STUDY OF CYCLIZATION OF 2-ACETYL-3-METHYLAMINO--N-BENZOYL-2-BUTENETHIOAMIDE

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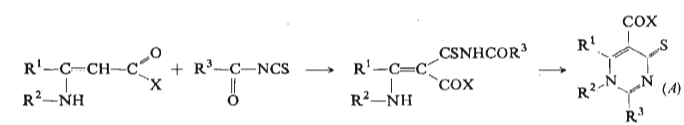
Kinetics has been studied of cyclization of 2-acetyl-3-methylamino-N-benzoyl-2-butenethioamide (*Ia*) and 2-acetyl-3-amino-N-benzoyl-2-butenethioamide (*Ib*) giving 5-acetyl-2-phenyl-1,6-dimethyl-4-(1*H*)pyrimidinethione (*IIa*) and 5-acetyl-2-phenyl-6-methyl-4-(3*H*)-pyrimidinethione (*IIb*), respectively, in aqueous buffers within pH 2 to 9. Formation of the cyclic intermediate is rate-limiting in the cyclization of *Ib* within the whole range. In the case of *Ia* the rate-limiting step consists in acid-catalyzed splitting off of water from the cyclic intermediate above pH 5 and in base-catalyzed splitting off of hydroxyl ion above pH 7.

Addition of enamino ketones or enamino esters to acyl isothiocyanates or alkoxycarbonyl isothiocyanates and cyclization of the products formed represent an advantageous method for preparation of substituted pyrimidinethiones[1-6] (*A*).



This paper deals with a kinetic study of cyclization of 2-acetyl-3-methylamino--N-benzoyl-2-butenethioamide (*Ia*) and 2-acetyl-3-amino-N-benzoyl-2-butenethioamide (*Ib*) in aqueous buffers.

EXPERIMENTAL

The ^{1}H-NMR spectra were measured with a Tesla BS 487 B spectrometer at 80 MHz using hexamethyldisiloxane as internal standard. The pH values of the reaction solutions were measured with a Radiometer pHm 4c apparatus (Copenhagen) using a combined glass and calomel electrode.

4-Methylamino-3-penten-2-one and 4-amino-3-penten-2-one were prepared by reaction of 2,4-pentanedione with aqueous methylamine[7] and ammonia[8] solutions, respectively. Benzoyl isothiocyanate was prepared by reaction of benzoyl chloride with ammonium thiocyanate[9]. The raw product was dissolved in benzene, ammonium chloride was removed by washing with water, and the product was dried and distilled in vacuum (b.p. 88°C/400 Pa).

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2-*Acetyl*-3-*methylamino*-N-*benzoyl*-2-*butenethioamide* (Ia): Solution of 11·3 g (0·1 mol) 4-methylamino-3-penten-2-one in 20 ml benzene was treated with solution of 16·3 g (0·1 mol) benzoyl isothiocyanate in 20 ml benzene (added dropwise). The mixture turned hot spontaneously (about 40°C). After cooling to 20°C the precipitated product was collected by suction, washed several times with a mixture benzene–acetone (1 : 1) and dried in a vacuum dessiccator. The compound *Ia* undergoes cyclization even in crystalline state to give 5-acetyl-2-phenyl-1,6-dimethyl-4-(1*H*)pyrimidinethione (*IIa*), and, therefore, it was kept in dark at 0°C. Yield 15·2 g (55%), m.p. 100—101·5°C. For $C_{14}H_{16}N_2O_2S$ (276·4) calculated: 60·87% C, 5·79% H, 10·14% N, 11·60% S; found: 61·22% C, 6·16% H, 10·46% N, 11·87% S. ^{1}H-NMR spectrum ($CDCl_3$, 25°C): $\delta(CH_3NH) = 12{\cdot}20$ (1 H), $\delta(NH) = 10{\cdot}67$ (1 H), $\delta(C_6H_5) = 7{\cdot}2$—$8{\cdot}0$ (5 H), $\delta(CH_3NH) = 2{\cdot}99$ (3 H), $\delta(CH_3) = 2{\cdot}15$; 2·17 (2 × 3 H).

2-*Acetyl*-3-*amino*-N-*benzoyl*-2-*butenethioamide* (Ib) was prepared in the same way. Yield 62%, m.p. 123—125°C (ref.[2] m.p. 156°C with decomposition). The sample kept in refrigerator for 4 months began to melt at 115°C, however, the melt crystallized during further heating and the new crystals melted at 153—159°C with decomposition. For $C_{13}H_{14}N_2O_2S$ (262·4) calculated: 59·52% C, 5·38% H, 10·68% N; found: 59·63% C, 5·77% H, 10·89% N. ^{1}H-NMR spectrum ($CDCl_3$, 50°C): $\delta(C_6H_5) = 7{\cdot}2$—$8{\cdot}0$ (5 H), $\delta(CH_3) = 2{\cdot}15$; 2·19 (2 × 3 H).

5-*Acetyl*-2-*phenyl*-1,6-*dimethyl*-4-(1*H*)*pyrimidinethione* (IIa): 3 g thioamide *Ia* was dissolved in about 10 ml warm methanol. After three days standing at the room temperature the crystalline product was collected by suction. Repeated crystallization from methanol gave the product melting at 251—253°C. For $C_{14}H_{14}N_2OS$ (258·4) calculated: 65·12% C, 5·43% H, 10·85% N; found: 64·90% C, 5·74% H, 10·47% N. ^{1}H-NMR spectrum ($CDCl_3$, 50°C): $\delta(C_6H_5) = 7{\cdot}0$—$7{\cdot}5$ (5 H), $\delta(CH_3N) = 3{\cdot}49$ (3 H), $\delta(CH_3) = 2{\cdot}57$; 2·21 (2 × 3 H).

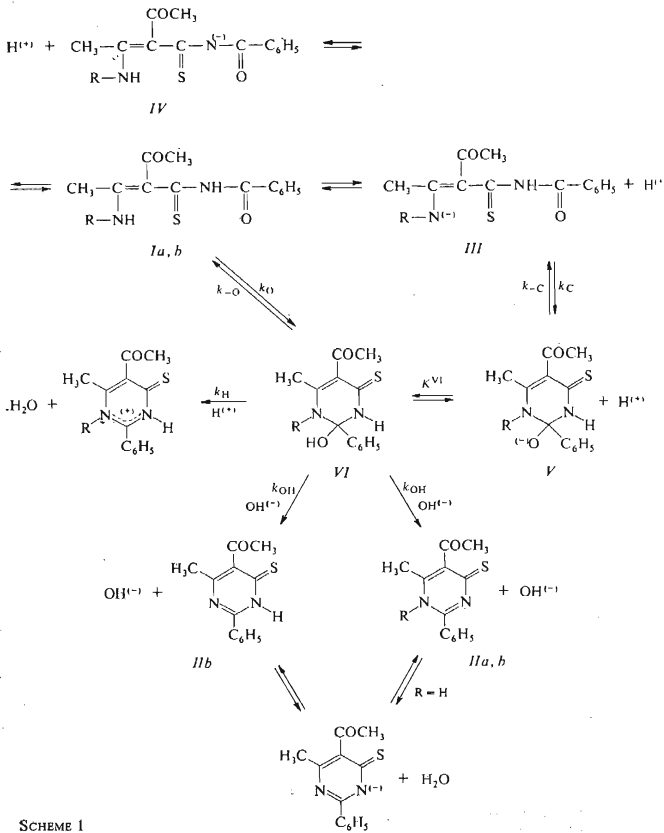
5-*Acetyl*-2-*phenyl*-6-*methyl*-4-(3*H*)*pyrimidinethione* (IIb) was prepared in the same way. M.p. 214—216°C (ref.[2] m.p. 216—218°C).

Kinetic measurements. 2 ml aqueous buffer solution (chloroacetate, acetate, phosphate, morpholine, borax) was temperated at 25°C, and 0·1 ml 10^{-3}M fresh methanolic solution of thioamide *Ia* or *Ib* was added thereto, whereafter the absorbance decrease was measured at 300 nm using a Zeiss VSU-2P spectrophotometer. The rate constants k_{obs} were calculated from the relation $k_{obs} \cdot t = -2{\cdot}3 \log (A_t - A_\infty) + \text{const}$. Ionic strength of the buffers used was adjusted at 0·2 by addition of 1M-KCl except for the series of the acetate buffers 1 : 3 ([HA] : [A^-]) in which the ionic strength was 0·5.

RESULTS AND DISCUSSION

The cyclization kinetics of the compounds *Ia* and *Ib* to the substituted pyrimidinethiones *IIa* and *IIb*, respectively, were measured in aqueous buffer solutions within pH 2 to 9. The reactions had pseudomonomolecular course in all the cases, and the spectra of the reaction mixtures agreed with those of the compounds *IIa* and *IIb* measured under the same conditions. Except for the cyclization of the compound *Ia* in acetate buffers (pH about 4·7 – 5·6) the observed rate constants k_{obs} were either quite independent of the buffer concentration (the compound *Ib* in the whole pH range measured) or slightly increased with the buffer concentration. Catalytic effect of acetic acid on cyclization of the compound *Ia* was measured in acetate buffers 1 : 3 ([HA] : [A^-]). The dependence of k_{obs} on the buffer concentration was a concave

curve with respect to O_x axis, as increasing acetic acid concentration results in a gradual change in the rate-limiting step from a general acid-catalyzed to specifically base-catalyzed step. The value of the Brönsted coefficient α estimated from the initial slope of the curve and from the rate constant of the proton-catalyzed reaction is about 0·7.



SCHEME 1

Figure 1 gives the pH dependence of log k_{obs} of the cyclization of the compounds *Ia* and *Ib*. In the pH region in which the catalytic effect of the buffers was significant the k_{obs} values were extrapolated to zero buffer concentration. The reaction mechanism of the cyclization of the compounds *Ia* and *Ib* is given in Scheme 1, wherefrom kinetic equation (*1*) was derived for the cyclization rate

$$k_{obs} = \frac{(k_H[H^+] + k_{OH}[OH^-])\left(\frac{k'_c K'}{K' + [H^+]} + \frac{k_o[H^+]}{K' + [H^+]}\right)}{k_{-o} + k_H[H^+] + k_{OH}[OH^-] + \frac{k_{-c}K^{VI}}{[H^+]}}, \qquad (1)$$

where $K' = ([III] + [IV])[H^+]/[I]$, $K^{VI} = [V][H^+]/[VI]$, $k'_c = k_c[III]/([III] + [IV])$.

The rate-limiting step of cyclization of the compound *Ib* is formation of the cyclic intermediate *VI* at lower pH values, whereas at higher pH values formation of the intermediate *V* is rate-limiting. At pH 5·2 the rates of formation of the both intermediates are the same. The kinetic equation is reduced to the form (*2*) in this case. The theoretical dependence log k_{obs} *vs* pH (Fig. 1, curve *1*) was calculated from Eq. (*2*) using the values $pK' = 7{\cdot}5$, $k'_c = 1{\cdot}6\ s^{-1}$, and $k_o = 7 \cdot 10^{-3}\ s^{-1}$.

$$k_{obs} = (k_o[H^+] + k'_c K')/(K' + [H^+]). \qquad (2)$$

The dependence log k_{obs} *vs* pH is much more complicated for cyclization of the compound *Ia*. At the lowest pH values the rate-limiting step consists in formation of the intermediate *VI* from the starting substance *Ia* (the rate constant k_o). Increasing pH value results in gradually increasing contribution of cyclization of the anion *III*,

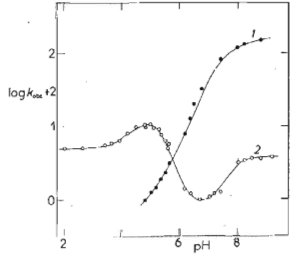
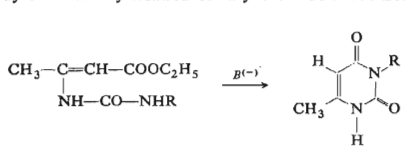


FIG. 1

pH Dependence of Logarithms of Rate Constants (k_{obs}) of Cyclization of *1* 2-Acetyl-3-amino-N-benzoyl-2-butenethioamide and *2* 2-Acetyl-3-methylamino-N-benzoyl-2-butenethioamide

and the k_{obs} value is increased. Above pH 5 the ring opening of the compound $V(k_{-c})$ is faster than the acid-catalyzed splitting off of water from the intermediate *VI* which becomes the rate-limiting step, and the k_{obs} value decreases with decreasing H^+ concentration. Above pH 6·7 another path becomes kinetically significant – the base-catalyzed splitting off of hydroxyl ion from the intermediate *VI*, and the k_{obs} value increases with increasing concentration of hydroxyl ion. Above pH 7·5 the increase of k_{obs} with pH is gradually slowed down, because dissociation of the compound *Ia* begins to make itself felt. At the highest pH values the k_{obs} value is almost pH independent. For calulation of the theoretical dependence log k_{obs} *vs* pH (Fig. 1, curve 2) we used the values $pK' = 7{\cdot}74$, $k_c' = 122\ s^{-1}$, $k_o = 5 \cdot 10^{-2}\ s^{-1}$, $k_{OH}/k_{-c} \cdot K^{VI} = 3{\cdot}63 \cdot 10^{10}\ l^2\ mol^{-2}$, $k_H/k_{-c} \cdot K^{VI} = 10^{10}\ l^2\ mol^{-2}$.

At low pH values the cyclization of *Ia* is much faster than that of *Ib*. However. later on the rate-limiting step of the cyclization of *Ib* is changed, and consequently at pH 5·8 the cyclization of *Ib* becomes faster (Fig. 1). From the given values of the rate constants it is obvious that the non-catalyzed cyclization of the compound $Ia(k_o)$ is faster by about one order of magnitude, and the base-catalyzed cyclization (k_c') is by almost two orders of magnitude faster, as compared with the corresponding reactions of *Ib*. The great reactivity difference can be due (to a considerable extent) to different relative abundances of the anions *III* and *IV*. A faster cyclization of N-methyl derivative (as compared with the non-substituted substrate) was observed earlier[10] in a study of similar cyclization of ethyl 3-ureido-2-butenoates (*B*).



(*B*)

Different character of the dependences log k_{obs} *vs* pH for the cyclizations of the compounds *Ia* and *Ib* is obviously due to two factors: *a*) In the cyclic intermediates *V* and *VI* there are greater sterical requirements, if N-methyl group is present, and, therefore, the reverse ring opening (k_{-c}) is faster, and the rate-limiting step can be changed. *b*) In the cyclic intermediate *VIb* there are two NH groups, the N—H bond at $N_{(1)}$ being split much more easily (the free electron pair being formed is conjugated with both C=O and C=S groups, whereas that at $N_{(3)}$ is only conjugated with C=S group). Therefore, the base-catalyzed splitting off of hydroxyl ion from the intermediate *VIb* is faster than the reverse ring opening even at lower pH values. Thus the cyclization remains rate-limiting. It is, however, impossible to determine to what extent the both factors make themselves felt.

In order that the operation of sterical effect of methyl group in cyclization of *Ia* might be confirmed, we measured the cyclization rate of N-ethyl, N-butyl, and

N-(1-methylpropyl) derivatives of the substrate *Ib* within pH 2 to 4. Cyclization of the ethyl and butyl derivatives was 3× and 5× slower, respectively, than that of the methyl derivative *Ia*. The cyclization of the N-(1-methylpropyl) derivative was so slow that side reactions predominated, and the cyclization rate constant could not be determined.

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