Technologies of Acylation of Hydroxyanthraquinones

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Abstract—In review the generalized data about different methods of synthesis of biological activity acylated hydroxyanthraquinones is presented. The basic regularity of a synthesis is analyzed. Action of temperature, pH, solubility, catalysts and other factors on a reaction product yield is revealed.

Keywords—Aminoacidic acylation, hydroxyanthraquinones, nucleophile exchange, physiologically active substances.

I. INTRODUCTION

Among high-performance low-toxicity medicine preparations, especially, preparations of selective action, an important place is occupied by the derivatives of anthraquinone. This is well proven in the literature on biological activity of anthracene-containing plants, natural anthraquinones, their synthetic analogues and phytopreparations, and it should be noted that synthetic analogues have wider spectrum of biological activity.

One of the most perspective directions of chemical modification of hydroxyanthraquinones is acylation reaction.

II. RESULTS AND DISCUSSION

The process of acylation of hydroxyanthraquinones enhances stability of aromatic system against oxidation, protects hydroxyl groups from further transformations thereby reducing the number of by-products, increases solvability of compounds, which is important for the choice of conditions of biological tests of any compounds weakly soluble or insoluble in water and physiological solution.

Hydroxyanthraquinones are acylated by aliphatic and aromatic aldehydes, ketones, acids, anhydrides. An important role plays reducing acylation by acetic anhydride or benzoil chloride in the dioxane solution in the presence of zinc dust. Acylation reactions may be carried out selectively in one of two α-, hydroxy-, in α-hydroxy- in the presence of β-hydroxy and vice versa, in pyridine [see in Fig. 1].

Reactions of acylation of chrysophanol, aloe-emodin, emodin, physcion, their amino- and halogen substitutes were carried out with acetic anhydride, benzenesulfochloride, alkyl halogenides in the presence of triethylamine. Aminoacidic acylation, hydroxyanthraquinones, nucleophile exchange, physiologically active substances.

It should be noted that in these reactions different reactivity of 4- and 5-OH-groups was most clearly pronounced, i.e. all experiments gave 2-mono- and di-substituted, with the yield of isomer in 4-OH group of chrysophanol and in 5-OH group of emodin and physcion up to 50%. The usage of pyridine in contrast to other alkaline agents enabled to get only monoacylated products after 4-5 hour heating, and if the temperature raised quickly, the products of complete acylation dominated in the reaction [1]. 2-methyl-4,5-bis-benzilaminoanthraquinone was detected in the reverse reaction of chrysophanol with benzamide and in the reaction of 2-methyl-4,5-diaminoanthraquinone with benzoil chloride [2].

Reactions of phosphorylation of hydroxyanthraquinones significantly widen possibilities of directed changes in biological activity of modified products as compared with traditional activity of P-organic substances and other classes of compounds. There are very few publications devoted to phosphorylation of anthraquinones, therefore we studied all parameters which could increase the yield of target products in interactions with various phosphorous syntons [3]. For example, phenols and thiophenols with PCl3, phosphorylation of chrysophanol gives yield of 40-47% [see in Fig. 2].

Chloroanhydrides of phosphorous acid are thermolabile; at temperatures above 70⁰ they give partial resinification in all solvents, therefore optimal solvents are tetrahydrofuran and dioxane in the presence of triethylamine [see in Fig. 3].
The sum of monosubstituted dialkylphosphates was divided into the mixtures of sorbents chromatin/Silicic acid 1:1 with the usage of eluents of opposite polarity. Dichloroanhydrides into the mixtures of sorbents chromatin/Silicic acid 1:1 with the main directions of fragmentation of anthraquinone molecules [see in Fig. 5]:

In spite of actively developing chemistry of isocyanates, we could not find publications on phosphorylation of hydroxyanthraquinones by isocyanato-phosphorous acids and carried out such reactions in the presence of triethylamine at temperatures varying from room temperature to 60°C [3] [see in Fig. 8].

We have worked out conditions of selective monophosphorylation in aromatic system, in carbonyl and

\[ \text{R} = \text{C}_{12} \text{H}_{25} \]

in the yield of target phosphates in the series C₁₋C₃ and → C₆H₅ → C₆H₅CH₃ [5].

The increase in temperature promotes increase in the yield, it should be noted that the best catalytic admixture in these reactions turned out to be one-valence copper [see in Fig. 6]:

[Fig. 3] Chloroanhydride P-acylation of anthraquinones

[Fig. 4] P-acylic dimerization of chrysophanol

[Fig. 5] MS-fragmentation of P-acylic anthraquinones

[Fig. 6] Thiophosphorylation of chrysophanol

[Fig. 7] Alkylthiophosphorylation of anthraquinones

[Fig. 8] Isocyanatophosphorylation of anthraquinones
hydroxyl groups of anthraquinone molecules, which considerably extend possibilities of targeted creation of biologically active compounds.

Most interesting in terms of biological activity are dimeric structures with phosphorous-containing fragments, isocyanates, alkylidithio-phosphonates and biophosphites. It was shown that the presence of anthraquinone fragment reduced toxicity of such derivatives [1], [7].

Interactions of chrysophanol, physcion and emodin with dimethyl- and trimethylphosphites go easily with acetyl derivatives [see in Fig. 9]:

Fig. 9 Alkoxyphosphorylation of anthrquinones

Salts of phosphorous monothio-acids with isomeric anions, i.e. anions constructed similar to thion-thiol ambident triads, may exhibit dual reactivity in alkylation and acylation reactions. For example, in the interactions with bromides of hydroxyanthraquinones high yield of exchange products of reaction of haloid atoms both in aminoacid residue can be also inserted through the exchange groups or their exchange for the aminoacid residue. The presented below [see in Fig. 10].

Fig. 10 Aminoacylation of hydroxyanthraquinones

III. CONCLUSION

The aforesaid enables to consider the acylation methods as a perspective for modifications of biologically active anthraquionones with a number of useful properties.

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REFERENCES