Carbobenzoxy-β-benzyl-L-aspartyl-L-serine p-methoxyphenacyl ester had mp 145–150°; 75%; ir (CHCl₃) 3400, 1755, 1725, 1680 cm⁻¹. *Anal.* Calcd for C₃₁H₃₂N₂O₁₀: C, 62.83; H, 5.44; N, 4.73. Found: C, 62.98; H, 5.36; N, 4.65.

Photolysis of p-Methoxyphenacyl Esters of N-Blocked Amino Acids and Peptides.—These photocleavage reactions were carried out in the same way as described for p-methoxyphenacyl benzoate with solvents and irradiation times as indicated in Table I.

α-Methylphenacyl Esters.—The products were prepared from α-methylphenacyl bromide and the corresponding carboxylic acid in the same way as described for p-methoxyphenacyl benzoate.

α-Methylphenacyl benzoate had mp 108°; 76%; ir (CCl₄) 1730, 1705 cm⁻¹. *Anal.* Calcd for C₁₆H₁₄O₃: C, 75.57; H, 5.55. Found: C, 75.25; H, 5.39.

α-Methylphenacyl phthaloylglycinate had mp 86°; 76%; ir (CCl₄) 1770, 1740, 1710 cm⁻¹. *Anal.* Calcd for C₁₉H₁₅NO₅: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.53; H, 4.49; N, 4.13.

α-Methylphenacyl *tert*-butoxycarbonylglycinate had mp 87°; 91%; ir (CCl₄) 3460, 1760, 1725, 1705 cm⁻¹. *Anal.* Calcd for C₁₆H₂₁NO₅: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.48; H, 6.68; N, 4.49.

α-Methylphenacyl ester of *tert*-butoxycarbonyl-L-alanine was recrystallized from petroleum ether: mp 79–83°; 62%; ir (CCl₄) 3450, 1750, 1720, 1710 cm⁻¹. *Anal.* Calcd for C₁₇H₂₃NO₅: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.28; H, 7.00; N, 4.72.

α-Methylphenacyl ester of *tert*-butoxycarbonyl-L-phenylalanine was an oil: 80%; ir (CCl₄) 1750, 1725, 1700 cm⁻¹.

Photolysis of α-Methylphenacyl Benzoate.—A solution of 1.06 g (4.0 mmol) of α-methylphenacyl benzoate in 300 ml of dioxane was irradiated for 6 hr at 12°. After removal of the sol-

vent under reduced pressure, 60 ml of ethyl acetate was added. The solution was extracted with 1 N aqueous potassium carbonate. Upon acidification of the alkaline extract with 2 N hydrochloric acid, the product was extracted with ether. After the removal of ether, the colorless solid was triturated in petroleum ether. Filtration gave 0.382 g (78.2%) of benzoic acid, mp 102°.

The ethyl acetate solution after the extraction was dried and evaporated. The residue was chromatographed on 50 g of Florisil (100–200 mesh) using cyclohexane–ethyl acetate (4:1) to give 0.190 g (35.4%) of propiophenone: ir (CCl₄) 1690 cm⁻¹; nmr δ 8.2–7.9 (m, 2 H), 7.7–7.3 (m, 3 H), 3.1 (q, 2 H), 1.3 (t, 3 H); tlc R_f 0.73 (cyclohexane–EtOAc (4:1)].

The other reactions of α-methylphenacyl esters were similarly conducted with solvents as indicated in Table II.

Quenching Experiments of p-Methoxyphenacyl Benzoate Photocleavage Reactions.—A solution of 1.2 g (4.45 mmol) of p-methoxyphenacyl benzoate and 38.4 g (0.30 m) of naphthalene in 300 ml of dioxane was irradiated for 17 hr. After the removal of the solvent, 200 ml of benzene was added. The solution was extracted with 1 N aqueous potassium carbonate. Upon acidification of the alkaline extract with 2 N hydrochloric acid, the solution was extracted with ether. The thin layer chromatography of the ether solution using cyclohexane–ethyl acetate (4:1) showed no product. After the removal of ether, no benzoic acid was obtained.

Reaction Kinetics of 3-Thenoyl Chloride with Anilines in Benzene

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The rate of the reaction of 3-thenoyl chloride with substituted anilines has been measured in benzene at different temperatures. The reaction follows a second-order kinetics. The activation parameters and the slopes of the Hammett (−3.21) and Brønsted (1.08) plots are similar to those of the reactions of benzoyl and 2-thenoyl chlorides with aniline. In the 3-thenoyl chloride reaction the effect of the substituents in the aniline is to modify the activation energy, log A remaining approximately constant. The reaction mechanism of the 3-thenoyl chloride with aniline is the same as for the reactions of benzoyl and 2-thenoyl chlorides. 3-Thenoyl chloride, however, does not react as expected from the pK_a of 3-thenoic acid. The Tommila equation points out that the carbonyl carbon atom of 3-thenoyl chloride is less electrophilic than that of benzoyl chloride but more electrophilic than that of 2-thenoyl chloride.

The Hammett relation is valid for correlating the reaction data of 3-thenoic and 3-furoic acid esters.[1]

Oae and Price[2] found that the ethyl ester of 3-thenoic acid saponified as expected from the pK_a of 3-thenoic acid. Imoto and coworkers[3] studied the hydrolysis of thiophene and furancarboxylic acid esters and they found a linear relationship between the hydrolysis rates and the dissociation constants for the 3-carboxylic acids; the 2-analogs, instead, deviated from the straight line. The same results were obtained recently by Ten Thije and Janssen.[4]

In a previous paper we reported the rates of the reaction of 2-thenoyl chloride with various substituted anilines in benzene solution in order to investigate whether 2-thenoyl chloride, in comparison with benzoyl

chloride, reacted as expected from the pK_a of 2-thenoic acid.[5] We found that 2-thenoyl chloride reacted more slowly than benzoyl chloride, although 2-thenoic acid was stronger than benzoic acid. The Tommila equation pointed out that the carbonyl carbon atom of 2-thenoyl chloride was less positively charged than that of benzoyl chloride.

Recently we reported the data relating to the reactions of 3-thenoyl 2- and 3-furoyl chlorides with aniline in benzene.[6] We found that only 2-furoyl chloride reacted as expected from the pK_a of 2-furoic acid. The reactivity decreased from benzoyl to 3-thenoyl, 3-furoyl, and 2-thenoyl chlorides, while the order of the acidity constants was 2-thenoic acid > 3-furoic acid > 3-thenoic acid > benzoic acid.

In the present paper we report a study of the reaction

(1) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 80 (1963).

(2) S. Oae and C. C. Price, *J. Amer. Chem. Soc.*, **79**, 2547 (1957).

(3) Y. Otsuji, Y. Koda, M. Kubo, M. Furukawa, and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1293 (1959).

(4) P. A. Ten Thije and M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, **84**, 1169 (1965).

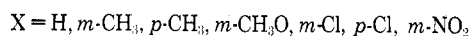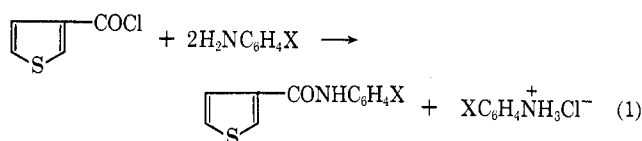(5) A. Arcoria, S. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, **38**, 32 (1973).

(6) A. Arcoria and S. Fisichella, *Gazz. Chim. Ital.*, in press.

TABLE I
SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF 3-THENOYL CHLORIDE WITH META- AND
PARA-SUBSTITUTED ANILINES IN BENZENE

Registry no.	No.	Substituent	$pK_a[5]$	$10°$	$15°$	$17.5°$	$20°$	$25°$	$35°$	$45°$
							$k_2 \times 10^2$, l. mol^{-1} sec^{-1}			
62-53-3	1	H	4.58		2.71			4.38	6.63	
108-44-1	2	m-CH$_3$	4.69		4.86		5.84	7.32	10.6	
106-49-0	3	p-CH$_3$	5.12	9.98		13.0		18.1	25.7	
536-90-3	4	m-CH$_3$O	4.20		1.96		2.49	3.13	4.83	
108-42-9	5	m-Cl	3.34					0.257	0.450	0.675
106-47-8	6	p-Cl	3.98					1.03	1.61	2.48
99-09-2	7	m-NO$_2$	2.50					0.0272	0.0456	0.0752

between 3-thenoyl chloride and anilines in benzene to give further information about this reaction.

The reaction of the acid chloride with aniline takes place quantitatively according to stoichiometric eq 1.

$$\text{[COCl-thiophene]} + 2H_2NC_6H_4X \longrightarrow$$

$$\text{[CONHC}_6\text{H}_4\text{X-thiophene]} + X C_6H_4\overset{+}{N}H_3Cl^- \quad (1)$$

$X = H, m\text{-CH}_3, p\text{-CH}_3, m\text{-CH}_3O, m\text{-Cl}, p\text{-Cl}, m\text{-NO}_2$

The reaction was followed kinetically, as previously described,[5,7] by filtering the completely insoluble aniline hydrochloride, dissolving it in water, and estimating the chloride ion by mercuric nitrate, using a mixture of diphenylcarbazone and bromophenol blue as indicator (see Experimental Section).

We found that the reaction of 3-thenoyl chloride with anilines follows a second-order kinetics. The reaction mechanism of 3-thenoyl chloride with aniline was the same as for benzoylation reaction. The differences in rate were due only to changes in activation energy, log A remaining approximately constant.

The 3-thenoyl chloride reaction was slower than that of benzoyl chloride, but it was faster than that of 2-thenoyl chloride. The Tommila equation showed that the carbonyl carbon atom of 3-thenoyl chloride was less electrophilic than that of 2-benzoyl chloride, but more electrophilic than that of 2-thenoyl chloride.

Results and Discussion

The reaction between 3-thenoyl chloride and anilines in benzene took place quantitatively according to eq 1; no other products were observed.

In all cases the compounds gave excellent second-order kinetics. The second-order rate constants were calculated with constant molar ratio of the reactants (1:2): 1 mol of acid chloride with 2 mol of aniline, in agreement with eq 1.

The rate constants at different temperatures, listed in Table I, show that electron-donating substituents accelerate and electron-withdrawing groups retard the reaction.

A comparison of these results with those of the benzoyl[8-10] and 2-thenoyl chlorides[5] reactions shows that 3-thenoyl chloride does not react as expected from the pK_a of 3-thenoic acid. In fact, 3-thenoyl chloride ($k_{25} \times 10^2 = 4.38$ l. mol^{-1} sec^{-1}) is less reactive than

benzoyl chloride ($k_{25} \times 10^2 = 6.27$ l. mol^{-1} sec^{-1})[10] but it is more reactive than 2-thenoyl chloride ($K_{25} \times 10^2 = 2.52$ l. mol^{-1} sec^{-1})[5], while the order of the acidity constants of the corresponding acid in aqueous solution is 2-thenoic acid (p$K_a = 3.53$) > 3-thenoic acid (p$K_a = 4.10$) > benzoic acid (p$K_a = 4.21$).[11]

The activation parameters, listed in Table II, were calculated in the usual way[5,7] from a least-squares treat-

TABLE II
ACTIVATION PARAMETERS FOR THE REACTION RATES IN TABLE I

Substituent	E_A, kcal mol^{-1}	ΔS^* at $25°$, cal mol^{-1} °K^{-1}	Log A
H	7.49	−41.6	4.12
m-CH$_3$	6.94	−42.4	3.95
p-CH$_3$	6.64	−41.6	4.12
m-CH$_3$O	7.94	−40.7	4.32
m-Cl	9.11	−41.6	4.09
p-Cl	8.27	−41.8	4.08
m-NO$_2$	10.24	−42.4	3.95

ment of log k against T^{-1} and they show a regular variation with the substituent in the aniline.

The results show that in the 3-thenoyl chloride reaction, as for that of benzoylation,[11] the effect of the substituents in the aniline is to modify the activation energy, log A remaining approximately constant. In Figure 1 log k at $25°$ is plotted against the experimental values of E_A. All the points lie close to the theoretical line of slope -2.303 RT drawn through the point representing the unsubstituted aniline, showing that the frequency factor is very nearly constant. According to Hinshelwood and coworkers[12,13] the substituent effects are consistent with the assumption that variation of the repulsion between the reactants is the principal factor determining the changes in activation energy.

The large negative entropies of activation are similar to those found for the reactions of benzoyl[10] and 2-thenoyl[5] chlorides with anilines and they are as expected by bimolecular reactions with a highly polar transition state.[14]

The values of the rate constants of the reaction of 3-thenoyl chloride with anilines show that the reaction rate depends on the electron density on the nitrogen atom. Since the basicity also depends on the electron density, one should expect a correlation between rate and basicity of the anilines. It is interesting to

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(8) E. G. Williams and C. N. Hinshelwood, _J. Chem. Soc._, 1079 (1934).
(9) F. J. Stubbs and C. N. Hinshelwood, _J. Chem. Soc._, 71 (1949).
(10) E. Tommila and T. Vihavainen, _Acta Chem. Scand._, **22**, 3224 (1968).

(11) G. Marino, _Advan. Heterocycl. Chem._, **13**, 242 (1971).
(12) H. S. Venkataraman and C. Hinshelwood, _J. Chem. Soc._, 4977 (1960).
(13) H. S. Venkataraman and C. Hinshelwood, _J. Chem. Soc._, 4986 (1960).
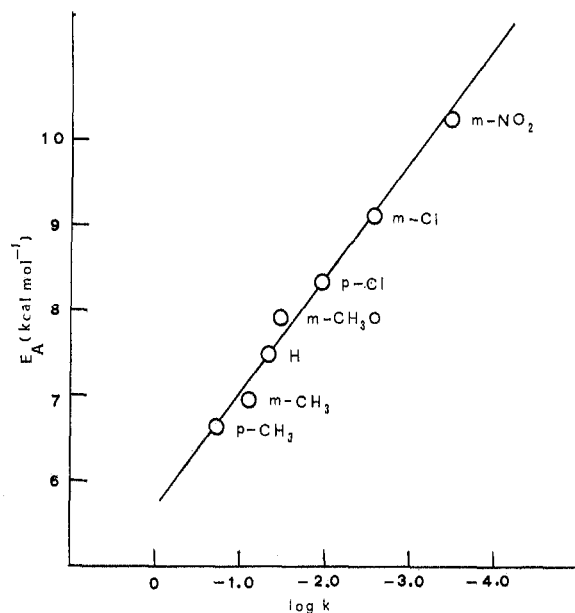(14) A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, Chapter 7.

Figure 1.—Plot of the experimental values of E_A against log $k_{25}°$ for the reaction of 3-thenoyl chloride with substituted anilines in benzene. The line is of theoretical slope $-2.303\, RT$.
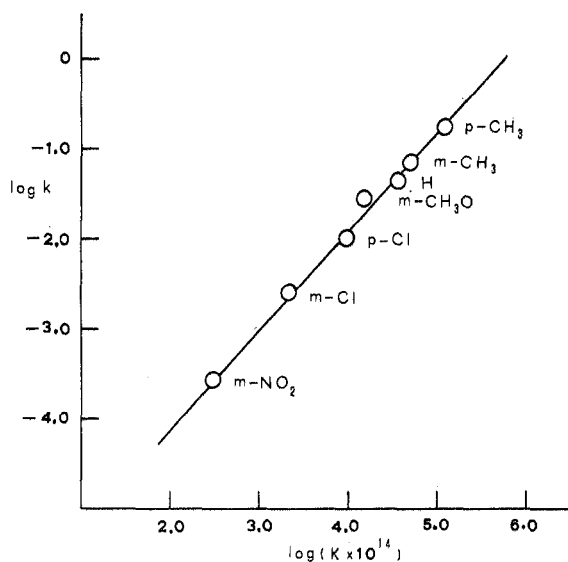

Figure 2.—Plot of log $k_{25}°$ for the reaction of 3-thenoyl chloride with substituted anilines in benzene against the logarithm of their dissociation constants in water at 25° (Brønsted plot).

observe that, as for the 2-thenoyl chloride reaction, for 3-thenoyl chloride was also found a linear relationship between log k at 25° and the pK_a at 25° in water of the corresponding protonated aniline[15] (Figure 2). The sign of the Brønsted slope is as expected for a nucleophilic substitution and its value (1.08) is similar to those found for the benzoylation (0.97) and 2-thenoyl chloride reactions[5] (1.14), but, as previously noted, we cannot discuss the value of the Brønsted coefficient, since the reaction rates were measured in benzene and the pK_a values in water.

The plot of log k at 25° against Hammett's σ constants is linear with a slope of -3.21 (Figure 3). This value is comparable to those found for the reactions of 2-thenoyl[5] and benzoyl[16-18] chlorides with anilines.

(15) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 144.
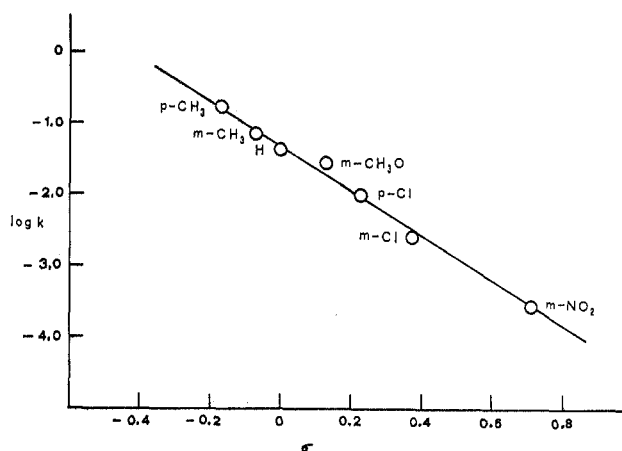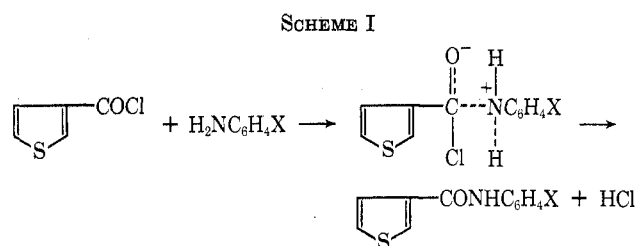

Figure 3.—Hammett plot for the reaction of 3-thenoyl chloride with substituted anilines in benzene at 25°.

From these results we can conclude also that the reaction of 3-thenoyl chloride with aniline in benzene is similar to benzoylation reaction involving the attack of the lone pair of the electrons of the amino group to the carbonyl carbon atom (Scheme I).

SCHEME I

In order to give further information about the reactivity of 3-thenoyl chloride we have made use of a simplified Tommila equation (eq 2),[10,19] where k_s =

$$2.303 \log \frac{k_s}{k_u} = -\frac{e_X \delta e_C}{RT r_{1\epsilon}} - \frac{\Delta W}{RT} \qquad (2)$$

rate constant of the reaction between 3-thenoyl chloride and aniline and k_u = rate constant of the reaction between benzoyl chloride and the same aniline. The results, listed in Table III, where also the log (k_s/k_u)

TABLE III

VALUES OF LOG (k_s/k_u) AT 25° FOR THE REACTION OF 2- AND 3-THENOYL CHLORIDES WITH META- AND PARA-SUBSTITUTED ANILINES IN BENZENE[a]

Substituent	3-Thenoyl chloride	2-Thenoyl chloride[b]
H	−0.23242	−0.47250
m-CH₃	−0.27537	−0.58357
p-CH₃	−0.24008	−0.49536
m-Cl	−0.22955	−0.42997
p-Cl	−0.18306	−0.39449
m-NO₂	−0.21281	

[a] The rate constants values at 25° for the reaction of benzoyl chloride with meta- and para- substituted anilines were those from ref 9.

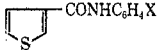(16) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(17) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

(18) G. V. Semenyuk, N. M. Oleinik, and L. M. Litvinenko, *Reakts. Sposobnost Org. Soedin.*, **4**, 760 (1967); *Chem. Abstr.*, **70**, 2931 (1969); *Zh. Obshch. Khim.*, **38**, 2009 (1968); *Chem. Abstr.*, **70**, 19475 (1969).

(19) E. Tommila, *Ann. Acad. Sci. Fennicae, AII*, No. 139 (1967).

TABLE IV

PHYSICAL CONSTANTS OF 3-THIOPHENECARBOXANILIDES[a]

CONHC₆H₄X (structure)

Registry no.	No.	X	Mp, °C	Formula	N, % Calcd	N, % Found	Ref
	1	H	141				b
41507-30-6	2	m-CH₃	126	C₁₂H₁₁NOS	6.44	6.38	
41507-31-7	3	p-CH₃	163	C₁₂H₁₁NOS	6.44	6.36	
41507-32-8	4	m-CH₃O	138	C₁₂H₁₁NO₂S	6.00	6.02	
41507-33-9	5	m-Cl	132	C₁₁H₈NOSCl	5.89	5.87	
41559-39-1	6	p-Cl	178	C₁₁H₈NOSCl	5.89	5.93	
41507-34-0	7	m-NO₂	172	C₁₁H₈N₂O₃S	11.28	11.26	

[a] All the compounds were crystallized from aqueous ethanol. [b] S. Nishimura, R. Motoyama, and E. Imoto, *Bull. Univ. Osaka Prefect., Ser. A-6,* 127 (1958); *Chem. Abstr.,* **53,** 4249 (1959).

values for the reaction of 2-thenoyl chloride with aniline[5] are reported, clearly show that the log (k_s/k_u) values for 2- and 3-thenoyl chlorides are negative, indicating that the effective electric charge of the carbonyl carbon atom of these heterocyclic acid chlorides is less positive than that of benzoyl chloride and, therefore, they are less reactive toward aniline. The log (k_s/k_u) value for 3-thenoyl chloride, less negative than that for 2-thenoyl chloride, shows that the carbonyl carbon atom of 3-thenoyl chloride is more positively charged than that of 2-thenoyl chloride, and, therefore, it is more reactive than 2-thenoyl chloride.

The slower reaction rate of 3-thenoyl chloride, in comparison with that of benzoyl chloride, can be due to the mesomeric interaction between the thiophene ring and the carboxyl group that makes it more stabilized and, therefore, less reactive than the carbonyl group of benzoyl chloride. The reactivity of 3-thenoyl chloride, higher than that of 2-thenoyl chloride, is ascribed to the lower conjugation of the thiophene ring with the carbonyl group in the 3 position than in the 2 position.[6,20]

Experimental Section

Materials.—3-Thenoyl chloride was prepared by refluxing 2 g of 3-thenoic acid (a K & K commercial product) with 10 ml of thionyl chloride for several hours. The excess of thionyl chloride was removed by water-bath distillation and the acid chloride was purified by distillation under reduced pressure, bp 204° (748 mm).[21]

The anilines were purified to constant melting point or boiling point by recrystallization or fractionation. The solvent was benzene (R. P. Carlo Erba).

Kinetic Procedure.—The reaction was followed kinetically, as previously described,[5,7] by filtering the completely insoluble aniline hydrochloride, dissolving it in water, and estimating the chloride with 0.01 *N* mercuric nitrate, using a mixture of diphenylcarbazone and bromophenol blue as indicator.[22,23]

The second-order rate constants are derived from the formula

$$k_2 = \frac{1}{2 \times 60t}\left(\frac{1}{100-X} - \frac{1}{100}\right)\frac{100}{a}$$

where t is the time in minutes, X is the percentage change, k_2 is the velocity constant (liters/mole seconds), and a is the initial concentration of the acid chloride in moles/liter.[5,7]

For the rate measurements the initial concentrations of the reactants after mixing were thus 3-thenoyl chloride 0.005 *M*, aniline 0.01 *M*. For compounds no. 2 and 3 in Table I, for which the reactions were too fast to be measured accurately at this concentration, the initial concentrations were 0.005 *M* aniline and 0.0025 *M* 3-thenoyl chloride. All compounds gave excellent second-order kinetics. All rates were run in duplicate to the last 80% completion with less than 3% deviation between the two rate constants.

At temperature other than 15 or 25°, rate coefficients were corrected for thermal expansion or contraction of the solvent. All rate constants were calculated by a least-squares computer program with an Hewlett-Packard 9100B. The activation parameters were calculated from a least-squares treatment of log k against T^{-1}.

The estimated precision is ca. ±0.5 kcal mol⁻¹ in E_A and ±2 cal mol⁻¹ °K⁻¹ in ΔS^*.

Product Analysis.—Standard solutions of the appropriate aniline and 3-thenoyl chloride in benzene were placed in a glass-stoppered bottle and maintained at the kinetic temperature until completion.

After concentration of the benzenic solution to small volume, the 3-thiophenecarboxanilide was filtered, washed free from aniline hydrochloride with water, dried, and recrystallized from aqueous ethanol. In all cases the amount of 3-thiophenecarboxanilide was ≥95% of that expected from the formation of 1 mol of anilide per mol of acid chloride consumed. Physical constants and analytical data of 3-thiophenecarboxanilides are reported in Table IV.

Registry No.—3-Thenoyl chloride, 41507-35-1; 2-thenoyl chloride, 5271-67-0.

(20) D. P. Ambler, *Phys. Methods Heterocycl. Chem.,* **II,** 312 (1963).
(21) E. Campaigne and W. M. LeSeur, *J. Amer. Chem. Soc.,* **70,** 1555 (1948).
(22) F. E. Clarke, *Anal. Chem.,* **22,** 553 (1950).
(23) A. I. Vogel, "A Textbook of Quantitative Inorganic Analysis," 3rd ed, Longmans, Green and Co., New York, N. Y., 1961, p 274.