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Anionic Condensations of 3,5-Di-*tert*-butyl-4(2)-hydroxybenzaldehydes in the Presence of Weak Bases

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Abstract—Products of the reactions of 4- and 2-hydroxy-3,5-di-*tert*-butyl-benzaldehydes with malonic acid, diethyl malonate, and acetic anhydride in the presence of weak bases were isolated and identified. The reactions of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde with malonic acid and acetic anhydride in the presence of sodium acetate and piperidine gave 3,5-di-*tert*-butyl-4-hydroxycinnamic acid. The reaction of its 2-hydroxy isomer with acetic anhydride stopped at the stage of formation of the corresponding O-acetyl derivative, while in the reaction with malonic acid the corresponding substituted cinnamic acid and its lactone (coumarin derivative) were formed as intermediate products in a transformation sequence finally leading to 3-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-3-piperidinopropionic acid and 6,8-di-*tert*-butyl-2-oxo-3,4-dihydro-2*H*-chromen-4-ylacetic acid. Analogous differences were typical of reactions of isomeric 4- and 2-hydroxy-3,5-di-*tert*-butylbenzaldehydes with diethyl malonate. The transformations of the 2-hydroxy isomer were accompanied by hydrolysis and formation of an adduct of intermediate coumarin derivative with diethyl malonate and piperidine.

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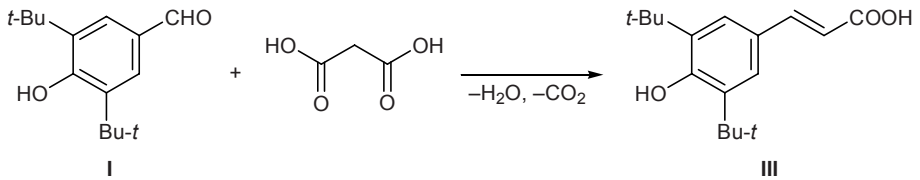
Anionic condensation of aromatic aldehydes, catalyzed by weak bases, such as Knoevenagel and Perkin reactions and their modifications, are used most frequently for the synthesis of unsaturated aromatic acids and ketones. Condensations of isomeric 4- and 2-hydroxy-3,5-di-*tert*-butylbenzaldehydes **I** and **II** with malonic acid and acetic anhydride seemed to provide a convenient route to cinnamic acids having a sterically hindered phenol fragment. In fact, the reaction of aldehyde **I** with malonic acid in the presence of 5–7% of piperidine smoothly afforded 3,5-di-*tert*-butyl-4-hydroxycinnamic acid (**III**) in high yield (Scheme 1).

Under similar conditions, aldehyde **II** reacted with malonic acid along different pathways, and neither the corresponding cinnamic acid **IV** nor its lactone, coumarin **V**, was obtained. Nevertheless, the structure of the isolated products suggests that cinnamic acid **IV** and coumarin **V** are formed as intermediates which take up piperidine or malonic acid molecule so rapidly that they could not be detected (Scheme 2). The ratio of the adducts with malonic acid and piperidine, 6,8-di-*tert*-butyl-2-oxo-3,4-dihydro-2*H*-chromen-4-ylacetic acid (**VI**) and 3-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-3-piperidinopropionic acid (**VII**), respectively, depends on the initial amount of malonic acid in the reaction mixture.

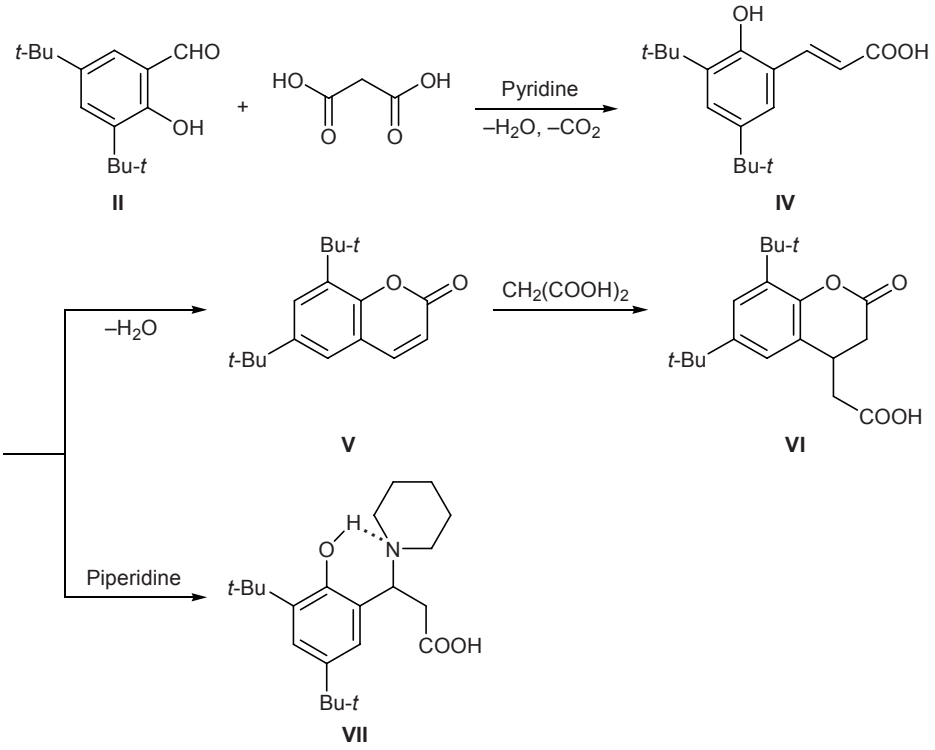
Ethyl 6,8-di-*tert*-butyl-2-oxo-3,4-dihydro-2*H*-chromene-4-carboxylate (**VIII**) isolated in the reaction of aldehyde **II** with diethyl malonate turned out to be more stable. The other product formed in this reaction was diethyl 2-[1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-3-oxo-3-piperidinopropyl]malonate (**IX**) (Scheme 3). Obviously, amide **IX** results from addition of piperidine and diethyl malonate to intermediate coumarin **V**

Scheme 1.

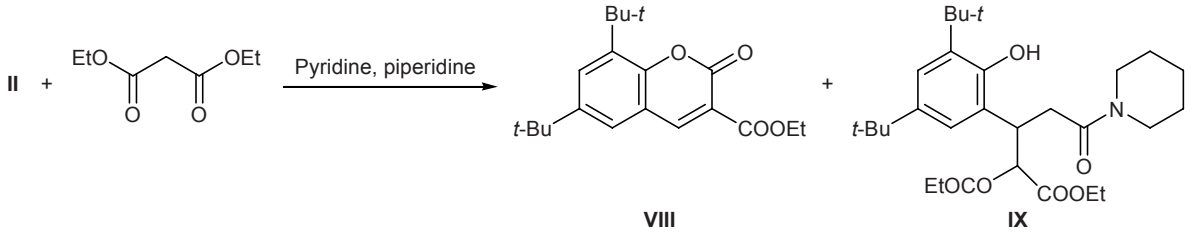


I **III**

Scheme 2.



Scheme 3.

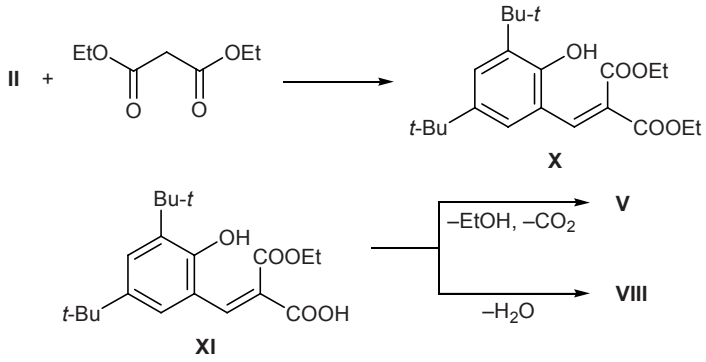


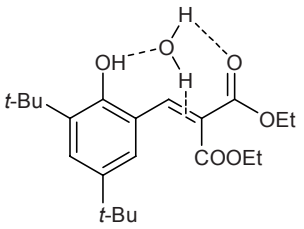
whose formation requires hydrolysis of at least one ester group in diethyl malonate (Scheme 4).

It is reasonable to presume participation of water molecule liberated in the first condensation stage yielding diethyl 2-(3,5-di-*tert*-butyl-2-hydroxybenzylidene)malonate (**X**). Such a fast reaction of water *in situ* indicates its high activity, which may be related to complex formation with diester **X**.

Presumably, retention of water molecule in the reaction complex is a specific property of ester **X**. In

Scheme 4.

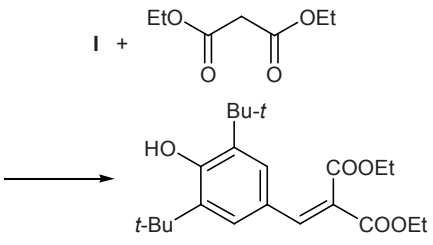




X

fact, the reaction of diethyl malonate with isomeric 4-hydroxy aldehyde **I** was not accompanied by hydrolysis, and the only product was diethyl 2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)malonate (**XII**) (Scheme 5). We have found no examples of analogous hydrolysis among vast published data on anionic condensations of diethyl malonate with various carbonyl compounds (for review, see, e.g., [1]).

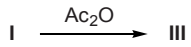
Scheme 5.



XII

An alternative method for the synthesis of cinnamic acids and related compounds is based on the condensation of aromatic aldehydes with acetic anhydride according to Perkin. Following this procedure, aldehyde **I** was converted into substituted cinnamic acid **III** (Scheme 6).

Scheme 6.

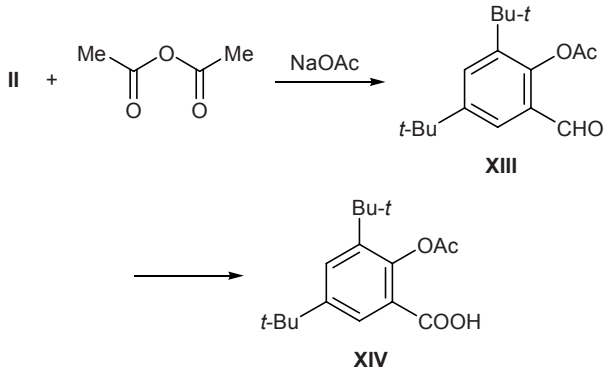


However, the reaction of aldehyde **II** with acetic anhydride under analogous conditions resulted only in acetylation of the hydroxy group to give aldehyde **XIII**. Elevated temperature and prolonged reaction time resulted in oxidation of aldehyde **XIII** to 3,5-di-*tert*-butylsalicylic acid (**XIV**) [2] (Scheme 7).

EXPERIMENTAL

The ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer at 250 MHz relative to tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were recorded on a Hitachi M-80A instrument. The reaction mixtures were ana-

Scheme 7.



XIII

XIV

lyzed by TLC using Silufol UV-254 plates (eluent hexane–diethyl ether, 15:1).

3-(3,5-di-*tert*-Butyl-4-hydroxyphenyl)prop-2-enoic acid (III). *a*. A mixture of 5 g (21 mmol) of aldehyde **I**, 6.7 g (60 mmol) of malonic acid, and 0.7 ml of piperidine in 18 ml of anhydrous pyridine was heated for 1.5 h on a water bath. The mixture was cooled, poured into water acidified with hydrochloric acid, and extracted with diethyl ether. The extract was washed with water and dried, the solvent was removed, and the residue was recrystallized from hexane–chloroform (5:1). Yield 4.2 g (71%), mp 213–214°C (sublimes). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.46 s (18H, *t*-Bu), 5.55 br.s (1H, OH), 6.31 d (1H, CH), 7.73 d (1H, CH, J_{trans} = 16.1 Hz), 7.40 s (2H, H_{arom}). Found, %: C 73.87; H 8.75. $C_{17}H_{24}O_3$. Calculated, %: C 73.80; H 8.75.

b. A mixture of 0.23 g (1 mmol) of aldehyde **I**, 0.16 g (1.5 mmol) of acetic anhydride, 0.1 g (1 mmol) of calcined sodium acetate, and 2 ml of pyridine was heated for 3 h on an oil bath at 180–190°C. The mixture was then treated as described above in *a* to isolate 0.12 g (48%) of compound **III**.

Reaction of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde with malonic acid. *a*. A mixture of 1.4 g (6 mmol) of aldehyde **II**, 2 g (20 mmol) of malonic acid, and 0.21 ml of piperidine in 6 ml of anhydrous pyridine was heated for 3 h on a water bath, the progress of the reaction being monitored by TLC. The mixture was then treated as described above to isolate 6,8-di-*tert*-butyl-2-oxo-3,4-dihydro-2*H*-chromen-4-ylacetic acid (**VI**). Yield 1.1 g (51%), mp 149–150°C (from hexane). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.27 s (9H, *t*-Bu), 1.37 s (9H, *t*-Bu), 2.55 d (2H, CH_2), 2.71 d.d and 2.98 d.d (1H each, CH_2, ^3J = 6.8, 8.5, ^2J = 16.6 Hz), 3.43 m (1H, 4-H, ^3J = 5.1 Hz), 7.20 d (1H, H_{arom}), 7.24 d (1H, H_{arom}, ^3J = 2.1 Hz),

12.45 br.s (1H, COOH). Mass spectrum: *m*/*z* 318 $[M]^+$. Found, %: C 71.37; H 8.18. $C_{19}H_{26}O_4$. Calculated, %: C 71.60; H 8.29. The mother liquor contained unreacted aldehyde **II** (TLC).

When the reaction was carried out under analogous conditions but at an aldehyde **II**–malonic acid ratio of 1 : 1.5, we isolated 3-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-3-piperidinopropionic acid (**VII**). Yield 46%, mp 151–152°C (from octane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 s (9H, *t*-Bu), 1.42 s (9H, *t*-Bu), 1.5 m (6H, CH_2), 3.4 m (4H, CH_2N), 2.65 d.d and 2.87 d.d (1H each, CH_2, *AB* system, ^3J = 3.0, 5.6, ^2J = 16.0 Hz), 4.06 m (1H, CH), 6.92 d (1H, H_{arom}), 7.19 d (1H, H_{arom}, ^3J = 2.3 Hz), 9.06 br.s (1H, OH), 12.07 br.s (1H, COOH); the position of the OH proton signal at δ 9.06 ppm did not change upon replacement of $CDCl_3$ as solvent by DMSO-d_6, indicating formation of a strong intramolecular hydrogen bond OH···N. Found, %: C 76.45; H 9.37. $C_{22}H_{33}NO_2$. Calculated, %: C 76.92; H 9.67. From the mother liquor we isolated lactone **VI** in 19% yield.

Reaction of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde with diethyl malonate. A mixture of 1 g (4 mmol) of aldehyde **II**, 2 g (12 mmol) of diethyl malonate, and 0.14 ml of piperidine in 4 ml of anhydrous pyridine was heated for 2 h on a water bath until complete conversion of aldehyde **II**. The mixture was poured into acidified water and extracted with diethyl ether. The extract was evaporated, and the crystals were separated and washed with hexane. Yield of diethyl 2-[1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-3-oxo-3-piperidinopropyl]malonate (**IX**) 0.4 g (21%), mp 191–192°C (from MeOH). ^{1}H NMR spectrum (pyridine-d_5), δ, ppm: 0.87 t (3H, C**H**$_3$CH$_2$), 1.14 t 3H, C**H**$_3$CH$_2$), 1.38 s (9H, *t*-Bu), 1.62 s (9H, *t*-Bu), 1.40 m (6H, CH_2), 3.3 m (4H, NCH_2), 3.06 d.d and 3.19 d.d (1H each, $COCH_2$, *AB* system, ^2J = 16.2 Hz), 3.91 m (2H, OCH_2), 4.21 q (2H, OCH_2, J = 7.0 Hz), 4.53 d (1H, CHCO), 4.95 m (1H, 1′-H, ^3J = 11.2 Hz), 7.40 d (1H, H_{arom}), 7.44 d (1H, H_{arom}, ^3J = 2.2 Hz), 10.21 s (1H, OH). Mass spectrum: *m*/*z* 503 $[M]^+$. Found, %: C 68.81; H 8.49. $C_{29}H_{45}NO_6$. Calculated, %: C 69.10; H 8.94. Evaporation of the mother liquor gave 0.78 g (57%) of ethyl 6,8-di-*tert*-butyl-2-oxo-2*H*-chromene-3-carboxylate (**VIII**), mp 118–119°C (from MeOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 s (9H, *t*-Bu), 1.51 s (9H, *t*-Bu), 1.41 t (3H, C**H**$_3$CH$_2$), 4.41 q (2H, C**H**$_2$CH$_3$, J = 7.0 Hz), 7.41 d (1H, H_{arom}), 7.68 (1H, H_{arom}, ^3J = 2.2 Hz), 8.51 s (1H, CH). Found, %: C 72.58; H 7.89. $C_{20}H_{26}O_4$. Calculated, %: C 72.66; H 7.93.

Diethyl 2-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)malonate (XII). A mixture of 1 g (4 mmol) of aldehyde **I**, 2 g (12 mmol) of diethyl malonate, and 0.14 ml of piperidine in 4 ml of anhydrous pyridine was heated for 1.5 h on a water bath. The mixture was treated with water acidified with hydrochloric acid and extracted with diethyl ether, and the extract was dried and evaporated to isolate 0.92 g (67%) of compound **XII**, mp 116–117°C (from MeOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.33 t (6H, C**H**$_3$CH$_2$), 1.43 s (18H, *t*-Bu), 4.29 q (2H, C**H**$_2$CH$_3$), 4.35 q (2H, C**H**$_2$CH$_3$, J = 7.3 Hz), 5.57 s (1H, OH), 7.34 s (2H, H_{arom}), 7.65 s (CH). Found, %: C 69.92; H 8.66. $C_{22}H_{32}O_5$. Calculated, %: C 70.00; H 8.51.

Perkin reaction of acetic anhydride with aldehyde II. A mixture of 0.47 g (2 mmol) of aldehyde **II**, 0.31 g (3 mmol) of acetic anhydride, 0.2 g of calcined sodium acetate, and 3 ml of anhydrous pyridine was heated for 4 h at 180–190°C on an oil bath. The mixture was cooled, treated with water acidified with hydrochloric acid, and extracted with diethyl ether. The extract was evaporated, and the residue was recrystallized from hexane. Yield of 4,6-di-*tert*-butyl-2-formylphenyl acetate (**XIII**) 0.7 g (91%), mp 88–89°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 s (9H, *t*-Bu), 1.39 s (9H, *t*-Bu), 2.42 s (3H, CH_3), 7.68 d (1H, H_{arom}), 7.70 d (1H, H_{arom}, ^3J = 2.4 Hz), 9.91 s (1H, CHO). Found, %: C 73.65; H 8.54. $C_{17}H_{24}O_3$. Calculated, %: C 73.87; H 8.75.

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