Synthesis and antioxidant activity of 5-hydroxycoumarans, 6-hydroxychromanes and sulfur-containing derivatives on their base

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A synthesis of 5-hydroxycoumarans, 6-hydroxychromanes and their dodecylthiomethyl-substituted derivatives was accomplished based on methylphenols through the intermediate preparation of 2-allyl-4-alkoxyphenols. The sulfur-containing compounds synthesized were shown to be highly efficient as inhibitors of autooxidation of methyl oleate.

Key words: 5-hydroxy-2,3-dihydrobenzofurans, 6-hydroxychromanes, sulfur-containing antioxidants, antioxidant activity.

By now, an increase in the intensity of the free-radical oxidation in living organisms (oxidation stress) was found to lead to the emergence and development of a wide range of diseases and pathological states.[1] The phenol-type antioxidants of natural (α-tocopherol, flavonoids) and synthetic origin (dibunol, mexidol)[2,3] are frequently used for prevention and correction of pathophysiological effects of the oxidation stress. The mechanism of the phenol antioxidant actions is based on their ability to inactivate free radicals.[4] Many authors[5—10] showed that the efficiency of synthetic phenol antioxidants can be increased by introduction in their molecules of thioalkyl groups capable of reducing peroxides, precursor of free radicals. At the same time, a possibility of the increase in the efficiency of natural phenol antioxidants, in particular, α-tocopherol, through the incorporation of sulfur-containing groups in their structure was studied little. Thus, the series of works[11—13] described the synthesis of α-tocopherol analogs, the chromane ring oxygen atom of which was substituted with the sulfur atom. According to the authors,[13] such compounds are somewhat inferior to α-tocopherol in the antiradical activity. At the same time, α-tocopherol derivatives containing methylthioethyl substituent or ethyl dimethyl sulfone group at position 2 inhibited oxidation of rat brain homogenates more efficient than vitamine E.[14]

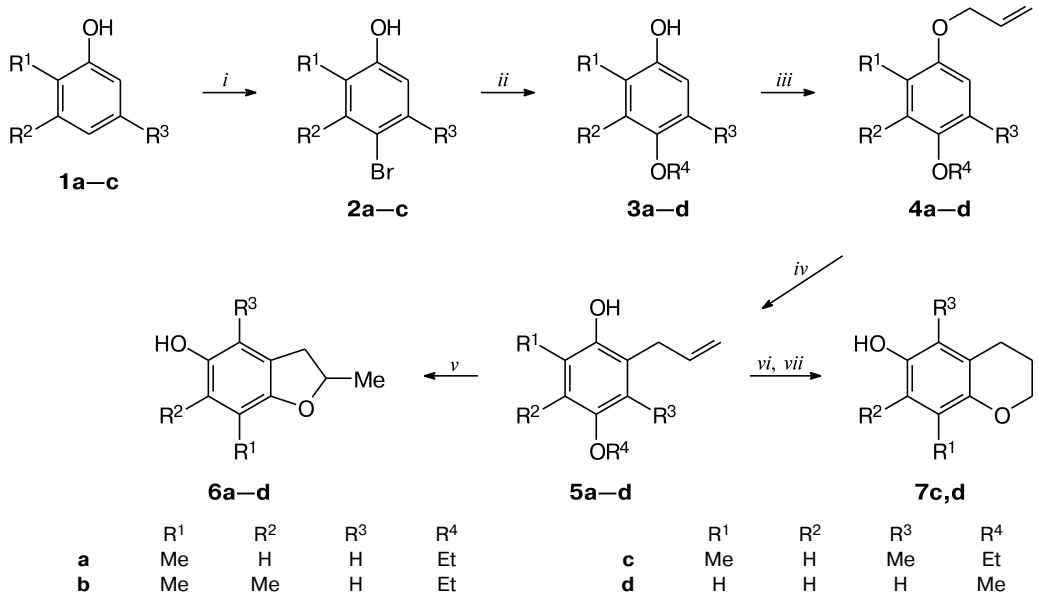
In this connection, in the present work we carried out a synthesis of new structural analogs of α-tocopherol, dodecylthiomethyl-substituted 5-hydroxycoumarans and 6-hydroxychromanes, and conducted comparative studies of their antioxidant properties.

The synthesis of 5-hydroxycoumarans and 6-hydroxychromanes was performed based on methylphenols **1a—c** (Scheme 1). Treatment of compounds **1a—c** with bromine at −10 °C furnished *para*-bromophenols **2a—c**. The reaction was carried out in chlorobenzene, since in the solvents commonly used for this conversion (CCl_4, $CHCl_3$) compounds **1a—c** are not soluble enough at lowered temperatures. The Ullmann reaction of bromophenols **2a—c** with sodium ethoxide led to compounds **3a—c** in high yields. This conversion was carried out in EtOH with DMF and TMEDA additives in order to increase the solubility of Cu^I compounds, that allowed us to apply milder conditions and increase selectivity of the reaction.[15] The reaction of the synthesized ethoxyphenols **3a—c**, as well as 4-methoxyphenol **3d**, with allyl bromide and the rearrangement of the thus formed phenyl allyl ethers **4a—d** were performed according to the procedure described earlier.[16] The resulting 2-allyl-4-alkoxyphenols **5a—d** were the key intermediate products in the synthesis of 5-hydroxycoumarans **6a—d** and 6-hydroxychromanes **7c**,**d**.

The heterocyclization and O-dealkylation reactions were carried out by heating of 2-allyl-4-alkoxyphenols **5a—d** with HBr in AcOH, which led to the target 5-hydroxy-2-methylcoumarans **6a—d**. This conversion could have proceed through the formation of the corresponding 5-alkoxycoumarans **8a—d** and/or allylhydroquinones **9a—d** as the intermediate products (Scheme 2). The GLC studies of the dynamics of the changes in the composition of the reaction mixture in the course of the conversion **5d** to **6d** showed that the process proceeded through the formation of one intermediate product, which was isolated and char-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1395—1400, June, 2013.

Scheme 1

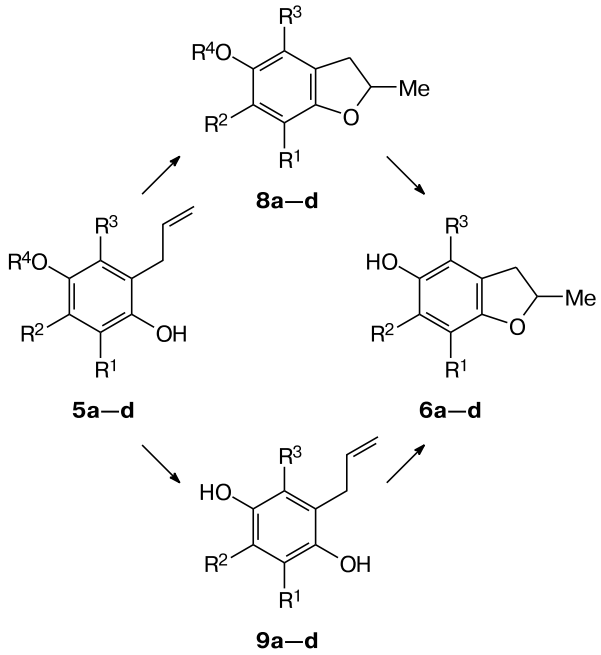


	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
a	Me	H	H	Et	**c**	Me	H	Me	Et
b	Me	Me	H	Et	**d**	H	H	H	Me

Reagents and conditions: *i*. Br_2, PhCl, −10 °C; *ii*. EtONa, CuI, TMEDA, DMF, EtOH, Δ; *iii*. C_3H_5Br, KOH, DMF; *iv*. 200—220 °C; *v*. HBr, AcOH, Δ; *vi*. $NaBH_4$, Me_2SO_4, THF, H_2O_2, NaOH, H_2O; *vii*. HBr, Δ.

acterized as 5-methoxy-2-methylcoumaran (**8d**). The fairly high yield of **8d** (74%) indicates that the rate of heterocyclization under the selected conditions is considerably higher than the rate of O-dealkylation.

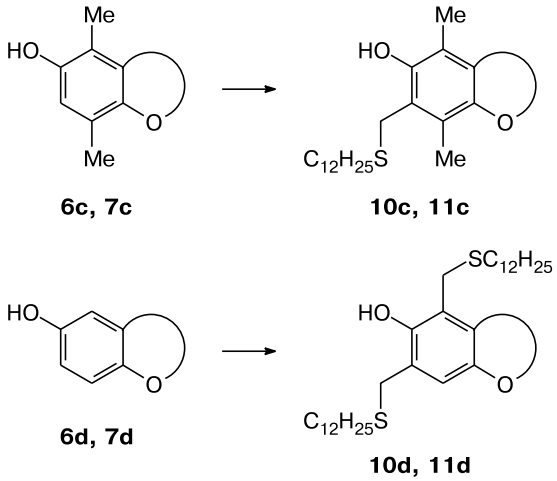
Scheme 2



The synthesis of 6-hydroxychromanes **7c**,**d** from **5c**,**d** was carried out in two steps: the hydroboration—oxidation process was the first step,[16] then the obtained products, 4-alkoxy-2-(3-hydroxypropyl)phenols, were heated with HBr.

The introduction of the dodecylthiomethyl group in the molecules of compounds **6c**,**d** and **7c**,**d** was performed according to the procedure suggested earlier,[17] which used an original reagent, (*N*,*N*-diethylaminomethyl) dodecyl sulfide (Scheme 3).

Scheme 3



Reagents and conditions: $Et_2NCH_2SC_{12}H_{25}$, Δ, AcOH.

The antioxidant activity of the compounds synthesized in comparison with α-tocopherol was tested in the model

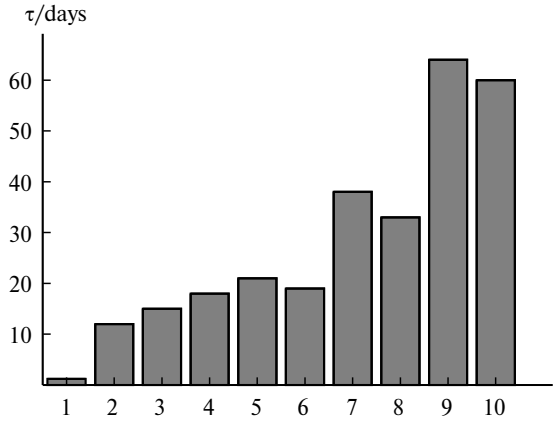


Fig. 1. Induction periods (τ) of autooxidation of methyl oleate at 60 °C without inhibitor (*1*), in the presence of α-tocopherol (*2*), **6c** (*3*), **7c** (*4*), **6d** (*5*), **7d** (*6*), **10c** (*7*), **11c** (*8*), **10d** (*9*), **11d** (*10*).

reaction of autooxidation of methyl oleate at 60 °C, which was earlier successfully used for the studies of antioxidant activity of sulfur-containing phenol antioxidants of various structure.[7,18—20] The data obtained show (Fig. 1) that compounds **6c**,**d** and **7c**,**d** in the concentration of 1 μmol g^{-1} possess inhibiting activity close to that of α-tocopherol. The introduction of the dodecylthiomethyl substituents in the molecules of hydroxycoumarans and hydroxychromanes, as we expected, led to the increase in the antioxidant activity: the induction periods of monododecylthiomethyl-substituted compounds **10c**, **11c** and bis-dodecyl thiomethyl derivatives **10d**, **11d** exceeded that of α-tocopherol by ~3 and 5 times, respectively. It should be noted that thiomethyl-substituted coumarans **10c**,**d** slightly exceeded the isomeric chromanes **11c**,**d** in the antioxidant activity. This result correlated with the known data,[4] according to which hydroxycoumarans containing no thio substituents exceed the corresponding hydroxychromanes in the rate constants of the reactions with free radicals.

In conclusion, in this work we suggested and successfully tested approaches to the synthesis of sulfur-containing analogs of α-tocopherol, *viz.*, dodecylthiomethyl-substituted 5-hydroxycoumarans and 6-hydroxychromanes from available methylphenols. The sulfur-containing compounds synthesized were shown to be highly efficient as inhibitors of autooxidation of methyl oleate.

Experimental

Reagents and solvents used in the work were commercially available from Fluka, Acros, Sigma-Aldrich, Reanal, Reakhim. Before use, solvents were purified according to the standard procedures. Dodecyl (diethylaminomethyl) sulfide was obtained according to the procedure published earlier.[17]

^{1}H NMR spectra were recorded on a Bruker AV-600 spectrometer (600 MHz) in $CDCl_3$, using $CHCl_3$ as a reference (δ 7.24). Chromatographic analysis was carried out on a LKhM-80 gas-liquid chromatograph, capillary column (SE-30, 12.5 m×0.22 mm), carrier gas nitrogen. Thin-layer chromatography was performed on Silufol (UV 254) plates. Melting points were determined in the capillary tube on a PTP appliance (PO Khimlaborpribor, Russia).

Oxidation of methyl oleate (Acros Organics) was carried out upon exposure to air at 60 °C. The sample to be oxidized weighed 5 g, the concentration of the compounds under study was 1 μmol g^{-1}. During the experiment, the samples of 0.1 g in weight were collected to determine the content of the peroxide compounds iron rhodanide method using a Specord UV VIS spectrophotometer. The time during which the peroxide number (PN) reached 0.05% I_2 was accepted as the induction period The starting PN for methyl oleate was 0.002% I_2. Plotting the structure and mathematical processing of kinetic curves were carried out using the Origin 6.0 program.

4-Bromo-2-methylphenol (2a). A solution of bromine (33.56 g, 0.21 mol) in chlorobenzene (100 mL) was added dropwise to a solution of *ortho*-cresol **1a** (21.61 g, 0.20 mol) in chlorobenzene (300 mL) at −10 °C over 4 h. Then, the mixture was heated to room temperature, followed by the addition of 10% aqueous solution of Na_2SO_3 (100 mL). The organic layer was separated, the aqueous phase was treated with chlorobenzene (2×50 mL), the organic phases were combined, washed with water, dried with Na_2SO_4, the solvent was evaporated, the residue (38 g, the content of the major compound (CMC) was 86% (GLC)) was recrystallized from light petroleum (200 mL) to obtain the product (29.27 g, 78%) with m.p. 63—65 °C (*cf.* Ref. 21: m.p. 63 °C). ^{1}H NMR, δ: 2.21 (s, 3 H, CH_3); 4.55 (s, 1 H, OH); 6.57 (d, 1 H, ArH, J = 8.4 Hz); 7.11 (dd, 1 H, ArH, J = 8.4 Hz, J = 2.4 Hz); 7.19 (d, 1 H, ArH, J = 2.4 Hz).

Compounds **2b,c** were obtained similarly to **2a**.

4-Bromo-2,3-dimethylphenol (2b). The yield was 74%, m.p. 89—91 °C (*cf.* Ref. 22: m.p. 91 °C). ^{1}H NMR, δ: 2.20 (s, 3 H, CH_3); 2.35 (s, 3 H, CH_3); 4.48 (s, 1 H, OH); 6.43 (d, 1 H, ArH, J = 8.4 Hz); 7.17 (d, 1 H, ArH, J = 8.4 Hz).

4-Bromo-2,5-dimethylphenol (2c). The yield was 76%, m.p. 85—86 °C (*cf.* Ref. 22: m.p. 87.5 °C). ^{1}H NMR, δ: 2.17 (s, 3 H, CH_3); 2.28 (s, 3 H, CH_3); 4.35 (s, 1 H, OH); 6.56 (s, 1 H, ArH); 7.19 (s, 1 H, ArH).

4-Ethoxy-2-methylphenol (3a). Sodium metal (9.20 g, 0.40 mol) was dissolved in EtOH (120 mL), then a solution of **2a** (18.70 g, 0.10 mol), CuI (4.00 g, 0.021 mol), and TMEDA (2.91 g, 0.025 mol) in DMF (20 mL) was added. The mixture was stirred for 5 h at 95 °C and cooled, followed by the addition of 2 *M* aqueous NH_4Cl (400 mL) and treatment with toluene (3×100 mL). The organic phase was washed with 2 *M* aq. NH_4Cl and brine, dried with Na_2SO_4, the solvent was evaporated. The residue (22.25 g, CMC 98% according to GLC) was distilled *in vacuo* to obtain the product (19.51 g, 85%) as a resin crystallizing upon cooling, m.p. 55—56 °C (*cf.* Ref. 23: m.p. 55—55.5 °C), b.p. 82—86 °C (1 Torr). ^{1}H NMR, δ: 1.37 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.19 (s, 3 H, $ArCH_3$); 3.91 (q, 2 H, $OC\underline{H}_2CH_3$, J = 6.6 Hz); 4.70 (br.s, 1 H, OH); 6.49 (dd, 1 H, ArH, J = 8.4 Hz, J = 3.0 Hz); 6.55 (d, 1 H, ArH, J = 8.4 Hz); 6.59 (d, 1 H, ArH, J = 3.0 Hz).

Compounds **3b,c** were obtained similarly to **3a**.

4-Ethoxy-2,3-dimethylphenol (3b). The yield was 90%, m.p. 113—114.5 °C, b.p. 98—113 °C (1 Torr). Found (%): C, 72.39; H, 8.40. $C_{10}H_{14}O_2$. Calculated (%): C, 72.26; H, 8.49. ^{1}H NMR, δ: 1.39 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.12 (s, 3 H, $ArCH_3$);

2.13 (s, 3 H, $ArCH_3$); 3.90 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.30 (br.s, 1 H, OH); 6.42 (d, 1 H, ArH, J = 8.4 Hz); 6.46 (d, 1 H, ArH, J = 8.4 Hz).

4-Ethoxy-2,5-dimethylphenol (3c). The yield was 86%, m.p. 80—82 °C (*cf.* Ref. 24: m.p. 80.5—81.5 °C), b.p. 111—115 °C (1 Torr). Found (%): C, 72.02; H, 8.31. $C_{10}H_{14}O_2$. Calculated (%): C, 72.26; H, 8.49. ^{1}H NMR, δ: 1.38 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.11 (s, 3 H, $ArCH_3$); 2.16 (s, 3 H, $ArCH_3$); 3.91 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.10 (s, 1 H, OH); 6.45 (s, 1 H, ArH); 6.48 (s, 1 H, ArH).

1-Allyloxy-4-ethoxy-2-methylbenzene (4a). Sodium hydroxide (3.15 g, 79 mmol) was added to a solution of **3a** (10.00 g, 66 mmol) in DMF (30 mL), the mixture was stirred for 30 min at 50 °C, followed by a dropwise addition of allyl bromide (15.90 g, 0.131 mol) and stirring for 2 h at 60 °C. The reaction mixture was cooled, acidified with aq. HCl, and treated with toluene (3×80 mL). The organic phase was washed with 15% aq. NaOH (3×50 mL) and brine, dried with Na_2SO_4. The solvent was evaporated to obtain compound **4a** (12.20 g, 96%) as a light liquid (CMC >99% according to GLC). Found (%): C, 75.12; H, 8.44. $C_{12}H_{16}O_2$. Calculated (%): C, 74.97; H, 8.39. ^{1}H NMR, δ: 1.37 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.20 (s, 3 H, $ArCH_3$); 3.91 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.44 (dt, 2 H, $C\underline{H}_2CH{=}CH_2$, J = 5.4 Hz, J = 1.2 Hz); 5.21 (dd, 1 H, $CH_2CH{=}C\underline{H}_2$, J = 10.2 Hz, J = 1.2 Hz); 5.37 (dd, 1 H, $CH_2CH{=}C\underline{H}_2$, J = 17.4 Hz, J = 1.2 Hz); 6.01 (m, 1 H, $CH_2C\underline{H}{=}CH_2$); 6.51 (dd, 1 H, ArH, J = 9.0 Hz, J = 2.4 Hz); 6.61 (m, 2 H, ArH).

Compounds **4b—d** were obtained similarly to **4a**.

1-Allyloxy-4-ethoxy-2,3-dimethylbenzene (4b). The yield was 95%. Found (%): C, 75.60; H, 8.86. $C_{13}H_{18}O_2$. Calculated (%): C, 75.69; H, 8.80. ^{1}H NMR, δ: 1.30 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.03 (s, 3 H, $ArCH_3$); 2.06 (s, 3 H, $ArCH_3$); 3.82 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.32 (dt, 2 H, $C\underline{H}_2CH{=}CH_2$, J = 4.8 Hz, J = 1.2 Hz); 5.11 (dd, 1 H, $CH_2CH{=}C\underline{H}_2$, J = 10.2 Hz, J = 1.2 Hz); 5.28 (dd, 1 H, $CH_2CH{=}C\underline{H}_2$, J = 17.4 Hz, J = 1.2 Hz); 5.92 (m, 1 H, $CH_2C\underline{H}{=}CH_2$); 6.32 (m, 2 H, ArH).

1-Allyloxy-4-ethoxy-2,5-dimethylbenzene (4c). The yield was 96%, m.p. 50—51.5 °C. Found (%): C, 75.62; H, 8.70. $C_{13}H_{18}O_2$. Calculated (%): C, 75.69; H, 8.80. ^{1}H NMR, δ: 1.38 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.14 (s, 3 H, $ArCH_3$); 2.17 (s, 3 H, $ArCH_3$); 3.93 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.43 (dt, 2 H, $C\underline{H}_2CH{=}CH_2$, J = 4.8 Hz, J = 1.2 Hz); 5.20 (dd, 1 H, $CH_2CH{=}C\underline{H}_2$, J = 10.2 Hz, J = 1.2 Hz); 5.36 (dd, 1 H, $CH_2CH{=}C\underline{H}_2$, J = 17.4 Hz, J = 1.2 Hz); 6.01 (m, 1 H, $CH_2C\underline{H}{=}CH_2$); 6.52 (s, 2 H, ArH).

1-Allyloxy-4-methoxybenzene (4d). The yield was 92%, b.p. 88—93 °C (1 Torr) (*cf.* Ref. 25: b.p. 92 °C (1 Torr)). ^{1}H NMR, δ: 3.73 (s, 3 H, OCH_3); 4.43 (dt, 2 H, $C\underline{H}_2CH{=}CH_2$, J = 5.4 Hz, J = 1.2 Hz); 5.22 (dd, 1 H, $CH_2CH{=}C\underline{H}_2$, J = 10.2 Hz, J = 1.2 Hz); 5.35 (dd, 1 H, $CH_2CH{=}C\underline{H}_2$, J = 17.4 Hz, J = 1.2 Hz); 5.99 (m, 1 H, $CH_2C\underline{H}{=}CH_2$); 6.74 (m, 4 H, ArH).

2-Allyl-4-ethoxy-6-methylphenol (5a). Compound **4a** (12.20 g, 63 mmol) was stirred for 2 h at 200 °C then distilled *in vacuo* (1 Torr) to obtain compound **5a** (10.72 g, 89%) as colorless light liquid, b.p. 82—86 °C. Found (%): C, 74.71; H, 8.23. $C_{12}H_{16}O_2$. Calculated (%): C, 74.97; H, 8.39. ^{1}H NMR, δ: 1.36 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2); 2.19 (s, 3 H, $ArCH_3$); 3.33 (d, 2 H, $C\underline{H}_2CH{=}CH_2$, J = 6.6); 3.91 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2); 4.41 (s, 1 H, OH); 5.15 (m, 2 H, $CH_2CH{=}C\underline{H}_2$); 5.95 (m, 1 H, $CH_2C\underline{H}{=}CH_2$); 6.43 (d, 1 H, ArH, J = 3.0); 6.50 (d, 1 H, ArH, J = 3.0).

Compounds **5b—d** were obtained similarly to **5a**.

6-Allyl-4-ethoxy-2,3-dimethylphenol (5b). The yield was 88%, m.p. 57.5—58.5 °C, b.p. 105—110 °C (1 Torr). Found (%): C, 75.79; H, 8.63. $C_{13}H_{18}O_2$. Calculated (%): C, 75.69; H, 8.80. ^{1}H NMR, δ: 1.39 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.11 (s, 3 H, $ArCH_3$); 2.13 (s, 3 H, $ArCH_3$); 3.32 (d, 2 H, $C\underline{H}_2CH{=}CH_2$, J = 6.0 Hz); 3.91 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.42 (s, 1 H, OH); 5.15 (m, 2 H, $CH_2CH{=}C\underline{H}_2$); 5.96 (m, 1 H, $CH_2C\underline{H}{=}CH_2$); 6.37 (s, 1 H, ArH).

2-Allyl-4-ethoxy-3,6-dimethylphenol (5c). The yield was 85%, m.p. 51—53 °C, b.p. 100—106 °C (1 Torr). Found (%): C, 75.51; H, 8.58. $C_{13}H_{18}O_2$. Calculated (%): C, 75.69; H, 8.80. ^{1}H NMR, δ: 1.39 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.11 (s, 3 H, $ArCH_3$); 2.19 (s, 3 H, $ArCH_3$); 3.39 (d, 2 H, $C\underline{H}_2CH{=}CH_2$, J = 4.2 Hz); 3.91 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.27 (s, 1 H, OH); 5.02 (m, 2 H, $CH_2CH{=}C\underline{H}_2$); 5.91 (m, 1 H, $CH_2C\underline{H}{=}CH_2$); 6.46 (s, 1 H, ArH).

2-Allyl-4-methoxyphenol (5d). The yield was 84%, b.p. 80—86 °C (1 Torr) (*cf.* Ref. 26: b.p. 95 °C (0.6 Torr)). Found (%): C, 73.36; H, 7.15. $C_{10}H_{12}O_2$. Calculated (%): C, 73.15; H, 7.37. ^{1}H NMR, δ: 3.35 (d, 2 H, $C\underline{H}_2CH{=}CH_2$, J = 6.6 Hz); 3.73 (s, 3 H, OCH_3); 5.10 (s, 1 H, OH); 5.19 (m, 2 H, $CH_2CH{=}C\underline{H}_2$); 5.96 (m, 1 H, $CH_2C\underline{H}{=}CH_2$); 6.59 (dd, 1 H, ArH, J = 8.4 Hz, J = 3.0 Hz); 6.63 (d, 1 H, ArH, J = 3.0 Hz); 6.65 (d, 1 H, ArH, J = 8.4 Hz).

5-Hydroxy-2,7-dimethyl-2,3-dihydrobenzofuran (6a). A 46% aq. HBr (0.15 mol, 22 mL) was added to a solution of **5a** (6.73 g, 35.0 mmol) in AcOH (350 mL), the mixture was refluxed for 4 h. Then, the solvent was evaporated on a rotary evaporator, the residue was dissolved in toluene (100 mL), washed with 20% aq. NaOH (3×60 mL), the aqueous layers were acidified with aq. HCl and treated with ethyl acetate (5×40 mL). The extract was washed with brine, dried with Na_2SO_4, the solvent was evaporated. The residue was distilled *in vacuo* to obtain a colorless resin (3.18 g, 55%) (CMC 99% according to GLC) crystallizing on cooling, m.p. 62—64 °C, b.p. 98—100 °C (1 Torr). Found (%): C, 73.36; H, 7.15. $C_{10}H_{12}O_2$. Calculated (%): C, 73.15; H, 7.37. ^{1}H NMR, δ: 1.43 (d, 3 H, $CH(C\underline{H}_3)CH_2$, J = 4.2 Hz); 2.10 (s, 3 H, $ArCH_3$); 2.71 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.18 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 4.76 (br.s, 1 H, OH); 4.80 (m, 1 H, $C\underline{H}(CH_3)CH_2$); 6.30 (d, 1 H, ArH, J = 2.4 Hz); 6.39 (d, 1 H, ArH, J = 2.4 Hz).

Compounds **6b—d** were obtained similarly to **6a**.

5-Hydroxy-2,6,7-trimethyl-2,3-dihydrobenzofuran (6b) was purified on a column with Al_2O_3 (5 degree of activity, eluent toluene). The yield was 42%, m.p. 127—128 °C (*cf.* Ref. 27: m.p. 126—128 °C). ^{1}H NMR, δ: 1.42 (d, 3 H, $CH(C\underline{H}_3)CH_2$, J = 6.0 Hz); 2.07 (s, 6 H, $ArCH_3$); 2.69 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.18 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.97 (s, 1 H, OH); 4.76 (m, 1 H, $C\underline{H}(CH_3)CH_2$); 6.34 (s, 1 H, ArH).

5-Hydroxy-2,4,7-trimethyl-2,3-dihydrobenzofuran (6c) was purified on a column with Al_2O_3 (5 degree of activity, eluent toluene). The yield was 56%, m.p. 96.5—98.5 °C (*cf.* Ref. 28: m.p. 97—99 °C). ^{1}H NMR, δ: 1.44 (d, 3 H, $CH(C\underline{H}_3)CH_2$, J = 6.0 Hz); 2.05 (s, 3 H, $ArCH_3$); 2.06 (s, 3 H, $ArCH_3$); 2.66 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.16 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 4.10 (s, 1 H, OH); 4.81 (m, 1 H, $C\underline{H}(CH_3)CH_2$); 6.24 (s, 1 H, ArH).

5-Hydroxy-2-methyl-2,3-dihydrobenzofuran (6d). The yield was 50%, b.p. 101—104 °C (1 Torr). Found (%): C, 71.61; H, 6.66. $C_9H_{10}O_2$. Calculated (%): C, 71.98; H, 6.71. ^{1}H NMR, δ: 1.42 (d, 3 H, $CH(C\underline{H}_3)CH_2$, J = 6.0 Hz); 2.69 (m, 1 H,

$CH(CH_3)C\underline{H}_2$); 3.17 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 4.82 (m, 1 H, $C\underline{H}(CH_3)CH_2$); 5.78 (s, 1 H, OH); 6.24 (dd, 1 H, ArH, J = 8.4 Hz, J = 2.4 Hz); 6.49 (d, 1 H, ArH, J = 8.4 Hz); 6.57 (d, 1 H, ArH, J = 2.4 Hz).

6-Hydroxy-5,8-dimethylchromane (7c). Sodium borohydride (2.27 g, 60 mmol) was added to a solution of **5c** (5.16 g, 25 mmol) in THF (35 mL), followed by a dropwise addition of Me_2SO_4 (3.15 g, 25.0 mmol). The mixture was stirred at room temperature for 1 h, cooled to 3—5 °C, and dropwise diluted with water (9.5 mL). Then, the mixture was heated to room temperatures, followed by a sequential dropwise addition of a 3 *M* aq. NaOH (3.00 g, 75 mmol) (25 mL) and 23% aq. H_2O_2 (13.6 mL, 75 mmol). The reaction mixture was stirred for 2 h, neutralized with aq. HCl and treated with toluene (3×80 mL). The combined organic phases were washed with brine and dried with Na_2SO_4. The solvent was evaporated to obtain the product 4-ethoxy-2-(3-hydroxypropyl)-3,6-dimethylphenol (5.61 g) as a colorless crystalline substance.

Further, the product obtained (5.61 g) was refluxed with 46% aq. HBr (21 mL, 0.175 mol) for 3 h, cooled, and treated with toluene (3×80 mL). The combined organic phases were washed with brine and dried with Na_2SO_4. The solvent was evaporated, the residue was recrystallized from light petroleum to obtain colorless crystals (2.97 g) with m.p. 124—126 °C (*cf.* Ref. 29: m.p. 126—127 °C). ^{1}H NMR, δ: 1.98 (m, 2 H, $OCH_2C\underline{H}_2CH_2Ar$); 2.02 (s, 3 H, $ArCH_3$); 2.05 (s, 3 H, $ArCH_3$); 2.61 (t, 2 H, $OCH_2CH_2C\underline{H}_2Ar$, J = 6.6 Hz); 4.04 (s, 1 H, OH); 4.06 (m, 2 H, $OC\underline{H}_2CH_2CH_2Ar$); 6.31 (s, 1 H, ArH).

6-Hydroxychromane (7d) was obtained similarly to **7c**. The yield was 62%, m.p. 98—100 °C (*cf.* Ref. 30: m.p. 99—100 °C), b.p. 115—122 °C (1 Torr). ^{1}H NMR, δ: 1.94 (m, 2 H, $OCH_2C\underline{H}_2CH_2Ar$); 2.67 (t, 2 H, $OCH_2CH_2C\underline{H}_2Ar$, J = 6.6 Hz); 4.07 (t, 2 H, $OC\underline{H}_2CH_2CH_2Ar$, J = 5.4 Hz); 5.39 (s, 1 H, OH); 6.39 (d, 1 H, ArH, J = 3.0 Hz); 6.46 (dd, 1 H, ArH, J = 8.4 Hz, J = 3.0 Hz); 6.55 (d, 1 H, ArH, J = 8.4 Hz).

5-Methoxy-2-methyl-2,3-dihydrobenzofuran (8d). A 46% aq. HBr (4.5 mL, 37.5 mmol) was added to a solution of **5d** (1.23 g, 7.5 mmol) in AcOH (95 mL), the mixture was refluxed for 1 h. Then, AcOH was evaporated on a rotary evaporator, the residue was dissolved in toluene (20 mL), washed with 20% aq. NaOH (3×20 mL) and brine, dried with Na_2SO_4. The solvent was evaporated to obtain the product (0.91 g, 74%) (CMC >97% according to GLC). Found (%): C, 73.22; H, 7.31. $C_{10}H_{12}O_2$. Calculated (%): C, 73.15; H, 7.35. ^{1}H NMR, δ: 1.42 (d, 3 H, $CH(C\underline{H}_3)CH_2$, J = 6.0 Hz); 2.74 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.23 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.70 (s, 3 H, OCH_3); 4.82 (m, 1 H, $C\underline{H}(CH_3)CH_2$); 6.53 (s, 2 H, ArH); 6.62 (s, 1 H, ArH).

6-Dodecylthiomethyl-5-hydroxy-2,4,7-trimethyl-2,3-dihydrobenzofuran (10c). Dodecyl (diethylaminomethyl) sulfide (1.58 g, 5.5 mmol) was added to a solution of **6c** (0.89 g, 5.0 mmol) in AcOH (2.5 mL), the mixture was stirred for 2 h at 140 °C and cooled, followed by the addition of water (30 mL) and treatment with toluene (3×10 mL). The combined organic phases were washed with 15% aq. NaOH (3×10 mL) and brine, dried with Na_2SO_4. The solvent was evaporated to obtain a resin (1.95g), which was purified on a column with Al_2O_3 (5 degree of activity, eluent light petroleum) to obtain a colorless resin (1.73 g, 88%) crystallizing on cooling, m.p. 32—33 °C. Found (%): C, 73.21; H, 10.07; S, 8.29. $C_{24}H_{40}O_2S$. Calculated (%): C, 73.42; H, 10.27; S, 8.17. ^{1}H NMR, δ: 0.88 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.25—1.35 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.43 (d, 3 H, $CH(C\underline{H}_3)CH_2$, J = 6.0 Hz); 1.56 (m, 2 H, $SCH_2C\underline{H}_2(CH_2)_9CH_3$); 2.08 (s, 3 H, $ArCH_3$); 2.11 (s, 3 H, $ArCH_3$); 2.40 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.68 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.18 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.73 (m, 2 H, $ArC\underline{H}_2SC_{12}H_{25}$); 4.78 (m, 1 H, $C\underline{H}(CH_3)CH_2$); 5.86 (s, 1 H, OH).

4,6-Bis(dodecylthiomethyl)-5-hydroxy-2-methyl-2,3-dihydrobenzofuran (10d). Dodecyl (diethylaminomethyl) sulfide (4.53 g, 15.8 mmol) was added to a solution of **6d** (1.13 g, 7.5 mmol) in AcOH (6 mL), the reaction mixture was stirred for 2 h at 140 °C then cooled, diluted with water (30 mL), and treated with toluene (3×10 mL). The combined organic phase were washed with 15% aq. NaOH (3×10 mL) and brine, dried with Na_2SO_4. The solvent was evaporated to obtain a resin (4.91 g), which were purified on a column with Al_2O_3 (5 degree of activity, eluent light petroleum) to obtain a colorless resin crystallizing on cooling, m.p. 44—46 °C. Found (%): C, 72.46; H, 10.91; S, 11.28. $C_{35}H_{62}O_2S_2$. Calculated (%): C, 72.60; H, 10.79; S, 11.08. ^{1}H NMR, δ: 0.88 (m, 6 H, $[S(CH_2)_{11}C\underline{H}_3]_2$); 1.24—1.33 (m, 36 H, $[S(CH_2)_2(C\underline{H}_2)_9CH_3]_2$); 1.43 (d, 3 H, $CH(C\underline{H}_3)CH_2$, J = 6.6 Hz); 1.53 (m, 4 H, $[SCH_2C\underline{H}_2(CH_2)_9CH_3]_2$); 2.35 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.40 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.76 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.27 (m, 1 H, $CH(CH_3)C\underline{H}_2$); 3.66 (m, 4 H, $Ar[C\underline{H}_2SC_{12}H_{25}]_2$); 4.83 (m, 1 H, $C\underline{H}(CH_3)CH_2$); 6.35 (s, 1 H, OH); 6.39 (s, 1 H, ArH).

7-Dodecylthiomethyl-6-hydroxy-5,8-dimethylchromane (11c) was obtained similarly to **10c** based on hydroxychromane **7c**. The yield was 90%, m.p. 49.5—51.5 °C. Found (%): C, 73.04; H, 10.15; S, 8.32. $C_{24}H_{40}O_2S$. Calculated (%): C, 73.42; H, 10.27; S, 8.17. ^{1}H NMR, δ: 0.90 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.25—1.35 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.56 (m, 2 H, $SCH_2C\underline{H}_2(CH_2)CH_3$); 1.98 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.07 (s, 3 H, $ArCH_3$); 2.10 (s, 3 H, $ArCH_3$); 2.40 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.62 (t, 2 H, $CH_2CH_2C\underline{H}_2$, J = 7.2 Hz); 3.76 (s, 2 H, $ArC\underline{H}_2SC_{12}H_{25}$); 4.06 (t, 2 H, $C\underline{H}_2CH_2CH_2$, J = 5.4 Hz); 5.89 (s, 1 H, OH).

5,7-Bis(dodecylthiomethyl)-6-hydroxychromane (11d) was obtained similarly to **10d** based on hydroxychromane **7d**. The yield was 76%, m.p. 44—46 °C. Found (%): C, 72.69; H, 10.97, S, 11.37. $C_{35}H_{62}O_2S_2$. Calculated (%): C, 72.60; H, 10.79, S, 11.08. ^{1}H NMR, δ: 0.88 (m, 6 H, $[S(CH_2)_{11}C\underline{H}_3]_2$); 1.24—1.33 (m, 36 H, $[S(CH_2)_2(C\underline{H}_2)_9CH_3]_2$); 1.51—1.57 (m, 4 H, $[SCH_2C\underline{H}_2(CH_2)_9CH_3]_2$); 1.99 (m, 2 H, $OCH_2C\underline{H}_2CH_2Ar$); 2.34 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.44 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.78 (t, 2 H, $OCH_2CH_2C\underline{H}_2Ar$, J = 6.6 Hz); 3.66 (s, 2 H, $ArC\underline{H}_2SC_{12}H_{25}$); 3.68 (s, 2 H, $ArC\underline{H}_2SC_{12}H_{25}$); 4.04 (t, 2 H, $OC\underline{H}_2CH_2CH_2Ar$, J = 5.4 Hz); 6.39 (s, 1 H, OH); 6.43 (s,1 H, ArH).

This work was financially supported by the City Council of Novosibirsk (Grant No. 47-12).

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Received December 3, 2012;
in revised form April 4, 2013