CROATICA CHEMICA ACTA CCACAA 51 (3) 213—223 (1978)

CCA-1115

YU ISSN 0011-1643
541.124
Original Scientific Paper

Kinetics of Cyclization of 2-(*N*-β-Bromoethyl)-amino-5-substituted Benzophenones into 1,4-Benzodiazepines[1]

J. Kuftinec

Institute for the Control of Drugs, 41000 Zagreb, Croatia, Yugoslavia

L. Klasinc

»Ruđer Bošković« Institute, 41001 Zagreb, Croatia, Yugoslavia

F. Kajfež, M. Mihalić, E. Decorte, and V. Šunjić

Department of Biomedical and Biochemical Research, CRC, Chemical Research Company, 33048 San Giovanni al Natisone (UD), Italy

Received May 8, 1978

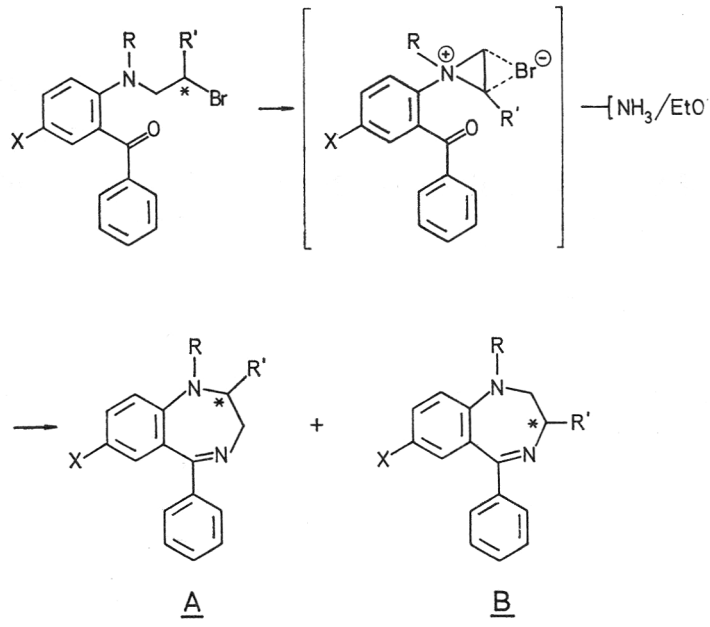
The overall pseudo-first order cyclization rates of 2-*N*-β-bromoethylamino-5-substituted benzophenones **1**—**3** into 1,4-benzodiazepines **7**—**9**, determined in 6% ethanolic ammonia at 100 °C, 115 °C, and 125 °C respectively, were found to range between 1.0×10^{-4} and 8.33×10^{-4} s^{-1} for **1**, between 1.6×10^{-4} and 5.83×10^{-4} s^{-1} for **2** and between 6.66×10^{-5} and 3.16×10^{-4} s^{-1} for **3**. Rate values calculated from the rising concentrations of cyclization products **7**—**9** were lower indicating the formation of stable intermediates. It is assumed that these are protonated aziridine derivatives **4**—**6**, since compounds **4** and **5** were identified as intermediates by TLC and GLC. The formation rate for the model compound 2-amino-5-chlorobenzophenone imine was found to be only 5.8×10^{-7} s^{-1} at 125 °C, which eliminates imine (C=NH) derivatives of **1**—**3** as possible intermediates. The ammonolysis rates of 3-phenylpropylbromide between 110 °C and 125 °C, were found to range from 1.5×10^{-4} to 4.16×10^{-4} s^{-1}. These values revealed that the β-participation of the *N*(2)-atom, being a relatively rapid equilibrium, does not enhance the overall cyclization rate. The following parameters characterize the overall cyclization process; $\Delta H^{\ddagger} = 50.0 \pm 4.0$ kJ mol^{-1} and $\Delta S^{\ddagger} = -156 \pm 5$ J mol^{-1} K^{-1} for **1**, $\Delta H^{\ddagger} = 89.9 \pm 4.0$ kJ mol^{-1} K^{-1} for **2**, $\Delta H^{\ddagger} = 75.3 \pm 4.0$ kJ mol^{-1} and $\Delta S^{\ddagger} = -89 \pm 4$ J mol^{-1} K^{-1} for **3**.

INTRODUCTION

2-Deoxy-1,4-benzodiazepines belong to an important class of the central nervous system (CNS) active compounds[2,3]. In previous papers[1,4], we gave stereochemical evidence for β-participation of vinylogous amide nitrogen during the cyclization of *N*-substituted 2-aminobenzophenone into these heterocycles (Scheme 1).

High regioselectivity in the ring opening of the intermediary aziridinium ion was observed. The retention of configuration in products **B** revealed the front side attack of ammonia on the intermediary ion pair. Another possibility

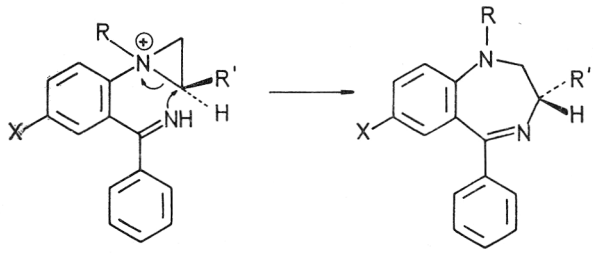
SCHEME 1.



X = H, Cl, NO_2
R = H, CH_3
R' = CH_3, C_2H_5

of the intramolecular front side attack by the intermediary formed ketimine according to Scheme 2, was proposed[5], however. In order to further clarify the cyclization pathway, we undertook a kinetic study, and in this paper we describe some results of this investigation.

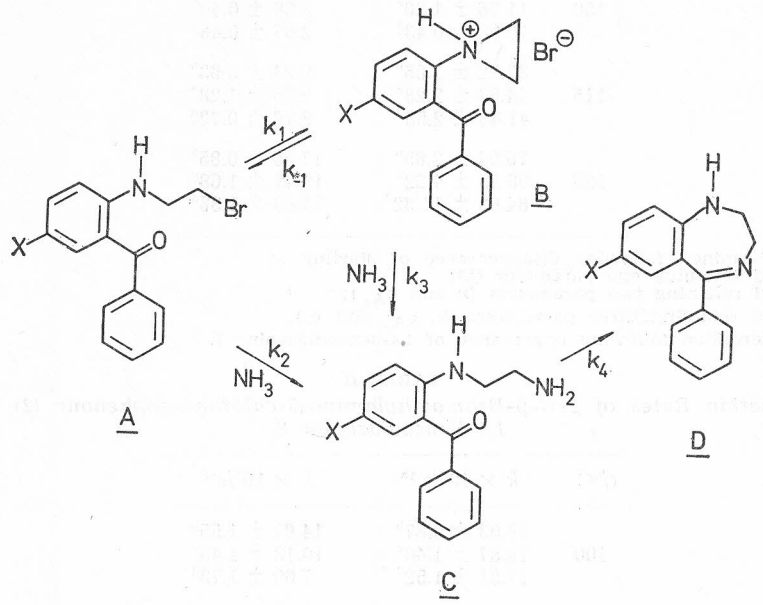
SCHEME 2.



RESULTS AND DISCUSSION

The kinetic scheme of the main steps during the ammonolysis and cyclization of 2-*N*-β-bromoethyl-5-substituted benzophenones is shown in Scheme 3.

SCHEME 3.



A full kinetic solution of such a multistep scheme requires a number of independent data on the concentrations of all involved species yielding the rates of particular steps by a sophisticated mathematical treatment[6,7]. Our main aims were, however, the following:

— to determine the overall cyclization rates of compound **A(1—3)**,

— to determine possible intermediates during the cyclization **A** → **D**.

— to determine the rate of formation of benzophenonimines of the corresponding *N*-unsubstituted benzophenones.

Thus, a simplified picture of the above scheme, based on some previous quantitative experimental results, turned to be satisfactory.

The relation $k_4 \gg k_2, k_3$ is based on our earlier experience[8] that the cyclization rate of 2-(*N*-α-aminoacyl)-amino-5-chlorobenzophenones at ambient temperature is very high, presumably much higher than any of the processes measured in this work. Moreover, compounds **C** were not identified under any experimental condition used, which indicates their undetectably low steady-state concentration caused by high k_4.

The total rate constants k were calculated as for the pseudo-first order reaction. The results are presented in Tables I—III where two constants, i. e. those obtained by following the disappearance of **A**, or those obtained by following the enhancement of concentration of **D** are presented. The difference

TABLE I

Cyclization Rates of 2-N-β-Bromoethylamino-benzophenone (**1**) *into 1,4-Benzodiazepine* **7**

t/°C	$k \times 10^5/s^{-1}$ [a]	$k \times 10^5/s^{-1}$ [e]
100	9.60 ± 0.45 [b]	3.67 ± 0.22 [b]
	11.76 ± 1.20 [c]	3.58 ± 0.40 [c]
	10.98 ± 0.43 [d]	2.57 ± 0.43 [d]
115	37.22 ± 1.05 [b]	9.23 ± 0.63 [b]
	44.67 ± 2.28 [c]	9.75 ± 1.28 [c]
	41.48 ± 2.55 [d]	6.78 ± 0.73 [d]
125	76.05 ± 2.85 [b]	17.58 ± 0.85 [b]
	88.55 ± 4.22 [c]	18.77 ± 1.68 [c]
	84.63 ± 11.52 [d]	14.63 ± 1.33 [d]

[a] Rates determined following disappearance of starting **1**;
[b] Calculated retaining one parameter (k);
[c] Calculated retaining two parameters (k and c_{A_o});
[d] Calculated retaining three parameters (k, c_{A_o} and c_A);
[e] Rates determined following appearance of 1,4-benzodiazepine **7**.

TABLE II

Cyclization Rates of 2-N-β-Bromoethylamino-5-chlorobenzophenone (**2**) *into 1,4-Benzodiazepine* **8**

t/°C	$k \times 10^5/s^{-1}$ [a]	$k \times 10^5/s^{-1}$ [b]
100	18.03 ± 0.87 [b]	14.67 ± 1.55 [b]
	19.87 ± 1.40 [c]	10.13 ± 1.43 [c]
	17.01 ± 1.52 [d]	7.60 ± 1.73 [d]
115	35.35 ± 1.00 [b]	21.47 ± 0.72 [b]
	38.72 ± 1.67 [c]	22.80 ± 1.47 [c]
	39.25 ± 2.15 [d]	22.48 ± 1.92 [d]
125	51.43 ± 2.27 [b]	22.97 ± 1.53 [b]
	59.80 ± 3.33 [c]	28.23 ± 3.53 [c]
	58.57 ± 4.38 [d]	13.30 ± 2.88 [d]

Subscripts a—e have the same meaning as in the Table I.

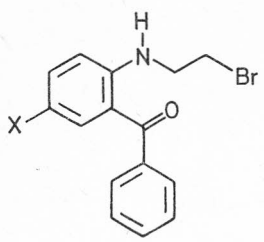
TABLE III

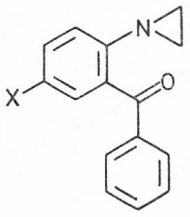
Cyclization Rates of 2-N-β-Bromoethylamino-5-nitrobenzophenone (**3**) *into 1,4-Benzodiazepine* **9**

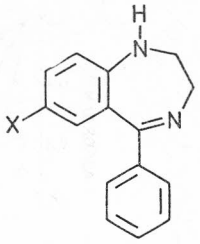
t/°C	$k \times 10^5/s^{-1}$ [a]	$k \times 10^5/s^{-1}$ [e]
100	6.50 ± 0.08 [b]	5.13 ± 0.23 [b]
	6.55 ± 0.15 [c]	5.00 ± 0.30 [c]
	6.47 ± 0.20 [d]	5.87 ± 0.52 [d]
115	16.43 ± 0.40 [b]	12.65 ± 0.70 [b]
	15.45 ± 0.68 [c]	11.42 ± 1.08 [c]
	16.77 ± 0.63 [d]	13.07 ± 1.15 [d]
125	31.03 ± 0.68 [b]	22.43 ± 1.10 [b]
	29.85 ± 1.18 [c]	20.63 ± 1.88 [c]
	31.00 ± 1.60 [d]	24.33 ± 2.12 [d]

Subscripts a—e have the same meaning as in the Table I.

in the values for k obtained by following these two components clearly reveals formation of some stable intermediates.







	1	2	3	4	5	6	7	8	9
X	H	Cl	NO_2	H	Cl	NO_2	H	Cl	NO_2

It turns out that these intermediates are aziridinium ions, i. e. protonated compounds **4**—**6**. They were identified by TLC, as free bases during the cyclization of compounds **1** and **2**. Since the high basicity of aziridine nitrogen is nearly unaffected on *N*-substitution[9], it could be proposed that protonated aziridines are real substrates for the nucleophilic ring (re)opening by bromide ion or ammonia. Figure 1 illustrates concentration changes of substrate **1**, of intermediary aziridine derivatives **4**, and of the product of cyclization **7**.
During the cyclization of **3**, the intermediary aziridinium compound **6** could not be detected, Figure 2 shows the absorption dependence of **3** at various temperature.

As already mentioned, other expected intermediates might be the corresponding ketimines of compounds **1**—**3**, as shown in Scheme 2. We were able, however, neither to identify them by TLC nor to determine their formation rate. Therefore the rate of formation of the model 2-amino-5-chloro-benzophenone--imine was determined. At 100 °C and 115 °C the reaction was too slow for

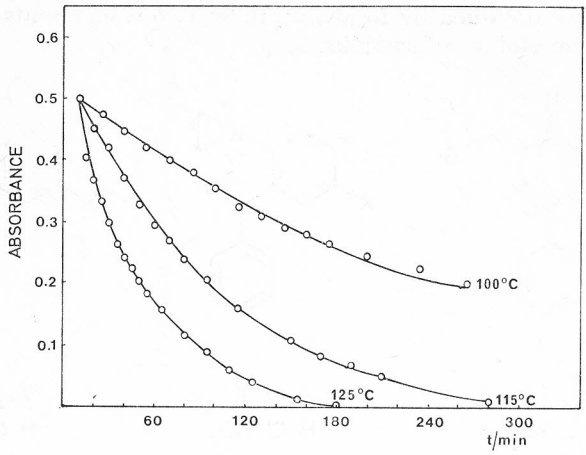


Figure 2. Concentration change of 3 during cyclization at 100 °C, 115 °C and 125 °C.

reproducible measurements, while at 125 °C k was determined to be 3.5×10^{-5} min^{-1}. Thus ketimine formation seems to be at least 10^3 times slower than the rate of the overall process of cyclization for 2-*N*-β-bromoethyl-derivative **2**. All attempts to isolate this ketimine failed, however, since it hydrolysed on standing on silicagel plates, or during chromatography on silicagel column, or during attempted crystallizations. In kinetic experiments it was quantitatively determined as benzophenone, after TLC separation from unreacted benzophenone, and subsequent hydrolysis.

Although we had thus kinetically confirmed β-participation postulated earlier[4], it remained open if it actually contributes to the enhancement of the overall cyclization rate. Therefore a parallel study of the ammonolysis rate of the simple model compound, 3-phenylpropylbromide, was undertaken. The results are given in Table IV.

TABLE IV

Ammonolysis Rates of 3-Phenyl-propylbromide

t/°C	$k \times 10^5$/s^{-1}[a]
100	14.73 ± 0.82[b] 14.65 ± 0.60[c]
115	15.52 ± 2.82[b] 16.55 ± 2.08[c]
125	17.67 ± 3.13[b] 18.75 ± 2.32[c]

Subscripts a—e have the same meaning as in the Table I.

These data revealed that only at 115 °C and 125 °C the overall cyclization rate for compounds **1**—**3** was somewhat higher than the rate of ammonolysis of the model compound. At 100 °C, however, only the most reactive compound **3**

exhibited a higher cyclization rate than ammonolysis of 3-phenyl-propyl-bromide. Thus, no significant enhancement of the overall cyclization rate by β-participation has been found, which is presumably a consequence of the rapid equilibrium established on β-participation. The subsequent nucleophilic attack by ammonia should be the rate determining step.

Temperature dependent rate determinations (see Figure 3) allowed the calculation of thermodynamic parameters given in the Table V.

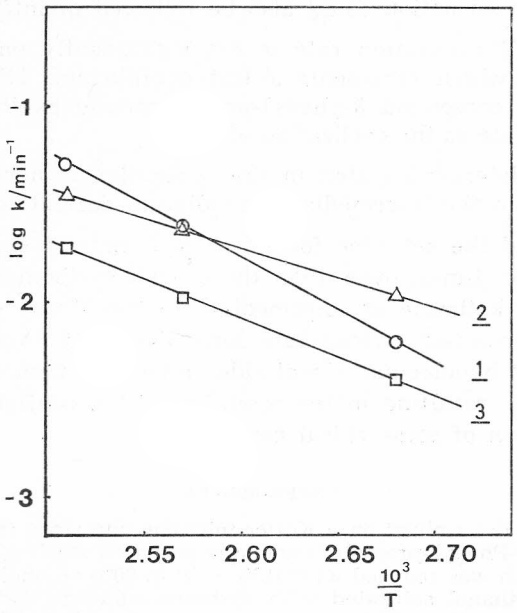


Figure 3. Temperature dependence of overall cyclization rates of the compounds 1—3.

TABLE V

Thermodynamic Parameters for Overall Cyclization Rates of the Compounds **1—3**

	$\Delta H^{\neq} \times 10^{-4}$/J mol^{-1}	$\Delta S^{\neq}$/J mol^{-1} K^{-1}
1	4.77 ± 0.2[a]	—156.5 ± 5.0[a]
	5.15 ± 0.08[b]	—145.2 ± 1.2[b]
	5.48 ± 0.54[c]	—137.2 ± 13.0[c]
2	9.29 ± 0.54[a]	— 39.7 ± 13.0[a]
	8.95 ± 0.58[b]	— 46.4 ± 15.0[b]
	9.21 ± 0.46[c]	— 40.6 ± 12.0[c]
3	7.62 ± 0.25[a]	— 89.5 ± 6.3[a]
	7.57 ± 0.54[b]	— 89.9 ± 13.3[b]
	7.49 ± 0.08[c]	— 92.5 ± 2.1[c]

[a] Values obtained from kinetic data using one, b-two, and c-three variables.

Since the activation parameters actually relate to a composite process, they should be considered with caution, consequently, we prefer to draw no conclusions therefrom.

CONCLUSION

From the results described above the following conclusions may be drawn:

(*a*) β-Participation of the *N*(2)-atom takes place during cyclization of compounds **1**—**3**. It gives rise to the formation of stable intermediates, protonated forms of **4**—**6**, which could be identified as free bases. In two cases their formation could also be followed quantitatively.

(*b*) The overall cyclization rate is not significantly enhanced by β-participation, which represents a fast equilibrium. The ammonolysis of the model compound 3-phenyl-propylbromide exhibits approximately the same rate as the cyclization of **1**—**3**.

(*c*) The rate determining step in the cyclization is nucleophilic attack of ammonia on the intermediary aziridinium derivatives of **4**—**6**.

(*d*) The rate of the ketimine formation of 2-amino-5-chloro-benzophenone is about 10^3 times lower than the overall cyclization rate. This result eliminates ketimine as intermediate in the »front side« ring opening of the intermediary aziridinium derivatives **4**—**6**. It confirms the earlier proposed[1,4] bimolecular »front side« attack of ammonia on aziridinium derivatives, resulting in the retention of the configuration during the recyclization of some chiral compounds.

EXPERIMENTAL

All mp.'s were determined on a Kofler microheating stage (Boetius), uncorrected values are given. 3-Phenyl-propylbromide was prepared starting from cinnamic acid (Fluka puriss.) which was reduced with 10% Pd/C in 90% ethanol (quantitative yield), and esterified in ethanol saturated with hydrogen chloride (78% yield of ester bp 135—140 °C/20—22 mm Hg)*. This ester was reduced with $LiAlH_4$ in ether using a standard procedure[10], giving 3-phenyl-propanole (bp 125—128 °C/8 mm Hg, lit.[11] bp 119 °C/12 mm Hg) in 96% yield. This alcohol was brominated in nitromethane using PBr_3 in great excess. 3-Phenyl-propylbromide was obtained in 75% yield after dilution with water, extraction with ether and, after drying and evaporation of the solvent, distillation at 68—72 °C/16 mm Hg (lit.[12] bp 110 °C/12 mm Hg). NMR (CCl_4) = δ in ppm; 2.10 (s, 2 H), 2.72 (t, 2 H), 3.26 (t, 2 H), 7.1 (s, 5 H).

Kinetics

All UV kinetic measurements were performed on Varian Techtron Mod. 635 UV-VIS spectrophotometer using 1 cm silica-grade cells. Samples were prepared by weighing 25.0 mg of the substrate, and dissolving them into 25.0 ml of 6% ethanolic solution of ammonia. This solution was divided into 15 ampoules, which were sealed under ice-water cooling. They were thermostated at reaction temperature using a block-thermostat BT-3, Grant Co., Cambridge, England. The reaction temperature was maintained within ± 0.2 °C. Quenching of the reaction was performed by cooling the samples in an ice bath. TLC's were performed on silicagel plates F254 (Merck), 20 × 20 cm. The separation of the components was performed using benzen-cyclohexane-ethanol (50 : 50 : 10, eluation system *A*), or the same solvents in the ratio 50 : 50 : 20 (eluation system *B*). In the first system, separation of the starting compounds **1**—**3** ($R_f \sim 0.8$) from intermediate aziridines **4**—**6** ($R_f \sim 0.4$) was achieved,

* 1 mm Hg ≈ 133.322 Pa

while 1,4-benzodiazepines remained on the start. In the second system, 1,4-benzodiazepines **7**—**9** moved up $R_f \sim 0.2$, while all other compounds moved with the front of the solvent mixture.

Chromatographic plates (20 × 20 cm) were divided into 8 vertical segments 15 mm wide. Within these segments, 50 μl of the solution from the ampoule was spotted on line 2 cm up from the edge of the plate. After eluation with system *A*, zones containing starting compounds **1**—**3**, and aziridines **4**—**6** were identified under a UV_{254} lamp, then scratched off from the plate and transferred into a centrifuge glass (10 ml volume) which contained 5 ml of ethanol. The stopped glass was shaken on the shaker at 80 cycles per minute for 10 min. Then it was centrifuged at 5000 revolutions per second, the ethanolic supernatant transferred into a UV cell and extinctions at particular wavelenghts (385 nm for **1**, 240 nm for **2** and 365 nm for **3**) were measured. For the first and last sample, the whole spectra between 300—450 nm were run.

Thereafter, the same TLC plate was eluated with system *B*, the zone of the 1,4-benzodiazepines identified and scratched off. It was transferred into a tube containing 5.0 ml 0.1 molar HCl, then shaken and the centrifugation was performed as described above. The extinctions were measured at 245 nm for **1**, 440 nm for **2**, and 365 nm for **3**.

The obtained ε_{max} values vs. time were used for calculating the pseudo-first order rate constants by iterative nonlinear regression using the least-square method. All attempts to determine the overall cyclization constants by UV spectrophotometry following the concentrations of the various components during cyclization without separation failed, although the maxima of all components were well separated. The measured ε_{max} vs. time values did not allow calculations of k's with more than 20% confidence (reliability).

Negative results were also obtained using GLC as a kinetical tool. Using Chromosorb 6 coated with 2% Dexyl, a GC 300 (Pye Unicam, Analbs) column was prepared according to the literature[13]. Samples (1 μl) from the ampoules were injected directly into the chromatograph, and separation was achieved at 200 °C for the cyclization of **1**, at 215 °C for the cyclization of **2**, and at 230 °C for the cyclization of **3**. The injection block temperature was always 260 °C, the carrier gas, argon, had a flow rate 50 ml/min, and area 450 ml/min. Good separation of the peaks was achieved, as shown in the Figure 4. Quantitative evaluation of the peaks was impossible, however, because of the concomitant decomposition of the compounds in the column.

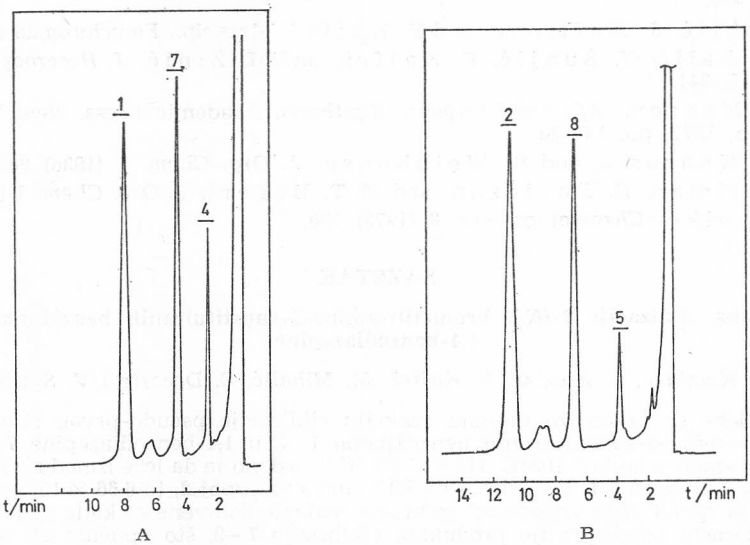


Figure 4. A. Gas chromatogram of the mixture of the compounds **1**, **4** and **7**. B. Gas chromatogram of the mixture of the compounds **2**, **5** and **8**.

Argentometric Titration of free bromide ions was used for the kinetics of ammonolysis of 3-phenyl-propylbromide. Titrations were performed using a TTT 2 titrator (Radiometer, Copenhagen) equipped with an ABU 13 automatic burette, and a SBR 2c recorder. A pair of electrodes Hg-$HgSO_4$/Ag-AgCl was used. The sample was pipetted from the ampoule, and acetonitrile (4 ml), and 2.5% nitric acid (10 ml) were added. The titration was then performed using 0.01 molar $AgNO_3$. The consumed reagent (ml) was plotted vs. time, and the k's of ammonolysis were calculated as described above. This method was not used for the determination of the kinetics of the bromine displacement in compounds **1**—**3**, since no reproducible titrations could be obtained. Some interaction of silver ions with the benzophenone moiety might be assumed.

Kinetics of formation of 2-amino-5-chlorobenzophenone-imine was determined using same reaction conditions (125 °C in the thermostat, ampoulation in 6% ethanolic ammonia) as for the cyclization procedures. After applying 10 μl of the reaction solution to TLC immediate eluation with dry benzene was performed. The zone of benzophenone-imine ($R_f \sim 0.2$) could then be quantitatively hydrolyzed back to the starting benzophenone by leaving the plate standing overnight, or by spraying it with 0.1 molar HCl. It was then scratched off, shaken and centrifuged with 5.0 ml of ethanole. 2-Amino-5-chlorobenzophenone was quantitatively determined at 238 nm.

Acknowledgement. — The authors are indebted to Dr. B. Ruščić for his valuable help in developing computer programs and rate constant calculations.

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SAŽETAK

Kinetika ciklizacije 2-(*N*-β-brometil)-amino-5-supstituiranih benzofenona u 1,4-benzodiazepine

J. Kuftinec, L. Klasinc, F. Kajfež, M. Mihalić, E. Decorte i V. Šunjić

Određene su brzine za ukupnu reakciju ciklizacije pseudo-prvog reda 2-(*N*-β--brometil)-amino-5-supstituiranih benzofenona **1**—**3** u 1,4-benzodiazepine **7**—**9** u 6% etanolnom amonijaku kod 100 °C, 115 °C i 125 °C, i nađeno je da leže između 1.0×10^{-4} s^{-1} i 8.33×10^{-4} s^{-1} za spoj **1**, 1.6×10^{-4} s^{-1} i 5.8×10^{-4} s^{-1} za spoj **2**, te 6.66×10^{-5} s^{-1} i $3.16 \times \times 10^{-4}$ s^{-1} za spoj **3**. Niže vrijednosti za brzine reakcije dobivene su kada su bile izračunane iz porasta koncentracije produkata ciklizacije **7**—**9**, što upućuje na nastajanje stabilnih intermedijara. To su protonirani aziridinski derivati **4**—**6**, a spojevi **4** i **5** su identificirani kao intermedijari koristeći kromatografiju na tankom sloju i plinsku kro-

matografiju. Brzina nastajanja imina modelnog spoja 2-amino-5-klor-benzofenona bila je kod 125 °C 5.8×10^{-7} s^{-1}, što je eliminiralo taj spoj kao mogući intermedijar. Brzina amonolize drugoga modelnog spoja, 3-fenil-propilbromida, određena između 110 °C i 125 °C, iznosila je od 1.5×10^{-4} s^{-1} do 4.16×10^{-4} s^{-1}. Te vrijednosti pokazuju da β-participacija atoma $N(2)$, budući da je to brzo ravnotežna reakcija, ne povećava brzinu ukupne reakcije. Slijedeći termodinamički parametri karakteriziraju ovu reakciju ciklizacije; $\Delta H^{\ddagger} = (50{,}0 \pm 4{,}0)$ kJ mol^{-1}, $\Delta S^{\ddagger} = (-156 \pm 5)$ J mol^{-1} K^{-1} za spoj **1**, $\Delta H^{\ddagger} = (89{,}9 \pm 4{,}0)$ kJ mol^{-1}, $\Delta S^{\ddagger} = (-41 \pm 4)$ J mol^{-1} K^{-1} za spoj 2, $\Delta H^{\ddagger} = (73{,}5 \pm 4{,}0)$ kJ mol^{-1}, $\Delta S^{\ddagger} = (89 \pm 4)$ J mol^{-1} K^{-1} za spoj **3**.

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CHIMICA, 33048 SAN GIOVANNI
AL NATISONE (UD), ITALIJA

Prispjelo 8. svibnja 1978.