

ABSTRACT

of the dissertation for the degree of the doctor of philosophy (PhD)
on the specialty 6D060600 – Chemistry

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Synthesis and physical and chemical properties of novel bicyclic bisureas.

The work is devoted to the synthesis and study of some of the physical and chemical properties of new bicyclic bisureas.

In this work, we studied the cyclization reactions of glyoxal, butanedione and benzyl with urea derivatives (urea, methyl- and 1,3 - dimethyl urea) under various conditions. Investigations of the most common derivatives of bicyclic bisureas to determine the enzyme-induced activity in relation to the mono-oxygenase liver system in experimental animals were carried out.

The relevance of the topic of dissertation research. Most biologically active compounds are characterized by a clear interconnection between their spatial structure and the manifestation of pharmacological activity, which is, in other words, the stereo-specific nature of their hypothetical bioscale. The foregoing is confirmed by the use in medicine of a number of well-known drugs (levomycetin, etc.), when only one of the isomers is acting as a current substance

In recent years, one of the intensively developing sections of the chemistry of heterocyclic compounds is the synthesis and study of bicyclic bisureas, in part of glycoluril, due to their polyfunctionality and the presence of practically valuable properties. They are used as drugs, antimicrobial agents, and additives to polymers. Glycoluril is used as a starting material for tetrachloroglycoluril and tetrabromoglycoluril, which are used as biocides in water purification, disinfection of swimming pools, and as agents for controlling sludge in papermaking. Glycoluril can be used as a biocide in water-based paints, in liquid detergents and in care and cleaning products (in concentrations of 0.1%). It also finds use as a cross linking agent for hydroxyl-containing polymers as an industrial fungicide and as an accelerator in cements.

It is particularly important to note that one of the intensively developing areas in the chemistry of glycoluril is the synthesis and study on their basis of supramolecular compounds. Thus, glycolurils are the basic components of such polycyclic condensed systems such as cucurbiturils and bambusurils, possessing a number of unique physical and chemical properties.

An analysis of the literature on glycoluril chemistry showed that investigators did not pay enough attention to the synthesis and investigation of the chemical properties of N-methyl glycoluril derivatives, some of which have now found wide application in the chemically-pharmaceutical industry.

For example, among the derivatives of glycoluril, its specific place is occupied by its N - methyl derivatives on the basis of which preparations of psychotropic action (mebicar, albicar) are developed.

Despite the high interest, the synthesis of N - methyl derivatives of glycoluril has not been well studied, especially in the separation and identification of its regioisomers. In connection with this, the development of new methods for the synthesis, separation and identification of the spatial isomers of N-methylglycoluril is of great importance.

The interaction of ureas with glyoxal, butanedione and benzyl leads to the formation of new bicyclic bisureas, including N - methyl derivatives, possessing not only biologically active properties, but also having the potential to be applied in various industries, which is a major factor of interest for further study.

Since today in the available literature there is a lack of information summarizing the methods of synthesis and research of the chemical properties of methyl glycoluril derivatives, in this dissertation the knowledge in this field has been systematized.

The degree of elaboration of the problem.

Close attention to bicyclic bisureas, their chemically modified derivative of the pharmaceutical, cosmetic and food industries are dictated by the fact, that these substances possess a whole set of biologically useful and unique properties, for example: the investigations revealed a promising antioxidant agent - 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo [3.3.0] octane-3,7-dione - tetramethyl glycoluril (mebicar).

To assess the current status of this line of research, we carried out a wide information search, which allowed us to determine the scale of scientific research and the prospect of continuing to develop in this direction.

A detailed analysis of the literature data showed that, despite the current interest in this area, the reactions of cyclization of urea derivatives with glyoxal, butanedione and benzyl have not been adequately studied.

In connection with this, the search and development of new convenient methods for the synthesis of bicyclic bisureas remains relevant.

The purpose of the study is to realize the synthesis and study the physical and chemical properties of the new derivatives of bicyclic bisureas.

In order to accomplish the set goal, the following tasks were defined:

- study of the reaction of cyclization of glyoxal with ureas and determination of the isomeric composition for N-methylglycoluril;
- study of the reaction of cyclization of butanedione with ureas in acidic and basic catalyzed conditions;
- investigation of the bicyclization reaction of benzyl and ureas in acid-catalyzed conditions;
- develop methods for HPLC and TLC analysis for the detection of spatial isomers of glycoluril;
- develop a method for the preparative separation of N-methyl glycoluril spatial isomers;
- identify synthesized bicyclic bisureas;
- to investigate the biological activity of some synthesized bicyclic bisureas.

The assigned tasks of identifying substances were resolved using a wide range of modern spectral research methods, such as IR spectrometry,

chromatography-mass spectrometry, ^1H and ^{13}C NMR spectroscopy, HPLC, DCC and melting point determination.

The subject of these studies is the chemical and physical and chemical properties of some bicyclic bisureas, which are of great importance for pharmaceutical production, biochemistry, cosmetic industry, food industry, clinical and experimental medicine.

The scientific novelty of the work is determined by the fact that for the first time:

- Optimal methods of glyoxal synthesis with ureas were developed and the isomeric composition of N - methylglycoluril was studied;
- The cyclization of butanedione with urea in acidic and basic catalyzed conditions was studied;
- The reaction of bicyclization of benzyl and ureas in acid-catalyzed conditions was carried out;
- HPLC and TLC techniques have been developed for the detection of spatial isomers of N-methylglycoluril;
- A method of preparative separation of glycoluril spatial isomers was developed;
- Synthesized bicyclic bisureas are identified;
- The enzyme-inducing activity of some synthesized bicyclic bisureas has been investigated.

The scientific and practical significance of the research is in the development of new methods for the synthesis of derivatives of bicyclic bisureas — glycoluril, dimethylglycoluril, tetramethylglycoluril, diphenylglycoluril.

The results obtained represent theoretical and practical interest and will make a significant contribution to solving a number of topical issues of modern organic chemistry of heterocyclic compounds.

According to the results of the study, the enzyme-inducing activity of some synthesized bicyclic bisureas on the monooxygenase system of the mouse liver was determined.

An act of testing was obtained in the laboratory of pharmacology of the Siberian State Medical University for a number of synthesized bicyclic bisureas on possessing enzyme-inducing activity on the cytochrome-R-450 monooxygenase system of the mouse liver.

Conclusions based on the results of the research:

1. It is established that the cyclization reaction of glyoxal with methyl urea in an acidic medium in various conditions is completed by the formation of a mixture of spatial isomers dimethyl-2,4,6,8-tetraazabicyclo [3.3.0] octane-3,7-dione with the predominant formation of the anti - isomer.

2. During the study of the reaction of butanedione with methyl urea in acidic and basic catalyzed conditions, it was found that, depending on the conditions of the medium, the process proceeds with the formation of either a mixture of 1,5 - dimethyl - 2,6 - dimethyl-2,4,6,8-tetraazobicyclo [3.3.0] octane-3,7 dione and 1,5 - dimethyl - 2,8 - dimethyl-2,4,6,8-tetraazobicyclo [3.3.0] octane-3,7 dione, or with

the formation of an intermediate product bi-cyclization of 1-methyl-4,5-dimethyl-4,5-dihydroxyimidazolidin-2-one.

3. It has been shown that the interaction of benzyl with ureas in acid-catalyzed conditions leads to corresponding bicyclic bisureas, moreover, the condensation with methyl urea leads to the formation of two N-methyl isomers of diphenylglycoluril, while the interaction with dimethyl urea leads to the formation of the monocyclic product of 1,3-dimethyl-5,5-diphenylhydantoin.

4. Methods for the qualitative and quantitative determination of the spatial isomers of N, N'-dimethylglycoluril were developed by TLC and HPLC, as well as methods of their separation using column chromatography and preparative HPLC.

5. Study by HPLC - control of alkaline hydrolysis of a mixture of 2,4-dimethyl - 2,4,6,8-tetraazabicyclo [3.3.0] octane-3,7-dione and 2,6-dimethyl - 2,4,6, 8-tetraazabicyclo [3.3.0] octane-3,7-dione revealed that the intermediate hydrolysis products of both isomers are methylhydantoin and methylurea, which ultimately fall to acetamide.

6. For the first time on the basis of NMR spectroscopic data, chromatography-mass spectrometry of thermal analysis reliably identified individual N-methylglycoluril isomers.

7. For the first time, the enzyme-inducing activity of some synthesized derivatives has been investigated and it has been established that 1,5-diphenyl-2,4,6,8-tetraazabicyclo [3.3.0] octane-3,7-dione exhibits the most pronounced activity.

The main provisions for the defense:

- Reactions of cyclization of glyoxal with ureas and determination of the isomeric composition of N - methyl glycoluril;
- Reactions of cyclization of butanedione with ureas in acidic and basic catalyzed conditions;
- Bicyclization reactions of benzyl and ureas in acid-catalyzed conditions;
- The results of the detection of N-methylglycoluril spatial isomers;
- Developed methods for the preparative separation of N-methylglycoluril spatial isomers;
- Methods of identification for synthesized bicyclic bisureas;
- Results of studies on the enzyme-inducing activity of some synthesized bicyclic bisureas.

Interrelation of work with the plan of state scientific programs.

Dissertation work is carried out in the framework of joint science research work conducted at the Department of Chemistry of the Eurasian National University named after L.N. Gumilyev and at the Department of Physical and Analytical Chemistry of the National Research Tomsk State University (Tomsk, Russia).

Approbation of work. The main results of the dissertation work were published in the journals "Chromatographia", «Bulletin of the KarSU»; «Bulletin of ENU», were reported at international scientific and practical conferences: materials of the XI International (Ukrainian) scientific conference of students, graduates and young scientists "Chemical Problems of Today" (Vinnitsa, 2018), materials of the VII International Scientific and Practical Conference "Innovations

in science and practice "(Barnaul, 2018), materials of the XXII International Scientific and Practical Conference" Fundamental and applied research in the modern world "(St. Petersburg, 2018).

The main results of the dissertation research. According to the results obtained, 9 works were published, including 5 articles in publications recommended by the Committee for Control in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, 1 article in foreign journals with impact factor (Q2), 3 reports in the materials of international conferences.

The volume and structure of the dissertation. Dissertational work is outlined on 90 pages of computer text, includes 71 figures and 2 tables. Dissertation consists of an introduction, the main part in which the literature review data are presented, the results of the discussion of the experimental data, experimental part, conclusions, list of used sources from 182 items and one act of investigations on the enzyme-induced activity of some new bicyclic bisureas.