DETERMINATION OF OPTIMUM CONDITIONS OF SYNTHESIS OF BUTADIONE DISULFAMIDE BY THE METHOD OF STEEPEST ASCENT

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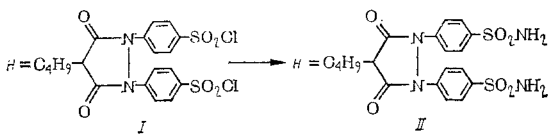
Despite broad use in medicinal practice, butadione has a series of significant disadvantages, as a result of which the search of low-toxicity analogs having high antiphlogistic activity is urgent. 4-n-Butyl-1, 2-di(p-sulfamidophenyl)-3,5-dioxopyrazolidine [butadione disulfamide (II)] synthesized earlier displayed, as do other sulfo derivatives of 3,5-dioxopyrazolidines [1], high antiphlogistic activity and low toxicity, in connection with which the necessity arose of obtaining a large batch of the preparation for a closer pharmacological study.

According to the method we developed earlier [1, 2] for obtaining (II), 13 g of 4-n-butyl-1,2-di(p-sulfophenyl)-3,5-dioxopyrazolidine (I) is added gradually to 70 ml of a cooled concentrated ammonia solution and the mixture is heated on a boiling water bath for 30-60 min. The cooled solution is acidified with 15% hydrochloric acid to pH 1.5. The precipitate is filtered and washed with water to a neutral reaction. After drying and crystallization 6.5 g of rose-white material having mp 195-197°C is obtained.



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The yield of recrystallized product varies in the region of 30-35%, in connection with which it was decided to carry out a search for optimum conditions of synthesis with the purpose of obtaining a maximum yield of the final product. One of the methods corresponding to the conditions of the problem is the Box-Wilson method of steepest ascent [3, 4].

The yield of recrystallized final product having mp not below 198-201° was chosen as a criterion for the quantitative evaluation of the effectiveness of obtaining (II). The assignment of varied variables, with the use of which the optimal region is found, was derived by analysis of a large number of factors affecting the process of obtaining (II). We carried out their classification, separating them into three groups: 1) controllable, yielding to quantitative evaluation, 2) controllable, not yielding to quantitative evaluation, and 3) uncontrollable. As uncontrollable variables are designated those which can not be changed by means at our disposal (percent content of initial material). Conditions of filtration, drying, and crystallization were assigned to controllable parameters, not yielding to quantitative evaluation. Ratio of reacting materials, temperature, and length of reaction were assigned to controllable parameters which could be evaluated quantitatively.

Use of the method of steepest ascent makes it possible to evaluate quantitatively the effect of the parameters being evaluated on criteria of effectiveness. However, its use requires stabilization of the varied variables at set levels with all other conditions of synthesis being constant. Therefore, the problem arises of choosing such a set of parameters (second group) which would give the largest yield of the final product for the designated set of values of the variables being evaluated quantitatively (third group). For this purpose a series of experiments was carried out preliminarily to clarify the effect of conditions of filtration, drying, and crystallization on the yield of (II), which made it possible to stop at the following

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TABLE 1. Variables and Interval of Their Variation

Value of variables	Variables		
	molar ratio of reacting materials	tempera-ture (deg)	length of reaction (h)
Base (initial) X_B	40	80	2
Variation step	10	20	1
Upper level	50	100	3
Lower level	30	60	1

TABLE 2. Initial Data and Results of Factoral Levelling of Experiments

Experiment No.	Molar ratio of starting materials	Temp.(deg)	Length of reaction (h)	Yield of final product (%)			Av. value of yield (%)	Calcd. value of yield (%)	Absolute error (%)	Relative error (%)
	X_1	X_2	X_3	Y_{n1}	Y_{n2}	Y_{n3}	$\bar{Y}_n$	Y_{calc}	$\Delta = Y_p - \bar{Y}_n$	$\delta = \frac{\Delta}{\bar{Y}_n} \cdot 100$
1	50	100	3	39,0	43,7	42,14	41,7	47,63	+5,9	14,2
2	30	100	3	26,2	32,5	29,9	29,2	33,23	+4,03	13,8
3	50	60	3	53,5	50,5	46,0	50,0	45,23	—4,77	9,55
4	30	60	3	33,9	35,1	39,0	36,0	30,83	—5,17	14,4
5	50	100	1	59,7	59,9	64,0	61,2	50,13	—11,07	18,3
6	30	100	1	37,8	35,5	30,45	34,6	35,63	+1,03	29,8
7	50	60	1	34,0	39,5	39,9	37,8	47,73	+9,93	26,2
8	30	60	1	33,34	33,34	33,34	33,34	32,3	—1,01	3,03

TABLE 3. Calculated Values of Yield and Absolute and Relative Errors

Expt. No.	Y_p	Δ	δ
1	44,67	2,97	8,8
2	26,25	2,95	8,40
3	47,05	2,95	8,40
4	38,95	2,95	8,40
5	58,35	2,85	8,12
6	37,45	2,85	8,12
7	40,75	2,95	8,40
8	29,37	3,97	15,76

conditions. 1) Dilution of the reaction mass after acidification with a three- to fivefold amount of water. 2) Drying of the precipitate at 50-60°. 3) Crystallization of dried (II) from a sixfold volume of a mixture of ethanol–benzene (4:2) with subsequent washing with a mixture of ethanol–benzene (1:5).

All preliminary experiments described above were carried out with 5.05 g of (I) at a molar ratio of ammonia and (I) equal to 30 at a temperature of 100° for 1 h. Yield of (II) amounted to 30-35%, mp 198-201°.

An interval of variation, determining the size of change of each factor relative to the initial (base) value assigned for it beforehand, was assigned for each of the three chosen factors (third group). Operating indices based on the existing methods [1, 2] and experiments of the authors were chosen as base values.

In order to exclude the effect of measurement errors, quite a large interval of variation of variables, exceeding by many times the absolute error of the control method, was assigned.

Corresponding data, also including base values of variables, are systematized in Table 1.

A matrix of factoral levelling of eight experiments was realized in agreement with literature data [3]. Initial data and also intermediate and final results of the executed experiments are presented in Table 2. (Each experiment corresponding to a certain combination of variables was carried out three times to increase the accuracy of measurement.)

Values of b_i coefficients of the equation, by which the connection between criteria of effectiveness of the process and the varied variables is approximated (surface response), were found from data of Table 2.

$$Y_p = 40.48 + 7.2Z_2 + 1.2Z_1 - 1.25Z_3, \qquad (1)$$

where

$$Z_1 = \frac{X_1 - X_1}{\lambda_1}; \quad Z_2 = \frac{X_2 - X_2}{\lambda_2}; \quad Z_3 = \frac{X_3 - X_3}{\lambda_3}.$$

TABLE 4. Calculated Values of Yield

Step	X_1	X_2	X_3	Y_p
1	50	83,5	1,8	52,50
2	60	87,0	1,6	64,52
3	70	90,5	1,4	76,54
4	80	94,0	1,2	88,56
5	90	97,5	1,0	100,58

TABLE 5. Variables and the Interval of Their Variation

Values of variables	Variables		
	X_1	X_2	X_3
Base	65	85	1,5
Variation step	10	10	0,5
Upper level	75	95	2,0
Lower level	55	75	1,0

TABLE 6. Initial Data and Results of Factoral Levelling of Experiments

Expt. No.	X_1	X_2	X_3	Y_{n1}	Y_{n2}	$\bar{Y}_n$	Y_p	$\Delta = Y_p - \bar{Y}_n$	$\delta = \frac{\Delta}{\bar{Y}_n} \cdot 100$
1	75	95	2	61,7	55,0	58,3	56,38	—1,92	3,3
2	55	95	2	60,0	54,6	57,3	55,94	—1,36	2,4
3	75	75	2	59,6	52,7	56,1	56,28	+0,18	0,32
4	55	75	2	52,1	53,3	52,7	55,84	+3,14	6,0
5	75	95	1	48,0	49,5	48,7	52,48	+3,78	7,75
6	55	95	1	52,6	52,6	52,6	52,64	—0,56	1,06
7	75	75	1	55,7	53,2	54,4	52,38	—0,02	0,057
8	55	75	1	51,0	55,4	53,2	51,34	+1,26	2,36

The calculated value of Y_p according to equation (1) gives a large relative error (up to 30%), which indicates the inadequacy of the equation of surface response. Properly, this indicates that immediately we fall into the region of the optimum point (stationary region). However, it was decided to improve the model of surface response by introducing nonlinear terms into equation (1). As a result the adequate equation was obtained:

$$Y = 40.48 + 7.2Z_1 + 1.2Z_2 - 1.25Z_3 + 2.58Z_1Z_2 - 0.57Z_1Z_3 - 4.97Z_2Z_3. \quad (2)$$

Calculated values of yield and absolute and relative errors calculated by equation (2) are presented in Table 3.

Evaluation of the significance of coefficients according to the Student criterion showed that only one coefficient of the equation at Z_1 Z_3 is insignificant, i.e., it is either doubtful or has an insignificant effect.

$$\sqrt{\sigma_{b_i}^2} \cdot t = 0.342 \cdot 1.895 = 1.1 > |b_i| = 0.57,$$

where σ_{b_i} is the average quadratic error of coefficient determinations; t is the table value of the Student criterion.

The possibility of approximating the real process of the obtained mathematical model was confirmed by the Fisher criterion.

Equation (2) can be regarded as an adequate real process, since the calculated value of the Fisher criterion $F_p = 6.81$ does not exceed the table value $F_{table} = 7.01$, i.e., the condition $F_p < F_{table}$ is fulfilled.

Equation (2) makes it possible to carry out a step shift in the guidance gradient, i.e., a maximum increase in Y. New steps of variation were calculated: $\lambda_1 = 10$; $\lambda_2 = 3.5$; $\lambda_3 = -0.2$.

Combination of independent variables assigned in this way were put into the initial equation and values of the yield parameter corresponding to them were calculated. These calculated values increase constantly in proportion to removal from the base point in the gradient direction, since the shift occurs along the plane (Table 4). However, the actual value of yield increases only to a known limit, since the real connection between parameters can be nonlinear. For this reason the calculated value of Y exceeded 100% at the fifth step.

Control verification showed that a significant deviation of experimental (48.6) and calculated (76.54) values of yield was already observed at the third step and, consequently, at this point a new series of experiments should be carried out.

Base values of variables for conditions similar to the third step are presented in Table 5.

Results of the second series of experiments are shown in Table 6. The following inadequate equation was obtained as a result of the experiment:

$$Y_p = 54,16 + 0,22Z_1 + 0,05Z_2 + 1,95Z_3. \qquad (3)$$

Calculated values of Y_p give a relative error up to 6%, and coefficients at Z_1 and Z_2 in equation (3) are not very reliable, as confirmation according to the Student criterion [5] showed.

$$\sqrt{\sigma^2_{b_i}} \cdot t = 0.81 \cdot 1.895 = 1.53 > |b_i|.$$

Since an increase of Y requires increases of Z_1, Z_2, and Z_3, it is natural to consider that the optimal conditions lie in the vicinity of values in the limits of the interval of variation:

$$65 \leqslant X_1 \leqslant 75; \qquad 85 \leqslant X_2 \leqslant 95; \qquad 1.5 \leqslant X_3 \leqslant 2.$$

Equation (3) describes the surface response well (see Table 6).

Experiments in the middle of the levelling matrix (at base values of variables) gave an average value of product yield of 57.6%, which does not differ from results obtained in the limits of the interval of variation.

Conditions of synthesis obtained in the second series of experiments were used to prepare (II) and made it possible to increase the yield of product by two times (up to 60%).

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