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METHODS OF ISOLATING ALKALOIDS OF THE COLCHICINE SERIES

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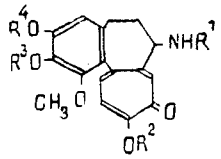
This review considers methods for the isolation of colchicine, colchamine, and colchicoside. The literature for the period from 1884 to 1997 has been used.

Colchicine, a long-known alkaloid of the autumn crocus, has appeared in the pharmacopeias of many countries [1]. Colchamine (synonyms: demecolcine, colcemide), which was discovered later [2, 3], is used in some cases of malignant neoplasms [4]. Colchicine is used for treating gout [1], amyloidosis [5], periodic disease [1, 6], and disseminated sclerosis. Some generalizations concerning the medical use of colchicine have been given in [8]. Colchicine has recently been used in the derivation of new varieties of plants [9].

Some artificial derivatives of colchicine have acquired medicinal value. Abroad, the drug Thiocolceran (deacetylthiocolchicine) is used [10]. Thiocolchicoside (Coltramyl) is employed in rheumatic and nonperiodic diseases [10]. For its pharmacology, see [11]. This drug is synthesized [12] from colchicoside, which is 3-glucosyl-3-demethylcolchicine [13]. Recent patents witness the unabating interest in the practical use of the biological properties of colchicine and its derivatives. In an American patent application antiphlogistic agents based on 2,3-didemethylcolchicine are described [14]. There are patents on medicinal forms of colchicine [15]. A solution of colchamine has been patented for lowering intraocular pressure [16].



	R^1	R^2	R^3	R^4
Colchicine	$COCH_3$	OCH_3	CH_3	CH_3
Colchamine	CH_3	OCH_3	CH_3	CH_3
Deacetylthiocolchicine	H	SCH_3	CH_3	CH_3
Thiocolchicoside	$COCH_3$	SCH_3	CH_3	$C_6H_{11}O_5$
Colchicoside	$COCH_3$	OCH_3	CH_3	$C_6H_{11}O_5$
2-Demethylcolchicine	$COCH_3$	OCH_3	H	CH_3
3-Demethylcolchicine	$COCH_3$	OCH_3	CH_3	H
2,3-Didemethylcolchicine	$COCH_3$	OCH_3	H	H
2-Demethylcolchamine	CH_3	OCH_3	H	CH_3
N-formyldeacetylcolchicine	HCO	OCH_3	CH_3	CH_3
17-Oxocolchicine	$COCH_2OH$	OCH_3	CH_3	CH_3
Colchiceine	$COCH_3$	OH	CH_3	CH_3

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RAW MATERIALS AND ITS DRYING

The colchicine alkaloids are basically obtained from the seeds and bulbs of autumn crocuses – plants of the genus Colchicum. The amounts of colchicine in the common autumn crocus Colchicum autumnale L. are as follows: seeds – 0.22-1.00% [17], dry bulbs – 0.08% [17, 18]. The fresh epigeal parts contain: moisture – about 87%; colchicine in the leaves – 0.004-0.008%; flowers – 0.05%; and the dry matter, respectively, 0.03-0.09 and 0.26% [17]. In the fresh bulbs of showy autumn crocus Colchicum speciosum Stev. there is 63-80% of water [19, 20]; in the flowering period the colchicine content is 0.03-0.14% and the colchamine content 0.01-0.05% [19, 20]; in the dry bulbs the amounts are, respectively, 0.04-0.4% and 0.01-0.08% [19, 20]. In the dry leaves, 0.08% of colchicine and 0.009% of colchamine have been found [19]. We may recall that the epigeal parts of the autumn crocus are the leaves in summer and the flowers in autumn. Colchicoside is obtained from the seeds of autumn crocus growing in Yugoslavia [13, 21].

The epigeal parts of yellow autumn crocus Colchicum luteum Baker have also been proposed for the isolation of colchicine [22]. Colchicine is also present in plants of the genus Merendera [23, 24]. The possibility of the use of the seeds of Gloriosa superba L. [21] and of some other tropical plants of the family Liliaceae [25, 26] has also been discussed.

The storage of the fresh bulbs for 2-3 months is permissible when the following conditions are observed: temperature, humidity, darkness, aeration. The drying of the bulbs of showy autumn crocus at 100°C involves a loss of colchicine of up to 25% and of colchamine of up to 39% [20]. Drying at a temperature not above 19-20°C has been recommended for yellow autumn crocus [27]. The impurities appearing on the drying of the bulbs of common autumn crocus at 100°C have been revealed with the aid of thin-layer chromatography [28]. Impurities are also formed in the slow drying (~25°C) of the leaves and flowers of the same plant. The amount of colchicine does not change but the amounts of 2- and 3-demethylcolchicine and of 2-demethylcolchamine increase. The authors explained this phenomenon by the fact that in the fresh raw material these demethylated derivatives are bound to substances of high molecular mass [17]. It was later found that the drying of the epigeal parts increases the amount of demethylated compounds and alters the amount of the main alkaloids. Demethylation also takes place on the storage of the dry flowers. During the first six months the amount of 2-demethylcolchamine rises, and then it falls [29]. This demethylation on drying must be regarded as irreversible. It has been proposed [17, 21] to methylate the byproducts arising with diazomethane. In this way it is possible to increase the yield of colchicine and colchamine at the expense of the natural demethylated derivatives.

EXTRACTION

In the isolation of colchicine and colchamine, water or aqueous solutions, alcohols, and weakly polar and mixed solvents are used. In one of the first publications the isolation of colchicine from the seeds of common autumn crocus was described. The seeds were then treated with rectified alcohol [18]. For other early publications, see [30, 31]. In the extraction of colchicine by organic solvents, the seeds are first defatted with weakly polar solvents such as petroleum ether [2, 24, 26, 32, 33]. After such treatment, the colchicine can be extracted with 80% ethanol [26]. Other alcohols are also used. For example, the dried epigeal parts of yellow autumn crocus are extracted with methanol [22]. The fresh or dry epigeal parts have also been treated with hot methanol [17, 34]. The use of weakly polar solvents (chloroform [2] and benzene [33]) has been described.

The aqueous extraction of the bulbs of showy autumn crocus has been proposed by Soviet workers [35]. According to thse authors, colchicine is obtained in higher yield and with a small amount of impurities, while the drying of the raw material and the corresponding losses of alkaloids are avoided. It has been proposed to extract bulbs freshly ground in a meat grinder at room temperature, with the addition of an aqueous solution of sodium bisulfate [36, 37]. Somewhat earlier, the aqueous extraction of dry bulbs was used in analysis [38]. Later, a patent was granted for the aqueous extraction of colchicine from the ground seeds of common autumn crocus with preheating to 40°C; and here it was mentioned that aqueous extraction gives a purer colchicine [39]. The same author had previously reported the use of aqueous extraction in the analysis [40]. Aqueous extraction is also recognized as the best in [41]. Here the method of the patent [39] is modified: it has been found more suitable to extract the unground seeds, but at a temperature of 50-60°C and for somewhat longer. The seeds and the water are charged in a ratio of 1:10 and are stirred continuously with a contin-

ued feed of preheated extractant at 1.6-2.0% of the volume of the charged liquid per minute [41]. At the outlet from the apparatus, the extract is pumped into a heat exchanger for cooling and then to a filter [41].

The process of extracting showy autumn crocus bulbs with aqueous extractants was considered in detail in [42]. The following conditions were selected: temperature 40-80°C at pH 11.5 (alkalinization with sodium carbonate or ammonia), at a ratio of solid and liquid phases of 1:3. In an industrial trial, an increase in the yield of colchicine by 30-40% was achieved [42].

The epigeal parts have been treated with water as described in [17, 19].

In the isolation of colchicoside, the ground seeds of common autumn crocus are defatted with petroleum ether and extracted with 70% ethanol [13]. A ternary mixture of benzene, ethanol, and water in a ratio of 3:1:1 has also been proposed. The ground seeds are extracted at 30-40°C. The method ensures a good yield of colchicine and colchicoside [43]. In the production of colchicoside by another patent, the seeds after defatting are treated with chloroform and then with a 1:2 mixture of ethanol and chloroform [44].

The extracts obtained by any of the methods described above contain alkaloids in low concentrations and are enriched with ballast substances. The nature of the latter depends on the features of the raw material and of the extractant used.

Extracts are reextracted with other solvents or are evaporated (see the reviews [30, 45] and the papers [2, 13, 17, 18, 22, 19, 43, 44]). Distribution in a liquid–liquid system is used for separating the nonalkaloid impurities: the residue after the organic solvent has been distilled off is treated with water and the insoluble impurities are separated off. Paraffin wax is used for absorbing resinous substances [30, 43]. The impurities are separated predominantly by the use of solvents not extracting the alkaloids [2, 22, 29, 45]. In this process, acidification has been used in some studies. For example, the residue from an ethanolic extract was stirred several times with 5% tartaric acid [18]. In more recent investigations acidification was likewise used, but the aqueous solution was not discarded; on the contrary, bases were isolated from it [25, 29, 46]. The aqueous phase has also been treated with lead acetate [2], but this involves the partial loss of the alkaloids [29].

As a rule, colchicine and colchamine are extracted from aqueous solutions with chloroform [2, 22, 35, 38, 39, 41] or dichloroethane [35, 43, 47].

Countercurrent extraction has been recommended [39, 47].

The extraction of alkaloids from the juice leaving the diffusor in three columns linked in series each being half-filled with chloroform has been described [41]. From the columns the juice runs into an intermediate tank where entrained chloroform separates. Then the juice is preheated and is again fed into the diffusor. Every 24 h the chloroform in the columns is replaced, and this is done three times. The total volume of chloroform consumed amounts to 0.8 with respect to the weight of the autumn crocus seed charged, and the loss of it at this stage is 12.5%. The chloroform extract obtained is evaporated to 0.04-0.05 of its initial volume [41].

In the isolation of colchicide, the evaporated extract was treated with chloroform, the aqueous phase was evaporated, and the residue was treated with a mixture of chloroform and ethanol (4:1). Both extracts were washed with water. Colchicoside was isolated from the combinded wash-waters after further purification [13].

The extraction of colchamine and colchicine from aqueous solutions has been studied [48-51] as functions of the pH of the medium [49], of features of the solvents [49, 51], of the temperature [51], and of the presence of an electrolyte [50, 51]. The partition coefficient of colchicine between organic and aqueous phases increaes with a rise in the polarity of the solvent [51]. In mixtures of chloroform–benzene with water, the partition coefficient rises with an increase in the amount of the former. The authors concerned explain this phenomenon by the fact that chloroform is a proton donor and colchicine, in view of its troponoid structure, acts as an acceptor [51]. With an increase in the temperature of the mixing of the phases, the partition coefficient rises [51]. When sodium chloride or ammonium or sodium sulfate is present in the aqueous phase, the partition coefficient in the benzene–water system increases, while sodium iodide lowers it [51]. The presence of sodium chloride or ammonium sulfate in the aqueous phase promotes extraction [50]. It is obvious that the main factor determining the course of extraction from the aqueous medium is the solubility of col-

chicine or colchamine in the organic solvent. This does not relate to acidic solutions of colchamine; however, it can pass from acidic solutions into chloroform in the form of a salt.

On the treatment of an aqueous extract of the bulbs or their expressed juice with chloroform or dichloroethane the main difficulty is caused by the stable emulsion arising, the cause of which is the precipitation of a protein-containing deposit [20]. To prevent emulsification, the proteins have been precipitated with ammonium sulfate. On the subsequent extraction of the mother solution with chloroform no emulsions were obtained, but it was found that the whole of the colchicine and almost the whole of the colchamine were precipitated with the protein. The alkaloid can be extracted from the protein precipitate in good yield by means of an organic solvent such as isopropanol [20]. An emulsion can also be eliminated with the aid of the fermentation of the aqueous phase with pancreatin or Taka-Diastase [52].

Another method of precipitating the alkaloids has been described for the isolation of colchamine: a 5-20% solution of tannin is gradually added to the aqueous extract until precipitation is complete. The precipitate is separated off and is treated 4-6 times with, for example, dichloroethane or chloroform at a ratio of the solid and liquid phases of 1:15. The colchamine is isolated from the extract [57].

ISOLATION AND PURIFICATION

The concentrates obtained as described above contain complex mixtures of alkaloids. In addition, other compounds are present, such as organic acids [17, 36, 54]. The isolation of individual alkaloids is therefore complicated and requires various methods. It has been recommended, after the concentration of the alkaloids in a chloroform extract, to treat it with dilute alkali [36, 47]. According to a patent [39] the residue after the evaporation of a chloroform extract is dissolved in ethanol. The resulting solution is poured into a tenfold volume of water. Sodium chloride is added to the mixture and the precipitate that deposits is filtered off. The filtrrate is treated with chloroform; colchicine is obtained from the extract.

Colchamine, unlike colchicine, shows a highly pronounced capacity for salt formation [3]. Independently of this work a separation of the total alkaloids of autumn crocus into fractions of substances of neutral and basic nature has been reported [55].

A method has been described for separating the total extractive substances from showy autumn crocus which presupposes the separation of the alkaloids according to basicity: a chloroform extract is treated with alkali to remove acids and phenols and then with dilute sulfuric acid. Alkali is added to the acid solution until a weakly alkaline reaction to Congo Red is obtained, and the weakly basic impurities are extracted with chloroform. Then the colchamine is precipitated with an excess of alkali and is extracted with chloroform. The phenolic bases remain in the alkaline solution [19, 56]. Colchamine is obtained in the same way by treating an evaporated dichloroethane extract with sodium phosphate buffer having pH 1.5-2.0. Then the acid solution is washed with chloroform and, at 10°C, is made alkaline with 25% ammonia to pH 8.0-9.0 and the colchamine is extracted with chloroform. The extract is treated 2-4 times with 1-10% alkali. The colchamine is isolated from the last extract. According to the authors of the method, its yield rises by 33-55% [47].

In [17], a purified acidic solution was made alkaline with ammonia to pH 12. Apparently, at this alkalinity there was an excess of ammonia, which must be considered undesirable, since ammonia is capable of reacting with cholchicine and with other alkaloids of this series, replacing a methoxyl of the tropone ring by an amino group. In the latest publication from the same laboratory [29], a purified acidified aqueous solution of the concentrate was treated with chloroform; the neutral and weakly acidic substances passed into the latter. The aqueous solution was made alkaline with ammonia and the bases passed into chloroform. A substance of phenolic nature was removed from both chloroform extracts, and then neutral substances and bases, respectively, were obtained [29]. The phenolic alkaloids have also been separated by the action of alkali in other procedures [46, 47].

The purified chloroform or other similar extracts are dried before chromatography, for example, with sodium sulfate [2, 22, 47].

Chromatography was first used for the purification of colchicine in [58]. Since then it has been widely employed in the isolation and purification of cholchicine and accompanying alkaloids [2, 3, 22, 29, 33, 46, 47, 57, 59]. Alumina is used for the purification of colchicine and colchamine [22, 33, 39, 41, 47]. The most important methodological schemes for

the separation of mixtures on columns containing alumina have been described in [60]. Elution is usually performed with various solvents or mixtures of them with a successive increase in the polarity of the eluent. Chloroform elutes colchicine first, while benzene initially separates out the colchamine.

For analyses and for research work the colchicine alkaloids have also been subjected to chromatography on cellulose [46, 61], and also on silica gel [63]. Magnesium silicate has also been used as sorbent [63]. The possibility has been shown of separating colchamine and colchicine on a cation-exchange resin consisting of a polymer of acrylic acid on a polypropylene mat [64].

After purufication, the alkaloids are crystallized. In some cases activated carbon is used, in addition. For example, the resinous residue from the chloroform eluate is dissolved at 60-70°C in a 10- to 12-fold amount of water, and the solution is filtered through activated carbon and evaporated to dryness. The residue is crystallized from ethyl acetate. This gives 0.28-0.30% of colchicine, calculated on the weight of the raw material; the amount in the initial seeds was 0.4% [41].

Colchicine is frequenty crystallized from ethyl acetate, and this was first done in [54]. According to a patent [43], the purified concentrate is redissolved in water and is crystallized from a 15-fold (volume/weight) amount of ethyl acetate; the amount of pure colchicine obtained is 0.346% of the weight of the raw material (seeds). In [36], a concentrate of purified chloroform extract was also crystallized from ethyl acetate. In this way it was possible to obtain colchicine only from ground bulbs collected in the period of autumn vegetation. Colchicine did not crystallize from other bulbs by this procedure; its derivative colchicerine [36], which consists of a molecular compound of colchicine and colchamine [3], was obtained.

Colchicine crystallizes from chloroform with two molecules of solvent [65]. According to the German Pharmacopeia [66], colchicine contains half a molecule of chloroform. Other pharmacopeias do not permit the presence of chloroform. Colchicine deposits from benzene with one molecule of solvent [58]. Crystal solvates of colchicine containing one molecule of methylene bromide or methylene chloride are known [67]. On the heating of its aqueous solutions, colchicine forms a sesquihydrate which is less soluble than the unhydrated alkaloid [68].

After the concentration of its purified chloroform solution, colchamine is crystallized from acetone [47, 56, 59] or ethyl acetate [3, 59].

The extraction of colchicoside and its concentration in aqueous solution has been mentioned above. To isolate this alkaloid the solution is treated with activated carbon and evaporated to dryness. The residue is crystallized from water, giving a yield of 0.25% on the weight of the raw material (seeds) [13]. According to a patent [43], the evaporated extract is treated with paraffin wax and then with carbon, after which the colchicine is extracted with dichloroethane. Colchicoside is obtained from the aqueous phase in an amount of 0.203% on the weight of the raw material. In the method of another patent [44], the purification of colchicoside is ensured thanks to the above-mentioned extraction of the raw material successively with three solvents: from the last, ethanolic chloroform, extract the colchicoside is eluted with water, the water is evaporated off slowly, and the residue is recrystallized from ethanol giving the same yield of colchicoside as in [13].

In a number of cases, impurities have been detected in colchicine stored for various times. The chromatography of colchicine corresponding to the requirements of the US Pharmacopeia of that time [58] showed the presence of 5% of impurities. Later, again with the aid of chromatography on alumina, it was found that colchicine of the same quality contains about 4% of 3-demethylcolchicine [69]. From another pharmacopeial sample, 1.5% of N-formyldeacetylcolchicine was isolated [70]; in the same paper the presence of other accompanying alkaloids was also reported. In an investigation of a commercial sample by high-resolution liquid chromatography 93.4% of colchicine, 2.9% of N-formyldeactylcholchicine, 1.8% of 17-hydroxycolchicine, and 0.84% of an unknown substance were found [71].

QUALITY INDICES

Colchicine is included in the pharmacopeias of the United Kingdom [72], the USA [73], Japan [74], and a number of other countries [1].

Tests for authenticity: IR spectrum [72, 73], the absorption of light in the 250-400 nm region [72], the formation of colchiceine [74, 75], and color reactions [72, 74, 75]. Determination of impurities: colchiceine – by the reaction with ferric chloride in an acid medium [72-75]; accompanying alkaloids – by thin-layer chromatography [72, 74] and by the test with picric acid [74]; solvents – by gas chromatography (chloroform, ethyl acetate) [72, 73] and the qualitative reaction forming isonitrile (chloroform) [74, 75].

The colchicine content has been standardized at 97-103% [72, 73], and not less than 98% [74]. Its amount is determined by potentiometric nonaqueous titration with perchloric acid [72-74]. A method of determining colchicine in the finished preparation has been proposed which is based on the precipitation of the alkaloids in an acid medium in the form of a complex with iodine [76].

The following identification reactions have been recommended for colchamine: with ferric chloride in an acid medium where a green coloration arises, after brief boiling; and with picric acid, when a precipitate appears on the mixing of saturated aqueous solutions [77]. A method for the quantitative determination of colchicine by titration by hydrochloric acid with Bromophenol Blue as indicator has been developed [77]. For determining a colchicine impurity, a color reaction with ferric chloride in an ethanolic medium has been proposed [77].

The quantitative determination of colchicine and colchamine based on a combination of thin-layer chromatography with spectrophotometric measurement of the concentration of acid extracts of the corresponding spots of a chromatogram has been recommended. The method is suitable for determining the amounts of both alkaloids in plant raw material and industrial solutions [78].

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STABILITY OF STATIONARY CATALYSTS IN THE HYDROGENATION OF RAPESEED OILS

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The stability of a nickel–copper–molybdenum–aluminum catalyst without additives and with the addition of promoting metals (chromium and titanium) in the hydrogenation of rapeseed oils has been investigated. It has been established that the addition of a promotor to the composition of a known catalyst raises the activity and improves the stability of the alloy. The possibility has been revealed of using catalysts that have been poisoned by sulfur compounds, after their regeneration.

In the evaluation of a catalyst in the hydrogenation of vegetable oils and fats, not only is its activity important but so also is its stability, i.e., its resistance to the action of catalyst poisons. The stability of a catalyst is an important technical and economic index of the desirability of its use.

It must be mentioned that the main catalyst poisons in refined rapeseed oil are organic compounds of sulfur, which are difficult to eliminate from the oil and are capable of interacting with products of its oxidation and hydrolysis [1]. In the hydrogenation of an oil, because of adsorption on the active centers, these compounds form with the metal or an ion of the metal of the catalyst a strong – more accurately, coordination – bond and thereby exclude it from the catalytic act [2].

We have investigated the stability of a nickel–copper–molybdenum–aluminum catalyst having an Ni:Cu:Mo:Al ratio of 22:20.5:7.5:50 without an additive (catalyst 1) and that of the same catalyst with the addition of promoting metals – chromium, giving an Ni:Cu:Mo:Cr:Al ratio of 22:18.5:7.5:2.0:50 (catalyst 2), and titanium, giving an Ni:Cu:Mo:Ti:Al ratio of 22:18.5:6.5:3:50 (catalyst 3) in the hydrogenation of erucic-acid-free and erucic-acid-rich rapeseed oils.

At the present time in industry the hydrogenation of rapeseed oils is performed mainly on pulverulent copper–nickel catalysts. The hydrogenation of the rapeseed oil is then com-

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