STUDY OF CYCLIZATION OF 1-BENZOYL-3-METHYL-3-(2-METHOXYCARBONYLPHENYL)THIOUREA TO 1-METHYL-2-THIOXO-4-QUINAZOLONE

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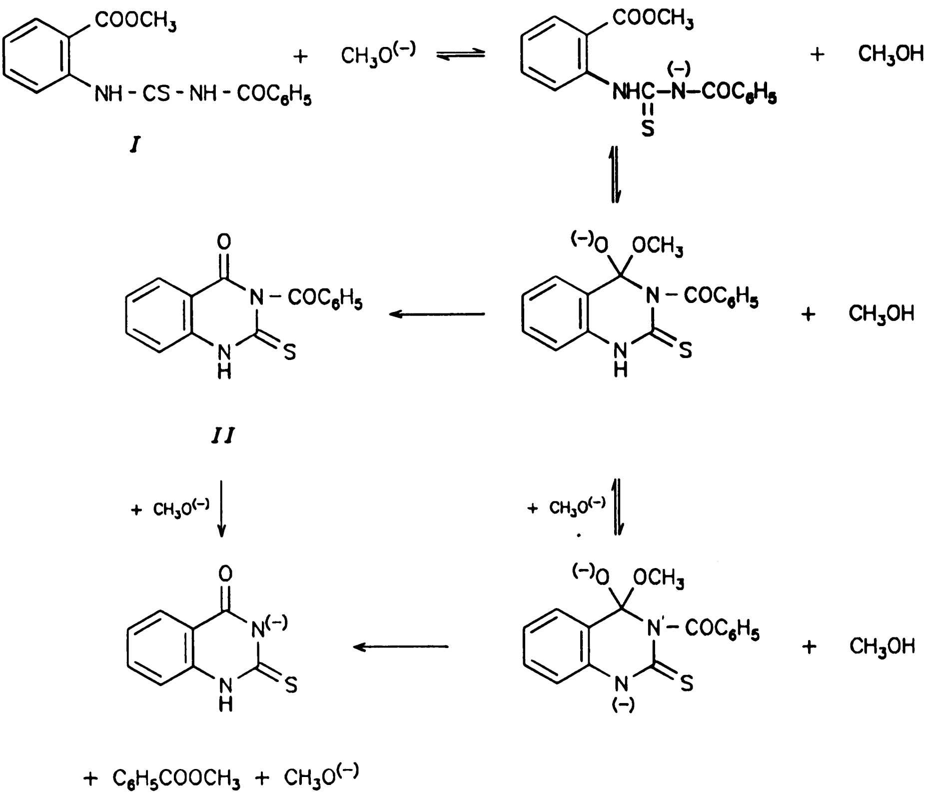
Received March 23, 1992
Accepted May 13, 1992

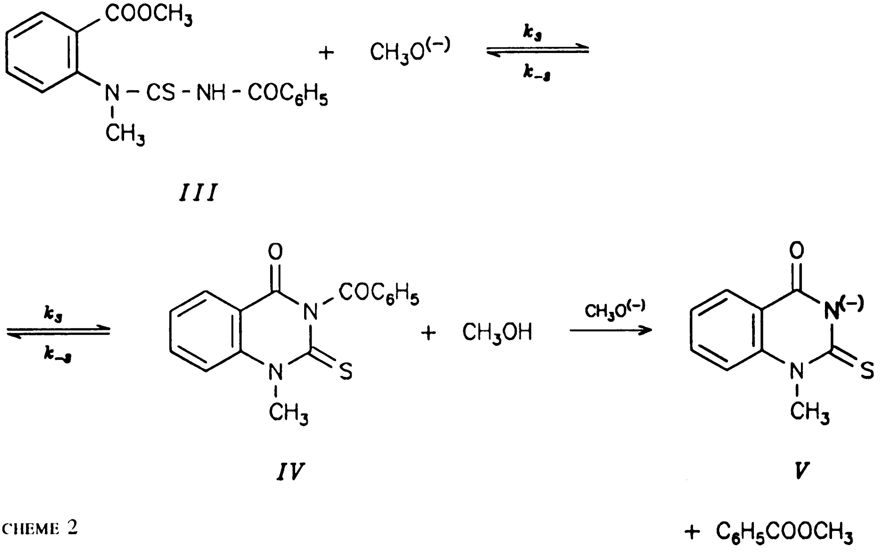
The reaction mechanism of the title reaction was proposed on the basis of the kinetic study. The reaction takes place in two stages considerably differing in rates. In the first, faster stage, the anion of initial substance cyclizes to 1-methyl-3-benzoyl-2-thioxo-4-quinazolone. The reaction is reversible, the concentration of 1-methyl-3-benzoyl-2-thioxo-4-quinazolone decreases with increasing concentration of methanolate. In the second stage, the benzoyl group rearrangement in the given substance from nitrogen to sulfur and subsequent methanolysis to 1-methyl-2-thioxo-4-quinazolone take place. The rate-determining step is the methanolysis for $[CH_3O^{(-)}] < 4 \cdot 10^{-3}$ mol l^{-1} and the benzoyl group rearrangement for higher methanolate concentrations.

In the framework of study of the cyclization reactions of ureides and thioureides leading to the biologically active substances, the cyclization of 1-benzoyl-3-(2-methoxycarbonylphenyl)thiourea (*I*) to 3-benzoyl-2-thioxo-4-quinazolone anion (*II*) catalyzed by methanolate ion was also studied[1]. The anion of substance *I* is subject to the cyclization, and therefore at lower methanolate concentrations, the rate of cyclization increased linearly with its concentration. At higher methanolate concentrations, when thiourea (*I*) is converted nearly completely to anion, the rate of cyclization should become independent of methanolate concentration; we have observed, however, further increase in the rate. The mechanism accounting for the kinetic behaviour described is given in Scheme 1.

To corroborate that the subsequent increase in the cyclization rate is caused by the proton abstraction from NH group of negatively charged tetrahedral intermediate and consequent splitting off of methanolate ion and benzoyl group, we studied the cyclization of methyl derivative of substance *I*, (1-benzoyl-3-methyl-3-(2-methoxycarbonylphenyl)thiourea) (*III*) to 1-methyl-3-benzoyl-2-thioxo-4-quinazolone (*V*) in methanolate solutions (Scheme 2). It appeared that the *III* → *V* reaction course is quite different from the cyclization of substance *I*. Results of the study of cyclization of 1-benzoyl-3-methyl-(2-methoxycarbonylphenyl)thiourea are subject of this work.



SCHEME 1



SCHEME 2

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.62 MHz using an AM-400 Bruker spectrometer. Chemical shifts are referred to the signal of hexamethyldisiloxane ($\delta(^1H)$ 0.05) and/or to the signal of solvent ($\delta(^{13}C)$ 77.0 for deuteriochloroform 39.6 for hexadeuteriodimethyl sulfoxide).

1-Benzoyl-3-methyl-3-(2-methoxycarbonylphenyl)thiourea (*III*)

Mixture of 1.8 g (11 mmol) methyl N-methylanthranilate[2] and 1.76 g (11 mmol) benzoylisothiocyanate was kept for 1 h in a closed flask at ambient temperature. After washing with 5 ml benzene, 2.2 g (62%) of raw crystalline substance with m.p. 108 – 113 °C was obtained. After crystallization from methanol, its m.p. was 122 – 124 °C. For $C_{17}H_{16}N_2SO_3$ (328.38) calculated: 62.17% C, 4.91% H, 8.53% N; found: 61.95% C, 5.00% H, 8.72% N. ^{13}C NMR (deuteriochloroform): 181.23 (C=S), 166.30 (CONH), 163.23 (COO), 143.73 (C_{kv}), 132.92 (CH), 132.72 (C_{kv}), 132.37 (CH), 130.69 (CH), 128.65 (CH), 128.46 (CH), 128.11 (CH), 127.50 (CH), 126.70 (C_{kv}), 52.96 (OCH_3), 45.66 (NCH_3).

1-Methyl-3-benzoyl-2-thioxo-4-quinazolone (*IV*)

Five ml 0.01 M sodium methanolate was added to the solution of 1.0 g (3 mmol) substance *III* in 15 ml methanol. The mixture was cooled with ice water. After 15 min, the dry product (650 mg, 72%) was sucked out. After crystallization from ethyl acetate, its m.p. was 229 – 230 °C. For $C_{16}H_{12}N_2SO_2$ (296.34) calculated: 64.84% C, 4.08% H, 9.45% N; found: 65.02% C, 4.12% H, 9.55% N.

1-Methyl-2-thioxo-4-quinazolone (*V*)

A solution of 0.33 g (1 mmol) benzoyl derivative *III* was refluxed with 25 ml 5 . 10^{-2} M sodium methanolate for 1.5 h. After cooling, the solution was neutralized with 13 ml 0.1 M HCl. The separated product (0.15 g, 79%) after crystallizing from methanol had m.p. 253 – 256 °C. For $C_9H_8N_2SO$ (194.24) calculated: 56.22% C, 4.20% H, 14.57% N; found: 56.50% C, 4.31% H, 14.80% N. ^{1}H NMR (hexadeuteriodimethyl sulfoxide): 12.67 b, 1 H (NH); 8.06 dd, 1 H (H-5, $J(5,6)$ = 7.7 Hz, $J(5,7)$ = 1.4 Hz); 7.87 dt, 1 H (H-6, $J(6,7)$ = 7.5 Hz); 7.63 d, 1 H (H-8, $J(7,8)$ = 7.5 Hz); 7.44 t, 1 H (H-7); 4.02 s, 3 H (NCH_3). ^{13}C NMR (hexadeuteriodimethyl sulfoxide): 175.92 (C=S), 158.40 (C=O), 141.55 (C-8a), 135.72 (C-7), 127.29 (C-5), 124.68 (C-6), 117.90 (C-4a), 116.45 (C-8), 36.78 (CH_3).

Kinetic Measurements

Electronic spectra were measured with a Specord UV-VIS spectrophotometer (Zeiss). Kinetic measurements for reactions with half-life $t_{1/2}$ > 20 s were carried out on the same apparatus, faster reactions (with half-life $t_{1/2}$ < 20 s) were monitored by the stopped-flow method on a Durrum D-150 spectrophotometer, all that at 25 °C.

Measurement of rate constants of cyclization of substance III *to substance* IV. An amount of 0.1 ml 1 . 10^{-3} M methanolic solution of substance *III* was added to 2 ml methanolic butylamine buffer and the increase at 290 nm was measured on the Specord UV-VIS apparatus. The kinetics of the reaction *III* $\rightleftharpoons$ *IV* $\rightarrow$ *V* was measured in an analogous way in sodium methanolate solutions, the absorbance increase (278 nm) or its decrease (250 nm) being observed. As the initial substrate, substances *III* and *IV* were used. The kinetics of reversible reaction *III* $\rightleftharpoons$ *IV* was measured with the Durrum D-150 spectrophotometer by the stopped-flow method. In one syringe there was the methanolate solution (1 . 10^{-1} to 1 . 10^{-3} mol l^{-1}), in the second the methanolic solution (1 . 10^{-4} mol l^{-1}) of substance *III* or *IV*. The absorbance change was recorded at 290 nm (for the initial substance *III*) or at 250 nm (for the initial substance *IV*). The rate constants, k_{exp}, were calculated in terms of Eq. (*1*).

$$k_{\mathrm{exp}}\,t \;=\; -2.3\,\log(A_t - A_\infty) \;+\; \mathrm{const} \qquad (1)$$

Measurement of Dissociation Constants

Dissociation constants, K_a, of substance *V* were measured spectrophotometrically by means of the Specord UV-VIS apparatus in methanolic methanolate solutions ($1.0 \cdot 10^{-3}$ to $3.5 \cdot 10^{-3}$ mol l^{-1}) at 332 nm and in aqueous solutions of borate buffers (pH 10.02 to 8.35) at 290 nm and ionic strength 0.5 mol l^{-1}. The dissociation constant, pK_a, in water (9.23 ± 0.04) was calculated from Eq. (*2*) where *A* are the measured absorbances

$$pK_a \;=\; pH_{\mathrm{buffer}} \;-\; \log\frac{A - A_{\mathrm{BH}}}{A_{\mathrm{B}} - A} \qquad (2)$$

of substance *V* in the buffer, A_{BH} in the acetate buffer and A_{B} in 0.1 M sodium hydroxide.

pK_a value of substance *V* in methanol (13.90 ± 0.05 mol l^{-1}) was calculated from Eq. (*3*), where *A* are the measured absorbances of substance *V* in methanolic methanolate solutions,

$$pK_a \;=\; \log[\mathrm{CH_3O^{(-)}}] \;+\; pK_s \;-\; \log\frac{A - A_{\mathrm{BH}}}{A_{\mathrm{B}} - A} \qquad (3)$$

A_{BH} in methanolic solutions of acetate buffer, and A_{B} of 0.1 M sodium methanolate and $K_s = [\mathrm{H^{(+)}}].[\mathrm{CH_3O^{(-)}}]$ is the autoprotolysis constant of methanol $10^{-16.92}$ (ref.[3]).

RESULTS AND DISCUSSION

The structure of substance *III* was verified by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum measured at 400 MHz (deuteriochloroform) can be interpreted only partly. The ester *III* exists in two relatively stable conformations which occur in approximate ratio 4 : 1. The conformations are interconverted slowly (on the NMR time scale) so that the signals are only mildly broadened owing to the interchange. The existence of two conformers is apparent from the signal pairs for groups $\mathrm{OCH_3}$, $\mathrm{NCH_3}$ and NH: 3.96 and 3.89; 3.74 and 3.53; 8.31 and 8.72 (the first of the signals of the pair belongs always to protons of more aboundant conformer). From the other signals, only the broadened doublets with δ 8.05, 7.90 and 7.78 are resolved. The other protons form a multiplet between δ 7.62 and 7.20.

The ester *III* cyclizes in the presence of methanolate reversibly to substance *IV* which splitts off benzoyl group several orders slower on forming the anion of substance *V* (Scheme 2). The rate determining step of formation of substance *IV* is the methoxy group splitting off from the tetrahedral intermediate (Scheme 3). For the rate of formation of substance *IV*, relation (*4*) is valid where $c_{\mathrm{III}} = [III] + [III^{(-)}]$;

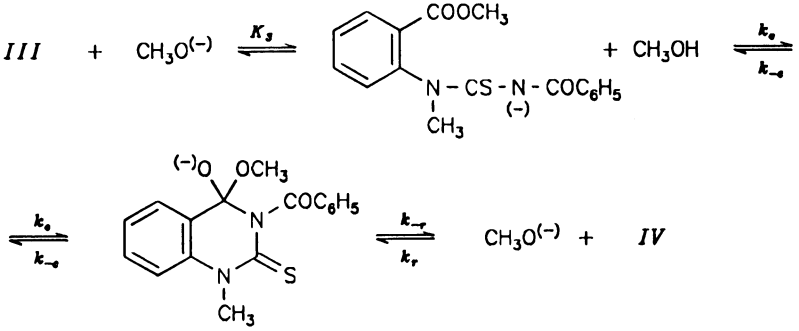
$$v_4 \;=\; \frac{K_3[\mathrm{CH_3O^{(-)}}]}{K_3[\mathrm{CH_3O^{(-)}}] + 1}\, c_{\mathrm{III}}\, k_4 \qquad (4)$$

$k_4 = (k_c/k_{-c})k_r$, ($[III^{(-)}]$ is the concentration of conjugate base of of substance *III*).

At very low methanolate concentrations ($c_{CH_3O^{(-)}} < 2 \,.\, 10^{-5}$ mol l^{-1}), $[III] >> [III^{(-)}]$ and the backward reaction is negligible so that the rate constant k_{exp} is defined by Eq. (*5*)

$$k_{exp} = k_4 K_3 [CH_3O^{(-)}] \,. \qquad (5)$$

The dependence of k_{exp} of cyclization on the concentration of butylamine buffers ($[C_4H_9NH_3Cl]/[C_4H_9NH_2]$ = 1, 2, 0.25) is illustrated in Fig. 1. The values of k_{exp} both extrapolated to the zero ionic strength and measured at a constant ionic strength are directly proportional to the ratio of buffer components and consequently also to the methanolate concentration.



SCHEME 3

At the methanolate concentration greater than 2 . 10^{-3} mol l^{-1}, nearly all ester *III* is converted to the anion, and the reverse reaction begins to manifest itself to the increasing degree so that k_{exp} is defined by Eq. (*6*) in which $k_{-4} = k_{-r}$.

$$k_{exp} = k_4 + k_{-4}[CH_3O^{(-)}] \qquad (6)$$

The rate-determining step of reverse reaction is the attack of methanolate ion on the carbon of carbonyl group of substance *IV*. The reversibility of reaction *III* $\rightleftharpoons$ *IV* was confirmed by measuring the rate constants of formation of the equilibrium mixture of substances $III^{(-)}$ and *IV* where as an initial component, beside the substance *III* (which in the given medium immediately undergoes a transition to the anion), also the substance *IV* was used (Fig. 2). The calculated values of constants are as follows: k_4 = 3.6 . 10^{-2} s^{-1}, k_{-4} = 11.7 . 10^{-1} l mol^{-1} s^{-1} and

$$K_4 = k_4/k_{-4} = [IV][CH_3O^{(-)}]/[III^{(-)}] = 3.1 \,.\, 10^{-2} \text{ mol l}^{-1} .$$

From the values of rate constants measured in butylamine buffers and extrapolated to the zero ionic strength (k^0_{exp}) and the found constant k_4, the dissociation constant, K_a, of substance *III* was calculated in terms of the equation

$$k^0_{exp} = k_4K_3[CH_3O^{(-)}] = k_4K_a/[H^{(+)}] , \qquad (7)$$

where $K_3 = [III^{(-)}]/[III][CH_3O^{(-)}]$, $K_a = [III^{(-)}][H^{(+)}]/[III]$, $[H^{(+)}] = r \,.\, 10^{-11.7 - 16.92}$; r is the ratio of concentrations of buffer components and the value $10^{-11.7}$ is the dissociation constant of butylamine ion in methanol[4]. In such a way found value of pK_a of substance *III* in methanol is 13.20 ± 0.05.

The methanolysis of substance *IV* (*IV* → *V*) was studied in methanolate solutions within 1 . 10^{-3} to 4 . 10^{-1} mol l^{-1}. Both the substance *III* and the cyclizate *IV* were used as a substrate. The course of reaction *IV* → *V* should be described by Scheme 4 ($V^{(-)}$ is the conjugate base of substance *V*) where the first stage is the fastly establishing pre-equilibrium.

$$III^{(-)} \rightleftharpoons IV + CH_3O^{(-)} \longrightarrow V^{(-)}$$

SCHEME 4

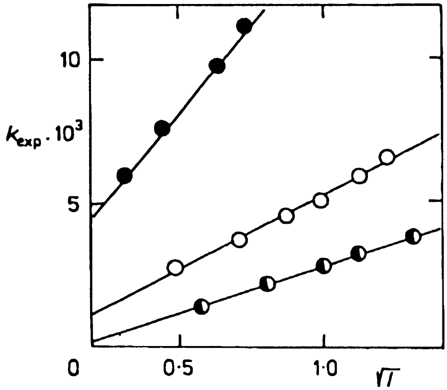


FIG. 1

The dependence of rate constant k_{exp} (s^{-1}) of reaction *III* ⇌ *IV* on ionic strength $\sqrt{I}$ in methanolic solutions of butylamine buffers 1 : 1 (○); 1 : 4 bas. (●) and 1 : 2 acid. (◐)

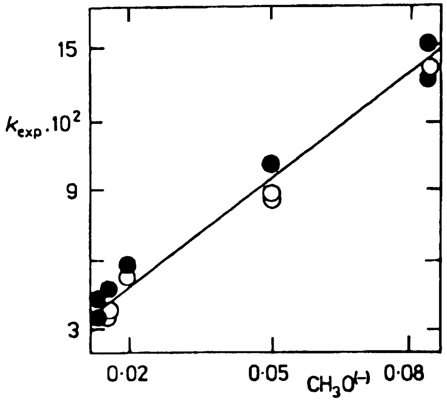


FIG. 2

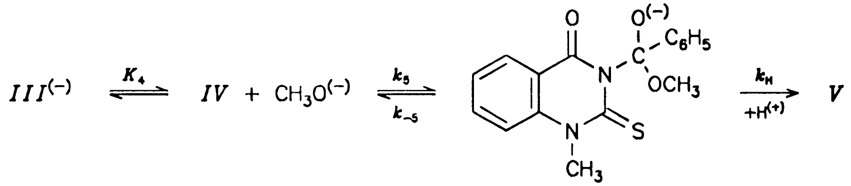
The dependence of rate constants k_{exp} (s^{-1}) (measured by the stopped flow method) of reversible reaction *III* ⇌ *IV* on the sodium methanolate concentration (mol l^{-1}). Substance *III* (○) or *IV* (●) was used as the initial substrate

At the lowest methanolate concentrations, the rate of formation of substance *V* or its anion increases with increasing methanolate concentration.

For $[CH_3O^{(-)}] > 1 \cdot 10^{-1}$ mol l^{-1}, when in pre-equilibrium ($III^{(-)} \rightleftharpoons IV + CH_3O^{(-)}$) nearly all the initial substance occurs in the form of anion $III^{(-)}$, the reaction rate should reach the maximum and should not change any more with further increase of $[CH_3O^{(-)}]$ (or should change only little at the highest methanolate concentrations owing to a change of the solvent solvation abilities – see ref.[5]).

In fact, the progressive decrease of k_{exp} took place at $[CH_3O^{(-)}] > 2.5 \cdot 10^{-2}$ mol l^{-1}, and the slope of dependence log k_{exp} vs log $[CH_3O^{(-)}]$ (see Fig. 3) approached the value -1 at the highest methanolate concentrations used.

The decrease of the dependence slope by unity may be caused either by a change in the rate-determining step when the activated complex of the new rate-determining step has negative charge a unity lower than the substrate (in this case the zero charge since the substrate is present in the form of anion) or by the formation od dianion in pre-equilibrium. No reasonable energetically advantageous structure with two negative charges from the initial substrate can be formulated. Therefore it is possible to exclude the second eventuality. For the reaction in which a change of the rate-determining step takes place with increasing methanolate concentration, we can consider two mechanisms outlined in Schemes 5 and 6. For the first case (Scheme 5), the rate constant, k_{exp},



SCHEME 5

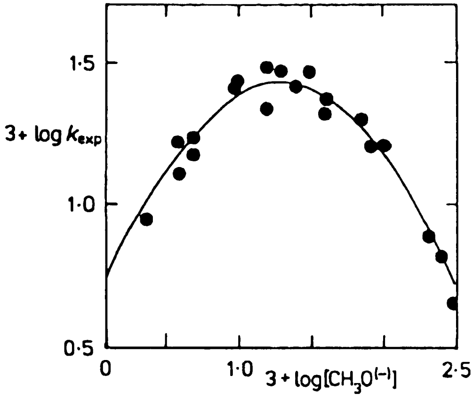


FIG. 3

The dependence of logarithms of rate constant k_{exp} (min^{-1}) of reaction *IV* → *V* on the logarithm of methanolate concentration (mol l^{-1})

$$k_{\mathrm{exp}} = \frac{K_4}{K_4 + [\mathrm{CH_3O^{(-)}}]} \, \frac{k_5[\mathrm{CH_3O^{(-)}}]\, k_{\mathrm{H}}[\mathrm{H^{(+)}}]}{k_{-5} + k_{\mathrm{H}}[\mathrm{H^{(+)}}]} \tag{8}$$

is defined by Eq. (*8*). At the highest methanolate concentration (decreasing part of the curve in Fig. 3), Eq. (*8*) is to be expressed by Eq. (*9*)

$$k_{\mathrm{exp}} = \frac{K_4}{[\mathrm{CH_3O^{(-)}}]} \, \frac{k_5[\mathrm{CH_3O^{(-)}}]\, k_{\mathrm{H}}[\mathrm{H^{(+)}}]}{k_{-5}} = K_4 K_{\mathrm{In}}\, k_{\mathrm{H}}[\mathrm{H^{(+)}}]\,, \tag{9}$$

where K_{In} is the equilibrium constant of formation of tetrahedral intermediate which must be <<1 because In is much less stable than substance *V*. When the values for k_{exp} and $[\mathrm{H^{(+)}}]$ from Fig. 2 are inserted into Eq. (*9*), we obtain the value $k_{\mathrm{H}} \approx 10^{13}/K_{\mathrm{In}}$. It means that $k_{\mathrm{H}} >> 10^{13}$ l mol^{-1} s^{-1}. The value of k_{H} is therefore several orders greater than the highest possible rate constant of proton transfer. In this way, this mechanism is excluded. Therefore, the mechanism described by Scheme 6 is probable.

$$III^{(-)} \xrightleftharpoons{K_4} IV + \mathrm{CH_3O^{(-)}} \xrightleftharpoons[k_{-6}]{k_6} VI + \mathrm{CH_3O^{(-)}} \xrightarrow{k_7} V^{(-)}$$

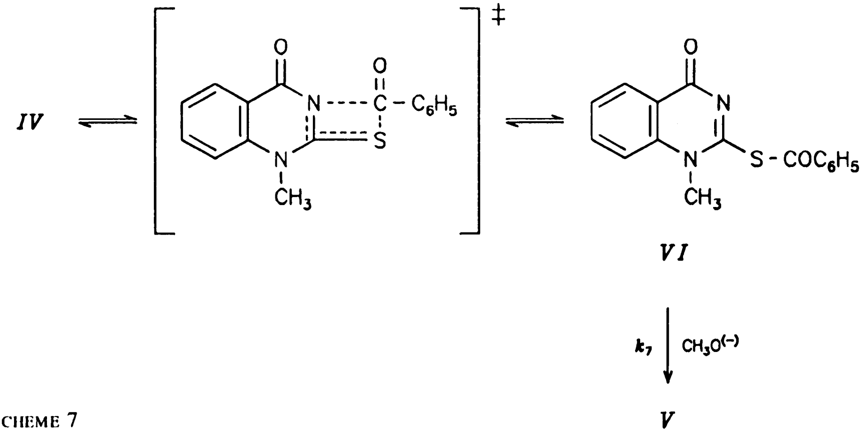
SCHEME 6

The neutral substance *IV* formed by the cyclization of anion $III^{(-)}$ is converted, with rate constant k_6, to another neutral substance *VI* which, reacting with methanolate, gives anion of the final product, $V^{(-)}$. For this mechanism, k_{exp} is expressed in terms of Eq. (*10*). Equation (*10*) was rearranged to the form of Eq. (*11*). The values of $k_6 = 1.2 \,.\, 10^{-3}$ s^{-1}

$$k_{\mathrm{exp}} = \frac{K_4}{K_4 + [\mathrm{CH_3O^{(-)}}]} \, \frac{k_6 k_7[\mathrm{CH_3O^{(-)}}]}{k_{-6} + k_7[\mathrm{CH_3O^{(-)}}]} \tag{10}$$

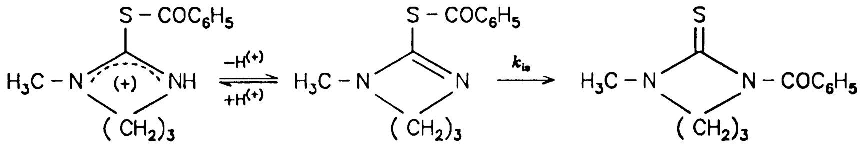
$$k_{\mathrm{exp}} = \frac{1}{1 + [\mathrm{CH_3O^{(-)}}]/K_4} \, \frac{k_6}{1 + k_{-6}/(k_7[\mathrm{CH_3O^{(-)}}])} \tag{11}$$

and $k_{-6}/k_7 = 2.3 \,.\, 10^{-4}$ mol l^{-1} were obtained by iterative method from Eq. (*11*) and experimental values of k_{exp}. Equation (*11*) can be interpreted as follows: The methanolate attack on the carbonyl of benzoyl group of substance *IV* takes place too slowly so this way is not kinetically significant. The adjacent groups C=O and C=S bring about the buckling of benzoyl group from coplanarity, and the attack of partially solvated methanolate ion on the carbon of benzoyl group is made sterically difficult by the atoms of oxygen and sulfur in the CO and CS groups. Therefore, the second reaction path in which the intermolecular attack on the carbon in carbonyl of benzoyl group with sulfur takes place first. The formed acyl derivative *VI* reacts very fast with methanolate as the S-acyl compounds are several orders more reactive than N-acyl derivatives. The above-mentioned steric hindrance is not applied here as well. The S-acyl derivative formed is thermodynamically less stable than the original N-acyl derivative *IV* (Scheme 7), and therefore it rearranges very fast backwards. At low methanolate concentrations, the attack of methanolate on the carbon in carbonyl of benzoyl group of S-acyl derivative *VI* is the rate-determining step. At higher methanolate concentrations, the methanolysis is faster than the backward S → N rearrangement, and the formation of S-benzoyl derivative *VI* with rate constant $k_6 = 1.2 \cdot 10^{-3}\ s^{-1}$ is the rate-determining step.



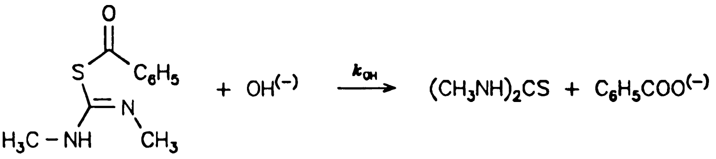
SCHEME 7

For an approximate estimation of backward isomerization constant k_{-6}, we can give here the analogous reaction in Scheme 8 with the constant of isomerization[6] $k_{is} = 316\ s^{-1}$ and the rate constant k_{OH} of hydrolysis of S-benzoyl-1,3-dimethylthiourea[7] catalyzed by

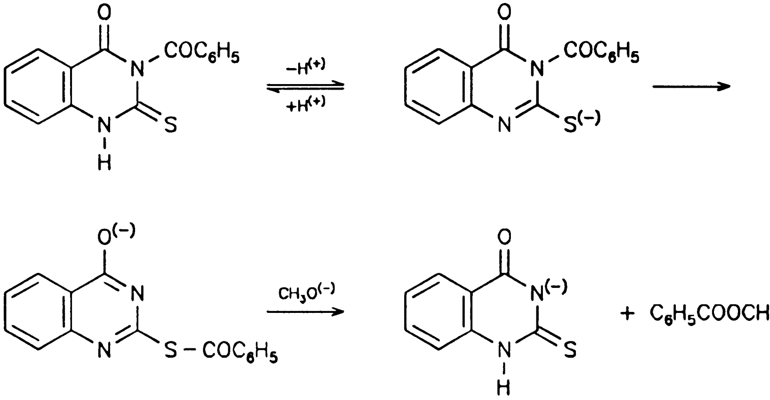


SCHEME 8

hydroxyl ion (Scheme 9), $k_{OH} = 293$ l mol^{-1} s^{-1}. In case of S-acyl derivative *VI*, the rate constant k_7 will be one to two orders greater because both nitrogen atoms are bound to the electron-acceptor carbonyl group and benzene ring. Unlike the mechanism of conversion of substance *III* to anion of substance *IV* catalyzed by methanolate ion when the reaction takes place in two stages, and the benzoyl elimination is several orders slower, the analogous reaction of 1-benzoyl-3-(2-methoxycarbonylphenyl)-thiourea *I* (ref.[1]) took place in one stage. The rate determining step was the cyclization of anion of substance *I* (taking place about one order slower than the cyclization of anion *III*$^{(-)}$), and the methanolysis of benzoyl was a subsequent very rapid stage. We assume that the reason of this diverse behaviour consists in the fact that in case of non-methylated substance *I* in the methanolate medium, the primary formed cyclizate was converted to S-anion (Scheme 10) which was rapidly rearranged to S-acyl derivative (the negatively charged sulfur atom is an internal nucleophile). This rapidly solvolyzed to the final product by the reaction with methanolate.



SCHEME 9



SCHEME 10

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Translated by J. Linek.