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Technologies of Amination of Hydroxyanthraquinones

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***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 participate in the processes of metabolism, respiration, division of cells, oxidative phosphorylation, complexation with DNA and RNA, and, perhaps, in other physiological processes of vital importance; they are parts of many medicines of the plant origin.

Besides medicinal preparations, the anthraquinones have found application as dyes, pigments, luminophores, analytical reagents, chemical means for plant protection, and so on.

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

II. Results and Discussion

Alkyl- (aryl-) aminoderivatives of hydroxyanthraquinones can be obtained in the exchange reactions of hydroxygroups in the interactions with ammonium or its compounds in the presence of dehydrating substances, in the reaction of saturation with gaseous ammonium, easily dissociating ammonium salts in the presence of reduction agents (for example, hydrosulfate), etc. Alizarin in 20% ammonium water solution at 180^0C in the presence of NaOH turns into 1-amino-2-hydrooxy-anthraquinone, in 40-50% ammonium at 140^0C it turns into 2-amino-1-hydroxyanthraquinone-9-imin, i.e. two dehydrating reactions proceed (OH → NH_2; C=O → C=NH).

2-hydroxyanthraquinone heated with ammonium water solution turns into 1-amino-2-hydroxyanthraquinone with 70% output. Commercial importance is the method of producing hydroxyanthraquinones by substitution of sulfogroups 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 nucleophilic 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.

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 25^0C and 3-day mixture storage enabled to avoid by-products and increase output of 2-dimethylamino-1,4-dihydroxyanthraquinone [1].

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].

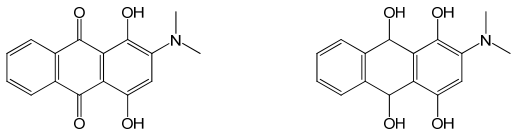

Fig. 1 Different structures of leuco-2-dimethylaminoquinizarin

We obtained amino-, alkyl- (aryl-) amino-derivatives in the ammonium medium in the presence of catalysts (NH_4C1, FAA, Cu, etc.), in liquid ammonium as well as in the reactions of OH- or Br exchange with alkyl- (aryl-) amines and NH_3 .

Addition of catalytic amounts of activated copper unlike other catalysts increases output by 18-25%.

The structures of most N-alkyl- (aryl-)-substituted were also determined by synthesis from amino-derivatives through reactions with RHal in the presence of substances binding HHal according to Figs. 2, 3.

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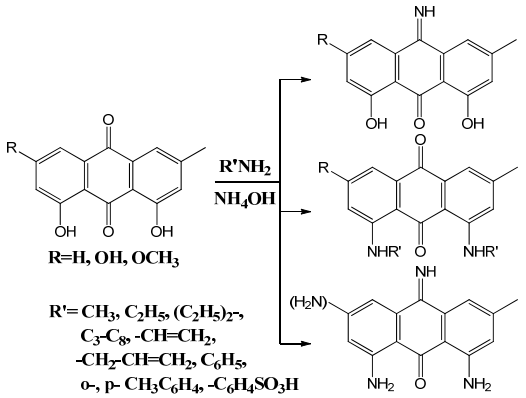

Fig. 2 Amination of natural hydroxyanthraquinones

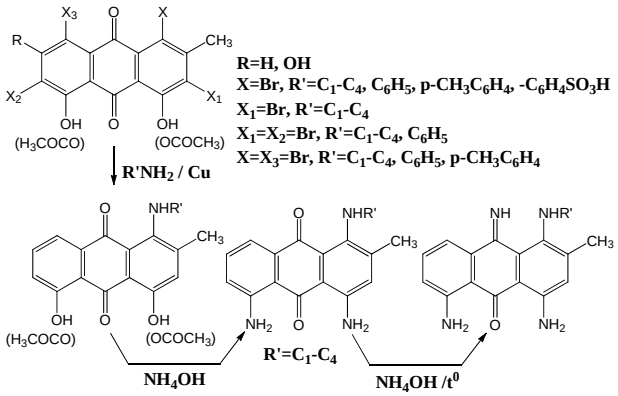

Fig. 3 Amination of modified hydroxyanthraquinones

Comparison of reactions conditions and outputs of products in the reactions in 25% ammonium solution witnessed in favor of liquid ammonium: reactions with CH_3NH_2 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, physcion, rhein and emodin were obtained in the interactions with concentrated ammonium solution in the presence of iron-ammonium alumens or ammonium chloride in autoclave at temperatures up to 80^0C, amination with liquid ammonium proceeded at lower temperatures up to 50^0C [1], [6].

N-alkylation and aramination 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-anthraquinones 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].

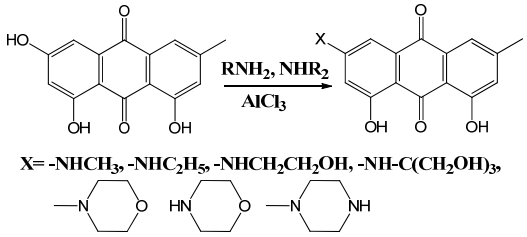

Fig. 4 Amination of emodin

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

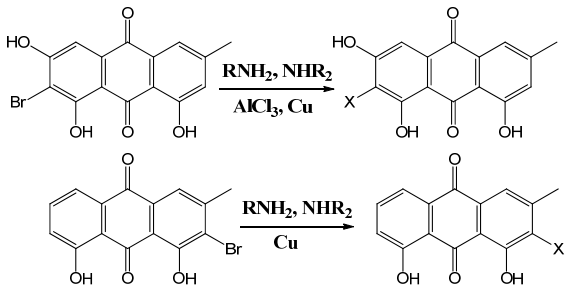

Fig. 5 Amination of 6-bromoemodin and 3-bromochrysophanol

Of all tested admixtures the presence of activated copper powder gave maximal output. Analogous derivatives (7-dimethylaminomethyl-, 5-diethylaminomethyl-, 7-piperidino-methyl-, 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 aramination reaction is activated by addition of H_3BO_3 or zinc chloride [9].

In polar solvents under all studied conditions reactions with RNH_2 went only through α-OH groups except the reaction of emodin with CH_3NH_2 in dioxane solution in the presence of H_3BO_3, 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.

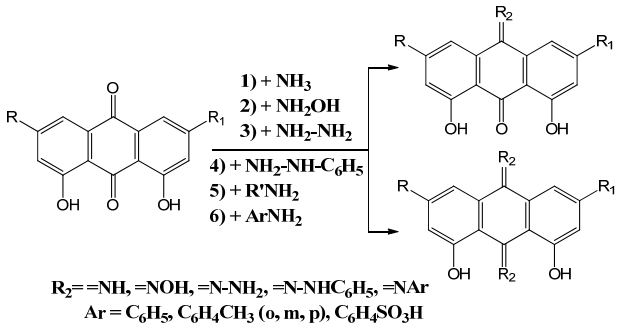

Fig. 6 Amination with participation of C=O groups of hydroxyanthraquinones

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 CH_3COOH and Fe-sawdust or $FeC1_3$ 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. Oxims 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 NH_2 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 NH_2, 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].

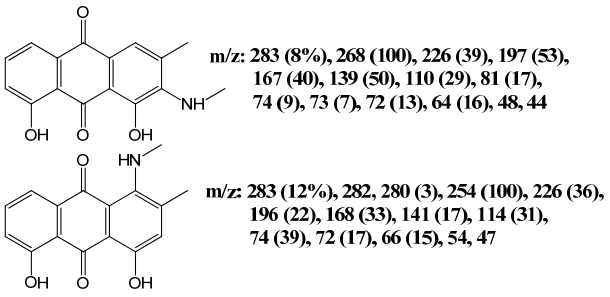

Fig. 7 Comparison of mass-spectral fragmentation of 1- or 3-aminosubstituted anthraquinones

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 (NCH_3) 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].

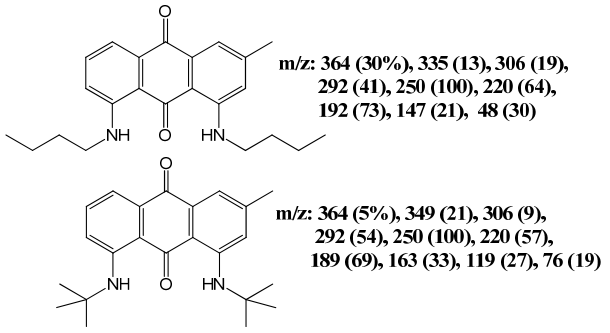

Fig. 8 Comparison of mass-spectral fragmentation of n- or iso-aminosubstituted anthraquinones

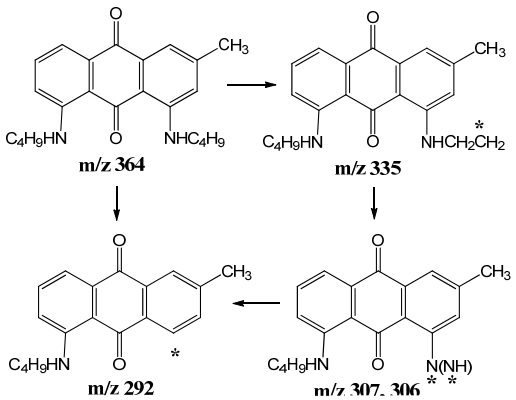

Fig. 9 Mass-spectral fragmentation of 4,5-di-N-aminosubstituted anthraquinone

A characteristic splitting of CH_3 (M-15) groups is observed for tertiary butyl, whereas C_2H_5 (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_4H_9, M-NHC_4H_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 chloride enabled to choose conditions for obtaining analogues of pirimidine-anthrones with high outputs [see in Fig. 10].

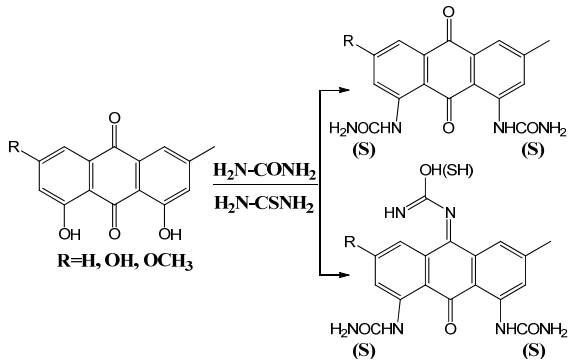

Fig. 10 Reactions with urea and thiourea derivatives

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_2CO_3 or H_2SO_4 increased the output by 12-19%, and in the presence of H_3BO_3 outputs 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_2CO_3 and Ag_2O proceeded easier in β-positions [see in Fig. 11].

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

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

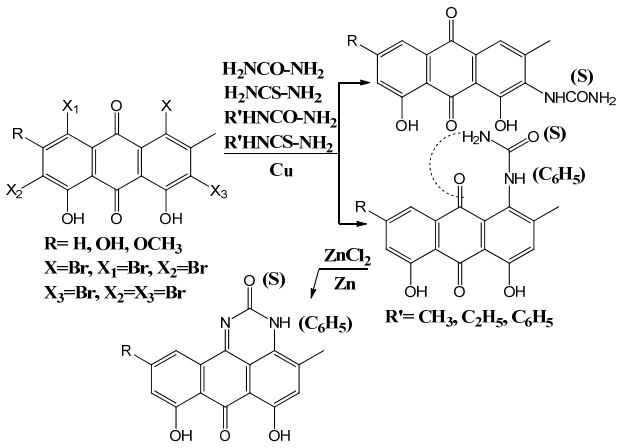

Fig 11 Amination of halogenated anthraquinones with urea and thiourea derivatives

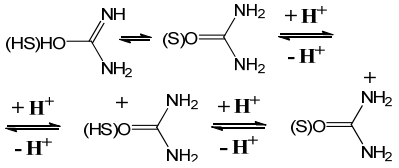

Fig. 12 Interaction of ureido- and thioureido- derivatives

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.

Acknowledgement

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