Study of methylation reactions of 2-phenylquinazoline-4-tion with "soft" and "hard" methylation agents and determination of its biological activity

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Abstract. Alkylation reactions of 2-phenylquinazoline-4-thion with methylation agents "soft" (methyl iodide) and "hard" (dimethyl sulfate, methyltozylate) were studied. It was found that the reaction proceeds with the formation of alkyl products at the N^3 - and S4 - reaction centers, depending on the methylation agent, solvent and temperature. This indicated the ambivalent nature of the 2-phenylquinazoline-4-tion anion. Prolongation of the reaction time leaded to the formation of a second isomeric product (VII). A slight increase in phenyl N^3-product (VII) yield was noted when dimethyl sulfate and methylfolate were used as methylation agents. In non-polar proton-free solvent DMF and dipolar proton-free solvent acetonitrile, only N-methyl product (VII) was formed because of the reaction. An increase in the polarity of the solvent and the "hardness" of the methylation agent leads to an increase in the yield of N^3 products.

1 Introduction

At present, the role of the science of chemistry of heterocyclic compounds in various areas of agriculture is important. For example, nitrogen fertilizers, phosphorus and potassium fertilizers, macro- and micronutrients play an important role in the normalization of biochemical processes in tissues and cells in the production of abundant crops and rapid ripening of fruits [1-2]. It allows to find compounds with different properties among the synthesized substances and to use them successfully in various sectors of the economy, including medicine, agriculture, food and light industry and other fields. 5-Methyluracil is widely used in medicine as a biologically active compound found in cancer, as well as among heterocyclic compounds, and has been successfully used as a pesticide herbicide, fungicide, insecticide, attractant, repellent, and plant-repellent [4, 6-7]. The number of chemicals has now reached 13 million in the period of the continuous development of organic chemistry and rising to the supramolecular level. About 80% of them are carbon, H, O, N, S, P and halogens. The unique feature of the carbon atom, such as its ability to

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combine not only with other elements, but also with each other to form long straight and branched chains, various rings and carcass structures that makes it possible to synthesize innumerable compounds [3-4, 8]. This, in turn, leads to the search for compounds with different properties among the synthesized substances and their successful application in the economic sectors, such as medicine, agriculture, food and light industry.

It is necessary to emphasize the role of chemistry of heterocyclic compounds, which is an integral part of organic chemistry, in achieving these successes, because 60-65% of the achievements in organic chemistry in recent years fall on the chemistry of heterocyclic compounds [5, 9]. Pyrimidine and its derivatives, which contain two nitrogen atoms in their molecules from heterocyclic compounds, occupy one of the leading positions in this regard. Quinazoline, an analogue of pyrimidine with a benzene ring, and its various derivatives are among the compounds of both practical and theoretical importance. Their practical significance is determined by their physiological activity. Biologically active compounds found among quinazoline derivatives have been successfully used as medicinal agents, pesticides, herbicides, fungicides, insecticides, attractants, repellents and substances with plant growth properties [1]. The theoretical significance of quinazoline derivatives is explained by the presence of several potential reaction centers in the molecule (N^1-, C^2-X, N^3-, C^4-X, (X = O, S, Se, NH).

2 Material and methods

In this research, the alkylation reactions of 2-exchange quinozoline-4-ons was studied, and N^3-alkyl was formed due to alkylation reaction of 2-Oxo (amino) quinazolin-4 [2-5]. Quinazoline-4-tion was used as a "soft" (methyl iodide) and "hard" (dimethyl sulfate, methylfolate (OTs)) in order to determine the direction of the alkylation reaction with methylation agents in the presence of a sulfur atom in the 4^{th} position of the quinazoline ring and the factors influencing it [2-4]. Alkylation reactions were carried out under two different conditions (by heating at room temperature for 24 hours and in a water bath for 4 hours) and in polar proton-soluble ethanol, non-polar proton-free solvent-dioxane-1.4, and bipolar proton-free solvents in acetonitrile and dimethylformamide (DMF). IR spectra were recorded on a UR-20 spectrometer in tablets with KBr and PERKIN ELMER System 2000 FT-IR, PMR spectra on JNM-4H-400 and Tesla Bs-567A (internal standard - TMC, GDMS, d scale). Rf-values were determined on plates "Silyfol" UV-254 (ChSSR), Disclosure: iodine vapors. Solvents (ethanol, acetonitrile, dioxane-1.4, dimethylformamide) were purified and absolute according to the standard method [7, 9-10]

2.1. Synthesis of N-phenylanathanyl acid

A 70.7 ml solution of 13.7 gram (0.1 mol) of anthranyl acid in benzene was prepared in a two-mouth flask equipped with a 200 ml reverse coolant and heated to boiling, then 0.05 mol of benzoic anhydride was added. White crystals of N-phenylanthranyl acid were formed. The reaction mixture was cooled and filtered, washed 2-3 times in benzene and dried [10].

2.2. 2-Phenylquinazoline-4-on synthesis (A-method)

In a 150 ml flask equipped with a reverse air cooler, 0.1 mol of N-phenylanthranyl acid and 0.8 mol of NH_4Cl were added. The reaction mixture was heated at 250–280 °C over the Wood alloy for 4–5 hours. At the end of the reaction time, the reaction mixture was cooled and dissolved in several parts using boiling water. The solutions were combined,

neutralized with NH_4OH to pH 7.8 and cooled. The precipitates formed were filtered and dried at room temperature [2-3, 9].

2.3. 2- Phenylxinazoline-4-on synthesis (B-method)

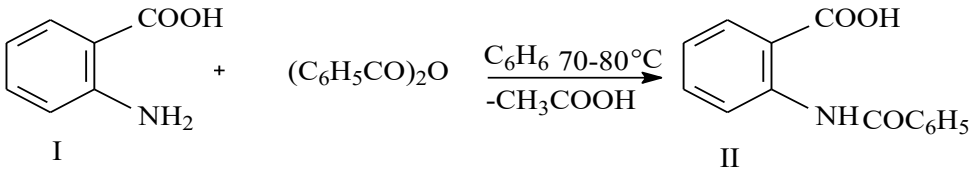
In a 100 ml flask equipped with a reverse air cooler, a mixture of 0.1 mol of benzamide with 0.1 mol of anthranil acid was added. The reaction mixture was heated at 250–280 °C for 4–5 h. Synthesis of 2-phenylquinazoline-4-tion (experiment is carried out in a tubular cabinet). A 150 ml flask equipped with a reverse air cooler was filled with 16 g (0.1 mol) of 2-phenylquinazoline-4-on, 0.1 mol of phosphorus (V) sulfide and 50 ml of absolute m-xylene and boiled at 140-150 °C for 2 hours [6, 9-10]. The reaction mixture was cooled; the precipitate was filtered and washed with m-xylene. Then 7ml 10% NaOH was treated.

2.4. General methylation method of 2-phenylquinazoline-4-thion

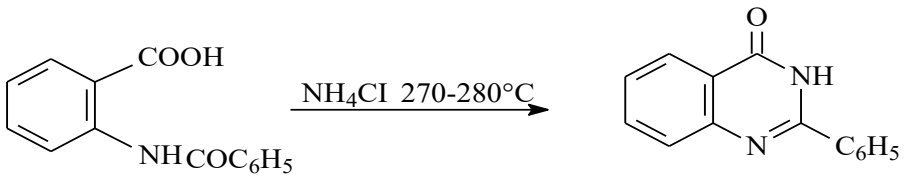
Equipped with a reverse cooler and mechanical agitator with calcium chloride tube, the volume was poured 150 ml of absolute solvent (ethanol, dioxane-1.4, acetonitrile, DMF) on top of the 0.01 mole 2-phenylxinazoline-4-tion into a three-mouth tube of 50 ml. In the mixture to the solution (suspension), 0,001 mole of NaH was added and mixed again for 30 minutes. 0.01 mole of methylation agent methyl iodide or dimethyl sulfate, 5ml of methyltosylates in the corresponding solution is added dripping to the solution the solution (suspension) of the formed salt [1, 7-8]. The reaction mixture was stirred at room temperature for 24 hours or heated in a water bath for 4 hours. At the end of the reaction time, it was cooled and 100 ml of cold water was added. The precipitate was filtered off. The percentage of isomer methyl products formed was determined using the N-PMR method [3-5].

3 Results and discussion

The results showed that methylation reactions occur with the formation of N^3- and S^4-methyl products, depending on the methylating agent, solvent and temperature used. It was found that the yield of methyl product on the N^3 atom with high polarity is high. In the 2nd position of the pyrimidine ring, when there was an electron acceptor phenyl group, the factors influencing the reaction direction was studied [6-7]. For this, 2-phenyl quinazoline-4-tion was synthesized. According to the first method, 2-phenylquinazoline-4-on (III) was first obtained by the action of NH_4Cl on N-phenylanthranyl acid (II) through the reaction of anthranil acid (I) with benzoic anhydride:

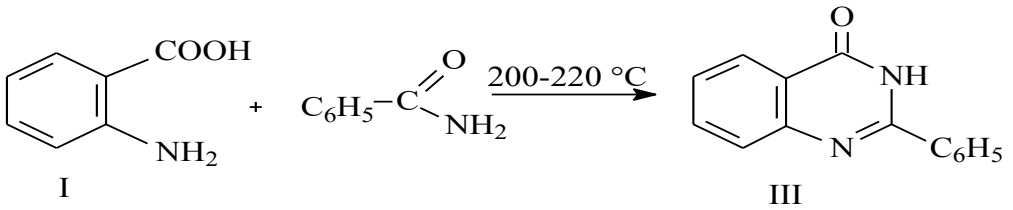


I II



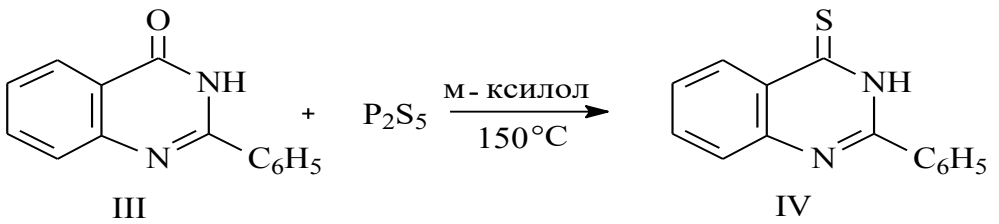
II III

The second method was obtained by heating a mixture of anthranilic acid and benzamide.



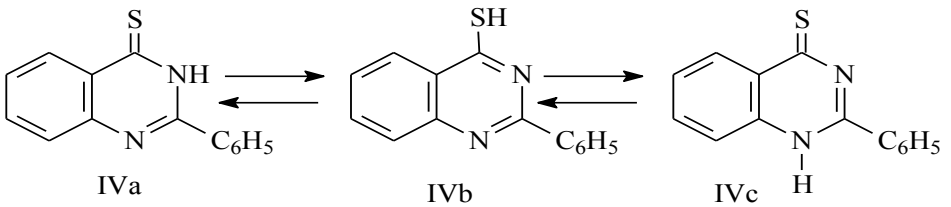
I III

2-phenylquinazoline-4-tion was synthesized with 62.5% yield by heating 2-henylquinazoline-4-on with phosphorus (V) sulfide.



III IV

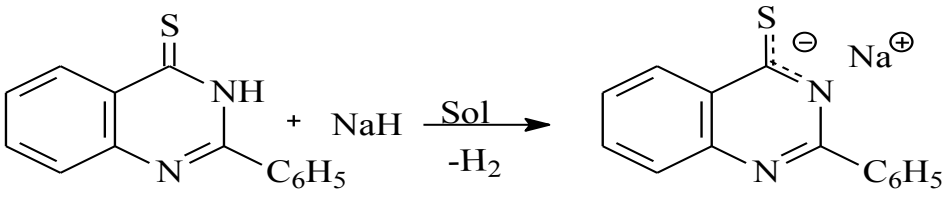
It was found that the 2-phenylquinazoline-4-tion (IV) molecule could exist in three different tautomeric states:



IVa IVb IVc

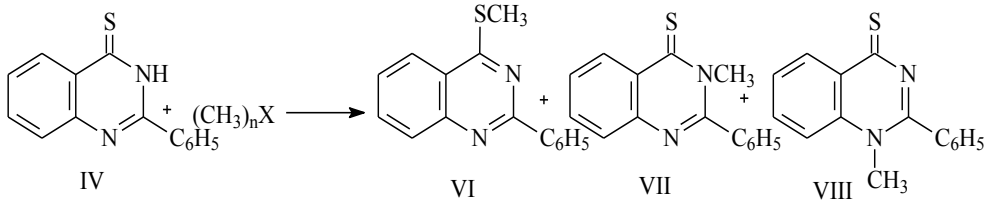
The study of the structure of the 2-phenylquinazoline-4-thionic anion (V) and its neutral molecule showed that the delocalization of a negative charge in a ring in crystalline salts

(sodium, potassium) was accompanied by the distribution of electron density in the S ------ C^4 ----- N^3 fragment. The N1 nitrogen atom had no protons; it did not participate in the N^1 process. Therefore, in the alkylation reaction of 2-phenylquinazoline-4-thion, the formation of the anion S ------ C^4 ----- N^3 was occurred:



IV V

In the alkylation reactions of 2-phenylquinazoline-4-thion, there was a possibility of formation of three different phenyl products:



IV VI VII VIII

n=1, X=I, OTs

n=2, X=SO_4

Only N-phenyl product (VI) was formed when the polar proton solvent was alkylated by heating in a water bath with methyl iodide in ethanol. Prolongation of the reaction time leaded to the formation of a second isomeric product (VII). A slight increase in phenyl N^3-product (VII) yield was noted when dimethyl sulfate and methylfolate were used as methylation agents. In non-polar proton-free solvent DMF and dipolar proton-free solvent acetonitrile, only N-methyl product (VII) was formed because of the reaction. An increase in the polarity of the solvent and the "hardness" of the methylation agent leads to an increase in the yield of N^3 products. For example, methylation with methyl iodide in DMFA resulted in the formation of only N^3-methyl product, while the use of dimethyl sulfate and methylfolate increased the yield of N^3-product. The formation of N^1-methyl product (VIII) as a result of the reaction was observed in none of cases (Table 1).

Table 1. Methylation of 2-Phenylxinazoline-4-thionine in various solvents.

#	Name of methylated substance	Methylation agent	Solvent	Tempera-ture °C	Duration, hour	N^3/S^4, %
1	2-phenyl-xinazoline-4-tion	CH_3I	ethanol	20-25	24	S^4-100
2	2-phenyl-xinazoline-4-tion	CH_3I	ethanol	80-90	4	S^4-100
3	2-phenyl-xinazoline-4-tion	$(CH_3)_2SO_4$	ethanol	20-25	24	N^3- S^4-99
4	2-phenyl-xinazoline-4-tion	$(CH_3)_2SO_4$	ethanol	80-90	4	N^3-19 S^4-81
5	2-phenyl-xinazoline-4-tion	CH_3OTs	ethanol	20-25	24	N^3-4 S^4-96
6	2-phenyl-xinazoline-4-tion	CH_3OTs	ethanol	80-90	4	N^3-38 S^4-81
7	2-phenyl-xinazoline-4-tion	CH_3I	Acetonitrile	20-25	24	S^4-100
8	2-phenyl-xinazoline-4-tion	CH_3I	Acetonitrile	80-90	4	S^4-100
9	2-phenyl-xinazoline-4-tion	$(CH_3)_2SO_4$	Acetonitrile	20-25	24	S^4-100
10	2-phenyl-xinazoline-4-tion	$(CH_3)_2SO_4$	Acetonitrile	80-90	4	S^4-100
11	2-phenyl-xinazoline-4-tion	CH_3OTs	Acetonitrile	20-25	24	S^4-100
12	2-phenyl-xinazoline-4-tion	CH_3OTs	Acetonitrile	80-90	4	S^4-100
13	2-phenyl-xinazoline-4-tion	CH_3I	DMF	20-25	24	N^3-6 S^4-94
14	2-phenyl-xinazoline-4-tion	CH_3I	DMF	80-90	4	N^3-20 S^4-80
15	2-phenyl-xinazoline-4-tion	$(CH_3)_2SO_4$	DMF	20-25	24	N^3-17 S^4-83
16	2-phenyl-xinazoline-4-tion	$(CH_3)_2SO_4$	DMF	80-90	4	N^3-26 S^4-74
17	2-phenyl-xinazoline-4-tion	CH_3OTs	DMF	20-25	24	N^3-28 S^4-72
18	2-phenyl-xinazoline-4-tion	CH_3OTs	DMF	80-90	4	N^3-35 S^4-65
19	2-phenyl-xinazoline-4-tion	CH_3I	Dioxane-1.4	20-25	24	S^4-100
20	2-phenyl-xinazoline-4-tion	CH_3I	Dioxane-1.4	80-90	4	S^4-100
21	2-phenyl-xinazoline-4-tion	$(CH_3)_2SO_4$	Dioxane-1.4	20-25	24	S^4-100
22	2-phenyl-xinazoline-4-tion	$(CH_3)_2SO_4$	Dioxane-1.4	80-90	4	S^4-100
23	2-phenyl-xinazoline-4-tion	CH_3OTs	Dioxane-1.4	20-25	24	S^4-100
24	2-phenyl-xinazoline-4-tion	CH_3OTs	Dioxane-1.4	80-90	4	S^4-100

The results of the experiment showed that an increase in the polarity of the solvent shortens the reaction time, as well as leads to a significant increase in the yield of N^3-alkyl product. It was found that the polarity of the reaction center had a major effect on the direction of the reaction. The IR spectrum of the structure of the 2-phenylquinazoline-4-tion neutral molecule and its salts was determined. The percentage content of isomeric products formed in methylation reactions was determined by obtaining their N-PMR spectra. The substances were dissolved in chloroform, hydrogen chloride gas was transferred from the solution and 2-phenylxinazoline-4-tion hydrochloride, and 2.3-imethylfenylxinazoline-4-tion hydrochlorides were formed. It was found that this drug had an antigelement property to gelmentosis and fascioliosis in domestic animals, such as young lambs

4 Conclusions

In non-polar proton-free solvent DMF and dipolar proton-free solvent acetonitrile, only N^3-methyl product was formed as a result of the reaction, although the increase in temperature leads to an increase in product yield, but the reaction yield is relatively low when converted to dioxane. When tested in young lambs, the drug was found to have anti-helminthic and anti-fascial properties. An increase in the polarity of the solvent and the "hardness" of the methylation agent leads to an increase in the yield of N^3 products. For example, methylation with methyl iodide in DMF resulted in the formation of only N^3-methyl product, while the use of dimethyl sulfate and methylfolate increased the yield of N^3-product. The formation of N^1-methyl product (VIII) as a result of the reaction was observed in none of cases

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