chloric acid and extracted three times with methylene chloride. The extracts were dried over $CaCl_2$ and concentrated and the residue was distilled under reduced pressure to yield 17.2 g (68%) of liquid: bp 55–57° (14 mm); $n^{20}D$ 1.4809; nmr (CS_2), δ 1.25 (t, J = 7.5 Hz, CH_3CH_2), 1.31 (d, J = 7.5 Hz, CH_3CS), 1.57 (d, J = 6 Hz, CH_3CCl). The mixture was calculated to contain 86% 2-chloro-4-thiahexane (**12a**) and 14% 1-chloro-2-ethylthiopropane (**12b**).

Reaction of the Mixture of 12a and 12b with Thiourea.—A solution of 9.0 g (0.065 mol) of **12a** and **b** (86:14) obtained above with 5.5 g (0.072 mol) of thiourea in 100 ml of ethanol was heated to reflux for 16 hr and concentrated under reduced pressure. The solid residue was dissolved in water and was treated with 3.2 g (0.08 mol) of sodium hydroxide in 25 ml of water. An oil which separated was removed and the aqueous layer was extracted with ether. After combining the oil and the ether extract, drying ($CaCl_2$), and concentrating, the residue was distilled under reduced pressure to yield 5.1 g (58%) of liquid: bp 60–62° (2.5 mm); $n^{20}D$ 1.5127. Gas chromatography of this sample on column A at 125° showed, in addition to several minor impurities, a large peak at 11.2 min with a shoulder at 10.7 min. The shoulder was shown to correspond to the secondary thiol **13a**. The nmr spectrum (CS_2) confirmed the presence of the secondary thiol **13a** by the presence of a doublet at δ 1.90 (J = 5 Hz) due to the secondary thiol proton. A triplet at δ 1.62 (J = 8.5 Hz) was assigned to the primary thiol proton of **13b**. Integration of these two sets of peaks indicated that **13a** and **b** were present in the ratio 16:84. The ir spectra of **13a**, obtained from the base-catalyzed addition of ethanethiol to propylene sulfide, and of the mixture of **13a** and **b** obtained above, were very similar showing only some minor differences.

Lithium Aluminum Hydride Reduction of Propylene Sulfide.—Propylene sulfide (10 g, 0.135 mol) in an equal volume of dry ether was added with stirring to 5.0 g (0.13 mol) of lithium aluminum hydride in 40 ml of dry ether which was being cooled in an ice–water bath. When the addition was completed the mixture was heated to reflux for 1 hr. The mixture was then cooled and the excess hydride was destroyed by the careful addition of 220 ml of 3 N hydrochloric acid. After separation and drying over magnesium sulfate, the ether layer was analyzed by glpc (column A at 60°). The major monomeric product (99.5%) had a retention time identical with that of authentic 2-propanethiol while a trace component (0.5%) had a retention time identical with that of 1-propanethiol.

Registry No.—**1a**, 1561-70-2; **1b**, 16621-19-5; **2a**, 16621-20-8; **2b**, 16621-21-9; **3a**, 16621-22-0; **3b**, 814-64-2; **4a**, 16621-24-2; **4b**, 16621-25-3; **5a**, 16621-26-4; **5b**, 2386-59-6; **6a**, 16622-60-9; **6b**, 16621-28-6; **7a**, 16621-29-7; **7b**, 16621-30-0; **8a**, 16621-31-1; **8b**, 16621-32-2; **9a**, 16621-33-3; **9b**, 16621-34-4; **10a**, 3001-64-7; **10b**, 1068-47-9; **11**, 16621-37-7; **12a**, 692-30-8; **12b**, 16621-39-9; **13a**, 16621-40-2; **13b**, 16621-41-3; **14a**, 16621-42-4; **14b**, 16621-43-5; **15a**, 16621-44-6; **15b**, 16621-45-7; **16a**, 16621-46-8; **16b**, 16621-47-9; **17**, 16621-48-0; **18a**, 1561-69-9; **18b**, 16621-50-4; **19a**, 16621-51-5; **19b**, 7763-79-3; **20a**, 16621-53-7; **20b**, 16621-54-8.

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Acid-Catalyzed Brominations, Deuterations, Rearrangements, and Debrominations of Thiophenes under Mild Conditions

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Bromination and deuteration of some substituted thiophenes have been accomplished under remarkably mild conditions. Upon treatment with N-bromosuccinimide in acetic acid–chloroform solution at room or slightly elevated temperatures, 3-methyl, 3-phenyl, 3-phenylthio, and 3-bromothiophenes are rapidly brominated in the 2 position in nearly quantitative yields. Bromination of 2-methyl, 2-phenyl, 2-phenylthio, and 2-bromothiophenes under the same conditions yields the 5-bromo derivatives. In refluxing deuterioacetic acid 3-alkyl-, 3-phenyl-, and 3-phenylthio-substituted thiophenes undergo deuterium–hydrogen exchange at the 2 position while the corresponding 2-substituted derivatives are exchanged at the 5 position. In solutions of hydrogen bromide in acetic acid some 2-bromothiophenes undergo rearrangements. 2-Bromo-3-phenylthiophene, for example, forms 2-bromo-4-phenylthiophene, 3-phenylthiophene, and 2,5-dibromo-3-phenylthiophene. Preliminary investigations of the mechanism of this reaction have been made. Substitution of 3-phenylthiophene at the 2 position is the kinetically controlled reaction under all conditions investigated. When the bromine acceptor phenol is added to the hydrogen bromide–acetic acid mixture, bromothiophenes which are subject to rearrangement can be debrominated in good to high yields.

In the course of studies of the mechanisms of the photochemically induced rearrangements of thiophenes[1] we have needed a number of deuterium-labeled starting materials.[2,3] Our normal technique of introducing deuterium at a specific position in the thiophene ring involves conversion of a bromo into a deuterio substituent. The necessity of having isomer-free bromothiophene precursors led us to investigate conditions necessary to obtain selective, high-yield brominations. The possibilities of direct deuterium-hydrogen exchange were also explored. We find that with certain thiophene derivatives both bromination and direct hydrogen–deuterium exchanges occur under remarkably mild conditions to give selectively substituted products of kinetic control.[4] We have furthermore observed that some bromothiophenes readily undergo rearrangement in the presence of strong acid catalysts.

Bromination.—When treated with N-bromosuccinimide (NBS) in a 50:50 (v/v) mixture of chloroform and glacial acetic acid, 3-alkyl, 3-phenyl-,[5] and 3-phenylthiothiophenes are brominated nearly quantitatively at the 2 position (eq 1). Reaction is complete

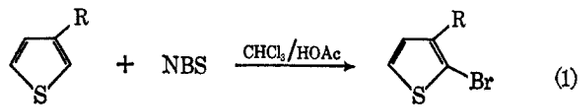
(1) See, for example, H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhuis, *J. Amer. Chem. Soc.*, **89**, 3501 (1967).

(2) R. M. Kellogg and H. Wynberg, *ibid.*, **89**, 3495 (1967).

(3) R. M. Kellogg, J. J. C. Vermeer, and H. Wynberg, unpublished work.

(4) See, for an excellent review of bromination as well as other aspects of thiophene chemistry, S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 1 (1963).

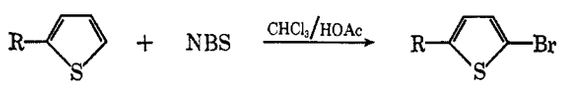
(5) Selective bromination of 3-phenylthiophene with NBS in carbon tetrachloride has recently been reported: S. Gronowitz, N. Gjös, R. M. Kellogg, and H. Wynberg, *J. Org. Chem.*, **32**, 463 (1967).



$R = CH_3, C_6H_5,$[5] C_6H_5S, Br

within a matter of minutes at ambient or slightly elevated temperatures. The reaction of 3-bromothiophene was slower and was about 80% complete after 30 min of refluxing.[6]

Under similar conditions some 2-substituted thiophenes were brominated in the 5 position (eq 2).[7]



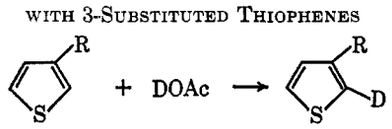
$R = C_6H_5,$[7] CH_3, C_6H_5S, Br, H (2)

Thiophene was converted primarily into 2-bromothiophene but the overbromination product, 2,5-dibromothiophene, was formed as well.

Similar results are obtained using carbon tetrachloride–acetic acid mixtures.[8] Reactions in carbon tetrachloride or chloroform alone give the same products but proceed many times slower than in mixtures with acetic acid. The strongly deactivated acetylthiophenes could not be brominated with NBS under the reaction conditions used by us.

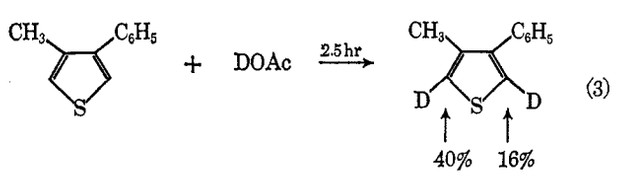
Deuterium–Hydrogen Exchange.—In refluxing deuterioacetic–deuterium oxide solutions various 3-substituted thiophenes undergo exchange exclusively at the 2 position. Results with some representative thiophenes are shown in Table I.

TABLE I
DEUTERIUM-HYDROGEN EXCHANGE WITH 3-SUBSTITUTED THIOPHENES



R	Time, hr	% exchange
CH_3	5	100
t-Bu	24	67
C_6D_5[8]	5	34
C_6H_5S	5	100

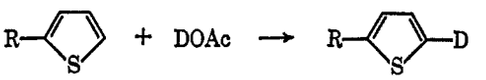
Exchange in 3-phenyl-4-methylthiophene occurred 2.5 times faster α to methyl as compared to substitution α to phenyl (eq 3).



(3)

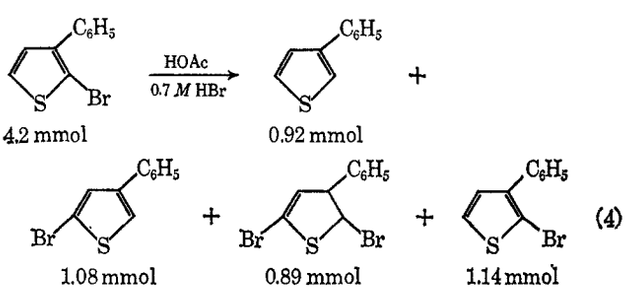
Exchange at the 5 position was observed with various 2-substituted thiophenes. The results of these experiments are summarized in Table II.

TABLE II
DEUTERIUM–HYDROGEN EXCHANGE WITH 2-SUBSTITUTED THIOPHENES



R	Time, hr	% exchange
CH_3	5	42
t-Bu	5	25
C_6H_5	5	40
C_6H_5S	5	33

Acid-Catalyzed Rearrangements.—Recently Gronowitz, Gjös, and two of the present authors[5] in a joint publication reported that 3-phenylthiophene gave exclusively 2-bromo-3-phenylthiophene when treated with NBS in carbon tetrachloride and a mixture consisting mainly of 2-bromo-4-phenylthiophene when treated with bromine in refluxing acetic acid. Although correct as reported, the reaction has since been found to be considerably more complex than was originally assumed. In refluxing acetic acid containing hydrogen



(4)

bromide, 2-bromo-3-phenylthiophene is transformed into a mixture of 2-bromo-4-phenylthiophene, 2,5-dibromo-3-phenylthiophene, and 3-phenylthiophene plus starting material. After 20 min reflux in acetic acid (0.7 *M* in hydrogen bromide) the product mixture shown in eq 4 was obtained.[9] Appreciable rearrangement could be detected after only 5 min reaction. In refluxing acetic acid alone no rearrangement of 2-bromo-3-phenylthiophene was detected after *ca.* 1 hr. Perchloric acid in acetic acid induced rearrangement, but considerably more decomposition took place than when hydrogen bromide was used.

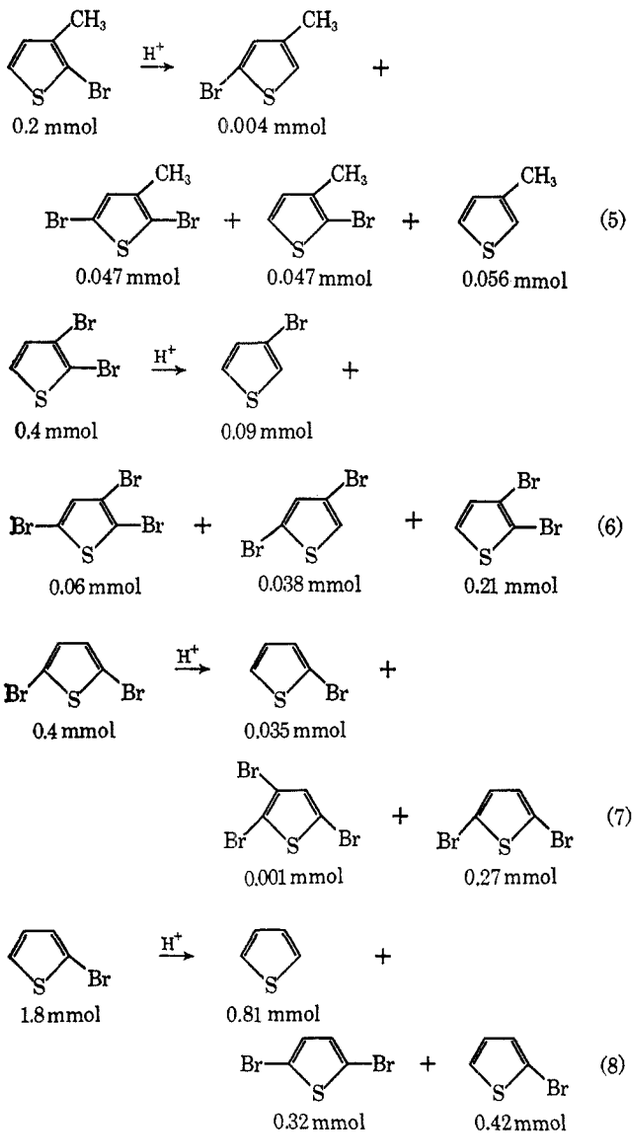
The reactions of a number of other brominated thiophenes in solutions of acetic acid containing hydrogen bromide were examined. Results of these experiments are shown in eq 5–8. Only a slight amount of rearrangement of 2,4-dibromothiophene was noted while 3,4-dibromothiophene and 3-bromothiophene seemed to be completely stable under the conditions used (see Experimental Section).

(6) Compare, however, with a recommended procedure for the preparation of 2,3-dibromothiophene which involves a 9.5 hr reaction between bromine and 3-bromothiophene: S. Lawesson, *Ark. Kemi*, **11**, 373 (1957).

(7) Preparation of 2-phenyl-5-bromothiophene by bromination of 2-phenylthiophene with NBS in carbon tetrachloride containing benzoyl peroxide has been reported: A. Kosak, R. J. F. Palchak, W. A. Steele, and C. M. Selwitz, *J. Amer. Chem. Soc.*, **76**, 4450 (1954).

(8) In one case (see Experimental Section) dibromodimethylhydantoin was used in place of NBS with excellent results. Both bromine atoms of the hydantoin were reactive. We thank Philips Duphar N.V. (The Netherlands) for a gift of dibromodimethylhydantoin.

(9) Some of these results were presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967. This rearrangement was simultaneously and independently discovered by Gjös and Gronowitz who have communicated their results in brief form: N. Gjös and S. Gronowitz, *Acta Chem. Scand.*, in press. We thank Professor Gronowitz for making their results available to us prior to publication. The previous rationalizations of the dependence of product on solvent did not take the possibility of a rearrangement into account.



Acid-Catalyzed Debrominations.—The products obtained from acid-catalyzed rearrangement of bromothiophenes suggested an intermolecular transfer of the bromo substituent. We reasoned that if this were the case a reaction in the presence of a good bromine (or bromonium ion) acceptor should induce debromination of bromothiophenes. Using an equimolar amount of phenol (based on bromothiophene) as acceptor, 2-bromo-3-phenylthiophene was debrominated in refluxing acetic acid containing hydrogen bromide to give an 84% yield (isolated) of 3-phenylthiophene (eq 9). Neither 2-bromo-4-phenylthiophene nor 2,5-dibromo-3-phenylthiophene were formed in detectable amounts. Debromination was noted even at room temperature. The results of debromination of some bromothiophenes are shown in Table III.

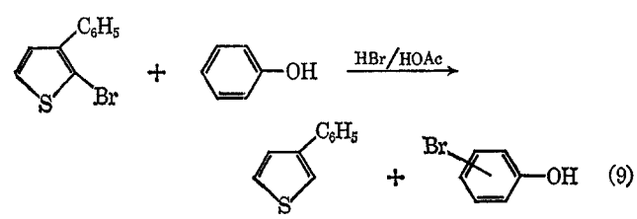


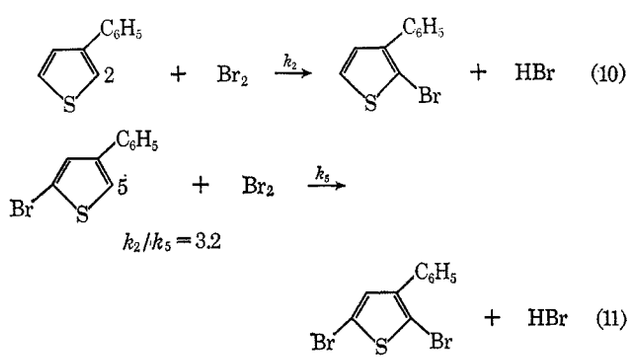
TABLE III
REACTIONS OF BROMOTHIOPHENES WITH PHENOL IN ACIDIC MEDIA[a]

Reactant	Product (yield)
2,3-Dibromothiophene	3-Bromothiophene (90%)
2,4-Dibromothiophene	3-Bromothiophene (20%) + starting material (30%)
2-Bromothiophene	Thiophene (72%)
2,5-Dibromothiophene	Thiophene (51%) + 2-bromothiophene (13%)
2,3,5-Tribromothiophene	2,3-Dibromothiophene (25%) + 3-bromothiophene (trace) + starting material (18%)
2-Bromo-3-methylthiophene	3-Methylthiophene (35%)

[a] Conditions were 0.2 *M* solutions of bromothiophene and phenol in acetic acid 1 *M* in hydrogen bromide. Reaction times were 5 hr.

Mechanism of Rearrangement of Bromothiophenes.—A preliminary study of the mechanism of rearrangements of bromothiophenes was deemed worthwhile. The rearrangements of the various bromo derivative of 3-phenylthiophene were chosen for detailed study. A solution of 3-phenylthiophene in chloroform–acetic acid held at 0° was treated with 0.1 equiv of bromine and the reaction was quenched with thiosulfate solution after 1 min. Reaction was complete within this time as shown by the disappearance of the bromine color. The ratio of 2-bromo-3-phenylthiophene to 2-bromo-4-phenylthiophene in the reaction mixture was *ca.* 660 to 1. A similar reaction carried out in refluxing acetic acid (*ca.* 120°) gave, after 1 min, 2-bromo-3-phenylthiophene and 2-bromo-4-phenylthiophenes in a ratio of *ca.* 190 to 1 (a small amount of 2,5-dibromo-3-phenylthiophene was also detected). These experiments show the 2 position of 3-phenylthiophene to be, dependent on temperature, 200–700 times more reactive than the 5 position toward bromination and 2-bromo-3-phenylthiophene to be, therefore, the primary *kinetically controlled* bromination product.

The relative reactivities of the 2 position in 3-phenylthiophene compared to the 5 position in 2-bromo-4-phenylthiophene were determined (eq 10 and 11).



Equimolar amounts of 3-phenylthiophene and 2-bromo-4-phenylthiophene were allowed to react at 0° for 1 min with 0.1 equiv of bromine (based on total thiophene); 2-bromo-3-phenylthiophene and 2,5-dibromo-3-phenylthiophene were formed in 3.2:1 molar ratio. This product ratio becomes the rate constant ratio under the assumption that the thiophene concentrations are large and unchanging compared to the bromine concentration.

The subsequent fate of 2-bromo-3-phenylthiophene under acid-catalyzed conditions was investigated

under the standard conditions of 70 ± 1° and 1 *M* hydrogen bromide in acetic acid. The change of composition with time of a reaction mixture originally 0.099 *M* in 2-bromo-3-phenylthiophene is shown in Figure 1. The disappearance of 2-bromo-3-phenylthiophene between 20 and 200 min follows a first-order rate plot well with a first-order rate constant for disappearance of 1.0×10^{-4} sec^{-1}. Deviation from first-order kinetics is serious after this time. A run 0.35 *M* in 2-bromo-3-phenylthiophene gave a first-order rate constant of 0.86×10^{-4} sec^{-1} over the first 200 min of reaction. 3-Phenylthiophene, the most important reaction product over the first stages of reaction (see Figure 1), failed to depress the initial rate of disappearance of starting material as shown by a run 0.093 *M* in 2-bromo-3-phenylthiophene and 0.018 *M* in 3-phenylthiophene; the first-order rate constant was 0.90×10^{-4} sec^{-1} for disappearance of 2-bromo-3-phenylthiophene over the first stages of reaction.

The reactions of 2,5-dibromo-3-phenylthiophene were investigated to determine whether this material is an intermediate in the rearrangements. Difficulties were experienced in the preparation of 2,5-dibromo-3-phenylthiophene; a sample, *ca.* 15% contaminated with 3-phenylthiophene and the monobromo isomer, was isolated by preparative gas chromatography. The first-order rate constant for disappearance of 2,5-dibromo-3-phenylthiophene in a 0.0084 *M* solution was 3×10^{-5} sec^{-1}. The products were 2-bromo-4-phenylthiophene and 2-bromo-3-phenylthiophene in a ratio of *ca.* 2 to 1. A trace of 3-phenylthiophene was also formed. Material balances accounted for 90–110% of the starting material.

Under the reaction conditions 2-bromo-4-phenylthiophene was not stable; the first-order rate constant for disappearance was 3×10^{-5} sec^{-1} for a 0.0324 *M* solution. The major reaction product was 3-phenylthiophene but in addition small amounts of 2-bromo-3-phenylthiophene as well as 2,5-dibromo-3-phenylthiophene could also be detected. Material balances accounted for roughly 90% of the starting material.

Discussion

Three aspects of this investigation need further comment: (a) the highly specific bromination and deuterations of various thiophenes under very mild conditions,[10] (b) the scope and mechanism of the facile acid-catalyzed rearrangements of some bromothiophenes under more rigorous conditions, and (c) the acid-catalyzed debrominations not requiring a strong reducing agent.

Brominations.—The exclusive formation of ring substitution products, the apparent catalysis by acetic acid,[11] the lack of substituent bromination with methylthiophenes, and the complete agreement of the position of substitution with that found in electrophilic deuterium–hydrogen exchange, all point to an electrophilic bromination by NBS under our conditions. Some confusion exists, however, regarding the reactions of NBS with thiophenes since allylic brominations *via* a free-radical mechanism may also be accomplished with this reagent. Bromination of 2-methyl- or 3-methylthiophenes with NBS in carbon tetrachloride solution, for example, gives side-chain bromination in addition to substantial quantities of ring-brominated products.[12] Allylic substitution is clearly a free-radical reaction but the ring-substitution products could, in principle, arise either from homolytic aromatic substitution or, alternatively, from the concurrent operation of an electrophilic bromination mechanism. Our results show ring substitution to be the exclusive reaction under conditions conducive to electrophilic reaction.[13,14] Electrophilic substitution has also been observed in the ring brominations of some other aromatics in reactions with NBS in the polar solvent, propylene carbonate.[15]

Gronowitz[4] has summarized the theoretical, mechanistic, and preparative aspects of most electrophilic substitutions of thiophene in 20 admirable pages. The preparative aspects of electrophilic bromination of thiophene have received more attention than the mechanism

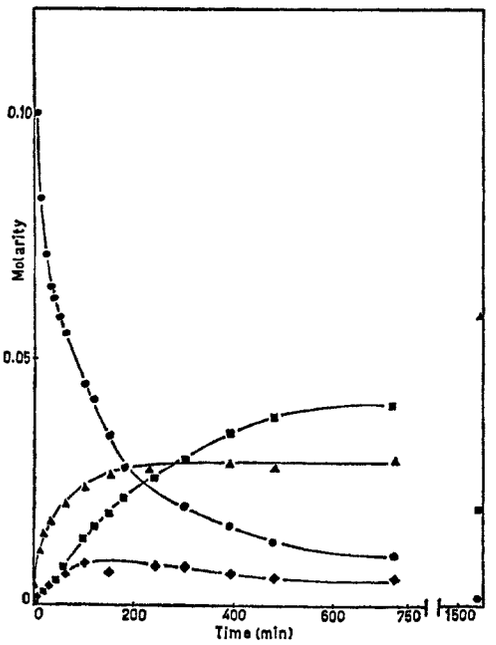


Figure 1.—Change of composition with time of 0.1 *M* 2-bromo-3-phenylthiophene in acetic acid 1 *M* in HBr: ●, 2-bromo-3-phenylthiophene; ▲, 3-phenylthiophene; ■, 2-bromo-4-phenylthiophene; ◆, 2,5-dibromo-3-phenylthiophene.

(10) Bromination, deuteration, and lithiation applied to the dithienyls will be reported separately: R. M. Kellogg, A. P. Schaap, and H. Wynberg, unpublished data.

(11) Our experience has been that reactions of 3-phenylthiophene, for example, with NBS in carbon tetrachloride proceed with unreproducible reaction times varying from 10 to 80 hr.[5] The recommended procedure for the bromination of 2-bromothiophene with NBS in carbon tetrachloride involves a reaction time of 30 hr.[5]

(12) See, for typical references (a) K. Dittmer, R. P. Martin, W. Herz, and S. J. Cristol, *J. Amer. Chem. Soc.*, **71**, 1201 (1949); (b) T. W. Campbell and W. W. Kaeding, *ibid.*, **73**, 4018 (1951); (c) E. Campaigne and B. F. Tullar, *Org. Syn.*, **33**, 96 (1953).

(13) A slight modification of the known[14] mechanism of free-radical allylic or benzylic bromination by NBS provides an attractive rationalization of thiophene brominations. The free-radical reactions require free bromine in low concentrations as the active brominating agent; in our reactions the combination of polar medium and reactive substitution could promote electrophilic substitution by bromine (or bromonium ion) but the details of bromine formation could be analogous to the free-radical mechanism. We have no direct evidence for free bromine as an intermediate and only offer this as a tentative mechanistic suggestion.

(14) (a) C. Walling, A. L. Rieger, and D. D. Tanner, *J. Amer. Chem. Soc.*, **85**, 3129 (1963); (b) G. A. Russell and K. M. Desmond, *ibid.*, **85**, 3139 (1963); (c) R. F. Pearson and J. C. Martin, *ibid.*, **85**, 3142 (1963).

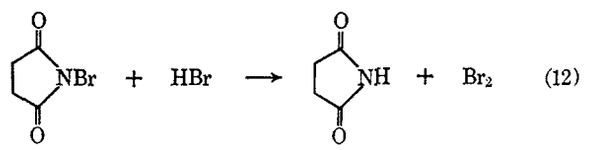
(15) S. D. Ross, M. Finkelstein, and R. C. Petersen, *ibid.*, **80**, 4327 (1958).

up to the present.[16] Our data with 3-substituted thiophenes indicate a selective activation of the 2 position to substitution. All the groups investigated (alkyl, phenyl, phenylthio, bromo) are capable of stabilizing the adjacent positive center that would be formed upon electrophilic substitution at the 2 position. This may, in part, explain the position of substitution.[17]

No selective activation is obvious with 2-substituted derivatives since, in any case, substitution should occur at the 5 position.[18] The mildness of the conditions necessary to obtain substitution with 2-substituted as well as 3-substituted thiophenes are noteworthy and have important implications particularly in synthetic applications.

Deuteration.—Thiophene and some other unsubstituted heterocycles are reported to be unaffected by refluxing deuterioacetic acid.[19] We have confirmed this observation for thiophene but have found that certain substituted derivatives are readily subject to exchange.[20,21] The position of substitution is analogous to that observed in kinetically controlled brominations. However, only thiophenes with activating substituents undergo exchange; bromothiophenes are unaffected by deuterioacetic acid while brominated by NBS in acidic media. The possibilities of synthesis of specifically labeled deuteriothiophenes *via* exchange are not to be overlooked.[22]

Acid-Catalyzed Rearrangements and Debrominations of Bromothiophenes.—Thiophenes brominated in the α positions are particularly sensitive to strong acid. The conditions under which rearrangements occur closely approximate those obtaining in brominations with bromine in acetic acid. Acetic acid alone is not sufficiently acidic but the hydrogen bromide generated during reaction can catalyze rearrangement of bromothiophenes. This problem is avoided in brominations using NBS since the hydrogen bromide generated during reaction is immediately consumed, most probably by reaction with NBS (eq 12).[13,23] The implicit dangers of all thiophene bromination methods which liberate hydrogen bromide should be apparent.



(12)

The acid-catalyzed rearrangements almost certainly proceed by *inter*- rather than *intra*molecular processes.[24-31] This is best shown by the debrominations in the presence of phenol in which bromo substituents are removed from acid-sensitive α positions without detectable formation of rearranged thiophenes whereas under identical conditions in the absence of phenol, rearrangement is observed. These reductive debrominations using phenol may also provide an alternative synthetic method when groups sensitive to other reducing agents are present in the molecule.[32]

For the case of 3-phenylthiophene, bromination in the 2 position is obviously the kinetically controlled reaction. The subsequent rearrangement of 2-bromo-3-phenylthiophene is best explained by initial protonation followed by loss of the bromo substituent *via* a disproportionation to give 3-phenylthiophene and 2,5-dibromo-3-phenylthiophene (eq 13). The *apparent* first-order kinetics for disappearance of starting material are not in conflict with this mechanism; the complex rate expression obtained for this process predicts *apparent* first-order kinetics if the rate of disproportionation is rapid compared to deprotonation.[33] In the first stages of the reaction debromination of 2,5-dibromo-3-phenylthiophene likely accounts for most of the rear-

(16) Thiophene is 10^7 and 10^9 times more reactive than benzene toward chlorination and bromination, respectively: G. I. Marino, *Tetrahedron*, **21**, 843 (1965). A substitution mechanism analogous to that involved in the bromination of benzene has been suggested: G. Marino, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis. Mat. Nat.*, **38**, 700 (1965). Studies of the relative reactivities of thiophene and furan toward electrophilic acylation have recently been published: P. Linda and G. Marino, *Tetrahedron*, **23**, 1739 (1967). Relative rates of deuterium exchange in thiophenes and other heterocycles have been measured: K. Schwetlick, K. Unverferth, and R. Mayer, *Z. Chem.*, **7**, 58 (1967).

(17) Note that 3-acetylthiophene is not substituted under the conditions used and that 3-bromothiophene appears to react more sluggishly than, for example, 3-methylthiophene (see Experimental Section).

(18) S. Gronowitz, *Ark. Kemi*, **13**, 295 (1958); S. Gronowitz and R. A. Hoffmann, *ibid.*, **16**, 539 (1960).

(19) B. Bak, *J. Org. Chem.*, **21**, 797 (1956).

(20) Several studies have been made of hydrogen–deuterium or hydrogen–tritium exchange in the presence of strong acid in thiophenes and these show the 2 position to be much more reactive than the 3 position: K. Halvarson and L. Melander, *Ark. Kemi*, **8**, 29 (1955); B. Östman and J. Olsson, *ibid.*, **15**, 275 (1960). Stable cations from thiophene protonated exclusively in the 2 position have been observed: H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, **85**, 1072 (1966). For hydrogen–deuterium exchange over Adams catalyst, see J. L. Garnett and W. A. Sollich, *Aust. J. Chem.*, **15**, 56 (1962). No exchange studies as a function of substituent appear to have been published.

(21) Bak[19] describes the reduction of bromothiophenes with Zn and deuterioacetic acid to prepare specifically deuterated thiophenes; Gronowitz[18] has also made extensive use of this technique to prepare specifically deuterated thiophenes. Neither author reports direct exchange with the thiophene ring and we have also never observed extraneous deuterium–hydrogen exchange in syntheses *via* these reductions[3] but did accidentally discover that "blind" exchange occurred at the position at which deuterium had been introduced by reduction of the bromo substituent. We have recently observed that deuterated thiophenes are subject to exchange over neutral aluminium oxide.[3]

(22) This method has been applied on a preparative scale for syntheses of 2-deuterio-3-*t*-butylthiophene and 2,4-di-*t*-butyl-5-deuteriothiophene: R. M. Kellogg, J. K. Dik, and H. Wynberg, unpublished results.

(23) The ionic reaction of hydrogen bromide with NBS is reportedly "instantaneous" even at $-78°$ in neutral solvent.[14c]

(24) Precedence exists in the literature for acid-catalyzed substituent elimination and/or rearrangement of bromothiophenes. The $SnCl_4$ catalyzed acetylation of 5-bromo-2-ethylthiophene is known to give 2-ethyl-5-acetylthiophene.[25] Chloromethylation of 2,5-dibromothiophene gives, in addition to 2,5-dibromo-3-chloromethylthiophene, also 2-bromo-5-chloromethylthiophene.[26] The phosphorus oxychloride catalyzed formylation of bromothiophenes leads to exchange of bromine for chlorine at either the α[27] or β positions.[28] All of these reactions involving the loss of a bromo substituent under acid-catalyzed conditions could be related to the rearrangements of bromothiophenes reported here. A not unprecedented rationalization of the formation of 4-bromo-2-thiophene carboxaldehyde from thiophene carboxaldehyde and bromine in the presence of excess aluminium chloride[29] in place of 2-bromo-5-thiophene carboxaldehyde formed in direct bromination[30] would involve rapid acid-catalyzed debromination of this latter product and slow accumulation of the more stable 4-bromo-2-thiophene carboxaldehyde. Disproportionation reactions also occur with bromobenzenes but under much more drastic conditions.[31]

(25) Ya. L. Gol'dfarb and P. A. Konstantinov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 113 (1957).

(26) S. Gronowitz, *Ark. Kemi*, **8**, 441 (1955).

(27) A. W. Neaton and R. J. Michaels, *J. Amer. Chem. Soc.*, **72**, 1422 (1960).

(28) S. Gronowitz, P. Moses, A.-B. Hörnfeldt, and R. Håkansson, *Ark. Kemi*, **17**, 165 (1961), quoted in ref 4.

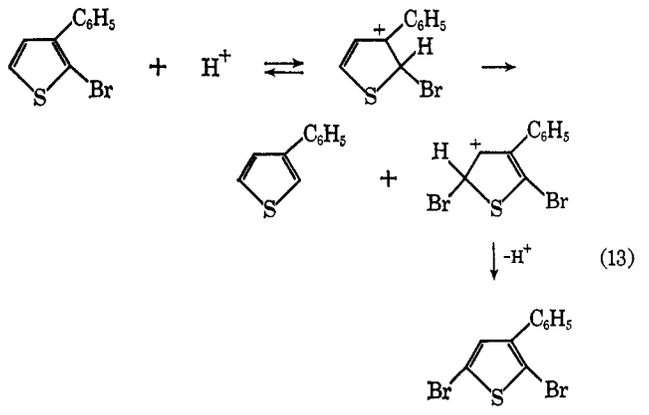
(29) Ya. L. Gol'dfarb, Yu. B. Vol'kenshtein, and B. V. Lopatin, *Zh. Obshch. Khim.*, **34**, 969 (1964); *Chem. Abstr.*, **61**, 629*d* (1964).

(30) S. Gronowitz, *Ark. Kemi*, **8**, 87 (1955).

(31) See, for example, G. J. P. Augustijn, E. C. Kooyman, and R. Louw, *Rec. Trav. Chim. Pays-Bas*, **82**, 965 (1963); E. C. Kooyman and R. Louw, *ibid.*, **81**, 365 (1962).

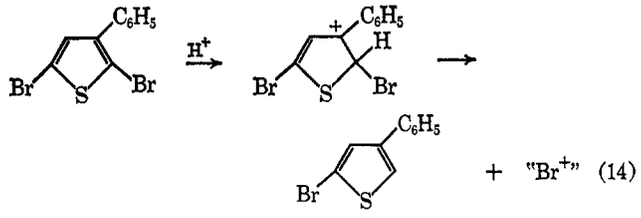
(32) Speculations can be made about the effect of other agents such as zinc which are used in reductive debromination. It could be that the first step is acid-catalyzed loss of "bromonium ion" and the zinc (or other agent) serves only as a trap for the eliminated substituent.

(33) See, for a solution of essentially the same kinetic problem: A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, New York, N. Y., 1961, pp 335–350.



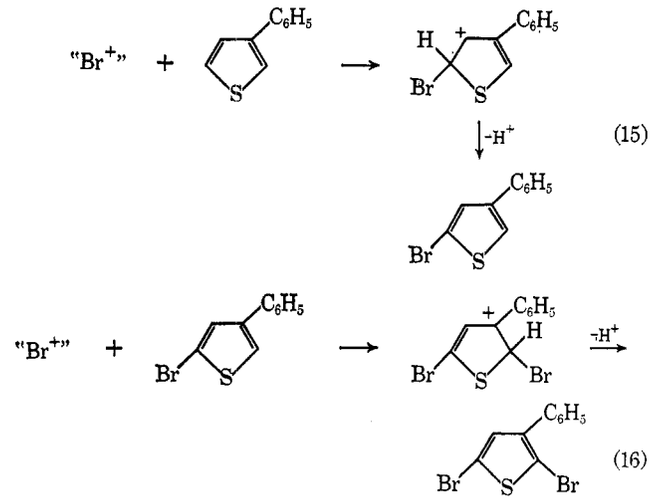
(13)

ranged 2-bromo-4-phenylthiophene (eq 14). Either 3-phenylthiophene or 2-bromo-3-phenylthiophene can be acceptors of the eliminated bromonium ion (represented as "Br^+" in eq 14–16; it is quite likely that



(14)

"Br^+" is not a simple bromonium ion, but the kinetic evidence does not allow positive identification of the bromonium ion carrying species). In later stages of the reaction 2-bromo-4-phenylthiophene probably also accumulates through bromination of 3-phenylthiophene in the 5 position in a slow but certainly real step (eq 15). Another kinetic complication is formation of 2,5-dibromo-3-phenylthiophene by rapid bromination of 2-bromo-4-phenylthiophene (eq 16). Since none



(15)

(16)

of the reaction products are completely stable, after *ca.* 200 min various complicated equilibria must be set up about which the present data justify no speculation.

Experimental Section

Melting points and boiling points are uncorrected. Ultraviolet spectra (uv) were obtained with a Zeiss PMQ II spectrophotometer. Infrared spectra (ir) were taken either on Perkin-Elmer Model 125 or Perkin-Elmer Model 257 infrared spectrophotometers. Nuclear magnetic resonance (nmr) spectra were measured with a Varian A-60 instrument with tetramethylsilane (TMS) as an internal standard. Spectra were taken at 500, 250, and 100 Hz sweep widths and integrations were done two times going from low to high field and two times from high to low field. The average value of the integrations was used. Gas chromatography (glpc) was done with an F & M Model 810 gas chromatograph equipped with hydrogen flame detectors. Preparative glpc separations were carried out on a Wilkens A-700 Autoprep.

Microanalyses were carried out by the analytical section of this department under the direction of Mr. W. Hazenberg.

Compounds cited without reference were either prepared by standard procedures or were available in stock.

3-(Phenylthio)thiophene was prepared from the reaction of 3-bromothiophene and benzene thiol with cuprous oxide in dimethyl formamide containing KOH following the general procedure given in the literature.[34] A 75% yield was obtained of 3-(phenylthio)thiophene: bp 88–94° (0.3 mm); $n^{20}D$ 1.6530; uv spectrum (C_2H_5OH), 247 mμ (ε 10500) and 268 (6400).

Oxidation with hydrogen peroxide–acetic acid gave the sulfone: mp 117.5–119°; uv spectrum (C_2H_5OH), 242 mμ (ε 12700), 266 (sh) (1400), and 274 (sh) (900).

Anal. Calcd for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59; S, 28.59. Found: C, 53.45; H, 3.61; S, 28.57.

2-Bromo-3-methylthiophene was obtained from the reaction of 3-methylthiophene (4.9 g, 50 mmol) and NBS (9.4 g, 52.7 mmol) in 60 ml of a 50:50 (v/v) solution of chloroform–acetic acid. Reaction occurred spontaneously at room temperature and was over within 2 min. The reaction mixture was diluted with an equal volume of water; the chloroform layer was separated, washed once with KOH solution and once with water, and dried over magnesium sulfate. Distillation gave 7.45 g (84%) of 2-bromo-3-methylthiophene: nmr (CCl_4), δ 7.82 (s, 3, CH_3), 3.30 (d, 1, J = 5.5 Hz, H-4), and 2.93 (d, 1, J = 5.5 Hz, H-5). No other peaks were detected in the nmr spectrum. Glpc under conditions capable of separating the different bromothiophenes (6 ft DEGS, 100°) showed the product to be >99% pure.

2,3-Dibromothiophene[6] was formed from the reaction of 3-bromothiophene (8.15 g, 50 mmol) with NBS (8.9 g, 50 mmol) in 60 ml of 50:50 (v/v) chloroform–acetic acid. The reaction mixture was gently refluxed for *ca.* 30 min. A deep red color formed indicative of free bromine. Work-up as described above gave, after distillation, 10.1 g of material consisting of 20% of starting bromide and 80% of 2,3-dibromothiophene (as determined by nmr spectroscopy). In addition a trace (2–3%) of 2,4-dibromothiophene could be detected by glpc (6 ft DEGS, 160°). This small amount of 2,4-dibromothiophene was also detected in 2,3-dibromothiophene prepared by addition of bromine to 3-bromothiophene.

2-Bromo-3-phenylthiophene[35] was formed in the reaction of 3-phenylthiophene (489 mg, 3.06 mmol) with NBS (543 mg, 3.06 mmol) in 16 ml of a 50:50 (v/v) mixture of chloroform–acetic acid. Reaction occurred upon mixing. The mixture was gently warmed for *ca.* 0.5 hr and worked up as described above to give 690 mg (94%) of 2-bromo-3-phenylthiophene shown to be pure by nmr spectroscopy.[2,3]

3-Phenylthiophene (320 mg, 2.0 mmol) in 12 ml of a 50:50 (v/v) mixture of chloroform–acetic acid when treated with dibromodimethylhydantoin (300 mg, 1.01 mmol) gave, after work-up, 455 mg (95%) of 2-bromo-3-phenylthiophene.

2-Bromo-3-(phenylthio)thiophene was prepared from the reaction of 3-(phenylthio)thiophene (174 mg, 0.91 mol) with NBS (167 mg, 0.94 mmol) in 6 ml of a 50:50 (v/v) solution of carbon tetrachloride–acetic acid. The mixture was warmed mildly for about 5 min. Work-up as described above gave 224 mg (91%) of 2-bromo-3-(phenylthio)thiophene: uv max (96% C_2H_5OH), 246 mμ (ε 13,000) and 274 (sh) (5600); nmr (C_3D_6O), δ 6.90 (d, 1, J = 5.6 Hz, H-4), 7.52 (d, 1, J = 5.6 Hz, H-5), and 7.27 (m, 5, C_6H_5).

Oxidation of the above product with H_2O_2–acetic acid gave 2-bromo-3-thienylphenyl sulfone: mp 71–73°; uv max (96% C_2H_5OH), 223 mμ (ε 13,100), 243 (14,400), and 267 (6600).

Anal. Calcd for $C_{10}H_7BrO_2S_2$: C, 39.61; H, 2.33; Br, 26.35; S, 21.15. Found: C, 39.47; H, 2.34; Br, 26.81; S, 21.01.

2-Bromo-5-phenylthiophene[7] was prepared from the reaction of 2-phenylthiophene (495 mg, 3.09 mmol) with NBS (546 mg, 3.07 mmol) in 6 ml of a 50:50 (v/v) mixture of chloroform–

(34) E. Jones and I. M. Moodie, *Tetrahedron*, **21**, 2413 (1965). We thank Dr. Jones for details of this procedure.

(35) The properties of this compound and the isomeric 2-bromo-4-phenylthiophene have been described.[5]

acetic acid. The solution was briefly warmed. Work-up gave 705 mg (95%) of 2-bromo-5-phenylthiophene: mp 82–84° (lit.[7] 84–85°).

2-Methyl-5-bromothiophene was prepared from the reaction of 2-methylthiophene (9.53 g, 0.097 mol) and NBS (18.9 g, 0.106 mol) in 120 ml of a 50:50 (v/v) mixture of chloroform–acetic acid. The solution was mildly heated. After work-up and flash distillation 17.82 g (103%) of 2-methyl-5-bromothiophene was obtained: $n^{19.8}$D 1.5575 (lit.[12a] n^{20}D 1.5687); nmr (C_3D_6O) δ 2.43 (d, 3, J = 1.2 Hz, CH_3), 6.62 (m, 1, J = 1.2, 3.5 Hz, H-3) and 6.92 (d, 1, J = 3.5 Hz, H-4). No extraneous peaks were observed in the nmr spectrum and glpc (6 ft DEGS, 100°) under conditions capable of separating the isomeric methyl bromothiophenes showed the product to be >99% pure.

2-Bromo-5-(phenylthio)thiophene was prepared from the reaction of 2-(phenylthio)thiophene[36] (161 mg, 0.84 mmol) with NBS (153 mg, 0.86 mmol) in 6 ml of 50:50 (v/v) mixture of CCl_4–acetic acid. Work-up gave 206 mg (90%) of 2-bromo-5-(phenylthio)thiophene: uv max (C_2H_5OH), 245 mμ (ϵ 16,300) and 276 (sh) (3640); nmr (C_3D_6O), δ 2.79 (s, 2, H-3,4), 2.69 (s, 5, C_6H_5).

A portion of this product was oxidized with H_2O_2–acetic acid to the sulfone: mp 116–118.5°; uv max (C_2H_5OH), 223 mμ (ϵ 9200), 252 (8600), and 276 (14,500).

Anal. Calcd for $C_{10}H_7BrO_2S_2$: C, 39.61; H, 2.33; Br, 26.35; S, 21.15. Found: C, 39.55; H, 2.45; Br, 26.27; S, 21.22.

2-Bromo-5-(*t*-butyl)thiophene[37] was prepared from the reaction of 2-(*t*-butyl)thiophene (210 mg, 1.50 mmol) with NBS (267 mg, 1.50 mmol) in 6 ml of a 50:50 (v/v) mixture of carbon tetrachloride–acetic acid. The material was worked up and the 2-bromo-5-(*t*-butyl)thiophene was concentrated in carbon tetrachloride: nmr, δ 1.35 (s, 9, $(CH_3)_3C$), 6.51 (d, 1, J = 3.6 Hz, H-4), and 6.77 (d, 1, J = 3.6 Hz, H-5) [lit.[36] nmr (CCl_4), δ 2.34 (s, 9, $(CH_3)_3C$), 6.50 (d, 1, J = 3.8 Hz, H-4), and 6.75 (d, 1, J = 3.8 Hz, H-3)]. The yield was estimated by nmr spectroscopy to be >95%.

2,5-Dibromothiophene[38] was prepared by allowing thiophene (13.0 g, 0.16 mol) to react with NBS (60.5 g, 0.34 mol) in 200 ml of a 50:50 (v/v) mixture of chloroform–acetic acid. The solution was held at *ca.* 30° and the NBS was added in small portions. After addition, the solution was heated to reflux for 10 min, allowed to cool, and worked up as described above. Distillation gave 32.2 g (86%) of 2,5-dibromothiophene shown to be absolutely pure by nmr spectroscopy and glpc (6 ft DEGS, 100°). An initial distillation fraction of *ca.* 2.5 g was not counted in the yield even though its refractive index was identical with that of the main fraction.

Bromination of thiophene occurred rapidly when a mixture of NBS (17.8 g, 100 mmol) and redistilled thiophene (8.4 g, 100 mmol) was gently refluxed for 0.5 hr with magnetic stirring in 120 ml of a 50:50 (v/v) solution of chloroform–acetic acid. After work-up as described above, the reaction mixture was rapidly distilled to give 10.9 g of product which contained 85% 2-bromothiophene and 15% 2,5-dibromothiophene as determined both from glpc (6 ft DEGS, 100°) and nmr analysis.

Attempted reactions of 2-acetyl and 3-acetylthiophenes under the conditions described above led only to the recovery of unchanged starting materials.

Deuterium exchange with 3-methylthiophene was carried out by refluxing a mixture of 3-methylthiophene (1.5 g, 15.2 mmol) for 5 hr in a mixture of 9 ml acetic anhydride and 11 ml of D_2O. After this time the reaction mixture was cooled, diluted with water, extracted with ether, and neutralized with Na_2CO_3 solution. After drying over magnesium sulfate the residue was distilled to give 1.4 g of exchanged 3-methylthiophene: nmr (C_3D_6O), δ 6.84 (d, 1, J = 5.0 Hz, H-4), 7.20 (d, 1, J = 5.0 Hz, H-5) and 2.21 (s, 3, CH_3). The peak at δ 7.20 was broadened due to coupling to deuterium at position 2. This identified the material as 2-deuterio-3-methylthiophene. No exchange occurred upon stirring 3-methylthiophene in deuterioacetic acid solution for 24 hr at room temperature.

Deuterium exchange with 3-pentadeuteriophenylthiophene[2,3] was carried out by refluxing 3-pentadeuteriophenylthiophene (90 mg, 0.545 mmol) with 2.25 ml of acetic anhydride and 2.75 ml of D_2O for 5 hr. The nmr spectrum of the worked up material in acetone showed a singlet located precisely at the point expected for 2-deuterio-3-pentadeuteriophenylthiophene.[23] From integration ratio 34% deuterium exchange at the 2 position was calculated.

Deuterium exchange with 3-*t*-butylthiophene (100 mg, 0.72 mmol) in 2.5 ml of acetic anhydride and 3.0 ml of D_2O for 5 hr led to 24% deuterium exchange as estimated from nmr. The same experiment carried out for 24 hr gave exchanged product: nmr (CCl_4), δ 6.95 (d, 1, J = 4.8 Hz, H-4), 7.12 (d, 1, J = 4.8 Hz, H-5), and 1.29 (s, 9, $(CH_3)_3C$–). Other peaks in the aromatic region were completely accounted for by the spectrum of unrearranged material. From integration ratios 67% exchange was calculated.

Deuterium exchange with 3-(phenylthio)thiophene was carried out by refluxing 3-(phenylthio)thiophene (195 mg, 1.01 mmol) for 5 hr in a mixture of 2.5 ml of acetic anhydride and 2.5 ml of D_2O. Work-up in the usual manner gave 174 mg of exchanged 3-(phenylthio)thiophene: nmr (C_3D_6O), δ 2.97 (d, 1, J = 5.1 Hz, H-4), 2.51 (d, 1, J = 5.1 Hz, H-5) and 2.79 (s, 5, C_6H_5). The doublet at δ 2.51 was slightly broadened owing to coupling with the deuterium in the 2 position. That exchange had only taken place in the 2 position was further confirmed by conversion of the product into 2-bromo-3-(phenylthio)thiophene whose nmr spectrum was completely identical with that of material prepared from undeuterated product.

Deuterium exchange with 3-phenyl-4-methylthiophene[39] was carried out by refluxing this compound (100 mg, 0.60 mmol) in a mixture of 2.5 ml of acetic anhydride and 3.0 ml of D_2O for 2.5 hr (longer refluxing led to complete deuteration). The reaction mixture was worked up in the usual manner: nmr (CCl_4), δ 6.90 (m, 40% reduced in intensity) 7.05 (m, 16% reduced in intensity), 7.25 (s, 5, C_6H_5), and 2.22 (d, 3, J = ~1 Hz, CH_3). The δ 6.90 peak was identified as being α to methyl group by the extra splitting arising from allylic coupling to the methyl protons.

Deuterium exchange with 2-methylthiophene was carried out by refluxing 2-methylthiophene (1.5 g, 15.2 mmol) in 9 ml of acetic anhydride and 11 ml of D_2O for 5 hr. The reaction mixture was worked up as normal: nmr (C_3D_6O), δ 2.91 (m, 0.58, H-5), *ca.* 3.2 (m, 2.0, 3,4-protons), 7.59 (d, 3.0, J = *ca.* 1 Hz, CH_3). The loss of integration in the low-field portion indicates 5 substitution (42%).

Deuterium exchange with 2-phenylthiophene was carried out with 2-phenylthiophene (164 mg, 1.02 mmol) in 2.5 ml of acetic anhydride and 2.5 ml of D_2O. After refluxing for 5.5 hr the reaction mixture was worked up in the usual manner to give 153 mg (0.96 mmol) of 2-phenylthiophene. The nmr (C_3D_6O) was substantially different from that of undeuterated 2-phenylthiophene. The deuterated product was converted into 2-bromo-5-phenylthiophene by treatment with an equivalent amount of NBS in chloroform–acetic acid. The nmr (C_3D_6O) of this product was identical with that of undeuterated 2-bromo-5-phenylthiophene indicating exchange only in the 5 position. Comparison of the nmr spectra of the partially deuterated and undeuterated 2-phenylthiophenes allowed calculation (using a section of the phenyl absorptions as standard)[2,3] of 40% deuterium content at the 5 position.

Deuterium exchange with 2-*t*-butylthiophene was carried out by refluxing 2-*t*-butylthiophene (203 mg, 1.45 mmol) for 5 hr in a mixture of 2.5 ml of acetic anhydride and 2.5 ml of D_2O. The reaction mixture was worked up in the usual manner. The solution was carefully concentrated to a 3-ml volume and an nmr spectrum was taken of the concentrated material. The complex aromatic region was appreciably changed and the integration for the aromatic protons was 25% reduced in intensity.

The solution above was diluted with 3 ml of acetic acid, NBS (255 mg, 1.43 mmol) was added, and the solution was warmed briefly. The product was extracted into carbon tetrachloride solution, and this solution was concentrated to a 3-ml volume. The nmr spectrum (CCl_4) was identical with that of authentic 2-bromo-5-*t*-butylthiophene; no trace of exchange in the 3,4 positions could be seen. Exchange is thus confined to the 5 position and is 75% complete after 5 hr.

Deuterium exchange with 2-(phenylthio)thiophene was carried out by refluxing 2-(phenylthio)thiophene (192 mg, 1.0 mmol) in 2.5 ml of acetic acid and 2.5 ml of D_2O. After work-up 161 mg of material was obtained: nmr (C_3D_6O), δ 2.40 (m, 33% de-

(36) H. Burton and W. A. Davy, *J. Chem. Soc.*, 525 (1948).

(37) A.-B. Hörnfeldt, *Acta Chem. Scand.*, **21**, 1952 (1967).

(38) We thank Mr. F. de Jong of these laboratories for carrying out this reaction.

(39) A. S. Broun, M. G. Voronkov, and F. G. Gol'dburt, *Nauchn. Byul. Leningr. Gos. Univ.*, **18**, 14 (1947); *Chem. Abstr.*, **43**, 5392*d* (1949); H. Wynberg, G. E. Beekhuis, H. van Driel, and R. M. Kellogg, *J. Amer. Chem. Soc.*, **89**, 3498 (1967).

creased in intensity compared to starting material) and *ca.* 7.2 (m, rest of protons).

The deuterated product was treated with an equimolar amount of NBS in carbon tetrachloride–acetic acid. The product obtained had a nmr spectrum completely identical with that of authentic 2-bromo-5-(phenylthio)thiophene. Exchange is thus confined to the 5 position and is 33% complete.

Deuterium exchange failed to take place with thiophene or bromothiophenes when under the conditions described above.

Acid-catalyzed rearrangement of 2-bromo-3-phenylthiophene was carried out with 2-bromo-3-phenylthiophene (1.0 g, 4.2 mmol) in 20 ml of acetic acid *ca.* 0.7 *M* in HBr. The acid solution was brought to reflux and the 2-bromo-3-phenylthiophene was added. At the end of 5 and 20 min 0.5-ml samples were withdrawn which were injected into a mixture of 1 ml of carbon tetrachloride and 5 ml of water in a test tube; these were washed once with KOH solution and twice with water, and the carbon tetrachloride layer was dried over magnesium sulfate. The samples were analyzed by glpc (6-ft Apiezon, 200°) using a trace of biphenyl as an internal standard. At the end of 5 min the reaction mixture consisted of 2.3 mmol of starting material, 0.76 mmol of 3-phenyl thiophene, 0.34 mmol of 2-bromo-4-phenylthiophene, and 0.75 mmol of 2,5-dibromo-3-phenylthiophene. After 20 min, 1.14 mmol of starting material remained and 0.92 mmol of 3-phenylthiophene, 1.08 mmol of 2-bromo-4-phenylthiophene, and 0.89 mmol of 2,5-dibromo-3-phenylthiophene were present. No other products were detected.

Rearrangement failed to occur with 2-bromo-3-phenylthiophene in refluxing acetic acid over a period of *ca.* 1 hr. Rearrangement occurred in mixtures of perchloric acid in acetic acid but was accompanied by considerable decomposition. Refluxing of 2-bromo-3-phenylthiophene in carbon tetrachloride solution in the presence of aqueous 48% HBr led to no apparent reaction.

Acid-catalyzed rearrangement of 2-bromo-3-methylthiophene was carried out by refluxing 2-bromo-3-methylthiophene (35 mg, 0.2 mmol) for 1.5 hr in 1 ml of acetic acid (*ca.* 0.5 *M* in HBr). Work-up as described above and analysis by glpc (6 ft Apiezon, 90°) showed 0.047 mmol of starting material, 0.004 mmol of 2-bromo-4-methylthiophene, 0.056 mmol of 3-methylthiophene, 0.047 mmol of 2,5-dibromo-3-methylthiophene to be present. Longer reaction times led to extensive decomposition.

General Procedure for Acid-Catalyzed Reactions of Bromothiophenes.—Solutions (0.2 *M*) of 2,3-dibromothiophene, 2,4-dibromothiophene, 2,5-dibromothiophene, and 2-bromothiophene in acetic acid (1 *M* in HBr) were made up. (Reactions failed to occur in 0.1 *M* HBr solutions.) A 2-ml sample of each of these solutions was gently refluxed with magnetic stirring for 5 hr. The solutions were cooled, diluted with 2 ml of 1 *N* KOH solution, and extracted with 1 ml of carbon tetrachloride. Analyses were carried out by glpc (6 ft DEGS, programmed at 6°/min from 100 to 185°). An appropriate internal standard was weighed into each reaction mixture; relative responses were determined by comparison with known mixtures. The product distributions given in the results were found.

Acid-catalyzed reactions of 3,4-dibromothiophene and 3-bromothiophene failed to give any detectable products other than recovered starting materials.

The acid-catalyzed debromination of 2-bromo-3-phenylthiophene was carried out by refluxing 2-bromo-3-phenylthiophene (50 mg, 0.21 mmol) for 3.5 hr in 1 ml of acetic acid (*ca.* 1 *N* in HBr containing phenol (20 mg, 0.21 mmol)). The solution was diluted with H_2O and extracted with carbon tetrachloride, the carbon tetrachloride layer was washed with KOH solution and then with water and dried over $MgSO_4$, and the solvent was removed to leave pure 3-phenylthiophene (28 mg, 84% yield). Examination of the reaction mixtures by glpc (6-ft Apiezon, 200°) showed that no 2-bromo-4-phenyl or 2,5-dibromo-3-phenylthiophene had been formed.

General Procedure for Debrominations with Phenol.—Solutions (0.2 *M*) of 2,3-dibromothiophene, 2,4-dibromothiophene, 2,5-dibromothiophene, 2,3,5-tribromothiophene and 2-bromo-3-methylthiophene were made up in acetic acid which was 1 *M* in HBr and 0.2 *M* in phenol. The reaction mixtures were refluxed 5 hr after which time 2 ml of 1 *N* KOH solution was added. The resulting mixture was extracted with 1 ml of carbon tetrachloride. Analysis was carried out by glpc (6-ft DEGS, programmed at 6°/min from 100 to 185°). An appropriate internal standard was added to the reaction mixture so as to allow yield calculations. The quantitative results of these experiments are given in the Results.

The debromination of 2-bromo-3-methylthiophene carried out as described above led to the formation of 3-methylthiophene (0.14 mmol, 35% yield). No other identifiable products could be detected. A considerable amount of black decomposition material was formed during the course of the reaction.

Kinetic studies of the acid-catalyzed reactions of 2-bromo-3-phenylthiophene were carried out normally at 70° in an automatic temperature-regulated water bath (*ca.* ± 1° control). The various bromophenylthiophenes were prepared as described[5] and purified by preparative glpc when necessary. A much improved synthesis of 2,5-dibromo-3-phenylthiophene has been described by Gronowitz.[9] 2-Bromo-3-phenylthiophene was dissolved in an acetic acid solution 1 *M* in HBr and 0.005 *M* in adamantanone (used as an internal standard and shown to be unreactive under the conditions used). Samples of this solution (0.5–0.8 ml) were put in glass tubes provided with a rubber seal. Four to seven of these tubes were held in the water bath by means of a large cork containing holes for each tube. At various time intervals samples (usually 50 μl) were withdrawn from a tube by means of a hydrodermic syringe which punctured the rubber stoppers. Samples were injected in sufficient Na_2CO_3 solution to neutralize the acid. Chloroform (50 μl) was added, the tube was centrifuged, and the chloroform layer was withdrawn by means of a syringe. The tubes were protected from light and stored in the freezer. The samples were subjected to gas chromatographic analysis (6 ft Carbowax on Chromosorb, 170°). A disk integrator was used to indicate relative peak areas and relative response factors calculated from gas chromatograms of known mixtures. The same technique was used to study the behavior of 2-bromo-4-phenylthiophene and 2,5-dibromo-3-phenylthiophene under acid-catalyzed conditions.

Competitive reactions of 3-phenylthiophene or the various bromo isomers were carried out by dissolving the components in a chloroform–acetic acid mixture held at the temperature stated in the discussion. An insufficient amount of bromine was added and the reaction was quenched as quickly as possible with sodium thiosulfate solution. Analyses of the reaction mixtures were by glpc.

Registry No.—Sulfone of 3-(phenylthio)thiophene, 16718-05-1; 2-bromo-3-methylthiophene, 14282-76-9; 2-bromo-3-(phenylthio)thiophene, 16718-07-3; 2-bromo-3-thienylphenyl sulfone, 16718-08-4; 2-bromo-5-(phenylthio)thiophene, 16718-09-5; sulfone of 2-bromo-5-(phenylthio)thiophene, 16718-10-8; thiophene, 110-02-1; 3-(phenylthio)thiophene, 16718-11-9; 3-methylthiophene, 616-44-4; 3-*t*-butylthiophene, 1689-79-8; 2-methylthiophene, 554-14-4; 2-phenylthiophene, 825-55-8; 2-*t*-butylthiophene, 1689-78-7; 2-(phenylthio)-thiophene, 16718-12-0; 2-bromo-3-phenylthiophene, 10341-87-4.

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