Chemistry of Heterocyclic Compounds, Vol. 36, No. 8, 2000

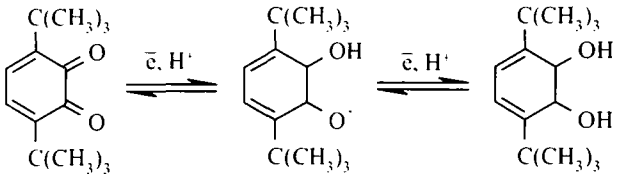
SYNTHESIS OF HETEROCYCLIC DERIVATIVES OF 3,6-DI-*tert*-BUTYL-*o*-BENZOQUINONE BY CATALYTIC DEHYDROCONDENSATION WITH ETHYLENE GLYCOL, GLYCEROL, AND DIETHANOLAMINE

T. I. Prokof'eva, V. B. Vol'eva, A. I. Prokof'ev, S. Belostotskaya, N. L. Komissarov, and V. V. Ershov

The dehydrocondensation of 3,6-di-tert-butyl-o-benzoquinone with ethylene glycol, glycerol, its chlorhydrin, and with diethanolamine, catalyzed by MnO_2–NaOH, has been carried out in an alcohol–DMF medium with the formation of 7,10-di-tert-butyl-2,5-dioxabicyclo[4.4.0]deca-1,6-diene-8,9-dione, its 4-hydroxymethyl and 4-chloromethyl derivatives, and 7,10-di-tert-butyl-5-(β-hydroxyethyl)-2-oxa-5-azabicyclo[4.4.0]deca-1,6-diene-8,9-dione.

Keywords: manganese dioxide, 3,6-di-*tert*-butyl-*o*-benzoquinone, 7,10-di-*tert*-butyl-5-(β-hydroxyethyl)-2-oxa-5-azabicyclo[4.4.0]deca-1,6-diene-8,9-dione, derivatives of 2,5-dioxabicyclo[4.4.0]deca-1,6-diene-8,9-dione, catalytic dehydrocondensation.

3,6-Di-*tert*-butyl-*o*-benzoquinone (**1**) and the redox-linked 3,6-di-*tert*-butylpyrocatechol (**2**) have become widespread as models for investigating fundamental problems of solid phase and structural chemistry, radiospectroscopy, catalysis, and medical biology (see, for example, [1,2]). This is due to a significant extent to the redox activity of the **1,2** pair, to the ease of electronic transitions in the quinone–semiquinone–pyrocatechol triad, to the coordinating activity of the *o*-carbonyl (or hydroxyl) groups, and to the relative simplicity of recording and identifying derivatives. The introduction of substituents into positions 4 and 5 of the ring broadens the scope of applying the pair. In particular, biologically active compounds and complexones for special purposes have been discovered among the amino and alkoxy substituted derivatives of quinone [3].

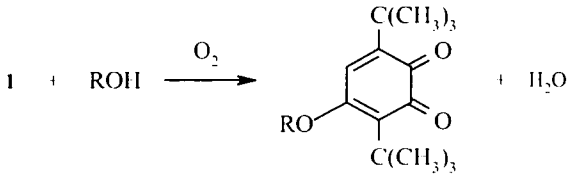


1 **2**

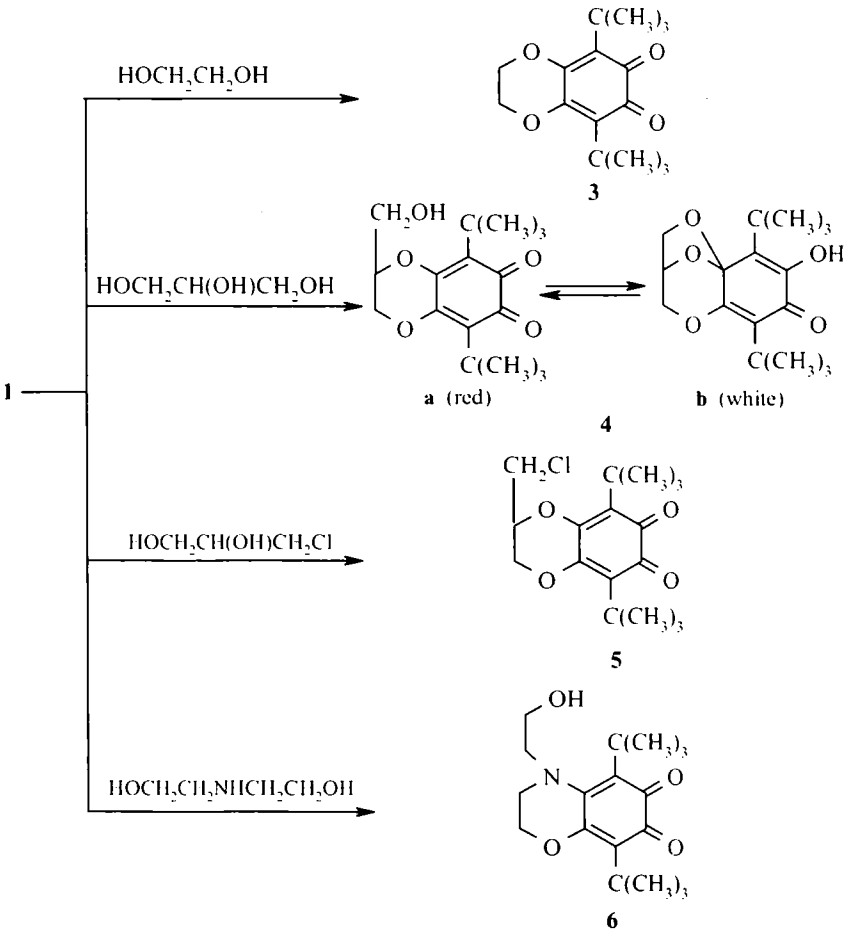
N. M. Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, Moscow 117977, Russia; e-mail: chembio@chph.ras.ru, chembio@glasnet.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1057-1065, August, 2000. Original article submitted January 13, 1999.

0009-3122/00/3608-0923$25.00©2000 KluwerAcademic/Plenum Publishers

The alkoxylation of quinone **1** by the lower alcohols is effected as a spontaneous oxidation–reduction process with the participation of atmospheric oxygen.



The rate of such autoalkoxylation is extremely small, however the process may be catalyzed by low valency ions of the transition metals. We have obtained alkoxy substituted quinone derivatives by interaction with methanol and ethanol in the presence of $MnOAc_2$ [4]. The applicability of this method, combining the use of alcohol as reactant and solvent is limited by the poor solubility of quinone **1** in the majority of higher and substituted alcohols. Investigation of alkoxylation in binary mixtures of alcohol and solvent with various catalysts (Mn, Co, Fe, Cu acetates and halides) showed that the best results were achieved in an alcohol–DMF medium using the twin catalyst MnO_2–NaOH. The following 4,5-disubstituted heterocyclic derivatives of quinone **1** were obtained for the first time by the reaction of quinone **1** with ethylene glycol, glycerol, glycerol chlorohydrin, and diethanolamine: 7,10-di-*tert*-butyl-2,5-dioxabicyclo[4.4.0]deca-1,6-diene-8,9-dione (**3**), 4-hydroxymethyl-7,10-di-*tert*-butyl-2,5-dioxabicyclo[4.4.0]deca-1,6-diene-8,9-dione (**4**), 4-chloromethyl-7,10-di-*tert*-butyl-2,5-dioxabicyclo-[4.4.0]deca-1,6-diene-8,9-dione (**5**), and 5-(β-hydroxyethyl)-7,10-di-*tert*-butyl-2-oxa-5-azabicyclo[4.4.0]deca-1,6-diene-8,9-dione (**6**).



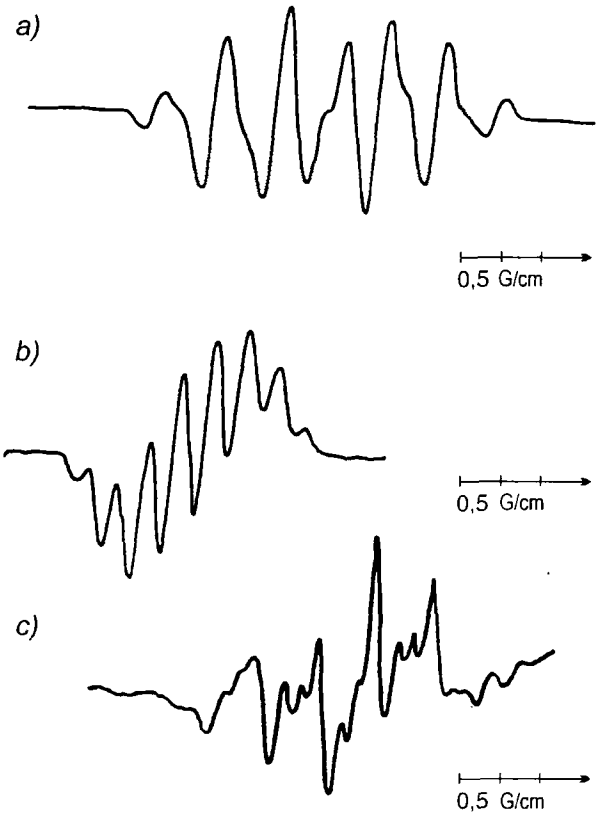


Fig. 1. The ESR spectrum of the products of one-electron reduction of quinone **3**:
a) semiquinone; b) Na semiquinolate; c) deuterosemiquinone.

One of the methods for structural identification in the chemistry of quinones is ESR analysis of the paramagnetic compounds formed in the one electron reduction, *viz.* semiquinones or semiquinolates. The semiquinone and deuterosemiquinone corresponding to quinone **3** were obtained directly in the resonator of the ESR spectrometer on irradiating solutions of quinone in toluene with a small addition of H_2O (D_2O) with UV light.

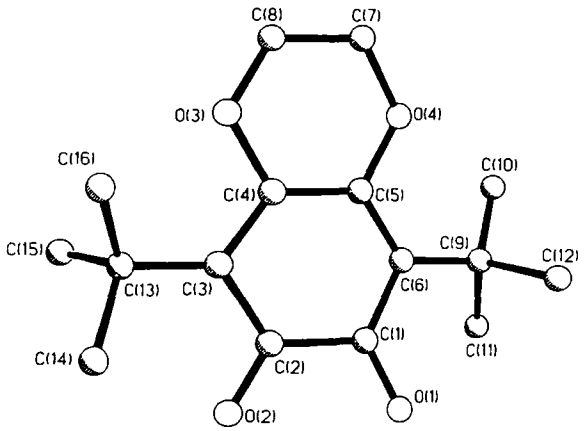
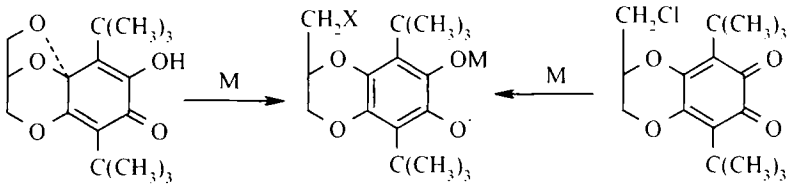


Fig. 2. Molecular structure of 7,10-di-*tert*-butyl-2,5-dioxabicyclo[4.4.0]deca-1,6-diene-8,9-dione **3**.

The ESR spectrum of the semiquinone (Fig. 1a) corresponds to the interaction of an unpaired electron with the proton of a hydroxyl group and with four methylene protons of the heterocyclic fragment with parameters $\alpha_H^{CH_2} = 0.65$ and $\alpha_H^{OH} = 1.4$ G. The spectrum of the deuterosemiquinone (Fig. 1c) is characterized by the constant $\alpha_D^{OD} = 0.2$ G. On reduction of quinone **3** with metallic sodium in THF the spectrum of the semiquinolate is observed (Fig. 1b), corresponding to the interaction of the unpaired electron with the four methylene protons and the ^{23}Na nucleus ($J = 3/2$), $\alpha_H^{CH_2} = \alpha_{Na} = 0.35$ G.

The identity of quinone **3** was also confirmed by data of X-ray structural analysis (Fig. 2).

The ESR method proved to be particularly useful in the identification of the structure of the dehydro adduct of quinone **1** with glycerol, which exists as the *ortho*-quinone **4a** (red) only in melts and in the presence of bases, but under normal conditions has the structure of the tricyclic isomer **4b** (white). The cryptoquinone structure causing the thermo- and pH-chromic properties of the tricycle **4b**, confirmed by ESR analysis of the semiquinolates formed on reduction of it with sodium and thallium amalgam, were spectrally identical to the semiquinolates obtained from quinone **5** under analogous conditions.



4b M = Na, Tl; X = Cl, O⁻ **5**

The observed spectra of the sodium semiquinolates correspond to the interaction of the unpaired electron with two equatorial protons of the heterocycle and with the ^{23}Na nucleus ($\alpha_{Na} = \alpha_H = 0.45$ G, Fig. 3a). In the spectra of the thallium semiquinolates a doublet was observed from the ^{199}Tl nucleus ($\alpha_{Tl} = 27.2$ G, $g_{iso} = 1.9327$, Fig. 3b).

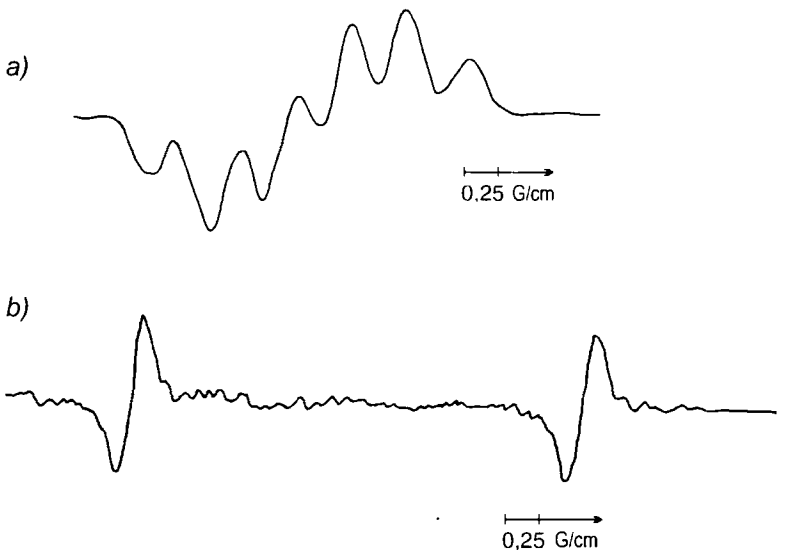


Fig. 3. The ESR spectrum of the reduction products of compounds **4** and **5**:
a) Na in THF; b) thallium amalgam in THF.

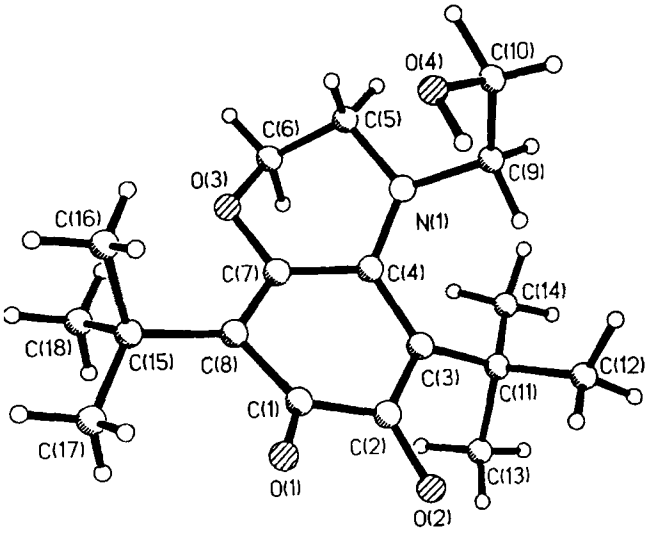


Fig. 4. Molecular structure of 7,10-di-*tert*-butyl-2-oxa-5-azabicyclo[4.4.0]deca-1,6-diene-8,9-dione **6**.

The structural identification of the dehydro adducts **4** and **5** was confirmed by ^{1}H NMR data. An interesting feature of quinone **5** is the nonequivalence of the chloromethyl group protons, indicating the hindrance to its free rotation.

The identification of *o*-quinone **6** was based on data of the ^{1}H NMR spectrum and X-ray structural analysis (Fig. 4).

TABLE 1. Bond Lengths (d) in Structure **3**

Bond	d, Å	Bond	d, Å
O(1)–C(1)	1.20(1)	O(1')–C(1')	1.22(2)
O(2)–C(2)	1.23(1)	O(2')–C(2')	1.20(2)
O(3)–C(4)	1.36(2)	O(3')–C(4')	1.36(1)
O(3)–C(8)	1.42(2)	O(3')–C(7')	1.40(2)
O(4)–C(5)	1.34(1)	O(4')–C(5')	1.35(1)
O(4)–C(7)	1.41(2)	O(4')–C(8')	1.45(2)
C(1)–C(6)	1.45(2)	C(1')–C(6')	1.43(2)
C(1)–C(2)	1.53(2)	C(1')–C(2')	1.51(2)
C(2)–C(3)	1.47(2)	C(2')–C(3')	1.49(2)
C(3)–C(4)	1.37(2)	C(3')–C(4')	1.36(2)
C(3)–C(13)	1.51(2)	C(3')–C(9')	1.59(2)
C(4)–C(5)	1.47(2)	C(4')–C(5')	1.49(2)
C(5)–C(6)	1.35(2)	C(5')–C(6')	1.35(2)
C(6)–C(9)	1.51(2)	C(6')–C(13')	1.52(2)
C(7)–C(8)	1.38(2)	C(7')–C(8')	1.44(2)
C(9)–C(10)	1.51(2)	C(9')–C(12')	1.46(2)
C(9)–C(12)	1.52(2)	C(9')–C(11')	1.50(2)
C(9)–C(11)	1.53(2)	C(9')–C(10')	1.53(2)
C(13)–C(15)	1.50(2)	C(13')–C(15')	1.42(2)
C(13)–C(16)	1.52(2)	C(13')–C(16')	1.49(2)
C(13)–C(14)	1.54(2)	C(13')–C(14')	1.55(2)

TABLE 2. Valence Angles (ω) in Structure **3**

Angle	ω, deg.	Angle	ω, deg.
C(4)–O(3)–C(8)	120(1)	C(4')–O(3')–C(8')	119(1)
C(5)–O(4)–C(7)	120(1)	C(5')–O(4')–C(8')	121(1)
O(1)–C(1)–C(6)	126(2)	O(1')–C(1')–C(6')	124(2)
O(1)–C(1)–C(2)	115(1)	O(1')–C(1')–C(2')	111(2)
C(6)–C(1)–C(2)	119(1)	C(6')–C(1')–C(2')	124(1)
O(2)–C(2)–C(3)	122(1)	O(2')–C(2')–C(3')	121(2)
O(2)–C(2)–C(1)	116(1)	O(2')–C(2')–C(1')	119(2)
C(3)–C(2)–C(1)	122(1)	C(3')–C(2')–C(1')	120(2)
C(4)–C(3)–C(2)	110(1)	C(4')–C(3')–C(2')	112(1)
C(4)–C(3)–C(13)	126(1)	C(4')–C(3')–C(9')	125(1)
C(2)–C(3)–C(13)	124(1)	C(2')–C(3')–C(9')	122(2)
O(3)–C(4)–C(3)	116(2)	O(3')–C(4')–C(3')	118(1)
O(3)–C(4)–C(5)	117(1)	O(3')–C(4')–C(5')	118(1)
C(3)–C(4)–C(5)	127(1)	C(3')–C(4')–C(5')	125(1)
O(4)–C(5)–C(6)	117(1)	C(6')–C(5')–O(4')	117(1)
O(4)–C(5)–C(4)	118(1)	C(6')–C(5')–C(4')	127(2)
C(6)–C(5)–C(4)	124(1)	O(4')–C(5')–C(4')	117(1)
C(5)–C(6)–C(1)	115(2)	C(5')–C(6')–C(1')	111(1)
C(5)–C(6)–C(9)	126(1)	C(5')–C(6')–C(13')	125(1)
C(1)–C(6)–C(9)	119(1)	C(1')–C(6')–C(13')	123(1)
C(8)–C(7)–O(4)	115(1)	O(3')–C(7')–C(8')	114(2)
C(7)–C(8)–O(3)	112(1)	C(7')–C(8')–O(4')	107(2)
C(10)–C(9)–C(6)	114(1)	C(12')–C(9')–C(11')	104(2)
C(10)–C(9)–C(12)	111(2)	C(12')–C(9')–C(3')	110(2)
C(6)–C(9)–C(12)	108(1)	C(11')–C(9')–C(3')	112(1)
C(10)–C(9)–C(11)	105(2)	C(12')–C(9')–C(10')	109(2)
C(6)–C(9)–C(11)	111(1)	C(11')–C(9')–C(10')	106(2)
C(12)–C(9)–C(11)	108(1)	C(3')–C(9')–C(10')	115(2)
C(15)–C(13)–C(3)	109(1)	C(15')–C(13')–C(16')	111(2)
C(15)–C(13)–C(1)	109(2)	C(15')–C(13')–C(6')	111(1)
C(3)–C(13)–C(16)	113(1)	C(16')–C(13')–C(6')	115(1)
C(15)–C(13)–C(14)	109(2)	C(15')–C(13')–C(14')	110(2)
C(3)–C(13)–C(14)	111(1)	C(16')–C(13')–C(14')	101(2)
C(16)–C(13)–C(14)	106(2)	C(6')–C(13')–C(14')	109(1)

TABLE 3. Bond Lengths (*d*) in Structure **6**

Bond	*d*, Å	Bond	*d*, Å
N(1)–C(4)	1.360(6)	C(3)–C(11)	1.545(6)
N(1)–C(5)	1.462(6)	C(4)–C(7)	1.494(6)
N(1)–C(9)	1.482(6)	C(5)–C(6)	1.477(7)
O(1)–C(1)	1.218(6)	C(7)–C(8)	1.343(6)
O(2)–C(2)	1.251(6)	C(8)–C(15)	1.535(7)
O(3)–C(7)	1.357(5)	C(9)–C(10)	1.511(8)
O(3)–C(6)	1.433(6)	C(11)–C(14)	1.526(7)
O(4)–C(10)	1.383(6)	C(11)–C(12)	1.547(7)
C(1)–C(8)	1.451(7)	C(11)–C(13)	1.556(7)
C(1)–C(2)	1.517(7)	C(15)–C(17)	1.461(8)
C(2)–C(3)	1.417(6)	C(15)–C(18)	1.505(8)
C(3)–C(4)	1.396(3)	C(15)–C(16)	1.533(9)

TABLE 4. Valence Angles (ω) in Structure **6**

Angle	ω, deg.	Angle	ω, deg.
C(4)–N(1)–C(5)	120.4(4)	C(8)–C(7)–C(4)	125.1(4)
C(4)–N(1)–C(9)	120.8(4)	O(3)–C(7)–C(4)	116.1(4)
C(5)–N(1)–C(9)	116.1(4)	C(3)–C(8)–C(1)	112.0(5)
C(7)–O(3)–C(6)	117.3(4)	C(7)–C(8)–C(15)	123.5(4)
O(1)–C(1)–C(8)	123.9(5)	C(1)–C(8)–C(15)	124.4(5)
O(1)–C(1)–C(2)	116.7(4)	N(1)–C(9)–C(10)	111.6(4)
C(8)–C(1)–C(2)	119.4(5)	O(4)–C(10)–C(9)	114.0(5)
O(2)–C(2)–C(3)	123.7(5)	C(14)–C(11)–C(3)	114.0(4)
O(2)–C(2)–C(1)	114.7(5)	C(14)–C(11)–C(12)	110.1(4)
C(3)–C(2)–C(1)	121.5(4)	C(3)–C(11)–C(12)	111.4(4)
C(4)–C(3)–C(2)	112.5(4)	C(14)–C(11)–C(13)	105.5(4)
C(4)–C(3)–C(11)	127.6(4)	C(3)–C(11)–C(13)	108.0(4)
C(2)–C(3)–C(11)	119.8(4)	C(12)–C(11)–C(13)	107.4(4)
N(1)–C(4)–C(3)	124.6(5)	C(17)–C(15)–C(18)	109.0(7)
N(1)–C(4)–C(7)	115.7(4)	C(17)–C(15)–C(16)	106.9(8)
C(3)–C(4)–C(7)	119.7(5)	C(18)–C(15)–C(16)	107.2(5)
N(1)–C(5)–C(6)	109.0(4)	C(17)–C(15)–C(8)	113.0(5)
O(3)–C(6)–C(5)	107.4(5)	C(18)–C(15)–C(8)	112.5(5)
C(8)–C(7)–O(3)	118.7(4)	C(16)–C(15)–C(8)	107.9(5)

TABLE 5. Characteristics of 7,10-Di-*tert*-butyl-2,5-dioxabicyclo[4.4.0]deca-1,6-diene-8,9-diones **3-5** and 7,10-di-*tert*-butyl-5-(β-hydroxyethyl)-2-oxa-5-azabicyclo[4.4.0]deca-1,6-diene-8,9-dione **6**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	^{1}H NMR spectrum, $CDCl_3$, δ, ppm
		C	H		
3	$C_{16}H_{22}O_4$	69.20 / 69.06	8.01 / 7.89	173-174	1.29 (9H, s, CMe_3); 4.35 (2H, s, CH_2O)
4	$C_{15}H_{24}O_5$	66.11 / 66.23	7.75 / 7.79	169-170	1.36 (9H, s, CMe_3); 4.09 (4H, br. s, J = 2.8 Hz, $2CH_2O$); 4.64 (1H, t, J = 2.8 Hz, CH); 7.65 (1H, s, OH)
5	$C_{16}H_{23}ClO_4$	62.43 / 62.38	7.15 / 7.03	186-187	1.3 and 1.32 (9H, s, CMe_3); 3.74 (1H, dd, J = 11.5 and 6.5 Hz, $2CH_2Cl$); 3.78 (1H, dd, J = 11.5 and 5.5 Hz, $2CH_2Cl$); 4.24 (1H, dd, J = 8.2 and 11.6 Hz, CH_2O); 4.44 (1H, dd, J = 3.1 and 11.6 Hz, CH_2O); 4.61 (1H, m, CH)
6	$C_{18}H_{31}NO_4$	67.11 / 67.29	8.33 / 8.41	187-188	1.28 and 1.30 (9H, s, CMe_3); 3.6 (4H, br. s, $2CH_2N$); 3.85 (4H, t, J = 6.1 Hz, $2CH_2O$)

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM 400 instrument, the solvent was $CDCl_3$. The ESR spectra of deoxygenated specimens in THF or toluene were recorded on a Varian E 12A spectrometer. Thin layer chromatography of reaction mixtures was carried out on Silufol UV-254 plates in the system hexane–ether 4 : 1. The X-ray structural analysis was carried out with collaborators O. V. Shishkin and E. V. Solomovich (A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences). The molecular structures of compounds **3** and **6** are given in Figs. 2 and 4, and the bond lengths and valence angles in

Tables 1-4. The results of the X-ray structural analysis will be presented elsewhere in more detail. Synthesis of the heterocyclic dehydroadducts of 3,6-di-*tert*-butyl-*o*-benzoquinone (**1**) with ethylene glycol, glycerol, glycerol chlorohydrin, and diethanol-amine was carried out by the following general procedure. Alcohol (5-6 ml), NaOH (0.02 g, 0.5 mmol), and MnO_2 (0.05 g, 0.5 mmol) were added to a solution of quinone **1** (1.1 g, 5 mmol) in DMF (50 ml) and the mixture was stirred for 8-10 h until disappearance of the initial quinone (check by TLC). The solution was decanted, diluted with water, and extracted with chloroform. The yields of quinines **3-6** were 65-70%, and their characteristics are given in Table 5.

The work was carried out with the financial support of the Russian Fund for Fundamental Investigations (grant 96-03-33253a).

REFERENCES

1. V. B. Vol'eva, A. I. Prokof'ev, V. A. Zhorin, T. I. Prokof'eva, I. S. Belostotskaya, N. L. Komissarova, A. Yu. Karmilov, and V. V. Ershov, *Khim. Fiz.*, **15**, 16 (1996).
2. M. I. Kabachnik, N. N. Bubnov, S. P. Solodovnikov, and A. I. Prokof'ev, *Usp. Khim.*, **53**, 487 (1984).
3. R. R. Rakhimov, N. N. Benetis, A. Lund, J. S. Hwang, A. I. Prokof'ev, and Y. S. Lebedev, *Chem. Phys. Lett.*, **255**, 156 (1996).
4. V. B. Vol'eva, I. A. Novikova, E. V. Ivanova, and V. V. Ershov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1**, 215 (1986).