ANESTHESIN SYNTHESIZED BY HYDROGENATION OF *p*-NITROBENZOIC ACID ETHYL ESTER ON PALLADIUM CATALYSTS

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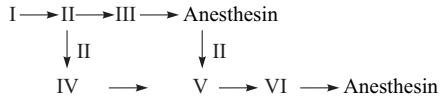
A technological scheme used for the commercial synthesis of anesthesin (*p*-aminobenzoic acid ethyl ester) includes the stage of reduction of *p*-nitrobenzoic acid ethyl ester (I) by iron cuttings in the presence of acetic acid. The reduction of ester I leads to the formation of anesthesin acetate, which is treated with sodium carbonate to obtain the target compound. The product is purified by recrystallization from ethanol in the presence of activated charcoal and sodium hydrosulfite in order to reduce and decolorize the soluble impurities [1].

The impurities present in the anesthesin represent for the most part the products of incomplete reduction of the nitro group, including *p*-nitrobenzoic acid ethyl ether (II), *p*-hydroxyaminobenzoic acid ethyl ester (III), and diethyl esters of azoxybenzene- (IV), azobenzene- (V), and hydroazobenzene- (VI) 4,4′-dicarboxylic acids. The formation of anesthesin and semiproducts II – VI from the initial nitro compound I can be described by the following scheme:



The rate of formation and the amount of the products of incomplete reduction of nitro groups depend on the temperature, solvent type, and nature of the reducing agent.

In order to increase the yield of anesthesin, we have studied the process of hydrogenation of *p*-nitrobenzoic acid ethyl ester and the products of its incomplete reduction. The hydrogenation of ester I to the target compound (*p*-aminobenzoic acid ethyl ester) was carried out in the presence of a heterogeneous palladium catalyst Pd/C and palladium-containing anion exchangers AN-1 and AV-17-8 (an advantage of using the latter system in hydrogenation reactions was pointed out in [2, 3]).

The results of preliminary investigations showed that, under the conditions selected, the hydrogenation of compounds I – VI proceeds in the kinetic regime and is a first-order process with respect to catalyst and hydrogen. However, dependence of the reaction rate on the substrate concentration was variable: when the substrate concentration became comparable to the concentration of active centers on the catalyst surface, the reaction order changed from zeroth to first.

The plots of the effective hydrogenation rate constant for the initial nitro compound I versus palladium content in the catalyst (Fig. 1) exhibits an extremal shape. The reaction rate constant increases in proportion to the palladium content in the range of metal concentrations below 4 wt.%. The further increase in the metal content is accompanied by a decrease in the reaction rate, probably, because of a decrease in the catalytic activity caused by the growth of microcrystals. Thus,

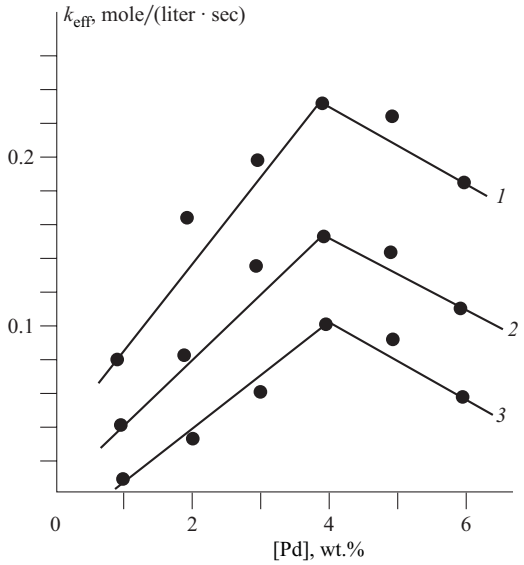


Fig. 1. Plots of the hydrogenation rate of *p*-nitrobenzoic acid ethyl ester versus palladium content for various catalyst systems: (*1*) Pd/C; (*2*) AV-17-8-Pd; (*3*) AN-1-Pd. The process conditions are indicated in Table 1.

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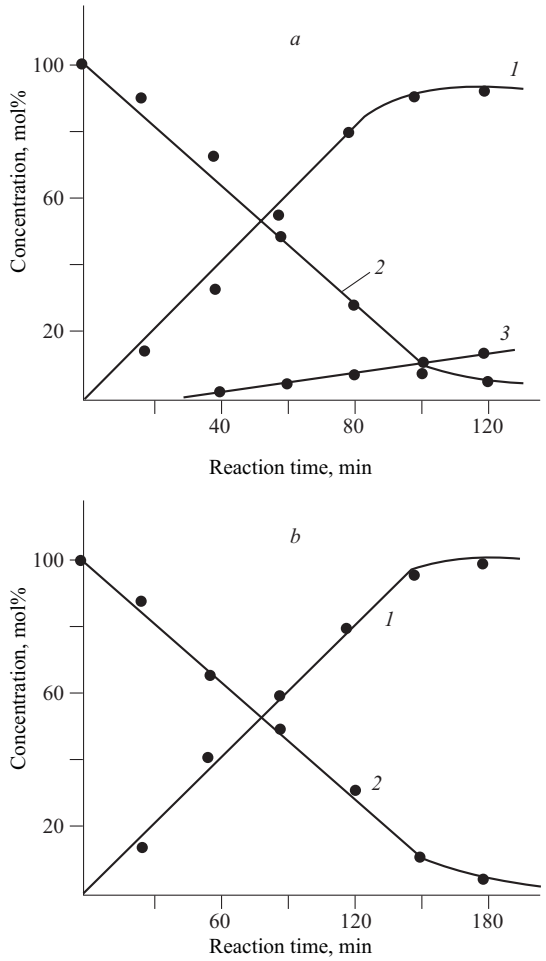

Fig. 2. Time variation of the concentration of the initial reagent, the intermediate product, and the target product of hydrogenation on (*a*) Pd/C and (b) AV-17-8-Pd catalysts: (*1*) anesthesin; (*2*) *p*-nitrobenzoic acid ethyl ester; (*3*) *p*- N,N-diethylaminobenzoic acid ethyl ester. The process conditions are indicated in Table 1.

the optimum palladium content in the catalyst system is 4 wt.%.

For all the catalysts studied in our experiments, the reduction of nitro compound I to anesthesin proceeded without the formation of significant amounts of the products of incomplete reduction of nitro groups (Figs. 2*a* and 2*b*). The effective reaction rate constants calculated per unit catalyst weight (1 kg) are presented in Tables 1 and 2.

In order to confirm the absence of the products of incomplete reduction of nitro groups (that is, compounds II – VI), we studied the hydrogenation of these semiproducts (Table 1). It was established that, other conditions being equal, all these compounds converted into anesthesin via certain intermediates, which were well detected by gas chromatography (GC). For example, the kinetics of reduction of the azoxy compound IV (Fig. 3) shows that the slowest stage of this process is the hydrogenolysis of hydroazo compound VI, while the fastest stage is the hydrogenation of compound IV. This results in accumulation of the intermediate products in the reaction mixture, the maximum content of compounds V and VI reaching 30 – 50% depending on the substrate, catalyst, and temperature.

The data in Table 1 also indicate that the rate of hydrogenation of nitro compound I for all catalysts is higher that the reaction rates for other substrates (II – VI). Therefore, accumulation of the latter products would be unavoidable if these compounds appeared in the reaction mass as kinetically independent components. Thus, we may ascertain that the reaction of reduction of the initial nitro compound I proceeds without the formation of the intermediate products of incomplete reduction of nitro groups. Additional evidence is provided by the high yields of the target product (Table 2).

It was found that a decrease in selectivity of the process observed in the presence of Pd/C is explained by the side reaction of alkylation of the amino group in anesthesin by the solvent. This reaction is favored by temperature increase above 45°C (Table 2). For the AV-17-8-Pd system, the tem-

TABLE 1. Effective Reaction Rate Constants for Hydrogenation of Compound I and the Products of Its Incomplete Reduction on Various Palladium Catalysts in Ethanol and Toluene

Compound	$k_{eff} \pm (5 – 12\%)$, mole/(liter · sec)					
	AN-1-Pd		AV-17-8-Pd		Pd/C	
	Ethanol	Toluene	Ethanol	Toluene	Ethanol	Toluene
I	0.100	0.020	0.150	0.025	0.23	0.16
II	0.077	0.018	0.120	0.016	0.21	0.14
III	0.080	0.015	0.130	0.013	0.22	0.14
IV	0.060	0.013	0.010	0.011	0.18	0.12
V	0.056	0.009	0.090	0.010	0.17	0.11
VI	0.030	0.007	0.060	0.008	0.15	0.10

Notes: Process conditions: solvent volume, 10 – 50 ml; substrate concentration, 0.1 – 0.5 mole/liter; hydrogen pressure, ~ 1 atm; temperature, 45°C; catalyst weight, 0.2 g (particle size, d = 0.075 – 0.102 mm); reaction time, 100 – 300 min.

TABLE 2. Effective Reaction Rate Constants and Yields for Hydrogenation of Compound II on Various Palladium Catalysts in Ethanol

Experiment No.	T, °C	Pd/C		AN-1-Pd		AV-17-8-Pd	
		k_{eff}	Yield, %	k_{eff}	Yield, %	k_{eff}	Yield, %
1	20	0.04	88.5	0.015	99.2	0.02	99.6
2	25	0.09	88.3	0.03	99.1	0.04	99.5
3	30	0.15	88.0	0.05	99.4	0.07	99.4
4	35	0.17	88.6	0.07	99.5	0.10	99.5
5	40	0.20	88.8	0.09	99.6	0.12	99.7
6	45	0.23	89.4	0.10	99.8	0.15	100
7	50	0.27	88.0	0.09	99.8	0.11	99.3
8	60	0.35	87.0	0.08	99.3	0.095	99.4

Notes: $k_{eff} \pm (6 – 10\%)$, mole/(liter · sec); process conditions the same as indicated in Table 1.

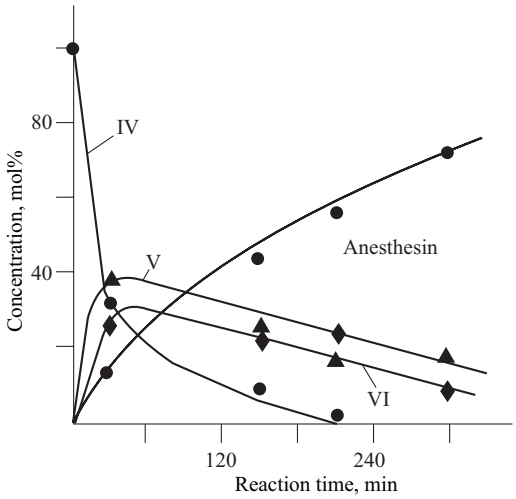

Fig. 3. Time variation of the concentration of various compounds during the hydrogenation of *p*-azoxybenzene-4,4′-dicarboxylic acid diethyl ester (IV) on an AV-17-8-Pd catalyst. The process conditions are indicated in Table 1.

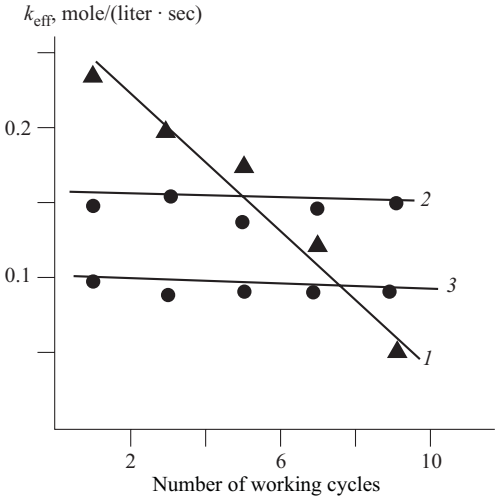

Fig. 4. Stability of various palladium-containing hydrogenation catalysts: (*1*) Pd/C; (*2*) AV-17-8-Pd; (*3*) AN-1-Pd. The process conditions are indicated in Table 1.

perature dependence exhibits an extremal character with a maximum precisely at 45°C. Further temperature rise leads to a decrease in the rate of the side reaction (Table 2). Apparently, this maximum is due to the interplay of increasing partial pressure of the solvent vapors (leading to a decrease in the effective hydrogen concentration in the reaction mixture), on the one hand, and the polymeric nature of catalysts of the AN-1-Pd and AV-17-8-Pd type, on the other.

For all the catalysts studied, the intensity and selectivity of the hydrogenation of nitro compound I was significantly affected by the type of solvent. For example, the reaction rate was considerably greater in ethanol than in toluene (Table 1); however, the process in the former medium was accompanied by the alkylation of anesthesin.

With respect to stability, the catalyst systems studied can be arranged in the following order: AV-17-8-Pd > AN-1-Pd > Pd/C (Fig. 4). Note, however, that the initial hydrogenation rate was markedly higher for Pd/C than for the palladium-containing anion exchangers. The decrease in activity during the repeated use of Pd/C is related to the palladium wash-off from the catalyst surface. No such removal of the metal takes place in anion exchangers where palladium atoms are strongly bound to functional groups of the polymer matrix.

Thus, the hydrogenation of *p*-nitrobenzoic acid ethyl ester (I) should be carried out in ethanol at 45°C on AV-17-8-Pd or AN-1-Pd catalysts. These catalysts exceed the Pd/C system with respect to both selectivity and stability and provide for obtaining high-quality anesthesin without additional special purification.

EXPERIMENTAL PART

The experiments were performed with *p*-nitrobenzoic acid ethyl ester (reagent grade) purified by recrystallization from ethanol. Individual compounds II – VI were synthesized and purified by conventional methods [4]. The heterogeneous palladium catalysts supported on charcoal were prepared by a standard method [5]. The degree of purity of the target product (anesthesin), assessed by GC and nitritometric titration [6] and checked by determining the melting temperature (89 – 91.5°C), was not less than 99.5%.

Preparation of Palladium-Containing Anion Exchangers AN-1 and AV-17-8.

Anion exchanger conversion into the OH form. Anion exchanger AN-1 or AV-17-8 (10 g) was treated with 1 N hydrochloric acid (20 ml) in a 100-ml cone-shaped flask, after which the resin was separated by filtration and washed with distilled water until the filtrate showed no acid reaction. The washed anion exchanger was transferred into a 100-ml flask, poured with 60 ml of 1 N sodium hydroxide solution and kept with periodical stirring for 3 h. Then the resin was separated by filtration and washed with distilled water until the filtrate showed no acid reaction. Finally, the anion exchanger was sequentially washed with acetone (50 ml) and diethyl ether or ethanol (50 ml) and dried in air. If necessary, anon exchanger fractions of desired size can be obtained by crushing in a mortar and sieving via standard sieves.

Synthesis of potassium tetrachloropalladate. The anion exchanger based catalysts were prepared using potassium tetrachloropalladate prepared from 2 g of palladium chloride dissolved on heating in 50 ml of 0.1 N hydrochloric acid. To this solution were added 1.68 g of potassium chloride and the mixture volume was reduced by evaporation to approximately 1 ml. The precipitated golden bright crystals were

separated by filtration, washed with ethanol (20 ml) and ether (20 ml), and dried in air. Yield, 3.17 g (88% of the theoretical value).

Preparation of palladium-containing anion exchanger. A solution of potassium tetrachloropalladate (120.8 mg) in 10 ml of water was poured into a 50-ml flask containing 1 g of the ion exchanger in the OH form in 1 ml of water. The mixture was stirred with a magnetic stirrer for 1 – 2 h at 20 – 25°C. Then the catalyst was separated by filtration, washed with water (100 ml) and acetone (50 ml), and dried in air. Palladium content in the catalyst, 3.99 ± 0.01%. Catalysts with different metal concentrations were obtained similarly.

Catalyst activation. A weighed amount of the catalyst (10 g) was charged into an all-glass temperature-controlled reactor equipped with a stirrer. Upon adjusting the temperature at 45°C, the reactor was charged with 50 ml of ethanol and 0.5 g of sodium borohydride. While the mixture was intensively stirred, the reactor was purged with hydrogen for 60 min. Then the catalyst was separated by filtration and washed with water and acetone (50 ml). The ready-to-use activated catalyst is kept in acetone.

Determination of palladium in the catalyst. The content of palladium in a catalyst sample was determined by measuring the decrease in the concentration of tetrachloropalladate ions in the course of immobilization on the carrier. The concentration of tetrachloropalladate ions in the initial solution was determined spectrophotometrically. The measurements were performed on a Specord UV-VIS spectrophotometer at a wavelength of $\lambda = 280$ nm using 1 cm quartz cells. The salt concentration in a sample solution was determined using an optical density calibration plot constructed preliminarily for the same wavelength.

Analysis and Synthesis

Gas chromatography. The hydrogenation products were analyzed on a Model 3700 chromatograph equipped with a plasma ionization detector and a glass column (2000 × 3 mm). The column was filled with Lukopren G-1000 (5%) on Chromaton. Temperature regime: evaporator, 250°C; column, 200°C. Carrier gas, helium; gas flow rate, 1.6 liter/h. Sample volume, 0.1 – 0.5 μl; duration of analysis, 30 – 60 min. Internal standard, tridecane. The calibration coefficients were determined from preliminary analyses of artificial mixtures with preset compositions. The percentage content of each component was determined with respect to the internal standard and normalized to the calibration coefficient.

Hydrogenation process. An all-glass reactor with thermostat jacket, a magnetic stirrer, and a hydrogen purging facility was charged with catalyst under a layer of solvent and the system was activated for 20 – 30 min in a flow of hydrogen. Then a weighed amount of the substrate was introduced in a hydrogen flow and the reaction mixture was intensively stirred throughout the process at a constant rate of 900 – 1000 rpm and a hydrogen pressure of 98 – 103 kPa (~ 1 atm). The reaction rate was determined volumetrically (by measuring the hydrogen uptake) and analytically (GC of the reaction mixture samples). The kinetic curves were constructed with the GC data. The effective reaction rate constants for the catalytic hydrogenation process at low hydrogen pressure were calculated with an allowance for the partial pressure of solvent vapors.

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