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Development of a One-Stage Synthesis of 2,6-Di-*tert*-4-ethylbutylphenol from 2,6-Di-*tert*-butylphenol

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Abstract—Investigation of the catalyzed reaction of 2,6-di-*tert*-butylphenol with ethanol, ethylene glycol, oligomeric glycols, and paraldehyde in a strongly basic medium permitted to develop a technologically suitable procedure for manufacture of 2,6-di-*tert*-4-ethyl-butylphenol, used in the synthesis of Antioxidant-425.

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2,6-Di-*tert*-butyl-4-ethylphenol (**I**) is a structural homolog of a well-known antioxidant 2,6-di-*tert*-butyl4-methylphenol **II**. They are used in the manufacture of a great number of stabilized polymeric compositions and generally patented under a common name 4-alkyl-2,6-di-*tert*-butylphenols [1]. Compounds **I** and **II** have recently been found in the foam of seas and limnetic rivers in Europe and America. Compound **I** was found among pollutants the ground waters in Sweden [2], China, and Israel. This finding means that compound **I** is present in industrial wastes and is widely used in agriculture and as polymer additive. The large-scale industrial production of compounds **I** and **II** necessitated development of ecologically safe methods of their use. Note such negative properies of compounds **I** and **II** as the tendecy for water migration, high solubility in fats, and slow biological degradation under natural conditions.

No reviews on the manufacture and properties of compound **I** have been published. It is noted that this compound is a promising antioxidant additive to monomeric olefins, which provides polymerization of the latter under heating [4]. It is nontoxic and due to that principally differs from 2,6-di-*tert*-butyl-4-methylphenol [5]. When advertizing compound **I**, Ethyl Co. states that it possesses a unique ability to preserve a natural color of polymeric articles during their use and is safe in contact with food [6]. This latter property of compound **I** is widely used for protecting fruits from oxidation and putrefaction on storage [7], as well as for prolonging the useful life of medicinals, creams, food stuff, and perfumes.

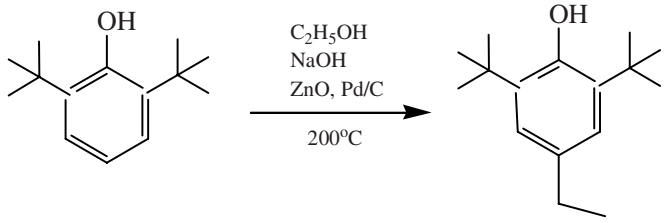
Among the previously developed methods of manufacturing compound **I** we can mention its synthesis by *tert*-butylation of 4-ethylphenol with isobutylene in the presence of acidic catalysts at 70–80°C [8, 9]. The reaction of these compounds taken in an equimolar ratio gives a mixture containing 6% of compound **III**, 10% of compound **I**, and 80% of 2-*tert*-butyl-4-ethylphenol (**IV**) used for manufacturing Antioxidant-425 (**V**) [9]. The main problem is to obtain starting compound **III** free of isomers. By now three approaches have been suggested. The furst involves the acylation of phenol, leading to 4-acetylphenol (60% yield), and its subsequent reduction [10]. The second is sulfonation of ethylbenzene followed by alkaline melting of the resulting mixture of sulfonic acids [11]. The third approach involves oxidation of 1,4-diethylbenzene to form hydroperoxide and decomposition of the latter [12]. The purest compound **III** could be obtained by the first procedure [10].

With 2,6-di-*tert*-butylphenol (**VI**), a number of highly selective two-stage syntheses of compound **I** become available. The acylation of compound **VI** with acetic anhydride in the presence of magnesium perchlorate in an acidic medium yields 4-acetyl-2,6-di-*tert*-butylphenol (**VII**). The latter is reduced with hydrogen in the presence of $Pd/BaSO_4$ to obtain compound **I** in a nearly quantitative yield. The acylation of compound **VI** with acetyl chloride and the

subsequent reduction of product **VII** with $LiAlH_4$ was reported by Volod'kin et al. [14].

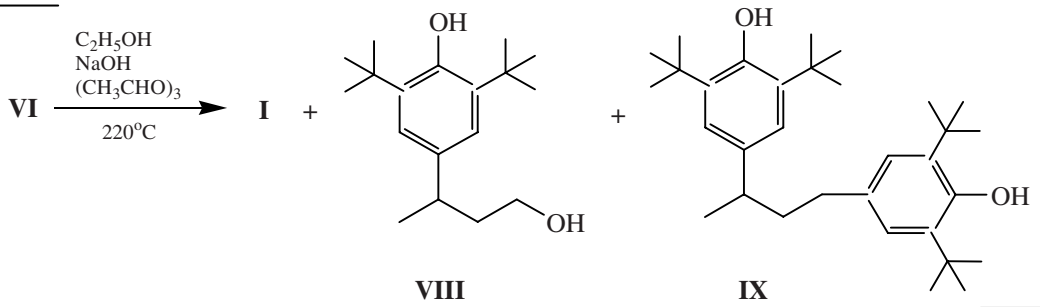
More attractive are one-stage syntheses of **I**, starting from 2,6-di-*tert*-butylphenol (**V**). Hence, the reaction of compound **VI** with ethanol in the presence of KOH gives a mixture containing 74% of **I** [3]. This process is catalyzed by zinc oxide [15]. As known, ZnO forms zincates in an alkaline medium. They catalyze redox methylation of compound **VI** with methanol [15]. Introduction of Pd/C accelerates reduction of the benzyl alcohol derivatives formed in the first stage [16].

We showed that using a mixture of the Pd/C and ZnO catalytic additives during the ethylation of compound **VI** with ethanol increases the fraction of target compound **I** in the reaction mixture from 70 to 85%. But the high reaction temperature (220–225°C) and pressure developed in the course of the process (4–10 MPa), as well as long reaction time (7 h) hinder commercialization of this procedure.



VI **I**

As known, compound **I** is formed in an alkaline medium when compound **I** is reacted with acetaldehyde and ethanol [17]. However, this process could not be optimized. In the presence of paraldehyde, this reaction proceeded under at 2–4 MPa and 230°C; under these conditions, the reaction time was 20 times shorter compared with the initial variant.



VIII **IX**

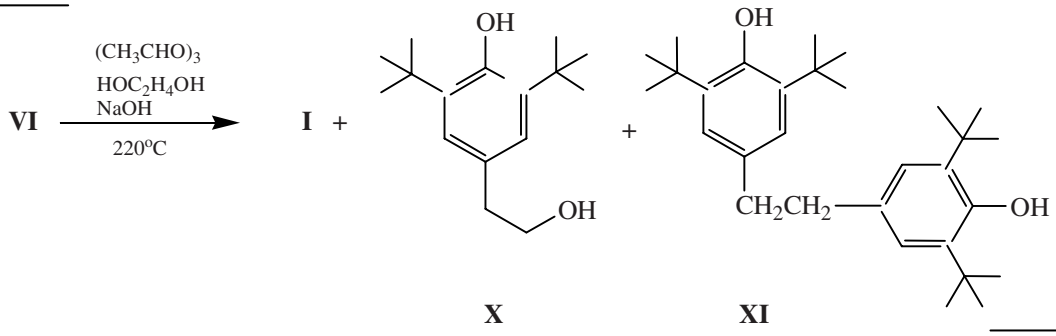
The by-product 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)butan-1-ol (**VIII**) and 1,3-bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)butane (**I**) are probably formed by condensation of compound **VI** with crotonaldehyde formed in its turn by dehydrocondensation of acetaldehyde. The primary condensation products undergo reduction in the course of the process. Really, short heating of an alkaline ethanol solution of compound **VI** and crotonaldehyde at 230°C in an autoclave gave a mixture of phenols. According to GC–MS data, the mixture contained 37% of 2-di-*tert*-butyl-4-ethylphenol, 16.4% of compound **VIII**, 13% of compound **IX**, and a series of other compounds. The composition of the reaction products is close to that formed under analogous conditions in the ethylation of compound **VI** in the presence of paraldehyde.

Since compound **VIII** can be used as the starting material for the synthesis of polymer thermostabilizers, while *tert*-butyl derivatives of bis(hydroxypenyl) propane, compound **IX** among them, are recommended for manufacture from polyesters of cast articles exhibiting enhanced whiteness, transparency, and thermostability [18], we resorted to a simplex approach to optimize the process and increase the fraction of compounds **VIII** and **IX** in the reaction mixture. As a result, the ethylation of compound **VI** gave a mixture containing 60–65% of compound **I**, 20–25% of alcohol **VIII**, and 10% of compound **IX**, easily separable by vacuum distillation.

It was found that the reaction of paraldehyde with compound **VI** in presence of ethylene glycol instead of

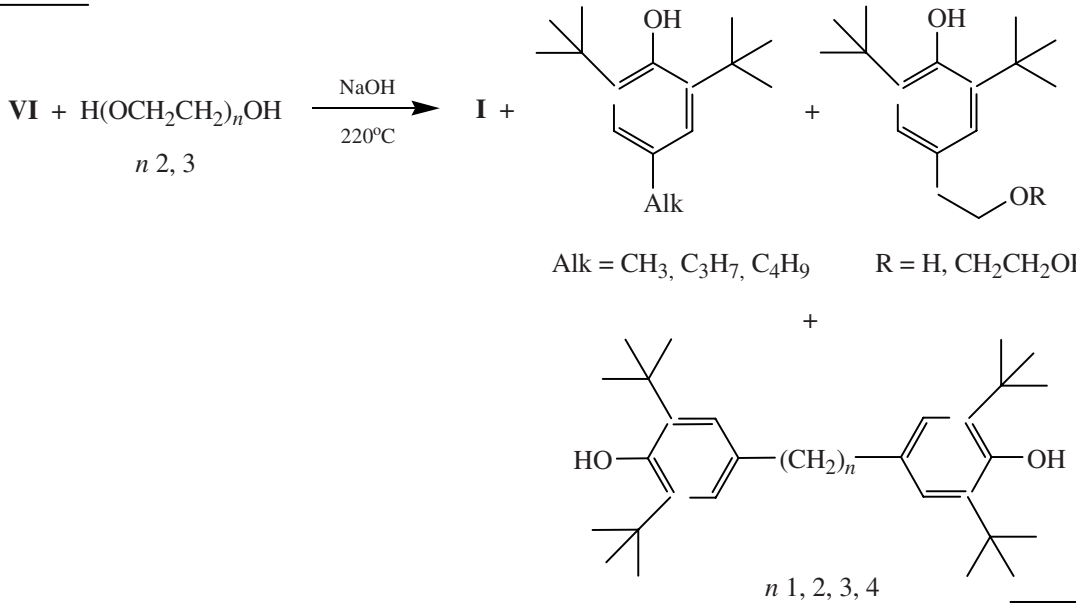
ethanol at a high temperature results in preferential formation of compound **I**. This process was accompanied by a significantly slower alkylation of compound **VI** with ethylene glycol, resulting in formation of 2,6-di-*tert*-butyl-4-(2-hydroxyethyl)phenol (**X**).

In the absence of paraldehyde, the reaction of compound **VI** with ethylene glycol under similar conditions gives little compound **I**. The only product isolated was compound **X** (yield 10%).



X **XI**

Further improvement of the synthesis of compound **I**, starting from **VI**, resulted in the development of an atmospheric-pressure process. It was found that compound **I** is formed as the main product upon refluxing of an alkaline solution of compound **VI** with excess di- or triethylene glycol.

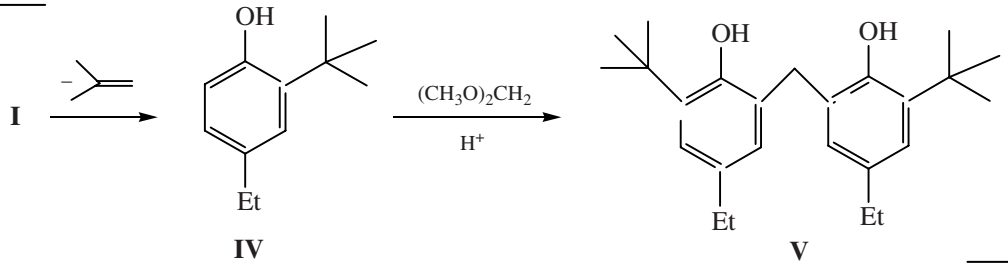


The process with triethylene glycol was realized at atmospheric pressure in a glass reactor. The fraction of compound **I**, the main reaction product, in the reaction mixture was 50–65%. According to GC–MS data, the mixture contained three groups of compounds. The first one was a mixture of 4-alkyl-2,6-di-*tert*-butylphenols with a C_1–C_4 alkyl radical, the second contained compound **X** and its ethers, and the third, bis-phenols with the aromatic fragments intervened by a C_1–C_4 alkyl chain and two unidentified products (fraction ca/10%) with the molecular masses 294 and 338.

We found no data in the literature, concerning C-alkylation of aromatic compounds with oligomeric glycols in an alkaline medium. The occurrence of this reaction is probably explained by an unusual way of generation of the alkylating agents from oligomeric glycols in an alkaline medium. The latter are known to form complexes with Li^+ and Na^+. Under ionizing irradiation, these complexes can generate radical species detected by tandem mass spectrometry [19]. It was established that the cleavage of oligomeric alkali metal glycolates proceeds via 1,4- and 1,5-hydride

shifts to form ethyl or hydroxyethyl radical. As judged from the composition of the reaction products, these species are also generated in our case and react with 2,6-di-*tert*-butylphenol to form its various C-alkylation products.

Compound **I** was manufactured at the Pilot Plant of the Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences (supervisor A.G. Khmel'nitskii), and a batch of product **I** was used for the synthesis of 2,2-methylenebis(6-*tert*-butyl-4-ethylphenol (**V**) via mono-de-*tert*-butylation of compound **I** [20, 21] followed by reaction of product **IV** with methylal in presence of an acidic catalyst. Compound **V** is used as a stabilizer for medical rubbers and transparent polymers [7].



The above-presented scheme was employed at the Sterlitamak Petrochemical Plant to manufacture from a batch of product **I** the first Russian butch of compound **V**, which was successfully tested at the Bobruisk Plant of General Rubber Goods.

EXPERIMENTAL

Gas chromatography–mass spectrometry analysis of phenols was performed on a Hewlett–Packard instrument comprising an HP 5890 gas chromatograph (11 series), an HP 5971 mass-selective detector. Separation was performed on an HP5MS 30 m × 0.25 × 0.25 μm capillary column, carrier gas helium. The composition of the reaction mixtures was determined on a Tsvet gas chromatograph.

The melting points were measured on a Kofler hot stage. The UV spectra were measured on a Specord UV-Vis spectrophotometer in ethanol (c 10^{-4} M). The ^{1}H NMR spectra were taken on a Bruker AV-300 (300.13 MHz) spectrometer for 10% $CDCl_3$ solutions at 25°C; the chemical shifts were measured against internal $CHCl_3$ (δ 7.24 ppm). The elemental analyses were obtained on a Carlo Erba CHN-analyzer (model 1106).

High-pressure synthesis of 2,6-di-*tert*-butyl-4-ethylphenol (I). Absolute methanol, 500 ml, 200 g of 98% 2,6-di-*tert*-butylphenol, 80 g of 85% KOH, 1.0 g of 4% Pd/C, and 10 g of zinc oxide were loaded in succession into a 2-l steel autoclave. The autoclave was heated at 200°C for 15 h. By the end of this time, the pressure inside the autoclave reached 10 MPa. The autoclave was cooled and depressurized. The reaction mixture was extracted with 0.5 l of petroleum ether.

The extract was washed with 5% HCl and water until neutral and evaporated to obtain 230 g of a solid material. According to GLC data, it contained 85% of 2,6-di-*tert*-butyl-4-ethylphenol and 0.5% of starting compound **VI**. The reaction product was purified by vacuum distillation. The fraction with bp 110–120°C (1–2 mm Hg) was collected. It contained 176 g (76%) of product **I** of 97% purity, mp 42–44°C (published data [11]: mp 44°C).

Synthesis of 2,6-di-*tert*-butyl-4-ethylphenol (I) with paraldehyde. Technical grade 95% 2,6-di-*tert*-butylphenol, 103 g, 230 ml of the 95% hydrolytic ethanol, 28 ml of paraldehyde, and 28 g of potassium hydroxide were loaded in a 0.5-l steel autoclave, and the autoclave was heated with rotation to 230°C and kept at this temperature for 20 min. By the end of this time (the highest pressure inside the autoclave was 4 MPa), the autoclave was cooled and unloaded. Excess ethanol was distilled off, and the residue was neutralized with 10% HCl and extracted with petroleum ether. The solvent was evaporated to leave 120 g of an oil. According to GLC data, it contained 59–63% of 2,6-di-*tert*-butyl-4-ethyl-phenol, 18–21% of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)butan-1-ol (**VIII**), 11–13% of 1,3-bis-(3,5-di-*tert*-butyl-4-hydroxyphenyl)butane (**IX**), 1% of the starting 2,6-di-*tert*-butylphenol, 2% of 2,4-di-*tert*-butylphenol, and 1–2% of other components.

Vacuum distillation gave three fractions.

First fraction. Yield 75 g, bp 110–120°C (2–3 mm Hg). According to GLC data, the material contained 96% of 4-ethyl-2,6-di-*tert*-butylphenol, mp 43–44°C (from *n*-heptane). Yield 65%.

Second fraction. Yield 20 g, bp 160–175°C (2–3 mm Hg). The material was dissolved in 25 ml of petroleum ether and cooled to 0°C. A precipitate formed and was filtered off and washed with petroleum ether to obtain 15 g (11.3%) of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)butan-1-ol (**VIII**), mp 74–76°C (from *n*-pentane). UV spectrum, λ_{max}, nm (log ε): 277 (3.20). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.82 s (2H, H_{arom}), 4.52 s (1H, ArOH), 3.48 t (2H, -CH_2CH_2OH, *J* 7), 2.72 m [1H, ArC*H*(CH_3)-], 2.02 s (1H, -CH_2O*H*), 1.72 m (2H, –CH_2CH_2OH), 1.40 s (18H, 3- and 5-*tert*-butyl groups), 1.14 d (3H, CHCH_3, *J* 7). Found, %: C 77.70, H 10.62. MM 278 (isothermic distillation). $C_{18}H_{30}O_2$. Calculated, C 77.73, H 10.86. MM 278.

Third fraction. Yield 12 g, bp 210–230°C (2–3 mm Hg). The material was dissolved in 25 ml of ethanol. After a day a precipitate formed and was filtered off to obtain 8 g (8%) of 1,3-bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)butane (**IX**), mp 132.0–132.5°C. UV spectrum, λ_{max}, nm (log ε): 279 (3.53). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.92 s and 6.83 s (2H each, H_{arom}), 4.84 s and 4.82 s (1H each, OH), 2.54 m [1H, ArC*H*(CH_3)-], 2.38 t (2H, ArCH_2-, *J* 7), 1.8 m (2H, -CH_2-), 1.40 s and 1.44 s (18H each, two *tert*-butyl groups), 1.20 d (3H, -CH_2CH_3, *J* 7). Found, %: C 82.54, H 10.41, MM 466. $C_{32}H_{50}O_2$. Calculated, %: C 82.35, H 10.80, MM 466.

Reaction of compound VI with crotonaldehyde. 2,6-Di-*tert*-butylphenol, 20 g, 7 g of crotonaldehyde, 7 g of 85% KOH, and 40 ml of ethanol were loaded in a 100 ml steel autoclave and kept at 230°C for 30 min. After that the reaction mixture was neutralized with HCl and extracted with *tert*-butyl methyl ether. The solvent was evaporated to leave 23.5 g of an oil. According to GC–MS data, it contained 14% of 2,6-di-*tert*-butylphenol, 37% of compound **I**, 16.5% of compound **VIII**, 13% of compound **IX**, 2.7% of bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)methane, 6% of 1,1-bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethane, and some other components (1% each). Vacuum distillation gave 10 g of compound **I** and 3 g of compound **VIII**.

Reaction of compound VI with ethylene glycol. A solution of 20 g of 2.6-di-*tert*-butylphenol and 5.6 g of NaOH in 40 ml of ethylene glycol was heated at 215°C for 7 h in a glass reactor equipped with a stirrer under an inert gas flow. The liberating water was distilled off over the course of the reaction. After neutralization of the reaction mixture 18 g of an oil was obtained. According to GLC data, it contained 78% of starting phenol **VI**, 10% of 2,6-di-*tert*-butyl-4-(2-hydroxyethyl)phenol (**X**), and 10% of a high-boiling bisphenol.

Reaction of compound VI with paraldehyde in the presence of ethylene glycol. Compound **VI**, 100 g, 200 g of ethylene glycol, 20 g of NaOH, and 15 g of paraldehyde were loaded into a 0.5 l steel rotating autoclave and heated at 240°C for 15 h. The autoclave was cooled, and the reaction mixture was neutralized and extracted with ether. The extract was evaporated to give 95 g of an oil containing 65% of compound **I**, 12% of 2-*tert*-butyl-4-ethylphenol (**IV**), 10% of compound **X**, and some other products (GLC data).

Synthesis of 2,6-di-*tert*-butyl-4-ethylphenol from 2,6-di-*tert*-butylphenol and triethylene glycol at atmospheric pressure. 2,6-Di-*tert*-butylphenol, 6 g, triethylene glycol, 6 ml, and 2 g of granulated NaOH were loaded into a three-necked flask equipped with a stirrer, an air cooler, and a collar trap. The mixture was heated with stirring under an inert gas flow for 5 h at 220°C, and the liberating water was collected in the trap. The reaction mixture was poured into water, acidified with HCl, and extracted with pertoleum ether. The extract was evaporated to give 6 g of an oil which was distilled in a vacuum. Two fractions were collected. The first fraction, 3 g, was an oil, bp 80–120°C (3–4 mm Hg). According to GC–MS data, it contained 0.5% of 2-*tert*-butyl-4-ethylphenol, 1% of 2,6-di-*tert*-butylphenol, 15.5% of 2,6-di-*tert*-butyl-4-methylphenol, 65.5% of 2,6-di-*tert*-butyl-4-ethylphenol, 12% of 2,6-di-*tert*-butyl-4-isopropylphenol, 2% of 2,6-di-*tert*-butyl-4-propylphenol, and 2% of 4-butyl-2,6-di-*tert*-butylphenol. The second fraction, 2.5 g, bp 120–210°C (3-4 mm Hg), contained 0.5% of 4-methyl-, 6.3% of 4-ethyl-, 2% of 4-propyl-, 4.3% of 4-*n*-butyl-, 3.3% of 4-(2-hydroxyethyl)-2,6-di-*tert*-butylphenol, 19.5% of 2,6-di-*tert*-butyl-4-(5-hydroxy-3-oxapentyl)phenol, 12% of a product with MM 294, 8.3% of a product with MM 338, and 30% of bisphenols with prevailing 1,2-bis(2,6-di-*tert*-butyl-4-hydroxyphenyl)ethane and 1,4-bis(2,6-di-*tert*-butyl-4-hydroxyphenyl)butane.

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