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NOVEL CONDENSED HETEROCYCLIC DERIVATIVES OF BENZOFURAN BASED ON 2,5-DIHYDROXY-3,4,6,7-TETRACHLORO-2,3-DIHYDROBENZO[*b*]FURAN

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We have synthesized novel condensed heterocyclic derivatives of benzofuran by reaction of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]*furan (I) with 4-phenyl- and 4-methylthiosemicarbazides, diphenylthiocarbazone, and also via cyclization of 2,5-dihydroxy-4,6,7-trichloro-3-(N,N-diethyldithio-carbamoyl)-2,3-dihydrobenzo*[b]*furan (obtained in the reaction of benzofuran I with sodium N,N-dithiocarbamate).*

Earlier we proposed [1] a general method for synthesis of trichloro-1,4-benzoquinonyl-substituted heterocycles (thiazoles [2], selenazoles [3], pyrazoles [4, 5], 4H-1,3,4-thiadiazines [5], and thiazoline-2-thiones [6]) based on a universal synthon: 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[*b*]furan (I) [7]. In molecules of these compounds, we observe intramolecular charge transfer between the electron-donor heterocycle and the electron-acceptor moiety of the benzoquinone, which is reflected in the electronic spectra of the considered compounds. For a systematic study of this phenomenon, we set ourselves the goal of extending the proposed method for obtaining other heterocycles connected by a C—C bond with the trichlorobenzoquinone residue.

Wide-ranging possibilities for obtaining such compounds are provided by the reactions of benzofuran I with thiosemicarbazide and its substituted derivatives. We know [8-10] that α-halocarbonyl compounds (benzofuran I is the cyclic tautomeric form of the aryl-substituted α-chloroacetaldehyde [7]) in reactions with thiosemicarbazide may form derivatives of 2-amino(6H or 4H)-1,3,4-thiadiazines, 3-amino-2-iminothiazolines, and 2-hydrazinothiazoles, and also pyrazole derivatives, if the process of formation of 1,3,4-thiadiazine is accompanied by "extrusion" of the sulfur atom.

Recently we showed [5] that in the reaction of benzofuran I with 1-phenylthiosemicarbazide in ethanol solution, 2-amino-6-(2,5-dihydroxy-3,4,6-trichlorophenyl)-4-phenyl-4H-1,3,4-thiadiazine is formed; and in acetone solution, 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-imino-3-phenylaminothiazoline hydrochloride is formed. Upon oxidation, both compounds are converted to the corresponding benzoquinonyl-substituted 1,3,4-thiadiazine.

Upon reaction of benzofuran I with 4-phenylthiosemicarbazide in ethanol or acetonitrile solution, we isolated a product which, according to PMR spectral data, has the structure of 8-hydroxy-2-phenylamino-6,7,9-trichloro-4*a*,9*b*-dihydro-4H-1,3,4-thiadiazino[5,6-*b*]benzo[*d*]furan hydrochloride (IIIa). We presume that compound IIIa is formed via cyclization of the intermediate (II) of nucleophilic substitution of the chlorine atom in the benzofuran molecule I. The reaction of benzofuran I with 4-methylthiosemicarbazide occurs similarly, with formation of 8-hydroxy-2-methylamino-6,7,9-trichloro-4*a*,9*b*-dihydro-4H-1,3,4-thiadiazino[5,6-*b*]benzo[*d*]furan hydrochloride (IIIb). For the example of the hydrochloride IIIa, we have shown that upon treatment with triethylamine, deprotonation occurs and the free base IVa is formed.

Recently we obtained [6] the tricyclic compound VI via intramolecular addition of the phenol hydroxyl at the C=C bond of thiazoline in the molecule of 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-3-methylthiazoline-2-thione (V).

When treated with phenyliodosodiacetate in DMF or nitrogen dioxide solution, in compounds IIIa,b opening of the benzofuran ring occurs followed by oxidation of the hydroquinone moiety to benzoquinone; but due to the extreme instability of the oxidation products, we could not isolate them in pure form.

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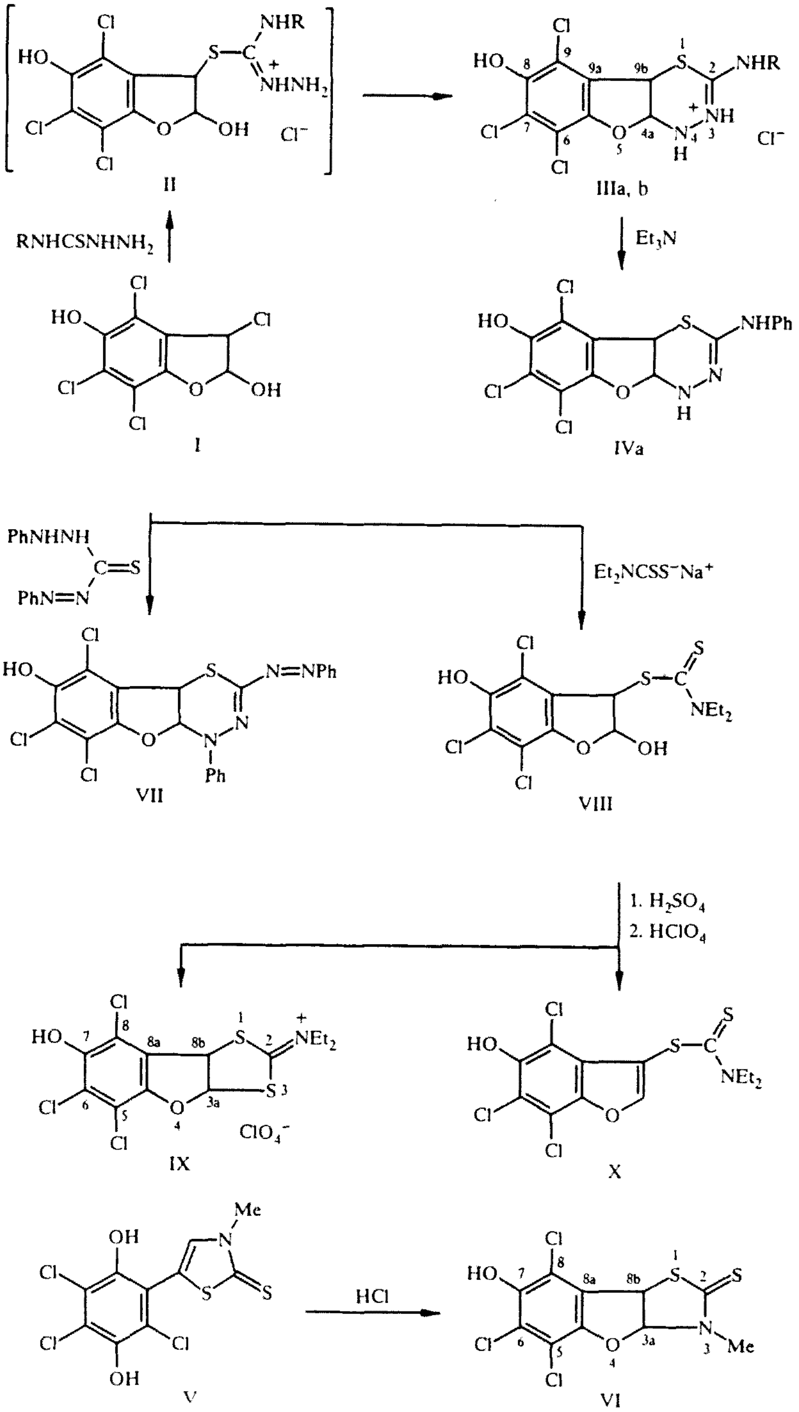

In the reaction of benzofuran I with diphenylthiocarbazone (Dithizone) in ethanol, 8-hydroxy-4-phenyl-2-phenylazo-6,7,9-trichloro-4*a*,9*b*-dihydro-4H-1,3,4-thiadiazino[5,6-*b*]benzo[*d*]furan (VII) is formed.

With the goal of obtaining trichlorobenzoquinonyl-substituted 2-dialkylamino-1,3-dithiolium salts [11, 12], we reacted benzofuran I with sodium N,N-diethyldithiocarbamate and obtained 2,5-dihydroxy-4,6,7-trichloro-3-(N,N-diethyldithiocarbamoyl)-2,3-dihydrobenzo[*b*]furan (VIII). After cyclization of compound VIII in concentrated sulfuric acid and conversion of the hydrosulfate to the less soluble perchlorate (see [12]), instead of the expected 4-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-(N,N-diethylimmonio)-1,3-dithiolium perchlorate, we obtained as the major product 7-hydroxy-5,6,8-trichloro-2-(N,N-diethylimmonio)-3*a*,8*b*-dihydro-1,3-dithiolo[4,5-*b*]benzo[*d*]furan perchlorate (IX); and as a byproduct we obtained 5-hydroxy-4,6,7-trichloro-3-(N,N-diethyldithiocarbamoyl)benzo[*b*]furan (X). The latter compound may be formed either via dehydration of the starting compound VIII or as a result of opening the dithiolium ring in the molecule of compound IX due to breaking of the C—S bond. Possibly the fact that the C—S is easier to break than the C—O bond is also the reason why we could not oxidize compound IX to the perchlorate of 4-(3,5,6-trichloro-1,4-benzoquinon-2-yl)-2-(N,N-diethylimmonio)-1,3-dithiolium.

In the IR spectra of compounds IIIa,b, we observe an intense immonium band at 1680-1670 cm^{-1}, and also a narrow N—H band near 3300 cm^{-1} and broad bands in the 3180-2860 cm^{-1} region, corresponding to vibrations of the associated O—H group and the N^+-H group. The deprotonation IIIa → IVa leads to a shift of the immonium band (1672 cm^{-1}) to 1632 cm^{-1}, which corresponds to vibrations of the C=N bond and serves as good proof for the presence of such a bond in the molecule of the heterocycle.

In the UV spectra of compounds IIIa,b, we observe a band near 315 nm, which can be assigned to absorption of the dihydrodithiazine ring [5, 10]. In the spectrum of compound VII, in addition to the band mentioned above there is a band at 406 nm, due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions in the conjugated system PhN=N–C=N–NPh.

In the PMR spectra of all the condensed heterocycles IIIa,b, VI, VII, and IX, there are two characteristic doublets in the interval δ 5.26-7.52 ppm, corresponding to signals from the vicinal protons at the C–C bond which are common to the benzofuran ring and the heterocycle condensed with it. Large values of the spin–spin coupling constant (^3J = 5-7.5 Hz) between these protons, except for compound IIIb, are probably due to their *cis* configurations [13]. In the spectrum of compound IIIb, the value of the spin—spin coupling constant between these protons (^3J = 3 Hz) is significantly lower. For comparison, we can present data from the PMR spectrum for benzofuran I, which in DMSO-D_6 solution forms an equilibrium mixture of *trans—cis* isomers in 83:17 ratio [7]. In the PMR spectrum of benzofuran I, there are two intense doublets at δ 6.01 and 5.36 ppm (^3J = 0.5 Hz) from the C^2-H and C^3-H protons of the *trans* isomer, and two low-intensity doublets at δ 6.09 and 5.61 ppm (^3J = 4.5 Hz), which are assigned to the same protons in the *cis* isomer. In the *trans* isomer of the diacetate of benzofuran I in $CDCl_3$, we observe two doublets at δ 6.80 and 5.29 ppm (^3J = 0.5 Hz).

The methylene protons of both ethyl groups at the nitrogen atom in the PMR spectrum of compound VIII, and in the spectra of compounds IX and X the methyl and methylene protons of both ethyl groups are chemically nonequivalent, which is due to the geometry of the molecule of IX and hindered rotation about the thioamide bond CS—NEt_2 in the molecules of VIII and X.

In the PMR spectrum of compound VIII, taken in $CDCl_3$, we observe two broadened ($\Delta\nu_{1/2}$ = 4 Hz) singlet at 5.49 ppm (C^3-H) and 6.06 ppm (C^2-H). Probably the C^2-H and C^3-H protons are found in a *trans* configuration and the instrument does not resolve these signals into two lines due to the low value of the spin–spin coupling constant (^3J ~0.5 Hz). In DMSO-D_6 solution, these signals appear at 5.33 ppm ($\Delta\nu_{1/2}$ = 4 Hz, C^3-H) and 5.82 ppm ($\Delta\nu_{1/2}$ = 8 Hz, C^2-H). The significant broadening of the C^2-H signal obviously is due to spin–spin coupling with the OH proton (unresolved doublet of doublets); this is supported by the fact that after addition of D_2O, the widths of both signals become equal.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument for Nujol mulls (the region 1900-1500 cm^{-1}, NaCl prism) and hexachlorobutadiene mulls (the region 3800-2000 cm^{-1}, LiF prism) (microlayer). The electronic spectra were taken on a Specord M-40 instrument for solutions in methanol or ethanol. The PMR spectra were obtained on a Bruker H-90 instrument (^1H 90 MHz) in DMSO-D_6 solutions; the chemical shifts were measured relative to the internal standard TMS.

The purity of the compounds was monitored by TLC on plates with an adherent layer of silica gel Silufol UV-254; the eluents were ethylacetate–carbon tetrachloride and acetone–hexane, visualization in UV light and iodine.

The elemental analysis data for C, H, N, S, and Cl correspond to the calculated values.

2,5-Dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[*b*]furan (I) was obtained according to the technique in [7].

8-Hydroxy-2-phenylamino-6,7,9-trichloro-4*a*,9*b*-dihydro-4H-1,3,4-thiadiazino[5,6-*b*]benzo[*d*]furan Hydrochloride (IIIa). A mixture of 0.29 g (1 mmole) benzofuran I and 0.16 g (1 mmole) 4-phenylthiosemicarbazide in 7 ml acetonitrile was heated gently at 35°C until both reagents completely dissolved. The reaction mixture was held at 20°C for 24 h. The residue was separated, washed with acetonitrile, and dried. Colorless crystals of IIIa were obtained, yield 0.38 g (90%). mp 190°C (decomp.). IR spectrum: 3296 (NH), 3152 (OH), 2860 (N^+H), 1672 ($C=N^+$), 1586 cm^{-1}. UV spectrum (methanol, saturated solution), λ_{max}: 317 nm. PMR spectrum (DMSO-D_6): 5.81 (1H, d, ^3J = 7 Hz, $C^{4a}-H$), 6.68 (1H, d, ^3J = 7 Hz, $C^{9b}-H$), 7.0-7.5 (5H, m, arom. protons), 10.1 ppm (broad s, NH, OH).

Deprotonation of IIIa-IVa. Activated charcoal was added to a solution of 0.22 g (0.5 mmoles) hydrochloride IIIa in a mixture of 12 ml ethanol and 0.14 ml (0.1 mmoles) triethylamine. This was filtered and the filtrate was diluted with 50 ml water, neutralized with 6 N hydrochloric acid to pH 6-7. The precipitate was separated, washed with water, and dried. Colorless crystals, yield 0.18 g (90%). mp > 150°C (decomp.). IR spectrum: 3335 (NH), 3220 (OH), 1632 (C=N), 1592 cm^{-1}; in dioxane, 1640 (C=N), 1594 cm^{-1}.

8-Hydroxy-2-methylamino-6,7,9-trichloro-4*a*,9*b*-dihydro-4H-1,3,4-thiadiazino[5,6-*b*]benzo[*d*]furan Hydrochloride (IIIb). A mixture of 0.29 g (1 mmole) benzofuran I and 0.11 g (1 mmole) 4-methylthiosemicarbazide was dissolved in 5 ml acetonitrile with stirring at 20°C. After both reagents dissolved, a precipitate fell out of solution immediately. After 20 h, the solvent was decanted, the residue was washed with 5 ml acetonitrile and then boiled for 2 min with 5 ml ethanol. After cooling, the residue was separated, washed with ethanol, and dried. Colorless crystals, yield 0.23 g (61%). mp 190°C (decomp.). IR spectrum: 3366 (NH), 3182 (OH), 3026 (N^+H), 1680 ($C=N^+$), 1594, 1558 cm^{-1}. UV spectrum (methanol, saturated solution), λ_{max}: 316 nm. PMR spectrum (DMSO-D_6): 2.97 (3H, s, CH_3), 5.34 (1H, d, ^3J = 3 Hz, C^{4a}–H), 5.47 (1H, d, ^3J = 3 Hz, C^{4a}–H), 5.47 (1H, d, ^3J = 3 Hz, C^{9b}–H), 7.89 (1H, broad s, NH), 8.67 (1H, broad s, NH), and 9.20 ppm (2H, broad s, OH and NH).

8-Hydroxy-4-phenyl-2-phenylazo-6,7,9-trichloro-4*a*,9*b*-dihydro-4H-1,3,4-thiadiazino[5,6-*b*]benzo[*d*]furan (VII). A mixture of 0.29 g (1 mmole) benzofuran I, 0.26 g (1 mmole) diphenylthiocarbazone (Dithizone) in 10 ml ethanol was boiled for 3 h. This was cooled and held at 10°C for 20 h. The residue was filtered off, washed with ethanol, and dried. Yellow crystals, yield 0.3 g (61%). mp > 220°C (decomp.). R_f 0.36 (acetone–hexane, 1:2). IR spectrum: 3420(OH), 2952, 1598, 1578, 1502 cm^{-1}. UV spectrum (ethanol, $c = 5 \cdot 10^{-5}$ moles/liter), λ_{max} (log ε): 237 (4.40), 314 (4.13), 406 nm (4.13). PMR spectrum (DMSO-D_6): 5.26 (1H, d, ^3J = 5 Hz, C^{4a}–H), 6.90 (1H, d, ^3J = 5 Hz, C^{9b}–H), 7.2-7.9 ppm (10H, m, arom. protons).

2,5-Dihydroxy-4,6,7-trichloro-3-(N,N-diethyldithiocarbamoyl)-2,3-dihydrobenzo[*b*]furan (VIII). 1.15g (5mmoles) of a solution of sodium diethyldithiocarbamate in 10 ml methanol was added dropwise over the course of 0.5 h to a solution of 1.45 g (5 mmoles) benzofuran I in 20 ml methanol with stirring (magnetic stirrer) at 20°C. Stirring was continued for 3-4 h, then the reaction mixture was held at 20°C for 20 h. The solution was clarified with activated charcoal, poured into 150-200 ml water, and saturated with sodium chloride. This was extracted with 2 × 100 ml ether; the ether extracts were dried over calcium chloride for 20 h. Then the drying agent was recovered, the filtrate was evaporated under vacuum, and the residue was recrystallized from 200 ml carbon tetrachloride. Colorless crystals of VIII were obtained, yield 1.45 g (73%). mp 159-160°C (decomp.). R_f 0.72 (acetone–hexane, 1:2). IR spectrum: 3540 (2-OH), 3380 (5-OH), 2972, 2932, 2872, 1650, 1608, 1584 cm^{-1}. PMR spectrum ($CDCl_3$): 1.30 (6H, t, ^3J = 7.7 Hz, $2CH_3$), 3.69 and 4.03 (4H, two quartets, ^3J = 7.7 Hz, $2CH_2$), 5.49 (1H, s, C_3–H), 6.06 ppm (1H, s, C_2–H); (DMSO-D_6): 1.15 (6H, t, ^3J = 7.7 Hz, $2CH_3$), 3.69 and 3.96 (4H, two quartets, ^3J = 7.7 Hz, $2CH_2$), 5.33 (1H, s, $\Delta\nu_{1/2}$ = 4 Hz, C^3–H), 5.82 (1H, s, $\Delta\nu_{1/2}$ = 8 Hz, C^2–H), 8.13 (1H, broad s, C^2–OH), 10.0 ppm (1H, broad s, C^5–OH).

7-Hydroxy-5,6,8-trichloro-2-(N,N-diethylimmonio)-3*a*,8*b*-dihydro-1,3-dithiolo[4,5-*b*]benzo[*d*]furan Perchlorate (IX) and 5-Hydroxy-4,6,7-trichloro-3-(N,N-diethyldithiocarbamoyl)benzo[*b*]furan (X). 0.8 g (2 mmoles) of compound VIII and 5 ml concentrated sulfuric acid were heated at 60-70°C for 1 h. Then 8 ml 75% perchloric acid was added and the reaction mixture was poured over 100 g ice. The residue was separated, washed with water, and dried. 0.5 g of light yellow crystals were obtained, a mixture of compounds IX and X. The mixture was boiled for 5 min in 30 ml ethylacetate and the hot solution was filtered. The residue was boiled again with 30 ml chloroform and the hot solution was filtered. Colorless crystals of compound IX were obtained, yield 0.7 g (72%). mp 188-189°C (decomp.). After recrystallization from absolute ethanol, mp 193-194°C (decomp.). IR spectrum: 3360 (OH), 2990, 1610, 1586 cm^{-1}. PMR spectrum (DMSO-D_6): 1.31 and 1.33 (6H, two overlapping triplets, $2CH_3$), 3.84 and 3.93 (4H, two overlapping quartets, $2CH_2$), 6.76 (1H, d, ^3J = 7 Hz, C^{3a}–H), 7.53 (1H, d, ^3J = 7 Hz, C^{8b}–H), 9.69 ppm (1H, broad s, OH).

The filtrates of the ethylacetate and chloroform solutions were combined and evaporated under vacuum. 0.15 g (20%) compound X were obtained. mp 190-191°C. R_f 0.80 (acetone–hexane, 1:2). IR spectrum: 3270 (OH), 3146, 2978, 2934, 1668, 1640 (C=C), 1608, 1574, 1534 cm^{-1}. PMR spectrum (DMSO-D_6): 1.21 and 1.37 (6H, two overlapping triplets; $2CH_3$), 3.82-4.09 (4H, m, two overlapping quartets, $2CH_2$), 8.44 (1H, s, C^2–H), 10.29 ppm (1H, s, OH).

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