PREPARATION OF SYNTHETIC ISOVALERIC ACID

A. V. Luk'yanov, E. V. Van'kovich,
K. S. Borodina, L. I. Medvedeva,
V. S. Onoprienko, V. A. Zasosov,
V. P. Pakhomov, N. S. Kuryatov,
and T. E. Simonova

Suryatov,

UDC 615.31:547.295.1].012.1

Isovaleric acid is prepared by oxidation of isoamyl alcohol of natural origin, which contains 50% of an impurity of the isomeric optically active 2-methylbutanol. Because of this, considerable amounts (on the average, about 20%) of optically active methylethylacetic acid are present in the isovaleric acid. There are also a number of lower homologs in the isovaleric acid, plus isoamyl isovalerate; the total amount of these substances can reach 10%. The presence of these impurities in the isovaleric acid adversely affects the yield and quality of preparations (bromisoval, validol) which are synthesized starting from it.

Following a previously described [1] method, we have effected the synthesis of isovaleric acid (IV) by hydrolysis of isobutyl cyanide (III), which is formed on reaction of isobutyl bromide (II) with sodium cyanide. The isobutyl bromide was synthesized from the readily available isobutyl alcohol (I) and hydrogen bromide which was prepared directly in the reaction mixture from sodium bromide and sulfuric acid.

 $(CH_3)_2CHCH_2OH \rightarrow (CH_3)_2CHCH_2Br \rightarrow (CH_3)_2CHCH_2CN \rightarrow (CH_3)_2CHCH_2COOH$

Judging from literature data, none of the aliphatic bromides is obtained in such poor yield as II, especially when I is treated with an alkali metal bromide and sulfuric acid [2-6].

The low yield of II (in the best case 55-56% when gaseous hydrogen bromide is used [2]) is explained by the fact that, together with the replacement reaction, elimination reactions take place, and molecular rearrangements occur. As a result, along with II isomeric butyl bromides (secondary and tertiary) are formed, plus unsaturated hydrocarbons (isobutylene and pseudobutylene) and products of further transformations of these.

We have established that the maximum yield of II is attained at molar ratios of I, sodium bromide, and sulfuric acid of 1:1.3:1.6, a sulfuric acid concentration of 68%, a reaction time of 14 h, and a temperature of 87-89°. The isobutyl bromide obtained by distillation from the reaction mixture at atmospheric pressure contained isomeric butyl bromides, isobutyl alcohol, and unsaturated hydrocarbons.

Checks were made of the purity of II (and also of the products III and IV, from its further transformations) by gas-chromatographic methods which were developed for this purpose. Successive treatment of II with concentrated sulfuric acid and with a potassium permanganate solution at $10-15^{\circ}$ frees it from isobutyl alcohol and unsaturated hydrocarbons. The remaining mixture contains 70-75% of II, 20-25% tertiary butyl bromide, and up to 5% secondary butyl bromide; the yield of the mixture is 76-80%.

Hydrolysis of the mixture of bromides with water for 5 h at $18-20^{\circ}$ leads to decomposition of the tertiary butyl bromide to form tertiary butyl alcohol, which is soluble in water. Secondary butyl bromide cannot be hydrolyzed even on heating for a long time with aqueous sodium carbonate or sodium hydroxide solutions of various concentrations. The yield of refined II is 52-55%; it contains 94-97% of the base material, and 3-4% of secondary butyl bromide is present in it as an impurity.

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific-Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 10, pp. 29-31, October, 1972. Original article submitted May 20, 1971.

© 1973 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. All rights reserved. This article cannot be reproduced for any purpose whatsoever without permission of the publisher. A copy of this article is available from the publisher for \$15.00. On reaction with a twofold molar excess of sodium cyanide in aqueous-alcoholic medium, II forms III in quantitative yield; this is isolated by distillation from the reaction mixture, together with ethyl alcohol and water. The ternary mixture, which contains 66-73% ethyl alcohol, 9.5-16.6% water, 16.2-17.7% III, and 0.2-0.4% sec.-butyl cyanide (the latter is formed from the sec.-butyl bromide impurity), is hydrolyzed with a 50% sodium hydroxide solution. After removal of the alcohol, compound IV is isolated by treatment with 35% sulfuric acid, the yield being 79-84% based on III; the content of base material is 97-98%. Methylethyl-acetic acid, formed from the sec.-butyl cyanide, is contained in it as an impurity; the amount of it does not exceed 2%.

The bromisoval prepared from synthetic IV corresponds to the best samples in quality, and is formed in 20-22% higher yield than when IV prepared from fermentation isoamyl alcohol is used.

EXPERIMENTAL

Analysis of II was performed on a "Fractovap-C chromatograph under the following conditions: separating column, 300×0.3 cm; solid carrier, Chromosorb W HMDS, 45-60 mesh; liquid phase, 10% Reoplex-400; temperature of separating column and detector, 60° ; carrier-gas velocity, 50 ml/min.

Determination of the secondary butyl bromide content in II was performed in a column 500×0.3 cm; solid carrier, Chromosorb W HMDS, 60-80 mesh; liquid phase, 1.5% polyethylene glycol-300 and 12% hexadecane. The remaining conditions were like those given above.

Analysis of the aqueous-alcoholic solution of III was carried out on a "JGC-810" chromatograph under the following conditions: column dimensions, 300×0.3 cm; solid carrier, Chromosorb W HMDS, 45-60 mesh; liquid phase, 10% Reoplex-400; temperature in sample-introduction block and in detector, 150° ; column temperature, 80° ; carrier-gas velocity, 50 ml/min.

The purity of the IV was ascertained on a "Fractovap-C" chromatograph under the following conditions: column dimensions, 200×0.3 cm; solid carrier, Chromosorb PAW, 45-60 mesh; liquid phase, 2% stearic acid plus 10% polyethylene glycol adipate; temperature of column and of detector, 130°; temperature in sample-injectionblock, 250°; carrier-gas velocity, 40 ml/min.

To measure the methylethylacetic acid content in IV, we prepared the ethyl and methyl esters from the mixture; these were then analyzed in the "Fractovap-C" chromatograph. The ethyl esters of the individual acids were separated under the following conditions: column size, 500×0.3 cm; solid carrier, Chromosorb W AW, 45-60 mesh; liquid phase, 1.5% polyethylene glycol-400 plus 20% Vaseline oil; temperature of column and detector, 80°; temperature in injection block, 150°; carrier-gas velocity, 60 ml/min. The methyl esters of these acids were successfully separated at 140-150° in columns having a polyester liquid phase.

All the analyses were performed in instruments having thermal-conductivity detectors; the carrier gas was helium. In the analysis of the mixture of butyl bromides, the estimate of the content of components was made without allowing for correction coefficients; but in calculating the composition of the other mixtures, we experimentally determined the individual sensitivity coefficients for all the compounds present in the mixtures, and then used them.

Isobutyl Bromide (II). To a mixture of 4 moles of I and 5.2 moles of sodium bromide was added 621 ml of 65% sulfuric acid, with stirring, at a temperature not over 8-12°. The reaction mixture was heated to boiling (87-89°) and was kept at this temperature for 14 h, after which 400-450 ml of technical II (bp 75-105°) was distilled from the reaction mixture at atmospheric pressure; this was treated successively with 40 ml of concentrated sulfuric acid and 20 ml of 2% potassium permanganate solution at 10-15°. After washing with water, the 381 g of a mixture of II with tertiary and secondary butyl bromides was shaken with 700 ml of water at 18-20° for 5 h. When the hydrolysis was over, the II was separated and washed with water. The yield was 312 g; content of main substance, 94.2%, d_4^{20} 1.2580, n_D^{20} 1.4360. The yield calculated as 100% material was 53.4% based on I.

Isobutyl Cyanide (III). A mixture of 4 moles of sodium cyanide, 2 moles of II, 960 ml of 96% ethyl alcohol, and 240 ml of water was heated to boiling (75-80°) with stirring, and was kept at this temperature for 30 h, after which the ternary mixture was distilled off at atmospheric pressure over a period of 2-2.5 h (bp 76-90°). The mixture contained 73% ethanol, 10.1% water, and 16.9% III. The yield of mixture was 976 g (1205 ml). The yield of III calculated as 100% material was 165 g (99.5% of the theoretical based on II, or 53.25% based on I). <u>Isovaleric Acid (IV)</u>. A mixture of 976 g of 16.9% aqueous-alcoholic solution of III and 320 g of 50% sodium hydroxide solution was heated to boiling (80-82°) and was stirred at this temperature for 30-32 h, after which 950 ml of 94% ethyl alcohol was distilled off at atmospheric pressure. To the remaining thick mass was added 500 ml of 35% sulfuric acid solution, with cooling to 10-15°. The upper layer was separated, and it was distilled under vacuum, collecting the fraction of bp 80-82° (16 mm). The yield was 175.8 g; content of base material, 97%. Yield calculated as 100% material, 170.9 g (84.5% based on III, 84.1% based on II, or 45% based on I).

LITERATURE CITED

- 1. E. Schmidt and R. Sachtleben, Liebigs Ann., 193, 92 (1878).
- 2. V. Longinov and Kh. Lerman, Khim.-Farm. Prom., No. 1, 14 (1933).
- 3. C. R. Noller and R. Dinsmore, Org. Syntheses, Coll. Vol. 2 (1943), p. 358.
- 4. F. C. Whitmore and A. R. Lux, J. Am. Chem. Soc., 54, 3448 (1932).
- 5. A. I. Vogel, British Patent No. 565452; Chem. Abstracts, <u>40</u>, 5067 (1946).
- 6. A. Wurz, Ann. der Chem. und Pharm., 293, 114 (1855).