same in experiments with relatively low (~ 0.75 mole/liter) and high (up to 4.2 mole/liter) concentrations of alcohol in aqueous solutions of HBr, H_2SO_4, and H_2SO_4 with HBr.

As has already been mentioned above, its own standard state was chosen in calculating H_0 for each mixture of water and alcohol: a dilute solution of a strong monobasic acid in the mixture. If the values of h_0 of a dilute solution of the strong acid in water and in aqueous–propanol solutions containing up to 4.2 mole/liter C_3H_7OH are equal to the concentration of the acid then it may be asserted that, in these solutions, the true rate constant for the hydrobromination of alcohol is independent of the composition of the medium. If, however, at the same concentrations of the acid, the values of h_0 are different in the dilute aqueous and aqueous–alcoholic solutions of the strong acid then the result which is obtained is a consequence of a change in the acidity of the medium which has been referred to a single standard state and a change in the true rate constant.

CONCLUSIONS

1. The kinetic laws for the hydrobromination of $n\text{-}C_3H_7OH$ by hydrogen bromide at 80°C in a solution with and without additions of H_2SO_4 have been investigated.

2. A method is proposed for taking account of the reduction in the acidity of the medium due to the consumption of HBr from the solution during the hydrobromination reaction. The kinetic curves are described by a second order equation for the reactions involving the formation of $n\text{-}C_3H_7Br$ and its hydrolysis.

3. When the reagents are mixed, an equilibrium is rapidly achieved between $n\text{-}C_3H_7OH$, H_2SO_4, and $n\text{-}C_3H_7OSO_2OH$. The alkyl acid is unreactive in the hydrobromination of n-propyl alcohol.

4. The rate of reaction, referred to the current concentrations of HBr and the alcohol which is not bound up in the alkyl acid, varies proportionally to the acidity of the medium h_0. A dilute solution of the strong acid in the mixture was chosen as the standard state. At 80°C, this law is obeyed up to 4.2 mole/liter n-propanol in the solution.

LITERATURE CITED

1. S. A. Skakun, I. G. Tribrat, and M. I. Vinnik, Izv. Akad. Nauk SSSR, Ser. Khim., 2439 (1982).
2. M. I. Vinnik and S. A. Skakun, Izv. Akad. Nauk SSSR, Ser. Khim., 2434 (1982).
3. G. D. Johnson, A. R. Katritzky, and S. A. Shapiro, J. Am. Chem. Soc., 91, 6654 (1969).
4. K. N. Bascombe and R. P. Bell, Disc. Faraday Soc., 24, 158 (1957).
5. M. I. Vinnik, Usp. Khim., 35, 1922 (1966).

REACTION OF o-PHTHALONITRILE WITH ANILINE

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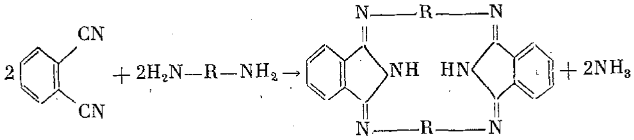
UDC 541.124:542.91:547.584:547.551

The work reported here is a continuation of our studies of the relationships and mechanism of formation of nitrogen-containing macroheterocycles, hexazocyclanes, which are obtained by the condensation of o-phthalonitrile with diamines in phenols



Since this reaction is complex and proceeds in many stages, it appeared desirable to investigate the reaction of phthalonitrile with a monoamine, aniline, as this reaction can be regarded as a model of the interaction of phthalonitrile with diamines.

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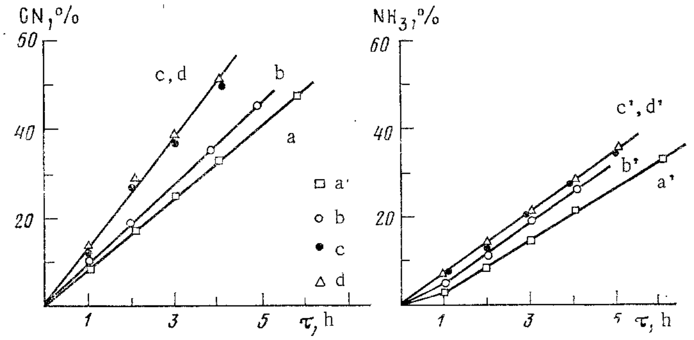
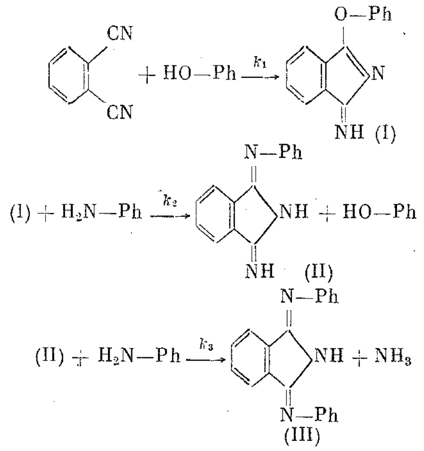


Fig. 1. Kinetic curves for conversion of C≡N groups of phthalonitrile (a-d) and degree of completion of reaction with respect to ammonia (a'-d') with a mole ratio PN/Cat = 4 (a, a'), 2 (b, b'), 1.33 (c, c'), and 1 (d, d') in reaction of phthalonitrile with aniline in phenol.

On the basis of the data reported in [1-3], the process under investigation can be represented as the following set of reactions:

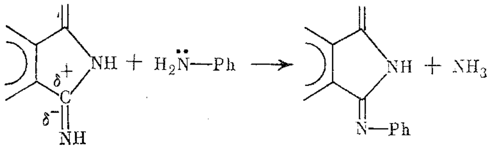


(A)

(B)

(C)

The mechanism of stage A was examined in detail in [3]. The interaction of aniline with the phenoxy group of 1-phenoxy-3-iminoisoindoline (I) (reaction B) apparently proceeds through a nucleophilic substitution mechanism [4]. It appears that nucleophilic attack on the carbon connected to the phenoxy group by the N atom of aniline is accompanied by rupture of the C−O bond and the splitting out of phenol. In stage C the aniline, as a stronger base than the exocyclic NH group, acts as a nucleophilic reagent with respect to the carbon atom of the C=NH group. As a result of the reaction of aniline and 1-phenylimino-3-iminoisoindoline (II), ammonia is liberated, apparently formed by the addition of protons of the aniline to the exocyclic NH group of 1-phenylimino-3-iminoisoindoline (II) [5], and 1,3-bis(phenylimino)isoindoline (III) is formed



We investigated the kinetics of phthalonitrile interaction with aniline at 140°C in the presence of various quantities of the complex catalyst isoquinoline·LiCl [3]. The course of the reaction was followed by the decrease in intensity of the absorption band for the C≡N group of the phthalonitrile in the IR spectrum of the reaction solution; the course of the reaction was also followed by the evolution of ammonia.

It can be seen from Fig. 1 that with increasing quantity of catalyst, the rate of phthalonitrile conversion increases significantly (without catalyst, the process goes forward very slowly, with a long induction period).

The data obtained in an investigation of the reaction of phthalonitrile with phenol in the absence of aniline [3] give us grounds for assuming that the reaction is autocatalytic. Therefore, in testing the catalytic activity

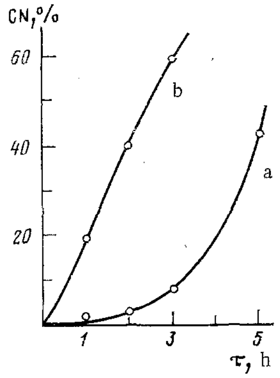


Fig. 2

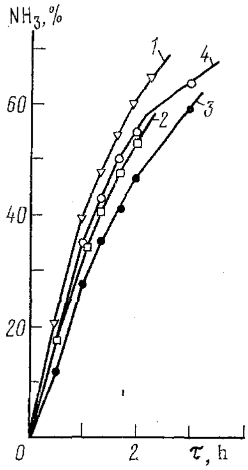


Fig. 3

Fig. 2. Conversion of C≡N groups of phthalonitrile in its reaction with phenol without catalyst (a) and in the presence of 10% (mole) of compound (II) (b).

Fig. 3. Kinetic curves for degree of completion of reaction with respect to ammonia in the interaction of 1-phenylimino-3-iminoisoindoline (II) with aniline with a mole ratio AN/Cat = 4 (1), 2 (2), and 1 (3); $C_{cat} = 0$ (4).

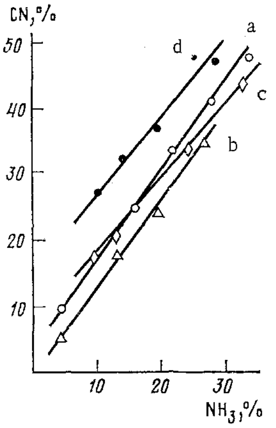


Fig. 4. Conversion of C≡N groups of phthalonitrile as a function of quantity of NH_3 evolved in reaction of phthalonitrile with aniline with a mole ratio PN/Cat = 4 (a), 2 (b), 1.33 (c), and 1 (d).

of (II) and (III) in stage A, the interaction of phthalonitrile with phenol was carried out in the presence of 10% (mole) of each of the compounds, monitoring the reaction by the disappearance of the C≡N groups of phthalonitrile. It was found that whereas (III) does not affect the course of the process, the presence of (II) eliminates the induction period (Fig. 2). This means that (II) is the autocatalyst of stage A.

From an investigation of the interaction of (II), obtained by counter-synthesis, with aniline in the presence of various quantities of the catalyst isoquinoline·LiCl, we were able to evaluate the influence of the catalyst on the rate of reaction C.

As can be seen from a comparison of the kinetic curves (Fig. 3), the catalyst, when introduced into the reaction mixture in amounts of 25-75% (mole) relative to one of the original compounds, does not affect the process rate; i.e., stage C is noncatalytic. With increasing amounts of the complex isoquinoline·LiCl, the reaction rate drops off.

In view of the capability of LiCl for forming strong complexes with the amino group [6], it appears that the decrease of the reaction rate with a mole ratio PN/Cat = 1 may be related to the increased concentration of this complex, in which the aniline has a lower nucleophilicity. This assumption is consistent with the proposed mechanism of reaction C.

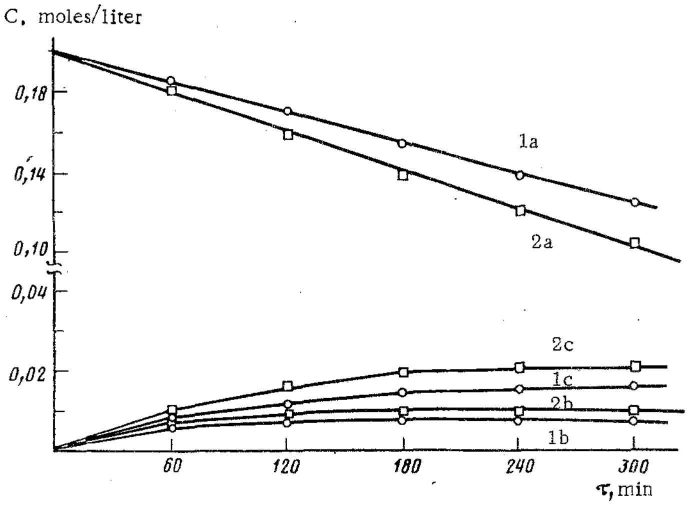
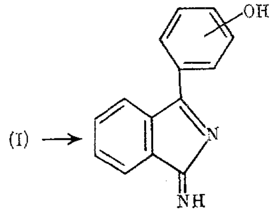


Fig. 5. Changes in concentrations of phthalonitrile (a), (I) (b), and (III)* (c) in reaction of phthalonitrile with aniline in phenol with a mole ratio PN/Cat = 4 (1), or 2 (2).

Since the condensation of the indoline (II) with aniline is performed under such conditions that the ammonia is removed almost completely, this reaction can be regarded as irreversible.

In examining the question of the effect of the catalyst on the reaction of stage B, we started with data obtained in studying the interaction of phthalonitrile and the indoline (II) with aniline. It was practically impossible to isolate the 1-phenoxy-3-iminoisoindoline (I) from the reaction medium in the interaction of phthalonitrile with phenol, since in the absence of the amine, the compound (I) undergoes rearrangement as soon as it is formed [1]



From the proposed process scheme it follows that if reactions B and C are noncatalytic, the yield of (III) with be determined solely by the degree of phthalonitrile conversion and will not depend on the quantity of catalyst at a given phthalonitrile conversion. As can be seen from Fig. 4, this relationship does actually exist with mole ratios Cat/PN from 0.25/1 to 0.75/1. Hence we can assume that reaction B is noncatalytic.

In order to investigate the reversibility of stage B, a solution of compound (II) in phenol was held for 3 h at 140°C, analyzing the solution periodically by TLC. Judging from the data obtained, aniline is not formed in the process of heating (II) in phenol, and this gives us grounds for regarding reaction B as irreversible.

The reaction scheme and the mechanism proposed for the reaction of phthalonitrile (PN) with aniline (AN) in phenol correspond to the following kinetic scheme for the process:

$$\frac{d\,[\mathrm{PN}]}{d\tau} = -k_1\,[\mathrm{PN}]$$

$$\frac{d\,[(\mathrm{I})]}{d\tau} = k_1\,[\mathrm{PN}] - k_2\,[(\mathrm{I})]$$

$$\frac{d\,[\mathrm{AN}]}{d\tau} = -k_2\,[(\mathrm{I})]\,[\mathrm{AN}] - k_3\,[(\mathrm{II})]\,[\mathrm{AN}]$$

$$\frac{d\,[(\mathrm{II})]}{d\tau} = k_2\,[(\mathrm{I})]\,[\mathrm{AN}] - k_3\,[(\mathrm{II})]\,[\mathrm{AN}]$$

$$\frac{d\,[(\mathrm{III})]}{d\tau} = k_3\,[(\mathrm{II})]\,[\mathrm{AN}]$$

By means of the nonlinear rating method of Marquardt, on an ES-1022 computer, we found the constants of the mathematical model to minimize the sum of the squares of deviations for the data on the degree of com-

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* As in Russian original; given as (II) in text – Translator.

pletion of the reaction according to $C\equiv N$ groups and NH_3. The best agreement between the calculated and experimental values was obtained with the following values of the constants: $k_1 = 0.0045\sqrt{C}_{Cat} + 0.035([(I) + [(II)])$, min^{-1}; $k_2 = 0.12$ liter/mole·min; $k_3 = 0.05$ liter/mole·min (C_{Cat} is the molar concentration of the catalyst).

The constant k_3 was determined, independent of k_1 and k_2, from a series of experiments (see Fig. 3); k_1 and k_2 were calculated on the basis of the data of Fig. 1, using the previously determined value of k_3.

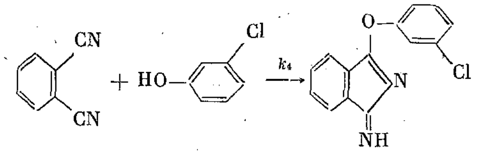
The Fisher statistical test for this model, defined as the ratio of the residual variance to the minimum possible general variance of the experiment due to the accuracy of analysis for the $C\equiv N$ groups and NH_3, proved to be 1.3850, which is less than the tabulated value with a significance level of 0.025 (the tabulated value is 1.4337). Fulfillment of this condition indicates that the model is adequate.

The mathematical description of the scheme provided a means for calculating how the rates of the individual stages and the contents of all reactants change during the course of the process. It can be seen from Fig. 5 that the quantity of 1-phenoxy-3-iminoisoindoline (I) in the reaction mixture is extremely small and remains almost unchanged during the course of the reaction; at each moment of time, the content of (II) is 2-2.5 times that of (I).

We also calculated the rates of formation of (I) in the absence of aniline [3] (ω_1) and in the reaction of phthalonitrile with aniline in phenol (ω_A). The calculations showed that $\omega_1/\omega_A \approx 100$. A comparison of the equations for the rate constants of the reaction of phthalonitrile with phenol with and without aniline gave us grounds for assuming that the aniline lowers the catalytic activity of the LiCl quite considerably and thereby, in effect, inhibits the reaction. This phenomenon is entirely understandable if we consider the possibility of forming the complex LiCl·aniline, which we mentioned previously.

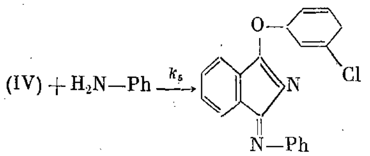
As has been shown previously, the nature of the substituent on the phenol has a major influence on its reaction with phthalonitrile [7]. Therefore, it appeared desirable to study the interaction of phthalonitrile with aniline in phenols with electron-donor and electron-acceptor substituents. As objects of investigation we selected m-cresol and m-chlorophenol. We found that the basic relationships and the reaction products are the same in m-cresol as in phenol. Condensation of the phthalonitrile and aniline in m-chlorophenol leads to the formation of 1-(m-chlorophenoxy)-3-phenyliminoisoindoline (IV).

On the basis of these data, the reaction of phthalonitrile with aniline in m-chlorophenol can be represented by the scheme



(IV)

(D)



(V)

(E)

We have obtained experimental evidence in favor of the proposed reaction scheme by conducting the process in stages. Compound (IV) was obtained by the interaction of phthalonitrile with m-chlorophenol and was identified by IR and mass spectrometry and elemental analysis; this is an important piece of evidence supporting the proposed mechanism of the reaction of phthalonitrile with phenols. Also noteworthy is the fact that (IV), based on a phenol with an electron-acceptor substituent, does not undergo any rearrangement in the absence of the amine, and that it can be isolated from the reaction mixture.

In carrying out the second stage of the reaction, it was found that the aniline interacts with (IV) only at the imino group. On the basis of the mechanism of reaction C that we have proposed, we can assume that the presence of an electron-acceptor substituent in the phenol leads to a decrease of polarity of the C–O bond, which makes it impossible for the aniline to interact with the other group of compound (IV).

Curves are shown in Fig. 6 for the conversion of $C\equiv N$ groups and the degree of completion of the reaction with respect to ammonia as functions of the reaction time and the quantity of catalyst in the interaction of phthalonitrile with aniline in m-chlorophenol. These data show that when the catalyst content in the reaction mixture

TABLE 1. Rates of Reactions A-E under Various Reaction Conditions in the Condensation of Phthalonitrile with Aniline ($\omega \cdot 10^4$, moles/liter·min)

τ, min	Catalyst concentration, moles/liter														
	0,05					0,10					0,15				
	ω_A	ω_B	ω_C	ω_D	ω_E	ω_A	ω_B	ω_C	ω_D	ω_E	ω_A	ω_B	ω_C	ω_D	ω_E
60	2,6	2,3	1,2	2,3	0,3	3,5	3,1	1,6	—	—	4,2	3,7	1,9	2,7	1,0
120	2,7	2,5	2,0	3,2	0,8	3,6	3,4	2,6	—	—	4,1	4,0	3,1	3,9	1,9

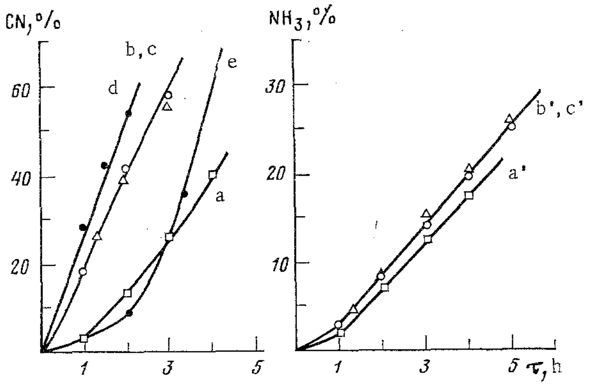


Fig. 6. Kinetic curves for conversion of C≡N groups of phthalonitrile (a-c) and degree of completion of reaction with respect to ammonia (a'-c') with mole ratio PN/Cat = 4 (a, a'), 1.33 (b, b'), and 1 (c, c') in reaction of phthalonitrile with aniline in m-chlorophenol, and in reaction of phthalonitrile with m-chlorophenol in the presence of (IV) (d) or (V) (e) with a ratio PN/Cat = 1.33.

is increased from 0.05 to 0.2 mole/liter (with a phthalonitrile concentration of 0.2 mole/liter), there are corresponding increases in both the rate of disappearance of the C≡N group and the rate of ammonia evolution.

In order to examine the catalytic properties of compounds (IV) and (V), the reaction of phthalonitrile in m-chlorophenol was carried out in the presence of 10% (mole) of each compound.

It can be seen from Fig. 6 that whereas (IV) accelerates reaction D, compound (V) does not manifest any catalytic activity.

The condensation of phthalonitrile with aniline in m-chlorophenol can be described by the system of equations

$$\frac{d[\mathrm{PN}]}{d\tau} = -k_4[\mathrm{PN}] = -(k_{4,0}C_{\mathrm{Cat}} + k_{4,1}[(\mathrm{IV})])\cdot[\mathrm{PN}]$$

$$\frac{d[\mathrm{AN}]}{d\tau} = -k_5[(\mathrm{IV})][\mathrm{AN}]$$

$$[(\mathrm{IV})] = [\mathrm{PN}]_0 - [\mathrm{PN}] - [\mathrm{AN}]_0 + [\mathrm{AN}]$$

From these equations we can find in explicit form the relationship between [AN] and [PN]:

$$[\mathrm{AN}] = [\mathrm{AN}]_0\left(\frac{[\mathrm{PN}]}{[\mathrm{PN}]_0}\right)^{k_5/k_{4,1}} \exp\left\{\frac{k_5 k_{4,0}}{k_{4,1}} C_{\mathrm{Cat}}\tau\right\}$$

After logarithmizing this equation, we determined the approximate initial values of $k_5/k_{4,1}$ and $k_5k_{4,0}/k_{4,1}$ and the order with respect to catalyst, which proved to be 1.

The expressions for the rate constants in the reaction of phthalonitrile with aniline in m-chlorophenol, found by the same method as was used for the constants k_1-k_3, have the following form: $k_4 = 0.0015\ C_{\mathrm{Cat}} + 0.047\ [(\mathrm{IV})]$, min^{-1}; $k_5 = 0.0170$ liter/mole·min.

The Fisher test for this model, calculated in the same manner as for the first model, was found to be 1.511. The tabulated value, with a significance level of 0.025, is 1.566, greater than the calculated value, indicating adequacy of the model. In Table 1 we have listed data on the rates of reactions A-E, calculated by means of the mathematical model.

It can be seen from these data that the rates of reactions A and B (ω_A and ω_B) are similar in magnitude, although ω_A is slightly greater than ω_B. The slowest stage of the interaction of phthalonitrile with aniline in phenol is reaction C. It can also be seen that ω_D is considerably smaller than ω_A.

An analysis of the equations for k_1 and k_4 indicates that in the reaction of phthalonitrile with m-chlorophenol, the catalyst manifests considerably lower activity than in the reaction of phthalonitrile with phenol. Moreover, since $\omega_E > \omega_D$, the concentration of compound (IV), which is the autocatalyst of stage D, at any moment of time in the reaction is extremely low. This is the apparent explanation for the considerable difference in reaction rates of phthalonitrile with phenol and with m-chlorophenol in the condensation of phthalonitrile with aniline in these solvents.

EXPERIMENTAL

The original phthalonitrile and phenols were purified by known methods. All of the constants of these compounds matched the literature values [8].

The IR spectra were taken in a Specord IR-75 instrument in CaF_2 cuvettes (d = 0.2 mm).

The reaction of phthalonitrile or (II) with aniline was carried out under homogeneous conditions in a stream of argon (15 ml/min) in a 20-ml two-necked flask with a reflux condenser, in a Wood's metal bath. The temperature was held to within ±0.5°C. The reactants were charged to the flask in the following order: first, 0.5 ml of absolute methanol, in which the calculated quantity of LiCl had been dissolved, was placed in the flask; the isoquinoline was added, then the aniline; the required quantity of phthalonitrile or (II) was added, and then 10 ml of the phenol, after which the flask was placed in the bath at the required temperature. The reaction mixture reached a constant temperature in 2 min. The loss of solvent during the reaction was no greater than 5% of the total quantity.

The degree of completion of the reaction was determined from the change in absorbance for the band of the $C\equiv N$ groups of the phthalonitrile in the 2230-2240 cm^{-1} region (the dependence of the absorbance on the concentration of $C\equiv N$ groups follows the Lambert–Beer law strictly [3]); the reaction was also followed by titrating the evolved ammonia with 0.1 N HCl solution.

Preparation of 1-Phenylimino-3-iminoisoindoline (II). To a solution of 0.93 g (0.01 mole) of aniline in 30 ml of absolute methanol containing 0.003 g Na as a catalyst, 1.28 g (0.01 mole) of phthalonitrile was added, while stirring and purging the mixture with argon. The reaction mixture was held in the stream of argon for 72 h at ~ 20°C, after which the mixture was poured onto ice, and the precipitate was filtered off and recrystallized from ethanol. Yield of (II) 1.77 g (80%), mp 201-203°C (decomp.). Found: C 75.94, H 5.09, N 19.05%. $C_{14}H_{11}N_3$. Calculated: C 75.99, H 5.01, N 18.99%.

Preparation of 1-(m-Chlorophenoxy)-3-iminoisoindoline (IV). A 1.28 g quantity (0.01 mole) of phthalonitrile was heated for 3 h in 10 ml of m-chlorophenol in a stream of argon at 160°C, after which the mixture was cooled and poured into 200 ml of ether. The precipitate was filtered off and dried. Yield of (IV) 1.49 g (60%). Found: C 65.09, H 3.87, N 10.63, Cl 13.69%. $C_{14}H_9N_2OCl$. Calculated: C 65.30, H 3.52, N 10.88, Cl 13.77%.

CONCLUSIONS

1. A mechanism has been proposed and a mathematical description has been given for the interaction of phthalonitrile with aniline in a medium of phenol or m-chlorophenol.

2. Aniline has an inhibiting effect on the first stage of the process, the reaction of the phthalonitrile with the phenol.

3. The nature of the substituent on the phenol determines the direction of the reaction of phthalonitrile with aniline.

LITERATURE CITED

1. R. K. Bartlett, L. V. Renny, and K. K. Chan, J. Chem. Soc., 129 (1969).
2. S. V. Vinogradova, S. A. Siling, and V. N. Solov'ev (W. N. Solowjöw), Macromolec. Chem., 177, 1905 (1976).

3. S. A. Siling, I. I. Ponomarev, V. V. Kuznetsov, B. V. Lokshin, S. V. Vinogradova, and V. V. Korshak, Paper deposited at VINITI, No. 452-83.
4. K. Ride, Course in Physical Organic Chemistry [Russian translation], Mir, Moscow (1972), p. 331.
5. B. A. Geller, Usp. Khim., 68, 537 (1978).
6. V. E. Plyushchev and B. D. Stepin, Chemistry and Technology of Compounds of Lithium, Rubidium, and Cesium [in Russian], Khimiya, Moscow (1970), p. 34.
7. V. V. Korshak, S. V. Vinogradova, S. A. Siling, and V. N. Solov'ev, Dokl. Akad. Nauk SSSR, 222, 114 (1975).
8. Dictionary of Organic Compounds [Russian translation], IL, Moscow (1949).

SYNTHESIS OF 5-S-CYSTEAMINE-6-HYDROXYTHYMINE AND EVIDENCE OF ITS FORMATION IN THE γ RADIOLYSIS OF AQUEOUS SOLUTIONS OF THYMINE AND CYSTEAMINE

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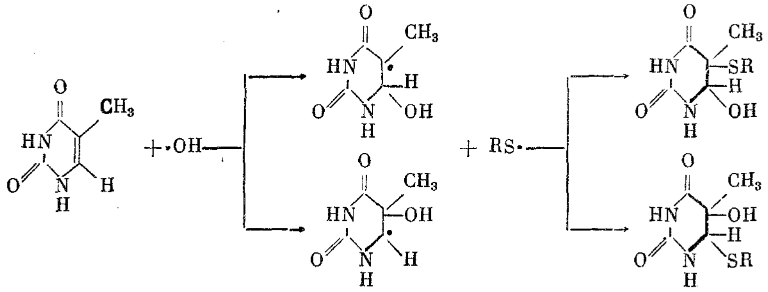
and G. I. Litvyakova

UDC 541.15:547.854.4

The photochemical and radiation-chemical addition of amino acids to nucleic acids is being investigated very thoroughly in connection with studies of the cross-linking of proteins with DNA in processes of cell aging [1]. Of all of the natural amino acids, only the sulfur-containing amino acids (cysteine and cystine) have proved to be the most reactive in photochemical bonding with uracil [2]. Many studies have been made of photochemical addition to nucleic acids and their components [1-7]. The principal products from the photochemical addition of cysteine to uracil and thymine have been identified as 5-S-cysteinedihydrouracil [8] and 5-S-cysteinedihydrothymine [3]. It has been suggested [3] that the formation of these compounds takes place by recombination of the thiyl radical with the radicals of thymine and uracil. It has been reported that cysteine adds to RNA and its components under the influence of ionizing radiation, but the addition products were not identified, and the fact was merely stated that cross-links between the cysteine and the RNA are formed [9]. It is well known that in the radiolysis of pyrimidine bases and their derivatives, hydroxyl radicals (formed by the radiolysis of water) add to the double bond of the pyrimidine ring to form OH-adducts. In the case of thymine, the reaction with OH radicals leads to adduct-radicals:



Hence we can assume that in the radiolysis of solutions containing a thiol and thymine, the recombination of the thiyl radical with OH-adducts of thymine will lead to the formation of thioethers.

Here we are reporting on the synthesis of 5-S-cysteamine-6-hydroxythymine (RST) and its identification in the radiolysis of solutions containing cysteamine and thymine.

EXPERIMENTAL

In this work we used cysteamine hydrochloride produced by Fehrak and thymine produced by Calbiochem. ^{35}S-Cysteamine with a specific activity of 5 mCi/mmole was synthesized in accordance with [11]. 2-^{14}C- Thymine brand "Izotop" with a specific activity of 60 mCi/mmole in the form of a 50% water–ethanol solution was

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