USE OF GAS–LIQUID CHROMATOGRAPHY IN THE SYNTHESIS OF 2-METHYL-4-METHOXYMETHYL-5-CYANO-6-HYDROXYPYRIDINE

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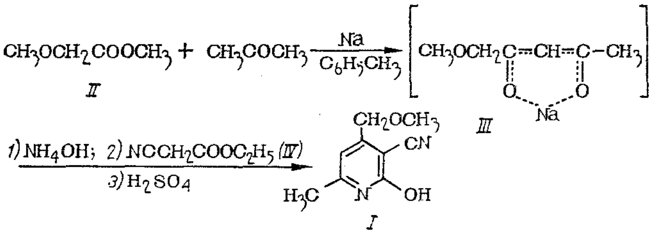
UDC 615.356:577.164.131].012.1.074:543.544

In one of the methods of producing vitamin B₆ [1], the synthesis of the intermediate product – 2-methyl-4-methox-methyl-5-cyano-6-hydroxypyridine (I) – is one of the most complex. The synthesis is conducted without isolation of the intermediate compounds and includes condensation of the methyl ester of methoxyacetic acid (II) with acetone in the presence of sodium in toluene medium with the formation of the sodium salt of methoxyacetylacetone (III), treatment of compound (III) with a 25% aqueous solution of ammonia, followed by interaction with the ethyl ester of cyanoacetic acid (IV) and the isolation of (I) by acidification with sulfuric acid.



To estimate the yield of the intermediate product at the intermediate stages of synthesis of I, we isolated the unpurified salt (III).

The conversion of (III) to (I) proceeds through three successive steps: formation of amino derivative of (III), its condensation with (IV), cyclization of the derivative obtained to (I), the yield of which is 81%. Consequently, if we consider at least only these three basic steps, then the yield at each of them is more than 90%.

In view of this, it was necessary to investigate in detail the step of formation of (III) from (II) and to determine the optimum conditions for conducting it. For this purpose we decided to select ratios of acetone and the methyl ester of methoxyacetic acid, with all other optimum systems of condensation [2], so as to obtain the maximum yield of (III) and the minimum yield of side products – products of the self-condensation of acetone and (II) – diacetone alcohol, mesityl oxide, farone, etc., as well as the sodium salt of the methyl ester of dimethoxyacetoacetic acid.

To monitor the condensation of acetone with (II), we used the method of gas–liquid chromatography. Quantitative methods of gas–liquid chromatography were developed for the determination of: a) acetone and (II) in the reaction mixture containing acetone, methanol, (II), toluene, and tridecane; b) (III)* and (II) in a reaction mixture containing acetone, methanol, (II), methoxyacetylacetone (V), toluene, and tridecane.

An analysis of the reaction mixture after the end of the condensation of (II) with acetone at an equimolar ratio of them showed the presence of unreacted (II). We found that

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*For the determination of (III), it is converted to methoxyacetylacetone (V) by treatment with 5 N hydrochloric acid.

All-Union Scientific-Research Vitamin Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 1, pp. 141-144, January, 1976. Original article submitted October 14, 1974.

for the reaction to go to completion it is necessary to increase the load of acetone to 1.17 moles per mole of (II) at the optimum reaction temperature 52-54°. This made it possible to obtain stable yields of (III) (70%) and (I) (52-55%). Moreover, no side products of the condensation of acetone and (II) were detected in the reaction mixture.

The method developed for the determination of (III) in the form of (V) made it possible to select the optimum concentrations of (IV) in the synthesis of (I), which led to a 25% reduction of the consumption of (IV).

EXPERIMENTAL METHOD

Preparation of Standard Methoxyacetylacetone (V). The standard sample of (V) for gas–liquid chromatography (GLC) was produced by converting (V) to the corresponding copper complex, followed by the isolation of (V) from it by acidification with 0.4 N hydrochloric acid, extraction with chloroform, and redistillation under vacuum. To 12.82 g (V) we added 50 ml of ether, and with mixing, poured in a solution of 110 g copper acetate and 155 ml of water, mixed for 6 h at 18-20°. After 12 h the precipitate was filtered off, washed with water, and dried at 70-80° to constant weight. The yield was 11.78 g (60%), mp 165-166°. Found, %: C 44.57, 44.66; H 5.49, 5.42. $C_{12}H_{18}CuO_6$. Calculated, %: C 44.78; H 5.64.

An 11-g portion of the copper salt of (V) was dissolved in 145 ml of chloroform. To the blue-green solution obtained, 370 ml of 0.4 N hydrochloric acid was added with mixing, whereupon the chloroform layer lightened, and then acquired a light-yellow color. The chloroform layer was removed and the aqueous layer extracted with chloroform (100 ml + 60 ml + 40 ml). The combined extracts were dried with magnesium sulfate and chloroform distilled off. The residue was dissolved under vacuum. Yield 6.65 g (51.7%), bp 55-56° (6 mm), n_D^{20} 1.4592. Literature data [3]: bp 68-69° (12 mm), $N_D^{23.5}$ 1.459.

Conditions of Analysis

The analysis was conducted on an LKhM-7A chromatograph with thermal conductivity detector. The stationary phase was 15% carbowax 20 M on Chromaton NAW DMCS. The length of the column was 2 m. Temperature of the column thermostat 100°, detector 150°, evaporator 200°, current of the detector 100 mA, sensitivity 1/2 (when the solvent emerges, the sensitivity decreases). The rate of flow of the carrier gas was 60 ml/min. Tridecane was an internal standard. The retention time of tridecane is 4 min 30 sec, (II) 3 min 20 sec, (V) 12 min 30 sec, acetone 30 sec, methanol 55 sec, and toluene 1 min 15 sec.

A. Construction of a Calibration Curve for Acetone and the Methyl Ester of Methoxyacetic Acid (II). The purity of acetone and (II) was verified under the conditions described above. Seven model mixtures of weighed samples of acetone, (II), and tridecane (exact weighed samples) were compiled, with weight ratios q_1/q_{st} from 0.3 to 3 and q_2/q_{st} from 0.6 to 4, where q_1 is the weight of the acetone (0.04-1.5 g), q_2 is the weight of (II) (0.15-2 g), and q_{st} is the weight of tridecane (0.2-1.5 g). To mix the layers, 0.5 ml of toluene was added to the mixtures to be calibrated. Each mixture was chromatographed five times, and the average ratio from five parallel determinations of the areas of the peaks of (II) and tridecane, acetone and tridecane was calculated. A calibration curve was constructed in a plot of q_1/q_{st} versus S_1/S_{st} for acetone and q_2/q_{st} versus S_2/S_{st} for the ester (II), where S_1 is the area under the peak of acetone, S_2 is the area under peak of (II), and S_{st} is the area under the peak of tridecane. The parameters of the calibration curve, the slope b and segment on the Y axis a, were found by the method of least squares [4]. The accuracy of the proposed method was characterized by the coefficient of variation 3.18 rel. % for acetone and 4.12 rel. % for (II).

B. Construction of a Calibration Curve for (V) and (II). The purity of (V) was verified under the conditions described above. Seven model mixtures were compiled from weighed samples of the standard (X) (exact weighed samples) with weight ratio q_1/q_{st} from 0.9 to 4 and q_2/q_{st} from 0.5 to 4, where q_1 is the weight of X (0.4-1.2 g), q_{st} is the weight of tridecane (0.2-0.8 g), and q_2 is the weight of the ester (II) (0.5-1.1 g). Further construction of the calibration curves was performed analogously to A. The accuracy of the method was characterized by a coefficient of variation 8.68 rel. % for (V) and 4.2 rel. % for (II).

Analysis of the Reaction Mixture after the Condensation of Acetone with (II)

A. Determination of Acetone and (II). For the analysis, a sample of about 5 g (exact weighed sample) was collected from the reaction mixture, about 2 g of tridecane (exact weighed sample) was added, and the precipitate was removed. About 1 μl of the solution was introduced into an evaporator; chromatography was conducted by the method described above. The analysis was repeated three times. The average values of the peaks of the substances to be analyzed and of tridecane were calculated. The content of acetone and (II) in the reaction mixture was calculated according to calibration curves.

B. Determination of (V) and (II). To a sample of the reaction mixture (about 2 g, exact weighed sample) we added about 0.3 g (exact weighed sample) of tridecane, and with cooling in an ice bath, added 5 N hydrochloric acid to pH 5.0-5.5. A sample was collected from the upper layer, 1-2 μl was introduced into the evaporator, and chromatography repeated three times. The average values of the peaks of the substances to be analyzed and tridecane were calculated. The content of (V) and (II) in the reaction mixture was calculated according to the calibration curves. At the end of the reaction, (II) should be absent.

2-Methyl-4-methoxymethyl-5-cyano-6-hydroxypyridine (I). A. To 8.2 g of metallic sodium in 58 ml of toluene, heated to 48-50°, we added a mixture of 37.3 g of the ester of (II) and 24.3 g of acetone, at a rate so as to maintain a temperature of 52-55°; mixing at 55-60° was continued for 1.5 h, the mixture cooled to 20°, and 90 ml of a 25% aqueous solution of ammonia added, the aqueous layer removed, and another 25 ml of a 25% solution of ammonia added to the toluene layer. Then 39 g of the ethyl ester of cyanoacetic acid (IV) was added to the combined aqueous ammonia solutions, whereupon there was an increase in the temperature of the reaction mixture to 39°. After 17 h, 125 ml of water was added, and 45 ml of sulfuric acid was added with mixing at a rate such that the temperature did not exceed 60°. After the end of the addition of sulfuric acid (pH 3.0), the reaction mass was heated at 80-90° for 45 min. The precipitate formed was removed, washed with 12 ml of hot water (90°), and then with water at 25-30° to the absence of SO_4^{2-} ions [test with $Ba(OH)_2$]. Yield 33.47 g (52.5%), mp 239-240°. The mixed melting point with an analytically pure sample of (I) gave no depression. B. An 8.2 g portion of metallic sodium in 58 ml of toluene was heated to 48-50°, and a mixture of 37.3 g (II) and 2.17 g acetone was added at a rate such that the temperature of the reaction mixture was 52-54°. Subsequent treatment of the reaction mass was performed according to A. Yield 23.45 g (46.2%), mp 239-240°.

Sodium Salt of Methoxyacetylacetone (III). To 8.2 g metallic sodium in 58 ml of toluene heated to 48-50°, we added a mixture of (II) (37.3 g) with acetone (24.3 g) at the temperature 52-54°. Mixing at 55-60° was continued for 1.5 h, then the mixture cooled to 6°, the precipitate removed, washed with toluene, and dried. Yield of (III) 38.7 g (70%), content of (III) 98.5% according to the GLC method of analysis described above.

2-Methyl-4-methoxymethyl-5-cyano-6-hydroxypyridine (I) from (III). To 5 g of (III) in 20 ml of a 25% ammonia solution, 4.5 ml (IV) was added with mixing. After 17 h of standing at 20°, 12 ml of water was added, and with mixing (temperature 50-60°) 7 ml of sulfuric acid, heated to 90°, and mixed at this temperature for 45 min. The precipitate was removed, washed with 1.5 ml of hot water (90°) and then with water with a temperature of 25-30° until the absence of SO_4^{2-} ions [test with $Ba(OH)_2$]. Yield of (I) 4.74 g (81%), mp 239-240°.

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