STUDY OF SOLVOLYSIS MECHANISM OF SOME UREAS DERIVED FROM 2-BENZOXAZOLONE*

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6-Nitro-, 6-chloro-, 6-bromo- and 6-amino-2-benzoxazolones *I* have been prepared and aminolyzed with piperidine and butylamine into the respective 2-hydroxy-4-nitro-, 4-chloro-, 4-bromo- and 4-aminophenylureas *II*, *III*. pK_a values of hydroxyl group of these ureas have been determined. The aminolysis and hydroxylaminolysis mechanism of the mentioned 2-benzoxazolones is discussed on the basis of kinetic data. Reaction of the 6-substituted-2-benzoxazolones with methyl, phenyl and *p*-toluenesulphonyl isocyanates and N,N-dimethylchloroformamide has been used for preparation of the respective ureas *V* to *VII* of the type of 3-alkylcarbamoyl- or arylcarbamoyl-2-benzoxazolone. Hydrolysis mechanism of these ureas possessing a good leaving (3-benzoxazolone) group in alkaline medium and behaviour of anions of ureas *VI* in alkaline medium are discussed.

In the previous work[1] we studied kinetics and mechanism of hydrolysis of N-methylcarbamates of phenols and proved it to be of ElcB mechanism. In the context of searching for further substrates which might hydrolyze by this elimination mechanism we chose benzoxazolone and its derivatives *I* which represent cyclic carbamates. The aim of this work was to follow behaviour of the benzoxazolones under the conditions of aminolysis in aqueous solutions of n-butylamine, piperidine and hydroxylamine. In the Discussion we have used also the results of hydrolysis of benzoxazolone and its 5-chloro and 5-nitro derivatives in alkaline medium[2]. Furthermore, we used the benzoxazolones *I* whose anions are good leaving groups[3] (pK'_a of benzoxazolone = 9·34) for preparation of the ureas *II* with the aim to find if their hydrolysis takes the usual BAc2 course (Scheme 1) or if they can hydrolyze by ElcB mechanism (Scheme 2).

As the N—H group in the urea *II* is not sufficiently acidic, we synthetized the ureas *VI* and presumed that behaviour of their anions would be possible to study in the media having the OH^- ion activities within the pH scale. For determination of hydrolytic stability of carbamates carrying ureido group in benzene ring we transformed the aminolysis product of benzoxazolone *I* (X = Cl) into hydroxyphenylurea *III*

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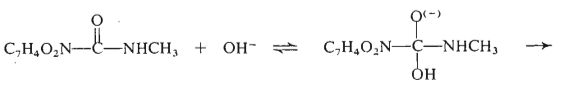
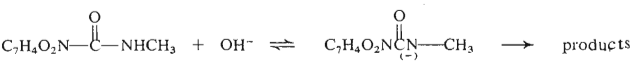
(X = Cl) and N-methylcarbamate *IV* which we submitted to hydrolytic splitting in alkaline medium (Scheme 3). We measured pK_a of the compounds *II* and *III* to obtain data for discussion of reactivity of the carbamate *IV*.



SCHEME 1



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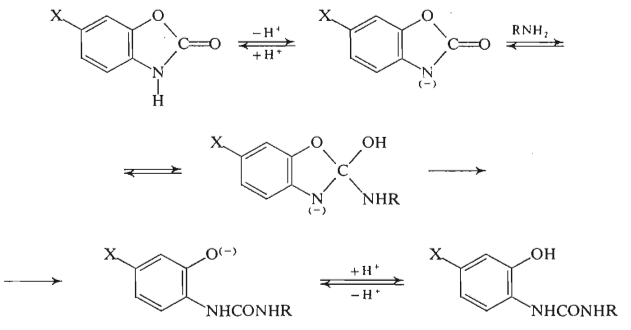


SCHEME 3

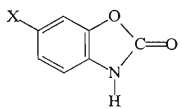
EXPERIMENTAL

Reagents

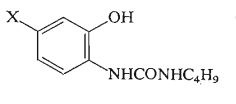
2-Benzoxazolone was prepared by melting of *o*-aminophenol with urea[4] at 150°C (60%), m.p. 136–137°C (benzene, dioxane). 6-Chloro-2-benzoxazolone (*Ia*) was obtained[5] by reaction of 2-benzoxazolone with sulphuryl chloride in acetic acid, m.p. 193–194°C (dioxane). 6-Bromo-2-benzoxazolone (*Ib*) was prepared[5] by direct bromination in benzene (70%), m.p. 194–196°C

(dioxane). 6-Nitro-2-benzoxazolone (*Ic*) was prepared[6] by direct nitration with 65% nitric acid in aqueous suspension (50%), m.p. 249—250°C (ethanol). Reduction with tin in hydrochloric acid gave 6-amino-2-benzoxazolone[7] (*Id*) (60%), m.p. 201—202°C (methanol).

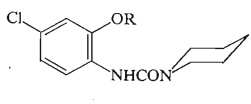
The 4-substituted N-2-hydroxyphenyl-N'-alkylureas *II*—*III* were prepared from the respective 2-benzoxazolones and alkylamines by refluxing for several hours. Solution 0·1M-$NaHSO_3$ was added to the reaction mixtures to prevent undesirable oxidation side reactions. After cooling the reaction mixture was diluted with water, the precipitate was extracted with ether to remove the unreacted 2-benzoxazolone, and the product was crystallized from toluene. Elemental analyses of the prepared ureas are given in Table I, the following ureas being prepared (80—90%): N-(2--hydroxy-4-nitrophenyl)-N'-n-butylurea (*IIa*) (m.p. 134—135°C); N-(2-hydroxy-4-bromophenyl)-*IIb* (m.p. 175—176°C); N-(2-hydroxy-4-chlorophenyl) — *IIc* (m.p. 206—207°C); N-(2-hydroxy--4-aminophenyl) — *IId* (m. p.169—172°C); N-(2-hydroxy-4-chlorophenyl)-N'-pentamethyleneurea (*III*) (m.p. 147—149°). Reaction of *III* with methyl isocyanate catalyzed with triethylamine in dioxane gave 2-(N'-pentamethyleneureido)-5-chlorophenyl methylcarbamate (*IV*) (95%), m.p. 119—120°C (dioxane).



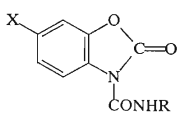
Ia, b, c, d,
X = Cl, Br, NO_2, NH_2



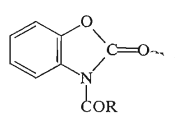
IIa, b, c, d,
X = NO_2, Br, Cl, NH_2



III, R = H
IV, R = $CONHCH_3$



Va, b, c, R = CH_3
VIa, b, c, R = $SO_2C_6H_4$—CH_3-*p*
X = H, NO_2, Cl



VII, R = NHC_6H_5
VIII, R = $N(CH_3)_2$
IX, R = CH_3

The 6-substituted 3-methylcarbamoyl-2-benzoxazolones (*V*) were prepared by reaction of methyl isocyanate with the respective 2-benzoxazolone in dioxane with catalysis of triethylamine and were crystallized from benzene. The following 2-benzoxazolones were prepared (90—95%): 3-(N-Methylcarbamoyl)-2-benzoxazolone (*Va*) (m.p. 155—156°C); 6-nitro-3-(N--methylcarbamoyl) — *Vb* (m.p. 192—195°C with decomp.); 6-chloro-3-(N-methylcarbamoyl) — *Vc* (m.p. 174—175°C). The 3-(N-*p*-toluenesulphonylcarbamoyl) derivatives of 6-substituted-2-benzoxazolones were prepared by reaction of the respective 2-benzoxazolone with *p*-toluenesulphonyl isocyanate in ether by standing overnight. The product was purified on alumina column (activity V, Voelm) and crystallized from benzene. The following substituted 2-benzoxazolones were prepared: 3-(N-tosylcarbamoyl)-2-benzoxazolone (*VIa*) (m.p. 178—179°C); 6-chloro-3-(N-tosylcarbamoyl) — *VIb* (m.p. 144—145°C); 6-nitro-3-(N-tosylcarbamoyl) — *VIc* (m.p. 240—242°C).

TABLE I
Elemental Analyses of the Prepared Ureas

Compound	Formula (mol.wt.)	Calculated/Found			
		% C	% H	% N	% Cl
IIa	$C_{11}H_{15}N_3O_4$	52·17	5·93	16·60	—
	(253·2)	52·30	6·08	16·85	—
IIb	$C_{11}H_{15}BrN_2O_2$	46·01	5·23	9·76	—
	(286·0)	46·40	5·28	10·02	—
IIc	$C_{11}H_{15}ClN_2O_2$	54·43	6·18	11·55	14·64
	(242·6)	53·85	6·32	11·75	14·20
IId	$C_{11}H_{17}N_3O_2$	59·19	7·62	18·83	—
	(223·1)	58·82	7·35	18·98	—
III	$C_{12}H_{15}ClN_2O_2$	56·60	5·90	11·00	13·95
	(254·6)	56·35	6·15	10·95	14·10
IV	$C_{14}H_{18}ClN_3O_3$	53·93	5·78	13·48	11·40
	(311·6)	54·11	5·55	13·11	10·95
Va	$C_9H_8N_2O_3$	60·67	4·49	7·89	—
	(178·2)	60·28	4·59	7·45	—
Vb	$C_9H_7N_3O_5$	45·45	2·95	17·87	—
	(237·3)	45·70	3·21	18·28	—
Vc	$C_9H_7ClN_2O_3$	47·68	3·09	12·36	15·67
	(226·6)	47·30	3·40	12·12	15·90
VIa	$C_{15}H_{12}N_2O_5S$	54·22	3·75	8·43	—
	(332·1)	53·98	3·98	8·11	—
VIb	$C_{15}H_{11}N_3O_7S$	47·75	2·92	11·14	—
	(377·2)	48·01	3·09	10·95	—
VIc	$C_{15}H_{11}ClN_2O_5S$	49·11	3·00	8·73	9·67
	(366·7)	49·32	3·25	8·42	9·92
VII	$C_{10}H_{10}N_2O_3$	58·19	4·85	13·59	—
	(206·2)	58·28	5·05	13·61	—
VIII	$C_{14}H_{10}N_2O_3$	66·09	3·93	11·01	—
	(254·2)	65·99	4·01	11·10	—

Yields of the compounds *V*— *VIII* varied within 30 to 50%. 3-(N-Phenylcarbamoyl)-2-benzoxazolone (*VII*) was prepared from phenyl isocyanate and 2-benzoxazolone in dioxane (m.p. 247 to 248°C).

3-Acetyl-2-benzoxazolone (*IX*) was prepared by acetylation of sodium salt of 2-benzoxazolone with acetanhydride in methanol[8] (90%), m.p. 80°C (methanol).

3-(N,N-Dimethylcarbamoyl)-2-benzoxazolone was prepared from 2-benzoxazolone and dimethylcarbamoyl chloride in pyridine (50% yield), m.p. 69°C (benzene).

The kinetic measurements were carried out with a Unicam SP 800 and a Specord UV VIS spectrophotometers in temperated cell compartments at 25°C. The kinetic dependence was evaluated up to 4 to 6 half-lives to obtain the k_{obs} hydrolysis constants. The reactions with half-lives shorter than 15 seconds were measured by the stopped-flow technique using a Durrum–Gibson apparatus, the rate constants being evaluated from the reaction half-lives. The aminolysis and hydroxylaminolysis of benzoxazolones to ureas were carried out in a thermostat at 70 to 90°C in sealed ampoules. At chosen time intervals samples were withdrawn and transferred to buffer, whereupon absorbance was measured with a VSU 2 spectrophotometer. The maximum of the first absorption band of the formed ureas was used, for which the validity of the Lambert–Beer law was checked. The pK values of the prepared ureas were determined spectrophotometrically,[9] too.

RESULTS AND DISCUSSION

Aminolysis of 2-Benzoxazolone

The aminolysis of 2-benzoxazolone is presumed to proceed by BAc2 mechanism with formation of tetrahedral intermediate from the amines and the conjugated base of the substrate (Scheme 3). Under the chosen conditions of aminolysis of 2-benzoxazolone the solution has pH about 11·8, and the substrates are present predominantly in their ionized form[3] (pK_a of 2-benzoxazolone is 9·43). In accord with the suggested mechanism in which bimolecular reaction is the rate-limiting step, the observed reaction rate in aqueous medium increases with increasing nucleophilicity of the reagents[10] (80°C; $c_{substrate} = 1 . 10^{-3}$M; ratio amine/substrate = 100 : 1):

amine	n-butylamine	piperidine	hydroxylamine
$k_{obs} . 10^4$ (s^{-1})	1·13	1·55	2·56

Electronwithdrawing substituents in benzene ring increase the aminolysis rate, as it follows from the calculated bimolecular constants k_2 (80°C; $c_{substrate} = 3 . 10^{-3}$M; ratio amine/substrate = 100 : 1; pH 11·79):

substituent	H	Cl	NO_2
$k_2 . 10^4$ (l mol^{-1} s^{-1})	0·36	0·80	2·11

The substituent polar effect agree with the BAc2 mechanism. Although these effects are transmitted to the reaction centre by two ways, the estimated reaction constant is low (ϱ about 0·3), hence it cannot be excluded that the rate-limiting step of the aminolysis consists in decomposition of the tetrahedral intermediate (the substituent polar effects on the 1. and the 2. reaction steps are mutually compensated).

Attack of the charged substrate by OH^- ions is slower by about 4 orders of magnitude than that of the neutral substrate[2], hence this side reaction of the OH^- ions present in the reaction mixture can be neglected. In the butylaminolysis of 6-chloro--2-benzoxazolone (90°C; $c_{substrate} = 3 . 10^{-2}$M) it was found that the reaction is 1. order in the amine:

c_{amine} (M)	6	9	12	14
$k_{obs} . 10^4$ (s^{-1})	3·41	5·22	6·09	7·30

This finding agrees with the bimolecular mechanism and contradicts to the elimination mechanism characterized by decomposition of the anion of benzoxazolone *I* to the corresponding isocyanate in the rate-limiting step. This isocyanate would not only give the products by the subsequent reaction, but it would also hydrolyze to *o*-aminophenol in the aqueous medium. However, the latter product was not detected spectrophotometrically.

2-Benzoxazolones, which represent cyclic carbamates, are thus hydrolyzed by another mechanism than that operating in case of acyclic carbamates. In our opinion one of the reasons is the possibility of delocalization of the electron pair at nitrogen of the conjugated base *I* into the aromatic ring, which decreases possibility of splitting of —O—CO bond in the heterocycle.

Hydrolysis of Carbamate IV

Values of the hydrolysis rate constants of the carbamate *IV* determined within pH 7 to 14 at 25°C in water are given in Table II. In order to be able to evaluate potential interaction of the ureide group in hydrolysis of the carbamate *IV*, we determined the pK_a value of hydroxyphenylurea *III* in water at 25°C. For comparison

TABLE II

Alkaline Hydrolysis of 2-(N'-Pentamethyleneureido)-5-chlorophenyl-N-methyl Carbamate ($c_{substrate} = 5 . 10^{-5}$M, temperature 25°C)

pH	$k_{obs} . 10^5$ / s^{-1}	pH	$k_{obs} . 10^5$ / s^{-1}
7·15	0·0315	10·80	105
8·07	0·288	12·70	970
9·00	2·30	13·34	1 500
0·36	28·00	13·98	2 190
9·83	51·6	14·20	2 300

we measured also dissociation constants of two *meta*-isomers (Table III). *o*-Hydroxyphenylureas generally have lower pK_a values by one unit than the corresponding *meta*- and *para*-isomers. As formation of hydrogen bond results in acidity decrease, the hydroxy group is presumed not to form intramolecular hydrogen bond to the ureido group. The acidity increase is ascribed to polar effect of *ortho*-substituents which behave practically in the same way as chlorine or bromine[11].

The higher hydrolysis rate of the carbamate *IV* agrees with the ureide group increasing acidity of the neighbouring hydroxy group in the urea *III*. However, the hydrolysis acceleration does correspond to polar effects of ureido group. Hence, direct assistance of the ureido group does not operate in the hydrolysis.

Hydrolysis of the Ureas

2-Benzoxazolone anion is a good leaving group (comparable with phenolate ion, as far as pK_a of the conjugated acids are considered). Mechanism ElcB (Scheme 2) cannot be excluded in case of hydrolysis of the ureas type *V* to *VII* with acidic N—H group. However, this mechanism cannot be differentiated kinetically from bimolecular hydrolysis by BAc2 mechanism (Scheme 1) involving attack of the non-dissociated substrate by OH^- ions. In the both cases linear dependence log k_{obs} *vs* pH is obtained with the slope equal to unity. Due to experimental reasons we could not follow the hydrolysis in media allowing complete ionization of the substrate. The criterion for differentiation between the BAcl and ElcB mechanisms, *i.e.* blocking of hydrogen at nitrogen atom, is obviously insufficient in the urea series in contrast to carbamates[1] where the rates of the two series differ by 4 orders of magnitude. It was found that dialkylureas type *VIII* are hydrolyzed more slowly than monoalkylureas type *V* (Fig. 1) by only about 0·5 order of magnitude. This difference can be due to increased sterical requirements connected with introduction

TABLE III

pK_a Values of the Substituted Hydroxyphenylureas

Compound	pK_a	Compound	pK_a
IIa	7·55	*III*	8·31
IIb	8·26	N-3-hydroxyphenyl-	9·59
IIc	8·24	-N′-methylurea	
IId	9·83	N-3-hydroxyphenyl-	9·54
II (X = H)	9·66	-N′,N′-dimethylurea	

of methyl group in neighbourhood of the reaction centre. Increase in the N—H acidity caused by substitution of methyl by phenyl group *VII* (which in case of carbamates results in the hydrolysis rate increase by 2 orders of magnitude[12]) makes itself felt by only five-fold acceleration in the case of ureas of this type (Fig. 1). Behaviour of the N-phenylureas in the pH region of complete ionization of the substrate could not be followed due to experimental difficulties, too. Therefore, *p*-toluenesulphonyl group was introduced as a substituent at nitrogen (*VI*), which strongly acidified the N—H group; break in the dependence log k *vs* pH (Fig. 2) indicates $pK_a \approx 7$. The broad plateau within pH 7·5 to 13 represents either spontaneous decomposition of the conjugated base of substrate to products or kinetically indistinguishable bimolecular reaction of the undissociated substrate with OH^- ion (Scheme 4). The BAc2 mechanism is supported by the value $\Delta S^* = -82{\cdot}97$ J mol^{-1} K^{-1}, which is typical for bimolecular reactions[10] and practically identical with the corresponding date for bimolecular hydrolysis of 3-acetyl-2-benzoxazolone *IX* ($\Delta S^* = -82{\cdot}22$ J . . mol^{-1} K^{-1}). In accord therewith we also found the carbonyl carbon atom to be sensitive to nucleophilic attack by hydroxylamine, as it can be seen from the following dependence of hydrolysis rate constant of 3-(N-*p*-toluenesulphonylcarbamoyl)--6-chloro-2-benzoxazolone on concentration of hydroxylamine at pH 12·30 at 25°C:

c_{NH_2OH}, M	0	0·1	0·2	0·4	0·6	0·8
k . 10^4, s^{-1}	9·24	23·1	30·4	41·3	48·2	57·5

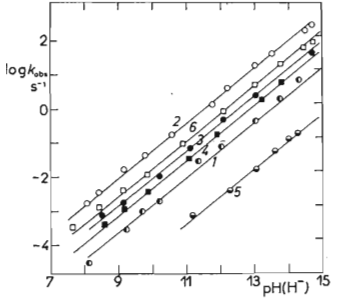


FIG. 1

Dependence of Logarithm of Hydrolysis Rate Constant of Ureas *V* to *VII* on pH at 25°C

1 Va, 2 Vb, 3 Vc, 4 VII, 5 VIII, 6 IX.

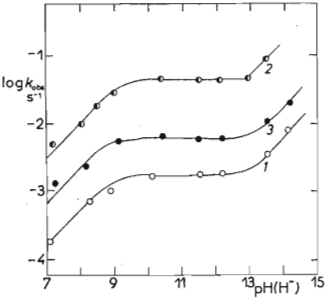
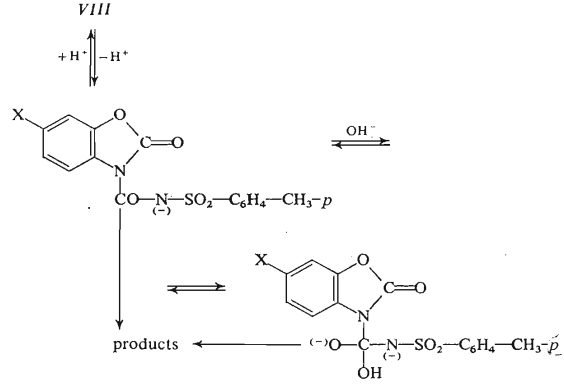


FIG. 2

Dependence of Logarithm of Hydrolysis Rate Constant of Ureas *VIIIa,b,c* on pH at 25°C

1 VIa, 2 VIb, 3 VIc.



SCHEME 4

In strongly alkaline region the reaction is 1. order in OH^- ion, $\Delta S^{\neq} = -82{\cdot}97$ J . . mol^{-1} K^{-1}, the completely dissociated substrate reacts by BAc2 mechanism (Fig. 2).

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