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## Physical Activation of Extraction and Organic Synthesis Processes

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### Abstract

The effect of various methods of physical action on the processes of extraction and organic synthesis is considered. The results of the authors' works are summarized, and it is demonstrated that the methods of mechanochemical, ultrasonic and microwave activation provide an increase in the yield of target products, a decrease in the volume of solvents used, in time and energy consumption, compared to traditional processes.

**Keywords:** mechanochemical, microwave and ultrasonic activation, extraction, organic synthesis

### PHYSICAL ACTIVATION OF THE PROCESSES OF EXTRACTION AND SYNTHESIS IN THE FORMAL OF GREEN CHEMISTRY

Energy input is required to stimulate chemical processes. As a rule, heating is used to overcome activation barriers in chemical reactions. However, during recent years, other methods to intensify chemical processes are increasingly frequently used. Among the most successful green strategies, it is necessary to stress the processes without any use of solvents in the reaction medium and the processes involving alternative methods of energy input for process activation, such as mechanical treatment in high-frequency mills of various types [1–4], microwave treatment [5–7], ultrasonic energy [8–10] and their joint use [11].

During recent years, much attention is paid to the requirements of green chemistry aimed at the promotion of ecological and sustainable growth of production, with a focus on the efficiency of the use of resources and energy saving, the development of cyclic economics [12].

Traditional extraction methods, such as maceration, percolation, fermentation, are now giving way to the advanced methods to enhance the efficiency of extraction and selectivity of the isolation of biologically active compounds to meet the growing demand on the market. Advanced technologies involve various approaches, for example, microwave and ultrasonic irradiation of reacting components and media, the application of pressure and supercritical liquids, electric fields, enzymes. Innovative methods of extraction allow obtaining final extracts selectively rich in target compounds, without artefacts, and these methods are distinguished by simplicity, rapidity, ecological safety in comparison with traditional methods of extraction [13].

During several recent decades, mechanochemistry has become a powerful tool providing ecologically safe chemical syntheses with small energy consumption. Mechanochemistry not only demonstrated alternatives to traditional synthesis in solutions but also proved its success in the enhance-

ment of the reactivity of raw materials and the possibility to unlock new compounds that are unavailable for extraction from complicated plant systems using usual methods. One of the strategies to meet the demand for more ecological synthetic methods implies a radical decrease or rejection of the use of solvents on all synthesis routes, from laboratory installations to large-scale production. In this respect, mechanochemical methods open enormous outlooks due to the development of synthetic routes to complicated molecules without the use of solvents or with their minimal use [14]. Solid-phase mechanochemical methods hold special advantages in obtaining antioxidants which are unstable in liquid media [15].

The principles of green chemistry imply changes in traditional chemical synthesis. First of all, it is the use of less toxic initial materials and solvents, an increase in the efficiency of synthetic methods, a decrease in the number of synthesis stages, and minimization of wastes. In this context, chemical synthesis becomes a part of efforts aimed at the sustainable development of society. Microwave synthesis made a revolution in chemical synthesis within a short time because it provides pure synthesis with the advantage of increased reaction rates, higher yields, higher selectivity and efficiency of the processes [16].

The goal of the present work was to study the effect of various methods of physical action on extraction and organic synthesis for the purpose of developing new green technologies for obtaining practically essential substances and materials, and to generalize the results obtained by the authors.

#### MECHANO-CHEMICAL EXTRACTION OF PLANT RAW MATERIALS

At present, many biologically active substances (BAS) are obtained from natural raw materials of plant or animal origin. In spite of the large number of highly efficient synthetic medicinal preparations, medicinal herbs are still leading in the production of therapeutic agents. Every third medicinal preparation among those present in the arsenal of modern medicine is a product of plant origin. Due to the complicated chemical structure of natural substances, their synthesis often appears to be too labour-intensive and economically unprofitable, so extraction is still a usual technology for the isolation of BAS from plant raw materials. Traditional extraction methods take much time and labour, require high consumption of toxic organic solvents, acids and alkalis, and pro-

duce wastes polluting environment. The low BAS content in plant raw materials and high labour intensity for their extraction bring complications to the production of medicinal substances, while the use of large amounts of solvents brings about ecological problems and reduces the safety of production.

The efficiency of extraction increases with an increase in the dispersity of raw materials. Mechanical treatment of plant raw materials involves first of all grinding. Grinding itself, to particle size less than the size of cells in the plant tissue, implies an increase in the yield, because the access of the solvent to BAS inside the cells is thus simplified. However, at the same time, the yield of ballast substances may increase, and the composition of the extracts may become more complicated because the substances previously inaccessible for the solvent would be extracted too.

We proposed to use solid-phase mechanochemical method to obtain preparations. The method involves mechanical treatment of powdered mixtures of plant raw materials and solid substances with various chemical properties [17]. It is assumed that the cells of plant raw materials are destroyed as a result of this kind of treatment, BAS travel over the particle of the raw material, come in contact with the solid phase which corresponds to the chemical nature of BAS, passes selectively to the solid phase and then may be easily isolated, concentrated and dried. The treatment is carried out in activator mills of planetary and roller types [18]. The high efficiency of mechanochemical technology allows using the plant raw materials with low BAS concentration, in particular large-scale wastes of agricultural production and food industry, which are economically unprofitable to be processed using existing methods [19].

One of the objects of our investigation was the medicinal plant aconite, *Aconitum septentrionale* Koelle. Its roots contain diterpene alkaloid lappaconitine, which possesses high physiological activity. Antiarrhythmic preparation with the commercial name Allapinin was developed on this basis [20]. The industrial method of obtaining this preparation is multistage liquid extraction. A method of lappaconitine extraction from the roots of aconite using the solid-phase mechanochemical method was developed. The advantages of the new method are evident: a sharp simplification of the scheme of isolation of the target product and an increase in the yield, decrease in the consumption of solvents, time, energy consumption, the

absence of hazardous acid-alkaline wastes. According to the data obtained by means of high-performance liquid chromatography, lappaconitine content in the primary extract obtained according to the traditional technology does not exceed 20 %, while lappaconitine content of the extract of the reaction mixture after mechanochemical treatment is 73 %. Evidently, it is much easier to isolate the target product from this concentrate.

Successful application of mechanochemical solid-phase extraction was demonstrated also during the isolation of berberin, an alkaloid possessing hepatoprotective properties (the corresponding preparation is Berberine sulphate) which is present in the roots of Siberian berberis, the extraction of alkaloid teobromine, an active component of a series of cardiostimulating preparations, from the husk of cocoa beans, and the extraction of a sum of sesquiterpene lactones possessing anti-helminthic action (Helenin preparation) from the roots of *Inula helenium*. The yields of BAS obtained by means of mechanochemical solid-phase extraction are 1.5–2 times higher than those from the traditional method (Table 1) [21].

The plants of *Sophora* genus, Fabaceae family are widespread over the territory of East Siberia, China and Tibet. They are used at all times as medicinal plants in folk and traditional medicine. The medicinal action of *Sophora flavescens* Soland. is due to BAS that are present in the plant:

quinolizidine alkaloids, flavonoids and saponins [22]. It was shown that mechanochemical treatment of the roots of sophora in the presence of adsorbent enhances the yield of the target low-molecular BAS (Table 2).

Attention should be paid to the fact that the maximal yield of extractable substances was obtained with the traditional method of extraction from roots, but alkaloids are poorly extracted using this method. A substantial increase in the yield of alkaloids is achieved in the case of mechanochemical treatment of the raw materials with the solid sorbent. During the treatment of the resulting mechanically activated mixture with chloroform, alkaloids are the first to be eluted, while more polar substances remain on the sorbent. Thus not only an increase in the yield of alkaloids is achieved but also a high selectivity of their isolation.

We studied the possibility to extract low-molecular BAS in the salt water-soluble form using solid-phase mechanochemical transformations of natural macromolecules with the major classes of reagents – alkalis and acids. The major component in the sum of alkaloids of sophora is matrin [23]. The roots of sophora were subjected to mechanochemical treatment together with acids in order to obtain water-soluble form of the basic alkaloid matrin. The best result was achieved when the roots were milled with succinic acid.

TABLE 1

Yields of target products after usual and mechanochemical extraction, % of raw material [21]

Target product	Extraction	
	Usual	Mechanochemical
Lappaconitine	0.3	1.3
Berberin	0.8	2.0
Teobromine	0.5	1.3
Sesquiterpenic lactones	2.0	5.0

TABLE 2

Effect of mechanochemical treatment on the isolation of alkaloids from the roots of *Sophora flavescens*

Extraction conditions	Yield of extract, % with respect to raw material	Alkaloid content, % in extract	Yield of the sum of alkaloids, % of raw material
Usual extraction	15.60	2.56	0.40
Preliminary mechanical treatment, desorption with dichloroethane	1.28	36.72	0.57
Mechanochemical treatment with the sorbent, desorption with chloroform	3.40	67.65	2.30

## MICROWAVE EXTRACTION

Microwave extraction (MWE) attracts increasing attention as an alternative for the extraction of secondary metabolites of plants. Unlike usual extraction of the solid raw material with a liquid, MWE promotes substantial increase in extraction time because microwave heating of the solvent occurs rapidly. In this case, the temperature gradient may be reduced to a minimum, and the rate of heat transfer may be increased substantially. In addition, the

use of MWE allows one to decrease the consumption of solvents and energy substantially, and to increase the efficiency of extraction [24].

Weak hydrogen bonds are destroyed during microwave heating due to activated rotation of molecular dipoles. Microwave radiation affects directly water molecules inside a plant cell *in situ*, due to which the temperature inside the cell rises quickly. Pressure arising due to the evaporation of water in the cell during microwave activation leads to the rupture of cell membranes and cell walls, and to the formation of channels which are flow paths. As a result, the diffusion of dissolved BAS from the cell is simplified, which enhances extraction efficiency [25].

The processes of BAS isolation from natural raw materials under microwave action were studied, and the conditions of MWE of alkaloids from the roots of *Sophora flavescens* Soland. were investigated. The dependence of the yield of a sum of alkaloids on MWE conditions (input power, activation time, temperature and the solvent involved) was demonstrated. Under the conditions of microwave activation for 20 min at the power of 200 W, temperature was varied within the range 50–70 °C. The maximal yield of root extract was 12.6 %, the sum of alkaloids – 0.5 %, herb extract – 16.0 %, the sum of alkaloids from the herb – 1.0 % at 70 °C. Results of the analysis of the sum of alkaloids, obtained with different MWE modes, by means of gas chromatography – mass spectrometry (GC-MS) show that matrin content is 65–84 %. In addition to the basic alkaloid matrin, GC-MS revealed also minor alkaloids: cytisine, sophoranol, sophoramine, sophoridine, caulophyllin, anagyrin, thermopsine, 5,6-dihydrospartein-2-one and isosophoramine [26].

#### ULTRASOUND EXTRACTION

One of the promising directions in the development of new processes for chemical and adjacent technologies is the use of the energy of ultrasonic (US) vibrations of high intensity. Ultrasound is elastic vibrations with the frequency above 15–20 kHz. The high efficiency of plant raw material processing involving US is due to the unique properties of US vibrations, namely the ability to generate local ruptures in liquid and liquid dispersed media, to form so-called cavitation bubbles, to provide the input of high energy into the media under treatment (up to 500 W/cm<sup>2</sup>) and to generate high local pressure. Ultrasonic waves may

accelerate chemical reactions due to emulsification of liquid components, dispersion of solid components and catalysts, erosion of their surface, degassing, prevention of precipitation or coagulation of the products, intense mixing etc. At present, it is confirmed that it is reasonable to carry out extraction in the field of high-power US, when active cavitation takes place in the medium, which leads to erosion and dispersion of plant raw materials due to pulsation and collapse of cavitation bubbles, in particular due to Bjerknes force, when a cavitation bubble interacting with two solid surfaces moved to the depth of a cavern (a slit) under the action of the resulting force, and there it collapses [27]. It is essential to stress that the use of US in comparison with other extraction methods not only accelerates the isolation of the major extractable component from the plant raw material but also increases the yield of side products [28, 29].

We used US extraction to isolate the sum of alkaloids from different vegetative organs of sophora. We studied the effect of time and power of US action on the yields of the sums of alkaloids. The optimal conditions of US activation of extraction process using ethanol are as follows: power, 60 W/cm<sup>2</sup>; activation time, 6 min. For US extraction of roots and pericarps of sophora under these conditions, the yield of alkaloids was substantially higher than the yield from usual extraction, for herb the yield was comparable, while for the seeds it turned out to be somewhat lower. It is possible that higher power of US action is necessary for seed dispersion (Fig. 1).

In all cases, a decrease in extraction time is indisputable advantage of US extraction. The yield of the sum of alkaloids from pericarps in the case of US extraction after 6 min was 1.7 %, while in the case of traditional extraction the yield was 1.2 % after 24 h. Alkaloids present in roots, herb, seeds and pericarps of sophora were identified by means of GC-MS [30].

#### MECHANOCHEMICAL ACTIVATION OF ORGANIC SYNTHESIS

Chemical reaction may be caused by the mechanical action of a solid reagent or a mixture of reagents. Under mechanical action, a strain field is formed in a solid body. When the time of mechanical action and the formation of strain field and its relaxation is shorter than the rate of chemical reaction, energy is accumulated in the solid body in the form of defects. In this case, mechanical activation is the correct term. When

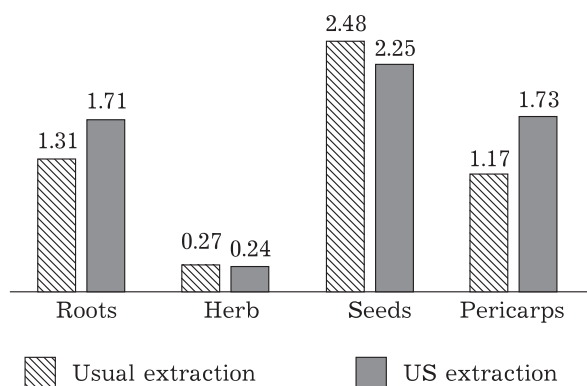


Fig. 1. Comparison of the yields of the sum of alkaloids of the vegetative organs of sophora after usual and ultrasonic (US) extraction, % [30].

reaction proceeds rapidly, directly during mechanical treatment, these processes are called mechanochemical [31].

Synthetic advantages of mechanochemistry are evident: elimination of solvents renders ecologically safe nature to the reactions and excludes wastes. Reactions are carried out at moderate temperatures, which requires less energy consumption than their analogues in solution. These factors are especially important in industry. The absence of solvents means also that the limitations of reagent solubility and solvolysis may be avoided, due to which a number of alternative initial raw materials become accessible, and process cost often decreases. There is no doubt that mechanochemistry may provide selectivity, as well as the synthesis of substances and materials which can hardly be obtained in solution [32–34].

The major role of mechanical action is reduced to forced transport of reacting particles and provision of contacts between them, though other mechanisms also contribute into reaction progress. Two mechanisms of mechanochemical reactions are most probable: 1) under the action of mechanical strain, mixing at the molecular level occurs, and 2) the product is formed on the surface of macroscopic reacting particles. Mechanochemical reactions in activator mills include three main stages: material grinding, which is necessary to provide the optimal particle size; reagent mixing, which is necessary for the maximal contact between particles; reaction itself. All the three stages take place in modern activator mills, though different levels of input energy are required for their implementation [31, 35].

Solvent-free reactions are of special interest. In some cases, organic synthesis may be carried

out without the use of any solvent, till the stage of product isolation [36]. Some solid-phase organic reactions proceed more efficiently and selectively than their analogues in solution. Reviews of various mechanochemical organic reactions without the use of solvents including catalytic reactions, condensation reactions, nucleophilic addition, cascade reactions, Diels–Alder reactions, oxidation, reduction, halogenation, aminohalogenation, *etc.* Mechanochemical approaches are used to synthesize calyxarenes, rotaxanes and carcass compounds, asymmetric synthesis, as well as for the transformation of biologically active compounds [37–39].

Lappaconitine (**I**) is alkaloid extracted from the roots of aconite; it possesses antiarrhythmic activity and reduces arterial pressure [40]. However, the application of the preparation based on lappaconitine must be strictly dosed due to its high toxicity and side effects [41]. For the purpose of improving the pharmaceutical properties of lappaconitine, we synthesized its derivatives: N-oxide of lappaconitine (**II**) and N-deethylappaconitine (**III**), possessing lower toxicity and conserving the physiological activity [42]. To exclude chlorine-containing solvents from the solvent-based synthesis, solid phase oxidation of lappaconitine under the action of *m*-chloro-perbenzoic acid (*m*-Cl-PBA) and deethylation under the action of N-bromosuccinimide (NBS) without the participation of a solvent under the conditions of mechanical activation were studied. The scheme of the synthesis of compounds **II** and **III** is shown in Fig. 2.

Mechanochemical synthesis was carried out using a vibratory mill SPEX-8000 (CertiPrep Inc., USA) for 30 min. Temperature rise and agglutination of the reaction mixture were observed. To achieve better mixing and to prevent agglutination,  $\alpha$ - $\text{Al}_2\text{O}_3$  was added into the reaction mixture as a loosener. The yield of the products was determined by means of high-performance liquid chromatography (HPLC) after the treatment of the reaction mixture, lappaconitine N-oxide **II** was synthesized with a yield of 64 %.

It was demonstrated that mechanochemical activation of a mixture of solid reagents lappaconitine **I** and NBS involves N-deethylation of lappaconitine with the formation of N-deethylappaconitine **III**. The effect of the duration of mechanical activation and the addition of a solid sorbent on the yield of target product was studied. The maximal yield of N-deethylappaconitine according to the data of HPLC was 47–50 % after mechanical activation of the reagents for 20 min [43].

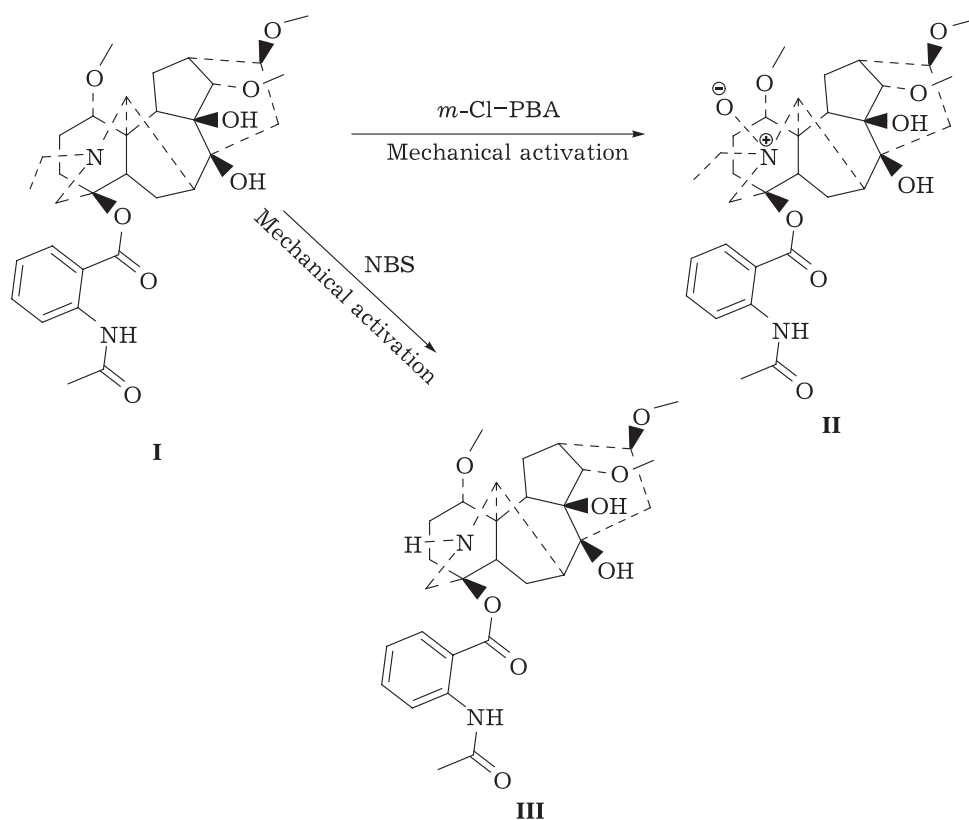


Fig. 2. Scheme of mechanochemical synthesis of lappaconitine N-oxide (II) and N-deethylappaconitine (III) [43].

The problem of improving the therapeutic properties of medicinal agents is rather relevant because long-term intake of medicines often cause side effects. Piroxicam (IV) is a nonsteroidal anti-inflammatory preparation belonging to the class of compounds of the N-heterocyclic carboxamide series. However, its long-term intake may lead to ulceration of stomach walls. As reported in the literature, some acylated derivatives of piroxicam possess improved therapeutic properties conserving antiinflammatory activity [44]. Mechanochemical acylation of piroxicam with benzoic, phthalic and maleic anhydrides did not lead to success. For this reason, more active solid acylating agents were chosen: 3,5-dinitrobenzoyl chloride and *p*-nitrobenzoyl chloride. Acylated derivatives of piroxicam were obtained according to the reaction presented in Fig. 3. Piroxicam was subjected to preliminary mechanical treatment to transform it into more reactive zwitter ion form (IVa) [45, 46].

As a result of the studies, the possibility of mechanochemical acylation of piroxicam was demonstrated. Through the joint mechanical activation of piroxicam with *p*-nitrobenzoyl chloride in the presence of triethylamine (TEA) supported

on  $\text{Al}_2\text{O}_3$ , *p*-nitrobenzoate of piroxicam (V) was obtained [47].

#### MICROWAVE ACTIVATION OF ORGANIC SYNTHESIS

Microwave (MW) chemistry is becoming a promising method allowing one to exclude the use of toxic solvents and reagents, and to decrease energy consumption in the technologies of organic synthesis. The efficiency of rapid MW heating consisting in a sharp decrease in reaction time (from days and hours to minutes and seconds) is only one of many advantages.

Microwave radiation is electromagnetic radiation within frequency range from 0.3 to 300 GHz. All modern specialized MW reactors for chemical synthesis operate at a frequency of 2.45 GHz (which corresponds to the wavelength of 12.24 cm), to avoid interference at the frequencies of telecommunication and mobile phones. The phenomenon of microwave dielectric heating depends on the ability of a specific substance (reagent or solvent) to absorb MW energy and transform it into heat [48].

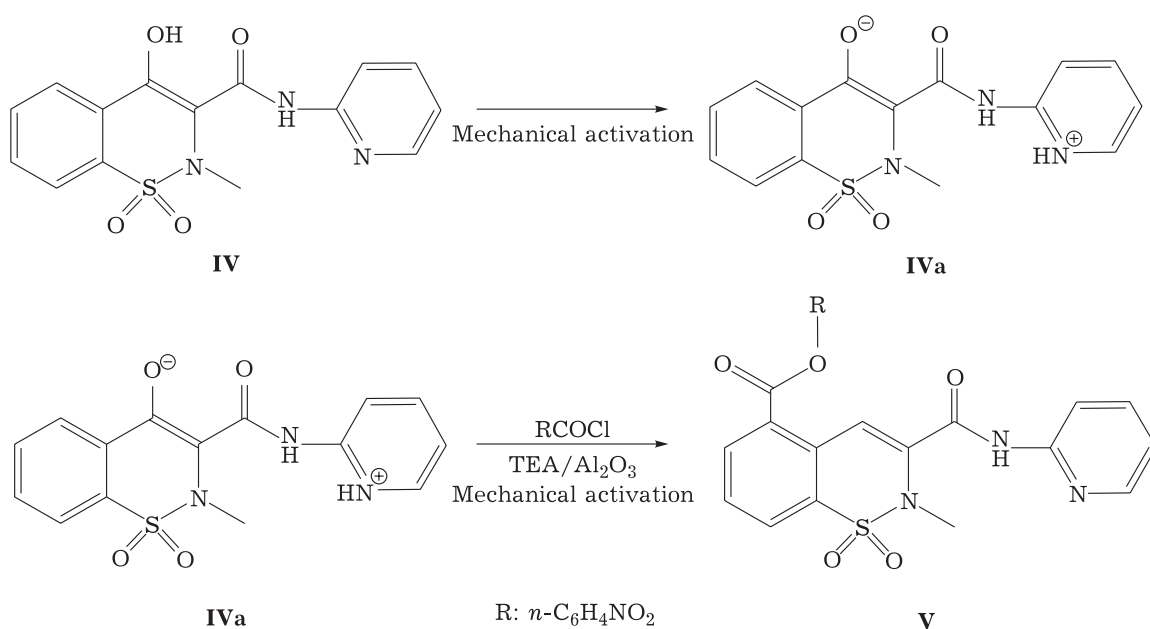


Fig. 3. Scheme of mechanochemical acylation of piroxicam (IV) [47].

At present, the use of the ability of some liquids and solids to transform MW energy into heat allows governing chemical reactions. The mode of energy transformation *in situ* is attractive for chemists because its scale is dependent on the dielectric properties of molecules. This opens the possibilities to control the properties of a material to some extent and to achieve selectivity of reaction. Organic reactions in the absence of solvents and in aqueous solutions attract increasing attention of chemists, especially from the viewpoint of green chemistry [49]. The use of MW activation in these reactions is one of the most convenient and efficient methods [50]. The synthesis of imides without the use of solvents under the action of MW radiation in a domestic MW furnace was described in one of the first communications as one of a more ecological method [51].

We carried out a thorough investigation of the interaction of phthalic anhydride with glycine under MW activation to understand the nature of the action of MW radiation on the reaction progress. The equipment provided continuous record of sample temperature, excess pressure in the reaction ampoule, and the dynamics of MW power changes in the achievement and maintenance of the necessary temperature values.

The dependence of heating rate separately for phthalic anhydride and glycine on MW power was determined. It was established that the efficiency of MW heating increases sharply during melting of the substances under study. This is clearly seen on

the curves of the dependence of heating dynamics on the power of MW radiation, where the point of inflection corresponds to the appearance of melt phase [52] (Fig. 4).

For an equimolar mixture of reagents, active absorption of MW energy starts from the appearance of the melt of phthalic anhydride. The synthesis of glycine phthalimide under the action of MW activation proceeds in a two-step mode: at first, reaction mixture is kept for 5 min at the temperature of the melt of phthalic anhydride, and then it is additionally kept for 5 min at the temperature of glycine melting. Under these conditions, at a temperature within the range 200–240 °C, power 200 W, glycine phthalimide was obtained within 10 min with the yield of 90% [53]. So, the method for the synthesis of phthalimides with MW activation without any use of solvents was developed, the boundary conditions for the synthesis were determined, and the general character of the conditions of the reaction of phthalimide synthesis was shown.

One of the most important problems of modern medicine is the arrest of bleeding during surgical operations and in the cases of traumatic injury of organs. Special attention is paid to local hemostatic agents that are efficient in local zones. Monocarboxylcellulose for use in medical practice as hemostatic agent able to get resorbed is obtained by the oxidation of cellulose with nitrogen oxides – nitrogen dioxide (NO<sub>2</sub>) or dinitrogen tetroxide (N<sub>2</sub>O<sub>4</sub>) in the gas phase and in the me-

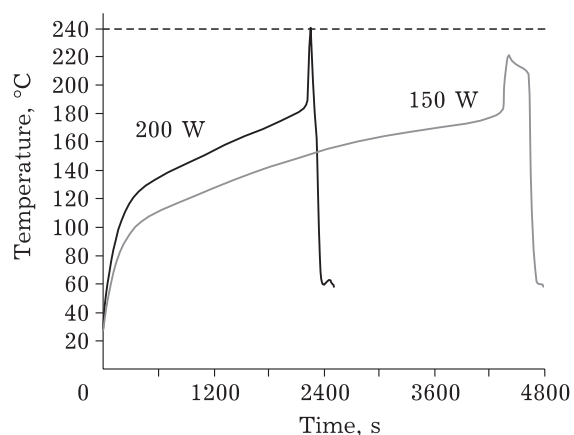


Fig. 4. Dependence of the rate of glycine heating on the power of microwave radiation [52].

dium of organic solvents. Oxidized cellulose with the content of carboxylic groups 12–25 % is suitable for use as biodegradable hemostatic means [54]. The major disadvantages of the methods known at present include the length of process duration (up to 70 h) and the low content of carboxylic groups in the product [55]. A method was developed to obtain hemostatic material based on oxidized cellulose under the action of  $\text{NO}_2$  with the use of MW radiation. Oxidation of cellulose (cloth, powder) was carried out with a solution of  $\text{NO}_2$  in hexane under the action of MW radiation with the constant power of 20–200 W at a temperature of 30–50 °C for 2–5 h. Cellulose oxidation degree equal to 19.0 % was achieved [56].

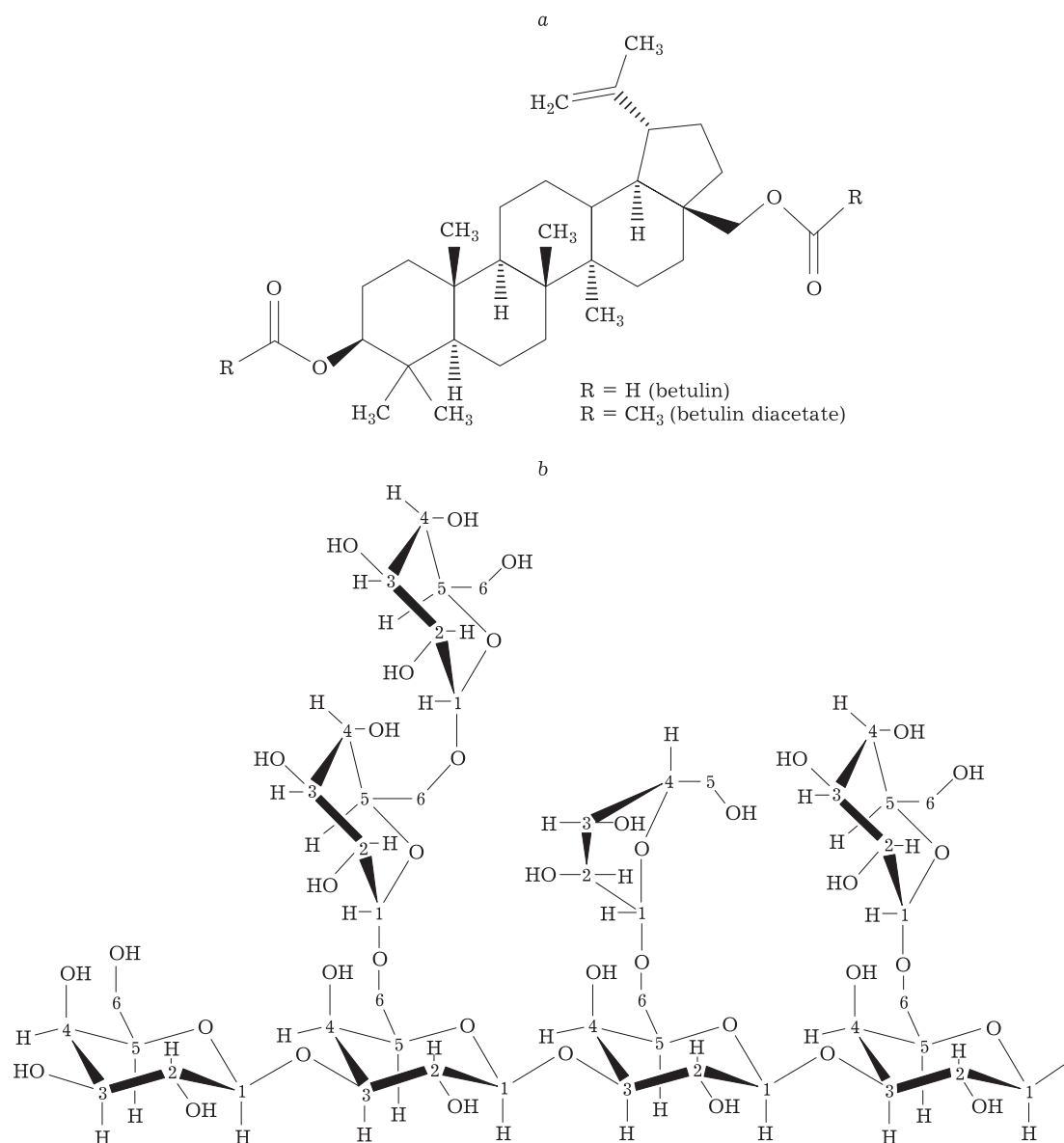


Fig. 5. Molecular structures of betulin, betulin diacetate (*a*) and a fragment of arabinogalactan structure (*b*) [58].



Microwave treatment may be used to activate heterogeneous reactions in the aqueous medium. Betulin diacetate (BDA), an ester of acetic acid and betulin, possesses diverse biological activity [57]. However, the poor solubility of BDA in water decreases its biological availability and limits its application. The composites of water-soluble polysaccharide arabinogalactan (AG) with BDA (Fig. 5) with higher solubility and high antitumour activity against A549 lung adenocarcinoma cells were obtained mechanochemically, though the preparation of BDA-AG complex in solution took much time [58].

For the purpose of improving the method of obtaining BDA-AG complex, decreasing the process duration and increasing the yield of the product, the effect of MW irradiation on the properties of AG and BDA and their interaction in the aqueous suspension was studied.

Under the conditions of MW irradiation, reaction time decreases from several hours to several minutes in comparison with the traditional synthesis. Changes of the size and morphology of the surface of BDA crystals during MW heating were observed. MW action is likely to promote the dissolution of BDA in water, which may promote high-rate synthesis of supramolecular complex. The BDA-AG complex, isolated in the form of thin film from the aqueous solution heated with MW radiation, exhibited antitumour activity against the cells of Ehrlich's ascitic carcinoma [59].

Developing the methods for the synthesis of lappaconitine derivatives [43] in the format of green chemistry, we used MW activation as an alternative method to carry out the reaction. Ox-

one ( $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ ) was chosen as the oxidizing as a highly active, non-toxic reagent soluble in water, organic solvents and aqueous-organic mixtures. The interaction of lappaconitine (I) with oxone under the action of MW radiation was carried out both in the absence of any solvent and in the solvent (water). The reaction was carried out under the conditions similar to those indicated in [60]. Lappaconitine N-oxide (II) was obtained in a yield close to the quantitative one [61]. Reaction scheme is shown in Fig. 6.

## CONCLUSION

The increasing attention to green chemistry caused the development of numerous ecological procedures for the isolation of BAS from natural sources and the synthesis of organic molecules of practical interest. Among green methodologies attracting attention, the methods of physical activation of extraction and synthesis occupy the key position. Mechanochemistry, microwave chemistry and the use of ultrasound become promising methods allowing an increase in the yield of target products, substantial decrease or elimination of the volumes of solvents used, a decrease in energy consumption and the cost of products.

Mechanochemical method of BAS extraction from plant raw materials was developed. The advantages of the new method were demonstrated: a sharp simplification of the scheme of isolation of target products and an increase in the yield, decrease in the consumption of solvents, time, energy, the absence of acid-basic wastes. The efficiency of the use of microwave and ultrasonic

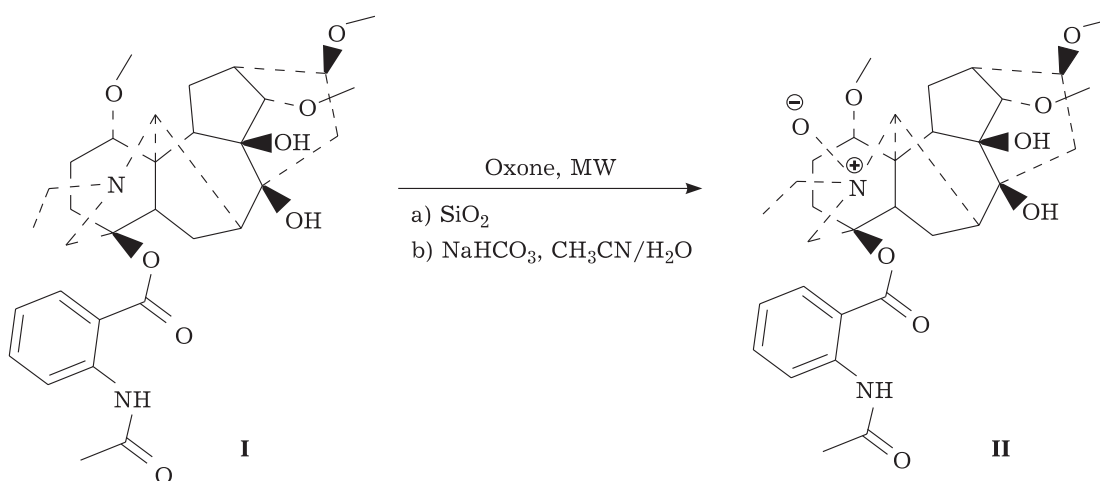


Fig. 6. Scheme of lappaconitine (I) oxidation by oxone under the action of MW radiation without solvent (a) and in aqueous medium (b) [61].

activation of extraction processes for the isolation of alkaloids from plants was demonstrated.

Examples of mechanochemical and microwave organic synthesis of the derivatives of natural and synthetic physiologically active compounds and a supramolecular complex of betulin diacetate with arabinogalactan are presented. A broad variability of synthesis conditions was demonstrated both in solution and without the use of solvents.

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## REFERENCES

- Aslam M. Sh., Ahmad M. S., Atanassova M. S., Ahmad M. A. Mechanochemical-assisted extraction method on medicinal plants: A brief review, *Adv. Environ. Biol.* 2017. Vol. 11, No. 2. P. 84–90.
- Wu K., Ju T., Deng Y., Xi J. Mechanochemical assisted extraction: A novel, efficient, eco-friendly technology. Review, *Trends Food Sci. Tech.* 2017. Vol. 66. P. 166–175.
- Shuling Wang, Rui Zhang, Xiaoyu Song, Mengmeng Wei, Tian Xie, and Jun Cao. Mechanochemical-assisted extraction of active alkaloids from plant with solid acids, *ACS Sustain. Chem. Eng.* 2018. Vol. 7, No. 1. P. 197–207.
- Lomovsky O. I., Lomovskiy I. O., Orlov D. V. Mechanochemical solid acid/base reactions for obtaining biologically active preparations and extracting plant materials, *Green Chem. Lett. Rev.* 2017. Vol. 10, No. 4. P. 171–185.
- Llompert M., Celeiro M., Dagnac T. Microwave-assisted extraction of pharmaceuticals, personal care products and industrial contaminants in the environment, *Trends in Analytical Chemistry*. 2019. Vol. 116. P. 136–150.
- Li Hong, Zhao Zhenyu, Xiouras Christos, Stefanidis Georgios D., Li Xingang, Gao Xin. Fundamentals and applications of microwave heating to chemicals separation processes, *Renew. Sust. Energ. Rev.* 2019. Vol. 114. 109316.
- Chaturvedi A. K. Extraction of nutraceuticals from plants by microwave assisted extraction, *Sys. Rev. Pharm.* 2018 Vol. 9, No. 1. P. 31–35.
- Teng Xiuxiu, Zhang Min, Devahastin Sakamon. New developments on ultrasound-assisted processing and flavor detection of spices: A review, *Ultrason. Sonochem.* 2019. Vol. 55. P. 297–307.
- Chemat F., Rombaut N., Sicaire A.-G., Meullemiestre A., Fabiano-Tixier A.-S., Abert-Via M. Ultrasound assisted extraction of food and natural products. Mechanisms, techniques, combinations, protocols and applications. A review, *Ultrason. Sonochem.* 2017. Vol. 34. P. 540–560.
- Albero B., Tadeo J. L., Perez R. A. Ultrasound-assisted extraction of organic contaminants, *TrAC*. 2019. Vol. 118. P. 739–750.
- Vinatoru M., Mason T. J., Calinescu I. Ultrasonically assisted extraction (UAE) and microwave assisted extraction (MAE) of functional compounds from plant materials, *Trends in Analytical Chemistry*. 2017. Vol. 97. P. 159–178.
- Zuin V. G., Segatto M. L., Ramin L. Z. Plants as resources for organic molecules: Facing the green and sustainable future today, *Curr. Opin. Green Sustain.* 2018. Vol. 9. P. 1–7.
- Belwal T., Ezzat Sh. M., Rastrelli L., Bhatt I. D., Daglia M., Baldi A., Devkota H. P., Orhan I. E., Patra J. K., Das G., Anandharamakrishnan C., Gomez-Gomez L., Nabavi S. F., Nabavi, S. M., Atanasov, A. G. A critical analysis of extraction techniques used for botanicals: Trends, priorities, industrial uses and optimization strategies, *Trends in Analytical Chemistry*. 2018. Vol. 100. P. 82–102. doi.org/10.1016/j.trac.2017.12.018.
- Tana D., Garcia F. Main group mechanochemistry: from curiosity to established protocols, *Chem. Soc. Rev.* 2019. Vol. 48. P. 2274–2292.
- Lomovsky O. I., Lomovsky I. O. Chapter 13. Mechanochemically Assisted Extraction. Contemporary Food Engineering Series. Enhancing Extraction Processes in the Food Industry, N. Lebovka, E. Vorobiev, F. Chemat (Eds.). Boca Raton, London, NY: CRS Press, Taylor & Francis Group, 2012. P. 361–398.
- Grewal A. S., Kumar K., Redhu S., Bhardwaj Sh. Microwave assisted synthesis: a green chemistry approach, *Int. Res. J. Pharm. App. Sci.* 2013. Vol. 3, No. 5. P. 278–285.
- Pat. RU 2176919 C2. 2001.
- Lomovsky O., Bychkov A., Lomovsky I. Chapter 2. Mechanical Pretreatment. Biomass Fractionation Technologies for a Lignocellulosic Feedstock Based Biorefinery, S. I. Mussatto (Ed.), Elsevier, 2016. P. 23–55.
- Bychkov A. L., Ryabchikova E. I., Korolev K. G., Lomovsky O. I. Ultrastructural changes of cell walls under intense mechanical treatment of selective plant raw material, *Biomass Bioener.* 2012. Vol. 47. P. 260–267.
- Yunusov M. S. Antiarrhythmics based on diterpene alkaloids, *Izv. AN. Ser. Khim.* 2011. Vol. 4. P. 620–624.
- Pankrushina N., Lomovsky O., Boldyrev V. The new “green” methodology for isolation of natural products from medicinal plants utilizing a mechanochemical approach, *Planta Med.* 2007. Vol. 73, No. 9. P. 931.
- Huang J., Xu H. Matrine: Bioactivities and Structural Modifications, *Curr. Top. Med. Chem.* 2016. Vol. 16, No. 28. P. 3365–3378.
- Sandanov D. V., Pankrushina N. A. Alkaloid content in different parts of *Sophora flavescens*, *Khim. Prirod. Soed.* 2011. Vol. 4. P. 585–586.
- Desai M., Parikh J., Parikh P. A. Extraction of natural products using microwaves as a heat source, *Sep. Purif. Rev.* 2010. Vol. 39, No. 1–2. P. 1–32.
- Veggi P. C., Martinez J., M. Meireles A. A. Chapter 2. Fundamentals of Microwave Extraction. Microwave-assisted Extraction for Bioactive Compounds. Theory and Practice, Boston MA: Springer, 2013. 238 p.
- Pankrushina N., Eroshenko Yu., Salnikova O., Mikheev A. The microwave assisted extraction of alkaloids from *Sophora flavescens* roots. Book of abstracts 4th Annual Russian-Korean Conference “Current issues of natural products chemistry and biotechnology”, Novosibirsk, Russia, 18–21 September 2012, P. 51.
- Chen D., Sharma S. K., Mudhoo A. Handbook on Applications of Ultrasound: Sonochemistry for Sustainability, Boca Raton: CRC Press, 2011. 739 p.
- Medina-Torres N., Ayora-Talavera T., Espinosa-Andrews H., Sanchez-Contreras A., Pacheco N. Ultrasound assisted extraction for the recovery of phenolic compounds from vegetable sources. A review, *Agronomy*. 2017. Vol. 7, No. 3. P. 47–65.
- Chuyen H. V., Nguyen M. H., Roach P. D., Golding J. B., Parks S. E. Microwave assisted extraction and ultrasound

- assisted extraction for recovering carotenoids from Gac peel and their effects on antioxidant capacity of the extracts, *Food Sci. Nutr.* 2018. Vol. 6. P. 189–196.
- 30 Pankrushina N., Korotkih M., Mikheev A. Mechanochemical, microwave, ultrasound assisted isolation of natural alkaloids. Book of Abstracts Int. Conf. “MedChem-2015”, Novosibirsk, Russia, 5–10 July 2015, P. 244.
- 31 Boldyrev V. V. Reactivity of solids and new technologies. Reactivity of Solids. Past, Present and Future. (IUPAC Series. Chemistry for 21st Century). Cambridge, Mass.: Blackwell Science, 1996. P. 267–285.
- 32 Wang G.-W. Mechanochemical organic synthesis, *Chem. Soc. Rev.* 2013. Vol. 42. P. 7668–7700.
- 33 Achar T. K., Bose A., Mal P. Mechanochemical synthesis of small organic molecules, *Beilstein J. Org. Chem.* 2017. Vol. 13. P. 1907–1931.
- 34 Ould M’hamed M. Ball milling for heterocyclic compounds synthesis in green chemistry: A review, *Synth. Commun.* 2015. Vol. 45, No. 22. P. 2511–2528.
- 35 Dubinskaya A. M. Transformations of organic substances under the action of mechanical strain, *Uspekhi Khimii.* 1999. Vol. 68, No. 8. P. 708–724.
- 36 Tanaka K., Toda F. Solvent-free organic synthesis, *Chem. Rev.* 2000. Vol. 100, No. 3. P. 1025–1074.
- 37 Friscic T. Supramolecular concepts and new techniques in mechanochemistry: Cocrystals, cages, rotaxanes, open metal-organic frameworks, *Chem. Soc. Rev.* 2012. Vol. 41. P. 3493–3510.
- 38 Tan D., Friscic, T. Mechanochemistry for organic chemists: An update, *Eur. J. Org. Chem.* 2018. Vol. 2018, No. 1. P. 18–33.
- 39 Leonardi M., Villacampa, M., Menendez J. C. Multicomponent mechanochemical synthesis, *Chem. Sci.* 2018. Vol. 9, No. 8. P. 2042–2064.
- 40 Mashkovskiy M. D. Medicinal agents. Moscow: Novaya Volna, 2010. 1216 p.
- 41 Sokolov S. F., Dzhakhangirov F. N. Antiarrhythmic preparation allapinin: a review of the results of clinical examination, *Kardiologiya.* 2002. Vol. 42, No. 7. P. 96–102.
- 42 Tolstikova T. G., Voevoda T. V., Dolgikh M. P. Psychotropic properties of alkaloid lappaconitine and some its derivatives, *Eksper. i Klin. Farmakol.* 2001. Vol. 64, No. 4. P. 7–9.
- 43 Pankrushina N. A., Nikitina I. A., Chernyak E. I., Boldyrev V. V. Mechanochemical synthesis of the derivatives of alkaloid lappaconitine, *Chem. Sust. Dev.* 2007. Vol. 15, No. 2–1. P. 149–155.
- 44 US Pat. No. 4309427, 1982.
- 45 Shakhtshneider T. P. Phase transformations and stabilization of metastable states of molecular crystals under mechanical activation, *Solid State Ion.* 1997. Vol. 101–103. P. 851–856.
- 46 Sheth A. R., Lubach J. W., Munson E. J., Muller F. X., Grant D. J. W. Mechanochromism of piroxicam accompanied by intermolecular proton transfer probed by spectroscopic methods and solid-phase changes, *J. Am. Chem. Soc.* 2005. Vol. 127. P. 6641–6651.
- 47 Pankrushina N., Nikitina I., Chernjak E., Myz C., Shakhtshneider T., Boldyrev V. Solvent-free mechanochemical modification of lappaconitine and piroxicam, *Mater. Manuf. Process.* 2008. Vol. 23. P. 561–565.
- 48 Kappe C. O., Stadler A., Dallinger D. Microwaves in organic and medicinal chemistry, 2nd Ed., John Wiley & Sons, 2012. 683 p.
- 49 Leadbeater N. E. (Ed.) Microwave heating as a tool for sustainable chemistry. Boca Raton, London, NY: CRC Press, Taylor & Francis Group, 2011. 278 p.
- 50 Loupy A. Solvent-free microwave organic synthesis as an efficient procedure for green chemistry, *C. R. Chimie.* 2004. Vol. 7. P. 103–112.
- 51 Borah H. N., Boruah R. C., Sandhu J. S. Microwave-induced one-pot synthesis of N-carboxyalkyl maleimides and phthalimides, *J. Chem. Res. (S).* 1998. Vol. 5. P. 272–273.
- 52 Mikheev A. N., Makotchenko V. G., Pankrushina N. A., Korotkih M. O., Arzhannikov A. V., Thumm M. K. A. Features of chemical reactions in the absence of solvents under microwave action, *Chem. Sust. Dev.* 2011. V. 19, No. 6. P. 669–677.
- 53 Tumanov N. A., Pankrushina N. A., Nefedov A. A., Boldyreva E. V. Nanoporous solvate of N,N-phthaloyl-glycine, *J. Struct. Chem.* 2012. Vol. 53, No. 3. P. 606–609.
- 54 Cheng W., He J., Wu Y., So C. Preparation and characterization of oxidized regenerated cellulose film for hemostasis and the effect of blood on its surface, *Cellulose.* 2013. Vol. 20. P. 2547–2558.
- 55 Wu Y. D., He J. M., Huang Y. D., Wang F. W., Tang F. Oxidation of Regenerated cellulose with nitrogen dioxide/carbon tetrachloride, *Fiber. Polym.* 2012. Vol. 13, No. 5. P. 576–581.
- 56 Pat. RU 2563279 C1, 2015.
- 57 WO Pat. No. 2013117137 A1, 2013.
- 58 Shakhtshneider T. P., Mikhailenko M. A., Kuznetsova S. A., Malyar Yu. N., Zamai A. S., Boldyrev V. V. New derivatives of betulin esters with arabinogalactan as highly potent anticancer agents, *Nat. Prod. Res.* 2016. Vol. 30. P. 382–1387.
- 59 Malyar Y. N., Mikhailenko M. A., Pankrushina N. A., Mikheev A. N., Eltsov I. V., Kuznetsova S. A., Kichkailo A. S., Shakhtshneider T. P. Microwave-assisted synthesis and antitumor activity of the supramolecular complexes of betulin diacetate with arabinogalactan, *Chem. Pap.* 2018. Vol. 72, No. 5. P. 1257–1263.
- 60 Hussain H., Green I. R., Ahmed I. Journey describing applications of oxone in synthetic chemistry, *Chem. Rev.* 2013. Vol. 113. P. 3329–3371.
- 61 Pankrushina N. A., Rakhmetali K. B. Synthesis of lappaconitine N-oxide under microwave activation, *Chem. Heterocycl.*