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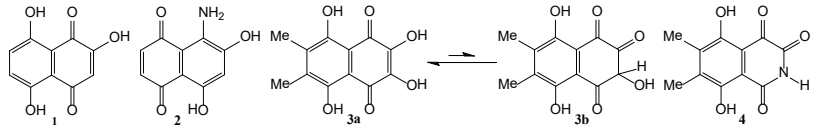
Reactions of polyhydroxynaphthazarins and their methyl ethers with aqueous ammonia

Key words: (poly)hydroxynaphthazarins, (poly)methoxynaphthazarins, amination, aminohydroxynaphthazarins, aminomethoxynaphthazarins.

Naphthazarins (5,8-dihydroxy-1,4-naphthoquinones) bearing a different number of hydroxy groups in the β-positions of their skeletons are widely distributed in nature. In most cases, they are produced by marine invertebrates. All polyhydroxynaphthazarins are antioxidants, the effectiveness of which depends on the number of β-hydroxy groups and their positions [7]. Echinochrome A is the most famous among them. On the basis of this pigment a new drug «Histochrome» was created [6]. Recently, previously unknown metabolites, echinamines A and B, and spinamine have been isolated from different sea urchin species. These metabolites contain NH_2 groups in the β-positions of the cyclic backbone [5]. Theoretical studies of the mechanisms of antioxidant action of echinamines A and B showed that they are much more active as antioxidants than the parent echinochrome A [2]. In this connection, the development of methods for the amination of functionally substituted naphthazarins is of considerable interest. These approaches can open the way for the synthesis of both natural and related compounds containing amino functions in different positions of the naphthazarin skeleton.

We have shown that the reaction of 2-hydroxynaphthazarin (**1**) (naphthopurpurin) with a 25% aqueous solution of ammonia at room temperature proceeds rapidly (10 - 20 min), giving product **2** with a quantitative yield [3].



In the case of substrates with vicinal OH groups, the interaction with ammonia leads to the formation of products of a different type. Under amination reaction conditions 2,3-dihydroxynaphthazarin **3** are converted to 5,8-dihydroxyisoquinoline-1,3,4(2*H*)-trione derivatives **4** [1]. This can be explained by the fact that the substrate **3** exists partially in the tautomeric form **3b**. The reaction of electrophilic C-atom of C(2)=O group of **3b** with NH_3 gives rise to amino intermediate that is turned to **4** by the action of O_2.

Substrates with three β-OH groups, for example, echinochrome A **5**, react with the formation of aminohydroxynaphthazarins **6** (48%) and **7** (47%) [3]. Because of the asymmetry of echinochrome A, the tautomeric forms **5b** and **5c** are not equivalent as a result of which the formation

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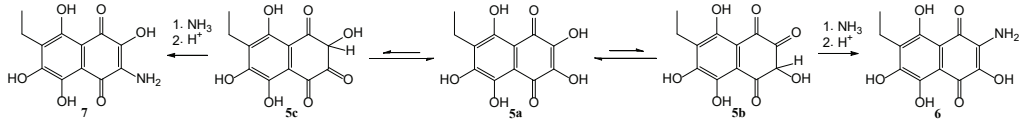
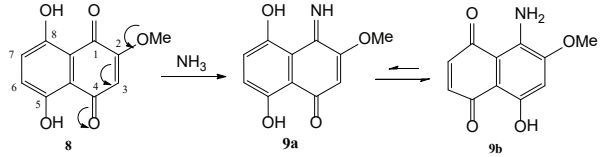
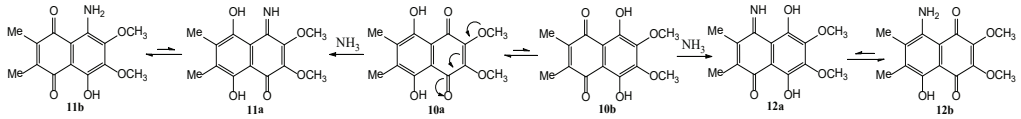
of isomers **6** and **7** is observed. In the case of substrate **5**, the reaction comes to rest at the stage of the formation of **6** and **7.** In the case of substrate **3**, the reaction proceeds via intermediates of the type **6** and **7** but is not brought to rest on this stage. We do not know yet why this happens. Undoubtedly, the nature of the C(6) and C(7) substituents at intermediates of these processes exerts a significant influence on the final result of these reactions. Substrate **3** has at these positions the relatively weak electronodonating substituents whereas substrate **5** has the ionized C(6) -OH group which is the strongest electronodonor.



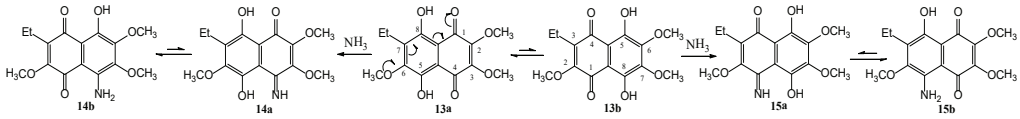
From the above, the question arises: will the aqueous solution of ammonia react with naphthazarin substrates where the β-OH groups are protected as OMe ethers? We found that the reaction of 2-methoxynaphthazarin **8** (naphthopurpurin monomethyl ether) with aqueous ammonia leads to the formation of aminonaphthoquinone **9** with a yield close to quantitative. In compound **8**, the most electrophilic center is the carbon atom of the C = O group at the position 1, since the electronodonating substituent at the position 2 partially desactivates the C = O group at the position 4.



Substrate **10** with vicinal OMe groups reacted with aqueous ammonia giving a mixture of products **11** (70%) and **12** (15%). As large as this difference in the yields of these products is a consequence of the strong dominance of tautomer **10a** in the tautomeric equilibrium of this substrate. This dominance is due to the electronodonating properties of OMe groups, that greatly exceed the same properties of Me groups. As a result, the electron density on the oxygen atoms of the C = O groups of tautomer **10a** will be larger than this density on the oxygen atoms of the C = O groups of tautomer **10b**. Such a electron density redistribution will increase the force of intramolecular hydrogen bond in tautomer **10a** compared to **10b** and will make **10a** dominate in the tautomeric mixture of the substrate **10**. Theoretical calculations have shown that the ratio of tautomers **10a** and **10b** in the alkaline medium is 70 to 30%.



As a result of the reaction of trimethyl ether of echinochrome **13** with aqueous ammonia, two products **14** (77%) and **15** (13%) were obtained. Their structures were assigned on the basis of the dates of IR-, NMR-, and mass – spectra [4]. By analogy with what has been said above regarding the ratio of tautomers **10a** and **10b** in the case of substrate **10**, for substrate **13**, a tautomer **13a** with two OMe groups in the quinoid nucleus should dominate in the solution. Obviously, in the case of tautomer **13b** an attack of the nucleophile will proceed on the carbon atom of the C = O group at the position 1, that will result in the formation of a minor product **15b** (13%). In the case of tautomer **13a**, the direction of the nucleophile attack is not obvious as for tautomer **13b**. Probably, a definite orienting effect in this case is exerted by the C (6)-OMe group whose donor effect reduces the positive charge on the carbon atom of the C = O group at the position 1 and, as would be expected, makes an attack on the C = O group at the position 4 more advantageous. As a result, the formation of the principal product **14b** (77%) takes place.



As is evident from the foregoing, naphthazarins with one β-OH group at the position 2 react with NH_3 giving derivatives with the NH_2 group at the position 5(8); with two β-OH groups at the positions 2 and 3 give 2(3)-amino derivatives that are further oxidized to the corresponding isoquinolinetrions by atmospheric O_2; with three β-OH groups at the positions 2, 3, and 6 give 2(3)-amino derivatives that are resistant to further oxidation with air oxygen. At the same time, OMe ethers of these naphthazarins react with NH_3 to form derivatives where the NH_2 group locates only at the position 5(8).

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