STUDY OF REACTION OF THIOUREA WITH ETHYL 3-OXOBUTANOATE

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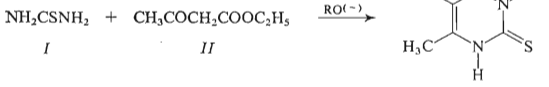
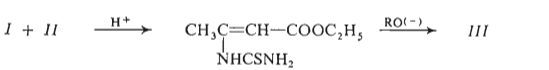
Base-catalyzed formation of 6-methyl-2-thiouracil (*III*) by reaction of thiourea (*I*) with ethyl 3-oxobutanoate (*II*) involves N-(3-oxobutanoyl)thiourea (*XI*) as the reaction intermediate. In acid medium the compounds *I* and *II* do not react. In contrast to literature data, base-catalyzed cyclization of ethyl 3-thioureido-2-butenoate (*IV*) does not produce the compound *III*, but produces 2-amino-4-methyl-6-oxo-1,3-thiazine.

Two procedures are given in literature for preparation of 6-methyl-2-thiouracil: Base-catalyzed reaction of thiourea (*I*) with ethyl 3-oxobutanoate giving immediately 6-methyl-2-thiouracil[1,2] (*III*) (*A*) and acid-catalyzed formation of ethyl 3-thioureido--2-butenoate[3] (*IV*) with subsequent base-catalyzed cyclization to the thiouracil *III* (*B*) (ref.[4]). The compound *IV* was not isolated[3]. Its formation was presumed on the basis of the finding that the compound *III* is formed on several hours heating of the raw reaction mixture in sodium methoxide medium. We repeated several times the described procedure, but we failed in proving the presence of the compound *IV* (even spectroscopically it was not detected, although the compound *IV* absorbs at substantially higher wavelength (λ = 340 nm) than the both starting substances). In addition





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to it we found that base-catalyzed cyclization of the compound *IV* (prepared by another method)[4] does not produce the thiouracil *III*.

This communication deals with study of reaction mechanism of the reaction of thiourea with ethyl 3-oxobutanoate, cyclization of the compound *IV*, and elucidation of differences between the literature data[3,4] and our results.

EXPERIMENTAL

The electronic spectra were measured with a Unicam SP 800 and a Zeiss VSU-2P spectrophotometers. The pH values of the reaction solutions were determined with a Radiometer pH M 4c using a combined glass and S.C.E. electrodes. The ^{1}H-NMR spectra were measured with a Tesla BS 487 B spectrometer at 80 MHz. For the measurements the compounds were dissolved in deuteriochloroform and hexadeuteriodimethyl sulphoxide with hexamethyldisiloxane as internal standard.

Reagents

Ethyl 3-thioureido-2-butenoate (IV) was prepared from ethyl 3-cyanamido-2-butenoate (the latter substance was obtained from cyanamide and ethyl 3-oxobutanoate (*II*)) by reaction with hydrogen sulphide[4]. Yield 39%, m.p. 170—171°C (ref.[4] gives m.p. 165—166°C).

6-Methyl-2-thiouracil (III) was prepared from the ester *II* and thiourea by cyclization in the presence of sodium methoxide[1]. Its m.p. 318°C agrees with ref.[2]. ^{1}H-NMR spectrum (hexadeuteriodimethyl sulphoxide, 24°C): $\delta(CH_3) = 2{\cdot}10$; $\delta(CH) = 5{\cdot}70$; $^4J = 0{\cdot}8$ Hz.

2-Amino-4-methyl-6-oxo-1,3-thiazine (V). The thioureido ester *IV* (0·18 g) was dissolved in 1·2 ml 1M-CH_3ONa and heated in a sealed ampoule at 80°C 30 min. Then the methanol was evaporated and the evaporation residue was dissolved in 2 ml water. After addition of 1 ml 1M-CH_3CO_2H the precipitated solid was isolated and crystallized from ethanol. Yield 0·1 g (70%), m.p. 200°C with decomposition. ^{1}H-NMR spectrum (hexadeuteriodimethyl sulphoxide, 24°C): $\delta(CH_3) = 2{\cdot}02$; $\delta(CH) = 6{\cdot}12$; $^4J = 0{\cdot}6$ Hz. For $C_5H_6OSN_3$ (142·2) calculated: 42·29% C, 4·26% H, 19·72% N; found 42·42% C, 4·38% H, 19·94% N.

S-Ethyl-6-methyl-2-thiouracil (VI) was prepared by alkylation of the thiouracil *III* with ethyl iodide in the presence of sodium methoxide. Its m.p. 145—147°C agrees with ref.[3].

2-Ethylamino-4-methyl-6-oxo-1,3-thiazine (VII) was prepared by alkylation of the thiazine *V* by the same procedure[4]. Yield 80%, m.p. 148—150°C. For $C_7H_{10}OSN_2$ (170·2) calculated: 49·39% C, 5·92% H; found: 49·63% C, 6·04% H. The mixed melting point of the compounds *VI* and *VII* was 90—130°C.

Ethyl 3-(N-methylcyanamino)-2-butenoate (VIII). 1·76 g (0·01 mol) sodium salt of ethyl 3-cyanamino-2-butenoate was dissolved in 10 ml methanol, and 2·8 g (0·02 mol) methyl iodide was added thereto. The solution was heated to boiling 6 h, the solvent was distilled off and the residue was extracted with chloroform. 0·8 g (45%) crystals were isolated from the extract and further purified by chromatography on a silica gel column using chloroform–acetone mixture (2 : 1) as eluent. M.p. 72—74°C. For $C_8H_{12}N_2O_2$ (168·2) calculated: 57·12% C, 7·19% H, 16·66% N; found: 56·91% C, 7·13% H, 16·44% N. ^{1}H-NMR spectrum ($CDCl_3$, 24°C): $\delta(CH_3) = 1{\cdot}26$ (triplet), $\delta(CH_3C{=}) = 2{\cdot}54$ (doublet, $^4J = 0{\cdot}8$ Hz), $\delta(CH_3N) = 3{\cdot}20$ (singlet), $\delta(OCH_2)$ = quartet, $\delta(HC{=}) = 5{\cdot}16$ (quartet).

1,6-Dimethyl-2-thiouracil (IX). The ester *VIII* (2 g) was dissolved in 25 ml ethanol, and hydrogen sulphide saturated with ethanol vapours was introduced therein at 30—40°C. During the

reaction 0·5 g (26·9%) compound *IX* separated, m.p. 258—260°C (ref.[5] m.p. 235—245°C). Ethanol was distilled off from the filtrate in vacuum, and the evaporation residue was separated chromatographically on a silica gel column (chloroform). 0·5 g ester *VIII* was recovered besides further 0·2 g (10·8%) compound *IX*, 0·2 g N-methylthiourea and 0·3 g yellow oily product of unknown composition. For $C_6H_8OSN_2$ (156·2) calculated: 46·14% C, 5·16% H; found: 46·02% C, 5·15% H. ^{1}H-NMR spectrum (hexadeuteriodimethyl sulphoxide, 24°C): $\delta(CH_3C=) = 2{\cdot}31$; $\delta(CH_3N) = 3{\cdot}69$; $\delta(HC=) = 5{\cdot}87$; $^4J = 1{\cdot}0$ Hz.

Kinetic Measurement

Reaction I + II → III. Solution of 0·76 g (0·01 mol) thiourea in 10 ml 0·15 to 1M-CH_3ONa was temperated at 25°C in a 100 ml closed flask. This solution was treated with 0·130 g (0,001 mol) ester *II* and, at suitable time intervals, samples 0·5 ml were withdrawn and diluted with methanol to the volume 10 ml. From the resulting solutions 0·2 ml was pipetted and adjusted with 0·1M-CH_3ONa to the volume 10 ml. Spectra of these samples were measured in the region 250—350 nm (or their absorbance at 315 nm only).

Reaction IV → V. 0·2 ml 10^{-3}M solution of ester *IV* and 4 ml solution of sodium ethoxide (concentrations 0·1; 0·25; 0·5 and 1M) were mixed and closed in a quartz cell ($d = 20$ mm) located in the thermostated cell compartment of the spectrophotometer (25°C); at suitable time intervals spectra were measured within 225 to 450 nm. The rate constants were calculated from the absorbance decrease at 337 nm.

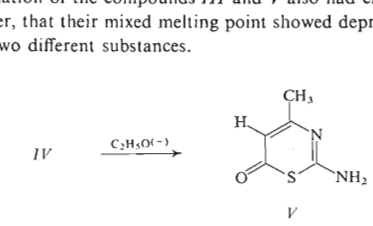
Reaction of thiourea with dimethyl propanedioate. 0·1 ml 0·1M solution of thiourea, 3 to 6 ml 1M methanolic solution of dimethyl propanedioate, 3 to 6 ml 1M-CH_3ONa were mixed, made up to 10 ml and placed in a flask in thermostat. At suitable time intervals 0·4 ml samples were withdrawn and diluted with 4 ml 0·1M-HCl. The absorbance increase was followed by measuring in a 1 cm quartz cell at 280 nm.

The dissociation constants were determined spectrophotometrically[6] in aqueous buffer solutions at the ionic strength adjusted at 0·5 by addition of KCl. *III*: $pK_{a1} = 8{\cdot}15 \pm 0{\cdot}02$ (morpholine buffer, 310 nm), $pK_{a2} = 13{\cdot}01 \pm 0{\cdot}02$ (sodium hydroxide, 310 nm). *IX*: $pK_a = 8{\cdot}33 \pm 0{\cdot}05$ (borax buffer, 238 nm). *V*: $pK_a = 13{\cdot}30 \pm 0{\cdot}06$ (sodium hydroxide, 330 nm).

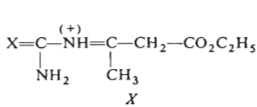
RESULTS AND DISCUSSION

The cyclization kinetics of the thioureidoester *IV* was followed in 0·1 to 0·5M-C_2H_5-.ONa solutions. The spectral records showed well-developed isosbestic points. The reaction took pseudomonomolecular course, and its velocity increased linearly with sodium ethoxide concentration. The calculated value of the rate constant k_2 is $(1{\cdot}65 \pm 0{\cdot}15) \cdot 10^{-2}$ l mol^{-1} s^{-1}. Electronic spectrum of the cyclization product was quite different from that of the thiouracil *III* prepared by the reaction (*A*) (spectra of the both substances were measured in the same medium). The compound prepared by cyclization of the ester *IV* melts at 200°C with decomposition whereas the compound *III* has m.p. 316—318°C. The compound *III* has two acidic hydrogen atoms ($pK_a = 8{\cdot}15$ and 13·01, respectively). On the contrary, the product obtained by cyclization of the ester *IV* has but one proton which can be split off in water ($pK_a = 13{\cdot}30$). The electronic spectrum (*i.e.* bathochromic shift indicating a longer conjugated system) as well as the pK_a value and chemical shifts in the ^{1}H-NMR spectrum

suggest that the product of the cyclization (*C*) of the ester *IV* is 2-amino-4-methyl--6-oxo-1,3-thiazine (*V*). Formerly the product of the reaction (*C*) was ascribed[4] the structure of thiouracil *III* (see (*B*)) on the basis of elemental analysis and analogy with cyclization reactions of other ureido and thioureido esters. The ethyl derivatives prepared by alkylation of the compounds *III* and *V* also had close melting points[4], we found, however, that their mixed melting point showed depression by about 30°, which indicates two different substances.

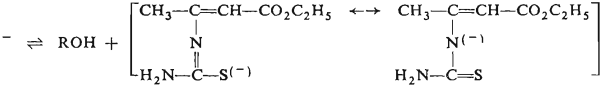


Formation of the thiazine *V* in base-catalyzed cyclization of the ester *IV* forms a further evidence of the fact that the compound *IV* is not produced in the acid-catalyzed reaction of thiourea with ethyl 3-oxobutanoate. The reaction mixture, which allegedly should have contained[3] the thioureido ester *IV*, gave, on boiling in ethoxide solution for several hours, the thiouracil *III* whose identity was unambiguously proved[3]. The only explanation is that the compounds *I* and *II* do not practically react in acid medium, so that the reaction mixture only contains the starting substances which (later in basic medium) give the compound *III* (ref.[2]).



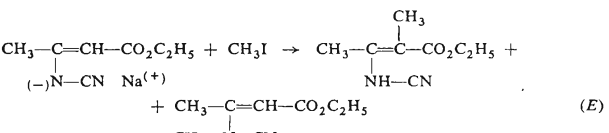
Ethyl 3-ureido-2-butenoate can be obtained under similar conditions in a good yield[7]. From the previous kinetic studies it follows that the rate-limiting step of the ureido ester formation consists in the C—H bond splitting at α-carbon atom in the intermediate *X* (X = O, S)[8-10]. Equilibrium constant of protonation of thiourea at nitrogen is smaller by 2·5 orders of magnitude than that of protonation of urea (the calculated pK_a constants are −6·2 and −3·7, respectively[11]). As in the activated complex of the rate-limiting step the predominant part of positive charge is concentrated at nitrogen (see *X*), reaching of the activated complex in the acid-catalyzed reaction of ethyl 3-oxobutanoate with thiourea is by about 2 orders of magnitude slower than that with urea. As the reaction with urea is very slow, too (the reaction time is about 1 week)[7], and the reaction is reversible with the equilibrium strongly shifted in favour of the starting reactants[8], the negative result of the reaction with thiourea is not surprising.

The thiourea derivatives take part in nucleophilic substitutions at aliphatic carbon atoms acting as S-nucleophiles. In reactions with esters, however, amides are formed. This fact can be explained by the thiourea being ambident nucleophile with amino group and sulphur as hard and soft base groups, respectively. Sulphur attacks preferably at sp^3 aliphatic carbon atom behaving, at the moment of the reaction, as a soft acid. The carbonyl carbon atom behaves as a relatively hard acid, and, therefore, it reacts preferably with amino group (hard base)[12]. In case of the base-catalyzed cyclization of thioureidoester *IV* the carbonyl group was attacked (against expectations) by sulphur (*IV*–*V*). The following explanation can be suggested. In basic medium the anion *IVa* is preferably formed (*D*). Electron density at the sulphur



IVa

atom is increased to a greater extent than that at the amino group, and consequently sulphur becomes stronger nucleophile. At the same time partial positive charge at carbonyl carbon atom is lowered, this centre becoming thus softer acid than that in the usual non-conjugated esters. In order to find the extent to which the mentioned effects operate in the cyclization reaction, we tried to prepare the N-methyl derivative of the compound *IV* and to study its base-catalyzed cyclization. Methylation of so-



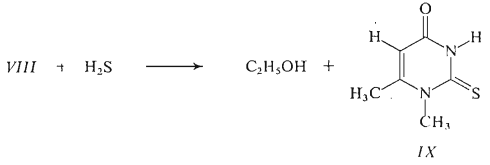
(*E*)

VIII

dium salt of ethyl 3-cyanamino-2-butenoate produces mixture of C- and N-methyl derivatives 4 : 1 (*E*). Neither of the reaction products is further methylated under the used reaction conditions. However, reaction of the N-methyl derivative *VIII* with hydrogen sulphide (*F*) gave besides 50% of the non-reacted compound *VIII* the cyclization product cyclized through nitrogen which was identified as 1,6-dimethyl-2-thiouracil (*IX*).* Its structure was confirmed by measuring of pK_a (8·33) (the product cyclized *via* sulphur atom would have no acidic hydrogen atom), by electronic spectrum (which

* In preparation of the thioureido ester *IV* the presence of the cyclized product was not confirmed, not even in traces.

has the same character as that of the 1-alkyl-2-thiouracils prepared by independent synthesis), and by ^{1}H-NMR spectra. Although in this case cyclization *via* nitrogen took place (*F*), it is impossible to make unambiguous conclusion that this is due to substitution of hydrogen at nitrogen by methyl group, because cyclization (*F*) proceeded under quite different conditions than (*C*).



IX (*F*)

The reaction $I + II \rightarrow III$ was followed spectrophotometrically by the absorbance increases of the anion of *III*. At $[CH_3O^{(-)}] > [II]$ the spectral records showed well-developed isosbestic points indicating that no intermediate is accumulated in the reaction mixture during the reaction. The reaction was pseudomonomolecular within the whole course. Values of the experimental rate constants k_{exp} were independent of methoxide ion concentration. With sufficient excess of methoxide almost all the ester *II* is present in the form of its anion, so that for the equilibrium reaction[13] $II + CH_3O^{(-)} \rightleftharpoons CH_3OH + II^{(-)}$ it follows ($II^{(-)}$ is enolate anion of ethyl 3-oxobutanoate):

$$K = 520 = [II^-]/[II]\,[CH_3O^-] \doteq [II]_{anal}/[II]\,[CH_3O^-] \qquad (1)$$

Kinetic equation of the base-catalyzed reaction $I + II \rightarrow III$ is thus simplified to the form (2).

$$v = k[I]\,[II]\,[CH_3O^-] = k_{exp}[II]_{anal} = k[II]_{anal}[I]/K \qquad (2)$$

$$k_{exp} = [I]\,k/K$$

The calculated value $k = (2{\cdot}4 \pm 0{\cdot}2)\,.\,10^{-2}\,l^2\,mol^{-2}\,s^{-1}$.

At $[CH_3O^{(-)}] < [II]$ the reaction rate decreases faster than it corresponds to pseudomonomolecular reaction. As the product *III* is a much stronger acid than the ester *II*, the methoxide ion concentration decreases in the reaction course. Under these conditions the simplified relation (2) is not valid, the reaction rate depends on a methoxide ion concentration, and the reaction stops at the moment when the ester *II* is not yet completely reacted. On addition of excess methoxide the reaction goes to completion.

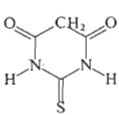
As the base-catalyzed cyclization of the thioureido ester *IV* produces the thiazine *V*, formation of the compound *IV* is excluded in the base catalyzed reaction of the compounds *I* and *II*. Also that variant is out of question that the thiazine *V* is the primary product of the reaction of *I* and *II* and is rearranged into the thiouracil *III* under the reaction conditions used. The compounds *III* and *V* are stable under the used reaction conditions. In reaction of the compounds *I* and *II* in basic medium N-(3-oxobutanoyl)thiourea (*XI*) is probably formed as intermediate (*G*). Reactions of amines with carbonyl group are usually acid-catalyzed[14], whereas ester amonolyses are base-catalyzed[15]. Therefore, *e.g.* reaction of the keto ester *II* with urea produces ethyl 3-ureido-2-butenoate in acidic medium which is cyclized to 6-methyluracil in alkaline medium[8].

$$I + II + CH_3O^{(-)} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3COCH_2CONHCSNH_2 + C_2H_5OH + CH_3O^{(-)}$$
$$\xrightarrow{k_2} V + C_2H_5OH + CH_3O^{(-)} \qquad (G)$$

To support the idea that the thioureide *XI* is the intermediate of the reaction (*G*), we measured the reaction rate of thiourea with dimethyl propanedioate (*XII*) (*H*) under the same reaction conditions as in (*G*). The reaction (*H*) must involve formation of thioureide as the first reaction step. As the inductive effects of the groups $-CH_2.CO_2CH_3$ and $-CH_2COCH_3$ are comparable, values of rate constants of the reactions (*G*) and (*H*) should be comparable, too.

$$I + CH_3O^{(-)} + \underset{XII}{CH_2(COOCH_3)_2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3OOCCH_2CONHCSNH_2 +$$

$$+ CH_3OH + CH_3O^{(-)} \xrightarrow{k_2}$$



$$+ CH_3OH + CH_3O^{(-)} \qquad (H)$$

$$v = [I][XII]\,k_1k_2[CH_3O^-]/(k_{-1} + k_2) = k'[I][XII][CH_3O^-] = k_{exp}[I] \qquad (3)$$

Real concentrations of dimethyl propanedioate (*XII*) and methoxide ion were calculated from the value of the equilibrium constant of the reaction of dimethyl propanedioate with methoxide ion ($K = 0{\cdot}5$) (ref.[13]). The value k' calculated from Eq. (*3*) is $(4{\cdot}3 \pm 0{\cdot}3) \cdot 10^{-3}$ l^2 mol^{-2} s^{-1}.

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