METHODS OF ANALYSIS AND QUALITY CONTROL

INVESTIGATION OF THE SYNTHESIS OF TROPINONE ACCORDING
TO THE ROBINSON-SCHOPF REACTION BY A POLAROGRAPHIC METHOD

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Tropine esters of a number of organic acids are widely used as drugs in world medical practice. Such preparations, approved for use in the USSR, include the natural alkaloid atropine and synthetic tropine esters: homatropine, tropaphen, and tropacine. Up to the present time, in the USSR tropine has been produced by hydrolysis of natural alkaloids. In view of the fact that the total demand for the preparations indicated above is far from satisfied by the plant raw materials that grow in the country, an urgent need has arisen for the development of an industrial method of production of tropine.

Chemists have been engaging in synthetic investigations in the field of propane, alkaloids for more than seventy years. The Robinson-Schöpf reaction, consisting of the condensation of succinic aldehyde, acetonedicarboxylic acid, and methylamine [1, 2], followed by catalytic reduction of the aminoketone tropinone obtained to the aminoalcohol tropine [3, 4], is used almost exclusively for the synthesis of tropine. The condensation reaction has been studied by many researchers, who moreover have widely varied the temperature conditions, pH of the medium, composition of the buffer solutions, concentrations of the reagents, and other factors [3, 4-6]. However, the absence of a reliable method of analysis of tropinone in the reacting mass hinders the quantitative evaluation of the step of condensation in tropinone synthesis and substantially complicates the selection of the optimum conditions for this reaction. The method of determining tropinone in the reaction mixture by precipitation with Reinecke salt, proposed earlier [5], seems insufficiently accurate to us, since in this case, in addition to tropinone, methylamine [7], which is always present in the solution in excess, is also trapped. The generally accepted methods of analysis of such compounds, such as oxime formation and titration, are also inapplicable in this case on account of the complexity of the composition of the reaction mixture. In our opinion, the use of a polarographic method, possessing high sensitivity and selectivity, is the most advisable for the analysis of tropinone in the reaction media. In view of this, we studied the polarographic behavior of tropinone.

In contrast to substituted 4-piperidones [8], the reduction of tropinone occurs in one step. In acid media, just as in the case of 4-piperidones, reduction is complicated by a preceding reaction of dehydration of the carbonyl group, and the wave is of a kinetic nature. With increasing pH, the reduction wave of tropinone increases, reaching a diffusion two-electron level at pH>6.5, while at pH>8.0, it again begins to decrease. The increase in the wave in the transition to neutral buffer media is determined by a decrease in the hydration of the carbonyl group, which is confirmed by the UV spectra. Simultaneously with the increase in the wave, $E_{1/2}$ is shifted toward negative potentials, and $\Delta E_{1/2}/\Delta pH$ is 70 mV. The value of pK_a of tropinone is determined po-

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*Deceased.

TABLE 1. Results of Statistical Treatment of the Calibration Curves

$j = m-1$	b	s_0^2	n	$\bar{x}$	$s_{\bar{x}}$	P	$t(P, f)$	$\Delta\bar{x}$	$\Delta\bar{x}$, rel. %
29	2,1366	0,001395	2	0,9139	0,01265	0,95	2,05	0,02593	2,84

TABLE 2. Influence of Temperature on the Rate of the Robinson-Schöpf Reaction

Item No.	Temp. (deg.)	Time of collection of sample after reaching of the reaction temp., min	Tropinone content in the reaction solution		Yield of tropinone	
			g	% of theoretical	g	%
1	60	30	18,4	88,2		
		60	18,2	87,2	17,5	83,7
2	60	15	18,3	87,5		
		30	18,8	89,8	17,1	81,9
		45	18,5	88,7	—	—
3	60	0	35,4	84,8		
		15	37,5	89,6	34,4	82,4
		30	36,3	87,0		
4	50	15	36,6	87,5		
		30	37,0	88,5	34,5	82,7
		45	37,2	89,0		
5	40	15	35,8	35,7		
		30	36,3	87,0	34,3	82,1
		45	36,2	86,8		
6	30	15	27,2	65,2		
		30	32,5	77,8		
		45	34,4	82,4	35,0	83,9
		60	36,7	87,8		
		90	36,4	87,2		

tentiometrically and proved equal to 7.5. Thus, at pH<5.5 practically all the tropinone in the volume of the solution is protonated on the nitrogen, while the displacement of $E_{1/2}$ toward negative potentials is determined by the preceding reaction of protonation of the carbonyl group. In the region of pH 6.5-8.0 the height of the wave remains constant while the value of $E_{1/2}$ does not depend on the pH. In this pH region, hydration of the carbonyl group already is not manifested, and the wave is of a quasidiffusion nature on account of the rather high rate of preceding protonation on the nitrogen. It is interesting to note that in the transition from citrate—phosphate to citrate buffer solutions, the rate of protonation decreases, which leads to a doubling of the wave. At pH>9.0 and in the volume of the solution tropinone is in a basic form. In this pH region the wave again acquires a kinetic nature, and in accord with Eq. [9]:

$$E_{1/2} = \text{const} + \frac{RT}{\alpha n_a F} \ln \frac{[H^+]}{K_A} + \frac{RT}{\alpha n_a F} \ln \frac{i_d}{i_k},$$

$E_{1/2}$ is shifted toward negative potentials with increasing pH.

The reduction of tropinone on a dropping mercury electrode can be represented by the scheme:

At pH < 5.5

In the pH interval 6.5-8
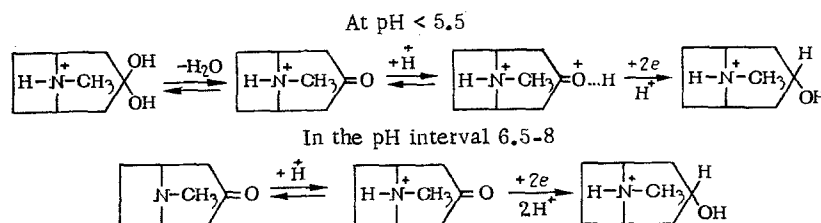
At pH>9.0, the preceding reaction of protonation determines the height of the wave of the reduction of tropinone. The wave of the reduction of the basic form of tropinone is covered by the discharge current of the supporting electrolyte; however, it can be observed in unbuffered solutions of lithium chloride and in anhydrous media (methanol, dimethylformamide).

The scheme of reduction of tropinone cited above is confirmed by experiments according to the method of latent limited currents of the hydrogen ion [10]. When a strong acid is added to aqueous unbuffered solutions of tropinone, depending on the H_3O^+ concentration, alternate reduction of the diprotonated, monoprotonated, and basic forms of tropinone can be observed, while calculation shows that two protons are consumed in the reduction. Such a nature of the reduction is also confirmed by a study of a model compound — N-methyltropinone. In acid media, N-methyltropinone is reduced in the same way as tropinone itself, while at pH>8.0, neither the height of the wave of N-methyltropinone nor $E_{1/2}$ depends on the pH. This is due to the presence of a fixed positive charge on the nitrogen atom in the N-methyltropinone molecule. In acid medium the reduction is preceded by a reaction of dehydration and protonation of the carbonyl group, while in alkaline medium there are no chemical steps before the transfer of an electron (at pH>11.0, just as in [11], we observed decomposition of N-methyltropinone under the action of the hydroxyl ion with the formation of an α,β-unsaturated ketone, reduced at more positive potentials).

From the aforementioned it follows that the optimum condition of the analysis of tropinone by a polarographic method is the use of citrate-buffer solutions with pH 7.0. In this region $E_{1/2}$ does not depend on the pH, which determines the stability of the wave. The limiting current plateau is rather pronounced, while the height of the wave is proportional to the tropinone concentration within broad limits. For an evaluation of the proposed method of determining tropinone, we conducted 30 parallel determinations of the value of the limiting current for solutions of tropinone of various concentrations. The results obtained were treated by the methods of regression analysis [12]. Using comparisons of the dispersion according to the Fisher criterion, it was established by the method of least squares that the calibration curve is described by the equation y=bx. The results of a statistical treatment are cited in Table 1 (the arbitrary notations are those generally used [12]).

To evaluate the applicability of the polarographic method in the analysis of reaction in the Robinson-Schöpf synthesis, we analyzed artificial mixtures, containing tropinone, methylamine, and acetonedicarboxylic acid, since the latter two compounds are always present in excess in the reaction solution. Under the conditions of the analysis, methylamine and acetonedicarboxylic acid are polarographically inactive; therefore, in the presence of these compounds neither the height of the wave of tropinone nor the value of $E_{1/2}$ is changed. When pure tropinone is added to a sample of the reaction solution, the increase in the height of the wave exactly corresponds to the amount of added tropinone. Thus, the polarographic method gives quite reliable results in the analysis of tropinone and can be used to study the Robinson-Schöpf reaction.

The trimolecular reaction of condensation of succinic aldehyde, acetonedicarboxylic acid, and methylamine, leading to the formation of tropinone, is one of the most complex and important steps in the production of tropine. The synthesis of tropinone according to Robinson-Schöpf is carried out in aqueous buffer solutions, using 1.4 moles of acetonedicarboxylic acid and methylamine per mole of succinic aldehyde [3-5]. The method described in the English patent [6] has important advantages. In the early investigations [2, 3], the synthesis of tropinone was conducted for a period of three days. According to the data of [5] the reaction takes 6 h at 22°, and 4 h at 32°. The essence of the patent [6] "consists of the heating of an aqueous solution of succinic aldehyde, acetonedicarboxylic acid, and methylamine at a temperature above room temperature." This permits an increase in the concentration of the initial 3,5-dimethoxytetrahydrofuran to 0.12-0.44 M and a decrease in the excess acetonedicarboxylic acid and methylamine to 25%. The authors of [6] believe that raising the temperature to 55-60° leads to a shortening of the reaction time to 90 min and to an increase in

the yield of tropinone to 74%. To verify this premise, we studied the dependence of the rate of the Robinson–Schöpf reaction on the temperature.

The results of a polarographic analysis of the tropinone in the reaction solution at various moments of time at four temperatures are cited in Table 2. It presents the amount of tropinone isolated in these experiments. The reaction ended after the collection of the last sample for analysis.

As can be seen from Table 2, at 60° the same amount of tropinone was found in all the samples, i.e., the reaction ends before the first sample was collected. At temperatures of 50 and 40° a 15-min exposure is sufficient for completion of the reaction. Even at 30° the reaction is practically ended in 1 h. Judging by the liberation of carbon dioxide, the reaction proceeds rather intensely at room temperature also. The experiments are readily reproducible. A change in the reaction temperature has practically no effect on the yield of tropinone. In the overwhelming majority of cases the tropinone content in the reaction solution after completion of the reaction is 87–89% of the theoretical. The losses in the isolation and redistillation of tropinone do not exceed 5%, average yield of tropinone 82%.

Thus, the Robinson–Schöpf reaction proceeds at a higher rate than was previously believed. Considering this circumstance, it is possible to decrease the excess of methylamine and acetonedicarboxylic acid and increase the concentration of the initial 2,5-dimethoxytetrahydrofuran. The experiments that we conducted are evidence that the yield of tropinone (82%) is maintained at a 0.7 M concentration of 2,5-dimethoxytetrahydrofuran, 3% excess of methylamine, and 15% excess of acetonedicarboxylic acid. This series of experiments was conducted at 40° and a 30-min exposure of the reaction solution. Thus, the decrease in the temperature and shortening of the time of the reaction with a simultaneous decrease in the excess of methylamine and acetonedicarboxylic acid lead to an increase in the yield of tropinone.

EXPERIMENTAL METHOD

Polarography was conducted in a thermostatically controlled cell at 25±0.1°. The dropping mercury electrode was equipped with a spatula for forced breakoff of the drop. Its characteristics are m:1.23 mg/sec, t:0.33 sec. The anode was a removable saturated calomel electrode. The polarograms were recorded with LP-60 and PO-4 polarographs from Radiometer. The pH values of the buffer solutions were monitored with a Radiometer PHM-22 meter. The number of electrons n was determined coulometrically, with the aid of the PAR-170 electrochemical system.

Procedure of Analysis. A 1 ml portion of the reaction mixture is collected in a 25-ml flask and brought up to the mark with distilled water. Then 1-1.5 ml of the solution obtained is transferred to a 25-ml volumetric flask, 12.5 ml of citrate–phosphate buffer, pH 7.0 and ionic strength 0.2, is poured in, and the mixture brought up to the mark with distilled water. The solution is introduced into a polarographic cell, dissolved oxygen is removed with a stream of special purity nitrogen, and the polarogram is taken in the interval 1.3-1.9 V. The tropinone concentration is determined according to a preconstructed calibration curve.

The tropinone used for the construction of the calibration curve was purified by two vacuum redistillations, followed by sublimation (mp 41-42°).

The polarographic method of analysis was also used to determine tropinone in the final product — tropine.

Production of Tropinone. Into a two-liter three-necked flask, equipped with a mechanical mixer, thermometer, and reflux condenser, we loaded 43 g of technical or 39.6 g 100% 2,5-dimethoxytetrahydrofuran, 20 ml of a 2 M solution of hydrochloric acid, and 400 ml of water. The reaction solution was boiled for 30 min and then cooled to 16-18°. Then 20 ml of a 2 M solution of sodium hydroxide was added (the solution obtained should have pH 6.0-5.0). A 96-g portion of crystalline sodium acetate was added, and then 50 g technical acetonedicarboxylic acid, with external cooling of the solution.

After complete solution of acetonedicarboxylic acid, 20.9 g of methylamine hydrochloride were added (the solution obtained should have pH in the range 4.0-4.5). The flask was heated, and after reaching the required temperature, samples were collected for analysis at definite time intervals. The reaction was ended in accord with the data of polarographic analysis, the reaction solution cooled, and 100 g of technical potash and 30 g sodium chloride added (specific gravity of the solution obtained 1.16). Then 150 ml of methylene chloride was added, and after 10 min of mixing the contents of the flask transferred to a separatory funnel and the layers separated. A total of four extractions was performed. The content of tropinone in methylene chloride and in the remaining mother liquors was also determined polarographically. The extract was dried overnight with anhydrous magnesium sulfate, filtered, and methylene chloride distilled off. After the methylene chloride was distilled off, the residue was transferred to a Claisen flask, and the remaining solvents distilled off under vacuum. The redistillation of tropinone was conducted at 7-12 mm of residual pressure. In the whole series of experiments, the load of 2,5-dimethoxytetrahydrofuran was doubled.

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