1,4-Benzodiazepines III (1). Cyclization Paths of Hexaminium Salts of 2-Chloroacetamido-5-chlorobenzophenone and its *N*-Methyl Derivative

N. Blažević, V. Šunjić, I. Crvelin, D. Kolbah, and F. Kajfež (2)

Compagnia di Ricerca Chimica SA., Chiasso, Switzerland, Institute of Organic Chemistry and Biochemistry, and Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Yugoslavia

Received November 22, 1971

This study reports the isolation and characterization of hexaminium salts of 2-chloroacetamido-5-chlorobenzophenone (I) and of 2-(*N*-methyl)chloroacetamido-5-chlorobenzophenone (II). The 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (VI) and 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (VII), respectively are of pharmacodynamic importance. Based on chromatographic separation of some intermediates, and on spectrophotometric monitoring of cyclizations I → VI and II → VII, respectively, two different pathways for these reactions have been proposed. Since the slowest step in the reaction sequence II → VII follows the quasi first order rate law, intramolecular nucleophilic attack of the benzophenone carbonyl group on the hexamine moiety proved to be decisive for the cyclization (scheme II). However, cyclization I → VI seems to incorporate quite different solvolytic pathways in addition to one corresponding to the sequence II → VII. Isolated 4-imidazolidinone intermediates *N,N'*-methylene-bis[3-(2'-benzoyl-4'-chloro)phenyl]-4-imidazolidinone (III), and 3-(2'-benzoyl-4'-chlorophenyl)-4-imidazolidinone hydrochloride (IV) recyclize into the 1,4-benzodiazepine VI. The optimal reaction conditions have been found to be between *p*H 6-7.

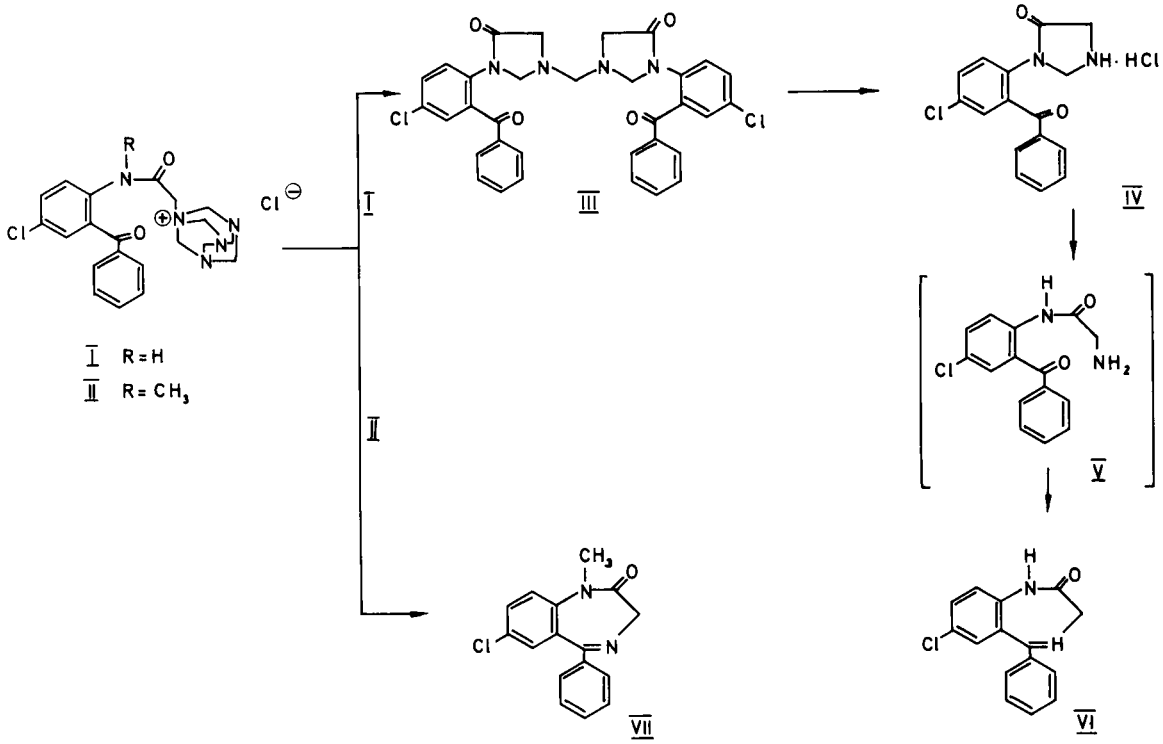
Introduction.

In earlier communications (3,4) a simple, unambiguous and economic procedure for the preparation of various 5-phenyl-7-substituted-1,4-benzodiazepines has been described. Starting from 2-(α-haloacetyl, or 2-(α-haloethyl)amino-5-substituted benzophenones and hexamine (hexamethylenetetramine), corresponding 1,4-benzodiazepines have been obtained in yields generally higher than 85-90%. Although corresponding hexaminium salts have been postulated as intermediates in these reactions, we have not been able so far to isolate these compounds in pure form. In this paper we describe a simple isolation procedure of the title compounds, I and II, as well as more detailed investigations of their cyclization pathways to the corresponding 1,4-benzodiazepin-2-ones, VI and VII. Once isolated, hexaminium salts I and II cyclize almost quantitatively under mild conditions, a neutral, slightly acidic or basic medium and temperatures between 25-35°. Similar conditions are present *in vivo*, and compounds I and II incorporate a physiologically compatible hexamine moiety, so that these compounds are of pharmacological importance. Hexaminium complexes of the type I and II, as potential *in vivo* precursors of 1,4-benzodiazepin-2-ones are of interest because of their strong hydrophilic character. This property is often unsatisfactorily shared by 1,4-benzodiazepines, causing some restrictions in their application (5). Therefore, a more detailed study of cyclization rate and cyclization pathways of the title hexaminium salts is of both chemical, and pharmacodynamical interest.

Results and Dicussion.

Following the cyclization rate of I and II in a neutral or slightly acid medium by thin-layer chromatography (see Experimental), an unexpectedly great difference in the reaction course was observed. The hexaminium salt I was converted into VI more slowly than II was into VII, and some isolable intermediates in the sequence I → VI were formed. On the other hand, II was converted into VII much faster without the formation of any observable intermediate (Scheme I). During the cyclization I → VI four substances were indicated by tlc; three of them disappeared during the reaction giving VI which was regularly isolated in a high yield. Of the three intermediates only III and IV were present in the reaction mixture for a longer time and in greater quantities. They were isolated by column chromatography after the reaction was stopped at an early stage. The third intermediate was present in traces only, and could not be

SCHEME I



isolated after repeated trials.

Compounds III and IV exhibited similar nmr and ir spectra. Nmr spectrum of the compound III revealed two groups of signals at δ about 3.20 ppm and 4.55 ppm in relation 3:2 and an unresolved multiplet in the aromatic region - δ 7.25-8.0 ppm. The signal at 3.20 ppm included two unresolved singlets at δ 3.20 and δ 3.17, respectively. The spectrum of compound IV showed two singlets at δ 4.27 and 5.52 ppm along with the same aromatic multiplet between *ca.* 7.25-8.0 ppm. Both compounds exhibited characteristic bands at 1710-1740, 1665-1673 and 1590-1595 cm^{-1}. Compound IV, isolated as the hydrochloride, revealed two additional strong bands at 3400-3450 and 2450-3000 cm^{-1}, respectively. Regarding the uv spectra of III and IV it could be noted that the spectrum of III exhibited a definite hyperchromic effect in relation to IV, however, without any observable bathochromic shift of the corresponding maximum, as had been expected for the weak conjugation of phenylimidazolidinone chromophores insulated by one methylene group (6). The amide bands of the lactam type at 1710-1740 cm^{-1}, as well as simple nmr spectra with isolated signals for methylene protons indicated imidazolidinone moiety to be included in the compounds III and IV. Since both compounds gave VI during chromatography on silica, or after short heating in an inert solvent (chloroform, acetonitrile), no analytically pure sample could be obtained. To prove their structure crude samples of *N,N'*-methylene-bis[3-(2'-benzoyl-4'-chloro)phenyl]-4-imidazolidinone and of 3-(2'-benzoyl-4'-chlorophenyl)-4-imidazolidinone hydrochloride were prepared according to the procedure from the patent literature (7). Their nmr, ir and uv spectra were identical with those of the intermediates III and IV. For the unstable third intermediate, structure V was proposed. Its structure was proved by the preparation of the crude sample of 2-glycylamido-5-chlorobenzophenone *via* hydrobromide according to the procedure described (8). Comparison by chromatography in different solvent systems indicated structure V for this intermediate. These results indicate that the cyclization pathways of I and II are different, both deviating from the course of the Delépine and Sommelet reactions of hexaminium salts (9).

A further insight into the reaction course has been obtained from chromatographic and spectrophotometric results. Ultraviolet spectra of the compound I-VI exhibited some characteristic features which were used for kinetic control. All spectra were measured in a strong acidic medium (0.1 *N* hydrochloric acid), since it was found that the spectra of the compounds investigated were practically unchanged within 3-4 hours. Cyclizations I →

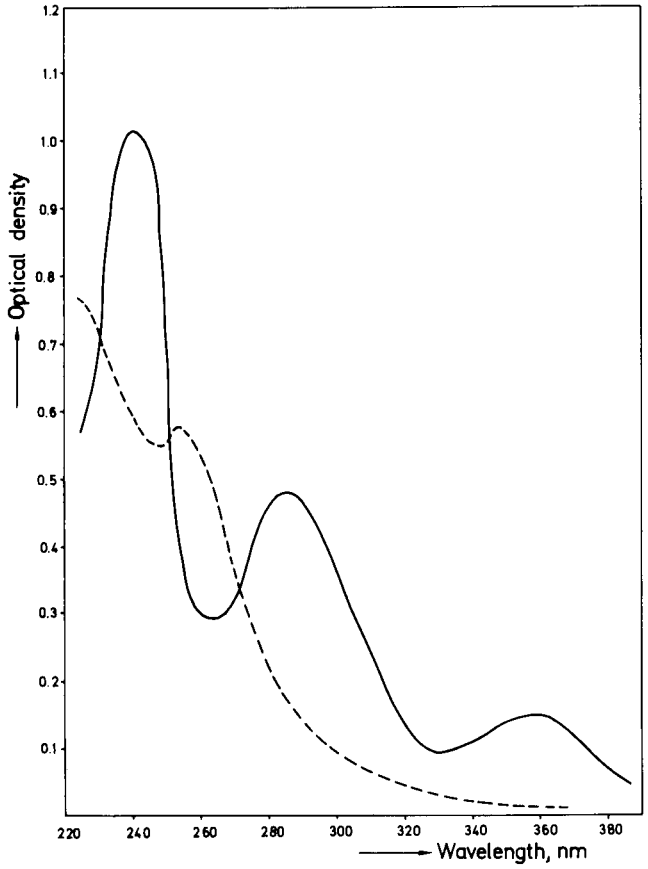


Figure 1. Ultraviolet spectra of II and VII (- - - II; ——— VII).

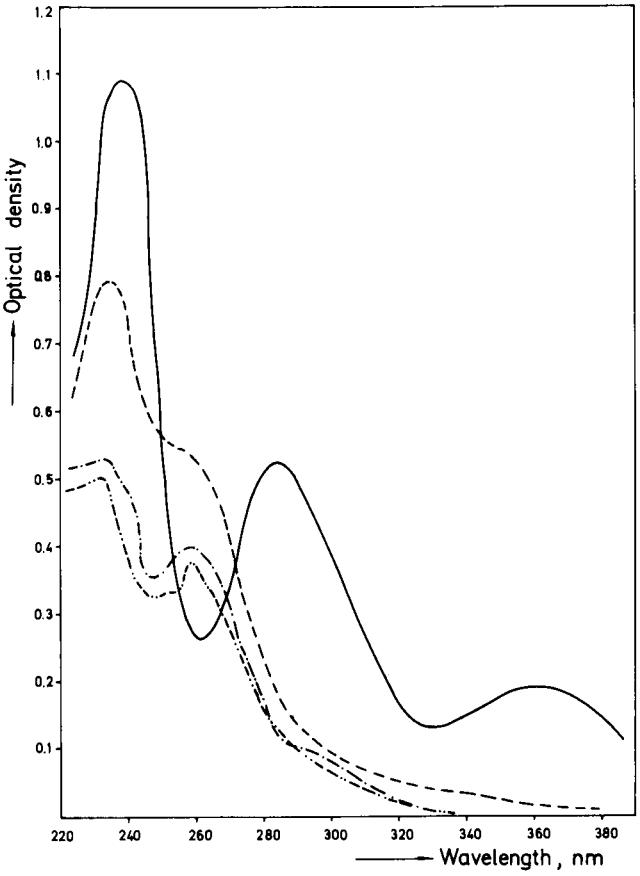


Figure 2. Ultraviolet spectra of I, III, IV, and VI (- - - I; ····· III; ····· IV; ——— VI).

VI and II → VII, respectively, were monitored at 285 and 359 nm, where characteristic maxima of the products appeared.

In Figure 3 a plot absorption-time is given for the cyclization of I and II at 37.0° and *p*H 7.45, *i.e.* under conditions approximating physiological systems. Compound II cyclizes into VII according to a quasi-monomolecular reaction and apparently follows a first order rate law. Absorption-time plot for the reaction I → VI was rather irregular indicating the rate determining formation of some intermediates. This is in agreement with chromatographically indicated and isolated intermediates III and IV.

The dependence on *p*H of cyclization IV → VI was investigated by tlc (see Experimental). Results from experiments carried out between *p*H 1.0 and 8.0 are given in Table I. The results reveal that the interval between *p*H 6-7 is optimal for the cyclization, and that the reaction is inhibited in a strong acidic medium. It was only in the experiments 5-8 that traces of the amino-derivative V were detected within 0.5-2 hours of the reaction time. Obviously, this can be a consequence of different reaction rates for the consecutive reaction IV → V and V → VI, the latter being more rapid. A detailed analysis of the

TABLE I

*p*H and Time Dependent Recyclization of IV → VI as Monitored by tlc (% of VI are given; temperature 30° ± 1°)

*p*H/hrs.	1	2	4	8	24	48
1.0	0	0	0	0	0	0
2.0	0	0	0	0	0	0
3.0	0	1.5	3	5	10	12
4.0	3	5	10	25	35	45
5.0	5	10	15	30	45	60
6.0	10	15	25	40	50	70
7.0	15	22.5	35	50	65	80
8.0	12.5	15	20	40	50	65

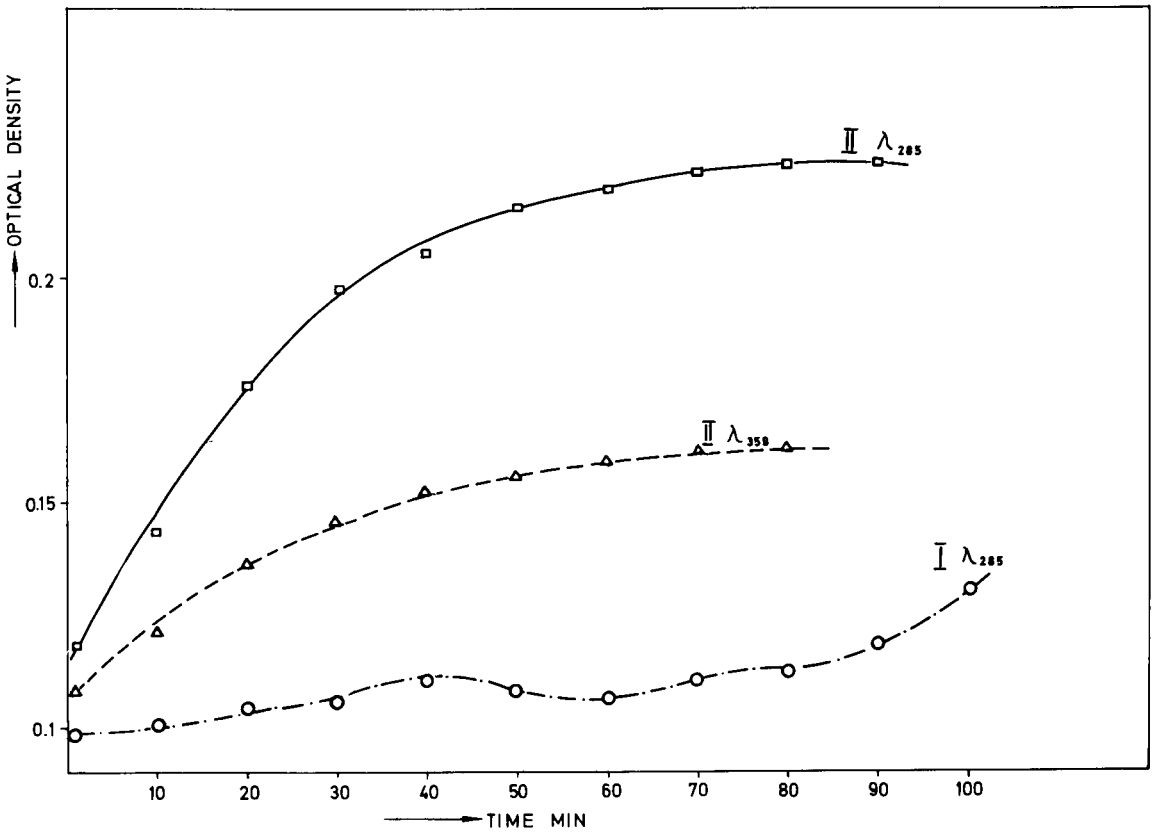


Figure 3. o---o---o Time - Optical Density Plot for Cyclization I → VI at 285 nm □-□-□ (285 nm) and △--△--△ (359 nm) Time Optical Density Plots for Cyclization II → VII.

time dependent concentration of V is difficult, because the first step in the sequence IV $\underset{k_2}{\overset{k_1}{\rightleftarrows}}$ V $\xrightarrow{k_3}$ VI is reversible (10). Preliminary results revealed that k_3 was of the order 10^{-4} sec^{-1}. Full investigation of this system and computations will be published separately.

These results indicate that the muscle-relaxing activity cited (7) for the compounds III and IV should be ascribed to the *in vivo* formed 1,4-benzodiazepine VI. On the other hand, cyclization II → VII is kinetically more simple and faster than I → VI. From the data in Figure 3 k_1 and $t_{1/2}$ are calculated:

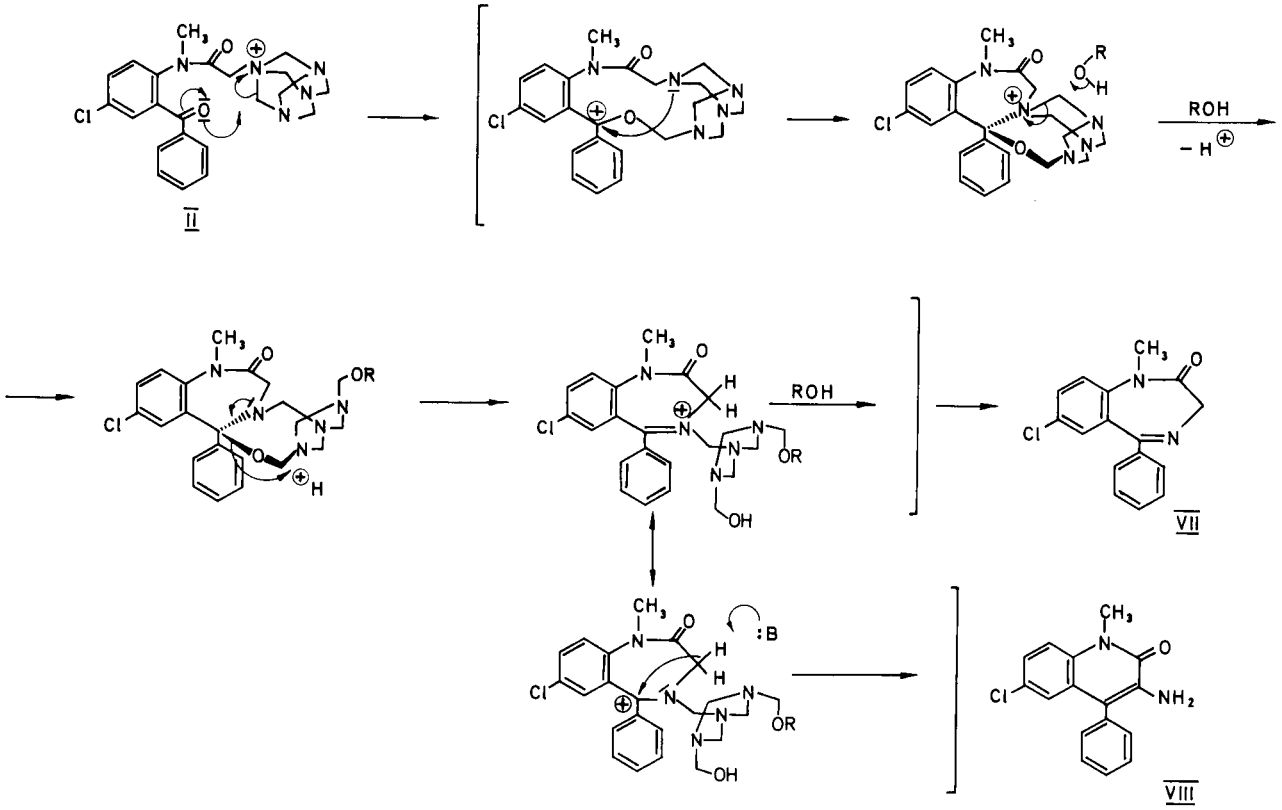
$$k_1^{285} = 5.68 \times 10^{-4} \text{ sec}^{-1}$$

$$k_1^{389} = 5.59 \times 10^{-4} \text{ sec}^{-1};\ t_{1/2} = 20.3 \text{ min.}$$

The proposed mechanism is shown in Scheme II and is envisioned as starting by intramolecular nucleophilic attack of the carbonyl group. Inspection of Dreiding, and of CPK-models of I and II reveal that the intramolecular attack on one of the α-methylene groups near the quaternized nitrogen in the hexamine moiety are sterically preferred.

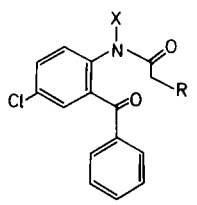
Due to the known polarization of the benzophenone carbonyl group (11), where the net charge on the oxygen atom was calculated as 0.4724, it is assumed that this group is the strongest nucleophile in this reaction. The formation of another product in somewhat altered reaction conditions as used for II → VII could be explained by the same mechanism (Scheme II). When a concentrated ethanolic solution of II was heated without additions of acid, formation of VIII, up to a yield of 85%, was achieved. This compound was described (12,13) earlier as a by-product in the cyclization of 2-haloacetamido-5-chlorobenzophenone into the 1,4-benzodiazepin-2-one with ammonia. On the other hand, base catalyzed recyclization of N^4-acetyl-1,4-benzodiazepin-2-one into the *N*-acetyl derivative of VIII has also been described (13). Therefore, in the base-catalyzed conversion of II into VIII, an intermediate with a positively charged nitrogen atom is proposed, as indicated in Scheme II. Heating of VII with

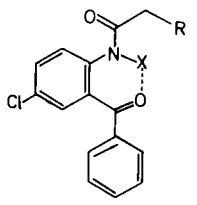
SCHEME II



hexamine under the same conditions gave no VIII as product, which excludes recyclization VII → VIII under the reaction conditions. Various fragments of hexamine decomposition could be proposed as base catalyst, *i.e.* ammonia or methylenimine, but an intramolecular C-3 deprotonation by secondary amino groups within partially decomposed hexamine moiety is also possible.

At the present, we can not fully explain which factors are responsible for the differences observed in cyclizations I → VI and II → VII, respectively. Conformational differences between the structures of complexes I and II seem to be of prime importance. Space-filling models reveal that conformation B cannot be achieved when X = CH_3 (as in II, where R is the hexaminium ion), but is possible when X = H, as in I (where R is the hexaminium ion).





The stabilization of the structure B by intramolecular hydrogen bonding seems to be participating in I. A typical shift of the carbonyl stretching band (14,15) appears in solid-state ir spectrum of I and IX, in relation to II and X, respectively, indicating strong intramolecular hydrogen bonding in these compounds (Table II). However, from these data it is not possible to conclude on the formation of such a hydrogen bond in the hydroxylic solvents used for cyclization of I and II.

TABLE II

Ir Carbonyl Frequences (cm^{-1}) of Some 2-Aminobenzophenones General Formulae A or B (in potassium bromide)

Compound	R	X	ν CO	$\Delta\nu$ CO
I	$(CH_2)_6N_4^+$	-H	1600	48
II	$(CH_2)_6N_4^+$	$-CH_3$	1648	
III	-bis-imidazolidinone		1673	8
IV	-mono-imidazolidinone		1665	
IX	-Cl (a)	-H	1631	24
X	-Cl (a)	$-CH_3$	1655	

(a) Compounds prepared according to ref. (16).

EXPERIMENTAL

Melting points were determined microscopically on a Boetius Mikroheiztisch apparatus. Ir spectra were recorded with a Perkin Elmer M 257 spectrophotometer. Nmr spectra were determined on a Varian A-60 instrument with TMS as an internal standard. The uv spectra, as well as the cyclization rates were measured on a Zeiss Opton PMQ II spectrophotometer. Thin-layer chromatography was performed on silica gel Merck HF_{254}, and for column chromatography silica gel Merck (70-325 mesh) was used. Fraction content was controlled by thin layer chromatography, spots being indicated under a uv lamp (254 nm) or by ninhydrin reaction. Elemental analyses were performed in the microlaboratory of the Department of Chemistry, Faculty of Pharmacy and Biochemistry, University of Zagreb.

Hexaminium Salt of 2-Chloroacetamido-5-chlorobenzophenone (I).

2-Chloroacetamido-5-chlorobenzophenone (5.0 g., 16.2 mmoles) and 2.45 g. (17.5 mmoles) of hexamine in 50 ml. of dry acetonitrile were stirred at room temperature for 72 hours. At the beginning of the reaction both reactants dissolved, after which the separation of the product began. The crude product was collected (7.2 g.), (m.p. 178-185°) and recrystallized by dissolution in hot chloroform and precipitation with ether. Pure product, opalescent plates, melted at 178-181°; ir: 3400, 2800, 1675, 1600, 1535, 1495, 1295, 1275, 1125, 1050, 1010, 950, 830, and 700 cm^{-1}; nmr (DMSO-d_6) δ 4.55 (s-broad, 6H), 4.86 (s, 2H), 5.22 (s-broad, 6H), 7.45-7.68 (unresolved multiplet, 8H), 9.95 ppm (s, 1H).

Anal. Calcd. for $C_{21}H_{23}Cl_2N_5O_2$ (448.36): C, 56.26; H, 5.17; N, 15.62. Found: C, 56.12; H, 5.27; N, 15.86.

Hexaminium Salt of 2-(*N*-Methyl)chloroacetamido-5-chlorobenzophenone (II).

A mixture of 2-(*N*-methyl)chloroacetamido-5-chlorobenzophenone (1.0 g., 3.1 mmoles) and 0.47 g. (3.4 mmoles) of hexamine was stirred in 50 ml. of dry acetonitrile at room temperature for 24 hours. The crude product which separated during the reaction was collected (1.15 g.) m.p. 159-166°. Recrystallization from cold chloroform and precipitation by ether gave an analytically pure product, m.p. 160-165°; ir (potassium bromide): 3300 (broad), 2850 (broad), 1665, 1648, 1490, 1270, 1115, 1010, 960 (doublet) and 850 cm^{-1}; nmr (DMSO-d_6) δ 2.92 (s, 3H), 4.60 (s-borad, 6H), 4.88 (s, 2H), 5.30 (s-broad, 2H), 5.47 (s-broad, 4H), 7.53-7.83 (unresolved multiplet, 8H).

Anal. Calcd. for $C_{22}H_{25}Cl_2N_5O_2$ (462.39): C, 57.16; H, 5.45; N, 15.15. Found: C, 56.93; H, 5.81; N, 14.90.

Chromatographic Analysis of the Reaction Mixture for the Reaction I → VI.

The hexaminium salt (0.476 g.) was dissolved in 10 ml. of 96% ethanol and gently heated on a steam bath for 1 hour. Silica gel (3 g.) was added, and the solvent was evaporated *in vacuo*. The residue was applied to the top of a silica gel column (50 g.) and eluted with benzene-acetone (2:1 v/v). Fractions 6-10 (5 ml. per fraction) gave 120 mg. of a substance with m.p. 200-205° whose nmr and ir spectra were identical with those of compound III. Fractions 11-19 gave 130 mg. of the mixture of two compounds, and fractions 20-31 gave 210 mg. of only one substance which was purified from cold ethanolic hydrochloric acid and precipitated with ether. Their ir and nmr spectra confirmed the structure IV on comparison with an authentic sample.

N,N'-Methylene-bis[3-(2'-benzoyl-4'-chloro)phenyl]-4-imidazolinone (III).

2-Glycylamido-5-chlorobenzophenone (prepared according to ref. (8) (1.42 g., 5 mmoles) was suspended in 7.0 ml. of methanol and 1.6 ml. of 36% aqueous formaldehyde was added. The reaction mixture was heated on a steam bath for 2 hours. After cooling, the crude product separated; 0.84 g. (55%), m.p. 204-208.5° (lit. (7) m.p. 213-215°); ir (potassium bromide): 1705, 1673, 1592, 1475, 1420, 1328, 829, and 800 cm^{-1}; nmr (deuteriochloroform): δ 3.17 ppm (s, 2H), 3.20 (s, 4H), 4.55 (s, 4H), 7.25-7.92 (m, 16H).

Further purification of this product by column, thin-layer chromatography or recrystallization from chloroform, benzene or acetonitrile failed. Two dimensional thin-layer chromatography revealed low stability of III in all the systems used; once separated III gave rise to two spots on elution in the other direction.

3-(2'-Benzoyl-4'-chlorophenyl)-4-imidazolidinone Hydrochloride (IV).

Compound III (0.23 g., 0.385 mmole) was dissolved in 5 ml. of absolute ethanol and a saturated solution of hydrogen chloride in ethanol was added, dropwise, until *p*H 2 was reached. Reaction solution was immediately evaporated *in vacuo* while the temperature was kept below 30°. The residual mass was slurried in 3 ml. of acetone, undissolved product was collected, washed with acetone and dried. The yield was 0.21 g. (82%) of IV, m.p. 159-160° (lit. (7) m.p. 162-183°); ir (potassium bromide): 3400-3500 (broad), 2400-3000 (broad), 1740, 1665, 1395, 1480, 1426, 1400, 1332, 1316, 1295, 1270, 1248, 1160, and 1150 cm^{-1}; nmr (deuterium oxide): δ 4.27 ppm (s, 2H), 5.52 (s, 2H), 7.50 (s, 1H), 7.7-8.0 (m, 8H).

6-Chloro-1-methyl-3-amino-4-phenyl-2-quinolone (VIII).

Compound II (1.50 g.) was added to 3 ml. of absolute ethanol and the suspension was heated under reflux for 6 hours. The solution thus obtained was evaporated to dryness under reduced pressure and the residue was partitioned between 50 ml. of water and 3 x 50 ml. of benzene. After evaporation of the dried organic fraction an oily residue remained, which was recrystallized from ethanol giving 0.79 g. (85%) of VIII, m.p. 138-140° (lit. (13) m.p. 136-138°); ir (potassium bromide): 3450, 3300, (NH_2), 1650 ($CO.N\text{-}CH_3$); nmr (deuteriochloroform): δ 3.75 ppm (s, 3H), 4.45 (s, 2H) 7.40 (m, 8H).

Anal. Calcd. for $C_{16}H_{13}ClNO_2$ (284.74): C, 67.48; H, 4.60; N, 9.84. Found: C, 67.50; H, 4.53; N, 9.83.

Experiments for Determining Dependence on *p*H of Cyclization IV → VI.

Eight solutions of *p*H 1.0-8.0 were prepared from Sörensen or McIlvine buffer, by addition of 0.1 *N* hydrochloric acid or 0.1 *N* sodium hydroxide. Because of the marginal solubility of IV and VI in water buffers, dioxane was used as a cosolvent, the ratio buffer-dioxane being 5:1 (v/v). All the experiments were performed at room temperature in closed Erlenmeyer flasks stirred by a magnetic stirrer. Each sample contained 50 mg. of IV dissolved in 10 ml. of buffer-dioxane (5:1). Samples were applied on HF_{254} coated plates (2.5 x 7.5, Fertigplatte-Merck). On elution by a mixture of benzene-acetone (1:1 v/v), IV had $R_f \sim 0.25$ and VI had $R_f \sim 0.69$. Visual comparison were performed relating to the standards, and average values were calculated for Table I - medium deviation being ± 3-5%.

Spectrophotometric Measurements of Cyclization I → VI and VI → VIII.

Compounds I and II (25.0 mg.) were dissolved in 25.0 ml. of the mixture buffer-dioxane (4:1 v/v). Sörensen buffer (*p*H 7.02) and dioxane mixed in the ratio 4:1 gave *p*H 7.45. From the thermostatically controlled reaction solution (37.0° ± 0.1°), 1 ml. samples were removed at regular time intervals and the reaction was quenched by putting the sample in 1.0 ml. of *N* hydrochloric acid and diluting it to 100.0 ml. A calibration curve was determined in 0.1 *N* hydrochloric acid; preliminary measurements at 285 and 359 nm revealed that the solutions of I and II in 0.1 *N* hydrochloric acid were entirely stable within 3-4 hours at room temperature.

Acknowledgments.

We thank Dr. L. Klasinc, of "Rudjer Bošković", Institute, Zagreb, for useful discussions and for the program for the rate constant calculations. Helpful assistance of Mr. J. Kuftinec for kinetic, and Mrs. J. Muhl for nmr measurements are gratefully acknowledged.

REFERENCES

(1) Papers cited in references 3 and 4 should be regarded as part I and II of this series.

(2) Correspondence should be addressed to this author; Compagnia di Ricerca Chimica SA., Chiasso, Via Motta 18, Switzerland.

(3) N. Blažević and F. Kajfež, *J. Heterocyclic Chem.*, 7, 1173 (1970).

(4) N. Blažević and F. Kajfež, *ibid.*, 8, 845 (1971).

(5) K. H. Beyer and W. Sadee, *Deutsch. Apoth. Ztg.*, 109, 312 (1969).

(6) A. Braude, *J. Chem. Soc.*, 1902 (1949).

(7) Swiss Patent, 465,621; *Chem. Abstr.*, 71, 61382g (1969).

(8) A. Stempel and F. W. Landgraf, *J. Org. Chem.*, 27, 4675 (1962).

(9) S. J. Angyal in "Organic Reactions" R. Adams, Ed., J. Wiley and Sons, Inc., New York, 1954, Vol. 8, Chapter 4, p. 197.

(10) Y. Katsura, *Yakugaku Zasshi*, 91, 12 (1971).

(11) M. J. S. Dewar and N. Trinajstić, *J. Chem. Soc. (A)*, 1220 (1971).

(12) R. I. Fryer, B. Brust, L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964).

(13) R. I. Fryer and L. H. Sternbach, *J. Org. Chem.*, 30, 524 (1965).

(14) K. Nakanishi "Infrared Absorption Spectroscopy Practical" Holden-Day, Inc., San Francisco, 1966, pp. 42-47.

(15) M. E. Derieg, R. M. Schweininger, and R. I. Fryer, *J. Org. Chem.*, 34, 179 (1969).

(16) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, 27, 3788 (1962).