

Alkaline hydrolysis of diethyl *N*-acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate

A. A. Volod'kin,* S. M. Lomakin, G. E. Zaikov, and N. M. Evteeva

N. M. Emanuel Institute of Biochemical Physics, Russian Academy of Sciences,
4 ul. Kosygina, 119991 Moscow, Russian Federation.
Fax: +7 (499) 137 4101. E-mail: chembio@sky.chph.ras.ru

Alkaline hydrolysis of diethyl *N*-acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate is accompanied by decarboxylation. The efficiency of this process depends on the temperature and ratio of the reactants. A possibility of tautomerism with migration of the proton of phenolic hydroxyl and the influence of the structure on the antioxidation properties were considered on the basis of analysis of the IR spectral data and quantum chemical (PM6) calculation of the structures. The energies of homolysis of the O–H bond of phenolic hydroxyl were calculated for a series of the synthesized compounds. It is proposed to predict the antioxidation activity on the basis of these values.

Key words: *N*-acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate, hydrolysis, decarboxylation, antioxidants.

The use of malonic acid derivatives in the synthesis of tyrosine analogs with *tert*-butyl substituents in the aromatic ring made it possible to consider this method as optimal for the preparation of water-soluble antioxidants promising in biology and medicine. It is known¹ that the formamide group in a molecule of 2-(*N*-formylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoic acid is deformylated by aniline to form 2-amino-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoic acid. Alkaline hydrolysis of diethyl *N*-acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate in a water–alcohol solution gives the corresponding acid in 63% yield. The thermolysis of the acid at 140–180 °C produces 2-(*N*-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoic acid. It is insufficient to identify the earlier synthesized compounds by the ¹H NMR spectra on the basis of multiplet signals from the protons of the –CH₂–CH– fragment, because this identification does not allow one to determine the vicinal and geminal constants. The single example for the alkaline hydrolysis of this diethyl ester does not elucidate the regularities of this reaction and its synthetic potentialities. Therefore, the further study of alkaline hydrolysis reactions and properties of the compounds formed seems topical.

In the present work, we found that decarboxylation occurs simultaneously with the alkaline hydrolysis of diethyl *N*-acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate, due to which the *N*-acetyltyrosine derivatives are formed along with the derivatives of acetylamino-malonic acid. The intermediate reaction products are cor-

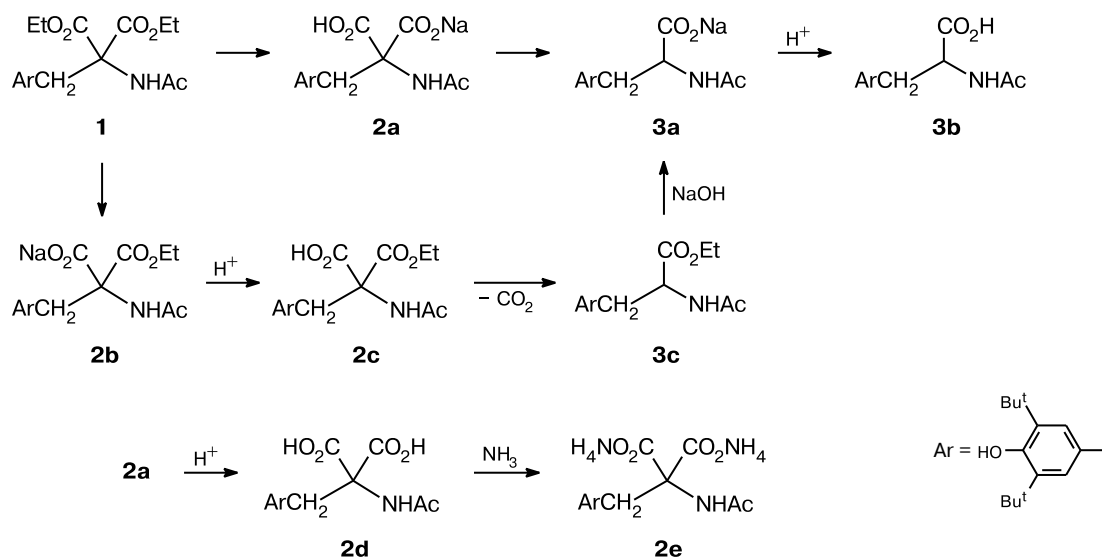
responding water-soluble sodium or potassium salts of this malonic acid. The acidification of these salts results in the corresponding substituted malonic acid, whose properties differed from those described earlier.¹

Results and Discussion

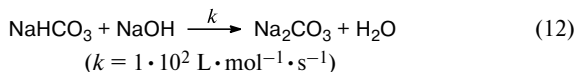
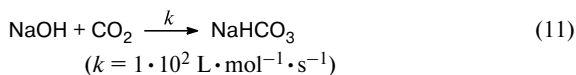
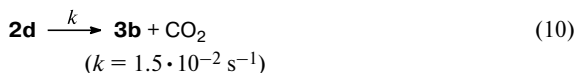
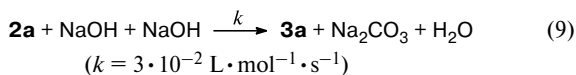
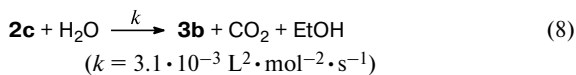
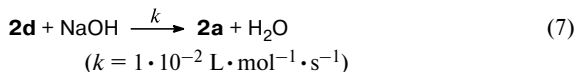
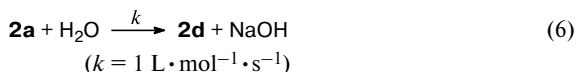
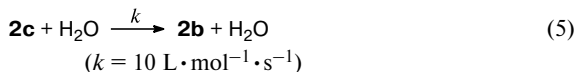
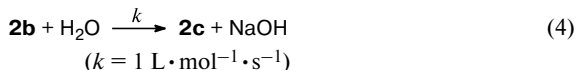
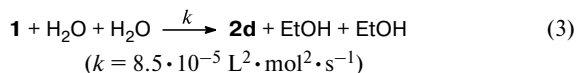
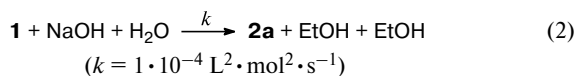
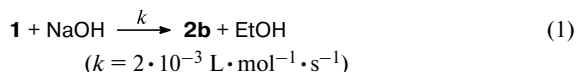
The alkaline hydrolysis of diethyl *N*-acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate (**1**) results in the saponification of ester groups followed by the decarboxylation of the substituted malonic acid formed (Scheme 1). Under the conditions of higher decarboxylation rates, the tyrosine analogs are formed, whose yield depends on the reactant ratio and reaction conditions. In a solution of aqueous dioxane at the mole ratio **1** : NaOH equal to 1 : 6 and temperature 100 °C, monosodium salt **2a**, sodium salt of tyrosine **3a**, and sodium salt of monoester **2b** are formed in the process of conjugated reactions. The rate constants for the conjugated reactions (Scheme 2) were determined from the data of changing the composition of the reaction mixtures in time and by the calculation of the kinetic scheme using modeling of the system of differential equations (Gear program²).

The kinetic scheme is presented by 12 reactions with the initial concentrations of compound **1**, NaOH, and H₂O, whose change affects the results of the consumption of the initial compounds and accumulation of the intermediate and final compounds. At the ratio of the initial molar concentrations of compound **1** and NaOH equal to 1 : 6, the corresponding salts of carboxylic acids are

Scheme 1



Scheme 2



formed, and the evolved CO_2 reacts with alkali, decreasing the concentration of NaOH . The kinetic scheme is presented by three blocks that describe the reactions of saponification and decarboxylation and the exchange reactions involving NaOH , H_2O , and CO_2 . Figure 1 presents the experimental data on the consumption of compound **1** and the accumulation of the reaction products (after neutralization to pH 4). Figure 2 shows the results of calculation of the kinetics of this reaction. Satisfactory coincidence of the experiment and calculation allowed us to use the kinetic scheme in the development of the method of synthesis of **2a**. It follows from the calculation of the kinetic scheme of the initial concentrations of compound **1** and NaOH equal to 1 : 1 that more than 50% of

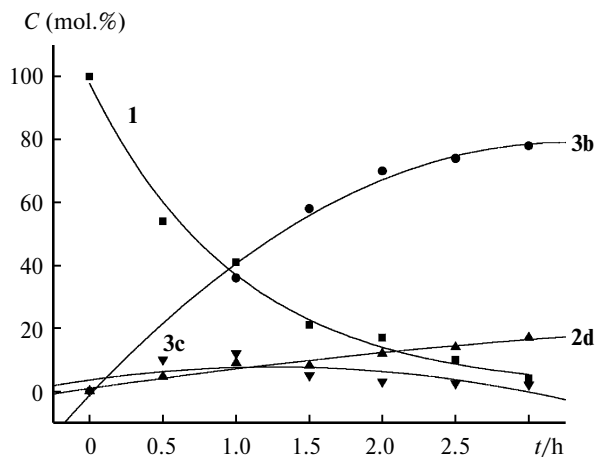


Fig. 1. Experimental data on the consumption of compound **1** and accumulation of **2d**, **3b**, and **3c** under the conditions of hydrolysis of compound **1** in aqueous dioxane at 100 °C. $[\mathbf{1}]_0 = 0.357 \text{ mol L}^{-1}$; $[\text{NaOH}]_0 = 2.24 \text{ mol L}^{-1}$; $[\text{H}_2\text{O}]_0 = 5.95 \text{ mol L}^{-1}$.

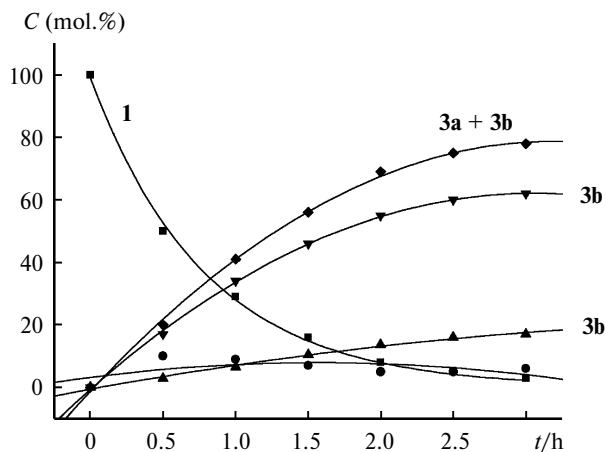


Fig. 2. Calculated data for the kinetics of the conjugated reactions under the hydrolysis conditions in aqueous dioxane at 100 °C; $[1]_0 = 0.357 \text{ mol L}^{-1}$; $[\text{NaOH}]_0 = 2.24 \text{ mol L}^{-1}$; $[\text{H}_2\text{O}]_0 = 5.95 \text{ mol L}^{-1}$.

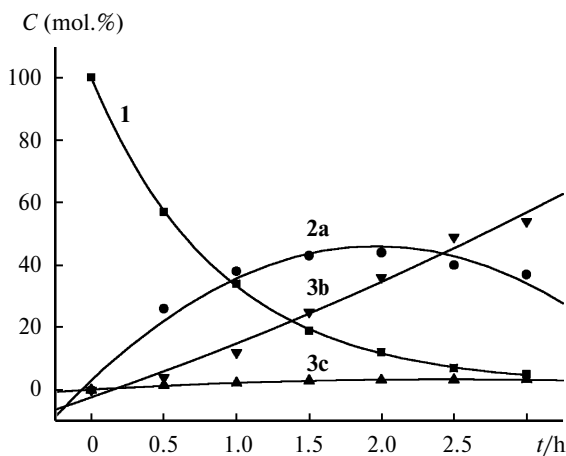


Fig. 3. Calculated data for the kinetics of the conjugated reactions under the conditions of hydrolysis of compound **1** in aqueous dioxane at 100 °C; $[1]_0 = 0.455 \text{ mol L}^{-1}$; $[\text{NaOH}]_0 = 0.455 \text{ mol L}^{-1}$; $[\text{H}_2\text{O}]_0 = 5.05 \text{ mol L}^{-1}$.

product **2a** are formed after 1.5–2 h (Fig. 3). In the preparative experiment, compound **2a** was obtained in 62% yield.

The hydrolysis conditions at room temperature in the presence of AcONa were developed for the preparation of compound **2c** in the individual form. On heating compound **2c** to 175–180 °C, decarboxylation occurs to form compound **3c**.

The IR and ^1H NMR spectral data present sufficient information on the structure and properties of the obtained compounds. It is known³ that the NH group in α -acetyl-amino acids appears in the region of 3390–3260 cm^{-1} , and vibrations of the C=O bond in the acetylamide group are observed at 1620–1640 cm^{-1} . These characteristic bands are observed in the IR spectra of the synthesized

compounds and, hence, no reactions occur at the acetyl-amide group under the experimental conditions. The corresponding signals in the ^1H NMR spectra of the synthesized compounds confirm the presence of the COCH_3 group (δ_{H} 1.91–1.75) and NH group (δ_{H} 7.69–7.05). The ^1H NMR spectra of the tyrosine derivatives indicate the presence of two nonequivalent hydrogen atoms in the CH_2 group, which are bound to the chiral atom, confirming the structures of synthesized compounds **3a**, **3b**, and **3c**. These protons in the ^1H NMR spectra appear as a doublet of doublets with vicinal and geminal constants that characterize the individual state of each compound. The diffuse reflectance solid-phase IR spectra make it possible to interpret the changes in the positions of the characteristic frequencies as a consequence of intermolecular interactions.⁴ Of the synthesized compounds, compound **3c** has an analogous property, and in its spectrum the H–O frequency of the phenolic hydroxyl shifts to the long-wavelength region of the spectrum (3189 cm^{-1}). In a solution of compound **3c** (CCl_4), the H–O frequency of the hydroxyl appears at 3435 cm^{-1} . It can be assumed that in a molecule of compound **3c** the hydrogen atom interacts with the oxygen atom of the functional group of the *para*-substituent and this interaction is accompanied by the enolation of the aromatic bonding system, which agrees with the IR spectra data of cyclohexadienones.^{5,6} The IR spectrum of salt **3a** contains intense bands at 1667, 1632, and 1596 cm^{-1} , whereas the band at 1550 cm^{-1} characteristic of the aromatic structure is absent. A similar effect related to the change in the position of the characteristic frequencies is manifested in the IR spectra of compound **2a** and corresponding potassium salt **4**. The IR spectra of these compounds contain no frequencies of the carboxyl group at 1700 cm^{-1} but have a broad band at 1550–1620 cm^{-1} . These data can be interpreted as a consequence of the interaction of the sodium (potassium) cation with π -electrons of the atoms of the six-membered ring and oxygen atoms of the functional groups. The data of quantum chemical calculation of structures **2a**, **3a**, and **4** in the PM6 approximation (Mopac 2007 program)⁷ confirm the participation of the metal cation in the coordination bond with the aromatic bonding system and oxygen atoms of the *para*-substituent (Fig. 4).

Thus, the above results show that the functional group of the *para*-substituent of sterically hindered phenol exerts a specific effect on the properties of the aromatic bonding system, which should manifest itself in the antioxidation properties of the synthesized compounds. The properties of the antioxidants depend on the reaction constants of the peroxide radicals with phenol and the backward reaction of the phenoxyl radical with hydroperoxide, which made it possible to use the calculation technologies for the prediction of the efficiency and choice of optimal structures for the synthesis.⁸ For this purpose, the energies of homolysis of the H–O bond of phenolic

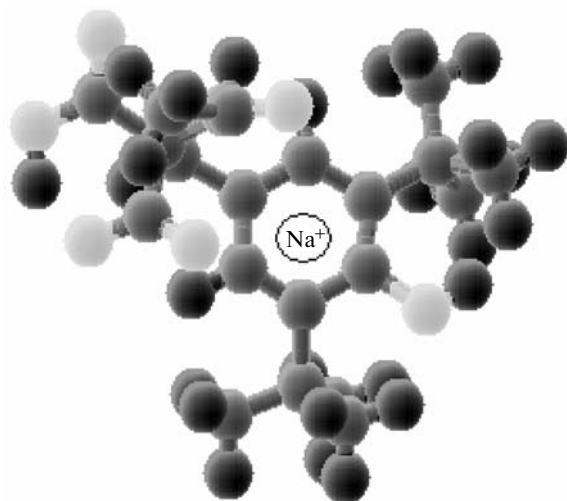


Fig. 4. Structure of compound **2a** according to the data of the PM6 calculation.

hydroxyl (D_{OH}) were calculated: $D_{\text{OH}} = \Delta H(\text{AlkArO}) + \Delta H(\text{H}) - \Delta H(\text{AlkArOH})$, where $\Delta H(\text{AlkArO})$ is the energy of formation of the phenoxyl radical, and $\Delta H(\text{AlkArOH})$ is the energy of formation of phenol (compounds **2a**, **2d**, **3b**, **3c**, and **4**). The results are listed in Table 1.

Cumene-soluble compounds **2d**, **3b**, and **3c** were used in the estimation of the influence of the intramolecular interaction on the antioxidation parameters: the period of oxidation inhibition involving the antioxidant (τ) and the chain termination factor (f) at the constant initiation rate $W_i = 1.5 \cdot 10^{-8} \text{ mol L}^{-1} \text{ s}^{-1}$. These parameters were related by the expression: $f = \tau W_i [\text{InH}]^{-1}$, where InH are compounds **3b**, **3c**, or **2d**. The results of determination of the induction period of cumene oxidation in the presence of InH are shown in Fig. 5. It follows from these results that the antioxidation properties (by the f value) increase in the series of compounds **2d** > **3b** > **3c**, whereas similar values of the f factor for compounds **2d** and **3c** should be expected from the results of calculation of the energy of homolysis of the O—H bond. In our opinion, this contradiction is due to tautomerism of compound **3c** between the aromatic and spirocyclic structures (Fig. 6), resulting

Table 1. Energies of homolysis of the O—H bond of phenolic hydroxyl in **2d**, **3a—c**, and **4** and cumene hydroperoxide

Compound	$D_{(\text{OH})}/\text{kcal mol}^{-1}$	$D_{(\text{OH})}/\text{kJ mol}^{-1}$
3b	80.0	334.7
2d	76.6	320.5
3c	76.6	320.5
3a	71.7	300.0
4	74.6	312.1
Cumene	75.2	314.6
hydroperoxide		

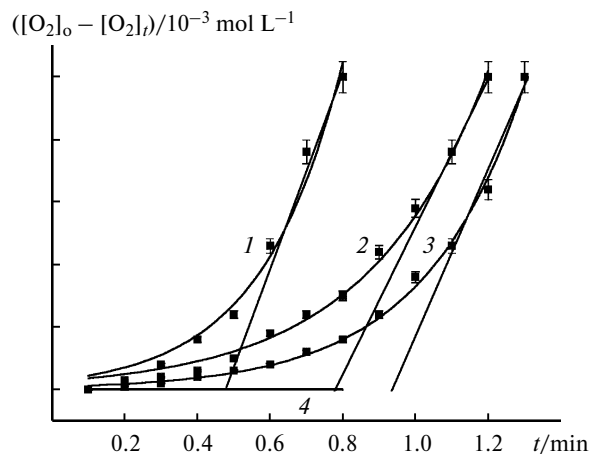


Fig. 5. Kinetic curves of oxygen absorption in the initiated oxidation of cumene at 50 °C in the presence of compounds **3c** (**1**), **3b** (**2**), and **2d** (**3**) and azobis-isobutyronitrile (AIBN) (**4**); $W_i = 1.5 \cdot 10^{-8} \text{ mol L}^{-1} \text{ s}^{-1}$, $C_0/\text{mol L}^{-1} = 2.4 \cdot 10^{-5}$ (**1**); $3.1 \cdot 10^{-5}$ (**2**); $3.3 \cdot 10^{-5}$ (**3**); $f = 1.71$ (**1**); 1.98 (**2**); 2.42 (**3**).

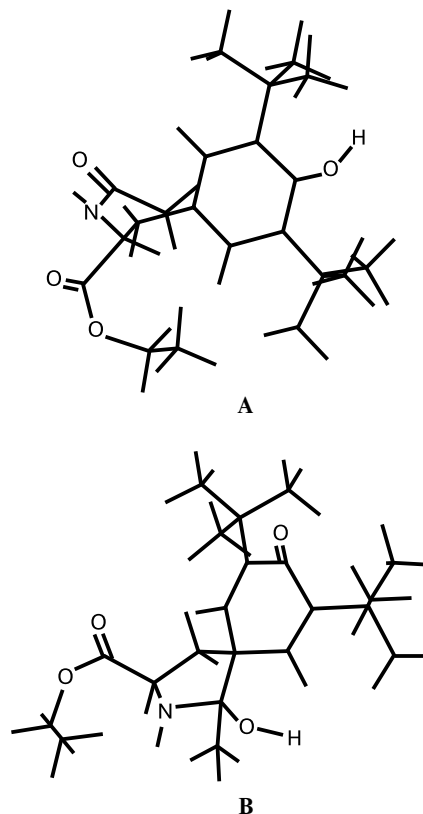


Fig. 6. Structures of tautomers **3c** (**A** and **B**) according to the data of quantum chemical calculations in the PM6 approximation.

in a decrease in the concentration of the aromatic structure under the experimental conditions. It follows from the energies of formation of aromatic structure **3c** (**A**) (−883.544 kJ) and spirocyclic structure **3c** (**B**) (−841.748 kJ)

that the difference is 41.796 kJ mol⁻¹ (9.98 kcal mol⁻¹). In the nonpolar solvent (cumene) structure **3c** (**B**) is more stable, because the dipole moment (*D*) of structure **3c** (**B**) is 3.47 D, which is lower than *D* **3c** (**A**) = 6.13 D.

The data in Table 1 show that compounds **2d**, **3b**, and **3c** are insufficiently efficient antioxidants, whereas compounds **3a** and **4** can be interest as water-soluble and efficient antioxidants.

Experimental

The parameters of the structures of the synthesized compounds were calculated using the Mopac-2007, Version 8.288W program in the PM6 approximation. ¹H NMR spectra were recorded on a Bruker WM-400 instrument (400 MHz) relative to the signal of residual protons of the deuterated solvent (acetone-*d*₆ or DMSO-*d*₆). IR diffuse reflectance spectra were recorded on a Perkin-Elmer 1725-X spectrometer for crystals. The antioxidation parameters of the synthesized compounds were determined by a known method⁹ under the conditions of inhibited oxidation of cumene with oxygen at 50 °C in the presence of the oxidation initiator (azodiisobutyronitrile).

Diethyl *N*-acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)-malonate (1**)** was synthesized by a known procedure,⁶ m.p. 130 °C. ¹H NMR (acetone-*d*₆), δ: 1.25 (t, 6 H, CH₂CH₃, *J* = 7.1 Hz); 1.40 (s, 18 H, Bu^t); 2.07 (s, 3 H, COCH₃); 2.89 (s, 1 H, CH₂); 4.20–4.23 (m, 4 H, CH₂CH₃); 6.01 (s, 1 H, OH); 6.82 (s, 2 H, Ar); 7.29 (br.s, 1 H, NH).

Alkaline hydrolysis of compound 1. Compound **1** (4.36 g, 0.01 mol) was added to a solution of NaOH (0.84 g, 0.06 mol) in dioxane (25 mL) and water (3 mL) at 100 °C in an argon flow, and samples for analysis were taken at an interval of 30 min for 3 h under the temperature-controlled conditions. The composition of the reaction mixtures was monitored (after neutralization to pH 4) using the comparison of the ¹H NMR spectra in an acetone-*d*₆ solution by the signals from *meta*-protons of the aromatic ring of the initial ester **1** (δ_H 6.820) and reaction products: δ_H 7.05 (**3b**), δ_H 6.95 (**3c**), and δ_H 6.92 (**2d**).

Synthesis of monosodium salt of *N*-acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonic acid (2a**) and 2-(*N*-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoic acid (**3b**).** A mixture of compound **1** (43.6 g, 0.1 mol), NaOH (4 g, 0.1 mol), water (20 mL), and dioxane (200 mL) was heated for 2 h at 85–90 °C in an argon flow. Then the reaction mixture was cooled down, and the precipitate formed was separated and recrystallized from aqueous ethanol (8 : 2). Crystalline hydrate of salt **2a** was obtained in a yield of 23.4 g (62%), m.p. 258–260 °C (with decomp.). ¹H NMR (DMSO-*d*₆), δ: 1.26 (s, 18 H, Bu^t); 1.79 (s, 3 H, COCH₃); 3.37 (s, 2 H, CH₂); 3.40–3.48 (br.s, HOH); 6.42–6.46 (br.s, 1 H, OH); 6.79 (s, 2 H, Ar); 7.20–7.27 (br.s, 1 H, NH). IR, ν/cm⁻¹: 3643 (OH); 3550–3100 br (HOH); 3321 (NHCOCH₃); 2957 (CH); 1550–1615 br (HNCO, COO⁻, C=C); 1507; 1433; 1417; 1287; 1234; 1215; 1156; 1123. Found (%): C, 56.96; H, 7.37; N, 3.52; Na, 5.55. C₂₀H₂₈NO₆Na · H₂O. Calculated (%): C, 57.27; H, 7.20; N, 3.34; Na, 5.48.

The mother liquor was treated with 10% HCl to pH 4, the solvent was evaporated, and the residue was crystallized from acetone. Compound **3b** was obtained in a yield of 5.37 g (17%), m.p. 205–206 °C (from EtOH). According to the literature

data,¹ m.p. 203 °C. ¹H NMR (acetone-*d*₆), δ: 1.42 (s, 18 H, Bu^t); 1.96 (s, 3 H, COCH₃); 2.94 (dd, 1 H_a, *J* = 7.6 Hz); 3.11 (dd, 1 H_b, *J* = 5.0 Hz); 4.63–4.69 (m, 1 H_c); 5.90 (s, 1 H, OH); 7.05 (s, 2 H, Ar); 7.45 (d, 1 H, NH, *J* = 5.0 Hz). IR, ν/cm⁻¹: 3639 (OH); 3332 (NHCOCH₃); 2954, 2913, 2872 (CH); 1715 (COOH); 1624 (HNCO); 1550 (C=C), 1433, 1269, 1218, 1188, 1157, 1120. Found (%): C, 67.84; H, 8.85; N, 4.16. C₁₉H₂₉NO₄. Calculated (%): C, 68.03; H, 8.72; N, 4.18.

Ethyl hydrogen *N*-acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate (2c**).** A mixture of compound **1** (43.6 g, 0.1 mol) and AcONa (8.2 g, 0.1 mol) in water (30 mL) and propan-2-ol (200 mL) was stored for 3 days at room temperature, after which 10% HCl (35 mL) was added. Compound **2c** was obtained in a yield of 26.1 g (64%), m.p. 175–176 °C (from toluene). ¹H NMR (DMSO-*d*₆), δ: 1.24 (t, 3 H, CH₂CH₃, *J* = 7.1 Hz); 1.34 (s, 18 H, Bu^t); 1.89 (s, 3 H, COCH₃); 3.22 (s, 2 H, CH₂); 4.13 (2 H, CH₃CH₂, *J* = 7.1 Hz); 6.34 (s, 1 H, OH); 6.76 (s, 2 H, Ar); 7.39 (s, 1 H, NH). IR, ν/cm⁻¹: 3633 (OH); 3345 (NHCOCH₃); 2954 (CH); 1749 (COOC₂H₅); 1714 (COOH); 1619 (HNCOCH₃); 1533 (C=C); 1435, 1235, 1212, 1149. Found (%): C, 64.89; H, 8.33; N, 3.31. C₂₂H₃₃NO₆. Calculated (%): C, 64.85; H, 8.16; N, 3.44.

Ethyl 2-(*N*-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoate (3c**)** is formed on heating monoethyl ester **2c** to temperatures higher than 176 °C due to decarboxylation. M.p. 135–136 °C (from toluene). ¹H NMR (acetone-*d*₆), δ: 1.68 (t, 3 H, CH₃CH₂, *J* = 7.1 Hz); 1.42 (s, 18 H, Bu^t); 1.91 (s, 3 H, COCH₃); 2.02 (dd, 1 H_a, *J* = 6.2 Hz); 3.11 (dd, 1 H_b, *J* = 6.3 Hz); 4.09 (2 H, CH₃CH₂, *J* = 7.1 Hz); 4.60–4.64 (m, 1 H_c); 5.98 (s, 1 H, OH); 6.95 (s, 2 H, Ar); 7.34 (d, 1 H, NH, *J* = 7.15 Hz). IR, ν/cm⁻¹: 3354 (NHCOCH₃); 3189 br (OH); 2948 (CH); 1732 (COOC₂H₅); 1647 (HNCO); 1548 (C=C); 1435; 1253; 1211; 1039. Found (%): C, 69.59; H, 9.13; N, 3.94; C₂₁H₃₃NO₄. Calculated (%): C, 69.40; H, 9.15; N, 3.85.

***N*-Acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonate (**2d**).** A solution of compound **2a** (4.2 g, 0.01 mol) in water (50 mL) was treated with 10% HCl (5 mL). The precipitate formed was separated, dried at 25–30 °C, and crystallized from a toluene–EtOH (9 : 1, vol.) mixture. The yield was 92–96%, m.p. 198–200 °C (from toluene). According to the literature data,¹ m.p. 148 °C. ¹H NMR (DMSO-*d*₆), δ: 1.34 (s, 18 H, Bu^t); 1.87 (s, 3 H, COCH₃); 3.22 (s, 2 H, CH₂); 6.74 (s, 2 H, Ar); 7.69 (s, 1 H, NH). IR, ν/cm⁻¹: 3637 (OH); 3338 (NHCOCH₃); 2954, 2913, 2872 (CH), 1716 (COOH); 1623 (HNCOCH₃); 1536 (C=C), 1435, 1214, 1155, 1121. Found (%): C, 63.24; H, 7.95; N, 3.86. C₂₀H₂₉NO₆. Calculated (%): C, 63.31; H, 7.70; N, 3.69.

***N*-Acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonic acid diammonium salt (**2e**).** Ammonia (2.2 mL, 0.1 mol) was added to a solution of acid **2d** (3.37 g, 0.01 mol) in EtOH (15 mL). The reaction mixture was stirred for 30 min, and ammonia and solvent excess were distilled off. Water (10 mL) was added to the residue, and the mixture was heated and filtered. The filtrate was cooled to 5–6 °C and stored until precipitation, and the precipitate was separated by filtration. Compound **2e** was obtained in a yield of 3.1 g (83%), m.p. 177–178 °C (from EtOH). ¹H NMR (DMSO-*d*₆), δ: 1.29 (s, 18 H, Bu^t); 1.75 (s, 3 H, COCH₃); 2.52 (s, 2 H, CH₂); 3.85–4.01 (br.s, 8 H, NH₄⁺); 6.80 (s, 2 H, Ar); 7.04–7.06 (br.s, 1 H, NH). Found (%): C, 57.95; H, 8.71; N, 10.26. C₂₀H₃₅N₃O₆. Calculated (%): C, 58.01; H, 8.53; N, 10.16.

***N*-Acetylamino(3,5-di-*tert*-butyl-4-hydroxybenzyl)malonic acid monopotassium salt (4)** was synthesized similarly to **2a** in 56% yield, m.p. 250–252 °C (with decomp.). ¹H NMR (DMSO-*d*₆), δ: 1.27 (s, 18 H, Bu^t); 1.80 (s, 3 H, COCH₃); 2.48 (s, 2 H, CH₂); 3.41–3.46 (br.s, 3 H, HOH); 6.42–6.47 (br.s, 1 H, OH); 6.79 (s, 2 H, Ar); 7.22–7.26 (br.s, 1 H, NH). IR, ν/cm⁻¹: 3644 (OH); 3550–3100 br. (HOH); 3323 (NHCOCH₃); 1550–1620 br. (HNCO, COO⁻, C=C). Found (%): C, 54.04; H, 7.03; N, 3.15; K, 8.60. C₂₀H₂₂KNO₆ · 1.5H₂O. Calculated (%): C, 54.32; H, 7.21; N, 3.06; K, 8.75.

Sodium 2-(*N*-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoate (3a). **A.** Sodium hydroxide (0.4 g, 0.01 mol) was added to a solution of compound **3b** (3.16 g, 0.01 mol) in water (10 mL). The mixture was heated until the precipitate dissolved, and then the solvent was distilled *in vacuo*. Ethanol (10 mL) was added to the residue, NaCl was separated by filtration, the mother liquor was evaporated, and the crystals of compound **3a** were washed with EtOH and dried in a desiccator over P₂O₅. Compound **3a** decomposes on heating above 250 °C. ¹H NMR (DMSO-*d*₆), δ: 1.32 (s, 18 H, Bu^t); 1.75 (s, 3 H, COCH₃); 2.69 (dd, 1 H_a, *J* = 7.6 Hz); 2.94 (dd, 1 H_b, *J* = 5.0 Hz); 4.01–4.06 (m, 1 H_c); 3.52–3.57 (br.s, H, H₂O); 6.96–6.98 (br.s, 1 H, OH); 6.87 (s, 2H, Ar); 7.43–7.45 (br.s, 1 H, NH). IR, ν/cm⁻¹: 3646 (OH); 3285 br. (HOH); 3103 (NHCOCH₃); 2956, 2914, 2874 (CH); 1667 (C=O); 1632 (HNCOCH₃); 1596 (C=C); 1435; 1400; 1316; 1400; 1316; 1234; 1158; 1121. Found (%): C, 55.64; H, 8.15; N, 3.46; Na, 5.64. C₁₉H₂₈NO₄Na · 3H₂O. Calculated (%): C, 55.45; H, 8.34; N, 3.40; Na, 5.59.

B. A solution of compound **2a** (4.2 g, 0.01 mol) in water (20 mL) was heated to boiling and stored for 35–40 min, then the solvent was evaporated, and the residue was crystallized from an EtOH–water (1 : 1) mixture. The yield of compound **3a** was 3.78 g (92%). The ¹H NMR spectrum of the sample coincides with that of compound **3a** obtained by method *A*.

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