REACTIONS OF N-BENZOYL ISOTHIOCYANATE WITH ANTHRANILIC ACID AND METHYL ANTHRANILATE

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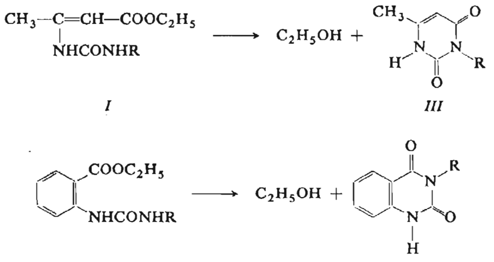
N-Benzoyl-N'-(2-carboxy- and -2-methoxycarbonylphenyl)thioureas have been obtained by the reaction of N-benzoyl isothiocyanate with anthranilic acid and methyl anthranilate, respectively. Kinetics of cyclization of these compounds into 2-mercapto-3,4-dihydro-4-quinazolone have been studied in water and in methanol. In the base-catalyzed cyclization of N-benzoyl-N'-(2-carboxyphenyl)thiourea the proper cyclization is preceded by solvolysis of the benzoyl group. In the case of N-benzoyl-N'-(2-methoxycarbonylphenyl)thiourea the reaction rate is limited by the base-catalyzed cyclization of the starting benzoyl derivative; the benzoyl group is split off in a subsequent rapid step.

The ureido derivatives of 2-butenoic (*I*) and benzoic (*II*) acids are cyclized to give the uracil derivatives *III* and *IV*, respectively (reaction (*A*))[1-3].



I *III*

II *IV*

(*A*)

The reaction is subject to specific base catalysis, and its velocity increases with increasing value of the σ constant of the substituent[2,3] R. The cyclization of ethyl 3-thioureido-2-butenoate (*V*) gave 2-amino-4-methyl-6-oxo-1,3-thiazine (*VII*) instead of the expected 6-methylthiouracil (*VI*) (reaction (*B*))[4].

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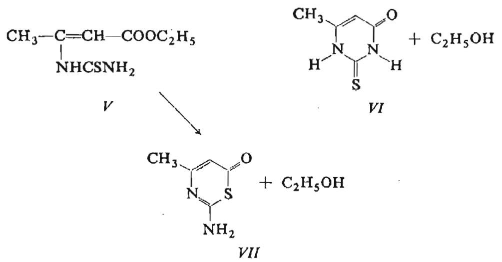
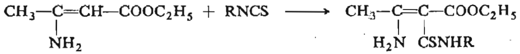


(B)

We tried to prepare the thioureido esters with a substituent at 1-nitrogen atom to find the conditions under which the cyclization *via* the sulphur atom takes place. However, we obtained either the cyclization products[4] or the products of addition to the carbon atom (reaction (*C*)).



$$CH_3-\underset{NH_2}{C}=CH-COOC_2H_5 + RNCS \longrightarrow CH_3-\underset{H_2N}{C}=\underset{CSNHR}{C}-COOC_2H_5 \qquad (C)$$

Therefore, in further experiments we used anthranilic acid or its methyl ester, because in this case no addition to carbon atom is possible. The attempts to prepare N-alkyl- and N-aryl-2-thioureidobenzoic acids and their methyl esters only gave the cyclization products, *i.e.* 1-alkyl- and 1-aryl-2-mercapto-3,4-dihydro-4-quinazolones (reaction (*D*)), respectively, even under the conditions when isocyanates give exclusively the non-cyclized ureido derivatives. Therefore, we prepared N-benzoyl derivatives of 2-thioureidobenzoic acid or its methyl ester and studied kinetics and mechanism of their cyclization reactions.

X = H; CH_3

VIII, R = CH_3

IX, R = C_6H_5

(*D*)

EXPERIMENTAL

Reagents

Methyl anthranilate was prepared by esterification of anthranilic acid with methanol[5]. Methyl isothiocyanate was prepared from methylamine, chloroformiate and carbon disulphide[6]. Benzoyl isothiocyanate was prepared from ammonium thiocyanate and benzoyl chloride[7].

2-*Mercapto*-3-*methyl*-3,4-*dihydro*-4-*quinazolone* (VIII) was prepared by mixing equimolar amounts of methyl anthranilate and methyl isothiocyanate at room temperature without solvent. The reaction took 3 days, the yields being almost quantitative; m.p. 271—273°C (recrystallization from ethanol; ref.[8] m.p. 267°C).

2-*Mercapto*-3-*phenyl*-3,4-*dihydro*-4-*quinazolone* (IX) was prepared in similar way as the methyl derivative *VIII*. The reaction was finished within about 5 h at room temperature. M.p. 306 to 307°C in accordance with ref.[8].

N-*Benzoyl*-N'-(2-*methoxycarbonylphenyl*)*thiourea* (X) was obtained by mixing equimolar amounts of methyl anthranilate and benzoyl isothiocyanate at room temperature without solvent. The reaction was finished within a few minutes. The yield was almost quantitative, m.p. 146·5 to 147°C after recrystallization from methanol. For $C_{16}H_{14}N_2O_3S$ (314·4) calculated: 61·13% C, 4·49% H; found: 61·11% C, 4·67% H.

N-*Benzoyl*-N'-(2-*carboxyphenyl*)*thiourea* (XI) was prepared from anthranilic acid and benzoyl isothiocyanate in acetone. After several hours standing at room temperature the product was filtered off and recrystallized from methanol; m.p. 160—161°C in accordance with ref.[9].

2-*Mercapto*-3,4-*dihydro*-4-*quinazolone* (XII) was prepared by dissolving 3·14 g (0·01 mol) of the compound *X* in 30 ml 1M-CH_3ONa. After 10 min the solution was diluted with about 60 ml water and neutralized with acetic acid to pH 7. The separated product was collected by suction and recrystallized from methanol. Yield 1·4 g (75%), m.p. 278—284°C in accordance with refs[9,10].

Kinetic Measurements

Cyclization of X. A quartz cell was charged with 2 ml temperated (25°C) solution of sodium methoxide ($1 . 10^{-3}$ to $5 . 10^{-1}$M, the ionic strength was not adjusted) or aqueous solution of morpholine, borax, carbonate or phosphate buffer (ionic strength adjusted at 0·5 by addition of KCl), whereupon a drop of methanolic solution of the compound *X* (about $5 . 10^{-3}$M) was added, and the absorbance increase at 294 nm was measured by means of a VSU-2P spectrophotometer (Zeiss, Jena).

Methanolysis of XI. A 1 cm quartz cell was charged with 2 ml sodium methoxide solution ($2 . 10^{-3}$ to $2 . 10^{-1}$M), whereupon a drop of methanolic solution of the compound *XI* (about $5 . 10^{-3}$M) was added, and the time-absorbance decrease was followed at 263 nm.

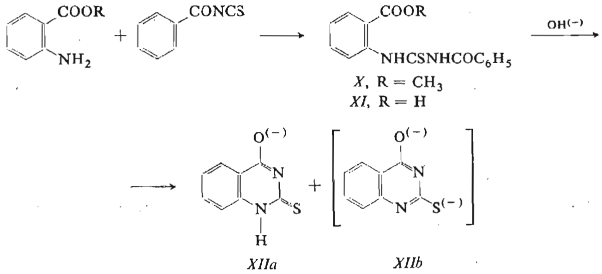
Hydrolysis of XI. A 1 cm quartz cell was charged with 2 ml sodium hydroxide solution (0·1 to 0·01N) or borax (carbonate) buffer with ionic strength 0·5, a drop of methanolic solution of *XI* was added, and the absorbance decrease was followed at 312 nm.

Cyclization of XIII. A calibrated flask was charged with 0·5 ml 0·1M-CH_3ONa, 3 ml 10^{-2}M methanolic solution of *XI* and 6 ml methanol. The methanolysis course was followed spectrophotometrically after a 100 fold dilution with methanol (0·1 ml to 10 ml) using a Specord UV-VIS spectrophotometer (Zeiss, Jena). After the methanolysis was finished (4 h), 1 drop of the reaction mixture was added to 2 ml sodium methoxide (0·1-2·8M) or to aqueous sodium hydroxide (pH 11—13·5) in a 1 cm quartz cell, and the absorbance increase was followed at 294 nm. The influence of ionic strength on the cyclization rate of the compound *XIII* in water was investigated in several experiments carried out in 0·02M-NaOH with the ionic strength adjusted at the values within 0·02 to 1 by addition of potassium chloride.

The dissociation constants were measured spectrophotometrically[11] by absorbance measurements of the compounds in buffers using a VSU-2P apparatus (Zeiss, Jena). The ionic strength was adjusted at 0·5 by addition of KCl. The pH values of the buffers used were measured with a Radiometer pH M-4 apparatus using a glass and a calomel electrodes. Conditions of the measurements and the results are given in Table I.

RESULTS AND DISCUSSION

Reactions of methyl anthranilate or anthranilic acid with benzoyl isothiocyanate gave the N-benzoylthioureido derivatives *X* and *XI* in good yields (*E*).



(*E*)

The both compounds *X* and *XI* are cyclized in alkaline medium to give the anion *XIIa* (pK_{a1} 8·23 in water) or, at higher base concentrations, its mixture with the dianion *XIIb* (pK_{a2} 13·37 in water). The monoanion is presumed to be formed

TABLE I

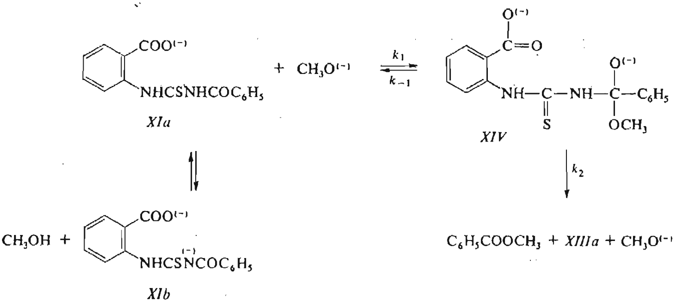
Experimental Conditions and Results of Measurements of the Dissociation Constants

Compound	Buffer	Ionic strength	λ_{anal} nm	pK_a
VIII	borax	0·5	282	9·02 ± 0·01
IX	borax	0·5	270	8·35 ± 0·012
X	bromophenolate	0·045	360	13·81 ± 0·015[a]
XI	CH$_3$ONa	[c]	360	14·64 ± 0·02[a,b]
XI	borax	0·5	310	9·85 ± 0·04[b]
XII	morpholine	0·5	288	8·23 ± 0·015
XII	NaOH	[c]	256	13·37 ± 0·016[b]

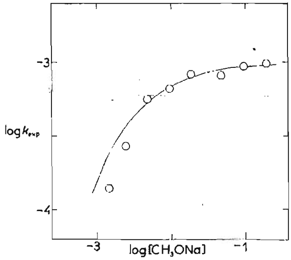
[a] In methanol; [b] the second dissociation constant; [c] not adjusted.

predominantly by splitting of the N—H bond near the carbonyl group (3-position), because pK_a of the 3-methyl derivative *VIII* (in which 1-hydrogen only can be split off) is by almost one unit higher (9·02).

The base-catalyzed cyclization of the N-benzoylthioureido derivative *XI* in methanol goes by two kinetically distinguishable steps. The first one consists in methanolysis of benzoyl group giving methyl benzoate and 2-thioureidobenzoate anion *XIIIa* (Scheme 1).



SCHEME 1



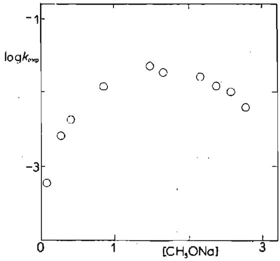


FIG. 1

Rate of Methanolysis of N-Benzoyl-N′-(2--carboxyphenyl)thiourea (*XI*) at 25°C

FIG. 2

Rate of Cyclization of N-Benzoyl-N′-(2--carboxyphenyl)thiourea (*XI*) in Sodium Methoxide at 25°C

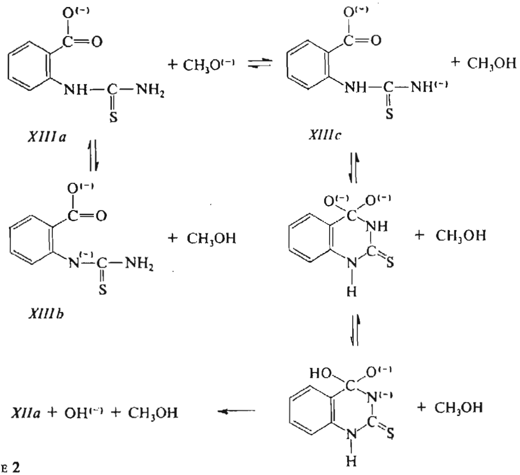
The dependence of k_{exp} vs log $[CH_3O^{(-)}]$ is given in Fig. 1, the full line representing the theoretical dependence calculated from Eq. (*1*).

$$v = k_{exp} \cdot c_{XIa} = \frac{k_1 \cdot k_2}{k_{-1} + k_2} \cdot c_{XIa} \, [CH_3O^{(-)}] \frac{[H^+]}{K_a + [H^+]} =$$

$$= (k_1 k_2 / (k_{-1} + k_2)) (K_s / (K_a + [H^+])) \, c_{XIa} \,, \qquad (1)$$

where $K_S = 1{\cdot}21 \cdot 10^{-17}$ is the ionic product of methanol[12], $K_a = 2{\cdot}29 \cdot 10^{-15}$ is the dissociation constant of the anion *XIa*. The value $k_1 k_2 / (k_{-1} + k_2)$ was determined by comparison of the calculated and the experimental values of k_{exp}.

Cyclization of the compound *XIIIa* was measured at higher methoxide concentrations, and the dependence of log k_{exp} on the alcoholate concentration is given in Fig. 2. A probable mechanism of this reaction is given in Scheme 2.



SCHEME 2

The rate constant of the base-catalyzed cyclization (k_3) was calculated from the k_{exp} values found at low methoxide concentration *i.e.* in the region of the linear dependence (*2*)

$$k_{exp} = k_3[CH_3O^{(-)}] . \qquad (2)$$

The constant $k_3 = (8{\cdot}7 \,.\, 10^{-3} \pm 0{\cdot}4)$ involves the dissociation pre-equilibrium of the compound *XIIIa* and the subsequent cyclization of the dianion (Scheme 2). The considerable decrease of the k_{exp} values at higher concentrations (Fig. 2) is due to two reasons: *a*) The starting substance *XIIIa* is partially transformed into the dianion *XIIIb*. *b*) The tetrahedral intermediate splits off a hydroxyl ion in the course of the reaction. This process needs considerable solvation with methanol molecules to be energetically reasonable. At higher alkoxide concentrations the methanol activity strongly decreases, hence the solvation energy decreases, and the reaction, having higher energy requirements, becomes slower.

The base-catalyzed cyclization of the compound *XI* in aqueous medium under the conditions used appears kinetically one-step reaction, because cyclization of the thioureido derivative (formed by hydrolysis of the compound *XI*) is faster than its formation. Direct measurement of cyclization of the compound *XI* gave the rate constant of the hydrolysis only, which is rate determining. The dependence of k_{exp} on the $OH^{(-)}$ concentration is similar to that in methanol, the reaction mechanism being analogous, too, as it is seen in Scheme 1. The rate and dissociation constants of the compound *XI* are summarized in Table II.

TABLE II

Dissociation Constants and Rate Constants ($l\ mol^{-1}\ s^{-1}$) of the Reactions (Schemes 1 and 2) of Anion *XIa* in Methoxide and in Water at 25°C

Parameter	H_2O	CH_3OH
$k_1k_2/(k_{-1} + k_2)$	0·64	0·174
K_a	$1{\cdot}41 \,.\, 10^{-10}$	$2{\cdot}29 \,.\, 10^{-15}$
k_3	$8{\cdot}7 \,.\, 10^{-1}$	$8{\cdot}7 \,.\, 10^{-3}$

TABLE III

Dissociation Constants and Rate Constants of Cyclization of Ester *X* at 25°C

Parameter	H_2O	CH_3OH
k_2, $l\ mol^{-1}\ s^{-1}$	$9{\cdot}38 \,.\, 10^2$	3·33
k_3, $l^2\ mol^{-2}\ s^{-2}$	$1{\cdot}28 \,.\, 10^6$	33·30
K_a	$4{\cdot}47 \,.\, 10^{-10}$	$1{\cdot}55 \,.\, 10^{-14}$

Although the calculated value of rate constant is about four times greater in water than in methanol, the maximum hydrolysis rate is about twenty times smaller than the maximum methanolysis rate. The reason is in that the anion *XIa* is converted into the non-reactive dianion *XIb* in water at the lyate ion concentration lower by two orders of magnitude than that in methanol.

For study of the cyclization kinetics the thioureido derivative *XIII* was prepared in advance in the solution *via* base-catalyzed methanolysis of the anion *XIa*. Dependence of k_{exp} of the cyclization on concentration of $OH^{(-)}$ was linear within the whole measured range (pH 11 to 13). The rate constant k_3 ($8{\cdot}7 \,.\, 10^{-1}$) is higher than that in methanol by two orders of magnitude. The cyclization rate constant of 2-ureidobenzoate anion measured in water at 30°C at the ionic strength 1·0 (ref.[3]) is lower by 3 orders of magnitude than the k_3 value found by us. This considerable lowering of the cyclization rate is mainly due to the fact that carbonyl group activates far less than the C=S group the splitting of the neighbouring N—H bond, and hence the concentration of the reactive dianion type *XIIIc* (C=O instead of C=S) is lower than that of the thio derivative *XIIIc*. Although the reaction proceeds between two anions (*XIa* and $OH^{(-)}$), the k_{exp} value increases with ionic strength very slowly. At the ionic strength 1·0 the rate constant k_{exp} is higher than that at I = 0·02 by

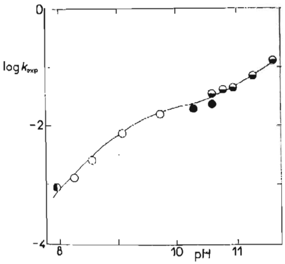


FIG. 3

Rate of Cyclization of N-Benzoyl-N'-(2-methoxycarbonylphenyl)thiourea (*X*) in Aqueous Buffers at 25°C at Ionic Strength 0·5

◐ Morpholine buffer, ○ borax buffers, ● carbonate buffers, ◒ phosphate buffers.

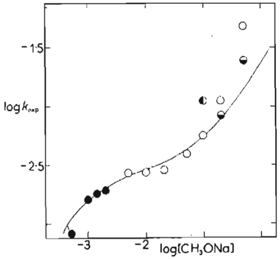


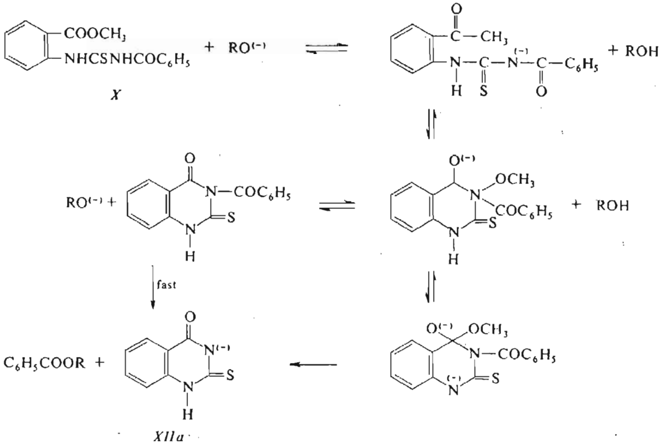
FIG. 4

Rate of Cyclization of N-Benzoyl-N'-(2-methoxycarbonylphenyl)thiourea (*X*) in Methanolic Solutions of Sodium Methoxide and Bromophenolate Buffers at 25°C

● Bromophenolate buffers, ◐ 0·1M-CH_3 . ONa, I = 0·5, ○ sodium methoxide (ionic strength not adjusted), ◒ correction for the ionic strength effects.

only 42%. This fact indicates that the negative charge of the activated complex is dispersed over a greater number of water molecules (similar to the reaction in methanol).

The base-catalyzed cyclization of the ester *X* proceeds kinetically as a one-step reaction both in water and in methanol. The dependences log k_{exp} *vs* pH or log $CH_3O^{(-)}$ are given in Figs 3 and 4. These dependences agree with the mechanism given in Scheme 3. At higher lyate ion (RO^-) concentrations the transformation of the negatively charged intermediate into products is catalyzed by a further lyate ion (the increasing section of the second part of the curve).



SCHEME 3

Splitting off of benzoyl group (in the form of methyl benzoate) from the negatively charged intermediate cannot be catalyzed by a further methoxide ion, and, hence, the rate-limiting step of the reaction measured in methanol cannot be the methanolysis of the starting ester *X*. As the dependence of the cyclization rate on the lyate ion concentration in water is similar to that in methanol, we presume that the reaction mechanism is similar, too. This presumption is supported by the finding that k_{exp} values of cyclization of the ester *X* are higher than those of hydrolysis of the acid anion *XI* by several orders of magnitude.

On the basis of the given reaction mechanism we derived the kinetic equation (*3*) wherefrom the theoretical dependence k_{exp} *vs* lyate ion concentration was calculated (full lines in Figs 3 and 4).

$$v = k_{exp} \cdot c_X = (k_2 + k_3[RO^-]) \frac{K_S}{K_a + [H^+]} c_X\,, \qquad (3)$$

where K_S mean the ionic product of the solvent, k_2 and k_3 are the rate constants of formation of the product *via* the tetrahedral intermediates carrying one and two negative charges, respectively.

The K_a value in methanol was determined separately by direct measurement of the acid–base equilibrium of the compound *X*, the other constants (k_2, k_3 and K_a in water) were determined by comparison of the calculated and the experimental k_{exp} values (Table III).

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