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Catalytic Hydrogenation of Persubstituted *p*-Nitrosophenols

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Abstract—Catalytic hydrogenation of dialkyl 2-hydroxy-4,6-dimethyl-5-nitrosobenzene-1,3-dicarboxylates over Pd/C gave the corresponding previously unknown dialkyl 5-amino-2-hydroxy-4,6-dimethylbenzene-1,3-dicarboxylates. The first-order rate constants for the hydrogenation process were found to be linearly related to steric constants of the alkyl groups.

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We previously reported on exhaustively substituted nitrosophenols having ethoxycarbonyl groups in the *ortho* positions with respect to the hydroxy group [1, 2]. We synthesized analogous nitrosophenols with methoxy-, propoxy-, and butoxycarbonyl groups and performed their hydrogenation with a view to obtain new *p*-aminophenols. The expected products contain both salicylic acid ester and *p*-aminophenol fragments that are typical of known medicines [3]; therefore, they attracted interest from the viewpoint of synthesis of biologically active compounds.

Dialkyl 2-hydroxy-4,6-dimethyl-5-nitrosobenzene-1,3-dicarboxylates **Ia–Id** were subjected to hydrogenation over carbon-supported palladium in anhydrous ethyl acetate. The reactions were carried out in a reduction cell maintained at a constant temperature. The cell was charged with the solvent, initial nitrosophenol, and catalyst, and hydrogen (from a steel cylinder) was bubbled through the mixture. The target products were isolated as follows: the reaction mixture was filtered from the catalyst and was saturated with dry





hydrogen chloride. Dialkyl 5-amino-2-hydroxy-4,6-dimethylbenzene-1,3-dicarboxylate hydrochlorides separated from the solution and were filtered off.

We also performed kinetic measurements. Kinetic curves were plotted for the consumption of hydrogen, and dependences of $\ln(V_0 - V_x)$ versus time were obtained. The regression equation for the hydrogenation of compound Ia was as follows: v = -0.05x + 3.38, r =0.994. The dependences for other substituted nitrosophenols **Ib–Id** of this series were also linear and were characterized by high correlation coefficients, indicating that catalytic hydrogenation of compounds Ia-Id under the given conditions conforms to first-order kinetics. From the obtained dependences we calculated the first-order rate constants (k, s^{-1}) for hydrogenation of all the examined dialkyl 2-hydroxy-4,6-dimethyl-5nitrosobenzene-1,3-dicarboxylates Ia-Id: Ia, 5.01; Ib, 3.03; Ic, 0.92; Id, 0.83. It is seen that the hydrogenation rate constant strongly depends on the length of the alkyl radical in the ester moiety: it decreases in going from methyl to butyl esters.

We revealed a linear relation between the logarithms of hydrogenation rate constants and steric constants of alkyl groups E_s . The following steric constants E_s were used: 0.00 (Me), -0.09 (Et), -0.30 (Pr), and -0.34 (Bu) [4]. The regression equation was y = 2.35x + 1.30, r = 0.998. We can conclude that the difference in the rates of catalytic hydrogenation is determined exclusively by the size of the alkyl group in the ester fragments.

EXPERIMENTAL

The ¹H NMR spectra were recorded on a Bruker Avance DRX-200 spectrometer (200 MHz) at the Krasnoyarsk Regional Collective Use Center (Siberian Division, Russian Academy of Sciences). Gas chromatographic–mass spectrometric analysis was performed on an Agilent Technologies GC–MS system consisting of a Hewlett–Packard HP 6890N gas chromatograph and a mass-selective detector; HP-5MS quartz capillary column, 30 m×0.25 mm, film thickness 0.33 μ m; injector temperature 230°C, detector temperature 270°C; oven temperature programming from 70 to 280°C at a rate of 20 deg/min; carrier gas helium; electron impact ionization, 70 eV; total ion current measurement.

Dimethyl, diethyl, dipropyl, and dibutyl acetonedicarboxylates were synthesized from anhydrous citric acid and oleum with subsequent esterification of acetonedicarboxylic acid with the corresponding alcohols according to the procedure described in [5].

Dialkyl 2-hydroxy-4,6-dimethyl-5-nitrosobenzene-1,3-dicarboxylates Ia-Id were synthesized in a way similar to cyclization of isonitrosoacetylacetone with dialkyl acetonedicarboxylates [2]. Isonitrosoacetylacetone, 5 mmol, and the corresponding dialkyl acetonedicarboxylate, 10 mmol, were added to a solution of 5 mmol of potassium hydroxide in 5 ml of anhydrous alcohol. The mixture was kept for 20 min at 18-20°C, and it changed from orange to green. Anhydrous diethyl ether was added to the solution until it became turbid, the bright green crystals were filtered off, dried over Na₂SO₄ under reduced pressure, and dissolved in 4 ml of water. The solution was acidified with dilute (1:3) hydrochloric acid, and an oily material separated and rapidly crystallized to form colorless crystals.

Dimethyl 2-hydroxy-4,6-dimethyl-5-nitrosobenzene-1,3-dicarboxylate (Ia). Yield 0.6 g (45%), white crystals, mp 125–127°C. ¹H NMR spectrum (CDCl₃), δ , ppm: 2.45 s (6H, CH₃), 3.97 s (6H, CH₃), 11.87 s (1H, OH). Mass spectrum, *m*/*z* (*I*_{rel}, %): 265 (40), 233 (100), 218 (20), 202 (50), 175 (30), 147 (50), 119 (30), 91 (15), 67 (35), 52 (10).

Diethyl 2-hydroxy-4,6-dimethyl-5-nitrosobenzene-1,3-dicarboxylate (Ib). Yield 0.75 g (51%), white crystals, mp 103–105°C. ¹H NMR spectrum of potassium salt (D₂O), δ , ppm: 1.30 t (6H, CH₃), 2.35 s (6H, CH₃), 4.34 q (4H, CH₂). Mass spectrum, *m/z* (I_{rel} , %): 293 (25), 247 (50), 221 (10), 202 (50), 175 (100), 147 (10), 119 (10), 91 (15), 67 (10), 51 (10). **Dipropyl 2-hydroxy-4,6-dimethyl-5-nitrosobenzene-1,3-dicarboxylate (Ic).** Yield 0.42 g (89%), white crystals, mp 80–82°C. ¹H NMR spectrum of potassium salt (D₂O), δ , ppm: 0.89 t (6H, CH₃), 1.63– 1.73 m (4H, CH₂), 2.36 s (6H, CH₃), 4.25 t (4H, CH₂). Mass spectrum, *m/z* (*I*_{rel}, %): 321 (30), 292 (15), 276 (10), 261 (65), 219 (20), 202 (70), 175 (15), 147 (15), 119 (10), 91 (10), 67 (10), 51 (10).

Dibutyl 2-hydroxy-4,6-dimethyl-5-nitrosobenzene-1,3-dicarboxylate (Id). Yield 0.8 g (88%), white crystals, mp 65–67°C. ¹H NMR spectrum of potassium salt (D₂O), δ , ppm: 0.83 t (6H, CH₃), 1.26–1.38 m (4H, CH₂), 1.56–1.70 m (4H, CH₂), 2.36 s (6H, CH₃), 4.28 t (4H, CH₂). Mass spectrum, *m/z* (*I*_{rel}, %): 349 (55), 292 (100), 276 (45), 265 (55), 249 (10), 221 (40), 202 (10), 175 (15), 147 (10), 121 (10), 97 (15), 75 (30), 56 (15).

Dialkyl 5-amino-2-hydroxy-4,6-dimethylbenzene-1,3-dicarboxylates IIa-IId (general procedure). Compounds Ia-Id were hydrogenated in a static system under atmospheric pressure at 298 ± 0.1 K under stirring. A 20-ml glass cell was charged with a suspension of 0.1 g of 0.5% Pd/C in 5 ml of ethyl acetate. The cell was evacuated, and filled with hydrogen, this procedure was repeated five times, and a solution of 0.5 mmol of nitrosophenol Ia-Id in 5 ml of ethyl acetate was added in a stream of hydrogen. The mixture was stirred, and the volume of absorbed hydrogen was measured. The mode of stirring did not affect the rate of hydrogenation, and the rate of hydrogen absorption did not exceed 3 ml/min. When the reaction was complete (hydrogen was no longer absorbed), the mixture was filtered from the catalyst, the filtrate was saturated with dry hydrogen chloride, and the precipitate of dialkyl 5-amino-2-hydroxy-4,6-dimethylbenzene-1,3-dicarboxylate hydrochloride (white crystals) was filtered off and washed with toluene. Aminophenols IIa-IId as free bases (for GC-MS analysis) were isolated by adding triethylamine to a solution of the corresponding hydrochloride in benzene.

Dimethyl 5-amino-2-hydroxy-4,6-dimethylbenzene-1,3-dicarboxylate (IIa). Yield of hydrochloride 0.1 g (74%), white crystals, mp 178–180°C. ¹H NMR spectrum (acetone- d_6), δ , ppm: 2.34 s (6H, CH₃), 2.97 br.s (2H, NH₂), 3.99 s (6H, CH₃), 11.40 s (1H, OH). Mass spectrum, m/z (I_{rel} , %): 253 (50) [M]⁺, 221 (100), 189 (80), 161 (10), 133 (20), 106 (25), 77 (15), 53 (10).

Diethyl 5-amino-2-hydroxy-4,6-dimethylbenzene-1,3-dicarboxylate (IIb). Yield of hydrochloride 0.25 g (68%), white crystals, mp 168–170°C. ¹H NMR spectrum (acetone- d_6), δ , ppm: 1.43 t (6H, CH₃), 2.39 s (6H, CH₃), 3.01 br.s (2H, NH₂), 4.49 q (4H, CH₂), 11.55 s (1H, OH). Mass spectrum, m/z (I_{rel} , %): 281 (50) [M]⁺, 235 (100), 207 (15), 189 (85), 163 (30), 133 (20), 106 (30), 77 (15), 53 (10).

Dipropyl 5-amino-2-hydroxy-4,6-dimethylbenzene-1,3-dicarboxylate (IIc). Yield of hydrochloride 0.1 g (60%), white crystals, mp 135–137°C. ¹H NMR spectrum (acetone- d_6), δ , ppm: 1.05 t (6H, CH₃), 1.79–1.89 m (4H, CH₂), 2.39 s (6H, CH₃), 3.01 br.s (2H, NH₂), 4.40 t (4H, CH₂), 11.69 s (1H, OH). Mass spectrum, m/z (I_{rel} , %): 309 (45) [M]⁺, 249 (100), 189 (80), 163 (30), 133 (15), 106 (25), 77 (10), 59 (10).

Dibutyl 5-amino-2-hydroxy-4,6-dimethylbenzene-1,3-dicarboxylate (IId). Yield of hydrochloride 0.08 g (45%), white crystals, mp 110–112°C. ¹H NMR spectrum (aceton- d_6), δ , ppm: 0.99 t (6H, CH₃), 1.42–1.61 m (4H, CH₂), 1.74–1.87 m (4H, CH₂), 2.36 s (6H, CH₃), 2.98 br.s (2H, NH₂), 4.44 t (4H, CH₂), 11.61 s (1H, OH). Mass spectrum, m/z (I_{rel} , %): 337 (100) [M]⁺, 307 (10), 281 (45), 263 (55), 235 (10), 207 (55), 189 (45), 163 (20), 133 (15), 106 (20), 75 (20), 56 (80).

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