SYNTHESIS AND CONVERSIONS OF 5-(3,5,6-TRICHLORO-1,4-BENZOQUINON-2-YL)-2-ISOPROPYLIDENEHYDRAZINO-THIAZOLE AND 2-ISOPROPYLIDENAZINOTHIAZOLINES

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When 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan interacts in acetone with thiosemicarbazide or its 4-methyl or 4-phenyl derivative, the respective products are 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-(isopropylidenehydrazino)thiazole and 3-R-2-(isopropylidenazino)thiazolines, respectively. It has been shown that hydrolysis of these compounds forms 3-amino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-imino(or 2-R-imino)thiazolines. These products of hydrolysis and their predecessors are oxidized to the corresponding 2-hetaryl-substituted 3,5,6-trichloro-1,4-benzoquinones.

The work reported here is a continuation of systematic studies [1, 2] of the synthesis of hetaryl-substituted trichloro-1,4-benzoquinones on the basis of a universal synthon, 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan (I) [3]. Intramolecular charge transfer is observed in the molecules of these compounds between the electron-donor heterocycle and the electron-acceptor benzoquinone fragment; this is reflected in their electronic spectra.

The reactions of the benzofuran I with thiosemicarbazide and its derivatives open up broad possibilities for obtaining various heterocycles connected by a C–C bond with a trichlorobenzoquinone group.

It is known [4-6] that α-halocarbonyl compounds (the dihydrobenzofuran I is a cyclic tautomeric form of an aryl-substituted α-chloroa acetalddehyde [3]) in reactions with thiosemicarbazides may form derivatives of 2-amino-4H(6H)-1,3,4-thiadiazines, 2-hydrazinothiazoles, and 3-amino-2-iminothiazolines, and also pyrazole derivatives, if the process of forming the 1,3,4-thiadiazine is accompanied by extrusion of the sulfur atom.

As a result of the interaction of the dihydrobenzofuran I with unsubstituted thiosemicarbazide in ethanol, we obtained a mixture of 2-hydrazino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazole and 3-amino-2-imino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazolone [1]. We were unable to separate this mixture or isolate the isomers in individual form, apparently because of their facile interconversion. As a consequence of side reactions, we were not successful in oxidizing these compounds to the corresponding derivatives of 1,4-benzoquinone.

In the present work, when the reaction of these same reagents was performed in acetone, the product that was formed was 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-isopropylidenehydrazino)thiazole (II), isolated in the form of the hydrochloride (II·HCl). Evidently, the initial step is the condensation of thiosemicarbazide with acetone, leading to 1-isopropylidenethiosemicarbazide, which then enters into a nucleophilic substitution reaction (the reaction mechanism will be discussed subsequently).

By oxidation of compound II with ferric chloride in aqueous dimethylformamide, we obtained 2-(isopropylidenehydrazino)-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazole (III). When compound II is subjected to acid hydrolysis (refluxing with hydrochloric acid in ethanol), the isopropylidene group splits out, and the resulting hydrochloride of 2-hydrazino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazole (IV) is isomerized to the hydrochloride of 3-amino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-iminothiazoline (V). This is a manifestation of the higher stability of the 2-iminothiazoline ring in comparison with the 2-hydrazinothiazole ring.
Upon oxidation of compound V with ferric chloride in aqueous dimethylformamide, 2-amino-6-(3,5,6-trichloro-1,4-benzoquinon-2-yl)-4H-1,3,4-thiadiazine (VI) is formed. Oxidation of the hydroquinone fragment is accompanied by isomerization of the thiazoline ring to a 4H-1,3,4-thiadiazine ring. We had shown previously that upon refluxing the hydrochloride of 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-imino-3-phenylaminothiazoline in ethanol, hydrogen chloride splits out, with subsequent isomerization to 2-amino-6-(2,5-dihydroxy-3,4,6-trichlorophenyl)-4-phenyl-4H-1,3,4-thiadiazine [7]. Evidently, protonation of 3-amino-2-iminothiazoline stabilizes its structure in comparison with the isomeric 2-amino-4H-1,3,4-thiadiazines, and deprotonation acts in the opposite direction (see also [5, 6]).

We had shown rather recently that when the benzofuran I interacts with 4-methyl- or 4-phenylthiosemicarbazide in ethanol or acetonitrile, new condensed heterocyclic derivatives of benzofuran are formed, namely the hydrochloride of 8-hydroxy-2-methyl(phenyl)amino-6,7,9-trichloro-4a,9b-dihydro-4H-1,3,4-thiadiazino[5,6-b]benzofuran [8].

When the reactions of the benzofuran I with 4-methyl- or 4-phenylthiosemicarbazide are carried out in acetone, 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-isopropylidene-4-methyl(phenyl)thiosemicarbazide (VIIa,b) are obtained. The methyl derivative VIIa is recovered from the reaction mixture in the form of the hydrochloride (VIIa·HCl), the phenyl derivative VIIb in the form of a solvate with a molecule of acetone. Upon recrystallization of compound VIIb from ethanol, a solvate with a molecule of ethanol is formed. Here also, the first step is the condensation of the corresponding thiosemicarbazide with acetone, after which the 1-propylidene-4-methyl(phenyl)thiosemicarbazide enters into a reaction of nucleophilic substitution of the chlorine atom in the molecule of the benzofuran. The intermediate product VIII is further subjected to intramolecular cyclization to form a thiazoline ring, with simultaneous opening of the benzofuran ring (VIII → VII). Closure of the six-membered ring of the 4H-1,3,4-thiadiazine is impossible here because of structural considerations, and formation of the condensed system IX (compare [8]) is not observed.

Compounds VIIa,b are oxidized smoothly by ferric chloride in aqueous dimethylformamide to 2-isopropylidenediazino-3-methyl(phenyl)-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazolines (Xa,b). Upon refluxing with hydrochloric acid in an ethanol solution, the thiazolines VIIa,b are subjected to hydrolysis, splitting out the isopropylidene group in the form of acetone; formed as intermediate products are the hydrochlorides of 2-hydrazono-5-(2,5-dihydroxy-2,4,6-trichlorophenyl)-3-methyl(phenyl)thiazolines (XIIa,b), which are rearranged to the hydrochlorides of the isomeric 3-amino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-methyl(phenyl)iminothiazolines (XIIa,b). This sort of isomerization had been observed previously in the hydrolysis of 3-alkyl-2-isopropylidenediazino-4-phenylthiazolines: Under the action of 2 N hydrochloric acid, the 3-alkyl-2-hydrazono-4-phenylthiazolines that were formed were converted to 3-amino-2-alkylimino-4-phenylthiazolines [4]. The high stability of the 3-amino-2-alkyl(aryl)iminothiazolines in comparison with the isomeric 3-alkyl(aryl)-2-hydrazonothiazolines had also been noted in a number of other cases [5, 6].