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## **SYNTHESIS OF NEW BIOLOGICALLY ACTIVE COMPOUNDS BASED ON 6-METHYLURACIL-5-SULFOCHLORIDE AND ALKYLAMINES**

*Об'єктом дослідження є 6-метилурацил-5-сульфохлориду та синтези на його основі моно- і дизаміщених сульфонамідів. Синтезовано ряд нових сполук, які не описані в літературі, тому не виключна можливість, що серед синтезованих сполук знайдуться і такі, які можуть в певній мірі проявляти і біологічну активність.*

*Виявлено дві проблеми, які вирішувалися в процесі дослідження. До першої проблеми належить те, що більшість попередніх робіт характеризувалися низьким виходом метилурацилсульфохлориду і це стримувало його широке використання в органічному синтезі. Підібравши певні умови синтезу, тобто проводячи реакцію взаємодії метилурацилу з хлорсульфоною кислотою в середовищі інертного органічного розчинника (дихлоретан, тетрахлорметан, хлороформ), вдалося досягти виходу МУСХ понад 96 %.*

*Другим проблемним місцем виявилася взаємодія МУСХ з амінами. Виявилось, що для підвищення виходу продукту реакції синтез краще проходить в середовищі інертних органічних розчинників (діоксан, диметилформамід, диметилсульфоксид) в присутності основ (сода, поташ, ацетат натрію). Гарні результати отримані при проведенні синтезу в піридині, який одночасно служить і розчинником, і основою.*

*Для підтвердження будови та складу отриманих сполук використовували фізико-хімічні методи аналізу (ІЧ- та ЯМР-спектроскопію), а також дані елементного складу.*

*Отримано ряд нових, не описаних в літературі, сульфонамідів. Це пов'язано з тим, що запропонований метод має ряд особливостей, зокрема, запропоновано новий метод введення сульфохлоридної групи в ароматичні сполуки.*

*Завдяки цьому забезпечується можливість отримання нових органічних препаратів, які можуть знайти певне застосування в різних галузях промисловості. У порівнянні з аналогічними відомими методами це забезпечує такі переваги, як збільшення виходу продуктів реакції, їх чистота та індивідуальність, доступність методу синтезу та ряд інших переваг.*

**Ключові слова:** біологічно активні сполуки, 6-метилурацил-5-сульфохлорид, первинні і вторинні алкіламінів, дезенфікуючі засоби, реакційна здатність.

### **1. Introduction**

Sulfanilamide preparations are a group of chemically synthesized compounds used for the treatment of infectious diseases, mainly of bacterial origin [1, 2]. Sulfanilamides were the first drugs that allowed successful prevention and treatment of a variety of bacterial infections. In 1935, the chemotherapeutic properties of one of the first sulfonamides, Prontosil, were discovered in the treatment of streptococcal infections. The effect of this drug was also observed in pneumococcal, gonococcal, E. coli, dysentery rods, typhoid fever and other infections. Several thousand different sulfonamides have been synthesized, of which only a few dozen are used in medical practice. This is due to the fact that the main constituent of such sulfonamides is benzene or aniline, which has increased toxicity, which limits their use.

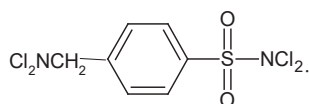
Sulfanilamide preparations are close in chemical structure to para-aminobenzoic acid (PABA), a necessary growth factor for microorganisms, in the absence of which they can't reproduce. The main mechanism of action of sulfanilamide preparations is competition with PABA for binding to certain enzymes in a microbial cell. As a result of the compounds of sulfonamide preparations with

enzymes, the bacteria lose the ability to synthesize the vitamin-folic acid they need and perform other transformations of substances that normally occur with the PABA participation. Since these enzymes have a higher affinity for PABA than sulfanilamide preparations, a therapeutic effect is achieved with sufficiently large doses of the preparations.

Thanks to sulfamides, a broad basis for a decisive attack on infectious diseases caused by bacteria has been created. The discovery of sulfamides had a tremendous stimulating effect on subsequent studies in the field of antibiotics.

Thanks to these drugs, entered into medical practice since the 1930s, it was possible to significantly reduce the death rate from pneumonia, infection of blood and many other bacterial infections. Their widespread use during the World War II saved many lives.

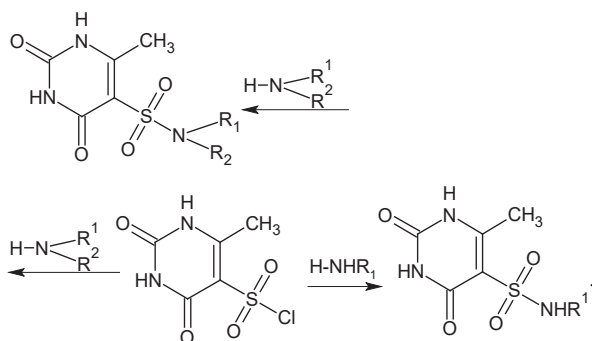
Among the amides of sulfonic acids, substances with different physiological activity have been found [3–5]. N, N-Dimethylamide-4-chlorobenzenesulfonic acid has acaricidal action and it is not inferior to the esters of this acid in activity. Bactericidal and fungicidal activity has N, N-dichloro-N', N'-dichloramine methylbenzenesulfonamide structure:



Widespread use for disinfection is found in chloramines T and B, the strong bactericidal action of which is based on the ability to release active chlorine. These substances are obtained by chlorinating the corresponding amines in an aqueous-alkaline medium.

Preparations of the sulfonamide group were invented long ago, and today they practically lost their importance, as they are inferior to modern antibiotics. Also, their limited use is due to the high toxicity and resistance of certain bacteria to them. But nevertheless at treatment of some diseases these agents till now are applied in a chemotherapy.

Therefore, the search for new compounds that have shown biological activity and at the same time were less toxic than current preparations is a very topical direction in bioorganic chemistry. Such compounds can be products obtained by reaction of 6-methyluracil-5-sulfochloride (MUSCH) and primary or secondary alkylamines. Such transformation can be represented by a general scheme:



## 2. The object of research and its technological audit

The object of research is 6-methyluracil-5-sulfochloride and syntheses based on it mono- and disubstituted sulfonamides. Sulfanilamide preparations have antibacterial effect on many Gram-positive and Gram-negative bacteria, in particular meningococci. The antibacterial effect of sulfonamides is due to the similarity of their structure to para-aminobenzoic acid (PABA), as a result of which sulfonamide preparations compete with it, blocking the metabolic processes of microorganisms.

One of the most problematic places was the method of sulfo-chlorination of methyluracil. Even with a tenfold excess,  $\text{HSO}_3\text{Cl}$  of methyluracil sulfochloride did not exceed 25–28 %.

## 3. The aim and objectives of research

The aim of research is studying the possibility of an improved synthesis of the initial 6-methyluracil-5-sulfonyl chloride (MUSCH).

To achieve this goal it is necessary to accomplish the following tasks:

1. To determine the synthesis conditions of MUSCH.
2. To determine the conditions for improving the quality of synthesized sulfonamides.

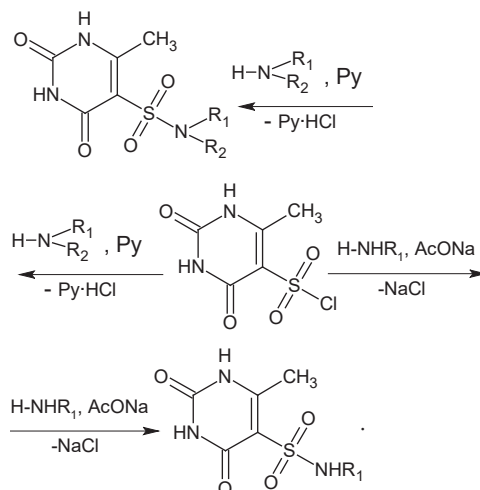
3. To confirm the structure of the reaction products and the obtained compounds.

## 4. Research of existing solutions of the problem

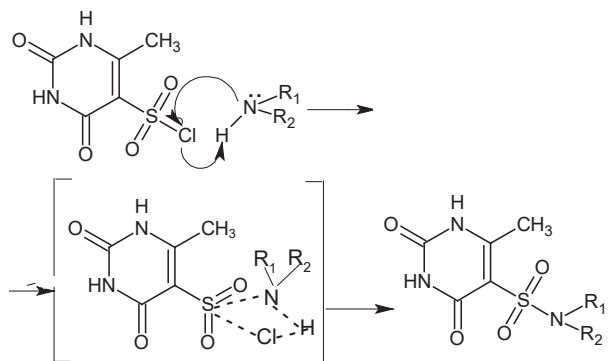
When working out the synthesis conditions for MUSCH with a higher yield [6–9], qualitatively MUSCH can be determined by the method [8].

The introduction of the sulfonyl chloride group –  $\text{SO}_2\text{Cl}$  into the molecule of an organic compound is widely used in organic synthesis both for the preparation of sulfochlorides of  $\text{ArSO}_2\text{Cl}$  and for the production of functional sulfonated groups (sulfonamides, sulphoesters and others). Sulfochlorides are important intermediates in the synthesis of sulfanilamide preparations. Compounds of this type are widely used for the preparation of amides, anilides, esters of sulfonic acids, herbicides, fungicides and other compounds. Among the various sulfonic acids and their derivatives, compounds with high pesticidal activity are found [10]. Fungicidal properties are found in many aromatic sulfonates [11]. But practical application has not yet been found, which is due to their high phytocytosis.

Sulfonic acid salts possess herbicidal properties [12, 13]. It is possible that among the sulfonamides. Sulfamides are usually obtained by reacting amines (primary or secondary) with sulfochlorides in the presence of bases (pyridine, triethylamine, dimethylaniline, sodium acetate):



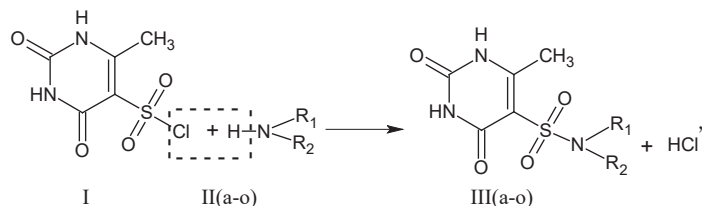
This reaction is often carried out at room temperature or at a lower temperature. It was found that in the case of MUSCH, the same regularities are observed as for the ammonolysis of aryl sulfochlorides. When studying the reaction of MUSCH with alkylamines, which are stronger bases than water, it is established that the ammonolysis proceeds like the hydrolysis of sulfochlorides and passes along the  $\text{S}_\text{N}2$  mechanism. However, the reaction rate in the first case is much smaller. The influence of the nature of the amine on the kinetics of ammonolysis of MUSCH shows that with increasing length of the aliphatic radical, the basicity of the amine increases and the rate constant of the formation of sulfonamides increases. In this case, the ammonolysis reaction can proceed through the stage of formation of the intermediate complex of the structure:



The repulsion and attraction of electrons within a molecule are most appropriate to be considered with respect to any standard, in which the type of hydrogen is usually chosen. On the basis of this analysis, the induction effect of hydrogen in this work is assumed to be zero and selected as the basis for comparison with other atoms and groups of atoms.

According to Ingold, the inductive effect is considered negative ( $-I$ -effect) if  $X$  in  $\text{CH}_3\text{-X}$  is more electronegative than carbon and positive ( $+I$ -effect) if the carbon is more negative than  $X$ . With the extension of the carbon chain and its branching, the inductive effect which, in turn, leads to an increase in the degree of dissociation of amines in the homologous series [14, 15].

The alkylamines are capable of reacting with sulfonic acid chlorides in the presence of bases or in the presence of an excess of the corresponding amine necessary to bind the evolved hydrogen chloride:



where  $R_1 = \text{H}$  or *alk*;  $R_2 = \text{alk}$ .

As the bases for the binding of hydrogen chloride, pyridine is most often used, which simultaneously acts as a nucleophilic catalyst. Instead of pyridine, aliphatic or aromatic tertiary amines are often used for this purpose, for example triethylamine, triethanolamine, *N,N*-dimethylaniline, pyridine.

## 5. Methods of research

When investigating the possibility of an improved synthesis of the initial 6-methyluracil-5-sulfochloride (MUSCH), chlorosulfonic acid was previously dissolved in an inert organic solvent (chloroform, carbon tetrachloride, dichloroethane).

To the resulting reaction mixture, methyluracil was added in small portions with stirring. The end of the reaction was determined chromatographically.

For the synthesis of *N*-alkylsulfonamides, MUSCH, prepared according to a technology developed by the authors, was previously purified by recrystallization from glacial acetic acid. The individuality of the product was determined by melting temperature and chromatography on plates of Silufol-254 (Czechoslovakia). Amines were purified by distillation in vacuum using a medium frac-

tion with a constant boiling point. The solid amines were crystallized from a suitable solvent or from several solvents to a constant melting point and chromatographic purity.

## 6. Research results

**Synthesis of 6-methyluracil-5-sulfonyl chloride.** 50 ml of dichloroethane is charged into the apparatus with a mechanical stirrer, a contact thermometer, a reflux condenser with a chloroalkium tube and a dropping funnel. While stirring, dissolve 20 ml (35.3 g, 0.30 mol) of freshly distilled chlorosulfonic acid.

With vigorous stirring, 12.6 g (0.10 mol) of methyluracil, previously dried at 105–110 °C, are added in small portions to the solution. The temperature rises to 40–45 °C. After 20–30 minutes, methyluracil completely dissolves and the reaction mass becomes homogeneous. The reaction mass is heated to the boiling point of dichloroethane (80–85 °C) and allowed to hold for 4.5–5 hours until the hydrogen chloride evolution ceases and the original methyluracil is not removed (by chromatography on Silufol-254, ethyl acetate system,  $R_f = 0.88$ ).

The contents of the flask are cooled to room temperature and carefully, with vigorous stirring, poured onto 100 g of finely powdered ice.

The precipitated precipitate of 6-methyluracil-5-sulfonyl chloride is filtered, washed 2–3 times with isopropyl alcohol (10 ml each) and dried in a vacuum desiccator over sulfuric acid (to constant weight).

22.10 g (96.1 % of theory) are recovered.  $T_m = 243\text{--}243.5$  °C (from acetic acid). The literature indicates 235 °C (with destruction) [8, 9].

Found: C – 26.58, 26.65; H – 2.28, 2.33; Cl – 15.88, 16.05; S – 14.02, 14.16.

$\text{C}_5\text{H}_5\text{ClN}_2\text{O}_4\text{S}$ . Calculated: C – 26.72; H – 2.22; Cl – 15.81; S – 14.25.

**6-methyluracil-5-sulfonamide.** In 5 ml of water, 1.5 ml of concentrated ammonia was dissolved.

To the resulting solution, 2.25 g (0.01 mol) of methyluracil sulfonyl chloride was powdered into the powder with stirring. The reaction mass was stirred until the absence of the initial MUSCH by chromatogram. After the end of aging, the reaction mass was acidified, the precipitate was filtered off, washed, and dried. 1.87 g is isolated. Physical and chemical properties of the obtained compounds and their elemental analysis are given in Table 1.

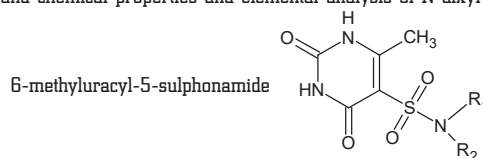
***N*-Ethyl-6-methyluracil-5-sulfonamide.** In 10 ml of glacial acetic acid, 2.25 g (0.01 mol) of methyluracil sulfonyl chloride was dissolved. To the resulting solution, 0.45 g (0.0125 mol) of ethylamine was added. The reaction mass was heated to 80–85 °C and allowed to stand at this temperature 2.5–3 hours before the absence of MUSCH.

After the end of aging, the contents of the flask were diluted three times with water. The precipitate was filtered off, washed with water, and with alcohol. 2.34 g is isolated. Physical and chemical properties are given in Table 1.

Based on the data from Table 1, it can be stated that the reduced elemental analysis of newly synthesized compounds practically coincides with the calculated content of these elements in the given compounds. This is one of the confirmations of the chemical structure of these structures.

Table 1

Physical and chemical properties and elemental analysis of N-alkyl-substituted

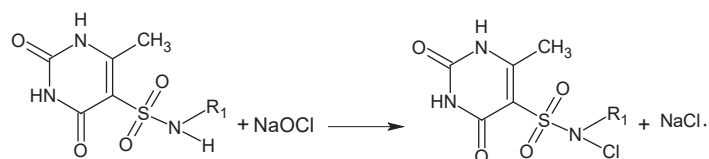


No. of compound	Radical – NR <sub>1</sub> R <sub>2</sub>	Yield, %	T <sub>m.</sub> , °C	Calculated %				Brutto-formula	Determined, %			
				C	H	N	S		C	H	N	S
III-a	NH <sub>2</sub>	91.4	289-00	29.57	2.46	20.68	15.63	C <sub>5</sub> H <sub>7</sub> N <sub>3</sub> O <sub>4</sub> S	29.32	2.41	20.77	15.54
III-b	NHCH <sub>3</sub>	93.4	220-22	32.87	4.14	19.17	16.62	C <sub>6</sub> H <sub>9</sub> N <sub>3</sub> O <sub>4</sub> S	32.96	4.15	19.26	16.71
III-c	N(CH <sub>3</sub> ) <sub>2</sub>	91.7	281-82	36.05	4.75	18.02	13.75	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub> S	36.00	4.78	18.20	13.83
III-d	NHC <sub>2</sub> H <sub>5</sub>	96.3	280-01	36.05	4.75	18.02	13.75	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub> S	36.15	4.82	17.94	13.87
III-e	NHCH <sub>2</sub> CH <sub>2</sub> OH	72.6	276-77	33.65	4.44	16.82	12.83	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> O <sub>5</sub> S	33.59	4.48	16.91	12.95
III-f	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	91.4	278-79	41.33	5.78	16.08	12.27	C <sub>9</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub> S	41.26	5.83	16.00	12.33
III-g	N(CH <sub>2</sub> CH <sub>2</sub> OH) <sub>2</sub>	77.6	301-02	36.86	5.15	14.33	10.93	C <sub>9</sub> H <sub>15</sub> N <sub>3</sub> O <sub>6</sub> S	36.94	5.10	14.26	11.03
III-h	N(CH <sub>2</sub> CH <sub>2</sub> Cl) <sub>2</sub>	84.1	291-93	32.74	3.97	12.73	9.71	C <sub>9</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>4</sub> S	32.68	4.00	12.63	9.87
III-j	N(CH <sub>2</sub> CH <sub>2</sub> Br) <sub>2</sub>	91.0	199-02	25.77	3.12	10.08	7.64	C <sub>9</sub> H <sub>13</sub> Br <sub>2</sub> N <sub>3</sub> O <sub>4</sub> S	25.67	3.10	9.92	7.73
III-k	NHCH <sub>2</sub> COOH	81.7	315-17	31.94	3.45	15.96	12.18	C <sub>7</sub> H <sub>9</sub> N <sub>3</sub> O <sub>6</sub> S	31.83	3.49	16.03	12.24
III-l	NHCH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H	79.3	325-27	34.60	4.00	15.16	11.56	C <sub>8</sub> H <sub>11</sub> N <sub>3</sub> O <sub>6</sub> S	34.71	3.94	15.24	11.43
III-m	NH(CH <sub>2</sub> ) <sub>3</sub> N(Et) <sub>2</sub>	88.6	222-24	45.10	6.94	17.53	10.03	C <sub>12</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub> S	45.01	6.91	17.65	10.15
III-n	N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> O	90.7	293-94	39.27	4.76	15.26	11.65	C <sub>9</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> S	39.16	4.70	15.18	11.76
III-o	N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>	94.5	278-79	43.95	5.53	15.37	11.73	C <sub>10</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub> S	43.86	5.56	15.44	11.63
III-p	NH-cyclohexyl	90.8	181-02	45.98	5.96	14.62	11.16	C <sub>11</sub> H <sub>17</sub> N <sub>3</sub> O <sub>4</sub> S	45.88	6.02	14.70	11.04

## 7. SWOT analysis of research results

**Strengths.** Most of the given compounds obtained by the interaction of methyluracil sulfonyl chloride with lower primary and secondary amines are not described in the literature. The use of lower alkylamines, which have a greater nucleophilicity than the arylamines, promotes a faster reaction of the nucleophilic substitution of the chlorine atom in the sulfochloride for the amino group. The more rapid exchange reaction between SO<sub>2</sub>Cl and alkylamine significantly shortens the reaction time, and the formation of a pure product removes the complexity of cleaning the reaction product from the researcher.

The interaction of synthesized N-alkyl-6-methyluracil-5-sulfonamides with a solution of sodium or potassium hypochlorite resulted in a number of completely new compounds not described in the literature. The synthesis was carried out according to the following scheme:



**Weaknesses.** Sulfochlorides are compounds with increased reactivity. Easily enter into reactions of nucleophilic substitution with alcohols, phenols, amines, especially – aliphatic ones. Aliphatic amines, in turn, also belong to compounds with increased reactivity and easily

replace the chlorine atom and the sulfonyl chloride group. Therefore, the weak side of this process is practically absent.

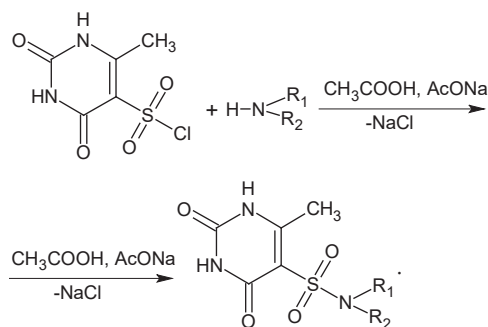
**Opportunities.** Preliminary screening using the PASS program for most of the obtained compounds showed their high biological activity [16–19]. Therefore, it is possible that among the synthesized compounds there are those that in the future will find practical application.

**Threats.** Methyluracil is used in medical practice as an energy stimulant, and also forms part of nucleic acids, therefore it does not pose a threat to the objects of research. Analogues devoted to the synthesis of products based on methyluracil sulfochloride and alkylamines have not been found in the literature.

## 8. Conclusions

1. In the course of the conducted studies, it was found that the increase in the yield and improvement of the quality of methyluracil sulfochloride depends to a large extent on the conditions for carrying out the sulfochlorination reaction. This can be achieved if the reaction of methyluracil with chlorosulfonic acid is carried out in a medium of inert organic solvents (chloroform, tetrachloromethane, dichloroethane), while replacing some of the chlorosulfonic acid with thionyl chloride.

2. It was shown that in order to improve the quality of synthesized sulfonamides and simplify the synthesis, the initial amines were used in the form of aqueous solutions in inert organic solvents (dioxane, acetone, acetic acid) in the presence of bases:



And also that the reaction of MUSCH interaction with water-soluble alkylamines with other amines easily passes in acetic acid in the presence of sodium acetate or in pyridine.

3. Elemental analysis of reaction products was determined to confirm the structure of the obtained compounds, and NMR and IR spectroscopy was partially used to confirm the structure of the reaction products. Using the PASS program, the preliminary biological activity of synthesized alkyl sulfonamides was determined and the possibility of their use as chemotherapeutic agents.

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