### INDUSTRIAL SYNTHESIS OF ISOVALERIC ACID

A. V. Luk'yanov, V. P. Pakhomov, E. V. Van'kovich, V. A. Zasosov, L. Sh. Gorodetskii, T. P. Kuz'micheva, and I. A. Kuznetsova

In a previously published article we described a laboratory method for synthesizing isovaleric acid from isobutyl alcohol (I) via isobutyl bromide (II) and isovaleronitrile (III) [1]. On the basis of this method, we have developed a semi-industrial method for preparing synthetic isovaleric acid (IV) and have solved a number of chemical-technological problems.

When we increase the scale of the batches in the stage involving the preparation of II, the reaction time at a temperature of  $82-84^{\circ}$  increases from 14 to 18 h. The necessity of increasing the reaction time is confirmed by gas-liquid chromatography (GLC) investigations. The composition of samples taken from the apparatus was determined from the variation in the height of the peaks of the initial I and the bromides formed. Figure 1 shows a chromatogram of the reaction mixture and an equilibrium plot of the relative content of butyl bromides in the mixture being analyzed versus the reaction time. The formation of II is complete in 15-17 h. An induction period (up to 7-8 h) is observed on the curve, evidently due to the formation of an oxonium compound. A sharp rise in the rate of II formation is characteristic in the 10-17 h range.

When the batch size is increased, the hydrolysis of the bromides with water for 5 h at 18-20° for the purpose of destroying the tertiary butyl bromide does not achieve this purpose because of insufficiently efficient mixing of the aqueous and organic layers. This difficulty was overcome by adding an alkali and increasing the hydrolysis temperature to  $25-28^{\circ}$ . The best results are obtained using sodium bicarbonate as the alkali; the use of caustic soda or sodium carbonate results in appreciable resinification of II. Moreover, the use of an aqueous sodium bicarbonate solution for purifying the technical II simplifies apparatus design in this stage since it allows stainless steel apparatus to be used instead of enamelled steel. As a result of these changes, the yield of II was increased from 52-55% [1] to 54-57%, the purity being 93%.

For the stage involving the cyanation of II, it was shown that a quantitative yield of III is achieved when a twofold molar excess of sodium cyanide is used. The yield of III decreases abruptly when the excess of sodium cyanide is decreased (Fig. 2).

The isolation of IV under semiindustrial conditions by acidifying the sodium salt with 35% sulfuric acid (according to the laboratory method of [1]) is accompanied by the formation of a solid monolithic mass, which leads to local overheating and losses of up to 15% IV. These difficulties are overcome by adding water until the reaction mixture has completely dissolved and subsequently extracting the IV with methylene chloride. The yield of IV is 86%, calculated on III, and the purity is 97%.

The purity of the IV depends substantially on the quality of the I used for its synthesis. From technical I, we obtain IV containingup to 8% of "heavy" impurities. When different batches of chemically pure grade I are used, the impurity content of IV ranges from 0.9 to 3%. Table 1 shows the results of a chromatographic analysis of several samples of I and IV.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 8, No. 9, pp. 25-28, September, 1974. Original article submitted October 11, 1973.

© 1975 Plenum Publishing Corporation, 227 West 17th Street, New York, N.Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$15.00.

UDC 615.31:547.295.1].012.1



Fig. 1. Chromatogram of reaction mixture (a) and plot of the relative content of butyl bromides in the mixture versus reaction time (b). (a): 1) butyl bromides; 2) I (the dotted line shows the peaks for the butyl bromides and I at the start of the reaction); (b):  $h_{br}$  is the peak height for the butyl bromides;  $h_{al}$  is the peak height for I.

Fig. 2. Plot of isobutyl cyanide (III) yield versus the amount of sodium cyanide used in the reaction. The x axis shows the yield of III (in %) and the y axis shows the molar ratio of sodium cyanide to II.

	Composition of I (in wt.%)			Composition of IV obtained from			
I sample	"light" impur- ities	1	n-butyl alcohol	"heavy" Impurities	"light" impur- ities	Ι٧*	"heavy" impur- ities
Technical Analytical grade Chemically pure	0,457 0,11 0,446 0,028	95,68 99,19 98,94 99,43	1,36 0,7 0,25 0,54	$2,5 \\ 0 \\ 0,35 \\ 0$	0,5 0,18 0,3 0,5	90,5 99,13 97,1 99	8,0 0,68 2,5 0,5

TABLE 1. Gas-Chromatographic Analysis Data for Isobutyl Alcohol (I) and Isovaleric acid (IV)

\* Together with methylethylacetic acid, the amount of which is not more than 2%.

#### EXPERIMENTAL

#### Gas-Chromatographic Investigations

1. Analysis of I (Fig. 3a): separation column  $500 \times 0.3$  cm; solid carrier Chromosorb WHMDS, 0.25-0.40 mm fraction; stationary liquid phase 1.5% polyethylene glycol 400 and 20% mineral oil, based on the weight of the solid carrier; column temperature  $80-85^\circ$ ; injection block temperature 200°; carrier gas flow rate 60 ml/min; volume of injected sample  $3-4 \mu l$ . The quantitative determination of impurities in the I samples was carried out by means of an internal standard; isopropyl alcohol was used as the standard. The relative sensitivity correction factors for the identified impurities were determined experimentally using synthetic mixtures. For the unknown components, the correction factors were taken to be equal to the sensitivity of the standard.

2. The analysis of the mixture of butyl bromides (Fig. 3b) was carried out under the same conditions, except that the chromatographic column temperature was reduced to 55-60°. The quantitative determination of the components of the butyl bromide mixture was carried out by a normalization method; the calibration factor for all the components was taken as unity on the basis of experimental data.



Fig. 3. Chromatograms of starting materials and intermediates in the synthesis of isovaleric acid (IV). a) I: 1) unidentified impurity; 2) isopropyl alcohol; 3) n-propyl alcohol; 4) I; 5) nbutyl alcohol; 6,7) unidentified impurities; b) II: 1) unidentified impurity; 2) tertiary butyl bromide; 3) secondary butyl bromide; 4) II; 5) n-butyl bromide; c) aqueous alcoholic solution of III: 1) water and ethanol; 2) III; 3) o-xylene (standard); d) synthetic IV: 1) ethyl alcohol; 2) methylene chloride; 3) water; 4) IV (together with methylethylacetic acid): 5) n-valeric acid; the impurities were registered at 8 times higher sensitivity than IV.

3. Investigation of the rate and termination of the formation of II: chromatography column  $100 \times 0.3$  cm; solid carrier Chromosorb WHMDS, 0.25-0.4 mm fraction; stationary liquid phase 15 wt.% triethanolamine; column and block temperatures 80 and 150°, respectively; carrier gas flow rate 40 ml/min.

4. Content of III in aqueous alcoholic solution (Fig. 3c): chromatography column  $200 \times 0.3$  cm; solid carrier Chromosorb WAWDMCS, 0.25-0.4 mm fraction; stationary liquid phase 10% polyethylene glycol adipate; column and block temperatures 80 and 140°, respectively; carrier gas flow rate 50-55 ml/min. The amount of III was determined using an internal standard, o-xylene being used as standard.

5. Monitoring the purity of IV (Fig. 3d): chromatography column  $200 \times 0.3$  cm; solid carrier Chromosorb P with a particle size of 0.25-0.35 mm modified with 2% stearic acid; stationary liquid phase 10 wt.% polyethylene glycol adipate; column and block temperatures 130 and 250°, respectively; carrier gas flow rate 40 ml/min. The impurity content was determined by normalization, taking into account correction factors determined experimentally.

The total analysis of the aqueous alcoholic solution and the determination of the methylethylacetic acid content of IV were carried out by methods described in [1].

With the exception of the total analysis of the aqueous alcoholic solution of III, all the gas-chromatographic investigations were carried out on Fractovar C and B instruments with thermal conductivity detectors. The carrier gas was helium, the flow rate of which was measured at the outlet of the column.

## Isovaleric Acid (IV).

Isobutyl Bromide (II). A suspension of 52.5 moles sodium bromide in 40 moles of pure I is treated with 6.2 liters of 65% sulfuric acid at 8-12°. The reaction mixture is heated to boiling (82-84°) and kept at this temperature for 18 h, after which 3.84 liters of technical II (bp 75-105°) is distilled off under atmospheric pressure. The II is treated successively with 450 ml of battery sulfuric acid, 200 ml water, 200 ml of 2% potassium permanganate and a further 200 ml

of water. After washing with water, 4.12 kg of the mixture of II with tertiary and secondary butyl bromide is stirred vigorously with 10.3 liters of 7% aqueous sodium bicarbonate solution at 25-28° for 5 h. After termination of hydrolysis, II is separated and washed with 200 ml water.

Yield 3.2 kg, purity 95%,  $D^{20}$  1.2530-1.2588;  $n_D^{20}$  1.4360-1.4370. The yield corrected for 100% pure substance is 55.5% calculated on I.

Isobutyl Cyanide (III). A mixture of 45 moles sodium cyanide, 22.2 moles II, 10.6 liters of 96% ethyl alcohol, and 2.66 liters water is stirred and heated to boiling (75-80° in the bulk) and kept at this temperature for 32 h, after which a ternary mixture is distilled off under atmospheric pressure for 10 h (bp 75-98°). The mixture contains about 73.4% ethyl alcohol, 10.1% water, and 16.5% III.

The yield of the mixture is 10.7 kg (13.2 liters). The yield of III calculated on 100% pure substance is 1.83 kg (quantitative).

Isovaleric Acid (IV). A mixture of 10.7 kg of 16.5% aqueous-alcoholic III solution and 4.04 kg of 44% technical caustic soda solution is heated to boiling (79-80° in the bulk) and stirred at this temperature for 32 h, after which 11 liters of ethyl alcohol (sp. gr. 0.834) was distilled off under atmospheric pressure.

The thick residue is cooled to  $80-81^\circ$ , treated with 9.5 liters of hot (60°) water, and stirred at this temperature for about 1 h. The resulting solution (13 liters) of the sodium salt of IV is cooled to 25° and treated with 5.55 liters of 35% sulfuric acid over 1 h, the temperature being kept at  $20-25^\circ$ .

After adding the sulfuric acid, the IV is extracted with .nethylene chloride  $(3 \times 1200 \text{ ml})$ . The extract obtained (5.9 liters) is distilled under atmospheric pressure for 6 h to remove 3 liters of methylene chloride (bp 37-44°). The residue (technical IV) was distilled in vacuo and the fraction with a bp of 83-85° (20-25 mm) collected.

The yield of IV is 1.95 kg, purity 97.14%. The yield corrected for 100% pure substance is 1.89 kg, i.e., 84% calculated on II or 45% calculated on I.

# LITERATURE CITED

1. A. V. Luk'yanov, V. P. Pakhomov et al., Khim.-Farmats. Zh., No. 10, 29 (1972).