# Synthesis of 2-methylquinazoline-4-thione with the purpose of alkylation of 3-propyl 2-methylquinazoline-4-thione with alkylating agents

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# Synthesis of 2-Methylquinazoline-4-Thione with the Purpose of Alkylation of 3-Propyl 2-Methylquinazoline-4-Thione with Alkylating Agents

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**Abstract.** In the given work, we present data on the alkylation of 2-methylquinazoline-4-thione. The anion of this compound, in contrast to abovementioned substances, exhibits an ambidentcharacter, that is negative charges in it is delocalized over the $S^4$-$C^4$-$N^3$ atoms. The anion of the compound is formed by the action of sodium hydride. The alkylation of 2-methylquinazoline-4-thione with propyl iodide in various solvents has been studied. It is shown that, depending on the nature of the alcating agent, solvent and temperature, the reaction happens in $C^4$, $N^3$, $S^4$ atom.

**Keywords:** synthesis, 2-methylquinazoline-4-thione, alkylation, propyl iodide, alkylating agent, solvent, temperature, anion, charge, sodium hydride, compounds, atom, negative charge, delocalization.

## INTRODUCTION

At the present time, the chemistry of heterocyclic compounds is rapidly developing, which is associated with the physiological properties of these compounds. Among them there are highly effective medicines, chemical agents for protecting plants from pests, diseases and weeds, chemical agents for protecting plants from ectozoic parasites. On their basis are created dyes, monomers, heat-resistant fibers, phytohormones and many other practically valuable substances. At the present time, more than 50% of publications on organic chemistry are related to the chemistry of heterocyclic compounds. Derivatives of quinazolin-4-one are one of the important classes of heterocyclic compounds.

A large number of medicinehave been created in recent years. More than 100 quinazoline derivatives have been proposed and used. There are several reviews on the chemistry of quinazoline and its benzo analogs, as well as naturally occurring quinazolin-4-ones, but they keep general character. The content of quinazolin-4-ones, which occupy a special place due to the possibility of tautomeric transformations and related reactions of nucleophilic and electrophilic substitution, is relatively small in the total volume of these publications [1].

Quinazoline derivatives have a broad spectrum of biological activity. Among them, drugs of anticholinesterase type of action, hypnotics and others have found their use. They are used in agriculture as fungicides, bactericides, etc. [2]. The quinazoline alkaloids deoxypeganine, peganine, and vazicinoneare used as medicines [3, 4].

It is known that the alkylation reaction strongly depends on the nature of the alkylating, alkylating agent, the effect of the environment, temperature, and other factors, for example, during methylation of the anions of 2- substituted quinazolin-4-ones, multiple reactivitycomes out, leading to the products of alkylation of this or that reaction center or by two heteroatoms.

We have previously studied the alkylation of 2-substituted (oxo, thioxo, selinoxo, amino, acylamino, etc.) quinazolin-4-ones [5-9].

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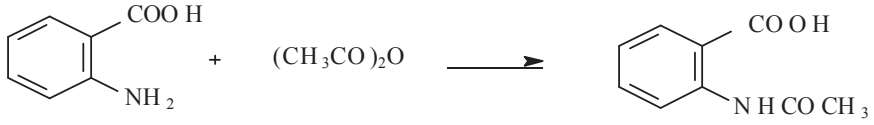
It was shown that in the case of2-oxo-, -aminoquinosolin-4-one, the reaction happens mainly with the N-3 atom. Alkylation of 2-thioxo-, -selenoquinazolin-4-one proceeds through a "softer" reaction center, that is an atom of sulfur.

**An Experimental Part. Method-A. Synthesis of N-Acetylanthranilic Acid.**

0.1 mole of anthranilic acid was dissolved in 70 ml of benzene. The solution was heated to boiling temperature in a water bath, then 0.05 mole of acetic anhydride was added by drops. There were formed white crystals. They were washed2-3 times with benzene, cooled, filtered and dried in an oven at 100°C for 1.5 hours.

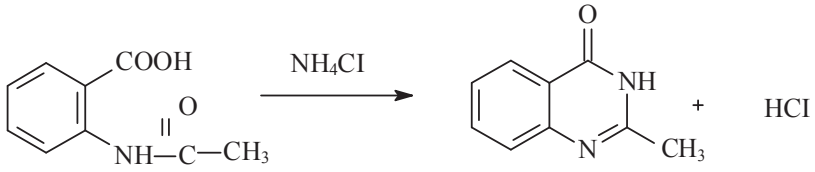
$R_f = 0.275$




**Synthesis of 2-Methylquinazolin-4-One.**

0.1 mole of N-acetylanthranilic acid was mixed with 0.8 mole of $NH_4Cl$, heated at 250-280°C for 4-5 hours using a sublimate condenser, cooled, dissolved by portions in the boiling water, the solutions were combined, neutralized with $NH_4OH$ to pH-8, cooled. The formed residual matterswere filtered off and dried at a room temperature.

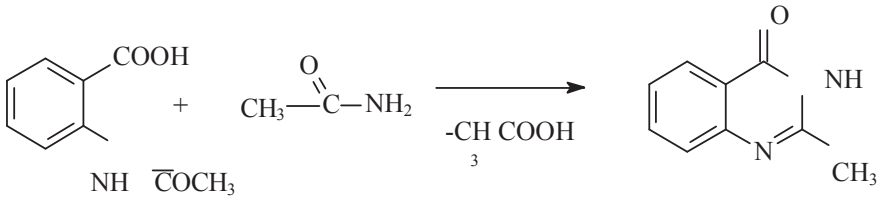
$R_f$=0,134




**Method-B. Synthesis of 2-methylquinazolin-4-one.**

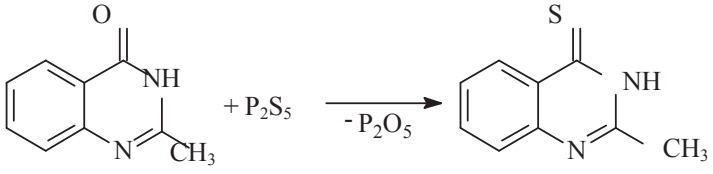
0.1 mole of anthranilic acid mixed with 0.1 mole of acetamidewas heated at 250-280 ° C for 4-5 hours using a sublimate condenser, cooled, filteredand dried.

$R_f$= 0,134




**Reaction of $P_2S_5$ with 2-Methylquinazoline-4-One.**

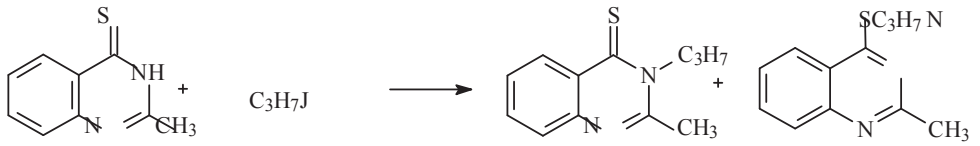
0.005 mole of 2-methylquinazoline-4-one (0.005 mole) $P_2S_5$ had been boiled for 2 hours in absolute m-xylene. The reaction mixture was filtered, the brakdown product was washed with m-xylene and treated with 7 ml of 10% NaOH. The residuewas filtered, washed with water and dried. It was recrystallized in hexane.



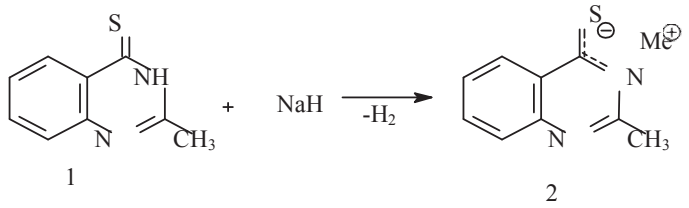

**Interaction of 2-Methylquinazoline-4-Thione with Propyl Iodide.**

0.05 mole of quinosoline-4-thione is dissolved in 50 ml of an absolute solvent (alcohol, dimethyl formamide, dimethyl sulfocxside, acetonitrile), 0.05 mole of NaHis added and shaken for 30 minutes, 1 mmole of propyl iodide is added to the resulting solution.

It was stirred for 24 hours or heated in a boiling water bath at 80-90°C for 3-4 hours through a sublimate condenser, the mixture was cooled and 50 ml of cold water was added, the risidue was filtered. T.of fluxion is 231°C



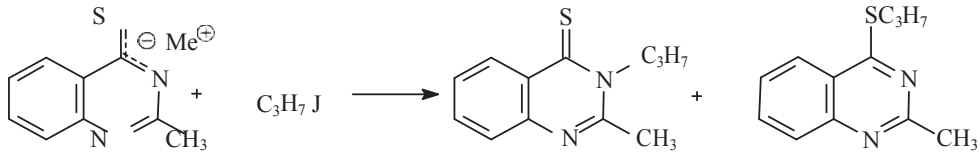

The anion of this compound, in contrast to the above shown substances, exhibits an ambidentcharacter, the negative charge in it is delocalized over the $S_4$-$N_3$ atoms. The anion of compound 1 (2) is formed by the influence of sodium hydride.




1 2

Me= Li, Na, K

Therefore, methylation of 2 can proceed at the nitrogen atom $N_3$, sulfur $S_4$. As a result, 2,3-dimethyl-3,4-dihydroquinazoline-4-thione (3), 4-thioxy-2-methylquinazoline (4) can be formed.




2 3 4

**TABLE 1.** Alkylation of 3-Propyl 2-Methylquinazoline-4-Thione.

| № | Name of alkylating matter | Alkylating agent | Solution | Temperature °C | time, hour | $N^3/S^4$, % |
|---|---|---|---|---|---|---|
| 1 | 2-methylquinazoline-4-thione | $C_3H_7I$ | ethanol | 20-25 | 24 | $S^4$-100 |
| 2 | 2-methylquinazoline-4-thione | $C_3H_7I$ | ethanol | 80-90 | 4 | $S^4$-100 |
| 3 | 2-methylquinazoline-4-thione | $C_3H_7I$ | dimethyl formamide | 20-25 | 24 | $S^4$-80 $N^3$-20 |
| 4 | 2-methylquinazoline-4-thione | $C_3H_7I$ | dimethyl formamide | 80-90 | 4 | $N^3$-19 $S^4$-81 |
| 5 | 2-methylquinazoline-4-thione | $C_3H_7I$ | dimethyl sulfoxside | 20-25 | 24 | $N^3$-40 $S^4$-60 |
| 6 | 2-methylquinazoline-4-thione | $C_3H_7I$ | dimethyl sulfoxside | 80-90 | 4 | $N^3$-38 $S^4$-62 |
| 7 | 2-methylquinazoline-4-thione | $C_3H_7I$ | acetonitrile | 20-25 | 24 | $S^4$-100 |
| 8 | 2-methylquinazoline-4-thione | $C_3H_7I$ | acetonitrile | 80-90 | 4 | $S^4$-100 |

## DISCUSSION OF OBTAINED RESULTS

It is known that the direction of the alkylating reaction is significantly influenced by the nature of the alkylating agent. In order to clarify the course of the reaction, depending on the structure of the alkylating agent, we used as "soft" iodide propyl.

To reveal the effect of temperature on the ratio of isomers, alkylation was carried out at 20°C and 80-90 ° C.

The nature of the solvent has a significant effect on the isomer ratio; therefore, we carried out the reaction in a protic solvent it is alcohol, aprotic dioxane, non-polar aprotic polar acetonitrile, and aprotic dipolar solventsdimethylformamide and dimethylsulfoxide.

Alkylation with propyl iodide, alcohol at 20°C, the reaction occurs completely S4, because ethyl alcohol is a protic solvent showing N3 of the nitrogen atom.

When alkylated with propyl iodide in dimethylformamide and dimethylsulfoxidealso at 20°C and at 80-90°C a mixture of product $N^3$ and $S^4$ is formed. Alkylation of 1 with propyl iodide in alcohol and acetonitrile at 80-90°C gives compound 4 with big amount of coming out.

NMR $^1$H spectrum in a Unity-400 device (operating frequency 400 MHz, internal GMDC standard, δ-scale) TPA + $CD_3COOD$, TPA + $(CD_3)_2SO$, Py-$d_5$ - were obtained in solutions, and thin-layer chromatography (TLC) was tested on plates Sorbfil (Russia) and Whatman® UV-254 (Germany),

PMR. 02.32 s (3H); 5.14 s (2H); 7.07-7.13 m (2H); 7.25-7.31 m (2H); 7.46 d (J = 8.1; 7.1; 1.2 Hz, 1H); 7.61 d(J = 8.3; 1.1 Hz; 1H); 7.71 d(J = 8.4; 7.1; 1.6 Hz; 1H); 8.18 d (J = 8.0; 1.5 Hz; 1H); 8.33 s (1H)

Thin layer chromatography (TLC) was tested on Sorbfil (Russia) and Whatman® UV-254 (Germany) plates.

## CONCLUSION

Thus, we have shown that the direction of the reaction of 2-methylquinazoline-4-thione depends on the nature of the alkylating agent, solvent and temperature regime; this is due to the formation of its ambident anion under the action of alkali metals.

Therefore, alkylation of 2 can occur at the nitrogen atom $N^3$, sulfur $S^4$. As a result, there can be formed 3- propyl 2-methylquinazoline-4-thione, 4-propylthioxy-2-methylquinazoline, or their mixtures.

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