The spectra characteristics of all of the compounds obtained are presented in Table 1.

LITERATURE CITED

1. V. I. Vysochin and G. V. Shishkin, Khim. Geterotsikl. Soedin., No. 2, 250 (1982).
2. G. V. Shishkin, A. A. Gall', and G. A. Zloba, Khim. Geterotsikl. Soedin., No. 11, 1538 (1981).
3. R. W. Alder, M. C. Goode, T. J. King, J. M. Mellar, and B. W. Miller, J. Chem. Soc., Chem. Commun., No. 5, 173 (1976).
4. S. F. Nelsen, E. L. Clennan, L. Echegoyan, and L. A. Grezzo, J. Org. Chem., 43, 2621 (1978).
5. T. S. Moore and I. Doubleday, J. Chem. Soc., 119, 1170 (1921).
6. G. V. Shishkin and A. A. Gall', Khim. Geterotsikl. Soedin., No. 6, 831 (1980).

DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS. 10.* INTRAMOLECULAR CYCLIZATION OF β-BROMOETHYL- AND γ-BROMOPROPYL-N,N'-ALKYLENE-o-PHENYLENEDIAMINES

A. A. Gall' and G. V. Shishkin

UDC 547.863.13'836.7'892.07:541.127.1:543.422

The overall scheme of the intramolecular cyclization of bromoalkyl derivatives of N,N'-alkylene-o-phenylenediamines in HBr was established, and the rates of the individual steps of this complex process were estimated. It is shown that N-(β-bromoethyl)-N,N'-trimethylene-o-phenylenediamine undergoes virtually irreversible cyclization at a high rate to give benzo[f]-1,5-diazabicyclo[3.2.2]-nonene in significant yield, while the cyclization of N-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoxaline proceeds at commensurable rates via two pathways, viz., C- and N-alkylation. This makes it impossible to use the latter reaction to obtain benzo[f]-1,5-diazabicyclo[3.2.2]nonene in high yield.

We have previously shown that N-acyl-N'-(β-hydroxyethyl)-N,N'-trimethylene-o-phenylenediamines undergo cyclization in hydrobromic acid to give benzo[f]-1,5-diazabicyclo[3.2.2]-nonene (I) [2], whereas the cyclization of N-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoxaline (II) leads primarily to 1,2,6,7-tetrahydro-3H,5H-pyrido[1,2,3-d,e]quinoxaline (III) [1] and only trace amounts of I.

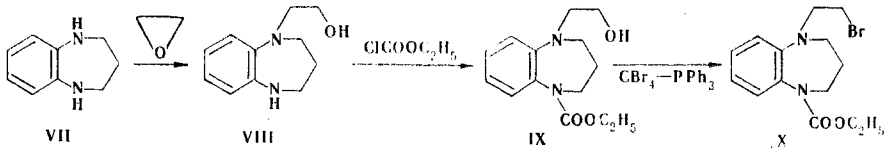
In order to find the optimum conditions for the synthesis of diazabicycloalkanes annelated with an aromatic ring and containing nitrogen atoms in the nodal positions and to determine more precisely the sequence of the reactions leading to heterocyclic system III we quantitatively evaluated, by means of our previously used chromatographic method [3], the rates of the reactions that occur in the intramolecular cyclization of bromoalkyl derivatives of N,N'-alkylene-o-phenylenediamines.

It is known that N-(β-bromoethyl)-1,2,3,4-tetrahydroquinoxaline (IV) upon heating in hydrobromic acid forms an equilibrium mixture with benzo[b]-1,4-diazabicyclo[2.2.2]octene (V) in a ratio of 3:7 [3], whereas N-acetyl-N'-(β-hydroxyethyl)-N,N'-trimethylene-o-phenylenediamine under these conditions undergoes cyclization to give only I [2]. To evaluate the possibility of the equilibrium N-(β-bromoethyl)-N,N'-trimethylene-o-phenylenediamine (VI) ⇌ benzo[f]-1,5-diazabicyclo[3.2.2]nonene (I) it was necessary to have VI at our disposal. With this in mind, we realized the synthesis of N-(β-X-ethyl)-N,N'-trimethylene-o-phenylenediamines — potential sources of VI — via the scheme

*See [1] for Communication 9.

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090.

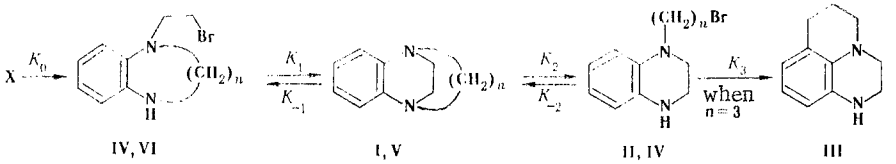
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 682-687, May, 1983. Original article submitted August 16, 1982.



VII VIII IX X

N-(β-Hydroxyethyl)-N,N'-trimethylene-o-phenyldiamine (VIII) was obtained by the reaction of N,N'-trimethylene-o-phenylenediamine (VII) with ethylene oxide. Attempts to exchange the hydroxy group in this compound for bromine by the action of phosphorus tribromide under the conditions used to obtain IV [3], as well as the use of milder conditions and other reagents, were unsuccessful. Compound I was formed in all cases. To protect the nitrogen atom from intramolecular N-alkylation under the conditions of exchange of the hydroxy group for a bromine atom we used the readily removable ethoxycarbonyl group. The reaction of VIII with ethyl chlorocarbonate in ethanol gave N-(β-hydroxyethyl)-N'-ethoxycarbonyl-N,N'-trimethylene-o-phenylenediamine (IX), treatment of which with a mixture of carbon tetrabromide and triphenylphosphine led to N-(β-bromoethyl)-N'-ethoxycarbonyl-N,N'-trimethylene-o-phenylenediamine (X). The spectral and analytical characteristics of all of the compounds obtained are in agreement with the expected structures. Considering the high lability of bromoethyl derivative VI, the ease of hydrolysis of the ethoxycarbonyl group, and the possibility of recording the total UV spectra of the individual components of the reaction mixture during chromatography we used stable urethane X as the source of VI to measure the rate of cyclization VI → I. Compound VI, which is observed chromatographically as an intermediate, is sufficiently stable under chromatographic conditions and has a UV spectrum that is similar to the spectrum of VIII; however, it differs from VIII with respect to its chromatographic mobility.

Observations of the behavior of diazabicycloalkanes condensed with an aromatic ring in hydrobromic acid [1-3] make it possible to propose the following scheme for the intramolecular cyclization of bromoalkyl derivatives of N,N'-alkylene-o-phenylenediamines:



IV, VI I, V II, IV III

I-III, VI, X n = 3; IV, V n = 2

To study the kinetics of this complex process we investigated separately the behavior of I, II, III, and X in hydrobromic acid; the behavior of IV and V under these conditions was previously investigated in [3]. All of the kinetic measurements were made under standard conditions at the boiling point of concentrated hydrobromic acid (125°C).

The qualitative pattern of the changes that occur with the investigated compounds is in good agreement with the proposed overall scheme. Compounds I and II form reaction mixtures with similar compositions in which I-III are easily determined; in both cases the III concentration increases during the reaction. Compound III remains unchanged under these conditions, while X is rapidly converted to a mixture of VI and I, in which virtually pure I remains with the passage of time. Quantitative treatment of the chromatograms obtained made it possible to evaluate the first-order and pseudofirst-order rate constants of the individual reactions; these constants are presented in Table 1.

It is apparent from Table 1 that II undergoes intramolecular N-alkylation to give I at a somewhat lower rate (K_{-2} $0.28 \cdot 10^{-4}$ sec^{-1}) than intramolecular C-alkylation in the aromatic ring to give III (K_3 $0.39 \cdot 10^{-4}$ sec^{-1}) and that the first reaction is reversible. The experimentally found concentrations of I-III in the isomerization of I to III in refluxing hydrobromic acid are presented in Fig. 1. It is apparent from Fig. 1 that the experimental results are in good agreement with the values calculated for a process of the A ⇋ B → C type [6], which confirms the previous assumption [1] regarding the isomerization pathway and is in good agreement with the proposed overall scheme of the behavior of bromoalkyl-N,N'-alkylene-o-phenylenediamines in hydrobromic acid.

To ascertain the role of hydrobromic acid in the intramolecular cyclization of II we carried out this reaction in sulfolane at 125°C in the presence of excess ethyldiisopropylamine as the weakly nucleophilic base. The rate of transformation of base II increases in

TABLE 1. Rate Constants for the Intramolecular Cyclization of N-(β-Bromoethyl)- and N-(γ-Bromopropyl)-N,N'-alkylene-o-phenylenediamines (IV, II, and X) and Opening of the Rings of Benzo[b]-1,4-diazabicyclo[2.2.2]octene (V) and Benzo[f]-1,5-diazabicyclo[3.2.2]nonene (I) in 8.8 N HBr at 125°C[a]

Starting compound	Rate constants, $K \cdot 10^4$, sec^{-1}					
	K_0	K_1	K_{-1}	K_2	K_{-2}	K_3
IV or V	—	4,4[b]	1,9[b]	1,9[b]	4,4[b]	—
X	20	58	<0,05[c]	—	—	—
I or II	—	—	—	0,036	0,28	0,39
II[d]	—	—	—	—	0,00	14

[a]The relative error in the determination of the constants was no more than ±10%; the constants were calculated under the assumption of first-order or pseudofirst-order of the reactions. [b]Calculated from the data in [3]. [c]The value of the constant was limited by the sensitivity of the method (see the experimental section). [d]In sulfolane with EtN(i-Pr)$_2$ at 125°C.

this case (K_3 $14 \cdot 10^{-4}$ sec^{-1}), but intramolecular cyclization is directed exclusively along the C-alkylation pathway to give III. Protonation of II in hydrobromic acid is probably necessary for the occurrence of intramolecular N-alkylation, which is in agreement with the available data [7] on the facilitation of the cyclization of haloethylpiperazines in the case of quaternization of the tertiary nitrogen atom.

It is apparent from the proposed scheme that the yields of the desired diazabicycloalkenes are determined by the ratios of the rates of the reactions in which the haloalkyl derivatives of N,N'-alkylene-o-phenylenediamines and the diazabicycloalkenes participate. The ratio of the reaction rates depends, in turn, on the conditions under which the process is carried out and the structures of the starting compounds. It is apparent from Table 1 that the rate of cyclization of VI is significantly higher than the rate of hydrolysis of urethane X, which explains the difficulties that we encountered in attempts to obtain bromoethyl derivative VI. A comparison of the rate of cyclization of substituted trimethylene-o-phenylenediamine VI (K_1 $58 \cdot 10^{-4}$ sec^{-1}) with the rate of the analogous reaction of substituted tetrahydroquinoxaline V (K_1 $4.4 \cdot 10^{-4}$ sec^{-1}) shows that decreasing the length of the alkylene chain by one CH_2 group leads to a decrease in the rate of intramolecular N-alkylation by a factor of more than 10. This is probably associated with the decrease in the basicity and steric accessibility of the reaction centers in V.

Diazabicycloalkenes I and V, which evidently exist in the form of hydrobromides in hydrobromic acid, differ substantially with respect to their electrophilic properties, i.e., with respect to their ability to undergo ring opening under attack by the bromide ion. In contrast to V, attack by the bromide ion at different alkylene bridges in I leads to different reaction products. We were unable to distinctly detect opening of the ethylene bridge in I on the background of the fast cyclization of VI, and the rate constant for this reaction was therefore estimated on the basis of the sensitivity of the method and was found to have a small value ($K_{-1} < 0.05 \cdot 10^{-4}$ sec^{-1}). Opening of the ring in I at the trimethylene bridge leads to N-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoxaline (II), which was identified from its chromatographic mobility and UV spectrum. The rate of this reaction is also lower by a factor of 50 than for opening of the diazabicyclooctene V ring. In order to explain this difference in the reactivities of the two structurally similar compounds we attempted to use the approach described in [4] for the analysis of the pathways and rates of opening of the rings of cyclic quaternary ammonium salts under nucleophilic attack. Cerichelli and co-workers [4] established that the rate of this process is higher, the higher the strain of the corresponding model cycloalkane. According to the literature data [5], the calculated strain energy in bicyclo[2.2.2]octane is 54.2 kJ/mole, as compared with 64.5 kJ/mole in bicyclo[3.2.2]nonane. This small difference in the strain energies should lead to only a small difference (several times) in the rates of opening of the rings of the quaternary ammonium salts and in the opposite direction [4] and cannot explain the significant

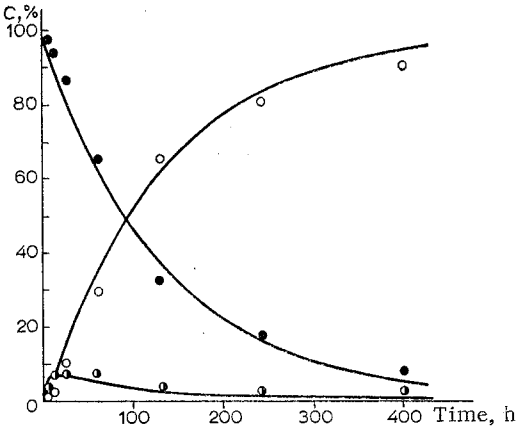


Fig. 1. Kinetics of the isomerization I ⇌ II → III in refluxing 8.8 N HBr (125°C). The relative percentages (C, %) in the reaction mixture of starting I (●), intermediate II (◑), and isomerization product III (○) with time are plotted. The calculated curves for the process A ⇌ B → C for the K_2, K_{-2}, and K_3 constants given in Table 1 are presented.

difference in the rates of opening of the rings of I and V in hydrobromic acid. A change in the structure probably leads to a change in the contributions of the various mechanisms of ring opening.

The results make it possible to evaluate various approaches to the synthesis of the benzo[f]-1,5-diazabicyclo[3.2.2]nonene (I) system. The high rate of cyclization of VI and the low rate of opening of the ring of reaction product I in hydrobromic acid make it possible to stop the reaction at the step involving the formation of I and isolate it in 95% yield. According to the kinetic data, the maximum concentration of I in the cyclization of II is reached after refluxing for 15 h in hydrobromic acid and amounts to only 37%. In practice, I was isolated in 11% yield under these conditions.

Thus in the development of methods for the synthesis of benzodiazabicycloalkene systems that contain an ethylene bridge it is most expedient to use intramolecular cyclization of β-X-ethylamines (X = OH, Hal) in hydrobromic acid.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Varian A 56/60 A spectrometer with tetramethylsilane as the external standard. Quantitative analysis of the composition of the reaction mixtures was carried out by ion-exchange chromatography on Aminex A-7 cation-exchange resin in a gradient of 2.0-4.0 N HCl by means of an Obi ultramicrospectrophotometer under the conditions described in [3]. Chromatography was carried out in an acidic medium, which excluded the possibility of transformation of the reaction products during analysis. Continuous spectrophotometry of the eluate at various wavelengths made it possible to quantitatively determine the relative percentages in the reaction mixture of all of the known components (up to 0.1%), which made it possible to thoroughly observe the initial sections of the kinetic reactions and to estimate the equilibrium constants up to 10^{-3}. The chromatograms were distinguished by comparing the areas of the peaks at the analytical wavelengths (210, 230, 250, 290, 300, 320, and 360 nm) with calibration data obtained from the chromatograms of artificial mixtures of the investigated compounds. Mathematical treatment of the results and calculation of the rate constants of the reactions were carried out with the formulas for a process of the A ⇌ B → C type [6]. Preparative chromatography was accomplished on plates with a loose layer of silica gel by elution with chloroform–ethanol [10:1 (system A) and 20:1 (system B)].

Benzo[f]-1,5-diazabicyclo[3.2.2]nonene (I) was obtained by the method in [8]. N-(γ-Bromopropyl)-1,2,3,4-tetrahydroquinoxaline (II) and 1,2,6,7-tetrahydro-3H,5H-pyrido[1,2,3,-d,e]quinoxaline (III) were obtained by the method in [1]. These substances were used as

references in the analysis of the reaction mixtures. N,N'-Trimethylene-o-phenylenediamine (VII) was obtained by the method in [9].

N-(β-Hydroxyethyl)-N,N'-trimethylene-o-phenylenediamine (VIII). A 0.65-ml (13.0 mmole) sample of ethylene oxide was added to a solution of 1.2 g (8.1 mmole) of VII in 12 ml of glacial acetic acid, and the mixture was maintained at 20°C for 3 days. It was then evaporated in vacuo, and the residue was neutralized with saturated sodium carbonate solution and extracted with 50 ml of chloroform. The extract was dried with magnesium sulfate and filtered, and the chloroform was removed by distillation in vacuo. The residue was chromatographed in system A with collection of the fraction with R_f 0.3-0.5. The product was eluted from the plate with 30 ml of chloroform–methanol (5:1) and recrystallized from 10 ml of toluene to give 0.8 g (51%) of VII in the form of a colorless crystalline substance with mp 95-97°C; its retention time in the column was 25 min. UV spectrum, λ (log ε): 210 (4.00), 230 (3.38), 250 (3.81), 290 (3.13), and 300 nm (2.81). IR spectrum: 763 (aromatic C–H), 1602 (aromatic C=C), 2817 (C–H), 3229 (N–H), and 3293 cm^{-1} (O–H). PMR spectrum (in $CDCl_3$): 6.5-7.0 (4H, m, aromatic protons), 4.0 (2H, s, NH, OH), 3.2-3.7 (8H, m, NCH_2, CH_2CH_2O), and 1.5-2.0 ppm (2H, m, CH_2). Found: C 68.8; H 8.6; N 14.7%. $C_{11}H_{16}N_2O$. Calculated: C 68.7; H 8.4; N 14.6%.

N-(β-Hydroxyethyl)-N'-ethoxycarbonyl-N,N'-trimethylene-o-phenylenediamine Hydrobromide (IX·HBr). A 0.8-ml (8.4 mmole) sample of ethyl chlorocarbonate was added with stirring and cooling to –20°C to a solution of 0.55 g (2.9 mmole) of VIII in 8 ml of absolute ethanol and 1.2 ml (8.6 mmole) of triethylamine, after which the mixture was warmed to 20°C in the course of 1 h and evaporated to dryness. The residue was chromatographed in system B with collection of the fraction with R_f 0.4-0.6. The product was eluted from the plate with 30 ml of chloroform–methanol (5:1), 0.3 ml (2.6 mmole) of 8.8 N HBr was added to the solution, and the mixture was dried by evaporation in vacuo with absolute ethanol three times at no higher than 50°C. The product was treated three times with 50-ml portions of absolute ether, and the mixture was filtered to give 0.77 g (77%) of IX·HBr in the form of a crystalline substance with mp 148-161°C (dec., from ethanol–ether); its retention time in the column was 18 min. IR spectrum: 778 (aromatic C–H), 1618 (aromatic C=C), 1712 (C=O), 2400-2600 (N^+–H), and 3348 cm^{-1} (O–H). PMR spectrum (in CD_3OD): 7.4-7.6 (4H, m, aromatic protons), 4.2 (2H, q, $COOCH_2$), 3.3-3.9 (8H, m, OCH_2), 1.9-2.5 (2H, m, CH_2), and 1.2 ppm (3H, t, CH_3). Found: C 48.6; H 6.1; Br 23.4; N 8.1%. $C_{14}H_{20}N_2O_3$. Calculated: C 48.7; H 6.1; Br 23.2; N 8.1%.

N-(β-Bromoethyl)-N'-ethoxycarbonyl-N,N'-trimethylene-o-phenylenediamine Hydrobromide (X·HBr). A 0.2-ml sample of diisopropylamine and 0.33 g (1.3 mmole) of triphenylphosphine were added to a suspension of 0.28 g (0.81 mmole) of IX·HBr in 3 ml of absolute chloroform, and 0.42 g (1.3 mmole) of carbon tetrabromide was added to the mixture with stirring, during which it became warmer and homogeneous. The solution was allowed to stand for 20 min, after which the product was isolated by chromatography in system B with collection of the fraction with R_f 0.7-0.8. The product was eluted from the plate with 20 ml of chloroform–methanol (5:1) and converted to the hydrobromide, which was recrystallized from a mixture of 2 ml of absolute ethanol and 5 ml of absolute ether to give 0.15 g (45%) of X·HBr with mp 133-151°C (dec.); its retention time in the column was 20 min. IR spectrum: 769 (aromatic C–H), 1608 (aromatic C=C), 1708 (C=O), and 2200-2400 cm^{-1} (N^+–H). PMR spectrum (in CD_3OD): 7.4-7.7 (4H, m, aromatic protons), 4.2 (2H, q, $COOCH_2$), 3.3-4.1 (8H, m, NCH_2, OCH_2), 1.9-2.5 (2H, m, CH_2), and 1.2 ppm (3H, t, CH_3). Found: C 41.2; H 5.0; Br 38.9; N 6.9%. $C_{14}H_{19}BrN_2O_2$. Calculated: C 41.2; H 4.9; Br 39.2; N 6.9%.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonene (I) and 1,2,6,7-Tetrahydro-3H,5H-pyrido[1,2,3,-d,e]quinoxaline (III). A solution of 0.48 g (1.4 mmole) of II·HBr in 4.8 ml of 8.8 N HBr was refluxed for 15 h, after which the solution was evaporated in vacuo, and the residue was neutralized with diisopropylamine and chromatographed in system A with collection of the fraction with R_f 0.2-0.4. The product was eluted with 30 ml of chloroform–methanol (5:1), the solution was evaporated, and I was extracted with ether and sublimed in vacuo at 100°C (2 mm). The yield of I was 28 mg (11%); its characteristics were in agreement with the data in [2]. Compound III was extracted from the fraction with R_f 0.5-0.6 and was sublimed at 120°C (2 mm). The yield of III was 0.10 g (40%); its characteristics were in agreement with the data in [1].

Benzo[f]-1,5-diazabicyclo[3.2.2]nonene Dihydrobromide (I·2HBr). A solution of 0.17 g (0.42 mmole) of urethane X·HBr in 3 ml of 8.8 N HBr was refluxed for 30 min, after which it was evaporated in vacuo, 2 ml of absolute ethanol was added to the residue, and the crystal-

line product was removed by filtration to give 0.13 g (95%) of I·2HBr with mp 210-215°C (dec., from ethanol). The characteristics of the product were in agreement with the data in [2].

Reaction of Urethane X in Hydrobromic Acid (Typical Method for the Study of the Kinetics of the Reactions). Samples (0.03-0.05 ml) of a solution of 3 mg (0.007 mmole) of urethane X·HBr in 0.3 ml of 8.8 N HBr were sealed in microampuls, which were then maintained in a thermostat at 125°C for the necessary time. During the reaction the ampuls were removed, and the composition of 1 μl of the reaction mixture was analyzed with a microcolumn. The concentration of VI in the reaction mixture was calculated on the basis of calibration with respect to an analytical sample of VIII using the similarity of the structures and UV spectra of these compounds. The maximum concentration of intermediate VI, which reached 21% of the initial concentration of urethane X, was observed in the reaction mixture after 4-5 min of thermostatting. The retention time of VI in the column was 30 min. UV spectrum, λ (log ε): 210 (3.98), 230 (3.38), 250 (3.81), 290 (3.13), and 300 nm (2.83). After thermostatting for 20 min, the reaction mixture consisted of 90% reaction product I, the retention time of which was 43 min. UV spectrum, λ (log ε): 210 (3.70) and 230 nm (2.22). The rate constants of the reactions calculated from the chromatographic data are presented in Table 1.

Kinetics of the Reactions of I and II in Hydrobromic Acid. The kinetics of the isomerization of I to III are presented in Fig. 1. The use of II as the starting compound made it possible to refine cyclization constants K_{-2} and K_3. The retention times of I-III in the column were, respectively, 43, 35, and 38 min. The substantial difference in the UV spectra of these compounds made it possible to distinguish the chromatograms even in the case of partial superimposition of the adjacent peaks. The calculated rate constants of the reactions are presented in Table 1.

Kinetics of the Cyclization of Base II in Sulfolane. A solution of 3 mg (0.009 mmole) of II·HBr and 7 mg (0.05 mmole) of ethyldiisopropylamine in 0.3 ml of sulfolane was sealed in microampuls, which were then maintained in a thermostat at 125°C. The kinetics of the reaction were studied by a typical method. The rate constant of the reaction is presented in Table 1.

LITERATURE CITED

1. A. A. Gall' and G. V. Shishkin, Khim. Geterotsikl. Soedin., No. 5, 677 (1983).
2. G. V. Shishkin, A. A. Gall', and G. A. Zloba, Khim. Geterotsikl. Soedin., No. 11, 1538 (1981).
3. G. V. Shishkin and A. A. Gall', Khim. Geterotsikl. Soedin., No. 6, 831 (1980).
4. G. Cerichelli, G. Illuminati, and C. Lillocci, J. Org. Chem., 45, 5952 (1980).
5. E. M. Engler, J. D. Andose, and P. R. Schleyer, J. Am. Chem. Soc., 95, 8005 (1973).
6. A. Rakowski, Z. Phys. Chem., 57, 321 (1906).
7. S. M. McElvain and T. A. Lies, J. Am. Chem. Soc., 82, 164 (1960).
8. G. V. Shishkin and A. A. Gall', Khim. Geterotsikl. Soedin., No. 6, 827 (1980).
9. H. Stetter, Chem. Ber., 86, 201 (1953).