THE SYNTHESIS OF SOME BENZO (b) THIOPHENESULFONAMIDES AND BENZO (b) THIOPHENESULFONYLUREAS

Thesis for the Degree of M. S.

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Edward S. Parsey

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THE SYNTHESIS OF SOME BENZO(b)THIOPHENESULFONAMIDES AND BENZO(b)THIOPHENESULFONYLUREAS

By

Edward S. Parsey

A THESIS

Submitted to the College of Science and Arts
of Michigan State University
in partial fulfillment of the requirements
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Department of Chemistry

1965

DEDICATION

To my wife Mary Lee and daughter Ann Marie
for their patience and encouragement
through the completion of this thesis.

ACKNOWLEDGMENT

Sincere appreciation for the aid and guidance given by Professor Robert D. Schuetz during the course of this investigation is expressed by the author.

THE SYNTHESIS OF SOME BENZO(b)THIOPHENESULFONAMIDES AND BENZO(b)THIOPHENESULFONYLUREAS

By

Edward S. Farney

AN ABSTRACT

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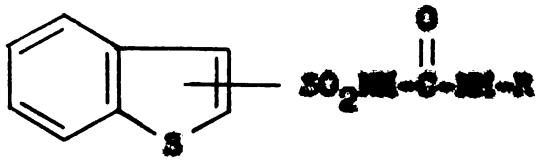
Approved

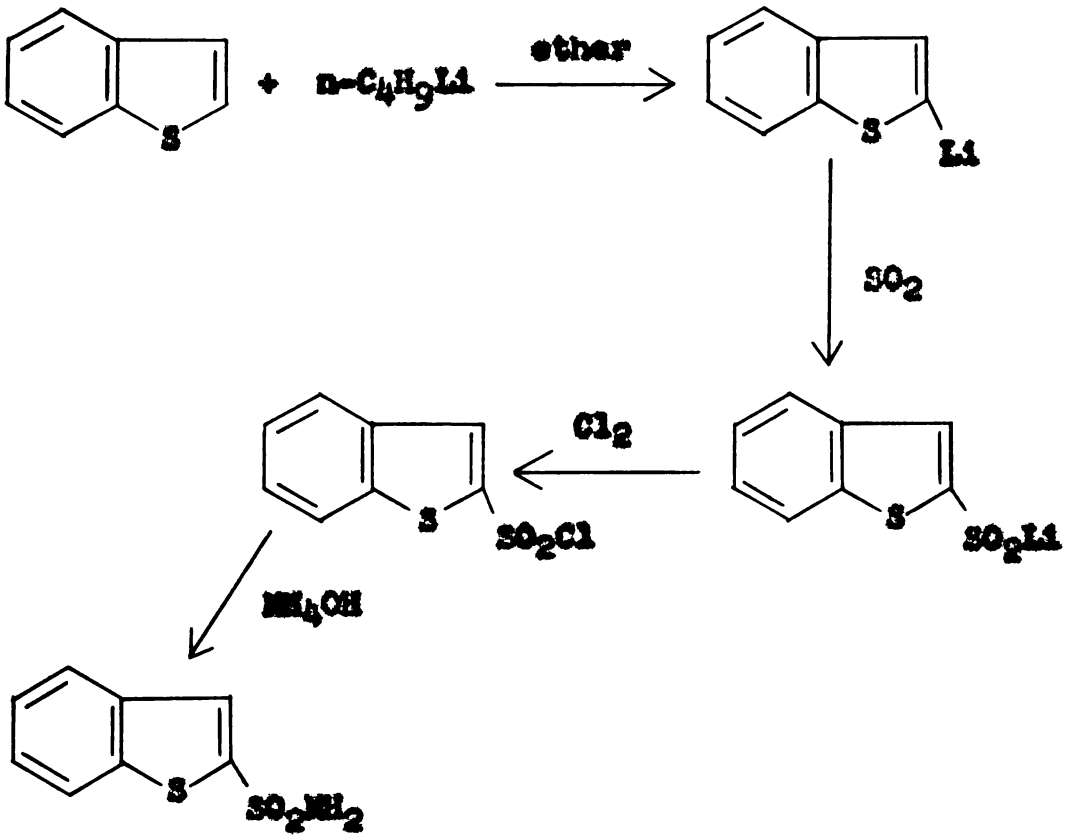
ABSTRACT

This study deals with an investigation of the synthesis of benzo(b)thiophenesulfonamides, and the synthesis from them of benzo(b)thiophenesulfonylureas. This study was undertaken for the purpose of preparing the sulfonylureas for possible use in the oral control of diabetes. These compounds may be represented by the general formula,

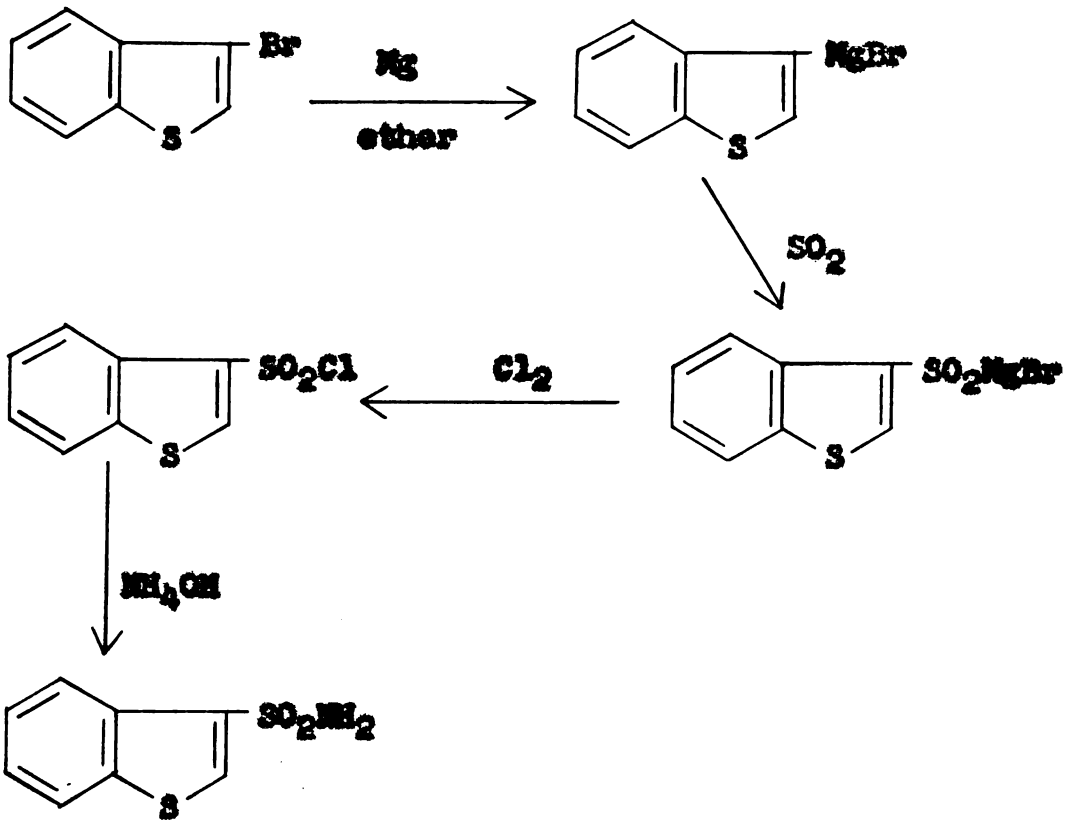


R = phenyl or n-butyl.

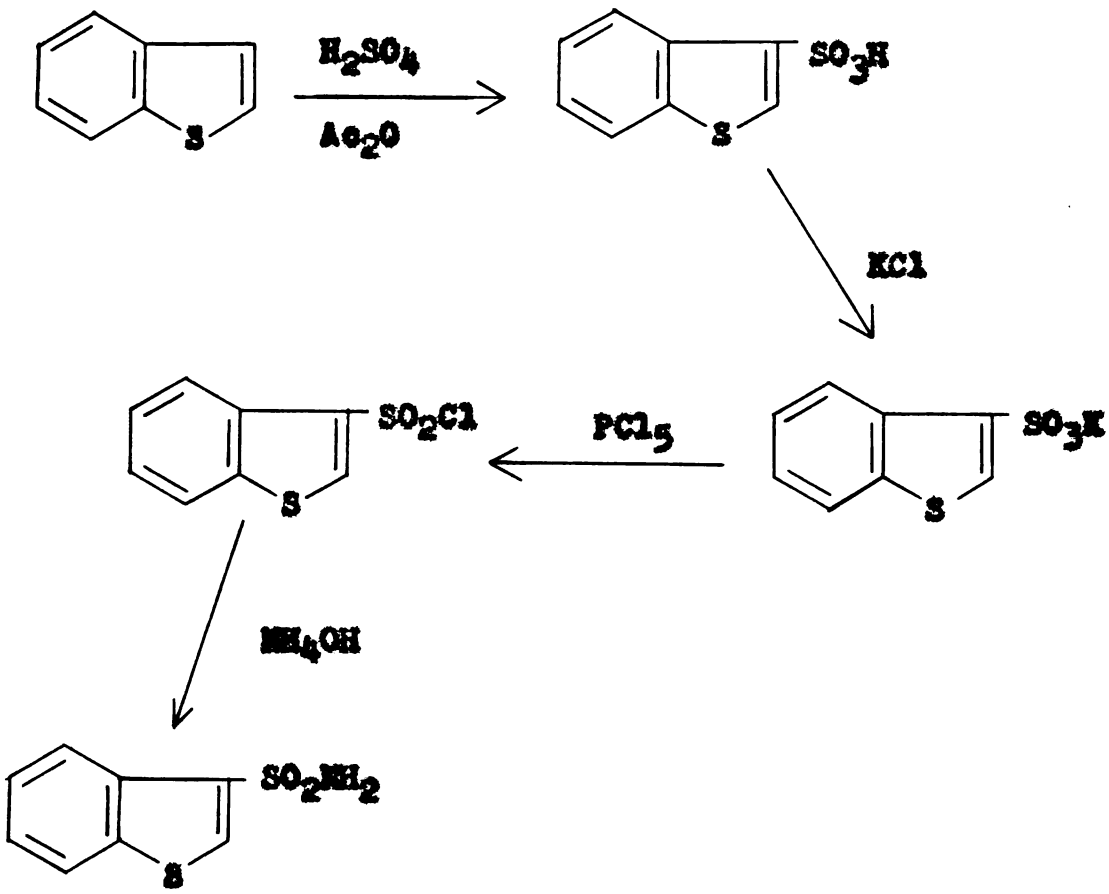
The benzo(b)thiophenesulfonamides, 2-benzo(b)thiophenesulfonamide, 3-methyl-2-benzo(b)thiophenesulfonamide, 3,5-dimethylbenzo(b)thiophenesulfonamide and 3,7-dimethylbenzo(b)thiophenesulfonamide, were prepared by the metalation of the appropriate benzo(b)thiophene derivative with n-butyl lithium, and subsequent reaction with anhydrous sulfur dioxide, then gaseous chlorine to yield the crude sulfonyl chloride which on interaction with excess ammonia gave the sulfonamide. The general reaction scheme is illustrated for the preparation of 2-benzo(b)thiophenesulfonamide,



The isomeric 3-benzo(b)thiophenesulfonamide was prepared by a series of reactions somewhat similar to those described for the synthesis of 2-benzo(b)thiophenesulfonamide. Employing a Grignard reaction starting with 3-bromobenzo(b)thiophene, the several steps involved in the synthesis can be summarized as,

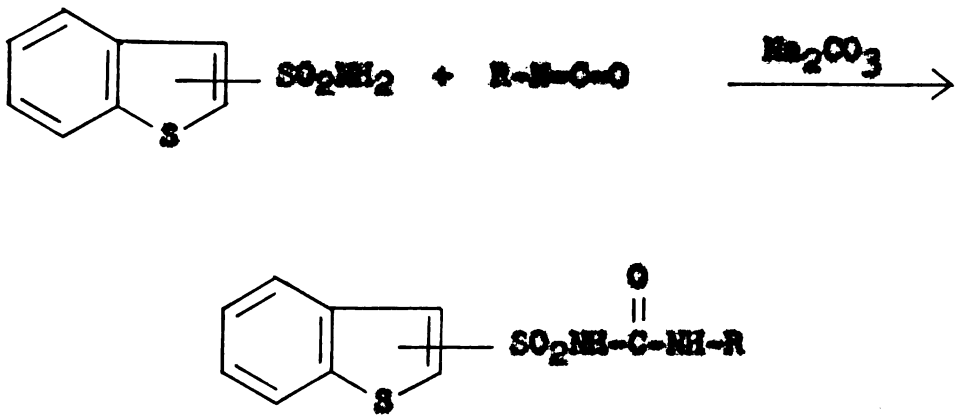


An alternative method for the preparation of 3-benzo-(b)thiophenesulfonamide involves the reaction of benzo(b)-thiophene with concentrated sulfuric acid in acetic anhydride as a reaction media. The general reaction scheme is illustrated for the preparation of 3-benzo(b)thiophene-sulfonamide.



By blocking the three position with a methyl group, the two-isomers were produced.

The sulfonylureas were prepared by the interaction of the appropriate sulfonamide with either phenyl- or n-butyl isocyanate in an aqueous or non-aqueous medium. The reaction may be represented as,



where R is equal to phenyl or n-butyl. All the sulfonamides prepared were employed in this reaction.

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INTRODUCTION

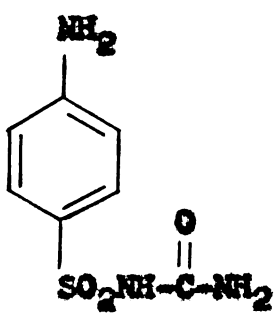
Benzo(b)thiophene was initially prepared by Gattermann and Lockhart in 1893 (1). Since then numerous investigations dealing with the chemistry of benzo(b)thiophene have been recorded in the literature. The majority of these studies has dealt with the hydroxybenzo(b)thiophenes and quinones which are essential intermediates in the synthesis of the commercially important thioindigo dyes. As a consequence, other phases of benzo(b)thiophene chemistry are still in need of investigation.

One such phase that has received very limited work is that of the sulfur derivatives of benzo(b)thiophene. To date, no sulfides, sulfoxides or sulfones have been reported in the literature, and only a few random cases of sulfonation have been published. Benzo(b)thiophenethiols were first prepared and described by Heyd (2).

The main objective of the present investigation was to develop synthetic methods to obtain benzo(b)thiophenesulfenamides and to utilize the sulfenamides in the preparation of sulfonylureas which could be useful in the oral treatment of diabetes.

HISTORICAL

Although a few isolated examples of sulfonylureas are recorded in the earlier literature, a more systematic study of the chemistry of sulfonyl derivatives of urea and thiourea is of rather recent origin. About 1940, increased interest in this class of compounds was aroused by the expectation that sulfanilylurea(I) and sulfanilylthiourea(II), because of their close structural resemblance to sulfanilamide(III), were compounds of potential chemotherapeutic value. A formal analogy, no less striking, exists between the highly active sulfathiazole(IV) and sulfanilylthiopseudoureas(V).



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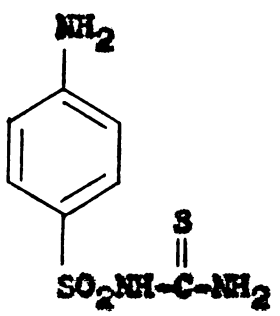

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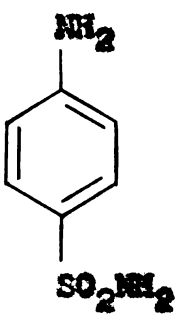

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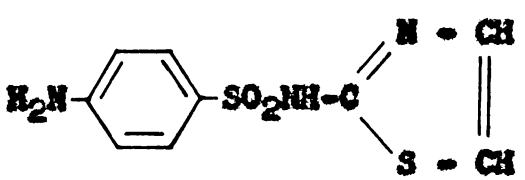

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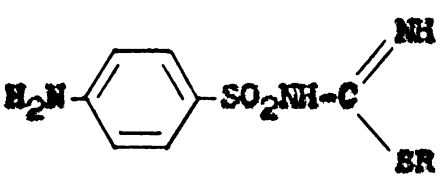
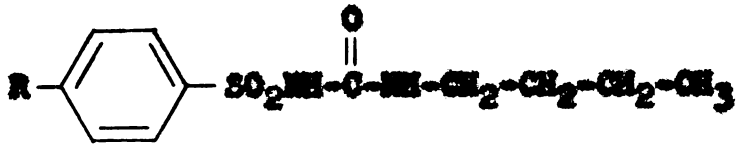


V

Kurzer (3) reviewed the literature on sulfonylureas and related compounds through 1951. He later contributed a chapter on sulfonylureas in a book on organic sulfur compounds edited by Kharasch (4).

Sulfanilylurea and sulfanilylthiourea are effective as bacteriostatic agents; their activity compares favorably to the related sulfonamide drugs, and their clinical use, particularly in the treatment of urinary infections is well established (5,6). Recent general and comparative studies of sulfanilylurea and sulfanilylthiourea, particularly the latter, confirm their usefulness as bacteriostatic agents against a broad spectrum of microorganisms (7).

Investigations on the chemotherapeutic aspects of both sulfanilylurea and sulfanilylthiourea have recently been overshadowed by the discovery that 1-sulfanilyl- (8) and 1-p-toluenesulfonyl-3-n-butylurea (9) possess hypoglycemic properties



R = NH_2 or CH_3

and are of definite value in the oral treatment of certain cases of diabetes. The announcement aroused widespread interest and resulted, in a short span of time, in the publication of considerable literature on these materials.

The drugs have been successfully introduced into clinical practice and have supplemented or even replaced, in some forms of diabetes, treatment by insulin injection. Of the two compounds extensively studied, the p-tolyl-homologue appears to be the more favored product. Because of the absence of the sulfanilyl moiety, it has no bacteriostatic action and thus does not affect the bacterial flora of the intestine during the inevitably prolonged therapy. Since it is excreted as the soluble carboxylic acid ($HOOC.C_6H_4.SO_2NHCONH.C_4H_9$), the danger of crystalluria occasionally associated with sulfonamide therapy is absent.

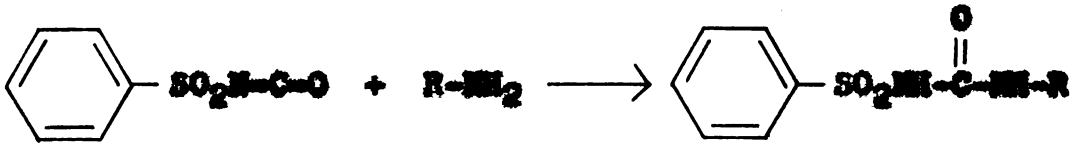
The mode of action of this drug is not fully understood, nor is sufficient information available for correlating its chemical structure with its blood-sugar lowering action. There can be no doubt, however, that the encouraging experiences in this important field will stimulate further investigations, in which the properties of the sulfonylureas will be held in focus.

A rather wide variety of methods for the synthesis of sulfonylureas is available. In contrast to the N-carbonylureas

which are easily prepared by the interaction of acid halides or anhydrides with the appropriate urea, the

sulfonylureas, unexpectedly, have not been obtained by the analogous reaction involving the sulfonyl halides (10). However, convenient alternative methods for obtaining the sulfonylureas have been developed; they are based on the numerous conventional urea syntheses and present, in certain cases, features of rather special interest.

Sulfonyl isocyanates can be prepared, with suitable experimental precautions, from sulfonyl chlorides and silver cyanate. They react readily with amines to yield the corresponding sulfonylureas. In 1904, Billeter (11) studied the interaction of benzenesulfonyl isocyanate with ammonia, amines, ethanol, and phenol, and obtained a series of sulfonylureas and sulfonylurethans. This work was the first reported systematic investigation dealing with compounds of this general type. Owing to the difficulties of preparing sulfonyl isocyanates, however, this method has not found wide application.

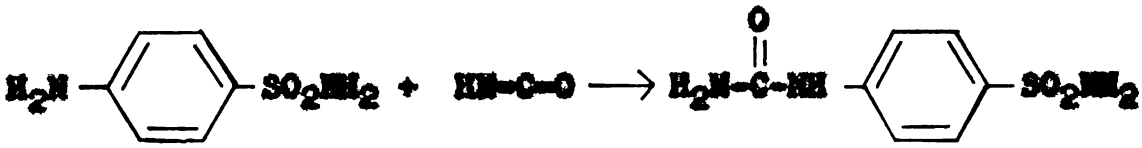


In the only other example reporting the experimental use of sulfonyl isocyanates, the procedure was simplified by omitting the isolation of the intermediate sulfonyl isocyanate (12); the nitrobenzene solution in which it had

been formed was used immediately in the condensation reaction with the amine.

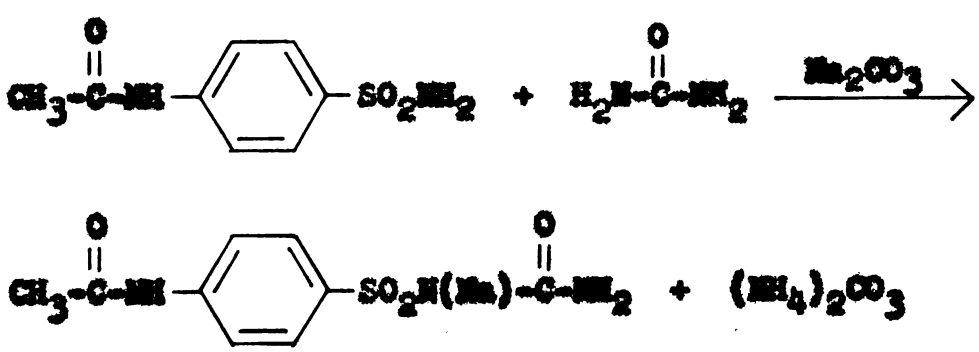
Sulfonylureas are obtained from sulfonamides by the methods generally used for converting amines into ureas. The reagents used for this purpose are cyanic acid, isocyanic esters, or compounds which decompose into these products under the reaction conditions of the synthesis. Urea, nitrourea, urethan, and carbamyl chloride may serve as sources of the elements of cyanic acid, while their N-alkyl- and N-aryl-substitution products, and certain azides and bromoamides, have been employed in place of the isocyanates.

The well-known extension of Wöhler's synthesis, involving the interaction of cyanic acid with amines, has not been successfully applied to the preparation of sulfonylureas. The first compounds of this type described in the literature were, in fact, prepared by this method (13). In contrast to amines, which condense rapidly with cyanates in acid media, sulfonamides fail to interact under these conditions. This is illustrated by the reaction of sulfanilamide with cyanic acid, in which p-sulfonamidophenylurea is produced, while the sulfonamide group remains unchanged (14). Sulfonamides are therefore condensed in neutral or alkaline media, but the reaction occurs considerably more slowly than with amines. Prolonged boiling of either benzene- or p-toluenesulfonamide



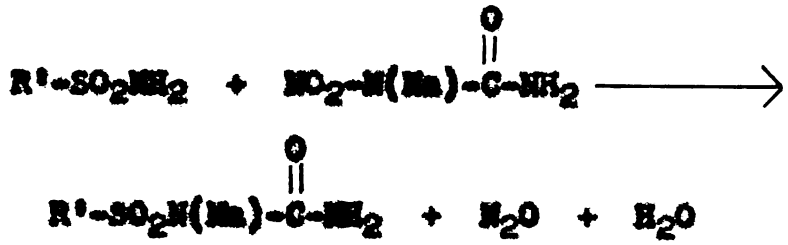
with an alkali cyanate in aqueous ethanol, for example, gives good yields of the appropriate arylsulfonylurea (10).

Sulfonylureas can often be prepared from urea itself by its interaction with sulfonamides. Owing to the acidic character of the latter reagents, the presence of an alkaline media is again necessary. Prolonged boiling of a mixture of p-acetaminobenzenesulfonamide, urea, and sodium carbonate in aqueous ethanol affords a nearly theoretical yield of acetylsulfanilylurea (15).

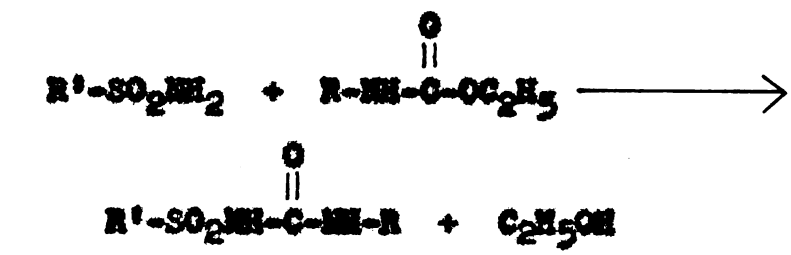


A convenient method of preparing substituted ureas with the aid of nitrourea has been used for synthesizing sulfonylureas (16). The sulfonamide is refluxed with sodium nitrourea, or with sodium carbonate and nitrourea, in 80 per cent ethanol until the evolution of nitrous oxide ceases. The desired sulfonylureas are usually obtained in

excellent yields (17).



Urethans readily decompose into cyanic acid or isocyanic esters and alcohols under suitable reaction conditions and in this way have been successfully used in the preparation of sulfonylureas. In practice, the reaction is carried out by heating the sulfonamide with urethan in the absence of a solvent to 100°C., until the evolution of ethanol is complete (17). In an alternate procedure using this method, the reactants are stirred in glycol monomethyl ether at 110-120°C. for prolonged periods (12).

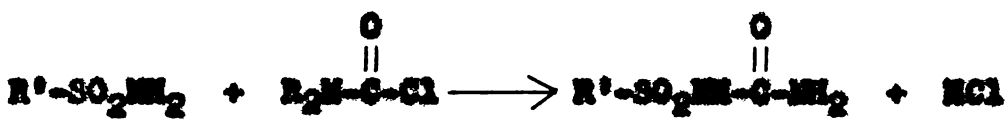


R' = alkyl, aryl or heterocyclic

R = H, alkyl or aryl

Carbamyl chloride and related compounds readily condense with sulfonamides to produce sulfonylureas. For

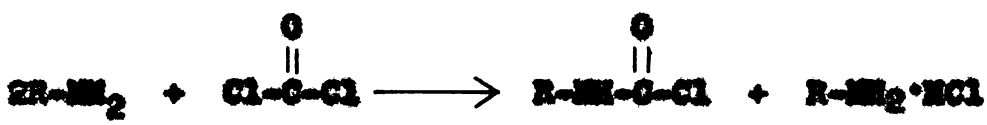
example, p-nitrobenzenesulfenamide reacts with carbamyl chloride in a dioxane solution, in the presence of pyridine as a catalyst, to yield p-nitrobenzenesulfenylurea (17). Condensation of the same amide with dialkylcarbamyl chlorides in nitrobenzene at 140-150°C. affords the trisubstituted sulfenylureas (18). In a variation



R^1 = alkyl or aryl

R = H or alkyl

of this general method, use is made of phosgene and the appropriate amine, without isolating the intermediate carbamyl chloride (10).



R = alkyl

The condensation of isocyanic esters with sulfenamides is a convenient method by which a great majority of sulfenylureas bearing a substituent on the amide nitrogen has been prepared.

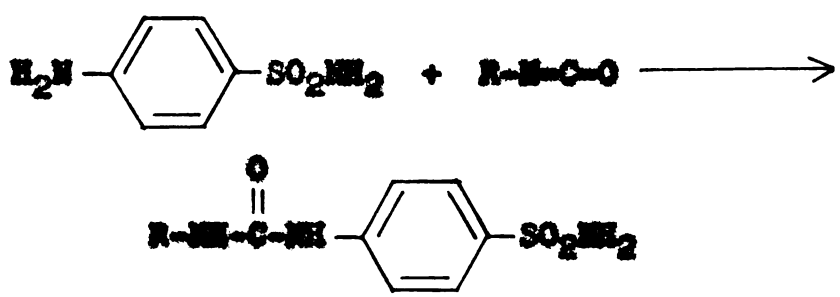
$$R'\text{-}SO_2NH_2 + R\text{-}N\text{=}C\text{=}O \longrightarrow R'\text{-}SO_2NH\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}R$$

R' = alkyl, aryl or heterocyclic

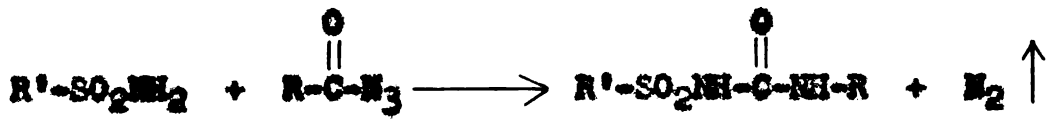
R = alkyl or aryl

The reaction may be carried out under a variety of experimental conditions with both aliphatic and aromatic isocyanates. Alkali metal salts of sulfonamides react in nitrobenzene (12), acetone (12), or ethanol (19), while free sulfonamides have been condensed in ethanolic sodium hydroxide (12) or in the absence of solvents (10). In the latter case, the addition of triethylamine, particularly in relatively large quantities, greatly accelerates the reaction resulting in improved yields (10). The catalyzing influence of tertiary amines in the condensation of isocyanates and hydroxyl-containing compounds is well known and its kinetics have been studied in detail (20). The interaction of isocyanates and amines, on the other hand, normally proceeds so readily that no attempts to employ tertiary amines as catalysts appear to be on record (21). It may be pointed out that in this reaction one of the reactants, the amine, is a base and is likely to be responsible for autocatalytic effects. With sulfonamides of essentially acidic character, however, the catalytic influence of a tertiary base becomes significant.

The great difference in the velocity with which amine and sulfonamide groups react with isocyanic esters is clearly illustrated by the observation of Roth and Degering (14) that approximately equimolar proportions of sulfanilamide and isocyanates react to form 1-aryl- or alkyl-3-p-sulfonamidophenylureas. The isocyanate is preferentially used up by the primary amino group of the molecule, while the sulfonamide group remains unaffected.



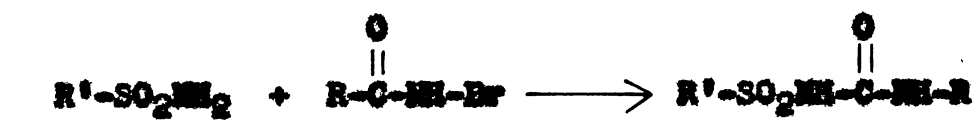
Substituted azides, capable of giving rise to isocyanates with attendant loss of nitrogen under suitable reaction conditions, provide still another method of adding the elements of isocyanates to sulfonamides. For this purpose the azide may be prepared in situ and need not be isolated. Thus, if phenylacetyl chloride is allowed to react with sodium azide in anhydrous benzene until the evolution of nitrogen ceases, followed by treatment of the resulting solution with sodium p-nitrobenzenesulfonamide and continued heating, it yields 1-benzyl-3-p-nitrobenzenesulfonylurea (12).



R' = p-nitrophenyl

R = benzyl

Similarly, sulfonylureas are obtainable by the reaction of sulfonamides with N-bromoamides in the presence of excess alkali. The N-haloamide, R-CO-NH-Br, first undergoes the Hofmann rearrangement on heating in an alkaline solution, alkali bromide is simultaneously lost, and the isocyanate thus formed reacts with the sulfonamide. For example, N-bromophenylacetamide has been used to prepare 1-arylsulfonyl-3-benzylureas (12).



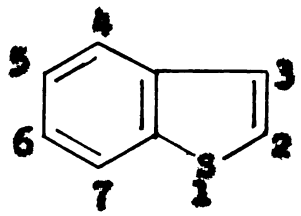
R' = aryl

R = benzyl

Since both the benzene and the thiophene nuclei (22) have been incorporated separately into arylsulfonylureas with chemotherapeutic uses, it was anticipated that the preparation of sulfonylurea derivatives containing both these structural features in a single molecule, as

found in benzo(b)thiophene, could have medicinal value in the oral control of diabetes.

Benzo(b)thiophene is the name currently used by Chemical Abstracts to designate the ring system(I). The alternate ring system(II) is found occasionally reported in the early literature. Benzo(b)thiophene is also called thianaphthene, thionaphthene, thiocoumarone and benzothiofuran. The numbering system used in this thesis report is that now in common usage by Chemical Abstracts, and shown in I.



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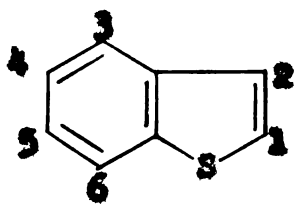
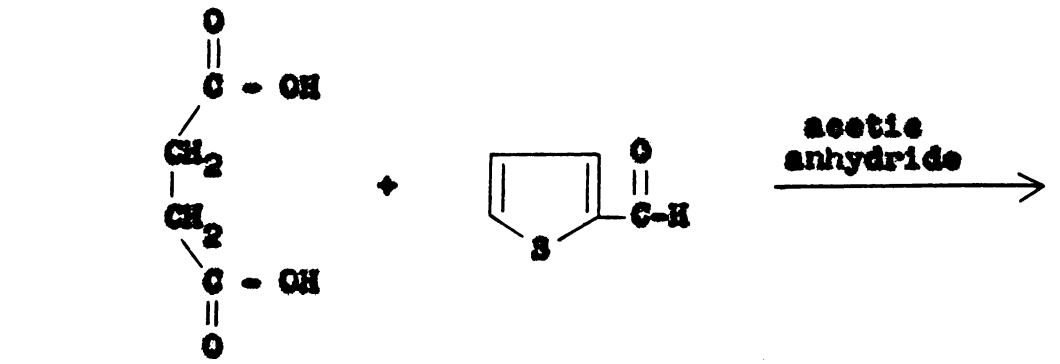


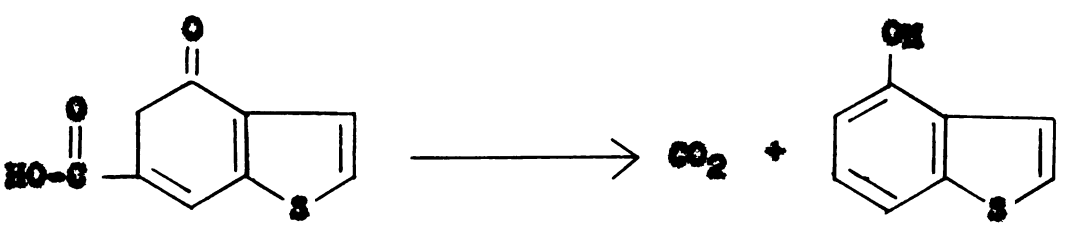
II

Detailed descriptions of the chemistry of benzo(b)-thiophene may be found in books by Steinkopf (23), and Fukushima (24). A fairly recent and excellent coverage by Hartough and Meisel (25) has been published containing the majority of references to benzo(b)thiophene through the first half of 1952. This sulfur heterocyclic occurs naturally in coal tar (26) and can be separated from the so-called "pure" commercial coal tar naphthalene (27).

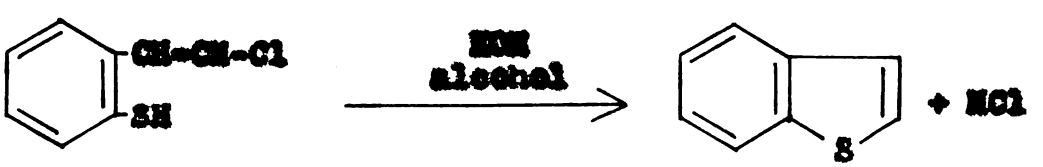
The first derivative of benzo(b)thiophene, 4-hydroxy-benzo(b)thiophene, was prepared in 1886 by Biedermann (28)

through the condensation of thiophene-2-aldehyde with sodium succinate. This reaction is similar to that used to prepare α-naphthol from benzaldehyde.



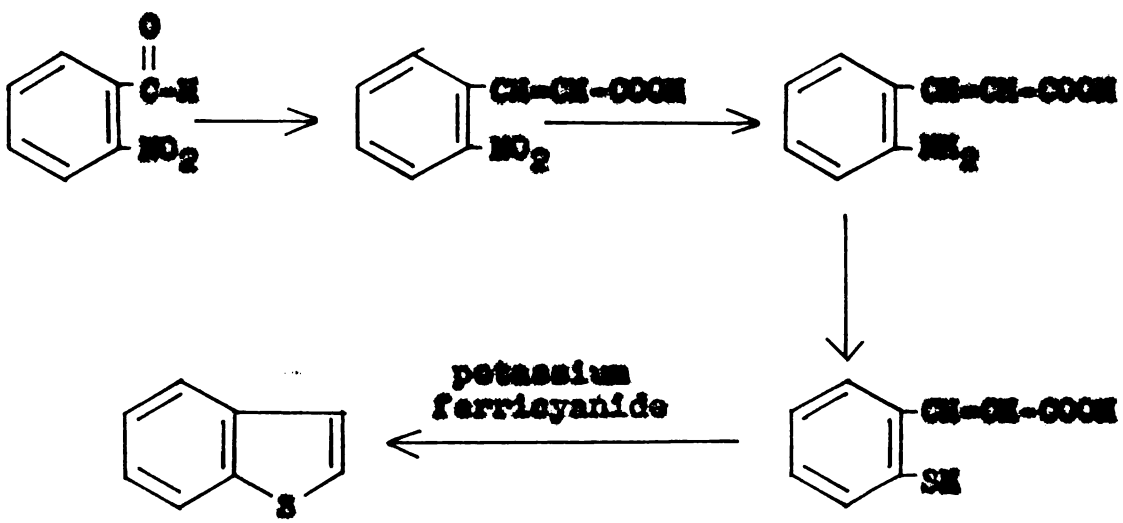


Benzo(b)thiophene was obtained synthetically prior to its isolation from natural sources. Initially, it was prepared by heating an alkaline alcoholic solution of o-mercapto-β-chlorostyrene at its reflux temperature (1).

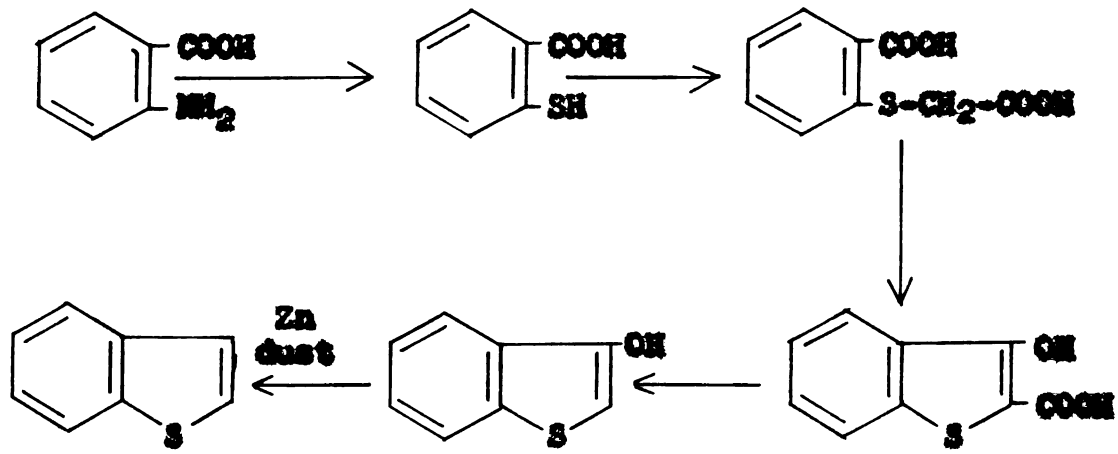


It was not until 1902 that Boes (29) was able to isolate benzo(b)thiophene from coal tar, separating it from the naphthalene fraction as its picrate derivative. Benzo(b)thiophene can be produced by the dehydrogenation of ethyl benzene and subsequent reaction of the styrene with hydrogen sulfide (30) or from styrene and hydrogen sulfide (31).

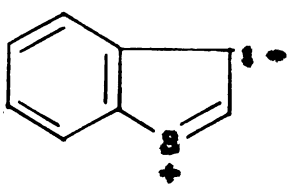
Friedlander (32) prepared benzo(b)thiophene by the oxidation of o-mercaptocinnamic acid with potassium ferricyanide.



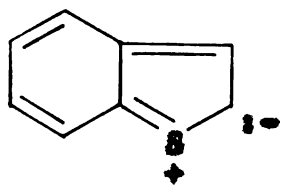
A widely used synthesis of benzo(b)thiophene involves the reduction of 3-hydroxythiophene by zinc dust (26).



The benzo(b)thiophenes undergo the usual aromatic type substitution reactions, with the formation of the 3-isomer, in contrast to thiophene, which undergoes substitution in the 2-position. Two resonance structures (I and II) involving the heterocyclic ring can be written for benzo(b)-thiophene. The stable Kekule structure present in I seems to control the orientation of substitution reactions to the 3-position.



I



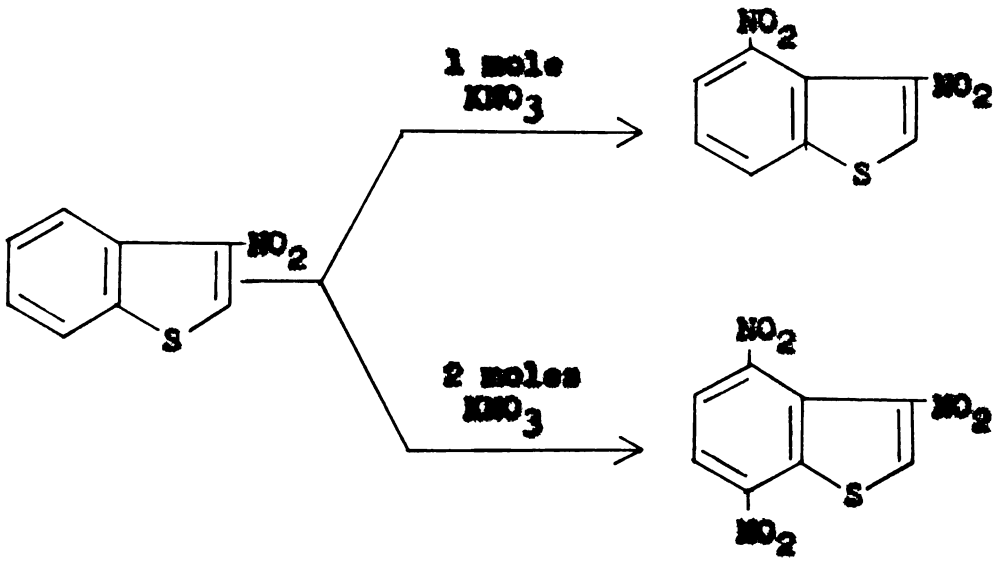
II

It is reported (33) that cyanoethylation, iodination with iodine monochloride, formylation and the Mannich reaction are unsuccessful with benzo(b)thiophene, but

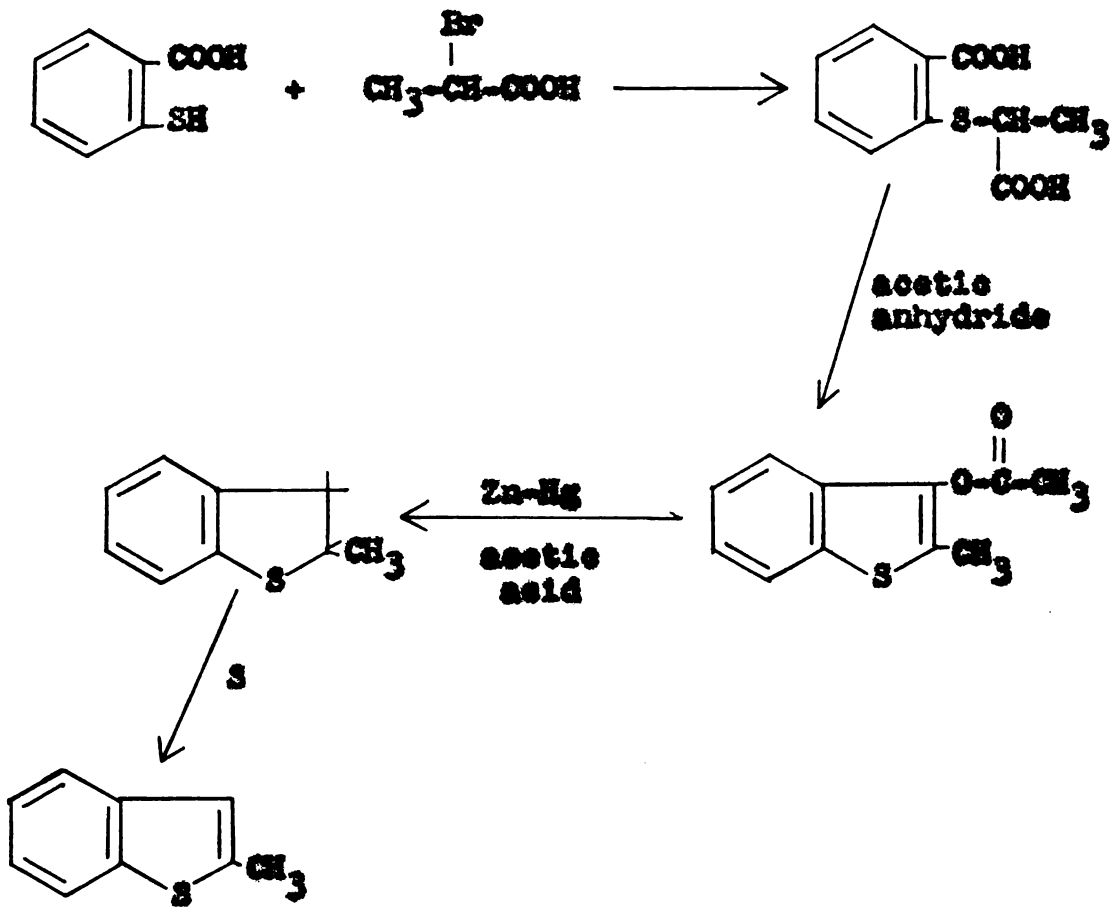
they do take place with thiophene itself indicating the more reactive character of thiophene.

If present, a 3-substituent determines the position of further substitution. When the 3-substituent is o,p-directing, further substitution occurs at the 2-position. Thus, nitration and bromination of 3-acetaminobenzo(b)-thiophene yields the 2-nitro- and the 2-bromo-derivatives, respectively (34).

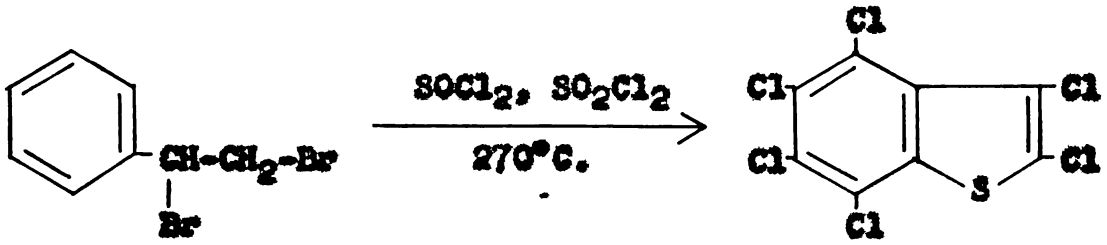
However, the presence of a meta-directing substituent in the 3-position, such as a nitro group, directs the entering group into the 4-position. The nitration of 3-nitrobenzo(b)thiophene with an equal molar quantity of potassium nitrate in sulfuric acid yields a mixture of dinitro derivatives from which the 3,4-dinitro compound has been identified; the use of a 2-molar excess of potassium nitrate results in the formation of the 3,4,7-trinitro derivative in an 85 per cent yield (35). The structure of the trinitro derivative has not been determined and the appearance of a third nitro group in a position para to one already present is unusual if the trinitro compound actually has the structure assigned to it.



Metalation of benzo(b)thiophene with sodamide in liquid ammonia (27), or with n-butyl lithium in ether (36) occurs in the two-position. That metalation occurs in the two-position has been verified by the fact that the 2-methylbenzo(b)thiophene obtained from the reaction of benzo(b)thienyllithium with methyl p-toluenesulfonate, and the 2-methylbenzo(b)thiophene prepared by Noth and Kiss (37) in the following unequivocal synthesis are identical.



Kruppa (38) was the first to report the chlorination of benzo(b)thiophene. He obtained a dichlorobenzo(b)thiophene, presumably the 2,3-derivative. Schlesinger (39) obtained 3-chlorobenzo(b)thiophene in low yield by the direct chlorination of benzo(b)thiophene in carbon tetrachloride as a solvent. The perchloro derivative of benzo-(b)thiophene, 2,3,4,5,6,7-hexachlorobenzo(b)thiophene, was prepared by Barger (40) according to the equation,

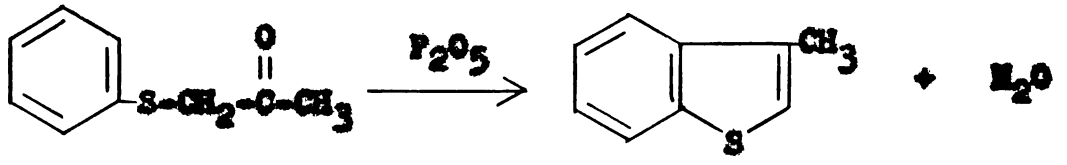


Bromination of benzo(b)thiophene yields a variety of products depending upon the reaction conditions. The mono-, di-, tri-, and tetrabromo derivatives are known. The monobromo derivative, 3-bromobenzo(b)thiophene, was first prepared (38) by treating benzo(b)thiophene with bromine in chloroform as a solvent at a reaction temperature of 30°C. The 2-bromobenzo(b)thiophene resulted from the interaction of 2-benzo(b)thienyllithium with bromine in ether solution (41).

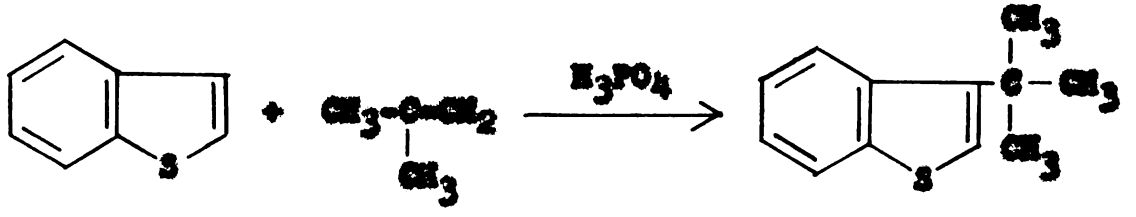
Only three iodo derivatives are reported in the chemical literature. The 2-iodobenzo(b)thiophene was obtained from the treatment, in an ether solution, of 2-benzo(b)thienyllithium with iodine (42). The 3-iodo derivative results from the treatment of benzo(b)thiophene with iodine and mercuric oxide (42).

The alkylbenzo(b)thiophenes are formed by either a ring closure reaction or by the direct alkylation of the benzo(b)thiophene nucleus. The monomethyl derivative, 2-methylbenzo(b)thiophene, is obtained from the reaction of 2-benzo(b)thienyllithium with methyl p-toluenesulfonate (41). It has also been prepared in low yields by the

vapor phase dehydrogenation of o-n-propylbenzenethiol (43). The alkyl derivative, 3-methylbenzo(b)thiophene, was obtained by Werner (44) by the dehydration of phenyl acetonyl sulfide.



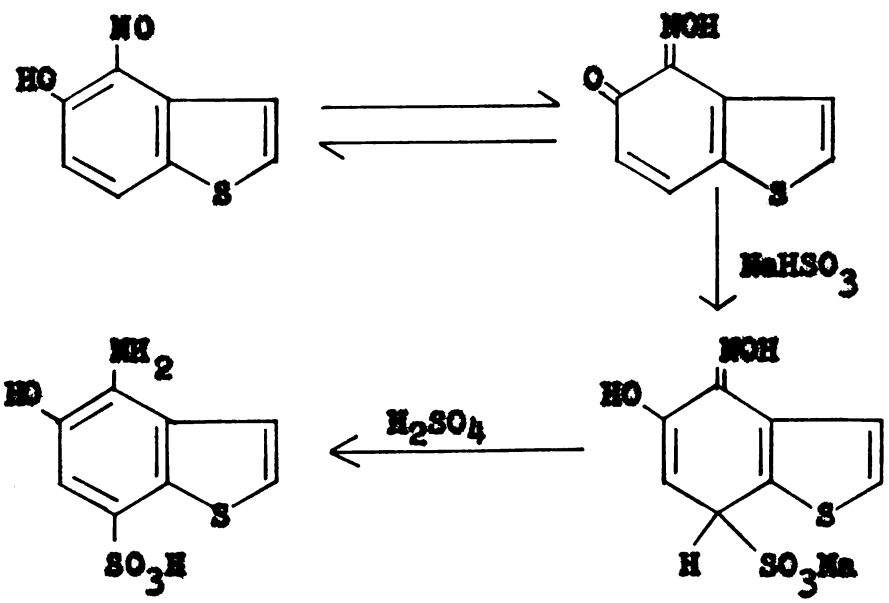
The alkylbenzo(b)thiophene, 3-t-butylbenzo(b)thiophene, reported by Coreen (45), was prepared by the acid catalyzed reaction of benzo(b)thiophene with isobutylene. The structure of this derivative of benzo(b)thiophene was established by desulfurization with Ramey nickel (46,47) to yield a known alkyl benzene.



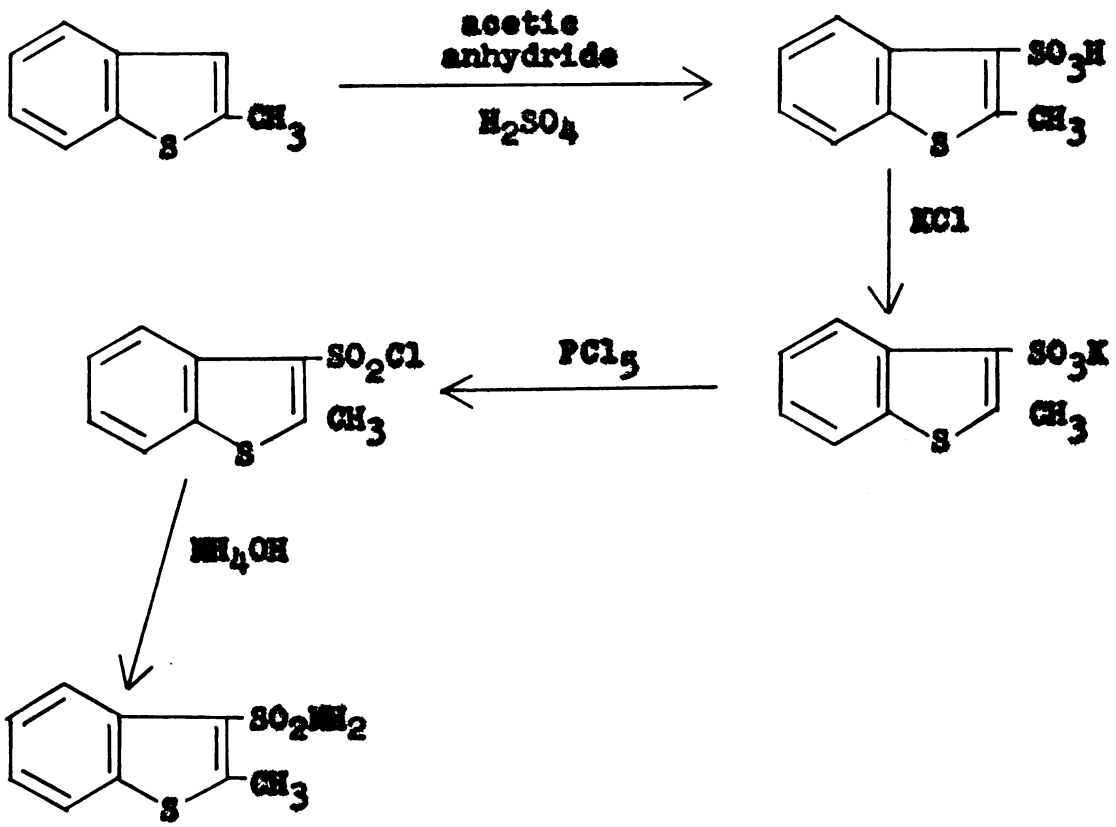
Only a very limited amount of work has been reported on the sulfur derivatives of benzo(b)thiophene. Meyd (2) was the first to prepare the 2- and 3-thiols by the reaction of sulfur with the 2-lithium derivative and the

3-Grignard reagent. Elemental analysis of the liquid thiols prepared in this study was carried out on their 2,4-dinitrophenyl sulfide derivatives since the thiols themselves were observed to be quite unstable. Komppa (38) treated benzo(b)thiophene with 75 per cent sulfuric acid and obtained a monobenzo(b)thiophene sulfonic acid, isolated as its sodium salt. He also reported some disulfonic acid was formed during the reaction. However, he reported no structure studies on any of these compounds.

Only a single benzo(b)thiophene derivative containing a sulfonic acid group in the benzene ring has been reported prior to 1961. Fieser prepared it by the following sequence of reactions (48),

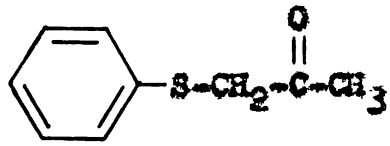


More recently, sulfonic acid derivatives have been reported. Pailer and Romberger (49) have synthesized several derivatives of methylbenzo(b)thiophenes. Using 95 per cent sulfuric acid in acetic anhydride as a reaction solvent, the following methyl derivatives were sulfonated, 2-methyl-, 3-methyl-, 5-methyl-, and the 2,3-dimethylbenzo(b)thiophenes. The sulfonyl chlorides, sulfonamides and sulfonanilides of these sulfonic acids were also prepared. The reactions involved are illustrated with 2-methylbenzo(b)thiophene.



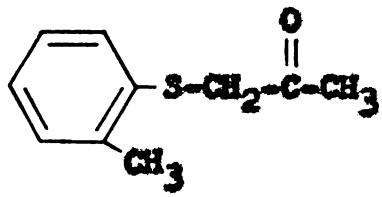
EXPERIMENTAL

Preparation of Acetonyl Phenyl Sulfide



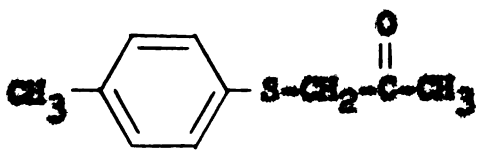
In a one-liter three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel was placed 40 g. (1.0 mole) of sodium hydroxide dissolved in 100 ml. of distilled water. The alkaline solution was cooled to 25°C. and 110 g. (1.0 mole) of thiophenol was quickly added. A 92.5 g. (1.0 mole) quantity of 1-chloro-2-propanone was then added during a half-hour period to the sodium thiophenolate solution while the reaction temperature was maintained in the range 20-25°C. Following the addition of the 1-chloro-2-propanone, the reaction mixture was stirred for an hour to complete the reaction. The product was extracted into 200 ml. of ether, separated from the aqueous layer, washed with 100 ml. of water, and dried over calcium chloride. Following removal of the ether on a steam bath, the residue was vacuum distilled to obtain 134 g. (0.81 mole, 81%) of a clear yellow colored liquid boiling at 139-140°C./16 mm. The reported boiling point (44) of acetonyl phenyl sulfide is 142°C./17 mm.

Preparation of Acetonyl-o-Tolyl Sulfide



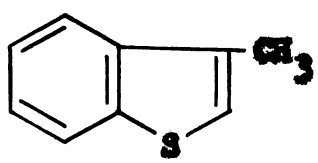
This compound was prepared by utilizing the experimental procedure described above for the synthesis of acetonyl phenyl sulfide. The amounts of the several reagents used were, 40 g. (1.0 mole) of sodium hydroxide dissolved in 100 ml. of distilled water, 124 g. (1.0 mole) of o-toluenethiol, and 92.5 g. (1.0 mole) of 1-chloro-2-propanone. Vacuum distillation of the crude product gave 140 g. (0.778 mole, 77.8%) of a pale yellow colored liquid having a boiling point of 154-155°C./15 mm. The reported boiling point (2) of acetonyl-o-tolyl sulfide is 154-155°C./15 mm. The 2,4-dinitrophenylhydrazone of this ketosulfide was prepared and after recrystallization from ethanol it melted at 114-115°C.

Preparation of Acetonyl-p-Tolyl Sulfide



This compound was prepared following the experimental procedure previously described for the synthesis of acetonyl phenyl sulfide. The quantities of the several reagents used were, 40 g. (1.0 mole) of sodium hydroxide dissolved in 100 ml. of distilled water, 124 g. (1.0 mole) of p-toluenethiol and 92.5 g. (1.0 mole) of 1-chloro-2-propanone. Vacuum distillation of the crude aryl keto-sulfide gave 144 g. (0.80 mole, 80%) of a pale yellow colored liquid boiling at 151-153°C./15 mm. The reported boiling point (50) of this ketosulfide is 150-151°C./15 mm.

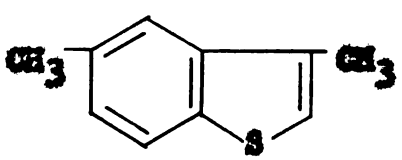
Preparation of 3-Methylbenzo(b)thiophene



In a 500 ml. three-necked flask fitted with a stirrer, reflux condenser and dropping funnel, was placed 28.4 g. (0.20 mole) of phosphorous pentoxide. In the dropping funnel was placed 74.0 g. (0.45 mole) of acetonyl phenyl sulfide. Approximately a quarter of the sulfide was added initially and then the reaction mixture was

cautiously heated with a bunsen burner to initiate the reaction. Reaction was initiated when the mixture reached a temperature of about 100°C. The exothermic reaction caused the reaction temperature to rise to about 200°C. causing it to take on a very dark coloration. After allowing the reaction temperature to fall to 170°C., the remainder of the sulfide was added dropwise, after which the reaction mixture was heated at 160-180°C. for an additional three-quarters of an hour. The dark colored reaction mixture was cooled to room temperature and 250 ml. of water was added. The reaction mixture was then extracted with four 100 ml. portions of ether. The combined extracts were washed with water and dried over magnesium sulfate. The ether was removed on a steam bath and the residual oil distilled under reduced pressure to yield 42.3 g. (0.29 mole, 64.4%) of a pale yellow colored liquid boiling at 75-78°C./2 mm. The boiling point reported in the literature (44) for 3-methylbenzo(b)thiophene is 63-72°C./0.3 mm.

Preparation of 3,5-Dimethylbenzo(b)thiophene

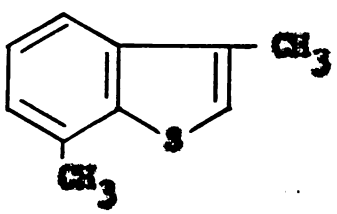


This material was prepared employing the experimental procedure previously described for the synthesis of 3-methylbenzo(b)thiophene. The reagents used were,

70.0 g. (0.49 mole) of phosphorous pentoxide and 140.0 g. (0.778 mole) of acetonyl-p-tolyl sulfide. Distillation of the crude product under reduced pressure gave 87.0 g. (0.54 mole, 69.4%) of a pale yellow colored liquid boiling at 118-120°C./9 mm. The reported boiling point (51) of 3,5-dimethylbenzo(b)thiophene is 118°C./9 mm.

A picrate of this compound was prepared and after recrystallization from ethanol it melted at 112-113°C. The melting point (51) reported in the literature for this picrate is 113-114°C.

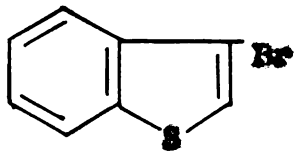
Preparation of 3,7-Dimethylbenzo(b)thiophene



Preparation of this substance was accomplished by following the experimental method used for the synthesis of 3-methylbenzo(b)thiophene. The following quantities of reagents were used, 56.8 g. (0.40 mole) of phosphorous pentoxide and 140.0 g. (0.77 mole) of acetonyl-o-tolyl sulfide. Distillation of the impure product under vacuum gave 98.0 g. (0.61 mole, 79.2%) of a nearly colorless liquid which boiled at 127-129°C./12 mm. (2).

A picrate of the product was prepared and after recrystallization from ethanol it melted at 113-114°C. Its reported melting point is 114-115°C. (2).

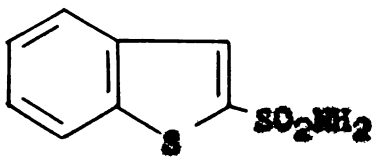
Preparation of 3-Bromobenzo(b)thiophene



In a two-liter flask fitted with a stirrer, dropping funnel and reflux condenser with an attached drying tube was placed 71.9 g. (0.5 mole) of benzo(b)thiophene, 73.0 g. (0.89 mole) of anhydrous sodium acetate and 380 ml. of chloroform. A solution of bromine (28 ml. of bromine dissolved in 70 ml. of chloroform) was added dropwise to the stirred benzo(b)thiophene solution during a 35 minute period. Intermittent external cooling was required to control the reaction. When the reaction had subsided, stirring was continued for an hour, and 100 ml. of water was added to dissolve the inorganic salts. The chloroform layer was separated, washed with 200 ml. of water, next with 100 ml. of 5 per cent sodium hydroxide, again with 200 ml. of water and finally with 200 ml. of a saturated sodium chloride solution. The chloroform layer was dried over anhydrous sodium sulfate. The chloroform was removed by distillation at atmospheric pressure and the residue was vacuum distilled to obtain 84.0 g. (0.39 mole, 78.0%) of

a light yellow colored oil boiling at 94-96°C./1.5 mm. The reported boiling point (52) of 3-bromobenzo(b)thiophene is 95°C./1.5 mm.

Preparation of 2-Benzo(b)thiophenesulfonamide



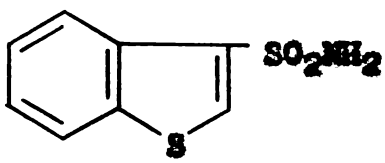
Benzo(b)thiophene was metalated according to the method of Shirley and Cameron (41).

A 500 ml. three-necked flask was fitted with a stirrer and two Y-adapter arms. One of the adapters carried a calcium chloride drying tube and thermometer while the other was fitted with a dropping funnel and a nitrogen gas inlet tube. In the reaction flask was placed 4.5 g. (0.65 mole) of lithium metal chips and 100 ml. of dry ether. A solution of 41.1 g. (0.3 mole) of redistilled n-butyl bromide dissolved in 60 ml. of dry ether was gradually added. As soon as reaction commenced, the reaction flask was immersed in an isopropyl alcohol-dry ice bath to lower the temperature of the reaction mixture to -10°C. The remainder of the n-butyl bromide solution was added during an hour, after which the reaction solution was stirred for an additional hour and a half at -10°C. The n-butyl lithium solution was filtered through glass

wool into a 500 ml. three-necked flask previously swept with nitrogen and precooled in an ice bath. The filtered n-butyl lithium solution was cooled to -10°C. and 26.8 g. (0.2 mole) of benzo(b)thiophene dissolved in 50 ml. of dry ether was added during a twenty minute period after which the reaction mixture was stirred for an additional hour and a half at -10°C. Anhydrous sulfur dioxide gas was bubbled slowly into the reaction mixture for 2 hours during which the reaction temperature was kept around 0°C. Then dry chlorine gas was bubbled slowly into the reaction mixture for an additional 3 hours after which the reaction mixture was stirred at room temperature for another 2 hours. About 200 ml. of water was added cautiously to the reaction to dissolve inorganic salts and excess sulfur dioxide and chlorine. The ether layer was separated and the ether removed on a steam bath. The residue was cooled and 150 ml. of concentrated ammonium hydroxide was added to it with rapid stirring. The stirred ammonical reaction mixture was heated on a steam bath for 2 hours, cooled to room temperature, and set aside overnight, with stirring being maintained. About 150 ml. of 10 per cent sodium hydroxide was added to the reaction mixture, and any insoluble material was removed by filtration. The filtered basic solution was decolorized twice with norite and acidified with 10 per cent HCl, precipitating the product as a white solid. This was allowed to digest for 2 hours, after which it was recovered by filtration and recrystallized from

dilute ethanol. The white solid product, 24.0 g. (0.113 mole, 56.5%), had a melting point of 206-207°C. Elemental analysis for $C_8H_7NO_2S_2$ gave the following results. Calculated: C, 45.05; H, 3.31; N, 6.57; S, 30.07. Found: C, 44.98; H, 3.43; N, 6.61; S, 30.05.

Preparation of 3-Benzo(b)thiophenesulfonamide



Method A:

In a one-liter three-necked flask fitted with a stirrer, reflux condenser and dropping funnel was placed 24.3 g. (1.0 mole) of magnesium chips and 100 ml. of dry ether. To this mixture was added dropwise 176.5 g. (0.83 mole) of 3-bromobenzo(b)thiophene dissolved in 200 ml. of dry ether. Reaction was initiated with 8 drops of ethyl bromide, and the reaction solution was heated at its reflux temperature for 2 hours following the addition of 3-bromobenzo(b)thiophene. The reaction solution was cooled, then filtered through cotton, to remove unreacted magnesium, into another one-liter flask equipped as above except for the substitution of a gas inlet in place of the dropping funnel. Anhydrous sulfur dioxide was bubbled into the stirred Grignard solution at room temperature for 2 hours, followed by dry chlorine gas for 3 hours. The reaction

mixture was stirred for another hour after the addition of the gases had been completed. About 200 ml. of water was added to the reaction mixture to dissolve any inorganic salts, excess sulfur dioxide and chlorine. The ether layer was separated from the aqueous layer and the ether was removed by distillation on a steam bath. The solid residue was stirred and heated on a steam bath for 2 hours with 250 ml. of concentrated ammonium hydroxide and then set aside overnight at room temperature with continuous stirring. About 200 ml. of 15 per cent sodium hydroxide solution was then added to the alkaline reaction mixture and the whole was treated with norite and filtered. The filtrate was cooled and on acidification with dilute HCl caused a white precipitate to form. This was allowed to digest for 2 hours, then recovered by filtration and washed with water on the filter. The solid was recrystallized from dilute ethanol to obtain 81.0 g. (0.38 mole, 45.8%) of a white solid which had a melting point of 158-160°C. Elemental analysis for $C_8H_7NO_2S_2$ gave the following results. Calculated: C, 45.05; H, 3.31; N, 6.57; S, 30.07. Found: C, 45.12; H, 3.86; N, 6.60; S, 30.02.

Method B:

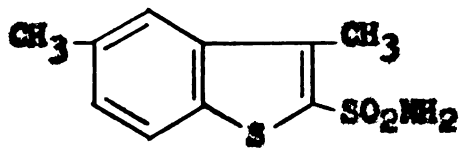
Into a 500 ml. three-necked flask fitted with a stirrer, condenser and dropping funnel was placed 50.0 g. (0.37 mole) of benzo(b)thiophene dissolved in 50.0 g. of acetic anhydride. The reaction mixture was cooled to

5°C. by immersion in an ice-salt bath. To the stirred chilled reaction mixture, 28.2 g. (0.37 mole) of 95 per cent concentrated sulfuric acid was carefully added. The reaction temperature was held in the range 5-15°C. during the addition of the acid. When this had been completed, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred at that temperature for an hour. The reaction mixture was again cooled by immersion in an ice-salt bath, and 25 g. of crushed ice was added to the reaction flask, which caused the temperature to rise to about 25°C. Then 100 ml. of water was added and the reaction mixture was extracted with two 75 ml. portions of chloroform. The aqueous layer was transferred to a distillation flask and it was concentrated to about one-quarter of its volume by the removal of water under vacuum. To the aqueous residue, 55.2 g. (0.74 mole) of potassium chloride as a warm saturated solution was added. The reaction slurry was stirred for 10 minutes, cooled to 10°C. and filtered. The solid was dried in an oven to yield 90.0 g. (0.357 mole, 96.5%) of the potassium salt of 3-benzo(b)thiophene sulfonic acid.

In a 500 ml. three-necked flask fitted with a stirrer, condenser and thermometer was placed 90.0 g. (0.357 mole) of potassium 3-benzo(b)thiophene sulfonate and 104.0 g. (0.50 mole) of phosphorous pentachloride. The reaction mixture was stirred at room temperature until it became liquid, and then it was heated at 100°C. for 2 hours.

gently heated until it became liquid. The reaction mixture was then stirred and heated at 100°C. for seven hours. The phosphorous oxychloride formed during the reaction was removed under vacuum distillation. After cooling the reaction flask by immersion in an ice bath, 150 ml. of ice water was cautiously added to the stirred contents followed by 100 ml. of benzene; stirring was continued for 15 minutes after adding the benzene. The benzene layer was separated and the aqueous layer was extracted with 100 ml. of benzene. The benzene extracts and original benzene layer were combined in a flask and the benzene was removed by distillation on a steam bath. The residue was cooled and 200 ml. of concentrated ammonium hydroxide was added to it with rapid stirring. The ammoniacal mixture was heated on a steam bath for 3 hours and then stirred at room temperature for a day. A solution of 150 ml. of 10 per cent sodium hydroxide was next added to the reaction flask. The mixture was heated gently and then filtered to remove insoluble material. The basic solution was decolorized twice with charcoal and acidified with dilute HCl to precipitate a pale yellow colored solid which was collected on a filter and washed with water. The crude product was recrystallized from dilute ethanol to yield 54.9 g. (0.242 mole, 72.7%) of an off-white colored solid which melted at 200-202°C. A mixed melting point with material prepared in Method A above showed no depression indicating that the two compounds were identical.

Preparation of 3,5-Dimethyl-2-Benzo(b)thiophenesulfonamide



Method A:

A 500 ml. three-necked flask was fitted with a stirrer and two Y-adapters. One of the adapters carried a calcium chloride drying tube and thermometer; the other was fitted with a dropping funnel and a nitrogen gas inlet. In the flask was placed 5.21 g. (0.75 mole) of lithium chips and 125 ml. of dry ether. A solution containing 68.5 g. (0.50 mole) of redistilled n-butyl bromide dissolved in 70 ml. of dry ether was added slowly to the lithium ether suspension. As soon as reaction had started, the reaction flask was immersed in an isopropyl alcohol-dry ice bath to lower the temperature of the reaction mixture to -10°C. The remainder of the n-butyl bromide solution was then added during an hour after which the reaction was stirred for an additional hour and a half at -10°C. The n-butyl lithium solution was filtered through glass wool directly into a 500 ml. three-necked flask which had been previously swept with nitrogen and prechilled in an ice bath. The filtered n-butyl lithium solution was cooled to -10°C. and 42.0 g. (0.26 mole) of 3,5-dimethylbenzo(b)thiophene dissolved in 60 ml. of dry ether was added during twenty minutes after which the reaction mixture was stirred for

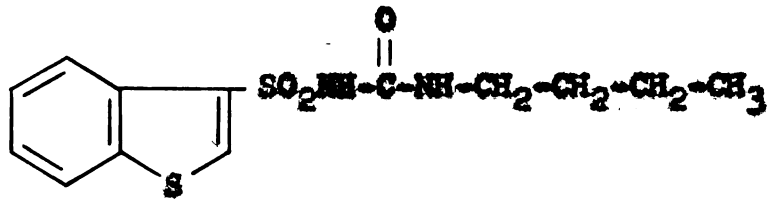
an additional 2 hours at -10°C. Anhydrous sulfur dioxide gas was then bubbled slowly into the reaction mixture for 3 hours. Next, dry chlorine gas was bubbled slowly into the reaction mixture for 5 hours, after which it was stirred at room temperature for an additional 4 hours. Two hundred ml. of water was added cautiously to the mixture to dissolve inorganic salts, excess sulfur dioxide and chlorine. The ether layer was separated and the ether removed by distillation on a steam bath. The residue was cooled and 200 ml. of concentrated ammonium hydroxide was added with rapid stirring. The stirred ammoniacal reaction mixture was heated on a steam bath for 2 hours, then set aside at room temperature for 12 hours with continuous stirring. About 150 ml. of 10 per cent sodium hydroxide solution was added to the reaction mixture and insoluble material was removed by filtration. The basic solution was treated with norite and acidified with 10 per cent HCl to precipitate a pale tan colored solid; this was collected on a filter and washed with cold water. The crude sulfonamide was recrystallized from boiling water to give 28.2 g. (0.12 mole, 46.1%) of a pale tan colored solid melting at 208-209°C. Elemental analysis for $C_{10}H_{11}NO_2S_2$ gave the following results. Calculated: C, 49.77; H, 4.60; N, 5.81; S, 26.58. Found: C, 50.03; H, 4.72; N, 5.89; S, 26.50.

Method B:

Into a 500 ml. three-necked flask fitted with a stirrer, condenser and dropping funnal was placed 50.0 g. (0.31 mole) of 3,7-dimethylbenzo(b)thiophene dissolved in 50.0 g. of acetic anhydride. The reaction mixture was cooled to 5°C. by immersion in an ice-salt bath. To the chilled reaction mixture, 31.4 g. (0.31 mole) of 95 per cent concentrated sulfuric acid was added slowly with stirring. The reaction temperature was kept below 20°C. during addition of the acid. Following addition of the acid, the reaction mixture was stirred at room temperature for two hours during which some solid formed in the reaction mixture. The reaction was cooled by immersion in an ice-salt bath and 25 g. of crushed ice was added to the reaction flask holding the reaction temperature below 25°C. Then, 100 ml. of water was added and the reaction mixture was extracted with two 75 ml. portions of chloroform. The aqueous layer was separated and transferred to a flask and about three-quarters of the water removed by distillation under vacuum. To the aqueous concentrate, 46.2 g. (0.62 mole) of potassium chloride as a warm saturated aqueous solution was added. The reaction slurry was stirred for a half hour, cooled to 10°C. and filtered. The solid was dried in an oven to yield 74.9 g. (0.267 mole, 86.2%) of the potassium salt of 3,7-dimethyl-2-benzo(b)thiophene sulfonic acid.

In a 500 ml. three-necked flask fitted with a stirrer, condenser and thermometer was placed 74.9 g. (0.267 mole) of potassium 3,7-dimethyl-2-benzo(b)thiophene sulfonate and 78.0 g. (0.37 mole) of phosphorous pentachloride. The solids were stirred at room temperature for about 10 minutes, after which the reaction mixture was heated at 100°C. for seven hours. The phosphorous oxychloride formed during the reaction was removed by distillation. To the residue, 150 ml. of ice water was added; the aqueous solution was extracted with two 75 ml. portions of benzene. The benzene extracts were combined and the benzene removed by distillation on a steam bath leaving a solid residue. With vigorous stirring, 200 ml. of concentrated ammonium hydroxide was added to the residue. The ammonical solution was stirred and heated on a steam bath for two hours and then set aside at room temperature for eight hours with continuous stirring. It was diluted with water and filtered. The solids collected on the filter were dissolved in 10 per cent sodium hydroxide solution, treated twice with norite and the alkaline solution was acidified with 10 per cent HCl to precipitate the crude product. The pale yellow colored solid weighed 51.1 g. (0.212 mole, 68.5%) and had a melting point of 211-213°C. after a single recrystallization from dilute ethanol. A mixed melting point of this compound with material prepared in Method A above showed no depression indicating that the two compounds were identical.

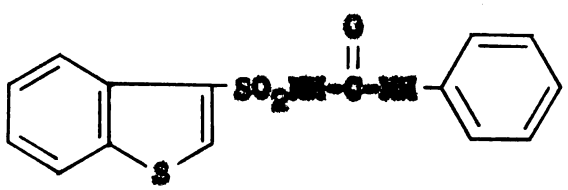
Preparation of 1-Butyl-3-[3-Benzo(b)thienylsulfonyl]urea



In a 500 ml. three-necked flask fitted with a condenser, stirrer and dropping funnel was placed 21.3 g. (0.10 mole) of 3-benzo(b)thiophenesulfonamide, 29.0 g. (0.21 mole) of ground anhydrous potassium carbonate and 200 ml. of dry acetone. This mixture was stirred and heated at its reflux temperature for an hour. To this mixture at its reflux temperature, 9.9 g. (0.10 mole) of n-butyl isocyanate dissolved in 20 ml. of dry acetone was slowly added during a half hour. After adding the isocyanate solution, the reaction mixture was stirred at its reflux temperature for an additional five hours to complete the reaction. The acetone was removed by distillation under vacuum. The dry residue was dissolved in 250 ml. of distilled water, and filtered to remove insoluble material. The filtrate was treated with charcoal, cooled and acidified with very dilute HCl, giving a white flocculent precipitate. The fine suspension was set aside overnight and filtered. The solid was dissolved in 5 per cent ammonium hydroxide solution and filtered to remove any insoluble material. The filtrate was acidified with dilute HCl in the cold and again filtered. The solid was

washed with 50 ml. of cold water and dried in an oven at 110°C. Recrystallization of the crude product from absolute ethanol gave 20.1 g. (0.064 mole, 64.0%) of a white solid which melted at 145-147°C. Elemental analysis for $C_{13}H_{16}N_2O_3S_2$ gave the following results. Calculated: C, 49.98; H, 5.16; N, 8.97; S, 20.53. Found: C, 50.03; H, 4.96; N, 9.01; S, 20.28.

Preparation of 1-Phenyl-3-[3-Benzo(b)thienylsulfonyl]urea



In a 500 ml. three-necked flask fitted with stirrer, dropping funnel and condenser was placed 10.6 g. (0.05 mole) of 3-benzo(b)thiophenesulfonamide and 60 ml. of acetone. An alkaline solution containing 2.0 g. (0.05 mole) of sodium hydroxide dissolved in 100 ml. of water was added to the amide solution in the flask. The reaction mixture was cooled to 20-25°C. and 5.95 g. (0.05 mole) of phenyl isocyanate dissolved in 20 ml. of acetone was slowly added with stirring. After adding the isocyanate solution, the reaction mixture was stirred at room temperature until isocyanate odor had disappeared. The reaction mixture was poured into a liter erlenmeyer flask, diluted with about 500 ml. of water and heated to about 65°C.

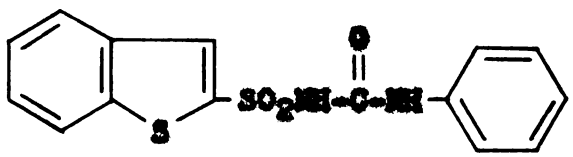
The hot solution was filtered and the filtrate was cooled and acidified with dilute HCl. The precipitate was collected on a filter, washed with water and then oven dried. The crude product was purified by several reprecipitations to give 11.2 g. (0.0338 mole, 67.6%) of a white powder melting at 153-155°C. Elemental analysis for $C_{13}H_{12}N_2O_3S_2$ gave the following results. Calculated: C, 54.20; H, 3.64; N, 8.43; S, 19.29. Found: C, 54.11; H, 3.60; N, 8.58; S, 19.06.

Preparation of 1-Butyl-3-[2-Benzo(b)thienylsulfonyl]urea

In a 500 ml. three-necked flask fitted with a stirrer, condenser and dropping funnel was placed 10.6 g. (0.05 mole) of 2-benzo(b)thiophenesulfonamide, 13.8 g. (0.10 mole) of ground anhydrous potassium carbonate and 200 ml. of dry acetone. The stirred mixture was heated at its reflux temperature for one hour. To this mixture at its reflux temperature, was added 5.9 g. (0.06 mole) of n-butyl isocyanate dissolved in 20 ml. of dry acetone during a half hour. After adding the isocyanate solution, the reaction mixture was stirred and heated at its reflux temperature for an additional five hours to complete the

reaction. The acetone was removed by distillation under vacuum. The dry residue was dissolved in 300 ml. of distilled water and filtered to remove insoluble material. The filtrate was acidified with dilute HCl to yield a white precipitate. This precipitate was collected on a filter, washed with water and recrystallized from absolute ethanol to give 10.3 g. (0.033 mole, 66.0%) of a white solid melting at 186-188°C. Elemental analysis for $C_{13}H_{16}N_2O_3S_2$ gave the following results. Calculated: C, 49.98; H, 5.16; N, 8.97; S, 20.53. Found: C, 50.24; H, 5.27; N, 9.12; S, 20.30.

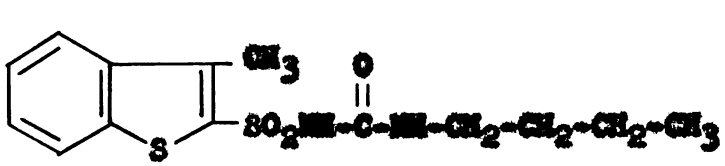
Preparation of 1-Phenyl-3-[2-Benzo(b)thienylsulfonyl]urea



In a 500 ml. three-necked flask fitted with a stirrer, dropping funnel and condenser was placed 15.0 g. (0.071 mole) of 2-benzo(b)thiophenesulfonamide and 60 ml. of acetone. A basic solution containing 2.82 g. (0.071 mole) of sodium hydroxide dissolved in 100 ml. of water was added to the reaction flask. The reaction mixture was cooled to 15-20°C. and 8.9 g. (0.75 mole) of phenyl isocyanate was slowly added to the cooled reaction mixture. A solid formed in the reaction mixture after all the isocyanate

had been added. The reaction was stirred at room temperature until the odor of isocyanate had disappeared. A 100 ml. volume of water was added to the reaction flask and the reaction mass was poured into a liter erlenmeyer flask and the mixture was further diluted with water to a final volume of about 600 ml. The diluted solution was heated to about 60°C. and filtered to remove any insoluble material. The filtrate was cooled to room temperature and filtered again. The filtrate was added slowly to excess ice cold 10 per cent HCl solution. The white flocculent precipitate which formed was collected on a filter and washed with water. The crude product was recrystallized from dilute methanol to yield 15.8 g. (0.048 mole, 67.2%) of an off-white colored solid which melted at 190-192°C. Elemental analysis for $C_{15}H_{12}N_2O_3S_2$ gave the following results. Calculated: C, 54.20; H, 3.64; N, 8.43; S, 19.29. Found: C, 54.30; H, 3.65; N, 8.49; S, 19.13.

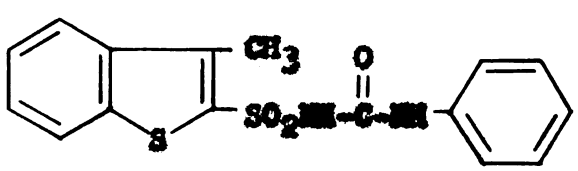
Preparation of 1-Butyl-3-[3-Methyl-2-Benzo(b)thienyl-sulfonyl]urea



In a 500 ml. three-necked flask fitted with a stirrer, condenser and dropping funnel was placed 11.35 g. (0.05 mole) of 3-methyl-2-benzo(b)thiophenesulfonamide, 13.8 g.

(0.10 mole) of ground anhydrous potassium carbonate and 200 ml. of dry acetone. The reaction was stirred and heated at its reflux temperature for an hour. To this stirred mixture at its reflux temperature was cautiously added 5.0 g. (0.05 mole) of n-butyl isocyanate during a half hour. When the isocyanate had been added, the reaction was stirred at its reflux temperature for another five hours to complete the reaction. The acetone was removed by distillation under vacuum. The residue was dissolved in 300 ml. of water, decolorised with charcoal twice and acidified with dilute HCl in the cold to precipitate the crude product. This was collected on a filter, washed with distilled water and recrystallised from methanol to give 10.1 g. (0.031 mole, 62.0%) of an off-white coloured solid which melted at 170-172°C. Elemental analysis for $C_{14}H_{18}N_2O_3S_2$ gave the following results. Calculated: C, 51.51; H, 5.56; N, 8.58; S, 19.65. Found: C, 51.30; H, 5.47; N, 8.70; S, 19.53.

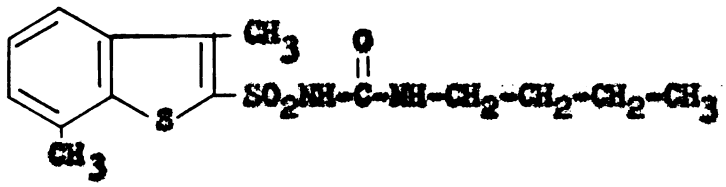
Preparation of 1-Phenyl-3-[3-Methyl-2-Benzo(b)thienyl-sulfonyl]urea



In a 500 ml. three-necked flask fitted with a stirrer, condenser and dropping funnel was placed 11.35 g.

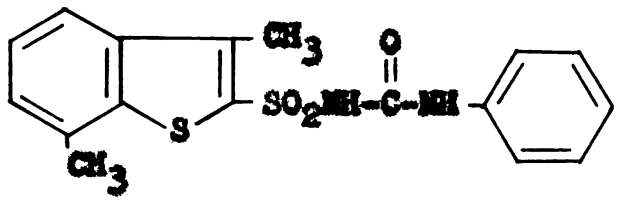
(0.05 mole) of 3-methyl-2-benzo(b)thiophenesulfonamide and 40 ml. of acetone. A solution containing 2.0 g. (0.05 mole) of sodium hydroxide dissolved in 100 ml. of water was added to the flask. The reaction mixture was cooled to 15-20°C. and 8.9 g. (0.075 mole) of phenyl isocyanate was slowly added to the precooled reaction mixture. A precipitate formed in the reaction mixture when all the isocyanate had been added. The reaction was stirred until the odor of isocyanate had disappeared. It was then diluted with water, heated to 40°C. and filtered. The filtrate was decolorized with charcoal twice, cooled and poured into ice cold dilute HCl. The precipitate was collected on a filter, water washed and air dried. The crude product was purified by several reprecipitations. The pure product weighed 8.9 g. (0.026 mole, 51.5%), was cream colored and had a melting point of 156-158°C. Elemental analysis for $C_{16}H_{14}N_2O_3S_2$ gave the following results. Calculated: C, 55.47; H, 4.07; N, 8.09; S, 18.51. Found: C, 55.37; H, 4.14; N, 8.30; S, 18.64.

Preparation of 1-Butyl-3-[3,7-Dimethyl-2-Benzo(b)thienyl-sulfonyl]urea



In a 500 ml. three-necked flask fitted with a stirrer, condenser and dropping funnel was placed 12.05 g. (0.05 mole) of 3,7-dimethyl-2-benzo(b)thiophenesulfonamide, 13.8 g. (0.10 mole) of ground anhydrous potassium carbonate and 200 ml. of dry acetone. The stirred reaction mixture was heated at its reflux temperature for two hours. To the refluxing mixture, 5.0 g. (0.05 mole) of n-butyl isocyanate was slowly added during a half hour. Following the addition of the isocyanate, the reaction was stirred for nine hours at its reflux temperature to complete the reaction. The acetone was removed by distillation under vacuum and the dry residue was taken up in 300 ml. of water, treated with charcoal and filtered. The filtrate was acidified with dilute HCl and the precipitated product was collected on a filter, washed with water and then dried in an oven. The product was recrystallized from methanol to obtain 10.3 g. (0.031 mole, 62.0%) of a white solid melting at 198-200°C. Elemental analysis for $C_{15}H_{20}N_2O_3S_2$ gave the following results. Calculated: C, 52.91; H, 5.92; N, 8.23; S, 18.84. Found: C, 52.84; H, 5.97; N, 8.33; S, 19.03.

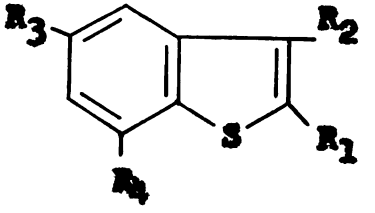
Preparation of 1-Phenyl-3-[3,7-Dimethyl-2-Benzo(b)-thienylsulfonyl]urea



In a 500 ml. three-necked flask fitted with a stirrer, condenser and dropping funnel was placed 12.05 g. (0.05 mole) of 3,7-dimethyl-2-benzo(b)thiophenesulfonamide and 30 ml. of acetone. A solution containing 2.0 g. (0.05 mole) of sodium hydroxide dissolved in 100 ml. of water was added to the flask. The reaction mixture was cooled to 20°C. and 6.55 g. (0.055 mole) of phenyl isocyanate was added slowly during a half hour. After adding the isocyanate, the reaction mixture was stirred at room temperature for three hours to complete the reaction. The reaction mixture was then diluted with 100 ml. of water and filtered. The filtrate was decolorized twice with charcoal and acidified with dilute HCl to precipitate the crude product. This was collected on a filter, washed with water and dissolved in 5 per cent ammonium hydroxide and filtered again. The filtrate was added to ice cold acetic acid. The precipitated product was collected on a filter and washed with water, dried in an oven and recrystallized from dilute ethanol. The yield obtained was 8.4 g. (0.0234 mole, 46.8%) of a pale yellow colored solid melting at

139-140°C. Elemental analysis for $C_{17}H_{16}N_2O_3S_2$ gave the following results. Calculated: C, 56.64; H, 4.47; N, 7.77; S, 17.79. Found: C, 56.54; H, 4.59; N, 7.64; S, 17.82.

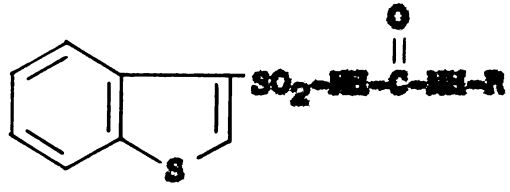
Table I: Properties and Analysis[a] of Benzo(b)thiophenesulfonamides



R_1	R_2	R_3	R_4	Formula	% Yield A	% Yield B	M.P., °C.		Carbon %	Hydrogen %	Nitrogen %	Sulfur %
H	SO_2NH_2	H	H	$C_8H_7NO_2S_2$	45.8	78.5	158-160	Calcd.	45.05	3.31	6.57	30.07
								Found	45.12	3.26	6.60	30.02
SO_2NH_2	H	H	H	$C_8H_7NO_2S_2$	56.5	--	206-207	Calcd.	45.05	3.31	6.57	30.07
								Found	44.98	3.43	6.61	30.05
SO_2NH_2	CH_3	H	H	$C_9H_9NO_2S_2$	62.9	72.7	202-203	Calcd.	47.55	3.99	6.16	28.22
								Found	47.44	4.17	6.10	28.30
SO_2NH_2	CH_3	CH_3	H	$C_{10}H_{11}NO_2S_2$	46.1	29.5	208-209	Calcd.	49.77	4.60	5.81	26.58
								Found	50.03	4.72	5.89	26.50
SO_2NH_2	CH_3	H	CH_3	$C_{10}H_{11}NO_2S_2$	46.0	68.5	212-214	Calcd.	49.77	4.60	5.81	26.58
								Found	49.78	4.64	5.72	26.66

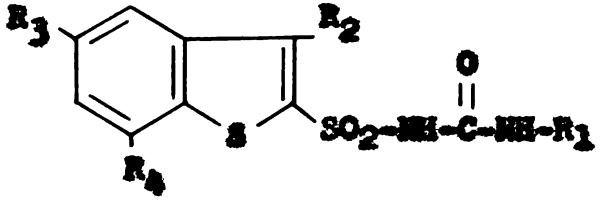
[a]Microanalysis by Microtech. Labs., Skokie, Illinois.

Table XI: Properties and Analysis of 3-Benzo(b)thiophenesulfonylureas



R	Formula	M.P. °C.		Carbon %	Hydrogen %	Nitrogen %	Sulfur %
C_6H_5	$C_{15}H_{12}N_2O_3S_2$	153-155	Calcd.	54.20	3.64	8.43	19.29
			Found	54.11	3.60	8.58	19.06
n-C_4H_9	$C_{13}H_{16}N_2O_3S_2$	145-147	Calcd.	49.98	5.16	8.97	20.53
			Found	50.03	4.96	9.01	20.28

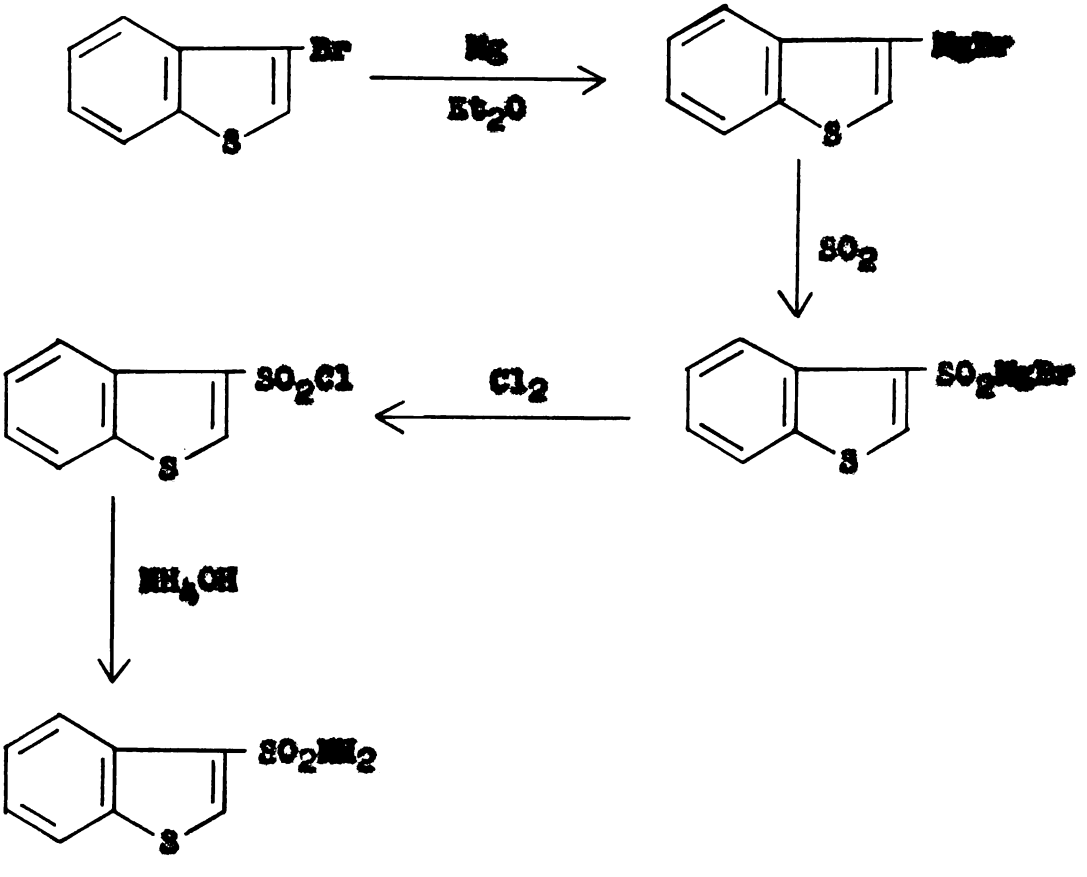
Table III: Properties and Analysis of 2-Benzo(b)thiophenesulfonylureas



R_1	R_2	R_3	R_4	Formula	M.P. °C.		Carbon %	Hydrogen %	Nitrogen %	Sulfur %
n-C_4H_9	H	H	H	$C_{13}H_{16}N_2O_3S_2$	186-188	Calcd.	49.98	5.16	8.97	20.53
						Found	50.24	5.27	9.12	20.30
n-C_4H_9	CH_3	H	H	$C_{14}H_{18}N_2O_3S_2$	170-172	Calcd.	51.51	5.56	8.58	19.65
						Found	51.30	5.47	8.70	19.53
n-C_4H_9	CH_3	H	CH_3	$C_{15}H_{20}N_2O_3S_2$	198-200	Calcd.	52.91	5.92	8.23	18.84
						Found	52.84	5.97	8.33	19.03
C_6H_5	H	H	H	$C_{15}H_{12}N_2O_3S_2$	190-192	Calcd.	54.20	3.64	8.43	19.29
						Found	54.30	3.65	8.49	19.13
C_6H_5	CH_3	H	H	$C_{16}H_{14}N_2O_3S_2$	156-158	Calcd.	55.47	4.07	8.09	18.51
						Found	55.37	4.14	8.30	18.64
C_6H_5	CH_3	H	CH_3	$C_{17}H_{16}N_2O_3S_2$	139-140	Calcd.	56.64	4.47	7.77	17.79
						Found	56.54	4.59	7.64	17.82

DISCUSSION

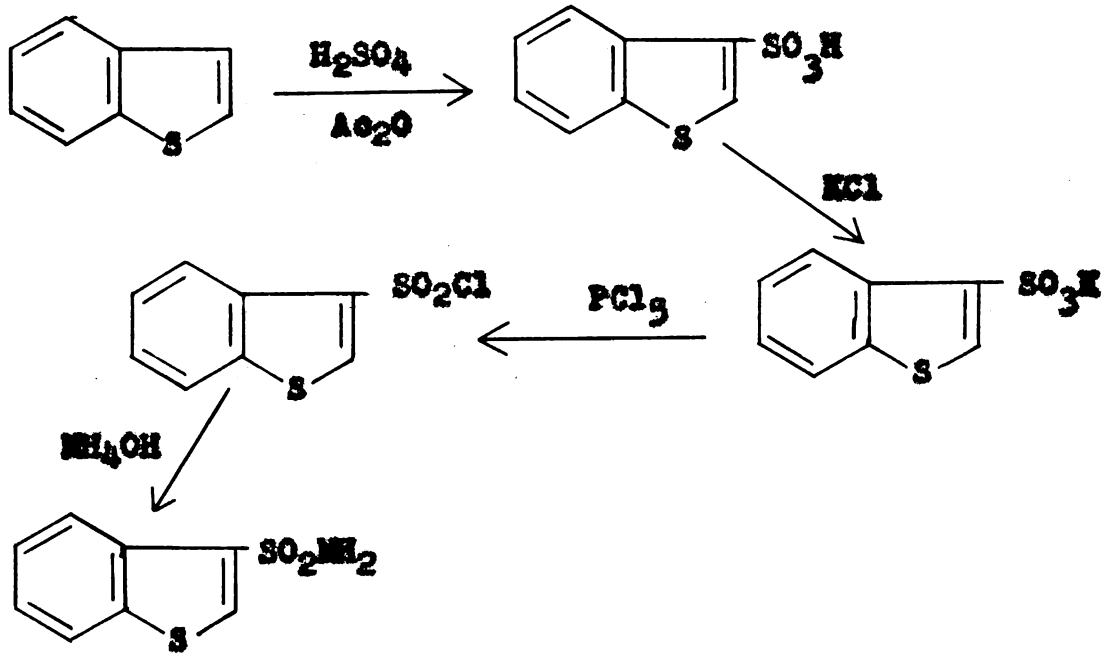
The preparation of 3-benzo(b)thiophenesulfonamide was accomplished by the reaction of 3-benzo(b)thiophene magnesium bromide with anhydrous sulfur dioxide to obtain bromomagnesium-3-benzo(b)thiophene sulfonate. Treatment of the latter with gaseous chlorine yielded the crude sulfonyl chloride which on interaction with excess ammonia gave the sulfonamide.



This general sequence of reactions is similar to those employed by Scott (54) to prepare several aliphatic sulfonyl chlorides. In utilizing 3-bromobenzo(b)thiophene, an appreciable amount of unreacted magnesium was always

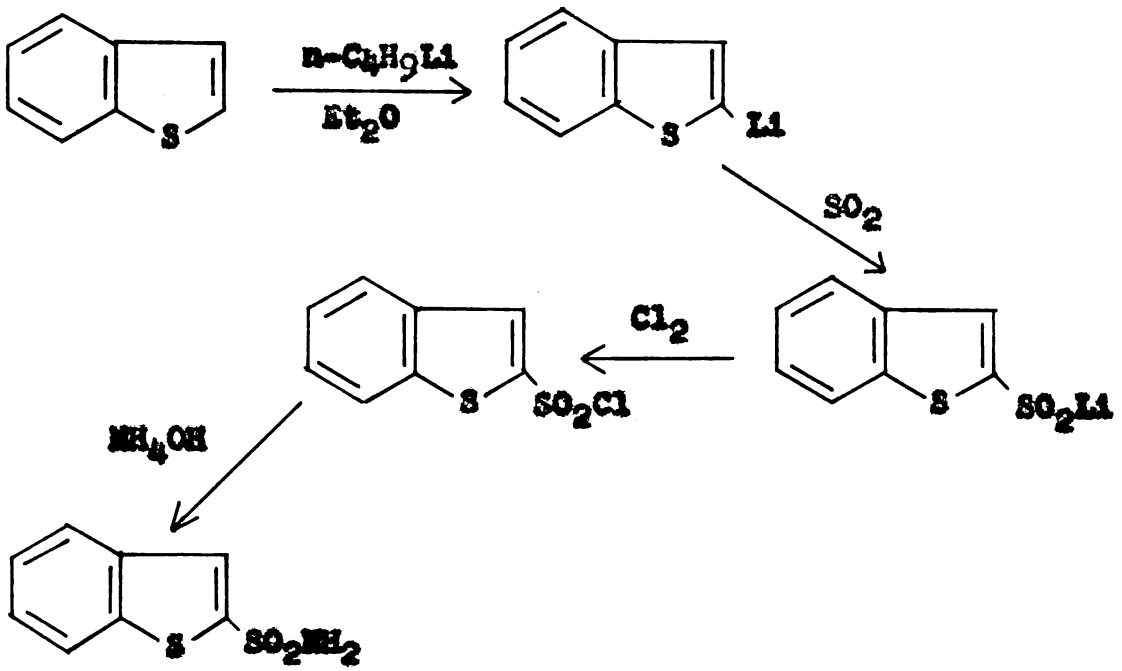
present at the completion of the Grignard reaction. The use of 3-bromobenzo(b)thiophene in preparing the Grignard reagent requires the presence of a simple alkyl halide to promote the reaction. Attempted distillation of the crude sulfenyl chloride leads to its decomposition with an attendant lowering of the yield. The sulfonamide was readily prepared from the crude sulfenyl chloride by reaction with ammonia yielding the heterocyclic sulfonamide as a white crystalline solid.

An alternative preparation of 3-benzo(b)thiophenesulfonamide involves the reaction of benzo(b)thiophene with 95 per cent concentrated sulfuric acid in acetic anhydride as a reaction media. The yield of the benzo(b)thiophenesulfonic acid by this method was good and the position of sulfonation (55) was fixed. In the sulfonation



of benzo(b)thiophene the reaction is conducted in the presence of sufficient acetic anhydride to combine with the total water present in the reaction system, that is in the sulfuric acid used and the water formed during the reaction. The 3-benzo(b)thiophenesulfonic acid is a viscous mass, crystallizable with difficulty. The acid was isolated as its potassium salt which crystallized in the form of colorless platelets. The sulfonamide was prepared by the usual method from the potassium salt via its sulfonyl chloride.

The preparation of the isomeric 2-benzo(b)thiophene-sulfonamide was accomplished by a series of reactions somewhat similar to those described for the synthesis of 3-benzo(b)thiophenesulfonamide. Benzo(b)thiophene was metalated according to the method of Shirley and Cameron (41). The several steps involved in the synthesis can be summarized as,



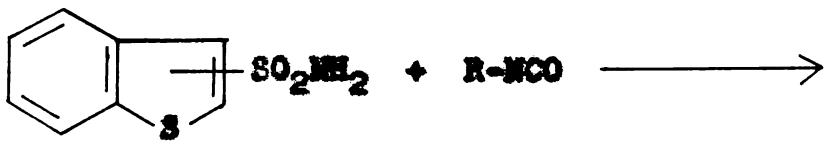
Three additional substituted benzo(b)thiophenesulfonamides were prepared by this general procedure, namely, 3-methyl-2-benzo(b)thiophenesulfonamide, 3,5-dimethyl-2-benzo(b)-thiophenesulfonamide, and 3,7-dimethyl-2-benzo(b)thiophene-sulfonamide. In these cases, the three position of the heterocyclic ring was first blocked by a methyl group, and thus, on direct sulfonation with concentrated sulfuric acid in acetic anhydride only the two isomer was produced.

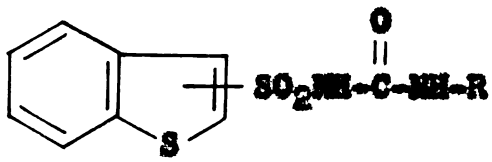
A similarity noted in all of these reactions was the large amount of tarry residue resulting in the sulfonation step. No attempt was made to investigate the residues but it can be reasonably assumed they contained some sulfones. The yields of products obtainable were fair in the majority of the reactions.

In each case the isolation of the desired sulfonamide was accomplished by extraction of the reaction mixture with dilute sodium hydroxide and isolation of the solid product on acidification. Purification of the crude sulfonamides was accomplished by their recrystallization from dilute ethanol. The sulfonamides prepared in this investigation are summarized in Table I. Preparation by Method A refers to either the Grignard or lithium procedures while Method B refers to the procedure involving direct sulfonation with concentrated sulfuric acid in acetic anhydride media.

The 3-alkylbenzo(b)thiophenes used in the preparation of the 3-alkyl-2-benzo(b)thiophenesulfonamides were prepared by a ring closure reaction using phosphorous pentoxide with the appropriate acetonyl phenyl sulfides. The experimental procedure described by Werner (44) was utilized for the synthesis of the alkylbenzo(b)thiophenes used in this study. The ring closure reaction was always accompanied by rather extreme discoloration and darkening of the reaction mixture with some apparent decomposition.

The sulfonylureas described in this investigation were prepared by the interaction of the appropriate sulfonamide with either phenyl or n-butyl isocyanate in an aqueous or non-aqueous medium. The reaction involved may be indicated in the following manner, where R represents phenyl or n-butyl.





The sulfur heterocyclic sulfonylureas prepared for the first time and characterized in the course of this investigation are summarized in Table IX and Table XII. All of the ureas obtained were white crystalline compounds. The sulfonyl urea derivative of 3,5-dimethylbenzo(b)thiophenesulfonamide could not be isolated in a pure form. The crude product was an oil which tended to revert to the sulfonamide and isocyanate on attempted purification. Dilute methanol or ethanol were found to be satisfactory solvents for the recrystallization of the majority of the heterocyclic sulfonylureas.

These compounds have been submitted to an independent laboratory for pharmacological evaluation, and these results will be reported elsewhere.

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