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Heterocycles Synthesis Based on Arylation Products of Unsaturated Compounds: XII.* Reactions of 2-Aryl-1,4-benzoquinones with Dithiol Compounds

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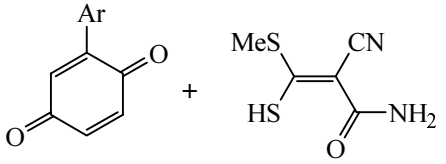
Abstract—Reactions of 2-aryl-1,4-benzoquinones with disodium (2,2-dicyano-1,1-ethylene)dithiolate gave rise either to 1,3-benzodithiol or 1,3-benzoxathiol depending on the character of the aryl substituent. 2-Aryl-1,4-benzoquinones reacted with 3-methylsulfanyl-3-sulfanyl-2-cyanoacrylamide with a higher selectivity: 2-(7-Aryl-5-hydroxy-1,3-benzoxathiol-2-ylidene)-2-cyanoacetamides were obtained in a high yield.

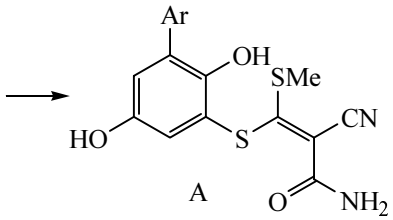
Reactions of S-nucleophiles with 1,4-benzoquinone derivatives are sufficiently documented [2–4]. A special attention attract processes involving quinones and S-nucleophiles with several functional groups since these reactions often result in a heterocycle formation [5–17]. The monosubstituted quinones were poorly studied since the isomers formation complicated these investigations. Note that the experimental data were summarized and compared with quantum-chemical calculations concerning the effect of the substituent character in the quinone ring on the regioselectivity of nucleophilic addition to the monosubstituted 1,4-benzoquinones [18]. However no unambiguous conclusions were reached with respect to the reactivity of the 1,4-benzoquinones possessing substituents with a system of conjugated multiple bonds.

We previously studied the cyclization selectivity of arylquinones in reactions with bifunctional nucleophilic reagents [19–21]. As for the reactions of the monoaryl-substituted 1,4-benzoquinones with S-nucleophilic reagents, the main point of attack is the position *6* of the quinone ring [4,19]. In the present study we investigated the trends in the regioselectivity of addition of some dithiocarboxylic acids derivatives to 2-aryl-1,4-benzoquinones.

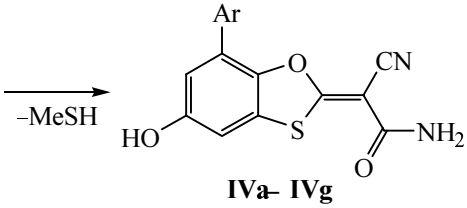
Arylquinones **Ia–Ig** were prepared by arylation of 1,4-benzoquinone with arenediazonium salts by Meerwein reaction [22]. We applied as dithiol components 3-methylsulfanyl-3-sulfanyl-2-cyanoacrylamide (**II**) and disodium (2,2-dicyano-1,1-ethylene)dithiolate (**III**) synthesized from the corresponding derivatives of the cyanoacetic acid [23,24]. Reagent **II** was established to undergo addition under relatively mild conditions to 2-aryl-1,4-benzoquinones **Ia–Ig** into the *meta*-position with respect to the aryl substituent (position *6*). Apparently an intermediate monosubstituted hydroquinone **A** formed where the CH_3S group easily suffered an intramolecular nucleophilic replacement by a hydroxy group resulting in a fused heterocyclic system, 2-(7-aryl-5-hydroxy-1,3-benzoxathiol-2-ylidene)-2-cyanoacetamides (**IVa–IVg**). The reaction is selective: In the most cases we obtained



Ia– Ig **II**



A



IVa– IVg

Ar = C_6H_5 (**a**), 4-MeC_6H_4 (**b**), 3-$CF_3C_6H_4$ (**c**), 4-BrC_6H_4 (**d**), 4-$NO_2C_6H_4$ (**e**), 2,4-$Cl_2C_6H_3$ (**f**), 3,4-$Cl_2C_6H_3$ (**g**).

* For communication XI see [1].

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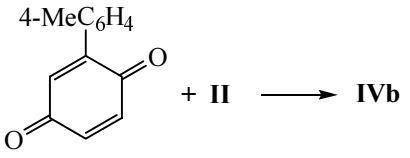
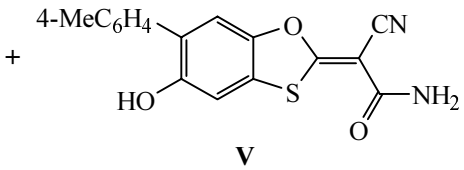
a single isomer (from three probable ones) corresponding to the addition of the bifunctional S-nucleopphile into the position *6* of the quinone ring.



Ib

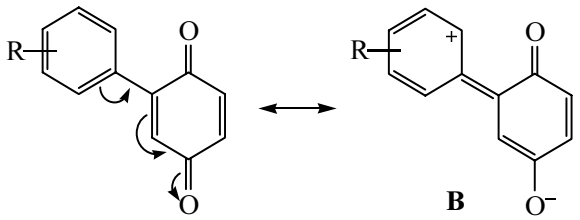


V

Only at the use of 2-(4-methylphenyl)-1,4-benzoquinone (**Ib**) two isomers **IVb** and **V** were obtained in a ratio 40 : 60 (according to ^{1}H NMR data).

The regioselectivity of the nucleophilic attack in the reaction of 2-aryl-1,4-benzoquinones with thiourea occurring in acid medium [19] may be due to the prevailing protonation of the carbonyl group in the position *4*. Then the electron density distribution in the quinone ring favors the nucleophile addition to the position *6*.

The reaction of arylquinones with reagent **II** was not carried out in acid medium, but its regioselectivity was the same: The nucleophile added predominantly to the position *6* of the quinone ring. Taking into account the conjugation of the aryl substituent with the system C=C–C=O a resonance structure **B** is presumable where the excessive charge on the oxygen in the position *4* would obviously passivize the positions *3* and *5* with respect to the nucleophile attack. Thus the position *6* would be the most active as is really observed.



B

The decrease in the selectivity in the presence of an electron-donor substituent resulting in formation of isomers **IVb** and **V** may evidence the high sensitivity to the electronic effects of this reaction occurring under mild conditions. The nucleophilic attack on position *5* in the presence of an electron-donor substituent is consistent with the published data [4].

The direction of nucleophile addition is easily established by the ^{1}H NMR spectroscopy. Alongside the proton signals from the aromatic ring characteristic doublets of protons H^4 and H^6 with a coupling constant 2.1–2.4 Hz appear in the spectra, and also a downfield singlet of the hydroxy group and a broad singlet belonging to the NH_2 group. Isomeric benzoxathiol **V** is easily identified by the clear singlets of protons H^4 and H^7 shifted downfield by 0.2–0.3 ppm with respect to the signals of compounds **IVa–IVg**.

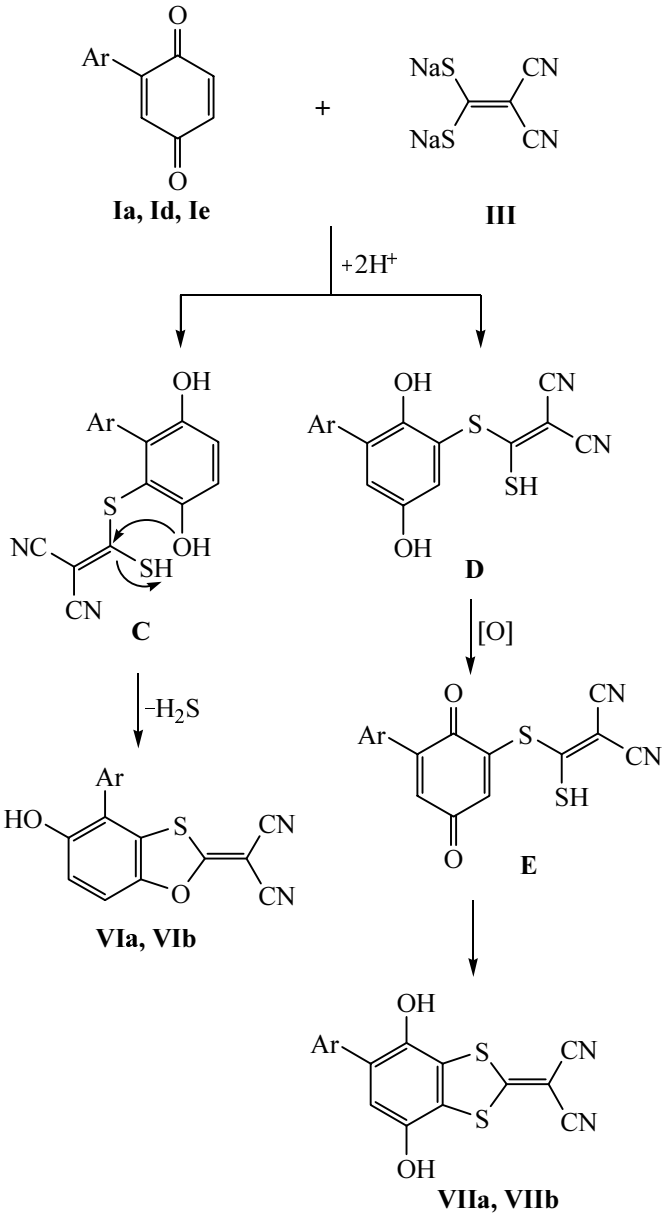
The specific feature of reagent **III** consists in generation of two SH groups at acidifying the water solution of the disodium salt. These SH groups readily react with the 1,4-benzoquinone derivatives [10,11]. We established that in the reaction of 2-aryl-1,4-benzoquinones **Ia, Id**, and **Ie** with reagent **III** depending on the character of the aryl substituent either 1,3-benzoxathiol **VIa** and **VIb** or 1,3-benzodithiol **VIIa** and **VIIb** derivatives were obtained.

In the case of 2-(4-nitrophenyl)-1,4-benzoquinone (**Ie**) mercapto compound **III** added into the *ortho*-position with respect to the aryl substituent (position *3*) giving intermediate **C** that further underwent cyclization into 1,3-benzoxathiol (**VIb**). A compound of similar structure **VIa** was obtained at the use in the reaction of 2-(4-bromophenyl)-1,4-benzoquinone (**Id**). However the reaction here was less selective: 1,3-Benzodithiol **VIIb** also was isolated. According to the ^{1}H NMR data compounds **VIa** and **VIIb** formed in a ratio 85:15. The reaction of 2-phenyl-1,4-benzoquinone (**Ia**) with reagent **III** furnished benzodithiol (**VIIa**).

The formation of 1,3-benzodithiols **VIIa** and **VIIb** occurred apparently due to the oxidation of adduct **D** in excess of arylquinone into a "quinone-adduct" **E** where the second SH group enters into the addition reaction. 1,3-Benzoxathiols **VIa** and **VIb** result from the intramolecular nucleophilic substitution of the SH group by a hydroxy group in the intermediate **C**.

The structure of reaction products was deduced from ^{1}H NMR and mass spectra. In ^{1}H NMR spectra of compounds **VIIa** and **VIIb** appear two signals of hydroxy groups and of H^6 proton, and in the spectra of benzoxathiols **VIa** and **VIb** the coupling constant of protons H^6 and H^7 equal to 9 Hz is characteristic for it evidences that they are located mutually in the *ortho*-position.

Thus the reaction of 2-aryl-1,4-benzoquinones with reagent **III** is very sensitive to the electronic effects of the substituents. This is favored by the mild conditions of the reaction. The electron-acceptor substituent ($4\text{-}O_2NC_6H_4$) reduces the electron density in the position *3* of the quinone ring and assists in the nucleophile



Ar = 4-BrC_6H_4 (**VIa, VIIb**), 4-$NO_2C_6H_4$ (**VIb**), C_6H_5 (**VIIa**).

attack to this position yielding adduct **C**. At Ar = 4-BrC_6H_4 this reaction route also proved to be dominant.

EXPERIMENTAL

^{1}H NMR were registered on spectrometers Bruker at operating frequencies 500 (**VIIa**), 300 (**IVb–IVg**, **V**, **VIa, VIb**, and **VIIb**), 250 MHz (**IVa**) for solutions in DMSO-d_6 or in a mixture DMSO-d_6–CCl_4. Chemical shifts were measured with respect to the solvent signal (DMSO, 2.50 ppm). Mass spectra were obtained on a GC-MS Finnigan MAT INKOS-50 instrument, ionizing electrons energy 70 eV.

2-Aryl-1,4-benzoquinones Ia–Ig were prepared by procedure [25]; the constants of compounds **Ia**, **Id**, and **Ie** were consistent with those published in [25, 26]. Yields of compounds were as follows: **Ic**, 82%, mp 60–61°C (ethanol); **Id**, 77%, mp 112°C (ethanol); **If**, 88%, mp 110–111°C (acetone) [27]; **Ig**, 81%, mp 162–163°C (AcOH) (publ.: mp 163–164°C [28]).

Reactions of 2-aryl-1,4-benzoquinone Ia–Ig with 3-methylsulfanyl-3-sulfanyl-2-cyanoacrylamide (II). Compound **II** (1.74 g, 10 mmol) was dissolved in a mixture of 10 ml of DMF, 2 ml of water, and 7 ml of methanol. To the solution obtained was gradually added within 30 min at 0–5°C a solution of 10 mmol of arylquinone **Ia–Ig** in 10 ml of DMF. The reaction mixture was left standing for 24 h at room temperature, then water was added, the separated precipitate was filtered off, analyzed by ^{1}H NMR spectroscopy for possible isomers, and recrystallized from an appropriate solvent

2-(5-Hydroxy-7-phenyl-1,3-benzoxathiol-2-ylidene)-2-cyanoacetamide (IVa). Yield 97%, mp 314–315°C (decomp., DMSO). ^{1}H NMR spectrum, δ, ppm: 6.91 d (1H, H^4, *J* 2.2 Hz), 7.10 d (1H, H^6), 7.26 br.s (2H, NH_2), 7.39–7.56 m (3H, Ph), 7.70 d (2H, Ph, *J* 7.2 Hz), 9.75 s (1H, OH). Found, %: C 61.88; H 3.19; N 9.11. $C_{16}H_{10}N_2O_3S$. Calculated, %: C 61.93; H 3.25; N 9.03.

2-[5-Hydroxy-7-(3-trifluoromethylphenyl)-1,3-benzoxathiol-2-ylidene]-2-cyanoacetamide (IVc). Yield 92%, mp 334–335°C (decomp., DMF). ^{1}H NMR spectrum, δ, ppm: 6.99 d (1H, H^4, *J* 2.4 Hz), 7.22 d (1H, H^6), 7.28 br.s (2H, NH_2), 7.73–7.80 m (2H, C_6H_4), 8.00 d (1H, C_6H_4, *J* 7.3 Hz), 8.04 s (1H, C_6H_4), 9.84 s (1H, OH). Found, %: C 54.09; H 2.43; N 7.29. $C_{17}H_9F_3N_2O_3S$. Calculated, %: C 53.97; H 2.40; N 7.40.

2-[7-(4-Bromophenyl)-5-hydroxy-1,3-benzoxathiol-2-ylidene]-2-cyanoacetamide (IVd). Yield 95%, mp 328–329°C (decomp., DMF–EtOH, 2:1). ^{1}H NMR spectrum, δ, ppm: 6.91 d (1H, H^4, *J* 2.1 Hz), 7.13 d (1H, H^6), 7.26 br.s (2H, NH_2), 7.66 s (4H, C_6H_4), 9.78 s (1H, OH). Found, %: C 49.17; H 2.28; N 7.13. $C_{16}H_9BrN_2O_3S$. Calculated, %: C 49.37; H 2.33; N 7.20.

2-[5-Hydroxy-7-(4-nitrophenyl)-1,3-benzoxathiol-2-ylidene]-2-cyanoacetamide (IVe). Yield 90%, mp >340°C (decomp., DMF). ^{1}H NMR spectrum, δ, ppm: 7.02 d (1H, H^4, *J* 2.4 Hz), 7.14 br.s (2H, NH_2), 7.21 d (1H, H^6), 8.00 d (2H, C_6H_4, *J* 8.7 Hz), 8.34 d (2H, C_6H_4), 9.77 s (1H, OH). Found, %: C 54.01; H 2.43; N 11.98. $C_{16}H_9N_3O_5S$. Calculated, %: C 54.08; H 2.55; N 11.83.

2-[5-Hydroxy-7-(2,4-dichlorophenyl)-1,3-benzoxathiol-2-ylidene]-2-cyanoacetamide (IVf).

Yield 94%, mp >340°C (decomp., DMF). ^{1}H NMR spectrum, δ, ppm: 6.94 d (1H, H^4, *J* 2.4 Hz), 7.14 d (1H, H^6), 7.25 br.s (2H, NH_2), 7.65–7.82 m (3H, C_6H_3), 9.80 s (1H, OH). Found, %: C 50.42; H 2.09; N 7.24. $C_{16}H_8Cl_2N_2O_3S$. Calculated, %: C 50.68; H 2.13; N 7.39.

2-[5-Hydroxy-7-(3,4-dichlorophenyl)-1,3-benzoxathiol-2-ylidene]-2-cyanoacetamide (IVg). Yield 91%, mp 329–330°C (decomp., DMF). ^{1}H NMR spectrum, δ, ppm: 6.93 d (1H, H^4, *J* 2.4 Hz), 7.15 d (1H, H^6), 7.29 br.s (2H, NH_2), 7.68 br.s (2H, C_6H_3), 7.92 s (1H, C_6H_3), 9.82 s (1H, OH). Found, %: C 50.51; H 2.04; N 7.31. $C_{16}H_8Cl_2N_2O_3S$. Calculated, %: C 50.68; H 2.13; N 7.39.

In reaction of compound **II** with arylquinone **Ib** compounds **IVb** and **V** were obtained in 37 and 56% yield respectively.

2-[5-Hydroxy-7-(4-methylphenyl)-1,3-benzoxathiol-2-ylidene]-2-cyanoacetamide (IVb). ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 6.90 d (1H, H^4, *J* 2.4 Hz), 7.06 d (1H, H^6), 7.18 br.s (2H, NH_2), 7.31 d (2H, C_6H_4, *J* 7.8 Hz), 7.61 d (2H, C_6H_4), 9.62 s (1H, OH).

2-[5-Hydroxy-6-(4-methylphenyl)-1,3-benzoxathiol-2-ylidene]-2-cyanoacetamide (V). ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H, CH_3), 7.18 br.s (2H, NH_2), 7.19 d (2H, C_6H_4, *J* 7.5 Hz), 7.24 C (1H, H^4), 7.41 s (1H, H^7), 7.46 d (2H, C_6H_4), 9.70 s (1H, OH). Found, %: C 63.12; H 3.78; N 8.51. $C_{17}H_{12}N_2O_3S$. Calculated, %: C 62.95; H 3.73; N 8.64.

Reactions of 2-aryl-1,4-benzoquinones Ia, Id, and Ie with disodium (2,2-dicyano-1,1-ethylene)dithiolate (III). To a vigorously stirred solution of 1.86 g (10 mmol) of compound **III** in 4 ml of DMF, 8 ml of water, and 1.2 ml of glacial acetic acid was gradually added at 0°C 20 mmol of an appropriate arylquinone **Ia, Id**, and **Ie** in 20 ml of DMF. The reaction mixture was kept for 24 h at 0°C, then it was poured into 500 ml of water, the oily substance was separated and boiled in chloroform. The separated precipitate was filtered off, analyzed by ^{1}H NMR spectroscopy for possible isomers, and washed with ethanol.

2-[5-Hydroxy-4-(4-nitrophenyl)-1,3-benzoxathiol-2-ylidene]malononitrile(VIb). Yield 39%, mp >300°C (decomp., DMSO). ^{1}H NMR spectrum, δ, ppm: 7.16 d (1H, H^6, *J* 9.0 Hz), 7.72 d (1H, H^7), 7.82 d (2H, C_6H_4, *J* 8.7 Hz), 8.37 d (2H, C_6H_4), 10.65 s (1H, OH). Found, %: C 56.83; H 2.04; N 12.33. $C_{16}H_7N_3O_4S$. Calculated, %: C 56.97; H 2.09; N 12.46.

2-(4,7-Dihydroxy-5-phenyl-1,3-benzodithiol-2-ylidene)malononitrile(VIIa), complex with DMF, 1:1. Yield 41%, mp 309–312°C (decomp., arueous DMF). ^{1}H NMR spectrum, δ, ppm: 6.83 s (1H, H^6), 7.38 t (1H, C_6H_5), 7.46 t (2H, C_6H_5), 7.50 d (2H, C_6H_5, *J* 8.1 Hz), 9.50 c (1H, OH), 10.63 s (1H, OH); DMF, δ, ppm: 2.76 s (3H, CH_3), 2.92 C (3H, CH_3), 7.94 C (1H, CHO). Mass spectrum *m/z* (I_{rel}, %): 324 $[M]^+$ (100), 215 (6), 162 (6), 131 (9), 115 (8), 103 (11), 102 (14), 85 (11), 77 (16). Found, %: C 57.19; H 3.72; N 10.50. $C_{16}H_8N_2O_2S_2 \cdot C_3H_7NO$. Calculated, %: C 57.42; H 3.80; N 10.57.

2-[4-(4-Bromophenyl)-5-hydroxy-1,3-benzoxathiol-2-ylidene]malononitrile (VIa). Yield 50%. ^{1}H NMR spectrum, δ, ppm: 7.11 d (1H, H^6, *J* 9.0 Hz), 7.47 d (2H, C_6H_4), 7.65 d (1H, H^7), 7.73 d (2H, C_6H_4), 10.44 s (1H, OH).

2-[5-(4-Bromophenyl)-4,7-dihydroxy-1,3-benzodithiol-2-ylidene]malononitrile (VIIb). Yield 9%. ^{1}H NMR spectrum, δ, ppm: 6.83 s (1H, H^6), 7.46 d (2H, C_6H_4), 7.66 d (2H, C_6H_4), 9.73 s (1H, OH), 10.88 s (1H, OH). Mass spectrum of mixture of compounds **VIa** and **VIIb**, *m/z* (I_{rel}, %): 404 and 402 $[M]^+$ (12), 372 and 370 $[M]^+$ (100), 199 (74), 183 (27), 171 (90), 155 (40), 127 and 126 (44). Found, %: C 50.96; H 1.81; N 7.32. Calculated [for (**VIa**):(**VIIb**) = 85:15], %: C 51.11; H 1.88; N 7.45.

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