SYNTHESIS AND ANTI-TUBERCULOSIS PROPERTIES OF 5`-NITROTHIAZOLYL-2-AMIDES OF 1-R-2-OXO-4-HYDROXYQUINOLINE-3-CARBOXYLIC ACIDS

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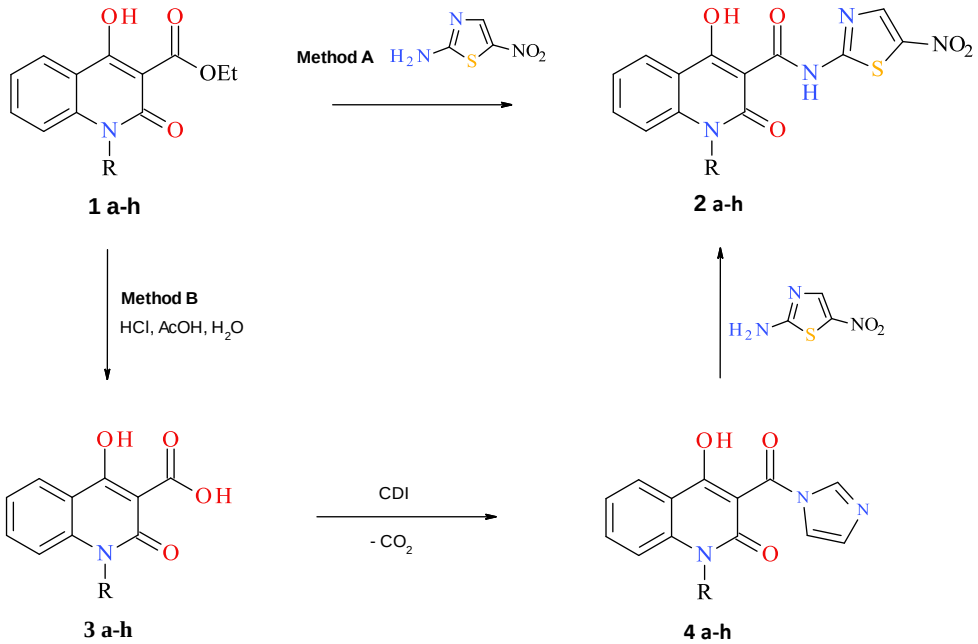
Introduction. One of the most pressing socio-political and medical problems of society at present is tuberculosis (TB)**.** According to the World Health Organization about 1.5 million people died from tuberculosis in 2018. Tuberculosis is one of the 10 main causes of death and the main cause from one infectious agent. About a quarter of the world's population has latent tuberculosis.

The high incidence of TB in many countries due primarily socio-economic and health factors, including high levels of poverty and, consequently, malnutrition, lack of medical facilities and qualified medical staff, HIV/AIDS and the spread of resistance to antimycobacterial drugs forms of mycobacteria tuberculosis (MBT).

That is why the problem of finding anti-tuberculosis drugs has become so urgent and obvious today that it does not require any special justification. Interesting objects of study in this regard are thiazole and quinoline derivatives. Particular attention is drawn to the ability of some of them, such as alkylamides of thiazolyl-2-oxamic acid to actively inhibit Mycobacterium tuberculosis. On the other hand, numerous amidated derivatives of 2-oxo-4-hydroxyquinoline-3-carboxylic acids have the same effect.

Aim. The aim of this work is to synthesize the nitroso derivatives of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acid thiazolyl-2-amides and to study their antimycobacterial properties.

Materials and methods. The initial substances for the synthesis of the target compounds are 5-nitrothiazolyl-2-amine and ethyl esters of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids. Method A: Amidation of 1-R-2-oxo-3-ethoxycarbonyl-4-hydroxyquinolines (1) by thermolysis. However, the compounds thus obtained have a brown color, which cannot be lost even after repeated crystallization. Therefore, the synthesis was also carried out according to method B, which is a three-stage synthetic scheme that provides for acylation under milder conditions. The first stage of the synthesis of the conversion to the corresponding acids 3 was carried out in a solution of hydrochloric acid in acetic anhydride. Subsequent activation of the acid component of 3 N, N'-carbonyldiimidazole (CDI) compounds allowed the target 5'-nitrothiazolyl-2-amides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids via intermediate acylimidazoles 4 with preparatively high outputs and a much higher degree of purity:



1 a-h **2 a-h** **3 a-h** **4 a-h**

1-4: **a** R = H; **b** R = CH_3; **c** R = C_2H_5; **d** C_3H_7; **e** R = C_4H_9; **f** R = *i*-C_4H_9; **g** R = C_5H_{11}; **h** R = C_6H_{13}

The anti-tuberculosis properties of synthesized substances were performed at the National Institute of Allergic and Infectious Diseases of the United States under the TAACF (Tuberculosis Antimicrobial Facility) & Coordinating Program.

Results and discussion. 5-nitroso-thiazolyl-2-amides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids were synthesized and their antituberculosis activity was studied.

Conclusions. During investigation of antituberculosis activity two substances showed high level of antimicrobial action against Micobacterium tuberculosis – compounds 2a and 2h.

TRANSFORMATION OF BENZYLIC ACID DERIVATIVES: KNOWN AND UNEXPECTED OUTCOMES

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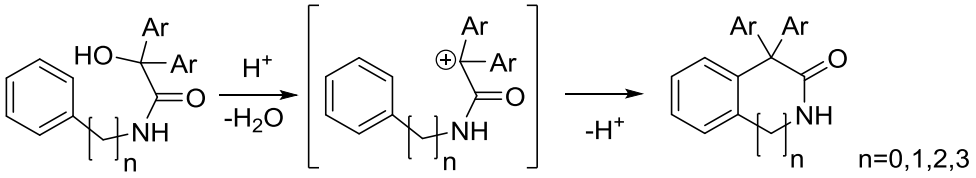
Introduction. So-called acidochromic condensation of diarylglycolic acids amides have been in focus of scientists of National University of Pharmacy for a long time. Some of the results turned out to be unusual and this fact stimulated us to give a brief overview of known transformations of benzylic acid and its derivatives.

Aim. To make a short overview of reactions of benzylic acid derivatives and to investigate the issue of how conditions applied to these interactions (catalyst nature, temperature mode, duration etc.) affect their outcome.

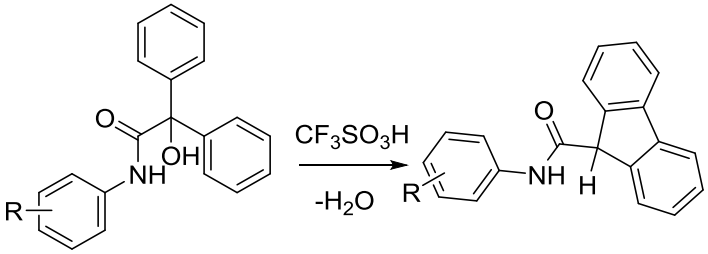
Materials and methods. Literature data dedicated to transformations of benzylic acid derivatives; systematization of the information found.

Results and discussion. Analysis of literature data revealed many possible ways of how benzylic acid derivatives can be transformed. Acidochromic condensation is one of possible reactions of benzylic acid amides. It results into benzolactames with various size of lactame cycle (Scheme 1). The latter display wide range of pharmacological activities.



Scheme 1

When CF_3SO_3H (TFSA) is used as a catalyst condensation proceeds giving another product – fluorene-9-carboxylic acid amides (Scheme 2).



Scheme 2

TFSA catalyzed transformation of (□-methoxycarbonyl)diphenylmethanol at 50°C also leads to a fluorene-9-carboxylic acid derivative, namely its methyl ester. When the reaction is conducted in a more concentrated solution (TFSA, 100 equiv, 50°C) the products are abovementioned methyl ester (41%) and the fluorene dimer (37%) (Scheme 3).