KINETICS AND MECHANISM OF REARRANGEMENT AND METHANOLYSIS OF ACYLPHENYLTHIOUREAS

Jaromír KAVÁLEK, Josef JIRMAN and Vojeslav ŠTĚRBA

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

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S-Acyl-1-phenylthioureas and their 3-methyl derivatives are rearranged to 1-acyl derivatives of thiourea in methanolic solution. The rearrangement of the 1-acyl-1-phenyl derivative to the thermodynamically more stable 3-acyl derivative is subject to specific base catalysis. The rearrangement of acetyl group is about 2 orders of magnitude slower than that of benzoyl group. 1-Acetyl-1-phenylthiourea undergoes base-catalyzed methanolysis (giving phenylthiourea and methyl acetate) instead of the rearrangement. The methanolysis rates of 1-acyl-3-phenylthioureas and their N-methyl derivatives have been measured. The acetylthioureas react at most 3× faster than the benzoyl derivatives. The methyl group at the nitrogen adjacent to acyl group accelerates the solvolysis by almost 2 orders of magnitude; the methyl group at the other nitrogen atom retards the solvolysis by almost 1 order of magnitude. Replacement of hydrogen atom by methyl group at the phenyl-substituted nitrogen increases acidity of the phenylacetylthiourea by 2 orders of magnitude. The same replacement at the benzoyl-substituted nitrogen increases the acidity by 3 orders of magnitude, the increase in the case of the acetyl derivative being as large as 4 orders of magnitude.

S-Acylthioureas are rearranged very rapidly to N-acylthioureas in solutions[1-3]. From asymmetrical S-acylthioureas the rearrangement can give two isomers and, moreover, the acyl group can be rearranged from the thermodynamically less stable N-acyl derivative to the more stable isomer. Besides that, in protic solvents there takes place the corresponding solvolysis giving thioureas and the respective acyl derivatives. The aim of this communication is to find the primary rearrangement product of 1-phenyl-S-acylthioureas, to study kinetics and mechanism of the acyl migration from one nitrogen to the other, the solvolysis kinetics in methanol, and to determine the substituent effects on the two reactions and on dissociation constants of acylphenylthioureas.

EXPERIMENTAL

The melting points of the substances prepared were measured in a pre-heated Kofler apparatus.

Reagents

1-*Benzoyl*-3-*phenylthiourea* (I). Procedure *a*) Equimolar amounts of acetonic solutions of benzoyl isothiocyanate and aniline were mixed and cooled, and the precipitated crystals were recrystallized from a benzene–cyclohexane mixture (5 : 1) (ref.[4]). M.p. 142–143°C in accordance with ref.[5]. Procedure *b*) 1 g 1-benzoyl-1-phenylthiourea (*II*) was dissolved in the minimum amount of warm methanol and treated with methanolic solution of sodium acetate (0·4 ml, 0·5 mol l^{-1}). The isomerization course was followed by the absorbance increase at 312 nm. After the reaction was finished (5 min at 50°C), the solution was cooled, and the separated crystals were collected by suction. Yield 0·5 g (50%), m.p. 141–144°C. The mixed melting point with the substance prepared by the procedure *a*) was 141–143°C. The ^{13}C NMR spectrum: δ_1 137·50; δ_2 124·02; δ_3 128·82; δ_4 126·83; δ_6 178·22; δ_9 166·89; δ_{10} 113·64; δ_{11} 127·64; δ_{12} 129·11; δ_{13} 131·50.

1-*Benzoyl*-1-*phenylthiourea* (II). A suspension of 6 g (40 mmol) phenylthiourea in 12 ml acetone was treated with 5·6 g (40 mmol) benzoyl chloride. The mixture became clear for a moment, whereupon crystals were separated. After addition of 20 ml benzene and cooling the yield was 6 g (52%) 1-phenyl-S-benzoylisothiouronium chloride, m.p. 63–66°C. This compound (5 g, 20 mmol) was added to a solution of 2·5 g (30 mmol) sodium acetate in 20 ml methanol with stirring. The separated crystals were collected by filtration after 5 min, washed with water and with ice-cold methanol. Yield 2 g (46%), m.p. 133–137°C. The ^{13}C NMR spectrum: δ_1 135·79; $\delta_2\delta_3\delta_{12}$ 127·72 or 127·43 or 128·42; δ_4 128·42; δ_6 186·63; δ_9 173·70; δ_{10} 141·47; δ_{11} 130·59; δ_{13} 130·24. For $C_{14}H_{12}N_2OS$ (256·2) calculated: 65·63% C, 4·68% H; found: 65·84% C, 4·50% H.

1-*Acetyl*-1-*phenylthiourea* (III). A suspension of 6 g (40 mmol) phenylthiourea in 12 ml acetone was treated with 3·6 g (46 mmol) acetyl chloride added with stirring. The 1-phenyl-S-acetylisothiouronium chloride precipitated on cooling was collected by suction and washed with acetone. Yield 6·4 g (70%), m.p. 92–95°C (ref.[6]). This compound (5 g) was added to a solution of 3·2 g (38 mmol) sodium acetate in 45 ml methanol. After 5 min, the separated solid was collected by suction, washed with water, and recrystallized from ethanol. Yield 3·2 g (76%), m.p. 142 to 145°C (ref.[7] gives m.p. 140°C). The ^{1}H NMR spectrum: δ_{COCH_3} 1·95. The ^{13}C NMR spectrum: δ_1 142·05; $\delta_2\delta_3$ 129·24 or 129·36; δ_4 128·95; δ_6 174·41; δ_7 168·17; δ_8 28·57.

1-*Acetyl*-3-*phenylthiourea* (IV). 2 g (20 mmol) acetyl isothiocyanate[8] was dissolved in 3 ml benzene, and 2 g (22 mmol) aniline was added thereto. The crystals separated on cooling were collected by suction, washed with benzene, and recrystallized from ethanol. Yield 2·1 g (54%), m.p. 172–173°C (ref.[7] gives m.p. 169–170°C). The ^{1}H NMR spectrum: δ_{COCH_3} 2·18. The ^{13}C NMR spectrum: δ_1 127·26; δ_2 124·45; δ_3 128·83; δ_4 127·02; δ_6 178·56; δ_7 172·00; δ_8 24·41.

1-*Acetylthiourea* (V), m.p. 168–169°C, was prepared by acetylation of thiourea with acetic anhydride and subsequent partial hydrolysis[3].

1-*Benzoyl*-1-*phenyl*-3-*methylthiourea* (VI). Acetonic solution of 5 g (30 mmol) 1-phenyl-3-methylthiourea (*VII*) (prepared by addition of aniline to methyl isothiocyanate in hexane) was treated with 4·1 g (30 mmol) benzoyl chloride added with stirring. The 1-phenyl-3-methyl-S-benzoylisothiouronium chloride separated on cooling was collected by filtration and washed with acetone. Yield 8·5 g (93%), m.p. 89–95°C. This compound was dissolved in a solution of 1·64 g (20 mmol) sodium acetate in 20 ml methanol. After a while, crystals began to separate which were collected by suction, washed with methanol and ether. Yield 4·7 g (63%), m.p. 128 to 130°C. For $C_{15}H_{14}N_2OS$ (266·1) calculated: 66·66% C, 5·22% H, 10·37% N; found: 66·60% C, 5·23% H, 10·31% N. The ^{1}H NMR spectrum: δ_{CH_3} 3·23. The ^{13}C NMR spectrum: δ_1 136·38; $\delta_2\delta_3\delta_{12}$ 127·72 or 127·20 or 128·37; δa 128·19; δ_5 33·24; δ_6 185·29; δ_9 173·65; δ_{10} 141·65; δ_{11} 130·82; δ_{13} 129·89.

Isomerization of compound VI. The compound *VI* (2 g, 7·5 mmol) was dissolved in the minimum amount of methanol at 40°C, one drop of 0·5 mol l^{-1} methanolic sodium acetate was added thereto, and the isomerization course was followed spectrophotometrically at 312 nm. After 10 min, the reaction was finished. The solution was diluted with water (40°C) until the first turbidity, whereupon it was left to free crystallization. The separated solid was collected by suction and washed with water. Yield 1·9 g (95%), m.p. 100—102°C. According to the ^{1}H NMR spectrum, the product represents a mixture of the isomers *VIII* and *VI* (3 : 1). The spectra of compound *VIII*: ^{1}H NMR δ_{CH_3} 3·59. ^{13}C NMR: δ_1 138·43; $\delta_2\delta_{11}$ 124·97 or 126·90; $\delta_3\delta_1\alpha$ 128·77; δ_4 126·68; δ_5 41·48; δ_6 183·47; δ_9 174·82; δ_{10} 135·74; δ_{13} 131·35.

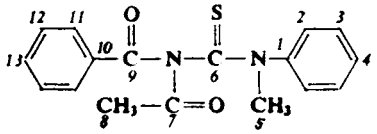
1-*Acetyl*-1-*phenyl*-3-*methylthiourea* (IX). A solution of 5 g compound *VII* in 10 ml acetone was treated with 3 ml (38 mmol) acetyl chloride. The crystals separated on cooling (1-phenyl-3-methyl-S-acetylisothiouronium chloride) were collected by suction and washed with benzene. Yield 6·4 g (80%), m.p. 71—74°C. This S-acetyl derivative was introduced into a solution of 2·2 g sodium acetate in 10 ml methanol. After 2 min, 30 ml ice water was added, the crystals were collected by suction and washed with water. Yield 1·5 g (28%), m.p. 63—65°C. For $C_{10}H_{12}N_2OS$ (208) calculated: 57·70% C, 5·77% H; found: 58·13% C, 5·99% H. The ^{1}H NMR spectrum: δ_{N-CH_3} 3·74; δ_{COCH_3} 2·41. The ^{13}C NMR spectrum: δ_1 138·72; δ_2 125·21; δ_3 128·72; δ_4 126·67; δ_5 38·51; δ_6 183·42; δ_7 175·40; δ_8 27·10.

1-*Acetyl*-1-*methyl*-3-*phenylthiourea* (X). The compound *IX* (5 g, 21 mmol) was dissolved in 80 ml cold methanol, and 20 ml 2 mol l^{-1} sodium methoxide was added thereto with stirring. After 20 s, the solution was neutralized with 50 ml 1M-HCl, whereupon 50 ml ice water was added. The solid separated on cooling (compound *X*) was collected by suction and recrystallized from a cyclohexane–benzene mixture (3 : 1). Yield 2 g (40%), m.p. 69—70°C. For $C_{10}H_{12}N_2OS$ (208) calculated: 57·70% C, 5·77% H; found: 58·04% C, 6·00% H. The ^{1}H NMR spectrum: δ_{NCH_3} 3·74; δ_{COCH_3} 2·41. The ^{13}C NMR spectrum: δ_1 138·72; δ_2 121·21; δ_3 128·72; δ_4 126·67; δ_5 38·51; δ_6 183·42; δ_7 175·40; δ_8 27·10.

1-*Benzoyl*-3-*phenyl*-3-*methylthiourea* (XI) was prepared by addition of N-methylaniline to benzoyl isothiocyanate in benzene solution. After crystallization from a cyclohexane–benzene mixture (1 : 5), the product melted at 134—136°C (ref.[9] gives m.p. 134°C). The ^{1}H NMR spectrum: δ_{NCH_3} 3·73. The ^{13}C NMR spectrum: δ_1 144·92; $\delta_2\delta_{11}$ 127·43 or 125·26; $\delta_3\delta_{12}$ 129·13 or 128·42; δ_4 127·60; δ_5 45·35; δ_6 180·37; δ_9 162·66; δ_{10} 132·40; δ_{13} 132·41.

Measurements

The electronic spectra were measured with a Specord UV VIS and a Unicam SP 800 spectrophotometers. The ^{1}H and ^{13}C NMR spectra were measured with a JNM-FX 100 JEOL apparatus at 99·602 and 25·047 MHz, respectively, at 25°C. The ^{1}H NMR spectra were measured in deuteriochloroform with hexamethyldisiloxane as the internal standard (δ = 0·05). The ^{13}C NMR spectra were measured in saturated solutions of the substances in deuteriochloroform. The carbon



P

chemical shifts were related to internal tetramethylsilane. The ^{1}H NMR spectra of compound *VIII* were measured in solutions in hexadeuteriodimethyl sulphoxide, hexadeuteriobenzene, pentadeuteriopyridine, perdeuteriomethanol with hexamethyldisiloxane as the internal standard in each case. The ^{1}H NMR spectra of compounds *VI* and *IX* were measured in solutions in perdeuteriomethanol with addition of sodium acetate and with hexamethyldisiloxane as the internal standard. The numbering of carbon atoms for values of the chemical shifts in the ^{13}C NMR spectra (see Reagents) is given in the above given general formula *P*.

Measurement of the dissociation constants: The dissociation constant of compound *XI* was measured spectrophotometrically in methanolic 4-bromophenolate buffers at a constant concentration of the bromophenolate (0·01 mol l^{-1}) using the Specord apparatus at 339 nm at 25°C. The dissociation constant value was determined graphically form Eq. (*1*).

$$pK_A = pH_{buffer} - \log R = pK_{A\,bromophenol} - \log \frac{C_{bromophenol}}{C_{bromophenoxide}} - \log R \qquad (1)$$

The concentration ratio of the conjugated base and acid of the substance measured was calculated from the absorbances according to Eq. (*2*)

$$R = (A - A_{NH})/(A_{N^-} - A)\,, \qquad (2)$$

where A_{NH}, A_{N^-}, and A are absorbances of the substrate, its conjugated base, and the solution measured, respectively. The pK_A value of 4-bromophenol in methanol is 13·61 (ref.[10]), and that of methanol is 16·916 (ref.[11]). The dissociation constant of compound *X* was measured at 312 nm in methanolic 1-butanamine buffers with constant ionic strength (0·05). After extrapolation of the absorbance to zero time, the value of the dissociation constant was calculated in similar way as that of *XI*. The pK_A value of 1-butanamine in methanol is 11·7 (ref.[12]).

TABLE I

Values of dissociation constants of compounds *I*—*XI* of the type $C_6H_5NR^1$–CS–NR^2R^3 in methanol and of their methanolysis or isomerization rate constants (k_2) at 25°C

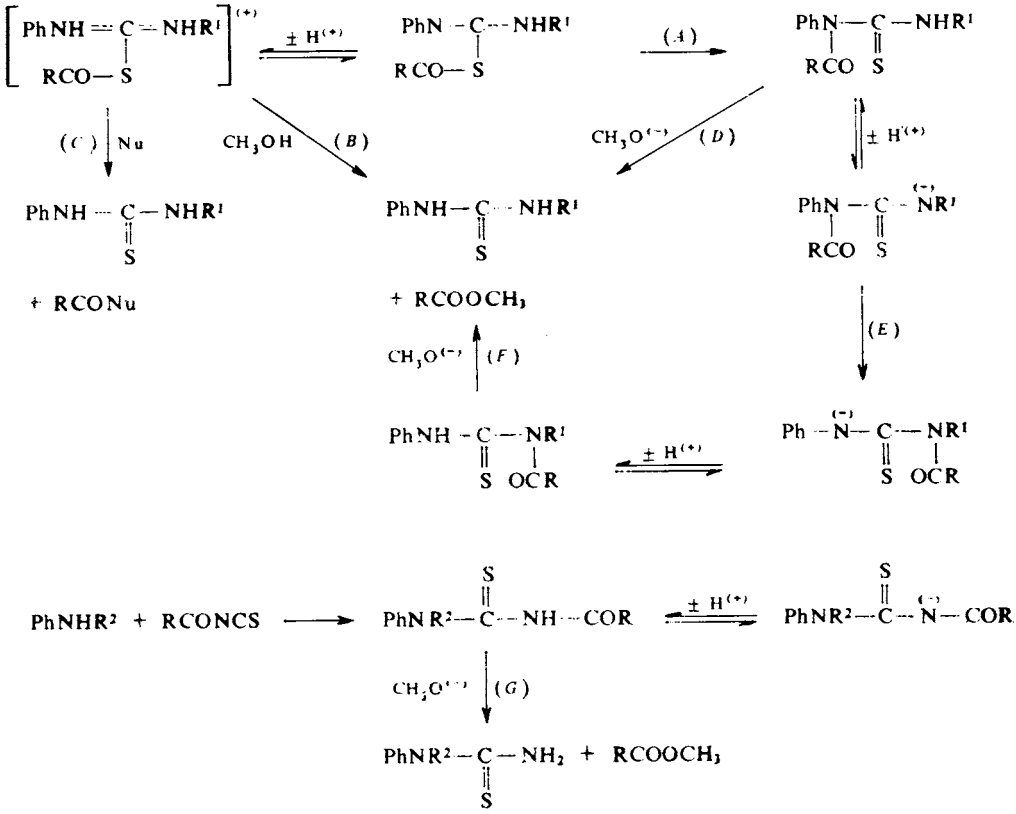
Compound	R^1	R^2	R^3	λ_{anal} nm	pK_A	k_2 s^{-1}
I	H	H	C_6H_5CO	—	14·56[a]	2·9[a]
II	C_6H_5CO	H	H	303	—	9·99 . 10^2 ± 16[b]
III	CH_3CO	H	H	250	15·64 ± 0·04	13·92 ± 0·46
IV	H	H	CH_3CO	330	15·57 ± 0·03	8·59 ± 0·22
V[c]	H	H	H	278	16·27 ± 0·06	5·27 ± 0·33
VI	C_6H_5CO	H	CH_3	303	—	1·74 . 10^4 ± 515[b]
VIII	H	CH_3	C_6H_5CO	302	11·77 ± 0·06	280 ± 14
IX	CH_3CO	H	CH_3	312	14·89 ± 0·03	0·38 ± 0·02[d]
X	H	CH_3	CH_3CO	312	11·70 ± 0·04	265 ± 18
XI	CH_3	H	C_6H_5CO	339, 245	12·96 ± 0·04	0·51[a]

[a] The values taken from ref.[4]; [b] k'_{iso} (1 mol^{-1} s^{-1}); [c] 1-acetylthiourea; [d] k_{iso} (s^{-1}).

Kinetic measurements: Before the kinetic measurement itself, spectra of the compounds studied were examined in suitable media within the wavelength range from 200 to 400 nm. These experiments verified the isosbestic point and enabled a selection of suitable wavelengths for the measurements of the kinetics. According to the rate constants expected, the measurements were carried out either with the Durrum D 150 apparatus (the reactions with the half-lives below 5 s) or with the Specord apparatus in closed quartz cells ($d = 10$ mm) located (with the buffer) in the temperated cell compartment of the spectrophotometer. A certain amount of stock solution of compound *II* in methanol or acetonitrile was added to the buffer, and the absorbance changes were recorded. The rate constants were calculated by the Guggenheim method[13]. In the measurements of effect of ionic strength on the isomerization of compounds *II* and *VI* and on solvolysis of compound *VIII*, the ionic strength was adjusted by addition of methanolic sodium chloride (0·15 mol l^{-1}). The analytical wavelengths are given in Table I.

RESULTS AND DISCUSSION

The reactions taking place during preparation of phenylacylthioureas and during their solvolyses and/or isomerizations are given in Scheme 1. The 1-acyl-1-phenyl-



SCHEME 1

thioureas could only be prepared by isomerization of the S-acylthiouronium salts, the acyl group migrating exclusively to the nitrogen atom adjacent to phenyl group. The neutral form of the thiouronium salt can only be rearranged (reaction (*A*)). The salt itself is solvolyzed very rapidly in methanol (reaction (*B*))[3], or it reacts with the basic buffer component (Nu = acetate ion) (reaction (*C*)). If the alkalinity of medium is increased, there takes place solvolysis (reaction (*D*)) of N-acylthiourea and/or its isomerization (reaction (*E*)).

The rearrangement of the S-benzoyl derivatives proceeded with good yields. Greater difficulties were encountered with the preparation of the N-acetyl derivatives, because the S-acetylthiouronium salts are solvolyzed and react with nucleophiles about ten times faster, and the acetyl groups migrates more slowly than benzoyl group in the corresponding benzoyl analogues.

1-Acyl-3-phenylthioureas could be obtained either by the direct reaction of the acyl isothiocyanate with aniline or N-methylaniline (reaction (*G*)) or by rearrangement of 1-acyl-1-phenylthiourea (reaction (*E*)). The rearrangement can only be utilized, if solvolyses of both the starting substrate and the product are slower than the rearrangement itself. If the solvolysis of the starting substrate is faster than the rearrangement, no suitable conditions can be found for the rearrangement, because the dependence of the rate constants on methoxide concentration is the same for the two reactions.

With the compound *IX* it was impossible to prepare the second isomer *X* at usual conditions (sodium acetate in methanol), because solvolysis of *X* was faster than isomerization of *IX*. From kinetic experiments (a system of competitive consecutive reactions of the 1.order) it was possible to construct the dependence of log *k vs* logarithm of methoxide concentration for both the solvolysis and isomerization (Fig. 1). This dependence was used for selection of the optimum conditions of the preparation of pure isomer *X* by rearrangement.

Kinetics of Rearrangement and of Methanolysis

Both the rearrangement and the methanolysis proceeded always as the 1. order reactions with respect to the substrate, which was confirmed by well-developed isosbestic points in the preliminary experiments examining the wavelength range of 200–400 nm. The only exception was the isomerization kinetics of compound *IX* at lower methoxide concentrations, when there also took place solvolysis of the compound *X* formed in the course of the measurement, so that kinetically the reaction proceeded as a system of consecutive reactions. In case of 1-acyl-3-phenylthiourea, solvolysis is only possible, whereas with 1-acyl-1-phenylthiourea the both reactions are conceivable. The question, whether the reaction followed is the rearrangement or the solvolysis, was answered in the following ways: *a*) on the basis of spectra of the products (the electronic spectrum of 1-acyl-3-phenylthiourea differs substantial-

ly from that of phenylthiourea), *b*) by realization of the subsequent reaction (*i.e.* solvolysis of the rearranged acyl derivative by increased alcoholate concentration) in the case of the isomerization being the reaction measured, *c*) by isolation of products in the experiments on preparative scale, *d*) by comparison of ^1H and ^{13}C NMR spectra of the starting compounds, products, and phenylmethylthiourea (*VII*) in the case of compounds *VI* and *IX* or 1-phenylthiourea in the case of compounds *II* and *III*. For compounds *VI* and *IX* the reactions were followed by means of ^1H NMR in perdeuteriomethanol solution and by identification of the products by means of chemical shifts of methyl groups in the case of compound *IX*.

Base-Catalyzed Reactions of 1-*Acyl*-1-*arylthioureas*

With both the benzoyl derivatives *II* and *VI* in diluted methoxide solutions there takes place the isomerization (*E*) followed by the solvolysis (*F*). The isomerizations were followed in buffer solutions where the subsequent solvolysis practically does not take place. The non-methylated derivative *II* and the methylated compound *VI* were measured in butanamine and acetate buffers, respectively. The k_{obs} values increased with concentration of the butanamine buffer, and they decreased with concentration of the acetate buffer. Therefore, the k_{obs} values were extrapolated to zero buffer concentration. In parallel experiments, the dependence of k_{obs} on ionic strength was measured at constant buffer concentration. From Figs 2 and 3 it can be seen that the decisive factor is the change of ionic strength with increasing buffer concentrations. In acetate buffers, the decrease of k_{obs} is probably due to the decrease

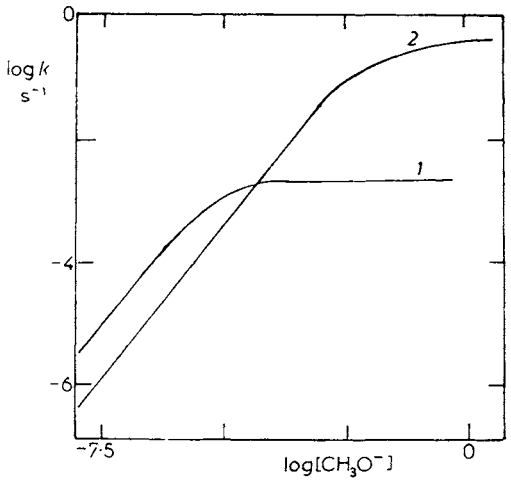


FIG. 1

The calculated logarithmical dependences of solvolysis *1* and isomerization rates *2* of compounds *X* and *IX* on molar concentration of methoxide

of the isomerization rate constant with increasing ionic strength. In the butanamine buffers, another factor begins to operate which has an opposite and predominant effect, *viz.* the increase of concentration of the substrate anion, because the equilibrium $BuNH_2 + SH \rightleftharpoons BuNH_3^{(+)} + S^{(-)}$ is shifted to the right-hand side with increasing ionic strength. The acetylphenyl derivative *IX* also undergoes isomerization, but with compound *III* the solvolysis is much faster, so that the isomerization rate could not be determined. The isomerization of acetyl derivative *IX* proceeds much slower than that of the two benzoyl derivatives *II* and *VI*, hence it could be measured also in diluted methoxide solutions. The isomerization mechanism of the substrate SH to product PH is given in Scheme 2, and its kinetics is described by Eqs (*3*)–(*7*).

$$SH + CH_3O^{(-)} \overset{K}{\rightleftharpoons} S^{(-)} + CH_3OH$$

$$S^{(-)} \xrightarrow{k_{iso}} P^{(-)} \xrightarrow[CH_3OH]{} PH + CH_3O^{(-)}$$

SCHEME 2

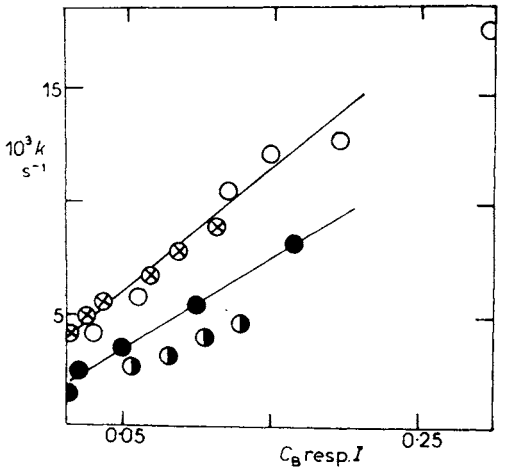


FIG. 2

Effect of concentration of 1-butylammonium chloride (c_B, mol l^{-1}) (○; ●) and of ionic strength (*I*, KBr) (⊘; ◑) on the isomerization rate constant *k* (s^{-1}) of compound *VI* at the buffer ratio $[BuNH_3^{(+)}]/[BuNH_2] = 2:3$ (pH 11·87) (○; ⊘) or 1 : 2 (pH 11·39) (●; ◑)

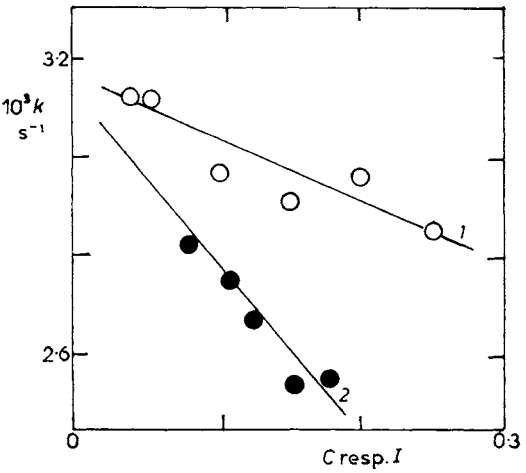


FIG. 3

Effect of concentration of sodium acetate (*c*, mol l^{-1}) (○) and of ionic strength (*I*, KBr) (●) on the isomerization rate constant *k* (s^{-1}) of compound *VI* at the buffer ratio $[AcO^{(-)}]/[AcOH] = 4:1$ (pH 10·12)

$$v = k_{obs}[S^T] = k_{iso}[S^{(-)}] \quad (3)$$

$$[S^T] = [S^{(-)}] + [SH] \quad (4)$$

$$[S^{(-)}] = K[CH_3O^{(-)}][S^T]/(K[CH_3O^{(-)}] + 1) \quad (5)$$

$$K \,.\, K_{CH_3OH} = K_A \quad (6)$$

The Eq. (7) follows from Eqs (3) and (5).

$$k_{obs} = k_{iso} \,.\, K \,.\, [CH_3O^{(-)}]/(K[CH_3O^{(-)}] + 1) = k_{iso} \,.\, K_A/(K_A + [H^+]) \quad (7)$$

The dependence of log k_{obs} on logarithm of the alcoholate concentration is given in Fig. 4 for compound *IX*. The constants k_{iso}, K, and K_A were obtained by optimizing the said two parameters by means of a program for non-linear regression. In the whole range of investigation of compounds *II* and *VI* it is $K[CH_3O^{(-)}] \ll 1$, hence it is $k_{obs} = k_{iso} \,.\, K \,.\, [CH_3O^{(-)}] = k'_{iso}[CH_3O^{(-)}]$. In calculating k'_{iso} of compound *VI* measured in acetate buffers we obtained the methoxide concentration with the use of $pK_A = 9{\cdot}52$ for acetic acid[14]. The isomerization rate constants k_{iso} and k'_{iso} are given in Table I. The k'_{iso} value of compound *VI* is higher than that of *II* by about one order of magnitude. From analogy with acetylthioureas (Table I) it can be presumed that compound *VI* is more acidic than compound *II* by about one order of magnitude, hence the k_{iso} constants of the two benzoyl derivatives are approximately the same. The k_{iso} values of the benzoyl derivatives *II* and *VI* could not be mea-

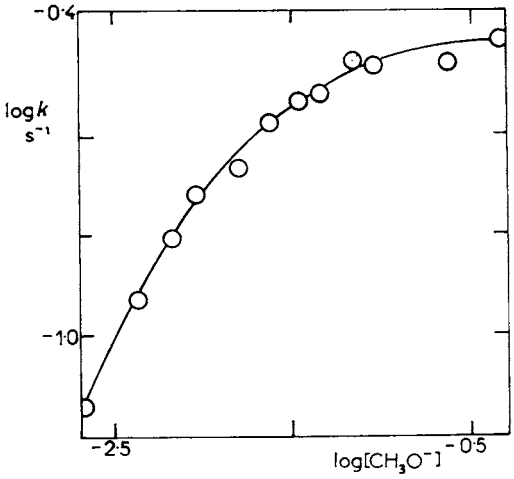
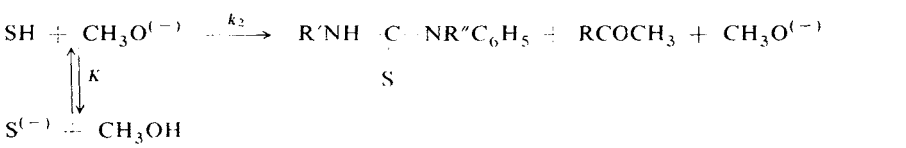


FIG. 4
Logarithmical dependence of the isomerization rate of compound *IX* on molar concentration of methoxide

sured because of the high isomerization velocity in methoxide solution. Comparison of dissociation constants of acetyl and benzoyl derivatives of thiourea (Table I) enables to estimate that the rearrangement of benzoyl group is faster than that of acetyl group by two orders of magnitude. A higher migration rate of benzoyl group was also found in rearrangements of S-acylthioureas[3]. With the acetyl derivative *II* the rearrangements were practically quantitative, but with the benzoyl derivative *VI* the final reaction mixture contained 70% of the rearranged compound *VIII* and 30% of the starting substance *VI*. This mixture exhibits a relatively sharp melting point, and (according to ^{1}H NMR spectra) the equilibrium of the isomers is practically the same after dissolution of the product in C^2HCl_3, $C_6{}^2H_6$, $(C^2H_3)_2SO$, $C_5{}^2H_5N$, and $C^2H_3O^2H$, the two isomers being solvolyzed in the last two solvents mentioned.

If compound *VI* is dissolved in perdeuteriomethanol and sodium acetate is added, the equilibrium is established between the isomers *VI* and *VIII* corresponding to the above-mentioned composition, the changes of methoxide concentration or temperature only affecting the solvolysis rate of the *VI* + *VIII* mixture formed. Compound *IX* is rearranged in perdeuteriomethanol in the presence of sodium acetate, and, at the same time, the isomer *X* formed is solvolyzed. The ratio of the isomers to the starting substance is less than 1, which corresponds to the ratio of the isomerization rate of compound *IX* to the solvolysis rate of isomer *X*.

The methanolysis course of acylphenylthioureas (SH) is represented in Scheme 3.



SCHEME 3

The reaction rate is given by Eq. (*8*).

$$v = k_{obs}[S^T] = k_2[SH][CH_3O^{(-)}] \qquad (8)$$

$$[SH] = [S^T]/(K[CH_3O^{(-)}] + 1) \qquad (9)$$

and the rate constant k_{obs} is then defined by the kinetic equation (*10*) calculated from Eqs (*8*) and (*9*).

$$k_{obs} = k_2[CH_3O^{(-)}]/(K[CH_3O^{(-)}] + 1) = k_2K_{CH_3OH}/(K_A + [H^+]) \qquad (10)$$

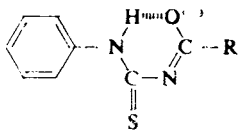
The empirical kinetic equation is the same as that of the isomerization reaction, hence also the dependence of k_{obs} on the methoxide concentration has similar shape.

The two constants, k_2 and K (or K_A) were obtained by similar optimizing procedure as that used in the isomerization kinetics, and they are given in Table I. The calculations concerning the experiments carried out in buffers solutions used the k_{obs} values extrapolated to zero buffer concentrations.

Both in esters[15,16] and in thioesters[7], acetyl group reacts with nucleophiles fasters than benzoyl group by one order of magnitude. The rate constants of the attacks of carbonyl groups of acetyl- and benzoylthioureas by methoxide ion are comparable. The k_2 value is at most 3× higher for the acetyl derivatives in the case of compounds *I* and *IV*. The methanolysis rate is strongly affected by introduction of a methyl group on the nitrogen atom. If the methyl group and the acetyl group are located at different nitrogen atoms (compounds *I* and *XI*), the k_2 rate constant is 6× lower; if they are on the same nitrogen atom (compounds *IV* and *X*), then the k_2 is 30× higher.

Effect of Structure on Acidity of N–H *Hydrogen Atoms*

1-Acyl-3-phenylthioureas contain acidic protons at the both nitrogen atoms, and it is a question which of them is split off preferably in basic medium. Acyl group attracts electrons more strongly than phenyl group, which can be seen from comparison of pK_A values of 4-nitroacetanilide[17] (pK_A 13·8) and 4-nitrodiphenylamine[18] (pK_A 15·9), so the N–H group adjacent to acyl group should be split preferably. Another reason consists in strong intramolecular hydrogen bond in the anion formed by splitting of the N–H bond adjacent to acyl group (structure *Q*).



Q

If the N–H bond adjacent to phenyl group is split, no intramolecular hydrogen bond is formed.* The same conclusion was also made from results of investigation of substituent effects in phenyl ring on dissociation constants of 1-benzoyl-3-subst. phenylthioureas[4]. High value of the reaction constant (ϱ = 1·53) was explained by parallel effects of substituents on strength of the intramolecular hydrogen bond.

* A strong intramolecular hydrogen bond was also found in the neutral molecule of 1-acyl-3-phenylthiourea in deuteriochloroform and hexadeuteriobenzene. It is possible, however, that in methanol solution preferably formed is the intermolecular hydrogen bond with a methanol molecule as the proton acceptor.

A detailed study of structural effect on acidity of substituted thioureas revealed that the difference between the effects of acetyl and phenyl groups is relatively small in these compounds. The pK_A value of 1-acetylthiourea (16·27) is lower than that of 1-phenylurea[19] by 0·7 only.

3-Nitrophenylthiourea (pK_A 15·32)[19] is even more acidic than 1-acetyl-3-phenylthiourea (pK_A 15·77) (Table I). It cannot be excluded that the both monoanions are formed in basic medium, and that increasing value of σ constant of the substituent in phenyl ring makes the PhN–H bond splitting increasingly more significant. As far as the ϱ constants of the N–H bond splitting at the two nitrogen atoms are not substantially different, the dependence of log K_A *vs* σ constants remains practically linear within the whole range measured. A partial splitting of the N–H bond adjacent to phenyl group is also indicated by the fact that the ϱ constant value found[4] is the same (1·53) as that for dissociation constants of substituted formanilides measured in sodium hydroxide solutions[20].

Further studies of structural effects on dissociation constants of acylphenylthioureas brought an unexpected result, *viz.* that 1-acetyl-1-phenylthiourea (*III*), whose N–H bond splitting is not activated by close vicinity of any of the groups mentioned, has practically the same pK_A value (15·64) as the derivative *IV*, 1-acetyl-3-phenylthiourea. In the anion formed from compound *III* no strong intramolecular hydrogen bond can be presumed.

One way of determination of the N–H bond splitting consists in replacement of the other hydrogen atom by a methyl group. According to older ideas, a replacement of hydrogen atom by methyl group in the vicinity of the X–H bond being split caused a slight acidity decrease due to inductive effect of methyl group. Recently it has been found that the effect of methyl group is far more complicated. Besides the inductive effect, also polarizability can make itself felt (which stabilizes the anion formed[21]), and, moreover, steric effect can operate, too (*e.g.* the effect on stability of individual conformers), as well as difference in changes in X–H and X–CH_3 bond connected with the hybridization change[22,23].

Replacement of one hydrogen atom of 1-acetyl-1-phenylthiourea *III* by methyl group resulted in a pK_A decrease by almost one order of magnitude (pK_A = 14·89 for the methyl derivative *IX*).

Replacement of hydrogen atom at 3-position of 1-benzoyl-3-phenylthiourea by methyl group (the methyl derivative *XI*) results in a much less influence of inductive effect and polarizability of methyl group on the N—H bond splitting, because the two groups are substantially more distant. The corresponding value pK_A = 12·96 for the methyl derivative *XI* is lower than that of the non-methylated compound *I* (14·56) by 1·5 units. This result was explained by sterical hindrance to resonance between the electron pair at 3-nitrogen atom and thiocarbonyl group[8].

With 1-acyl-3-phenylthioureas we presumed preferable splitting of the N–H bond adjacent to acyl group for the reasons that acyl group attracts electrons more strongly

and that a strong intramolecular hydrogen bond is formed in the anion. As the introduction of methyl group into the AcN–H group (compounds *X* and *VIII*) should be connected with no such steric effect of methyl groups as in the previous case (compound *XI*), the acidity decrease should be substantial. In fact, the pK_A value of the methyl derivative *X* is lower than that of the non-methylated compound *IV* by 4 orders of magnitude. Practically the same value was found with the corresponding methylated benzoyl derivative *VIII* ($pK_A = 11{\cdot}77$).

As far as we know, this is yet the biggest anomalous effect of methyl group on acidity, and we have no acceptable explanation for it.

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