REACTIONS OF ETHYL 2-ALKYL-3-OXOBUTANOATE WITH THIOUREA AND METHYLTHIOUREA

Jaromír KAVÁLEK, Vladimír MACHÁČEK and Vojeslav ŠTĚRBA

Department of Organic Chemistry,
Institute of Chemical Technology, 532 10 Pardubice

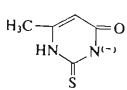
Received October 6th, 1982

The reaction of ethyl 3-oxobutanoate with N-methylthiourea in alkoxide medium gives a mixture (1 : 20) of 1,6-dimethyl-2-thiouracil and 3,6-dimethyl-2-thiouracil: the latter isomer has been isolated from the mixture and the former isomer has been prepared by independent synthesis. Dissociation constants of ethyl 2-alkyl-3-oxobutanoates (alkyl = methyl, butyl, or isopropyl) have been measured in methanol. Reaction of these esters with thiourea and N-methylthiourea gives the corresponding alkyl derivatives of 6-methyl-2-thiouracil. Kinetics of these reactions have been measured in methoxide medium. Effects of the alkyl groups on the reaction rates have been investigated, and a reaction mechanism is suggested.

Reactions of substituted thioureas with ethyl 3-oxobutanoate and its 2-alkyl derivatives in the presence of alkoxide represent a method of preparation of substituted uracils[1,2]. Mechanism of the reaction of thiourea (*I*) with ethyl 3-oxobutanoate (*III*) is given in Scheme 1 (ref.[3]).

$$I + CH_3O^{(-)} \rightleftarrows NH_2CSNH^{(-)} + CH_3OH$$

$$NH_2CSNH^{(-)} + III \rightleftarrows CH_3COCH_2CONHCSNH_2 + C_2H_5O^{(-)} \rightarrow$$

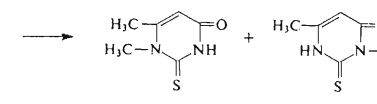


$$+ C_2H_5OH + H_2O$$

SCHEME 1

N-Methylthiourea (II) can react with the ester *III* to give two thiouracil derivatives (*A*).

The aim of this communication is to determine composition of products of the reaction of *II* + *III* and specify effects of alkyl groups at nitrogen atom of thiourea



(A)

or at 2-carbon atom of ethyl-3oxobutanoate on the reaction rate. Reaction mechanism is discussed on the basis of the results of these kinetic experiments.

EXPERIMENTAL

Reagents

1-Methylthiourea (*II*) was prepared from methyl isothiocyanate and ammonia; yield 89%, m.p. 119–120°C. The 2-alkyl derivatives (methyl (*IV*), isopropyl (*V*), butyl (*VI*)) of ethyl 3-oxobutanoate were prepared by alkylation of ethyl 3-oxobutanoate (*III*) according to refs[4,5].

3,6-*Dimenthyl-2-thiouracil* (VII). Compound *II* (4·7 g) was dissolved in 60 ml methanolic sodium methoxide (1 mol l^{-1}) and treated with 6·7 g ester *III*. The mixture was heated on water bath 2 h. Methanol was distilled off, and the residue was dissolved in 20 ml water, filtered, and acidified with 4 ml acetic acid. The solid was collected by filtration and recrystallized three times from methanol. Yield 5·1 g (61%); m.p. 265·5–267°C. For $C_6H_8N_2OS$ (156·2) calculated: 46·09% C, 5·12% H; found: 45·81% C, 5·25% H, ^{1}H NMR spectrum: δ(C—CH_3) = 2·11, δ(N—CH_3) = = 3·53, δ(C—H) = 5·73.

Analogous procedure was used for the following preparations: 5,6-Dimethyl-2-thiouracil (*IX*) from thiourea (*I*) and ester *IV*; m.p. 247·5–250°C; for $C_6H_8N_2OS$ (156·2) calculated: 46·09% C, 5·12% H; found: 45·86% C, 5·30% H. 5-Isopropyl-6-methyl-2-thiouracil (*X*) from *I* and *V*; m.p. 227–230°C; for $C_8H_{12}N_2OS$ (184·2) calculated: 52·12% C, 6·51% H; found: 51·81% C, 6·65% H. 5-Butyl-6-methyl-2-thiouracil (*XI*) from *I* and *VI*; m.p. 201–203°C; for $C_9H_{14}N_2OS$ (198·2) calculated: 54·49% C, 7·06% H; found: 54·16% C, 7·01% H. 3,5,6-Trimethyl-2-thiouracil (*XII*) from methylthiourea *II* and ester *IV*; m.p. 189–192°C; for $C_7H_{10}N_2OS$ (170·2) calculated: 49·39% C, 5·88% H; found: 49·09% C, 6·02% H. 3,6-Dimethyl-5-isopropyl-2-thiouracil (*XIII*) from *II* and *V*; m.p. 211–213°C; for $C_9H_{14}N_2OS$ (198·2) calculated: 54·54% C, 7·06% H; found: 54·69% C, 6·92% H. 3,6-Dimethyl-5-butyl-2-thiouracil (*XIV*) from *II* and *VI*; m.p. 148–151°C; for $C_{10}H_{16}N_2OS$ (212·2) calculated: 56·59% C, 7·54% H; found: 56·30% C, 7·70% H.

1,6-*Dimethyl-2-thiouracil* (VIII). 1·76 g sodium salt of ethyl 3-cyanamino-2-butenoate[6] was suspended in 10 ml methanol and treated with 2·8 g methyl iodide. The mixture was refluxed 6 h, the solvent was distilled off, and the residue was extracted with boiling chloroform. Chloroform was distilled off, and 0·8 g (45%) ethyl 3-(N-methylcyanamino)-2-butenoate was isolated and purified by column chromatography (silica gel; chloroform–acetone 2 : 1). M.p. 72–74°C. For $C_8H_{12}N_2O_2$ (168·2) calculated: 57·12% C, 7·20% H, 16·66% N; found: 56·91% C, 7·13% H, 16·64% N. The said ethyl ester (2 g) was dissolved in 25 ml ethanol, and the solution was treated with hydrogen sulphide saturated with ethanol vapours at 30–40°C. The product *VIII* precipitated during the reaction in the yield 0·5 g, m.p. 258–260°C (ref.[7] gives m.p. 235–245°C). The filtrate was vacuum-distilled to remove ethanol, and the residue was separated chromatographically (silica gel; chloroform) to give 0·5 g starting ethyl ester, 0·2 g thiouracil, and 0·2 g methylthiourea *II*. For $C_6H_8N_2OS$ (156·2) calculated: 46·09% C, 5·12% H; found: 46·00% C, 5·16% H. ^{1}H NMR spectrum: δ(C=CH_3) = 2·13, δ(N—CH_3) = 3·70, δ(C—H) = 5·86.

Methods

Kinetics measurements: Compound *I* or *II* (about 0·8 g) was dissolved in 10 ml methanolic sodium methoxide (0·5—1·5 mol l^{-1}), the solution was temperated at 25°C, and 1 ml 20% (v/v) methanolic solution of ester *III* (or *IV*—*VI*) was added. At suitable time intervals (2—30 min), 0·5 ml samples were withdrawn from the reaction mixture and their volume was adjusted at 10 ml by addition of methanol. The resulting solution was diluted (from 0·2 to 10 ml) by addition of 0·1 mol l^{-1} methoxide solution and submitted to spectral measurements: with a Unicam SP 800 apparatus spectra were measured in the range 250—350 nm, and with a Zeiss VSU-2P spectrophotometer absorbance was measured at 320 nm.

Measurement of dissociation constants: Spectra of esters *IV*—*VI* were measured in methanol (the non-dissociated form) and in 2·2—3 mol l^{-1} sodium methoxide (the dissociated form) using the Unicam SP 800 spectrophotometer, and the obtained spectra were used for determination of suitable analytical wavelength (275 nm for the ester *V*; 285 nm for the esters *IV* and *VI*). 0·5 ml methanolic solution (about 10^{-4} mol l^{-1}) of compound *IV* (or *V* or *VI*) was placed in a 1 cm quartz cell and mixed with 1·5 ml sodium methoxide solution (0·02—2·24 mol l^{-1}), and the absorbance was measured at λ_{anal} with the Zeiss VSU-2P apparatus. The reference cell contained sodium alkoxide of the same concentration. The pK_a values were determined from the dependence of logarithms of the measured absorbance ratios of the non-dissociated to the dissociated forms on the H_M function[8]. The pK_a values are 16·15, 16·51, and 17·80 for the derivatives *IV* (methyl), *VI* (butyl), and *V* (isopropyl), respectively. Ref.[9] gives the value 14·20 for the non-substituted ester *III*.

^{1}H NMR *spectra*: the samples were dissolved in hexadeuteriodimethyl sulphoxide and measured at 70°C using a Tesla BS-487B spectrometer at 80 MHz with hexamethyldisiloxane as internal standard.

RESULTS AND DISCUSSION

The ^{1}H NMR spectra of the non-crystallized reaction product from compounds *II* and *III* contain pairs of signals of the both methyl groups and the proton of C—H groups at the intensity ratio 1 : 20. Chemical shifts of the more intensive signals are identical with those of the *VII* isomer, which indicates that the main reaction pathway consists in formation of 1-methyl-1-(3-oxobutanoyl)thiourea (*XV*) according to Eq. (*B*).

$$II + III \rightarrow \underset{XV}{CH_3COCH_2CON(CH_3)CSNH_2} \rightarrow VII \qquad (B)$$

$$III + H_2N{-}CN \xrightarrow{CH_3ONa} \underset{\displaystyle NC{-}N^{(-)}Na^{(+)}}{\underset{|}{CH_3{-}C{=}CH{-}COOC_2H_5}} \xrightarrow{CH_3I}$$

$$\longrightarrow \underset{\displaystyle NC{-}N^{(-)}Na^{(+)}}{\underset{|}{CH_3{-}C{=}C{-}COOC_2H_5}} + \underset{\displaystyle NC{-}N{-}CH_3}{\underset{|}{CH_3{-}C{=}CH{-}COOC_2H_5}}$$

$$\underset{XVI}{\underset{|}{CH_3}} \qquad\qquad \underset{XVII}{}$$

$$XVII + H_2S \rightarrow VIII$$

SCHEME 2

Structure of the two isomers was proved in the following way: the 1,6-dimethyl derivative *VIII* was prepared by independent synthesis (Scheme 2).
The reaction with methyl iodide gives a mixture of the C- and N-methyl derivatives *XVI* and *XVII*. The compound *XVII* is soluble in chloroform. After its extraction from the solid portion, ethyl 2-methyl-3-cyanamino-2-butenoate was liberated by action of tartaric acid, and its structure was verified by ^{1}H NMR spectra.

The kinetic measurements were carried out with a great excess of thiourea *I* or *II*. The reaction followed 1. order kinetics, and the spectral records always contained clear isosbestic points. The observed rate constants k_{obs} (s^{-1}) are directly proportional to concentration of *I* (or *II*), which indicates the first-order kinetics with respect to these substances. The reaction rate of *I* with *III* (ester *III* has the lowest pK_a value (14·2) of all the esters used) is independent of alkoxide concentration. With decreasing acidity of the esters the influence of methoxide concentration on k_{obs} is increasingly significant.

Besides the reactions given in Scheme 1, equilibrium (*C*) also makes itself felt in the presence of alkoxide, which causes concentration decrease of the reactive non-dissociated esters *III* – *VI*.

$$CH_3CO{-}CHR{-}COOC_2H_5 + CH_3O^{(-)} \rightleftarrows CH_3CO{-}\overset{(-)}{C}R{-}COOC_2H_5 + CH_3OH \quad (C)$$

The reaction rate is defined by Eq. (*1*) in which C_{ester} means analytical concentration of the ester whose effective concentration is given by Eq. (*2*).

$$v = k[\text{thiourea}]\,[\text{ester}]\,[\text{methoxide}] = k_{obs}C_{ester} \qquad (1)$$

$$[\text{ester}] = C_{ester}[CH_3O^{(-)}]/(K_a + [CH_3O^{(-)}]) \qquad (2)$$

The rate constant k can be expressed by Eq. (*3*).

$$k = k_{obs}\frac{K_a + [CH_3O^{(-)}]}{[CH_3O^{(-)}]} \cdot \frac{1}{[I \text{ or } II]\,[CH_3O^{(-)}]} \qquad (3)$$

Effective concentration of the thiourea *I* (or *II*) is practically equal to analytical concentration, because dissociation of NH bond proceeds to slight extent only ([*I*] or [*II*] = $C_{(\text{thiourea})}$). Effective methoxide concentration was calculated from Eq. (*4*) and Eq. (*2*) by the method of gradual approximation.

$$[CH_3O^{(-)}] = C_{CH_3O^{(-)}} - C_{ester} + [\text{ester}] \qquad (4)$$

Table I gives values of the rate constants k and k_{obs} for analytical concentrations 1 mol l^{-1} of sodium methoxide and thiourea *I* (or *II*). The rate constant k involves

both the pre-equilibrium $RNHCSNH_2 + CH_3O^{(-)} \rightleftharpoons \overset{(-)}{R}NCSNH_2 + CH_3OH$ and subsequent reaction of anion of *I* (or *II*) with ester group, or possibly also cyclization of the intermediate formed.

The reaction of methylthiourea *II* with ester *III* giving 3,6-dimethyl derivative *VII* is 3·4 times slower than the reaction of ester *III* with thiourea *I*; if statistical factor is taken into account, the said finding means a rate reduction to one half. The reaction intermediate from *II* + *III* is compound *XV*, which indicates that the N-methyl group retards somewhat the reaction, not taking into account whether the rate-limiting step consists in formation of intermediate *XV* or in cyclization Eq. (*B*).

$$II + III \overset{\text{fast}}{\rightleftharpoons} \underset{XX}{CH_3COCH_2CONHCSNHCH_3} \xrightarrow{\text{slow}} VIII \qquad (D)$$

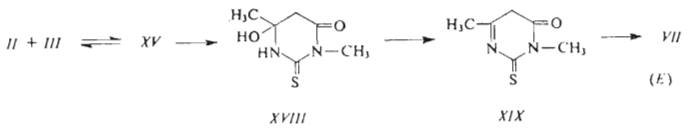
The isomeric 1,6-derivative *VIII* is formed about 70× more slowly (35× after correction with respect to statistical factor). As the first step of reaction (*D*) involves an attack of ester group of *III* by non-methylated amino group of the nucleophile *II*, the large retardation cannot be due to this step but to the subsequent cyclization which thus represents the rate-limiting step in the reaction (*D*) producing *VIII*. The large difference between rates of formation of the two isomers *VII* and *VIII* indicates a possibility that another factor is operating besides steric effect of methyl group. In the case of the cyclic intermediate *XVIII* (Eq. (*E*)) formed from compound *XV*, the proton is split off from nitrogen atom, and hydroxyl is splitt off from the adjacent carbon atom to give the cyclizate *XIX* which rearranges rapidly to final product *VII*.

TABLE I

Rate constants of the reactions of esters *III*—*VI* with thiourea *I* or methylthiourea *II* (k^{I}_{obs} and k^{II}_{obs} (s^{-1}), respectively, and k^{I} and k^{II} ($s^{-1}\,l^{2}\,mol^{-2}$), respectively in the presence of sodium methoxide at 25°C

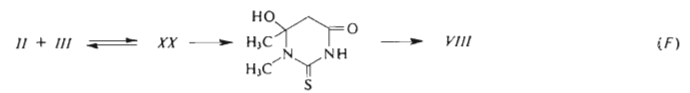
Ester	$10^4 k^{I}_{obs}$	$10^4 k^{II}_{obs}$	$10^3 k^{I}$	$10^3 k^{II}$	k^{I}/k^{II}	k^{I}/k^{I}_{III-VI} [a]
III	0·5	0·13	24	7·6	3·4	1·0
IV	11·0	5·3	16·5	9·0	1·78	1·57
VI	1·8	1·0	1·2	0·68	1·76	23·2
V	0·91	0·38	0·125	0·06	2·12	208

[a] Ratio of k^{I} of ester *III* to k^{I} of esters *III*—*VI*.



XVIII XIX

In the case of the cyclizate *XXI* formed from 1-methyl-3-(3-oxobutanoyl)thiourea (*XX*) (Eq. (*F*)) the dehydratation involves splitting off of the proton from CH_2 group, which requires higher energy, and so the reaction (*F*) is slower than (*E*).



XXI

The reactions of esters *IV–VI* show great decrease in rate with increasing steric demands of alkyl group. Also it is interesting that the reactivity ratio of thiourea *I* and its methyl derivative *II* is about 2 for all the alkyl esters (Table I), which would indicate that the retardation is only due to the statistical factor. The reaction rates of the alkyl esters *IV–VI* are, even in the case of isopropyl derivative *V*, greater (under the given reaction conditions) than that of the non-substituted ester *III*, although the rate constants decreased by more than two orders of magnitude (Table I). This result is due to the fact that increasing steric demands of the substituents are accompanied by increase in pK_a values of the ester and, hence, by concentration increase of the non-dissociated reactive ester in the reaction mixture.

REFERENCES

1. Robinson R., Tomlinson M. L.: J. Chem. Soc. *1935*, 1283.
2. Foster H. M., Snyder H. R.: Org. Syn. Coll. Vol. *IV*, 638 (1963).
3. Kaválek J., Said El Bahaie, Macháček V., Štěrba V.: This Journal *45*, 732 (1980).
4. Folkers K., Adkins H.: J. Amer. Chem. Soc. *53*, 1416 (1931).
5. Renfarow W. B.: J. Amer. Chem. Soc. *66*, 145 (1944).
6. Brigl P.: Chem. Ber. *45*, 1557 (1912).
7. Lacey R. N.: J. Chem. Soc. *1954*, 839.
8. Rochester C. H.: *Acidity Functions*, p. 247. Academic Press, London 1970.
9. Kaválek J., Macháček V., Lyčka A., Štěrba V.: This Journal *41*, 590 (1976).

Translated by J. Panchartek.