METHODS OF SYNTHESIS AND TECHNOLOGY OF DRUG PRODUCTION

DEVELOPING A CATALYST FOR HYDROGENATION OF p-NITROBENZOYL-L[+]-GLUTAMIC ACID

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The catalytic hydrogenation of p-nitrobenzoyl-L[+]-glutamic acid (I) is one of the stages in the synthesis of folic acid.

$$\underset{\text{I}}{O_2NC_6H_4C(O)HNCH(COOH)CH_2CH_2COOH} \xrightarrow{H_2(Ni)} \underset{\text{II}}{H_2NC_6H_4C(O)CH(COOH)CH_2CH_2COOH}$$

The pyrophoric Raney-Ni catalyst used at present for this purpose cannot be activated, and is not suitable for repeated use [7]. Doped catalysts for the hydrogenation of nitro groups of aromatic nitriles, dinitriles, etc. are known [9, 10]. By changing the structure of the catalyst by introducing other hydrogenating components into its composition, both an increase in catalytic activity and change in its strength characteristics are achieved. Catalysts containing Pt, Pd, Rh and rare earth elements have the highest activity [9, 13, 14].

The aim of the present work was to determine the optimal composition of the catalyst for hydrogenation of I. In selecting the hydrogenation catalysts of I, we studied doped catalysts containing Pd as the hydrogenating component. To lower the consumption of Pd, we studied the influence of the addition of Ni and for the most comprehensive application of the properties of the hydrogenating components and to prevent their penetration into the catalyst, we also studied the influence of the addition of Cr.

The investigations were carried out in a laboratory reactor (glass vessel with a rocking device) at a temperature of 50°C, in the presence of H_2, with continuous agitation (more than 350 rpm or rockings) up to the cessation of H_2 absorption. The yield of II was determined after crystallization, filtration, and drying of the product.

The samples of the catalyst were prepared by impregnating aluminum oxide with a hydrochloric acid solution of $PdCl_2$ and aqueous solutions of Ni and Cr salts, followed by activation in a H_2 current at 60°C. The content of the hydrogenating components in the catalyst was determined by atomic adsorption analysis.

To evaluate the influence of the catalyst components on the hydrogenating properties and selection of its optimal composition, we used mathematical experiment planning [1-6, 8, 11, 12]. As independent factors, we took the concentration of Cr (X_1), Pd (X_2), Ni (X_3) in the catalyst (in wt. %), as the output parameter (y) – the rate of hydrogenation (rate of consumption of H_2 in ml/min). The change intervals ($\Delta X_1 = 0.5$, $\Delta X_2 = 1.75$, $\Delta x_3 = 2$) and main levels ($X_{01} = 1.5$, $X_{02} = 2.25$, $X_{03} = 3$) were selected according to preliminary experiments. The planning was carried out according to a plan of complete factor experiment at two levels. The planning matrix and the experimental results are listed in Table 1.

The following regression equation was obtained from the experimental data:

$$\hat{y}=3.1-0.04\,x_1-0.23x_2+0.67x_3-0.37x_1x_2+0.82x_1x_3+0.29x_2x_3.$$

An incomplete quadratic equation was used as the regression equation to evaluate the influence of the interaction of factors in pairs.

A statistical treatment of the experimental results, carried out for the data of parallel measurements ($S_0^2 = 0.085$ for 5 experiments), showed that the dispersions of the

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TABLE 1. Experiment Planning Matrix and "Steep Ascent"

No. of expt.	X_0	Plan						Variable of state	
		X_1	X_2	X_3	X_1X_2	X_1X_3	X_2X_3	Y_E	$\hat{Y}$
1	+	+	+	+	+	+	+	3,11	4,28
2	+	—	+	+	—	—	+	4,58	3,38
3	+	+	—	+	—	+	—	6,00	5,48
4	+	—	—	+	+	—	—	1,43	2,5
5	+	+	+	—	+	—	—	1,85	0,72
6	+	—	+	—	—	+	—	2,00	3,09
7	+	+	—	—	—	—	+	1,33	2,5
8	+	—	—	—	+	+	+	4,60	3,40
"Steep ascent"									
9			1,65	5				3,71	4
10			1,05	7				4,38	7,36
11			0,45	9				4,7	0,237

experimental values are of the same type. The influence of the catalyst components on the rate of hydrogenation could be evaluated by checking the significance of the regression equation coefficients. The coefficients at x_1 was found to be insignificant, i.e., change in the Cr concentration in the catalyst inappreciably influences increase in the rate of hydrogenation. By increasing the concentration of the Ni and Pd compound in the catalyst, the rate of hydrogenation can be increased to 4.58 ml/min. Increase in the Cr content lowers the rate of hydrogenation to 3.11 ml/min. Simultaneous increase in the Cr and Ni concentrations also leads to decrease in the rate of hydrogenation to 1.85 ml/min. With increase in the Cr and Pd content in the catalyst, the rate of hydrogenation noticeably increases (the coefficient at x_1x_3 is equal to 0.82) to 6 ml/min. However, increase in the Cr content in the catalyst is not permitted, since it leads to washing out of chromium into the catalyzate and deterioration in the quality of the product. Therefore, in optimization of the catalyst composition, the influence of the Ni and Pd content in the catalyst on the rate of hydrogenation was taken only into account; the concentration of Cr was kept constant. Checking the regression equation obtained according to the Fischer criterion showed that it is inadequate ($F_p > F_t$ at $f_{ag} = 1$, $f_0 = 4$, $g = 0.05$). For an adequate description of the process studied, a second order regression equation must be used, which involves carrying out additional experiments. To obtain an adequate description, a new plan with transfer of the plan center to the extremal point can be compared with the best value of the hydrogenation rate, while the variation intervals can be decreased proportionally to an absolute value of the regression coefficients [1, 2, 8]. Repeated production of a planning matrix involves appreciable expenditure for synthesis and analysis of the catalyst samples. Therefore, optimal conditions were investigated by the inadequate model [2]. To determine optimal values of the content of the catalyst components, the method of "steep ascent" (with spacings of −0.6 for X_2 and 2 for X_3) was used.

The experimental checking of the catalyst samples with compositions obtained in carrying out the "steep ascent" spacings (experiments No. 9-11) showed that the rate of hydrogenation in experiment No. 10 (7.36 ml/min) is higher than that obtained in producing the planning matrix.

The following optimal composition of the catalyst was found (in wt. %): Ni 7, Pd 1.05.

Experimental hydrogenation of I at 50°C and at atmospheric pressure using a catalyst with optimal composition and Raney-Ni showed that with the former catalyst the yield can be increased by 5%, compared to that with Raney-Ni, and the time of hydrogenation can be shortened by a factor of more than 2.

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RECTIFICATION PURIFICATION OF INTERMEDIATES OF THE MANUFACTURE OF HEXENAL ACID

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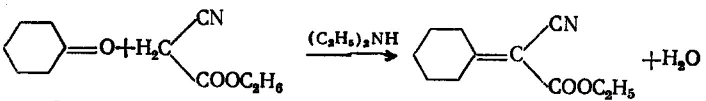
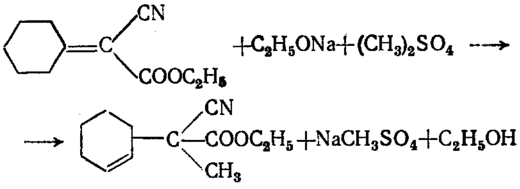
The starting materials for obtaining hexenal acids are cyclohexanone and cyanoacetic ester. In the presence of catalytic amounts of diethylamine, cyclohexylidenecyanoacetic ester (C-ester) is formed from them.



I II C-ester

After drying and purifying C-ester by distillation under vacuum it is passed on to the stage of alkylation with dimethyl sulfate in the presence of sodium ethylate.



M-ester

Methylcyclohexenylcyanoacetic ester (M-ester), purified by distillation under vacuum, was condensed with dicyandiamine with the formation of hexenal acid [1]. Distillation under vacuum (6.7-40.0 GPa) of C- or M-ester in equipment which contained a column with a Raschig ring and a packing of height 2 m made it possible to obtain a C-ester fraction with a content of main substance up to 92-93 wt. % (content of main substance in the crude was about 70 wt. %) and a fraction of M-ester differing little from the initial crude material (68-78 wt. %). The use of this M-ester in the synthesis of hexenal acid led to a reduction in the quality and yield of the desired product.

The need therefore arose for a rectification purification of C- and M-esters in manufacture.

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