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Reactions of 3,5-di-*tert*-Butyl-4-hydroxybenzyl Acetate with Weakly Basic Nucleophiles

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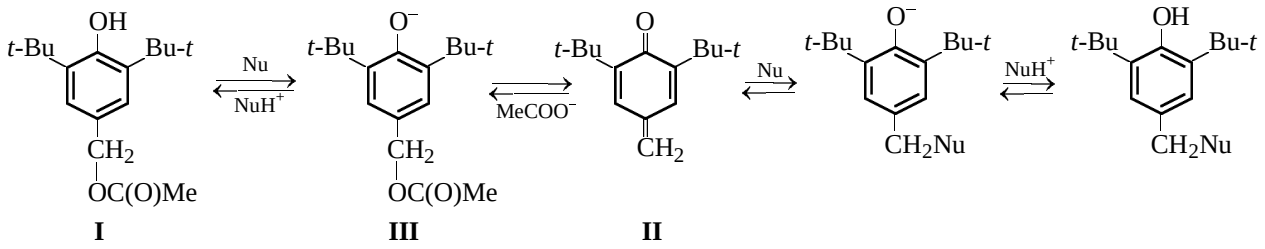
Abstract—The acid dissociation of 3,5-di-*tert*-butyl-4-hydroxybenzyl acetate in the presence of bases or in dimethylformamide favors reaction of this compound with weakly basic nucleophilies.

3,5-Di-*tert*-butyl-4-hydroxybenzyl acetate (**I**) is a highly active reagent which allows synthesis in mild conditions and in high yields of compounds comprising sterically congested phenol fragments [1]. Earlier we found that acetate **I** readily reacts with primary and secondary aliphatic amines to form benzylamines [2]. In the same way acetate **I** reacts with ammonia, yielding tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)amine rather than bis(3,5-di-*tert*-butyl-4-hydroxybenzyl) ether as reported in [2]. At the same time, aromatic amines, for example, aniline and benzidine, as well as hydrazine, fail to react with acetate **I** in inert solvents, such as chloroform, carbon tetrachloride, and benzene.

It is known that reactions with nucleophiles of sterically congested phenols containing a functional group at the α-carbon atom of the *para*-substituent proceed via intermediate formation of 2,6-di-*tert*-butylmethylenequinone (**II**) [3, 4].



I **III** **II**

In view of this scheme we assumed that the inertness of aromatic amines toward acetate **I** is associated with their insufficient basicity. It was therefore expected that addition to the reaction mixture of a stronger base facilitating formation of phenoxide anion **III** and its subsequent transformation into methylenequinone **II** but not forming adducts with the latter would favor benzylation of weakly basic nucleophiles. The following circumstance would be born in mind. It is known that the prevailing reaction route of methylenequinone **II**, and, therefore, the selectively of reaction of acetate **I** in the presence of bases depend on the nucleophilicity of the reagent used [4]. In this connection, acetate **I** and relatively weak nucleophiles (aromatic amines, phenylhydrazine) are best reacted in the presence of such basic agents which ensure a fairly slow formation methylenequinone **II** thus preventing its accumulation in concentrations sufficient for dimerization and disproportionation [3].

It was previously found that alkali additives in a solution of ester **I** favor the above transformations of methylenequinone **II** [5]. In these conditions, successful benzylation of aniline to form monobenzyl derivative **IV** is only possible with a great excess of aniline. The reaction at a 2:1 acetate **I**:aniline molar ratio occurs quite unselectively yielding an intractable mixture containing, by TLC data, benzylated anilines **IV** and **V**, as well as compounds **VI** and **VII** formed by side reactions of methylenequinone **II**.

At the same time, in a chloroform solution of ester **I** in the presence of triethylamine, methylenequinone **II** is accumulated fairly slowly (Fig. 1). As seen from

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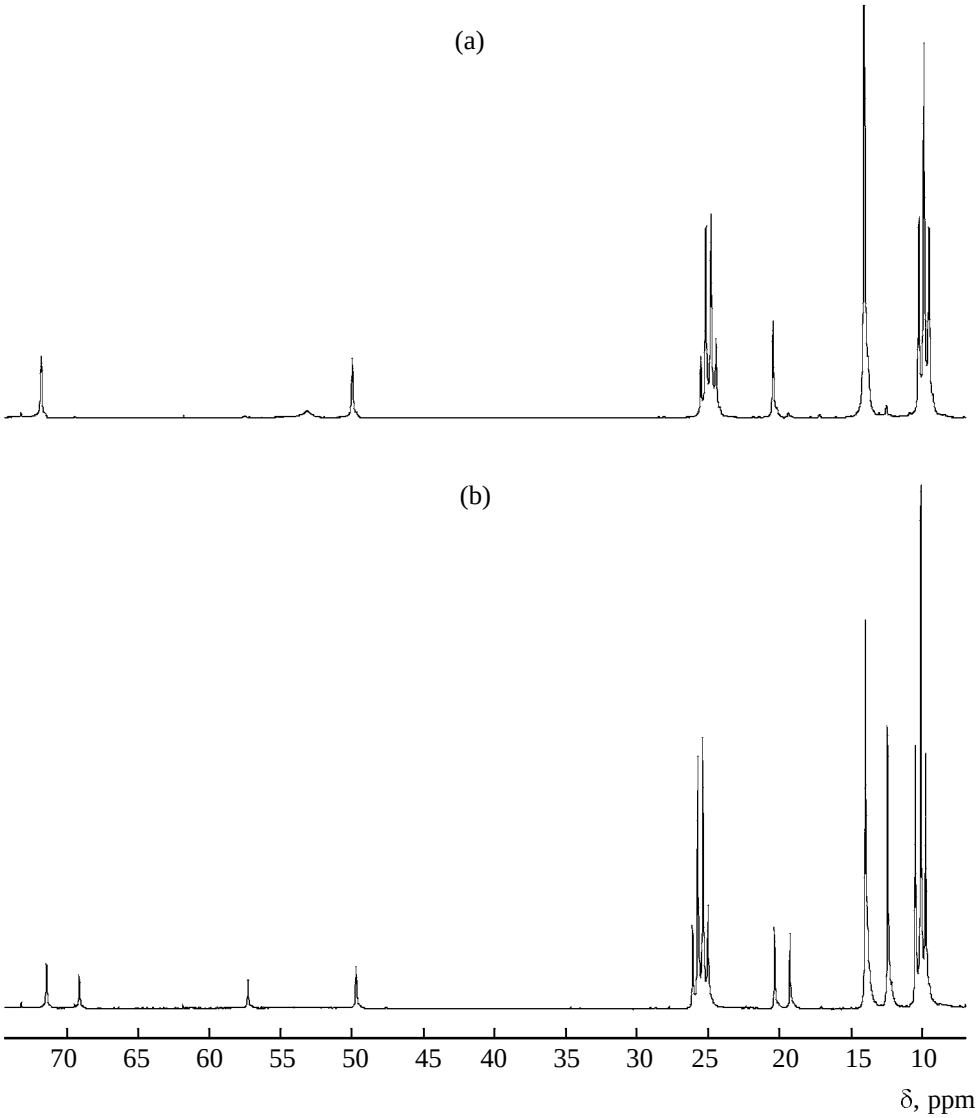
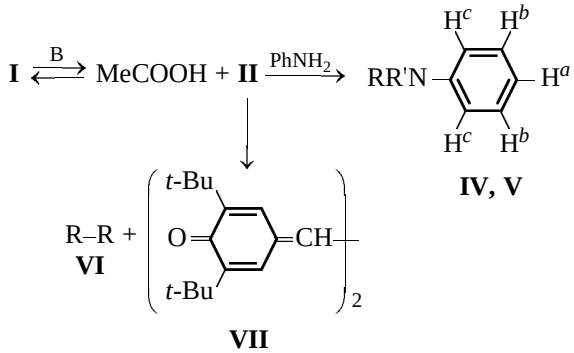


Fig. 1. ^{1}H NMR spectra of acetate **I** in $CDCl_3$ in the presence of triethylamine (a) immediately after prepration and (b) after 3 h. $c_{\mathbf{I}}$ 0.3 M and c_{NEt_3} 0.8 M.



R = $CH_2C_6H_2(Bu\text{-}t)_2$-3,5-OH-4; R' = H (**IV**), $CH_2C_6H_2 \cdot (Bu\text{-}t)_2$-3,5-OH-4 (**V**).

the ^{1}H NMR spectra, the intensity of signals of acetate **I** {δ, ppm: 1.40 s (SMe_3), 2.03 s [MeC(O)], 4.96 s (CH_2O), 7.13 s (Ar–H)} decreases with time compared to those of triethylamine. Simultaneously, the intensity of signals of methylenequinone **II** {δ, ppm: 1.22 s (CMe_3), 5.72 s (CH_2), 6.91 s (CH)} and of the acetate methyl group (δ, ppm: 1.92 s) increases. The ^{1}H NMR spectra were assigned relying on the chemical shifts of compounds **II**, reported in [6].

In view of the above findings, the synthesis of benzyl derivatives **IV** and **V** in the presence of triethylamine readily occurs at room temperature. Similarly, the use of triethylamine allows facile reactions of acetate **I** with C-nucleophiles.

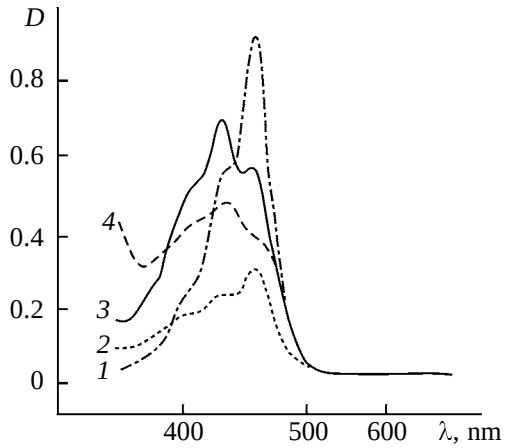
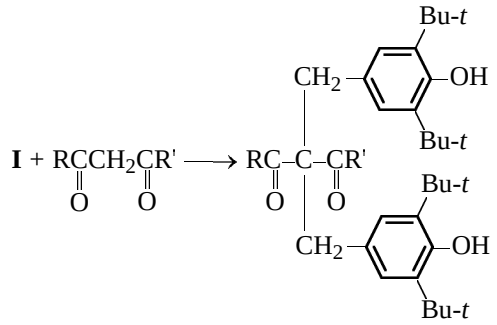


Fig. 2. Electronic absorption spectra in acetone. (*1*) Compound **VII**, (*2*) acetate **I** ($c_{\mathbf{I}}$ 0.15 M), (*3*) the same solution in the presence of KOH, and (*4*) DMF solution of ester **I** ($c_{\mathbf{I}}$ 0.2 M).



VIII–X

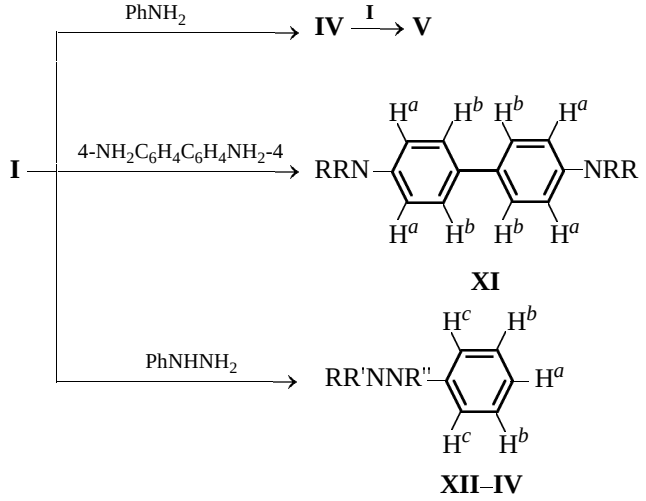
R = Me (**VIII, IX**), OEt (**X**); R' = Me (**VIII**), OEt (**IX, X**).

We found that the role of bases in reactions of ester **I** with weak nucleophiles can be played by some solvents, such as DMF. Dipolar aprotic solvents, DMF inclusive, can form hydrogen bonds with sterically congested phenols [7], thus facilitating ionization of the latter [8].

The electronic absorption spectra of solutions of acetate **I** in chloroform, carbon tetrachloride, benzene, and acetone show no absorption in the visible region and weak absorption of the 2,6-di-*tert*-butyl-4-[2-(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)ethylidene]cyclohexa-2,5-dien-1-one (**VII**) admixture. On addition of alkalis, the acetone solution of acetate **I** immediately acquired a light green color, and in its electronic absorption spectrum we observed, on the background of enhanced absorption of compound **VII** which is one of the products of dimerization and disproportionation of methylenequinone **II** [3] readily formed from acetate **I** under the action of alkalis [5], a new absorption band at λ_{max} 425 nm (Fig. 2). Acidification of the solution leads to its lightening and recovery of the initial absorption pattern at 370–480 nm. This finding allows the absorption band at λ_{max} 425 nm to be assigned to phenoxide anion **III**. The same band is present in the electronic absorption spectrum of a fresh solution of ester **I** in DMF. Within some time this band is obscured by enhancing absorption of compound **VII**.

Thus, regardless of the fact that DMF is a weaker base than aromatic amines, the formation of phenoxide anion **III** is made possible by the high concentration of DMF, which shifts the equilibrium to the side of this product. In addition, enhanced dissociation of ion pairs in DMF and its ability to solvation of delocalized anions should be taken into account [9]. As a result, slow accumulation of compound **VII**, a product of methylenequinone **II** transformations, in a DMF solution of acetate **I** takes place, which is detected by electronic spectroscopy.

The reactions of benzyl acetate **I** with aniline, benzidine, and phenylhydrazine in DMF occur under as mild conditions as in the presence of triethylamine, and, therewith, the degree of benzylation can be controlled by varying reactant ratio.



R = $CH_2C_6H_2(Bu\text{-}t)_2$-3,5-OH-4 (**XI**–**XIV**); R' = H (**XII**), $CH_2C_6H_2(Bu\text{-}t)_2$-3,5-OH-4 (**XIII, XIV**); R'' = H (**XII, XIII**); $CH_2C_6H_2(Bu\text{-}t)_2$-3,5-OH-4 (**XIV**).

Thus, the generation of methylenequinone **II** from acetate **I** under the action of bases or dipolar aprotic solvents, particularly DMF, allow reactions of compound **I** with weakly basic nucleophiles. Therewith, reaction success depends on whether the nucleophilic agent is able to add to methylenequinone **II**. Thus, for instance, such a weak nucleophile as urea, because of its poor reactivity toward methylenequinone **II**,

fails to react with benzyl acetate **I** even in the presence of bases or in DMF.

EXPERIMENTAL

The ^{1}H NMR spectra were measured on a Varian Gemini-200 spectrometer (200 MHz) with reference to residual proton signals of deuterated solvents. The electronic absorption spectra were run on a Specord UV-Vis spectrophotometer.

Dimethylformamide was purified as described in [10].

3,5-Di-*tert*-butyl-4-hydroxybenzylanilines (IV, V). A solution of 0.01 mol of acetate **I**, 0.01 mol of triethylamine, and 0.25 mol (synthesis of **IV**) or 0.005 mol (synthesis of **V**) of aniline in 15–20 ml of acetone was allowed to stand at room temperature for 5 h, after which it was poured into water. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from hexane.

***N*-(3,5-Di-*tert*-butyl-4-hydrohybenzyl)-*N*-phenylamine (IV),** yield 89%, mp 104–105°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.44 s (18H, CMe_3), 4.19 s (2H, CH_2), 5.21 s (1H, OH), 6.65– 6.85 m (3H, H^a, H^c), 7.18 s (2H, Ar–H), 7.21 t (2H, H^b). Found, %: C 80.87; H 9.31. $C_{21}H_{29}NO$. Calculated, %: C 81.03; H 9.32. Compound **V** was obtained in 80% yield with 1 ml of 20% aqueous KOH instead of triethylamine.

***N*,*N*-Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*-phenylamine (V)**, yield 81%, mp 166–168°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.38 s (36H, CMe_3), 4.49 s (4H, CH_2), 5.10 s (2H, OH), 6.69 t (1H, H^a), 6.84 d (2H, H^c), 7.02 s (4H, Ar–H), 7.19 t (2H, H^b). Found, %: C 81.46; N 9.62. $C_{36}H_{51}NO_2$. Calculated, %: C 81.66; H 9.64.

Di(3,5-di-*tert*-butyl-4-hydroxybenzyl)-substituted C-nucleophiles VIII–X. A solution of 0.02 mol of ester **I**, 0.04 mol of triethylamine, and 0.01 mol of acetylacetone or 0.01 mol of acetoacetic ester, or 0.01 mol of malonic ester in 20 ml of acetone was allowed to stand at room temperature for 5 h. The reaction mixture was then poured into 150 of water and acidified with 5 ml of acetic acid. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from methanol.

2,2-Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)-acetylacetone (VIII), yield 75%, mp 154–156°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.39 s (36H, CMe_3), 2.05 s (6H, Me), 3.20 s (4H, CH_2), 5.03 s (2H, OH), 6.78 s (4H, Ar–H). Found, %: C 78.11; H 9.68. $C_{35}H_{52}O_4$. Calculated, %: C 78.36; H 9.70. **Ethyl 2,2-bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)acetoacetate (IX)**, yield 73%, mp 135–137°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.13 t (3H, Me), 1.42 s (36H, CMe_3), 1.82 s [3H, Me–C(O)], 3.10 s (4H, CH_2), 4.03 q (2H, CH_2O), 5.02 s (2H, OH), 6.89 s (4H, Ar–H). Found, %: C 76.12; H 9.52. $C_{36}H_{54}O_5$. Calculated, %: C 76.33; H 9.54. **Diethyl 2,2-bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate (X),** yield 70%, mp 161°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 t (6H, Me), 1.42 s (36H, CMe_3), 3.18 s (4H, CH_2), 4.04 q (4H, CH_2O), 5.10 s (2H, OH), 7.03 s (4H, Ar–H). Found, %: C 74.43; H 9.37. $C_{37}H_{56}O_6$. Calculated, %: C 74.50; H 9.40.

3,5-Di-*tert*-butyl-4-hydroxybenzylamines IV, V, and XI–XIV. Aniline, benzidine, or phenylhydrazine was added with stirring to a 25% solution of acetate **I** in DMF. The reaction mixture was allowed to stand at room temperature for 12 h and then poured into water. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from hexane.

***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*-phenylamine (IV)**, molar ratio **I**:aniline 1:25, yield 91%. ***N*,*N*-Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*-phenylamine (V)**, molar ratio **I**:aniline 2.5:1, yield 84%. **4,4'-[*N*,*N*,*N*',*N*'-Tetra(3,5-di-*tert*-butyl-4-hydroxybenzyl)diamino]diphenyl (XI)**, molar ratio **I**:benzidine 4.5:1, yield 89%, mp 265°C. ^{1}H NMR spectrum ($C_6D_5CD_3$), δ, ppm: 1.53 s (72H, CMe_3), 4.71 s (8H, CH_2), 5.03 s (4H, OH), 7.09 d (4H, H^b, ^3J 8.8 Hz), 7.34 s (8H, Ar–H), 7.58 d (4H, H^a, ^3J 8.8 Hz). Found, %: C 81.50; H 9.44. $C_{72}H_{100}\cdot N_2O_4$. Calculated, %: C 81.82; N 9.47. ***N*-(3,5-Di-*tert*-butyl-4-hydroxybenzyl)-*N*'-phenylhydrazine (XII)**, molar ratio **I**:phenylhydrazine 1:25, yield 77%, mp 100–102°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.46 s (18H, CMe_3), 3.44 s (2H, NH), 4.50 s (2H, CH_2), 5.17 s (1H, OH), 6.80 t (1H, H^a), 7.08 s (2H, Ar–H), 7.10–7.35 m (4H, H^b, H^c). Found, %: C 77.21; H 9.19. $C_{21}H_{30}N_2O$. Calculated, %: C 77.30; H 9.20. ***N*,*N*-Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*'-phenylhydrazine (XIII)**, molar ratio **I**:phenylhydrazine 1.5:1, yield 76%, mp 167–168°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 s (36H, CMe_3), 3.78 s (4H, CH_2), 4.62 s (1H, NH), 5.08 s (2H, OH), 6.74 t (1H, H^a), 6.88 d (2H, H^c), 7.10–7.35 m (6H, H^b, Ar–H). Found, %: C 79.29; H 9.53. $C_{36}H_{52}N_2O_2$. Calculated, %: C 79.41; H 9.56. ***N*,*N*,*N*'-Tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*N*'-phenylhydrazine (XIV)**, molar ratio **I**:phenylhydrazine 3.5:1, yield 79%, mp 160–162°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 s (18H, CMe_3), 1.40 s (36H, CMe_3), 3.90 s (4H, CH_2), 4.54 s (2H, CH_2), 4.96 s (1H, OH), 4.99 s (2H, OH), 6.75 t (1H, H^a), 6.91 s (2H, Ar–H), 7.13 s (4H, Ar–H), 7.14–7.35 m (4H, H^b, H^c). Found, %:

C 80.23; H 9.70. $C_{51}H_{74}N_2O_3$. Calculated, %: C 80.31; H 9.71.

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