AN INVESTIGATION OF THE PROCESS OF CHLORINATION OF 4-METHYL-5-(β-HYDROXYETHYL)THIAZOLE. II.

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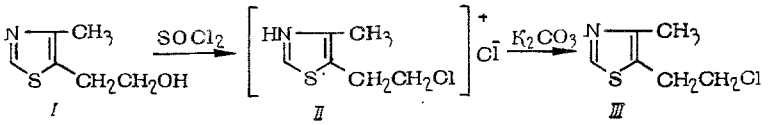
The synthesis of a new soporific and sedative agent, viz., hemithiamine, has been effected [1] based on 4-methyl-5-(β-chloroethyl)thiazole (III). Several methods of obtaining (III) are known [2-5]. In the majority of studies (III) was obtained by the chlorination of 4-methyl-5-(β-hydroxyethyl)thiazole (I) with thionyl chloride (II).



Previously we investigated the chlorination of industrial samples of (I) [6]. The synthesis occupied about 40 h and the yield of product was 68-71%. Up to the present time a detailed study has not been carried out of the influence of temperature and the duration of the reaction and the proportions of reagents in this process.

The aim of the present work was to clarify the influence of these factors on the yield of desired product and to study the possibility of curtailing the time for carrying out the process. The yield of (III) from (I) was chosen as the criterion for optimization. The effect of the following factors was investigated: duration of keeping at the boiling point in hours (X_1); the excess of thionyl chloride over the stoichiometric amount in moles (X_2); the reaction temperature in degrees (X_3). When selecting the basic levels and intervals of variation, account was taken of literature data [2,3], the technological possibility of effecting the process in industry, and also of previous experimental data. These factors, their basic levels, and intervals of variation are given in Table 1 (lines 1-4).

The experiments were all carried out in one laboratory installation. The first series consisted of 8 experiments according to a type 2^3 plan (see Table 1, lines 6-13). Each experiment, corresponding to a definite combination of variation levels, was carried out three times. Thus, the size of V represents an average value of the yield of three parallel experiments. Experiments were set in random order [7,8] (see Table 1, figures in parentheses).

The results of the experiments obtained in the matrix are given in the form of the linear part of the regression equation

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3. \quad (1)$$

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TABLE 1. Factors, Intervals, and Their Variation in the Planning Matrix for the Experiments and Steepest Ascent

Line No.	Named factor value		X_1	X_2	X_3				Yield (%) $\bar{Y}$	Calculated value $\hat{Y}$ (%)
1	Basic level	—	2	2	5					
2	Interval of variation λ_i	—	1	0,5	5					
3	Upper level (+1)	—	3	2,5	10					
4	Lower level (−1)	—	1	1,5	0					
5	Coded value of factors	x_0	x_1	x_2	x_3	x_1x_2	x_1x_3	x_2x_3		
6	Experiment No. 1 (5)	+	+	+	+	+	+	+	67,91	70,95
7	» No. 2 (1)	+	−	+	+	−	−	+	85,67	82,65
8	» No. 3 (8)	+	+	−	+	−	+	−	63,16	60,12
9	» No. 4 (7)	+	−	−	+	+	−	−	67,14	70,17
10	» No. 5 (2)	+	+	+	−	+	−	−	83,04	80,01
11	» No. 6 (6)	+	−	+	−	−	+	−	74,23	74,27
12	» No. 7 (3)	+	+	−	−	−	−	+	63,59	66,61
13	» No. 8 (4)	+	−	−	−	+	+	+	65,25	62,23
14	Coefficients of regression equation (b_i)	71,25	−1,83	6,47	−0,28	−0,41	−3,61	−0,64		
15	Steepest ascent $b_i\lambda_i$		X_1 −1,83	X_2 3,23	X_3 −1,40					
	Step		−0,3	0,5	−0,022					
16	Rounded-off step		−0,3	0,5	0					
17	Experiment No. 9		1,7	2,5	5				72,41	78,15
18	» No. 10		1,4	3,0	5				85,07	85,77
19	» No. 11		1,1	3,5	5				82,70	93,38
20	» No. 12		0,8	4,0	5				84,76	101,27
21	Statistical analysis	S^2_{rep}	S_{rep}	$S(b_i)$	$t(S_{b_i})$	F_{calc}	$F_{0,05\,calc}$			
		6,19	2,48	0,88	2,08	16,6	3,8			

Calculated regression coefficients (b_0, b_1, b_2, and b_3) are given in line 14 of Table 1. Substituting values in Eq. (1), we obtain

$$\hat{Y}=71.25-1.83X_1+6.47X_2-0.28X_3. \quad (2)$$

The coefficients b_1 and b_2 have the greatest value. A complete factor experiment made it possible to estimate quantitatively the double factor interactioneffects $X_1X_2(b_{12} = -0.41)$, $X_1X_3(b_{13} = -3.61)$, $X_2X_3(b_{23} = -0.64)$.

Statistical analysis [9] of the experimental results and the regression equation (see Table 1, line 21) showed that the standard deviation of the experiments was $\pm$ 2.48%, which is fully adequate; the coefficients b_1, b_3, b_{12}, and b_{23} are insignificant for a 5% level of significance, and the linear model is inadequate.

From Eq. (2) it follows that the yield of (III) depends most of all on the excess of thionyl chloride (b = +6.47), which must be increased since this regression coefficient is preceded by a plus sign. The coefficient b_{13} implies that any combination of different signs of X_1 and X_2 leads in the present case to a rise in the optimization parameter (experiments No. 2 and 5).

It was decided to carry out a steepest ascent. Calculation of the step, the program of the steepest ascent, and the results of the experiments are given in lines 15-20 of Table 1.

The results obtained from the matrix and in the steepest ascent showed the following. The yields of (III) in experiments No. 2 and 5 were the greatest and exceeded the yield given in the literature by 12-14%. The steepest ascent failed to improve these results. Experiment No. 11 was put into practice. This gave a yield of (III) close to the yield in experiment No. 5.

Thus, with the aid of eight experiments in a matrix and four experiments in a steepest ascent, we succeeded in raising the yield from 71 to 85%.

EXPERIMENTAL

4-Methyl-5-(β-chloroethyl)thiazole (III). To a solution of 5 g freshly distilled (I) in 10 ml dry benzene cooled to 10° was added, with stirring, 10.4 g thionyl chloride in 10 ml dry benzene over 1 h, ensuring that the temperature does not rise above 10° during the reaction. After adding all the thionyl chloride, the reaction mixture was heated on a water bath to boiling and kept boiling for 1 h. The excess of thionyl chloride and the solvent was distilled off in the vacuum of a water jet pump. The residue was diluted with water (1:1) and treated with potassium carbonate to an alkaline reaction. The product was extracted three times with ether (1:2 in proportion to the reaction mixture). The ether extract was dried with magnesium sulfate. The ether was distilled off, and the residue distilled in vacuum. The yield of (III) was 47.8 g [85% of bp 76-79° (3 mm)].

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