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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-chloroacetaldehyde [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)thiazoline [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.

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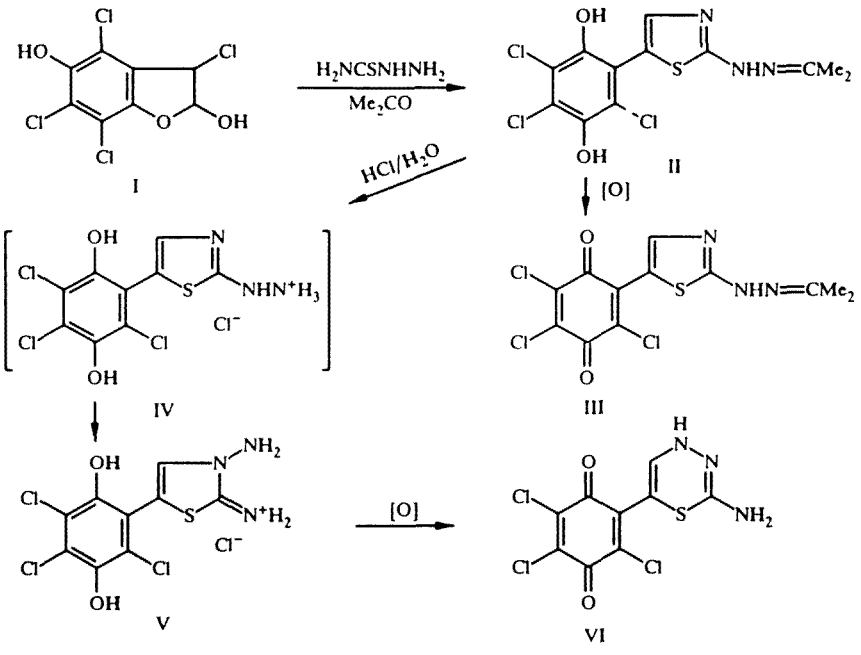
Scheme 1



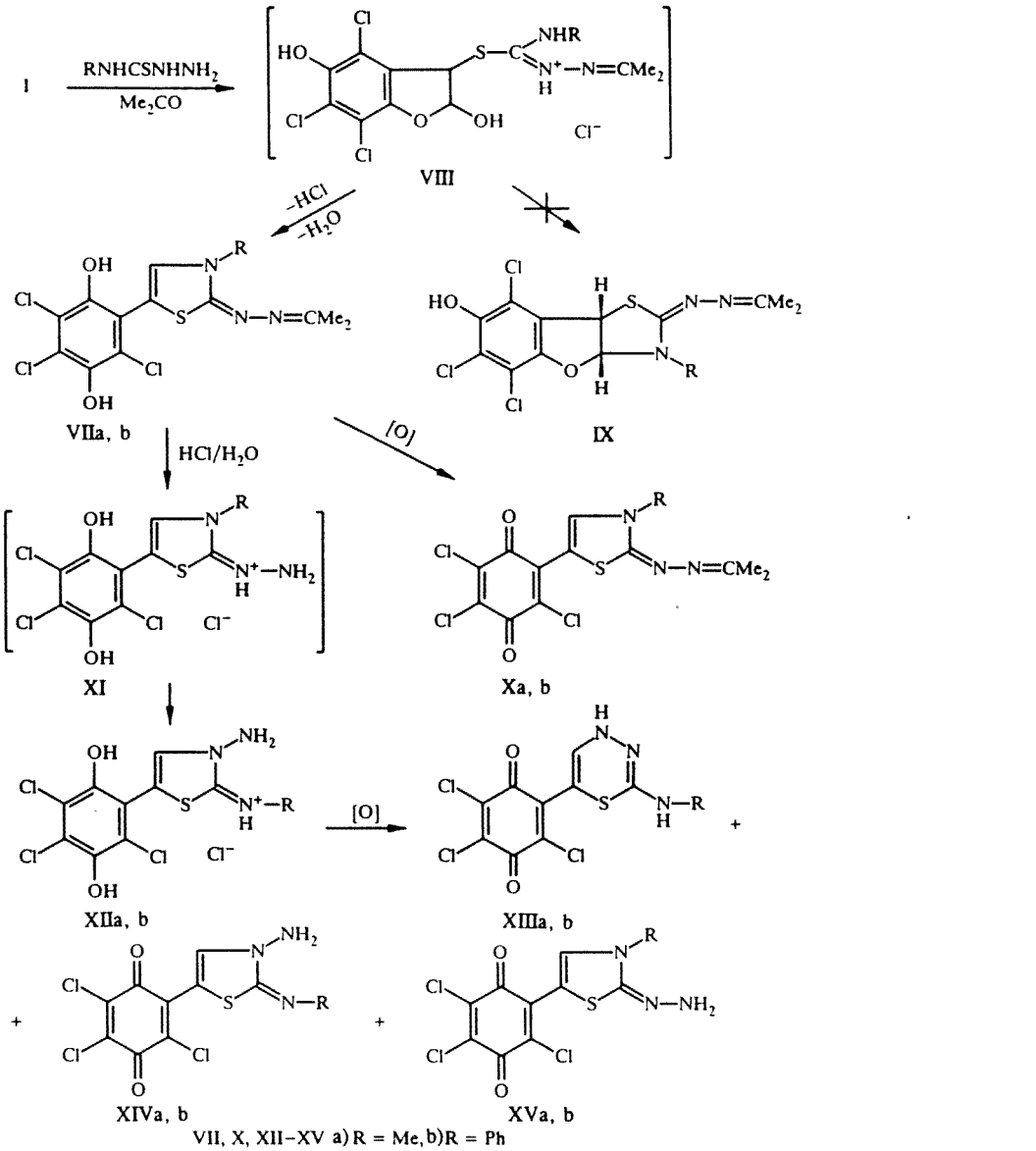
Upon oxidation of compound V with ferric chloride in aqueous dimethylformamide, 2-amino-6-(3,5,6-trichloro-1,4-benzoquinon-2-yl)-4H-1,3,4-thiadiazine (VI) is formed. Oxidation of the hydroquinone fragment is accompanied by isomerization of the thiazoline ring to a 4H-1,3,4-thiadiazine ring. We had shown 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]benzo[d]furan [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-isopropylidenazino)-3-methyl(phenyl)thiazolines (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-isopropylidenazino-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 (XIa,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-isopropylidenazino-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].

Scheme 2



VII, X, XII–XV a) R = Me, b) R = Ph

In the oxidation of the iminothiazolines XIIa,b with ferric chloride in aqueous dimethyl sulfoxide, the main products were 2-methyl(phenyl)amino-6-(3,5,6-trichloro-1,4-benzoquinon-2-yl)-4H-1,3,4-thiadiazines (XIIIa,b). The low yields of these compounds (about 40%) apparently reflect the occurrence of side reactions, including reactions that form water-soluble compounds. The oxidation products contain, in addition to the thiadiazines XIIIa,b, the isomeric 3-amino-2-methyl-(phenyl)imino-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazolines (XIVa,b) and 2-hydrazono-3-methyl(phenyl)-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazolines (XVa,b). Owing to the facile interconversion of the isomers, separation of this mixture encounters serious difficulties.

In the IR spectra of the crystalline compounds II and VIIa,b (Table 1), the most intense band, which can be assigned to absorption of the $Me_2C=N$ group, is observed at 1620-1610 cm^{-1}; there are also broad bands in the 3300-3000 cm^{-1} interval, corresponding to vibrations of associated OH groups and the N^+H group. In the spectra of the hydrochlorides V and XIIa,b, obtained after hydrolysis of compounds II and VIIa,b, respectively, there are two intense bands at 1672-1664 and 1582-1578 cm^{-1}, the first of which can apparently be attributed to vibrations of the protonated imino group ($C=N^+$), and the second to stretching vibrations of the iminothiazole ring [9]. Also observed in these spectra is an absorption band of the amino group (3362-3310 cm^{-1}) and broad bands of an associated OH group and the N^+H group in the interval 3400-2800 cm^{-1}.

In the PMR spectra of compounds II and VIIa,b (Table 1), there are two singlets corresponding to signals of the protons of two nonequivalent methyl groups of the isopropylidene fragment, a singlet of the 4-H proton of the heterocycle, and broad

TABLE 1. Characteristics of 2-Hetaryl-Substituted 3,5,6-Trichlorohydroquinones II, V, VIIa,b, XIIa,b

Compound	Empirical formula	mp, °C (decomp.)	IR spectrum (thin layer), ν, cm^{-1}	PMR spectrum (DMSO-d_6), δ, ppm	Yield, %
II·HCl	$C_{12}H_{10}Cl_3N_3O_2S \cdot HCl$	>230	3270 br. 3120, 2905, 1620, 1557	2,02 (3H, s, CH_3); 2,05 (3H, s, CH_3); 7,47 (1H, s, 4-H); 10,2 (4H, br. s, 2OH, NH_2, N^+H_2)	94
V	$C_9H_7Cl_4N_3O_2S$	219...220	3362, 3200...3000 br. 1667, 1618, 1578, 1562	7,32 (1H, s, 4-H); 9,5 (6H, br. s, 2OH, NH_2, N^+H_2)	93
VIIa·HCl	$C_{13}H_{12}Cl_3N_3O_2S \cdot HCl$	206...207	3200...3000 br., 3106, 2778, 1610, 1550	2,09 (3H, s, CH_3); 2,18 (3H, c, CH_3); 3,71 (3H, s, NCH_3); 7,53 (1H, s, 4-H); 8,95 (3H, br. s, 2OH, N^+H)	99
VIIb·$(CH_3)_2CO$	$C_{18}H_{14}Cl_3N_3O_2S \cdot (CH_3)_2O$	180...182	3400...3200 br., 2930 br., 2620 br.,1714, 1588, 1530	1,98 (3H, s, CH_3); 2,06 (3H, s, CH_3); 2,09 (6H, s, CH_3-acetone); 7,42 (1H, s, 4-H); 7,3...7,8 (5H, m, C_6H_5)	80
VIIb·C_2H_5OH	$C_{18}H_{14}Cl_3N_3O_2S \cdot C_2H_5OH$	175...177	3300...3100 br.,3102, 2974, 1618, 1596, 1566, 1552	1,07 (3H, t, CH_3-ethanol); 1,96 (6H, s, $2CH_3$); 3,47 (2H, q, CH_2-ethanol); 4,18 (1H, br. s, OH-ethanol); 7,38 (1H, s, 4-H); 7,3...7,8 (5H, m, C_6H_5); 9,64 (1H, br. s, OH); 9,84 (1H, br. s, OH)	70
XIIa	$C_{10}H_9Cl_4N_3O_2S$	217...218	3326, 3200...2800 br., 1666, 1622, 1582, 1550	3,56 (3H, s, NCH_3); 7,47 (1H, s, 4-H); 10,0 (5H, br. s, 2OH, NH_2, N^+H)	92
XIIb	$C_{15}H_{11}Cl_4N_3O_2S$	218...219	3310, 3400...2900 br., 1672, 1626, 1598, 1578	7,58 (6H, m, C_6H_5, 4-H); 9,98 (5H, br.s, 2OH, NH_2, N^+H)	89

TABLE 2. Characteristics of 2-Hetaryl-substituted 3,5,6-Trichloro-1,4-benzoquinones III, VI, X, XIII

Compound	Empirical formula	mp, °C* (decomp.)†	R_f ($CHCl_3$)	IR spectrum (thin layer), ν, cm^{-1}	UV spectrum, λ_{max}, nm (and log ε)		PMR spectrum ($CDCl_3$)‡, δ, ppm	Yield, %
					ethanol	chloroform		
III	$C_{12}H_8Cl_3N_3O_2S$	>240	0,20	3138, 2926, 1674, 1650, 1604, 1562, 1514	263 (4,11), 335 (4,18), 624 (3,76)	303 (4,25), 334 (4,10), 615 (3,68)	2,03 (3H, s, CH_3); 2,13 (3H, s, CH_3); 8,42 (1H, s, 4-H)	94
VI	$C_9H_4Cl_3N_3O_2S$	154...155	0,70	3334, 3142, 2926, 1670, 1606, 1562, 1548, 1510	277 (4,22), 334 (3,66), 450 (3,37)	276 (4,23), 338 (3,62), 472 (3,48)	8,51 (1H, s, 5-H)	67
X a	$C_{13}H_{10}Cl_3N_3O_2S$	>190	0,36	3142, 2918, 1662, 1636, 1552, 1534, 1512	293 (4,31), 348 (4,22), 720 (4,02)	298 (4,29), 358 (4,16), 762 (4,02)	2,08 (6H, s, $2CH_3$); 3,54 (3H, s, NCH_3); 8,22 (1H, s, 4-H)	95
X b	$C_{18}H_{12}Cl_3N_3O_2S$	165...168	0,62	3158, 2918, 1668, 1650, 1626, 1606, 1566, 1518	300 (4,27), 334 (4,15), 698 (3,90)	306 (4,14), 334 (4,01), 758 (3,85)	1,96 (3H, s, CH_3); 2,07 (3H, s, CH_3); 7,50 (5H, m, C_6H_5); 8,36 (1H, s, 4-H)	85
XIIIa	$C_{10}H_6Cl_3N_3O_2S$	143...145	0,37	3330, 3142, 2924, 1662, 1530	290** 334, 527	297** 361, 561	3,38 (3H, s, NCH_3) 7,96 (1H, s, 5-H)	44
XIIIb	$C_{15}H_8Cl_3N_3O_2S$	>210	0,70	3330, 3070, 2930, 1674, 1596, 1548	283** 335, 401, 523	287** 334, 401, 579	7,53 (5H, m, C_6H_5); 8,02 (1H, s, 5-H)	42

*Compounds III and Xa,b were recrystallized from 1:2 benzene–hexane mixture, VI from carbon tetrachloride.

†Compound VI melts without decomposition.

‡PMR spectra of compounds XIIIa,b, were taken in CD_3CN solution.

**UV spectrum was taken for saturated solution of compound, owing to its poor solubility and its instability.

signals of protons of the OH and NH groups. In addition, the spectrum of the thiazoline VIIa contains a singlet signal of NMe-group protons; and the spectrum of the thiazoline VIIb contains a multiplet of protons of the phenyl substituent. In the spectra of the hydrochlorides V and XIIa,b, the singlet of the 4-H proton of the heterocycle is preserved, and also the broadened signals of the protons of the OH and NH groups.

In the IR spectra of the quinones III and Xa,b (Table 2), we observe two bands of carbonyl absorption at 1674-1662 and 1650-1636 cm^{-1} (C=O of quinone) and also a band at 1566-1552 cm^{-1} (C=C of quinone) [10]; there are no bands of OH groups. In the spectra of the quinones VI and XIIIa,b, absorption of the C=O group is observed in the form of a single broad band in the 1678-1662 cm^{-1} interval.

The PMR spectra of the quinones III and Xa,b (Table 2) contain signals of protons of methyl groups of the isopropylidene fragment (two singlets for compounds III and Xb, one singlet for compound Xa) and a singlet of the 4-H proton of the heterocycle. In the spectra of the quinones VI and XIIIa,b, we observe a singlet of the 5-H proton of the heterocycle, and also a signal of protons of the NMe group for compound XIIIa or a signal of protons of the phenyl substituent for compound XIIIb.

In the UV spectra of the quinones VI, Xa,b, and XIIIa,b (Table 2) there are two bands in the 280-335 nm interval, where the absorption of the benzoquinone system overlaps that of the iminothiazoline or thiadiazine ring. The most intense of these bands may pertain to a $\pi \rightarrow \pi^*$ transition in the benzoquinone system [11], the less intense band to a $\pi \rightarrow \pi^*$ transition in the iminothiazoline or thiadiazine ring [12]. In the spectrum of the quinone III (in ethanol) there are two bands corresponding to absorption of the benzoquinone system (335 nm) and the thiazole ring (263 nm). In addition to these bands, the spectra of all of the quinones exhibit a band of intramolecular charge transfer from the heterocycle to the benzoquinone fragment. When the molecule contains a thiazole ring (compound III) or a thiazoline ring (compounds Xa,b), this band is located in the interval 624-720 nm (in ethanol) or 615-762 nm (in chloroform); in the case of a thiadiazine ring (compounds VI and XIIIa,b), we note a hypsochromic shift of this band to 450-527 nm (in ethanol) and 472-579 nm (in chloroform). It is pertinent to emphasize that for the quinones Xa,b, in comparison with all of the 2-heteryl-substituted 3,5,6-trichloro-1,4-benzoquinones that we had synthesized previously (see [1, 2]), the charge transfer band appears at longer wavelengths.

EXPERIMENTAL

IR spectra were recorded in a Specord M-80 instrument on suspensions of the samples in white mineral oil (1900-1500 cm^{-1} interval, NaCl prism) or hexachlorobutadiene (3800-2000 cm^{-1} interval, LiF prism, microlayer). The electronic spectra were taken in a Specord M-40 instrument on solutions in ethanol or chloroform (concentration $2.5 \cdot 10^{-5}$ M). PMR spectra were obtained in a Bruker H-90 instrument (^1H 90 MHz) in DMSO-d_6 or $CDCl_3$ solutions. Internal standard TMS.

The individuality of the compounds was monitored by TLC on Silufol UV-254 plates with an anchored layer of silica gel, eluent chloroform or ethyl acetate/carbon tetrachloride, development with UV light and iodine.

2,5-Dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan I was obtained by a procedure given in [3].

5-(2,5-Dihydroxy-3,4,6-trichlorophenyl)-2-isopropylidenehydrazinothiazole (II·HCl) and 5-(2,5-Dihydroxy-3,4,6-trichlorophenyl)-2-isopropylideneazino-3-methyl(phenyl)thiazolines (VIIa·HCl, VIIb) (Table 1). A mixture of 0.58 g (2 mmoles) of the benzofuran I and 2 mmoles of the appropriate thiosemicarbazide in 10 ml of acetone was refluxed 5 h, cooled, and held at 15-20°C (or 0°C for the thiazoline IXb) for a period of 20 h. The precipitated product was separated, washed with acetone, and dried. Compound VIIb was recrystallized from 60% ethanol. The reaction products were obtained in the form of colorless crystals.

Hydrochlorides of 3-Amino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-iminothiazoline (V) and 3-Amino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-methyl(phenyl)iminothiazolines (XIIa,b) (Table 1). A mixture of 1 mmole of compound II, IXa, or IXb with 5 ml of concentrated hydrochloric acid was refluxed for 0.5 h after which refluxing was continued for 2 h with a Dean and Stark head. As the ethanol and the acetone that were formed in the reaction mixture were driven off, a precipitate formed. The reaction mixture was held for 20 h at 0°C, and the precipitated product was separated, washed with water, ethanol, and ether, and dried. The reaction product darkened during storage.

2-Isopropylidenehydrazino-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazole(III),2-Isopropylidenazino-3-methyl-(phenyl)-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazolines (Xa,b), 2-Amino-6-(3,5,6-trichloro-1,4,-benzoquinon-2-yl)-4H-1,3,4-thiadiazine (VI), and 2-Methyl(phenyl)amino-6-(3,5,6-trichloro-1,4-benzoquinon-2-yl)-4H-1,3,4-thiadiazines (XIIIa,b) (Table 2). To a solution of 1 mmole of compound II, V, or VIIa,b in 10 ml of dimethylformamide, or XIIa,b in 10

ml of dimethyl sulfoxide, while mixing with a magnetic stirrer at 20°C, 20 ml of 20% aqueous ferric chloride solution was added dropwise. The reaction mixture was stirred for another 2 h at 20°C, after which 20 ml of water was added, and the precipitated product was separated, washed with water, and recrystallized. Obtained intensely colored crystals: blue III, red VI, blue-green Xa,b, and violet XIIIa,b.

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