Reactions of 3,5-di-*tert*-butyl-1,2-benzoquinone with mercapto carboxylic acids

L. Yu. Ukhin,[a] K. Yu. Suponitsky,[b] E. N. Shepelenko,[c] L. V. Belousova,[a] D. V. Alekseenko,[a] G. S. Borodkin,[a] and L. N. Etmetchenko[a]*

[a] *Institute of Physical and Organic Chemistry, Southern Federal University, 194/2 prosp. Stachki, 344090 Rostov on Don, Russian Federation. Fax: +7 (863) 243 4700. E-mail: may@ipoc.sfedu.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. E-mail: kirshik@yahoo.com*
[c] *Southern Scientific Center, Russian Academy of Sciences, 41 ul. Chekhova, 344006 Rostov on Don, Russian Federation. E-mail: dubon@ipoc.sfedu.ru*

Heating of an equimolar mixture of 3,5-di-*tert*-butyl-1,2-benzoquinone with thiosalicylic acid led to 2-[(4,6-di-*tert*-butyl-2,3-dihydroxyphenyl)thio]benzoic acid. In the case of β-mercaptopropionic acid, 2-[(4,6-di-*tert*-butyl-2,3-dihydroxyphenyl)thio]propionic acid was formed, which upon reflux in Ac_2O was converted to 6,8-di-*tert*-butyl-9-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-2-one.

Key words: 3,5-di-*tert*-butyl-1,2-benzoquinone, mercapto carboxylic acids, lactonization, 6,8-di-*tert*-butyl-9-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-2-one.

3,5-Di-*tert*-butyl-1,2-benzoquinone (**1**) is easily available and promising compound[1,2] due to its ability to be involved in different reactions, leading to unexpected structures. The formation of β-tropolones in the reaction of **1** with 2-methylquinoline derivatives[3,4] is one of the examples.

Another interesting example was the conversion of 3-[(2-aminophenyl)amino]-5,5-dimethylcyclohex-2-en-1-one in the reaction with quinone **1** to earlier unknown macrolactone of the oxonine series.[5] In these examples, the reaction begins from the attack by C- or N-nucleophile on the quinone C(2)-carbonyl carbon atom.

In the reaction with S-nucleophiles, the attack was directed on another electrophilic center of quinone **1**: the C(6) carbon atom (see Refs 2 and 6), thus following the Michael addition reaction. In the case of thioglycolic acid, 4,6-di-*tert*-butyl-2,3-dihydroxyphenylthioacetic acid was obtained, undergoing ready lactonization to 5,7-di-*tert*-butyl-8-hydroxy-1,4-benzoxathiin-2(3*H*)-one. These both compounds possess antioxidant properties, especially pronounced in the lactone, which is regarded by the authors as the structural analogue of tocopherol.[2] Apart from that, the acid and its complex with Ag^I exibit antimicrobial activity.[7] We did not find information in the literature on the reaction of quinone **1** with thiosalicylic acid (**2**).

We found that an equimolar mixture of quinone **1** and thiosalicylic acid (**2**) triturated in a mortar and subjected to heating, after partial melting undervent conversion to a loose colorless mass without complete melting. The IR and mass spectra of the material obtained indicate the formation of a linear product of addition of thiosalicylic acid to quinone at position C(6). However, the ^{1}H NMR spectrum of the product recrystallized from MeCN exhibited signals conflicting with the structure.

The X-ray diffraction study of the crystal grown from MeCN unambiguously confirmed that this is 2-[(4,6-di-*tert*-butyl-2,3-dihydroxyphenyl)thio]benzoic acid (**3**, Scheme 1, Fig. 1). The cause of the discrepancy of the ^{1}H NMR spectrum was the presence of disulfide **4** in the sample. Compound **4** was formed simultaneously with the main product by the oxidation of thiosalicylic acid. The impurity of disulfide **4** cannot be removed by recrystallization from MeCN.

The spectrally pure product **3** was obtained by recrystallization of the reaction mixture from acetone. The compound is very poorly soluble in refluxing acetic acid, but crystallizes from a mixture of AcOH—Ac_2O (6 : 1). Refluxing acetic anhydride decomposes compound **3**.

The asymmetric unit cell of compound **3** contains one molecule. The phenyl rings bound by a sulfide bridge are arranged almost perpendicular to each other because of the steric factor. Both hydroxy groups are almost coplanar to the phenyl ring, to which they are attached. The hydro-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 0727—0730, March, 2016.

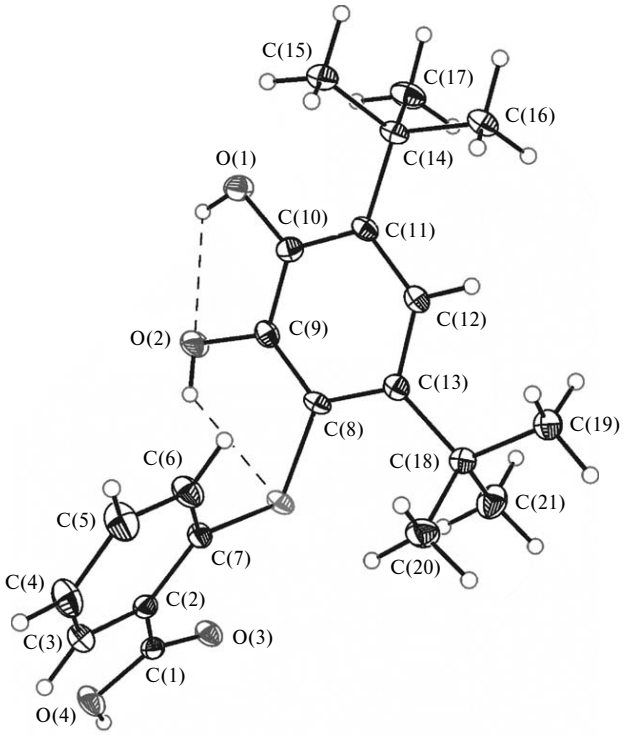
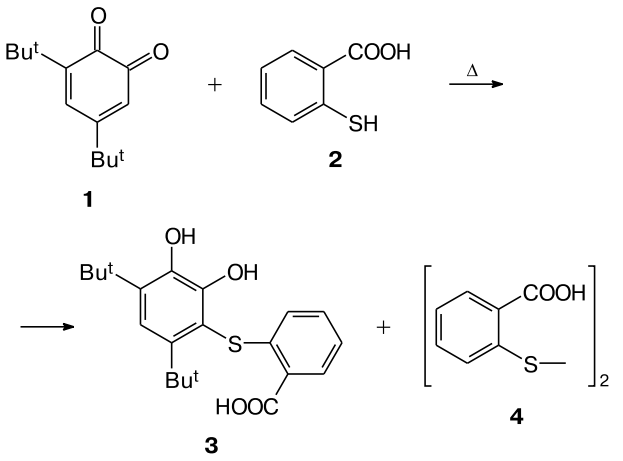


Fig. 1. General view of compound **3** in representation of atoms by ellipsoids of atomic displacements with 50% probability.

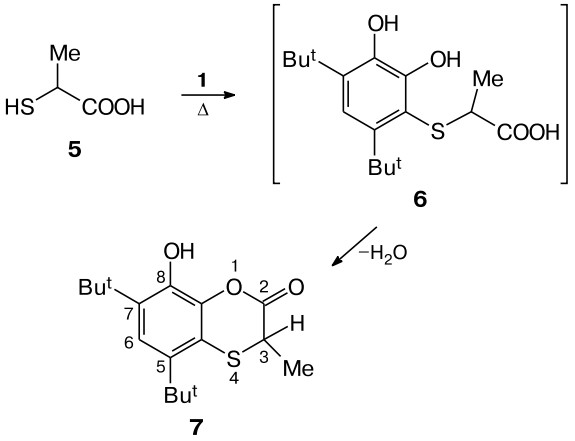
Scheme 1



gen atoms of these groups are not involved in the formation of intermolecular hydrogen bond (because of the steric hindrance posed by the close *tert*-butyl groups), but form the weak intramolecular bonds O(2)—H(2)...S(1) (O—H, 0.82(2), O...S, 2.920(2), H...S, 2.35(2), <OHS, 127(2)°), O(1)—H(1)...O(2) (O—H, 0.81(2) Å, O...O, 2.619(2) Å, H...O, 2.13(2) Å, <OHO, 118(2)°). At the same time, the proton of the carboxy group is involved in the strong direct intermolecular H-bond O(4)—H(4)...O(3) (O—H 0.83(2), O...O, 2.683(2) Å, H...O, 1.86(2), <OHO, 173(2)°), which leads to the formation of centrosymmetric dimers bound by a hydrogen bond typical of carboxylic acids.[8—10]

It was found that a short-time heating of quinone **1** with 2-mercaptopropionic acid (**5**) led to 5,7-di-*tert*-butyl-8-hydroxy-3-methyl-1,4-benzoxantiin-2(3*H*)-one (**7**) (Scheme 2).

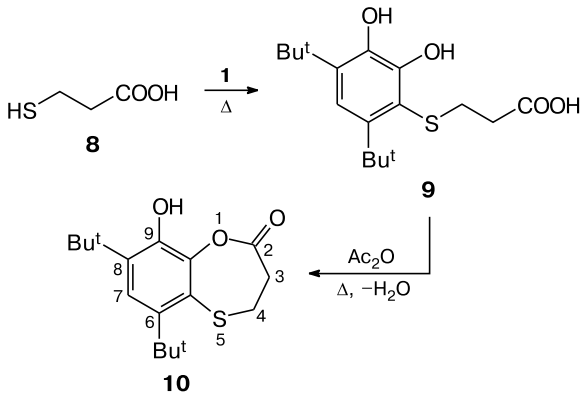
Scheme 2



Apparently, compound **7** is formed by lactonization of the intermediate acid **6**, similarly to the reaction of **1** with thioglycolic acid.[2]

The product of heating of quinone **1** with 3-mercaptopropionic acid (**8**) was 3-[4,6-di-*tert*-butyl-(2,3-dihydroxyphenyl)thio]propionic acid (**9**). Its reflux in Ac_2O causes lactonization to the earlier undescribed 6,8-di-*tert*-butyl-9-hydroxy-3,4-dihydro-2*H*-benz-1,5-oxathiepin-2-one (**10**) (Scheme 3).

Scheme 3



Compound **10** is isomeric to compound **7**. If a suggested intermediate compound **6** undergoes lactonization just upon heating, the acid **9** remains unchanged upon reflux in acetic acid, from which it can be recrystallized. The structure of **10** was inferred from its ^1H and ^{13}C NMR

spectra by the complete assignment of the signals (see Experimental). The complete assignment of chemical shifts in the ^{1}H NMR spectra was made using a 2D pulse sequence COSY.

The complete assignment of chemical shifts in the ^{13}C NMR spectra was made using a 2D pulse sequences HSQC and HMBC.

Experimental

IR spectra were recorded on a Varian Excalibur 3100 FT-IR spectrometer using FTIR method. ^{1}H NMR spectra were recorded on a Varian UNITY-300 spectrometer. Mass spectra were obtained on a Shimadzu GCMS-QP2010 SE spectrometer with direct injection of the sample into the source of ions (EI 70 eV). The signals in the NMR spectra of compound **9** were assigned based on the experiments recorded on a Bruker Avance-600 spectrometer, which was also used for recording ^{13}C NMR spectra for compounds **7** and **9**. The starting compounds and solvents were purchased from Alfa Acear.

2-[(4,6-Di-*tert*-butyl-2,3-dihydroxyphenyl)thio]benzoic acid (3). A mixture of quinone **1** (0.44 g, 2 mmol) and thiosalicylic acid (0.31 g, 2 mmol) was triturated in a mortar, then placed into a 25-mL round-bottom flask, and heated in a heater with the temperature set to 300 °C. A partially melted mixture, without complete melting, turned to a loose colorless mass. After cooling, ethyl acetate (5 mL) was added, a precipitate formed was triturated, filtered, sequentially washed with ethyl acetate, diethyl ether, and light petroleum ether. The yield of the product containing a disulfide **4** admixture was 0.4 g (53%). To obtain spectrally pure compound, the product was recrystallized from acetone, hot-filtered through a dense filter to obtain a colorless compound with m.p. 245 °C (from acetone). IR, ν/cm^{-1}: 3527, 3365 (OH); 2961 (Bu^t); 1681 (CO). ^{1}H NMR (300 MHz, DMSO-d$_6$), δ: 1.36 (s, 9 H, Bu^t); 1.38 (s, 9 H, Bu^t); 6.43 (d, 1 H, CH$_{arom}$, J = 8.4 Hz); 6.93 (s, 1 H, C(5′)H); 7.09 (t, 1 H, CH$_{arom}$, J = 7.5 Hz); 7.30 (dt, 1 H, CH$_{arom}$, ^3J = 8.4 Hz, J = 1.5 Hz); 7.91 (dd, 1 H, ^3J = 7.5 Hz, J = 1.5 Hz); 8.12 (s, 1 H, OH); 8.45 (s, 1 H, OH); 13.05 (s, 1 H, OH). MS, *m/z*: 374 [M]$^+$.

5,7-Di-*tert*-butyl-8-hydroxy-3-methyl-1,4-benzoxathiin-2(3*H*)-one (7). A mixture of quinone **1** (0.22 g, 1 mmol) and 2-mercaptopropionic acid (0.15 mL) was heated until dissolution and turning colorless, followed by addition of EtOH (2 mL). Then, the mixture was heated to homogenization and cooled, resulting in solidification of the mass. The material obtained was placed on a filter, washed with cold EtOH, light petroleum ether, and dried to obtain a colorless compound (0.11 g) with m.p. 150—152 °C (from EtOH). The filtrate was treated with water to precipitate another 0.12 g of the compound with an identical IR spectrum. A total yield was 0.23 g (74%). Found (%): C, 66.34; H, 7.93; S, 10.28. $C_{17}H_{24}O_3S$. Calculated (%): C, 66.20; H, 7.84; S, 10.40. IR, ν/cm^{-1}: 3438 (OH); 2965, 2954 (Bu^t); 1763 (CO). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.37 (s, 9 H, Bu^t); 1.41 (s, 9 H, Bu^t); 1.56 (d, 3 H, CH_3, J = 6.9 Hz); 3.40 (q, 1 H, CH, J = 6.9 Hz); 5.76 (s, 1 H, OH); 7.08 (s, 1 H, C(6)H). ^{13}C NMR (600 MHz, $CDCl_3$), δ: 13.81, 29.31, 30.26, 35.17, 36.15, 36.29, 116.87, 120.01, 134.22, 138.15, 139.23, 141.42, 166.23. MS, *m/z*: 308 [M]$^+$.

3-[(4,6-Di-*tert*-butyl-2,3-dihydroxyphenyl)thio]propionic acid (9). A mixture of quinone **1** (0.22 g, 0.2 mmol) and 3-mercaptopropionic acid (0.2 mL) was heated until dissolution and turning colorless and cooled, resulting in solidification of the mixture. Light petroleum ether (3 mL) was added, the precipitate was triturated, filtered, and washed with light petroleum ether to obtain a colorless compound with m.p. 161—165 °C (from light petroleum ether), the yield was 0.25 g (77%). Found (%): C, 62.73; H, 8.28; S, 9.61. $C_{17}H_{26}O_4S$. Calculated (%): C, 62.54; H, 8.03; S, 9.82. IR, ν/cm^{-1}: 3539, 3342 (OH); 2953 (Bu^t); 1698 (CO). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.40 (s, 9 H, Bu^t); 1.49 (s, 9 H, Bu^t); 2.74 (t, 2 H, CH_2, J = 6.6 Hz); 2.92 (t, 2 H, CH_2, J = 6.6 Hz); 5.65 (br.s, 1 H, OH); 6.91 (s, 1 H, C(5)H); 7.50 (br.s, 1 H, OH). ^{13}C NMR (600 MHz, DMSO-d$_6$), δ: 29.24, 30.75, 31.27, 33.02, 34.59, 36.31, 114.68, 116.70, 135.07, 141.54, 142.18, 147.39, 173.35. MS, *m/z*: 326 [M]$^+$.

6,8-Di-*tert*-butyl-9-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-2-one (10). A mixture of compound **9** (0.293 g, 0.89 mmol) and Ac_2O (1 mL) was heated to reflux, a clear solution formed was cooled. Light petroleum ether (3 mL) was added to the reaction mixture with a precipitate formed. The precipitate was filtered, washed with light petroleum ether, and dried. The yield of crude product was 0.115 g (42%). Recrystallization from light petroleum ether (70—100 °C) (15 mL) gave chemically pure compound **10** (0.081 g, 29%), a colorless compound, m.p. 194 °C (from light petroleum ether). Found (%): C, 65.94; H, 8.03; S, 10.02. $C_{17}H_{24}O_3S$. Calculated (%): C, 66.20; H, 7.84; S, 10.40. IR, ν/cm^{-1}: 3370 (OH); 2991, 2959 (Bu^t); 1757 (CO). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 1.41 (s, 9 H, Bu^t); 1.51 (s, 9 H, Bu^t); 2.76 (t, 2 H, C(3)H$_2$, J = 7.1 Hz); 3.17 (t, 2 H, C(4)H$_2$, J = 7.1 Hz); 5.91 (s, 1 H, OH); 7.27 (s, 1 H, C(7)H). ^{13}C NMR, δ: 29.23 (C(8)—C($\underline{C}$H$_3$)$_3$); 31.20 (C(6)—C($\underline{C}$H$_3$)$_3$); 31.61 (C(4)); 32.75 (C(3)); 35.46 (C(8)—$\underline{C}$Me$_3$); 37.00 (C(6)—$\underline{C}$Me$_3$); 118.09 (C(5a)); 122.20 (C(7)); 137.66 (C(8)); 142.95 (C(9)); 143.25 (C(9a)); 144.06 (C(6)); 169.46 (C(2)). MS, *m/z*: 308 [M]$^+$.

X-ray diffraction study of compound 3. Crystals $C_{21}H_{26}O_4S$ at 120 K are monoclinic, space group $P2_1/c$: a = 10.5940(4) Å, b = 9.9657(4) Å, c = 17.9939(7) Å, β = 92.4570(10)°, V = = 1897.99(13) Å^3, Z = 4, M = 374.48, d_{calc} = 1.311 g cm^{-3}, wR_2 = 0.0841, the structure was solved on F^2_{hkl} and on 4139 independent reflections with 2θ < 54°, GOOF = 1.032 (R = 0.0330, was solved on F_{hkl} on 3679 reflections with $I > 2\sigma(I)$). Crystallographic data (except structural factors) for this the structure were deposited with the Cambridge Crystallographic Data Center (CCDC 1411565).

Spectroscopic studies were carried out using facilities of the Molecular Spectroscopy Multi-access Center of the Southern Federal University.

This work was financially supported by the Ministry of Education and Science of the Russian Federation within the Project part of the State Assignment in Academic Area for the Southern Federal University according to the Theme 4.196.2014/K.

References

1. W. Flaig, T. Ploetz, Y. Biergans, *Lieb. Ann.*, 1955, **597**, 196.
2. L. A. Maslovskaya, D. K. Petrikevich, V. A. Timoshchuk, V. A. Shadyro, *Zh. Obshch. Khim.*, 1996, **66**, 1899 [*Russ. J. Gen. Chem.* (*Engl. Transl.*), 1996, **66**].

3. V. N. Komissarov, Dyong Nghia Bang, V. I. Minkin, S. M. Aldoshin, V. V. Tkachev, G. V. Shilov, *Mendeleev Commun.*, 2003, **13**, 219.
4. V. I. Minkin, S. M. Aldoshin, V. N. Komissarov, I. V. Dorogan, Yu. A. Sayapin, V. V. Tkachev, A. G. Starikov, *Russ. Chem. Bull.* (*Int. Ed.*), 2006, **55**, 2032 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2006, 1956].
5. L. Yu. Ukhin, K. Yu. Suponitsky, E. N. Shepelenko, L. V. Belousova, G. S. Borodkin, *Tetrahedron Lett.*, 2012, **53**, 67.
6. L. A. Maslovskaya, D. K. Petrikevich, V. A. Timoshchuk, V. A. Shadyro, *Zh. Obshch.. Khim.*, 1996, **66**, 1893 [*Russ. J. Gen. Chem.* (*Engl. Transl.*), 1996, **66**].
7. N. V. Loginova, F. A. Chernyavskaya, G. I. Polozov, T. V. Kovalchuk, E. V. Bondarenko, N. P. Osipovich, A. A. Cheryakov, O. I. Shadyro, *Polyhedron*, 2005, **24**, 611.
8. (a) L. Turi, J. J. Dannenberg, *J. Phys. Chem.*, 1993, **97**, 12197; (b) L. Turi, J. J. Dannenberg, *J. Am. Chem. Soc.*, 1994, **116**, 8714.
9. C. H. Gorbitz, M. C. Etter, *J. Am. Chem. Soc.*, 1992, **114**, 627.
10. K. Yu. Suponitsky, T. V. Timofeeva, M. Yu. Antipin, *Russ. Chem. Rev.*, 2006, **75**, 457.

Received August 28, 2015;
in revised form December 23, 2015