World Academy of Science, Engineering and Technology
International Journal of Chemical and Molecular Engineering
Vol:9, No:4, 2015

Technologies of Halogenation of Hydroxyanthraquinones

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***Abstract*—**In review the generalized data about different methods of synthesis of biological activity halogenated di-, tri- and tetra-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*—**Electrophilic substitution, halogenation, hydroxyanthraquinones, physiologically active substances.

I. Introduction

CHEMOTHERAPEUTICAL and pharmacological tests as well as experience of folk medicine show that individual natural and modified anthraquinones have versatile physiological activity, and the highest effect was registered for glycosided mono-, dimer, and reduced forms and for anthracycline antibiotics. Oxidized forms of aglycones exhibit depending on dose astringent and (or) purgative effect, moderate antitumor, anti-inflammatory and antibacterial action [1]-[3].

Our group was the first to discover growth-regulating, hormonal, radiation sensitizing, radioprotective, mycocide, insecticide and antioxidant activities, selectivity of action against some types of tumors and microorganisms and low toxicity in the series of hydroxyanthraquinone derivatives.

We have showed the possibility and efficiency of usage for several hydroxyanthraquinone derivatives as radiation protectors of animals and plants under prolonged action of Cs-137 γ-quanta as antitumor agents in combination with radiation treatment, as a means for plant selection, killer of weeds and plant pathogens in agriculture, and a means of potato protection against dry rot during storage [4], [5].

Scientists in many countries search for biologically active compounds extracted from natural materials with synthetic methods as well as synthesized as a result of structure change in well-known biologically active compounds by inclusion of new functional groups, replacement of heteroatoms, creation of new types of chemical bonds and other processes.

One of the most perspective directions of chemical modification of hydroxyanthraquinones is halogenation reaction [4].

II. Results and Discussion

Halogenation reactions are performed using electrophilic, nucleophilic substitution and reactions of substitution for other functional derivatives; an important factor in these reactions is that all they obey the rules of orientation for introduced substitutes. Taking into account the influence of the environment on the dominating orientation of reactions it is possible to get α– or β–substitutes in the nucleus or in the side chain [4].

Each of the hydroxyanthraquinones has several reaction centers, which enable to make practically all types of organic reactions on their base.

Thus, the molecule of chrysophanol has two unequal α>H, 3 unequal β-H in aromatic rings, 2 unequal C=O groups, group CH_3 and, because of such arrangement, unequal reactivity of aromatic rings.

Emodin and physcion have practically the same reactivity in all reaction centers. Aloe-emodin and rhein have additional reaction centers: alcoholic hydroxyl and carboxyl groups.

In this work, we present quantum-chemical calculations of effective charges on atoms of some hydroxy-derivatives of anthraquinone. Calculations of charge distribution in the atoms of chrysophanol and emodin molecules were made using AM1 and AMPAC [see in Fig. 1]:

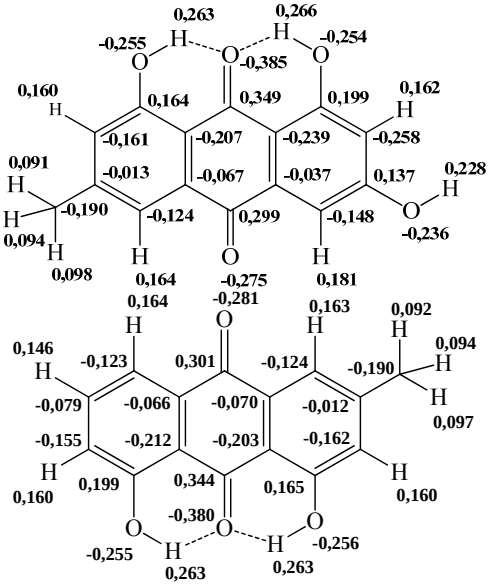

Fig. 1 Chrysophanol (0.974 D) and emodin (0.202 D) dipole moments

As it is seen, presence of just one β-OH group in emodin molecule as compared with that of chrysophanol causes considerable difference in distribution of charges in atoms and dipole moments of the molecules. The donor OCH_3-group in the physcion molecule has the same effect. Knowledge of the contribution of each structural element is useful in molecule

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reactivity estimations and in choice of reaction conditions.

Using multifunctionality of natural hydroxyanthraquinones, it is possible to carry out directed chemical transformations to study the role of the structure of anthraquinones, various inserted functional groups or chemical bonds.

Based on the values of effective charges of atoms (q), for example, it is obvious that in the emodin molecule proton C_7 is preferable for electrophilic exchange, OH-1,6 and 8, C=O 9 and 10 have unequal reactivity, and it can be used for selective formation of corresponding derivatives [see Table I].

TABLE I
EFFECTIVE CHARGES OF ATOMS IN THE EMODIN

Atom	q	Atom	q	Atom	q
C-1	0.164	C-10	0.299	H-6	0.228
C-2	-0.161	C-11	-0.037	H-7	0.162
C-3	-0.013	C-12	-0.239	H-8	0.266
C-4	-0.124	C-13	-0.207	H-9	0.263
C-5	-0.148	C-14	0.069	O-1	-0.255
C-6	0.137	C-15	0.019	O-6	-0.236
C-7	-0.258	H-2	0.160	O-8	-0.254
C-8	0.199	H-4	0.164	O-9	-0.385
C-9	0.349	H-5	0.181	O-14	-0.275

Chlorination unlike bromination mainly occurs in α-position independent of the environment. Nucleophilic exchange of OH- groups in the aromatic system of rings and in CH_2OH group with high output proceeds in the presence of red phosphorous.

Chlorination of α-hydroxyanthraquinones by chlorosulfonic acid in nitrobenzene without catalysts mainly gives α–hydroxy- β-chlorine-derivatives, whereas in the presence of catalysts it gives α- and α-substitutes. In halogenation by a haloid in presence of phosphorous, a mixture of ε-isomers is formed. The same reagents in the medium of organic solvents under heating may give exchange reactions, for example, exchange of hydroxy-groups. To produce isomers, chemists also use the method of chlorination of hydroxyanthraquinones by hypochlorites in water-alkaline solutions in cold medium or heating the reaction mixture to the boiling state, or chlorination by chlorate in hydrochloric acid at heating; in both cases, temperature regime influences the ratio of isomer chlorine substitutes. It is convenient to use oleum as a solvent during chlorination since it binds released HCl into $ClSO_3H$ [4], [6], [7].

It has been revealed that the processes of photobromination in presence of initiator – peroxide – are different not only by the amount of formed bromides but also by the rate of accumulation of various products.

In case of UV irradiation the main factors influencing the rate of products accumulation are the power of UV source and temperature: at room temperature a prevailing compound in the output of bromides is monobromide; at a lamp power of 250 W monobromide is formed for 20 minutes, at a power of 375 W monobromide is produced during the second minute. If there is an excess of bromine, three bromides with close rates are formed, and three reaction products are registered on the chromatograph as early as 20 minutes after the reaction starts. In the presence of peroxide, dibromide (88%) dominates in the reaction products. We suggested optimal conditions of alkaline hydrolysis of α- and β-bromides.

We showed clear differences in the character of fragmentation of halogen-derivatives depending on the nature of halogen and type of substitution, which enables us to identify them by M+ and isotope lines of the corresponding halogens [8]-[10].

Among natural ones, only chlorine derivatives such as nalhyolacsione (1-chloro-), mono- and dichloro-derivatives with β- and α,β-orientation (2- and 7-chloroemodins, 7-chloro-metoxyemodin, 7-chlorophyscion and 7-chlorofallacinal, 7-chloro-6-hydroxyaloe-emodin, 6,8-dichloroemodin, papulosin; dimeric structures of flavoobskurines and bromine-containing dimers (gymnochromes A-D) are described [4], [5].

Bromination of three-O-methyl ether of emodin gives 8-monobromide. 6-chloroemodin was obtained by heating emodin with pyridine hydrochloride at 100-160^{0}C. Aloe-emodin, its acetate and dimethyl ether brominated in acetic acid turn into 1-monobromine-derivatives with 97% output. Bromine was inserted into the side chain of aloe-emodin by nucleophilic exchange during heating with 48% hydrobromic acid. Exchange by OH-groups in reaction with HF (60-hour saturation with output up to 32%) occurs less readily.

In the excess of bromine the main products (up to 90%) are three- and tetrabromides [4], [11].

The common scheme to produce halogen-derivatives of chrysophanol, emodin, physcion, rhein and aloe-emodin was as follows [see Figs. 2 and 3]:

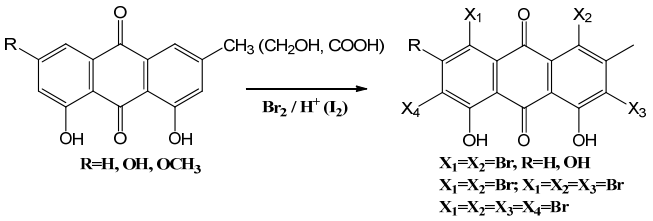

Fig. 2 Halogenation of hydroxyanthraquinones with bromine in the acid medium

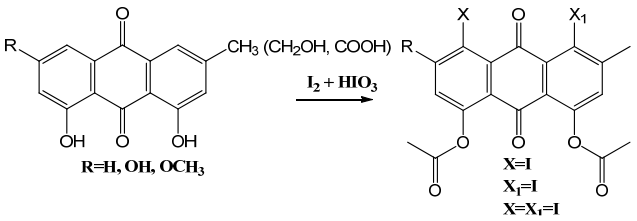

Fig. 3 Halogenation of hydroxyanthraquinones with iodine in the HIO_3 medium

It is possible to carry out monobromation reaction using N-bromosuccinamide in the presence of reaction initiators, in particular, azodiizobutironitrile at light exposure in boiling carbon tetrachloride and dioxandibromide [4], [12], [13].

Complexation, for example, with boric acid facilitates nucleophilic substitution and increases substance stability in the reaction conditions [14].

Chlorination and bromination of purpurine, 2-metoxy-purpurine, quinizarine, alizarine gives mixtures of mono- and dihalogeno-derivatives of α- and mixed orientation (α- and β-). Bromination of emodin and its trimetoxy-derivative enabled to obtain only α-oriented mono- and dibromides [15], [16].

Chlorination of physcion and trimetoxyemodin in the chloroform solution and acetic acid proceeded with formation of α-mono, α,α-di-, β-mono- and α,β-trichlorides, which were separated by the methods of preparatory chromatography.

Natural hydroxyanthraquinones easily undergo the reactions of nucleophilic exchange of two and three chlorine or bromine atoms [see Fig. 4].

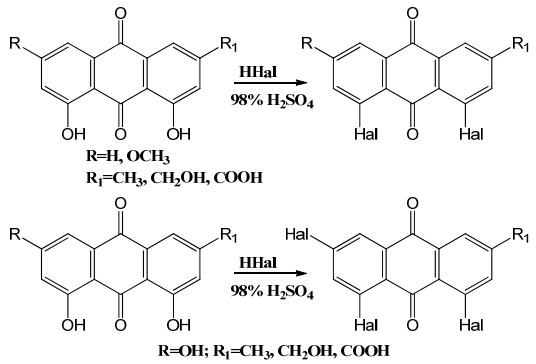

Fig. 4 Hydrohalogenation of hydroxyanthraquinones

Interactions of chrysophanol, physcion and emodin with chlorine and bromine go easily with dioxane-dibromide or low-polar solvents [see Fig. 5]:

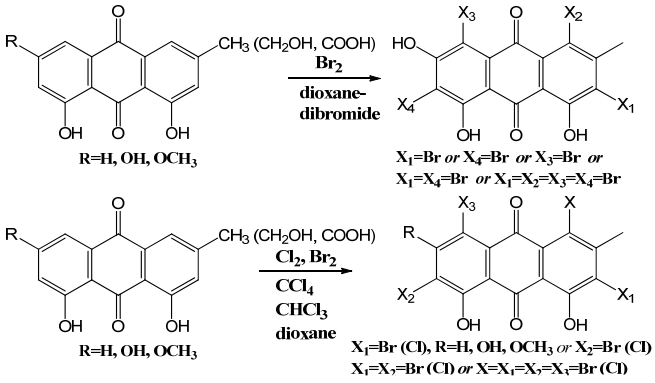

Fig. 5 Halogenation of hydroxyanthraquinones with low-polar solvents

The scheme of radical halogenation of natural hydroxy-anthraquinones was as Fig. 6.

2-halogeno- and 1,8-dihalogenosunstituted anthraquinones were detected in the reaction of chrysophanol, emodin, physcion, rhein and aloe-emodin with phospourus red [see Fig. 7].

The structures of obtained bromides were determined on the base of alkaline splitting, by hydrolysis products and data of physical-chemical methods (ultraviolet, infrared, NMR and mass-spectroscopy).

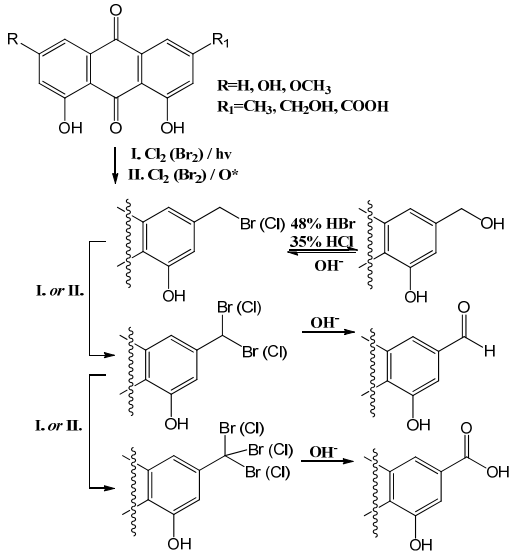

Fig. 6 Radical halogenation of hydroxyanthraquinones

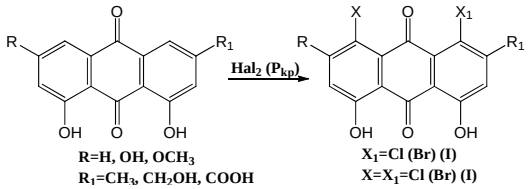

Fig. 7 Halogenation of anthraquinones with phosphorus

Biological tests of obtained halogen-derivatives of various structures showed their high antioxidant, antibacterial and fungicide activity as well as action on the central nervous system (bromides) [4], [16].

The following methods may be used to obtain sulfo-derivatives of hydroxyanthraquinones: sulfonation in different conditions including oxidizing sulfonation and substitution of other functional groups, for example, nitro-, amino-, halogen-, and others [4].

The presence of electron-donor substitutes facilitated the reaction and, first, turned the sulfo-group mainly in the orto-position with respect to the substitute, then to the para-position, except the examples with the influence of spatial effects.

It was also noticed that the reaction direction and the ratio of obtained products depended on the environment.

Thus, when hydroxyanthraquinones were treated with oleum or chlorosulfonic acids in presence of tertiary amines without a reducer, sulfuric ethers, mainly β-oriented, were formed. Addition of phosphoric acid during sulfonation contributed to inhibition of possible side hydroxylation reactions [4], [17].

Reactions of α-sulfocations proceeded in the presence of catalysts: Hg, HgO, Hg_2SO_4, Ti (III), Pd (II), Se (III), Cr (III), and others. However, such reactions were not strictly selective. Studying the influence of such factors as concentration of sulfuring agent, temperature regime, duration of processes and other characteristics it was shown that the number of different isomeric α-sulfoacids reached maximum

at the temperature of 140-150^{0}C during a short period of time (15-20 minutes), after which selectivity was violated, products of β- and mixed α-,β- sulfonation appeared. In presence of 0.01-0.1% PtO_2 in 4-6% oleum medium, the sum of α-sulfoacids of aloe-emodin, chrysophanol, alizarin, emodin and physcion was about 90-93% [4], [18].

In exchange reactions, for example, exchange by nitro-groups and halogens in water or water-alcohol solution of sodium sulfate, not only functional groups are exchanged but also products of β-sulfonation are formed [19].

β-sulfonation is carried out in conditions similar to the conditions of α-sulfonation but with a wider range of conditions and absence of catalysts.

For example, heating of 2-hydroxyanthraquinone with 20% oleum produced 2-hydroxyanthraquinone-3-sulfoacid; heating of 1,2-dihydroxyanthraquinone (alizarin) at the same conditions gave isomeric 1,2-dihydroxy-3- and 4-sulfoacids. Heating of 1,5-dihydroxyanthraquinone gave 1,5-dihydroxy-2,6-disulfoacid with 92% output, heating of 1,8-dihydroxyanthraquinone (chryzazin) with 100% sulfuric acid gave 1,8-dihydroxyanthraquinone-2,7-disulfoacid with the same high output [4].

A similar dependence was noticed for heating hydroxyanthraquinones in oleum in presence of concentrated sulfuric acid and for sulfonation by chlorosulfonic acid in nitrobenzene and without it.

Electron-acceptor effect of two C=O groups reduces rings reactivity during electrophilic substitution and activates them with respect to nucleophilic reagents. 9,10-anthraquinones are characterized by rigid geometry of molecules and enhancement of steric influence of C=O group on the neighboring positions of aromatic rings.

When one of aromatic rings contains an electron-donor substitute in α-position, electrophilic substitution occurs in o- and p- positions what results in unequal reactivity of C=O groups. On the other hand, relative autonomy of rings hampers formation of individual mono- and di-halogeno-substituted rings, i.e. in all known chemical reactions with participation of hydroxy-anthraquinones, a specific direction is observed, and sometimes a decisive role plays the choice of conditions in certain reactions.

Presence of just one β-OH group in emodin molecule as compared with that of chrysophanol causes considerable difference in distribution of charges in atoms and dipole moments of the molecules. The donor OCH_3-group in the physcion molecule has the same effect.

Formation of intramolecular hydrogen bonds affects acid-base properties of molecules, chemical stability and reactivity of perioxy-, periamino- and perimercapto-substituted anthraquinones. For example, in the presence of HMHB α-hydroxygroups are etherified less readily, whereas ethers are hydrolyzed easier than in β-positions. Differences are also observed for orto- and amphi-substituted halogenated hydroxyanthraquinones.

III. Conclusion

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

Analysis of intensity and character of biological activity enabled to establish some interrelations with the structure of molecules, which may help to develop the schemes of targeted syntheses of substances with predetermined properties.

Acknowledgment

Thanks to project: 2029/GF financial support by The Science Committee of the Ministry of Education and Science of Republic of Kazakhstan.

The authors are very much indebted to the Center of Physico-Chemical Methods of Research and Analysis for having provided the equipment where the work has been developed.

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