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SYNTHESIS OF 4-HYDROXIBENZOIC ACID DERIVATIVES WITH AMINO ACIDS AND THEIR POTENTIAL PHARMACOLOGICAL PROPERTIES

Abstract. Derivatives of 4-hydroxybenzoic acid with glycine and 4-aminobutanoic acid have been synthesized. To increase the solubility of substances, salts with potassium were poured. It is shown that the synthesized substances have biological activity. Synthesized substances were studied using computer programs Gausview, Passonline, which showed the activity of molecules and biological activity. Experiments will be conducted to confirm the activity.

Keywords: 4-hydroxybenzoic acid, glycine, 4-aminobutanoic acid, salt, synthesis, biological activity.

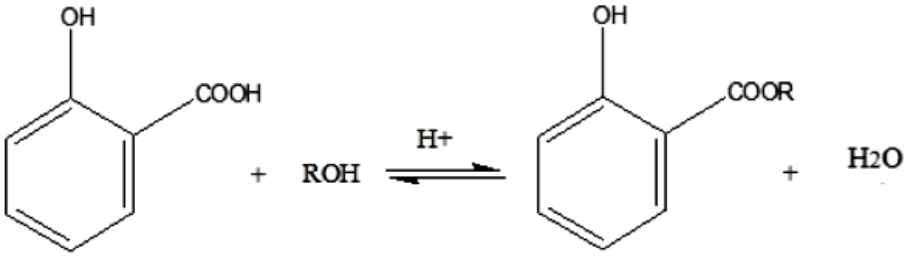
Introduction

Today, the synthesis of drugs is one of the current problems of chemistry. Since the middle of the 19th century, salicylic acid (SA) has been isolated from salicin. Aspirin was developed and patented by Bayer specialists during the synthesis of its compounds in order to study the biologically active properties of SA. Although aspirin was synthesized and used for over 150 years, it is still used as one of the most widely used pharmacological drugs in the world. Acetylsalicylic acid (ASA) has specific biological properties (anti-inflammatory, antipyretic, antithrombotic, analgesic). In the body ASA inhibits cyclooxygenase and irreversibly inhibits the metabolic pathway of cyclooxygenase (COX-1 and COX-2) of arachidonic acid, i.e. it stops the synthesis of several prostaglandins [1]. Usually the origin of the term aspirin is associated with hyperthermic properties, from the ancient Greek "pyro" – fire. However, there is another idea, namely, that salicylic acid was first isolated by C. Lovig from a plant called Spirae Ulmaria. In this case, the letter "a" (acylation) was added before the word "spir" and then the suffix "in" was added to make it sound better [2]. According to recent data, SA products are synthesized in the body and act as a bioregulator and have a protective function, which, in turn, means that the role of SA in human and animal pathophysiology should be reviewed [3; 4].

In this regard, one of the urgent tasks is the synthesis of new substances and their derivatives based on oxybenzoic acids, creation of new methods of synthesis and development of existing ones. It is also important to target therapeutic agents based on oxybenzoic acids with low toxic properties and high biologically active properties.

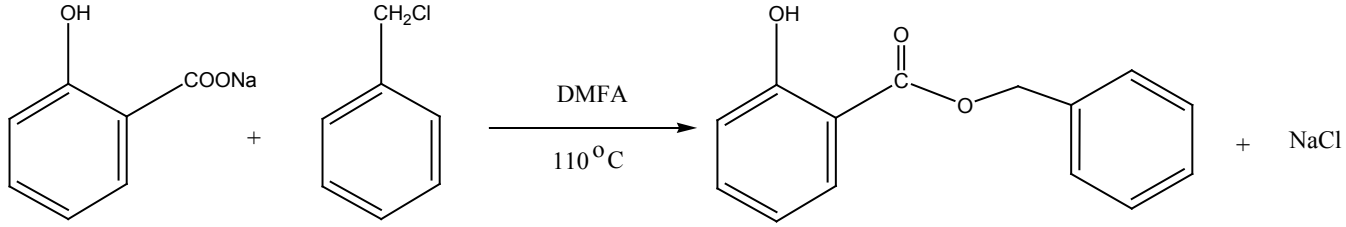
Materials and Methods

It is known that SA derivatives are obtained by different methods, one of which is the production of esters, i.e., alkyl ethers, carried out in the presence of catalytic sulfuric acid with the corresponding alcohols:



The duration of the esterification reaction according to the classical method is 5–12 hours, and the yield of the reaction is from 55% to 80%, depending on the ortho-, meta-, and para-states of the -OH and -COOH groups, as well as the molecular weight of the alcohol [5; 6].

However, another way to obtain esters is the application of silver and sodium salts to halogen derivatives, for example, the interaction of sodium salicylate and benzyl chloride produces benzylsalicylate. In this reaction dimethylformamide 110^0C the yield was 79% when conducted in the environment [7; 8].

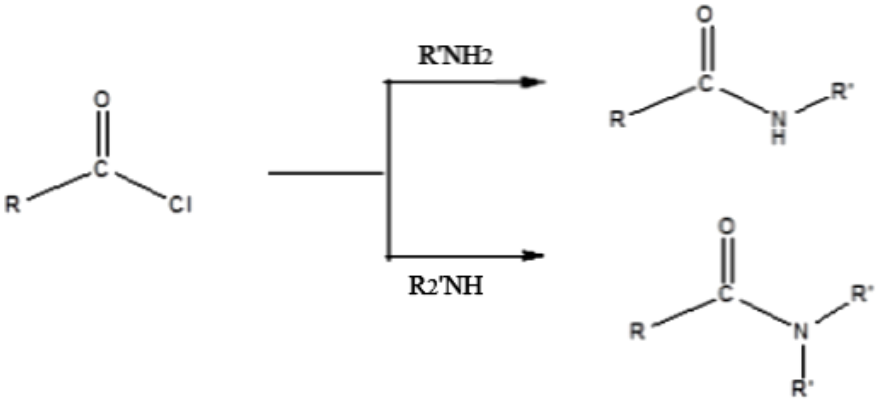


SA amides and its derivatives has a variety of pharmacological activities: antipyretic, sedative, anti-vibration, and high diaphoretic activity [7; 8].

Therefore, intermediate derivatives of SA are very important because they facilitate the synthesis of substances of a given composition. In our opinion, carbonic acid chlorohydride is an intermediate for the synthesis of the corresponding amides because it forms an amide corresponding to ammonia. The reaction requires a lot of ammonia and additionally hydrochloric acid. In general, the reaction scheme can be written as follows:

$$RC(O)Cl + 2NH_3 \rightarrow RC(O)NH_2 + NH_4Cl$$

However, amides are also obtained by the interaction of amines with chlorohydrides in the following reaction:



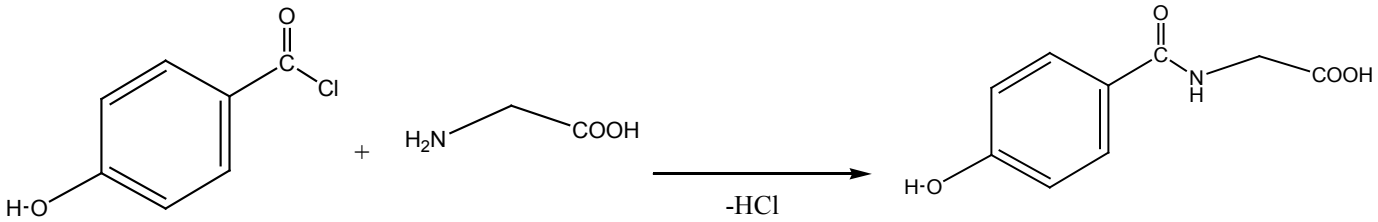
Synthesis of preservative derivatives of SA nitrogen compounds is a promising area of search for new effective and non-toxic long-acting drugs. The role of amino acids in the body is very broad; complex substances such as amino acids, peptides and proteins are structural components of enzymes, coenzymes, hormones and receptors [9; 10]. Amine derivatives exhibit a variety of biological activities, including psychotropic, analgesic, anti-inflammatory and others. Today in practice there is increasing interest in

γ-aminobutyric acid (GABA) and its derivatives, many drugs based on GABA have neuroprotective activity [11; 12].

Therefore, the synthesis of hydroxybenzoic acid derivatives with amino acids is relevant. For this purpose, a 4-hydroxybenzoic acid-based SA derivative was synthesized and their potassium salts were obtained to increase the water solubility of the synthesized substance.

Synthesis of N-(4-hydroxybenzoyl)glycine

The obtained 4-hydroxybenzoyl chloride is introduced dropwise for 1.5–2 h with a glycine solution (5.00 g g glycine in 28.30 ml water). The mixture is cooled, then stirred for another 1.5 hours, keeping the pH > 7. The resulting mixture is poured on ice. Hydrochloric acid is added to pH = 5. The resulting precipitate is filtered and dried. The yield is 76%. Tm = 220–223 °C.



Synthesis of N-(4-acetoxybenzoyl)glycine

A stirrer, reflux condenser and thermometer are placed in a three-neck flask.10.00 g (72.40 mmol) of 4-oxybenzoylglycine, 25.00 ml of acetic acid and 0.20 ml of sulfuric acid. To the 6.8 mL mixture was added (72.40 mmol) acetic anhydride and stirred at 45 °C for 2 hours. The precipitated crystals are recrystallized with isopropanol, filtered and dried. The yield is 73%. Tm = 194–197 °C.

Synthesis of 4-[(N-4-acetoxybenzoyl)amino] butanoic acid

N-(4-acetoxybenzoyl) is obtained as glycine. The yield of the reaction is 76%. Tm = 195–197 °C.

Potassium salt of N-(4-acetoxybenzoyl)glycine

4.6 g (100 mmol) of potassium ethylate (potassium metal treated with absolute ethanol), 100.00 g of benzene and 2.70 g (100 mmol) of N-(4-acetoxybenzoyl)glycine in a three-neck flask with stirrer, reverse cooler and thermometer are added. The mixture in the flask is stirred at 100 °C for 30 minutes. After cooling the mixture is filtered, washed with a slightly alkaline alcohol solution and dried. The resulting substance is a white crystal. The yield is 72%. Tm = 203–205 °C.

Potassium salt of 4- [N-(4-acetoxybenzoyl) amino]butanoic acid

The yield of the reaction is 78%. Tm = 235 – – 237 °C.

Conclusion

Some quantum-chemical properties of substances were studied. The results of the studies show complex interactions of functional groups in the molecules of substances. Based on the structure of the obtained substances, it can be concluded that they can form complex compounds. The structure of the obtained 4-hydroxybenzoic acid derivatives was confirmed by IR, H^1NMR, C^{13}NMR spectroscopy, the physical and chemical properties of compounds were studied [13; 14]. The PASS Online program was used to predict the biological activity of the synthesized substances. From the prediction follows the need for preclinical studies to confirm the pharmacological properties of the substances obtained [15; 16].

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