Alkylation of Ethyl 4-Thiomorpholineacetate and Ethyl 1-(4-Methylpiperidine)acetate with Ethyl Bromoacetate

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The alkylation of ethyl 4-thiomorpholineacetate (I) and ethyl 1-(4-methylpiperidine)acetate (II) at 30, 40, 50, and 60° with ethyl bromoacetate in absolute methanol follows second-order kinetics. The quaternization of reactant I was complicated by a competing reaction of sulfonium salt formation. The k_2 and ΔE and ΔS values at 40° are 3.75 and 34.4 × 10^{-6} l./(mol sec), 16.4 and 16.7 kcal/mol, and −33.4 and −27.6 eu, respectively, for the quaternization of the I and II amines. The k_2' and ΔE and ΔS values for the sulfonium salt formation at 40° were 10.6 × 10^{-6} l./(mol sec), 18.5 kcal/mol, and −24.2 eu, respectively.

This study investigated the quaternization of ethyl 4-thiomorpholineacetate (I) and ethyl 1-(4-methylpiperidine)acetate (II) with ethyl bromoacetate in absolute methanol. The reaction rate constants, energies of activation, and entropies of activation were determined and compared to literature values for ethyl 1-piperidineacetate (III) and ethyl 4-morpholineacetate (IV).[1]

The kinetics of the reaction were determined by potentiometric titration of the bromide ion with a Sargent Model C constant rate buret capable of delivering 0.05-ml increments of titrant with an accuracy of 0.05% as determined in this laboratory. Sample preparation, sample aliquots, and experimental determinations were performed in the same manner as previously described.[1] The rate constants were obtained from the second-order reaction plots and by a CHEM/2 Fortran IV G computer program developed at Illinois State University for the treatment of second-order reaction data.

Activation energies were determined from the Arrhenius equation, and the entropies of activation were calculated from the Eyring equation.

Results

The experimental rate constant data for the quaternization reaction are summarized in Table I. The bimolecular rate constant, k_2, is defined by the familiar equation

$$\frac{dx}{dt} = k_2(a - x)^2 \tag{1}$$

where a is the initial molar concentration of ethyl bromoacetate and the tertiary amine in absolute methanol, and x is the concentration of the bromide ion.

Fractional lifetime analysis of the initial products of II by the Fortran program indicated the reaction followed second-order kinetics. Output included several estimates of the reaction order based on pairs of time intervals during which the concentrations of the reactants decreased by 25%. First and second indications of the 40° reaction order for II were calculated to be 2.3 and 1.9, respectively. These were typical data for the results obtained.

The data for II represents quaternization reactions of 59% completion at 30°, 81% at 40°, 84% at 50°, and 74% at 60°. The average percentage error in determining the concentration between three identical samples was 2.3% with a standard deviation of 2.8%. This is based on a population of 144 samples for the four different temperatures.

TABLE I

REACTION RATE CONSTANTS[a] FOR THE QUATERNIZATION

OF X NCH$_2$CO$_2$Et[b] WITH BrCH$_2$CO$_2$Et

Temp, °C (±0.1°)	$k_I \times 10^6$	$k_{II} \times 10^6$	$k_{III} \times 10^6$ [c]	$k_{IV} \times 10^6$ [c]
30	1.69 ± 0.12[e]	12.9 ± 0.5	13.2[d]	1.33[d]
40	3.75 ± 0.13	34.4 ± 0.3	33.9	4.00
50	8.43 ± 0.43	69.8 ± 1.1	80.5	10.0
60	17.6 ± 0.1	171.0 ± 1.0	150.0	23.1

Comparison of Reaction Rates

Temp, °C (±0.1°)	k_I/k_{IV}	k_{II}/k_{IV}	k_{III}/k_{IV}	k_{III}/k_{II}	k_{III}/k_I
30	1.27	9.69	9.92	1.02	7.80
40	0.937	8.63	8.46	0.986	9.04
50	0.843	6.98	8.08	1.15	9.53
60	0.762	7.41	6.46	0.888	8.82

[a] Average and average deviations of three determinations unless otherwise noted. [b] I, X = S; II, X = CHCH$_3$; III, X = CH$_2$; and IV, X = O. [c] Data from ref 1. [d] The reaction rate was calculated from the linear plot of $-\log k$ *vs.* $1/T$ from data at 20, 25, 40, 50, and 60° (ref 1). [e] Value extrapolated from the linear plot of $-\log k_2$ *vs.* $1/T$ (Figure 2).

The reaction data indicated a positive deviation from linearity at 60° after 110 hr (78% reaction). This discrepancy can be attributed to two possible sources: evaporation of the solvent and the competing methanolysis of ethyl bromoacetate which was found to be 6.68% at 60° after 240 hr and 0.55% at room temperature.[1]

The points for the 30° reaction became scattered after 1000 hr (70% reaction) but seemed to indicate a downward curvature with a 25% deviation from the initial slope after 2700 hr (82% reaction). The reaction of pyridine with isopropyl iodide in nitrobenzene has been reported to proceed to an equilibrium at 60 and 121°;[2] however, this explanation is questionable in this study because the downward curvature was not observed at the higher temperatures. Consequently, in order to calculate accurate rate constants only the linear portion of the rate curves were utilized.

Second-order plots of the data for I are shown in Figure 1. These graphs indicate complex kinetics by curving downward until approximately 30% of each reaction is complete. At this time a linear slope develops which eventually increases in the 50 and 60° reactions. The final upward trend is undoubtedly

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[1] R. C. Duty and R. L. Gurnea, *J. Org. Chem.*, **35**, 1800 (1970).

[2] K. Laidler and C. N. Henshelwood, *J. Chem. Soc.*, 858 (1938).

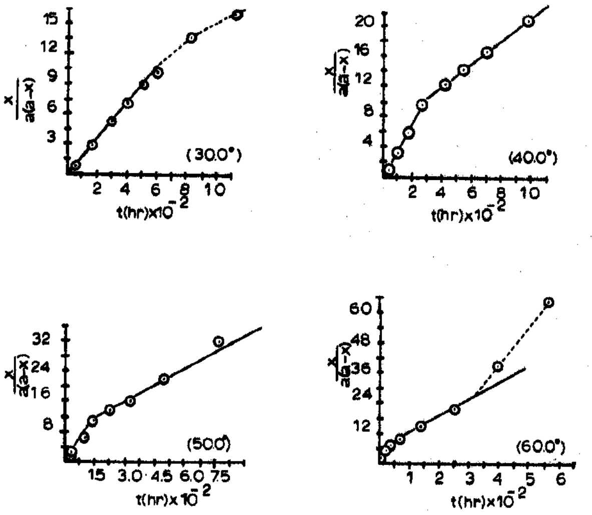
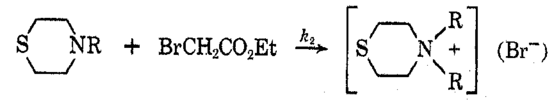
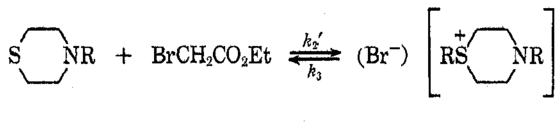


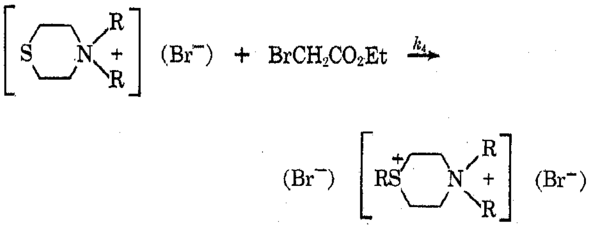
Figure 1.—Second-order kinetic plots for ethyl 4-thiomorpholineacetate with ethyl bromoacetate.

evidence for the methanolysis reaction noted previously.[1] The time required to reach the linear region of the curves is inversely related to the increase in temperature and is barely evident at the lower reaction temperature of 30°.

Since sulfides are known to form sulfonium salts with alkyl halides, the above observations suggest that the quaternization reaction of I_8 is complicated by the formation of a sulfonium salt formed from the electrophile, ethyl bromoacetate. Thin layer chromatographic analysis of the salts (see Experimental Section) recrystallized from reaction I solutions definitely established that two products were formed. The following reactions, therefore, may be written for the above observations.


(2)


(3)


(4)

Equation 4 undoubtedly occurs to a negligible extent since the positive charge produced in eq 3 would reduce the reactivity of the heterocyclic ring to further electrophilic attack. Additionally, the thin layer chromatograms revealed only two products instead of three.

Equation 3 is written as an equilibrium reaction because the literature supports a reversible reaction of sulfonium salts as reported by Balfe and coworkers.[3] They found that 1-ethylmethylphenacylsulfonium mercuritetraiodide readily racemized in an acetone solution and contributed this racemization to the following equilibria

$$(\mathrm{PhCOCH_2SMeEt})_2\mathrm{HgI_4} \rightleftharpoons 2(\mathrm{PhCOCH_2\overset{+}{S}MeEt}) + \mathrm{HgI_3^-} + \mathrm{I^-} \quad (5)$$

$$(\mathrm{PhCOCH_2\overset{+}{S}MeEt}) + \mathrm{I^-} \rightleftharpoons \mathrm{PhCOCH_2SMe} + \mathrm{EtI} \quad (6)$$

Consequently, one can justify the reversible reaction in eq 3 based on the equilibrium reaction of eq 6 above. Equation 2 is not written as a reversible reaction because aliphatic quaternary ammonium salts, as reported by Coleman and Fuoss,[4] are typically nonreversible and follow second-order kinetics in their formation.

Reactions 2, 3, and 4 enable the following rate equation to be written

$$\frac{dx}{dt} = k_2(A)(B) + k_2'(A)(B) - k_3(C)(x) \quad (7)$$

where $(x) = [\mathrm{Br}^-]$, $(A) = [\text{amine}]$, $(B) = [\mathrm{BrCH_2CO_2Et}]$, and $(C) = [\text{sulfonium ion}]$, along with the equilibrium constant equation

$$K_e = \frac{k_2'}{k_3} = \frac{(C)(x)}{(A)(B)} \quad (8)$$

Equations 7 and 8 combine to produce the second-order equation

$$\frac{dx}{dt} = k_2(A)(B) = k_2(a - x)^2 \quad (9)$$

where a is the initial concentration of A and B.

It is seen from these assumptions that, once equilibrium is established, the rate of bromide ion formation is related to second-order kinetics through eq 9. The concentration of the sulfonium ion is small during the initial stages and produces a nonlinear graph. However, once the sulfonium salt concentration has reached equilibrium, a plot of $x/a(a - x)$ *vs.* time should become linear. The experimental plots for these reactions (Figure 1) are in agreement with this hypothesis. Since the 30° reaction had evidently not reached equilibrium, only the 40, 50, and 60° reactions produced a linear region. The 30° graph represents data for 44% conversion to the quaternary salt, the 40° graph 50%, the 50° graph 61%, and the 60° graph 75%. The average percentage error between three identical samples was 1.5% with a standard deviation of 1.9%. This was based on a total population of 128. For the calculation of the rate constants for compound I in Table I, the average percentage error for the 36 samples was 1.9% with a standard deviation of 2.0%.

A more careful examination of eq 7 above reveals that at the beginning of the reaction the term $k_3(C)(x)$ is quite small and enables the rate equation to be expressed as

$$\lim_{t \to 0} \frac{dx}{dt} = (k_2 + k_2')(A)(B) \quad (10)$$

Consequently, we constructed tangents to the initial slopes of the curves in Figure 1 and calculated the term $(k_2 + k_2')$ for temperatures of 30, 40, 50, and 60°. Since we had previously determined the rate constants, k_2, from the linear portion of the curves of Figure 1, values for the reaction rate constants for the sulfonium

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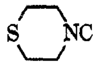
(3) M. P. Balfe, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 2554 (1930).

(4) B. D. Coleman and R. M. Fuoss, *J. Amer. Chem. Soc.*, **77**, 5472 (1955).

salt formation (k_2') could be calculated. These rate constants are given in Table II along with their limits of error.[5]

TABLE II
REACTION RATE CONSTANTS FOR THE FORMATION OF QUATERNARY AND SULFONIUM SALTS OF



S NCH₂CO₂Et WITH BrCH₂CO₂Et[a]

Temp, °C (±0.1°)	$(k_2 + k_2') \times 10^6$	$k_2' \times 10^6$
30	5.85 ± 0.01	4.16 ± 0.13
40	14.3 ± 0.6	10.6 ± 0.7
50	35.5 ± 1.3	27.1 ± 1.7
60	71.6 ± 0.9	54.0 ± 1.0

[a] See eq 2 and 3.

Since the tangents to each graph coincided with the initial experimental points in the Figure 1 graphs, experimental errors were calculated by constructing tangential graphs through the limits of error of the first experimental points of each graph.

The energies of activation (E_a) for the I and II quaternization reactions were calculated from an Arrhenius plot of the rate constants at the different temperatures. In the case of I, only three rate constants were available because of the inability to establish a reversible sulfonium salt equilibrium at 30° (see Figure 2). The values for E_a were calculated as the average of the minimum and maximum slopes drawn in such a manner that the lines passed through the areas of deviation of each point.[6] The close agreement of the activation energy of I with II, III and IV, which are given in Table III, lends additional support for the above reaction scheme.

An Arrhenius plot of $-\log k_2'$ *vs.* $1/T$ is also shown in Figure 2. A straight line resulted which helps support the interpretation of the kinetic data for the equilibration of the sulfonium salt. The datum point at 60° is slightly higher than the linear slope and is undoubtedly the result of contributions from the term, (C)(x), which was assumed to be negligible (see eq 10). The 60° second-order kinetic plot (Figure 1), also suggests the term (C)(x) would be significant during the early stages of the reaction. The limits of error were established in the same manner as for the quaternization reaction using three experimental temperatures of 30, 40, and 50°.

The entropies of activation, $\Delta S^{\ddagger}$ (Table III), were calculated by the method of Eyring[7] with the experimental errors calculated from the differential changes in the independent variables.[8]

$$\Delta S^{\ddagger} = \frac{E_a}{T} + 2.3R\left(\log k - \log \frac{k'T}{h}\right) - R$$

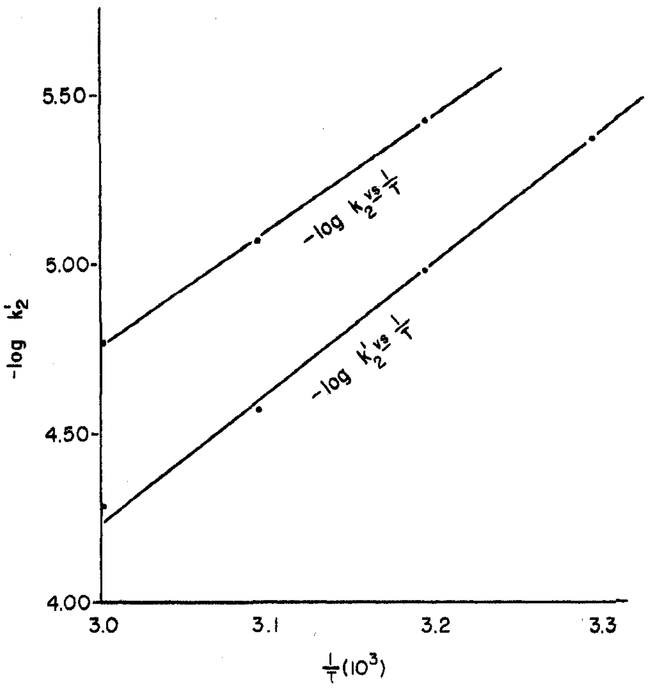


Figure 2.—Arrhenius plot for the sulfonium salt reaction (k'_2) and the quaternization reaction (k_2) with ethyl bromoacetate.

Ratios of the rate constants for I and II as compared with ethyl 1-piperidineacetate (III) and ethyl 4-morpholineacetate (IV) are given in Table I.

Discussion of Results

The reaction ratios for II and III ($k_{\text{III}}/k_{\text{II}}$), Table I, fluctuate about unity and are consistent with the postulate that the polar effect of the methyl substituent in II is equal to that of hydrogen. The inductive effect of the methyl group has traditionally been described as electron donating in solution. Such an effect is well established when the methyl group is directly bonded to an unsaturated system, but the picture is not so clear with saturated systems. Recent experimental evidence seems to support the view that the polar effect of the methyl substituent is small and electron withdrawing when bonded to an sp^3 hybridized carbon.[9-11] In a study of the dissociation constants of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids, Holtz and Stock determined σ_I of the methyl group to be −0.008.[12] Such a low value indicates the polar influence of the methyl group is minor.

In addition, the three carbon bonds separating the substituent from the nucleophilic nitrogen would also diminish the electronic effect of the methyl group. It is pertinent also to note that analyses have shown that the inductive effect is completely dampened by three carbon–carbon bonds.[13] Quadrupole resonance spectra of 1-chloroparaffins have established that the methyl group has no effect on the charge distribution of the chlorine nucleus when separated by more than two carbons.[14] Therefore, the small rate differences found

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[5] A point considered by a reviewer was that the sulfonium salt reaction would not establish equilibrium if k_2' is only three times faster than k_2. Consequently, we calculated K_e by a numerical integration of eq 7, and the computer results will appear immediately following this article in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-73-2453. Remit check or money order for $3.00 photocopy or $2.00 for microfiche.

[6] D. P. Shoemaker and C. W. Garland, "Experiments in Physical Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1967, p 34.

[7] K. J. Laidler, "Chemical Kinetics," 2nd ed, McGraw-Hill, New York, N. Y., 1965, p 90.

[8] F. Daniels, J. W. Williams, P. Bender, R. A. Alberty, and C. D. Cornwell, "Experimental Physical Chemistry," McGraw-Hill, New York, N. Y., 1962, p 398.

[9] R. C. Fort, Jr., and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 4194 (1964).

[10] V. W. Laure and J. S. Muenter, *ibid.*, **88**, 2883 (1966).

[11] H. Kwart and L. J. Miller, *ibid.*, **83**, 4552 (1961).

[12] H. D. Holtz and L. M. Stock, *ibid.*, **87**, 2404 (1965).

[13] K. Bowden, *Can. J. Chem.*, **41**, 2781 (1963).

[14] H. O. Hooper and P. J. Bray, *J. Chem. Phys.*, **33**, 334 (1960).

TABLE III

ACTIVATION ENERGIES AND ENTROPIES FOR THE QUATERNIZATION REACTION OF TERTIARY AMINES WITH ETHYL BROMOACETATE AT 40°

Amine	ΔE_a, kcal/mol	$-\Delta S$, eu	ΔE_a,[a] kcal/mol	$-\Delta S$,[a] eu
Ethyl 4-thiomorpholineacetate (I)	16.4 ± 0.4	33.4 ± 0.8	18.5 ± 1.1	24.2 ± 1.3
Ethyl 1-(4-methylpiperidine)acetate (II)	16.7 ± 0.3	27.6 ± 1.0		
Ethyl 1-piperidineacetate (III)[b]	17.2	26.0		
Ethyl 4-morpholineacetate (IV)[b]	18.1	27.6		

[a] Sulfonium salt formation. [b] Reference 1.

above ($k_{\text{III}}/k_{\text{II}}$) cannot be assigned to a polar effect of the methyl substituent.

The reaction rate ratio for I and III ($k_{\text{III}}/k_{\text{II}}$) is 9.04 at 40° and remains essentially constant with temperature. This trend is in agreement with an inductive model for the thioether group which exhibits electron-withdrawing ability. Taft's inductive constant, σ_{I}, is reported as +0.19 for $-SCH_3$,[15] and Hall reported that the pK_a of thiomorpholine is 2.31 units less than for piperidine.[16]

The fact that the rate constants of IV are predominantly greater than those of I ($k_{\text{I}}/k_{\text{IV}} < 1$) indicates that other factors in addition to an inductive effect are operative. The Taft inductive constants for $-OCH_3$ and $-SCH_3$ are +0.27 and +0.19, respectively,[15] and the pK_a for thiomorpholine and morpholine are 9.00 and 8.36, respectively.[16] These data suggest that the ratio ($k_{\text{I}}/k_{\text{IV}}$) should be greater than one, which is only true for the 30° reaction.

One of the original purposes of this research was to substantiate a hypothesis that the temperature-dependent ratio, $k_{\text{III}}/k_{\text{IV}}$, was caused by a reversed substituent effect.[17] The previous study[1] explained the smaller ratios at higher temperatures as the result of an increasing contribution of the field effect to the total polar effect of the oxygen atom. Since a greater percentage of the boat conformation of the six-membered ring occurred at higher temperature, the direct electrostatic repulsion of the nitrogen electron cloud by oxygen would increase and, consequently, enhance the rate of quaternization for IV over that for II and III. If sulfur replaced oxygen in the six-membered ring, this would lessen the reversed substituent effect by raising the activation energy of the ring inversion.

It is well known that six-membered rings exist in equilibrium mixtures of boat and chair conformations with the chair form the more stable.[18] When one substitutes a sulfur atom for a carbon atom in a carbocyclic ring, the barrier to ring inversion is increased whereas for oxygen the opposite is true.[19] In addition, it is also known that replacement of ring hydrogens with an alkyl substituent raises the barrier of ring inversion.[20] Therefore, it is not unreasonable to assume that at any one temperature the concentration of boat conformers for III and IV would exceed those for I and II.

One can observe from Table I that the ratio $k_{\text{III}}/k_{\text{I}}$ does not change appreciably with temperature whereas the ratio $k_{\text{I}}/k_{\text{IV}}$ decreases by 40% from 30 to 60° and the ratio $k_{\text{III}}/k_{\text{IV}}$ has decreased 35%. These decreases indicate the reaction rate of the oxygen analog, k_{IV}, is increasing faster with temperature than the reaction rate for the sulfur analog, k_{I}, and the methylene analog, k_{III}. If the larger size of the atom is decreasing the boat conformer concentration relative to that for the oxygen heterocylic ring, this decrease in reaction rate ratio is understandable if one examines the field effect model. In the field effect model of IV,[1] the ether dipole moment in the boat conformation enhances the reaction rate (k_{IV}) in parallel with a temperature increase. The sulfur dipole for I operates predominantly from a chair conformation and, consequently, its rate enhancement ability with temperature does not increase as is reflected in the reaction rate ratios. These conclusions are certainly not unequivocal proof for the field effect, but it does impart a reasonable explanation for the reaction ratios.

The activation energies reported for I and II (Table III) are in agreement with those reported in the earlier study.[1] The entropy value for I (−33.4 eu) is 23% more negative than the average of the three other amines. This entropy term is undoubtedly more negative because of the steric interference that results from the heterosulfur atom and the two *N*-carbethoxymethyl groups in the final product. The entropy term is even more enhanced for the sulfur atom in I than the oxygen atom in IV because of the difference in sizes of the two atoms (S = 1.04 Å and O = 0.66 Å).[21]

The rate constants, activation energy, and entropy for the sulfonium salt formation, to our knowledge, are the first to be reported for this type of reaction. Consequently, no comparison of these parameters can be made with literature values. The only comparison that appears to be reasonable is the comparison between the quaternization reactions of this study. Compound IV makes a reasonable model because it has an oxygen atom in the 4 position for the quaternization reaction, and a tertiary nitrogen in the 4 position of compound I for the sulfonium salt reaction. For these two compounds, surprisingly close agreement exists between the activation energies and entropies whereas the rate constants are three orders of magnitude larger for the sulfonium salt formation.

Experimental Section

Compound I, bp 83° (0.5 mm), was prepared by reacting $BrCH_2CO_2Et$ (0.068 mol) (Eastman White Label) with one molar excess of thiomorpholine (0.133 mol) in refluxing CH_3CO_2Et for 1 hr. Fraction distillation yielded 7.9 g (28%) of I. Compound I was further purified by preparative vpc on a Beckman GC-2A chromatograph with a 3 ft × $^5/_8$ in. o.d. column packed with 10% SE-30 substrate on a Chromosorb P (60/80 mesh) sup-

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[15] P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

[16] H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2570 (1956).

[17] R. Golden and L. M. Stock, *ibid.*, **88**, 5928 (1966).

[18] J. B. Hendrickson, *ibid.*, **83**, 4537 (1961).

[19] F. G. Riddel, *Quart. Rev., Chem. Soc.*, **21**, 364 (1967).

[20] E. L. Eliel, N. L. Allinger, S. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1967, p 42.

[21] F. A. Cotton and G. Wilkenson, "Advanced Inorganic Chemistry, 2nd ed, Interscience, New York, N. Y., 1966, p 103.

port. Purity of the sample as checked by vpc was 99%. The ir spectrum confirmed the structure by comparison with the ir spectrum of compound IV:[1] ir ν (film) 2945, 2840, 1740, 1460, 1425, 1190, 1040, 965, and a weak 663-cm^{-1} band (C–S–C) (lit.[22] 658 cm^{-1}); nmr ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.3 Hz, OCH_2CH_3), 2.75 (m, 8 H, methylene ring protons), 3.35 (s, 2 H, NCH_2CO_2Et), and 4.18 ppm (m, 2 H, J = 7.3 Hz, OCH_2CH_3).

Thiomorpholine was prepared by the $LiAlH_4$ reduction of thiomorpholin-3-one (Aldrich). A 105-g (0.896 mol) sample of thiomorpholin-3-one was slowly shaken into an ether solution of 48.5 g (1.28 mol) of $LiAlH_4$ (Ventron). After the excess $LiAlH_4$ was decomposed and the solid was filtered, the solution was rotary evaporated and vacuum distilled to yield 14.0 g (14.6% yield) of thiomorpholine, bp 82–83° (2.9 mm).

Compound II, bp 51° (0.2 mm), was prepared by adding $BrCH_2CO_2Et$ (0.302 mol) (Aldrich) to an excess of 4-methylpiperidine (0.510 mol) (Aldrich) dissolved in CH_3CO_2Et. Fractional distillation of the mother liquor produced a 75% yield of product. Preparative gas chromatographic analysis as previously described for compound I produced 7.2 ml of product of 99.7% purity. The ir spectrum compared favorably with that for compound III:[1] ir ν (film) 2940, 2820, 1740, 1460, 1380, 1190, 990, and 830 cm^{-1}; nmr ($CDCl_3$) δ 1.30 (m, 11 H, ring hydrogens and methyl hydrogens), 2.70 (m, 4 H, ring hydrogens adjacent to nitrogen, 3.35 (s, 2 H, NCH_2CO_2Et) and 4.25 (m, 4 H, J = 7.0 Hz, OCH_2CH_3).

Kinetic Procedure.—Initial concentration for the amines and $BrCH_2CO_2Et$ was 0.0500 M. Three independent samples of each compound were prepared and studied at the same time. Sample preparations and potentiomatic titrations were similar to the procedures as reported in the previous study.[1]

Reaction Products *via* Tlc.—In order to establish that two products were formed in the quaternization of I, a 50-ml sample of 0.0500 M reaction solution was heated at 60° for 427 hr. After removal of the solvent the product was recrystallized into fine white crystals from a solvent of ethyl acetate and ether (2:1) containing a small amount of methanol. The crystals (60-μg spots) were chromatographed on 4 × 7^3/$_4$ in. glass plates coated with Silicar TLC 7G (Mallinckrodt). The mobile phase was absolute CH_3OH, and the plates were developed in an I_2 chamber. The R_f values for the two compounds were 0.64 ± 0.03 and 0.57 ± 0.02 (average and average deviation for two plates containing three spots per plate).

A similar tlc analysis was made from the reaction product of II. However, only one compound was resolved with R_f value of 0.51 ± 0.03.

Registry No.—Compound I, 39981-80-1; compound II, 39981-81-2; ethyl bromoacetate, 105-36-2; thiomorpholine, 123-90-0; thiomorpholin-3-one, 20196-21-8; 4-methylpiperidine, 626-58-4.

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[22] E. A. Allen, N. P. Johnson, O. T. Rosevear, and W. Wilkinson, *J. Chem. Soc. A*, 2137 (1970).

Reaction Kinetics of 2-Thiophenesulfonyl Chloride with Anilines in Methanol

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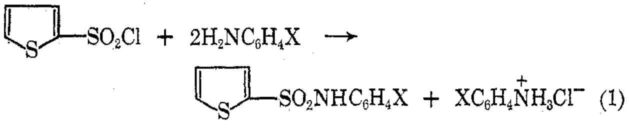
The reaction rate constants of 2-thiophenesulfonyl chloride with some substituted anilines have been measured in methanol at different temperatures. The reaction is second order overall and pseudo first order with respect to each reactant. The rate constants value is greater with electron-donating substituents, while it is lower with electron-withdrawing groups. The activation parameters and the slopes of the Hammett (−2.25) and Brønsted (0.53) plots are similar to those of the reaction of benzenesulfonyl chloride with anilines, showing that the reaction mechanism is the same for the two substrates, although 2-thiophenesulfonyl chloride reacts more slowly. The Tommila equation points out that the sulfur atom, the reaction center, is less positively charged, and thus less reactive toward nucleophiles, than that of benzenesulfonyl chloride.

Previously the mechanism of the reaction of 2-thenoyl chloride with some meta- and para-substituted anilines was investigated.[1] Following this research we report in this paper the kinetics of the reaction of 2-thiophenesulfonyl chloride with a series of substituted anilines to verify the reactivity in comparison with the analogous reaction of benzenesulfonyl chloride, which have been widely studied recently.[2–7]

The reaction between 2-thiophenesulfonyl chloride and aniline in methanol takes place quantitatively according to eq 1.



X = H, m-CH_3, p-CH_3, m-OCH_3, p-OCH_3, m-Cl, p-Cl

The rate of reaction 1 was measured by continuous titration of the acid produced (see Experimental Section).

We found that the reaction of 2-thiophenesulfonyl chloride with anilines follows second-order kinetics, first order with respect to each reactant.

By the comparison of the slopes of the Hammett and Brønsted plots it seems that the reaction mechanism is the same as for benzenesulfonyl chloride and anilines,[2] although the rates observed with 2-thiophenesulfonyl chloride are lower, probably because of the thiophene conjugative effect on the sulfonyl group which also makes the sulfur atom less electrophilic than that of benzenesulfonyl chloride as the Tommila equation shows.

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