REACTIONS OF 1,3-DIACYLTHIOUREAS WITH METHOXIDE ION AND WITH AMINES

Jaromír KAVÁLEK, Josef JIRMAN and Vojeslav ŠTĚRBA

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

Dedicated to Prof. J. Klikorka on the occasion of his 65th birthday.

Rate constants of base-catalyzed methanolysis and dissociation constants in methanol have been determined for benzoylthiourea (*II*), 1,3-diacetylthiourea (*III*), 1,3-dibenzoylthiourea (*IV*), and 1-acetyl-3-benzoylthiourea (*V*). With the diacyl derivatives *III* and *IV*, the reaction of methoxide ion with the neutral substrate is accompanied by that of methoxide with the substrate anion (at higher alkoxide concentrations). Above $0.1 \; mol \; l^{-1} \; CH_3O^{(-)}$, the rate constants are also affected by medium. The rate of the reaction of neutral diacyl derivative is decreased, and that of the reaction of methoxide with the substrate anion is rapidly increased. The dissociation constant of *II* is higher than that of acethylthiourea (*I*) by about one order of magnitude, but the attack of methoxide on the carbonyl group of *II* is about three times slower than that in *I*. The benzoyl group at the N^1 nitrogen exhibits a greater activating influence (in both the rate and the equilibrium constants) on the other NHCOR group than the acetyl group does. With *V* the ratio of methanolysis rate constants is 9 : 1 in favour of the acetyl group. The reaction of diacetyl derivative *III* with 1-butanamine has been followed in butanamine buffers. At the lowest butanamine concentrations, the reaction is second order in the amine, and the rate-limiting step is the proton transfer from the intermediate to the second amine molecule. At the highest butanamine concentrations the reaction becomes first order in the amine, and the rate-limiting step changes to the attack of butanamine on the carbonyl group of diacetyl derivative *III*.

In the previous papers[1,2] we dealt with reactions of substituted monoacylthioureas and -ureas with methoxide ion. The aim of the present paper is a quantitative determination of the effect of acyl group on the acidity of the other NHCOR group and on reactivity of this acyl group in its reactions with nucleophiles.

EXPERIMENTAL

Reagents

1-*Acetylthiourea* (I) was prepared by acetylation of thiourea with acetanhydride and subsequent partial hydrolysis[3]. 1-*Benzoylthioura* (II) was prepared from benzoyl isothiocyanate and ammonia[3]. 1,3-*Diacetylthiourea* (III) was prepared by heating (1 h, 120°C) the acetyl derivative *I* with acetanhydride. Yield 70%, m.p. 150—151°C (in accordance with ref.[4]).

1,3-*Dibenzoylthiourea* (IV): A mixture of 100 ml dried acetone, 3·2 g (0·02 mol) diacetyl-thiourea *III* and 5·64 g (0·04 mol) benzoyl chloride was distilled from a water bath with simultaneous addition of acetone to keep its volume constant. The acetyl chloride formed was distilled off along with acetone during the heating. Thereafter, the reaction mixture was concentrated to the volume of 30 ml, cooled, and mixed with 30 ml ether or petroleum ether. The separated crystals of dibenzoylthiourea *IV* were filtered off and recrystallized from acetone. Yield 4 g (70%), m.p. 160—163°C. For $C_{15}H_{12}N_2OS$ (284·3) calculated: 63·37% C, 4·26% H, 9·85% N; found: 63·31% C, 4·50% H, 9·81% N.

1-*Acetyl-3-benzoylthiourea* (V): A mixture of 18 g (0·1 mol) benzoylthiourea (*II*), 41 g (0·4 mol) acetanhydride, and 7·9 g (0·1 mol) pyridine was heated on boiling water bath 10 min. The crystals formed on cooling were filtered off (a mixture of *I* and *III*), and the filtrate was diluted with 200 ml water, whereupon the mixture was refluxed until it became homogeneous. The solution was filtered again and cooled in an ice bath. The separated crystals were filtered off, digested with boiling ether, and crystallized from an acetone–ether (2 : 1) mixture. Yield 3 g (13·5%), m.p. 134—138°C (decomp.). Ref.[5] gives m.p. 105°C after recrystallization from chloroform. Structure of the compound *V* prepared was verified by means of ^1H and ^{13}C NMR spectra. For $C_{10}H_{10}N_2O_2S$ (22·3) calculated: 54·03% C, 4·54% H, 12·60% N; found: 54·17% C, 4·72% H, 12·83% N.

1-*Benzoyl-3-phenylthiourea* (VI) was prepared from benzoyl isothiocyanate and aniline according to the known procedure[1].

Measurements of Kinetics and of Dissociation Constants

The kinetic measurements were carried out in methanolic solutions by means of a Zeiss Spe-cord UV-VIS with closed quartz cells ($d = 1$ cm) at 25°C.

The kinetics in sodium methoxide solutions. The cell was charged with 1·8 ml sodium methoxide ($5 . 10^{-4}$ to $1·0$ mol l^{-1}), and 0·2 ml freshly prepared methanolic solution of compounds *I— V* ($5 . 10^{-4}$ to $2 . 10^{-3}$ mol l^{-1}) was injected thereto, whereupon the absorbance decrease was followed at suitable wavelength (Table I).

TABLE I
Dissociation constants K_A of acylthioureas *I— V* in methanol and rate constants k_m (1 mol^{-1} s^{-1}) of their methanolyses in sodium methoxide solutions measured at 25°C at the wavelengths λ_{anal} (nm)

Compound	pK_A	pK_A[a]	k_m	λ_{anal}
I	16·27	16·27	5·27[e]	—
II	15·18	15·18	1·4	278
III	13·68	13·89	85; 42·5[a]	310
IV	12·31	12·61	87; 43·5[a]	350
V	12·81	12·91[b]; 13·5[c]	110; 11[d]; 99[d]	287; 333

[a] Recalculated for one acyl group; [b] the value assessed from the effect of benzoyl group; [c] the value assessed from the effect of acetyl group; [d] the values calculated from the product composition (%); [e] the value from ref.[1].

The kinetics in piperidine buffers. a) At a constant ionic strength 0·12 adjusted by addition of methanolic sodium chloride (0·15 mol l^{-1}); 0·2 ml 10^{-3} mol l^{-1} compound *III* was injected into 1·8 ml piperidine buffer (piperidine and its hydrochloride 1 : 1 to 4 : 1 (basic)), and the absorbance decrease was followed at 307 nm. *b)* At variable ionic strength equal to the piperidine hydrochloride concentration: 0·2 ml 10^{-3} mol l^{-1} solutions of compounds *III — V* were injected into 1·8 ml piperidine buffer solutions (the piperidine hydrochloride concentration was 0·01 to 0·15 mol l^{-1} for compounds *IV* and *V* and 0·125 mol l^{-1} for *III*), and the absorbance decrease was measured at 307, 320, and 333 nm for compounds *III*, *IV*, and *V*, respectively.

The reaction kinetics of the diacetyl derivative III *in butanamine buffers.* The ionic strength 0·12 was kept constant by addition of a sodium chloride solution. Fresh solution (0·2 ml) of compound *III* was injected into 1·8 ml buffer solution (1-butanamine and its hydrochloride 1 : 1 or 1 : 2 (acidic)), and the absorbance decrease was followed at 310 nm.

Measurements of dissociation constants of compounds IV *and* V *in piperidine buffers.* A solution (1·8 ml) of the piperidine buffer (2 : 1 basic for compound *V* and 1 : 1 for compound *IV*; the piperidine hydrochloride concentration 0·0025—0·08 mol l^{-1}) was placed in the cell, and, at the time $t = 0$, 0·2 ml 10^{-3} mol l^{-1} fresh solution of diacetylthiourea *IV* or *V* was injected thereto, whereupon the absorbance — time dependence was followed at 330 nm (compound *V*) or 310 nm (compound *IV*) for 2 min. The absorbances of neutral forms of compounds *IV* and *V* were estimated by the measurement in pure methanol, those of their anions by measurements in 10^{-2} mol l^{-1} methoxide. The reference cell always contained the same solution as the sample cell but without the substance measured.

Estimation of relative basicity of piperidine and 1-butanamine *in methanol.* 3-Nitrophenol solution (0·5 ml 4 . 10^{-4} mol l^{-1}) was added to 1·5 ml butanamine or piperidine buffer 1 : 1 or 1 : 2 (basic), and the absorbance was measured at 395 nm. The absorbances of nitrophenol and its anion were measured in methanol and in 10^{-2} mol l^{-1} methoxide. Again the reference cell contained the same solution but with methanol instead of nitrophenol.

Identification and Determination of Products

Methanolysis of compound V *in piperidine buffers.* A solution was prepared from 24 ml methanol, 24 mg acetylbenzoyl derivative *V*, and 1 ml piperidine buffer 2 : 1 (basic; $\mu = 0·1$), and 1 μl samples were withdrawn therefrom after 2, 30, 50, and 70 min. The samples were injected into the column (Sepharon Six C18 ∅ 5 μm) of a liquid chromatograph (Laboratorní přístroje, Prague), and 70% aqueous methanol was used as the eluent at a flow rate of 0·3 l min^{-1} at 25°C. An LCD detector (Laboratorní přístroje, Prague) was used for the detection at 254 nm where the compounds *I* and *II* have the same extinction coefficient. The elution times of compounds *I*, *II*, and *V* were 7·65, 9·33, and 10·66 min, respectively. The *I* : *II* ratio was 1 : (9·0 ± 0·2) at the four time intervals.

The reaction products from diacetyl derivative III *in butanmine buffers.* 80 mg (5 . 10^{-4} mol) diacetyl derivative *III* was dissolved in a solution of 1 ml 1M 1-butanamine, 1 ml 1M its hydrochloride, and 1 ml methanol. After 30 min, N-butylacetamide content was determined in the reaction mixture by means of gas chromatography using a Carlo Erba GV 200 apparatus with an FID detection; the column $l = 2$ m, ∅ 4 mm, packing Chromosorb W of 0·2—0·25 mm grain wetted with 3% KOH + 15% Apiezon L. The column temperature 160°C, nitrogen flow rate 50 ml min^{-1}.
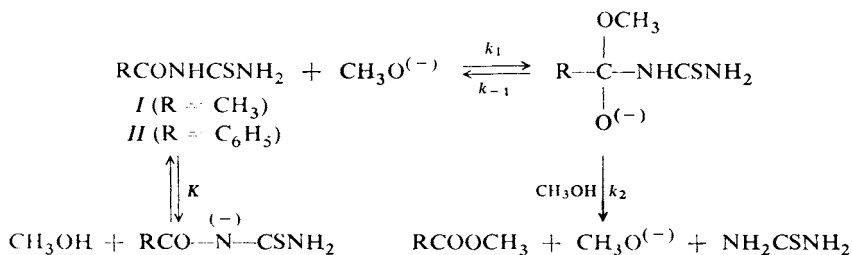
Solvolysis of compound IV *in* 0·9 *mol l^{-1}* methoxide. A stock solution of dibenzoyl derivative *IV* was prepared by dissolving 0·1 g in 10 ml methanol at 30°C, and 1 ml of this stock solution

was added to 10 ml 1M sodium methoxide. After 30 s, 20 ml 1M acetic acid (methanolic) was added. The reaction products were identified by means of TLC (Silufol UV 254, Kavalier) using dichloromethane–ethyl acetate 6 : 1 as the eluent (R_F of compound *II* 0·59, *IV* 0·79). Thiourea (as well as sodium acetate) has $R_F = 0$ in this solvent system, and, therefore, it was identified in the ethyl acetate–acetone 6 : 1 system (thioura R_F 0·28, both compounds *II* and *IV* the same R_F 0·8).

RESULTS AND DISCUSSION

Methanolysis of Mono- and Diacylthioureas I – V in Methanolic Sodium Methoxide Solutions

The dependence of log k_{exp} on log $[CH_3O^{(-)}]$ is presented in Fig. 1. With all the thioureas *I – V* the methanolysis proceeds as a 1st order reaction with respect to the substrate. Scheme 1 represents the reaction course for the monoacyl derivatives *I, II*.

$$RCONHCSNH_2 + CH_3O^{(-)} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\underset{O^{(-)}}{\overset{OCH_3}{-C-}}NHCSNH_2$$

I (R = CH₃)
II (R = C₆H₅)

$$\Big\updownarrow K$$

$$CH_3OH + RCO-N^{(-)}-CSNH_2$$

$$CH_3OH \Big\downarrow k_2$$

$$RCOOCH_3 + CH_3O^{(-)} + NH_2CSNH_2$$

SCHEME 1

On the basis of Scheme 1 it is possible to define the observed rate constant k_{exp} by Eq. (*1*), where $k_m = k_1 k_2/(k_{-1} + k_2)$;
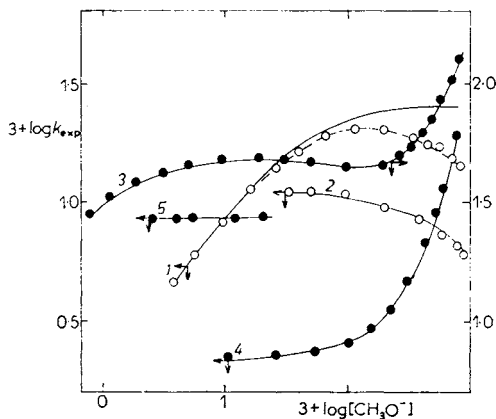

FIG. 1

Dependence of the rate constants log k_{exp} (s^{-1}) on log $[CH_3O^{(-)}]$ (mol l⁻¹) for the methanolyses of compound *1 II, 3 III, 4 IV, 5 V*, and *2 VI*

$$k_{exp} = \frac{k_m[CH_3O^{(-)}]}{1 + [CH_3O^{(-)}]K} = \frac{k_m[CH_3O^{(-)}]}{1 + [CH_3O^{(-)}]K_A/K_S} . \qquad (1)$$

$K_A = KK_S$ means the dissociation constant of compound *I* or *II*, K_S stands for the ionic product of methanol[6] (16·91), and $(1 + [CH_3O^{(-)}]K)^{-1}$ gives the ratio of real to analytic concentration of compound *I* (or *II*). The curve *1* in Fig. 1 represents the dependence of k_{exp} calculated from Eq. (*1*) for the reaction of compound *II*. At the lowest methoxide concentrations, k_{exp} increases almost linearly with the methoxide concentration. When the predominant part of compound *II* is present in the form of its anion ($[CH_3O^{(-)}] > 0·2 \text{ mol } l^{-1}$), the k_{exp} value should become practically independent of the methoxide concentration, because the concentration of undissociated benzoyl derivative *II* is inversely proportional to methoxide concentration. In reality, however, the experimentally determined k_{exp} decreases at $[CH_3O^{(-)}] = 0·2 \text{ mol } l^{-1}$, and the decrease is more and more steep with increasing alkoxide concentration (the dot-and-dash part of curve *1*). This decrease is not caused by a change in the mechanism, but is due to the fact that the activity coefficients of the reactive components are affected in different ways by increasing alkoxide concentration. The activity coefficient of the anion increases more slowly than that of the activated complex, and the result is that increasing methoxide concentration decreases the concentration ratio of the activated complex to anion[2] (the anion concentration is practically constant already).

The rate and equilibrium constants (Table I) were calculated from Eq. (*1*) at $[CH_3O^{(-)}] \leqq 5 . 10^{-2} \text{ mol } l^{-1}$ when the effect of methoxide concentration on the ratio of activity coefficients of the reacting components already is negligible. As the deviation of the found k_{exp} value (the dot-and-dash line) from the calculated one (heavy line *1* in Fig. 1) becomes already significant in the regions where the calculated k_{exp} still considerably increases, the solvolysis rate of 1-benzoyl-3-phenylthiourea (*VI*) was measured at $[CH_3O^{(-)}] > 0·05 \text{ mol } l^{-1}$ (curve *2* in Fig. 1). From the figure it can be seen that at the highest methoxide concentrations (when the concentration of the anions of both the compounds *II* and *VI* is constant) the decrease in k_{exp} is the same for both the compounds.

The reactions of the diacylthioureas with methoxide proceed in two steps. In the first step the respective monoacylthiourea is formed which is further solvolyzed to thiourea and ester. The kinetics of the first step was measured at the wavelengths (Table I) at which neither the monoacyl derivative nor thiourea absorb, so that the subsequent reaction (the solvolysis of the monoacyl derivative) is not detected spectroscopically. In the case of the diacetyl derivative *III* (curve *3* in Fig. 1) the k_{exp} value increases with increasing methoxide concentration in accordance with Eq. (*1*). At $[CH_3O^{(-)}] > 5 . 10^{-2} \text{ mol } l^{-1}$ a decrease in k_{exp} is observed which is caused by the same effect as in the case of the monoacyl derivatives *II* and *VI*. Thereafter, however, the k_{exp} value increases more and more steeply. With the dibenzoyl

derivative IV (curve 4) k_{exp} is constant at the lowest methoxide concentrations, because the anion concentration already is practically equal to the analytical concentration of the substrate IV. In this case no decrease in k_{exp} could be observed at high methoxide concentrations but only an abrupt increase at $[CH_3O^{(-)}] >$ $> 0\cdot1 \text{ mol l}^{-1}$. This increase observed with both diacyl derivatives III and IV is explained by operation of another reaction pathway at higher methoxide concentrations, $viz.$ the reaction of the monoanion with methoxide ion (Scheme 2).

$$RCO—\overset{(-)}{N}—CSNHCOR + CH_3O^{(-)} \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} \overset{OCH_3}{\underset{\underset{O^{(-)}}{|}}{R—\overset{|}{C}—NHCS—\overset{(-)}{N}—COR}}$$

$$+ CH_3OH \Big\downarrow k_4$$

$$CH_3O^{(-)} + RCOOCH_3 + RCO—\overset{(-)}{N}—CSNH_2$$
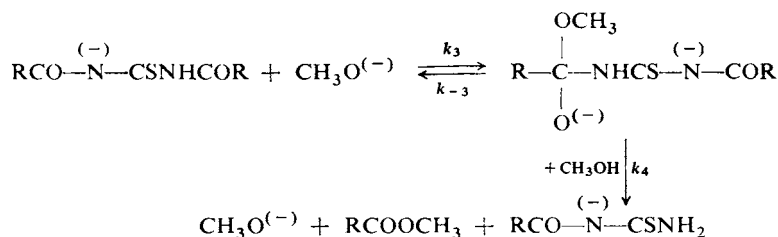
SCHEME 2

The rate constant of methanolysis of diacylthiourea anion in Scheme 2, $k_a = k_3k_4/$ $/(k_{-3} + k_4)$, is defined by the Eq. (2),

$$k_a = (k_{exp} - k_{corr})/[CH_3O^{(-)}], \tag{2}$$

where k_{corr} means the rate constant of the reaction of neutral substrate with methoxide corrected for the effect of medium on the basis of curve 2 in Fig. 1. As the reaction is one between two anions (Scheme 2), the k_a value depends strongly on the ionic strength μ which is determined by the methoxide concentration.

The dependence of $\log k_a$ on the expression $\sqrt{\mu}/(1 + \sqrt{\mu})$ is given in Fig. 2. The dependence is linear in both the cases (compounds III and IV), and the straight lines are parallel. The rate constant of the reaction of anion of compound III is greater by a factor of $4\cdot5$ than that of anion of compound IV. At the ionic strength $\mu = 1$ the rate constant values are $1 . 10^{-1}$ and $2\cdot2 . 10^{-2} \text{ l mol}^{-1}\text{s}^{-1}$ for the compounds III and IV, respectively. The rate constant values for $\mu = 0$ were determined from Fig. 2 under the presumption that the dependence is linear until zero ionic strength: $k_a = 4 . 10^{-3}$ and $9\cdot0 . 10^{-4} \text{ l mol}^{-1} \text{ s}^{-1}$ for the compounds III and IV, respectively. Although the anion of compound IV reacts more slowly with methoxide than anion of III, at lower methoxide concentrations this reaction becomes kinetically significant for IV, because the dissociation constant of IV is much higher than that of III (Table I). Therefore, also the concentration ratio of anion to neutral compound is much greater for IV than for III. Hence, with compound III no decrease was observed in k_{exp} (curve 4, Fig. 1).

Reaction of Diacetylthiourea III *in Piperidine Buffers*

Diacetyl- and dibenzoylthiourea (III, IV) are so strong acids that their dissociation constants cannot be determined by the measurements in methoxide solutions. Substituted phenols cannot be used as buffers, because they strongly absorb at the wavelength suitable for the spectrophotometric measurements. Therefore, piperidine and 1-butanamine (along with the respective hydrochlorides) were examined as buffers. In the first experimental series the measurement was carried out with diacetylthiourea *III* which is almost completely present in the neutral form in the given medium, so that estimation of the buffer effect is substantially simpler in this case. In the butanamine buffers N-butylacetamide is formed (see below). In the piperidine buffer $(1 : 1)$, k_{exp} increased approximately linearly with increasing buffer concentration (Table II). The k_{exp} value extrapolated to zero buffer concentration (and, hence, to zero ionic strength) is $8 . 10^{-4} s^{-1}$. The pK_A value of piperidine found by comparison with 1-butanamine $(pK_A = 11.70)$ $(ref.[7])$ in methanol is 11.75.
From these two values we calculated the value of $k_m = (8 . 10^{-4}) s^{-1} . (10^{16.91-11.75})$. $. 1 mol^{-1} = 115 l mol^{-1} s^{-1}$ which agrees well with the value of $85 l mol^{-1} s^{-1}$ found by the measurement in methoxide solutions. The approximately linear increase

TABLE II

The rate constants $k_{exp}(s^{-1})$ of solvolysis of diacetylthiourea (II) in methanolic piperidine buffers $(1 : 1)$ at various buffer concentrations $(c_b, mol l^{-1})$ at 25°C

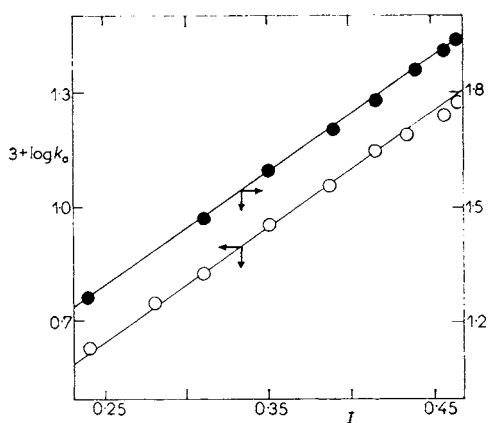| $10^2 . c_b$	1·25	2·50	5·00	7·50	10·00	11·25	12·50
$10^2 . k_{exp}$	0·15	0·21	0·33	0·44	0·56	0·61	0·69

FIG. 2

Dependence of the rate constants $\log k_a$ (defined by Eq. (2)) on the ionic strength I $(I = \sqrt{\mu}/(1 + \sqrt{\mu}))$ for the methanolyses of compound *III* (●) and compound *IV* (○) in sodium methoxide solutions

in k_{exp} with increasing piperidine concentration can be due either to a catalytic effect of piperidine, or to an effect of increasing ionic strength, or to both the effects.

In the next experimental series the dependence was examined between k_{exp} and the piperidine concentration at constant ionic strength (0·12; adjusted by addition of methanolic sodium chloride) (Fig. 3). From the figure it can be seen that k_{exp} increases only very slowly with the piperidine concentration. This means that the increase of the rate constant in the previous case (Table II) was due to the influence of increasing ionic strength. The decrease observed at the lowest concentrations of piperidine buffer (Fig. 3) is due to the fact that the solutions of sodium chloride in methanol were almost saturated, in which case ions undergo considerable association to ionic pairs which less affect the activity coefficients of the reacting components. The extrapolated k_{exp} value is $5 . 10^{-3} s^{-1}$ for the piperidine buffer (1 : 1). From the theory of the activated complex it is possible to derive Eq. (*3*) for k_{exp},

$$k_{exp} = k_0/\gamma_p \gamma^{\neq} , \qquad (3)$$

where γ_p and $\gamma^{\neq}$ are the activity coefficients of the protonated piperidine and of the activated complex of the addition of methoxy group to diacetyl derivative *III*, resp., and $k_0 = 8 . 10^{-4} s^{-1}$ is the k_{exp} value for the zero ionic strength. Owing to lower relative permittivity of methanol as compared with water, the effect of ionic strength on logarithm of the activity coefficients is about $3\times$ greater in methanol than in water[8]. That is why the observed rate constant is increased by the factor of six when changing μ from the value of 0 to $0·12 \ mol \ l^{-1}$.

The dissociation constants of diacetyl- and dibenzoylthioureas (*III*, *IV*) can be determined by measuring the methanolysis rate constants in the piperidine buffers on the basis of Eqs (*4*) and (*5*).

$$K_A = (H^{(+)}) k_{exp}/(k_{extr} - k_{exp}) = (H^{(+)}) [S^{(-)}]/[SH] \qquad (4)$$

$$k_{extr} = k_m(K_S/K_A) \qquad (5)$$

The k_{extr} constant is the k_{exp} value at $[H^{(+)}] \ll K_A$. The dependence of k_{exp} on the buffer concentration is presented in Fig. 4 for four different buffer ratios. Another way to K_A consists in spectrophotometric estimation of the $[S^{(-)}]/[SH]$ ratio by measuring the absorbances of the reaction solutions in a buffer series. This method is experimentally more exacting in this case, because it is necessary to extrapolate the absorbances measured to zero time and, in addition to it, to continuously check the absorbance of the substrate stock solution, because even traces of basic impurities cause its absorbance to decrease. Therefore, at first we examined the kinetic method of determination of the dissociation constant, and the pK_A values calculated were plotted against the expression $\sqrt{\mu}/(1 + \sqrt{\mu})$. The decrease of the pK_A values

with increasing concentration of the piperidine buffer was gradually more and more steep, especially so with the most basic buffer used $(2 : 1$ for compound V). This fact is obviously due to a catalytic effect of piperidine on k_{exp}. Therefore, it was impossible to carry out any reliable extrapolation to zero ionic strength I, and the spectral method had to be used for the determination of pK_A. In this case the dependence of pK_A on $\sqrt{\mu}/(1 + \sqrt{\mu})$ was linear for both the compounds (IV, V), its slope being close to the theoretical value[8]. The pK_A and k_m values obtained are presented in Table I.

Comparison of Effects of Acetyl and Benzoyl Groups

Acetylthiourea (I) is a weaker acid than benzoylthiourea (II) by more than one order of magnitude, but it reacts almost 4 times faster with methoxide ion as a nucleophile. The acidity of diacetyl derivative III is higher than that of the monoacetyl derivative I by 2·3 orders. The acidity difference between the dibenzoyl (IV) and monobenzoyl derivative (II) is even greater (2·6 orders).

The rate constant of the reaction of diacetylthiourea III with methoxide ion is 8 times greater than that of the monoacetyl derivative I. Dibenzoylthiourea IV reacts 30 times faster than the monobenzoyl derivative II with the same nucleophile. The much greater effect on acidity than on reactivity (towards nucleophiles) is
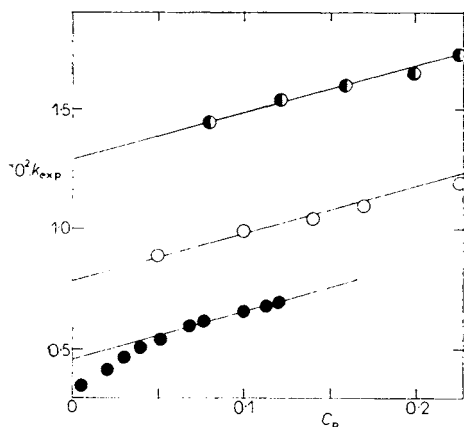
FIG. 3

Dependence of the rate constants k_{exp} (s^{-1}) of solvolysis of diacetylthiourea (III) in piperidine buffers $1 : 1$ (●), $1 : 2$ basic (○), and $1 : 4$ basic (◖) on the concentration of piperidine c_p $(mol\,l^{-1})$ at the constant ionic strength $\mu = 0·12$
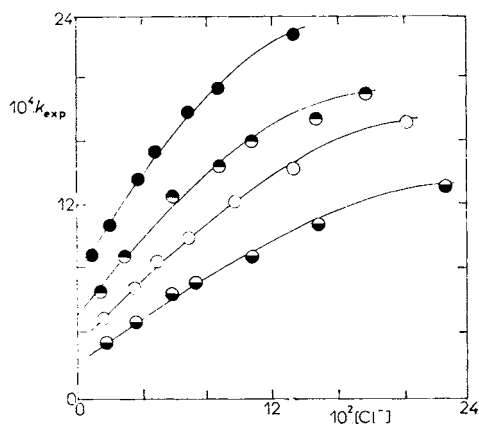
FIG. 4

Dependence of the rate constants k_{exp} (s^{-1}) of solvolyses of compound IV in piperidine buffers $1 : 1$ (●), $2 : 1$ acidic (◒), $3 : 1$ acidic (○), and $5 : 1$ acidic (◓) on the ionic strength determined by the piperidine hydrochloride concentration $([Cl^{(-)}], mol\,l^{-1})$

probably due to the fact that in the case of the dissociation constant the substituent effect is determined by the difference of the effects on the substrate and reaction product, whereas in the case of methanolysis the reactivity difference is determined by the difference of substituent effects on the starting substrate and on the activated complex of the rate-limiting step.

The introduction of the second benzoyl group has a greater effect on both the rate and the equilibrium constants of the reaction than the introduction of the second acetyl group has. This is distinct especially with the effect on the methanolysis rate constants of compound *V*, in which acetyl group reacts 9 times faster than benzoyl group. Hence, the reactivity ratio has increased almost by the factor of 3 as compared with the monoacyl derivatives *I* and *II*, the acetyl group in compound *V* reacting about 2 times faster than that in *III*. Therefrom it follows that the substitution of one acetyl group by benzoyl group in compound *III* increases the reactivity of the remaining acetyl group. On the other hand, the benzoyl group of compound *V* reacts about 4 times more slowly than that of the dibenzoyl derivative *IV*.

The dissociation constant of compound *V* is by 0.2 pK_A unit greater than that of the NH bond in the dibenzoyl derivative *IV*. This means that the substitution of one benzoyl group of compound *IV* by acetyl group substantially decreases the acidity of the NH bond adjacent to the other benzoyl group.

Reaction of Diacetylthiourea III in Butanamine Buffers

The influence of the butanamine buffer on k_{exp} was followed, from the beginning, at constant ionic strength in order to eliminate its effect on the k_{exp} value. The dependence of k_{exp} on the butanamine concentration in the buffers $1 : 1$ and $2 : 1$
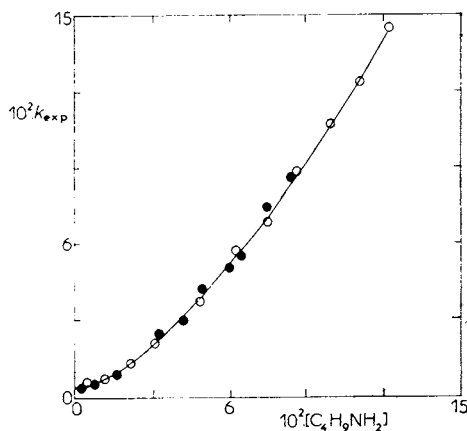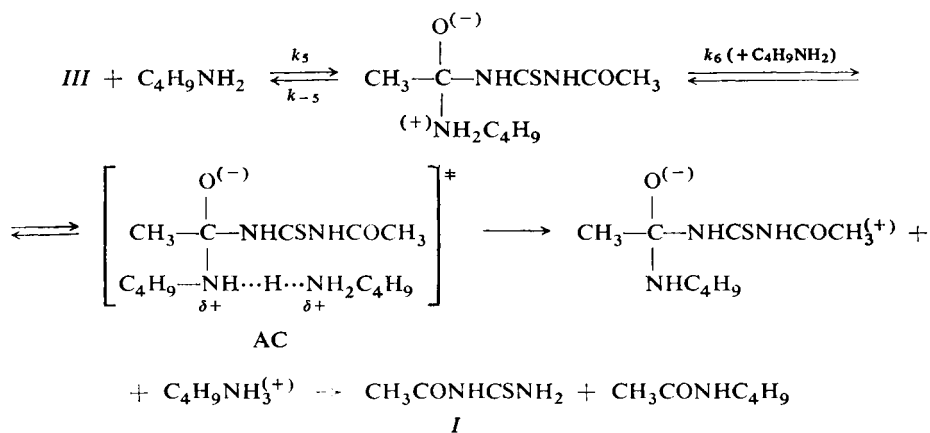
Fig. 5

Dependence of the rate constants k_{exp} (s^{-1}) of aminolysis of compound *III* in butanamine buffers $1 : 1$ (●) and $2 : 1$ acidic (○) on the butanamine concentration ([$C_4H_9NH_2$], $mol\,l^{-1}$). The heavy line denotes the dependence defined by Eq. (6)

(acidic) is presented in Fig. 5 and expressed by Eq. (6),

$$k = k_5 k_6 [C_4H_9NH_2]^2/(k_{-5} + k_6[C_4H_9NH_2]) + k', \qquad (6)$$

where k' means the k_{exp} value extrapolated to zero concentration of the butanamine buffer (1 : 1). It has the value of $4 \cdot 5 \cdot 10^{-3} \, s^{-1}$ and corresponds to the rate constant of the reaction of diacetyl derivative *III* with methoxide at the given ionic strength (0·12). This value is by about 10% lower than the extrapolated rate constant in the piperidine buffers of the same ionic strength in accordance with the pK_A of 1-butan-amine (in methanol) being by 0 05 smaller than the pK_A of piperidine. The first expression (fraction) at the right-hand side of Eq. (6) corresponds to the reaction of the diacetyl derivative *III* with butanamine giving N-butylacetamide and mono-

$$III + C_4H_9NH_2 \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \begin{array}{c} O^{(-)} \\ | \\ CH_3\!-\!C\!-\!NHCSNHCOCH_3 \\ | \\ {}^{(+)}NH_2C_4H_9 \end{array} \xrightarrow{k_6 \, (+C_4H_9NH_2)}$$

$$\overset{}{\rightleftharpoons} \left[\begin{array}{c} O^{(-)} \\ | \\ CH_3\!-\!C\!-\!NHCSNHCOCH_3 \\ | \\ C_4H_9\!-\!NH\!\cdots\!H\!\cdots\!NH_2C_4H_9 \\ {}_{\delta+} \qquad {}_{\delta+} \end{array} \right]^{\ddagger} \longrightarrow \begin{array}{c} O^{(-)} \\ | \\ CH_3\!-\!C\!-\!NHCSNHCOCH_3^{(+)} + \\ | \\ NHC_4H_9 \end{array}$$

$$AC$$

$$+ \, C_4H_9NH_3^{(+)} \cdots CH_3CONHCSNH_2 + CH_3CONHC_4H_9$$

$$I$$

SCHEME 3

acetylthiourea *I*. At the lowest butanamine concentrations, the value of the fraction increases with the square of butanamine concentration. At the highest butanamine concentrations, the value of the fraction increases almost linearly with the butan-amine concentration. The heavy line in Fig. 5 expresses the calculated dependence of k_{exp} on butanamine concentration (in the 1 : 1 buffer) with the values $k_5 = 1 \cdot 8 \, l$. $. \, mol^{-1} \, s^{-1}$ and $k_{-5}/k_6 = 0 \cdot 075 \, mol \, l^{-1}$. In the more acidic buffer (2 : 1), the k_{exp} values lie (at the higher butanamine concentrations) practically at the same line as those for the 1 : 1 buffer. The reason is in the fact that with these k_{exp} values the difference in k' already is negligible (in both the buffers).

The reaction mechanism of diacetyl derivative *III* with butanamine is represented in Scheme 3. At the lowest butanamine concentration the rate-limiting step is the proton transfer from the intermediate to the second amine molecule. At the highest butanamine concentrations the rate-limiting step consists in the attack of the carbonyl

group of compound *III* by butanamine (k_5). The k_6 value is about $10^8 \, \text{l} \, \text{mol}^{-1} \, \text{s}^{-1}$ (ref.[9]). Hence, the rate constant of decomposition of the first intermediate (k_{-5}) is about $10^7 \, \text{s}^{-1}$.

The slight nucleophilic reactivity of piperidine, as compared with butanamine, is explained by the steric hindrance in this secondary amine[10]. However, it can also be explained by the relatively strong hydrogen bond in the intermediate In.
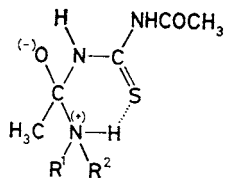
In

In the case of 1-butanamine $(R^1 = H)$ the hydrogen is split off, whereas in the reaction with piperidine the hydrogen bridge must be destroyed first, and the k_6 rate constant (and hence also k_{exp}) is smaller.

REFERENCES

1. Kaválek J., Jirman J., Štěrba V.: This Journal *50*, 766 (1985).
2. Kaválek J., Said El Bahaie, Štěrba V.: This Journal *49*, 2103 (1984).
3. Kaválek J., Novák J., Štěrba V.: This Journal *47*, 2702 (1982).
4. Hugershoff A.: Chem. Ber. *58*, 2482 (1925).
5. Dixon A. E., Taylor J.: J. Chem. Soc. *117*, 726 (1919).
6. Rochester C. H., Rossel B.: J. Chem. Soc. B *1967*, 743.
7. Goodhue L. D., Hixson R. M.: J. Am. Chem. Soc. *56*, 1329 (1934).
8. Gordon J. E.: *The Organic Chemistry of Electrolyte Solutions*, p. 40. Wiley, New York 1975.
9. Satterthwait A. C., Jencks W. P.: J. Am. Chem. Soc. *96*, 7018 (1974).
10. Crampton M. R., Gibson B.: J. Chem. Soc., Perkin Trans. 2, *1981*, 533.

Translated by J. Panchartek.