METHODS OF SYNTHESIS AND TECHNOLOGY OF DRUG PRODUCTION

KINETICS OF HYDROGENATION OF 2-METHYL-3-NITRO-4-METHOXYMETHYL-5-CYANO-6-CHLOROPYRIDINE, AN INTERMEDIATE IN THE SYNTHESIS OF VITAMIN B_6.

II. INVESTIGATION OF HYDROGENATION ON Pd/C IN DILUTE HYDROCHLORIC ACID

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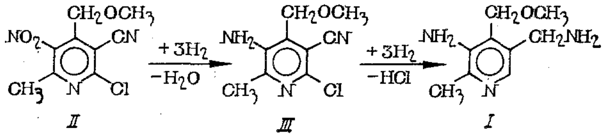
As a result of investigating the influence of various factors in the catalytic properties of Pd/C in aqueous hydrochloric acid medium the optimal catalyst was found for the synthesis of 2-methyl-3-amino-4-methoxymethyl-5-aminomethylpyridine (1) [1]. In this work it was noted that deviation from optimal conditions or use of an insufficiently active catalyst led to the appearance in the hydrogenation product of undesirable contaminants, namely hydrogenation intermediates or side products of 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (II).

The proposed mechanism of hydrogenation of (II) may be represented as two sequential stages: reduction of the nitro group of (II) and then hydrogenation of the cyano group with simultaneous hydrogenolysis of the C—Cl bond at position 6:



The possibility of forming (III) was confirmed by synthesizing 2-methyl-3-amino-4-alkoxymethyl-5-aminomethylpyridines through the corresponding 2-methyl-3-amino-4-alkoxymethyl-5-cyano-6-chloropyridines [2-5]; however, there is no other information on intermediate or side products of the hydrogenation of (II).

TABLE 1. Characteristics of Industrial Samples of (II) in the Hydrogenation Reaction on Optimal Catalyst under Optimal Conditions

Sample	Activity		Final catalyst characteristics		Yield I, %
	$A_{1/2}$	A_c	w_k	$\Delta\varphi_k$	
	liter/(g· h)		ml/min	mV	
Chromatographically pure	104,8	55,8	0,27	—5,6	99,5
No. 1	82,6	52,7	0,26	—4,0	99,8
No. 2	83,1	45,3	0,27	—4,0	99,2
No. 3	72,0	39,5	0,27	—3,2	99,8
No. 4	66,5	35,8	0,25	—7,2	99,7
No. 5	66,1	33,2	0,27	—4,8	98,0
No. 6	63,7	29,0	0,26	—4,0	99,8

Note. $A_{1/2}$ and A_c are activities referred to half and complete conversion of (II) into (I). W_k and $\Delta\varphi_k$ are the reaction rate at the end of hydrogenation and the corresponding change in saturation potential of the catalyst with hydrogen under these conditions.

All-Union Scientific-Research Institute for Vitamins, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 13, No. 2, pp. 60-68, February, 1979. Original article submitted July 13, 1978.

TABLE 2. Hydrogenation of Cyanopyridines (2.07 mole) on 4% Pd/C-OU-A (Pd 0.00366 g) in Hydrochloric Acid (0.8 ml concentrated acid in 14.4 ml water) at 34°C

Compound	W_{max}, ml/min	$\Delta\varphi_{max}$, mV	Final characteristic		V_{com}/V_{theor}	A_M^* liter/(g · h)	Yield of final product, %
			W_K, ml/min	$\Delta\varphi_K$, mV			
II	11,0	83,2	0,27	—7,2	1,09	71,0	99,5
III	8,0	43,2	0,25	—4,0	1,11	78,8	99,6
IIa	7,0	96,5	0,6	8,0	1,00	38,1	—
IV	9,5	70,4	0,3	—12,0	1,12	35,0	—
V	6,0	47,2	0,26	13,6	0,80	10,1	—
VI	8,5	57,5	0,35	20,0	1,00	27,8	—
VIII	6,5	70,5	0,25	0,0	1,11	55,4	—

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*A_M is molar activity of cyanohydrins referred to V_{theor}.

Between them molecules (II) and (III) contain several functional groups able to undergo various conversions under conditions of hydrogenation (hydrolysis, hydrogenolysis); consequently the present work was undertaken with the aim of identifying the compounds formed in the hydrogenation process and of a quantitative assessment and investigation of the reasons for their appearance. Furthermore we have determined the influence of these compounds and possible contaminants in (II) on the activity of Pd/C and have clarified the possibility of using the spent catalyst.

1. Influence of Contaminants in (II) and Substances Formed in the Hydrogenation Process. For the assessment of the influence of contaminants on the hydrogenation kinetics of (II), technical samples of (II) were used of mp 72-74°C differing in external form with a 98% content of main product, sulfur < 0.12%, and organic contaminants < 1% of which 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-hydroxypyridine (IV) and 2-methyl-4-methoxymethyl-5-cyano-6-chloropyridine (V) were identified. The activity of Pd/C on hydrogenating these samples of (II) (Table 1) varied within wide limits and was 52.0-94.2% of the activity for a chromatographically pure sample. However, its selectivity in this was not altered and the yield of (I) was not less than 98%. A final characteristic of the catalyst for all the samples investigated was its stability and suitability for the normal course of the process [1].

To clarify the influence of individual contaminants which may be present in initial (II) or are formed in the process of hydrogenation, the kinetics of the hydrogenation of (II) and its structural isomer 2-methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine (IIa) were studied; also studied were the product of incomplete hydrogenation (III); (IV) and (V), which are possible contaminants in (II); 2,4-dimethyl-3-nitro-5-cyano-6-chloropyridine (VI), as a result of the hydrogenation of which 2,4-dimethyl-3-amino-5-aminomethylpyridine (VII) was formed, which is a side product of the hydrogenation of (II); and 2,4-dimethyl-5-cyano-6-chloropyridine (VIII), the starting material for 2,4-dimethyl-5-aminomethylpyridine (IX), which is the deamination product of (VII) (Fig. 1).

The greater activity of Pd/C was shown in the hydrogenation of (III), i.e., the process of hydrogenation was not limited by the rate of hydrogenation of the intermediate compound. However, all the remaining compounds investigated may reduce the rate of hydrogenation of (II) since they may be arranged in an activity series in the sequence (III) > (II) > (VIII) > (IIa) > (IV) > (VI) > (V) (Table 2).

The reactivity of the studied nitrocyanopyridines in the process of reducing the nitro group changes in the series (II) > (IV) > (VI) > (IIa), and evidently the deciding factor in the case in question is the nature of the substituent in the para position to the ring nitrogen.

The reactivity of cyanopyridines in the hydrogenation of the cyano group is different. For (VIII), where a methyl group is found in the para position to the ring nitrogen, it is five times greater than for (V) with a methoxymethyl substituent.

It is evident from Fig. 1 that the potentiometric curves are a reflection of the kinetics of hydrogenation of the cyanopyridines and may be used for checking the process. The potentiometric curve for (II) was located in the region of most positive values of potential compared with the hydrogenation of the remaining cyanohydrins. This may be the result of the large proportion of reactive hydrogen. For (IV) it indicates the rapid adsorption displacement of the reaction products by hydrogen depending on the extent of reduction of the nitro group. It is possible to form an opinion on the maximum deactivating action of (V) and (VII) (hydrogenation products of VI) from $\Delta\varphi_K$ (it is more positive by far than φ_{H_2}).

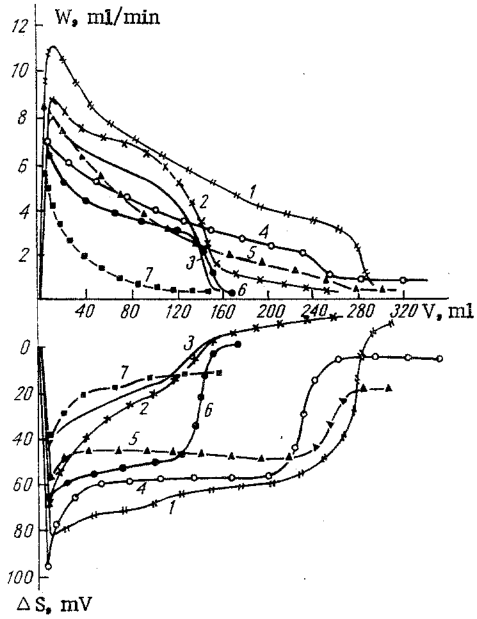

Fig. 1. Kinetics and potentiometric curves for the hydrogenation of cyanopyridines on 4% Pd/C-OU-A. 1) (II); 2) (IV); 3) (III); 4) (IIa); 5) (VI); 6) (VIII); 7) (V). Here and in Fig. 2 conditions of reaction were Pd 3.66 · 10^{-3} g, concentrated hydrochloric acid 0.8 ml, water 14.4 ml, 35°C.

2. Composition of Hydrogenation Mixture and Proposed Mechanism of Forming Hydrogenation Products of (I). The following compounds, in addition to (I), were detected and identified in the composition of technical samples: products of incomplete hydrogenation (III) and 2-methyl-3-amino-4-methoxymethyl-5-cyanopyridine (X)*, (VII), luminescent contaminants from hydrolysis products of (III) and (X): 2-methyl-3-amino-4-methoxymethyl-5-cyano-6-hydroxypyridine (XI) and presumably 2-methyl-3-amino-4-methoxymethyl-5-carboxy-6-hydroxypyridine (XII) or the lactone (XIIa) corresponding to it, and 2-methyl-3-amino-4-methoxymethyl-5-hydroxymethylpyridine (XIII), with traces of contamination by 2-methyl-3-amino-4-methoxymethyl-5-formylpyridine (XIV). Compound (XIII) (< 0.5%) was detected in all samples of hydrogenation product irrespective of the catalyst activity and hydrogenation conditions. Its presence indicated the occurrnce of a side reaction of hydrolysis of the intermediate 2-methyl-3-amino-4-methoxymethyl-5-iminomethylpyridine (XV) to (XIV) by reduction of which (XIII) was formed [8].

Hydrogenolysis of the ether linkage leading to the formation of (VII) is a consequence of the catalytic action of palladium catalyst in acid medium. The quantity of this contaminant grew with increasing hydrogenation time since the process did not stop on absorption of the amount of hydrogen theoretically required but continued further although at a comparatively low rate (10-30 times less than initially).

The presence, in the hydrolysate, of products of incompletely reduced (II) may indicate either inadequate activity of the catalyst (on maintaining optimal conditions for the process) or, when using active catalyst, disturbance of the optimal conditions for hydrogenation. An increase in the temperature of hydrogenation and acidity of the medium above optimal intensified the hydrolysis of (III) and (X) which led to deactivation of the catalyst and aided accumulation of (XI, XII) and other luminescent contaminants in the hydrogenation product.

Comparative characteristics of crude samples of the hydrogenation product are given in Table 3. Data for samples 1 and 2 were obtained under nonoptimal conditions of hydrogenation with a check on the end of the reaction at the end of hydrogen absorption. Data for sample 3 were obtained under optimal conditions with a potentiometric method of checking.

On the basis of the material stated and data on the synthesis in the opposite manner of appropriate compounds, the following scheme may be proposed for the formation of (I) and the intermediate and subsidiary products of hydrogenation of (II):

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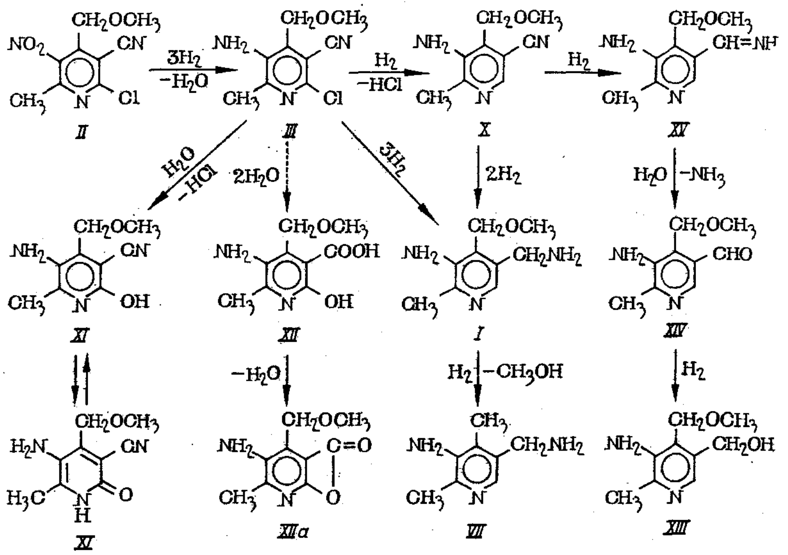
*Compound (X) was isolated by preparative chromatography on silica gel L 40/100 from the mixture obtained on hydrogenation of (II) on Raney nickel catalyst in ethyl alcohol.

TABLE 3. Characteristics of Crude Samples of (I)

Sample number	I	III	VII	XI	Other contaminants
1	79,43	13,1	6,51	0,86	0,1
2	81,50	—	10,89	—	7,61
3	99,8	—	—	—	0,2

Note. Increase of temperature above optimal leads to the appearance of (III) and (XI) in the hydrogenation product. Increase in hydrogenation time above optimal leads to accumulation of (VII) in the hydrogenation mixture.



3. The Possibility of Using Spent Catalyst. No more than 3.9% of the catalyst mass was organic residue – this was a mixture of unreacted (II) and (III). This residue remained on the catalyst after removing it from the solution and washing with water when using active catalyst under the optimal hydrogenation conditions. When using insufficiently active catalyst and on disturbing the optimal regimen for the hydrogenation of (II) the content of organic residue varied from 8 to 25%.

Since the catalyst does not change its activity in the presence of (III), it is then possible to return the organic residue taken from the catalyst back into the process.

The regenerated catalyst (washed with methyl alcohol and chloroform) was tested in the process of hydrogenating (II). Extraction of spent catalyst with chloroform was more effective for the complete removal of (II) and (III) but caused significant deactivation of the catalyst and made it unsuitable for hydrogenation (II). The relative activity of catalysts treated with methanol was 40.2-76.5% of the initial activity and the yield of (I) from 95.6 to 99.9% was determined by the catalysts/(II) ratio and by the percentage content of Pd on the support (Table 4).

The potentiometric method of checking these catalysts was also representative. For catalysts the hydrogenation potential of which did not reach φ_{H_2} in this solution, the yield of (I) was less and the product (III) of incomplete hydrogenation appeared in the hydrogenation product.

Thus it is possible to use both the organic residue and the actual spent catalyst after regeneration.

4. The Deactivating Action of (I) and Adsorption Characteristics of Pd Catalyst. As already mentioned, addition of (III) to (II) did not in practice affect the catalytic properties of Pd/C but introduction of (I) caused an appreciable drop in catalyst activity (Fig. 2). A second portion of (II) using the same portion of catalyst was hydrogenated at a rate 3.5 times lower and incompletely (70% of theory). In the products of hydrogenation,

TABLE 4. Characteristics of Regenerated Samples of Pd/C

Sample No.	Mass, g	Pd catalyst, % (on carbon)	Wt. of Pd, g × 10^{-3}	Activity		Yield I, %	Final characteristic of catalyst		Relative activity, %	Contaminants
				$A_{1/2}$ liter/(g·h)	A_c		W_K, ml/min	$\Delta\varphi_k$, mV		
1	0,1	6,79	6,8	30,0	13,7	95,6	0,4	24,8	76,5	III, XIII
1	0,2	6,79	13,6	28,2	13,2	99,0	0,26	2,4	73,7	XIII
1	0,4	6,79	27,2	25,5	6,7	99,9	0,25	—4,8	37,4	XIII
2	0,1	8,48	8,5	18,6	8,5	96,8	0,3	2,4	47,5	III, XIII
3	0,15	12,7	19,0	17,6	9,1	99,0	0,25	—0,8	64,1	XIII
4	0,15	8,45	12,6	14,1	7,2	99,9	0,26	—3,2	40,2	XIII

Note. Reaction conditions: 0.5 g (II), 0.8 ml conc. hydrochloric acid, 14.4 ml water, 35°C.

(III) was detected in significant amounts and the yield of (I) was less than 50%. Thus deactivation of the catalyst by the required hydrogenation product took place.

Starting from the stepwise procedure for the hydrogenation of (II) and taking advantage of the Langmuir equation for uniformly heterogeneous surfaces [6] it is possible to calculate the ratio of the adsorption coefficients of the initial, intermediate, and final products and the hydrogenation rate constants. The results of calculations for various catalysts and conditions of carrying out the process are given in Table 5.

It is seen from Table 5 that the ratio of the adsorption coefficients of (I), (II), and (III) depends on the state of the catalyst and the hydrogenation conditions. All the relationships obtained previously [1] of the change of activity on changing the state of the catalyst or the hydrogenation conditions were also characteristic for the values of rate constants. For example, K_1 and K_2 for Pd/C-OU-A was greater than for Pd/C-OU-B and AG-5. The drop in activity of catalysts with increase in percent Pd correlated with the reduction in rate constants for the first and second parts of the process (from 5 to 10.3%).

The ratio of adsorption coefficients has acquired great importance for assessing the selectivity of catalysts. The greatest value of b_{III}/b_I was a characteristic of catalysts giving the greatest yield of (I). Reduction of this ratio led to the fact that (I) became competitively available for the adsorption displacement of (III) into the solution preventing its further conversion. Hence the presence of the product of incomplete hydrogenation was a characteristic of insufficiently active catalysts.

A reduction in the amount of water and acid or deviation of temperature from optimal caused a reduction in b_{III}/b_I which indicated displacement of the adsorption equilibrium $I_{solution} \rightleftharpoons I_{surface}$ in the direction of the surface.

Thus the appearance of (III) in the hydrogenation product is a consequence of the increase in adsorptivity of (I) and is accompanied in the majority of cases by a drop in the activity of the system.

Hence the conclusion may be drawn that the conditions most favorable for hydrogenation will be those increasing the solubility of (I) and not causing thereby a reduction in the adsorption ability of (II) and of its intermediate hydrogenation products.

EXPERIMENTAL

Thin-layer chromatography was carried out on Silufol UV-254 plates in the systems: a) acetone–dioxane–ammonia (9 : 9 : 2), b) hexane–acetone (2 : 1), c) butanol–ethanol–5% aqueous ammonia–acetic acid (10 : 10 : 10 : 1), and d) methyl ethyl ketone–dioxane–ammonia (9 : 9 : 2).

Detection of spots was effected in UV light and by treatment with a 0.5% solution of ninhydrin in acetone.

UV spectra were taken on Specord UV-Vis and SF-4A instruments, IR spectra (suspension in Nujol) were taken on a UR-10 instrument (DDR).

2-Methyl-3-amino-4-methoxymethyl-5-cyano-6-chloropyridine (III) [7]. To (II) (2.65 g) was added Raney nickel catalyst (4 g) and methyl alcohol (70 ml). Air was displaced from the system and the mixture was hydrogenated with stirring at room temperature for 2.5 h until absorption of 1.05 times the theoretical volume of hydrogen. The catalyst was removed from the hydrogenation product and washed with methanol. The filtrate was added to the hydrogenation product and evaporated in vacuum until the appearance of the first

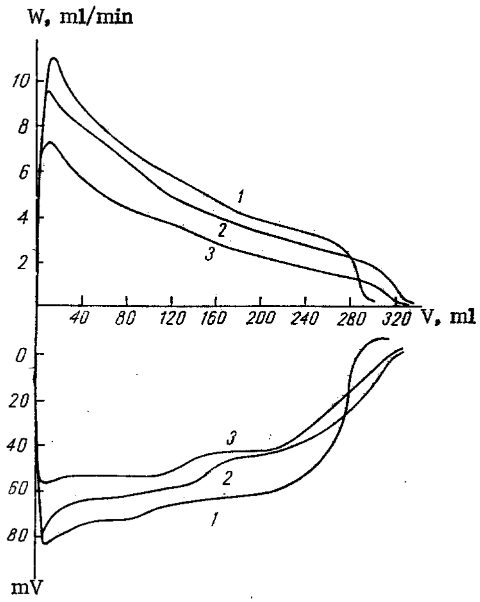


Fig. 2. Kinetic and potentiometric curves for hydrogenating 0.5 g (II) on 1) 4% Pd/C-OU-A with added 2) 0.05 g (III) and 3) 0.064 g (I).

crystals. The precipitated solid was separated, washed with cold alcohol, and recrystallized. Compound (III) (2.1 g: 90.5%) was obtained having mp 120-121°C, chromatographically homogenous in systems a and b.

IR spectrum, cm^{-1}: 3350, 3450, 2220, 1560, 1630, 1295, 1245, 1090. UV spectrum λ_{max}, nm(ε): (in alcohol) 211 (19770), 266 (10970), 340 (5715); (in chloroform) 264.4 (5627), 331 (3408); (in 0.1 N hydrochloric acid) 210 (2020), 264 (9560), 331 (5005). Found, %: C 50.85; H 4.72. $C_9H_{10}ClN_3O$. Calculated, %: C 51.06; H 4.76.

2-Methyl-3-amino-4-methoxymethyl-5-cyano-6-pyridone (XI) Hydrochloride. Compound (III) (0.4 g) was boiled with concentrated hydrochloric acid (4 ml) for 4 h. After cooling, the precipitated solid was separated and washed with a small volume of cold absolute ethyl alcohol. A product (0.27 g: 62.4%) of mp 249°C was obtained. The compound possessed a bright green fluorescence and was chromatographically homogeneous in systems a and c.

IR spectrum, cm^{-1}: 2580, 2220, 1770, 1660, 1590, 1560, 1510, 1330, 1115, 1090. UV spectrum, λ_{max}, nm (ε): (in 0.1 N hydrochloric acid) 213 (14280), 335 (8970). Found, %: C 46.71; H 5.39. $C_9H_{11}N_3O_2 \cdot HCl$. Calculated, %: C 47.05; H 5.27.

In a mixing test with a sample isolated by preparative chromatography from a crude hydrogenation product no depression of melting point was observed. UV and IR spectra were identical.

2,4-Dimethyl-3-amino-4-methoxymethyl-5-aminomethylpyridine (VII) Dihydrochloride. To a suspension of activated carbon (0.8 g) in distilled water (80 ml) was added with stirring a solution of palladous chloride in concentrated hydrochloric acid (0.2 g in 2 ml). Air was displaced from the system and the catalyst was reduced with stirring for 30 min. Then (VI) (3 g) was added and was hydrogenated for 4.5 h at room temperature until absorption of 1.05 times the theoretical volume required. The catalyst was removed and washed with water. The obtained filtrate was added to the hydrogenation product and evaporated to dryness in vacuum. After recrystallization from ethyl alcohol (VII) (1.87 g: 59.0%) was obtained having mp 255-256°C, chromatographically homogeneous in system a.

UV spectrum, λ_{max}, nm (ε): (in 0.1 N hydrochloric acid) 212 (20960), 256.5 (5240), 312 (6650). Found, %: C 42.84; H 5.84; N 18.74. $C_8H_{13}N_3 \cdot 2HCl$. Calculated, %: C 42.92; H 5.97; N 18.92.

2-Methyl-4-methoxymethyl-5-aminomethylpyridine (XVI) Dihydrochloride. The synthesis of (XVI) was carried out in a similar manner to that of (VII) using (V) as starting material. Yield was 67.8% of mp 125-127°C. Found, %: C 45.45; H 6.69; N 11.49; Cl 29.23. $C_9H_{14}N_2O \cdot 2HCl$. Calculated, %: C 45.25; H 6.74; N 11.71; Cl 29.65.

TABLE 5. Dependence of the Adsorption and Kinetic Characteristics of Pd/C on Its Nature and on the Conditions of Hydrogenation of (II) (0.5 g)

Varied parameter	Reaction conditions	b_{II}/b_{III}	b_{III}/b_I	K_1 ml/min	K_1 ml/min
Carbon					
OU-B	5 % Pd/C, 0,0077 g Pd, H_2O — 11,8 ml HCl — 0,45 ml, 35° C	19,4	3,4	9,7	5,1
OU-A		13,6	4,9	10,6	7,1
AG-5		18,6	4,7	4,5	2,4
Quantity of water, ml					
11,8	3,5% Pd/C 0,00036 g Pd, HCl — 0,8 ml, 35° C	7,2	3,4	6,6	3,9
14,4		8,3	5,2	8,6	4,8
% Pd on carbon:					
2,0	Pd—0,0077 g, H_2O—11,8 ml, HCl—0,8 ml	8,9	2,3	14,1	8,8
5,0		12,3	5,2	13,1	8,9
10,3		7,9	17,4	7,7	3,9
Reaction temperature					
25	4% Pd/C, 0,0036 Pd H_2O—14,4 ml, HCl—0,8 ml, active addition 0,01 g	7,4	4,1	6,7	4,4
35		9,0	18,8	8,2	3,9
45		3,3	1,7	5,6	1,6
Acidity of medium (amount of hydrochloric acid, ml):					
0,45	5% Pd/C 0,0077g Pd, Carbon OU-A, H_2O — 11,8 ml	17,7	2,9	12,3	8,2
0,80		12,3	5,2	13,1	8,9

Note. K_1 and K_2 are hydrogenation rate constants for stages I and II respectively.

2-Methyl-3-amino-4-methoxymethyl-5-hydroxymethylpyridine (XIII) Hydrochloride. A sample isolated after preparative chromatography on silica gel* and recrystallized three times from alcohol had mp 196-197°C. According to literature data [9], (XIII) has mp 197-198°C. Found, %: C 49.07; H 6.97; N 12.91; Cl 16.25. $C_9H_{14}N_2O_2 \cdot 2HCl$. Calculated, %: C 49.43; H 6.91; N 12.81; Cl 16.21. IR spectrum, cm^{-1}: 3460, 3360, 3200, 2690, 1615, 1540, 1275, 1100. PMR spectrum (D_2O), ppm: 8.27 (6-H, singlet); 4.9 (4-CH_2O, singlet); 4.85 (5-CH_2O, singlet); 3.55 (4-OCH_3 singlet); 2.7 (2-CH_3, singlet).

Thin-Layer Chromatography with Subsequent Spectrophotometry. For quantitative determination of the composition of crude (I) (obtained by evaporation of a hydrogenation product in vacuum) thin-layer chromatography by the ascending method was used (Silufol plates with solvent system a) with subsequent elution of the separated products from definite adsorption zones. Rf: (I) 0.48-0.50; (II) 0.98-0.99; (III) 0.93-0.94; (X) 0.76-0.78; (XIII) 0.62-0.64; (VII) 0.42-0.44; (XI) 0.23-0.25; (XVI) 0.57-0.59; (XII) 0.15-0.16. Chloroform was used as eluent for removing (III) and 0.1 N hydrochloric acid for (I, VII, and XI). Eluates were filtered through a No. 4 glass filter and the volume made up to 100 ml for (I), 10 ml for (III), 4 ml for (XI), and 10 ml for (VII). The optical density of the filtrates was measured relative to a reference eluate obtained from a clear zone on a similar Silufol UV-254 plate at the height of the appropriate spot, on an SF-4A spectrophotometer in cuvettes of thickness 1 cm at wavelengths of 325 nm for (I), 331 nm for (III), 335 nm for (XI), and 312 nm for (VII). Each determination was the mean result of three measurements. Relative error was 5%.

Determination of the Percentage Content of Organic Residue on Spent Catalyst. Spent catalyst (10 g), previously washed with water, was boiled in methanol or chloroform (100 ml) for 30 min. The catalyst was filtered off. Extraction was repeated twice. The percentage content was determined from the difference in mass of the spent catalyst before extraction and after it.

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INVESTIGATION OF PROCESSES FOR REGENERATING BUTYL ACETATE IN PENICILLIN MANUFACTURE

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Butyl acetate (BA) is the most widely consumed solvent in antibiotic manufacture [1]. A significant amount of it is used in obtaining salts of penicillin. In the last ten years BA has been used as the main solvent in this area due to the growth in manufacture of semisynthetic penicillins and also to the continuing manufacture of penicillin as a pharmacological preparation.

In spite of the fact that the process of regenerating BA on an industrial scale has already been carried out for some time, there are no data up to the present permitting an objective assessment of the technical and economic features of the various methods of regenerating this solvent.

The present study was undertaken with the aim of filling the indicated gap, including the development of the optimal technological scheme for regenerating BA allowing for the actual resources of plants.

In penicillin manufacture, spent BA to be regenerated is mainly a mixture of BA, butanol (up to 10%), and water (up to 3%) containing contaminants the composition of which will be indicated below.

According to literature data [2, 3], the liquid–vapor phase diagram for the system m-butyl acetate–butanol–water is characterized by the presence of three binary azeotropes with boiling point minima and one ternary heteroazeotrope. Consequently complex equipment is required for the isolation of individual components from the ternary mixture mentioned. This consists of several continuous-action rectification columns.

As experiments at the plants showed, it is possible to use regenerated BA containing up to 10% butanol and up to 2.5% water for the extraction of penicillin without endangering the yield or quality of the desired product.

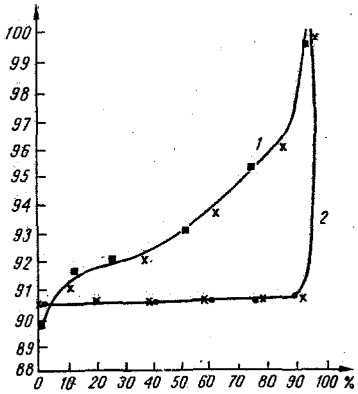

Fig. 1. Change of solvent vapor temperature on regenerating BA by the methods of azeotropic distillation and rectification. 1) Distillation; 2) rectification.

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