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HYDROGENATION OF ETHYL ESTERS OF 4-PHENYL- AND (2-FURYL)-SUBSTITUTED 2,4-DIOXOBUTYRIC ACIDS AT PALLADIUM BLACK

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The hydrogenation of ethyl 4-R-2,4-dioxobutyrates (R = phenyl, 2-furyl) at 5% Pt/Al_2O_3 catalyst, modified with cinchonidine, and at palladium black was investigated. The former had low activity under the conditions we tested. The main products during the hydrogenation of these compounds at palladium black are ethyl 4-R-2-hydroxy-4-oxobutyrates. The yield of the phenyl derivative amounts to 68.5%, while the yield of the corresponding 2-furyl derivative amounts to 97%. In the last case ethyl 2-hydroxy-4-oxo-4-(2-tetrahydrofuryl)butyrate was detected as impurity. The optimum conditions for the formation of ethyl 2-hydroxy-4-phenylbutyrate (yield 88.2%) were determined.

Keywords: ethyl 4-substituted 2,4-dioxobutyrates, platinum and palladium catalysts, hydrogenation.

The derivatives of 4-substituted 2-hydroxybutyric acids are valuable synthons for the production of antihypertensive substances, homoamino acids, hydroxamic acids, and other compounds [1, 2].

We studied the hydrogenation of sodium 2-oxo-4-phenyl-, 4-(2-furyl)-2-oxo-, 2-oxo-4-(2-thienyl)-, and 2-oxo-4-(3-pyridyl)butenoates at nickel and palladium catalysts.

During the hydrogenation of sodium 2-oxo-4-phenylbutenoate at nickel catalysts the corresponding salt of 2-hydroxy-4-phenylbutyric acid is formed [3].

The use of palladium black and 10% Pd/C catalyst leads to the formation of sodium 2-oxo-4-phenylbutyrate. During the hydrogenation of sodium 4-(2-furyl)-2-oxobutenoate at Raney nickel catalyst the corresponding 4-(2-furyl)-2-oxobutyrates and 4-(2-furyl)-2-hydroxybutyrates and aliphatic compounds from hydrogenolysis of the molecule of the original compound are formed [4].

During the hydrogenation of sodium and ethyl 2-oxo-4-(2-thienyl)butenoates at Raney nickel the corresponding derivatives of 2-oxo-4-(2-thienyl)butyric acid and 2-hydroxy-4-(2-thienyl)butyric acid are formed [5]. Palladium catalysts secure the more selective formation of the corresponding oxo compound than Raney nickel. The formation of ethyl 2-oxo-4-(2-tetrahydrothienyl)butyrate in addition to the above-mentioned compounds was also observed during the hydrogenation of ethyl 2-oxo-4-(2-thienyl)butenoate at palladium black.

During the hydrogenation of sodium 2-oxo-4-(3-pyridyl)butenoate at palladium black the reaction products were sodium 2-oxo-4-(3-pyridyl)butyrate and 2-hydroxy-4-(3-pyridyl)butyrate and hydrogenolysis products. The reaction takes place by a parallel–consecutive mechanism [6].

During the hydrogenation of derivatives of 4-substituted 2-oxobutenoic acids the double bond is saturated, and the carbonyl group is partly hydrogenated. The latter depends on the composition of the catalyst and on the structure of the initial compound.

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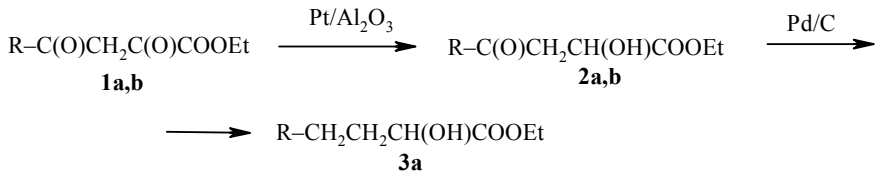
The second direction for the synthesis of the synthons [the (*R*)-enantiomers of the respective 2-hydroxybutyric esters] for the production of antihypertensive products and other biologically active substances is hydrogenation of the esters of 4-substituted 2,4-dioxobutyric acids [7]. These compounds are more readily obtainable than the corresponding derivatives of butenoic acids.

In this case hydrogenation takes place in two stages:



1-3 a R = Ph; **1**, **2 b** R = 2-furyl

At the first stage hydrogenation of the 4-substituted 2,4-dioxobutyric esters **1** occurs under mild conditions, and the corresponding 2-hydroxy compounds **2** are obtained. The enantiomers are separated by crystallization, and the *R* isomer is hydrogenated under more drastic conditions to the esters of 4-substituted 2-(*R*)-hydroxybutyric acids **3**.

We studied the hydrogenation of ethyl 4-phenyl-2,4-dioxobutyrate (**1a**) and 4-(2-furyl)-2,4-dioxo-butyrate (**1b**) at palladium black and Pt/Al_2O_3. (The reaction conditions are given in Table 1.)

Under the conditions recommended in [8] the 5% Pt/Al_2O_3 catalyst modified with 10,11-dihydrocinchonidine is characterized by low activity. (The conversion of the raw material does not exceed 17%.) During the hydrogenation of compounds **1a** and **1b** at palladium black at room temperature with a

TABLE 1. The Hydrogenation of Ethyl 4-Substituted 2,4-Dioxobutyrates **1a**,**b***

Compound	Catalyst*[2]	c_{in} of **1**, mol/l	Time reaction, h	Reactions products		Unreacted **1a**,**b**, %
				2	**3a**	
1a	5% Pt/Al_2O_3	0.303	3	5.5	—	83.0
	Pd black	0.182	4	—	88.2	—
	Pd black	0.061	0.5	68.5	—	9.6
	Pd black	0.062	0.3	38.5	—	45.5
1b	5% Pt/Al_2O_3	0.27	4	4.6	—	84.0
	Pd black	0.06	1	96.6	—	—
	Pd black	0.06	4	88.4*[3]	—	—

* At 5% Pt/Al_2O_3, modified with 10,11-dihydrocinchonidine (catalyst–modifier, 10:1), in toluene (H pressure 60 atm) and Pd black in ethanol (H pressure 1 atm) at room temperature.

*[2] Before use the 5% Pt/Al_2O_3 catalyst was activated in a stream of hydrogen at 400°C for 2 h. After activation it was cooled and quickly transferred to the reaction flask, the 10,11-dihydrocinchonidine and the initial substance were added, and the hydrogenation was performed.

*[3] Ethyl 2-hydroxy-4-oxo-4-(2-tetrahydrofuryl)butyrate was detected in the catalyzate by chromatography (yield ~5%). Mass spectrum, *m/z* (*I*, %): 216 $[M]^+$ (4); 143 $[M–COOC_2H_5]^+$ (4); 125 (3); 71 $[3CH_2–O–CH]^+$ (100); 43 (54).

hydrogen pressure of 1 atm in ethanol solution the first reaction products are ethyl 2-hydroxy-4-oxo-4-phenylbutyrate (**2a**) (yield 68.5%) and ethyl 4-(2-furyl)-2-hydroxy-4-oxobutyrate (**2b**) (yield up to 97% with total conversion of the raw material). In the last case small amounts of ethyl 2-hydroxy-4-oxo-(2-tetrahydrofuryl)butyrate are found as impurities.

During prolonged hydrogenation of the ester **1a** (4 h) with the initial compound at a concentration of 0.182 M (ratio of initial compound and catalyst 1:0.5) in ethanol solution ethyl 2-hydroxy-4-phenylbutyrate (**3a**) (yield 88.2%), which was not observed during the hydrogenation of compound **1b**, was obtained.

Thus, the first stage in the production of the (*R*)-enantiomers of the of the respective 4-substituted 2-hydroxybutyric esters can be realized under mild conditions with palladium black.

EXPERIMENTAL

The initial substances were obtained by the method in [9]: **1a** by the condensation of acetophenone with diethyl oxalate, and compound **1b** by the condensation of 2-acetylfuran with diethyl oxalate. The contents of the main products were 98 and 99% respectively. The catalyst 5% Pt/Al_2O_3 (supplied by Acros) was modified with 10,11-dihydrocinchonidine by the method in [10].

The initial substances and the reaction products were determined by HPLC on Rainin chromatographic apparatus; Dynamax-300A analytical column (4.6×250 mm), C_8 reverse phase at λ 220 nm; eluant 34% acetonitrile in 0.25 N triethylammonium phosphate. The esters **2a**,**b** were purified for analytical purposes on a Buchi preparative chromatograph, 26×470 mm column filled with Silasorb C_{18} sorbent. The eluant was acetonitrile, 0.1% trifluoroacetic acid.

The ^{1}H NMR spectrum of compound **3a** was recorded on a Bruker WH-90 spectrometer (90 MHz) in $CDCl_3$, internal standard TMS. The ^{1}H NMR spectra of the esters **2a** and **2b** were recorded on a Varian Mercury-200 BB spectrometer (200 MHz) with TMS as internal standard.

The mass spectra were obtained on a Kratos MS-25 chromato-mass spectrometer at 70 eV.

Hydrogenation of Ethyl 2,4-Dioxo-4-phenylbutyrate 1a in the Presence of Pt/Al_2O_3 Modified with 10,11-Dihydrocinchonidine. In an autoclave we placed compound **1a** (1.88 g, 8.54 mmol), dissolved in toluene (30 ml). We added 10,11-dihydrocinchonidine (0.005 g) and 5% Pt/Al_2O_3 (0.05 g) catalyst that had been previously activated at 400°C for 2 h in a stream of hydrogen. The mixture was hydrogenated at a hydrogen pressure of 60 atm at room temperature. At the end of the reaction the catalyst was filtered off, and the catalyzate was evaporated. We obtained 1.80 g of the product, which contained 0.11 g of the ester **2a** (yield 5.8%) and 83.0% of the unreacted initial substance.

Hydrogenation of Ethyl 2,4-Dioxo-4-phenylbutyrate (1a) in the Presence of Pd Black. A. We dissolved the ester **1a** (0.60 g, 2.73 mmol) in ethanol (45 ml), added moist palladium black (0.3 g), and hydrogenated the mixture at atmospheric pressure at room temperature. At the end of the reaction the catalyst was filtered off, and the catalyzate was evaporated. We obtained 0.54 g of the product, which contained 0.06 g of the unreacted initial compound (9.6%) and 0.42 g of the ester **2a** (yield 68.5%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.2, CH_3); 3.37 (2H, d, *J* = 6.2, CCH_2C); 4.10 (2H, q, *J* = 7.2, OCH_2); 4.54 (1H, t, *J* = 6.2, CHO); 5.7 (1H, br. s, OH); 7.4-7.7 (5H, m, C_6H_5).

B. We dissolved the ester **1a** (0.06 g, 2.73 mmol) in ethanol (15 ml) and added moist palladium black (0.3 g). The mixture was hydrogenated for 4 h at atmospheric pressure and room temperature. At the end of the reaction the catalyst was filtered off, and the catalyzate was evaporated. We obtained 0.52 g of the product, which contained 0.50 g of the ethyl ester **3a** (yield 88.2%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.19 (3H, t, *J* = 7.6, CH_3); 1.88 (2H, m, C–CH_2–C); 2.65 (2H, t, *J* = 8.0, Ph–CH_2); 3.98 (1H, m, CH–O); 4.07 (2H, q, *J* = 7.6, OCH_2); 4.2 (1H, br. s, OH); 7.23 (5H, m, C_6H_5).

Hydrogenation of Ethyl 4-(2-Furyl)-2,4-dioxobutyrate 1b in the Presence of Pt/Al_2O_3 Modified with 10,11-Dihydrocinchonidine. In an autoclave we placed the ester **1b** (1.68 g, 8.00 mmol), dissolved in toluene (29.6 ml), and we added 10,11-dihydrocinchonidine (0.008 g) and 5% Pt/Al_2O_3 catalyst (0.08 g) that had been previously activated at 400°C for 2 h in a stream of hydrogen. The mixture was hydrogenated for 3 h 30 min at a hydrogen pressure of 60 atm and at room temperature. At the end of the reaction the catalyst was filtered off, and the catalyzate was evaporated. We obtained 1.52 g of the product, which contained 0.08 g of the ester **2b** (yield 4.6%) and 1.41 g of the unreacted ester **1b**.

Hydrogenation of Ethyl 4-(2-Furyl)-2,4-dioxobutyrate (1b) in the Presence of Pd Black. We dissolved the ester **1b** (0.5 g, 2.38 mmol) in ethanol (40 ml) and added moist palladium black (0.3 g). The mixture was hydrogenated with molecular hydrogen for 1 h at atmospheric pressure and room temperature. At the end of the reaction the catalyst was filtered off, and the catalyzate was evaporated. We obtained 0.50 g of the product, which contained 0.49 g of the ester **2b** (yield 96.6%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.1, CH_3); 3.30 and 3.39 (2H, AB part of ABM system, *J* = 7.0, *J* = 6.4, *J* = 4.4, C–CH_2–C); 4.26 (2H, q, *J* = 7.1, OCH_2); 4.65 (1H, M part of ABM system, *J* = 6.4, *J* = 4.4, CHOH); 5.7 (1H, br. s, COH); 6.55 (1H, dd, *J* = 3.6, *J* = 1.8, H-4 of furan); 7.24 (1H, dd, *J* = 3.6, *J* = 0.9, H-3 of furan); 7.61 (1H, dd, *J* = 1.8, *J* = 0.9, H-5 of furan).

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