PREPARATION OF 2,6-DINITRO-p-TOLUIC ACID FROM p-TOLUIC ACID

V. Yu. Dolmatov, P. S. Zubarev,
M. E. Veretennikova, and B. A. Lebedev

UDC 615.31:547.583.44].012.1

2,6-Dinitro-p-toluic acid (2,6-DNTA) can be used for the preparation of 3,5-dinitrobenzoic acid (3,5-DNBA), which is a starting compound for the synthesis of x-ray contrast preparations of the triombrast type, and also of vitamin D_2.

Several methods for the preparation of 3,5-DNBA are known [3, 5-7]. However, these methods have a number of important disadvantages: extremely high excesses of acid (15-60 parts of volume), low yield of desired product (6-50%), etc. In connection with what is said above one of the competitive methods for the preparation of 3,5-DNBA may be the method of oxidation of 2,6-DNTA that we have developed.

A method for the preparaton of 2,6-DNTA described in the literature [1, 4] consists of nitration of p-toluic acid (p-TA) with concentrated nitric acid in sulfuric acid at 50°C for 30 min. In that case the excess of nitric acid above the stoichiometric amount is 40%, the modulus of 92-96% sulfuric acid is eight. The 2,6-DNTA is isolated by diluting the reaction mixture with water. The yield of product with mp 152-153°C reaches 90%.

We have studied the nitration step of p-TA to 2,6-DNTA with a nitrating mixture more comprehensively. Thereby we initially used the traditional one-factor method in which we varied the fundamental parameters that determine the yield of final product (concentration and modulus of sulfuric acid, modulus of nitric acid, temperature, and reaction time). Each parameter was varied separately in a certain range of variation while the other parameters remained constant.

It is clear from Fig. 1 that the optimal temperature for the nitration is 50°C, while lowering it to 40°C leads to considerable lowering of the yield of product, and that increasing it to 80°C has practically no influence on the yield, that is reacting at that temperature is not practical.

Figure 2 shows that the optimal sulfuric acid concentration is 92-96%. Decreasing and increasing the acid concentration lowers the yield of final product.

Optimal with respect to yield of final product is an excess of acid of 3 parts per part of p-TA (Fig. 3). Increasing the excess of sulfuric acid to more than three is not economical because the yield of final product remains constant also at an excess of eight. Lowering the modulus below three gives a reaction mixture that is difficult to stir.

A reaction time of 30 min is optimal because on lowering the time to 15 min a decrease in yield of final product is found and increasing the time to 45 min practically does not change it (Fig. 4).

As optimal may be chosen an excess of nitric acid of 5% of the stoichiometric amount because when it is lowered the yield of final product decreases considerably and when it is increased to up to 40% the yield does not change (Fig. 5).

Attempts to obtain the maximum yield by nitrating under optimal conditions found for the parameters were not crowned with success. Thus, the process carried out with reaction time 30 min, temperature 50°C, sulfuric acid modulus 3, excess of nitric acid 5% of the stoichiometric amount, and sulfuric acid concentration 94% led to a 88.2% yield of 2,6-DNTA of low purity (mp 142-151°C instead of 152-153°C).

Therefore, for the optimization of the process under consideration we have used the method of statistical planning of the experiment – complete factorial experiment (CFE) – and the simplex procedure. That created the possibility to shorten the investigation scheme with realization of all possible combinations of factors on all the levels chosen for the investigation [2].

Lensovet Leningrad Technological Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 12, pp. 55-58, December, 1990. Original article submitted December 12, 1989.

0091-150X/90/2412-0931$12.50

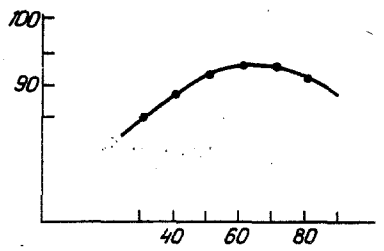

Fig.1

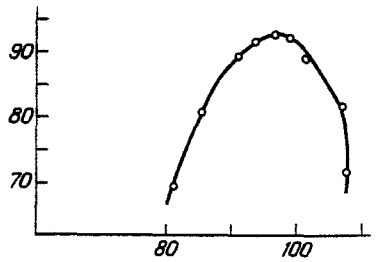

Fig. 2

Fig. 1. Dependence of the yield of final product on the temperature. Reaction time 30 min; modulus of nitric acid 1.05; sulfuric acid concentration 94%; sulfuric acid modulus 4.0. On the x-axis the temperature, °C; on the y-axis, here and in Figs. 2-5, the yield, %.

Fig. 2. Dependence of the yield of 2,6-DNTA on the sulfuric acid concentration. Reaction time 30-60 min; temperature 50-80°C. On the x-axis the sulfuric acid concentration, %.

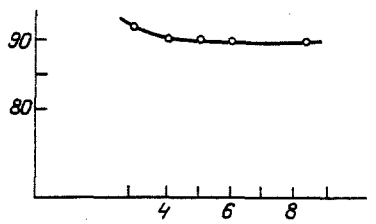

Fig. 3

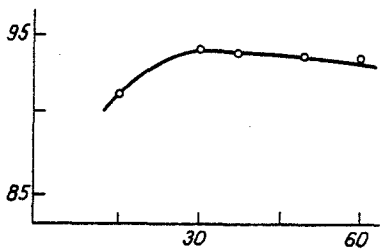

Fig. 4

Fig. 3. Dependence of the yield of 2,6-DNTA on the excess of sulfuric acid in the mixture of acids. Reaction time 30 min; temperature 50°C; nitric acid modulus per part of p-TA 1.4; sulfuric acid concentration 94% (the same data were also obtained in the case of reacting at 80°C for 60 min). On the x-axis the excess of sulfuric acid, parts per part of p-TA.

Fig. 4. Dependence of the yield of 2,6-DNTA on the reaction time. Temperature 50°C; sulfuric acid concentration 94%; sulfuric acid modulus 4; nitric acid modulus 1.05. On the x-axis the reaction time.

CFE was carried out in local regions of the factorial range lying in the neighborhood of the chosen points with the coordinates: temperature of the process 50°C, time of nitration 30 min, and mass modulus of sulfuric acid four. A factor such as an excess of nitric acid of 5% was taken by us as the minimally possible and not subject to optimization. A sulfuric acid concentration of 94 ± 2% corresponds with the industrially manufactured product "oil of vitriol"; moreover, in our opinion analysis of the obtained data (Fig. 2) also rules out the necessity to optimize that factor.

To assess the reproducibility we carried out two series of parallel experiments of which the results are listed in Table 1.

There was found a function of the responses Y and their mean arithmetical values:

$$\bar{Y} = \frac{1}{k} \sum_{1}^{k} Y_{ji}, \tag{1}$$

then the dispersion for each series of parallel experiments was determined:

$$S_j^2 = \frac{1}{k-1} \sum_{i=1}^{k} (Y_{ji} - \bar{Y}_j)^2 \tag{2}$$

and the Cockren number was calculated:

$$G_p = \frac{\max S_j^2}{\sum_{j=1}^{N} S_j^2}, \qquad (3)$$

$$G_p = \frac{1.12}{0.845+0.500+1.12} = 0.423.$$

The tabular value of the Cockren number in the case of confidence level P = 0.95, total number of evaluation variance N = 4, and number of degrees of freedom f = 1, is $G_T = 0.907$.

Thus, in our case $G_p < G_T$ and this means that the experiments are reproducible.

Then the error mean square was determined:

$$S_Y^2 = \frac{1}{N} \sum_{j=1}^{N} S_j^2. \qquad (4)$$

In our case $S_T^2 = 0.66$.

The evaluation variance is linked with the degrees of freedom:

$$f_1 = N(k-1). \qquad (5)$$

In our case:

$$f_1 = 4(2-1) = 4.$$

In order to obtain a mathematical model of the process use was made of the mathematical description of the process under investigation by the CFE method in some local regions of the factorial range lying in the neighborhood of the chosen points with coordinates (x_{01}, x_{02},..., x_{0n}).

The mathematical description is expressed by the regression equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3, \qquad (6)$$

in which the coded variables are coupled with the temperature, the reaction time, and the sulfuric acid modulus by the following relationships:

$$X_1 = \frac{x_1 - x_{01}}{\Delta x_1}; \quad X_2 = \frac{x_2 - x_{02}}{\Delta x_2}; \quad X_3 = \frac{x_3 - x_{03}}{\Delta x_3}. \qquad (7)$$

When carrying out CFE the conditions specified in Table 2 were set.

The planning matrix and the results of CFE are given in Table 3.

On the basis of CFE the regression coefficients were calculated with the equations:

$$b_0 = \frac{1}{N} \sum_{j=1}^{n} Y_j \qquad (8)$$

and

TABLE 1. Assessment of the Reproducibility of the Experiments

No. of series of experiment	Conditions			Results of the experiments		$\bar{Y}_j$, %	S_j^2
	x_1, °C	x_2, min	x_3, parts	Y_1	Y_2		
1	50	30	4	94.1	95.4	94.75	0.845
2	30	30	4	86.1	87.1	86.6	0.500
3	50	15	4	92.8	93.4	93.1	0.180
4	50	30	3	92.3	93.8	93.05	1.120

TABLE 2.

Characteristic	X_1, °C	X_2, min	X_3, parts
Basic level	50	30	4
Interval of variation	10	15	1
Upper level	60	45	5
Lower level	40	15	3

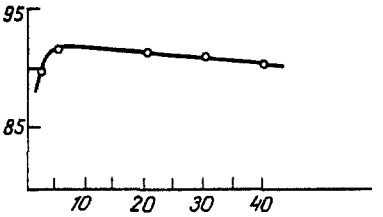

Fig. 5. Dependence of the yield of 2,6-DNTA on the excess of nitric acid. Temperature 50°C; sulfuric acid concentration 94%; sulfuric acid modulus 4; reaction time 30 min. On the x-axis the excess of nitric acid, parts per part of p-TA.

TABLE 3. Complete Factorial (four-factorial) Experiment

Experiment No.	X_1	X_2	X_3	x_1, °C	x_2, min	x_3, parts	Response function Y_j
1	−1	−1	−1	60	45	5	94,4
2	+1	−1	−1	40	45	5	90,8
3	−1	+1	−1	60	15	5	95,4
4	+1	+1	−1	40	15	5	89,2
5	−1	−1	+1	60	45	3	94,4
6	+1	−1	+1	40	45	3	91,6
7	−1	+1	+1	60	15	3	93,3
8	+1	+1	+1	40	15	3	88,7

TABLE 4. Values of the Levels of the Factors and the Variation Steps

Factor	Basic level	Variation step
x_1, (t_0), °C	50	10
x_2, (τ), min	30	15
x_3 (M)parts	4	1

TABLE 5. Matrix of the Starting Simplex

Experiment No.	X_1	X_2	X_3
1	K_1	K_2	K_3
2	$-K_1$	K_2	K_3
3	0	$-R_2$	K_3
...	...	...	...
$n-1$	0	0	0
	0	0	0
$n+1$	0	0	0

$$b_i = \frac{1}{N}\sum_{i=1}^{n} x_{ij} y_j \qquad (9)$$

In our case we got:

b_0=92.23; b_1=−2.15; b_2=−0.575 and b_3=−0.188.

The error in the regression coefficients were calculated with the formula:

$$S_b = \sqrt{\frac{\delta_y^2}{N}} \qquad (10)$$

In our case: $S_b = \sqrt{\frac{0.66}{8}} = 0.287$.

For P = 0.95 and f = 4 we found the value t = 2.78 for Student's t test. Then $S_b \cdot t = 0.798$.

We determined the significance of the regression coefficients by using the comparison $|b| \geq S_b \cdot t$.

In our case:

$|b_0| = 92.23 > 0.798$ (significant);
$|b_1| = 2.15 > 0.798$ (significant);
$|b_2| = 0.575 < 0.798$ (not significant);
$|b_3| = 0.188 < 0.798$ (not significant).

Thus, the required equation has the form:

$$Y = 92.23 - 2.15 \cdot X_1. \tag{11}$$

It can be seen from the equation that only one factor occurs (temperature).

To check the adequacy of the regression equation we initially determined the calculated values of the response function with the equation:

$$Y_j^p = 92.23 - 2.15 X_j. \tag{12}$$

Then we calculated the regression variance of the adequacy:

$$S_{ad}^2 = \frac{1}{N-B} \sum_{j=1}^{N} (Y_j^e - Y_j^p)^2, \tag{13}$$

in which B is the number of regression coefficient of the desired equation including also the free terms; Y_j^e and Y_j^p are the experimental and calculated values of the response function in the j-th experiment; and N is the number of experiments of CFE.

In our case $S_{ad}^2 = 1.93$.

Then we determined the calculated value of Fisher's variance ratio

$$F_p = \frac{\max (S_{ad}^2; S_Y^2)}{\min (S_{ad}^2; S_Y^2)}. \tag{14}$$

In our case $F_p = \frac{1.93}{0.66} = 2.92$.

The tabular value of Fisher's variance ration at a number of degrees of freedom in the numerator $f_1 = 1$ and in the denominator $f_2 = 4$ is $F_T = 7.71$.

Hence, $F_P < F_T$ and this means that Eq. (12) is adequate.

This equation may be used for optimization of the process under investigation.

We used the simplex method and chose the basic levels and variation steps of the factors and have listed them in Table 4.

The matrix of the starting simplex is in the form of Table 5 in coded variables.

The values that are in Table 5 are calculated with the following formula:

$$K_i = \sqrt{\frac{1}{2i(i+1)}}; \tag{15}$$

$$R_i = i \cdot K_i. \tag{16}$$

The results of the calculations carried out on the basis of Table 5 and formulae (15) and (16) are listed in Table 6.

When beginning the optimization by means of an initial series of experiments with physical variables, we used the formula

$$x_i = x_{0i} + \Delta x_i \cdot X_i, \tag{17}$$

in which x_i is the coded variable, Δx_j the scale on the X-axis, and i the number of the factor.

The obtained results are listed in Table 7.

When comparing the results of the first four experiments, we excluded the worst (3rd) experiment.

We replaced it by experiment No. 5, of which the conditions were calculated with the formula

$$x_i = -\frac{2}{n} \left(\sum_{n}^{n+1} x_{ji} - x_i^{\dagger} - x_i^{*}, \right. \tag{18}$$

TABLE 6. Conditions of an Initial Series of Experiments

Experiment No.	X_1	X_2	X_3
1	0,5	0,289	0,204
2	−0,5	0,289	0,204
3	0	−0,578	0,204
4	0	0	−0,612
5	0	0	0

TABLE 7. Optimization with the Simplex Method

Experiment No.	x_1	x_2	x_3	Response function, %
1	55	34,3	4,2	95,4
2	45	34,3	4,2	91,9
3	50	21,3	4,2	84,6
4	50	30	3,4	92,5
5	50	44,4	3,7	91,0

in which n is the number of factors in the planning matrix, j the number of the experiment, i the number of the factor, and x_i^* the value of the factor in the most "unsuccessful" experiment of the preceding simplex.

The result of experiment No. 5 showed that the extreme of the optimality criterion is reached and the motion of the simplex stops.

Thus, the conditions of experiment No. 1 were considered optimal, namely: nitration temperature 55°C; reaction time 33.4 min; sulfuric acid modulus 4.2 parts of acids per one part of p-TA; excess of nitric acid 5% of the stoichiometric amount; and concentration of the sulfuric acid 94 ± 2%.

When these conditions are realized the yield of 2,6-DNTA with mp 154-156°C is more than 95%; impurities are not present according to TLC.

EXPERIMENTAL

In a thermostated glass reactor of a volume of 150 ml is placed a weighed quantity of sulfuric acid or oleum of known concentration. Then, at the specified temperature and with vigorous stirring a weighed portion of p-TA is added in 1 min, after which the calculated amount of 98% nitric acid is added in 2-3 min. To stop the reaction at the specified temperature the reaction mixture is cooled to 20°C and the calculated amount of water is added. The precipitated product is filtered off, washed with water until the pH of the wash water is at least 6, and dried to constant weight at 90°C. The quality of the obtained product was determined by measuring the melting point on a PTP TU 25-11-1144-76 instrument and by TLC (on Silufol plates, eluent chloroform–hexane 10:1).

LITERATURE CITED

1. USSR Author's Cert. 215924, 1968; Byull. Izobret. No. 14 (1968).
2. S. L. Akhnazarov and V. V. Kafarov, Methods of Optimization of an Experiment in Chemical Technology [in Russian], VSh (1985).
3. B. A. Lebedev, V. Yu. Dolmatov, P. S. Zubarev et al., Khim.-farm. Zh., No. 5, 589-591 (1988).
4. E. Yu. Orlova, Khimiya, Leningrad (1973), p. 162.
5. F. Beilstein and A. Kurbatow, Justus Liebigs Ann. Chem., 202, 213-229 (1880).
6. A. Cahours, J. Prakt. Chem., 46, 321-353 (1849).
7. W. Stoedel, Justus Liebigs Ann. Chem., 217, 153-181 (1883).