CYCLIZATION KINETICS AND MECHANISM OF N-BENZOYL-N'-(1,2-DIMETHYL-3-OXO-1-BUTENYL)THIOUREA

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Received April 1st, 1982

Cyclization kinetics of N-benzoyl-N'-(1,2-dimethyl-3-oxo-1-butenyl)thiourea have been studied in aqueous and methanolic solutions of acids and bases. In all cases the cyclization product is 4,5,6-trimethyl-2,5-dihydro-2-thioxopyrimidine or its protonated or deprotonated forms. In dilute methanolic and aqueous hydrochloric acid the substrate reacts in its monoprotonated form. The cyclization in basic media is catalyzed by methoxide or hydroxyl ion and also by primary and secondary amines at such pH values where the catalysis by lyate ion is practically insignificant. Tertiary amines and acetate ion do not catalyze the cyclization.

In the last few years we dealt with studies of kinetics and mechanisms of cyclization reactions of thioureido-[1] and N-benzoylthioureido esters[2], ureido esters and ketones[3,4]. As in the case of thioureido derivatives the cyclization reactions with ester group have only been studied so far, we considered it useful to investigate analogous cyclizations with carbonyl group of ketones, too. The aim of this communication is a study of cyclization kinetics of N-benzoyl-N'-(1,2-dimethyl-3-oxo-1-butenyl)-thiourea (*II*) to 4,5,6-trimethyl-2,5-dihydro-2-thioxopyrimidine (*III*), estimation of the reaction mechanism and effect of catalysts, and comparison with the cyclization reactions studied earlier.

EXPERIMENTAL

Reagents. 4-Amino-3-methyl-3-penten-2-one (*I*) was prepared from 3-methyl-2,4-pentanedione and ammonia. Yield 80%, m.p. 111·5—112·5°C in accordance with ref.[4]. N-Benzoyl-N'-(1,2-dimethyl-3-oxo-1-butenyl)thiourea (*II*) was prepared from 9 g enamine *I* and 12 ml benzoyl isothiocyanate[5] in 90 ml benzene. After 24 h a solid separated (7 g), m.p. 175—175·5°C (methanol). The compound was identified as N-benzoylthiourea by its m.p., mixed m.p., electronic and ^{1}H NMR spectra. The filtrate was vacuum-distilled to remove benzene, and the evaporation residue was separated by column chromatography (silica gel L 40/100, benzene–ethyl acetate 10 : 1). The fraction corresponding to compound *II* was crystallized from chloroform to give 3·7 g (17% with respect to enamine *I*) compound *II*, m.p. 114·5—115°C. For $C_{14}H_{16}N_2O_2S$ (276·1) calculated: 60·87% C, 5·80% H, 10·14% N; found: 60·49% C, 6·02% H, 10·20% N. ^{1}H NMR spectrum: $\delta(C_6H_5)$ 7·06—8·31; $\delta((CH_3)_2)$ 2·26; $\delta(CH_3)$ 2·23.

4,5,6-Trimethyl-2,5-dihydro-2-thioxopyrimidine (*III*)

A) Solution of 1·16 g compound *II* in 15 ml 1 mol l^{-1} sodium methoxide was left to react 1 h and neutralized with acetic acid to pH 7. On concentrating and cooling the solution separated the compound *III* (0·45 g, 70%), m.p. 206–210°C (water).

B) Solution of 6 g thiourea in 200 ml ethanol was treated with 11·4 g 3-methyl-2,4-pentanedione and 20 ml conc. hydrochloric acid and refluxed 4 h. On cooling the solution separated 11·5 g (76% with respect to thiourea) hydrochloride of compound *III* as yellow crystals. M.p. 230°C (decomp.), ^{1}H NMR spectrum: δ(NH) 6·69; $\delta((CH_3)_2)$ 2·53; $\delta(CH_3)$ 2·06. The hydrochloride of compound *III* (3·8 g) was dissolved in 25 ml water at 60°C and treated with solution of 0·7 g sodium hydroxide in 5 ml water, whereupon sodium carbonate solution was added to adjust pH 6–7. After filtration (charcoal) and cooling the product separated as 1·2 g crystals, m.p. 206–210°C. The mother filtrate gave further 0·4 g product by extraction with ethyl acetate. Overall yield 64%, m.p. 208–212°C (water). For $C_7H_{10}N_2S$ (154·1) calculated: 54·56% C, 6·49% H, 18·19% N; found: 54·50% C, 6·52% H, 18·49% N. Identity of the compounds *III* prepared by the two procedures was proved by mixed melting point (206–210°C) and by comparison of electronic spectra in acidic, neutral and basic media.

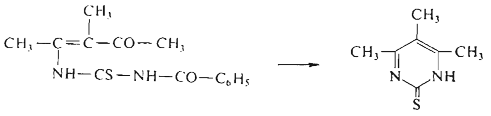
Methods

The electronic spectra were measured with a Unicam SP 800 and a Zeiss VSU-2P apparatus. The pH values of reaction solutions were determined with a Radiometer pHm 4c using a combined glass and calomel electrode. The ^{1}H NMR spectra were measured with a Tesla BS 487 B apparatus at 80 MHz in solutions of deuteriochloroform or hexadeuteriodimethyl sulphoxide with hexamethyldisiloxane as internal standard.

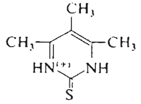
The dissociation constant of compound *IIIa* was measured spectrophotometrically at 25°C in aqueous solutions of hydrochloric acid, chloro acetate, and acetate buffers at 293 nm. The dissociation constant of compound *III* was measured in aqueous solutions of sodium hydroxide and carbonate and borate buffers at 285 nm. The ionic strength 0·5 was adjusted by addition of 1 mol l^{-1} potassium chloride. The values of dissociation constants of compounds *III* and *IIIa* were calculated from the relation $pK_a = pH - \log I$, where I means the concentration ratio of conjugated acid and base of the measured substance (calculated from the measured absorbances). pK_a of compound *III* and its protonated form *IIIa* are 8·84 ± 0·02 and 2·91 ± 0·03, respectively. The cyclization kinetics of compound *II* to *III* or the respective protonated (*IIIa*) or deprotonated (*IIIb*) forms were followed in methanolic solution of 1-butanamine, 2-butanamine or morpholine buffer at 290 nm, in methanolic solution of hydrochloric acid (0·05 to 1 mol l^{-1} HCl) at 295 nm, and in aqueous solution of hydrochloric acid (0·1 to 5 mol l^{-1} HCl) at 290 nm, in aqueous carbonate buffers (pH 9·44 to 10·21) and sodium hydroxide (2.10^{-3} to 10^{-2} mol l^{-1} NaOH) at 280 nm. The rate constants were calculated from the relation $kt = -2{\cdot}303 \log (A_\infty - A_t)$, where A_t and A_∞ mean absorbances measured at time t and after about 7 half-lives, respectively.

RESULTS AND DISCUSSION

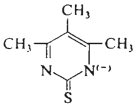
The compound *II* is cyclized in acidic and basic media in similar way as ureido ketones[4], the reaction taking place (slowly) even in methanol alone. Product of the cyclization reaction (*A*) is always 4,5,6-trimethyl-2,5-dihydro-2-thioxopyrimidine (*III*) or its protonated or deprotonated forms (*IIIa,b*).



II *III* (*A*)



IIIa



IIIb

Formation of compound *III* in kinetic experiments was proved spectrophotometrically. Electronic spectra of the products obtained in acidic, neutral and basic media were compared with those of the compound *III* (Fig. 1) (at 260–325 nm) prepared by condensation of thiourea with 3-methyl-2,4-pentanedione. The spectra of the compared substances were identical in each medium. Moreover, the spectrum of reaction mixture after cyclization of compound *II* in methanol was found to contain absorption band of methyl benzoate (λ_{max} 229 nm).

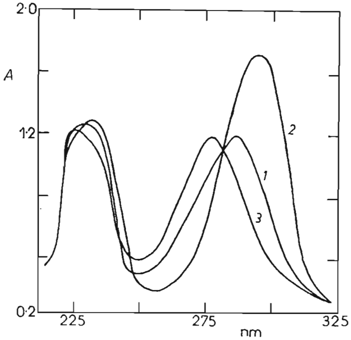


FIG. 1

Electronic spectra of compound *III* (curve *1*), its protonated form *IIIa* (curve 2) and its anion *IIIb* (curve *3*) in methanolic solutions

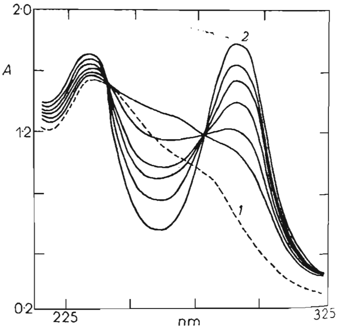
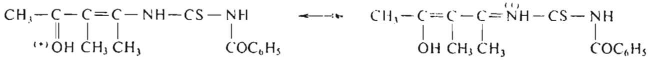


FIG. 2

Spectral recordings of cyclization of compound *II* to *IIIa* in aqueous hydrochloric acid (2 mol l^{-1}) at 25°C (curve *1* compound *II* in water; curve 2 compound *IIIa*)

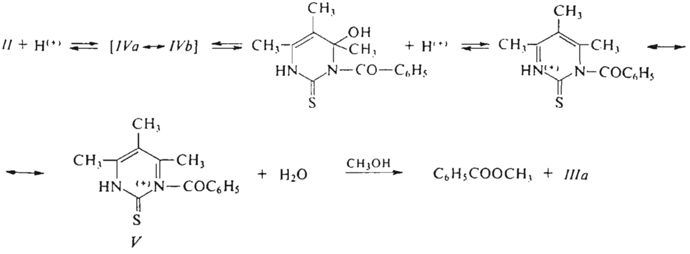
For the study of cyclization in acidic media we used methanolic and aqueous solutions of hydrochloric acid. Addition of hydrochloric acid to solution of compound *II* causes an immediate absorbance increase (Fig. 2) which continues with increasing acid concentration. If the acid was neutralized immediately after its addition, the absorbance value fell almost to its original value, which can be explained by a rapid protonation preequilibrium. The protonation probably takes place at carbonyl oxygen atom to give mesomeric cation *IVa,b*.



$$CH_3-\underset{^{(+)}OH}{\overset{}{C}}-\underset{CH_3}{C}=\underset{CH_3}{C}-NH-CS-\underset{COC_6H_5}{NH} \longleftrightarrow CH_3-\underset{OH}{C}=\underset{CH_3}{C}-\underset{CH_3}{C}=\overset{(+)}{N}H-CS-\underset{COC_6H_5}{NH}$$

IVa *IVb*

Analogous protonation of oxygen with formation of mesomeric cation also takes place with 4-alkylamino-3-penten-2-ones[6], of course, at proton concentrations lower by several orders of magnitude. From spectral records it follows that cyclization of compound *II* in acidic media produces cation *IIIa*, the benzoyl group being split off in the course of the reaction. Two alternatives can be considered for this splitting: either the benzoyl group is split off in the first rate-limiting step followed by rapid cyclization of the benzoyl-free intermediate, or the cyclic benzoyl derivative is formed first, and the benzoyl group is split off in subsequent rapid step. We investigated effect of methanolic hydrochloric acid on N-(3-nitrophenyl)-N'-benzoylthiourea (prepared according to ref.[7]) to differentiate between the two alternatives. Polar effect of 3-nitrophenyl group is roughly comparable with that of 1,2-dimethyl-3-oxo-1-butenyl. Therefore, the methanolysis rates of the two substrates can be presumed to be comparable, too. In the case of the 3-nitrophenyl derivative of benzoylthiourea in methanolic hydrochloric acid, no spectral change was observed even after a time corresponding to several half-lives of the cyclization reaction of compound *II*. This finding could suggest that the benzoyl group is split off after cyclization (Scheme 1).



SCHEME 1

From dependence k_{obs} *vs* $[H^+]$ it follows that in methanolic hydrochloric acid the cyclization proceeds as a non-catalyzed (or methanol-catalyzed) and a proton-catalyzed reaction. The k_{obs} increase with increasing proton concentration is gradually smaller (as the protonated form gradually increases), and at $[H^+] > 1$ the cyclization rate becomes independent of the proton concentration. The said dependence can be expressed by Eq. (*1*)

$$v = k_{obs}[II]_{anal} = k_0[II] + k_{H^+}[IV]\,, \tag{1}$$

where $[II]_{anal}$ means analytical concentration of compound *II*. After introduction of concentrations of *II* and *IV*, Eq. (*1*) is converted to Eq. (*2*)

$$k_{obs} = (k_0 K_a + k_{H^+}[H^+])/(K_a + [H^+])\,, \tag{2}$$

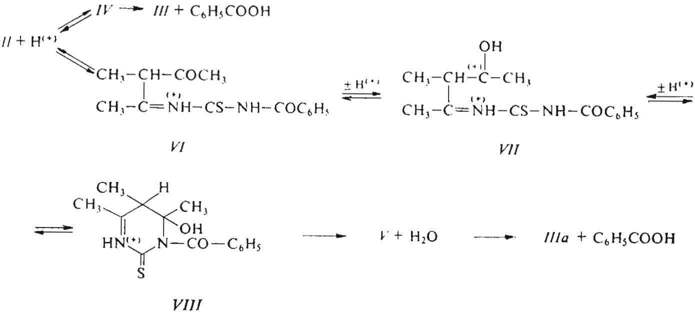
where k_0 is rate constant of the non-catalyzed reaction, k_{H^+} is rate constant of cyclization of compound *IV*, and K_a is dissociation constant of compound *IV*. Using Eqs (*1*) and (*2*) and the measured constants k_{obs}, the following values were obtained: $k_0 = (1.65 \pm 0.15) \cdot 10^{-4}\,s^{-1}$; $k_{H^+} = (8.1 \pm 0.2) \cdot 10^{-4}\,s^{-1}$; $K_a = (2.7 \pm 0.3) \cdot 10^{-2}$ mol l^{-1}. The dependences of the cyclization rate constant *vs* concentration of hydrochloric acid are different in aqueous and methanolic media. The initial trend in water is the same as in methanol, *i.e.* attaining of the reaction rate independent of the proton concentration at $[H^+] \sim 0.5$ (with the value about 4 times smaller), whereafter, however, an abrupt increase in rate is observed, the reaction rate being by two orders of magnitude greater in 5M-HCl than in 0·5M-HCl. From this fact it follows that at higher concentration of hydrochloric acid the activated complex of the rate-

TABLE I

Rate constants of base-catalyzed cyclization *II*→*IIIb* in aqueous carbonate buffers and sodium hydroxide at ionic strength $I = 1$ at 25°C

pH	$10^2 \cdot [OH^-]$ mol l^{-1}	$10^3 k_{obs}$ s^{-1}
9·44	—	0·77
9·80	—	1·56
10·21	—	3·56
—	0·2	10·90
—	0·5	28·88
—	1·0	57·76

-limiting step has two positive charges. The following explanation seems to be acceptable: In analogy with 4-alkylamino-3-penten-2-one[6], protonation of compound *II* takes place at oxygen or carbon atom to give compounds *IV* and *VI*, respectively (Scheme 2).



SCHEME 2

The protonated form *VI* is much more stable in water, having practically no tendency for cyclization. At higher concentrations of hydrochloric acid protonation takes place at carbonyl oxygen atom to give the dication *VII* which is converted very rapidly to the cyclic intermediate *VIII* (Scheme 2).

The anion *IIIb* is formed in aqueous sodium hydroxide or in sodium methoxide. If the reaction is followed spectrometrically, all lines cross in isosbestic points, which

TABLE II

Rate constants k_B of cyclization *II*→*III* catalyzed by amines in methanol at 25°C

Amine	k_B $l\ mol^{-1}\ s^{-1}$	pK_a[a]
1-Butanamine	14·7 ± 0·7	11·70
2-Butanamine	2·44 ± 0·03	—
Morpholine	0·615 ± 0·016	8·69
Morpholine[b]	0·775 ± 0·025	8·45

[a] The values taken from ref.[9]; [b] the values obtained by measurement in aqueous buffers.

means that the reaction mixture only contains the starting substance *II* (as the anion) and the reaction product *IIIb* in spectroscopically detectable concentrations. The reaction kinetics was followed in aqueous carbonate buffers and sodium hydroxide (Table I). In the whole range measured the reaction takes pseudomonomolecular course (at least for 3–4 half-lives), and the observed rate constant increases linearly with activity of OH^- ion (in carbonate buffers) or with concentration of hydroxyl ion (in hydroxide solutions). Both the values of rate constants and the dependence on sodium hydroxide concentration allow to exclude the reaction mechanism in which benzoyl group would be split off in the first rate-limiting step followed by rapid cyclization. With benzoylthioureido derivatives[1,8] the splitting off of benzoyl group is much slower than in the given case, and its rate is independent of hydroxide concentration at the used concentrations of sodium hydroxide[1,8]. As the starting substance *II* is present predominantly as monoanion under the conditions used*, and the rate increases linearly with hydroxyl ion concentration, the activated complex of the rate -limiting step must carry two negative charges. So far no acceptable mechanism fits the said findings. The base-catalyzed cyclization of compound *II* followed in buffers composed of amines and their hydrochlorides revealed that the reaction is strongly accelerated by the amines. It is considerably fast even at such pH values when catalysis by alkoxide ion is practically insignificant. Figure 3 presents spectral record of the reaction course catalyzed by 1-butanamine buffer. The reaction is catalyzed by both primary and secondary amines, but it is not catalyzed by

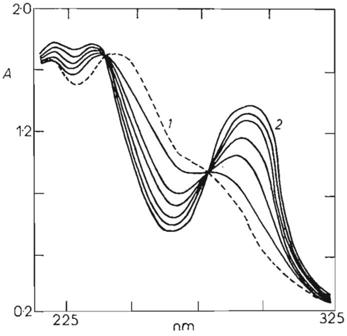


FIG. 3

Spectral recordings of cyclization of compound *II* (curve 1) to *III* (curve 2) in methanolic 1-butanamine buffer (0·2 mol l^{-1}; amine : ammonium salt 1 : 8) at 25°C

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* Its pK_a was estimated about 9·0–9·5 on the basis of analogy with similar compounds given in refs[1,8].

tertiary amines and by acetate ion. The reaction rate increases linearly with concentration of the basic buffer component, being independent of the respective acidic component and independent of pH. Values of the bimolecular rate constants k_B were calculated from Eq. (*3*) and are given in Table II.

$$v = k_{obs}[II] = k_B[\text{amine}][II] . \qquad (3)$$

The finding that the reaction is not catalyzed by tertiary amines and acetate ion and that primary and secondary amines are as efficient (or even more efficient) catalysts as alkoxide ion suggests that the catalysis is not a general base catalysis but a nucleophilic catalysis by amine. As far as we know, this is the first instance of nucleophilic catalysis in this type of cyclizations. It is possible that protonated imino derivative acts as the reactive intermediate, which would explain why tertiary amines do not catalyze the cyclization.

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Translated by J. Panchartek.