ISSN 1070-4280, Russian Journal of Organic Chemistry, 2015, Vol. 51, No. 5, pp. 623–628. © Pleiades Publishing, Ltd., 2015.
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Synthesis of Unsymmetrical Hydroxybenzylphenols from 2-Isobornyl-4-methylphenol

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Received February 17, 2015

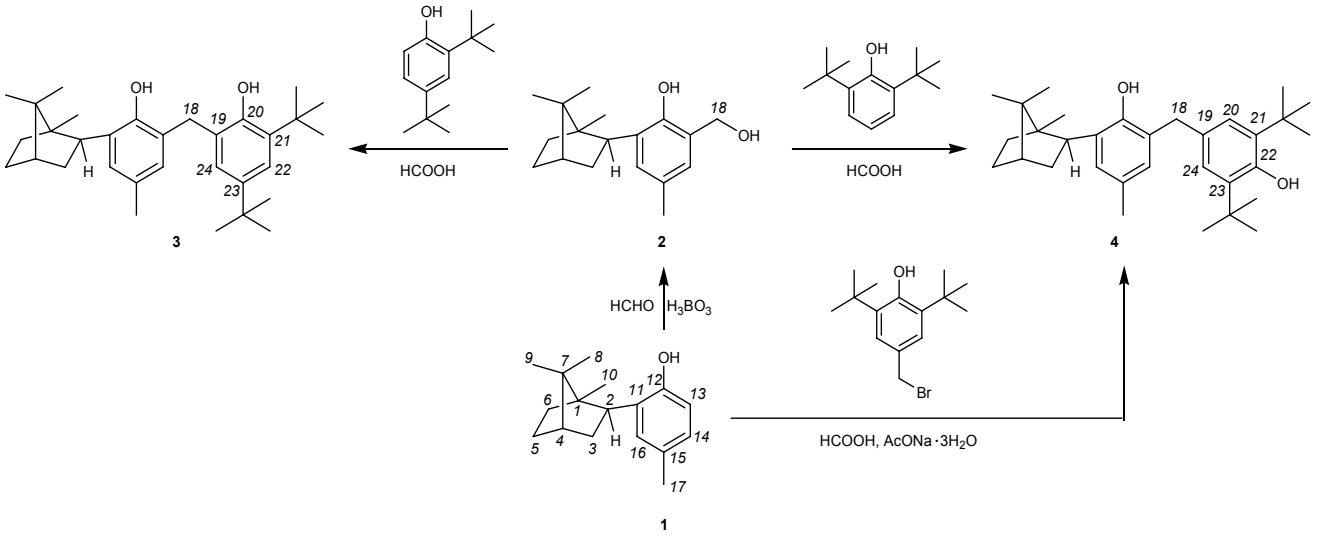
Abstract—2-Hydroxymethyl-6-isobornyl-4-methylphenol was synthesized from 2-isobornyl-4-methylphenol. Reactions of this hydroxymethyl derivative with 2,4- and 2,4-di-*tert*-butylphenols gave new unsymmetrical hydroxybenzylphenols.

DOI: 10.1134/S1070428015050061

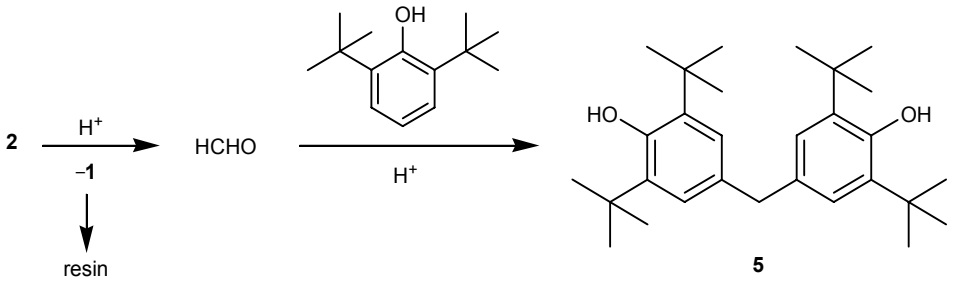
Previously we reported on the synthesis of unsymmetrical hydroxybenzylphenols basing on 4-(hydroxymethyl)- and 4-(bromomethyl)-2,6-diisobornylphenol under catalysis with formic acid. As a result hydroxybenzylphenols with various positions of alkyl and phenol OH groups were obtained [1]. These compounds along with symmetrical 2,2'- and 4,4'-methylenebisphenols with alkyl substituents may be interesting for the investigation of their antioxidant properties.

In the present study we describe the synthesis of new unsymmetrical hydroxybenzylphenols proceeding from 2-isobornyl-4-methylphenol **1**. By the method [2] from compound **1** and paraformaldehyde in the presence of H_3BO_3 2-(hydroxymethyl)-6-isobornyl-4-methylphenol **2** was synthesized in 92% yield. Its interaction with 2,4- and 2,6-di-*tert*-butylphenols at reflux in chloroform in the presence of formic acid leads to the formation of hydroxybenzylphenols **3** and **4** (Scheme 1) (numeration of atoms is

Scheme 1.



Scheme 2.



introduced for convenient interpretation of NMR spectra).

Compound **3** is isolated in 53% yield by precipitation from pentane. Compound **4** was purified by column chromatography with further precipitation.

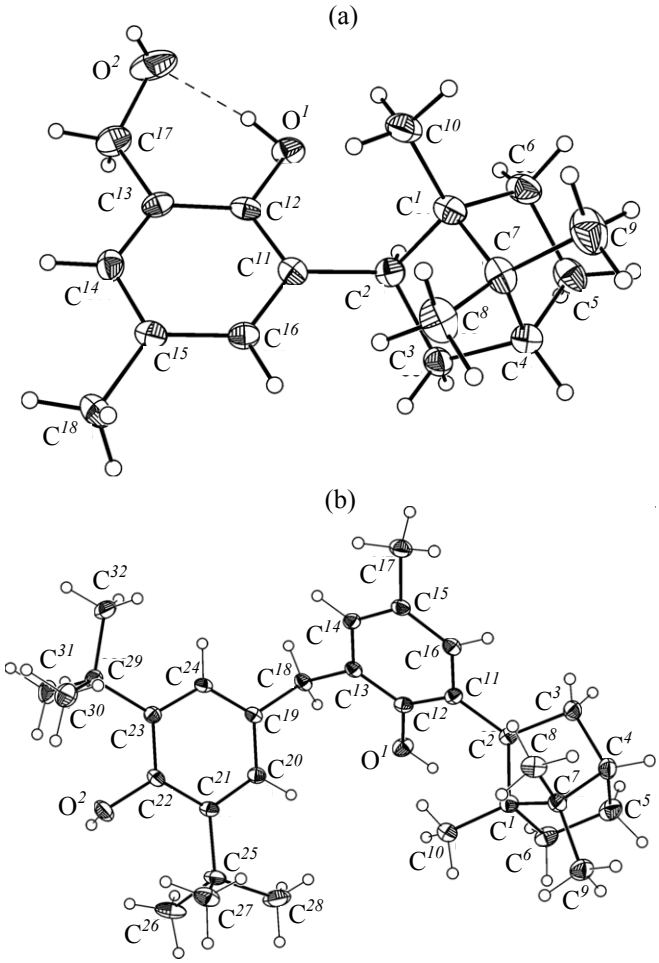


Fig. 1. Molecular structures of 2-(hydroxymethyl)-4-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol **2** (a) and 2,6-di-*tert*-butyl-4-{2-hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo-[2.2.1]hept-*exo*-2-yl)benzyl}phenol **4** (b) according to the X-ray diffraction data. Thermal ellipsoids are shown with 50% probability. For compound **2** the appearance of the first independent molecule is presented.

Yield of hydroxybenzylphenol **4** was 59% at 70% conversion of compound **2**. In mother liquor after precipitation of the main amount of phenol **4** 4,4'-methylenebis(2,6-di-*tert*-butylphenol) **5** was found, which was identified by ^{1}H and ^{13}C NMR spectra.

Its generation may be due to a side reaction of formaldehyde elimination followed by condensation of the latter with 2,6-di-*tert*-butylphenol (Scheme 2). However in the reaction mixture cresol **1** has not been found although it is the second product of the formaldehyde elimination from alcohol **2**. Its absence may be caused by resinification.

At boiling the 2,6-di-*tert*-butylphenol in a system HCOOH–$CHCl_3$ in the absence of alcohol **2** the generation of compound **5** was not observed. By the gas chromatography and ^{1}H NMR spectroscopy in the reaction mixture after processing only initial phenol and its dealkylation product, 2-*tert*-butyl-phenol, was detected. This may be regarded as a proof of the participation of alcohol **2** in the generation of 4,4'-methylenebisphenol **5**.

Compound **4** was obtained by authentic synthesis from cresol **1** and synthetically available 4-(bromomethyl)-2,6-di-*tert*-butylphenol (Scheme 1) in 78% yield at a full conversion of initial phenols. 4,4'-Methylenbisphenol **5** was not present in the reaction mixture.

For compounds **2** and **4** single crystals were obtained for X-ray diffraction (XRD) analysis. The general appearance of molecules of these compounds is shown in Fig. 1. In symmetrically independent part of crystal cell of compound **4** there is one molecule, while compound **2** crystallizes with the location in the unit cell of two independent molecules **A** and **A'** (main component of disordered molecule). Relative orientation of the terpene and the phenyl fragment in compounds **2** and **4** and in previously studied derivatives of *o*-isobornylphenols [1, 3–5] is practically the same [torsion angle $C^{16}C^{11}C^{2}C^{3}$ –19.5(2), 22.9(4),

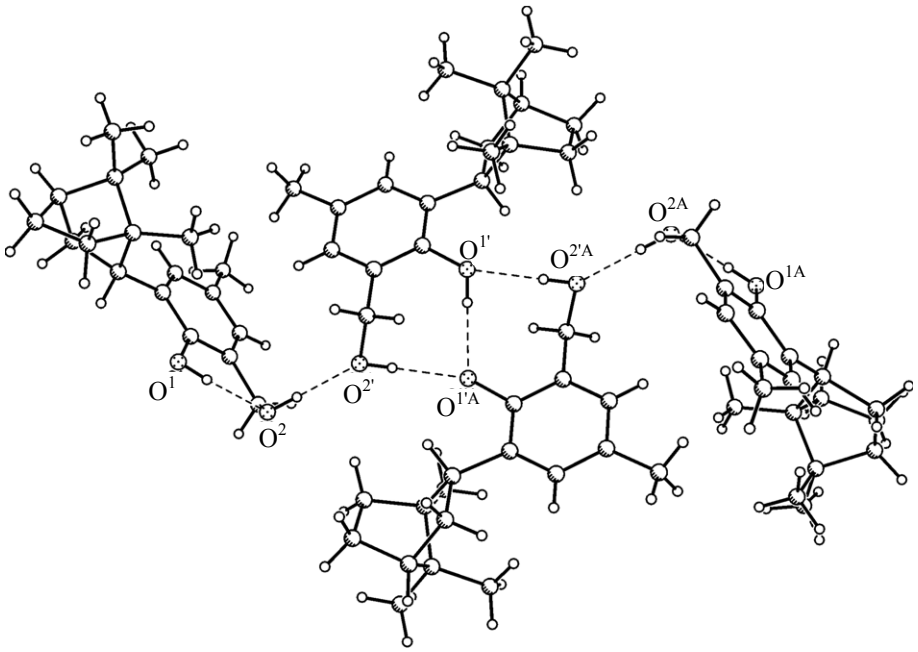


Fig. 2. H-bonded tetramer in crystal structure of compound **2**.

–15.0(6)° in compounds **4**, **2A** and **2A'** respectively] and, according to calculated data [6], is mostly determined by intramolecular forces. In the minor component (30%) of the disordered molecule of compound **2** the terpene substituent is turned by an angle $C^{16}C^{11}C^{2}C^{3}$ of 109(2)°. In crystal packing of both compounds the associates are formed connected by hydrogen bonds. In compound **4** the bond $O^{2}H^{2}O^{1}$ [O···O 3.051(4), H···O 2.29 Å, angle CHO 149°] is fairly weak, while the other acid proton (H^{1}) does not take part in H-bonding that is caused by steric hindrances created by bulky *tert*-butyl and isobornyl groups. In previously studied of 4,4'-methylenebisphenol [5] and hydroxybenzylphenol [1] the hydroxy groups located between two *tert*-butyl or isobornyl substituents did not form hydrogen bonds in the crystal.

The structure of H-bonding in the crystal packing of compound **2**, where both hydroxy groups participate, is more complex. The bond O^{1}–H^{1}···O^{2} [O···O 2.610(5), H···O 1.77 Å, angle CHO 169°] in molecule A is intramolecular. In the second independent molecule A' this hydroxy group participates in the formation of a bond between molecules A'···A' [$O^{1'}$–$H^{1'}$···$O^{1'}$, O···O 2.774(7), H···O 1.93 Å, angle CHO 180°] and leads to generation of dimers additionally stabilized by the $O^{2'}$–$H^{2'}$···$O^{1'}$ [O···O 2.819(9), H···O 1.97 Å, angle CHO 179°] bond. Besides, the hydrogen bond O^{2}–H^{2}···$O^{2'}$ [O···O 2.675(8), H···O 1.83 Å, angle CHO 179°] binds symmetrically independent molecules A···A', resulting in generation of tetrameric H-bond associates (Fig. 2), and, evidently, is responsible for generation of two symmetrically independent molecules in the unit cell. Sufficiently strong intermolecular interactions between symmetrically independent molecules we have already observed before [7–10].

The structure and composition of compounds **2–4** are confirmed by spectral data and elemental analysis. Compounds **2–4** are racemates because the racemic 2-isobornyl-4-methylphenol **1** was used to obtain them.

EXPERIMENTAL

IR spectra were recorded on Shimadzu IR Prestige 21 instrument from pellets with KBr. ^{1}H and ^{13}C NMR spectra of the solutions of compounds in $CDCl_3$ were registered on a spectrometer Bruker Avance II 300 (300.17 and 75.48 MHz respectively). Chemical shifts were measured from the residual signals of $CHCl_3$ (δ_H 7.26, δ_C 77.00 ppm). The assignment of signals was carried out using the ^{13}C NMR spectra in the mode of *J*-modulation and by HSQC method. The purity of the initial 2,4- and 2,6-di-*tert*-butylphenols and cresol **1** was monitored by gas chromatography on Shimadzu GC-2010AF instrument using flame-ionization detector (carrier gas helium) and capillary column HP-1

(Agilent, 60 m × 0.25 mm × 0.25 μm, oven temperature programming 100–240°C, heating rate 6 deg/min). Melting points were determined on a Sanyo Gallenkamp MDP350 device and were not corrected.

The reaction course was monitored by TLC on Sorbfil plates. Chromatograms were developed treating with $KMnO_4$ solution (15 g of $KMnO_4$, 300 mL of H_2O, and 0.5 mL of conc. H_2SO_4). For column chromatography silica gel Alfa Aesar 70/230μ was used (eluent is indicated in each particular case).

Chemically pure chloroform, pure grade formic acid, diethyl ether, sodium acetate trihydrate, and boric acid pure for analysis were used without additional purification. Petroleum ether was distilled, bp 65–70°C. 2-Isobornyl-4-methylphenol **1**, 2,4-di-*tert*-butylphenol, 2,6-di-*tert*-butylphenol according to GC data contained more than 97% of the main compound. 4-(Bromomethyl)-2,6-di-*tert*-butyl-phenol was obtained by method [11]. Values of R_f and spectral characteristics of 4,4'-methylenebis(2,6-di-*tert*-butylphenol) **5** coincide with characteristics of the compound sample that was synthesized previously [12].

Single crystals of compound **2** after prolonged storage at room temperature were taken from the solution, washed with pentane, and dried; single crystals of compound **4** were obtained by slow evaporation of the solution of this compound in pentane. Experimental intensity of the reflections was measured on a diffractometer SmartApex II CCD (graphite monochromator, ω-scanning) using the MoK_α-radiation (λ 0.71073 Å). Processing of the initial array of the measured intensities was performed applying programs SAINT and SADABS, included in APEX2 [13] program package. Structures were solved by the direct method and refined using full-matrix least-squares method in anisotropic approximation for nonhydrogen atoms with respect to F^2_{hkl}. Solving and refining of the structures was performed with program SHELXTL [14]. Coordinates of the atoms and temperature factors for compounds **2** and **4** were deposited in Cambridge Crystallographic Data Center (CCDC nos. 1046442 and 1046443).

2-(Hydroxymethyl)-4-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol (2). A mixture of 2.5 g (10 mmol) of 2-isobornyl-4-methylphenol **1**, 0.46 g (15 mmol) of paraformaldehyde, 0.95 g (15 mmol) of boric acid in 15 mL of toluene was refluxed for 9 h in a flask equipped with a Dean-Stark trap. Every 4 h portions of 0.22 g (7.3 mmol) of paraformaldehyde and 10 mL of toluene were additionally added. By the end of the reaction the solvent was removed at a reduced pressure, 30 mL of water was added to the precipitate and the reaction mixture was left overnight for hydrolysis of intermediate borosilicate ether. Diethyl ether was used for extraction (3 × 20 mL), the extract was washed with water (30 mL), dried with Na_2SO_4, the solvent was removed at a reduced pressure. The residue was subjected to column chromatography (eluent petroleum ether–Et_2O, 100 : 1→35 : 1, then the polarity was raised by adding CH_2Cl_2). Yield 2.57 g (92%). Light-yellow crystals, mp 68–70°C. IR spectrum, cm^{-1}: 3514, 3368 ν(OH), 2951, 2876 ν(CH_3, CH_2), 1609 ν(C=C), 1468, 1383 δ(CH_3, CH_2),1186 ν(C–O), 771 δ(=C–H). ^{1}H NMR spectrum, δ, ppm: 0.83 s (3H, $C^{10}H_3$), 0.89 s, 0.94 s (3H each, $C^{8,9}H_3$), 1.37–1.44 m, 1.50–1.69 m, 1.87–1.88 m (6H, H^3, H^4, C^5H_2, C^6H_2), 2.24 s (1H, $CH_2O\underline{H}$), 2.20–2.30 m (1H, H^3), 2.30 s (3H, $C^{17}H_3$), 3.30 t (1H, H^2, J 9.0 Hz), 4.55 s (2H, $C^{18}H_2$), 6.71 s, 7.12 s (1H each, $H^{14,16}$), 7.28 s (1H, ArOH). ^{13}C NMR spectrum, δ, ppm: 12.33 (C^{10}), 20.41, 21.47 ($C^{8,9}$), 20.86 (C^{17}), 27.54 (C^3), 34.04 (C^5), 39.80 (C^6), 44.94 (C^2), 45.75 (C^4), 47.99 (C^1), 49.84 (C^7), 65.08 (C^{18}), 125.61, 128.82, 131.04 ($C^{13,14,16}$), 123.66, 127.89 ($C^{11,15}$), 153.12 (C^{12}). Found, %: C 79.02; H 9.36. $C_{18}H_{26}O_2$. Calculated, %: C 78.79; H 9.55.

Crystals of compound **2** ($C_{18}H_{26}O_2$) at 120 K are triclinic, a 7.3629(9), b 14.419(2), c 15.347(2) Å, α 71.093(2), β 88.245(3), γ 82.340(2)°, V 1527.6(3) Å^3, Z 4, space group P-1, d_{calc} 1.193 g/cm^3, μ 0.075 mm^{-1}, 20404 reflections were measured in the range from 1.51 to 27.00 deg by θ for a single crystal of the size 0.18 × 0.12 × 0.02 mm. The convergence of refinement for all independent reflections wR_2 0.2061, calculated with respect to F^2_{hkl} for 6657 independent reflections (R_{int} 0.0579) [GOF 1.105, R_1 0.0967 calculated with respect to F_{hkl} for 4931 reflection with $I > 2\sigma(I)$]. The structure contains two symmetrically independent molecules, one of them is fully disordered by two positions with the population 0.7 : 0.3. Also the hydroxy group HO^2 of the first independent molecule is also disordered by two positions with the same population. The minor component of the disordered fragments was refined in isotropic approximation. The hydrogen atom at $O^{1'}$ of both components of disordered molecule is additionally disordered by two positions. Hydrogen atoms of the disordered hydroxy groups were geometrically placed (basing on the H-bonding system), only the H atom at O^1 was localized from the

differential synthesis of deformation density. All hydrogen atoms were refined in the *rider* model.

2,4-Di-*tert*-butyl-6-{2-hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)-benzyl}phenol (3). Formic acid was added to a solution of 0.137 g (0.5 mmol) of compound **2** and 0.103 g (0.5 mmol) of 2,4-di-*tert*-butylphenol in 2 mL of $CHCl_3$, and the mixture was heated for 3.5 h under reflux with vigorous stirring. By the end of the reaction the mixture was poured in 10 mL of $CHCl_3$, the organic phase was washed with water (3 × 15 mL) to remove acid, dried with Na_2SO_4, solvent was removed at a reduced pressure. The reaction product was isolated by precipitating from cold pentane. Yield 0.123 g (53%). Colorless powder, mp 148–150°C. IR spectrum, cm^{-1}: 3595, 3505, 3375 ν(OH), 2953, 2874 ν(CH_3, CH_2), 1464 δ(CH_3, CH_2), 1186, 1146 ν(C–O). ^1H NMR spectrum, δ, ppm: 0.76 s (3H, $C^{10}H_3$), 0.84 s, 0.86 s (3H each, C^8H_3, C^9H_3), 1.32 s, 1.40 s (9H each, 2*t*-Bu), 1.16–1.49 m, 1.52–1.76 m, 1.78–2.01 m (2H each, $H^{3,4}$, C^5H_2, C^6H_2), 2.16–2.32 m (1H, H^3), 2.26 s (3H, $C^{17}H_3$), 2.92 t (1H, H^2, *J* 8.6 Hz), 3.92 d, 3.96 d (1H each, $C^{18}H_2$, *J* 14.7, 14.7 Hz), 5.40 s, 6.56 s (1H each, 2 OH), 6.96 br.s, 6.97 br.s, 7.18 d, 7.20 d (1H each, $H^{14,16,22,24}$, *J* 2.2, 2.2 Hz). ^{13}C NMR spectrum, δ, ppm: 12.36 (C^{10}), 20.17, 21.39 ($C^{8,9}$), 21.04 (C^{17}), 27.55 (C^5), 29.86, 31.66 [2 C($\underline{C}H_3)_3$], 32.33 (C^{18}), 34.06 (C^3), 34.25, 34.83 [2 $\underline{C}(CH_3)_3$], 40.27 (C^6), 45.44, 46.26 ($C^{2,4}$), 48.28, 49.72 ($C^{1,7}$), 122.70, 125.12, 127.14, 128.57 ($C^{14,16,20,24}$), 125.82, 126.23, 129.04, 129.80, 135.71, 142.33 ($C^{11,13,15,19,21,23}$), 149.26, 150.46 ($C^{12,20}$).Found, %: C 83.31; H 9.87. $C_{32}H_{46}O_2$. Calculated, %: C 83.06; H 10.02.

2,6-Di-*tert*-butyl-4-{2-hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)benzyl}-phenol (4). *a*. The preparation procedure was similar to that of compound **3** using the 2,6-di-*tert*-butylphenol. The fraction containing the main component was isolated by column chromatography (eluent petroleum ether–Et_2O, 150 : 1). The target product was precipitated from cold pentane. After removing the solvent from mother liquor the residue contained additionally about 40% of compound **4** (by the ^1H NMR data) in a mixture with compound **5** (mass of the mixture 0.043 g). General yield considering the conversion was 0.097 g (59%). Light-yellow crystals, mp 129–131°C. IR spectrum, cm^{-1}: 3640, 3582, 3510 ν(OH), 2953, 2874 ν(CH_3, CH_2), 1464, 1435 δ(CH_3, CH_2), 1190, 1153 ν(C–O). ^1H NMR spectrum, δ, ppm: 0.70 s (3H, $C^{10}H_3$), 0.84 s, 0.91 s (3H each, C^8H_3, C^9H_3), 1.40 s (18H, 2 *t*-Bu), 1.17–1.48 m, 1.50–1.67 m, 1.73–1.94 m (2H each, $H^{3,4}$, C^5H_2, C^6H_2), 2.14–2.32 m (1H, H^3), 2.20 s (3H, $C^{17}H_3$), 2.11 t (1H, H^2, *J* 8.9 Hz), 3.89 s (2H, $C^{18}H_2$), 4.59 s, 5.12 s (by 1H, 2 OH), 6.81 s, 7.02 s (1H, 3H, $H^{14,16,20,24}$). ^{13}C NMR spectrum, δ, ppm: 12.41 (C^{10}), 20.28, 21.48 ($C^{8,9}$), 21.02 (C^{17}), 27.52 (C^5), 30.27 [2C($\underline{C}H_3)_3$], 33.93 (C^3), 34.32 [2 $\underline{C}(CH_3)_3$], 37.35 (C^{18}), 39.77 (C^6), 45.38, 45.63 ($C^{2,4}$), 48.01, 49.73 ($C^{1,7}$), 124.98 ($C^{20,24}$), 127.10, 128.77 ($C^{14,16}$), 125.93, 128.50, 129.56, 129.79 ($C^{11,13,15,19,21,23}$), 151.07, 152.60 ($C^{12,22}$). Found, %: C 83.20; H 9.96. $C_{32}H_{46}O_2$. Calculated, %: C 83.06; H 10.02.

b. Formic acid (3 mL) and 0.095 g (0.7 mmol) of AcONa·$3H_2O$ were added to a solution of compound **1** and 0.105 g (0.35 mmol) of 4-(bromomethyl)-2,6-di-*tert*-butylphenol in 2 mL of $CHCl_3$. The mixture was heated for 3.5 h under reflux with vigorous stirring. Further processing and isolation of the reaction product was carried out as in the experiment *a*. Yield 0.127 g (78%). Colourless crystals, mp 130–132°C. Spectral characteristics are the same as characteristics of the sample obtained by the *a* method.

Crystals of compound **4** ($C_{32}H_{26}O_2$) at 120 K are monoclinic, *a* 16.9971(11), *b* 15.2093(10), *c* 20.8281 (14) Å, β 98.0770(10)°, *V* 5330.9(6) $Å^3$, *Z* 8, space group *C*2/*c*, d_{calc} 1.153 g/cm^3, μ 0.069 mm^{-1}. 31516 reflections were measured in the range from 1.80 to 29.00 deg by θ for a single crystal of the size 0.34 × 0.26 × 0.24 mm. The convergence of refinement for all independent reflections wR_2 0.1450, calculated with respect to F^2_{hkl} for 7093 independent reflections (R_{int} 0.0320) [*GOF* 1.157, R_1 0.0629 calculated with respect to F_{hkl} for 6174 reflections with $I > 2\sigma(I)$].

Authors express their thanks to E. N. Zainullina (Laboratory of physicochemical research methods) for registering the NMR spectra.

K. Yu. Suponitskii is grateful to the Russian Foundation for Basic Research for the financial support (project no. 15-03-06931).

REFERENCES

1. Buravlev, E.V., Chukicheva, I.Yu., Suponitskii, K.Yu., and Kutchin, A.V., *Russ. J. Org. Chem*., 2014, vol. 50, p. 361.
2. Belyanin, M.L., Filimonov, V.D., and Krasnov, E.A., *Russ. J. Appl. Chem*., 2001, vol. 74, p. 103.
3. Buravlev, E.V., Chukicheva, I.Y., Suponitsky, K.Y., Vikharev, Y.B., Grishko, V.V., and Kutchin, A.V., *Lett. Org. Chem*., 2011, vol. 8, p. 301.

4. Buravlev, E.V., Chukicheva, I.Yu., Shevchenko, O.G., Suponitsky, K.Yu., and Kutchin, A.V., *Russ. J. Bioorg. Chem*., 2011, vol. 37, p. 614.
5. Buravlev, E.V., Chukicheva, I.Yu., Suponitsky, K.Yu., and Kutchin, A.V., *Russ. J. Gen. Chem*., 2013, vol. 83, p. 1345.
6. Chukicheva, I.Yu., Fedorova, I.V., Buravlev, E.V., Suponitskii, K.Yu., and Kuchin, A.V. *Russ. J. Gen. Chem*., 2012, vol. 82, p. 1425.
7. Sheremetev, A.B., Aleksandrova, N.S., Suponitsky, K.Yu., Antipin, M.Yu., and Tartakovsky, V.A., *Mendeleev Commun*., 2010, vol. 20, p. 249.
8. Griffith, D.M., Duff, B., Suponitsky, K.Yu., Kavanagh, K., Morgan, M.P., Egan, D., and Marmion, C.J., *J. Inorg. Biochem*., 2011, vol. 105, p. 793.
9. Nelyubina, Yu.V., Dalinger, I.L., and Lyssenko, K.A., *Angew. Chem., Int. Ed*., 2011, vol. 50, p. 2892.
10. Palysaeva, N.V., Kumpan, K.P., Struchkova, M.I., Dalinger, I.L., Kormanov, A.V., Aleksandrova, N.S., Chernyshev, V.M., Pyreu, D.F., Suponitsky, K.Yu., and Sheremetev, A.B., *Org. Lett*., 2014, vol. 16, p. 406.
11. Coppinger, G.M. and Campbell, T.W., *J. Am. Chem. Soc*., 1953, vol. 75, p. 734.
12. Buravlev, E.V., Chukicheva, I.Yu., Borisenkov, M.F., and Kutchin, A.V., *Synth. Commun*., 2012, vol. 42, p. 3670.
13. *APEX2 and SAINT software package*, Madison, Wisconsin, USA: Bruker AXS Inc., 2005.
14. Sheldrick, G.M., *Acta. Cryst*., 2008, vol. A64, p. 112.