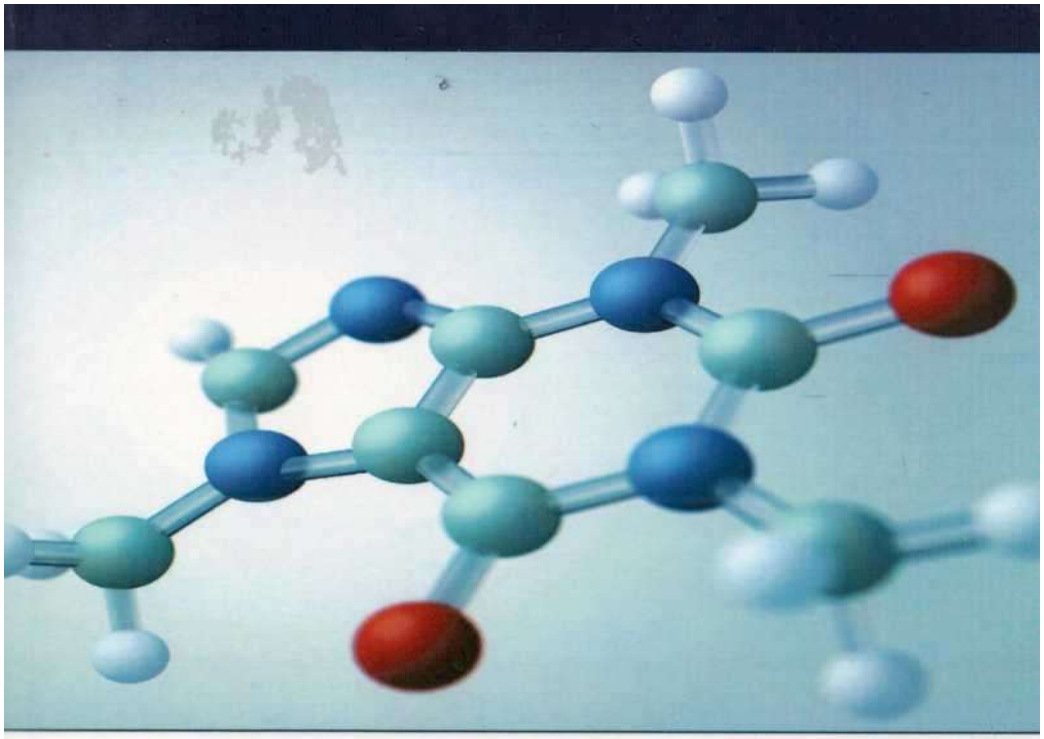

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Problem of synthesis and the development of waste-free technology of derivatives bis-urea

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SYNTHESIS AND TECHNOLOGY OF BIS-UREA DERIVATIVES AND THEIR APPLICATION

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Secretary of the Council, Associate Professor: N.A. Nasirdinova

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INTRODUCTION

Relevance of the topic: Ureas are used in many industries: medicine, agriculture, technology, rubber industry, organic synthesis. On their basis, various preparations were obtained for the needs of the national economy. Recent research on derivatives of ureas and bis-ureas, carried out at the present time, is prompted not only by theoretical, but also by practical needs. From this point of view, urea derivatives are of undoubted interest for substances with various biological activities. They are widely used in agriculture and have found application as herbicides, fungicides, insecticides, bactericides, dyes, growth stimulants, etc. Of particular interest is the use of these compounds in medicine as antitumor, antiviral, anti-inflammatory, antiarrhythmic, vasodilator and other drugs.

Today, most of the derivatives of urea, the search on their basis for new highly effective low-toxic biologically active compounds is constantly ongoing, as can be judged by the large number of publications in the world scientific and patent literature.

Therefore, the development of this branch of organic chemistry is the highest urgent task that requires new developments in synthesis, technology and scientifically grounded approaches. The synthesis of new compounds based on aromatic secondary amines and isocyanates, as well as their practical application, has broad prospects in solving priority problems: the development, first of all, agriculture, as well as the entire national economy and the growth of the well-being of the people of the Republic of Uzbekistan.

The degree of knowledge of the problem: This work is a complete scientific research. Chemistry, technology and properties of bis-urea derivatives attract the attention of world researchers looking for biologically active substances. A number of works are devoted to this direction. Nevertheless, to date, there is no information in the literature on the synthesis of bis - [(aminoaroyl) ureas] derivatives, as well as a waste-free technology for obtaining bis-aminoaroylurea derivatives for the search for highly effective biologically active substances.

Relationship of dissertation work with thematic research plans.

The dissertation work was carried out according to the grant of the Center for Science and Technology under the Cabinet of Ministers of the Republic of Uzbekistan № A-6-338 of 2006 on the topic: "Development of an import-substituting environmentally friendly technology for obtaining new, highly effective reagents that stimulate plant growth (for vegetable crops, tomatoes, cucumbers, cotton, etc.) on the basis of products and wastes of the chemical industry".

Purpose of the research: development of a simple, affordable synthesis method and waste-free technology for the production of previously unknown derivatives of bis-aromatic ureas; study of their properties, as well as growth-stimulating activity; development of practical proposals for the introduction of growth stimulators in the agriculture of our republic.

Research objectives:

- synthesize new bis-aminoaroylureas based on the interaction of secondary aromatic amines with HMDI;
- to develop a simple, affordable waste-free technology for the production of hexamethylene bis-[(dibenzylamino) ureas];
- to study the influence of various factors on the yield of bis-aminoaroylureas, to establish the dependence of the product yield on the nature of the solvent, temperature and reaction time;
- to study the chemical properties of N-H centers: dinitrosation, dihalogenation and dialkylation;
- describe the proposed mechanisms of reactions for the formation of bis-aminoaroyl-ureas, their derivatives, and the types of their course;;
- find biologically active compounds among the newly synthesized bis-ureas, test them and recommend them as a growth stimulant in agriculture, as well as determine their coloring properties.

Object and subject of research: The object of research is hexane-1,6-diisocyanate. The subject of the study are secondary aromatic amines: diphenylamine, dibenzylamine, 5-bromisatin, isatin, p-ferrocenylphenylamine and carbazole.

Research methods: The dissertation uses modern physicochemical research methods, elemental analysis, IR and PMR spectroscopy, quantum chemical calculations Hyper chem. 7.01 (AM1) and TLC, as well as methods of organic chemistry, technological processes. The main provisions for defense:

- the results obtained in the interaction of secondary aromatic amines of various structures with hexane-1, 6-diisocyanate;
- the supposed theoretical concept of the formation mechanism of N,N^1-hexamethylene bis - [(aminoaroyl) ureas];
- the results of N,N^1-dichlorination, -dibromination, -dinitrosation, and -dialkylation at N-H reaction centers of bis-urea derivatives;
- the results of studies to identify various factors (nature aromatic amine solvents, temperature and duration reactions) on the direction of the reaction;
- the results of the study of the electronic structure and quantum-chemical calculations of the compounds used;
- the results of studies to identify practically valuable properties (in agriculture and industry) for the first time synthesized compounds.

Scientific novelty: A simple, convenient method for the synthesis of N,N^1-hexamethylene bis - [(aminoaroyl) ureas] based on aliphatic diisocyanate with secondary aromatic amines in dimethylformamide (DMF), triethylamine in fairly high yields has been proposed. For the first time, the reaction of bis-carbamoylation of diphenylamine, dibenzylamine, isatin, 5-bromisatin, carbazole and ferrocenylphenylamine was studied;

- the proposed theoretical concept of the mechanism of formation of N,N^1-hexamethylene bis - [(aminoaroyl) ureas];
- for the first time studied the chemical properties of the N-H reaction center: N,N^1-dialkylation, -dinitrosation and -dihalogenation;
- for the first time a new, waste-free production of bis-urea derivatives was developed, a technological scheme of the process was proposed and developed.

Scientific and practical significance of the research results:

Developed and recommended new methods for the synthesis of N,N^1-hexamethylene bis - [(aminoaroyl) ureas] based on the interaction of highly reactive hexane-1,6-diisocyanate with diphenylamine, dibenzylamine, isatin, carbazole, p-ferrocenylphenylamine and 5-bromisatin with high yields.

A technology for the production of N,N^1-hexamethylene bis - [(dibenzyl-amino) ureas] has been developed. On the basis of the developed synthesis methods, new, previously undescribed derivatives of N,N^1-hexamethylene bis - [(aminoaroyl) ureas] were obtained.

We have identified drugs that are valuable for practical use as growth stimulants in agriculture (on wheat, cotton, tomatoes and cucumbers), which have coloring properties and are recommended for use in the polymer industry.

Implementation of the research results. Highly effective growth stimulator of cotton, wheat variety "Kroshka", vegetable crops (tomatoes, cucumbers). After the permission of the Commission of the Chemical Committee of the Republic of Uzbekistan, it can be used in agriculture.

Approbation of work: The main results of the study were reported and discussed at various conferences: « The prospects of the current development of analytical chemistry» Materials of the jubilee MNC dedicated to 90th anniversary of NU RUz and 100th anniversary of Acad. Talipova Sh.T., Tashkent, 2008; «Classification and certification of tokens on the basis of their chemical composition» RIAK materials, Andijan, 2008; collection of articles Rita" technologies of processing of local raw materials and products", Tashkent, 2008. "Actual problems of Chemical Technologies of oil and gas industry" Riakin materials Karshi, 2009; "the role of modern pedagogical technologies in improving the quality of Personnel: experience and prospects "RIAK materials collection, Namangan, 2009; "hopeful chemists-2010» Proceedings of the Scientific and Technical Conference XIX, Tashkent, 2010; in 2010, the discussion of the work was carried out on the basis of AndGosMI at a meeting of the problem commission, the work was discussed at a seminar at the Specialized Council D. 067.24.02 at the Tashkent Chemical-Technological Institute

Publication of results: 10 scientific papers were published on the topic of the dissertation, including 2 scientific articles and 8 theses.

The structure and scope of the thesis: The thesis is presented on 106 pages of computer text, contains 33 figures, 15 tables and consists of an introduction, a description of the structure, properties and production of biologically active substances based on urea, methods of obtaining N,N1-hexamethylene bis - [(aminoaroyl) ureas] and their derivatives, development of technology and production of hexamethylene bis - [(dibenzylamino) ureas], biological and technical activity of derivatives of N,N^{1}-hexamethylene bis - [(aminoaroyl) ureas], conclusions, conclusions, references (188 titles) and applications.

CHAPTER I. STRUCTURE, PROPERTIES AND OBTAINING BIOLOGY UREA-BASED ACTIVE SUBSTANCES

1.1. Reactivity of mono- and diisocyanates in reactions with amines

The reactions of isocyanates with compounds containing an active hydrogen atom are increasingly attracting the attention of researchers. This is due to the fact that among the products of this reaction, substances with various valuable properties were found [1-10].

Currently, there are several reviews on the reactivity of isocyanates [11-13]; however, the kinetics and mechanism of these reactions are still poorly understood.

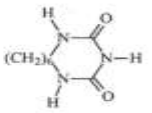
Mono - and diisocyanates are among the compounds with extremely high reactivity. Primary and secondary amines have the greatest reactivity towards isocyanates. Peterson [14] arranged the compounds according to their reactivity in the following order: amines> water> alcohols> urea derivatives> phenols> mercaptans> compounds with an active methylene group.

In addition, he also showed that carbamides, sulfamides, oximes, formaldehyde and hydrocyanic acid and acetylenic protons can react with isocyanates (R – C≡C –H).

As reported by Sounders [15] and Michael [17], isocyanates react with water much more slowly than with ammonia and amines, therefore, as a result of the reaction, urea derivatives are formed:

$$R\text{-}N{=}C{=}O + NH_3 \longrightarrow R\text{-}NHCONH_2$$

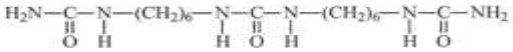
By slowly passing an excess of dry ammonia into an ethereal solution of hexamethylene diisocyanate, crystalline pro accession ducts. Peterson for products of this type suggested two formulas:



I

II

Reacts similarly with diisocyates and CH_3NH_2. The described products are very unstable, they cannot recrystallize without decomposition. The product corresponding to formula (II), when heated with water, cleaves CO_2 and forms a difficultly soluble compound, which Peterson presumably attaches to the formula:



Strepikheev et al. [16] reports that diamines react with diisocyanates at high rates.

Gravchikova V.A. et al. [19] determined the relative rate of reaction of primary aliphatic amines and ammonia with phenylisocyanate. The results obtained give a quite definite picture showing that an increase in the length of the amine radical (from C_2H_5-NH_2 до $C_5H_{11}NH_2$) has little effect on the speed of the described reaction. Aniline reacts with phenylisocyanate more slowly than aliphatic amines, about 20 times.

I.V. Nageli with sotr. [9], having studied the reactions of aromatic isocyanates with aromatic amines, established the effect of substituents in the benzene ring of the isocyanate and amine on the reactivity of these compounds. It was shown that the reactivity of the isocyanate increases with the increase in the acceptor ability of the substituent contained in its molecule. If the substituent is in the amine ring, the opposite picture is observed, and the substituted amines, from the point of view of their activity, can be located in the next ascending row:

$2,4\text{-}(NO_2)_2 < 2\text{-}NO_2 < 3,5\text{-}(NO_2)_2 < 4\text{-}NO_2 < 3\text{-}NO_2 < 3\text{-}OCH_3 < \text{-}H < 4\text{-}CH_3$

Their data are consistent with previously published data. For example, Mihael [17] found that 2,4-dinitroaniline and 2,4,6-trinitro-aniline do not react with phenylated cyanate even at a temperature of 1000C. He also observed a greater reaction rate of chloramines compared to nitroamines, thus, the reaction rate between isocyanate and amine depends on their structure.

According to Van Goldersen [18], the rate of reaction of phenyl isocyanate with various amines depends on the basicity of the amine. Negeli states that the rate of attachment of various compounds to isocyanate cannot be considered from

the point of view of the hydrogen mobility alone, without taking into account other factors characterizing the state of the molecule. The reaction rate of isocyanates with aromatic amines is highly dependent on the presence of catalysts. Pyridine or organic bases are recommended as catalysts. However, the mechanism of the reaction catalyzed by organic bases has not been established by the authors..

1.2. Nucleophilic addition (A_N) to isocyanates

Analysis of the literature data showed that in the absence of catalytic bases, the reactivity of various nucleophilic compounds with respect to isocyanate changes in the following order:

$R\text{-}NH_2 > R\text{-}OH > H_2O > Ph\text{-}OH > R\text{-}SH > R\text{-}COOH > R\text{-}C{\equiv}C\text{-}H$

for amines: $R_2NH > R\text{-}NH_2 > NH_3 > Ph\text{-}NH_2$,

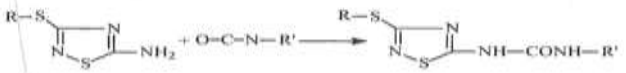
and in a series of nitrogen-containing compounds:

$R\text{-}NH\text{-}R^1$ > $R\text{-}NHCONH\text{-}R^1$ > $R\text{-}NHCO\text{-}R^1$ > $R\text{-}NHCOOR^1$

Secondary amine urea derivatives amide carbamate

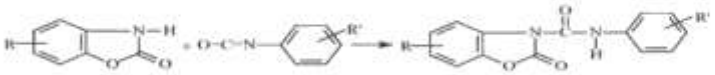
The structure of the R radical in the R-NCO molecule has a significant effect on the activity of the isocyanate group. The presence of electron-attracting groups will increase the proportion of the positive charge on carbon, electron-suppressing decrease it. According to literature data, aromatic isocyanates are more active than aliphatic and arylalkyl isocyanates [19]. However, quantitative comparisons of their reactivity, according to different authors, differ significantly from each other.

Isocyanates can also interact with various heterocyclic compounds. For example, in [20], the synthesis of ureido derivatives of 1,2,4-thiadizole was carried out, in the study of the reaction of 3-alkyl (allyl, benzyl) -thio-5-amino-1,2,4-thiadizole with phenyl- and naphthyl isocyanates at room temperature.



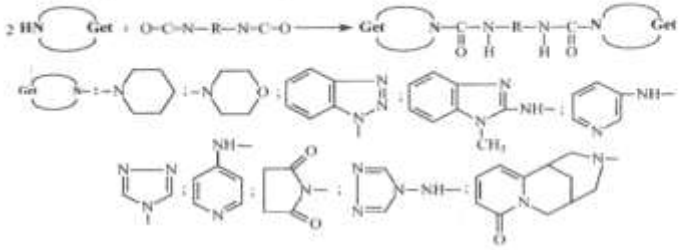
where R: CH_2= CH-CH_2-; $C_6H_5CH_2$- ; R^1= C_6H_5-; $C_{10}H_7$-

Benzoxazolin-2-ones, also interacting with aromatic isocyanates, form the corresponding 3- (phenylcarbamoyl) - benzoxazolin-2-ones [21, 35].

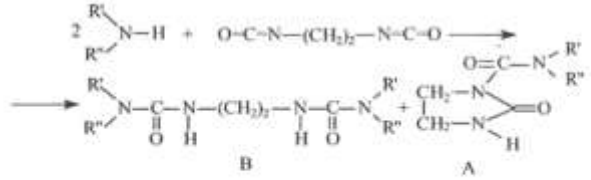


Where R: — -H; 5- Cl; 6- Cl-; 4,5,6- три-Cl ; R^1:-H; 4-Br-; 3-Cl; 3,5-ди-Cl;3,4-ди-Cl.

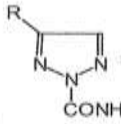
Makhsumov A.G. et al. [22-34] obtained bis-urea derivatives of interaction of hexamethylene diisocyanate with heterocyclic amines and their derivatives at room temperature according to the scheme:



Analysis of the literature data shows that the reactions of ethylene diisocyanate with amines have been relatively little studied. Many examples have shown that this reaction proceeds ambiguously. According to many authors, its direction depends on the basicity of the reacting amines. During the interaction of ethylene diisocyanate with primary or secondary aliphatic, alicyclic amines, the possibility of the formation of monoadducts N-carbamoylimidazolidones-2 (A) and bis-adducts (B) was shown.

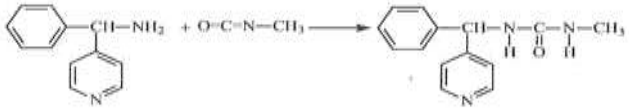


Abdugafurov I.A. with sotr. [36], 1,2,3-triazolo-phenyl-ureas were synthesized by interaction of 1,2,3-triazole derivatives with phenylisocinate:

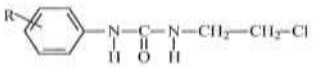


где: R:C_6H_5; 4- BrC_6H_4; 3- Cl- C_6H_4-;

They showed that the synthesized compounds have high wfficiancy and low toxicity. The authors of [37] obtained urea derivatives in 80% yields:

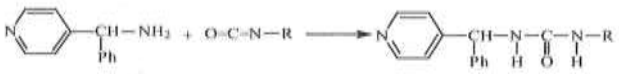


The results of studying the acute toxicity and neurotropic activity of the obtained derivatives are presented. A series of N-aryl (2-chloroethyl) -ureas and their derivatives has been synthesized [38]. Revealed their antitumor activity. The structure activity ratio (SAR) was investigated for the following substituents: branched alkyl chain or halogen in the 4-positions of the phenyl ring. It was shown that N-aryl N^1-(2-Chloroethyl) -urea is part of a new class of anti-mite agents.



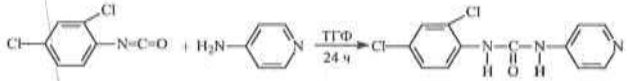
R=alkyl, benzyl;

Shamshin V.P. with employees [39] carried out the following reaction

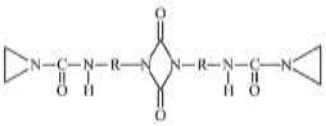


R=CH_3; C_6H_5;

in the presence of Et_3N and got the product with a yield of 80%. The results [40,41] of studying the acute toxicity and neurotropic activity of the derivatives obtained are presented. American scientists [42] synthesized urea derivatives by the interaction of 4,6-dichlorophenyl isocyanate with 4-aminopyridine

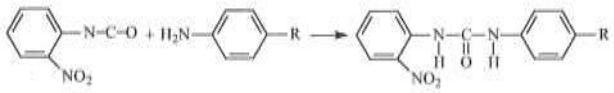


The patent [43] describes a compound obtained by the reaction of isopherone diisocyanate with ethyleneimine in the presence of 0.5% $(C_2H_5)_3N$



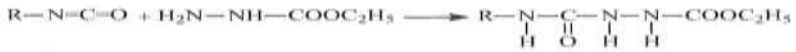
at 85-90 C, aziridine in 80-85% yield, recommended as a vulcanizing agent.

Chinese scientists Li et al. [44] synthesized aryl-2-nitrophenylurea derivatives with a yield of 87-95% by the interaction of 2-nitrophenylisocyanate with aniline derivatives:



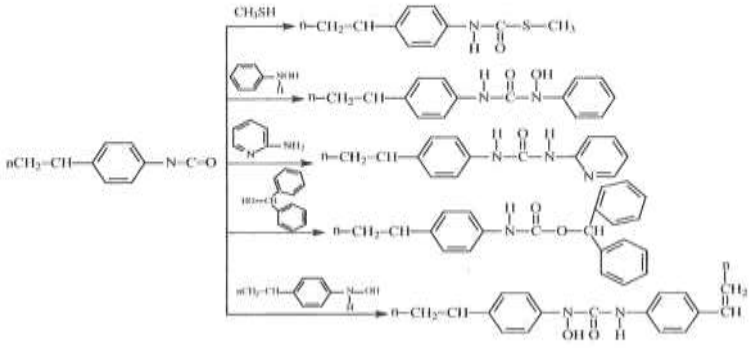
The reaction was carried out in the solid phase by grinding the reagents in a mortar for 10-30 minutes.

In work [45-48] under microwave irradiation, the synthesis of 1-ethoxycarbonyl-4-substituted semicarbazides was carried out according to the scheme:

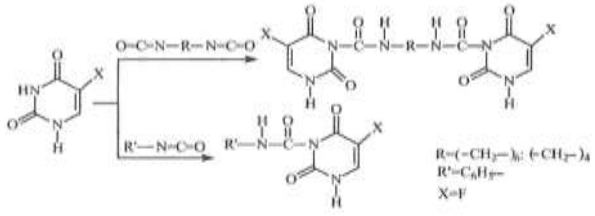


где R= 4- Cl- C_6H_4-; 3,4- Cl_2 -C_6H_3-; C_6H_{11}-и C_3H_7-; The reaction time is 2 minutes. The product yield is 82-96%.

Moldovan scientists [49] by the reaction of p-vinylphenyl isocyanate with compounds containing various functional groups and radicals, obtained products in rather high yields (82-98.5%):

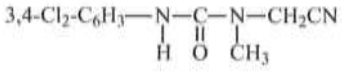


A number of patents [46-51] describe the reactions of interaction of uracil derivatives with mono- and diisocyanates according to the following scheme:



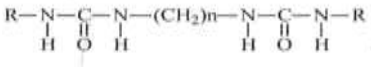
The reaction was carried out by heating $CHCl_3$, in the presence of pyridine or DMAC. The yield is 48-81%. The obtained compounds have an antitumor effect and strengthen the immune system..

In [52], the reaction of 3,4-dichlorophenyl isocyanate 3,4-Cl_2- $C_6H_3N{=}C{=}O$ c CH_3NHCH_2CN in the presence of toluene (t=0-40^{0}C; Et_3N), product received:



having herbicidal activity when applied before and after germination of plants. It is recommended for use (in doses of 0.5-3.0 kg/ha) when processing crops such as soybeans, beets, peanuts and sorghum. Japanese researchers [53] proposed as herbicides that suppress the development of weeds in rice fields, compounds of the formula 3-[CH_3 (HNCONH)]-C_6H_4-X-C_6H_4-п.

British scientists [54] synthesized new bis-urea derivatives in order to obtain compounds with anticancer activity:

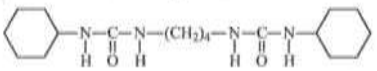


where R: -CH_2-CH_2Cl; cyclogexyl;

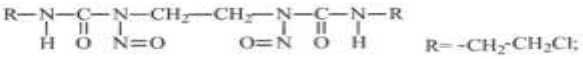
n= 2,3,4,5,6,7 and their nitro derivatives.

Tetramethylene diisocyanate is added to the solution Cl-CH_2-CH_2NH_2, which was treated with 50% NaOH и Et_3N, the mixture was stirred for 0.5 hour at 5 ° C, then 7 hours at 20 ° C.

$ClCH_2CH_2$–NHCONH-$(CH_2)_4$–NHCONH-CH_2–CH_2Cl with a yield of 98%. Under the same conditions, from tetramethylene diisocyanate and cyclohexylamine, a compound of the following structure was obtained in 87% yield:

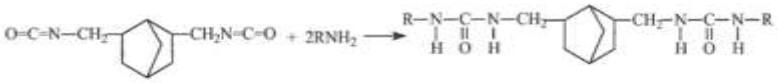


This analogous compound is also obtained from ethylenediamine, Et_3N Cl-CH_2-CH_2N=C=O on air with stirring for 7 hours at 20C, $ClCH_2CH_2$-NHCONH-$(CH_2)_2$-NHCONH-CH_2CH_2Cl with a yield of 62%. Nitrogenation was carried out c NaNO2 in the presence of HCOOH in cold water at 50C for 30-40 minutes. Allocated nitroso products of the structure:

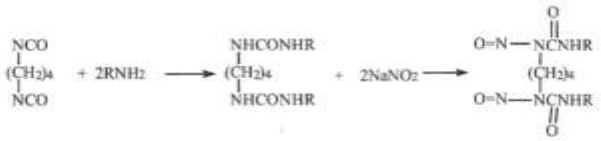


Bulgarian researchers [55-62] describe the synthesis of derivatives N- (R-pyridyl-2) -N1-phenylureas in high yield by the reaction of PhNCO with R-2-aminopyridines. It has been shown that these compounds are growth-regulating substances.

American scientists [63] have isolated urea derivatives in high yields when a polycyclic diisocyanate interacts with amines, ureas, alcohols when heated for 5-10 hours according to the following scheme:



The obtained derivatives of bis-urea and others are high-melting substances. In 1970-1990, interest in the study of N-nitrosourea derivatives increased in connection with their unique mutagenic activity [64-70] and antitumor action [71,72]. Later, in order to study carcinolytic activity, a number of N,N1-dimetyl, N,N^1- di (2-haloethyl) substituted alkylene-, cycloalkylene- and arylene-bis- (N-nitrosoureides) [73-74]. Lutsenko et al. [72] studied the nitrosation of the N,N^1-disubstituted tetramethylenediureas:

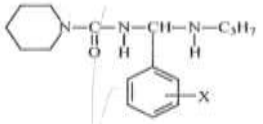


I II-a-d III-a-d

где II: а) R=H;б)R=C_6H_5; в) R=C_6H_{11}; г) R=-CH_2 -CH_2OH; д) R=-CH_2 -CH_2Cl.

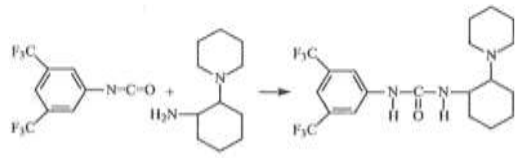
Initial N,N^1- disubstituted tetramethylenediureas (II a-e) were obtained by the reaction of tetra-methylene diisocyanate (I) c NH_3, C_6H_5-NH_2, u-C_6H_{11}-NH_2, H_2NCH_2-CH_2OH and 2-chloroethylamines, respectively. Tetramethylenediureas (II a-e) were easily nitrosated $NaNO_2$ in anhydrous HCOOH, forming tetramethylene bis - (N,N^1- dinitrosoureas) (III a-e). Both under the action of an excess and an equivalent (for the formation of a mononitroso-substituted) amount $NaNO_2$, obtained only dinitroso-substituted tetramethylenedimojins (III a-e); the corresponding mononitroso derivatives could not be isolated in any case. All synthesized or N,N^1-disubstituted tetramethylene bis- (N,N^1-dinitrosoureas) are fairly stable crystalline substances that recrystallize from organic solvents. Welldried compounds were kept unchanged for several weeks in a cool and dark place. The N-nitrosation of tet-ramethylenediurea (II) was probably carried out by the authors in two directions. However, the rationale they made regarding this or that structure N,N^1 -dinitrosoureas, based on the relative nucleophilicity of nitrogen atoms, sometimes led them to erroneous results [75,76].

To prove the structure of N-nitroso compound (III a-e), the authors of the work used their reactions with amines. The interaction of tetra-methylene bis- (N-nitrosoureas) (III a-e) with aqueous solutions of ammonia, methyl- and cyclohexylamines, mono- and 1,3-disubstituted ureas were obtained. Australian patent [77] describes urea derivatives,



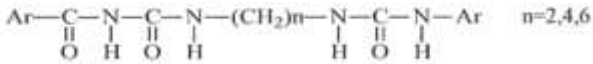
suggested to treat alopecia or stimulate hair growth.

In [78], urea derivatives with a yield of 84% are obtained without a solvent according to the scheme:



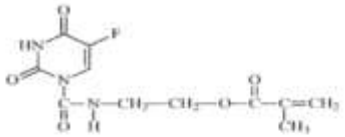
To study the quantitative relationships between the structure and biological activity of N-containing heterocyclic compounds (imidazolyl-, benzimidazole, etc.) on the basis of molecular topological theory, new mathematical models have been proposed with the calculation of the valence values of atoms at the vertex points, construction of the topological index connectivity of structural molecular information and good agreement between the calculated and experimental values of biological activity [79].

Tran Kevin et al. [80] propose a new simple accessible method for obtaining N,N^1-diphenylureas in high yield. They improved the method of obtaining Ph-NHCONHPh from PhNCO, carrying out the reaction in anhydrous benzene or toluene without a catalyst. The authors of [81] found an efficient method for the synthesis of polymethylene bis-arylurea derivatives. Under the conditions of phase-transfer catalysis by the interaction of aryl isocyanate with H_2N-$(CH_2)_n$-NH_2 with a yield of 78-92%, substances were obtained



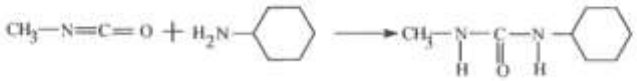
n=2,4,6

The compound [82] recommended as an anticancer drug and suitable for the production of polymers and copolymers on its basis is being patented:



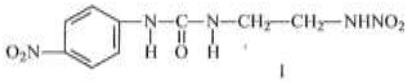
The polymerization is carried out in the presence of polymerization initiators.

In [83], the interaction CH_3-N=C=O with cyclohexylamine in the presence of ether at room temperature. N-methyl-N1-cyclohexylurea was obtained in 67.3% yield. T. pl. 160-161^{0}C.



B work [84] to study the effect on plant growth by the addition reaction (3 hours, 60-70oC) R^1-NH_2 (everywhere R^1-5- trifluoromethyl-1,3,4-thiadiazol-2-yl) to R^2CONCO in CH_3CN synthesized R^1-$NHCONHCOR^2$.

Substituted phenylaminocarbonylaziridines react with N-nitro-ethylcarbamate and then with ammonium, and after acidification it is obtained N-aryl-N ^{1}- nitro-aminoethylurea [92]:

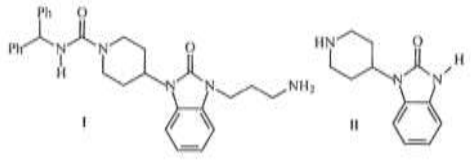


I

Moroz N.E. with sotr. [85] studied the interactions of ureides with quinones, which is of particular interest for the synthesis of biologically active compounds. Both ureides and quinones in the initial state are known to be very active biologically. Therefore, it can be assumed that the products obtained as a result of their interaction will also be biologically active. Ureides were obtained by acylation of urea. Acylation can be carried out with carboxylic acids, their esters, anhydrides and halogen hydrides. If dibasic acids are used as acylating agents, cyclic ureides can be formed. For example, oxalylurea is obtained by the interaction of urea and oxalic acid.

The authors of [86] proposed the use of polyhexamethylene guanidine (I) and polyhexamethylene ureas (II) as a growth stimulant for the development of corn and wheat, including pre-sowing seed treatment by spraying. Spraying of corn and wheat seeds is carried out with an aqueous solution with a molecular weight of 5 to 9 thousand. including when grown on a herbicidal background.

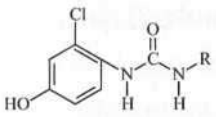
In [87], a five-stage method for the synthesis of urea derivatives (I) from compound (II) with a total yield of 40% was developed. Compound I is a selective antagonist of the vasopressin 1 a receptor.



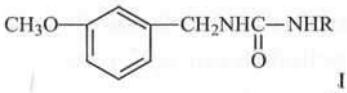
I II

Its effectiveness in Vivo (in rodents) for the treatment of states of anxiety, fear, etc. has been previously studied.

Patent [88] formulas of compounds that are key intermediates in the synthesis of medicinal substances.

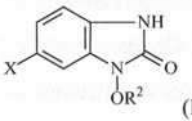


British scientists [89] patented oxidation-resistant lipids or oils containing an effective amount of an antioxidant-urea derivative of the formula



I

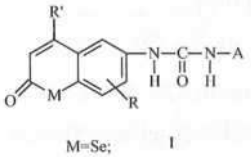
Synthesize [90] N-chloro-N-alkoxyureas $R^1NHCON(OR^2)Cl$ (everywhere R^1=H, 4-NO_2-C_6H_4-; 4-$C_2H_5C_6H_4$-; 4-Cl-C_6H_4-; $PhCH_2$; R^2=CH_3-, C_2H_5) with reaction $R^1NHCONH(OR^2)$ with BuOCl in CH_2Cl_2, yields 79-83%. Connections I (R^1=Y,-CH_2Ph; R^2=CH_3, C_2H_5) in reactions with CH_3COONa in CH_3CN or in reactions with CH_3OH in the presence CH_3COONa give N- or O-acyl products as a result of chlorine substitution H_2N-CO-$N(OCH_3)_2$ выходы 89-95%. Reaction I (R^1=4-$NO_2C_6H_4$-; 4-Cl-C_6H_4-; R^2=$C(CH_3)_2$-$COOCH_3$, C_2H_5-) under the same conditions leads to (II, X=NO_2; Cl; R^2= $C(CH_3)_2COOCH_3$, $C_2H_5O^-$), yields 61-94%.



(II)

Work [91] proposes 1- (5-chloro-2-hydroxyphenyl) - 3-cyclohexylurea and its analogs used in drugs for the treatment of proliferative diseases.

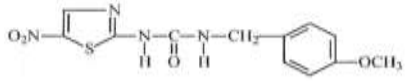
Patent [92] compounds (I), which can be substituted with halogen.



M=Se; I

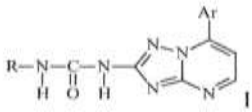
where R^1=H, alkyl, alkoxy, R^2= галоген, CN^-, OH^-. A= H, alkyl, alkynyl, which are antagonists of androgen receptors and are used in medicines for the treatment of benign

hyperplasia of the prostate, prostate cancer, baldness and many others. dr. Compound (I), its pharmaceutically acceptable salt, used as an active ingredient in the composition of drugs for the treatment of neurodegenerative diseases, including dementia, Alzheimer's disease, was similarly patented [93]. The method of obtaining compound (I) is given,



I

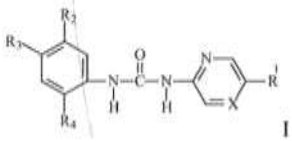
In [94], compounds I are proposed, which can be substituted by various substituents; used in medicines for the treatment or prevention of autoimmune diseases.



I

The authors of [95] synthesized new series of sulfur analogs of benzoylphenylurea and evaluated their antitumor activity. Some of the analogs increase this activity 10-fold compared to NSC-639829 against cancer cells. If we compare the sulfur analogs of benzoylurea with other drugs of a similar mechanism of action, then they have the ability to inhibit the formation of tubulin with IC_{50}, equal to 2.1 mm. In particular, aniline derivatives were obtained by the reaction of substituted aminophenols with substituted 2-chloropyrimidines in the presence of K_2CO_3 and DMSO. Condensation of substituted benzoyl isocyanates with aniline derivatives gives a series of benzoylphenylurea analogs. Group recovery 2-NO_2 when using Fe and CH_3COOH promotes the formation of derivatives with 2-NH_2. All compounds are identified by spectral analysis data.

Compounds I inhibiting protein kinase are patented [96]:



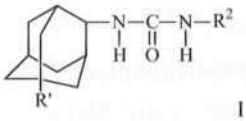
I

где R^1= H, alkyl, alkoxy, -NH_2,- CN, -COOH; R^2= галоген, -CN; R^3= H, -OR, alkyl,- NH_2used in medicinal products for treatment

cancer.

Work [97] patented compounds (I), as well as a method for their preparation, including dissolving I in an organic solvent, including ethyl acetate, bringing the solution to a boil, cooling to 20oC and filtering the precipitated crystals (I). Compounds I are useful in drugs for the treatment of diseases mediated by overexpression of cytokines, including osteoarthritis, atherosclerosis, bone resorption, dermatitis, multiple sclerosis, psoriasis, etc..

E.I. Goryunov c sotr. [98] found that the reaction of diphenylphosphorylisocyanate with n-alkylamines at 20-25 ° C, the solvent of which is acetonitrile. The method allows you to obtain a high-purity product while reducing energy and economic costs. The urea derivatives mentioned in the patent are used in radioactive waste treatment technology. The authors of [99] propose adamantanamo-chevin derivatives of the formula I:



I

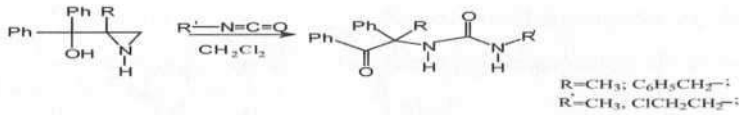
used in the composition of medicines for the prevention and treatment of metabolic syndrome, diabetes,ожи-

insulin resistance, glaucoma, osteoporosis, cognitive impairment, etc.

From 1-methyl-3-ethyl-4-chloro-5-pyrazolylcarboxylic acid and 4,6-disubstituted 2-aminopyrimidine, 10 new derivatives of N- (4,6-disubstituted pyrimidin-2-yl) -N^1- (1-methyl-3-ethyl-4-chloro-5-pyrazolyl) carbonylureas, characterized by IR and PMR spectra; studied acaricidal and herbicidal activity [100].

Chinese scientists [101] synthesized 9 new derivatives of N1- (4,6-disubstituted 2-pyrimidyl) -N-cinnamoylurea, characterized by IR - and PMR spectra.

Polish scientists [102] propose obtaining compounds of urea derivatives:

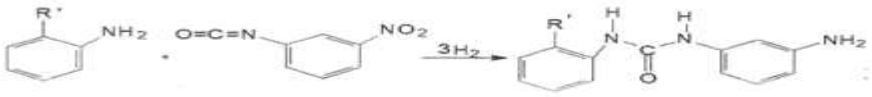


R=CH$_3$; C$_6$H$_5$CH$_2$–;
R'=CH$_3$, ClCH$_2$CH$_2$–;

They proposed a reaction mechanism.

In [103], the addition of anilines (I) to nitro-substituted isocyanates (II) and subsequent reduction promotes the production of aniline-substituted ureas (III), which, upon repeated treatment with ArN = C = O and NaH + MeI, can be

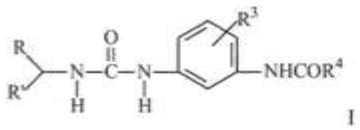
"stretched" by one-dimensional and two-dimensional ways to oligomeric ureas (contain up to 8 urea bonds). The crystal structure is presented and the conformation of the "STO-HA" type is considered. 1H-NMR data show that such a conformation exists in solution:



Chinese specialists [104] to study the fungicidal activity by reaction (3 hours, t = 400C) 2-R-5- (4-pyridyl) - 1,3,4-thiadiazole 4-Cl-$C_6H_4CON{=}C{=}O$ synthesized in DMF I. Cl-C_6H_4CONH-CO-NH-R (I);

In the patent [105] formulas (I) are given that are applicable in the composition of drugs for the treatment of asthma, allergic diseases, rheumatoid arthritis, atherosclerosis.

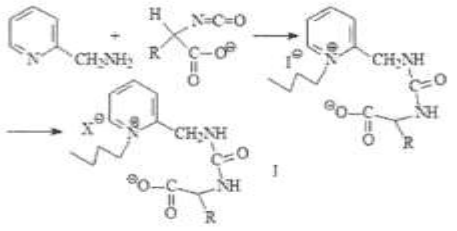
American specialists [106] describe compounds of formula I used in the treatment of oncological and immune diseases,



I

diabetes, atherosclerosis, osteoporosis, etc. Synthesis of I is described. The data of mass spectra and results are given.

biotesting. The synthesized ionic liquids of the formula I are prepared from 2-methyl-aminopyridine and isocyanates. The resulting preparations of I serve as an effective reaction medium as a chiral catalyst in asymmetric reactions. [107].

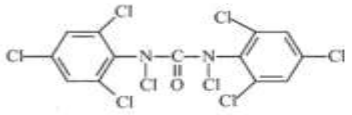


I

To study [108] bactericidal, insecticidal and herbicidal activity from $ClCH_2COOH$, 3-и 4-$CH_3C_6H_4OH$ through R-X-OCH_2COOH (I), R-X-OCH_2COCl (II) и O=C=N-X-OCH_2CON=C=O syntezied R NHCONHCO-X-$OH_2CONHCONHR$ (III) и R-NHCONHCO-X-OCH_2CONHR(IV) X=O; S;. More than 10 new bis-urea derivatives have been obtained.

Chinese experts [109] review the data on the physicochemical and detonation properties of N-guanylurea dinitride (CsUDN) (FOX-12). CsUDN has high energy (close to RDX), low sensitivity, exceptional thermal stability, CsUDN is not hygroscopic, does not dissolve in water, and forms a large amount of gas. CsUDN is acceptable for use as additives for other energetic materials. CsUDN is used as propellant, gas generator and explosive.

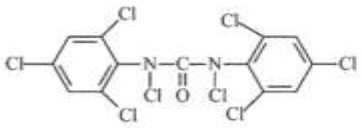
Specialists [110] described one-pot synthesis N,N^1- dialkylphosphoramidites (DADAR) from dialkylphosphites and dialkylamines when using N,N^1- dichloro-bis - [(2,4,6-trichlorophenyl) -urea] as



chlorination agent. DAADAP is a chemical weapon marker (herd and its analogues).

The paper presents an improved spectral database for certification of the chemical weapons convention. The described synthesis strategy can be adapted to obtain analogs of DADAP.

[111] described a simple, efficient, fast and gentle method for the synthesis of 2-chloronitroso compounds using bis (2,4,6-trichlorophenyl) -urea (CC-2):



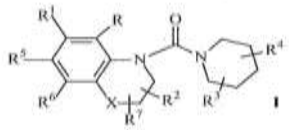
Silicon-bound thiocarboms are obtained by rearrangement of Curtius carbon

acids in the presence of a thiol from silica gel. Such solid supports of thiocarbamates are stable isocyanate equivalents which, when treated with amines,

give di- and trisubstituted ureas. The urea products are released from the trap, and the released substrate in most cases with 95% purity can be used further [112].

Alkyl nitrosoureas are a well-known class of anticancer drugs, the action of which is based on their ability to generate diazonium ions during hydrolytic decay particles, alkylating DNA. The ability of most drugs in this group to penetrate the blood-brain barrier makes it possible to effectively use them in complex chemotherapy of certain types of tumors. Recent studies have shown that the decomposition of N-nitroso-N-cyclopropylureas (NCU) in protic solvents differs significantly from other alkylnitrosoureas. For example, the dinitrosation reaction plays a significant role, which makes it possible to consider the NCM as NO donors [113].

The authors [114] for the treatment of type 2 diabetes, suggest compounds I,

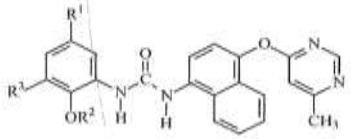


I

used in the composition of medicines for the treatment of type 2 diabetes.

Spiridonov Y. Ya with sotr. [115] studied the results of 25-year studies of the Herbology Department of VNIIF of fourth generation herbicides and came to the following conclusions. The dose of sulfonylurea derivatives is 1-2 orders of magnitude lower compared to other drugs, which makes it possible to increase safety and reduce the cost of their use. It has been established that the behavior of sulfonylurea derivatives in soil largely depends on its type. Research of this class of herbicides of sulfonylurea derivatives with other pesticides, growth regulators, antidotes continues; new preparative forms of domestic herbicides are being studied.

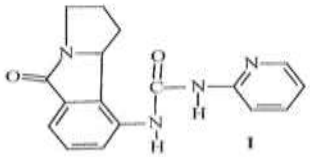
The authors of [116] patented the compounds described below, used



as part of medicines for the treatment of chronic inflammatory diseases.

The authors of [117] carried out studies on the creation of new series of Cdk-4 inhibitors using the LEGEND program, established new candidates as

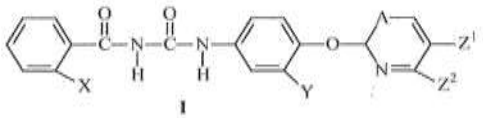
building blocks for obtaining new inhibitors, thus, N- (9 -oxo-9-n-fluoren-4-yl) - N^1-pyridin-2-ylurea. The result of a computer search for active structures led to the establishment of a stronger derivative (I). Yield- 30%. Structure I is confirmed by X-ray diffraction data.



I

[118] patented powders, capsules, tablets, oral solutions, parenteral or rectal dosage forms for the treatment of viral diseases, as well as for use in chemotherapy for cancer of the stomach, liver, gallbladder, rectum, bones, internal glands. secretions, uterus and other organs.

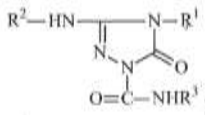
The preparations contain, as active ingredients, calculated amounts of benzoylurea derivatives of formula (I) (x = Cl) in combination



I

with various surfactants acting as stabilizers.

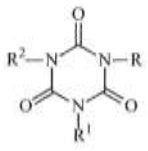
Compounds of formula (I)



I, где R^2= CH_2-CH=CH_2; -CH_2-C≡CH

have herbicidal activity in doses of 0.01-10 kg / ha against a wide range of weeds on plantings of citrus and fruit trees, coffee, tea, cocoa, etc. [119].

The work [120] describes compounds with the general formula:

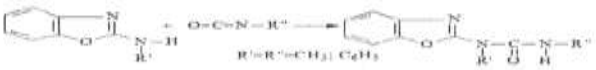


where k 0.054 mole 4-CH_3O-C_6H_4CH(изо-C_3H_7)-CH_2NH_2 в 100 ml of toluene add 0.065 mol t-BuCH_2-N=C=O in 10 ml of toluene, boiled for 15 min, filtered, obtained in the residue with a yield of 83%

4-CH_3O-C_6H_4CH(изо-C_3H_7)-CH_2NHCONHCH_2-But, with so pl. 132^{0}C, which

have contact and systemic action against Pyricularia oryzal. The authors of [121] presented the results of the formation of mathematical models for predicting herbicidal activity in acute toxicity (LD50); the relationship between the structure, herbicidal activity and the toxic effect of compounds of the aryl (heteryl) classes of urea and sulfanylurea derivatives was studied.

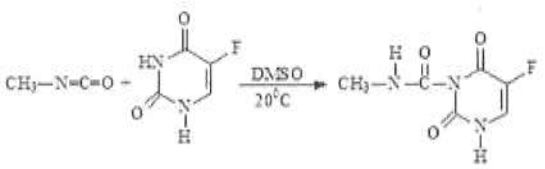
In order to synthesize potential biologically active compounds [122] carried out the interaction of 2-alkyl (phenyl) aminobenzoxazole with methyl and phenyl isocyanates.



I a-g II a-z

They found that the reactivity of amines in acylation reactions substantially depends on the basicity of the substrates. Since the amines I a-g used in this work had a low basicity, they were able to react with isocyanates under rather harsh conditions. With prolonged reflux of the reagents (amine: isocyanate ratio = 1:2) in a dry inert solvent, the yields of ureido derivatives II a - h were 55-86%.

1-R-5-F-uracils [123-126] used for the treatment of lymphatic leukemia are being patented. Yield 65.5%.

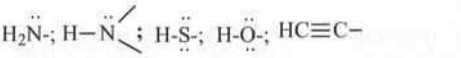


Maksumova N.A. [127] synthesized more than 50 bis-urea derivatives with various heterocycles (piperidine, morpholine, benzimide-zol, succinimide, cytis-

ine, 4-aminopyridine, 1-amino-1,2,4-triazole, 3-aminopyridine, 1-methyl-2-aminobenzimidazole), with high yields (80-98%). The chemical properties of NH reaction centers (reactions N-nitrosation, -methylation, -alkylation) have been studied in detail, -halogenation). Studied and recommended for field trials as a growth stimulator for plants.

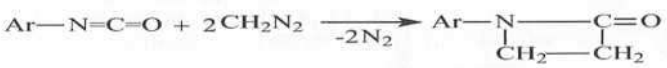
1.3. Interaction of isocyanates and diisocyanates with compounds containing a mobile hydrogen atom in functional groups (halogenation). Studied and recommended for field trials as a growth stimulator for plants

As noted above, mono- and diisocyanates are among the compounds with exceptionally high reactivity. Typical for mono- and diisocyanates are reactions with compounds containing mobile active hydrogen, in particular, with compounds containing functional groups:



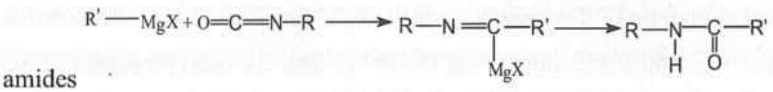
Bayer [128] arranged compounds containing active mobile hydrogen according to their reactivity in the following series:
amines> alcohols > water> mercaptans> acids> urea derivatives> phenols> and other compounds with an active methylene group. In addition to these, he also proposed the following compounds capable of reacting with isocyanates: carbonamides, sulfamides, oximes, formaldehyde, HCN, R-MGX, HC≡C-, etc.

For example, when aromatic isocyanate interacts with diazomethane, □-lactams are formed:



According to Johnston [129], NH3 interacts with isocyanates both in the presence of organic solvents and in an aqueous medium.

The addition of the Grignard reagent to isocyanates [130] proceeds smoothly with a yield of 80-90% of the theoretically corresponding acid



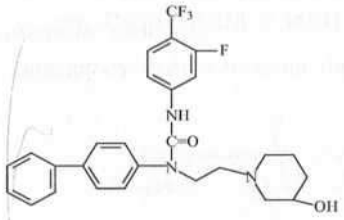
amides

in the presence of traces of the main catalysts, of which pyridine is the most suitable, Et3N.

The reaction with HCN is recommended to be carried out with PhN = C=O according to the following scheme:

The cyanformanilide formed in this case with the second phenylisocyanate molecule easily forms 4-amide-1,3-diphenyl-parabanic acid [131].

To search for fungicides with high activity and low toxicity from 4-H_2N-C_6H_4 O-CH_2-$CONHC_6H_4R$ (R=CH_3, 4-OCH_3; CF_3) c 2,6-F_2 C_6H_3CON=C=O (II) synthesized 4-(2,6-$F_2C_6H_3CONHCONH$) $C_6H_4OCH_2CONHC_6H_4R$ (III). The data of IR and PMR spectra are given [132]. Derivatives of substituted phenylbarylurea have been synthesized [132] and evaluated as MSN-1 antagonists for interaction in obesity.

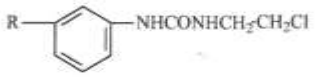


The relationship between structure and activity in this series has been studied. Urea (I) has been identified as a potential and selective antagonist of MSN-R_I.

By the interaction of isocyanates (C_6H_5N=C=O или $C_{10}H_7N$=C=O) urea derivatives were obtained with substituted anilines [134-135]. A series of [136-137] N-aryl –N^1-(2-chloroethyl) urea and their derivatives were synthesized. Their antitumor activity was revealed. The ratio, structure, and activity (SAR) of the following substituents were studied: a branched alkyl chain or a halogen at position 4 of

the phenyl ring, a fluorene-ilrendanyl group. It is shown that N-aryl -N^1-(2- chloroethyl) urea is part of a new class of anti-tick agents.

In this regard , compounds with the general formula have been synthesized:



It was shown in [138] that the combination of KNO_3, $NaNO_2$ and wet SiO_2 (50% by volume) in CH2Cl2 forms an effective reagent for N-nitrosation of secondary amines, with a yield of up to 99%.

A new solid-phase addition of isocyanates and aromatic amines has been studied [139]. Synthesized 14 aryl urea with high yields at 20^0C. This method is characterized by simplicity and short reaction time,

therefore compounds with a general formula have been synthesized.

By joining R^1-NH_2 к R^2-N=C=O в $CHCl_3$ synthesized R^1- NHCONHR^2 (где R^1=1- naphthol; R^2= Ph and etc) [140]. The cytokinin-inhibiting activity of Ia-e to slow down the growth of surepica roots was studied. The results of quantum chemical calculations using the MORAS software and the results of the study of inhibitory activity allowed us to establish quantitative relationships between the structure and biological activity.

The authors [141-142] synthesized a series of phenylallyl-substituted asymmetric urea in a single-reactor procedure by reactions of cinnamoi-lysocyanate, which is obtained from cinnamoylazide by Curtius rearrangement with various aromatic amines 2-amino-5-aryl-1,3,4-thiadiazoles and 2-amino-5-aryloxymethylene-1,3,4-thiadiazoles under micro-wave irradiation. In comparison with conventional methods, this synthesis is characterized by mild reaction conditions, high yields of urea derivatives. The products were identified by IR and 1H NMR spectroscopy data.

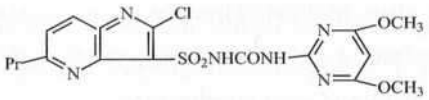
The authors [143-144] obtained salts of N-alkoxy-N-(1-pyridinium) urea I. It was found that N-acetoxy-N-methoxyurea is converted to N,N1-dimethoxyurea

H2NCON(OCH3)2, and N-propyloxy-N-(1-pyri-dinium) N1,N1-dimourea chloride into N,N-dimethoxy- N1,N1-dimethyl urea.

To study herbicidal activity and search for environmentally safe herbicides from 5-NH_2-2-$CH_3OOCC_6H_3SO_2NH_2$ through the intermediate 5-R^1-CO-2-$CH_3OOCC_6H_3SO_2NH_2$ (I) синтезирован [145]

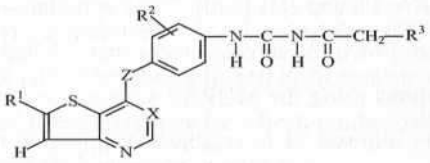
5-R^1-CONH-2- $CH_3OOCC_6H_3SO_2NHCONHR^2$ (II).

It is proposed [146] a weed control agent with herbicidal activity - flumioxazine:

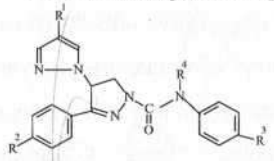


Flumioxazine is used in a ratio of 1:0.01-1:100, respectively, examples of the composition of compositions, test results of herbicidal activity are given.

Compounds with the following formula or their pharmaceutically acceptable salts or solvates with antitumor effect are patented [147]:

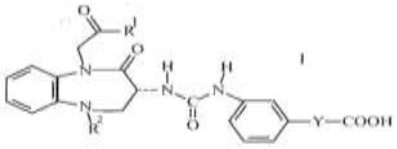


Patented compounds I [148] with the general formula used as part of insecticidal compositions. The methods of obtaining compounds and the results of insecticidal activity tests are given.



The review [149] presents drugs having an asymmetric urea as a functional group. The importance of developing new methods using more environmentally friendly, effective reagents instead of toxic and unstable phosgene and its derivatives is distinguished.

An antitumor composition containing as an active ingredient a compound of its pharmaceutically acceptable salt used in combination with radiotherapy for the treatment of leukemia is proposed,

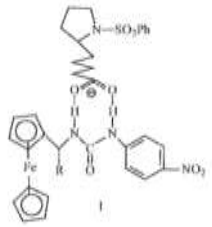


I

neuroastrocytomas, thyroid cancer, gastrointestinal tract, etc.

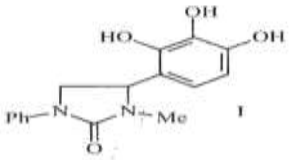
The results of tests of the biological activity of compounds in vitro and toxicity in vivo (on rats) are presented [150].

The authors [151] study the complexation of chiral ferrocenyl urea I (I R=i-Pr, t-Bn-, Bn) containing a redox-active ferrocene group with chiral carboxylates from spectroscopic data and voltammetry. Enantioselectivity of the complexation of protected N-benzenesulfanylproline with the Intra molecule (R=$PhCH_2$-) enough high to distinguish opposite isomers electrochemically.



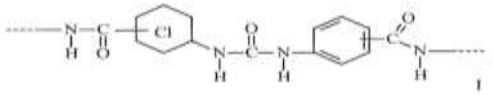
I

Interaction $PhNHCON(Me)CH_2CH(OMe)_2$ with $1,2,3\text{-}(HO)_3C_6H_3$ in the presence of CF_3COOH ($CHCl_3$, 60^0, 8 ч.) receive (I), output 47% [152].



I

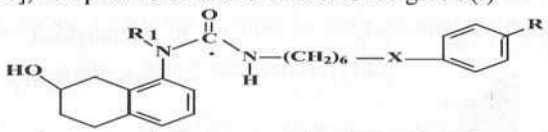
The authors [153] propose the use of compounds (I), urea derivatives of pharmaceutically acceptable salts in the composition of medicines for the treatment of cardiovascular and immune diseases.



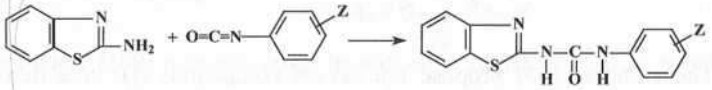
I

In [154], synthesis methods and the results of preliminary studies of the effect on plant growth and antibacterial activity in 8 new aromatic acylaminoureas with N,N1-naphthalenacil substitutes characterized by IR and PMR spectra were reported. 2-(4-R-phenyl)-1(carboxy-4-methyl-4-cyclohexenecarbonyl-hydrazides) were synthesized from monohydrazides of cyclohexendicarboxylic acid and sodium nitrite in acetic acid, which were used as starting compounds to produce, unknown in the literature, cyclohexengroup containing disaminated urea in their reactions with derivatives of 2-aminopyridine. They form N-[2-(4-R-phenyl)-1-carboxy-4-methyl-4-cyclohexene]-N1-(3-R1-5-R2-pyridyl-2)-urea, as well as N-[2-(4-R-phenyl)-4-methyl-4-cyclohexene]-N1-(3-R1-5-R2-pyridyl-2)-urea, since at the boiling point of toluene both the formation of disubstituted urea derivatives and the decarboxylation of the acid group occurs [155].

In patents [156], compounds of urea derivatives are given (I)



and their tautomers, pharmaceutically acceptable salts used in the composition of medicines for the treatment of urological diseases, including bladder hyperactivity. Reaction of 2-amino-benzimidazoles (X=4-OMe, 5-OMe, 6-OMe, 6-CF_3/NO_2, 5-Me-; Y=H, Z=Me) with NaH in DMFA, then with benzoyl chloride (Z=Me, OMe, CN, CF_3, NO_2) at 200C, amide derivatives with yields of 60-70% are obtained for 5 hours. Interaction with substituted phenylisocyanates (Z=2-Me, 4-Me-, H, 2-F,3-NO_2) (Et_3N, 20^0, 8ч) synthesize the compound

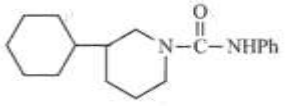


I-V

(X=6-F/Me/Cl; 5-Me-;Y= H; 6-Me) with a yield of 40-60%. The antiproliferative properties of the obtained compounds have been studied [157,158]. The authors [159,160] described easy access to a wide list of original saturated N-heterocyclic urea with use as a key stage of the Michael type reaction. The latter

includes isocyanates or amines on the piperidine skeleton, which have [illegible] unsaturated essential functionality.

In [161], the cyclization reaction CH_2=CH(R) $(CH_2)_n$ R^1,R^2)CH(R^3)NHR^4



in dioxane and water in the presence of a mixture AgCl and $AgOSO_2CF_3$ (15-24 ч. 20^0 C we get with yield 83-100 %.

8 new derivatives of N 1-(tert-butylaminocarbonyl) were synthesized to study the inhibition of proliferation of leukemia cells k562-N- [5-(substituted phenyl)-2-furyl] urea characterized by IR and PMR spectra [162].

The authors [163] propose the use of N{2-[(2,1,3-benzothiadiazole-5-ilamino)]-6-(2,6-dichlorophenoxy) pyrido [2,3-d] pyrimidine-7-yl]-N1- [1,1-dimethylethyl] urea}, its hydrate, solvate as part of the drug means that can be made in the form of tablets, solutions for intravenous administration.

A general technique for the synthesis of alkyl and arylalkyl carbamates is described [164] R-NHCOOAr (R=CH_3-,C_2H_5-, C_4H_9-, C_6H_{13}-), based on S-methyl-N-alkylthiocarbamates R-NHCOS-CH_3. The technique consists of three stages, which proceed in one reactor without the release of intermediate N-alkylcarbamoyl chlorides R-NHCOCL or R-N=C=O. All products are obtained with high yields (16 examples, average yield 91 %).

As can be seen from the above, the chemistry and technology of urea derivatives are rapidly developing in a large number of research centers abroad and in our country.

Thus, the analysis of the literature data shows that the reactions of GMDI with aliphatic, aromatic, heterocyclic amines are relatively little studied. Many examples show that the reaction of AN is ambiguous. According to many researchers, its direction depends on the basicity of reacting amines. By reacting hexamethylenediisocyanate with primary or secondary aliphatic, alicyclic, aromatic amines, we have shown the possibility of forming bis-aroylurea derivatives.

It has been established that the majority of published patents, articles and monographs from 1954-2010 are mainly devoted to the reaction of isocyanates with substituted H2N-, H-N< containing aliphatic, aniline derivatives and heterocyclic amines in a medium of various solvents, such as CH_2Cl_2, $CHCl_3$, toluene, ether, etc.

Research in this field of chemistry, on the one hand, allows us to discover fundamentally new patterns in the behavior of organic urea compounds and reaction mechanisms and, thus, contribute to the development of new theoretical concepts in organic synthesis.

On the other hand, the enormous practical significance of these unique studies as the basis for the creation of new biologically active drugs, dyes, plant growth regulators, semi-products of fine organic synthesis and technology is quite obvious.

Hence the wide range of tasks that are solved by chemists working in this field, from deep theoretical research to purely applied issues.

In the light of the above, the purpose of this work was to develop a simple, convenient method of synthesis and a waste-free technology for the production of previously unknown derivatives of bis-aromatic urea. The study of their properties, as well as growth-stimulating activity and the development of practical proposals for the introduction of growth-stimulating agents in agriculture of our republic will increase the economic efficiency of the economy as a whole.

Research objectives:

- synthesize new bis-aroylureas based on the interaction of secondary aromatic amines with GMDI;
- to develop a simple, convenient waste-free technology for the production of hexamethylene bis-[(dibenzylamino) urea];
- to study the influence of various factors on the yield of bis-aminoaroylureas, to establish the dependence of the product yield on the nature of the solvent, temperature and duration of the reaction;

- to study the chemical properties of NH centers: denitrosation, dehalogenation and dealkylation;
- describe the proposed mechanisms of reactions of the formation of bis-aminopropyl-urea, their derivatives and varieties of their course;
- to find biologically active compounds among newly synthesized bis-urea, to test them and recommend them as a growth stimulator in agriculture, as well as to determine their coloring properties.

CHAPTER 2. OBJECTS AND METHODS OF RESEARCH

2.1. OBJECTS OF RESEARCH

Initial reagents, devices, equipment used to establish the structure of synthesized compounds Carbon tetrachloride (carbon tetrachloride) CCl_4 – as a solvent; ethanol - x h. -TU 6-09-1710-77: $T_{boiling}$ =78,33°C: $n_д^{20}$=1,3616: d_4^{20}=0,7890; THF (tetrahydrofuran) stable. – h. -TУ 6-09-3986-77; benzene -– ch.d.a.- GOST 5789-51, T.boiling.78°C; dimethylformamide - hc. - GOST 20-289-74 Kharkiv Chemical Reagents Plant; acetone - ch.d.a. - GOST 2603-994; hexane - ch. TU 6-093375-78; dioxane – ch. Shostka chemical reagents plant - GOST 10455-80; methanol - hc -GOST 6995-92; dimethyl sulfoxide- hc; DMSO - hygroscopic liquid, colorless and odorless; ethyl acetate - ch.d.a. - GOST 22300-96; diphylamine - hc., t.pl.=53°S;

$T_{boiling}$ =302°S; dibenzylamine- C.D.a, $T_{кип.}$=300°S, M_M=197,29; carbazol-x, $T_{boiling.}$= 238 °S, $T_{кип}$ =354,8 °C; M_M = 167,21; isatin - hc; 5-bromisatin -hc; hexane-1,6-diisocyanate; (hexamethylenediisocyanate, GMDI); colorless, oily liquid with a pungent odor, em-pyric formula – $C_8H_{12}N_2O_2$; structural formula –O=C =N-$(CH_2)_6$- N=C=O, $M_м$ – 168,20; $T_{melting.}$ = - 67°S; $T_{boiling.}$ = 255-258°S; 127°C, 10 mm Hg. art.; density - d_4^{20}; г/см^3- 1,0465, $n_д^{20}$ =1,4533; GMDI - mixes with most organic solvents, reacts c H_2O, R-OH, R_2NH, RNH_2, it has all the properties of isocyanates. All reagents were purified by transfer in vacuum, or at atmospheric pressure, or by recrystallization of the corresponding solvent.

2.2 Research methods

IR spectra were obtained on a Fourier spectrometer model 2000 (Regkin Elmer) in KBr tablets, as well as "Spekord -75" in KBr tablets. PMR spectra were taken on the proton resonance spectrometer "Iroll C-60 HI" with a frequency of 60 MHZ. The purity of the products and the course of the reaction were controlled by TLC on Silufol UV-254 plates in different solvent systems:

System 1: HCOOH: $CHCl_3$: CCl_4=0.5:0.5:0.4;

System 2: Gexan: $CHCl_3$ = 1:9;

System 3: C_6H_6:C_6H_{14} = 5:1;

System 4: $CHCl_3$:C_6H_{14}=7:1;

System 5: $CHCl_3$:C_6H_6 = 6:1;

System 6: C_6H_6 :$CH_3COOC_2H_5$ = 4:1;

System 7: $CHCl_3$: C_2H_5OH = 4:1.

Developer: Iodine vapor.

2.3. Synthesis and chemical transformations N,N^1- hexamethylene bis-[(aminoaryl) urea]

Synthesis N,N^1- hexamethylene bis-[(aminopropyl) urea]

N,N^1- Hexamethylene bis-[(diphenylamino) urea] (1)* (XIOX-1)

In a four-necked flask equipped with a reverse refrigerator with a chlorocalcium tube, a mechanical stirrer, a thermometer and a drip funnel, 16.9 ml (0.1 mol) of diphenylamine was placed in 70 ml of dimethylphoramide, 20 ml of triethylamine and, with intensive stirring, 8.5 ml (0.05 mol) of GMDI was added drop by drop from the drip funnel. The reaction lasted for 4 hours at a temperature of 26-36°S. The precipitate was filtered, washed with distilled water 2-3 times and dried at room temperature. Appearance: White powdery product. Output 23.2 g (92%): T. pl. 224-225°S.

The individuality of the resulting product was tested by TLC on a fixed layer (Al_2O_3) II degree of purity in the system 6. R_f=0,72

Found %: C 75,68 H 6,49 N 10,78

Calculated for $C_{32}H_{34}N_4O_2$, % : C 75,89 H 6,72 N 11,06

(1)-and further to (36) the numbering corresponding to the number of the formula (characteristics b of this substance) in Tables 3.1, 3.3, 3.4, 3.5 and 3.8.

N,N^1- Hexamethylene bis-[(dibenzylamino) urea] (2) (XIOX-2)

19.7 ml (0.1 mol) of dibenzylamine in 55 ml of DMFA, 18 ml of triethylamine were placed in a four-throated flask equipped with a reverse refrigerator with a chlorocalcium tube, a mechanical stirrer, a thermometer and a drip funnel, 8.5 ml (0.05 mol) GMDI. The reaction lasted for 4 hours at a temperature of 25-38°S. The precipitate was filtered, washed with distilled water 2-3 times and dried at room temperature. Appearance: snow-white powdery product. Yield-26.5g (94%); t.pl.=190-191^{0}S. The individuality of the resulting product was tested by TLC on a fixed layer (Al_2O_3) of II degree of purity in system 3. R_f=0.69.

Found, %: C 76,51 H 7,23 N 9,31

Calculated for $C_{36}H_{42}N_4O_2$, %: C 76,82 H 7,47 N 9,56

N,N^1- Hexamethylene bis-[(carbazolyl) urea] (3) (XIOX-3)

In a four-necked flask equipped with a reverse refrigerator with a chlorocalcium tube, a mechanical stirrer, a thermometer and a drip funnel, 16.7 ml (0.1 mol) of carbazole was placed in 60 ml of dimethylformes-yes, 25 ml of triethylamine and, with intensive stirring, 8.5 ml (0.05 mol) of GMDI was added drop by drop from the drip funnel. The reaction lasted for 4 hours at a temperature of 23-39°S. The precipitate was filtered, washed with distilled water 2-3 times and dried at room temperature. Appearance: white-grayish powdery product. Output- 22.75 g (90 %); t.pl.=230-232 °S; the individuality of the resulting product was tested by TLC on a fixed layer (Al_2O_3) of II degree of purity in system 6. R_f=0,79;

Found, %: C 76,19; H 5,68; N 10,88

Calculated for $C_{32}H_{30}N_4O_2$, % : C 76,49; H 5,97; N 11,15

N,N^1- Hexamethylene bis-[(isatinyl) urea] (4) (XIOX-4)

To 14.7g (0.1 mol) of isatin in 60 ml of DMFA and 25 ml of triethylamine with intensive stirring, 8.5 ml (0.05 mol) of GMDI was added drop by drop from a drip funnel. The reaction lasted for 4 hours at a temperature of 24-37°S. The pre-

cipitate was filtered, washed with distilled water 2-3 times and dried at room temperature. Appearance bright red powdery product. Yield - 18.53g (89%): t.pl.=163-164°S. The individuality of the resulting product was tested by TLC on a fixed layer (Al_2O_3) of II degree of purity in the system 5. R_f=0,57.

Found % : C 62,06; H 4,44; N 11,87

Calculated for $C_{24}H_{22}N_4O_6$, %: C 62,33; H 4,76; N 12,12

N,N¹--Hexamethylene bis-[(5-bromisatin il) urea] (5) (XIOX-5)

To 23.6g (0.1 mol) of 5-bromisatin in 55 ml of DMFA and 24 ml of triethylamine with intensive stirring, 8.5 ml (0.05 mol) GMDI was added drop by drop from the drip funnel. The reaction lasted for 3.5 hours at a temperature of 25-42°S. The precipitate was filtered, washed with distilled water 2-3 times and dried at room temperature. Appearance - brown-reddish powdery product. Yield - 26.9g (85%): t.pl.=174-175oC.

Found % : C 46,23 H 3,01 N 8,74

Calculated for $C_{24}H_{20}Br_2N_4O_6$: C 46,46 H 3,22 N 9,03

N,N¹-Hexamethylene bis-[(p-ferrocenylamine)urea] (6) (XIOX-6)

8.5 ml (0.05 mol) GMDI was added to 27.68g (0.1 mol) of p-ferrocenyl phenyl amine in 100 ml of DMFA with intensive stirring by drops from a drip funnel. The reaction lasted for 3.5 hours at a temperature of 26-44°S. The precipitate was filtered, washed with distilled water 2-3 times and dried at room temperature. Appearance- brick-brownish powdery product. Yield -32.26g (89%);

t. melting= 211-212°S; R_f=0,58

Found % : N 8,96

Calculated for $C_{40}H_{38}N_4O_2$, %: N 9,24

2.4. Chemical transformations N,N¹- hexamethylene bis-[(aminoaryl) urea]

Synthesis N,N¹- Dichloro-substituted hexamethylene bis-[(aminopropyl) urea] (7-12) (General procedure)

N,N¹--dichloro hexamethylene bis-[(diphenylamino) urea] (7)

5.06g (0.01 mol) N,N^1-hexamethylene bis-[(diphenylamino) urea], 60 ml of tetrachloro-methane, 25.0 g of wet aluminum oxide were placed in a threenecked flask equipped with a reverse refrigerator with a calcium chloride tube, an auto mixer and a thermometer, and 4.7 g of calcium hypochlorite was added drop by drop at a temperature of 370C for 4 hours. Then the reaction mass was left for 24 hours. The precipitate was filtered out and washed with sulfuric ether. Received 6.26g (96 %). t. mt. =178-179^{0}S.

Found, %: N 9,52

Calculated for $C_{32}H_{32}Cl_2N_4O_2$, %: N 9,73

Similarly , according to the above method , the following results were obtained: N,N^1- dichlor - N,N^1- hexamethylene bis-[(dibenzylamino) urea], N,N^1- dichlor - N,N^1- hexameethylene bis-[(carbazolyl) urea], N,N^1-dichlor- N,N^1- hexamethylene bis [(isatinyl) urea],N,N^1-dichlor- N,N^1- hexamethylene bis-[(5-bromisatinil) urea], N,N^1-dichlor-N,N^1- hexamethylene bis-[(p- ferrocenyl phenyl amino) urea] (**8-12**).

Synthesis N,N^1- dibromosubstituted hexamethylene bis-[(aminoaryl) urea] (13-18) (General technique)

N,N^1-dybrom -N,N^1- hexamethylene bis-[(diphenylamino) urea] (13)

5.06g (0.01 mol) of N,N^1- hexamethylene bis-[(diphenylamino) urea], 65 ml of chlorophore, 30 g of wet alumina were placed in a three-necked flask equipped with a reverse refrigerator with a calcium chloride tube, an auto mixer and a thermometer, and 10 g of calcium hypobromite was added drop by drop at a temperature of 600C for 3.5 hours. Then the reaction mass was left for 48 hours. The precipitate was filtered out and washed with sulfuric ether. Received 5.73g (86%). T.mt. =217-218^{0}S.

Found, %: N 8,19

Calculated for $C_{32}H_{32}Br_2N_4O_2$, %: N 8,43 N

Similarly, according to the above method, the following were obtained: N,N^1-dibromo- N,N^1-hexamethylene bis-[(dibenzylamino) urea], N,N^1-dibromo-N,N^1-hexamethylene bis-[(carbazolyl) urea], N,N^1-dibromo-N,N^1-dibromo-N,N^1-

dibromo-N,N^1-hexamethylene bis-[(5-bromisatinyl) urea] and N,N^1-dibromo-N,N^1-hexamethylene bis-[(p-ferrocenylphenylamino) urea] **(14-18)**.

2.5. Synthesis N,N^1-hexamethylene bis-[(aminoaryl) urea] (19-24)

(General technique)

N,N^1- diisopropyl -N,N^1- hexamethylene bis-[(diphenylamino) urea]

(19)

5.06g (0.01 mol) N,N^1-hexamethylene bis-[(diphenylamino) urea] in 30 ml of benzene was mixed into a three-necked flask equipped with a reverse refrigerator with a chlorocalcium tube, an auto mixer and a thermometer. With slow stirring, 3.4 ml (0.02 mol) of isopropyl iodide was added drop by drop. Then the mixture was stirred for 13 hours when heated in a boiling water bath. After cooling, 25 ml of water was poured, the precipitate was separated and recrystallized with 50% alcohol. Received- 5,42 r (92,0%).

Found , %: N 9,23

Calculated for $C_{38}H_{46}N_4O_2$, %: N 9,49

Similarly , according to the above method , the following results were obtained: N,N^1 - diisopropyl - N,N^1-bis hexamethylene-[(dibenzylamino) urea], N,N^1 - diisopropyl - N,N^1-bis hexamethylene-[(ve carbazolyl) urea], N,N^1 - diisopropyl - N,N^1 - bis hexamethylene-[(estinyl) urea], N,N^1 - diizo-propyl - N,N^1 - bis hexamethylene-[(5-bromoisatin) urea], N,N^1 - diizo-propyl-N,N^1-hexamethylene bis-[(p- ferrocenylethylamine) urea] (20-24).

N,N^1-diamide, N,N^1-hexamethylene bis-[(diphenylamino) urea] (25)

5.06g (0.01 mol) of N,N^1-hexamethylene bis- [(diphenylamino) urea] and 30 ml of abs. benzene were placed in the flask. With slow stirring, 3.4 g (0.02 mol) of amyl iodide was added drop by drop. Then the mixture was stirred for 15 hours when heated in a boiling water bath. After cooling, 50% alcohol was poured. Obtained- 6.14 g (95%) N,N^1-diamide- N,N^1-hexamethylene bis- [(diphenylamino) urea].

T. pl . = 181-182°S.

Found, %: N 9,23

Calculated for $C_{38}H_{46}N_4O_2$, %: N 9,49

Similarly, according to the above method, the following were obtained: N,N^1- diamylo - N,N^1-hexamethylene bis-[(dibenzylamino) urea], N,N^1- diamylo - N,N^1-hexamethylene bis-[(carbazolyl) urea], N,N^1-diamylo - N,N^1-diamylo- N,N^1-hexamethylene bis-[(isatinyl) urea], N,N^1- diamylo - N,N^1- hexamethylene bis- [(5-bromisatinyl) urea], N,N^1- diamyl -N,N^1-hexamethylene bis-[(p- ferrocenylphenyl-amino) urea] **(26-30).**

2.6. Synthesis of N,N^1-dinitrosubstituted N,N^1-hexamethylene bis-[(amino aryl) urea] (31-36) (General procedure)

N,N^1-dinitroso-N,N^1-hexamethylene bis-[(diphenylamino) urea] (31)

To a suspension of 5.06 g (0.01 mol) N,N^1-hexamethylene bis-[(diphenylamino) urea) in 50 ml of 36% (method A) or 60 ml of 18% (method B) hydrochloric acid, or 70 ml of 98% formic acid (method B), or 60 ml of 50% caustic acid (method D), with stirring and cooling to 0-5^{0}C, a portion was added for 1 hour 0.1 mol $NaNO_2$, then, stirring at the same temperature, the reaction was continued for 1 hour. Every 6-10 minutes, the reaction mixture was analyzed by TLC method. The resulting precipitate was filtered, washed with 50 ml of ice water and dried in air at room temperature. For methods (A-D), the filtrate was extracted with ethyl cetate (2x50ml), washed with ice water and 5% aqueous soda solution, dried with magnesium sulfate and evaporated dry. For all methods (A-D), precipitates and residues after evaporation of extracts were combined. The obtained N,N^1-dinitroso compounds N,N^1-hexamethylene bis-[(diphenylamino) urea] were determined by R_f, washed off with acetone sorbent. The solvent is evaporated dry at room temperature in the vacuum of the desiccator. N,N^1-dinitrous derivative N,N^1-hexamethylene bis-[(diphenylamino) urea] was recrystallized from hexane and ethyl acetate. Output - 5.01g (89%). t.pl.=294^{0}C (different).

Found, %: N 14,63

Calculated for $C_{32}H_{32}N_6O_4$, %: N 14,89

Similarly, according to the above method, the following were obtained: N,N^1- dinitroso- N,N^1-hexamethylene bis-[(dibenzylamino) urea], N,N^1- dinitroso -

N,N^1-hexamethylene bis-[(carbazolyl) urea], N,N^1- dinitroso - N,N^1- hexamethylene bis-[(isatinyl) urea], N,N^1 - dinitroso - N,N^1- hexamethylene bis- [(5-bromisatinyl) urea], N,N^1- dinitroso -N,N^1-hexamethylene bis-[(p-ferrocenylphenylamino) urea] **(32-36)**.

CHAPTER 3. STRUCTURE, PROPERTIES AND METHODS OF OBTAINING N,N^1- HEXAMETHYLENE BIS-[(AMINOPROPYL) UREA] AND THEIR DERIVATIVES

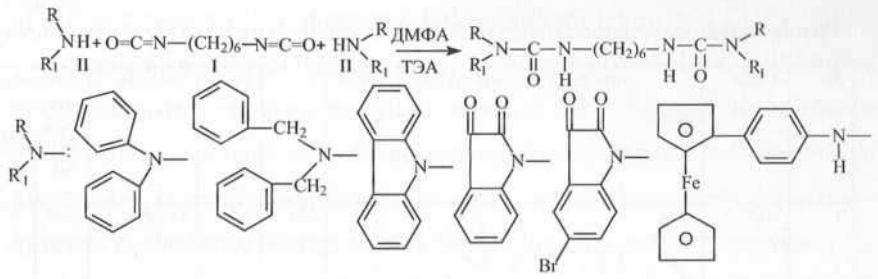
Today in agriculture, urea derivatives are used as herbicide, pesticide, fungicide, defoliant and biofertilizers. In organic synthesis based on urea with other reagents, hard-to-reach heterocyclic compounds (barbitals, phenobarbital, mineral, etc.) were obtained. This list can be continued, so wide is the scope of use of urea derivatives, bisureas and polyureas.

Based on the above, we have started searching for the synthesis and technologies for the production of urea derivatives, or rather bis-aminoaroylureas, which are little-studied, new directions in the world of organic synthesis and production technologies. Continuing research on the synthesis of previously unknown new derivatives of bis-urea and the study of their chemical properties and activity, as well as systematic studies of rare produced urea, we found it interesting to develop waste-free technologies for the synthesis and reaction of GMDI with HN< or H2N-containing compounds of the aromatic series.

3.1. Synthesis N,N^1- - hexamethylene bis-[(aminopropyl)-urea] and their derivatives. Reactions of A_N- (nucleophilic addition) aromatic secondary amines to hexane-1,6-diisocyanate

To continue research in the field of neglected synthesis of derivatives of urea-based aromatic compounds containing amino groups, we have developed a simple preparative method for the synthesis of derivatives of N,N^1 –bis hexamethylene-[(aminoalkyl) urea] based on the reaction of a diisocyanate (I) secondary aromatic amines (II) carried out with a molar ratio of the reagents I:II= 1:2 at room temperature for 3.5 - 4.0 hours according to the following

scheme:

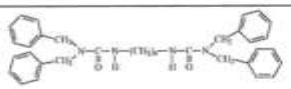
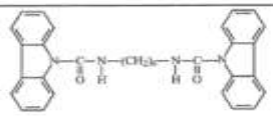
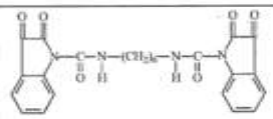
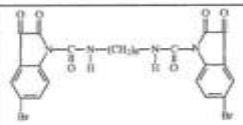


For the first time synthesized products are colorless substances, hardly soluble in water and easily soluble in organic solvents (DMAC, DMSO, DMFA, pyridine, NSOON, CCl4, etc.), which confirms the presence of two urea groups and aromatics soluble in heteropolar solvents. The physico-chemical characteristics of N,N^1-hexamethylene bis-[(aminoaroyl) urea] are given in Table 3.1.

Table 3.1 shows that the yields of N,N^1- hexamethylene bis-[(aminoaroyl) urea] (I-VI) depend on the nature of the radical in the molecule of aromatic secondary amines, as well as the basicity and solubility constants. For example, in the case of dibenzylamine, diphenylamine, carbazole, isatin, p-ferrophenylphenylamine, 5-bromisatin yields are 85-94%. A slight decrease in the yield of the product, apparently, can be explained, firstly, by the increased basicity of aromatic amines, since the reactivity of aromatic secondary amines increases with increasing basicity, and consequently, the yield of reaction products increases (Table 3.1). Secondly, the high yield of the obtained N,N1-hexamethylene bis- [(aminoaroyl) urea] is apparently due to the high density and light mobility of the electron cloud of the conjugated (-N=C=O) group. feasts of hexane-1,6-diisocyanate, which leads to an increase in steric obstacles.

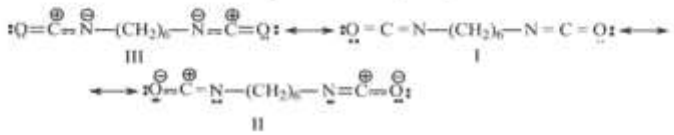
Table 3.1

Physico-chemical characteristics of N,N^1- hexamethylene bis-[(amino aryl) urea]

№ n/n	Code	Structural formula and the name	Yield, %	T mt., °C	R_f	Formula Gross	Elemental analysis, N,%	
							Calculate.	Found
1	HUH -1	 N,N^1- hexamethylene bis-[(diphenylamino)- urea]	92	224-225	0,7	$C_{32}H_{32}N_6O_2$	11,06	10,78
2	HUH -2	 N,N^1- hexamethylene bis-[(diphenylamino)- urea]	94	190-191	0,69	$C_{36}H_{40}N_6O_2$	9,56	9,31
3	HUH -3	 N,N^1- hexamethylene bis-[(carbazolyl) urea]	90	230-232	0,79	$C_{32}H_{30}N_6O_2$	11,15	10,88
4	HUH -4	 N,N^1- hexamethylene bis-[(isatinoylo) urea]	89	163-164	0,70	$C_{34}H_{32}N_6O_6$	12,12	11,87
5	HUH -5	 N,N^1- hexamethylene bis [(5-bromoisatinoyl) urea]	85	174-175	0,76	$C_{34}H_{30}Br_2N_6O_6$	9,03	8,74
6	HUH -6	 N,N^1- hexamethylene bis-[(p-ferrocenyl-phenylamino) urea]	89	211-212	0,58	$C_{48}H_{48}Fe_2N_6O_2$	9,24	8,96

Probable mechanism of interaction of aromatic secondary amines with hexane-1,6-diisocyanate

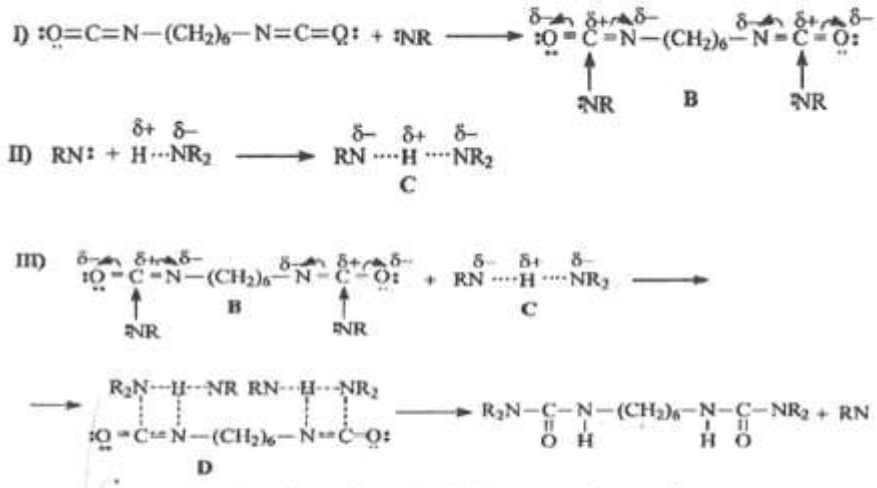
It is known from the literature data [13] that the structure of the radical R in the grouping -N=C=O has a significant effect on the activity of the isocyanate group. At the same time, electron-acceptor substituents increase the reactivity of diisocyanates in addition reactions to the nucleophilic reagent, electron-donating - decrease. A number of foreign authors believe that this pattern is explained, respectively, by an increase and decrease in the positive charge on carbon -N=C=O groups. So, for example, S.G. Entelis with col. [13] it is shown that in the case of substitution of arylisocyanates, the charge density on the carbon atom ($C^{\delta+}$) correlates with the δ-constants of the substituent. An increase in the fraction of the positive charge δ^+ on this atom, when electron acceptor substituents are introduced into the nucleus, is consistent with changes in the reactivity of arylisocyanates when the substituent changes. An increase in the electron density deficit on the carbon atom of the -N=C=O group leads to an increase in the rate constant of the nucleophilic reagent $(Ph)_2NH$ to diisocyanates. However, in the course of work, a rigid structure is also used for the isocyanate group in a static state. Based on quantum chemical calculations, it is assumed that the charge density on the atoms of the -N=C=O group does not change when a substituent is replaced in the R-N=C=O molecule. The effect of substituents on the reactivity of isocyanates is explained either by a change in the length of bonds in the isocyanate group, or by a different stabilization of the transition state in the reactions of nucleophilic addition (A_N) to diisocyanates. The chemical behavior of the diisocyanate is most fully consistent with such a distribution of the electron density in the -N=C=O group, which is described by the combination of the following structures (I-III):



III I

II

Nitrogen and oxygen in the –N=C=O group carry mainly a negative charge and have electron-donating properties, so this group is susceptible to both nucleophilic and electrophilic attacks. In some cases, diisocyanates can also play the role of electrophilic agents. The most typical reactions for them are nucleophilic addition involving oxygen- and nitrogen-containing substances. The NH group, for example, of diphenylamine, having a free electron pair, attacks the electrophilic center in the GMDI molecule with the formation of an intermediate (B), which rearranges into bis-urea. Therefore, based on the literature data, the probable mechanism of interaction of aromatic secondary amines with hexane-1,6-diisocyanate, in our opinion, can be represented by the following scheme:



where RN: is a solvent, R_2NH is a secondary amine.

For the final solution of the question of the mechanism of attachment of heterocyclic amines to endi, additional study of the reaction dynamics is necessary.

The structure of the first synthesized N,N^1-hexamethylene bis-[(aminoaryl) urea] proved by IR and PMR spectroscopy (Table 3.2) (Appendix) and confirmed by elemental analysis data.

Table 3.2

IR and PMR spectra of some bis-urea derivatives

№ п/п	Structural formula and name	IR spectrum, ν_{max}, $см^{-1}$			PMR spectrum, δ, м.д.		
				$(CH_2)_6$			
1	N,N^1- hexamethylene bis-[(diphenylamino) urea]	1622	3330	768-734	2,81	1,28-1,06	3,29
2	N,N^1- hexamethylene bis-[(dibenzylamino) urea]	1624	3334	770-736	2,77	1,24-1,02	3,59
3	N,N^1- hexamethylene bis-(carbazolyl) urea]	1626	3335	772-728	2,76	1,26-1,04	3,61
4	N,N^1- hexamethylene bis-[(izatinoylo) urea]	1623	3331	767-733	2,98	1,40	3,47
5	N,N^1- hexamethylene bis-[(5-bromoisatinoyl) urea]	1625	3333	771-730	2,91	1,39-1,06	3,59
6	N,N^1- hexamethylene bis-[(p-ferrocenyl phenyl amino) urea]	1630	3330	765-728	-	-	-

Influence of various factors on the yield of bis-urea derivatives

In order to establish optimal conditions for the synthesis of bis-urea derivatives, the effect of reaction duration, temperature, and solvent type on the yield of the target products was studied. To clarify the effect of the reaction duration, experiments were conducted with hexane-1,6-diisocyanate in a thermostat under comparable conditions at a temperature of 330C. The duration of the process was changed from 1 to 5 hours (Fig. 3.1).

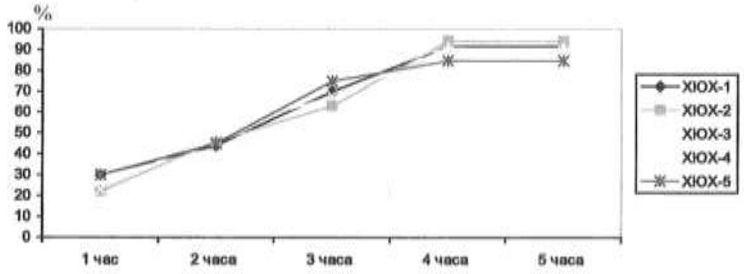


Fig.3.1. Effect of reaction duration on the yield of bis-aminoaroyl-chevin

From the results obtained, it was found that the optimal duration of the reaction providing the highest yield of the product is 4 hours, and during the 5th hour the yield of the product did not change.

Effect of reaction temperature

The effect of temperature on the yield of the target products was studied by conducting a reaction at different temperatures of the reaction medium (Fig. 3.2). As can be seen from the figure, during the reaction at 00C, the yields of the target products ranged from 4 to 6%. With an increase in temperature, the yield began to increase: so, at a temperature of 15^0 C, the yield was from 17 to 25%, at a temperature of 22^0C - 50-60%, at 28^0C - up to 94%. At a temperature of 33^0 C, the yield of the product did not in-

crease.

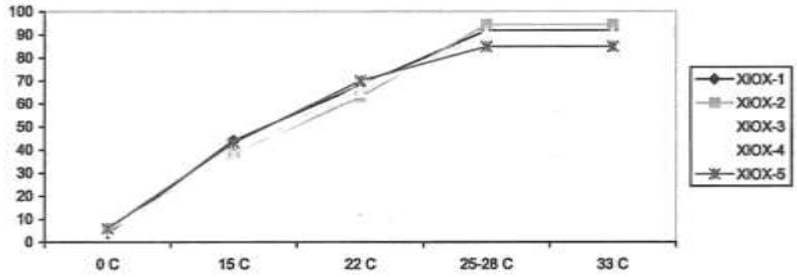


Fig.3.2. The effect of temperature on the yield of bis-aminoaroylureas

The high yield rates at a temperature of 25-280 C can be explained, apparently, by the fact that at such a temperature the mobility of the reaction center of the N-H groups is high, which causes the absence of intra- and intermolecular hydrogen bonding. In this case, a certain amount of solvent binds and activates the -N=C=O grouping and the free H-N< group with hexane-1,6-diisocyanate, followed by the formation of bis-urea derivatives. At a temperature of 330C, the mobility of the reaction center N-H does not change.

Influence of solvent nature

To study the effect of the nature of the solvent, in addition to dimethylformamide, a number of electron-donating solvents (THF, pyridine, dioxane, acetonitrile) supporting the ionization of reacting components were used, which apparently significantly intensified the reaction. It has been experimentally established that the yield of hexamethylene bis-[(aminoaroyl) urea] is significantly influenced by the nature of the solvent. Thus, with an increase in the dipolar moments of aprotic bipolar solvents, the yield of the target product changed in the following order: DMFA (3,8) > Py (2,19) > THF (1,7) > Dioxane (0) increases (Fig. 3.3). It was found that at 280C hexane-1,6-diisocyanate in DMFA easily reacts with N-N< group-containing aromatic secondary amines to form N,N^{l}-hexamethylene bis-[(aminoaroyl) urea]. According to the "like-in-kind" dissolution principle, the interaction of DMFA with heterocycles proceeds especially regioselectively, which apparently contributed to the formation of strong stable stable complexes between -N=C=O and H-N< groups of aromatic amines. Thus, it has been established that bipolar aprotic solvents with large dipole moments and high dielectric permittivity are capable of forming strong donor-acceptor complexes that contribute to an increase in the yield of target products.

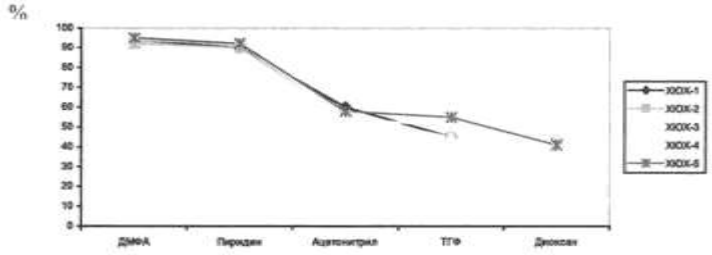


Fig.3.3. Dependence of the yield of bis-aminoaroylureas on the nature of the solvent

It was found that during the reaction of specific solvation with carbonyl carbon of the isocyanate group, the basicity of the H-N< imino group is enhanced due to donor-acceptor complexation. Thus, in THF and dioxane, the reaction proceeds with

a lower yield of the target product of N addition than in DMFA. Solvation with DMFA and pyridine is easier than with THF and dioxane, so the yield increases.

Thus, it was found that the optimal reaction conditions for the formation of N,N^1-hexamethylene bis-[(aminoaryl)urea] are: temperature 28^{0}C; solvent - DMFA, reaction duration 4 hours.

3.2. Chemical transformations of N,N ^{1}- hexamethylene bis-[(amino aryl) urea]

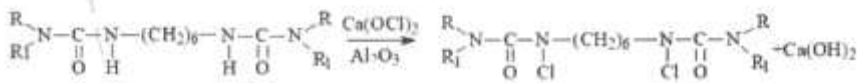
To study the chemical properties of the H-N< reaction center of the synthesized bis-urea derivatives, their N,N^1-digalogenation and N,N^1-dinitrosation were carried out.

3.2.1. N,N 1-dihalogenylation of substituted N,N^1-hexamethylene bis-[(amino aryl) urea]

Preparation of N,N ^{1}-dichloro-substituted N,N^1-hexamethylene bis- [(amino aryl) urea]

Derivatives of N,N^1-hexamethylene bis-[(aminoaroyl) urea] are the most valuable raw materials for the synthesis of nitrogen-containing aromatic compounds with a diverse chemical structure, which are of interest to many specialists - chemists, physicians, pharmacologists, biologists, biochemists and many others - due to the presence of a vital, highly reactive center (>N-H group) in the composition of bis-aminoaroyl urea, necessary for reactions nucleophilic and electrophilic substitution.

In order to obtain N,N^1-dichloro-substituted N,N^1-hexamethylene bis-[(aminopropyl) urea] [7-12] a highly effective, affordable, cheap, fast, stable, environmentally friendly method of N,N^1-dichlorination of bis-[(aminoaroyl) urea] with calcium hypochlorite in the presence of wet aluminum oxide has been developed for the first time [140].

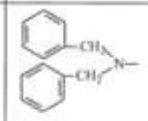
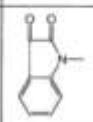
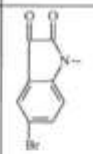
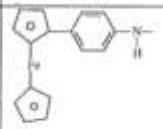


7-12

The physico-chemical parameters of N,N^1-dichloro derivatives of N,N^1-hexamethylene bis-[(aminoaroyl) urea] are given in Table. 3.3.

Table 3.3

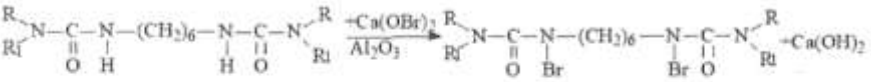
Physico-chemical characteristics of N,N^1- dichloro-substituted N,N^1- hexamethylene bis-[(amino aryl) urea]

№ n/n	R, R'N—:	Yield %	T mt.,° C	Gross Formula	Elemental analysis, N, %	
					Calc.	Found
7		96	178-179	$C_{32}H_{32}Cl_2N_4O_2$	9,73	9,52
8		98	159-160	$C_{36}H_{40}Cl_2N_4O_2$	8,87	8,52
9		95	184-185	$C_{32}H_{28}Cl_2N_4O_2$	9,80	9,53
10		89	163-164	$C_{24}H_{20}Cl_2N_4O_6$	10,54	10,29
11		84	174-175	$C_{24}H_{18}Cl_2Br_2N_4O_6$	8,13	7,88
12		91	249-250	$C_{40}H_{36}Fe_2Cl_2N_4O_2$	7,08	6,86

To prove the structure of N,N^1-dichloro-substituted N,N^1-hexamethylene bis-[(aminoaroyl) urea], IR spectra, elemental analysis were taken and a classical qualitative reaction was carried out with $AgNO_3$.

Preparation of N,N^1-dibromo-substituted N,N^1-hexamethylene bis- [(aminopropyl) urea]

In order to obtain N,N^1-dibromo-substituted N,N^1-hexamethylene bis-[(aminopropyl) urea] (13-18), we have for the first time developed a highly effective, easily accessible, cheap, environmentally friendly method of N,N^1-dibromation of bis-[(aminoaroyl) urea] with calcium hypobromide in the presence of wet alumina, according to the scheme:



13-18

Physico-chemical parameters of N,N^1-dibromo-substituted N,N^1-hexamethylene bis-[(amino aryl) urea] are given in Table 3.4.

To prove the structure of newly synthesized N,N^1-dibromo-substituted N,N^1-hexamethylene bis-[(amino aryl) urea] (13-18) IR spectra were taken, elemental analysis and qualitative reactions with $AgNO_3$.

Qualitative reaction to the bromide ion (Br^-)

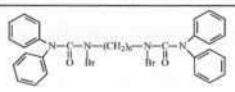
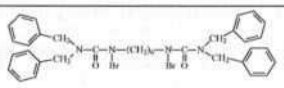
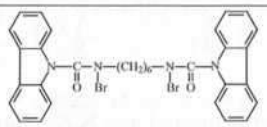
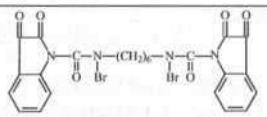
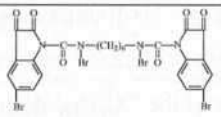
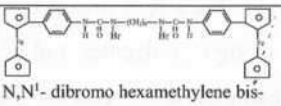
To confirm the structure of the N,N^1-dibromo-substituted- N,N^1-dibromo-N,N^1-hexamethylene bis-[(aminoaroyl) urea] formed, the obtained compounds were reacted with a solution $AgNO_3$. A pale yellowish precipitate of ApVkb fell out, to which a solution of ammonium hydroxide was added in small quantities. The Apc precipitate dissolved to form silver ammonia:

$$AgBr + 2\ NH_4OH = [Ag\ (NH_3)_2]\ Br + 2H_2O$$

This chemical method fully confirms the formation of N,N^1-dibromosubstituted- N,N^1-hexamethylene bis-[(aminoaroyl) urea].

Table 3.4

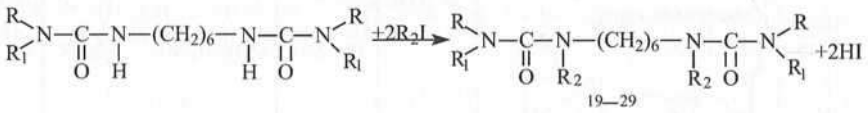
Characteristics of N,N^1-dibromo-substituted N,N^1-hexamethylene bis-[(amino aryl) urea]

№ п/п	Structural formula and name	Yield, %	T mt ^{0}C	Formula Brutto	Element. analysis,N, %	
					Calc.	Found
13	 N,N^1- dibromo hexamethylene bis-[(diphenylamino) urea]	86	217-218	$C_{32}H_{32}Br_2N_4O_2$	8,43	8,19
14	 N,N^1- dibromo hexamethylene bis-[(dibenzylamino) urea]	84	226-227	$C_{36}H_{40}Br_2N_4O_2$	7,78	7,47
15	 N,N^1 dibromo hexamethylene bis-(carbazolyl) urea	95	189-190	$C_{32}H_{20}Br_2N_4O_2$	8,48	8,31
16	 N,N^1- dibromo hexamethylene bis-[(isotino il) urea]	84	177-178	$C_{24}H_{20}Br_2N_4O_6$	9,03	8,79
17	 N,N^1- dibromo hexamethylene bis-[(5-bromoisatinoyl) urea]	80	196-197	$C_{24}H_{18}Br_4N_4O_2$	7,20	7,01
18	 N,N^1- dibromo hexamethylene bis-[(p-ferrocenylphenylamino) urine-wine	87	202-203	$C_{40}H_{36}Br_2\ Fe_2N_4O_2$	6,36	6,09

3.2.2. N,N^1-dealkylation of N,N^1- hexamethylene bis-[(amino aryl) urea] N,N^1-disopropyl and deamidation of N,N^1-hexamethylene bis-[(amino aryl) urea]

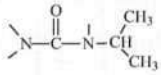
N,N^1-dealkylation of the bis-urea group by alkyl halides by N-H is of undoubted interest for elucidating the reactivity of compounds containing >N-H of the reaction center.

The alkylation reaction is carried out by the interaction of iso-propyl iodide or n-amyl iodide with N,N^1- hexamethylene bis-[(aminoaroyl) urea] in a molar ratio of 2.5:1 in benzene at a temperature of 27-30^{0}S for 4 hours according to the scheme:



19—29

Physico-chemical characteristics of N,N^1-diisopropyl and N,N^1-diamyl substituted N,N^1-hexamethylene bis-[(amino aryl) urea] are shown in Table 3.5.
Strong absorption bands are detected in the IR spectra:

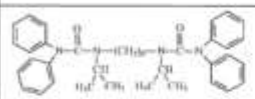
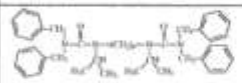
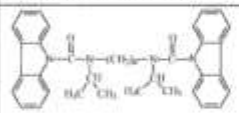
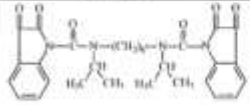
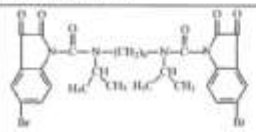
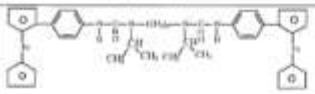


1294-1308 sm^{-1}; C=O - 1720-1730 см$^{-1}$; (-CH_2-)$_6$ 758-724 см$^{-1}$; a для -CH_2-2420-2860 см$^{-1}$. It has been experimentally established that the course of the reaction of N,N1-dialkylation of N,N1-hexamethylene bis-[(aminoaroyl) urea] strongly depends on the nature of the radical of secondary aromatic amines, amyl halide R-I, solvent, "hardness" or "softness", mobility of the "X" (halide) – alkylating agent, etc.

In particular, the increased ability of alkyl halides R-X to substitution reactions is associated with the structural features of their molecules and depends on the structure of the radical, the nature of the halogen, as well as on the reaction conditions and the nature of the solvent in which the reaction is carried out (Table 3.6).

Таблица 3.5

Physico-chemical characteristics of N,N^1-diisopropyl- and N,N^1-diamyl derivatives of N,N^1-hexamethylene bis-[(aminoaryl) urea]

№ п/п	Structural formula and name	Yield o,д, %	T mt.,$^\circ$C	R_f	Formula Brutto	Elemental analysis, N, %	
						Calc	Found
19	 N,N^1- diisopropyl hexamethylene bis-[(diphenylamino) urea]	92	191-192	0,64	$C_{38}H_{48}N_4O_2$	9,46	9,23
20	 N,N^1 diisopropyl hexamethylene bis-[(dibenzylamino) urea]	94	196-197	0,58	$C_{42}H_{54}N_4O_2$	8,66	8,38
21	 N,N^1- diisopropyl hexamethylene bis-(carbazolyl) urea]	90	187-188	0,71	$C_{38}H_{42}N_4O_2$	9,55	9,31
22	 N,N^1- diisopropyl hexamethylene bis-[(isatinoyl) urea]	86	179-180	0,66	$C_{30}H_{34}N_4O_6$	11,61	11,46
23	 N,N^1- diisopropyl hexamethylene bis-[(5-bromisatinoyl) urea]	85	186-187	0,56	$C_{30}H_{32}Br_2N_4O_6$	7,95	7,68
24	 N,N^1–diisopropyl hexamethylene bis-	95	314-315	0,76	$C_{46}H_{50}Fe_2N_4O_2$	6,53	6,29

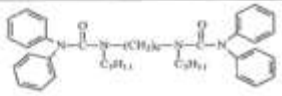
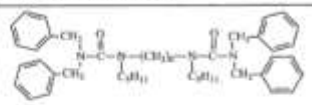
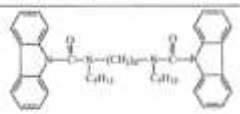
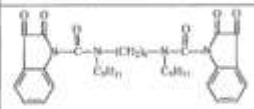
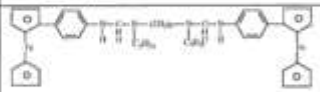
	[(p-ferrocenyl phenyl amino) urea						
25	 N,N¹- diamylhexamethylene bis- [(diphenylamino) urea]	92	181-182	0,67	$C_{42}H_{54}N_4O_2$	8,66	8,36
26	 N,N¹- diamylohexamethylene bis- [(dibenzylamino) urea]	94	189-190	0,54	$C_{46}H_{62}N_4O_2$	9,77	9,50
27	 N,N¹- diamylhexamethylene bis- [(carbazolyl) urea]	95	203-204	0,66	$C_{42}H_{50}N_4O_2$	8,72	8,47
28	 N,N¹- diamyl hexamethylene bis- [(isatin-yl) urea]	89	173-174	0,54	$C_{34}H_{42}N_4O_6$	9,30	9,04
29	 N,N¹- diamyl hexamethylene bis- [(p-ferrocenyl phenyl amino) urea	90	217-218	0,74	$C_{58}H_{62}Fe_2N_4O_2$	6,50	6,24

Table 3.6

Physical properties of R-X

Halogen derivatives	T. boiling. °C				d_4^{20}			
	F	Cl	Br	J	F	Cl	Br	J
CH_3-CHX-CH_3	-10,1	36,5	59,3	89,5	Col. gas	0,87	1,32	1,70
CH_3-$(CH_2)_4$-X	62,8	108,2	129	156	0,788	0,88	1,25	1,52

The table shows that R-I has a higher relative density and boiling point than the corresponding brominated ones. And the bromine-substituted ones, in turn, have a higher density and boiling point than the chlorine-substituted analogues.

The relative density of R-X increases with an increase in the atomic weight of "X", which is part of the molecule, the relative density also depends on the binding energy, its length, etc. (Table 3.7).

Table 3.7

Physical properties R-X

Connection	Ccal	Length, A°	Polarity	Polarizability
C-F	102	1,40	2,3	1,7
C-Cl	78	1,76	2,3	6,5
C-Br	65	1,91	2,2	9,6
C- I	57	2,12	2,0	14,6

Organic molecules are characterized by the so-called polarizability, i.e. the ability to increase the polarity of the bond when an attacking agent approaches. The greater the polarizability of the bond, the more voluminous and mobile the electron shell of the atoms forming the bond. The ability to polarize is well traced in a number of C-X connections. So, if the polarity of the R-F, R-Cl, R-Br and R-I bonds is quite close, then the polarizability of the C-I bond is significantly greater than the C-F bond. Therefore, in exact accordance with the polarizability in all nucleophilic substitution reactions (S_N) bonds C-I is as active as possible than other C's. Therefore, the alkylation reaction with R-I proceeds faster and leads to the formation of >N-CH(CH_3)CH_3 with high yields (Table 3.5).

Thus, the study of the reaction of N,N^1-dialkylation of N,N^1-hexamethylene bis-[(aminoaroyl) urea] with isopropyl iodide (n-amyl) showed that in all cases there is a selective formation of the final products of N,N^1-dialkylation. The predominant N,N^1-dialkylation with iodalkyl is explained by the thermodynamic control of the N,N^1-dialkylation process, i.e. the thermodynamic stability of the obtained N,N^1-diisopropyl (diamyl) N,N^1-hexamethylene bis-[(aminoaroyl) urea] due to the presence of an alkyl group [180,185].

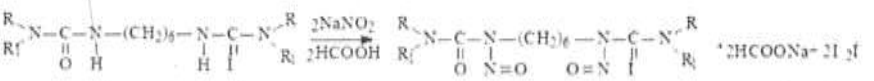
3.2.3. N,N¹- denitrosation of N,N¹- hexamethylene bis-[(amino aryl) urea 3.2.4.]

The reaction of N,N¹-nitrosation of bis-urea derivatives has been relatively little studied in the world literature [77-78]. One of our previous reports was devoted to N,N¹-denitrosation of derivatives of bis-alkyl carbamates of urea [29, 32, 186].

N,N¹-denitrosation of bis-[(aminopropyl) urea] was carried out using sodium nitric acid in an acidic medium (HCl) of concentrated, 5 and 1 n. and formic (anhydrous) acid with stirring and cooling to 0-50C. The products of N,N¹-dinitrosation precipitated. For more complete control over the filtration process after separation of the sludge, the filtrate was repeatedly washed with dichloromethane, chloroform or ethyl acetate.

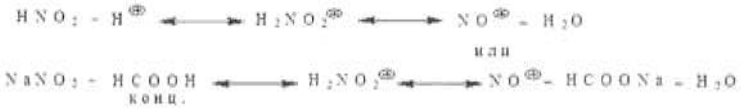
Further, both white precipitates and ethyl acetate extracts were investigated. During the experiments, we expected that reactions would go through all N-H reaction centers to form a mixture of products.

Therefore, in order to clarify the structure of the products of N,N¹-dinitrosation N,N¹-hexamethylene bis-[(amino aryl) urea] PMR spectra were taken. This method made it possible to quickly establish the presence of N,N¹ isomers, as well as by the integral signal intensities of methylene and >N-H groups located at x-positions to N-H or >N-N=About groups, to establish their quantitative ratios. At the same time, on the basis of chemical shifts, the nature of the multiplicity of signals and in combination with the double resonance technique, the structure of N,N¹-dinitro derivatives was unambiguously proved. When carrying out the reaction in the presence of HCOOH from N,N¹-hexamethylene bis-[(amino aryl) urea] with $NaNO_2$, only N,N¹-dinitroso-substituted N,N¹-hexamethylene bis-[(aminoaroyl) urea were obtained]:

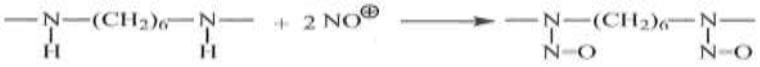


Installed: both under the action of an excess and an equivalent amount of sodium nitrite, only N,N¹-dinitroso-substituted N,N¹-hexamethylene bis-[(aminoaroyl)

urea] is obtained. The corresponding mono-nitros derivatives could not be isolated in any case. N,N^1-dinitrosation proceeds by the mechanism of electrophilic substitution (SE). The corresponding agent is nitrosonium ion NO^+, since nitrous acid, which is the most common nitrosating agent, does not exist in its free form, sodium nitrite and strong acid (HCOOH) are used for the process. The nitrogenous acid formed in this case, by connecting the proton, generates the NO ion$^+$.



Further interaction proceeds by analogy with other electrophilic substitution reactions.



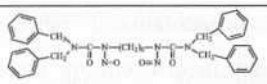
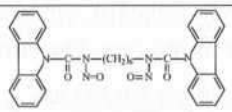
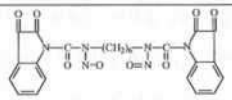
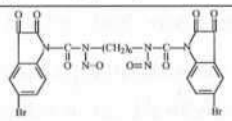
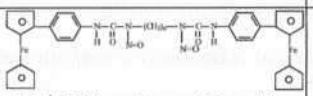
N,N^1 - denitrosation is carried out when the reaction mixture is cooled. An increase in temperature is undesirable, since this reduces the yield of the target product, and sometimes affects the direction of the reaction. The use of nitrous acid as a nitrosating agent, due to its low stability when heated, requires a reaction at low temperatures.

Physico-chemical parameters of the obtained N,N^1- and nitrososubstituted N,N^1-hexamethylene bis-[(amino aryl)urea] are given in Table 3.8.

Table 3.8

Physico-chemical parameters of N,N^1-dinitrosubstituted N,N^1-hexamethylene bis-[(aminoaryl) urea]

№ n/n	Structural formula and name	Yield, %	T.boiling., ^{0}C	Formula Brutto	Elemental analysis, N, %	
					Calc.	Found
30	 N,N^1- dinitroso hexamethylene bis-[(diphenylamino) urea]	89	294 (разл.)	$C_{30}H_{30}N_6O_4$	14,89	14,63

31	 N,N^1-dinitroso hexamethylene bis-[(dibenzylamino) urea]	91	144-146 (разл.)	$C_{36}H_{40}N_6O_4$	13,55	13,36
32	 N,N^1- dinitroso hexamethylene bis-[(carbazolyl) urea]	92	189 190 (разл)	$C_{32}H_{28}N_6O_4$	15,00	14,81
33	 N,N^1- dinitroso hexamethylene bis-[(carbazolyl)urea]	87	192-194	$C_{24}H_{20}N_6O_8$	16,15	16,01
34	 N,N^1- dinitroso hexamethylene bis-[(5-bromisatinoyl) urea]	91	246-247 (разл)	$C_{24}H_{18}Br_2N_6O_8$	12,39	12,18
35	 N,N^1- Dinitroso hexamethylene bis-[(ferrocenyl phenyl amino) urea]	92	296-297	$C_{40}H_{36}Fe_2N_6O_4$	10,77	10,54

Absorption bands were detected in the IR spectra (appendix): - for >N-N=O from 1435-1525 cm^{-1} - strong absorption band, for $(CH_2)_6$–722-768 sм$^{-1}$, for C=O groups from 1690 to 1720 cm $^{-1}$, а для - CH_2- 2927-2946 см$^{-1}$ (табл. 3.9).

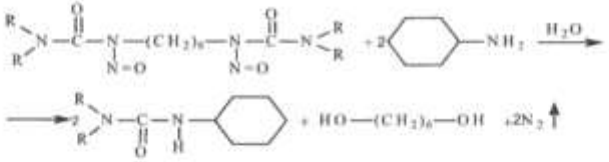
Таблица 3.9

IR spectra of N,N1-dinitroso-substituted N,N^1-hexamethylene bis- [(aminoaroyl) urea]

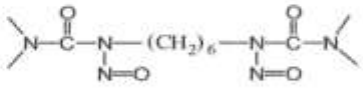
№ п/п	Structural formula	IR spectrum, ν, см$^{-1}$			
		-CH_2-	>N-N=O	C=O	(-CH_2-)$_6$
30	N,N^1- dinitroso hexamethylene bis- [(di-phenylamino) urea]	2940	1458-1550 1248-1310	1690	758-721

31	N,N¹- dinitroso hexamethylene bis-[(dibenzylamino) urea]	2944	1460-1550 1243-1310	1691	762-736
32	N,N¹- dinitroso hexamethylene bis-[(carbazolyl) urea]	2938	1456-1545 1244-1311	1688	757-724
33	N,N¹- dinitroso hexamethylene bis-[(iso-tinoyl) urea]	2942	1460-1552 1242-1315	1691	762-731
34	N,N¹- dinitroso hexamethylene bis- [(5-bromisatinoyl) urea]	2940	1456-1551 1244-1316	1693	764-728
35	N,N¹- Dinitroso hexamethylene bis-[(ferrocenyl phenyl amino) urea]	2946	1459-1550 1246-1320	1690	758-726

In addition to the spectral data, the structure of N,N¹-dinitroso compounds (36-41) was additionally confirmed by a chemical method, i.e. by the reaction of N,N¹-dinitrosation products with amines [186]. Mono- and 1,3-disubstituted urea were obtained by the interaction of N,N¹-dinitroso- N,N¹-hexamethylene bis-[(aminoaroyl) urea] with aqueous ammonia solutions and cyclohexylamine:



Thus, the formed compounds prove once again that at N,N¹-denitrosation of N,N¹-hexamethylene bis-[(aminoaroyl) urea] nitrogen atoms associated with the polymethylene chain undergo nitrosation:



These conclusions are quite consistent with the literature data [186].

3.4. Study of the electronic structure and quantum chemical calculations of the compounds used

Currently, in the natural sciences, including chemistry, using various computer-chemical programs based on the results of quantum chemical and

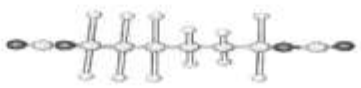
molecular dynamic calculations, it is possible to comprehensively characterize molecules. Based on such results, it is possible to assume in advance the features of the properties, reactivity, and, most importantly, the __ reaction centers of the studied molecules [173]. It should be noted that quantum-chemical and especially molecular-dynamic calculations have not yet received proper distribution in organic chemistry and chemical technology.

The results obtained using quantum chemistry methods provide important information about the distribution of the electron charge density, total energy, energy of formation, heat of formation, electron energy, nuclear energy and dipole moment of the studied molecules.

In addition, the method of quantum chemistry is cheaper, more accessible and universal for studying the properties of a molecule [174, 175]. Nevertheless, it should be pointed out that we cannot completely abandon chemical experimental research methods, since the conduct of quantum chemical research is based on key experimental results.

The activity of a molecule in chemical reactions mainly depends on its composition, structure and energy characteristics. Prediction of the reaction centers of organic molecules is an important and urgent task. With the use of modern quantum chemical methods, chemists have the opportunity to plan experimental studies and conduct targeted synthesis of important chemical products.

Based on these considerations, we investigated the 3D structures, charge distribution and electron density of the initial nitrogen-containing compounds: from the reagents hexane-1,6-diisocyanate, diphenylamine, dibenzyl-amine, carbazole, isatin, 5-bromisatin and p-ferrocenylamine, which were used in the synthesis of urea derivatives. In all the reactions studied, hexane-1,6-diisocyanate is the starting compound. In Fig.3.4 3D structures, charge distribution and electron density in a hexane-1,6-diisocyanate molecule are given (рис.3.4).



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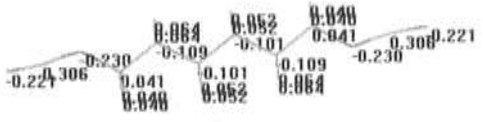

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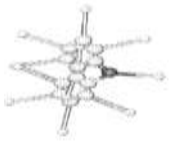
a) 3D structures; b) charge distribution; c) electron density distribution in a hexane-1,6-diisocyanate molecule

Figure 3.4. Structures of charge distribution and electron density

Analysis of the results showed that in the hexane-1,6-diisocyanate molecule, the most negative charge is observed in the nitrogen atom (Fig. 4b), whose values are -2.30 (the charge of the oxygen atom is -2.21). It should be noted that in this molecule, both nitrogen atoms have the same negative charge. Based on these data, it can be assumed that the reaction involving hexane-1,6-diisocyanate proceeds at the expense of both nitrogen atoms. 3D structures, charge distribution and electron density of the initial heterocyclic amines were also investigated. The data obtained are shown in Fig. 1.1-1.23 in appendix 1.



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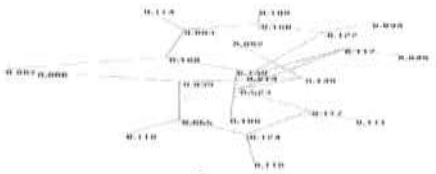

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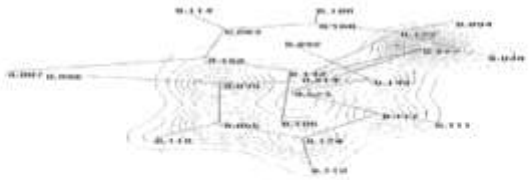

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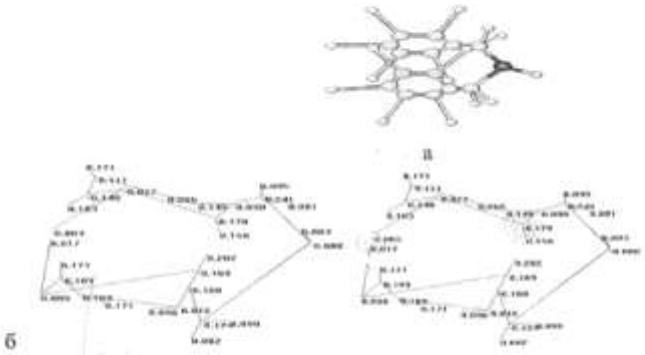
a) 3D structures; b) charge distribution; c) electron density distribution in a diphenylamine molecule

Figure 3.5. A nitrogen atom in a diphenylamine molecule having a pyramidal state

Analysis of the results showed that in the diphenylamine molecule, the nitrogen atom has an sp3 pyramidal state and is in the same plane with two phenyl rings (Fig. 3.5 b). The electron density distribution (Fig. 3.5 c) showed that the greatest concentration of the electron cloud is collected around the nitrogen atom, which is the reaction center of the diphenylamine molecule.

In addition, the dibenzylamine molecule was studied, which is shown in Fig.3.6.



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a) 3D structures; b) charge distribution; c) electron density distribution in the dibenzylamine molecule

Figure 3.6. Structures of charge distribution and electron density

The quantum-chemical characteristics of the studied compounds were also considered. At the same time, the total energy, energy of formation, heat of formation, electron energy, nuclear energy, dipole moment and atom charge in the

molecules of the initial and target compounds were studied. The results obtained are shown in Table 3.11.

The data on the calculation of the quantum-chemical characteristics of the initial compounds are used to clarify (predict) the nature and direction of the reaction, as well as the reaction center of the molecule involved in the reaction. For example, hexane-1,6-diisocyanate is the starting reagent in all studied reactions with secondary amines. In its molecule, the nitrogen atom has a negative charge of -0.230. It can be assumed that it is a reaction center during the nucleophilic addition of aromatic secondary amines to hexane-1,6-diisocyanate.

The second starting compound in the studied reactions are secondary aromatic amines (diphenylamine, dibenzylamine, carbazole, isatin and 5-bromisatin). Among them, the nitrogen atom in the dibenzylamine molecule has the highest negative charge, the value of which is -0.088 (Table 3.11). It is assumed that dibenzylamine is the most reactive in the medium of used amines in reactions with hexane-1,6-diisocyanate.

It should be noted that the above considerations on the quantum-chemical and molecular-dynamic characteristics of the compounds used are confirmed by the experimental data obtained by us.

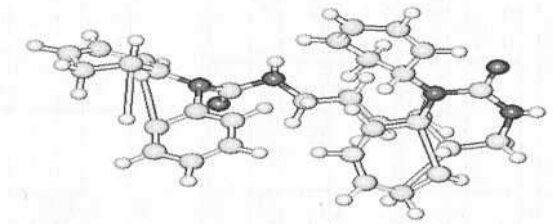
For example, in the reaction of hexane-1,6-diisocyanate with dibenzylamine, N,N^1-hexamethylene bis-[(dibenzylamino) urea] is formed, i.e. the bonding proceeds due to the nitrogen atom of the reacting substances. The yield of the product with the participation of dibenzylamine is higher (94%) than with the participation of other amines.

The quantum-chemical and molecular-dynamic characteristics of the obtained compounds are also investigated. At the same time, the obtained data can be used for further studies involving these molecules, as well as as reference data for those working in the field of computer chemistry.

Quantum chemical calculations of the studied compounds **Table 3.11**

The nature of the connection	Total energy, kcal/mol	Energy of formation, kcal/mol	Heat of formation, kcal/mol	Electron energy,B	Core energy, kcal/mol	Dipole moment (D)	The charge of the nitrogen atom
Hexane-1,6-diisocyanate	-47140,61	-2387,79	-50,328	-224669,01	177528,39	9,485	-0,230
Diphenylamine	-40235,48	-2503,60	233,201	-243565,9	203330,42	2,803	0,117
Dibenzylamine	-46848,58	-2780,61	506,37	-243113,26	196264,71	0	-0,088
Carbazole	-39706,68	-2577,76	54,837	-229233,71	189527,04	1,411	0,236
Izatin	-40905,01	-1897,25	-37,511	-191939,35	151034,35	4,585	0,040
5-bromizatin	-48699,83	-1863,63	-29,253	-223294,96	174595,12	3,996	0,041
N,N`- hexamethylene bis-[(carbazolyl) urea]	-126500,2031	-7489,5273	113,1304	-1349161,125	1222660,875	6,216	-0,038
N,N`- dinitroso-N,N`-hexamethylene bis-[(carbazolyl) urea]	-146693,0938	-7670,8759	172,6961	-1602912,5	1456219,375	7,762	-0,140
N,N`- hexamethylene bis-[(diphenylamino) urea]	-129320	-7897,5126	121,961	-1422843,875	1293523,875	6,554	-0,041
N,N`- dinitroso-N,N`-hexamethylene bis-[(diphenylamino) urea]	-149517,75	-8083,7207	176,6671	-1675196,125	1525678,375	8,709	-0,139
N,N`- dichloro-N,N`-hexamethylene bis-[(diphenylamino) urea]	-143279,0156	-7922,0664	51,18349	-1573909,625	1430630,625	5,426	-0,119
N,N`- dibromo-N,N`-hexamethylene bis-[(diphenylamino) urine-wine]	-144996,25	-7916,8642	51,8859	-1573684	1428687,75	5,379	-0,104
N,N`- diisopropyl-N,N`-hexamethylene bis-[(diphenylamino) urea]	-150052,75	-9622,1025	47,9366	-1873370,62	1723317,87	1,117	-0,113
N,N`- diamyl-N,N`-hexamethylene bis- [(diphenylamino) urine-wine]	-163846,4063	-10743,6484	26,7656	-2152937,75	1989091,25	1,042	-0,130
N,N`- hexamethylene bis-[(isatinyl) urea]	-128787,1172	-6018,7973	38,1607	-1085994,37	957207,18	9,192	-0,097

N,N`-dinitroso-N,N`-hexamethylene bis-[(isatinyl) urea]	-148978,2188	-6198,3427	99,5294	-1317129,5	1168151,25	11,63	-0,191
N,N`- hexamethylene bis [(5-bromisatin il) urea	-144379,8281	-5954,6035	51,6305	-1207149	1062769,125	7,571	-0,075
N,N`- dinitroso-N,N`-hexamethylene bis- [(5-bromisatinyl) urea	-164568,4531	-6131,684	115,4637	-1449550,5	1284982,125	10,1	-0,184
N,N`- hexamethylene bis-[(dibenzylamino) urea]	-142481,7188	-8990,0761	25,5701	-1655439,625	1512957,875	4,074	-0,016
N,N`- dinitroso-N,N`-hexamethylene bis-[(dibenzylamino) urea]	-162643,5625	-9140,3681	116,1917	-1933932,375	1771288,875	3,841	-0,218



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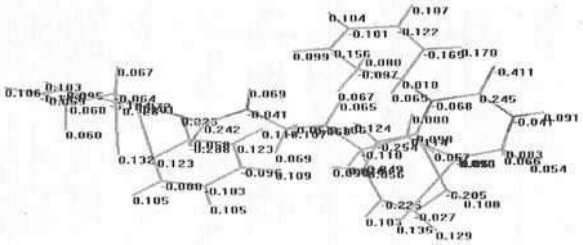

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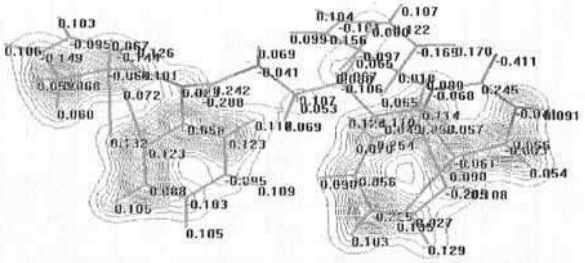

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a) 3D structures; b) charge distribution;
c) electron density distribution in the molecule N,N1-hexamethylene bis-[diphenylamine) urea]

Picture 3.7. Structures charge distribution and electron density

a) 3D structures; b) charge distribution; c) electron density distribution in the molecule N,N^1-hexamethylene bis-[(dibenzylamino) urea]

Picture 3.8. Structures of charge distribution and electron density

Thus, the quantum chemical characteristics and molecular dynamic calculations of the studied compounds have been studied. Based on these data, an assumption is made about the direction of the reaction with their participation and the reaction center in which the process of nucleophilic attachment takes place. The stated considerations are confirmed by the experimental results obtained.

CHAPTER 4. DEVELOPMENT OF PRODUCTION TECHNOLOGYHEX-AMETHYLENE BIS-[(DIBENZYLAMINO) UREA]

The technology for obtaining N,N^1-hexamethylene bis-[(dibenzylamino) urea] was developed in the laboratory of organic synthesis, according to the grant of the Center for Science and Technology under the Cabinet of Ministers of the Republic of Uzbekistan No. A-6-338 from 2006-2009 on the topic: "Development of an import-substituting environmentally friendly safe technology for the production of new, highly effective plant growth stimulant reagents (for vegetable crops, tomatoes, cucumbers, cotton, etc.) based on products and waste from the chemical industry""

To implement this program, a pilot plant has been installed at the department, which consists of one technological line with a periodic process.

The method developed by us for obtaining N,N^1-hexamethylene bis-[(dibenzylamino) urea] consists in nucleophilic addition of dibenzylamine to hexane-1,6-diisocyanate at a temperature of 26-38°C in the presence of a solvent and a catalyst (base), in filtration and drying of the product at a temperature of 156-158 °S.

In the process of obtaining N,N^1-hexamethylene bis-[(dibenzylamino) urea], gaseous and solid waste are not formed. As a liquid waste, a solvent and a base catalyst are formed, which after regeneration is used in subsequent operations.

4.1. Characteristics of finished products

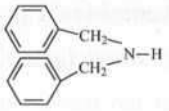
The final finished product- N,N1-hexamethylene bis-[(dibenzylamino) urea] is a colorless powder with a melting point of 190-191°C (Table.3.1), soluble in many organic solvents: DMFA, DMSO, DMAC, HCOOH, nitrobenzene, dioxane.

Characteristics of raw materials and intermediates

1. Dimethylformamide. Formula – C_3H_7NO; structure formula $HCON(CH_3)_2$; colorless. hygroscopic liquid; $M_м$=73,09; Т.кип.=153°S; d_4^{25}=0,9445; n_4^{25}=1.4269; weak base; bipolar aprotic solvent.

2. **Calcium hypochlorite** – $Ca(OCl)_2$; colorless crystals. Resistant to dry atmosphere in the absence of CO_2. Solubility in water (g per 100 g): 27,9 (0°S); и 33,3 (25°S). The industry produces $Ca(OCl)_2$ (50-70 % of active chlorine) and 3 $Ca(OCl)_2$ x 2 $Ca(OH)_2$ x 2 H_2O (50-55 %) active chlorine.

3. Dibenzylamine – colorless liquid with a specific odor.

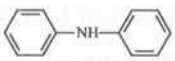


Empirical formula – $C_{14}H_{15}N$.

Molecular weight – 197,29.

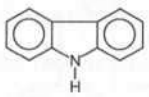
Boiling point – 300°S.

4. **Diphenylamine** – colorless crystals with a specific smell.



Empirical formula – $C_{12}H_{11}N$, $M_м$ =169,23; Т.пл.=54-55°S; T.boiling.=302°S; 179°S/22 мм рт.ст.; d_4^{64}=1,0513; d_4^{25} =1,159; n_D^{64} =1,16189; pKa in water = 0,9. Diphenylamine with concentrated mineral acids forms salts.

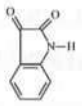
5.Carbazole



M_m = 167.2; colorless crystals; t.pl.=247-248 °S; weak acid; pKa in water -16.7; in DMSO-19.6; Carbazole is characterized by the properties of NH acid;

carbazole is easily alkylated by a nitrogen atom, with CO_2 forms carbazole-9 carboxylic acid. Nitrosation of carbazole proceeds along the N atom with the formation of 9-nitrosocarbazole under the action of HCl and, when heated, regroups into a 3-nitros derivative.

6. **Isatin (2,3-indolindion)**



$M_м$ = 147,12; red crystals; t.pl.=205 °S; density = 1.51 g/cm3.

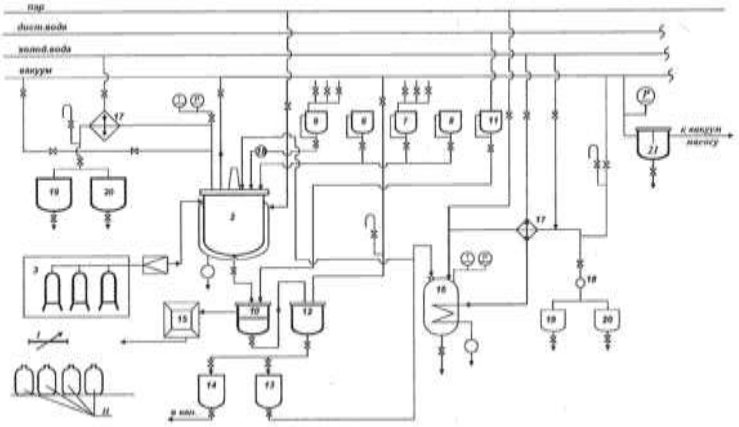
Hexane-1,6-diisocyanate;(hexamethylenediisocyanate, GMDI); a colorless, oily liquid with a pungent odor. Empirical formula - $C_8H_{12}N_2O_2$; structural formula - O=C=N-$(CH_2)_6$-N=C=O; Molecular weight -168.20; t. pl.= -67°C; t. kip.=255-258 °S; 127°C, 10mm Hg. art.; Density: d_4^{20}=1.0465 g/cm3; n_D^{20} =1.4533; GMDI mix-

es with most organic solvents, reacts with water, R-OH, R_2NH, it has all the properties of isocyanates.

4.2. Scheme and description of the technological process

The proposed method for obtaining the growth stimulator of technical plants XIOX-2 includes the preparation of N,N^1-hexamethylene bis-[(dibenzylamino) urea] by the interaction of hexane-1,6-diisocyanate with dibenzylamine in the presence of a dimethylformamide solvent, as well as a small amount of triethylamine.

4.3. Flow chart of the technological process



1-scales; 2-reactor; 3-nitrogen frame; 4,5-tanks; 6,7,8,9-measuring gauge for hexane-1,6-diisocyanate, dibenzylamine, dimethylformamide, triethylamine; 10-Nut filter; 11-distilled water; 12,13,14,19,20-collectors; 15-dryer, 16-alembic; 17-condenser; 18-viewing lantern; 21-trap

Рис. 4.1. The basic technological scheme of the production of N,N^1-hexamethylene bis-[(dibenzylamino) urea]

Description of the technological process for the production of N,N^1-hexamethylene bis-[(dibenzylamino) urea]

The dibenzylamine solution is prepared in the R-2 reactor. To do this, 3.6719 kg (3.5788 l) of dibenzylamine and 10.2516 kg (10.5982 L) of dimethylformamide (DMFA) are loaded by gravity from the M-6 measuring tube from the

M-7 measuring tube, all this is mixed for 20-25 minutes until the complete dissolution of dibenzylamine in dimethylformamide.

Before starting work, all equipment and communications of the installation are washed with water and, if necessary, purged with nitrogen. Nitrogen is supplied from the nitrogen frame AR-3 through a step-down reducer. The components are loaded into the measuring cup from the container E 4.5 by the vacuum created by the vacuum pump. The preparation of the solution and the production of HX-2 is carried out in the R-2 reactor, equipped with a condenser, a steam jacket for heating and a stirrer for mixing. 3.35551 kg (4.6412 l) of triethylamine catalyst is loaded into the R-2 reactor with a prepared dibenzyl-mine solution in DMFA by gravity from the M-8 measuring tube and, with intensive stirring, 1.5843 kg (1.5139 l) of hexamethylenediisocyanate is slowly loaded from the M-9 measuring tube through an inspection lamp. The reaction proceeds at a temperature of 25 - 35^0S by supplying steam to the reactor jacket. The duration of the reaction is 4 hours. Then the reactor shutdown is stopped, the reaction products are cooled, and then they lag behind. Then they are transferred for filtration and washing. The reaction products are filtered on the NF-10 nut filter, which consists of NF-10 and a collector 12. The filter paper is soaked with water and the filter is coated. Then the reaction products are passed through a filter from the reactor. The filtrate is collected on the filter in the collection of 12 pos. sat. 13. The sediment on the filter is washed with distilled water, which is supplied from the measuring tube M-11 by gravity. Distilled water can be heated to 30 - 35^0S to accelerate filtration. The washed sediment enters the drying. The drying of the precipitate of HUX-2 is carried out in a drying cabinet SH-15 at a temperature of 100 - 110^0S for 2 - 3 hours. The filtrate from the Sb-13 collector is loaded into the R-2 reactor, consisting of a mixture of dimethylformamide and triethylamine, then vacuum is taken into the PK-16 alembic, equipped with a heating coil, and brought to a boil. The vapors are removed to the condenser 17. Distillate fractions are fed through the inspection lamp into separate collections (Sb-19 and Sb-20). The first fraction, the catalyst

triethylamine , is distilled at a temperature of 89.5^{0}S. After distilling triethylamine, the mixture is cooled. A vacuum is created in the alembic. At a residual pressure of 35 mm Hg, dimethylformamide is distilled at a temperature of 76^{0}S. At the end of the operation, the remainder is drained from the cube, after which the separated mixture is reloaded into it. The washing water containing traces of triethylamine is collected in the Sb-14 collection and thrown into the sewer. The same operation can be carried out in the R-2 reactor.

Material balance

Initial data for the calculation of the material balance of the production of N,N^1-hexamethylene bis-[(dibenzylamino) urea] (XIOX-2):

1. Production capacity 100 tons/year.
2. The number of production days in a year is 120.
3. Technological and mechanical losses can be assumed to be equal to 5%.
4. The duration of one operation for the synthesis of N,N^1-hexamethylene bis-[(dibenzylamino) urea] 120 hours.
5. The humidity of the finished bis-urea is not more than - 2%.
6. Average hourly plant capacity - 42 kg/hour.

Table 4.1

Material balance

№	Name of raw materials and product	Loaded, in kg	Received, in kg
1	Hexane-1,6-diisocyanate	176	-
2	Dibenzylamine	204	-
3	Dimethylformamide	40	38
4	Triethylamine	10	9
5	N,N^1- hexamethylene bis-[(dibenzylamino) urea]	-	383
	Total	430	430

Table 4.2

Consumption rates of raw materials and intermediates per 1 ton of finished product

№	Type of costs	Unit measurements, t	Consumption of a ton of N,N¹-hexamethylene bis-[(dibenzylamino) urea
1	Hexane-1,6-diisocyanate	t	0,255
2	Dibenzylamine	t	0,604
3	Dimethylformamide	t	0,1
4	Triethylamine	t	0,041

Mathematical description of the technological process and devices

Synthesis of N,N¹-hexamethylene bis-[(dibenzylamino) urea] is carried out in a batch device.

The duration of the operation - is the time from the start of loading the starting substances of the previous operation to the start of loading the starting substances of the subsequent operation, is the sum of the duration of the individual stages.

The main operations are as follows:

Preparation of raw materials:

Loading of dibenzylamine, Hexane-1,6-diisocyanate, solvent and base.....τ_1.

Mixing ..... τ_2.

Chemical transformation of raw materials, heat removal of reaction τ 3= τ II=Tp

Preparation of the reaction mixture and isolation of the product:

cooling of the reaction mass...t4

unloading of the reaction mass ... τ 5

filtration .... τ 6 } τ_{III}

drying, crushing and screening... τ_7

the duration of the operation... τ op

The duration of operation of the reaction apparatus during the operation is less than the total duration of the operation.

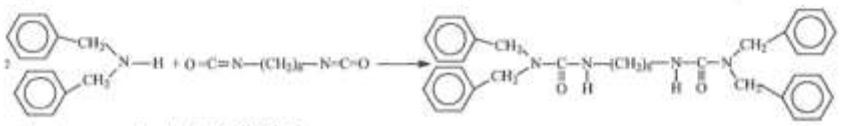
The degree (coefficient) of using the reactor for its intended purpose is expressed by the ratio:

$$\eta = \frac{\tau_1}{\tau_{o\ddot{i}}} = < 1$$

For reactionary spaces:

$$\eta = \frac{\tau_p}{\tau_{o\ddot{i}}} = \frac{\tau_p}{1+\tau_p} \quad \text{ãäå} < + \quad \tau_I = \tau_{III}$$

The formation of N,N^1-hexamethylene bis-[(dibenzylamino) urea] by the interaction of hexane-1,6-diisocyanate with dibenzylamine is generally described by the equation:



or in the symbols A+B (C) D,

where A - hexane-1,6-diisocyanate; B - dibenzylamine; C - DMFA; D - N,N^1-hexamethylene bis-[(dibenzylamino) urea].

$$V=K\,[A][B][C]$$

From this equation it can be seen that the rate of formation of N,N^1-hexamethylene bis-[(dibenzylamino) urea] is directly proportional to the concentrations of dibenzylamine and hexane-1,6-diisocyanate.

Currently, the well-known plant growth stimulator α-NUC (α-naphthylacetic acid) is imported at a price of $3000,0 per 1 kg.

The economic effect in the production of a plant growth stimulator (cotton, wheat, cucumbers and tomatoes) of the drug HYUKH-2 with a capacity of 10 kg per year is: Ee = (Qc-C) x Q= (3000-800) x10=22,000 US dollars, where Qc-selling price; C - cost; Q - installation capacity.

Thus, in the production of the domestic Uzbek growth stimulator XIOX-2 in the amount of 10 kg, the expected economic effect is $22,000.

Calculation of the expected economic effect from the production of N,N[1]-hexamethylene bis-[(dibenzylamino) urea]

Table 4.3

Cost calculation of N,N[1]- hexamethylene bis-[(dibenzylamino) urea]

№ п/п	Name of the article	Unit of measurement	Consumption rate, g/kg	Consumption rate, g/kg	Amount per 1 ton, in US dollars
1.	Raw materials and main materials:				
	Hexane-1,6-diisocyanate	kg	0,255	144	36,7
	dibenzylamine	kg	0,604	13,0	7,85
	solvent	kg	0,1	6,0	0,6
	footing	kg	0,041	2,5	0,10
	Total				45,27
2.	Fuel and energy for technology:				1,5
	A) electricity	t/kvt	0,4	4,0	1,6
	B) reverse water	t/m^3	0,01	6,0	0,6
	C) steam		1,2	1,0	1,2
	D) Kip and A air		0,002	3,0	0,06
	E) nitrogen		0,002	12,0	0,024
	Total				4,98
3.	Basic and additional salary	USD			32
4.	Payroll tax	-//-			12,8
5.	Equipment maintenance and operation costs	-//-			5,6
6.	Shop expenses	-//-			12
7.	Shop cost	-//-			163,7
8.	General factory expenses	-//-			45
9.	Non - production expenses	-//-			12
10.	Full cost price	-//-			283,1
11.	Profit, 20%	-//-			44,15
12.	Wholesale price	-//-			327,25
13.	Unaccounted expenses, 20%	-//-			53
14.	VAT 18%	-//-			57,2
15.	Wholesale price	-//-			375
16.	Retail price	-//-			800

CHAPTER 5. BIOLOGICAL AND TECHNICAL ACTIVITY OF SYNTHESIZED COMPOUNDS AND DERIVATIVES N,N^1-HEXAMETHYLENE BIS-[(AMINOARYL) UREA]

As is known from the literature and patent data, substances with different activity have been identified and introduced among urea derivatives [8, 38,42,46,47,49-52,77,79,83,125].

Herbicides, defoliants, pesticides, growth regulators, pharmacological preparations and many others are present in this series.

5.1. Growth-stimulating activity

Laboratory testing of drugs

The growth-stimulating activity of the synthesized compounds was studied in the Laboratory of Phytotoxicology of the Institute of Plant Chemistry of the Academy of Sciences of the Republic of Uzbekistan.

The primary screening was carried out according to the method of Yu.V. Rakitin, because this method allows you to quickly determine the degree of physiological activity of chemical compounds, which is detected by stimulating or inhibiting the germination of plant seeds, as well as by changing the length of the roots and the length of the stem part. The preparations were tested by the method of soaking seeds in solutions of different concentrations, followed by germination in Pet cups. The control seeds were soaked in distilled water (control).

5 new previously unknown derivatives of N,N^1-hexamethylene bis-[(aminoaroyl) urea] have been studied. The studies were carried out in three-fold repetition in order to experimentally determine the sensitivity of cultures to the action of drugs and to establish their optimal effective concentration. It is known that stimulating concentrations can be taken by those under the action of which maximum stimulation is observed. The maximum stimulation of the roots and stems of tomato seedlings of the Temp-8 variety was obtained by soaking the seeds in 0.00001% solution (75,000 times) of XIOX-2 N,N^1-hexamethylene bis-[(dibenzylamino) urea]. Stimulation of the growth of the roots was 106.5%, and

the stem part was 103.2% compared to the control. And when the seeds were soaked in a 0.1% solution of XIOX-2, the stimulation of root growth was 125.3%, and the stem part was 106.2% compared to the control.

The study of the drugs of the class of XIOX for growth-stimulating activity on cucumber seeds (variety "Uzbekistan") gave very good results. The stalk showed the greatest increase in the preparations of XIOX-2: N,N^1-hexamethylene bis-[(dibenzylamino) urea] and XIOX-1: N,N^1-hexamethylene bis-[(diphenylamino) urea] at a concentration of 0.00001% (i.e., in 75,000 times dilution); compared with the control (Roslin drug), the increase increased, respectively, by 9.0%.

Studies of the studied drugs on the growth-stimulating activity of cotton showed that the drugs contributed to seed germination and the development of the root system of seedlings. Thus, the drug HYUKH-1 [N,N^1-hexamethylene bis-[(diphenylamino) urea] in a concentration of 0.01% accelerated seed germination on day 3 from 11.5 to 14.3% above the control (Table 5.1).

Thus, among the tested preparations, XIOX-1 and XIOX-2 are the most effective growth-stimulating preparations of vegetable crops in the laboratory and are recommended for further, more in-depth study in the field.

Table 5.1

The effect of preparations XIOX-1 and XIOX-2 on seed germination and growth of seedlings of tomatoes, cucumbers and cotton

Code	Name of prepa	Concentrations, %	Seed germination 2/3 5 day, %	Seedling growth on the 10th day,%	
				root	stem
BIOTEST TOMATO					
	Control	**H_2O**	**50,0**	**100,0**	**100,0**
HYUH - 1	N,N^1- hexamethylene bis - [(diphenylamino) urea]	0,1	37,5	88,9	69,2
		0,01	40,0	96,1	98,2
		0,001	50,0	**105,4**	**100,1**
		0,0001	47,5	**109,9**	95,5
		0,00001	50,0	**102,0**	83,5
HYUH - 2	N,N^1- hexamethylene bis - [(diben-	0,1	40,0	**125,3**	**106,2**
		0,01	45,0	**112,0**	**109,7**

	zylamino) urea]	0,001 0,0001 0,00001	50,0 47,5 40,5	**109,6** **105,3** **106,5**	**107,5** **108,7** **103,3**

BIOTEST OF CUCUMBERS

	Control	**H_2O**	**100,0**	**100,0**	**100,0**
HYUH - 1	N,N[1]- hexamethylene bis- [(diphenyl-amino) urea]	0,01 0,001 0,0001 0,00001	100,0 100,0 100,0 100,0	96,1 **110,6** **106,4** **100,3**	90,3 **105,4** **101,4** **104,3**
HYUH - 2	N,N[1]- hexamethylene bis- [(dibenzyl amino) urea]	0,01 0,001 0,0001 **0,00001**	100,0 100,0 100,0 100,0	86,3 **105,9** **108,7** **109,9**	96,7 98,9 **100,0** **102,3**

COTTON BIOTEST

HYUH - 1	N,N[1]- hexamethylene bis [(diphenyl-amino) ureas]	**0,01** **0,001** **0,0001** **0,00001**	86,7 93,3 **80,0** **80,0**	**111,5** **114,3** **108,2** **110,5**	**107,0** **103,6** **104,6** **105,2**
HYUH - 2	N,N[1]- hexamethylene bis [(dibenzyl-amino) ureas]	0,01 0,001 0,0001 0,00001	87,3 44,6 **95,6** -	**109,7** **114,3** **116,2** **120,2**	**102,1** **106,3** **104,1** **107,2**

5.2. Field trials of drugs

Field trials of preparations on wheat

Wheat of the autumn variety "Kroshka" treated with the preparation HYUH -2 was sown on October 15, 2008 in the farm "Uchtosh" of the Asaka district of the Andijan region. Seven days after sowing wheat, seed growth was 50%, and after 15-18 days, wheat grew by 100%. The difference between wheat treated with 0.1% HYUH -2 preparation and wheat not treated with preparations (i.e. control) is immediately noticeable. The well-known "Roslin" was used as a reference in the control. The growth of wheat treated with our preparation was 86.7 cm, and in control the height was 83.2 cm. The number of wheat stalks per square meter was 648.6 pcs., And in control - 601.1 pcs. As a result, the yield as of June 12, 2009 was 67.5 c /

ha, and on the control field, the yield was 57.1 c / ha. Thus, wheat cultivar "Kroshka" treated with a 0.1% solution of XIOX-2 under field conditions showed a positive effect; from each hectare gave 10.4 c / ha more than the control.

The preliminary economic effect of the introduction of the XYuh-2 preparation in the field on wheat is 57,200 sums per hectare..

Field trials of the drug on cotton

In the field conditions of a number of districts of the Andijan region (including Asake), the effect of the drug on cotton was studied with pre-planting soaking of seeds in optimal concentrations (0.1; 0.01; 0.001%). The well-known Roslin was used as a reference. Plants grown from seeds treated with drugs were distinguished by more intensive growth, a more developed root system, due to which the number of boxes on the cotton stalk increased. Pre-planting seed treatment with XYUX-2 at a concentration of 0.01% provided an increase in yield in relation to the control by 2.2-2.4 centners / ha (%). The expected economic efficiency in agriculture in Asaka district alone from each hectare is 440,000 soums (for cotton).

5.3. Coloring activity of the preparation XIOX-5

N,N^1-hexamethylene bis - [(5-bromisatinyl) urea] for dyeing polyethylene (RU -342)

This dye belongs to the aniline paint industry, in particular to the synthesis of a new dye N,N^1-hexamethylene bis - [(5-bromisatinyl) urea]. It is suitable for dyeing synthetic polymers (polyethylene, polypropylene, polystyrene, polyamides, polyurethanes, as well as polyacrylates and polymethacrylates).

The dye was tested for dyeing polymer boxes in the Andijan region at the Andijanpolimer enterprise, Khodjaabad). The dyeing was carried out in the factory, while the dyeing technology was followed. Painted boxes correspond to physical-chemical, physical-mechanical and rheological properties. The appearance of polymeric boxes complies with GOST.

Since the well-known dyes are imported and expensive, the new local synthesized dye is much cheaper. Painted polymer boxes are transparent, the paint is

resistant to long-term storage to the external environment, as well as to the effects of flue and atmospheric gases.

As a result of the carried out factory tests, it was revealed that the proposed dye is low-toxic (for mice and other rodents LD_{50} = 4080-4100 mg / kg), which is very important for polymer products.

CONCLUSION

1. A procedure has been developed for the synthesis of previously unknown bis - [(aminoaroyl) uvines] in high (85-94%) yields. The influence of a number of factors (duration of the process, temperature, nature of the solvent) on the yield of reaction products has been studied and the optimal conditions for this process have been determined.

A probable mechanism for the formation of N,N^{I}-hexamethylene bis - [(aminoaroyl) ureas] has been proposed.

2. Developed and studied the chemical properties of the N-H reaction centers of new derivatives of N,N^{I}-hexamethylene bis - [(aminoaroyl) ureas], N,N^{I}-disubstituted derivatives and established the probable directions of these reactions.

3. A technology for the synthesis of a growth stimulator for plants N,N^{I}-hexamethylene bis - [(dibenzylamino) urea] has been developed. The basic technological scheme of the process is proposed.

4. The structure of the synthesized compounds has been proven by modern physicochemical methods of IR and PMR spectroscopy and confirmed by elemental analysis. Based on quantum chemical calculations Hyper chem. 7.01 (AM1), ball-and-stick, molecular conformations and configurations were established, which additionally confirms the structure of the obtained substances.

5. Among the synthesized compounds, substances have been identified that have a growth-stimulating activity for industrial crops and low-toxic dyes of polymer materials, some of which are recommended for use in agriculture and polymer industry.

6. Compounds XIOX-1, XIOX-2 were tested at concentrations of 0.01% and 0.1% in field conditions of the Andijan region in order to determine their influence on the growth, development and productivity of cotton and wheat. The expected economic efficiency in agriculture in Asaka district alone from each hectare is 440,000 soums (for cotton) and 57,200 soums (for wheat).

BIBLIOGRAPHY

1. Melnikov N.H., Baskakov Yu.A., Bokarev K.S. Chemistry of herbicides and plant growth stimulators. Moscow: Goskhimizdat, 1954. -261 p.

2. Melnikov N.H., Novozhilov K.B., Pylova T.N. Chemical plant protection products (handbook). M.: Chemistry, 1980. 288 p.

3. Melnikov N.H. Pesticides. M., 1976. - pp.306-363

4. Barkan Ya.G. Organic chemistry.- M.: Higher School, 1973. - pp. 447-450.

5. Melnikov N.H. Pesticides: chemistry, technology, application. M., 1987. - pp. 255-288

6. Baibetova G.Sh., Lyapunov V.V., Solomin V. A. Analysis of urea and carbamate pesticides by liquid chromatography-mass spectrometry. // Chemical Journal of Kazakhstan. Almaty, 2006. No. 2. - pp. 48-61.

7. Patsak Y. Organic chemistry. M., 1986. 324 p.

8. Poltsev A.V. Thiourea as a seed germination stimulator. //Doc. USSR Academy of Sciences, 1952. Vol. 84. pp. 614-622.

9. Negeli I.B. Herbicides based on phenylureas // VestnikAN Kaz SSR.-Almaty, 1981. No. 5. pp. 44-50.

10. Michael I.A. Synthesis of new aliphatic derivatives of urea // Rev. roum. chim., 1977, 22. №6. Pp. 885-888.

11. Nesterov O.V., Entelis S.G. Kinetics and catalysis, 1965, № 6. _178 S.

12. Baker W. Holdsworth I. B. Kinetic examination of the reaction of Arylisocyanates with methyl alcohol // J. Chem. soc.- 1947.__P. 713-726.

13. Entelis C. G., Nesterov O. V. Kinetics and mechanism of reactions of isocyanates with compounds containing active hydrogen // Uspehi himii, 1966. So XXXV, Vol. II, -pp. 2178- 2203.

14. Petersen. Organometallic Reactions. part II. The addishion of alcohols to isocya-nates //Ann.-1949. v. 562, P.205.

15. Sounders J.H., Frish K.C. Polyurethanes: Chemistry and technology. part 1. Chemistry. N-Y, 1962, P. 208.

16. Strepikheev A.A., Artemyev A.A., Schmidt Ya.A. Research in the field of Naval Forces, M., Publishing House of the USSR Academy of Sciences. 1949.

17. A. Michael. The reaction ot sadium pheynlacetylide isocyanic esters. // Ann, 1908, V. 363. P. 89.

18. Van Goldersen, Jurgens Sabine. N-acyl- and N-aryl-N-alkylidenureas as precursors of isocyanates // Frch. pharm, 1987, 320, No. 9. C. 846-850.

19. Gravchikova V.A., Rudakov G.F., Zhilin V.F. Synthesis and reactivity of azidomethyl urea // Successes of chemistry and chemical technology. M., 2001. Vol. 15. -Issue 4.-pp. 80-82.

20. Sheehan J.C. Chem. Abstr., 1999, 130, 57245.

21. Lutsenko V.V., Blum R.A., Knunyants I.L. // Journal organich. Chemistry, 1971. --№ 7. _ P. 1152.

22. Maksumova N.A., Sulaimonov B.I., Juraev A.J., Boboev I.D., Makhsumov A.G. Synthesis and research of properties of derivatives of N,N1-di (heterocyclo) poly-alkylene bis-urea // Bulletin of the Osh State. university. Osh, 2003. Series 5, issue 2. - pp. 103-106.

23. Makhsumov A.G., Sulaimonov B.I., Chorieva N.B., Maksumova N.A., Bobo-Vi.D. Yalliglanishga karshi faol thiourea va urea hosilalarini sin-tezi // Kimyo va farmatsiya, T., 2003.- No.2 pp. 18-21.

24. Maksumova N.A., Boboev I.D., Juraev A.J., Makhsumov A.G. Synthesis of pro-isodic hexamethylene bis (N,N1-substituted) urea and their properties // "Kimyo va kimyo texnologiyasi", _ T.- 2003.- No.2 pp. 18-21.

25. Maksumova N.A., Boboev I.D., Shukurullaev K., Juraev A.J., Makhsumov A.G. Bis-urea derivatives and their anti-inflammatory activity // Pharmaceutical Journal. Tashkent, 2005. - No.1. pp. 20-23.

26. Maksumova N.A., Boboev I.D., Maksumov A.G., Juraev A.J., Boltaboev U.A., Waste-free synthesis of productsthe requirement of time. International Conference "Applied Ecology and Sustainable Development", Karshi, 2005. pp. 127-128.

27. Makhsumov A.G., Maksumova N.A., Boboev I.D., Juraev A.J., Selective N,N1-dinitrosation of hexamethylene bis-[(heteroylo)-urea] // Analitik kime fanning dolzarb muammolari: Ilmiy makolalar tuplami. Termiz, 2005. - pp. 241-243..

28. Maksumova N.A., Ibragimov A.A., Haidarova Z.G., Juraev A.J., Ubaydullaeva M.U. Development of technology for the synthesis of environmentally friendly, non-polluting organic compounds // Modern technologies for processing local raw materials and products: Rep. NTK, T., 2005. Vol.1. pp. 41-42.

29. Makhsumov A.G., Boltaboev U.A., Maksumova N.A. Synthesis of bis-urea derivatives and the mechanism of their formation// Chemical Journal of Kazakhstan _ Almaty, 2006. No. 3 . pp. 65-71.

30. Maksumova N. A., A. G. Makhsumov, J. A. Juraev. N,N1-dinitropyridine derivatives of bis-ureido // Chemical journal of Kazakhstan, spec. vol.16.
Almaty, 2007. Pp. 144-149.

31. A. G. Makhsumov, Maksumova N. And. Production technology hexamethylene bis-[(piperidyl) urea], and its chemical properties // Chemical journal of Kazakhstan. Special issue. 16. Almaty, 2007.- pp. 224-230.

32. Maksumova N.A., Makhsumov A.G., Juraev A.J. Technology of obtaining polyalkylene bis-[(morpholilo) ureida] // Chemical technology, theses of the MK on chemical technology reports HT-07. M., 2007, -Vol. 5 - pp.201-202.

33. Maksumova N.A., Makhsumov A.G., Turobzhonov S.M. et al. Diphenylamine derivatives as a growth stimulator for vegetable crops and cotton // The sovereign. Patent Office of the Republic of Uzbekistan. License # TAR 2007, 0027 19.01.2007 G.

34. A. G. makhsumov, ubaydullaeva M. C., H. A. Maksumova On the reaction of 3-and 4 - aminopyridines with HMDI // Materials NPK "Integration of science, education and production in pharmacy",T., 2007. P. 152-153.

35. Davlatyan V. V., Gevorkyan, R. A. a Method of producing GC of acylhydrazines // AV. Holy, CL. 07 with 109/02, No. 595298, Appl. 24.10.72., publ. 20.03.78.

36. Abdugafurov I.A., Madikhanov N., Makhsumov A.G., et al. Antiinflammatory activity of new 1,2,3-triazole derivatives.// Materials of the I-th MK: Chemistry and biological activity of nitrogenous heterocycles and alkaloids. M., 2001.T.2. pp. 8-9.

37. Vauthey Isabelle, Valot Frederic, GOZZi Christel. An environment-friendly approach to carbamates and urea. // Tetrahedron Lett., 2001, 41, No. 33, pp. 6347-6350.

38. Maune tou Emmanuelle, Lagault Jean, et al. Anti-tick, anti-tumor agents: Synthesis, correlation structure activity and biological identification of N-aryl-N1-(2-chloroethyl) urea as new selective alkylating agents // J. Med. Chem. 2001, 44, No. 5, pp. 694-702

39. Shamshin V.P., Alyoshina V.A., Sukhanova S.A., Kabanova T.I. Synthesis and neurotropic activity (heteryl-phenyl-methyl)-amines and urea // Himiko-pharmacist. zh-l, 2001. Issue. 35, - №7. ___ S.3-6.

40. H.Elgemeie Gatal, El-Ezbawy, R.Samia, Ati Hany A. Reactions ot chlorocarbonyl isocyanate fe with 5-aminopyrazales and active methylene nitriles // Sinth. Commun 2001,31. No. 22. S. 3459-3467.

41. Veselov V. R., Savelyev, Yu., A. P. Greeks To the question of the manifestation of the effect in the reactions of 1,1-disubstituted hydrazine with phenylisocyanate in benzene // Ukrain. chem. W-l, 2000. Vol. 66, No. 7-8.- P. 118-121.

42. Warner-Lambert, Tayber Harles, Price, Weber Mark Lawrence. Methods of treatment of diseases neurogenerative c using N-(2,6-disubstituted aromatic radical) -N-(of peridiniaceae and other anticoagulants // Pat. 6133249 USA MPK7 A 61 K 31/44 wilted. 25.02. 1993; publ. 17.10.2000.

43. Ling Hao-Jan Chen, Kan-Nan, Lai Jian-Zei, Lai Jian-Zei, Lin Yun-shar. Methods of obtaining uredin derivatives and vulcanizing resin compositions based on them // application 1106613 EPO, IPC7 From 07 D 403/14, From 09 J 175/04. application 07.12.1999; publ. V.06.2000.

44. Li Jing, Wang Yu-Lu, Sun-Ting. Solid-phase synthesis of aryl-2-nitrophenyl urea // J.Chem. Res Synop., 2003, No. 4, pp.220-221..

45. Mallakpour Shadpour, Hajipur Abdol Reza, Taikhizaden Hedayat A. Synthesis of 4-substituted 1-ethoxycarbonyl-semicarbazides from ethyl carbamate and isocyanates by microwave irradiation// Monatskh. Chemistry., 2003.134.No. 7, pp.1015-1017.

46. Yoshida Taka, Takemato Kazuki, etc. Phenylurea derivatives, methods of their preparation and herbicides and fungicides based on them // Yapon. application, cl. C 07c 127/19, A 01 No. 47/30, No. 55-62058, application 30.10.78; publ.10.05.90.

47. Tan Wei-Fan, Lu Tao, Ni Pei-jeong, Zhang Yu-Mer Synthesis and diuretic and antihypertensive activities of new anilinopyridal-sulfonylurea derivatives// J.Chim. pharm. Univ. 2003, 34, No. 3, pp. 208-213.

48. Ignatov V.A., Koltsov N.I. Synthesis of hydroxyethyl-substituted urea based on aliphatic diisocyanates // All-Russian Symposium on Organic Chemistry: "Organic chemistry__decline or rebirth?", Theses of pre-treasures. _ Moscow, 2003. p. 66.

49. Korzha I.D., Barba N., Shur A.M., Manole S.F. Synthesis of some derivatives of p-vinylphenylisocyanate // Izv. AN Moldov. SSR, Ser. biol. and Chemical Sciences, 1975.- No.3.- pp.74-77

50. V.Demlow Ekehad is it possible to obtain azetinone by adding alkyne to isocyanate? // Z. Nafur forsh., 1975, p.30, No. 9, pp. 822-823.

51. Ozaki Shoichiro, Mori Haruki. Derivatives of 1-carbamoyl -5-fluorouracil // Pat. USA, cl. 260 -254.4 P.07 D 239/10, No. 4032524, application 24.09.76, No. 725196. publ. 28.06.90 (Yap.)

52. Albrecht Conrad, Frenchman Heinz, Schumacher Hans. Herbicide preparation // application. FRG. Kl. A 01 N 47/30 application. 12.04.79; 16.10.1980.

53. Mitsuno seruyuki, Takahashi Yosei, Kaneko Junji. Preparations with a slow release of herbicide // Yapon. application, cl A 01 N 25/10; A 01 N 25/12; application 13.11.78, publ. 20.05.80.

54. Barak Ileana, Narnauchanu Yustanta, Nikilescu Duvas. Potential anti-cancer agents. XIII synthesis of new aliphatic and cycloaliphatic N-nitrosoureas// Reverend Rum. chim., 1977,. 22, № 6. Pp. 885-898 .

55. R.D.Dillard, D.R.Cassidy, N.R.Easton. // J. Med. Chem.. 10. pp. 1180-1184 (1967).

56. N.R.Easton, D.R.Cassidy, D.Dillard// J. Org. Chemistry., 1964,29, _ p.1851-1856.

57. N.Shachat, J.J.Bagnell. // J.Org . Chemistry., 1963, 28. C. 991-994.

58. P.J.Stoffel, A.J.Specialty// J.Org . Chemistry. 1962, 27, p.3079.

59. Yu.Yura// Chem. pharm. Bull. Japan, 1962, 10, pp.1087-1093.

60. N.Shachat, J.J.Bagnell. // J. Org. Chemistry.., 1963, 28. pp.991.

61. R.D.Dillard, D.R.Cassidy, N.R.Istom// J. Med. Chemistry, 1967.10. pp.1180-1184

62. S.L.Shapiro, V.Bandurko, L.Fredmann// J.Org.chemistry. 1961,26. pp. 3710-3714.

63. Chemicals Mitsui., Aso Shinji., Noguchi Takeshi., Ogawa Shinji. Urethane compound and a method for obtaining polycyclic aliphatic diisocinate // pat.6204409 USA, IPC7 From 07 to 271/20. application 30.03.1999; pub. 20.03.2001.

64. I.A. Rapoport. // Collection. "Supermutagens" M,. 1966. p.9.

65. U.A.Skinner, H.F.Karam, M.O.Grene// J.Med. Farm.chemistry, 1960, 2. pp.292.

66. K.A.Hyde, E.Acton, W.A.Skinner, L.Gudnann. idr.// J. med. Farm. Chemistry.., 1962, 5.Pp.1-5.

67. H.Leffer, Broz V.,//Nafurvi., 1949. pp. 57-61.

68. T.Lizer, Beck S.S.// chemical.ber., 1950,83.__.137-m

69. S.M.Samur, J.F.// J. Amer. Chemical. soc., 1954.76 p. 441-446.

70. V Lutsenko.V., R Blum.A., Knunyants I.L. N-nitrosoureides.

II. N-nitrosation of some x-ureidoacids.// Organ. chemistry, 1971, -Vol.VII, -Issue 6 pp. 1152-1159.

71. In Lutsenko.V., R Blum.A., Knunyants I. L. N-nitrosoureides.

I. N,N1-disubstituted hexamethylene bis-(nitrosoureas).// Organ. chemistry, - M. 1971, -Vol. VII, -Issue 6, pp. 1149-1152.

72. T.P.Yohuston, G.S.Mekaleb, J.A.Montgomery.// J.Med. Chemistry.., 1963, 6. R. S. 669-674.

73. W.A.Skinner, H.F.Graham, M.O.Green, B.R.Baker, // J.med. Farm. Chemistry.., 1960, 2. pp. 292-296.

74. K.A.Hyde, E.Akgon, W.A.Scanner, L.Goodman, // J. ved. Farm. Chemistry.., 1962, 5.pp.1-6.

75. W.A.Skinner, H.F.Graham, M.O.Green, B.R.Baker// J.med. Farm. Chemistry.., 1960, 2; pp.292-296.

76. K.A.Hyde, E.Akfon, Skinner et al.// J med. Farm. Chemistry.1962, 5.pp.1-6..

77. S.Hamilfon Gregory, P.Steiner Josepf. Compositions for hair growth containing small carbamate or urea molecules and their application // pat-764032 Australia, MPK6 A 61 K1 007/43 G A 61 K 031/27; application 03.06.1998; publ 07.08.2003.

78. Okipo tomafaka, Hoashi Yasufaka, Takemofo. Synthesis, molecular structure and chemical reactivity of urea derivatives// J. Amer. Chem.. soc. 2003,125, No.42 pp.12672-12673.

79. Yi chang-hai, Zhou Xiang-chan, Yu Xun-min. The study of quantitative relationships between the structure and biological activities of nitrogen-containing heterocyclic compounds // J. Jianghan Pttral Ingt., 2003, 25, No. 1, pp. 126-128.

80. Tran Kevin, Berlin K. A new simple method for obtaining N,N1-diphenylurea// Ogd. Prep. And prosed. Int., 2004, 36, №1. C.71-73.

81. J.W.Baker, J.B. Holdsworth// J. chem. Soc, 1964. p.4000-4005

82. Wei Tai-Bao, Zhang You-Ming, Wu Jia-Wai.Effective synthesis of polymethylene bis-aroylurea derivatives under conditions of interphase catalysis// chem. Res. Chim. Vniv., 2001, 17,No.3. C. 194-195.

83. Narumoto Ryuji, Furuyva Sumiyasub, Kaban Kiyohisa. Anti-inflammatory and analgesic agents// application 60-149523, application 28.11.84; publ. 7.08.85. MKI A-61 To 31/505; From 07 D 498/04;

84. Song xin-jian, tan xiaj-Hong, Yu Ai-Nong, Wang Yan-Gang Chin. J.org. chem.., 2006, N6.__C. 803-807.

85. B.Unterhalt, T.Adat, Bagyerzaden. Nitroamines related to suosan as potential sweeteners// Sei. Pharm, 2001,69, N2. C.119-122

86. Moroz N.E., Volodina O.I. Interaction of acylated urea with quinones// 4-MNK "Innovations in science and education 2006": Proceedings of the scientific conference. Part 1, 2006. C.284-285

87. Filonik I.A., Aprasyukhin A.I. Stimulator of growth and development of grain crops and a method of stimulating the growth and development of corn and wheat.// Application 13. 09. 2005 publ. 20. 03. 2009.

88. Guillaume Miehel A quick way to improve the synthesis of manufactured urea// org. Process Res. And Dev., 2006, 10, N6. C.1227-1230.

89. Naifo Toshihiko, Yfshizawa kazuhiro. Urea derivatives and the method of their preparation//Application 1683785 EPO, IPC 7 FROM 07 TO 275/34; No. 04818213.3;APPLICATION 08.11.2004; APUBA. 26.07.2006;

90. P.Abbott Thomas, wohlman Alan. Derivatives of 3-methoxybenzylurea and improved lipid compositions containing them //Pat. 7169815 USA, IPC7 A 61 To 31/09/5; No. 10/426122; application 29.04.2003; publ. 30.01.2007.

91. Shtamburg Vasiliy G., Shishkin Oleg V., et al. N-chloro-N-alkoxymo-wines: Synthesis, structure and properties // Mendeleev Commun., 2006, N6. C. 323-325.

92. A.G.Yirini, Kolle Jokep, Shutakavski Mike et al. Phenol derivatives and their use as rotamase inhibitors // Pat. 200511125/04 Russia, IPK7 From 07 to 275/34; application 18.09.2003; publ. 27.10.2006.

93. Y.Du Doniel, Procter Martin James, Fyte Matthew, etc. Derivatives of urine and thiourea // Pat. 7074933 USA, IPC8 From 07 D 215/38; A 61 To 31/47; application 10.02.2004; publ. 10.07.2006.

94. Stefan Berg, Sven Hellberg. 4-(4-metoksifenil) -N1- (5-nitro-1,3-have thiazolyl-2) urea and its use for the treatment of conditions associated with glycogen-synthase-kinase-3 // Pat. 7056939 USA, МПК8 A 61 K 31/427, 07 D 277/58; Appl. 03.07.2002; publ. 06.07.2006.

95. Masuda Akira, Yoshitaka Satoh, etc. Derivatives of 1,2,4-triazolo [1,5-a] pyrilidine-2-yl urea and their use // Application 1630165 EPO, IPC7 From 07 D 487/04 A 61 To 31/5377. application 02.06.2004; publ. 01.03.2006.

96. Hallur Gurulingappa, Jimeno Antonio, Dalrumple SuSan, Zhu Tao, etc. Sulfurous analogues of benzoyl phenylurea with potential antitumor activity // J.Med. Chem. 2006. 49. N7 pp. 2357- 2360.

97. Li Gaoquuan, Li Qun, Li Tongmei, Lin Nan-Horng, etc. Urea kinase inhibitor // Pat. USA. 7056925; MPK8 A 61 K 31/4965 ; From 07 D 241/00; application 13.08.2003; publ. 06.06 2006;

98. A.Smoliga John, Vitous Jana. Polymorphic forms. // Pat. 7091340 USA, IPC8 From 07 D 413/02. application. 13.12.2004; publ. 15.08.2006;

99. Goryunov E.I., Nifantiev E.U., Myasoedov B.F. Method of obtaining.

Nurmuhammad, [11/18/2021 12:40 AM]

100. Giefen, R.Schreiner Pefer, Wanka Lukas. Compounds of aminoadamantane // Application 102004035978 Germany, IPC8 From 07 To 7/04; A 61 To 31/95; application 23.07.2004; publ. 16.03.2006.

101. Wang Li-Zeng, Jiang Lin, etc. Synthesis and biological activity of N-(4,6-disubstituted purimidine-2-yl)-N1- (1-methyl-3-ethyl-4-chlorpyrazole-5-yl) carbonylurea //Chin. J. Appl. Chem. 2007, 24 No.11. pp.1284-1288.

102. Xue Si-Jia, Guo Yan-Ling, Li Jing-Zhi. Syntheses of derivatives of cinnamoilurea under ultrasonic irradiation // Chin., J.Appl. Chem., 2006, 23 N12. pp. 1381-1384.

103. B.Kryezka, S.Lesniak, B.Pasternak, Porwanski S. Reaction of (2-ethyl-aziridine-2-yl) diphenylmethanol and diphenyl-(2-phenyl-aziridine-2-yl) methanol with phenyl-and tert.-butylisocyanates and phenylisothiocyanate // Pol. J. Chem., 2007, 81, N11. pp. 1927-1934.

104. Clayden Jonathan, Lemiegre Loc. Synthesis and conformation of the "stack" type of symmetric and asymmetric oligoureas of metaphenylinediamine // J. Org. Chem., 2007, 72, No. 7. pp. 2302-2308.

105. Tan Xiao-hong, Sang Qiuzhang, Wang Ning. Synthesis and fungicidal activity of 1-(4-chlorobenzoyl)-3-5- (4-pyridyl) 1,2,4-thiadiazole-2-yl) urea // J.Hubei Inst. Nat. Natyr. Sci., 2006, 24 N1, C. 71-74.

106. G.Batt Douglas, H.Carter Percy, A.Wackor Dean. Substituted bicyclic condensed amines as modulators of chemokine receptor activity // Pat.7230022 USA, IPC A 51 K 31/4035; application 17.02.2005; publ. 12.06.2007.

107. Safar Pavel, Walser Armin, Shimshock Stephen James. Substituted Sulpalamidi and urea, inhibiting kinase activity // Pat. 7223763 USA, IPC A 61 K 31/496; C 07 D 241/04; Appl. 30.04.2004; publ. 29.05.2007.

108. Ni Bukuo, Qianying Zhang, Allan D. Headley J. Design and synthesis of chiral pyridine-ionic liquids containing functional group urine-guilt // J. Org. Chem. 2006.71.No. 26. pp. 9857-9860.

109. Li Ying-Jun, Zhang Zhi-Guang, etc. Synthesis, characterization and biological activities of acylurea derivatives // Acta Chemical Sin., 2007, 65, No. 9, pp. 834-840.

110. Lei Yong-peng, Yang Shi-qing, etc. Progress in sensitive high-energy materials of N-guanylurea dinitride (GUDN) // Chin J. Energ. Mater., 2007.15. No.3. C. 289-293 (Kit.)

111. K.Gupta Arvind, Pardasani Deepak, K.Guhta Hemendra, K.Dubey Devendra.N,N1-dichloro-bis[(2,4,6-trichlorophenyl)-urea]: an effective reagent for the synthesis of dialkyl-N,N1-dialkylphosphoramidites approved by the Chemical

Weapons Convention from dialkylphosphites // Austral. J. Chem., 2007, 60, No. 11. C. 879-882

112. A.K.Gupta, J.Acharya, D.Pardasani, D.K.Dubey, N,N1-Dichlorobis-(2,4,6-trichlorophenyl)-urea (CC-2): an effective reagent for the synthesis of chloro-nitroso compounds // Tetrahedron Lett., 2007, 48, No.5. C.767-770.

113. Bolshan Yurt, tomaszewski Miroslaw J., et al. Thiol-by silica gel as ULAW-liwayway and the released substrate for isocyanates receiving urea // Tetrahedron Lett., 2007, 48, No. 28, P. 4925-4927.

114. Klimenko I. P., Shulishov E. V. Tomilov, Yu. a Possible way of decomposition of N-nitroso - N-cyclopropylacetic in vivo // Chemistry and medicine,

-Ufa, 2005.-pp. 32-33.

115. Braun Alain Jean, Gussregen Stefan, etc. Piperidine or pyrroline-tions urea derivatives, their preparation and therapeutic use // application 2902790 France, МПК8 07 IN 401/14; A 61 K 31/47 Appl. 27.06.2006; publ. 28.12.2007.

116. Spiridonov, Y. J., Raskin, M. S. Herbicides fourth generation: results of the study and the implementation in production // Arpo XXI. 2006, № 7-9. S. 31-35.

117. Boehringer Ingelhein, Cirillo Pier Francesco, etc. Compounds of fluorinated diarylurea // Pat. 7279475 USA, IPC A 61 K 31/5377; From 07 D 403/06; application 14.09.2004: publ. 09.09. 2007.

118. Hanma Teruki, Hayashi Kyoko, Acyama Tetsuya, etc. Generation of a new class of strong Cdk-4 inhibitors based on structural study: New de novo design strategies and library design // J.Med. Chem., 2001, 44, No. 26. C. 4615-4617.

119. Nakajima Tsunetaka, Okamoto Tadao, Watanabe Nasahiro et al. Antiviral drugs // pat. 5036072 USA, MKI5 A 61 K 31/505; application 23.01.90; publ. 30.07.91..

120. Findeison Kurt, Linding Markus, Santel Hans. Замещенные триазолены.// заявка 3916208 ФРГ, МКИ[5] С 07 Д 409/12; А 01 № 43/453; заявл. 18.05.89; опубл. 22.11.1990.

120. Findeison Kurt, Linding Markus, Santel Hans. Substituted triazolenes.// forturnout 3916208 FRG, MKI5 From 07 D 409/12; A 01 No. 43/453; application 18.05.89; publ. 22.11.1990.

121. Uhr Hermann, Adler Alfons, Widding Arno. Tizanidine 1,3,5-triazine-2,4,6-trione // application 3933933 Germany, МКИ5 07 D 251/30; C 07 c 275/24.

122. Karimov, F. S., A. B. Karlan, Gilmanova V. T., Kirdan S. A. Production-ing urea as the objects of research, "the structure of biological activity," Part I. Structural analysis and integrated forecast potential herbicidal active substances // Bashkirs. chem. W-l, 2002.Vol. 9. - No. 1. pp. 33-38.

123. Sultonkulov A., Saprykina V.A., Abdurakhmonova K.R., Shokhidoyatov H.M.. On the reaction of substituted aminobenzoxazoles with methyl and phenylisocyanates // Pharmaceutica Journal, 2004. - No. 4. pp. 36-38.

124. Ozaki Shoichiro, Mori Haruki. Derivatives of 1-carbomoyl-5-fluorouracil // Pat. 2479097 USA, Cl. 260-256,4; From 07 D 239/10 No. 4032524; application 29.09.76; publ. 28.06.77.

125. Marumoto Ryuji, Furukawa Sumiyasub Kavan. Anti-inflammatory and analgesic agents // Application 60149523, application 28.11.84; publ. 07.08.1985.

126. Wang Shirong, Li Xiang-gao, He Li-li. Synthesis of N-(methyl substituted phenyl) N1-(2-oxy-3-naphthoyl)- Urea // Fine chem. 2007, 24, N10. pp. 948-951; 987; (Kit.)

127. Maksumova N.A. Synthesis and technology of hexamethylene bis-[(heteroylo) urea] and their properties // Dissertation for the degree of Candidate of Chemical Sciences Tashkent, 2008, 109 p

. 128. Vaueg Sgorseipse, Schnabel Gerhard. Effective herbicide // Application 10351234 Germany, application 03.11.03; publ. 16.06.2005.

129. T.P.Johnston, G.S.McCaleb, P.S.Opliger, etc. // J.Med. Chem., 1971, 14. _ C.600.

130. S.S.Mirkish // J. Nat. Canar. Inst., 1971, 46. C. 1183.

131. G.Greber, H.R.Kricheldorf // Angew. Chem.. Int. Edi., 1968, 7. _ C. 941.

132. Du Hai-Jun, Ou-Yang Csui-ping, Du Hai-tang , Shi-Da-bin, Wan Xido-qiang. Synthesis and characterization of phenoxyacetamide derivatives containing the urea bond.

133. Polani Anandan, Shapiro Sherry, D.Mevgiag Mark, W.Clader John, J.Csrulee William, Spar Brian. Biaryl urea as patently and orally effective receptor 1 antagonists concentrating the hormone melanin for the effect on obesity // J. Med.Chem., 2005, 48, No. 15. pp.4746-4749.

134. Kai Xiang, Lewis Timothy. N-(3-butynyl) -N-hydroxyurea // Application 2004122075/04. Russia MPK7 from 07 to 275/64; application 21.07.2004; publ.27.01.2006

135. Camerman Arthur, Hempel Andrew, Mastropalo Donald, Camerman Norman. N-phenyl-N1-pyridimoureas: stereochemical basis of anticonvulsant activity // Acta crystallogr. C. 2006, 62, No. 4. C. 190-192 (eng).

136. Ivanov Iliyan, Nikolova Stoyanka, Kochovskaya Ekaterina. The construction of the structure of quinazolinone from 1-(3,4-dimethoxyphenyl)-3-phenylurea and carboxylic acids inhibited by polyphosphoric acid // Heterocycles. 2006, 68, No. 7. C.1443-1444.

137. E.Mounetou, Legauet Jean, et al. Anti-tick, antitumor agents: Synthesis, ratios, structure, activity and biological identification of N-aryl-N1-(2-chloroethyl) urea as new selective alkylating agents // J. Med. Chem. 2001, 44, No. 5. pp. 694-702 (eng).

138. H.Elgemeie Csalal, R.El-EzBany Samia, A.Ani Hany. Reactions of chlorocarbonylisocyanate with aminopyrazoles and active methylene nitriles // Synth. Commun., 2001, 31, N22, pp. 3459-2967 (eng).

139. Zolfigal Mohammad Ali et al. N-nitrosation of secondary (NH) amines in mild heterogeneous conditions // Synth. Commun. 2001, 31. No.8. pp.1161-1168 (eng).

140. Li Jian-Ping, Wang Yu-Lu, etc. A new and effective solid-phase synthesis of diarylureas // Synth. Commun., 2001, 31, N5, pp. 781-785 (eng).

141. Wang Jin-Ling, Li Ai- Xiu, Li Yong-Hong, Zhai Xin-Hong, Miao Fang-Ming. Syntheses, biological activity and quantum chemical calculations of aromatic urea derivatives // Acta Chim. Sin. 2001, 59, N9, pp.1490-1494 (kit).

142. Cs.Shtamburg Vaciliy, V.Shishkin Oleg, V.Zubatyuk Roman, V.Shtamburg Victor. Synthesis, structure and properties of N-alkoxy-(1-pyridinium) urea salts,. N-alkoxy-N-acyloxyurea and N,N-dialkoxyurea // Mendeleev. Sommip. 2007, 17, N3, pp.178-180.

143. V.Shishkin Oleg, J.Zubatyuk Roman, Cs.Shtamburg Vasiliy, V.Tsygankov Alexander, A.Klofs Evgeny. Pyramidal amide nitrogen in acyloxy-N-alkoxyureas and N-acyl-oxy-N-alkoxycarbamates // Mendeleev Sommip.2006, N4. pp. 222-223.

144. Wang Mei-Yi, Mu Xiao-li, Csuo Wan-Cheng, Li Yong-hong, Li Jheng-ming. Synthesis and herbicidal activity of new 5-substituted phenylsulfonyl urea // Chem. Res. Chin. Univ. 2007. 23, N6, pp. 674-678 (eng).

145. Sada Yoshinao, Kizawa Satoru. Herbicidal agent// Application 102007019785 Germany, IPC A 01 N 43/90 A 01 43/54; application N.26.04.2006;-publ. 31.10.2007 (German).

146. K.K.Kirin Pharma, Kubo Kazuo., Furuta Takayuki. Derivatives of thienopyridine, quinoline or quinazoline with inhibition potential C-met autophosphorylation // Application 1870414 EPO, IPC c 07 D 495/04; A 61K 31/4709; application 28.03.2006. publ. 26.12.2007

147. A.Cs.Bayer Crop Sciense, Maurer Fritz, Fuchs Rainer, Erdelon Christoph, Lubod-Erdelen Angelika. Substituted 4-pyrazolylpyrizolines, applicable for pest control // pat. 7345080 USA, IPC A 01 N 43/56; c 07 D 403/04; application 23.02.2003; publ. 18.03.2008;

148. Csallou Isabelle. Asymmetric urea. Synthetic methodologies and applications for drug development // Org. Prep. and Proced. Int. 2007, 39. N4. C.355, 357-383.

149. Yoshinaga Koji, Kawasaki Daisuke, Emori Yutaka. Antitumor

agent // application 1839662 EPB, A 61 K 31/551; A 61 P 35/00 application.16.01.2006; publ.03.10.2007

150. Willener Yasmine, M.Joly Kevin, J.Moody Christopher, H.R. Tucker James. The use of ferrocenylureas as electrochemical sensors for chiral carbosylate anions // J. Org. Chem; 2008, 73, N4. C. 1225-1233 (eng).

151. Burilov A.R., Gazizov A.S., Khakimov M.S., Ludovik M.A. Interaction 1-(2,2-dimethoxyethyl)-1-methyl-3-phenylureas with pyrogallol // Zh. Chemistry, 2008, 78, No.12. pp. 2065-2066.

152. V.Kassack Matthias, Meis Sabine, Hongwiset Dagipee. Carbonylbisiminor derivatives for the treatment of immune diseases // Application 102006037920. Germany, IPC A 61 To 31/166; application 11.08.2006; publ.14.02.2008.

153. Wang Lin, Li Ru-Lin, Wang Hong-Wei, Xing Wen-Ru, Wen-Min. Synthesis and biological activity of aromatic acylaminoureas with N,N^1-naphthalenacyl substituents // Chin. J. Appl. Chem. 2007, 24, N10. pp.1145-1148 (kit).

154. Z.Tetere, I.Ravina, D.Zicane. The use of cyclohexanediacarboxylic acid monohydrazides for the synthesis of disubstituted urea // RTU Zinatniskie raksti. Ser. I. 2008, N16. pp. 54-57 (Latvian).

155. Yura Takeshi, Mogi Muneto, Fujishima Hiroshi, Urbahus Klaus, Masuda Tsutamu, Tsukimi Yasuhiro, Tajimi Masaomi. Hydroxytetrahyde derivatives-Ronaphthaline urea // Pat. 7423175 USA, IPC From 07 C 275/32; A 61 K 31/17. application 05.02.2004; publ. 09.09.2008.

156. Song Eun Young, Kaur Navneet, Park Mi-Young, Jin Yunglan, Lee Kyeong, Kim Csuncheol, Lee Ki Youn, Yang Jee Sun, Shin Jae Hong. Synthesis of amide and urea derivatives of benzothiazole as Raf-1 inhibitors // Eur. J. Med. Chem. 2008. 43, N7. C. 1519-1524.

157. Shulishov E.V., Klimenko I.P., I.P.Tomilov I.P. Synthesis of N-methyl-N-nitrosourea and its use for obtaining an essential solution of diazometh on // Syntheses of organic compounds. 3. Moscow: MAKS PRESS. 2008. pp. 266-269.

158. Baumann Delphine, Bennis Khalil, Ripoche Isabelle, Troin Yves. Simple and

effective synthesis of new cyclic urea // Tetrahedron Lett. 2007. 48. N47, C. 8363-8365 (eng).

159. Farmer Jan, Ford Mark James, Schlegel Gunter, Kübel Berris, Ort Ostwald. Halides of halosulfonyl benzoic acid, the method of their preparation and their application for the production of substituted phenylsulfonyl- urea // Pat. 2330027, Russia, IPC From 07 D 251/42; From 27.07.2008 (rus).

160. B. Fender Christopher, A.Widenhoefer Rosa. Hydroamination of N-alkenylureas catalyzed by gold (I)-N-heterocyclic carbene complex, at room temperature // Org. Lett. 2006. 8, N23. pp. 5303-5305.

161. Cai Zhi-Juan, Xue Si-Jia, Shin Jie-Feng, Wang Qing-Dong. Synthesis of N1-(tert-butylaminocarbonyl)-N-[5-(substituted phenyl)-2-furoyl] urea derivatives and inhibition or proliferation of K.562 cells // Chin. J. Appl. Chem. 2008, 25, N5. pp. 552-555.

162. S.A. Sanofi Aventis, Bourrie Bernard, Casellas Pierre. New application therapeutic agents for the treatment of leukemia // Application 29/08/3 France, IPC8 A 61 K 31/519; A 61 P 35/02. application. 12/28/2006; publ. 04. 07. 2008.(France).

163. Artuso Emma, Degani Iacapo, Fochi Rita. Single-reactor, three-stage preparation of alkyl- and arylalkyl carbamates from S-methyl-N-alkylthiocarbamates // Synthesis, 2008, N10. pp. 1612-1618.

164. Carlini Rina, Toma Eniko, Odell Reter Cs., Banning Jeffrey H.Cured trans-1,2-cyclohexane bis (urea-urethanes) // Pat. 7317122 USA, IPC From 07 To 261/00; application 04.12.2004; publ. 08.01.2008.

165. A.B.Astra Zeneca, Ashwell Susan, Csero Thomas. Substituted urea thiophenes and their use // Pat. 7423061 USA, IPC A 61 K 31/381; C 07 D 334/04; application 12.08.2004; publ. 09.09.2008.

166. Махсумов А.Г., Холбоев Ю.Х., Джиембаев Б.Д., Ауешов А.Т. Синтез и технология получения производных дифениламина и его свойства // Химический журнал Казахстана. – Алматы, 2008. -№ 3. – С.9-16.

167. Холбоев Ю.Х., Мирзабоев Э.А., Инаков Т.К., Ортиков М.Б., Махсумов А.Г. Синтез N,N^1- гексаметилен бис-[(изатиноило мочевины] в качестве красителя полистирола // Наука.Образование. Техника –Ош, 2008. -№ 4. — С. 84-85.

168. Холбоев Ю.Х., Махсумов А.Г., Мирзабоев Э.А., Инаков Т.К., Ортиков М.Б. Синтез N,N^1-гексаметилен бис-[(дибензилоило) мочевины] для овощных культур и хлопчатника // Наука. Образование. Техника. –Ош, 2008. -№ 4. – С.82-84.

169. Холбоев Ю.Х., Махсумов А.Г. Технология получения производного изатина // Кимёвий технология Назорат ва Бошқарув. Илмий техникавий журнал. – Тошкент, 2008. -№ 4. – С. 9-16.

170. Хожиматов М.М., Холбоев Ю.Х. Молекуласида ферроцен сақловчи гематологияда қўлланиладиган бирикмаларни сертификатлаш муаммолари // Товарларни кимёвий таркиби асосида таснифлаш ва сертификатлаш. Республика илмий амалий анжумани материаллари. –Андижон, 2008.– Б.98-99.

171. Мўйдинов Н.Т., Холбоев Ю.Х. Ферроцен асосида биологик фаол модда лар яратиш истиқболлари ва сертификатлаш муаммолари // Товарларни кимёвий таркиби асосида таснифлаш ва сертификатлаш. Республика илмий амалий анжумани материаллари. –Андижон, 2008. – Б. 103-104.

172. Мадумаров Т.А., Аскаров И.Р., Киргизов Ш.М., Жўраев А.М., Холбоев Ю.Х. Микроэлементлар асосида биостимуляторлар яратиш ва уларни сертификатлаш // Товарларни кимёвий таркиби асосида таснифлаш ва сертификатлаш. Республика илмий амалий анжумани материаллари. – Андижон, 2008. – Б. 22-23

173. Холбоев Ю.Х., Махсумов А.Г., Аскаров И.Р. П-ферроцениланилинни экологик ҳосиласини синтези // Аналитик кимёнинг ҳозирги замон ривожланиш истиқболлари. Материалы юбилейной международной конференции, посвященной 90-летию НУУз и 100-летию академика Талипова Ш.Т. –Ташкент, 2008. – Б.79.

174. Махсумов А.Г., Холбоев Ю.Х., Максумова Н.А., Миркомилов Ш.М.

Простой и эффективный метод синтеза производного изатина // Аналитик кимёнинг ҳозирги замон ривожланиш истиқболлари. Материалы юбилейной международной конференции, посвященной 90-летию НУУз и 100-летию академика Талипова Ш.Т. –Ташкент, 2008. — 98 с.

175. Холбоев Ю.Х., Махсумов А.Г., Максумова Н.А., Миркомилов Ш.М., Получение, свойства, производные дибензиламина // Маҳаллий хомашёлар ва маҳсулотларни қайта ишлашнинг технологиялари. Республика илмий-техника анжуманининг мақолалар тўплами. –Тошкент, 2008. – С. 71-73.

176. Холбоев Ю.Х., Махсумов А.Г., Максумова Н.А., Мирзабаев Э.А., Инаков Т.К. Синтез и технология получения полиметилен бис-[(5- бромизатиноило) мочевины] и ее свойства // Маҳаллий хомашёлар ва маҳсулотларни қайта ишлашнинг технологиялари: Республика илмий- техника анжуманининг мақолалар тўплами. – Тошкент, 2008. — С. 73-75.

177. Холбоев Ю.Х., Ахмедова М.Р., Махсумов А.Г., Миркомилов Ш.М., Абдурахмонов Э.Б. Синтез бис-замещеных бис-п-ферроценилфенола и их свойства // Наука. Образование. Техника. –Ош, 2009. -№ 4 – С. 119-121.

178. Сулаймонов Б.И., Махсумов А.Г., Холбоев Ю.Х., Сулаймонов И.А. Способ получения производного N,N^1-гексаметилен бис-[(дифенилоило) мочевин] и его химические свойства // Наука. Образование.Техника. –Ош, 2009. -№ 4 –С.110-112.

179. Холбоев Ю.Х., Махсумов А.Г., Мирзабоев Э.А., Инаков Т.К., Хамидов И.И., Бочаров С.С. ХЮХ-5 N,N^1-гексаметилен бис-[(5-бромизатиноил) мочевина)] препаратининг ўсимликларни ўсиши ва ривожланишини бошқарувчи (биостимулятор) сифатидаги роли // Наука. Образование. Техника. –Ош, 2009, - № 1 – Б.120-121.

180. Холбоев Ю.Х., Каримов А., Махсумов А.Г., Махсумова Н.А. Бис-мочевина ҳосилаларини N-H гуруҳи реакцион марказ бўйича алкиллаш реакцияси // Нефть ва газ саноати кимёвий технологияларининг долзарб муаммолари: –Республика илмий-амалий конференцияси материаллари - Қарши, 2009.– Б.22-23.

181. Махсумов А.Г., Ахмедова М.Р., Самадов С.Ж., Холбоев Ю.Х. П-ферроцениламин, п-ферроценилфенол ва уларнинг ҳосилаларининг реакциялари // Нефт ва газ саноати кимёвий технологияларининг долзарб Қарши, 2009. Б. 55-56.

182. Холбоев Ю.Х., Махсумов А.Г., Максумова Н.А., Каримов А. Селективный, удобный и эффективный метод синтеза производного карбазола // Нефть в газ саноати кимёвий технологияларининг долзарб муаммолари. –Республика илмий-амалий конференцияси материаллари -Қарши, 2009. – С. 41-42.

183. Холбоев Ю.Х., Максумова Н.А., Махсумов А.Г., Миркомилов Ш.М., Рахматов Х.Б. Разработка технологии синтеза экологически чистых, не загрязняющих окружающую среду, органических препаратов // Нефть ва газ саноати кимёвий технологияларининг долзарб муаммолари. Республика илмий-амалий конференцияси материаллари –Қарши, 2009.– С. 136.

184. Ахмедова М.Р., Холбоев Ю.Х., Махсумов А.Г. Экологик тоза темир органик бирикмаларини ишлаб чиқаришга мослаштирайлик // Нефт ва газ саноати кимёвий технологияларининг долзарб муаммолари. Республика илмий-амалий конференцияси материаллари -Қарши, 2009. – Б. 130.

185. Махсумов А.Г., Холбоев Ю.Х. Гексаметилен бис-[(карбазолил) мочевина] нинг N-H гурухи реакцион марказ бўйича алкиллаш реакцияси // Кадрлар сифатини оширишда замонавий педагогик технологияларининг роли: тажриба ва истиқболлар. Республика илмий-амалий конференцияси материаллари тўплами – Наманган, 2009– Б. 266-267.

186. Махсумов А.Г., Холбоев Ю.Х. Бис мочевина ҳосилаларини нитрозо ва хлорлаш реакциялари // Кадрлар сифатини оширишда замонавий педагогик технологияларининг роли: тажриба ва истиқболлар. Республика илмий-амалий конференцияси материаллари тўплами -Наманган, 2009. – Б. 268-269.

187. Холбоев Ю.Х. Мочевина ҳосилаларининг буғдой ҳосилдорлигига таъсири // Умидли кимёгарлар -2010: Труды научно-технической конференции молодых ученых.–Ташкент, 2010. –С. 211-212.

188. Холбоев Ю.Х. N,N[1]-гексаметилен бис- [(5-бромизатиноил) мочевина] синтези ва унинг хоссаларини ўрганиш // Умидли кимёгарлар -2010: Труды научно-технической конференции молодых ученых. –Ташкент, 2010. – С. 213-214.

Practical advice

1. The results of the interpretation of the waste-free synthesis technology and spectroscopic data of synthesized N,N^{1}-hexamethylene bis - [(aminoaroyl) uchevin] can be used in research, master's and educational works of universities and universities in the field of organic matter technology and in organic chemistry. when establishing the structure of new bis-urea derivatives

2. The results obtained on the biological activity of new compounds can be used in applied research: extended chemical-technological and biological research in order to create new plant growth stimulants, dyes and other substances.

3. The results obtained on the biological activity of bis-urea derivatives as a growth regulator of vegetable crops and cotton, as well as a dye preparation, were filed in the form of a patent application and submitted to the State Patent Office of the Republic of Uzbekistan.

Ureas are used in many industries: medicine, agriculture, technology, rubber industry, organic synthesis. On their basis, various preparations were obtained for the needs of the national economy. Recent research on derivatives of ureas and bis-ureas, carried out at the present time, is prompted not only by theoretical, but also by practical needs. From this point of view, urea derivatives are of undoubted interest for substances with various biological activities. They are widely used in agriculture and have found application as herbicides, fungicides, insecticides, bactericides, dyes, growth stimulants, etc. Of particular interest is the use of these compounds in medicine as antitumor, antiviral, anti-inflammatory, antiarrhythmic, vasodilator and other drugs.

Purpose of the research is development of a simple, affordable synthesis method and waste-free technology for the production of previously unknown derivatives of bis-aromatic ureas; study of their properties, as well as growth-stimulating activity; development of practical proposals for the introduction of growth stimulators in the agriculture of our republic.

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