ISOLATION AND PURIFICATION OF ALKALOIDS

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A literature review is given of methods of isolating and purifying alkaloids. Material is collected on the influence of the nature of the solvent on the isolation of alkaloids and on the interaction of alkaloids with acids and **alkalis.**

The high biological activity of alkaloids gives these compounds a special position among classes of natural substances. In the State Pharmacopoeia 11% of the total number of papers is devoted to alkaloid preparations and medicinal forms of them [1].

At the present time, more than a hundred alkaloids have been introduced into medical practice [2, 3].

The great diversity of the alkaloids with respect to structure and properties is responsible for a selection of methods for their isolation and purification. There are several publications in which technological methods of obtaining alkaloids are discussed [4-6].

In the present paper the advances of recent years in the field of the production and technology of manufacturing alkaloids are generalized.

METHODS OF ISOLATING ALKALOIDS

The principal scheme for the isolation of alkaloids, taking their individual characteristics into account, is based on the following steps: extraction of the plant raw material, separation of the total alkaloids from other extractive substances, separation of the alkaloids, and purification of the individual compounds. Alkaloids are distributed nonuniformally over the organs of plants: at the end of the vegetation period they accumulate in the overwintering parts, such as the root system, seeds, and bark, and at the beginning of the vegetation period they pass from the roots, seeds, and bark into the shoots and then also into the leaves. At the same time, the alkaloid composition also changes [7, 8], depending on the site and time of collection, the weather conditions, and the methods of drying the plant material. It is not recommended that some types of raw material, such as autumn crocus corms, should be subjected to drying, since the amount of active substances falls as the result of thermal treatment [9, 10]. In this case, for further working up it is preferable to use the juice from the fresh corms. In the production of pilocarpine only freshly dried leaves of *Pilocarpus* are used, since the amount of this alkaloid rapidly decreases on storage [11].

A feature of natural mixtures is the low content of active components in the plant raw material, only a few compounds being present in amounts greater than 1% (glaucine, berberine, hindarine). A technology of obtaining the antitumoral drugs vinblastine and vincristine has been developed that uses a raw material containing them in amounts not exceeding a few hundredths and ten-thousandths of a percentage part [12-14].

An important factor making an impression on the technological scheme of isolation is the multicomponent nature of the natural mixtures. For example, the total alkaloids of *Catharanthus roseus* contain about 90 compounds. With an increase in the molecular mass of the substances the differences in the physicochemical properties of the individual representatives become insignificant, which complicates the separation of such mixtures, particularly under factory conditions. Separation can be achieved by the combined use of known methods: extraction, countercurrent distribution, crystallization, separation according to basicity, the formation of crystalline derivatives, chromatography (absorption, liquid, gas-liquid, ion-exchange, and gel-filtration), molecular distillation, etc.

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The process of extraction from plant raw material is associated with the necessity for a large amount of solvent (7-10 times the amount of plant raw material, or less in continuous processes). When extraction is carried out batchwise, stirring [15], the temperature of the process, and the size of the particles, which affect the rate of extraction, are of great importance.

The choice of solvent depends on the type of alkaloids, their physicochemical properties, the type of plant raw material, and the problem posed. Where it is necessary to extract from a plant not only the alkaloids but compounds of other classes with the aim of the comprehensive utilization of the raw material, polar solvents such as alcohols are used with the subsequent separation of the alkaloids from the still residue by the passage of their salts into an aqueous phase and that of compounds of other classes into an organic phase. In many cases, the procedure is limited to the extraction of the alkaloids in the form of their bases from the alkalinized plant material with organic solvents of low polarity followed by treatment of the extract with a solution of an organic or a mineral acid.

Of the organic solvents for the treatment of plant raw material, dichloroethane is frequently used, being cheap and possessing universal properties. This solvent has been used in the isolation of many types of alkaloids such as peganine from common goat's rue [16], the tropane alkaloids [17], echinopsine from the common globe thistle [18], sanguinarine and chelerythrine [19], and others. A high yield of glaucine (90-94%) is obtained in the extraction of the yellow horned poppy with perchloroethylene [20]. One of the best solvents for the extraction of the alkaloids of belladonna, *Areca*, etc., is diethyl ether [21], but it is hardly used in industry at the present time because of its explosion and fire hazard. By extracting ergot alkaloids with 90-95% ethanol it is possible to achieve 90-95% of the alkaloids instead of the 80-85% when using benzene [22].

It is sometimes possible to select an extractant extracting a desired compound preferentially. For example, chloroform extracts the salts of certain alkaloids. This property is utilized in the technology of the production of glaucine from the yellow horned poppy: glaucine hydrochloride is extracted with chloroform from an aqueous solution of the hydrochlorides of the total alkaloids [23, 24].

In the choice of the solvent for extraction one must take into account the fact that chlorine-containing solvents are not inert to certain natural bases. For example, dichloroethane readily reacts at room temperture with secondary bases of the cytisine type with the formation of N-chloroethyl or hydroxyethyl derivatives [25]. There is information on the formation of quaternary ammonium derivatives of certain indole alkaloids with chloroform and of bisbenzylisoquinoline alkaloids with dichloroethane, and in the latter case, since extraction is carried out in an alkaline medium, products of Hofmann degradation are isolated [27].

Compounds that are active electrophiles, such as the benzophenanthridine alkaloids sanguinarine and chelerythrine readily react with alcohols and with acetone, forming, respectively, ethers of pseudobases and acetonyl derivatives [28, 29]. The protoberberine alkaloids react similarly but more slowly [30, 31]. The method of aqueous extraction appears to be the simplest and most economical. The extraction of the alkaloids in the production of securinine has been carried out in this way [32]. Extraction with 1% sulfuric acid has been used to obtain the alkaloid sarracine from the roots and rhizomes from broad-leaved ragwort [33]. The spray-drying of an aqueous extract of *Anabasis* has given anabasine [34].

However, in a number of cases, under industrial conditions extraction with water is accompanied by substantial technological difficulties. In particular, it is unsuitable for the extraction of active substances from plant tubers containing large amounts of starch which causes swelling of the raw material and interfere with filtration. Here it is more desirable to express the juice of the plant, as is done in the case of *Stephania glabra* [35], or to use organic solvents [36, 37]. Similar difficulties arise in the treatment of plant material containing water-soluble protein substances capable of forming emulsions on subsequent extraction with organic solvents. In these cases, some authors recommend the coagulation of the proteins [38, 39, 10].

Glycoalkaloids poorly withstand preliminary treatment in which they are subjected to enzymatic cleavage, and under laboratory conditions it is convenient to use the low-temperature extraction of the freshly frozen raw material with methanol with its simultaneous grinding under a layer of the solvent [40]. A method exists for the isolation of steroid glycoalkaloids with 5% acetic acid followed by precipitation with ammonia and extraction with methanol [41]. For the *Solanum lacineatum* used for working up for solasodine, which contains aglycones as well as glycosides, the method of aqueous extraction is ineffective. A procedure for the preliminary hydrolysis of the glycoalkaloids in the raw material before extraction has been developed which makes it possible to increase the yield of solasodine under factory conditions by a factor of 2-2.5 [42]. The method has also been formulated in a continuous variant [43].

In working with alkaloids one must bear in mind the action of atmospheric oxygen and light, which are capable of causing various type of transformations. Thus, 1-benzyl-3,4-dihydroisoquinoline derivatives are oxidized in alcoholic solutions by atmospheric oxygen to the corresponding 1-benzoyl derivatives. Indole bases are oxidized even more readily. On standing, solutions of the majority of *Rauwolfia* indole alkaloids become yellow and begin to fluoresce, the fluorescence increasing in intensity in an acid medium and in the light [44].

In recent years, it has been shown that the N-oxides of alkaloids are fairly widespread in plants and, apparently, play an important role in their metabolism [45]. The N-oxides are far less basic than the tertiary bases but far more polar and more soluble in water. As a rule, the N-oxides are difficult to isolate because of their poor solubility in organic solvents. They are therefore frequently converted into tertiary bases by reduction with sodium bisulfite, zinc dust, etc. Since the oxidized forms of alkaloids can be produced during the processing and storage of the raw material and intermediate products [46, 47], this expedient can considerably increase the yield of the desired reduced bases [48-50].

As extractants for alkaloids, in addition to the usual solvents, it has been proposed to use liquified gases. The extraction of pepper alkaloids, which have a sharp and burning taste and cause irritation of the mucous membranes, is inconvenient under industrial conditions. In view of this, extraction with liquid carbon dioxide is used, its low boiling point excluding the necessity for the preliminary comminution of the raw material [51].

METHODS OF EXTRACTION

The optimum apparatus for the extraction stage is an extractor with the maximum specific throughput ensuring the maximum yield of substance with the minimum volume of the apparatus. In the general case, the specific productivity of the apparatus for the substance being produced (g) is determined by the ratio

$$g = \frac{X_i \cdot \gamma_{\text{bulk}} \cdot \eta \cdot \varepsilon}{\tau},$$

where X_i is the initial concentration of substance in the raw material; γ_{bulk} is the bulk density of the raw material; η is the degree of extraction in the stage; τ is the residence time of the raw material in the apparatus; and ε is the coefficient of use of the volume of the apparatus.

An increase in the specific productivity of extracts is possible in practice only in the direction of increasing the degree of extraction of the active substance (η), shortening the residence time of the raw material in the apparatus (τ), and its rational design, including the completest possible utilization of its volume (ε) [52].

In a number of alkaloid factories, diffusion batteries are used. While being distinguished by simplicity of design, they have all the disadvantages of batch apparatuses: low productivity, difficulty in mechanizing the basic and auxiliary operations, and the production of extracts with a low concentration because of the high ratio of solvent to raw material. It is possible to eliminate these defects only by introducing continuous extraction apparatuses. For example, a vertical worm extractor has been used in the production of morphine from poppy capsules.

At the present time, many design modifications of continuous apparatuses for the extraction of substances from a solid phase have been proposed [53-55]. An analysis of extraction equipment, of methods of calculating apparatuses, and of conditions for extraction from medicinal plant raw material has been carried out by V. D. Ponomarev [56]. At the present time an extractor of carrousel type is considered to be the continuous apparatus with the most rational design [57, 58]. Its main advantage is the observance of counterflow between the phases, the low degree of breakdown of the particles during the extraction process, the complete utilization of the volume of the apparatus, and simplicity of construction. A rotary-pulsation apparatus has also been proposed [59]. The action of ultrasound considerably accelerates the extraction process [60, 61]; for example, the time of extraction of alkaloids from *Rauwolfia* root under these conditions is shortened from 120 to 5 h [62]. It has been established that the degree of extraction is affected not only by ultrasonic vibrations but also by an electromagnetic field, which can be demonstrated in the case of the extraction of alkaloids from *Cytisus laburnum* [63].

A method of extraction of belladonna alkaloids by water consisting in the successive raising and lowering of the pressure of water vapor is of interest. At the moment of boiling there is an efflux of extractive substances from the raw material into the solution. The authors report a high rate of the process [64].

Extraction from a liquid into a liquid is widely used in phytochemical manufactures in the concluding stages. The distribution coefficient between the organic and aqueous phases is of great importance in the choice of extractant. The quinolizidine alkaloids, the majority of which have $K < 1$, are extracted with difficulty from an aqueous phase, in view of which they must be salted out on extraction with solvents of low polarity, or saturated aqueous solutions of the alkaloid must be used. Liquid–liquid extraction (two-phase or multiphase) is an effective method of separating many types of compounds. An example of the use of countercurrent distribution in extraction columns is the isolation of the *Corydalis* alkaloids [65].

To choose the optimum conditions of the extraction process, wide use has been made recently of mathematical methods of planning experimental work [66, 67].

ISOLATION OF THE COMBINED ALKALOIDS AND SEPARATION INTO FRACTIONS; CONCENTRATION OF THE COMBINED ALKALOIDS

The separation of combined alkaloids or individual alkaloids from compounds of other classes is achieved by:

1) treating a water-immiscible extract with a solution of an organic or mineral acid followed by alkalinization and the extraction of the liberated bases by a suitable solvent;

2) the alkalinization of an aqueous or acid extract of the plant and the extraction of the alkaloids as in 1); or

3) the sorption of an aqueous or acid extract on a cation-exchanger followed by desorption by a suitable method (by an acid, by salts, by an alcoholic solution of ammonia, etc.) and the regeneration of the combined bases by the usual methods.

In each case one must reckon with the physicochemical properties of particular alkaloids. Thus, quaternary ammonium derivatives do not pass into organic solvents of low polarity. Ion-exchange methods or precipitation in the form of sparingly soluble salts are used for their separation from other extractive substances.

Another route for the isolation of quaternary heteroaromatic alkaloids is the reduction of aqueous solutions containing them to tetrahydro derivatives with zinc dust or other suitable reducing agents followed by the regeneration of the initial compounds by dehydrogenation of the purified tetrahydro compounds with iodine or atmospheric oxygen in the presence of a catalyst. This method has been used for the isolation of jatrorrhizine and sanguinarine [68].

SEPARATION ACCORDING TO BASICITY

An important criterion in the separation of alkaloids is the ionization constant pK_a, which permits the pH range within which the alkaloid is least ionized and passes into an organic phase from aqueous solutions to be determined. Since a single plant contains alkaloids with different basicities, they can be subjected to preliminary separation into fractions by performing extraction at various pH values of the solution. Weakly basic alkaloids are extracted at low pH values and strongly basic ones at high pH values, and alkaloids of medium basicity can be extracted from solutions with a close to neutral medium. Some alkaloids may have two pK_a values; for example, the bisindole alkaloids from *Catharanthus roseus*. It has also been proposed to use the value $pH_{1/2}$, denoting the pH of the solution at which the partition coefficient between water and the organic phase is equal to one, for characterizing alkaloids. An inverse relationship has been found between the $pH_{1/2}$ values and the chromatographic mobilities of alkaloids on silica gel in the solvent system used for the extraction of the alkaloids [5]. However, the inverse relationship is not complete, since it does not take into account the adsorption of the alkaloids on the sorbent, their interaction with the solvents, etc., No direct interrelationship between pK_a and $pH_{1/2}$ has been observed, either. As Aripov has shown [5], the $pH_{1/2}$ value is a universal characteristic which can be used in the selection of the technological method of separating alkaloids.

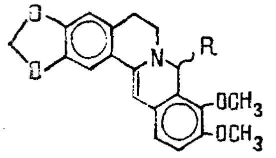
In view of the fact that in the process of extracting alkaloids from aqueous soluion the pH of the solution changes, buffer solutions are frequently used for a more accurate separation. In industry, the pH of the solution is usually brought to the required value and the desired fraction is then extracted. In the production of vincamine from *Vinca minor*, a toluene solution of the alkaloids is treated with a buffer solution having pH 4.0-5.5 whereupon the vincamine, in this case together with isovincamine, passes into the aqueous phase [69].

The separation of magnoline and magnolamine has been carried out by the fractional extraction of the alkaloids with a mineral acid from their solutions in an organic solvent [70]. On using countercurrent extraction with buffer solutions having different pH values, it is possible to separate mixtures of alkaloids in those cases when other methods prove to be not very effective. This method, which is known under the name of polybuffer separation, has been used in the extraction of the alkaloids of *Anabasis*, *Delphinium*, *Peganum*, *Heliotropium*, *Vinca*, *Petilium*, *Buxus*, and others [71-81]. In the extraction of anabasine from aqueous solutions by chloroform, it was found that for its selective separation from other alkaloids it is important to maintain not only a definite pH value (10.26), but also a definite concentration of the solutions. In concentrated solutions separation is ineffective [82].

The quaternary heteroaromatic alkaloids of the protoberberine and benzophenanthridine series behave peculiarly, having a tendency to exhibit tautomerism: carbinolamine form $\rightleftarrows$ quaternary ammonium derivative [83, 84]. The properties of these compounds are determined by the equilibrium of the two forms in the reaction medium, which depends on the charge on their electrophilic center and also on the acidity of the medium. Quaternary ammonium bases are readily soluble in water and are strong bases, while carbinolamines are weakly basic and are extracted by organic solvents. In an acid medium, the equilibrium is always shifted to the right.

On treatment with strong alkaloids followed by extraction with ether berberine can be converted into the carbinolamine form. For strong bases (palmatine), the equilibrium is shifted in the direction of the formation of the quaternary base, and therefore they remain in the aqueous phase in such an extraction and can be separated from berberine in this way. The phenolic alkaloid jatrorrhizine likewise remains in the aqueous solution, since it forms phenolates with strong alkalis. This method is used in the analytical determination of berberine in the roots of *Barbaris vulgaris* [85]. The weak base coptisine is converted into its carbinolamine form even when its solution is made alkaline with ammonium hydroxide (in which berberine remains in the quaternary form) and it can be extracted at lower pH values.

The carbinolamine form of berberine readily reacts with some solvents, forming with them covalently bound adducts, such as ethers of pseudobases (I, R = OR'), acetonides (I, R = CH_2COCH_3), berberine-chloroform (I, R = CCl_3), and others [86]. The benzophenanthridine alkaloids sanguinarine and chelerythrine react with such solvents even more readily

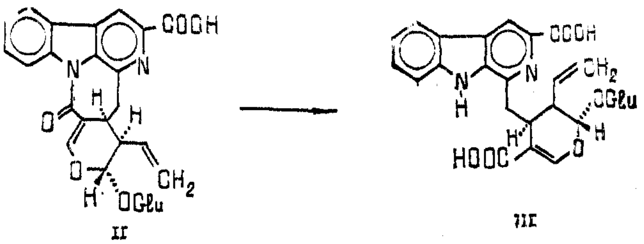


I

INTERACTION OF ALKALOIDS WITH ACIDS AND ALKALIS

The prolonged contact of protoberberine and benzophenanthridine alkaloids with alkalis causes a cross-Cannizzaro reaction with the formation of dihydro and oxo derivatives of the alkaloids in each case.

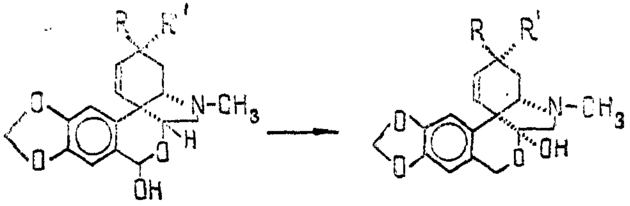
The glycosidic β-carboline alkaloid deoxycordifoline — a lactam from *Adina rubescens* (II) — is saponified in an alkaline medium to the dibasic acid (III) [87].



II

III

Tazettine (IV, R = OCH_3, R' = H), and criwelline (IV, R = H, R' = OCH_3) are artefacts formed from pretazettine (V, R = OCH_3, R' = H) and precriwelline (V, R = H, R' = OCH_3) by rearrangements when *Sprekelia formosissima* and *Ismene calathina* are treated in an alkaline medium. Pretazettine is also converted into tazettine in water at 70°C in 1 hour [88]. On prolonged treatment tazettine is converted further into isotazettine, which is apparently its epimer at the ketal carbon atom [89].

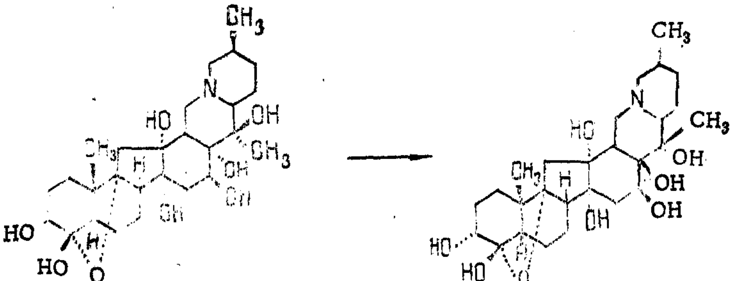


V

IV

In the presence of strong alkalis, the alkaloid veracevine (VI) isomerizes at C_3 (through an intermediate hydroxyketone) into cevine (VII) [90].

In the isolation of veratrine, the aqueous solutions must be made alkaline with ammonia very carefully, since an excess of ammonia causes an irreversible browning of the alkaloid [91].



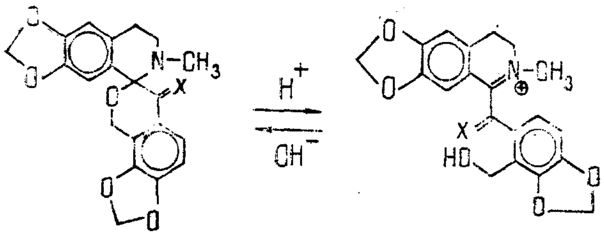
VI

VII

The benzophenanthridine alkaloid sanguinarine readily loses one methylene group in acid media, being converted into a dihydroxy derivative [92].

Some alkaloids containing asymmetric carbon atoms have been isolated only in the racemic form because of ready racemization. Examples of such alkaloids are hypecorine (IX, X = H_2), and hypecorinine (IX, X = O), which have a spiroaminoketal grouping only in an alkaline medium with the center of asymmetry at C_1 of the isoquinoline fragment, while in an acid medium the ring formed by this grouping opens to give a 3,4-dihydroisoquinolinium salt (X, X = H_2, O), in which there is no center of asymmetry [93]. (Formula, top, following page.)

The property of alkaloids of forming salts with acids is also used in ion-exchange methods of isolating these natural compounds from aqueous extracts of plant raw material. The basic investigations in this direction are connected with the search for ion-exchange materials possessing a high sorption capacity and selectivity, the development of improved apparatus, etc. Questions of the use of ion-exchange materials have been discussed in a number of reviews [94, 95].



IX X

Sorption on ion-exchange resins is used in the production of tubocurarine chloride, quinine, and the ergot alkaloids [6], scopolamine, lobeline, and cytisine [96-98], and the alkaloids of *vinca minor* [99]. The ion-exchange isolation of peganine from *Peganum harmala* [100], of lycorine from *Ungernia sewerzowi* [101, 102], and of fetidine [103] and other alkaloids [104-106] has been described. The use of an ion-exchange method has permitted a 3% increase in the yield of morphine and caffeine through the ion-exchange treatment of mother solutions [107]. The yields of the alkaloids salsoline and salsolidine from aqueous solutions using desorption with 1% hydrochloric acid has been increased by a factor of 1.3 as compared with the dichloroethane method. The consumption of dichloroethane has been reduced 50-fold. The total yield of these alkaloids has reached 96-97% [108, 109]. The best results were obtained when using the sulfonated cation-exchange resins KU-1 for d-β-hydrastine from *Corydalis pseudoadunca* [104] and for lycorine from *Ungernia tadshikorum* [110]; and KU-2 for cytisine from *Thermopsis lanceolata* [111, 112]. However, this method also has its limitations. For example, vincanidine is strongly adsorbed on cation-exchange resins and is difficult to elute from them.

ISOLATION OF THE TOTAL ALKALOIDS OR OF INDIVIDUAL ALKALOIDS FROM EXTRACTS IN THE FORM OF SPARINGLY SOLUBLE COMPOUNDS

In a number of manufactures, the total alkaloids can be isolated from extracts of a plant raw material in the form of sparingly soluble compounds.

The quaternary alkaloids sanguinarine and chelerythrine can be isolated in the form of sparingly soluble bisulfates when dichloroethane extracts are treated with sulfuric acid [19]. The quaternary dihydrofuroquinoline alkaloid O-methylptelefolonium is precipitated in the form of the picrate from aqueous extracts after the separation of the coumarines [113]. In the production of glycoalkaloids, precipitation of the alkaloids — for example, α-tomatidine — from methanolic solution by cholesterol, which forms with α-tomatidine a molecular compound in a ratio of 1:1, is used. The complex obtained is decomposed by hot dimethyl sulfoxide [114] or by acid [115, 116].

An original method of obtaining crystalline ergotaminine for subsequent conversion into ergotamine consists in placing an aqueous solution containing the combined alkaloids in a constant low-frequency electrical or magnetic field and a high-frequency electromagnetic field. Under these conditions, ergotamine deposits as a precipitate [117].

OTHER METHODS OF ISOLATION

Vacuum distillation can be used to isolate low-molecular-weight alkaloids [118]. For example, the distillation of the total alkaloids from *Anabasis* seeds in vacuum (3-4 mm) has given the liquid alkaloid anabasine and crystalline lupinine [119]. However, in a number of cases distillation may lead to undesirable processes. Thus, the dimeric quinolizidine alkaloid goebeline is the product of the thermal dimerization during distillation of the monomeric quinolizidine alkaloids present in a plant. This has been confirmed by synthesis [120, 121].

The steam volatility of ephedrine and pseudoephridine has been used in an analytical method for their determination [122].

A method has been described for obtaining matrine which consists in the saponification of the latter to matrinic acid, which is isolated in the form of a salt, with the subsequent regeneration of the alkaloid by acid cyclocondensation [123].

Alkaloids **of the matrine** series isomerize in the presence of metallic catalysts of the type of platinum and nickel. Thus, in the presence of platinum matrine is converted into allomatrine [124], and sophoridine in hydrochloric acid solution is converted into isosophoridine [125].

To separate alkaloids, the differences in the solubilities in organic solvents are frequently utilized. In this method a good separation is not achieved but there is only an enrichment of the fractions with individual alkaloids. The separating capacity of this method is inversely proportional to the amount of the components in the mixture. A solubility difference has been used in a laboratory method of separating the quinolizidine alkaloids of *Sophora* [126].

The property of the alkaloids anabasine [127] and cytisine [128] each of which contains a secondary amino group, for forming N-nitroso derivatives has been used in the technology of their isolation and purification. The initial alkaloids are regenerated from the nitroso derivatives by heating with an acid. Using this method, cytisine has been isolated from *Thermopsis lanceolata* with a yield of 90-95% [129].

Electrophoretic separation and liquid chromatography have been proposed for the technical monitoring of the production of alkaloids [130, 131].

METHODS OF PURIFYING ALKALOIDS

The modern severe demands on medicinal preparations relate primarily to their quality, and it is therefore preferred to obtain individual alkaloids. However, in a number of cases it is undesirable from the technological and economic points to separate compounds with similar properties and practically identical biological activities — for example, in the case of the drug Sangviritrin [Sanguiritrine] which consists of a mixture of the bisulfates of sanguinarine and chelerythrine [19, 131]. In each concrete case, the desirability of obtaining two-component preparations must be confirmed by biological, toxicological, and other studies.

As a rule, in the concluding stages of the production of a drug, salt formation, the formation of other crystalline derivatives, chromatography, and crystallization are used. A combination of two or more methods is frequently used for purification.

CHROMATOGRAPHIC METHODS

Chromatographic methods of separation are widely used in the chemistry of natural compounds for isolating individual substances and purifying them, for analytical control methods, for determination, etc. The most convenient sorbent is alumina thanks to its high sorption capacity [132-138]. Separation on columns of alumina is used in the production of vinblastine, vincristine, and vincamine [139-141], i.e., in those cases where the active components are minor ones. If it is required to free a crude product from more polar impurities, filtration through a layer of alumina is used.

Both the sorbent and the solvent system are selected in each concrete case individually in the light of the polarity of the compounds and their chemical properties. Highly polar compounds may be irreversibly adsorbed on alumina, and therefore either it is deactivated or other sorbents are used, such as cellulose, Sephadex, and silica gel. Cases are known of the occurrence of chemical reactions catalyzed by sorbents. For example, on alumina an ester group may be saponified, the Cannizzaro reaction may take place with compounds containing aldehyde groups, and intramolecular aldol condensations, etc., may occur. Because of partial racemization on alumina in the process of purifying alkaloids, this method has not found use in industry [141-146]. It has been shown that alumina is unsuitable for the isolation of reserpine from *Rauwolfia serpintina* roots. A more suitable sorbent in this case has proved to be kieselguhr [147].

Activated carbon is also used as a sorbent for chromatography. However, the latter is more frequently used for decoloring solutions in the recrystallization of alkaloids and their salts.

In addition to the sorbents mentioned, polyamide powder is used, for example, in the preparative separation of the polar alkaloids of *Menispermum canadense* [148]. The chromatography of alkaloids in a thin layer of polyamide has also been developed [149].

A method has been described for separating clavine from other alkaloids by gel filtration on Sephadex LH-20 in the solvent system ethanol–acetone–dimethylformamide–water [150].

The chromatography of alkaloids in a thin layer of sorbent with the aim of control and identification has been described fairly fully in Stahl's monograph [151]. For the preparation of the alkaloid chelidonine use is made of the adsorption of an acid extract of the *Chelidonium majus* on Wofatit followed by the desorption of the desired compound with a mixture of ethanol–chloroform (80:20) and 4% ammonia [152].

THE FORMATION OF SALTS, ADDUCTS, AND OTHER CRYSTALLINE DERIVATIVES

The choice of crystallization regimes, solvent systems, and rates of precipitation of crystals frequently requires special investigations. The configuration and dimensions of the crystals, which affect some physicochemical properties of the substances of the preparations, play a large role in the preparation of medicinal forms.

The majority of alkaloids are crystalline compounds, but they can rarely be obtained in the pure form by crystallization of combined alkaloids. In view of this, use is made of the capacity of the alkaloids for giving crystalline salts (basic, acid, or neutral salts) with mineral or organic acids which differ greatly in their properties. For example, berberine bisulfate is far more sparingly soluble in water and ethanol than berberine sulfate and can be separated from palmatine bisulfate, which remains in solution. Palmatine and jatrorrhizine can be separated from mother solutions in the form of iodides by adding potassium iodide. For their more complete separation from various parts of the plant *Berberis oblonga* it is proposed to precipitate them in the form of the iodides [153, 154]. Characteristic salts of alkaloids are the nitrate for pilocarpine, the sulfates for vinblastine and vincristine, etc.

The diastereomeric natural mixture of ephedrine and pseudoephedrine can be separated by virtue of the lower solubility of ephedrine oxalate in water [155], of ephedrine hydrochloride in chloroform [156], and of pseudoephedrine, in the form of the base, in water [157].

The quaternary alkaloids betaine and stachydrine are precipitated from aqueous solutions in the form of periodides by the addition of solutions of HI + I_2 or KI + I_2 [158]. The isolation of indole alkaloids by this method has been patented. However, some alkaloids, particularly of the phenolic type, readily undergo oxidation by iodine, which imposes limitations on this method. The aporphine alkaloid O-methylbulbocapnine undergoes dehydrodimerization on oxidation by iodine in ethanol [159].

The quaternary protoberberine alkaloids form double salts with heavy metals (iron, copper, lead, etc.), and this fact must be taken into account in the choice of the method of isolation and the material of the apparatus in the technology of their production.

Many natural compounds possess the capacity for retaining a certain amount of the solvent of crystallization, the energy of such affinity depending on the functional groups in the molecule and its spatial structures. For example, isochondodendrine hydrochloride, which possesses a macrocyclic structure, retains 15 molecules of water of crystallization. The sulfates of the bisindole alkaloids vinblastine and leurosine form a double crystal solvate with water and ethanol which slowly decomposes on heating in vacuum. Vinblastine in the form of the base gives a crystalline etherate. The formation of crystalline adducts of the ergot alkaloid with solvents is used for their purification (the crystal solvates of ergotamine with acetone, of ergotoxine with benzene [160], and of ergometrine with chloroform [161, 162]).

In working with crystalline derivatives the possibility of the formation of molecular compounds of the molecules of some alkaloids with others, which may lead to erroneous results, must be taken into account. For example, (–)-curine forms a molecular compound (1:1) with (–)-tubocurine which is not separated by crystallization [163].

Alkaloids readily soluble in water are difficult to isolate by the usual methods. However, a method has been developed for their precipitation in the form of sparingly soluble acid conjugates, and it has been reported that the conditions for their isolation are connected with their basicity constants pK_a. Thus, quaternary ammonium bases can be precipitated in the form of reineckates in alkaline media, and betaines (pK_a 7-11) and **tert-amine** oxides (pK_a 3-5) in media close to neutral and at acid pH values. The initial alkaloids can be regenerated by passing solutions of the conjugates in acetone or ethanol through columns containing an acidic cation-exchange resin [164-167].

SOME METHODS FOR INCREASING EFFICIENCY IN THE PRODUCTION OF ALKALOIDS

The prime cost of drugs can be lowered by the comprehensive utilization of the raw material. An indicative example is the production of the drugs morphine, codeine, thebaine, papaverine, narcotine, and others from poppy capsules and the production of ergometrine and ergotamine from ergot.

The yields of the desired compounds can be increased by converting accompanying compounds possessing a lower biological activity into these more active compounds. Thus, by isomerizing pseudoephedrine into ephedrine, converting ergonine into cocaine, oxidizing vinblastine to vincrisitine, etc., the yields of the desired products are substantially raised. In a number of cases, this method is the most rational, particularly for difficultly accessible alkaloids.

A method has been developed for the catalytic conversion of the *Anabasis* alkaloids aphylline and aphyllidine into pachycarpine under the conditions of their hydrogenation [168-170]. The performance of this process has enabled pachycarpine to be obtained in anabasine production and not from *Sophora* [171].

Thus, practically all known methods of isolating and purifying organic compounds are used in the chemistry and technology of the production of alkaloids. The choice of methods is based on differences in the structures, physicochemical properties, and reactivities of the compounds. The task of the chemist and the technologist is to combine known methods taking the individual properties of the alkaloids into account to ensure the maximum yield of desired compounds.

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