

Unsaturated  $\gamma$ -Thiolactones

## V.\* On the Rearrangement of Some 5-Alkyl-substituted Thiolenes-2-ones

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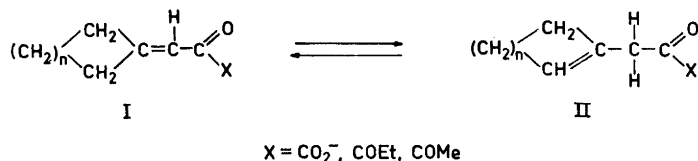
The tautomeric rearrangement of 5-methyl-4-thiolene-2-one and of 5-*tert.*butyl-4-thiolene-2-one has been studied at different temperatures.

The kinetics clearly indicate that in methanol solution with pyridine as base, the isomerizations are first-order in substrate and first-order in base. The tautomerization follows a two-stage mechanism and obeys both parts of the Hughes-Ingold rule. The activation parameters have been determined for both systems.

Unsaturated systems which undergo proton-transfer have been known for a long time. These systems have earlier been studied mainly from the equilibrium point of view, little attention having been paid to their kinetics. It is first during the last decade that different types of mechanisms have been understood. Earlier, two types of mechanisms were suggested, a two-stage unimolecular mechanism<sup>1</sup> and a single-stage bimolecular mechanism.<sup>2</sup>

The two-stage mechanism, suggested by Ingold, Shoppee and Thorpe, presumes a free mesomeric anion, which has a definite independent existence. In connection with this mechanism, Ingold and Hughes submit the generalization that "when a proton is supplied by acids to the mesomeric anion of weakly-ionizing tautomers of markedly unequal stability, then the tautomer which is the most quickly formed is the thermodynamically least stable, it is also the tautomer from which the proton is lost most quickly to bases".<sup>3</sup> This generalization is particularly successful when unsaturated carbanions are stabilized by charge distribution on the electronegative elements, as in the phenylnitromethane system, a classical school example of a tautomeric system.<sup>4</sup> Even the cyclic systems of type I and II (Scheme I) and the corresponding nitriles investigated by Kon *et al.* around 1930<sup>5</sup> obey the Hughes-Ingold rule, as does also the rearrangement of the vinylacetate anion to crotonate anion.<sup>6</sup> The diphenylpropene system and its nitrogen analogue, the azomethine or

\* Part IV. Ref. 21.

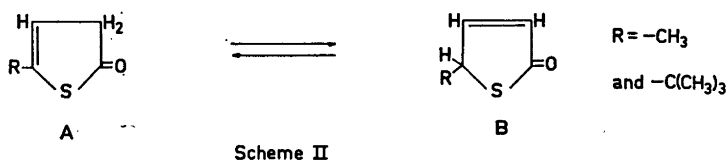


Scheme I

aza-allylic system, have been of great interest.<sup>7-11</sup> Some of the results of the studies of these systems seemed to favour the single-stage mechanism.<sup>12,13</sup> Even if de Sales and Wilson<sup>14</sup> threw some doubt on some of the results, the single-stage mechanism remained as an alternative in the discussions of mechanisms<sup>15,16</sup> until 1965, when Cram and Gutrie<sup>17</sup> showed that it was without secure foundation, and that under certain conditions some aza-allylic systems follow the Hughes-Ingold rule. In other systems, however, the first part of the rule fails because the ambident anion reacts faster at the side which provides the more thermodynamically-stable tautomer.<sup>15,18</sup> During the last years it has been shown that, besides the intermolecular mechanism, there exists a competing mechanism which under certain conditions becomes dominant. In this mechanism the proton-transfer is intramolecular and involves ion-pairs as intermediates. Weidler and Bergson<sup>19</sup> and Cram *et al.*,<sup>20</sup> the pioneers in this field, have in a series of investigations elegantly established the intramolecular nature of these tautomerizations.

#### KINETICS OF THE THIOLENE-2-ONE SYSTEM

The preparations of tautomeric 5-alkyl-substituted thiolene-2-ones (Scheme II) have been described earlier, and their structure and thermodynamic



Scheme II

equilibrium were established by NMR-spectroscopy.<sup>21</sup> In this paper, the kinetics of the tautomerization of the 5-methyl- and 5-*tert.* butyl-substituted systems will be studied.

Since the thiolene-2-ones are very reactive, suitable conditions for first-order kinetics are rather limited. It is usual to have alcohols as solvents and alkoxide ions as catalysts, but these bases cause some side reactions in the thiolene-2-one system. When amines are used as catalysts a tertiary amine is desirable in order to avoid reaction with the carbonyl group. Triethylamine was tried but in order to get measurable rates the amine concentration had

to be so low that it was difficult to keep it constant. Ethanol could not be used as solvent because in the NMR-spectra some of its sidebands were interfering with the analytical absorption bands of the thiolene-2-ones. However, by using pyridine as catalyst in methanol solution, the rates of the rearrangements in these systems are of such an order that NMR could be used for measuring the relative amounts of the two tautomers. As the substituents of the two tautomeric forms have different  $\tau$ -values (Scheme III), the course of the

R	$\tau_{AR}$	$\tau_{BR}$
-CH <sub>3</sub>	7.97	8.50
-C(CH <sub>3</sub> ) <sub>3</sub>	8.87	9.00

Scheme III

rearrangement could be followed by measuring the increase in intensity of the BR proton peak and the decrease in intensity of the AR proton peak.

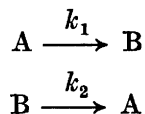
The thermodynamically-unstable unconjugated isomer, namely the 4-thiolene-2-one form (A), was obtained as the predominant component by acidifying the alkaline solution of the tautomeric 5-alkylthiolene-2-one mixture.<sup>21,22</sup>

In a qualitative experiment with deuterated methanol as solvent, it was found that the 4-thiolene-2-one isomer undergoes hydrogen-deuterium exchange more rapidly than the 3-thiolene-2-one form (B). Furthermore, exchange of the methylenic protons for deuterium in the 3-position of the 4-thiolene-2-one form was complete before any tautomerization to the 3-thiolene-2-one form could be observed.

In all the kinetic runs, methanol was used as solvent, pyridine as catalyst, and a thiolene-2-one concentration of 1.5 moles/litre. When the thiolene-2-one concentration was varied between 1.0 mole/litre and 2.0 moles/litre the variation in reaction rates was within the experimental errors. The experimental kinetic data satisfied function (1), showing that

$$\ln \frac{AK-B}{A_0K-B_0} = -(k_1 + k_2)t \quad (1)$$

the opposing reactions are first-order and describable in principle by the scheme



where  $k_1$  and  $k_2$  are the specific reaction rate constants for the consumption and production of A, respectively.  $K$  is the thermodynamic equilibrium constant and is related to the individual rate constants by

$$K = k_1/k_2$$

Table 1. Algebraically evaluated values for  $k_1 + k_2$ .

Compound	Temp. °C	Pyridine conc. M	$(k_1 + k_2) \times 10^4$ sec <sup>-1</sup>
5-Methyl-thiolene-2-one	0	0.2	$1.4 \pm 0.1$
	15	0.2	$3.2 \pm 0.2$
	31.6	0.2	$11.0 \pm 0.4$
	45	0.2	$28.0 \pm 0.9$
	31.6	0.1	$6.4 \pm 0.4$
	31.6	0.5	$26 \pm 0.6$
5-tert.Butyl-thiolene-2-one	0	0.2	$3.0 \pm 0.2$
	15	0.2	$6.9 \pm 0.4$
	31.6	0.2	$20 \pm 0.6$
	45	0.2	$37 \pm 3$
	31.6	0.1	$10.2 \pm 1$
	31.6	0.5	$54 \pm 2$

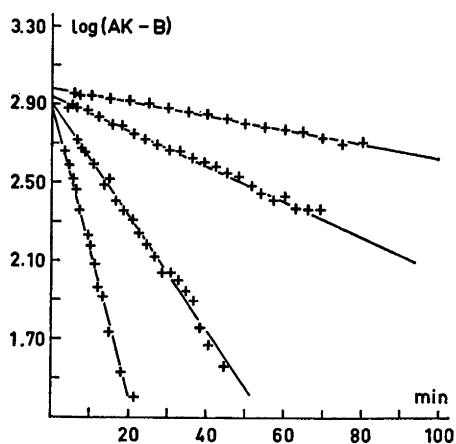


Fig. 1. Rate of tautomerization of 5-methyl-4-thiolene-2-one at different temperatures (45°, 31.6°, 15°, 0°).

In one series of experiments the base concentration was kept constant and the temperature varied. The least squares method was used to obtain the best fit of the experimental measurements to function (1). The algebraically evaluated values for  $(k_1 + k_2)$  and their standard deviations are given in Table 1. The sums  $(k_1 + k_2)$  can also be determined from the slopes of the curves in Figs. 1 and 2. Since the ratios  $k_1/k_2 = K$  are known, the individual rate constants at different temperatures could be determined. They are given in Table 2.

The Arrhenius activation energy,  $E_a$ , and transition-state theory functions have been calculated from the velocity constants for both the forward and the

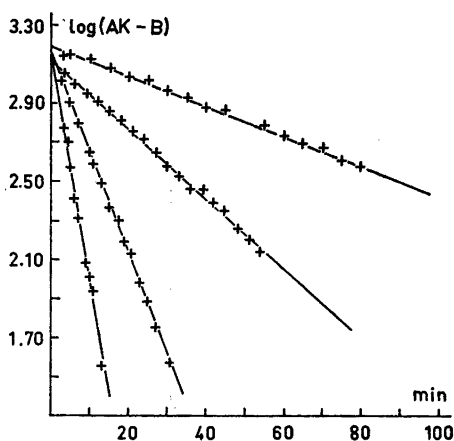


Fig. 2. Rate of tautomerization of 5-*tert.*-butyl-4-thiolene-2-one at different temperatures (45°, 31.6°, 15°, 0°).

Table 2. Equilibrium constants and specific rates at different temperatures. (Base conc. = 0.2 mole/litre).

Compound	Temp. °C	$K$	$k_1 \times 10^4$ sec <sup>-1</sup>	$k_2 \times 10^4$ sec <sup>-1</sup>
5-Methyl-thiolene-2-one	0	12.3 ± 0.6	1.3 ± 0.1	0.11 ± 0.01
	15	10.9 ± 0.6	3.0 ± 0.2	0.27 ± 0.03
	31.6	9.5 ± 0.5	9.9 ± 0.4	1.0 ± 0.1
	45	8.6 ± 0.5	25.3 ± 0.9	2.9 ± 0.3
5- <i>tert.</i> -Butyl-thiolene-2-one	0	23 ± 1	2.8 ± 0.2	0.12 ± 0.01
	15	20 ± 1	6.5 ± 0.4	0.32 ± 0.03
	31.6	18.7 ± 0.9	18.9 ± 0.6	1.0 ± 0.08
	45	16.0 ± 0.8	35.0 ± 3	2.2 ± 0.3

reverse processes of the two systems studied. The Arrhenius plots are given in Figs. 3 and 4, and the absolute rate equation was written as

$$\Delta S^\ddagger = \frac{E_a}{T} - 4.58 \log \frac{T}{k} - 49.20$$

The Gibbs free energy of activation could be calculated since  $\Delta F^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$  and  $\Delta H^\ddagger = E_a - RT$ . The activation parameters are collected in Table 3.

The equilibrium constants at different temperatures were found to satisfy function (2).

$$\ln K = -(\Delta H/RT) + C \quad (2)$$

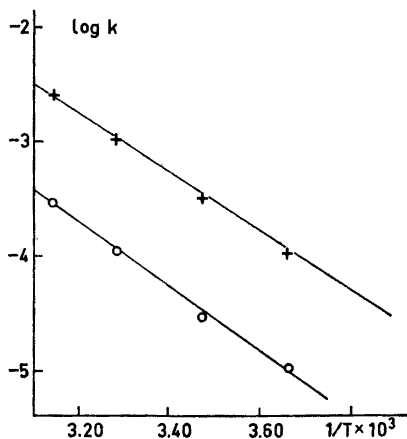


Fig. 3. + =  $\log k_1$  and O =  $\log k_2$  in the Arrhenius plots for 5-methyl-thiolene-2-one.

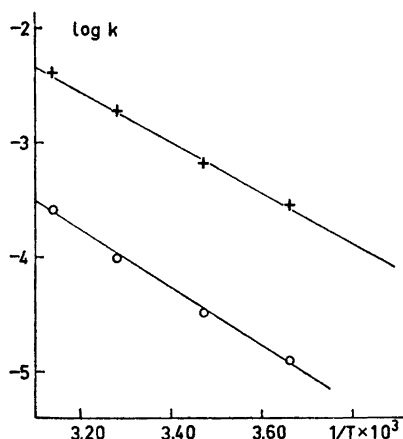


Fig. 4. + =  $\log k_1$  and O =  $\log k_2$  in the Arrhenius plots for 5-tert.butyl-thiolene-2-one.

This relation is plotted logarithmically in Fig. 5, for both systems, and the heat of reaction,  $\Delta H$ , was determined by the method of least squares. For the 5-methyl-thiolene-2-one system the thermodynamic constants at 31.6° was found to be  $\Delta H = -1.45 \pm 0.07$  kcal mole<sup>-1</sup>,  $\Delta F = -1.32 \pm 0.15$  kcal mole<sup>-1</sup>, and  $\Delta S = -0.30 \pm 0.03$  cal degree<sup>-1</sup> mole<sup>-1</sup>. The corresponding values for the 5-tert.butyl-thiolene-2-one system was  $\Delta H = -1.35 \pm 0.07$  kcal mole<sup>-1</sup>,

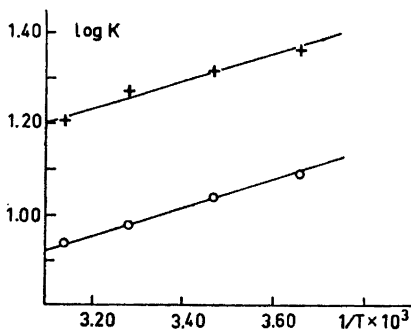


Fig. 5. (+) =  $\log$  equilibrium constant of 5-tert.butyl-thiolene-2-one and (O) =  $\log$  equilibrium constant of 5-methyl-thiolene-2-one against  $1/T$  degree<sup>-1</sup>.

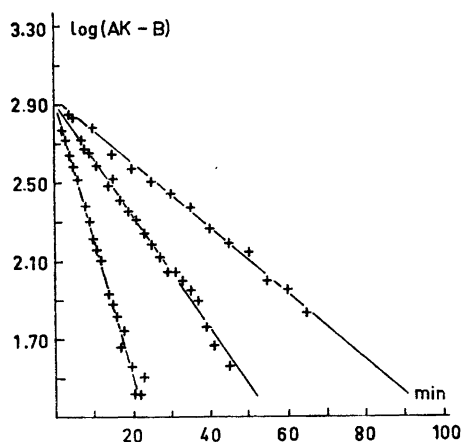


Fig. 6. Rate of tautomerization of 5-methyl-4-thiolene-2-one at different pyridine concentrations (0.5, 0.2, and 0.1 mole/litre).

Table 3. Enthalpies, free energies, and entropies of activation.

Compound	Temp. °C	$\Delta H^\ddagger$ kcal mole <sup>-1</sup>	$\Delta F^\ddagger$ kcal mole <sup>-1</sup>	$\Delta S^\ddagger$ cal degree <sup>-1</sup> mole <sup>-1</sup>	$\Delta H^\ddagger$ kcal mole <sup>-1</sup>	$\Delta F^\ddagger$ kcal mole <sup>-1</sup>	$\Delta S^\ddagger$ cal degree <sup>-1</sup> mole <sup>-1</sup>
Methyl-thiolene-2-one	0	11.5	20.8	-34.2	12.9	22.2	-34.1
	15	11.5	21.5	-34.9	12.9	22.6	-34.0
	31.6	11.4	22.0	-34.9	12.8	23.4	-34.8
	45	11.4	22.4	-34.8	12.8	23.8	-34.6
<i>tert.</i> Butyl-thiolene-2-one	0	9.7	20.4	-39.3	11.0	22.1	-40.5
	15	9.6	21.0	-39.5	11.0	22.8	-40.9
	31.6	9.6	21.6	-39.6	11.0	23.4	-41.0
	45	9.6	22.3	-40.1	10.9	24.0	-41.1

$\Delta F = -1.70 \pm 0.15$  kcal mole<sup>-1</sup>, and  $\Delta S = 1.30 \pm 0.15$  cal degree<sup>-1</sup> mole<sup>-1</sup>. The negative signs of  $\Delta H$  and  $\Delta F$  and the small values of  $\Delta S$  are expected for the rearrangement of the less stable isomer in a reversible process.

In another series of experiments, the base concentration was varied and the temperature was kept constant at 31.6°. The experimental results are given in Fig. 6, Fig. 7, and Table 4. By comparing the equilibrium constants obtained in the different media, it was once again verified that the polarity of the solvent

Table 4. Equilibrium constants and specific rate constants at different base concentrations. (Temp. 31.6°).

Compound	<i>K</i>	Pyridine conc. M.	<i>k</i> <sub>1</sub> + 10 <sup>4</sup> sec <sup>-1</sup>	<i>k</i> <sub>2</sub> × 10 <sup>4</sup> sec <sup>-1</sup>
5-Methyl-thiolene-2-one	9.5 ± 0.5	0.1	5.8 ± 0.4	0.6 ± 0.1
	9.5 ± 0.5	0.2	9.9 ± 0.4	1.0 ± 0.1
	8.7 ± 0.5	0.5	23.6 ± 0.6	2.7 ± 0.2
5- <i>tert.</i> Butyl-thiolene-2-one	18.7 ± 0.9	0.1	9.6 ± 0.6	0.52 ± 0.05
	18.7 ± 0.9	0.2	18.9 ± 0.6	1.0 ± 0.1
	17.7 ± 0.9	0.5	50.7 ± 2	2.9 ± 0.2

favours the conjugated 3-thiolene-2-one form.<sup>21</sup> When the pyridine concentration was as high as 0.5 mole/litre, the equilibrium constant was lowered (*cf.* Table 4). The tautomerization was faster for the 5-*tert.*butyl-4-thiolene-2-one than for the 5-methyl-4-thiolene-2-one, and in both systems the specific

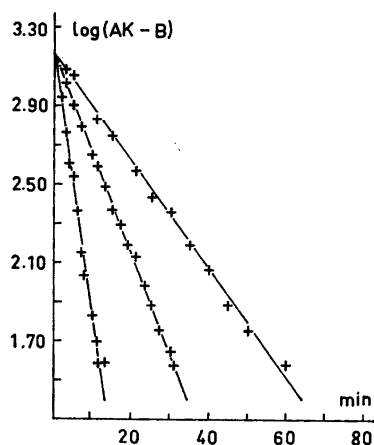


Fig. 7. Rate of tautomerization of 5-*tert.*butyl-4-thiolene-2-one at different pyridine concentrations (0.5, 0.2, and 0.1 mole/litre).

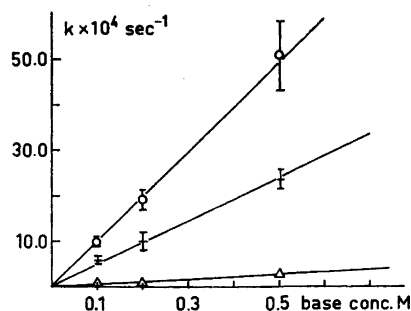


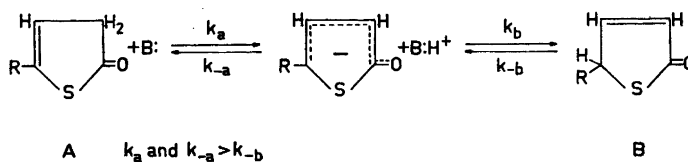
Fig. 8. Specific rate constants for (O) 5-*tert.*butyl-4-thiolene-2-one, (+) 5-methyl-4-thiolene-2-one, (Δ) 5-*tert.*butyl- and 5-methyl-3-thiolene-2-one at different pyridine concentrations.



rates of isomerizations were found to be proportional to the base concentration (Fig. 8), showing that the rearrangement is first-order even with respect to the base.

## DISCUSSION

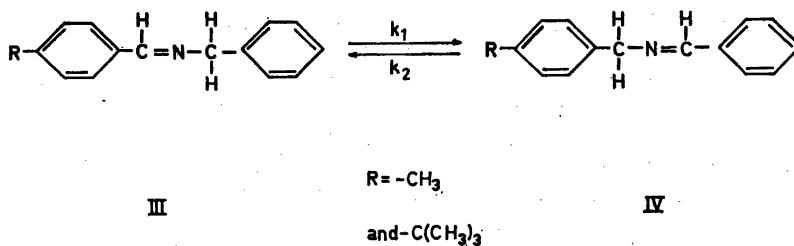
In the thiolene-2-one systems studied in this paper, the less stable 4-thiolene-2-one form (A) is first formed upon acidifying. From the deuteration experiment it is shown that the less stable form also donates protons to bases more rapidly than the stable form. Thus the thiolene-2-one system in methanol, with pyridine as catalyst, obeys both parts of the Hughes-Ingold rule. This is expected, as the carbonyl group in this system provides an additional location for the charge in the mesomeric anion (Scheme IV), which is formed as inter-



Scheme IV

mediate. In going from A to B,  $k_a$  and  $k_{-a}$  is greater than  $k_{-b}$ , thus the protonation at the 5-position giving the 3-thiolene-2-one form (B) is the rate determining step. The principle of microscopic reversibility then demands that deprotonation of B is the slowest and rate determining step in going from B to A.

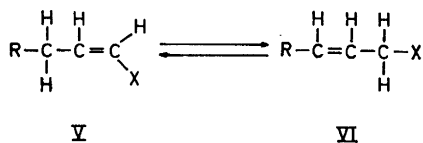
Compared with the aza-allylic system, III, IV (Scheme V), where a strong base such as an alkoxide ion is necessary in order to achieve tautomerization, the 5-alkylthiolene-2-one system is very labile, as it tautomerizes with about the same velocity in methanol with such a weak base as pyridine ( $pK_a = 5.23$ ). In the rearrangement of III to IV at  $85^\circ$  with ethoxide as catalyst, the sum ( $k_1 + k_2$ ) was  $0.9 \times 10^{-4} \text{ sec}^{-1}$  when R = methyl and  $1.7 \times 10^{-4} \text{ sec}^{-1}$  when R = *tert.*butyl.<sup>10</sup> The speed of the rearrangement is increased by a factor of



Scheme V

two when the substituent is *tert.*butyl instead of methyl, as in the case of thiolene-2-one  $(k_1 + k_2)_{\text{methyl}} = 11 \times 10^{-4} \text{ sec}^{-1}$  and  $(k_1 + k_2)_{\text{tert.butyl}} = 20 \times 10^{-4} \text{ sec}^{-1}$ . This similarity in substituent effect indicates similar mechanisms in both systems.

During recent years, several sulfur-containing tautomeric systems such as the unsaturated sulfides, sulfoxides and sulfones<sup>15,23-25</sup> shown in V and VI (Scheme VI), and the thiophene analogue of indene,<sup>26</sup> have been investigated.



Scheme VI

Although the reason for the tautomeric lability is due to different factors, it is interesting to note that the 5-alkylthiolene-2-ones appear to be the most easily tautomerized. As the structures of these three types of systems are quite different, it is not surprising that the mechanism for the tautomerization is dissimilar. Of what hitherto is known, the proton-transfer is intramolecular in the thiaindene system and intermolecular in the other two groups of systems. However, some of the unsaturated sulfoxides do not follow the Hughes-Ingold rule.<sup>24</sup>

As the errors of the rate constants are rather large (Table 1), the variations in entropy and enthalpy of activation as functions of temperature are within the range of experimental errors<sup>27</sup> (Table 3). The difference in the entropies of activations for the two thiolene-2-ones seems however to be significant. If substitution results in a crowded transition state in which freedom of motion of the substituents is unduly hindered the entropy of activation is lowered. For instance in the nucleophilic substitution of  $\text{RCH}_2\text{I}$  with an ethoxide group, the entropy of activation is  $-9.5 \text{ cal degree}^{-1}\text{mole}^{-1}$  when R is H and falls to  $-19.9 \text{ cal degree}^{-1}\text{mole}^{-1}$  if R is *tert.*butyl.<sup>28</sup> In the present case, the entropy of activation is lowered by  $6 \text{ cal degree}^{-1}\text{mole}^{-1}$  if the substituent is *tert.*butyl instead of methyl. The two extra methyl groups obviously contribute to the crowding in the transition state. This effect further testifies to the fact that the 5-position is involved in the rate determining step, both in the forward and the reverse process. If the rate determining step for the forward reaction were removal of the 3-hydrogen in A, such a large substituent effect would hardly be expected. The entropy of activation for reactions that involve proton abstraction by charged bases in the rate determining step have generally values that range from  $+10$  to  $-22 \text{ cal degree}^{-1}\text{mole}^{-1}$ .<sup>29,30,31</sup> In a recent work by Cram *et al.*,<sup>32</sup> however, an entropy of activation value as low as  $-27 \text{ cal degree}^{-1}\text{mole}^{-1}$  was obtained in *tert.*butyl alcohol dioxane-triethylenediamine, which is much more negative than the values obtained

with negatively-charged bases in non-polar solvents. This large negative entropy is probably associated with the fact that in the latter system two neutral molecules produce two charged species in the transition state, and the solvent molecules are "frozen out" in the process. When charged bases are used, the charge is not generated but only dispersed in the transition state. In the reverse step of the thiolene-2-one system, going from B to A, it is the two neutral molecules, pyridine and 3-thiolene-2-one, that produce two charged species in the transition state, and the entropies of activation are low, as expected. However, in the forward reaction, going from A to B, the same magnitudes of entropies of activation were obtained. In this case it is the capture of the proton that is involved in the rate determining step, where charge is destroyed. The negligible difference in entropies of activation when charge is created and destroyed may be due to the fact that methanol is used as solvent. As a polar solvent, methanol is capable of dispersing charge by solvation, and itself undergoes a little reorganisation. By comparing the rates, enthalpies, and entropies of activation for the two thiolene-2-ones, the *tert*.butyl-thiolene-2-one rearranges faster due to the fact that the less positive values for enthalpies of activation for this compound overcompensate the more negative values for the entropies of activation.

#### EXPERIMENTAL

5-Methyl- and 5-*tert*.butyl-4-thiolene-2-one were prepared as described in Ref. 21.

The NMR-spectra were obtained with a Varian A-60 high resolution spectrometer with a v-6057 variable temperature accessory. The temperature was measured before and after each kinetic run and each equilibrium determination out from the internal shift of methanol and ethylene glycol, respectively, in separate samples.

The numerical treatment of the rate data was done on the electronic digital computer SMIL at the Department of Numerical Analysis of the University of Lund.

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