Technologies of Amination of Hydroxyanthraquinones

Dmitry Yu. Korulkin, Raissa A. Muzychkina

Abstract—In review the generalized data about different methods of synthesis of biological activity aminated 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—Amination, hydroxyanthraquinones, nucleophilic 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.

Modified natural anthraquinones are distinguished by a large structural variety, wide range of biological activity, and low toxicity. They possess astringent, purgative, anti-inflammatory, moderate antitumor, and bactericide effects; they readily react with ammonium or water ammonium with addition of sulfuric or boric acid into the reaction space, and amination in the solution of liquid ammonium also gives two types of reactions: exchange of OH groups and oxygen in carbonyl groups.

Amination of hydroxyanthraquinones in the presence of boric acid in the nitrogen environment reduces reaction time, whereas under these conditions amination reactions proceed with higher selectivity and at lower temperatures. Heating of purpurin with aniline and its hydrochloride causes exchange of β-OH-group [2].

Earlier the reaction of amination and N-alkylation of quinizarine and 1-hydroxyanthraquinone in presence of oxygen in air has been studied [3]-[5]. Heating of quinizarine in alcohol solution of DMFA gave 35% 2-dimethylamino-1,4-dihydroxyanthraquinone. Reduction of temperature to 25°C and 3-day mixture storage enabled to avoid by-products and increase output of 2-dimethylamino-1,4-dihydroxyanthraquinone [1].

Fig. 1 Different structures of leuco-2-dimethylaminoquinizarin

Differences in the reaction directions are caused by instability, even in the absence of air oxygen, of primary product of amine addition to quinizarin – leuco-2-dimethylaminoquinizarin, which can form several structures [see in Fig. 1].

We obtained amino-, alkyl- (aryl-) amino-derivatives of hydroxyanthraquinones by substitution of sulfo-groups at high temperatures and production of amino-derivatives in the interaction with alkyl amines. Substitution of haloid atoms by amino-group is the most widely-spread reaction of nucleophile substitution [1], [2], which is used in the synthesis of coloring agents of anthraquinone series.

Natural hydroxyanthraquinones with 1,8-dihydroxygroup readily react with ammonium or water ammonium with addition of sulfuric or boric acid into the reaction space, and amination in the solution of liquid ammonium also gives two types of reactions: exchange of OH groups and oxygen in carbonyl groups.

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Dmitry Yu. Korulkin is with the Department Chemistry and Chemical Technology, al-Farabi Kazakh National University, Almaty, CO 050038 Kazakhstan (corresponding author to provide phone: 727-387-1751; fax: 727-292-3731; e-mail: Dmitry.Korulkin@kaznu.kz).

Raissa A. Muzychkina is with the Department Chemistry and Chemical Technology, al-Farabi Kazakh National University, Almaty, CO 050038 Kazakhstan (e-mail: rmuz@mail.ru).
temperatures up to 80 °C ammonium alums or ammonium chloride in autoclave at 
and emodin were obtained in the interactions with 
α-vanadium pentaoxide, in this case amination mainly occurs in 
concentrated sulfuric acid in the presence of, for example, 
anthraquinone one can use interaction with hydroxylamine in 
intermolecular bonds. 

Comparison of reactions conditions and outputs of products 
in the reactions in 25% ammonium solution witnessed in favor 
of liquid ammonium: reactions with CH₃NH₂ gave higher 
quantitative output. Elongation of the carbon radical chain in 
alkyl amines and its isomerism reduce the output of reaction 
products. Aryl amination in the α-position proceeds easier 
than in the β-position. The best solvent turned out to be 
dioxane able to polarize bonds and form intra- and 
intermolecular bonds. 

In order to insert aminogroups directly in the nucleus of 
anthraquinone one can use interaction with hydroxylamine in 
concentrated sulfuric acid in the presence of, for example, 
vanadium pentaoxide, in this case amination mainly occurs in 
α-positions. Direct amination is also possible in the presence of 
oxygen. 

High outputs of amino-substituted chrysophanol, phyocin, 
rhein and emodin were obtained in the interactions with 
concentrated ammonium solution in the presence of iron-
ammonium alums or ammonium chloride in autoclave at 
temperatures up to 80°C, amination with liquid ammonium 
proceeded at lower temperatures up to 50°C [1], [6]. 

N-alkylation and amination can be realized through 
substitution of haloid atoms, hydroxygroups, sulfogroups in 
the presence of substances binding water and halogens [7]. 
These reactions are selective practically for all hydroxy-
antraquinones and their substitutes; the reaction may have 
peculiarities for spatially hindered hydroxyanthraquinones or 
in the presence of various substitutes in α- and β-positions. 

Moreover, we have noticed that for reactions in liquid 
ammonium the exchange rate of hydroxygroups and haloid 
atoms in the same positions was practically the same. The 
length of alkyl chain and the structure of alkyl and aryl-amines 
influenced the output of target products. 

In the interaction of emodin with aliphatic and heterocyclic 
amines (morpholine, piperidine, piperazine) we obtained the 
products of nucleophilic exchange of β-OH-group with the 
output from 69 to 84% [1], [8] [see in Fig. 4]. 

Fig. 2 Amination of natural hydroxyanthraquinones 

Fig. 3 Amination of modified hydroxyanthraquinones 

Fig. 4 Amination of emodin 

The same amines were used in the reactions with 6-
bromoemodin and 3-bromochrysophanol [see in Fig. 5]. 

Fig. 5 Amination of 6-bromoemodin and 3-bromochrysophanol 

Of all tested admixtures the presence of activated copper 
powder gave maximal output. Analogous derivatives (7-
dimethylaminomethyl-, 5-diethylaminomethyl-, 7-piperidinomethyl-, 7-morpholinomethyl) of emodin were obtained in the 
conditions of Mannich reactions [1]. 

Exchange Br → alkyl- (aryl-) amine is catalyzed by 
activated copper, however, in these conditions in liquid 
ammonium there is also parallel exchange of OH- groups. In 
contrast to the literature data we showed that in liquid 
ammonium imines for 1,8-dihydroxyanthraquinones are 
formed only for 9 C=O group. 

The amination reaction is activated by addition of H₂BO₃ 
or zinc chloride [9]. 

In polar solvents under all studied conditions reactions with 
RNH₂ went only through α-OH groups except the reaction of 
emodin with CH₃NH₂ in dioxane solution in the presence of 
H₂BO₃, in which a small amount of the product of N-
alkylation in β-OH group was extracted [10]. 

N-nucleophiles such as hydrazine, hydroxylamine, 
phenylhydrazine, aromatic amino-compounds and others can
be used in the reactions with participation of carbonyl groups of hydroxyanthraquinones. The presence of electronodonor substitutes in α-positions facilitates these reactions as compared to those with unsubstituted anthraquinone, where interaction is observed only after long-term heating during many hours.

Thus, heating of chrysazine (1,8-dihydroxyanthraquinone) and other hydroxyanthraquinones with similar location of ox groups in water-alkaline solution containing 2% of ammonium results in formation of corresponding 9-imines [11]. It should be noted that if heating occurs in the excess of N-nucleophile, interaction goes in both C=O groups [1], [12]. Such transformations are generally described on a Fig. 6.

![Fig. 6 Amination with participation of C=O groups of hydroxyanthraquinones](image)

A mixture of mono- and diphenylhydrazones with the output of 56.4-58.9% and 41.4-49.0 %, respectively, was obtained by melting hydroxyanthraquinones in the ampoule with the ratio of initial substances 1:2 or 10-hour heating in alcohol with addition of CH₃COOH and Fe-sawdust or FeCl₃ with the ratio 1:1:1.

Biological tests showed that replacement of C=O bond with C=N one gave higher anti-inflammatory and antitumor activity at small doses of compound injections. Oximes showed wider biological activity as compared with the corresponding hydrazones and phenyl hydrazones. As these compounds have the same anthraquinone part and their C=N bonds differ only by the character of the fragment bound to the nitrogen atom, it is possible to make a conclusion about the influence of this nitrogen-containing fragment on the character and intensity of biological effect. It was also shown that replacement of a labile hydrogen atom by the acyl remainder reduces activity of obtained compounds [13].

Comparing mass-spectra of N-alkyl- and N-aryl-derivatives one clearly sees the difference in the direction of fragmentation: first, a fragment with the mass of phenyl radical with a substitute splits off, then phenyl substitute decays further and characteristic fragments of NH and NH₂ split off, then the decay repeats characteristic directions for anthraquinone molecules. The common fragmentation scheme does not differ significantly. Stable fragments are the fragments of NH₂, NHR, hydrogen and M-15. However, comparing mass-spectra of isomeric N-alkyl(aryl) derivatives it is possible to identify corresponding α- and β-monosubstituted and the structure of radical carbon skeleton if it has the same length [see in Fig. 7].

![Fig. 7 Comparison of mass-spectral fragmentation of 1- or 3-aminosubstituted anthraquinones](image)

As it is seen from the comparison of the spectra, α-isomer has more stable M’283 and its fragmentation reminds that of chrysophanol with cleavage of m/z 29 (NCH₃) and formation of a stable ion with mass 254 (chrysophanol), then follows cleavage of C=O groups and rearrangement of aromatic system typical of the most anthraquinone derivatives [see in Fig. 8].

![Fig. 8 Comparison of mass-spectral fragmentation of n- or iso-aminosubstituted anthraquinones](image)

Fig. 9 Mass-spectral fragmentation of 4,5-di-N-aminosubstituted anthraquinone

A characteristic splitting of CH₃ (M-15) groups is observed for tertiary butyl, whereas C₂H₅ (M-29) splits off from n-butyl. Both spectra have fragments with masses 306, 292, 220, 192-
189, which can correspond to splitting of M-C$_4$H$_9$, M-NHC$_2$H$_9$ according to Fig. 9.

Studying biological activity of anthraquinones with amino-, alkyl- and arylamino-substitutes chemists determined the influence of the length of carbon chain and its structure in the alkylamino-fragment on the intensity and selectivity of antitumor effect and discovered that location of the same fragments in α- or β-sites especially strongly affects antioxidant activity [1], [13], [14].

Reactions with urea and thiourea derivatives were studied in three directions: for OH- and C=O groups with splitting of water and splitting of HBr in α- and β- positions of the corresponding derivatives. As a catalytic admixture we used activated copper and carried out Br exchange with the output ranging from 73 to 93.5% depending on the halogen position. Heating ureido-, (phenyl) thioureido- derivatives with zinc activated copper and carried out Br exchange with the output corresponding derivatives. As a catalytic admixture we used water and splitting of HBr in three antioxidant activity [1], [13], [14].

Films in alkylamino-fragment on the intensity and selectivity of influence of the length of carbon chain and its structure in the alkyl- and arylamino-substitutes chemists determined the according to Fig. 9.

H$_2$S[e]- pyrimidinedions-2,7 (3H)) [see in Fig. 12].

To obtain pyrimidonoanthrones we used two tautomeric forms and showed that exchange of OH-groups proceeded easier through emodin β-OH-group, addition of K$_2$CO$_3$ or H$_2$SO$_4$ increased the output by 12-19%, and in the presence of H$_2$BO$_3$ output of target products amounted to 79-82%. After 5-hour heating in glacial acetic acid two reactions for OH- and C=O groups with water splitting occurred but the output of the target product for C-O group was 20%, whereas the output for acetates was 48.5%.

Exchange of halogens in presence of activated copper powder, Cu$^+$ salts, K$_2$CO$_3$, and Ag$_2$O proceeded easier in β-positions [see in Fig. 11].

Pyrimidon- and thiopyrimidonanthrones were obtained in the medium of waterless dioxane with output higher than 65%.

These are interaction of 1-chloro- and 1-aminoanthraquinones with urea in phenol, interaction of 1-aminoanthraquinones with urethanes in the presence of zinc chloride, transformation of salts of formamidine derivatives of 1-alkylanthraquinones with ammonium acetate with formation of alkylpyrimidonoanthronmines, which after heating in alkaline medium turn into pyrimidoanthrones (7-H-benzo[e]-pyrimidinedions-2,7 (3H)) [see in Fig. 12].

Fig 10 Reactions with urea and thiourea derivatives

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Fig 11 Amination of halogenated anthraquinones with urea and thiourea derivatives

Comparative analysis of our data on biological activity with the initial molecules of hydroxyanthraquinones enabled us to make some conclusions about the influence of ureal and thioureal fragments on the character of biological activity of such compounds. In particular, ureido- and thioureido-derivatives have high bactericide activity and analogues of pyrimidino-anthrones have high selective antitumor activity. Moreover, the presence of urea and thiourea fragment in α-, β-position or the side chain of hydroxyanthraquinones influences the character of antitumor effect [1], [11].

Thiourea derivatives are more toxic as compared to ureido-derivatives and more specific with respect to some microorganisms.

It is also necessary to note that replacement of hydroxyl-groups by alkyl- and aminogroups causes reduction in solubility of the compounds and, hence, difficulties in studying their biological activity.

III. CONCLUSION

The previously mentioned enables to consider the amination methods as a perspective for modifications of biologically active anthraquinones with a number of useful properties.

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