ISOAMYL ALCOHOL AS A RAW MATERIAL FOR THE PRODUCTION OF CERTAIN DRUG PREPARATIONS

V. S. Gershanovskii, Yu. G. Zelinskii,
A. V. Luk'yanov, V. P. Pakhomov,
and Ya. D. Zel'venskii

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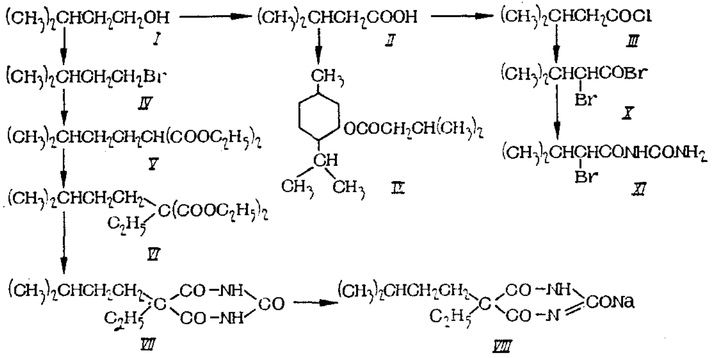
Isoamyl alcohol (I) is the initial raw material for the production of a number of drug preparations: barbamil (VIII), validol (IX), bromisoval (XI), corvalol, and amyl nitrite [1-2].



The industrial yields of some of them, especially VIII, IX, and XI, are insufficiently high; the main cause of this is the use of "fermentation" isoamyl alcohol, containing substantial amounts of impurities of optically active amyl alcohol (1-2-methylbutanol) as a raw material.

The results of our study of the composition of industrial samples of isoamyl alcohol by the method of gas-liquid chromatography are presented in Table 1. The different composition of "fermentation" isoamyl alcohol is determined by the source of origin of the potato spirits [3-4]. Thus, the raw material used for the synthesis of VIII, IX, and XI is chiefly a mixture of two alcohols (an average of 70% isoamyl and 30% optically active amyl), and therefore processes of the corresponding isomers occur during the synthesis, resulting in the necessity of purification of the preparations obtained.

TABLE 1. Composition of Industrial Samples of Isoamyl Alcohol

Sample of "fermentation" isoamyl alcohol	Content of alcohols (wt. %)					
	isoamyl	optically active amyl	n-butyl	isobutyl	isopropyl	ethyl
Technical						
1	48,81	41,71	7,85	1,128	0,27	0,22
2	72,1	27,9	—	—	—	—
3	71	27	2	—	—	—
Reagent						
4	72,95	27,05	—	—	—	—
5	70,5	29,5	—	—	—	—

We studied the influence of the quality of isoamyl alcohol on the yield of VIII. For this purpose we used specially prepared mixtures of isoamyl and optically active amyl alcohols (Table 2). In the synthesis of VIII we used the existing industrial methods.

Isoamyl alcohol, containing 47% of the basic substance, leads to the formation of isoamyl bromide (IV), in which the amount of 1-bromo-2-methylbutane is 27.8% and the amount of other amyl bromides is 5% (chiefly n-butyl bromide). With increasing content of isoamyl alcohol, the amount of 1-bromo-2-methylbutane decreases (the use of 97% alcohol leads to the formation of IV containing a total of 2% of the isomeric bromide); in this case the yield of the total bromides

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S. Ordzho-kidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 7, No. 4, pp. 36-40, April, 1973. Original article submitted June 16, 1972.

TABLE 2. Influence of an Admixture of Optically Active Amyl Alcohol on the Yield of Barbamil

Comp. of initial alcohol		Isoamyl bromide (IV)		Isoamylmalonic ester (V), yield (%), calc. on the basis of the initial bromides	Ethylisoamylmalonic ester (VI)		5-Ethyl-5-isoamylbarituric acid (VII)		
isoamyl alcohol (1) (wt. %)	optically active amyl alcohol (wt. %)	content (wt. %)	yield of total bromides, calc. on the basis of the total of initial alcohols (%)		content (wt. %)	yield of 100% VI, calc. on the basis of V (%)	yield of VII (%)		mp (deg)
							calc. on the basis of 100% VI	calc. on the basis of initial alcohols	
47	50*	67	64	57,7	79,6	63	80,7	18,8	148—150**
70,5	29,5	82	78,2	68,8	86,5	71	87	33,2	152—154
87	13	92	83	75,6	94,7	80,9	93,8	47,6	153,5—154,5
94,8	5,2	92	—	—	—	—	—	—	—
97,2	2,8	97,5	91	82,5	100	82,6	92,6	57,4	155—157

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* Contains 3% homologous alcohols (chiefly n-butyl).

† After purification by recrystallization from 50% isopropyl alcohol.

Note. The composition of I, IV, V, and VI was determined by gas chromatographic methods.

TABLE 3. Composition of Various Samples of Isovaleric Acid (II)

Sample II	Acid	II	Methylethylacetic acid	Other impurities
		% by weight		
1	Reagent grade	81,13	18,40	0,47
2	Pure	79,98	18,15	1,87
3	"	79,49	18,05	2,46
4	Technical	73,65	16,70	9,65
5	Synthetic	97,96	2,04	—

(calculated on the basis of the total initial alcohols) is substantially increased. Successive alkylation of malonic ester with compound IV, containing various amounts of 1-bromo-2-methylbutane, and with ethyl bromide leads to the formation of ethylisoamylmalonic ester (VI), in which various amounts of the isomeric ethyl(2-methylbutyl)malonic ester are present. In VI, produced from 47% isoamyl alcohol, there is 20.4% of the isomeric compound, whereas from 97% alcohol VI with a 100% content is obtained. Amytal acid (VII) is formed from various samples of VI with different yields. The larger the amount of optically active amyl alcohol, the lower the yield of VII; moreover, there is a decrease in the melting point of VII, since its isomer melts at 133-135° [5].

Thus, we should conclude that purified isoamyl alcohol, containing no less than 95% of the basic substance, must be used in the production of VIII, which in actual production leads to an increase in the yield of the preparation.

Isovaleric acid (II), which is used in the synthesis of IX and XI, is produced by the oxidation of "fermentation" isoamyl alcohol. In the process of oxidation, the impurities of other alcohols contained in isoamyl alcohol are also converted to the corresponding acids; in particular, optically active amyl alcohol forms methylethylacetic acid. More volatile acids can be partially removed by distillation, while isomeric II and methylethylacetic acid distill over together in view of their close physical properties. We established by methods of gas chromatographic analysis that the II obtained in this case contains about 20% methylethylacetic acid, as well as a whole series of homologous acids and esters, the total amount of which may reach 10%. The results of a study of various samples by the method of gas-liquid chromatography are presented in Table 3.

Technical XI from the third sample of II (see Table 3) was obtained with a yield of 72.8% and mp 136-141°. After purification by recrystallization from 85% isopropyl alcohol, XI has mp 147-148°, and its yield is only 47% (calculated on the basis of the technical product). Supplementary purification of XI through the adduct with salicylic acid [6] involves substantial losses. When a sample of II containing about 97% of the basic substance is used, however, technical XI is formed with a yield of 87% and mp 144-146°; after recrystallization from 85% isopropyl alcohol, XI is obtained with a yield of 76.5% (calculated on the basis of the technical product) and with mp 150-151°.

Validol (IX), produced from the third sample of II (see Table 3), contains up to 20% of the methyl ester of methylethylacetic acid; the use of a 97% sample of II reduces the amount of this ester to 2%. Thus, high percentage II should be used for the direct production of high-quality XI (with a yield 32% above the existing yield) and IX.

We have shown that the removal of an admixture of methylethylacetic acid from II by fractional distillation is extremely difficult. Therefore we studied the possibilities of obtaining purified II by a separation of their derivatives. The most promising is the separation of anhydrides of the corresponding acids, which is confirmed by the literature data [7], in which it is recommended that a mixture of aliphatic acids be converted to a mixture of their anhydrides, using acetic anhydride for this purpose. The acetic acid formed in the reaction is collected through the fractional distillation column, and then the mixture of anhydrides formed is separated on the same column. Since a mixture of methylethylacetic acid and II was not studied in the work of Koch and Leibnitz [7], we conducted experiments on the production and separation of a mixture of the corresponding anhydrides. Despite the use of a highly effective column (up to 40 theoretical plates) and work at reflux ratios of up to 60, we were unable to obtain sufficiently pure anhydride of II. It contained up to 10% of the anhydride of methylethylacetic acid, with a content of 20% methylethylacetic acid in the initial II.

Thus, at the present time we do not have available a sufficiently simple and safe method for producing purified II. This forces a more detailed consideration of the possibility of producing purified isoamyl alcohol, which can both be used directly for the production of VIII and be converted to II by the method of catalytic oxidation, well known and developed in industry. Therefore, the production and use of purified isoamyl alcohol will permit a solution of the problem of increasing the yields of all the abovementioned preparations.

In industry isoamyl alcohol is produced either from petroleum products or from products of alcohol fermentation. Abroad isoamyl alcohol for pharmaceutical preparations, in particular, for XI, is produced from petroleum products [8]. This process, consisting of steps of chlorination of the isopentene fraction of petroleum, its distillation, hydrolysis, and again distillation, is rather complex technologically. In the USSR the chief industrial method of producing isoamyl alcohol is alcohol fermentation, in which, as was indicated above, substantial amounts of optically active amyl alcohol are formed.

Of the methods of separation of the isoamyl alcohol–optically active amyl alcohol system described in the literature [8-12], the most promising is fractional distillation in a sufficiently efficient mass exchange apparatus. Since the boiling points of the indicated alcohols (128.9 and 132° [13]) are rather close, while the coefficient of relative volatility of the mixture, according to the literature data [14], is only about 1.08, the separation of the system of alcohols into pure components presents substantial difficulties. For example, according to the data of various authors [10-12], the production of a sufficiently pure (90-95%) optically active amyl alcohol requires a fractional distillation column with an efficiency of 70-100 theoretical plates. However, if we do not attempt to obtain both components of the system in individual form, but limit ourselves to the problem of obtaining only pure isoamyl alcohol, which is accumulated in the still, the required efficiency of the column is substantially reduced and is determined to a substantial degree by the set content of optically active amyl alcohol in the distillate. In view of the sharp increase in the yields of VIII when it is produced from high percentage isoamyl alcohol (see Table 2), the consumption of unpurified 70% isoamyl alcohol in this production can be increased without net crude expenditures. Since the cost of the alcohol (according to the existing technology of production of VIII) is only about 15% of the total cost of the raw materials, the amount of the unpurified alcohol consumed can be increased approximately 5-fold in this case without increasing the cost of the preparation. On the basis of this, on the operation of fractional distillation, the ratio between the still residue (purified isoamyl alcohol) and the distillate, enriched with optically active amyl alcohol (and not further used in the production of VIII), can be assumed equal to 4 : 1; in this case, at a content of 3% optically active amyl alcohol in the still residue, its content in the distillate is 36.7%. When the process is conducted in a periodic fractional distillation column, as is shown by tentative calculations [15], a column efficiency of approximately 30-40 theoretical plates is necessary to obtain such results. When effective packing, for example, spiral-prismatic packing [16], is used to fill the fractional distillation column, such efficiency is quite achievable even with a comparatively small height of the column.

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