CERTAIN IMPROVEMENTS IN THE SYNTHESIS OF VITAMIN B_2

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It is known that reduction in price and simplification of the technology at the last stages of production are very important. For the production of riboflavin (vitamin B_2 — I), these stages are the preparation of 3,4-xylyl-6-phenylazo-D-ribitylamine (II) from 3,4-xylyl-D-ribitylamine (III) and condensation in which I is formed.

1. Synthesis of 3,4-Xylyl-6-phenylazo-D-ribitylamine (II)

In recent years, great progress has been made in the production of dyes with regard to the automatic control of the course and finishing of diazotization and azo-coupling processes by using potentiometry, conductometry, etc., an increase in the capacity of the processes by shortening their duration and increasing temperatures, and also with regard to an increase in the yield as a result of the use of agents which decompose excess nitrous acid during diazotization [1, 4].

We tried to apply these results to the preparation of II. The experiments were carried out with control of diazotization of aniline from the change in the electrode potential difference. Platinum and silver chloride electrodes served as the measuring system. In parallel, diazotization was controlled as usual with starch iodide paper. The reaction was complete when a potential of 700-720 mV was reached, and the serrated curve on the diagram transformed into a vertical line (Fig. 1). We also verified the possible diazotization of aniline at 15-20°C, instead of the usual 0-3°C. It was found that such an increase in temperature is permissible (Table 1), while the time of the process can be halved (from 20-30 min to 10-15 min).

It is also known that for more complete diazotization, a small excess of sodium nitrite is necessary, but it is harmful later in the coupling reaction, since the nitrous acid formed lowers the yield of the diazo compound. Urea, sulfanilic or sulfamic acids, are usually used for its decomposition [2, 3, 5, 6]. We verified the possible use of these reagents for the process and found that amino-sulfonic acids, in particular sulfamic acid, are best for this purpose. The reagents were added with analyzing probes withdrawn from the reactor on a starch iodide paper (up to the disappearance of a blue color). In our case, the consumption of sulfamic acid was, on the average, 0.013 g per 1 g of III, and the yield of II reached 91.5% (Table 2).

TABLE 1. Yield of II Obtained by Using Phenyldiazonium Salt Prepared at Different Temperatures

Charged		Temperature during diazotization, °C	Yield of II, g	mp, °C	Yield of II, %
aniline hydrochloride, g	III, g				
16,8	26	0—3	31,2	173—174	85,7
16,8	26	0—3	30,10	170—172,5	82,6
Mean					84,1
16,8	26	15—20	32,8	175—176	90,1
16,8	26	15—20	30,95	175—176	85,0
16,8	26	15—20	30,0	175—177	82,4
16,8	26	15—20	30,85	175—176	84,8
16,8	26	15—20	31,3	175—176	86,0
Mean					85,6

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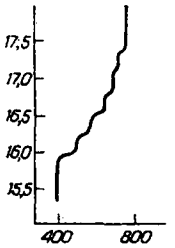

Fig. 1

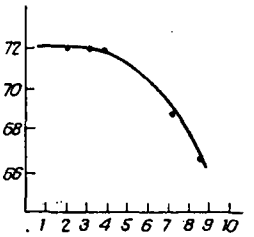

Fig. 2

Fig. 1. Curve for change in redox potential during diazotization of aniline. Abscissa) electromotive force (mV); ordinate) amount of 40% sodium nitrite solution (ml). Data are given for a series of experiments corresponding to those in Table 1.

Fig. 2. Influence of per-weight fraction of water in II on yield of I. Abscissa) per-weight fraction of water in II (%); ordinate) yield of I (%).

TABLE 2. Dependence of Yield of II on Nature of Reagent Added, Decomposing Excess of Sodium Nitrite

Charged				Yield of II	
aniline hydrochloride, g	III, g	reagent	weight of reagent, g	weight, g	yield, %
8,4	13	—	—	16,2	88,4
8,4	13	—	—	15,3	83,6
Mean				15,75	86,0
8,4	13	Urea	0,57	15,0	82,0
8,4	13		0,565	15,5	84,6
8,4	13		0,57	16,0	87,3
Mean			0,568	15,5	83,8
8,4	13	Sulfanilic acid	0,100	16,4	89,6
8,4	13		0,103	16,3	88,9
8,4	13		0,105	16,4	89,6
Mean			0,103	16,3	89,4
8,4	13	Sulfanilic acid	0,13	16,7	91,3
8,4	13		0,15	16,8	91,8
8,4	13		0,18	16,5	90,2
8,4	13		0,13	16,95	92,6
Mean			0,172	16,75	91,5

Thus, the preparation of the phenyldiazonium chloride salt in the synthesis of intermediate II was improved, and the duration of the diazotization was shortened, which led to savings in the refrigerating agent and an increase in the yield of II.

2. Riboflavin (I) Stage

Riboflavin is obtained by condensing II with barituric acid (IV) in a butanol–acetic acid medium, followed by treatment with hydrogen peroxide in an acid medium, and the precipitation of the product by water. The yield of I at the condensation stage depends on the amount of water introduced to the reaction mixture together with II. This influence is not evident when II containing up to 3% of water is used, but later, with increase in the moisture content, the yield of I sharply decreases (Fig. 2). A crude II, containing up to 3% of water and about 40% of butanol, can be obtained by thorough washing and pressing out of the intermediate product purified from butanol. A variant of the condensation of II with IV with azeotropic distillation of water was also tested. The yield of I could thus be increased by 2-4%, the time of condensation shortened from 7 to 4 h, and II could be used with a water content of up to 5% (Table 3).

TABLE 3. Preparation of I with Azeotropic Distillation of Water

Per weight fraction of water in II, %	Water separated, ml	Time of condensation, h	Yield of I in %*
1,4	—	7	71,3
1,4	5,0	7	75,5
5,0	4,9	7	74,2
6,0	5,0	7	71,5
10,0	6,5	7	64,6
5,0	2,7	5	74,2
5,0	3,0	4	74,2
5,0	2,8	3	69,8

*Arithmetic mean values of yields of I are given according to data of two experiments.

TABLE 4. Reduction in Amount of Water for Precipitation of I

Charged			Residual acidity, %	Amount of water per g of I, ml	Purified I obtained, g	Yield of I in purification, %*
technical grade I, g	water, ml	42% NaOH, ml				
13,2	750	—	2,76	56	11,6	87,9
13,2	375	14,5	2,28	28	11,6	87,9
13,2	300	14,0	3,10	22	11,6	87,9
13,2	300	15,0	3,00	22	11,7	88,6
13,2	200	21,5	3,00	15	11,5	87,2

*Yield calculated per 100% of I; in all cases during the analysis of samples of I according to State Pharmacopoeia X, the content of I was close to 100%.

During the purification of I, to use smaller, more available glazed reactors and to increase their efficiency, we tried to decrease the amount of water for precipitating I by partially neutralizing hydrochloric acid by sodium hydroxide solution and maintaining the acidity of the solution during the precipitation at about 3% (under these conditions the solubility of I is minimal). It was found that the amount of water can be decreased by a factor of 2.5 (from 56 to 22 ml per g of I) (Table 4).

EXPERIMENTAL

3,4-Xylyl-6-phenylazo-D-ribitylamine (II). An 8.4-g portion of aniline hydrochloride is stirred in a mixture of 26 ml of water and 10 ml of 34% hydrochloric acid to complete dissolution, and a 40% aqueous solution of sodium nitrite (90% of calculated amount, 7.5 ml) is added gradually, while the temperature is maintained at 15-20°C. The remaining amount is added in equal portions of 0.3 ml in the course of 1 min. To measure the redox potential, silver chloride and platinum electrodes are placed in the mixture. The reaction is complete at 700-720 mV, when the serrated curve on the self-recorder diagram transforms into a vertical line. Excess of sodium nitrite is removed by sulfamic acid (about 0.2 g). The solution of phenyldiazonium chloride thus obtained is then added, with stirring, to a suspension of III in water (13 g in 70 ml). A 20% aqueous solution of sodium acetate is gradually added to pH 3.6-3.9, and stirring is continued for 2 h. Compound II obtained is filtered, washed with water, and recrystallized from butanol. Yield, 16.75 g of II (91.5%, based on III), mp 175-176°C.

Riboflavin (I). A mixture of 15 g of II (with a moisture content of not more than 5%), 6.4 g of IV, 130 ml of a butanol—acetic acid mixture is heated to boiling. Water formed during the process is distilled azeotropically with the solvents. The reaction mixture is held for 4 h at the boiling point. Compound I obtained is filtered, washed with water, dissolved in 60 ml of 34% hydrochloric acid and 2 ml of a 15% solution of hydrogen peroxide are added. The hydrochloric acid solution of I is poured into 300 ml of water heated to 95°C, 14 ml of

a 42% aqueous solution of sodium hydroxide are added to a residual acidity of not more than 3%. The reaction mixture is held for 3 h at 95°C, then cooled to 20°C, compound I is filtered, washed with alcohol, and dried. Yield 11.65 g (74.2%, based on II). The quality of I corresponds to the requires of the State Pharmacopoeia X.

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