Synthesis and crystal structure of 5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,2,3,5-tetrahydrophenazine

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5-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,2,3,5-tetrahydrophenazine was synthesized by the reaction of 2,6-di-*tert*-butyl-1,4-benzoquinone-4-(*o*-aminophenyl)imine with cyclohexanone. The structure of the reaction product was established by X-ray diffraction.

Key words: *o*-phenylenediamine, 2,6-di-*tert*-butyl-1,4-benzoquinone, 2,6-di-*tert*-butyl-1,4-benzoquinone-4-(*o*-aminophenyl)imine, azomethines, enamines, 5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,2,3,5-tetrahydrophenazine, X-ray diffraction study.

Heterocycles with 2,6-di-*tert*-butyl-4-hydroxyphenyl substituents are potential biological antioxidants attracting considerable interest of researchers. Previously, we have described the related isoquinoline[1—3] and indazole[4] derivatives, which proved to be low-toxic and more efficient inhibitors of the peroxide oxidation of lipids compared to ionol and α-tocopherol.

It is known that *o*-phenylenediamine readily undergoes condensation with 2,6-di-*tert*-butyl-1,4-benzoquinone to form monoquinoneimine **1**, which vigorously reacts with aldehydes to give 2-substituted 1-(3,5-di-*tert*-butyl-4-hydroxy)phenylbenzimidazoles.[5]

It could be expected that the use of carbonyl compounds, whose azomethine derivatives can undergo the tautomeric transformation into enamines, in the reactions with quinoneimine **1** would lead to the alternative condensation resulting in the closure of the six- rather than five-membered ring. Due to the absence of hydrogen atoms at the carbonyl C atom in ketones, the analogous cyclization of the latter compounds is evidently the only possible pathway.

The short-term heating of quinoneimine **1** with cyclohexanone was found to afford 5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,2,3,5-tetrahydrophenazine **5**.

The completion of the reaction can easily be detected visually based on the change in the color of the reaction mixture from intense-blue to pale-yellow. The probable mechanism of condensation is presented in Scheme 1.

The reaction mechanism involves the formation of azomethine **3a**, the ring closure between enamine form **3b** and the quinoneimine moiety, and the dehydrogenation of intermediate hexahydrophenazine **4**.

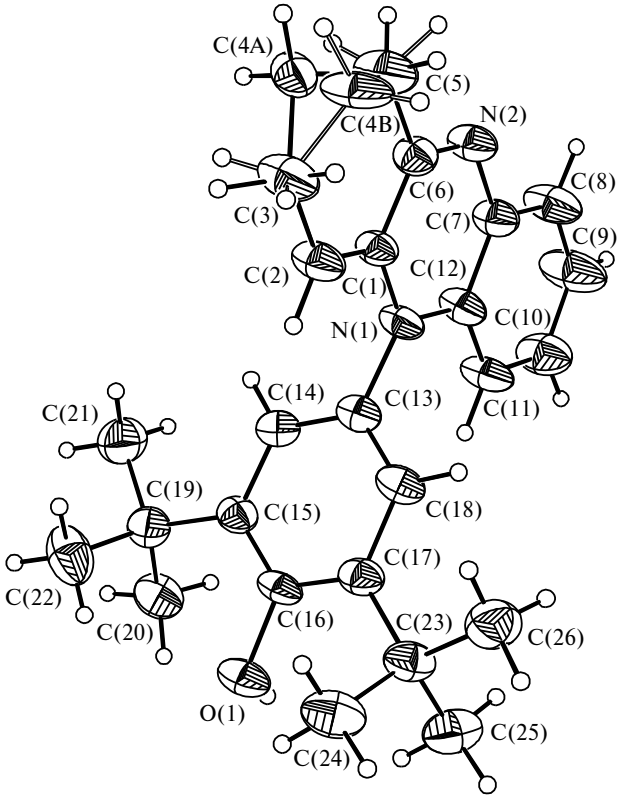

Fig. 1. Molecular structure of compound **5** with displacement ellipsoids drawn at the 50% probability level.

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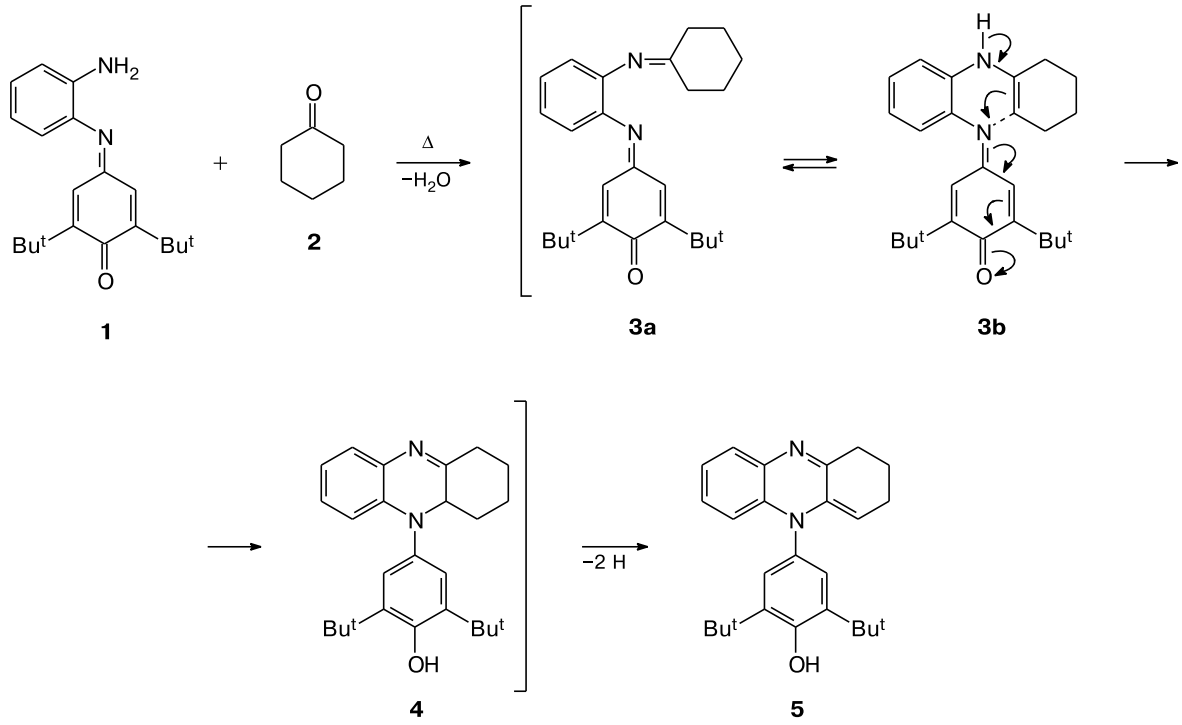
Scheme 1



The structure of tetrahydrophenazine **5** was established by X-ray diffraction.

The molecular structure of **5** is shown in Fig. 1. The fused tetrahydrophenazine system is planar, except for the cyclohexene fragment adopting an envelope conformation (the CH_2 group deviating from the plane is disordered over two positions with occupancies of 40 and 60% for the atoms labeled with the letters A and B, respectively). The N(1) atom has a planar configuration (the sum of the angles at N(1) is 360.0°), which is indicative of the involvement of the lone electron pair of the N(1) atom in the conjugation. This is also evidenced by the shortened N(1)—C(1) (1.406(2) Å) and N(1)—C(12) (1.393(3) Å) bonds, whereas the N(1)—C(13) bond (1.449(3) Å) corresponds to the standard C—N single bond (1.426 Å).[6] The 3,5-di-*tert*-butyl-4-hydroxyphenyl substituent is perpendicular (89.30(6)°) to the tricyclic system due in part to the steric repulsion between the H atoms in the *ortho* positions. Apparently, this orientation is additionally stabilized by the anomeric interaction between the lone pair of the N(1) atom and the π-system of the substituent and by the crystal field effect.

In the crystal structure, the molecules are linked to each other by the O(1)—H(1O)...N(2) hydrogen bonds ($0.5 + x$; $1.5 - y$; $1 - z$) (O...N, 2.814(2) Å; H...N, 1.97 Å; OHN, 173°) to form chains running along the crystallographic *a* axis. The fragment of the hydrogen-bonded chain is shown in Fig. 2. The solvent molecules (CH_3CN)

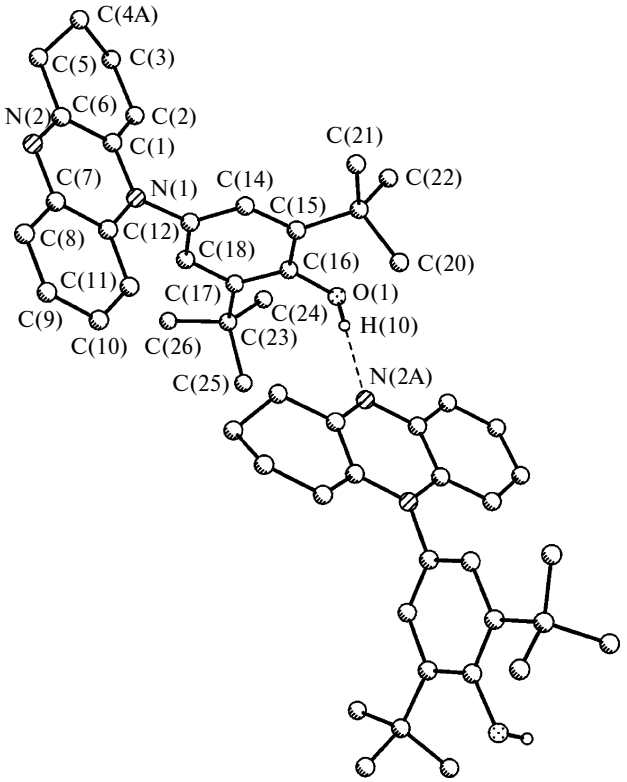


Fig. 2. Fragment of the chain in the crystal structure of compound **5** with the O(1)—H(1O)...N(2) hydrogen bond.

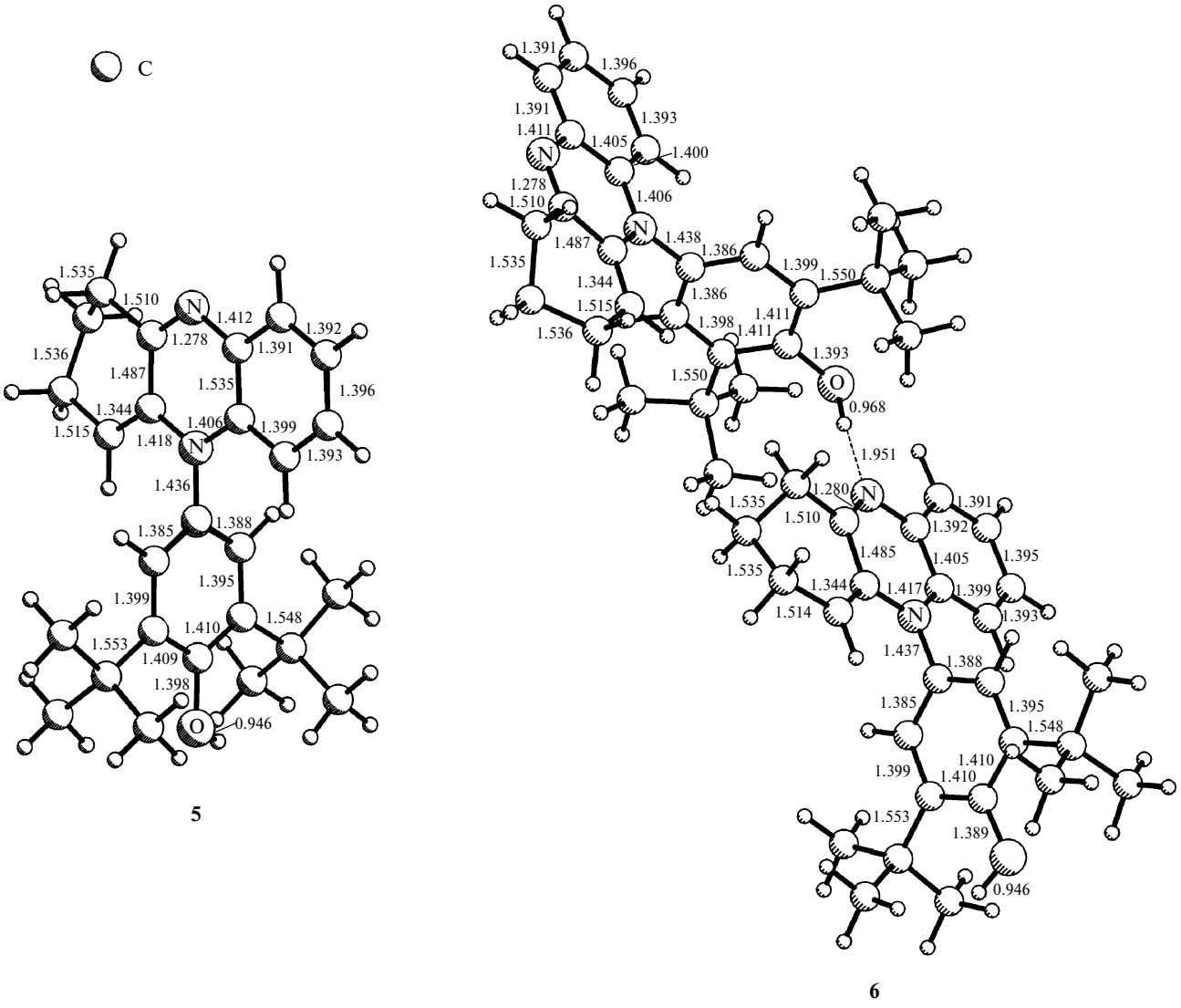


Fig. 3. Geometric characteristics and the minimum harmonic vibrational frequencies (ω_1) of monomer **5** and dimer **6a** calculated at the RHF/LanL2DZ level. The bond lengths are given in Å. For compound **5**, $\lambda = 0$ ($\omega_1 = 19.9$ cm^{-1}); for compound **6**, $\lambda = 0$ ($\omega_1 = 5.6$ cm^{-1}), $E_{complex} = 7.8$ kcal mol^{-1}.

are located between the chains, so that molecules **5** and the solvent molecules alternate along the crystallographic *b* axis.

The presence of the *tert*-butyl substituents adjacent to the hydroxy group in compound **5** should lead to steric hindrance to the hydrogen bonding. Hence, the formation of hydrogen-bonded chains established by X-ray diffraction is rather unusual. The IR spectrum of compound **5** is typical of the hydrogen-bonded hydroxy group characterized by a broad OH stretching band, which is not typical of sterically hindered phenols. At the same time, the formation of hydrogen bonds between molecules **5** should be accompanied by a large exothermic effect. To estimate the energy effects of the formation of hydrogen-bonded chains of molecules **5**, we performed quantum chemical calculations[7,8] for monomer **5** and its hydrogen-bonded dimer **6** (Fig. 3). As can be seen from Fig. 3, the calculated geometric characteristics of molecule **5** are consistent with the X-ray diffraction data. The results of calculations are in agreement with the experimental evidence of the perpendicular orientation of the 3,5-di-*tert*-butyl-4-hydroxyphenyl substituent with respect to the tricyclic tetrahydrophenazine system and the formation of rather strong hydrogen bonds between monomers **5**. The hydrogen bond energy in dimer **6** calculated as the difference between the total energy of dimer **6** and twice the energy of monomer **5** is rather large (7.8 kcal mol^{-1}). Therefore, the formation of hydrogen-bonded chains

should be accompanied by the exothermic effect of ~8 kcal mol^{-1} per hydrogen bond, resulting in the high total exothermic effect of this polymerization reaction.

Experimental

The IR spectra were recorded on a Varian Excalibur 3100 FT-IR instrument using attenuated total internal reflectance. The ^{1}H NMR spectra were measured on a Varian UNITY-300 spectrometer.

5-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,2,3,5-tetrahydrophenazine (5). A mixture of quinoneimine **1** (0.31 g, 1 mmol) and cyclohexanone **2** (0.3 mL, 2.8 mmol) was refluxed for 2 min. Then CH_3CN (2 mL) was added, and the reaction mixture was cooled with ice and ground with a rod. The resulting greenish-yellow crystalline precipitate was filtered off, washed with cold CH_3CN, and dried; m.p. 210—215 °C (from CH_3CN). The yield was 0.13 g (33.7%). To prepare the analytically pure compound, the substance was chromatographed on alumina using $CHCl_3$ as the eluent. The solvent was distilled off, and the residue was recrystallized from CH_3CN and dried *in vacuo* at 100 °C. Found (%): C, 80.27; H, 8.43; N, 7.14. $C_{26}H_{32}N_2O$. Calculated (%): C, 80.38; H, 8.30; N, 7.21. IR, ν/cm^{-1}: 3633 (OH), 1614, 1581 (arom.), 1234 (Bu^t). ^{1}H NMR ($CDCl_3$), δ: 1.42 (s, 18 H, Bu^t); 1.80 (m, 2 H, C(2)H$_2$); 2.14 (m, 2 H, C(3)H$_2$); 2.62 (t, 2 H, C(1)H$_2$, J = 6.4 Hz); 4.21 (t, 1 H, C(4)H, J = 4.8 Hz); 5.33 (s, 1 H, OH); 5.92 (dd, 1 H, C(6)H, ^3J = 8.1 Hz, ^4J = 1.1 Hz); 6.68 (m, 1 H, C(7)H); 6.83 (m, 1 H, C(8)H); 6.90 (s, 2 H, C(2′)H, C(6′)H); 7.22 (dd, 1 H, C(9)H, ^3J = 7.7 Hz, ^4J = 1.5 Hz).

X-ray diffraction study. Crystals suitable for X-ray diffraction study were grown by slow evaporation of a solution of compound **5** in CH_3CN at room temperature. The resulting crystals contained one CH_3CN solvent molecule per molecule **5**. The solvated crystals of compound **5** ($C_{26}H_{32}N_2O \cdot CH_3CN$) at 110 K are orthorhombic, a = 18.024(2) Å, b = 14.727(2) Å, c = 18.462(3) Å, V = 4900.5(11) Å^3, Z = 8, space group *Pbca*, μ = 0.071 mm^{-1}, d_{calc} = 1.165 g cm^{-3}. The intensities of 31557 reflections were measured on a SMART 1000 CCD diffractometer (λ(Mo-Kα) = 0.71073 Å, graphite monochromator, ω-scanning technique, the scan step was 0.3°, the exposure time per frame was 10 s, $2\theta < 54°$). The X-ray diffraction data were processed using the SAINT Plus[9] and SADABS programs.[10] The structure was solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for all nonhydrogen atoms based on F^2_{hkl}. The hydrogen atoms were positioned geometrically, except for the hydrogen atom of the OH group, whose position was located in difference electron density maps and then normalized to the distance of 0.85 Å. All hydrogen atoms were refined using a riding model (U_{iso}(H) = nU_{eq}(C,O), where n = 1.5 for the carbon atoms of the methyl groups and the oxygen atom, n = 1.2 for the other C atoms). The refinement was performed using 5328 independent reflections. The refinement based on all independent reflections converged to wR_2 = 0.0857 (R_1 = 0.0549 based on 1584 reflections with $I > 2\sigma(I)$). All calculations were carried out on an IBM PC AT using the SHELXTL program package.[11]

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