ETHOXYACETANILIDE SYNTHESIZED BY REDUCTIVE ACETYLATION OF ETHOXYNITROBENZENE ON PALLADIUM CATALYSTS

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Phenacetin, or 4-ethoxyacetanilide (I), has been known for a long time and is used as an antipyretic, analgesic, and antiinflammatory drug [1], entering into a number of combined preparations such as citramon, asphen, and caficyl. However, the administration of phenacetin alone has been restricted because of side toxicity manifestations related to an admixture of *p*-chloroacetanilide present in the as-synthesized parent compound [2]. In this context, the search for new effective methods for the synthesis of compound I free of toxic impurities is still important.

There are several pathways to the target compound I. Most widely used are the two schemes of synthesis proceeding from phenol [3] and *p*-nitrochlorobenzene [4]. In both cases, a key stage is the reduction of *p*-ethoxynitrobenzene (II) to *p*-phenetidine (III). The latter compound is subsequently distilled in vacuum and acetylated with acetic aldehyde or a 80 % aqueous acetic acid. Finally, the reaction mass is poured into water and the precipitated technical-purity compound I is separated by filtration and recrystallized from water.

However, even these commercially adopted optimum schemes are not free of disadvantages. The main drawbacks are related to a large number of intermediate stages, each involving a certain loss of the main component and leading to reduced total yield of the target compound. The relatively low yield of the pharmacopoeial product is caused not only by the presence of impurities of the initial substances and intermediate products: an additional negative factor is the appearance of products of incomplete reduction of the nitro group. The amount and rate of formation of these products depend on the conditions of reduction of II, and (to an even greater extent) on the nature of the reducing agent.

The above drawbacks can be completely or at least partly eliminated using the proposed method of one-stage synthesis of I from from II, based on the reductive acetylation of II on palladium catalysts according to the following scheme:

$$\text{II} \xrightarrow[-2\text{H}_2\text{O},\,\text{CH}_3\text{COOH (or} - 3\text{H}_2\text{O)}]{\text{Catalyst},\,\text{H}_2,\,(\text{CH}_3\text{CO})_2\text{O (or 80\% CH}_3\text{COOH)}} \text{I}$$

The catalysts represented a heterogeneous supported Pd/C system and palladium-containing anion exchangers AN-1 and AV-17-8 (AN-1-Pd and AV-17-8-Pd, respectively). The high efficiency of the latter catalysts in reactions of the type under consideration (including hydrogenation of the nitro group without formation of products of incomplete reduction) was repeatedly demonstrated in the previous papers [5 – 7].

In order to optimize the reaction conditions, it was preliminarily established that the reductive acetylation of II proceeds in the kinetic region and is a first-order process with respect to the catalyst and a zero-order process with respect to the substrate.

Data on the reaction kinetics (Fig. 1) obtained by gas chromatography showed that the reductive acetylation of II to the target product I under selected conditions proceeds

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TABLE 1. Effective Reaction Rate Constants (K_{eff}, M/sec; ± 15 – 27%) and Yields of Phenacetin (I) for the Reductive Acetylation of *p*-ethoxynitrobenzene (II) on Various Palladium Catalysts in Ethanol*

Experiment No.	Pd/C		AN-1-Pd		AV-17-8-Pd	
	K_{eff}	yield, %	K_{eff}	yield, %	K_{eff}	yield, %
1	0.17	62.5	0.08	77.6	0.14	85.0
2	0.19	64.1	0.07	78.1	0.12	85.5
3	0.15	64.4	0.07	79.3	0.13	85.1
4	0.15	65.3	0.09	78.5	0.14	87.3
5	0.16	61.7	0.08	78.0	0.14	86.6
6	0.18	60.8	0.09	79.0	0.12	87.8
7	0.16	65.2	0.07	78.8	0.14	85.9

* Process conditions: solvent volume, 10 – 70 ml; acid or acetic anhydride concentration, 0.1 – 0.5 M; hydrogen pressure, ~1 atm; temperature, 45°C; catalyst weight, 0.4 g; Pd content, 4 wt.% (particle size, d = 0.075 – 0.192 mm); concentration of II, 0.1 – 0.8 M.

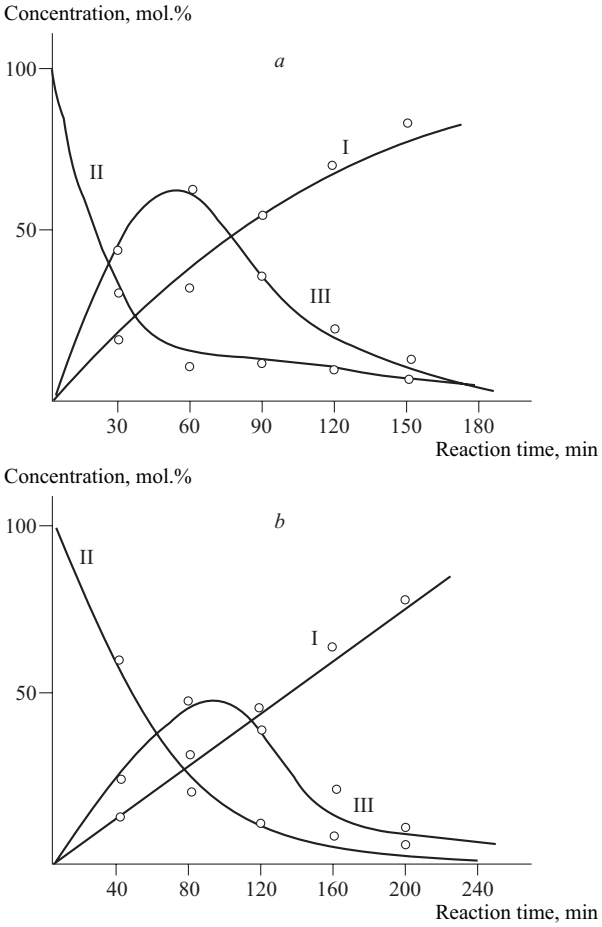

Fig. 1. Time variation of the concentration of the initial reagent II, the intermediate product III, and the target product I during the reductive acetylation on (*a*) Pd/C and (*b*) AV-17 – 8-Pd catalysts. The reaction conditions are indicated in Table 1.

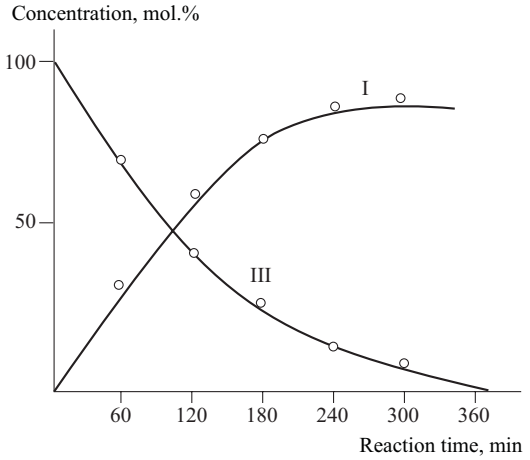

Fig. 2. Time variation of the concentration of the initial reagent III and the product I during acetylation on an AV-17 – 8-Pd catalysts. The process conditions are indicated in Table 1 (except for hydrogen).

without the formation of a significant amount of products of incomplete reduction of the nitro group. However, the accumulation of *p*-phenetidine (III) in the reaction mass indicates that a process other than hydrogenation of II is the limiting stage of the reductive acetylation process. The accumulation of III in a significant amount is due to the possibility of the acetylation reaction proceeding via two pathways: (i) reductive acetylation and (ii) acetylation of the primary amine III formed *in situ*.

In order to determine which of the two pathways dominates in a reaction mixture, we performed experiments on the acetylation of III in a hydrogen-free medium in the presence of various catalysts (Fig. 2). It was established that the rate of formation of product I, and especially the product yield from the equilibrium acetylation process, are significantly lower as compared to the case of reductive acetylation. Therefore, we may suggest that the first pathway is dominating.

The effective rate constants of the reaction of reductive acetylation of II to I, calculated per kilogram of catalyst, are presented in Table 1. As can be seen from these data, Pd/C is superior to the metal – polymer catalysts with respect to activity (K_{eff}), while offering a lower selectivity (percentage yield of I). Apparently, the relatively low selectivity of the reaction proceeding on the heterogeneous Pd/C catalyst is related to side reactions taking place in this system: alkylation of the amino group of III by the solvent (ethanol) and hydrolysis of the ethoxy group. Which of the two side reactions dominates depends on the process conditions. For example, the process of reductive acetylatrion in benzene, while excluding alkylation of the amino group, shows a decrease in the yield of I, which is evidence of a significant decrease in the selectivity (Table 2).

The variation of the activity of catalysts in response to a change of the solvent (ethanol versus benzene) is rather ambiguous. Indeed, the rate constants of the reaction on Pd/C in the two cases are virtually the same (Tables 1 and 2). In contrast, the rate of reductive acetylation on the metal – polymer

TABLE 2. Effective Reaction Rate Constants (K_{eff}, M/sec; ± 10 – 22%) and Yields of Phenacetin (I) for the Reductive Acetylation of *p*-ethoxynitrobenzene (II) on Various Palladium Catalysts in Benzene *

Experiment No.	Pd/C		AN-1-Pd		AV-17-8-Pd	
	K_{eff}	yield, %	K_{eff}	yield, %	K_{eff}	yield, %
1	0.15	58.4	0.06	70.2	0.08	80.0
2	0.14	59.6	0.05	70.5	0.08	80.1
3	0.13	57.7	0.05	70.8	0.07	80.5
4	0.14	58.0	0.06	73.3	0.07	81.7
5	0.14	58.5	0.05	71.8	0.07	83.8
6	0.15	60.0	0.05	71.6	0.08	80.5
7	0.13	59.3	0.06	72.7	0.08	81.4

* For the reaction conditions, see Table 1.

catalysts changes more significantly (drops) on passage from ethanol to benzene where the degree of polymer swelling is much lower as compared to that in ethanol [8]. With respect to stability, the catalyst systems reported here, as well as those studied previously [5 – 8], can be arranged in the following order: AV-17-8-Pd > AN-1-Pd > Pd/C

Thus, the synthesis of phenacetin (I) via reductive acetylation of *p*-ethoxynitrobenzene (II) 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 of operation. The proposed single-stage synthesis of I from II eliminates contamination of the target product by the main toxic impurity, *p*-chloroacetanilide.

EXPERIMENTAL PART

The preparation of catalysts, the reaction procedures, and the chromatographic conditions have been described in detail elsewhere [6]. The initial *p*-ethoxynitrobenzene (II) of reagent grade was additionally purified by recrystallization from ethanol. The degree of purity (98.7%) of the synthesized 4-ethoxyacetanilide (I) with m.p. = 134 – 136°C was evaluated by TLC and gas chromatography.

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