SYNTHESIS OF 4-METHYL-5-β-HYDROXYETHYLTHIAZOLE FROM α-CHLORO-α-ACETO-γ-BUTYROLACTONE AND THIOUREA

B. V. Passet, G. N. Kul'bitskii,
V. Ya. Samarenko, and L. I. Vekshina

UDC 615.356:577.164.11.012.1

Of the existing methods for preparation of 4-methyl-5-β-hydroxyethylthiazole (VII), which is an intermediate in the synthesis of vitamin B_1 [1-12], the condensation reactions of thiourea (IV) with α-chloro-α-aceto-γ-butyrolactone (I) and its acid hydrolysis products γ-chloro-γ-acetopropyl alcohol (II) and its dimeric ester are of particular interest [8-9, 13]. The hydrochloride of 2-amino-4-methyl-5-β-hydroxyethylthiazole (V) is formed in this case. An acidic solution of V is diazotized and the 4-methyl-5-β-hydroxyethylthiazolyl-2-diazonium salt (VI) is reduced to VII [4-5, 8-9].

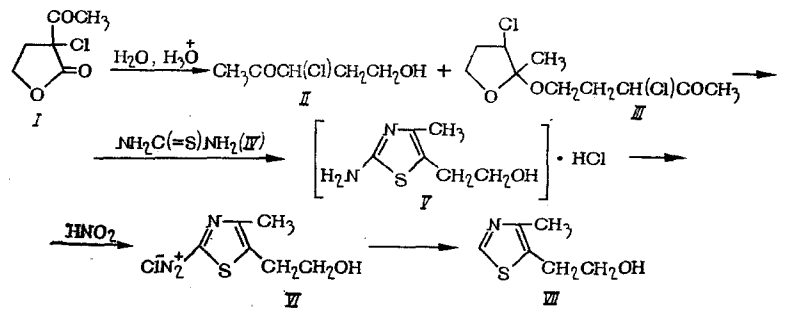

TABLE 1. Diazotization of V and Reduction of VI in a Solution of Hydrochloric (experiments Nos. 1-3) and Sulfuric (experiments Nos. 4-11) Acid*

Experiment No.	Method of conducting diazotization and reduction processes	Yield of VII calculated with respect to V, %	Concentration in crude product, %	
			VII	VIII
1	Additionof acidic solution of VI to a solution of sodium hypophosphite	27,3	63,7	36,3
2		26,9	59,2	40,8
3		24,5	60,8	39,2
4	Ditto	34,6	83,2	16,8
5		41,5	83	14,9
6		41,0	87,8	12,2
7	Additionof solution of sodium hypophosphite to an acidic solution of VI	38,2	84,3	15,7
8		40,3	83,4	16,6
9		41,2	86,8	13,2
10	Simultaneous diazotization of V and reduction of VI	23,7	79,5	20,5
11		22,4	81,2	18,8

*The concentrations of reagents per mole of V are: sodium hypophosphite 2 mole, hydrochloric acid 5.2 mole, sulfuric acid 2.6 mole.

Leningrad Pharmaceutical Chemistry Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 8, No. 11, pp. 48-52, November, 1974. Original article submitted May 3, 1973.

According to the literature data, one of the best reducing agents for VI is hypophosphorous acid [5, 7-9]. Diazotization of V in 12 N hydrochloric acid and subsequent reduction of VI with 30-32% hypophosphorous acid in the cold gives a yield of 70% VII calculated with respect to V [9]. According to the literature data [9], the required conditions for preparation of VII in satisfactory yield involve the use of a large excess of hypophosphorous acid (12-15 mole per mole of V) which makes the method uneconomic. The synthesis described in the literature involved separation of intermediate products, leading to additional losses and making the method unsuitable for industrial application.

The aim of the present work was the study of the influence of excess hypophosphorous acid on the yield of VII and also investigation of the possibility of synthesis of VII without separation and purification of the intermediate products II, III, V, and VI. At the same time a study was made of the different variants of the technological design of the stages of diazotization of V and reduction of VI. The principal experimental results are shown in Tables 1 and 2.

The product V was obtained by condensation of IV with the acid-hydrolysis products of I without isolation and purification of the latter. This made it possible to obtain V in a yield of not less than 90% of the theoretical calculated with respect to I because of elimination of loss of II through isolation and purification of III, the yield of which is around 70% with respect to I according to the data in [7]. From Table 1 it may be seen that the crude VII contains the product VIII as impurity. We established that this is 2-chloro-4-methyl-5-β-hydroxyethylthiazole. The concentration of VIII in the crude VII obtained by carrying out diazotization of V and reduction of VI in a solution of hydrochloric acid attains a value of 40%. This casts doubt on the yield and purity of VII given in a series of investigations [4-5, 8-9]. Substitution of hydrochloric acid by sulfuric acid leads to a considerable increase in the average yield of VII (to 39%) and in its quality. However, this does not exclude the formation of the by-product VIII (its concentration is only decreased to 12-17%) which is explained by the use of the hydrochloride V as starting product.

The results obtained in using different variants of the processes of diazotization of V and reduction of VI indicate that the process should be rationally carried out by addition of a solution of sodium hypophosphite to an acid solution of diazonium salt VI and this, in our opinion, is also more advantageous technologically since it allows both processes to be carried out in the one reactor. It may be seen from Table 2 that simultaneous diazotization and reduction by the addition of a solution of sodium nitrite to an acidic solution of V and sodium hypophosphite sharply decreases the yield of the required product VII and increases the concentration of secondary product VIII to 40-50%.

Table 2 presents the results of experiments on the synthesis of VII from I without isolation of the intermediate V for different mole ratios of sodium hypophosphite and I. Analysis of the results shows that with increase in the concentration of reducing agent the yield of VII increases; however, even a considerable increase in the concentration of sodium hypophosphite does not lead to such a marked increase in the yield of VII (results of experiments 12-14, 15-19, 22-23). Consequently, the maximum yield of VII cannot be a factor determining the optimum ratio of sodium hypophosphite and I. In the choice of the optimum ratio it is best to compare the consumption coefficients of the basic raw material (I, IV, sodium hypophosphite) which are presented in Table 3.

From Table 3 it follows that, from the point of view of material consumption, the optimum ratio of sodium hypophosphite and I lies in the range 1.5-3.

Since the crude VII obtained by the method indicated contains on average up to 12-17% of VIII, further condensation with 2-methyl-4-amino-5-bromomethylpyrimidine can give the 2-chloroderivative of vitamin B_1 as a secondary product. This may complicate the purification stage of the vitamin.

The methods described in the literature for replacement of the halogen by hydrogen in VIII [1, 14] and its acetate [14] by the action of zinc in glacial acetic acid with heating and also in 2-bromo-4-methyl-5-β-hydroxyethylthiazole [12] by a similar method or by reduction with hydrogen over palladium on charcoal in alcohol in the presence of alkali are distinguished by incompleteness of the data on yield and quality of the VII obtained. Meanwhile, reduction in a medium of glacial acetic acid will probably be accompanied by partial esterification of VII with the formation of its acetate.

For this reason we have developed a method of purification of crude VII by conversion of the impurity VIII into the required product VII using zinc dust in a medium of 15-20% hydrochloric acid at 50-59°C. The yield of VII at the stage of purification is not less than 85% (with respect to crude VII). Purified VII, according to the gas–liquid chromatography data, does not contain VIII (within the limits of accuracy of

TABLE 2. Results of Experiments on the Synthesis of VII from I without Isolation of Intermediate Product V and with Diazotization of V and Reduction of VI in a Solution of Sulfuric Acid*

Experiment No.	Method of conducting process of diazotization and reduction	Concentration of sodium hypophosphite per mole of I, mole	Yield of VII with respect to I, %	Concentration in crude product	
				VII	VIII
1			22,9	87,0	8,5
2	Addition of acidic solution of VI	1,48	24,6	88,8	11,2
3	to a solution of sodium hy-		26,5	89,2	8,4
4	pophosphite		23,0	85,0	8,1
5	Addition of sodiumhypophos-		35,8	85,5	8,5
6	phite solution to an acidic	1,48	30,1	84,7	7,7
7	solution of VI		34,1	87,3	6,8
8	Simultaneous diazotization of		7,06	56,0	41,0
9	V and reduction of VI	1,48	6,92	50,2	49,8
10	Addition of acidic solution of		29,7	83,5	15,2
11	VI of a solution of sodium	1,9	38,6	95,5	1,0
12	hypophosphite				
13	Addition of sodium hypophos-		39,7	84,0	13,9
14	phite solution to an acidic	1,9	42,3	87,5	4,4
15	solution of VI		36,9	88,8	7,32
16			47,2	87,3	9,8
16	" "		37,2	84,0	16,0
17		2,38	38,5	83,6	15,0
18			40,9	83,4	16,6
19			36,8	85,5	8,8
20	» »		47,8	91,5	8,5
21		2,85	46,9	86,7	10,2
22		5.02†	47,6	83,5	14,8
23	» »		50,0	85,5	9,3

*Concentrations of reagents per mole of I are: IV 0.99 mole, sodium nitrite 0.99 mole, and sulfuric acid 1.91 mole.
†3.5 mole sulfuric acid per mole of I.

TABLE 3. Consumption Coefficients of I, IV, and Sodium Hypophosphite per Unit of VII with Different Mole Ratios of Sodium Hypophosphite and I

Concentration of sodium hypophosphite per mole of I, mole	Average consumption coefficient per unit of 100% VII						Total consumption of raw materials (in kg) per kg of 100% VII
	I		Sodiumhyphosphite		IV		
	mole/mole	kg/kg	mole/mole	kg/kg	mole/mole	kg/kg	
1,48	3,49	3,97	5,17	3,83	3,47	1,84	9,64
1,9	2,9	3,29	5,53	4,1	2,88	1,53	8,92
2,38	2,93	3,32	7,0	5,18	2,91	1,55	10,05
2,85	2,37	2,7	6,75	5,0	2,35	1,25	8,95
5,0	2,43	2,75	12,15	9,0	2,40	1,28	13,03

the method of determination) and has a concentration of basic substance of not less than 97–98%.

Comparison of the data obtained with the literature data [15] indicates the high quality of the VII obtained.

EXPERIMENTAL

The percentage concentration of crude V after separation and in the reaction mixture was determined spectrophotometrically at 265 nm. The molar absorption coefficient of pure V is $\varepsilon_{265} = 7.7 \cdot 10^3$. As the principal method of analysis of the crude product we used the gas–liquid chromatography method. The chromatographs UKh-2 and Tswett-1 were used. In the UKh-2 the carrier-gas was helium, the inlet pressure 0.8 atm, thermostat temperature 204–210°C, and filament current 190 mA; the solid carrier was TNDM, fraction 0.143–0.250, and the stationary phase Apiezon M; the column length was 3 m; the volume of the samples was 2–3 μ liter. In Tswett-1, the carrier-gas was helium, the inlet pressure 0.9 atm, thermostat temperature 140°C, filament current 230 mA, and evaporator temperature 190°C; the solid carrier was Chromosorb, fraction 80–100 mesh, and the stationary phase E-30 (3%); the column length was 1 m; the sample volume was 0.4 μ liter. To confirm the presence of VII in the product we recorded a chromatogram of VIII obtained by the known method [14] and thus determined its retention time. Assignment of the peak of the basic product was carried out by comparison with the chromatogram of the product obtained by the thioformamide method [2, 11]. Determination of the percentage concentration of the product was carried out by relating the area of the peak of the basic product to the total area of all the peaks in the chromatogram.

2-Amino-4-methyl-5-β-hydroxyethylthiazole (V). A mixture of 19.6 g freshly distilled I [7, 11], 20 ml water, and 0.5 ml concentrated sulfuric acid was heated with stirring on a boiling water bath for 2 h. After cooling the reaction mixture 9.2 g IV were added and heating continued for a further 2 h at 98-100°C. The yield of V is not less than 93% (with respect to I). The solution of V obtained was submitted to separation or passed on without separation, to the diazotization stage. For separation of V from the solution the water was boiled off under vacuum (residual pressure 200 mm) with heating on a boiling water bath. 30 ml acetone were added to the cooled mass which then crystallizes. The residue is filtered off and washed with 15 ml acetone. The yield of crude V is 22.2 g with a concentration of not less than 95% (90% yield with respect to I). The melting point is 140-145°C; according to the literature data the melting point is 148-150°C [13] or 153-154°C [9].

4-Methyl-5-β-hydroxyethylthiazole (VII). a) 4-methyl-5-β-hydroxyethylthiazolyl-2-diazonium chloride (VI). A mixture of 22.2 g crude V, 16 ml concentrated sulfuric acid or 46.7 ml hydrochloric acid, and 25 ml water was cooled to −12 to −14°C and then over a period of 15-20 min a solution of 8.30 g sodium nitrite in 25 ml water added with cooling and stirring, keeping the temperature below −10°C. The mixture was held at this temperature for a further 15 min and then submitted to reduction.

b) Reduction of VI and Isolation of VII. A solution of sodium hypophosphite in 60 ml water cooled to −5 to −7°C was added over a period of 3-5 min to a solution of VI cooled to −14°C; the order of mixing may be changed (see Table 1). The reaction mixture foams intensely. The mixture is stirred at −5°C for a further 3-3$^1/_2$ h until complete disappearance of the diazo compound (absence of color reaction with Schaeffer's salt) and alkalized with a 42% solution of sodium hydroxide to a pH of 9.0-10.0. VII is formed as an oil and is extracted with chloroform (twice with 50 ml).

The chloroform extract is dried with 10 g anhydrous sodium sulfate and the sulfate filtered off. The main volume of chloroform (80-83%) is distilled off at normal pressure and the remainder removed under vacuum. The oil remaining is distilled under vacuum at a residual pressure of 1-5 mm and a still temperature of 150-155°C. The yield of VII is shown in Table 1.

Preparation of VII without Isolation of V. Concentrated sulfuric acid (13 ml) and 20 ml water are added to a solution of V obtained by the method above and the mixture cooled to −12 to −14°C. Then a solution of 8.3 g sodium nitrite and 25 ml water is added at −12°C over a period of 30 min and the mixture maintained at this temperature for a further 15 min. A solution of sodium hypophosphite in 100 ml water cooled to −5 to −7°C was poured into the cooled solution (the order of mixing may be changed, see Table 2). The reaction mixture is stirred at −5°C for a further 3-3$^1/_2$ h until complete disappearance of diazo compound (absence of color reaction with Schaeffer's salt). The mixture was alkalized to pH 9.0-10.0, the VII extracted with chloroform (twice with 75 ml) and treated as above. The yield of VII is shown in Table 2.

Separation of Impurity VIII from Crude VII. To a solution of 14 g crude VII in 60 ml 15-20% hydrochloric acid 5.3 g zinc dust added in small portions with stirring at 35-38°C at such a rate that the temperature did not exceed 50-55°C. The reaction mixture is then stirred at 50-55°C until the zinc is practically completely dissolved (1$^1/_2$-2 h). The mixture is cooled to 20°C, alkalized with a 42% solution of sodium hydroxide to pH 9.0-10.0, the VII extracted with chloroform (twice with 100 ml) and treated by the above method.

The yield of VII is 11.9-12.2 g (85-87% with respect to crude VII). According to the gas-liquid chromatography data the concentration of basic substance is 97-98% and there is no secondary product VIII.

LITERATURE CITED

1. V. M. Berezovskii, The Chemistry of Vitamins, [in Russian] Moscow (1959), p. 404.
2. L. O. Sneidman The Manufacture of Vitamins, [in Russian], Moscow (1958), p. 291.
3. A. M. Yurkevich, Uspekhi Khim., 33, 418 (1964).
4. G. Popp, Justus Liebigs Ann. Chem., Bd. 250, S. 273 (1889).
5. J. B. Hatcher, J. Am. Chem. Soc., 69, 465 (1947).
6. J. Low and R. Smit, British Patent No. 606026, 1948.
7. J. Stevens and G. J. Stein, Am. Chem Soc., 62, 1045 (1940).
8. M. J. Verret and L. R. Ceredo, J. Org. Chem., 22, 1695 (1957).
9. D. L. Williams and A. R. Ronzio, J. Am. Chem. Soc., 74, 2409 (1952).

10. B. I. Shapiro, A. A. Malina, G. Z. Yakovleva, et al., Khim.-Farmats. Zh., No. 6, 46 (1969).
11. I. A. Rubtsov and B. I. Shapiro, ibid., No. 3, 49 (1970).
12. Takeda, Tamamura, and Tone, J. Pharm. Soc. Jap., 71, 84 (1951); 74, 290 (1954); Ref. Zh. Khim., No. 47010 (1956).
13. A. R. Todd, F. Bergel, H. L. Fraenkel-Conrat, et al., J. Chem. Soc., 1601 (1936).
14. British Patent No. 456751, Chem. Zbl., Bd. 1, S. 2868 (1937).
15. B. I. Shapiro, A. K. Mukhina, I. N. Tsabashova, et al., Khim.-Farmats. Zh., No. 7, 42 (1967).