, we take for our analysis the same portion of the plant, and begin by having it well comminuted or pulverized.

Now let us consider for a moment in what chemical form or combination the alkaloid exists in the plant or in the powder, and what is the nature of the substances with which it is mixed and from which it is to be separated. The alkaloid never exists in the plant in the free state but is invariably combined in the form of a salt, and oftentimes as an acid salt, with one or other of the organic acids which are found so generally in plants, particularly malic acid and the varieties of tannic acid. Sometimes the acid with which it is combined is, like the alkaloid, peculiar to the plant in which it is found, as meconic acid in opium, quinic acid in cinchona; and occasionally the acid may be even inorganic, as, for example, the sulphuric acid with which some of the opium bases appear to be united. To whatever acid the alkaloid may be joined it almost invariably forms a salt which is readily soluble in water or in alcohol, and which therefore can be extracted by either of these menstrua.

The various substances with which the alkaloidal salt is mixed is dependent, of course, upon the nature of the plant, and may be thus arranged, and at the same time their solubility in the three most common menstrua represented:—

	WATER.	ALCOHOL.	ETHER.
Cellulose . . .	insol.	insol.	insol.
Starch	insol. in cold. sol. in hot.	insol.	insol.
Gums and pectose.	sol.	partly sol.	insol.
Sugars	sol.	sol.	insol.
Fixed oils . . .	insol.	partly sol.	sol.
Volatile oils . .	slightly sol.	sol.	sol.
Resins	insol.	partly sol.	partly sol.
Albuminoids, incl. mucus. . . .	sol.	insol.	insol.
Neutral principles.	partly sol.	partly sol.	partly sol.
Colouring matters.	sol.	sol.	partly sol.
Organic acids and salts	sol.	sol.	partly sol.
Other organic matter	partly sol.	partly sol.	partly sol.
Inorganic salts .	mostly sol.	mostly insol.	insol.

It can be perceived at a glance what portions of the plant, in addition to the alkaloidal salt, are likely to be met with in extracts made with water, alcohol, or ether.

Continuing the examination of our plant, we now make choice of what solvent or menstruum will most readily dissolve the alkaloidal salt out of the plant, and at the same time carry into solution as few and as little as possible of the other constituents of the plant. Were the natural alkaloidal salt freely soluble in ether, which it is not, and did the ether penetrate readily the particles of the pulverized drug, we would feel inclined on account of its dissolving so few of the other vegetable substances to adopt it as an extractive solvent. As, however, a perfect extraction of the alkaloid is the primary object, we commonly find it advisable to use water or alcohol in preference to ether. Pure hot water is in nearly every case the best extractive solvent, and, after the plant has been repeatedly exhausted with water, the solvent power of the water in the final extraction may be increased by the addition of a small quantity of sulphuric acid or of tartaric acid. Even when alcohol is used it is sometimes advantageous to add a little acid. But on the whole it is advisable to use as little acid as possible. It is well not to employ too large a bulk of the solvent, for it may necessitate prolonged evaporation in order to remove a portion of the alcohol or the water at a later stage of the process. The extraction may be made by mixing the powdered plant with three or four successive portions of the solvent and allowing each mixture to stand for some hours, then draining and pressing; or the extraction may be made with the help of a percolator, particularly if the drug at our disposal is small in quantity or if alcohol is employed as the solvent.

METHODS FOR SEPARATION OF ALKALOID.—We have now obtained a fluid extract of the plant, either watery or alcoholic, and its treatment for the separation of the alkaloid may take one of two different directions. We may endeavour to separate the alkaloid by precipitating it in the form of an insoluble salt, or we may remove it from the extract by means of solvents. The former method yields, as a rule, better results than the latter in respect of the purity of the product, although it is not generally so well adapted for the separation and detection of small quantities of alkaloids in chemico-legal investigations, where often the absolute purity of the product is of less account, provided it satisfies the tests and possesses the physiological action of the alkaloid sought for. As the more important for our purpose let us first consider in what manner the method by precipitation is to be followed.

A. METHODS BY PRECIPITATION.—*Purification of Extract.*—The watery extract (or the alcoholic extract deprived of its alcohol by evaporation and the residue exhausted with water) if it has been prepared from a portion of the plant, as, for example, certain woods and barks, which yields to the water not much else than extractive matter besides the alkaloidal salt, may at once be treated with the precipitant; and this is also in many cases the course pursued if the alkaloid is present in large quantity, and can, on account of its insolubility in water, be precipitated in an uncombined form by the addition of an alkali (*e.g.*, morphine). If, on the other hand, the precipitation of the alkaloid, on account of the solubility of the alkaloid in water, or its presence in small quantity, requires the use of some of the more complex but more effective reagents, as phospho-molybdic acid or the double iodide of potassium and mercury, it is always necessary to previously remove from the extract as much of its inert organic matter as possible. For this purpose nothing surpasses a combination of basic acetate of lead and of ammonia. The basic acetate can of itself form insoluble precipitates with most of the organic acids, as malic acid; with many glucosides, as tannin, and with all albuminoids, starches, and gums. It can also very effectually remove the colouring matter; but the presence of free ammonia is essential to its completely precipitating dextrine and the various sugars. The ammonia may be added either immediately after the addition of the basic acetate of lead without previous filtration; or the precipitated lead compounds may be first removed by draining or filtration, and the ammonia mixed with the filtrate which should contain an excess of the basic acetate. The ammonia is added until the fluid, after stirring, begins to smell distinctly of ammonia. No alkaloid is known to be precipitated by basic acetate of lead and ammonia. The fluid having been again filtered is now evaporated at a moderate heat over the water-bath to drive off the excess of ammonia and to diminish the bulk of the fluid, which may with advantage be reduced until the fluid becomes of a syrupy consistence, so that the ammonia may be almost completely removed. The partially evaporated fluid is, if syrupy, diluted with some water, and now treated with dilute sulphuric acid in sufficient quantity to precipitate all the lead in the form of the insoluble sulphate of lead, and the fluid is once more filtered. The fluid will generally at this stage be found pure enough to permit of the precipitation of the alkaloid by means of any form of precipitant. If it is still highly coloured and evidently contains a large proportion of extraneous organic matter, the process of precipitation with the basic acetate of lead and with ammonia may be repeated; but, generally, this is not needed.

Precipitants.—The stage has now been reached when we must select an alkaloidal precipitant. If the alkaloid be insoluble in water, a solution of any one of the alkalies or alkaline carbonates, or of the alkaline earths, will prove the most ready and effectual precipitant. But if, as it oftener occurs, the alkaloid is soluble to some extent in water—and, indeed, in most cases, whether soluble or not—we must resort to the use of some of those acids or salts, which have already been mentioned as forming insoluble precipitates with practically every alkaloid. These precipitants may be divided into four classes :—

(1.) Some *simple organic acids*, as tannic acid (Berzelius) and picric acid (Hager).

(2.) Some *compound inorganic acids*, as phospho-wolframic acid (Scheibler), phospho-molybdic acid (De Vrij, Sonnenschein), and phospho-antimonic acid (Schulze).

(3.) The *chlorides of the heavier metals*, as those of platinum (Dragendorff), gold, iridium, and palladium (V. Planta).

(4.) Certain *double metallic iodides*, as those of potassium and mercury (V. Planta, Mayer), potassium and bismuth (Dragendorff), and potassium and cadmium (Marmé).

The cost of the third group precludes their general use, but each of the precipitants of the other groups has its advocates. The best of them are probably phospho-wolframic acid, phospho-molybdic acid, the double iodide of potassium and mercury, the double iodide of potassium and bismuth, and tannic acid.

Precipitation.—Each of these precipitants, except the last, acts best in the presence of dilute mineral acid ; and the acid most commonly used is sulphuric, which, it so happens, is present in excess in the extract, on account of its having been used to remove the lead. Tannic acid must be added in a neutral or faintly acid solution, and sometimes, owing to the acid which is being set free from the precipitated alkaloid being large in amount and rendering the fluid too acid, a little alkali or alkaline carbonate may require to be added before complete precipitation can be secured. In the use of the other precipitants, no precaution is, as a rule, necessary, unless it is to take care that the fluid has a well-marked acid reaction, and that previous to filtering the fluid is allowed to stand for a day or so, in order to ensure the complete precipitation of the alkaloidal compound. It is important, as Schmiedeberg has remarked for the double iodide of potassium and mercury, that the solutions of the double iodides do not contain any more iodide of potassium than is sufficient for the solution of the heavier iodide, otherwise the excess of the iodide of potassium may, in certain cases, dissolve the alkaloidal precipitate. To avoid this, the solution should be made by adding excess of the heavier iodide to a solution of the iodide of the alkali, allowing the latter to dissolve as much of the former as it can, then filtering, to remove the undissolved iodide, and observing that the filtrate does not give a precipitate on dilution; if it does, dilute and again filter. The alkaloidal precipitate obtained by the use of tannic acid, or of one of the composite organic acids, or of one of the double iodides, is now separated by filtration. The tannic acid precipitate may be washed with a little water; the others must be washed with dilute sulphuric acid, as water alone is apt to decompose and dissolve them. The precipitate is then dried in the usual way by pressure between several folds of filter paper, and is transferred to a beaker and mixed with a little water.

Liberation of Alkaloid from Precipitate.—The means necessary for the liberation of the alkaloid from its insoluble salt varies with the nature of the precipitant, but is the same for the members of each of the different kinds or groups of precipitants; that is, there is one method to be followed in the treatment of the precipitate with tannin, another for all the precipitates with the double iodides, and a third for all those with the composite acids.

a. From Tannic Acid Precipitate.—The treatment of the precipitate with tannic acid is simple, and consists in gently digesting it for some time with moist and freshly precipitated oxide of lead, until a portion of the supernatant fluid or filtrate is no longer darkened by the addition of ferric chloride. If the alkaloid which has been set free is soluble in water, then it will all be contained in the filtrate, from which any trace of lead is removed by passing sulphuretted hydrogen through it, and again filtering. The filtrate, if gently heated for a short time over the water-bath, will have the excess of sulphuretted hydrogen readily dissipated. By continued slow evaporation, crystals of the alkaloid may be got; or it may be exactly neutralized with a dilute mineral acid, and a crystalline salt obtained by evaporation. The further steps necessary for the perfect purification of the alkaloid or of its salt, I shall immediately come to.

If the liberated alkaloid be insoluble, it remains mixed with the precipitated tannate of lead, and with the excess of lead oxide, and requires to be extracted with alcohol. The alcoholic extract is evaporated almost to dryness and dissolved in dilute sulphuric acid, any trace of lead remaining undissolved as sulphate of lead. The acid solution of the sulphate of the alkaloid is then treated with carbonate of barium to remove the acid, but of course at the expense of the precipitation of the alkaloid (as the carbonates of the alkalies or alkaline earths behave as bases towards solutions of alkaloidal salts). The mixture is filtered, and the alkaloid once more extracted with alcohol. Slow evaporation of the alcohol will, under favourable circumstances, yield crystals of the alkaloid.

b. From Double Iodide Precipitate.—If one of the double iodides has been employed for the original precipitation of the alkaloid, then the precipitate, which is a double iodide of the alkaloid and the heavier metal, requires a different process for the recovery of the alkaloid. It is mixed with a little water and with an equal volume of the moist hydrated oxide of barium, and a stream of sulphuretted hydrogen gas is passed through the mixture until the fluid, after being shaken, smells strongly of the gas, when the double iodide will have become completely decomposed, forming an insoluble sulphide of the heavy metal—mercury, bismuth or cadmium, as the case may be—the alkaloid being dissolved in the form of the simple iodide. The previous addition of the baryta facilitates the decomposing action of the sulphuretted hydrogen. The fluid is filtered to remove the insoluble sulphide, and the filtrate which contains the iodide of the alkaloid, and the iodide and the sulphide of barium, is treated with excess, either of moist and freshly prepared oxide of lead, or of sulphate of silver. The latter precipitates the hydriodic acid in the form of iodide of silver, the sulphuretted hydrogen in the form of sulphide of silver, and the barium as sulphate of barium, and leaves the alkaloid in the form of a soluble sulphate; whereas, the oxide of lead, whilst it precipitates with equal effectiveness the hydriodic acid and the sulphuretted hydrogen, and the barium as oxide of barium, yet it sets free the alkaloid in an uncombined state; and if the alkaloid be insoluble in water, it remains mixed with the precipitates.

Where the sulphate of silver has been employed, the filtrate, after the addition of this reagent, contains the unused excess of the reagent as well as the sulphate of the alkaloid. To remove the silver, the fluid is treated with an excess of barium hydrate, and sulphate of barium and oxide of silver are formed and the alkaloid is liberated, which, according as it is soluble or insoluble in water, is dissolved in the filtrate or remains precipitated with the barium and the silver. If it is dissolved in the filtrate, the small excess of barium hydrate is removed by a stream of carbonic acid gas, and the barium carbonate is then got rid of by filtration, and the filtrate gently evaporated, when the alkaloid will be obtained. If the alkaloid is insoluble in water and remains mixed with the precipitates, then, after filtration, the residue is exhausted with alcohol, and the alcoholic solution treated in the same manner as that obtained from the tannate of lead in the previous process.

If oxide of lead has been used for the precipitation of the iodine, it is advisable to previously render the fluid slightly acid with sulphuric acid, so as to precipitate the barium as sulphate of barium. The oxide should then be digested with the fluid, until the fluid has an alkaline reaction. The precipitate from the oxide of lead may, as already mentioned, contain the alkaloid, if it be insoluble. If it be soluble, it will be met with in the filtrate, which, in order to deprive it entirely of its lead, is treated with a little sulphuretted hydrogen and again filtered. The filtrate then requires the same treatment, in order to isolate the alkaloid, as was described in connection with the filtrate obtained at the same stage of the tannin method. The alkaloid if insoluble in water is also obtained from the mixed precipitate in the same manner as previously described.

c. From Precipitate with Composite Inorganic Acid.—The process required for the separation of the alkaloid from its precipitate with the composite inorganic acids is simpler than the preceding; and to that extent is one or other of these acids to be preferred for the precipitation of the alkaloid. The precipitate, after being pressed, is thoroughly mixed by frequent stirring with a little water and more than an equal volume of pure barium hydrate, until it is completely decomposed, which is readily indicated by the excess of the dissolved barium hydrate forming with the carbonic acid of the atmosphere an insoluble scum of carbonate on the surface of the fluid. The mixture is now filtered, and the alkaloid, if it be soluble in water, passes through in the filtrate mixed only with a little barium hydrate, which can be readily removed by precipitation with a stream of carbonic acid gas. The filtrate on gentle evaporation will yield the alkaloid; or, if it be previously neutralized with dilute sulphuric acid, or other simple acid, crystals of a salt of the alkaloid may be obtained. If the alkaloid be insoluble in water, it remains mixed with the insoluble wolframate of barium and with the excess of baryta, and can be removed by alcohol, and the alcoholic solution treated in the usual way.

Purification of Alkaloid.—By these various methods of precipitation it is possible to obtain, and in the manner described, a tolerably pure alkaloidal product. For its more complete purification it is sometimes necessary to make a solution of it in water and a little acid, and to repeat the process of precipitation and isolation; and, whether it be reprecipitated or not, if it possesses a tinge of colour it is often advantageous to treat its solution in water or in alcohol, or the solution of its salt in one of these menstrua, with pure animal charcoal, remembering that the charcoal is apt to remove a portion of the alkaloid, which can, however, be re-obtained by treating the charcoal with boiling alcohol. Also, repeated crystallization of the alkaloid or its salt from a solution in alcohol or in water may be required to furnish a perfectly pure product. The *technique* of the methods employed for this purpose is quite familiar in every department of chemistry, and, therefore, requires no further mention.

When it is desired to procure a very pure salt of the alkaloid of definite composition and of good crystalline form for the purpose of an elementary analysis, the double salt obtained by the addition of chloride of platinum or chloride of gold to a solution of the alkaloid, will generally be found to best meet the requirements.

These, then, are, shortly stated, the most reliable methods for the separation of the alkaloid by precipitation, and important modifications may be necessitated in each individual practical application of the methods, which can only be suggested in the course of the analytical investigation. For example, other solvents than alcohol may be required for the extraction of the alkaloid from the mixed precipitates, and it is an easy matter to try one after another until the most efficient is obtained.

Separation of Volatile Alkaloids.—I have described these methods as if the alkaloid were non-volatile, which in the great majority of instances it is; but there are exceptions, as I formerly mentioned. In such cases the separation of the alkaloid is generally most easily accomplished, often even without making a preliminary extract with alcohol or water, merely by mixing the drug with a little water and alkali or alkaline earth, and distilling, neutralizing the distillate, and again distilling to remove other volatile substances, the alkaloid remaining in the retort in the form of a non-volatile salt. This can be dissolved in water or alcohol and purified by crystallization, etc., in the usual way, and a perfectly pure alkaloid obtained from the salt by a final distillation with an alkali. The presence of a volatile alkaloid is generally to be perceived by its odour at that stage of the operations required for the separation of an alkaloid by precipitation, where oxide of lead or barium hydrate is being employed for the decomposition of the precipitated compound of the alkaloid, on the alkaloid being set free. If so, it is advisable to add excess of barium oxide and distil. A tolerably pure alkaloid will in this manner be obtained.

B. METHODS BY SOLUTION.—The other series of methods for the separation of alkaloids, and which mainly involves the use of solvents without precipitants, is that which, as I have already mentioned, is in one form or other most frequently employed for the medico-legal isolation of alkaloids. They were formerly the only methods used, but at the present time the precipitation methods are considered more serviceable in pharmaceutical research. These methods mainly depend on the following facts :—(1) When an acid solution of the alkaloid is shaken with ether, chloroform, amylic alcohol, benzol, acetic ether or petroleum ether, the alkaloid is not removed by these solvents; but, (2) when the solution is alkaline, the alkaloid is readily taken up by one or other of these solvents. In short, these methods rely on the solubility of the free alkaloid, and the insolubility of its salts, in certain menstrua which are non-miscible with water.

Purification of Extract.—When it is desired to separate an alkaloid by means of solvents, an extract of the plant is made with acidulated water or alcohol exactly as when precipitants are intended to be employed. The watery extract, which is the more preferable, is neutralized with carbonate of soda, and cautiously evaporated almost to dryness, and the residue is treated with acidulated absolute alcohol, which dissolves the alkaloid and leaves some albuminous and other matter. The filtrate is again neutralized with carbonate of soda and evaporated to dryness, and the residue dissolved in water. It is always strongly advisable never to evaporate fluids containing alkaloids without previously neutralizing them, otherwise the alkaloids are very prone to suffer decomposition.

Separation of Alkaloid.—The aqueous solution is now rendered acid with a little sulphuric acid or other simple acid, and is well shaken with successive portions of ether to remove fats and resins, and the ether poured off. The ether, as a rule, in the presence of acid dissolves none of the alkaloid; but there are one or two exceptions where a small portion of the alkaloidal salt is removed by the ether. If any of the alkaloid should chance to be thus removed, evaporate the ether and treat the residue with water: the watery extract will contain the alkaloid.

But, if, as almost invariably happens, the ether has removed none of the alkaloid, the acidified aqueous solution is now rendered alkaline by means of carbonate of soda or a little caustic soda, and is again well shaken with successive quantities of ether, which, in the great majority of cases, will completely dissolve out the alkaloid. Should the alkaloid prove to be insoluble in ether, it is necessary after pouring off the ether to neutralize the aqueous fluid and heat to drive off the ether, and again render it alkaline, and shake it with another of the alkaloidal solvents enumerated, as chloroform, or amylic alcohol, or benzol, or with a succession of them. The ethereal or other solution of the alkaloid, in order to purify it, is then shaken with an equal volume of slightly alkaline water. Sometimes, to ensure a still greater degree of purity, the ethereal or other solution is next shaken with water containing a little sulphuric or hydrochloric acid, which transfers the alkaloid to the water, and this may now be shaken with successive portions of pure ether, or whatever solvent has been previously used, to completely remove from it all substances soluble in the ethereal menstruum in the presence of acid. On adding an alkali or alkaline carbonate to the water, it readily gives up the alkaloid to a fresh portion of the ethereal solvent when shaken with it. Evaporation of this purified ethereal solution will generally yield the alkaloid in a tolerably pure condition. For its further purification, digestion with charcoal and crystallization of the alkaloid or its salts from their solution in water or alcohol may be necessary.

This is merely an illustrative outline of a process embodying the principles involved in the method of separating alkaloids by means of solvents. As this method is very largely employed in medico-legal investigations, several more detailed descriptions of processes will be found in the numerous works on toxicology (Husemann, Otto, Dragendorff, Taylor, etc.). Of these, the process or method of Stas, as improved by Otto, is the oldest and the best known, and, perhaps, still the most frequently employed. In it ether and amylic alcohol are successively employed as solvents. The method of Erdmann and Uslar, in which amylic alcohol is the main solvent employed, has been also favourably received. Dragendorff's method is, perhaps, of all the most thorough, and involves the use of nearly all the important alkaloidal solvents.

SEPARATION OF ALKALOIDS FROM ONE ANOTHER. —In the processes which I have described as being used for the separation of alkaloids, I have nearly always spoken as if but one alkaloid were to be met with in each plant. But, as a matter of fact, many plants, perhaps, it will be eventually found, most toxic plants, contain more than one alkaloid. The product obtained by the methods described may, therefore, consist of a mixture of alkaloids. If so, the alkaloids are to be separated from each other by taking advantage of the differences in the degree of the solubility of themselves or their salts in the various solvents mentioned, water included.

RECOGNITION OF ALKALOID.—When once the substance is supposed to have been isolated in a pure form, it is necessary to make certain that it is in reality alkaloidal. If it be an alkaloid or alkaloidal salt it will when heated to redness, like all organic matter, completely burn away. Mixed and heated with soda-lime (a mixture of caustic soda and lime) it will, unlike neutral active principles and other nitrogen-free organic substances, evolve the odour of ammonia. Further, a solution of the alkaloid or of its soluble salts, will give a precipitate with nearly all the substances already mentioned as generally forming insoluble salts with alkaloids. The physiological action of the separated product will also sometimes be of help in determining whether it is alkaloidal or not. One must guard against mistaking a salt of ammonia for a salt of an alkaloid, as the former behaves chemically in many respects quite like an alkaloid.

CONCLUSION.—These, then, are, briefly stated, the various processes or methods employed for the separation of alkaloids. It is impossible in the present state of our knowledge to lay down any single general method which will suffice for the separation of every alkaloid. It will therefore rest with each chemist to choose the method that may appear to him the most suitable for the plant he is about to examine, and to use his own discretion and ingenuity in modifying it when necessary. It has been mainly my aim in the present communication to lay before you the general principles which guide us in the separation of alkaloids.

In conclusion, allow me to say that, whilst only a few of you may have the opportunity of discovering an unknown alkaloid, yet many of you may be able to improve and cheapen the processes by which we at present obtain known alkaloids. Pure alkaloids of definite composition, and, therefore, of unvarying action, are what the therapeutist requires; and the chemist who can furnish him with these, and by the readiest and cheapest methods, benefits both therapeutics and pharmacy as much as he who brings to light a new alkaloid. For all new alkaloids are not of value medicinally.

To those who are proficient scientific chemists, and who devote themselves in great part to pharmaceutical research, there lies open the almost untrodden field of the artificial production of both known and unknown alkaloids. The syntheses of Schiff and Schmiedeberg cannot surely remain long unadded to. The capability of the artificial formation of all alkaloids is in the highest degree probable. And what synthetical chemistry is now in certain instances doing for the arts, we are all hopeful, and even confident, it will soon accomplish for the materia medica.

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