Polarographic Study Of Heterocyclic Compounds.

Citation

LATSHAW, DAVID RODNEY. *Polarographic Study Of Heterocyclic Compounds.* 1966, https://preserve.lehigh.edu/lehigh-scholarship/graduate-publications-theses-dissertations/theses-dissertations/polarographic-0.

LATSHAW, David Rodney, 1939–
POLAROGRAPHIC STUDY OF HETEROCYCLIC
COMPOUNDS.

Lehigh University, Ph.D., 1966
Chemistry, analytical

University Microfilms, Inc., Ann Arbor, Michigan

POLAROGRAPHIC STUDY OF HETEROCYCLIC COMPOUNDS

by
Carney
David R. Latshaw

A Dissertation
Presented to the Graduate Faculty
of Lehigh University
in Candidacy for the Degree of
Doctor of Philosophy

Lehigh University
1966

This dissertation is respectfully submitted to the Graduate Faculty of Lehigh University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

David R. Latshaw

David R. Latshaw

CERTIFICATE OF APPROVAL

Approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Sept. 15, 1966
Date

James Diefenderfer
Professor in Charge

Special committee directing the work of Mr. David R. Latshaw.

James Diefenderfer
A. James Diefenderfer, Chairman

Velmer B. Fish
Velmer B. Fish

William E. Ohnesorge
William E. Ohnesorge

Robert S. Sprague
Robert S. Sprague

Thomas E. Young
Thomas E. Young

ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Dr. A. James Diefenderfer for his guidance and advice throughout the course of this research. Thanks are also due members of his special committee, especially Dr. Velmer B. Fish and Dr. Thomas E. Young, for their many helpful discussions and suggestions. Appreciation is also extended to Mr. James A. Dougherty for the helpful discussions regarding this work.

Gratitude is expressed to Lehigh University, Institute of Research, for their financial support.

Thanks are also due to the author's parents without whose moral and material support over many years he would not have undertaken the challenge of advanced study.

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ABSTRACT

A large number of substituted bromothiophenes were studied polarographically in an attempt to correlate the polarographic half-wave potentials with the chemical reaction parameters. In correlating the half-wave potentials for a series of compounds measured under similar experimental conditions, the variation in half-wave potential was dependent upon the variation in electron distribution of the molecules. These changes were induced by placing substituents with different electron densities at different ring positions relative to the polarographically reducible group: the carbon-bromine bond. Data representing this effect have been obtained by studying the polarograms of 66 bromothiophene and 13 bromofuran compounds. From these data, substituent constants which were applicable in the thiophene and furan heterocyclic system have been calculated. These data served to provide a means whereby the half-wave potentials for polysubstituted bromothiophenes could be predicted. A study of the reaction constants provided an insight into the mechanism of the reduction process. The sign of these reaction constants indicated that the mechanism of the potential determining step was a nucleophilic one.

All compounds gave reduction waves; the number of waves being equal to the number of bromine atoms per molecule. Compounds substituted by bromine in the α position were more easily reduced than those with bromine in the β position.

All bromines (including adjacent ones) were reduced in a stepwise manner.

The polarographic study revealed a significant analytical application because it provided a method whereby the percentage of one bromothiophene isomer in another could be determined with an average deviation of less than 2%.

INTRODUCTION

The Hammett relationship (1,2) has been applied to a vast number of organic reactions. With meta and parasubstituted benzenoid reactants, the correlations have been remarkable. In the Hammett equation,

$$\log\left(K/K_0\right) = \rho\sigma \qquad (1)$$

sigma (σ), the substituent constant, is a measure of the electron-donating or electron-withdrawing power of the substituent. Rho (ρ), the reaction constant, is a measure of the sensitivity of the equilibrium constant to changes in the sigma value of the substituent, and K and K_0 are the equilibrium constants (or rate constants) of the substituted and unsubstituted reactants respectively.

Attempts have been made to correlate changes in polarographic half-wave potentials with structural changes because it is accepted (3, 4) that effects of substituents on reactivity are basically electronic in nature. Data have been collected by Bennett and Elving (5) which generally support the view that changes in polarographic half-wave potentials with structure are due to both electronic and steric effects. Zuman (6) has used polarography and a general equation from Taft (7) to determine the polar, steric, and mesomeric effects of substituents in the benzenoid system. Zuman (8) further made an attempt to correlate the shifts of the half-wave potentials of monocyclic heterocyclic compounds with structural changes. He found that the reduction on the side chain may be influenced by substituents on the ring, by the kind of heteroatom, by the size of the ring and, finally, by substituents on the side chain itself. However, very scanty experimental data (due to a lack of availability of some heterocyclic compounds) has imposed limitations on these treatments.

Because of the remarkable correlations obtained from the benzene series, there have been many attempts to apply these benzenoid sigma values to other systems, including thiophene. Recently Imoto et al. (9) have investigated the dissociation constants and the rates of alkaline hydrolysis of several substituted thiophenes. They found that sigma and rho values from parasubstituted benzenes could be used for 2,5-disubstituted thiophenes. Similar conclusions were drawn by Tirouflet and Chané (10) when studying the electrochemical reduction of substituted 2-nitrothiophenes. The changes in half-wave potential were correlated with sigma values taken from the benzene system. However, the experimental information was too scanty to allow any general conclusions to be drawn from this work.

There are a number of instances in the heterocyclic literature when use of sigma values from the benzene system has been ruled out. For instance, Gronowitz (11), who considers correlations of nuclear magnetic resonance (NMR) data with sigma values, has indicated that such general applicability is not justified. He studied the similarity of the chemical shifts of the para hydrogen in the benzene series with the shift of the 5-hydrogen in 2-substituted thiophenes. He found that the nitro group had similar effects on the electronic distribution of the two aromatic nuclei in question. However the amino group and the methoxy group had entirely different effects on the reactivity of the two aromatic nuclei in question.

Hartough (12) presents chemical evidence which shows that ortho positions in the thiophene system are not the same as the ortho positions in the benzene system. He has carried out nitrations of bromothiophenes by the HNO_3-H_2SO_4 method when both the 2- and the 5- positions were blocked. Nitration of 2,5-dibromothiophene, 2,5-dichlorothiophene or 2,5-dimethylthiophene proceeded with considerable ease in all cases to the 3,4-dinitro-2,5-disubstituted thiophene. This is contradictory to benzene chemistry, in which ortho-nitro groups are formed by substitution only in minute traces or not at all. In this respect, Steinkopf (13) considers that the 3,4- positions of thiophene should be compared to meta positions in the benzene nucleus.

Due to the inequality of reactivity of ring hydrogens in thiophene (namely the 2 hydrogen is much more reactive than the 3 hydrogen), the sigma values in a thiophene would not be expected to be the same as the similar values in the benzene series. It can be concluded that the ortho, meta, and para positions in thiophene are not always the same as ortho, meta, and para positions in benzene. Therefore it would not be rational to rely on σ_{meta} and σ_{para} values obtained from the benzenoid system to always be the same as the σ_{thio} values for the corresponding positions in thiophene.

The purpose of this work is to determine experimentally $\sigma_{2\text{-thio-N-R}}$ values. This value is the substituent constant for an R- substituent at the N- position while the reactant group is at the 2- position in the thiophene ring. These sigma values will then be applicable to thiophene chemistry. A polarographic study of bromothiophenes and correlation of the data by means of the Hammett equation would have the following purposes:

1. To experimentally determine sigma values directly on the thiophene system.
2. To determine rho values with the expectation that they will help elucidate the reaction mechanism.
3. To quantitatively separate polar, steric, and resonance effects, where possible.

THEORY

Polarography

Polarography may be defined as an electrochemical technique in which a microelectrode, usually a dropping mercury electrode, is polarized with respect to a reference electrode by applying a direct voltage. The current which results from the oxidation or reduction of the electroactive species in solution is measured as a function of the applied voltage. The fundamentals, techniques, instrumentation, and applications of polarography can be found in standard monographs (14-18).

The usual polarographic sign conventions will be used in this work. This is the I.U.P.A.C. convention in which reductions usually occur at potentials negative to a saturated calomel reference electrode (S.C.E.) and give rise to cathodic currents which are designated positive. Oxidations usually occur at potentials positive to the S.C.E. and give rise to anodic currents which are designated minus. This work deals exclusively with reductions and when it is stated that compound A is more easily reduced than compound B, or that A has a lower half-wave potential than B, this means that compound A reduces at a less negative potential than compound B (*i.e.*, less energy is necessary to effect the reduction).

In polarography of simple metal ions, reduction is a gain in electrons, and the reduction occurs as a change in the oxidation state of the electroactive species similar to the equation

$$Fe^{+3} + e^{-} \rightleftarrows Fe^{+2} \qquad (2)$$

In the reduction of organic substances, hydrogen ion is often involved in the electrode reaction. In a general case in which the oxidant and reductant are both uncharged molecules, the electrode reaction may be written

$$R + mH^{+} + ne^{-} \rightleftarrows RH_{m} \qquad (3)$$

When speaking of the reduction of an organic halogen compound at the dropping mercury electrode, reduction is used in the sense of a substitution of halogen by hydrogen according to the equation

$$RX + H^{+} + 2e^{-} \rightarrow RH + X^{-} \qquad (4)$$

Although H^{+} is included in Equation (4), the reduction of organic halogen compounds is usually pH independent. This general mechanism has been confirmed for a number of halogen compounds by von Stackelberg (19) using large scale controlled potential electrolysis. It should also be noted that most electrochemical reactions of organic compounds proceed in one direction with very little, if any, contribution to the overall process by the reverse reaction. These reactions are called totally irreversible.

Irreversible polarographic waves (where there is no contribution from the back reaction) have been treated theoretically by Delahay (20). The results of these treatments relate the half-wave potential of an irreversible process to the logarithm of the rate constant of the heterogeneous electrode process $k^{o}_{f,h}$, according to Equation (5)

$$E_{1/2} = \frac{RT}{\alpha nF} \ln 0.87\ k^{o}_{f,h}\sqrt{t/D} \qquad (5)$$

where t is the drop time in seconds and D is the diffusion coefficient in cm^2/sec. The rate constant $k_{f,h}$ for a cathodic process varies with the electrode potential and the rate constant of the electrode process according to the equation

$$k_{f,h} = k^{o}_{f,h} \exp\left(\frac{-\alpha n_a FE}{RT}\right) \qquad (6)$$

where n_a is the number of electrons involved in the activation step and α is the transfer coefficient.

The transfer coefficient is defined as the fraction of the applied potential which favors the rate of the forward reaction. It may also be defined as the fraction of the total energy which acts to increase the rate of the cathode reaction (21). By plotting **E** versus log (i/i_d-i), where i is the current at a voltage, E, and i_d is the limiting diffusion current, a straight line is obtained. The slope of this line is equal to $\frac{0.059}{\alpha n}$ where n is the number of electrons involved in the rate-controlling step of the reduction. The value of αn must remain constant if the Hammett sigma values are to be correlated with half-wave potentials of irreversible systems. If a series of similar compounds has a constant αn value, it is assumed that the same reduction mechanism is operative throughout the series.

The above method of determining αn is time consuming. However it can also be shown (22) that

$$E_{3/4} - E_{1/4} = \frac{-.05172}{\alpha n} \tag{7}$$

The latter method is used in this work because of its simplicity.

Hammett Equation

Hammett observed that plots of the logarithm of the rate or equilibrium constant for the reactions of a series of meta and parasubstituted derivatives of benzene versus the logarithm of the ionization constants for the correspondingly substituted benzoic acids in water at 25°C are very frequently linear (1). The equation of this straight line is

$$\log K = \rho \log K' + C \tag{8}$$

where K and K' are the ionization constants for an aromatic acid (*i.e.*, phenylacetic acid) and a benzoic acid, each bearing the same substituent. The slope of the line is ρ and C is the intercept. When hydrogen is used as the substituent, Equation (8) becomes

$$\log K_o = \rho \log K_o' + C \tag{9}$$

where K_o and K_o' are the ionization constants of the aromatic acid (*i.e.*, phenylacetic acid) and benzoic acid respectively.

Subtraction of Equation (8) from Equation (9) gives

$$\log \frac{K}{K_o} = \rho \log \frac{K'}{K'_o} \qquad (10)$$

$\log \frac{K'}{K'_o}$ is defined as sigma (σ), a constant for a given substituent. K' is the ionization constant for a substituted benzoic acid in water at 25°C and K'_o is the ionization constant for benzoic acid itself. Thus equation (10) can be written as

$$\log \frac{K}{K_o} = \rho \sigma \qquad (11)$$

The sigma values are associated with the effect of the substituent on the charge density of the carbon atom which bears the side-chain reaction center. Both classical electrostatic (inductive) and resonance interactions of the substituents with the benzene ring are reflected in sigma values (23). A positive value of sigma denotes net electron-withdrawal relative to the hydrogen atom, and a negative value denotes the opposite.

The reaction constant, rho (a property of the process involved), is a measure of the sensitivity of the equilibrium in question to a change in electron density at the reaction center.

Since the linear relationship involves the logarithm of equilibrium constants, this implies that the substituents exert their influence through changes of potential energy. Therefore equation (11) is referred to as a linear free energy relationship.

The Hammett equation can be applied to rate constants as well. The Hammett relationships are equivalent to the existence of linear relationships between the free energies (of reaction or of activation) for different series of reactions. The free energy of activation, $\Delta G^{\ddagger}$, (increase in Gibbs free energy in the passage from the initial state to the activated state) is related (24) to the rate constant $k_{f,h}$ by the equation

$$k_{f,h} = \frac{k_B T}{h} e^{\frac{-\Delta G^{\ddagger}}{RT}} \tag{12}$$

where $k_{f,h}$ is the reaction rate constant, h is Planck's constant and k_B is the Boltzman constant. The logarithm of the rate constant is given by

$$\log k_{f,h} = \log \frac{k_B T}{h} - \frac{\Delta G^{\ddagger}}{2.303\ RT} \tag{13}$$

Since the Hammett equation can be written in the form,

$$\log k = \log k_o + \rho\sigma \tag{14}$$

Equation (14) may be rewritten as,

$$\Delta G^{\ddagger} = \Delta G_o^{\ddagger} - 2.303\ RT\,\rho\sigma \tag{15}$$

Equation (15), with a particular value of ρ, applies to any reaction involving a reactant having a series of substituents. For a second series of homologous reactions, having the reaction constant ρ',

$$\Delta G'^{\ddagger} = \Delta G_o'^{\ddagger} - 2.303\ RT\,\rho'\sigma \tag{16}$$

Equation (15) and (16) may be written as

$$\frac{\Delta G^{\ddagger}}{\rho} = \frac{\Delta G_0^{\ddagger}}{\rho} - 2.303\ RT\sigma \qquad (17)$$

and

$$\frac{\Delta G'^{\ddagger}}{\rho'} = \frac{\Delta G_0'^{\ddagger}}{\rho'} - 2.303\ RT\sigma \qquad (18)$$

Subtraction gives

$$\frac{\Delta G^{\ddagger}}{\rho} - \frac{\Delta G'^{\ddagger}}{\rho'} = \frac{\Delta G_0^{\ddagger}}{\rho} - \frac{\Delta G_0'^{\ddagger}}{\rho'}$$

which may be written as

$$\Delta G^{\ddagger} - \frac{\rho}{\rho'}\Delta G'^{\ddagger} = \text{constant} \qquad (20)$$

Thus, there is a linear relationship between the free energies of activation for one homologous series of reaction rates and those for another.

Since Equation (11) is a linear free energy relationship, a technique which measures changes in free energy (of reaction or activation) can be used to determine sigma values. Changes in polarographic half-wave potentials are used here to measure the changes in reaction rates of substituted bromothiophenes. It is known that the half-wave potentials of reversible systems are proportional to the logarithmic values of the corresponding equilibrium constant. On the other hand, the half-wave potential of an irreversible process (25) is proportional to the logarithm of the rate constant of the heterogeneous electrode process $k_{f,h}^{o}$, as shown earlier in Equation (5). The condition necessary for the linear relationship between the half-wave potential and $\ln k^{o}_{f,h}$ is that T and α, the transfer coefficient, remain constant. In this work, these conditions have been fulfilled for numerous substituted bromothiophenes.

The Hammett equation is modified to accommodate polarographic half-wave potentials according to Equations (21) and (23). If the half-wave potential of the unsubstituted substance (denoted E_H) is compared with the half-wave potential of a similar compound containing a substance X (denoted E_x), then the difference is characterized as $\Delta E_{1/2}$. Equation (5) has shown that $E_{1/2}$ is related to $k^{o}_{f,h}$, therefore

$$E_x - E_H = \Delta E_{1/2} \approx \Delta \ln k^{o}_{f,h} = \ln \frac{(k^{o}_{f,h})_X}{(k^{o}_{f,h})_H} \qquad (21)$$

Equations (11) and (14) have shown

$$\log \frac{K}{K_o} = \log \frac{k}{k_o} = \rho \sigma \qquad (22)$$

Substituting Equation (22) into Equation (21) gives

$$\Delta E_{1/2} = \rho \sigma \qquad (23)$$

Equation (23) shows a relationship between changes in half-wave potentials with rho and sigma. This is the Hammett equation modified for polarographic half-wave potentials. The above equation has been verified a number of times (6, 8,10,26-38) by different investigators. The sigma value is a measure of the influence of the substituent on the half-wave potential of an irreversible electrode process. This then is the relative change of the forward rate constant (i.e., free activation energy) between the reactant state and the transition state.

In this work, the rho value will refer exclusively to the reaction of groups attached to the 2 position on the thiophene ring. Correspondingly, the sigma values for electrochemically inactive substituents (R) at various ring positions (N) will be reflected in changes in the half-wave potentials. Equation (23) can be rewritten in the following form

$$\Delta E_{1/2} = \rho_{\text{2-thio-Br}} \sigma_{\text{2-thio-N-R}} \qquad (24)$$

For polarographic reduction of bromothiophenes, the reaction constant, $\rho_{\text{2-thio-Br}}$, indicates the susceptibility of the reduction of the carbon to bromine bond in the 2 position to the effects of substituents in certain positions. The value of this constant depends on the kind of the polarographically active group, on its position relative to the heteroatom, on the type of the heterocyclic ring, and on reaction conditions. It is independent of the kind and position of the substituent R. The sigma value on the other hand depends on the kind of substituent, on its position relative to the reactant group, on its position relative to the heteroatom, and on the type of heteroatom.

Acid Dissociation

In order to establish a consistent set of sigma values, it was necessary to determine the acid dissociation constants for a number of substituted 2-thenoic acids. The acid dissociation constants of weak acids are determined by titrating them with a strong base. The pKa value is measured from the titration curve by measuring H^+ concentration at one-half the neutralization point (39, 40). Since

$$K_A = \frac{[H^+]\ [A^-]}{[HA]}, \qquad (25)$$

at one-half the neutralization point, $[A^-] = [HA]$, therefore

$$K_A = [H^+] \quad \text{or} \quad pKa = pH \qquad (26)$$

Dissociation constants of substituted and unsubstituted aromatic acids were used by many authors to calculate sigma values. Tables of sigma values established this way and other ways are found in the literature (1, 2, 23, 41-43). These sigma values vary slightly depending upon the method by which they were determined. Jaffé (42) estimated the overall precision of this correlation as only ± 15%.

Electronic Structure

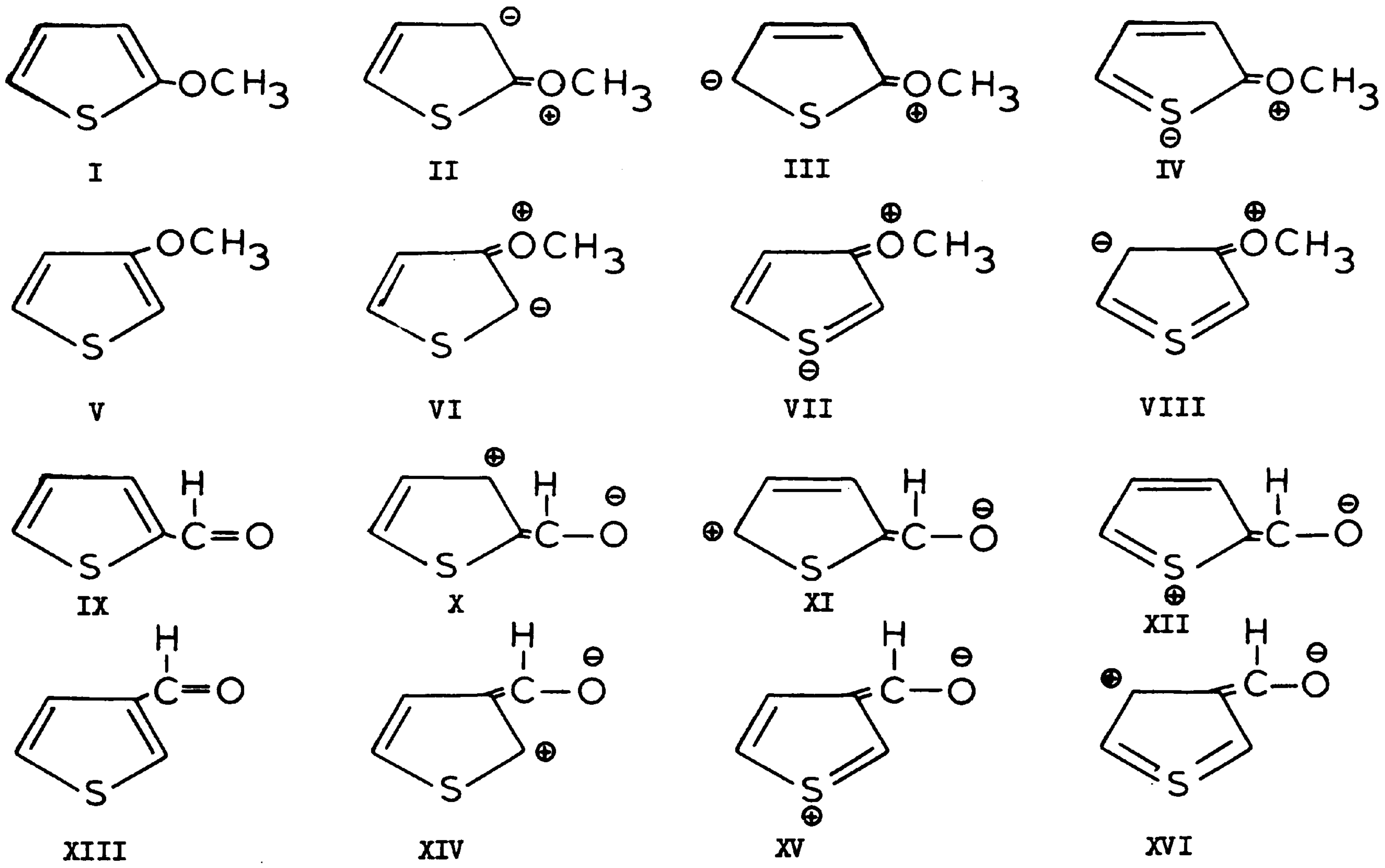
It has been pointed out earlier that effects of substituents on reactivity are basically electronic in nature. Chemists have devised a number of methods verbalizing upon electronic structure; one of the more preferred methods invokes the terms mesomeric and inductive effects. The mesomeric effect (designated ± M) controls the orientation of entering groups within the ring. By convention +M is established to be any group that supplies electrons to the ring through its resonating forms. Any group whose resonance forms act to pull electrons from the ring is designated -M. Figure 1 presents some of the resonance forms in thiophene when a -I-M group (aldehyde) or a -I+M group (methoxy) are situated at the 2 or 3 position. In Figure 1 structures IV, VII, VIII, XII, XV and XVI have been assumed (94) to have little influence because of the double-bonded sulfur.

The inductive effect (designated ±I) is a measure of the electronegativity of the substituent group. This effect accounts for the activating or deactivating influence of different groups on the ring. Groups that withdraw electrons from the ring are designated -I, while groups that supply electrons to the ring are designated +I.

Thiophene and benzene are iso-π-electronic (104). The resonance energy of benzene is 36 kcal/mole while that of thiophene is 29 kcal/mole (95). Therefore it can be concluded that the electrons in thiophene are more localized, and the resonance forms will not be as predominant in thiophene as they are in benzene. This will be verified in this work.

Figure 1

Resonance Forms of Substituted Thiophenes



EXPERIMENTAL

Chemicals

Tetramethylammonium chloride was obtained from J. T. Baker Chemical Company,(Phillipsburg, N. J.),and recrystallized twice from methanol. Lithium perchlorate was obtained from G. Frederick Smith Chemical Company,(Columbus, Ohio), and recrystallized from water. Phenyllithium used in these preparations was obtained from Alpha Inorganics Inc.

The following compounds used as starting materials in syntheses or as final reducible compounds were purchased from Marstan Chemical Laboratory,(Bethlehem, Penna.):

2-Acetyl-5-bromothiophene
3-Bromothiophene
2,5-Dibromothiophene
2-Iodothiophene
2-Methoxythiophene
2-Methylthiophene
3-Methylthiophene
2-Ethylthiophene
2-Propylthiophene
2-Chlorothiophene
2,5-Dichlorothiophene
2-Thiophenecarboxaldehyde
3-Thiophenecarboxaldehyde
2-Thenoic Acid
2,3,5-Tribromothiophene
Tetrabromothiophene

3-Thenoic acid was obtained from K&K Laboratories Inc., (Plainview, N. Y.).

2,3-Dibromothiophene was obtained from City Chemical Corporation,(New York, N. Y.).

The following compounds used as starting materials in synthesis or as polarographically reducible compounds were obtained from E. I. DuPont de Nemours & Company, Organic Chemicals Department,(Wilmington, Del.):

5-Bromo-2-dodecylthiophene
5-Dodecyl-2-thenoic Acid
2-Isopropylthiophene
5-Bromo-2-isopropylthiophene
5-Bromo-2-thenoic Acid
Methyl 5-bromo-2-thenoate
5-Isopropyl-2-thenoic Acid
5-Methyl-2-thenoic Acid
2-Thenoic Acid
5-Chloro-2-thenoic Acid
3,4-Dibromo-2,5-dimethylthiophene
3,4-Dibromothiophene-2,5-dicarboxylic Acid
2-Tert.-amylthiophene
5-Isooctyl-2-thenoic Acid
5-Bromo-2-isooctylthiophene
2-Tert.-octylthiophene
5-Bromo-2-tert.-octylthiophene
5-Bromo-2-tert.-butylthiophene
3-Bromo-2-chlorothiophene
3-Bromo-2,5-dichlorothiophene
3,4-Dibromo-2-chlorothiophene

The following compounds were furnished by Dr. Edward Amstutz, Lehigh University:

4,5-Dibromo-2-thenoic Acid
2-Furoic Acid
5-Methoxy-2-furoic Acid
5-Bromofuran-2,4-dicarboxylic Acid
5-Hydroxymethyl-2-furoic Acid
Methyl 4,5-dibromo-2-furoate
Sodium 5-bromo-2-furoate
Dimethyl 5-bromofuran-2,4-dicarboxylate
Allyl 5-bromo-2-furoate
5-Bromo-2-furoic Acid
5-Nitro-2-furoic Acid
5-Chloro-2-furoic Acid
5-Carbomethoxy-2-furancarboxylic Acid
Ethyl 5-bromo-2-furoate
Methyl 5-bromo-2-furoate
5-Nitro-2-thenoic Acid
Isopropyl 5-bromo-2-furoate

Chemical Synthesis

The following compounds were synthesized in this laboratory following the procedure given in the reference accompanying the compound. Data from NMR spectra appearing in Appendix II were taken as a confirmation of structure of some of these substituted bromothiophenes.

2,4-Dibromothiophene - b.p. 82-83° (9 mm.), [lit. (96) b.p. 83-85° (9-10 mm.)].

2,3,4-Tribromothiophene - b.p. 136-138° (11 mm.), [lit. (44) b.p. 132-134° (10 mm.)].

3,4-Dibromothiophene - n_D^{20} 1.6408; b.p. 96-97° (10 mm.), [lit. (45) n_D^{20} 1.6404; b.p. 96.5-99° (11 mm.)].

4-Bromo-3-methylthiophene - n_D^{20} 1.5792; b.p. 63-65° (11 mm.), [lit. (45) n_D^{20} 1.5795; b.p. 181-184°].

5-Bromo-2-methylthiophene - n_D^{20} 1.5700; b.p. 29° (1.8 mm.), [lit. (45, 46) n_D^{20} 1.5708; b.p. 55-56° (12 mm.)].

2,4,5-Tribromo-3-methylthiophene - b.p. 105.5-107.5° (2 mm.); m.p. 33-35°, [lit. (45) b.p. 137-140° (11 mm.); m.p. 33.5-34.5°].

5-Bromo-2-thiophenecarboxaldehyde - n_D^{21} 1.6287; b.p. 113° (10 mm.), [lit. (47) b.p. 80-83° (2 mm.)].

5-Bromo-2-thenaldoxime - m.p. 112-113°.

2-Bromo-3-methylthiophene - n_D^{20} 1.5720; b.p. 40-42° (3 mm.), [lit. (46) n_D^{20} 1.5714; b.p. 27° (1.8 mm.)].

2-Thenyl Bromide - n_D^{20} 1.6056; b.p. 54-55° (1.5 mm.), [lit. (46) n_D^{20} 1.6050; b.p. 55° (1.5 mm.)].

3-Thenyl Bromide - n_D^{20} 1.6025; b.p. 65° (3 mm.), [lit. (46) n_D^{20} 1.6035; b.p. 50° (1.5 mm.)].

5-Bromo-3-thenoic Acid - m.p. 115-118°, [lit. (48) m.p. 117-118°].

Methyl 5-bromo-3-thenoate - b.p. 132-136° (4 mm.).

5-Bromo-3-thiophenecarboxamide - m.p. 124-125°.

2,5-Dibromo-3-methylthiophene - n_D^{20} 1.6116; b.p. 67° (4 mm.), [lit. (46) n_D^{20} 1.6126; b.p. 55° (2 mm.)].

2-Bromo-5-chlorothiophene - n_D^{25} 1.5929; b.p. 52° (4 mm.), [lit. (49) n_D^{25} 1.5924; b.p. 69.5-70° (18 mm.)].

5-Bromo-2-thiophenecarboxamide

5-Bromo-2-thenoic acid, 1.0 g. (0.005 mole), was refluxed with an excess of thionyl chloride for 45 minutes. The excess thionyl chloride was evaporated and the crude carboxylic acid chloride was added dropwise to a cold and concentrated solution of ammonium hydroxide. Recrystallization from ethanol-water gave white crystals with m.p. 160-161°, [lit. (50) m.p. 163°].

3-Bromo-2-methylthiophene

To a stirred refluxing mixture of 229 ml. of water, 32 g. of zinc powder and 21.35 ml. of acetic acid was added in small portions 28.85 g. (0.113 mole) of 3,5-dibromo-2-methylthiophene. After addition was completed, the mixture was refluxed for 22 hours and then distilled from the reaction flask. The aqueous layer of the distillate was separated intermittently from the organic phase and returned to the reaction vessel. The organic phase was washed first with an aqueous 10% sodium carbonate solution, then water, and finally dried, and fractionally distilled to give 13.9 g. (70%) of 3-bromo-2-methylthiophene with b.p. 38° (2.3 mm.); n_D^{23} 1.5726, [lit. (51,52) b.p. 174-176°, 43° (4 mm.)].

3,5-Dibromo-2-methylthiophene

To 36.1 g. (0.20 mole) of 5-bromo-2-methylthiophene in 50 ml. of chloroform was added with cooling over a one hour period 11.15 ml. (0.20 mole) of bromine. The mixture was refluxed for 5 hours after which time 50 ml. of aqueous 2N sodium hydroxide was added cautiously, followed by an additional half-hour reflux period employing vigorous stirring. The mixture was allowed to cool to room temperature, transferred to a separatory funnel, and washed with successive portions of water, aqueous 2N sodium hydroxide solution, water, aqueous 10% sodium thiosulfate solution and water. The organic solution was dried over calcium chloride, filtered and then fractionally distilled to give 33.25 g. (64%) of 3,5-dibromo-2-methylthiophene with b.p. 82-83° (2.8 mm.); n_D^{23} 1.6120.

Anal. Calcd. for $C_5H_4Br_2S$: C, 23.46; H, 1.58

Found, C, 23.61; H, 1.70

3-Methyl-2-acetylthiophene

3-Methyl-2-acetylthiophene with n_D^{24} 1.5604; b.p. 68-70° (1.8 mm.), [lit. (53) n_D^{20} 1.5618; b.p. 79° (4 mm.)], was prepared in 65% yield by the reaction of 3-methylthiophene with acetic anhydride and orthophosphoric acid employing a procedure identical to that described for acylation of thiophenes by Hartough and Conley (53).

3-Methyl-2-thenoic Acid

3-Methyl-2-thenoic acid with m.p. 145-147°, [lit. (54) m.p. 148°], was prepared in 70% yield by the action of sodium hypobromite on 3-methyl-2-acetylthiophene by a method described for oxidation of acetyl groups by Newman and Holmes (54).

Methyl 3-methyl-2-thenoate

3-Methyl-2-thenoic acid, 5.0 g. (0.035 mole), was refluxed with an excess of thionyl chloride for 45 minutes. The excess of thionyl chloride was evaporated and the crude carboxylic acid chloride was added dropwise to a cold methanol solution. Evaporation of the methanol solution gave crude product which when recrystallized from methanol gave white crystals with m.p. 71-74°, [lit. (55, 56) b.p. 216-217°; m.p. 72-73°].

Methyl 5-bromo-3-methyl-2-thenoate

To a stirred mixture of 12.6 g. (0.081 mole) of methyl 3-methyl-2-thenoate in 50 ml. of chloroform, was added slowly 4.5 ml. (0.081 mole) of bromine. The mixture was refluxed for 1 hour, then cooled and water added. The organic phase was then washed with an aqueous 5% sodium thiosulfate solution and water, dried over calcium chloride, filtered and fractionally distilled to give 11.4 g. (60%) of methyl 5-bromo-3-methyl-2-thenoate with b.p. 114-117° (3 mm.).

Anal. Calcd. for $C_7H_7BrO_2S$: C, 35.74; H, 3.07; Br, 34.00.
Found, C, 35.52; H, 2.98; Br, 33.72.

5-Bromo-3-methylthiophene

With constant stirring, 2.8 gm. (0.012 mole) of methyl 5-bromo-3-methyl-2-thenoate and 100 ml. of aqueous 10% sodium hydroxide solution were refluxed for 90 minutes. After cooling, the solution was acidified with conc. hydrochloric acid to give crude product which was recrystallized from water to give 1.9 g. (72%) of 5-bromo-3-methyl-2-thenoic acid. Then 1.7 g. (0.0077 mole) of the acid, 1.0 g. of copper powder and 10 g. of quinoline in the usual decarboxylation apparatus (similar to reference 57) were put in an oil bath previously heated to 170°C. This was heated to 230°C for 30 minutes and the liquid product which distilled was collected. Fractionation of this product gave 0.5 g. (36.6%) of 5-bromo-3-methylthiophene with b.p. 35-37° (2 mm.).

Anal. Calcd. for C_5H_5BrS: C, 33.92; H, 2.85.

Found, C, 34.13; H, 2.99.

5-Bromo-2-ethylthiophene and 3,5-Dibromo-2-ethylthiophene

To 5.0 g. (0.045 mole) of 2-ethylthiophene in 10 ml. of chloroform was added dropwise 2.48 ml. (0.045 mole) of bromine in 10 ml. of chloroform. The solution was warmed to 50°C for 20 minutes and then cooled. Water was added, and the organic layer was washed with aqueous 5% sodium bicarbonate solution, water and dried over calcium chloride. Fractionation gave 3.1 g. (38%) of 5-bromo-2-ethylthiophene with b.p. 85° (4 mm.); n_D^{23} 1.5578, [lit. (97, 58) b.p. 195° n_D^{20} 1.5576], and 0.6 g. (2.2%) of 3,5-dibromo-2-ethylthiophene with b.p. 120° (4 mm.); n_D^{23} 1.5793.

Anal. Calcd. for $C_6H_6Br_2S$: C, 26.69; H, 2.24.

Found, C, 27.00; H, 2.33.

5-Bromo-2-propylthiophene and 3,5-Dibromo-2-propylthiophene

To 5.0 g. (0.04 mole) of 2-propylthiophene in 10 ml. of chloroform was added dropwise 2.18 ml. (0.04 mole) of bromine in 10 ml. of chloroform. The solution was warmed to 50°C for 20 minutes and then cooled. Water was added, and the organic layer was washed with aqueous 5% sodium bicarbonate solution, water and dried over calcium chloride. Fractionation gave 2.6 g. (32%) of 5-bromo-2-propylthiophene with b.p. 70° (2.5 mm.); n_D^{23} 1.5475, [lit. (97, 59) b.p. 189°], and 0.8 g. (2.8%) of 3,5-dibromo-2-propylthiophene with b.p. 103° (2.5 mm.); n_D^{23} 1.5847, [lit. (59) b.p. 248°].

4,5-Dibromo-2-thiophenecarboxaldehyde

To 45 g. (0.40 mole) of 2-thiophenecarboxaldehyde in 30 ml. of chloroform was added dropwise 45.6 ml. (0.83 mole) of bromine in 30 ml. of chloroform. The solution was warmed to 60°C and held there for 90 minutes. After the solution was cooled and neutralized with excess sodium acetate, the organic layer was washed with successive portions of aqueous 5% sodium thiosulfate solution, aqueous 5% sodium bicarbonate solution, water and then dried over sodium sulfate. Fractionation gave 26 g. (34%) of 5-bromo-2-thiophenecarboxaldehyde with b.p. 115-118° (10 mm.); n_D^{21} 1.6387, [lit. (60) 80-83° (2 mm.)], and 37 g. (34%) of 4,5-dibromo-2-thiophenecarboxaldehyde with b.p. 132-139° (4.5 mm.); m.p. 75-77°. Preparation of the oxime derivative of 4,5-dibromo-2-thiophenecarboxaldehyde gave white crystals with m.p. 136-137°, [lit. (60) m.p. 139°].

4,5-Dibromo-2-methylthiophene

4,5-Dibromo-2-thiophenecarboxaldehyde was reduced to 4,5-dibromo-2-methylthiophene, b.p. 91° (3.5 mm.); n_D^{25} 1.5977, with hydrazine monohydrate according to the method used by King and Nord (61) to reduce 2-thiophenecarboxaldehyde to 2-methylthiophene.

Anal. Calcd. for $C_5H_4Br_2S$: C, 23.46; H, 1.58; Br, 62.44.
Found, C, 23.70; H, 1.70; Br, 62.20.

4-Bromo-2-methylthiophene

To a stirred refluxing mixture of 30 ml. of water, 1.15 g. of zinc dust and 1.0 ml. of acetic acid, was added in portions 1.0 g. (0.004 mole) of 4,5-dibromo-2-methylthiophene. After addition the mixture was refluxed for 2-1/2 hours and the product was distilled from the reaction flask. The organic product was extracted with chloroform and these extracts were washed with aqueous 10% sodium carbonate solution, water and then dried over calcium chloride. Fractionation gave 0.6 g. (86%) of 4-bromo-2-methylthiophene with b.p. 38° (2.5 mm.).

Anal. Calcd. for C_5H_5BrS: C, 33.92; H, 2.85; Br, 45.13.
Found, C, 33.67; H, 3.00; Br, 45.02.

5-Ethyl-2-acetylthiophene

5-Ethyl-2-acetylthiophene with b.p. 121° (11 mm.); n_D^{25} 1.5473, [lit. (62) b.p. 248-250°, 116° (10 mm.)], was prepared in 64% yield by the reaction of 2-ethylthiophene with acetic anhydride and orthophosphoric acid employing a procedure identical to that described for acylation of thiophenes by Hartough and Conley (53).

5-Ethyl-2-thenoic Acid

5-Ethyl-2-thenoic acid with m.p. 67-68°, [lit. (55) m.p. 71°], was prepared in 34% yield by the action of sodium hypobromite on 5-ethyl-2-acetylthiophene by a method described for oxidation of acetyl groups by Newman and Holmes (54).

5-Propyl-2-acetylthiophene

5-Propyl-2-acetylthiophene with b.p. 115° (5 mm.); n_D^{26} 1.5388, [lit. (62) b.p. 257-260°, 126° (11 mm.); n_D^{20} 1.5438], was prepared in 78% yield by the reaction of 2-propylthiophene with acetic anhydride and orthophosphoric acid employing a procedure identical to that described for acylation of thiophenes by Hartough and Conley (53).

5-Propyl-2-thenoic Acid

5-Propyl-2-thenoic acid with m.p. 52-54°, [lit. (55, 59) m.p. 57°], was prepared in 42% yield by the action of sodium hypobromite on 5-propyl-2-acetylthiophene by a method described for oxidation of acetyl groups by Newman and Holmes (54).

2-Bromo-5-chlorothiophene

To 1.3 g. (0.011 mole) of 2-chlorothiophene in 10 ml. of chloroform was added 0.6 ml. (0.011 mole) of bromine in 5 ml. of chloroform. The solution was warmed to 50°C for 20 minutes. The solution was cooled, and the organic layer was washed with successive portions of water, aqueous 10% sodium thiosulfate solution and water. After drying over calcium chloride, fractionation gave 1.0 g. (46%) of 2-bromo-5-chlorothiophene with b.p. 52° (4 mm.); n_D^{25} 1.5929, [lit. (49) b.p. 70° (18 mm.); n_D^{25} 1.5924].

5-Bromo-2-methoxythiophene - n_D^{25} 1.5699; b.p. 68° (4 mm.), [lit. (63) n_D^{26} 1.5689; b.p. 92-93° (19 mm.)].

3,4-Dibromo-2,5-dichlorothiophene

To 2.1 g. (0.0137 mole) of 2,5-dichlorothiophene in 10 ml. of chloroform was added 1.5 ml. (0.0274 mole) of bromine. This mixture was heated for 5 hours, cooled and then 20 ml. of aqueous 2N sodium hydroxide solution was added. After refluxing for an additional one-half hour, the mixture was cooled and the organic phase was separated and washed with water and aqueous 10% sodium thiosulfate solution. After drying over calcium chloride, fractionation gave 1.0 g. (31%) of 3-bromo-2,5-dichlorothiophene with b.p. 73° (3.5 mm.); n_D^{22} 1.5984 and 0.4 g. (9%) of 3,4-dibromo-2,5-dichlorothiophene with m.p. 62-64°, [lit. (64) m.p. 65°].

2-Bromo-5-iodothiophene

To a beaker equipped with a stirrer, 10 g. (0.061 mole) of 2-bromothiophene and 20 ml. of petroleum ether were added. With constant stirring and cooling, 13.0 g. (0.06 mole) of mercuric oxide and 15.5 g. (0.061 mole) of iodine were added alternately in small amounts during a period of 20 minutes. The mixture was filtered and the residue was washed 3 times with 25 ml. portions of petroleum ether. The ether layer was shaken with aqueous 10% sodium thiosulfate solution and dried over calcium chloride. Fractionation gave 4.8 g. (27%) of 2-bromo-5-iodothiophene with b.p. 86-87° (3 mm.), [lit. (65) b.p. 116° (13 mm.)].

5-Iodo-2-acetylthiophene

5-Iodo-2-acetylthiophene with m.p. 127-129°, [lit. (66) m.p. 129-130°], was prepared in 17% yield by the reaction of 2-iodothiophene with acetic anhydride and orthophosphoric acid employing a procedure identical to that described for acylation of thiophenes by Hartough and Conley (53).

5-Iodo-2-thenoic Acid

5-Iodo-2-thenoic acid with m.p. 131-133°, [lit. (98) m.p. 133-134°], was prepared in 50% yield by the action of sodium hypobromite on 5-iodo-2-acetylthiophene by a method described for oxidation of acetyl groups by Newman and Holmes (54).

5-Carbomethoxy-2-thenoic Acid

To a solution of 3.6 g. (0.016 mole) of methyl 5-bromo-2-thenoate in 75 ml. of ether, at -60°C, was added 1.0 ml. of 2<u>N</u> phenyllithium in a fast stream similar to the procedure described for carboxylation of bromothiophenes by Lawesson (44). The solution was stirred for 4 minutes and then treated at once with an excess of powdered dry ice in ether. After the dry ice evaporated, water and dilute hydrochloric acid were added, and the ether layer was separated from the aqueous layer. The water solution was extracted with ether, and the ether extracts were washed with aqueous

5% sodium bicarbonate solution. The sodium bicarbonate extracts were made acidic with conc. hydrochloric acid, and recrystallization of the crude product from petroleum ether gave 0.2 g. (15%) of 5-carboxomethoxy-2-thenoic acid with m.p. 138-139°.

Anal. Calcd. for $C_7H_6O_4S$: C, 45.16; H, 3.25.
Found, C, 45.02; H, 3.37.

2,5-Diiodothiophene and 2-Iodothiophene

To a beaker equipped with a stirrer, 20.0 g. (0.24 mole) of thiophene and 40 ml. of petroleum ether were added. With constant stirring and cooling when necessary, 86.0 g. (0.40 mole) of mercuric oxide and 120.8 g. (0.48 mole) of iodine were added alternately (similar to references 67, 68) in small amounts during 90 minutes. The mixture was filtered and the residue was washed with 3 - 25 ml. portions of ether. The ether layer was shaken with aqueous 10% sodium thiosulfate solution and dried over calcium chloride. Fractionation gave 12.4 g. (25%) of 2-iodothiophene with b.p. 58-60° (7 mm.), [lit. (69) b.p. 66.5° (9 mm.)], and 42.3 g. (53%) of 2,5-diiodothiophene with m.p. 39-41°, [lit. (69) b.p. 139-140° (15 mm.); m.p. 40.5-41.5°].

5-Bromo-2-tert.-amylthiophene

To 20 ml. of dry CCl_4 and 2.5 g. (0.016 mole) of 2-tert.-amylthiophene, was added 3.03 g. (0.017 mole) of N-bromosuccinimide (NBS). The mixture was refluxed for 2-1/2 hours with constant stirring. After the mixture was cooled, the succinimide was filtered off and washed with carbon tetrachloride. Fractionation of the carbon tetrachloride mixture gave 1.3 g. (43%) of 5-bromo-2-tert.-amylthiophene.

Anal. Calcd. for $C_9H_{13}BrS$: C, 46.36; H, 5.62.
Found, C, 46.20; H, 5.48.

5-Methoxy-2-thenoic Acid

To 23.4 ml. (0.044 mole) of 1.87 M phenyllithium, was added 5.0 g. (0.44 mole) of 2-methoxythiophene. The mixture was stirred 80 minutes, and then the contents of the flask were poured onto a slurry of dry ice in ether. After the dry ice evaporated, the mixture was hydrolyzed with water and dilute hydrochloric acid, and the ether layer was separated from the aqueous layer. The water solution was extracted with ether and the ether extracts were washed with aqueous 5% sodium bicarbonate solution. The sodium bicarbonate washings were made acidic with conc. hydrochloric acid, and the recrystallization of the crude product from petroleum ether gave 2.3 g. (33%) of 5-methoxy-2-thenoic acid with m.p. 157-159°, [lit. (63) m.p. 160-161°].

5-Tert.-amyl-2-thenoic Acid

To 8.6 ml. (0.016 mole) of 1.87 M phenyllithium was added with stirring 2.5 g. (0.016 mole) of 2-tert.-amylthiophene. This was worked up similar to the preparation for 5-methoxy-2-thenoic acid described earlier. Recrystallization from petroleum ether gave 10.3 gm. (9.3%) of 5-tert.-amyl-2-thenoic acid with m.p. 90-92°, [lit. (55) m.p. 86.5-87.5°].

5-Tert.-octyl-2-thenoic Acid

To 6.8 ml. (0.013 mole) of 1.87 M phenyllithium was added with stirring 2.5 g. (0.013 mole) of 2-tert.-octylthiophene. This was worked up similar to the preparation for 5-methoxy-2-thenoic acid described earlier. Recrystallization from petroleum ether gave 0.35 g. (10%) of 5-tert.-octyl-2-thenoic acid with m.p. 118-120°, [lit. (50) m.p. 122-123°].

2,5-Diacetylthiophene

2-Acetylthiophene was prepared from thiophene by reaction with acetic anhydride and orthophosphoric acid according to the procedure given by Hartough and Conley (53). To 30.0 g. (0.24 mole) of 2-acetylthiophene were added 50.0 g. of 95% acetic anhydride and 1.0 g. of zinc. The mixture was heated at reflux for 2 hours, and then cooled and washed with aqueous 10% sodium carbonate solution and water. Fractionation gave much unreacted starting product and a few ml. of a yellow liquid, b.p. 138-145° (5 mm.), which solidified in the condenser. The solid product was dissolved in ethyl acetate and treated with decolorizing carbon. Recrystallization by the addition of petroleum ether gave 3.0 g. (7.5%) of 2,5-diacetylthiophene with b.p. 138-145° (5 mm.); m.p. 172-173°, [lit. (70) b.p. 138-145° (5 mm.); m.p. 172-173°].

5-Acetyl-2-thenoic Acid - m.p. 140-142°, [lit. (70) m.p. 142-143°].

2-Bromo-3-thenyl Bromide - n_D^{22} 1.6277; b.p. 93-96° (4 mm.), [lit. (71) n_D^{20} 1.6241; b.p. 113° (7 mm.)].

Hexamethylenetetramine Salt of 2-Bromo-3-thenyl Bromide

To 23.4 g. (0.092 mole) of 2-bromo-3-thenyl bromide in 75 ml. of dry carbon tetrachloride was added 13.0 g. (0.093 mole of hexamethylenetetramine. This was refluxed for 1 hour and worked up similar to the procedure for the preparation of 2-chloroveratraldehyde according to Hornbaker and Burger (72). Recrystallization gave 33.0 g. (91%) of the hexamethylenetetramine salt of 2-bromo-3-thenyl bromide with m.p. 170-172°, [lit. (71) m.p. 171-172°].

2-Bromo-3-thiophenecarboxaldehyde

A mixture of 30.0 g. (0.076 mole) of the hexamethylenetetramine salt of 2-bromo-3-thenyl bromide and 120 ml. of 50% acetic acid were refluxed for 3 hours. This was worked up similar to the procedure for the preparation of 2-chloroveratraldehyde according to Hornbaker and Burger (72). Recrystallization from petroleum ether gave 6.3 g. (43%) of 2-bromo-3-thiophenecarboxaldehyde with m.p. 33-34°, [lit. (71) m.p. 34°].

2-Bromo-3-thenoic Acid

Silver oxide was prepared according to the preparation given by Campaign and LeSuer (73). With good stirring, 3.6 g. (0.019 mole) of 2-bromo-3-thiophenecarboxaldehyde was added in small portions to the silver oxide. This was worked up similar to the procedure for the preparation of 3-thenoic acid according to Campaign and LeSuer (73). Recrystallization from water gave 3.4 g. (87.2%) of 2-bromo-3-thenoic acid with m.p. 170-172°.

Anal. Calcd. for $C_5H_3BrO_2S$: C, 29.01; H, 1.46: Br, 38.59.
Found, C, 28.76; H, 1.61; Br, 38.70.

2-Bromo-3-thiophenecarboxamide - m.p. 126-128°.

2-Bromo-3-thiophenecarboxylic Acid Chloride - m.p. 54-55°.

2-Bromofuran - b.p. 24-26° (50 mm.), [lit. (74) b.p. 52-54° (180 mm.)].

2,5-Dibromofuran - b.p. 59-61° (15 mm.), [lit. (74) b.p. 60-61° (15 mm.)].

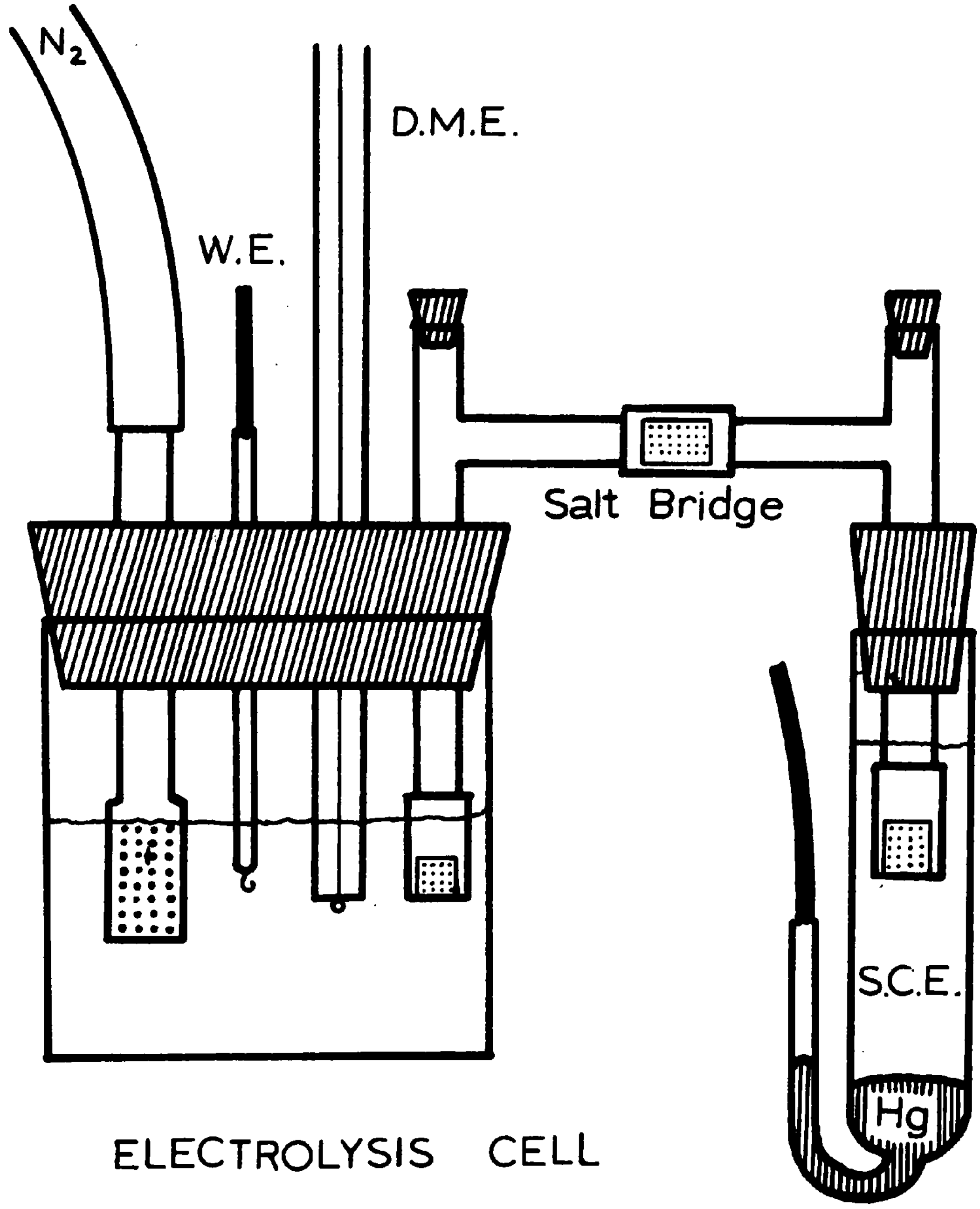
Apparatus

Polarograph - The electronic polarograph used was constructed in this laboratory from a design by Duffield (75). A three electrode system composed of a dropping mercury electrode (DME), a saturated calomel reference electrode (SCE), and an auxiliary electrode (WE) was used. A Houston model HR921 XY recorder with the scan range set at 100 mv/inch was used to record all current-potential curves.

The electrolysis cell, pictured in Figure 2, consisted of a four ounce jar with a rubber stopper which was used to support the dropping mercury electrode, the auxiliary electrode, a salt bridge, and a gas dispersion tube. The reference electrode was connected to the electrolysis cell by a salt bridge. Both the electrolysis cell and the standard calomel electrode were placed in a water bath which was thermostated at 25.0°C ± 0.1°. The salt bridge was constructed of 2 glass sections connected by Tygon tubing. Vycor plugs were used in the Tygon tubing to seal off the ends of the salt bridge and also to

Figure 2

Electrolysis Cell



separate the two sections of the salt bridge. The section of the salt bridge nearest the calomel contained a saturated solution of KCl, while the section of the salt bridge nearest the electrolysis cell contained 0.5 M $(CH_3)_4NCl$.

The DME was constructed from 0.05 mm. marine barometer tubing (Corning Glass Works). It had an m value of 0.89 mg./sec. and an open circuit time of 5.89 seconds with a 60 cm. head of mercury. The capillary constant under these conditions was 1.24 $\text{mg.}^{2/3}$ $\text{sec.}^{1/6}$. The auxiliary electrode consisted of a platinum wire sealed into a glass rod which contained mercury.

The gas dispersion tube was lowered into the solution for the initial deaeration with prepurified nitrogen, and then it was raised above the solution during the analysis in order to provide a layer of nitrogen which prevented oxygen from reentering the system.

Nuclear Magnetic Resonance - The NMR spectra were recorded with a Varian A-60 High-Resolution Spectrometer equipped with a 60 Mc. oscillator and a variable temperature probe. The data from these spectra are shown in Appendix II.

pH Meter - All pH measurements were made with a Beckman Model M pH meter equipped with a glass indicator electrode and a saturated calomel reference electrode.

Procedure

Polarograph - Stock solutions of the electroactive species were prepared by weighing 0.50 millimole of the bromothiophene and dissolving it in 100 ml. of methanol. This gave a 0.005 M solution.

Solutions for analysis, when a buffer was not used, were made by pipetting 10 ml. of 0.5 M $(CH_3)_4NCl$ electrolyte solution, 10 ml. of water, 20 ml. of methanol, and 10 ml. of the electroactive species stock solution into the cell. When a buffer was used, the solutions for analysis were made by pipetting 10 ml. of 0.5 M $(CH_3)_4NCl$ electrolyte solution, 10 ml. of pH 3.0 or pH 6.0 McIlvaine's Buffer (76), 20 ml. of methanol, and 10 ml. of the electroactive species stock solution into the cell. This gave a 1.0×10^{-3} M solution of electroactive species and a 1.0×10^{-1} M solution of electrolyte in a 60% methanol solution. The solution was then deaerated for one minute before the polarogram was run.

Nuclear Magnetic Resonance - The pure sample to be studied was diluted in the sample cell with an equal volume of $CDCl_3$ and 3 drops of tetramethylsilane (TMS) were added. Chemical shifts were measured using TMS as an internal reference.

pKa Determination - Stock solutions for measurement of pKa values of acids were prepared by weighing out 0.50 millimole of the acid and then dissolving it in enough 60% methanol-water solution to make 100 ml. of stock solution. For the actual determination of the pKa value, 25 ml. of this 0.005 M stock solution was titrated with aqueous 0.1 N NaOH.

DISCUSSION

Characteristics of Bromothiophenes

A thorough study of the polarographic reduction of the bromothiophenes has yielded the following overall characteristics.

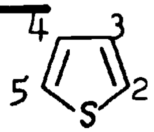
All bromothiophene compounds give a separate reduction wave for each bromine atom present in the molecule. The waves due to this reduction are pH independent, except when other groups such as an acetyl, carboxylic acid, aldehyde, or oxime are attached to the bromothiophene. In those cases the half-wave potential becomes pH dependent due to changes in structure of the substituent group at different pH values. Under such conditions, the electroactive species must be studied in a buffered solution.

The ease of reduction is considerably greater for compounds with the bromine in the α position than in the β position. This relative ease of reduction is due to the electron accepting character of the sulfur atom in thiophene.

Compared to bromobenzene, 3-bromothiophene is more easily reduced. This is believed to be due to the adsorption of bromothiophene on mercury (84) by way of the sulfur. Comparison of half-wave potentials of polybromo derivatives of thiophene indicates that the first bromine atom to be reduced is that in the α position. The half-wave potentials for a number of bromothiophenes are given in Table I. These half-wave potentials are the results of multiple determinations

TABLE I

$E_{1/2}$ VALUES OF BROMOTHIOPHENES



Compound	Buffer	$-E_{1/2}$ vs. SCE for Reduction of Br in "N" Position			
		N= 2	3	4	5
2-Bromothiophene	N.P.*A	1.544			
	pH 3.0	1.536			
	pH 6.0	1.535			
3-Bromothiophene	N.P.		1.917		
2,5-Dibromothiophene	N.P.	1.350			1.546
	pH 6.0	1.333			1.529
2,4-Dibromothiophene	N.P.	1.360		1.910	
	pH 6.0	1.345		X*B	
2,3-Dibromothiophene	N.P.	1.278	1.905		
	pH 6.0	1.234	X		
3,4-Dibromothiophene	N.P.		1.577	1.901	
	pH 6.0		1.572	X	
2,3,5-Tribromothiophene	N.P.	1.076	1.900		1.363
	pH 6.0	1.054	X		1.328
2,3,4-Tribromothiophene	N.P.	1.095	1.563	1.887	
	pH 6.0	1.073	1.562	X	
2,3,4,5-Tetrabromothiophene	N.P.	0.789	1.571	1.883	1.097
	pH 6.0	0.857	1.572	X	1.109

*A No buffer present (N.P.).

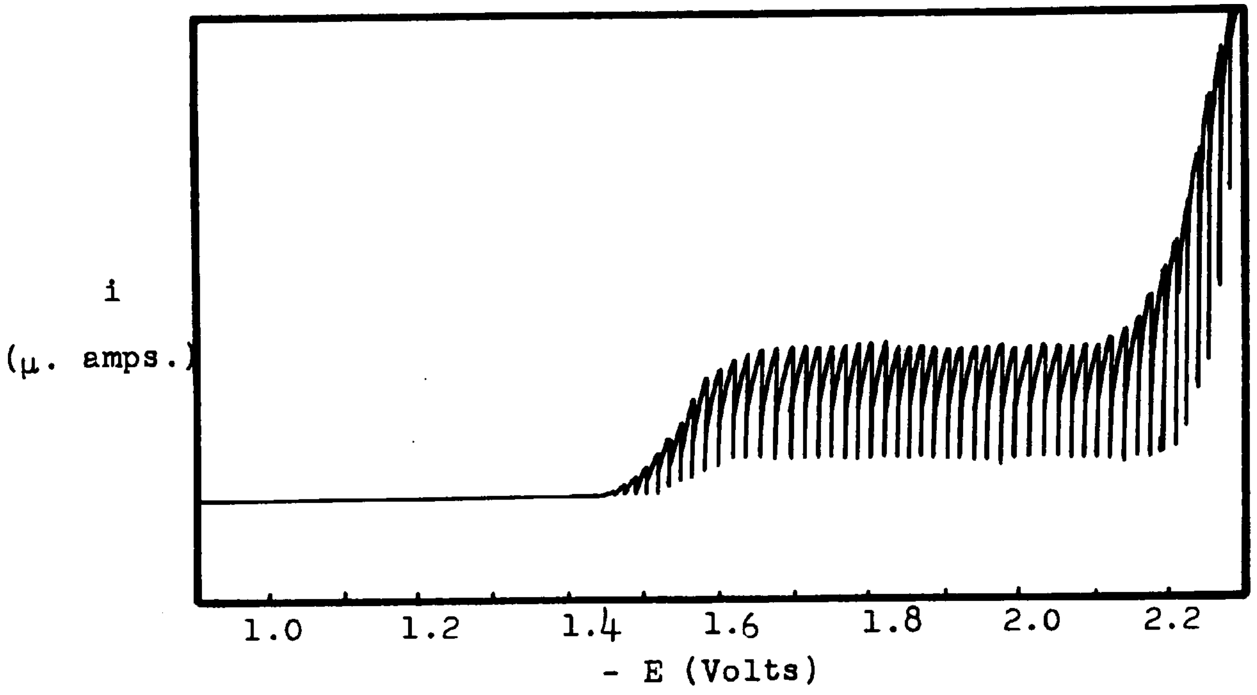
*B Buffer reduces before bromine reduces (X).

All $E_{1/2}$ values were measured in 60% methanol-water with 0.1 M $(CH_3)_4NCl$ as electrolyte.

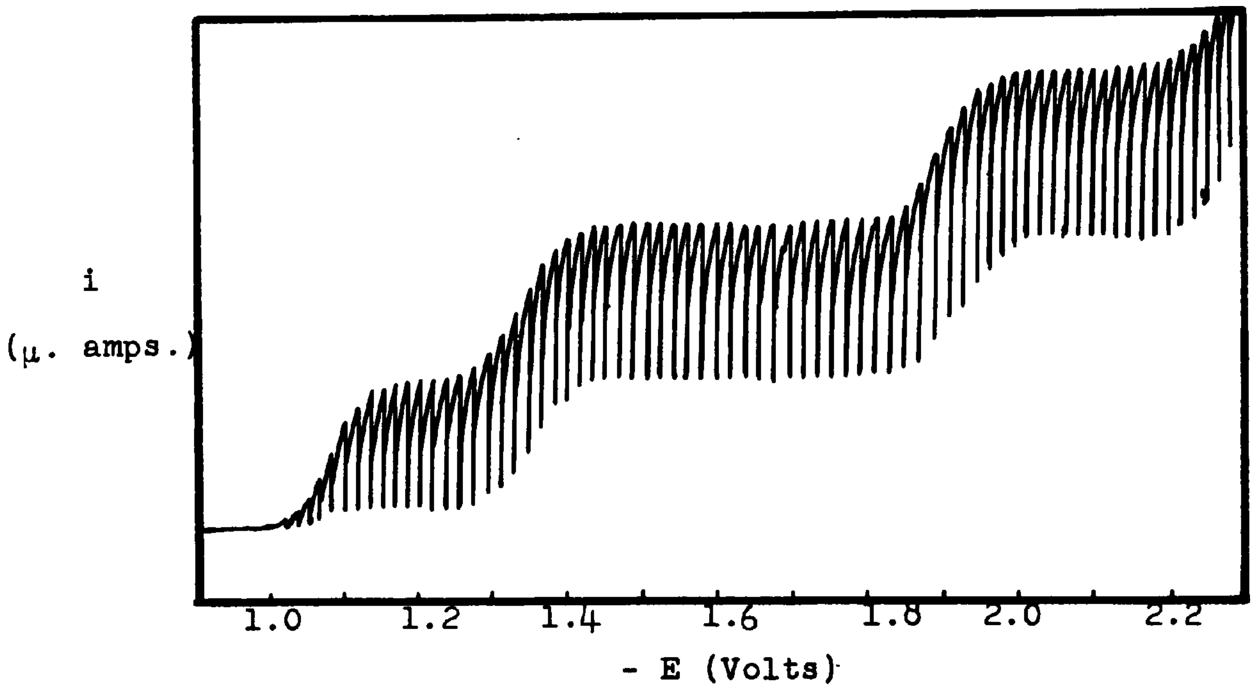
and are reproducible to within ± 6 mv. It is noted that the ease of reduction of the α bromine increases with the number of bromine atoms on the thiophene. In the case of the dibromo derivatives having at least one α bromine atom (*i.e.* 2,5-dibromothiophene, 2,4-dibromothiophene, and 2,3-dibromothiophene), the electrochemical reduction of the bromine is facilitated to the greatest extent by the introduction of the second bromine next to it in the vicinal position (position 3). The removal of the first bromine in the 2,5-dibromothiophene is somewhat more difficult and the least effect of the second bromine atom is in the 4 position. Likewise the electrochemical reduction of the α carbon-bromine bond in tribromoderivatives is considerably easier when the two remaining bromine atoms are in the 3 and 5 positions, and not in the 3 and 4 positions. The reduction of the 3 bromine in 3,4-dibromothiophene is also made easier by the introduction of the vicinal bromine atom in the 4 position.

Comparing the half-wave potentials, it is clear that the reduction of 2,3,5-tribromothiophene first gives 3,5-dibromothiophene which in turn is reduced to 3-bromothiophene. Likewise 2,3,4-tribromothiophene is first reduced to 3,4-dibromothiophene which in turn is reduced to 3-bromothiophene. As might be expected from this comparison, the reduction of 2,3,5-tribromothiophene is stepwise. This is shown in Figure 3 where the polarogram of 2,3,5-tribromothiophene is compared with the 1-step reduction polarogram of 2-bromo-

Figure 3



Polarogram of 2-Bromothiophene



Polarogram of 2,3,5-Tribromothiophene

thiophene. The stepwise reduction of vicinal bromines on thiophene is in direct opposition to the case of vicinal dihalides in alkyl compounds where both halogen atoms are removed at the same potential with the formation of the double bond (19, 85).

These changes in half-wave potentials produced by placing a second bromine atom at various ring positions are due almost entirely to changes in polar and mesomeric effects on the thiophene ring. It can be concluded that a carbon-bromine bond will reduce more easily than expected if a substituent group is added to the molecule which will draw electrons from the carbon-bromine bond which is being reduced. All -I groups (such as bromine) are capable of this electron withdrawal, provided they do not sterically interfere with the reduction process. Therefore the carbon-bromine bond reduces at a potential which is less negative than it would be for the corresponding unsubstituted bromothiophene.

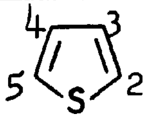
Characteristics of Bromoalkylthiophenes

The marked effect of a second bromine upon the reduction of a given bromothiophene suggested that a thorough study of the effect of other substituents be made. The methyl group was chosen as the second substituent to be studied because it is classified as a +I +M group while the bromine is a -I +M group.

A further assessment of the inductive and mesomeric effects in thiophene can be carried out if the half-wave

TABLE II

$E_{1/2}$ VALUES OF BROMOMETHYLTHIOPHENES



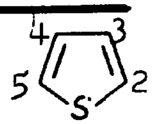
Compound	Buffer	$-E_{1/2}$ vs. SCE for Reduction of Br in "N" Position			
		N= 2	3	4	5
5-Bromo-2-methylthiophene	N.P.[*A]				1.586
	pH 6.0				1.578
5-Bromo-3-methylthiophene	N.P.				1.588
	pH 6.0				1.587
2-Bromo-3-methylthiophene	N.P.	1.623			
	pH 6.0	1.622			
3-Bromo-2-methylthiophene	N.P.		2.027		
	pH 6.0		X[*B]		
4-Bromo-3-methylthiophene	N.P.			2.014	
	pH 6.0			X	
4-Bromo-2-methylthiophene	N.P.			1.965	
	pH 6.0			X	
2,5-Dibromo-3-methylthiophene	N.P.	1.398			1.626
	pH 6.0	1.400			X
3,5-Dibromo-2-methylthiophene	N.P.		2.016		1.397
	pH 6.0		X		1.393
4,5-Dibromo-2-methylthiophene	N.P.			1.944	1.300
	pH 6.0			X	1.274
3,4-Dibromo-2,5-dimethylthiophene	N.P.		1.711	2.033	
	pH 6.0		1.698	X	
2,4,5-Tribromo-3-methylthiophene	N.P.	1.463		2.003	1.097
	pH 6.0	1.455		X	1.118

[*A] None present (N.P.).

[*B] Buffer reduces before bromine reduces (X).

TABLE III

$E_{1/2}$ VALUES OF BROMOALKYLTHIOPHENES



Compound	Buffer	$-E_{1/2}$ vs. SCE for Reduction of Br in "N" Position			
		N= 2	3	4	5
5-Bromo-2-ethylthiophene	N.P.*A				1.583
	pH 6.0				1.573
3,5-Dibromo-2-ethylthiophene	N.P.		2.011		1.394
	pH 6.0		X*B		1.375
5-Bromo-2-propylthiophene	N.P.				1.577
	pH 6.0				1.575
3,5-Dibromo-2-propylthiophene	N.P.		1.998		1.378
	pH 6.0		X		1.374
5-Bromo-2-isopropylthiophene	N.P.				1.575
	pH 6.0				1.579
3,5-Dibromo-2-isopropylthiophene	N.P.		2.079		1.379
	pH 6.0		X		1.358
5-Bromo-2-dodecylthiophene	N.P.				1.605
	pH 6.0				1.626
5-Bromo-2-tert.-amylthiophene	N.P.				1.576
	pH 6.0				1.595
5-Bromo-2-iso-octylthiophene	N.P.				1.594
	pH 6.0				1.610
5-Bromo-2-tert.-octylthiophene	N.P.				1.595
	pH 6.0				1.623
5-Bromo-2-tert.-butylthiophene	N.P.				1.598
	pH 6.0				1.629

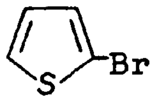
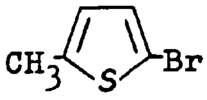
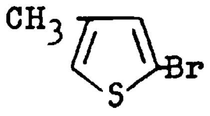
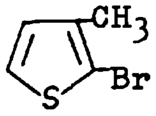
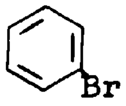
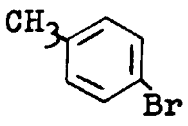
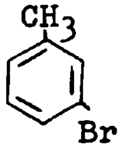
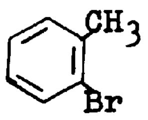
*A None present (N.P.).

*B Buffer reduces before bromine reduces (X).

potentials in Table II and III are studied. The six possible isomers of bromomethylthiophene were synthesized in hope of establishing a method whereby the inductive and mesomeric effects of a methyl group could be unequivocally measured. Due to an inability to separate the inductive and mesomeric effects into numerical terms, this hope was not realized. However, the half-wave potentials of these bromomethylthiophenes were compared with those determined by Hussey (27) for the bromotoluenes. This study shows the predominance of the inductive effect in thiophene as compared to that of benzene. Table IV shows that bromomethylthiophenes do not follow the trend established by the bromotoluenes. If inductive and mesomeric effects are the same in the thiophene system as they are in the benzene system, it would be expected that 5-bromo-3-

TABLE IV

Comparison of $E_{1/2}$ in Benzene and Thiophene Systems

Compound				
$-E_{1/2}$ vs. SCE*C	1.535	1.578	1.587	1.622
Compound				
$-E_{1/2}$ vs. SCE*D	2.07	2.11	2.09	2.12

*C All $E_{1/2}$ values measured at pH 6.0.

*D All $E_{1/2}$ values from work by Hussey (27).

methylthiophene would reduce before 5-bromo-2-methylthiophene (similar to the reduction of meta-bromotoluene before para-bromotoluene). However Table IV indicates that 5-bromo-3-methylthiophene reduces after 5-bromo-2-methylthiophene. It is also noted that the effect of addition of a methyl group to a molecule has a greater effect on the half-wave potential in the thiophene system than in the benzene system. All this suggests that the inductive effect is greater than the resonance effect in thiophene. Since it has been pointed out earlier that the resonance energy of thiophene is less than the resonance energy of benzene, it may be assumed that, for the substituents studied, the mesomeric effect of these substituents in thiophene is less than the mesomeric effect of these substituents in benzene. This may be summarized symbolically as: $I_{Thio} > M_{Thio}$, and $M_{Benzene} > M_{Thio}$. This effect will be demonstrated again later in this work when the sigma values for the methoxy group are compared in the benzene and in the thiophene systems. The 5-bromo-3-methylthiophene reduces with more difficulty than 5-bromo-2-methylthiophene simply because the methyl group is located closer to the reaction site. Therefore the electron density is increased at the carbon-bromine bond due to the increased inductive effect of the methyl group being closer to it. Thus the reduction is hindered. This is operationally similar, but opposite to that effect observed for dibromothiophene in which the -I second bromine withdraws electrons from the carbon-bromine bond being reduced, and thus facilitates the reduction.

In order to determine the validity of these conclusions one should be able to apply these effects to polysubstituted thiophenes as well as the disubstituted thiophenes already studied. 2,5-Dibromo-3-methylthiophene and 2,5-dibromothiophene can be used as a measure of the effect that a 3-methyl group has on the reduction potential of the bromine in the 5-position. This is obtained by calculating the difference in half-wave potentials of these two compounds for the reduction of the carbon-bromine bond in the 2-position. Table V gives the average change in half-wave potential that a methyl group at a given position has on the reduction of a carbon-bromine bond at another position. The trends observed in Table V are exactly the same as those observed in the case of the disubstituted bromothiophenes, but the values in Table V are considered more accurate since they were obtained from a larger number of compounds.

These effects are further borne out by observing Tables VI, VII, VIII, and IX, which include a large number of other substituents. The same effect as observed before for dibromothiophenes and bromomethylthiophenes is continued in these tables; <u>i.e.</u>, +I groups make reduction more difficult and -I groups facilitate reduction.

TABLE V

CHANGE IN $E_{1/2}$ WITH ADDITION OF METHYL SUBSTITUENTS

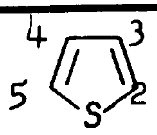
Substituent Group	Position	Reducible Group	Position	Number of $E_{1/2}$ Changes Measured	Average Change in $E_{1/2}$ (Volts)	Standard Deviation of Changes in Volts
CH_3	2	C-Br	5	4	-0.037	± 0.010
CH_3	3	C-Br	5	6	-0.060	± 0.005
CH_3	3	C-Br	2	2	-0.089	± 0.002
CH_3	2	C-Br	4	2*A	-0.041	± 0.004
CH_3	3	C-Br	4	2*A	-0.100	± 0.003
CH_3	2	C-Br	3	1*A	-0.110	---

All changes measured at pH 6.0 (unless noted otherwise).

*A Measured with no buffer present.

TABLE VI

$E_{1/2}$ VALUES OF HALOGEN SUBSTITUTED BROMOTHIOPHENES



		$-E_{1/2}$ vs. SCE for Reduction of Br in "N" Position			
Compound	Buffer	N= 2	3	4	5
2-Thenyl Bromide	N.P.*A pH 6.0	1.489 1.495			
3-Thenyl Bromide	N.P. pH 6.0		1.494 1.497		
2-Bromo-5-chloro-thiophene	N.P. pH 6.0	1.386 1.372			
3-Bromo-2-chloro-thiophene	N.P. pH 6.0		1.615 X*B		
3-Bromo-2,5-dichlorothiophene	N.P. pH 6.0		1.446 1.441		
3,4-Dibromo-2-chlorothiophene	N.P. pH 6.0		1.335 1.333	1.682 X	
3,4-Dibromo-2,5-dichlorothiophene	N.P. pH 6.0		1.145 1.144	1.423 1.423	
2-Bromo-5-iodo-thiophene*E	N.P. pH 6.0	1.410 1.396			

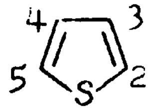
*A No buffer present (N.P.).

*B Buffer reduces before bromine reduces (X).

*E Calculated from $E_{1/2}$ values for 2-iodothiophene, 2-bromothiophene, 2,5-dibromothiophene, 2,5-diiodothiophene and 2-bromo-5-iodothiophene.

TABLE VII

$E_{1/2}$ VALUES OF ACID SUBSTITUTED BROMOTHIOPHENES



Compound	Buffer	$-E_{1/2}$ vs. SCE for Reduction of Br in "N" Position			
		N= 2	3	4	5
5-Bromo-2-thenoic Acid	N.P.[*A]				1.363
	pH 3.0				1.400
	pH 6.0				1.450
5-Bromo-3-thenoic Acid	N.P.				1.411
	pH 3.0				1.435
	pH 6.0				1.469
2-Bromo-3-thenoic Acid	N.P.	1.243			
	pH 3.0	1.268			
	pH 6.0	1.479			
Sodium 5-bromo-2-thenoate[*F]	N.P.				1.487
Sodium 5-bromo-3-thenoate[*F]	N.P.				1.506
Sodium 2-bromo-3-thenoate[*F]	N.P.	1.500			
4,5-Dibromo-2-thenoic Acid	N.P.			1.858	1.131
	pH 3.0			X[*B]	1.149
	pH 6.0			X	1.153
Sodium 4,5-dibromo-2-thenoate[*F]	N.P.			1.863	1.249
5-Bromo-3-methyl-2-thenoic Acid	N.P.				1.450
	pH 3.0				1.455
	pH 6.0				1.514
Sodium 5-bromo-3-methyl-2-thenoate[*F]	N.P.				1.552
3,4-Dibromothiophene-2,5-dicarboxylic Acid	N.P.		1.133	1.518	
	pH 3.0		1.288	X	
	pH 6.0		1.402	X	
Disodium 3,4-dibromothiophene-2,5-dicarboxylate[*F]	N.P.		1.537	1.751	

---

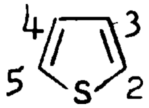
*A No buffer present (N.P.).

*B Buffer reduces before bromine reduces (X).

*F Salt of acid made by adding 0.2 ml. of 2N NaOH to the acid in solution.

TABLE VIII

$E_{1/2}$ VALUES OF AMIDE AND ESTER SUBSTITUTED BROMOTHIOPHENES

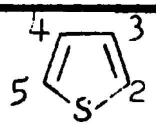


		$-E_{1/2}$ vs. SCE for Reduction of Br in "N" Position			
Compound	Buffer	N= 2	3	4	5
Methyl 5-bromo-2-thenoate	N.P.[*A] pH 3.0 pH 6.0				1.345 1.330 1.331
Methyl 5-bromo-3-thenoate	N.P. pH 6.0				1.390 1.383
Methyl 2-bromo-3-thenoate	N.P. pH 6.0	1.223 1.237			
Methyl 5-bromo-3-methyl-2-thenoate	N.P. pH 3.0 pH 6.0				1.403 1.388 1.388
5-Bromo-2-thiophene-carboxamide	N.P. pH 3.0 pH 6.0				1.345 1.340 1.351
5-Bromo-3-thiophene-carboxamide	N.P. pH 6.0				1.384 1.390
2-Bromo-3-thiophene-carboxamide	N.P. pH 6.0	1.089 1.092			

[*A] No buffer present (N.P.).

TABLE IX

$E_{1/2}$ VALUES OF MISCELLANEOUS SUBSTITUTED BROMOTHIOPHENES



Compound	Buffer	$-E_{1/2}$ vs. SCE for Reduction of Br in "N" Position			
		N= 2	3	4	5
5-Bromo-2-methoxythiophene	N.P.[*A]				1.530
	pH 6.0				1.520
5-Bromo-2-acetylthiophene	N.P.				1.280
	pH 3.0				0.915
	pH 6.0				1.209
5-Bromo-2-thiophenecarboxaldehyde	N.P.				1.135
	pH 3.0				0.807
	pH 6.0				1.067
5-Bromo-3-thiophenecarboxaldehyde	N.P.				1.187
	pH 3.0				0.888
	pH 6.0				1.205
2-Bromo-3-thiophenecarboxaldehyde	N.P.	1.145			
	pH 3.0	0.835			
	pH 6.0	1.106			
4,5-Dibromo-2-thiophenecarboxaldehyde	N.P.				0.934
	pH 3.0				0.637
	pH 6.0				0.845
5-Bromo-2-thenaldoxime	N.P.				1.423
	pH 3.0				0.856
	pH 6.0				1.108
Hexamethylenetetramine Salt of 2-Bromo-3-thenyl Bromide	N.P.	1.024			
	pH 6.0	1.016			

[*A] No buffer present (N.P.).

Development of Thiophene Sigma Values

In dealing with the six isomers of bromomethylthiophene and the four isomers of dibromothiophene, it was anticipated that measurements of the inductive and mesomeric effects of the methyl group and the bromo group could be estimated by comparisons of the half-wave potentials for these compounds. However due to the sulfur atom in the heterocyclic ring, the above mentioned quantitative measurements were not possible. One of the principal successes in benzenoid work has been the use of the Hammett relationship for quantitative measurement of these effects. It is obvious from the preceding discussion that a direct transposition from the benzene system to the thiophene system is highly questionable.

The approach followed by Hammett, however, is applicable to the thiophene system. The work by Hammett shows that it is possible to determine experimentally reaction parameters and then in turn apply them to other systems. Therefore, new substituent constants must be determined which will be applicable to the thiophene system.

In order to determine new $\sigma_{\text{2-thio-N-R}}$ constants which will be applicable to the thiophene system, the following approach is used. A number of substituted thenoic acids were synthesized and their pKa's (in 60% methanol-water) were determined. These results are given in Table X. At the same time, the pKa's of substituted benzoic acids were measured in the same solvent system. These results are also shown in Table X.

TABLE X

ACID DISSOCIATION CONSTANTS

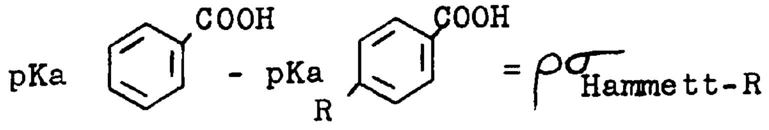
All measured in 60% methanol-water system

Acid	pKa
5-Nitro-2-thenoic Acid	4.05
4,5-Dibromo-2-thenoic Acid	4.11
5-Acetyl-2-thenoic Acid	4.22
5-Bromo-2-thenoic Acid	4.70
5-Chloro-2-thenoic Acid	4.71
5-Carbomethoxy-2-thenoic Acid	4.72
5-Iodo-2-thenoic Acid	4.80
5-Methoxy-2-thenoic Acid	5.27
2-Thenoic Acid	5.31
5-Propyl-2-thenoic Acid	5.50
5-Isopropyl-2-thenoic Acid	5.55
5-Ethyl-2-thenoic Acid	5.58
5-Methyl-2-thenoic Acid	5.62
5-Dodecyl-2-thenoic Acid	5.82
5-Isooctyl-2-thenoic Acid	5.82
5-Tert.-amyl-2-thenoic Acid	5.84
5-Tert.-octyl-2-thenoic Acid	5.98
3-Thenoic Acid	5.85
5-Bromo-3-thenoic Acid	5.33
p-Nitrobenzoic Acid	4.78
p-Bromobenzoic Acid	5.64
p-Chlorobenzoic Acid	5.65
Benzoic Acid	6.07
p-Toluic Acid	6.37
p-Isopropylbenzoic Acid	6.37
p-Hydroxybenzoic Acid	6.70
5-Nitro-2-furoic Acid	3.91
5-Carbomethoxy-2-furoic Acid	4.48
5-Bromo-2-furoic Acid	4.50
5-Chloro-2-furoic Acid	4.51
5-Methoxy-2-furoic Acid	4.74
2-Furoic Acid	4.78
5-Hydroxymethyl-2-furoic Acid	4.84

In order to obtain sigma values which are useful for the thiophene system, an assumption must be made. It is assumed that the reaction constant for the dissociation of parasubstituted benzoic acids is the same as the reaction constant for 5-substituted-2-thenoic acids. It is known that the reaction constant mainly depends on the distance from substituent to reactant group, the type of reactant group, the mechanism by which it reacts, the solvent, and the temperature of the experiment (86). The reactant group in both cases is a carboxylic acid. The acid is solvated in 60% methanol in both cases and the pKa measurements are taken at the same temperature. The distance from substituent to reactant group is similar in both cases. The distance between a methyl carbon and the hydrogen of the carboxylic acid in p-toluic acid is 9.47 A, while the similar distance around the carbon chain in 5-methyl-2-thenoic acid is 9.43 A. Therefore the reaction constant obtained from the dissociation of parasubstituted benzoic acids is used as the reaction constant for the dissociation of 5-substituted-2-thenoic acids.

This assumption has been shown to be valid by Imoto and co-workers (99). They have correlated (100-103) a number of reactions of thiophenes and benzenes. The reactions studied were the acid-base equilibria; the acid catalyzed methylation of thiophenecarboxylic acids, and the alkaline hydrolyses of their ethyl esters; the side-chain bromination of the α-acetylthiophenes; and the polarographic half-wave potentials for the reduction of the methyl esters of thiophenecarboxylic acids and of nitrothiophenes. The authors have compared, in every case, the values for the thiophene series (ρ_{thio}) with the corresponding value for the benzene series (ρ_b) under identical conditions. The ratios of ρ_{thio} to ρ_b varied between 0.83 and 1.20 with an average value of 0.99. This value indicates that the present assumption is justified in taking the ratio of ρ_{thio} to ρ_b for the dissociation of carboxylic acids in both these series to be 1.00.

First, the reaction constant for the dissociation of benzoic acids in 60% methanol-water is calculated. This is done by using the pKa values of substituted benzoic acids (shown in Table X) in Equation 27.



(27)

The sigma values used in this equation are given in Table XI. The sigma values in Table XI are Hammett's para sigma values which are applicable to the benzenoid system only.

TABLE XI
HAMMETT SIGMA VALUES

Substituent	para (41, 43)
NO_2	0.778
Br	0.232
Cl	0.227
H	0.000
i-Pr	-0.151
CH_3	-0.17
OH	-0.37

The reaction constant for the six p-substituted benzoic acids is found to be 1.809 ± 0.124. This value is then used as the reaction constant for the dissociation of 5-substituted-2-thenoic acids. With the reaction constant established, the pKa data for 5-substituted-2-thenoic acids are used to evaluate the sigma values for the thiophene substituents given in Table XII.

These newly evaluated sigma values can be plotted against changes in half-wave potentials. But, before polarographic data can be correlated with sigma values one must make sure that certain variables (*i.e.*, solvent, temperature, and transfer coefficient) are held constant. In this series of experiments the temperature is held constant at 25 ± 0.1°C. The solvent system, 60% methanol-water, remains the same. It was mentioned earlier that the reaction constant depends on the reduction mechanism. One way to observe if the reduction mechanism is held constant in polarographic processes is to measure the transfer coefficient. If the transfer coefficient remains constant, then it is assumed that the reduction mechanism does not change. Table XIII shows a summary of the αn values for a number of bromothiophene compounds reduced in this work. The average αn value from Table XIII is 0.57 ± 0.02. Since it is observed that the αn value remains constant for this series of similar compounds, it may be assumed that the same reduction mechanism is operative throughout this series, and therefore these polarographic data may be used with Hammett type correlations.

TABLE XII

THIOPHENE SIGMA VALUES CALCULATED FROM pKa DATA

$\rho_{2\text{-Thio-COOH}} = 1.809$

R = Substituent	2-Thio-5-R
t-C_8H_{17}	-0.370
t-C_5H_{11}	-0.293
$C_{12}H_{25}$	-0.282
i-C_8H_{17}	-0.282
CH_3	-0.171
C_2H_5	-0.149
i-C_3H_7	-0.133
C_3H_7	-0.105
H	0.000
OCH_3	0.022
I	0.282
$COOCH_3$	0.326
Cl	0.332
Br	0.337
$COCH_3$	0.602
NO_2	0.696

TABLE XIII

an VALUES OF SUBSTITUTED BROMOTHIOPHENES

Compound	an_2*G	an_5*H
2-Bromothiophene	.59	
5-Bromo-2-methylthiophene		.57
2-Bromo-3-methylthiophene	.58	
2,3-Dibromothiophene	.59	
2,5-Dibromothiophene	.55	.58
2,5-Dibromo-3-methylthiophene	.54	.54
2,3,5-Tribromothiophene	.57	.52
2,4,5-Tribromo-3-methylthiophene	.59	.56
2,3,4,5-Tetrabromothiophene	.56	.58
5-Bromo-3-methyl-2-thenoic Acid		.54
5-Bromo-2-thenoic Acid		.56
4,5-Dibromo-2-thenoic Acid		.59
2,3,4-Tribromothiophene	.57	

*G Reduction of carbon-bromine bond in 2 position

*H Reduction of carbon-bromine bond in 5 position

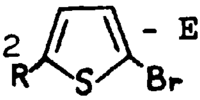
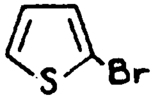
The sigma values from Table XII are then plotted against the changes in half-wave potential measured at pH 6.0. This change in half-wave potential for a certain substituent is the difference in half-wave potentials between 2-bromothiophene and the 5-substituted-2-bromothiophene. Figure 4 shows the curve obtained by plotting these sigma values against the changes in half-wave potentials. The best straight line in Figure 4, determined by the method of least squares, fits the equation,

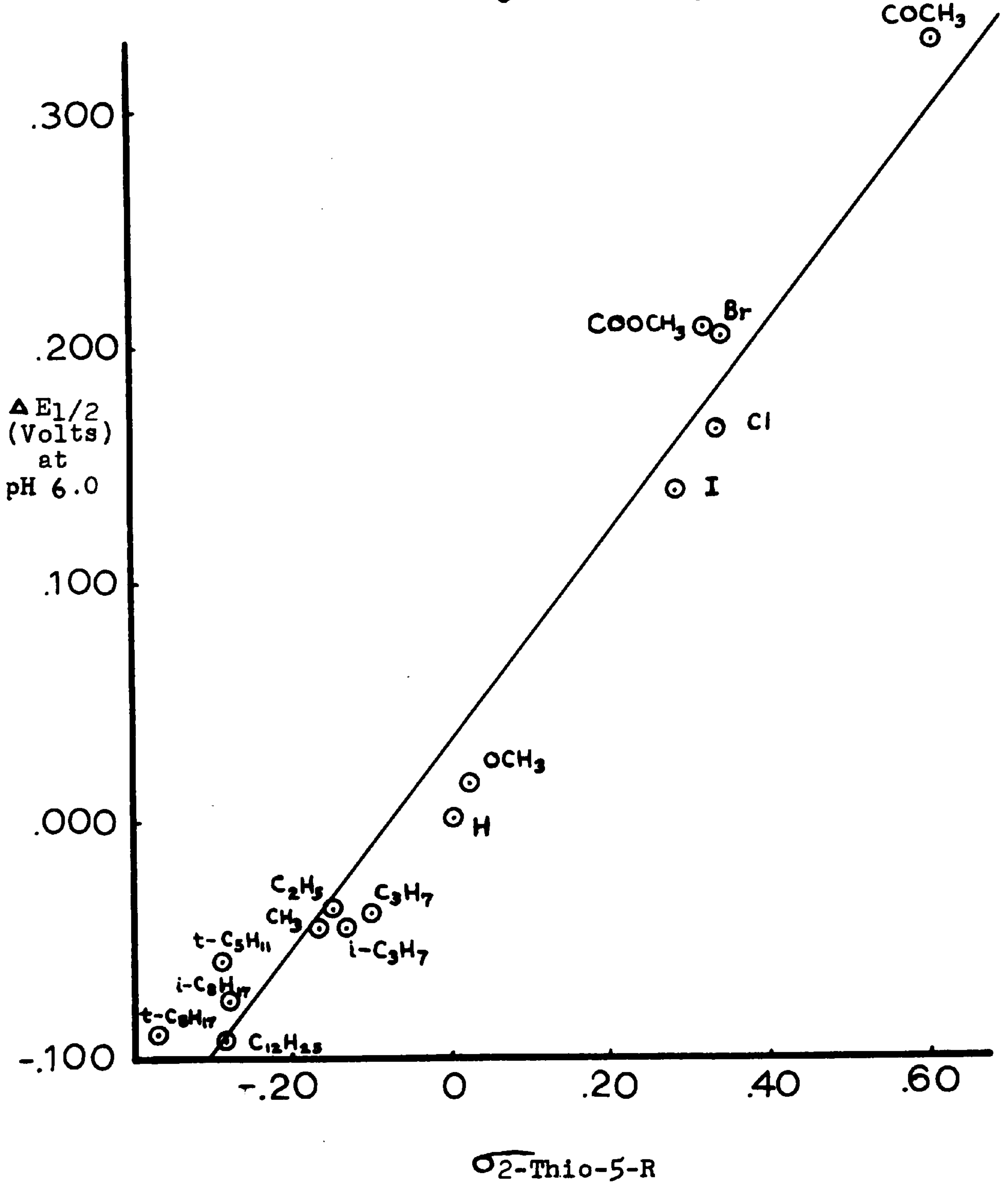
$$\Delta E_{1/2} = .041 + .438\,\sigma \qquad (28)$$

The correlation coefficient (r), for the above equation is 0.941 and the standard deviation from the best fit line is 0.080. Thus the reaction constant (the slope of this line) for the reduction of a carbon-bromine bond in the 2 position of thiophene is established as 0.438 volts. This reaction constant depends on the kind of polarographically-active group (bromine, in this case), on its position relative to the heteroatom (the two position, in this case), on the type of heterocyclic ring, and on reaction conditions; i.e., solvent and temperature. The reaction constant is, however, independent of the type and ring position of the substituent. The value of the substituent constant ($\sigma_{2\text{-thio-N-R}}$) will be dependent only on its position relative to the polarographically active group, on the type of heterocyclic system, and on the position of the substituent relative to the heteroatom.

Figure 4

$\Delta E_{1/2}$ vs. $\sigma_{2\text{-Thio-5-R}}$

$\Delta E_{1/2} = E_{1/2}$  $- E_{1/2}$ 



With the reaction constant established for the reduction of a substituted 2-bromothiophene, it is possible to calculate the substituent constant for any substituent at any ring position of a substituted 2-bromothiophene. The change in half-wave potential between a substituted-2-bromothiophene and 2-bromothiophene is determined. This change in half-wave potential can be used to determine the sigma value either graphically from Figure IV or mathematically from Equation 28. Table XIV summarizes the sigma values obtained for a number of substituents at different ring positions.

TABLE XIV

SIGMA VALUES FOR THIOPHENES

R = Substituent	2-Thio-5-R	2-Thio-4-R	2-Thio-3-R
t-C_8H_{17}	-0.37		
t-C_4H_9	-0.31		
t-C_5H_{11}	-0.29		
i-C_8H_{17}	-0.28		
$C_{12}H_{25}$	-0.28		
CH_3	-0.17	-0.21	-0.29
C_2H_5	-0.15		
i-C_3H_7	-0.13		
C_3H_7	-0.11		
H	0.00		
OCH_3	0.02		
COO^- (Na^+)*F	0.04*A	-0.01*A	0.01*A
COOH	0.10	0.06	0.03
	0.32*A	0.21*A	0.59*A
	0.22*I	0.14*I	0.52*I
I	0.28		
Cl	0.33		
$COOCH_3$	0.33	0.25	0.59
$CONH_2$	0.33	0.24	0.92
Br	0.34	0.36	0.59
$COCH_3$	0.60		
	0.51*		
	1.32*I		
CH=NOH	0.88		
	0.18*A		
	1.46*I		
CHO	0.97	0.66	0.89
	0.84*A	0.72*A	0.82*A
	1.57*I	1.39*I	1.51*I
NO_2	0.70		
$CH_2Br\ (CH_2)_6N_4$	1.09		

All sigma values are measured at pH 6.0 unless otherwise noted.

*A Measured with no buffer present.

*F Salt of the acid made by adding 0.2 ml. of 2<u>N</u> sodium hydroxide to the acid in solution.

*I Measured at pH 3.0.

Development of Furan Sigma Values

The utility of this approach suggests that it be extended to other systems. The substituted furan system was an obvious choice since effects of change in the heteroatom of the ring could be evaluated by comparison with the thiophene system. The $\sigma_{2\text{-furan-}5\text{-R}}$ values were calculated by a method similar to that used to calculate $\sigma_{2\text{-thio-}5\text{-R}}$ values. The previously determined reaction constant value of 1.809 is used as the reaction constant for the dissociation of 5-substituted-2-furoic acids. The pKa's of a number of 5-substituted-2-furoic acids are determined and are given in Table X. These pKa values and the reaction constant of 1.809 are used in Equation 27 to calculate $\sigma_{2\text{-furan-}5\text{-R}}$ values. These calculated values are shown in Table XV.

TABLE XV

FURAN SIGMA VALUES CALCULATED FROM pKa DATA

$\rho_{2\text{-thio-COOH}} = 1.809$

R = Substituent	2-Furan-5-R
CH_2OH	-0.033
H	0.000
OCH_3	0.022
Cl	0.149
Br	0.155
$COOCH_3$	0.166
NO_2	0.481

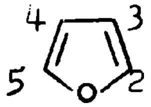
The established sigma values from Table XV are then used to determine additional sigma values by the polarographic procedure. The αn values for a number of bromofuran compounds used in this work were found to average 0.62 ± 0.02. Since it is observed that the αn value remains constant for this series of similar compounds, it may be assumed that the same reduction mechanism is operative throughout this series, and therefore these polarographic data may be used with Hammett type correlations. The sigma values from Table XV are then plotted against the changes in half-wave potential measured at pH 6.0 for similarly 5-substituted-2-bromofurans. The half-wave potentials for the bromofurans are found in Tables XVI and XVII. Figure 5 shows the curve obtained by plotting these sigma values against the change in half-wave potentials. The best straight line in Figure 5, determined by the method of least squares, fits the equation,

$$\Delta E_{1/2} = .003 + 1.630\,\sigma \qquad (29)$$

The standard deviation from the best fit line is 0.080. With the reaction constant established for the reduction of a substituted 2-bromofuran, it is therefore possible to calculate the substituent constant for any substituent at any ring position of a substituted 2-bromofuran. Equation 29 is used to calculate the sigma values for any substituted 2-bromofuran for which polarographic data can be obtained.

TABLE XVI

$E_{1/2}$ VALUES OF SUBSTITUTED BROMOFURANS



Compound	Buffer	$-E_{1/2}$ vs. SCE for Reduction of Br in "N" Position			
		N= 2	3	4	5
2-Bromofuran	N.P.[*A] pH 6.0	1.760 X[*B]			
2,5-Dibromofuran	N.P. pH 6.0	1.754 X			1.516 1.516
5-Bromo-2-furoic Acid	N.P. pH 3.0 pH 6.0				1.449 1.484 1.657
Sodium 5-bromo-2-furoate[*F]	N.P.				1.638
5-Bromofuran-2,4-dicarboxylic Acid	N.P. pH 3.0 pH 6.0				1.270 1.301 1.557
Disodium 5-bromo-furan-3,5-dicarboxylate[*F]	N.P.				1.558

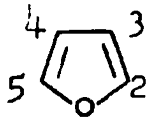
[*A] No buffer present (N.P.).

[*B] Buffer reduces before bromine reduces (X).

[*F] Salt of acid made by adding 0.2 ml. of 2N NaOH to the acid in solution.

TABLE XVII

$E_{1/2}$ VALUES OF ESTER SUBSTITUTED BROMOFURANS



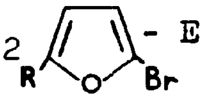
Compound	Buffer	$-E_{1/2}$ vs. SCE for Reduction of Br in "N" Position N= 2	3	4	5
Methyl 5-bromo-2-furoate	N.P.*A pH 6.0				1.471 1.474
Ethyl 5-bromo-2-furoate	N.P. pH 6.0				1.471 1.474
Isopropyl 5-bromo-2-furoate	N.P. pH 3.0 pH 6.0				1.483 1.474 1.477
Allyl 5-bromo-2-furoate	N.P. pH 6.0				1.468 1.472
Methyl 4,5-dibromo-2-furoate	N.P. pH 6.0			1.742 X*B	1.243 1.253
Ethyl 4,5-dibromo-2-furoate	N.P. pH 6.0			1.743 X	1.259 1.260
Dimethyl 5-bromofuran-2,4-dicarboxylate	N.P. pH 6.0				1.159 1.157

*A No buffer present (N.P.).

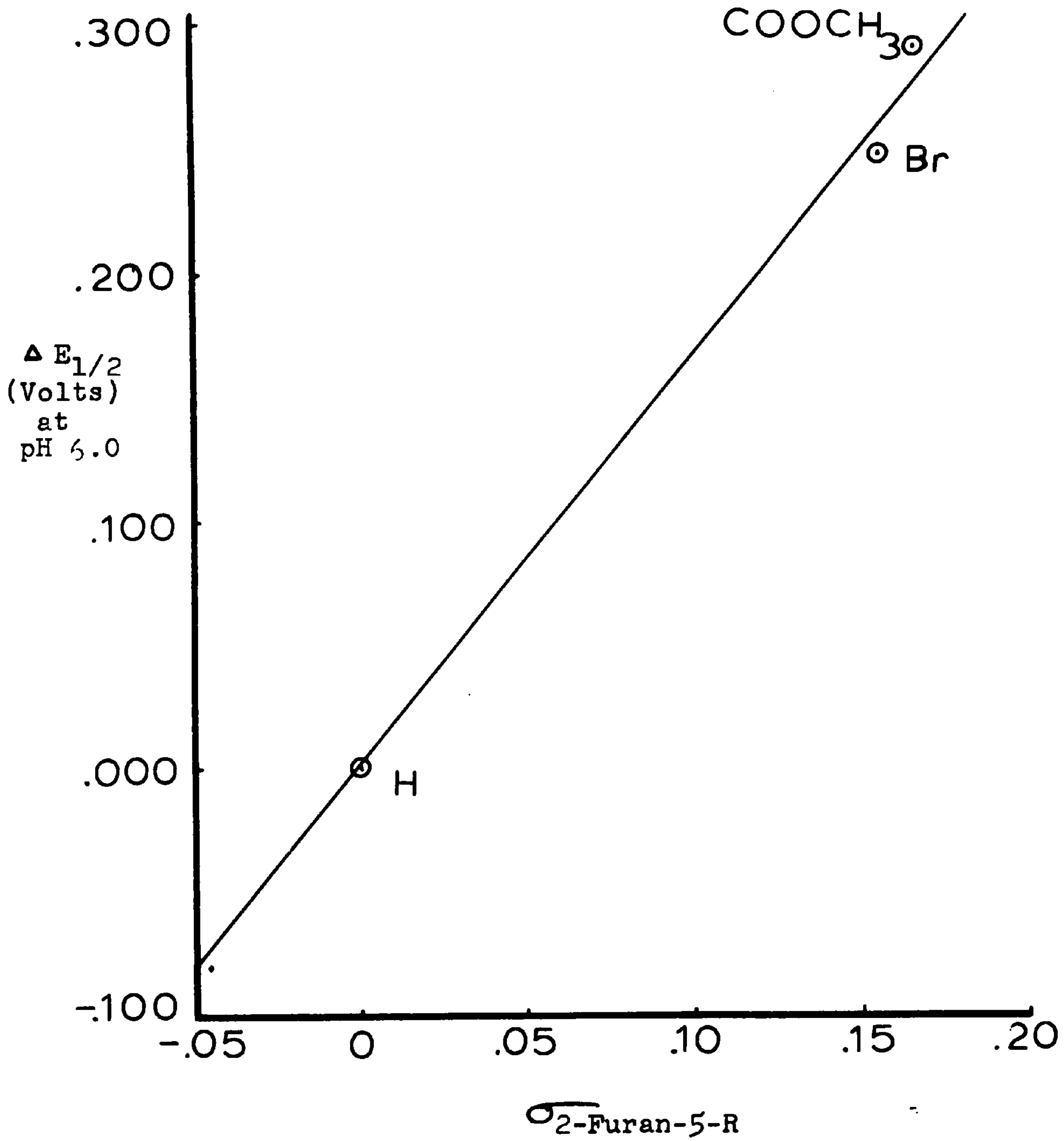
*B Buffer reduces before bromine reduces (X).

FIGURE 5

$\Delta E_{1/2}$ vs. $\sigma_{\text{2-Furan-5-R}}$

$\Delta E_{1/2} = E_{1/2}$


$- E_{1/2}$

The only measurement necessary, at this stage, is the change in half-wave potential between a substituted-2-bromofuran and 2-bromofuran. The sigma values obtained for a number of substituents at various ring positions are summarized in Table XVIII.

Comparison of Sigma Values

One of the reasons given for the acceptance of the Hammett equation is that it yields quantitative measures of the reaction parameters. Since these reaction constants and substituent constants have been determined, it would follow that these values should be examined with regard to their accuracy. Table XIX presents a compilation of sigma values for the thiophene series where the values calculated in this work are compared with other such sigma values taken from the literature. The methods used by these other workers to calculate the sigma values are given in the footnotes of Table XIX. Examination of this table shows that there is good agreement among workers for the thiophene sigma value for these substituents. Most of these values fall within the ± 15% error range as predicted by Jaffé (42) for the usual accuracy of this correlation.

Another way to estimate the accuracy of the thiophene sigma values is to calculate half-wave potentials of polysubstituted 2-bromothiophenes. These calculated half-wave potentials are then compared with the measured half-wave potentials for the same compound. It is known (89) that

TABLE XVIII

SIGMA VALUES FOR FURANS

R=Substituent	2-Furan-5-R	2-Furan-3-R
CH_2OH	-0.03	
H	0.00	0.00
OCH_3	0.02	
COO^- (Na^+)*F	0.07*A	0.05*A
COOH	0.06 0.19*A 0.17*I	0.06 0.11*A 0.11*I
Cl	0.15	
Br	0.16	0.13
$COOCH_3$	0.17	0.19
$COOCH(CH_3)_2$	0.17	
$COOCH_2CH=CH_2$	0.18	
$COOC_2H_5$	0.18	
NO_2	0.48	

All sigma values are measured at pH 6.0 unless otherwise noted.

*A Measured with no buffer present.

*F Salt of acid made by adding 0.2 ml. of 2<u>N</u> sodium hydroxide to the acid in solution.

*I Measured at pH 3.0.

TABLE XIX

COMPARISON OF SIGMA VALUES IN THIOPHENE

Substituent	*J	*K	*L	*M	*N
Cl	0.33	0.32	0.32	0.30	0.33
NO_2	0.70	0.63	0.63	1.03	0.72
CH_3	-0.17	-0.13	-0.13	-0.18	-0.09
Br	0.34				0.36

---

*J Values obtained from this work, $\sigma_{2\text{-thio-5-R}}$.

*K Measured difference in pKa of 5-substituted-2-thenoic acid, Zuman (8).

*L Measured difference in pKa of 5-substituted-2-thenoic acid, Price, Mertz and Wilson (87).

*M Measured rate of saponification of ethyl 5-substituted-2-thenoate (87).

*N Measured rate of hydrolysis of ethyl 5-substituted-2-thenoate, Thije and Janssen (88).

substituent constants are additive. Therefore changes in half-wave potential are calculated for tri- and tetrasubstituted bromothiophenes by using the modified Hammett equation in Equation 30.

$$\Delta E_{1/2} = .041 + 0.438 \Sigma \sigma \qquad (30)$$

These calculated reduction potentials for the reduction of the carbon-bromine bond in the 2-position are compared with the measured reduction potentials for the actual compound. The data collected in this exercise are shown in Table XX. The calculated half-wave potentials are plotted against the measured half-wave potentials in Figure 6. The average error of the data in Table XX is found to be ± 2.6% or ± 0.03 volts. The correlation coefficient, (r), for the line in Figure 6 is 0.993 and the standard deviation is 0.022. This indicates that the sigma values, obtained for a number of substituents, allow valid predictions of half-wave potentials for polysubstituted compounds with a high degree of accuracy. In addition, this acts to confirm the fact that sigma values obtained in Table XIV can be used with assurance.

It is informative to compare the sigma values for the same substituent when taken from the thiophene, furan, and benzene systems. These values are shown in Table XXI, and give an insight into the changes occurring as one passes from the thiophene to the benzene to the furan system.

It should be noted that most substituents remain in the same relative order and vary only in magnitude. However,

TABLE XX

COMPARISON OF CALCULATED AND MEASURED $E_{1/2}$ VALUES

Compound Number	Compound	Calculated $-E_{1/2}$	Measured $-E_{1/2}$	% Error
1	2,5-Dibromo-3-methylthiophene	1.457	1.400	4.1
2	3,5-Dibromo-2-ethylthiophene	1.402	1.375	2.0
3	2,3,5-Tribromothiophene	0.987	1.054	-6.4
4	3,5-Dibromo-2-isopropylthiophene	1.393	1.358	2.6
5	4,5-Dibromo-2-thiophenecarboxaldehyde	0.811	0.845	-4.0
6	4,5-Dibromo-2-thenoic Acid	1.102*A	1.131*A	-2.6
7	4,5-Dibromo-2-thenoic Acid	1.140*I	1.149	-0.8
8	4,5-Dibromo-2-thenoic Acid	1.192	1.153	3.4
9	Sodium 4,5-dibromo-2-thenoate*F	1.192	1.153	3.4
10	Methyl 5-bromo-3-methyl-2-thenoate	1.450	1.388	4.5
11	3,5-Dibromo-2-methylthiophene	1.411	1.393	1.3
12	4,5-Dibromo-2-methylthiophene	1.310	1.274	2.8
13	5-Bromo-3-methyl-2-thenoic Acid	1.455*A	1.450*A	0.3
14	5-Bromo-3-methyl-2-thenoic Acid	1.491*I	1.455*I	2.4
15	5-Bromo-3-methyl-2-thenoic Acid	1.542	1.514	1.8
16	Sodium 5-bromo-3-methyl-2-thenoate*F	1.577*A	1.552*A	1.6
17	2,4,5-Tribromo-3-methylthiophene	1.179	1.118	5.4
18	2,4-Dibromo-3-methylthiophene	1.463	1.455	0.5
19	2,3,4-Tribromothiophene	1.078	1.073	0.5

All measurements of $E_{1/2}$ were made at pH 6.0 unless otherwise noted.

*A Calculated and measured with no buffer present.

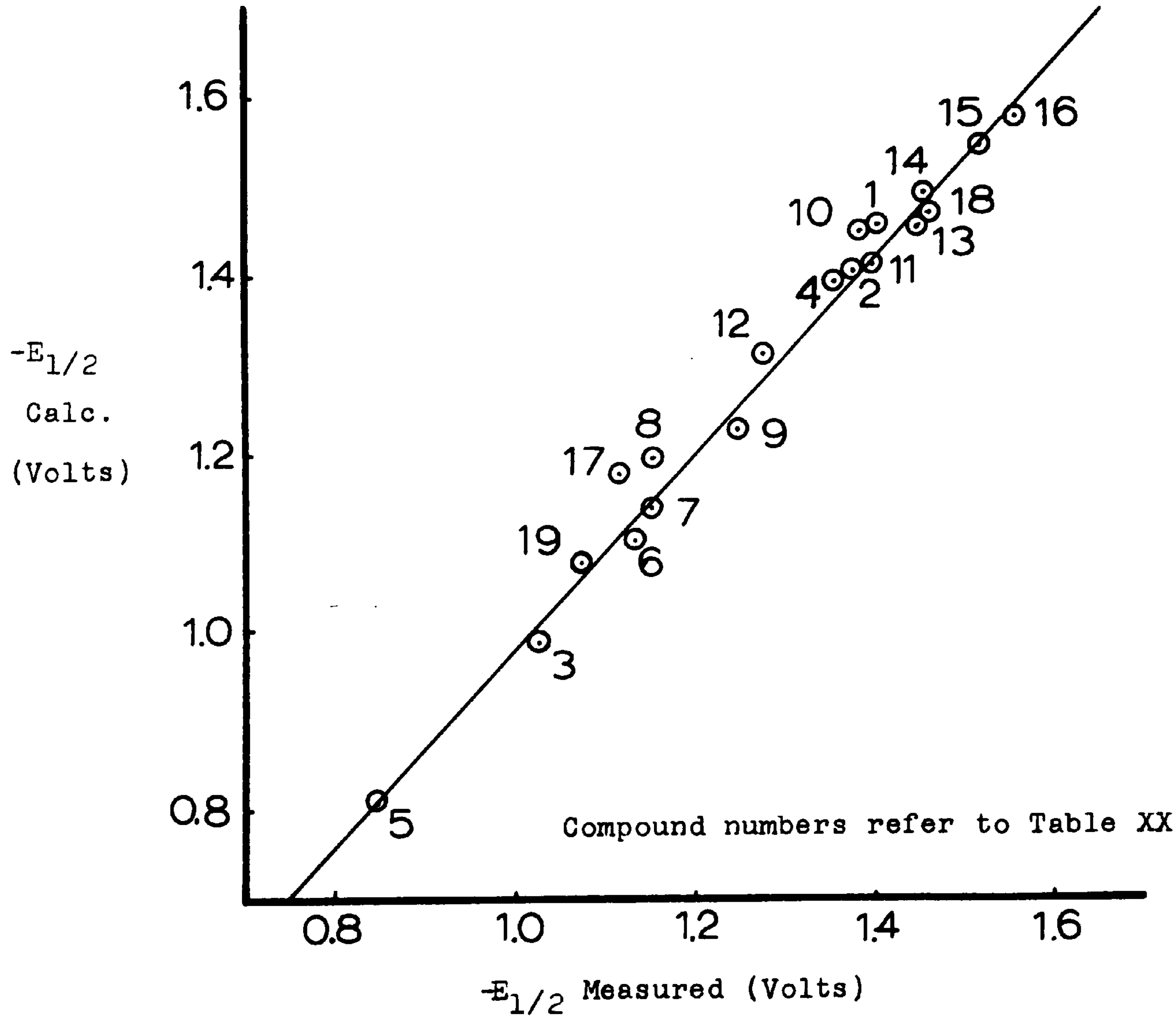
*F Salt of acid made by adding 0.2 ml. of 2N sodium hydroxide to the acid in solution.

*I Calculated and measured at pH 3.0.

Figure 6

$E_{1/2}$ Measured vs. $E_{1/2}$ Calculated

For Polysubstituted Bromothiophenes



Compound numbers refer to Table XX.

TABLE XXI

COMPARISON OF SIGMA VALUES ACROSS SYSTEMS

System	Thiophene	Furan	Benzene	
R=Substituent	2-Thio-5-R	2-Furan-5-R	Para	Meta
NO_2	0.70	0.48	0.78	0.71
$COCH_3$	0.51		0.50	0.38
$COOCH_3$	0.33	0.17	0.45	0.37
Br	0.34	0.16	0.23	0.39
Cl	0.33	0.15	0.23	0.37
COOH	0.32	0.19	0.45	0.37
COO^- (Na^+)	0.04	0.07	0.00	
OCH_3	0.02	0.02	-0.27	0.09
CH_3	-0.17		-0.17	-0.07
$t-C_4H_9$	-0.31		-0.20	-0.10

the sigma value for the methoxy group is +0.02 for both thiophene and furan, while in benzene it is -0.27. This rather large negative sigma value in the para position of benzene is mainly attributed to the large resonance effect of the methoxy group. Taft (23) has divided this para sigma value in benzene into a sigma inductive effect of 0.25 and a sigma resonance effect of -0.52. Addition of these two values gives a total sigma value of -0.27. Since the sigma value for the methoxy group is positive in both thiophene and furan, again this shows that the resonance forms are not as predominant in thiophene and furan as they are in benzene. Therefore the +I inductive effect becomes greater than the -M mesomeric effect and thus the sign of the sigma value for the methoxy group in these two heterocyclic systems is positive.

It is also noted in some instances that the thiophene sigma values in Table XXI compare more closely with the benzene σ_{meta} values than with the benzene σ_{para} values. This is noted in Table XXI for the Cl, NO_2, Br, $COOCH_3$, OCH_3 and COOH substituents. Thus, it may be possible to consider the 5-position relative to the 2-position in thiophene as a "psuedo" meta position. However before any firm conclusions can be drawn, more experimental work will have to be done comparing sigma values in all three systems.

Comparison of Reaction Constants

The Hammett relationship is extremely useful in evaluating substituent effects upon a vast number of reactions. In addition to this, it may be used to evaluate the character of the transition state. This latter approach examines the magnitude of the reaction constant. As discussed earlier, rho is a measure of the sensitivity of the reaction to substituent effects. Conversely, comparisons of various rho values for the same kind of reaction (reduction of a carbon-bromine bond in this case) under the same solution conditions can be used to suggest something about the degree of charge in the transition state. For example, the rho value (90) for the sulfation of alcohols is 4.60. Other work on this reaction strongly suggests a "fully" charged intermediate or carbonium ion. Correspondingly, reactions which have little carbonium ion character in the transition state have rho values on the order of 0.2 to 0.6. This has led a number of workers to correlate the character of the transition state with rho. Data have been compiled for a number of electrochemical reductions of carbon-halogen bonds. When the data obtained by Hussey (27), for parasubstituted iodobenzenes and bromobenzenes in 60% methanol-water, are plotted against Hammett sigma values, reaction constants of 0.197 volts and 0.286 volts are obtained respectively. The reaction constant for the 5-substituted-2-bromothiophenes (measured under similar experimental conditions) is 0.438 volts while that for the 5-substituted-2-bromofurans is 1.630 volts. It is noted first that all four rho values are positive. It has been shown (91) that a positive rho indicates that the reaction is facilitated by low electron density at the reaction site, and a negative rho implies a reaction favored by high electron density. This is verified in this work by observing that the acetyl group in 5-bromo-2-acetylthiophene draws electrons away from the reaction site (i.e. the carbon-bromine bond). Therefore less energy is needed to break the carbon-bromine bond in this particular case than would be needed for a substituent which pushes electrons toward the carbon-bromine bond. Hence, the reaction is facilitated by withdrawal of electrons at the reaction site and the rho value when calculated is positive as expected. Therefore it appears that the mechanism of the potential determining step in this case is a nucleophilic one. The most probable nucleophilic agent is the electron (or the electrode). The possibility of an electrophilic attack (e.g. by proton prior to electron transfer) is thus excluded.

Some insight into the fact that these rho values increase in going from iodobenzene, to bromobenzene, to bromothiophene, to bromofuran may be gained by studying the factors which Hammett has indicated (92) govern rho. He suggested that reaction constants have the form

$$\rho = \frac{B_1/D + B_2}{RT\ d^2} \qquad (31)$$

where R is the gas constant, T is the absolute temperature, D is the dielectric constant of the solvent, and d is the distance from the substituent to the reaction site. B_1 is assumed to depend on purely electrostatic interaction between the reacting derivative and the medium, and B_2 is assumed to measure the susceptibility of the reaction to changes in the charge density at the reaction site. Since rho depends on the effectiveness with which the side chain can transmit the electrical effect of the substituent to the reaction site, Hammett has attempted to treat this transmission term by including the factor $1/d^2$ in Equation 31. Thus the magnitude of the reaction constant is related with the distance from the substituent to the reaction site. The data collected in this work in which the rho value increases in going from iodobenzene to bromobenzene, to bromothiophene, to bromofuran can be explained in part by this factor. The distance from an iodine to the methyl carbon in p-iodotoluene is 7.77 A; the similar distance in p-bromotoluene is 7.60 A. The distance around the carbon chain in 5-methyl-2-bromothiophene is 7.56 A while the distance through the sulfur atom is 6.84 A. The distance around the carbon chain in 5-methyl-2-bromofuran is 7.54 A, while the distance through the oxygen atom is 6.14 A. Thus Equation 31 predicts correctly that rho would increase across this series.

Zuman (6) has also shown that the value of the reaction constant depends on the ionization state of the electroactive substance. He demonstrated this by obtaining different values of rho in different pH regions. Thus in electrochemical reduction it can be said that the rho value is a measure of the buildup of negative charge when the electrons come into contact with the electroactive species. The simplified accepted mechanism for the reduction, as determined by coulometric studies (84, 93) is:

$$RBr + 2e^- \rightarrow R^- + Br^- \qquad (32)$$

$$R^- + H_2O \rightarrow RH + OH^- \qquad (33)$$

The magnitude of the rho value would then be a measure of the buildup of negative charge on the R^- state caused by the attack of the two electrons. The greatest charge buildup would be expected on furan as compared to thiophene or benzene because this molecule holds the most electronegative element (oxygen has an electronegativity value of 3.5, while carbon and sulfur have values of 2.5).

From these data and other data (91), it can be concluded that rho is influenced by more than one factor. Therefore more systems should be studied in order to quantitatively determine the influence of these factors.

Future Work

An outgrowth of this work could be an attempt at dividing the thiophene sigma values into the polar, mesomeric, and steric portions. From the principles of organic chemistry, it is known (6) that the effects of substituents causing the shifts of half-wave potentials can be distinguished as polar, steric, and mesomeric. The polar, steric, and mesomeric contributions can often be treated as additive such as

$$\Delta E_{1/2} = P + S + M \qquad (34)$$

Equation 34 is the general equation expressing the shifts of half-wave potentials due to polar, steric and mesomeric effects of substituents. However the single value of half-wave potentials does not allow one to distinguish the various conditions of the substituent. In order to differentiate these contributions a proper choice of the electromeric effects for a given reaction series and also a choice of suitable substituents ought to be made. For instance, a substance can be chosen where only the polar effect is operative. This will give a measure of the polar effect. Then by choosing another substance where the polar and steric effects are operative, a measure of the steric effects can be obtained. By a similar process of addition and subtraction a measure of polar, steric and mesomeric effects operative in a substance can be obtained. So far, no reaction series has been found where only steric effect, mesomeric effect and both steric and mesomeric effects influence the shift of half-wave potentials. In order to obtain a quantitative value of these effects, methods will have to be devised whereby the mesomeric or steric effects can be measured separately.

Conclusion

This work has shown that the sigma values obtained from the benzenoid system cannot be reliably used in the thiophene system. As a result of this study, new substituent constants have been determined experimentally which are applicable to the thiophene and furan systems. Equations have been developed whereby additional sigma values can be easily determined by measuring the change in half-wave potential for the substituted 2-bromocompound. The new thiophene sigma values have been shown to be accurate and reliable. The accuracy of these values is verified by using the Hammett equation (Eq. 30) to predict half-wave potentials. These half-wave potentials can be predicted within ± 2.6% of the observed values. As a result of this work and earlier work, it has been clearly shown that in the thiophene system inductive effects operate to a higher degree than mesomeric effects. This is in opposition to the benzene system. Due to the work on sigma values, rho values were also calculated which give an insight into the charge buildup of the transition state. This work is helpful to analytical chemists because it provides a technique whereby the analysis of isomers of bromothiophenes can be accomplished with great precision.

APPENDIX I

Determination of Isomeric Mixture of Bromothiophenes

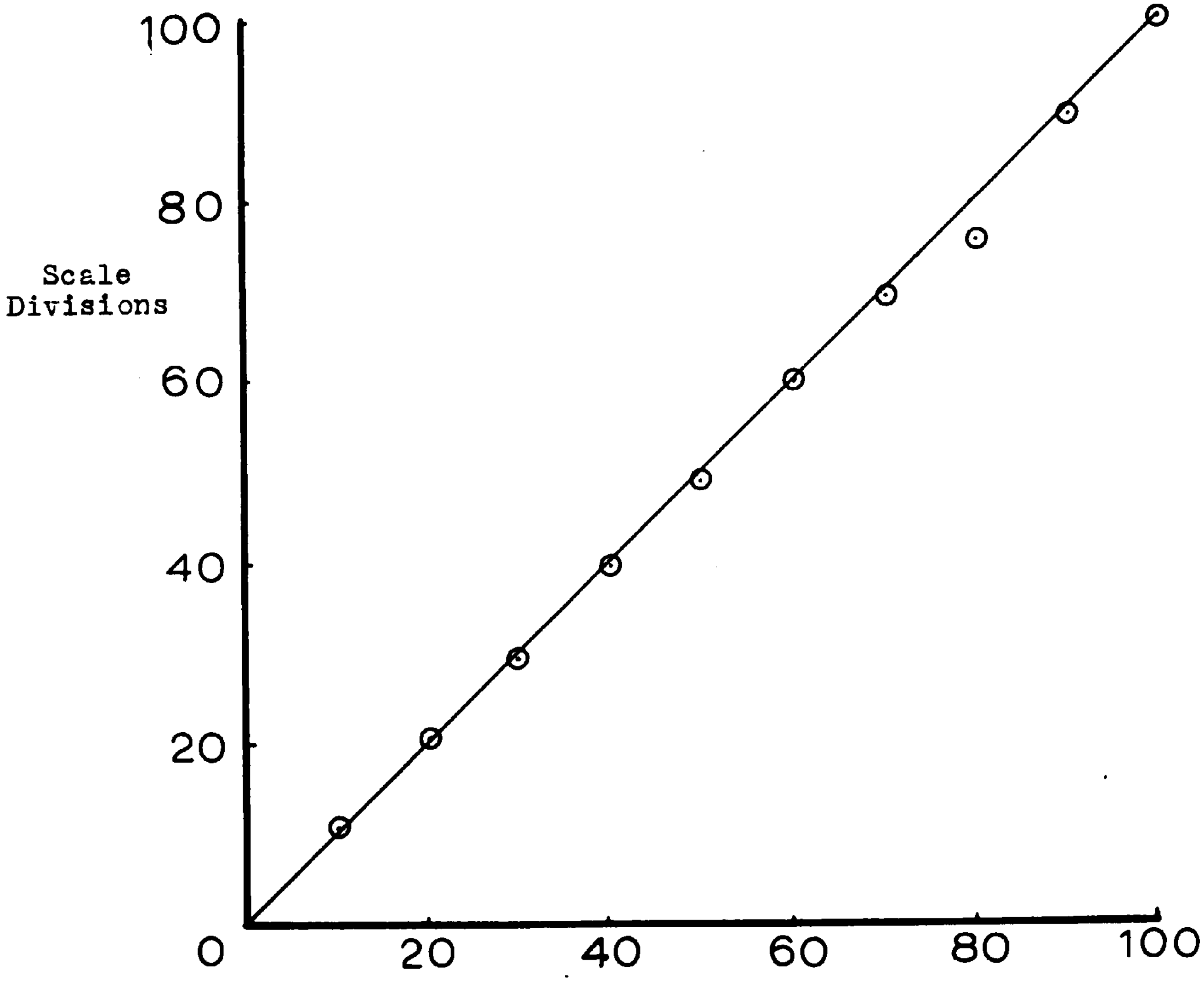
Due to the small difference in physical properties between monobromothiophenes, there is extreme difficulty in finding a method of analysis whereby the percentage of one isomer in the presence of the other can be determined. Polarography is appropriate in this particular situation. It provides, for example, a method whereby the amount of 2-bromothiophene in 3-bromothiophene can be determined with relative ease. A standard procedure for the determination of 3-bromothiophene in 2-bromothiophene is presented as an example of the utility of this approach.

Prepare standard solutions of known amounts of 3-bromothiophene in 2-bromothiophene. The total concentration of bromothiophene is 1.0×10^{-3} M. The electrolyte is 0.1 M $(CH_3)_4NCl$ and the solvent is 60% methanol-water. Polarograms of these solutions are obtained and the diffusion current is measured for the polarographic wave due to the reduction of 2-bromothiophene. A calibration curve (shown in Figure VII) is obtained by plotting the diffusion current of the 2-bromothiophene wave against the known concentration of 2-bromothiophene in 3-bromothiophene. For an unknown, a pure sample of a mixture of 2- and 3-bromothiophene is weighed so that the combined concentration is 1×10^{-3} M. A polarogram of the unknown is obtained in 0.1 M $(CH_3)_4NCl$ and 60% methanol-water and the diffusion current for the reduction of 2-bromothiophene is measured. From the calibration curve, the actual concentration of 2-bromothiophene in 3-bromothiophene can be determined.

Table XXII shows the results of such a determination of 3-bromothiophene in 2-bromothiophene carried out by a slightly different method. In Table XXII the percentage of 3-bromothiophene in 2-bromothiophene is determined by comparing the measured relative diffusion current heights for the 2-bromo-

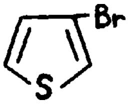
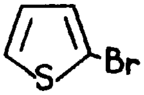
Figure 7

CALIBRATION CURVE FOR DETERMINATION OF 2-BROMOTHIOPHENE



Conc. of 2-Bromothiophene x 10^5

TABLE XXII

DETERMINATION OF  IN 

% 3 Known	Height of 2-Wave	Height of 2+3 Wave	% 3 Calc.	Absolute Deviation
100	0	100	100	--
90	11.5	106.5	89.20	0.8
80	21.0	102.0	79.41	0.6
70	30.0	102.0	70.59	0.6
60	40.0	104.5	61.72	1.7
50	49.0	100.5	51.24	1.2
40	60.5	103.0	42.23	2.2
30	69.5	103.0	32.52	2.5
20	75.0	96.5	21.24	1.2
10	89.0	100.0	11.00	1.0
0	100.0	100.0	0	--

Total combined concentration of 2-bromothiophene and 3-bromothiophene in the electrolysis cell is 1 x 10^{-3} M.

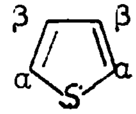
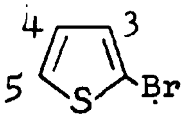
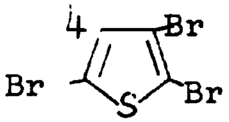
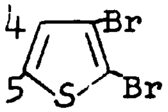
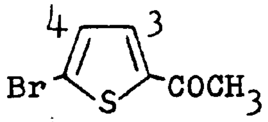
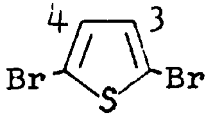
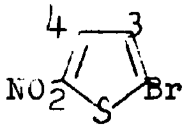
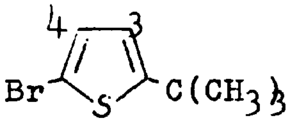
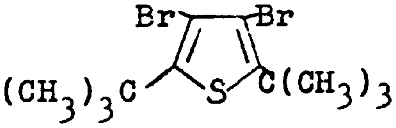
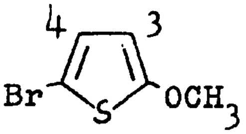
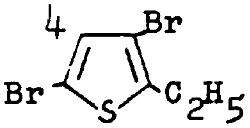
thiophene wave and the total height for the 2-bromothiophene and 3-bromothiophene waves together. The diffusion current height for the 2-bromothiophene wave is measured at -1.75 volts, while the total height for the 2- and 3-bromothiophenes is measured at -2.125 volts. The average absolute deviation between the known and calculated percentage of 3-bromothiophene from Table XXII is ± 1.3. A calibration curve is not needed when the percentages are calculated in this manner. However the isomeric mixture of bromothiophenes may not contain anything other than bromothiophenes for this method to apply. The determination of the amounts of dibrominated or tribrominated isomers in a mixture can also be performed by this procedure.

APPENDIX II

NMR SPECTRA

The chemical shifts (relative to TMS) and the coupling constants for the NMR spectra of a number of bromothiophenes are recorded in Tables XXIII and XXIV. These spectra were taken mainly as a confirmation of structure of the substituted bromothiophenes. The theory of NMR can be found in standard texts (77-83) and a thorough study of thiophene NMR spectra can be obtained from the work of Gronowitz (11).

TABLE XXIII
NMR SPECTRA OF BROMOTHIOPHENES

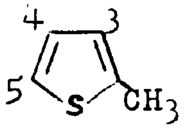
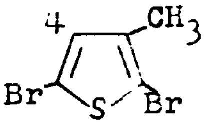
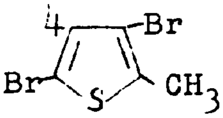
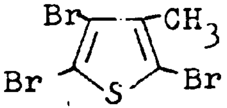
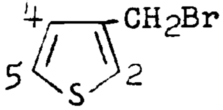
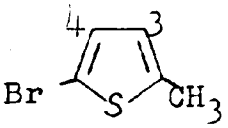
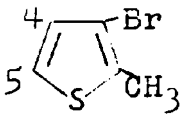
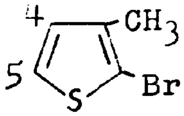
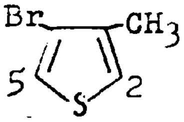
Compound	Position	δ	Simplicity	Coupling c/s	
	α-H β-H	7.23 7.04	m m		
	3H 4H 5H	6.91 6.67 7.01	q q q	J_{35} J_{34} J_{45}	1.5 3.7 5.4
	4H	6.83	s		
	4H 5H	7.14 6.81	d d	J_{45}	5.8
	2 CH$_3$CO 3H 4H	2.50 7.44 7.09	s d d	J_{34}	4.05
	3H 4H	6.74 6.74	s s		
	3H 4H	7.08 7.69	d d	J_{34} J_{34}	4.41 4.37
	2 C(CH$_3$)$_3$ 3H 4H	1.59 6.70 6.76	s d d		
	2 C(CH$_3$)$_3$ 5 C(CH$_3$)$_3$	1.28 1.28	s s		
	2 OCH$_3$ 3H 4H	3.81 5.94 6.67	s d d	J_{34}	4.0
	2 CH$_2$ 2 CH$_3$ 4H	2.73 1.24 6.82	q t s		

s = singlet; d = doublet, etc.; m = multiple splitting.

d-m = doublet with multiple splitting of each doublet peak.

TABLE XXIV

NMR SPECTRA OF BROMOMETHYLTHIOPHENES

Compound	Position	δ	Simplicity	Coupling c/s
	2 CH_3 3H 4H 5H	2.38 6.64 6.76 6.95	d m q-m q	J_{34} 3.5 J_{45} 4.95 J_{35} 1.45 J_{2CH_3-4} 0.3 ca. J_{2CH_3-3} 9.98
	3 CH_3 4H	2 06 6.59	s s	
	2 CH_3 4H	2.25 6.78	d m	J_{2CH_3-4} 0.35
	3 CH_3	2.21	s	
	3 CH_2	4.37	s	
	2 CH_3 3H 4H	2.33 6.42 6.75	d m d-m	J_{2CH_3-3} 1.17 J_{34} 3.5 J_{2CH_3-4} 0.32 ca.
	2 CH_3 4H 5H	2.32 6.94 6.78	d d m	J_{2CH_3-5} 0.3 ca. J_{45} 5.37
	3 CH_3 4H 5H	2.12 6.65 7.02	s d d	J_{45} 5.5
	2H 3 CH_3 5H	6.79 2.15 7.07	m d d-m	J_{25} 3.4 J_{3CH_3-2} 1.07 J_{3CH_3-5} 0.25 ca.

s = singlet; d = doublet, etc.; m = multiple splitting.

d-m = doublet with multiple splitting of each doublet peak.

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VITA

David Rodney Latshaw, son of Willis D. and Augusta M. Latshaw, was born on November 4, 1939, in Allentown, Pennsylvania. He attended public schools in Allentown, Pennsylvania until graduating from Allen High School in June 1957.

In September 1957, he entered Muhlenberg College, Allentown, Pennsylvania, and he received a Bachelor of Science degree in Natural Science in June 1961. While at Muhlenberg College he served as a laboratory instructor in Organic Chemistry, and he worked on a research project sponsored by Trojan Powder Company of Allentown, Pennsylvania.

Mr. Latshaw entered The Graduate School of Lehigh University, Bethlehem, Pennsylvania in September 1961.

During the Summer of 1962, Mr. Latshaw worked at the Homer Research Laboratories of Bethlehem Steel Company, Bethlehem, Pennsylvania, in the Chemical Engineering Division.

Upon returning to Lehigh University in Fall 1962, he continued working in the Chemistry Department of Lehigh University under the direction of Dr. A. James Diefenderfer. Mr. Latshaw received the Master of Science degree in Analytical Chemistry on October 13, 1963. His thesis was entitled, "Spectrophotometric Determination of Titanium Using Thiocyanate in Ethanol".

He continued working at Lehigh University and in November, 1963 he was appointed research assistant under Dr. Diefenderfer.

Mr. Latshaw is a member of the American Chemical Society and an associate member of Sigma Xi. In February, 1966, he presented a talk on his work at the First Middle Atlantic Regional Meeting, A.C.S., Philadelphia, Pennsylvania. He expects to receive the degree of Doctor of Philosophy in Chemistry on October 9, 1966.