THIOPHENE AND ITS DERIVATIVES

Part Three

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible, new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

In 1952, in the first volume of *The Chemistry of Heterocyclic Compounds*, Howard D. Hartough described the state of research on the chemistry of thiophene and its derivatives up to 1950. Selenophene and tellurophene were also included in this monograph which, except for two chapters, was written by Hartough alone. When this book was written, the explosive development triggered by the commercial process for thiophene from butane and sulfur, developed by Socony-Vacuum Oil Company in the 1940s, had just begun. The enormous amount of work carried out on this important aromatic five-membered heterocycle since 1950 makes it of course impossible for one person to cover all aspects, and an able group of specialists were assembled from all over the world to treat the entire field. This makes some minor overlaps between chapters unavoidable, but I think it is important to treat some topics from different angles of approach.

Because of the wealth of results and the rather large number of contributors, these volumes are not as strictly organized as some previous volumes in this series, but can be considered as a collection of topics on thiophene chemistry. Together, however, it is my hope that these chapters give as comprehensive a description as possible of the chemistry of thiophene and its monocyclic derivatives, based on the literature from 1950 to 1982. References to previous results, treated in Hartough's book, are also given when necessary.

The chapters fall in two categories: (1) those that treat syntheses, properties, and reactions of thiophenes, and (2) those that treat systematically functionalized simple thiophenes, such as alkylthiophenes, halothiophenes, aminothiophenes, thiophenecarboxylic acids, and so on. The latter chapters, as is customary in the Weissberger–Taylor series, contain tables of compounds with their physical properties, which should be very useful for all synthetic chemists. Part 1 of these volumes contains only chapters in category 1 and starts with a treatise on the preparation of thiophenes by ring-closure reactions and from other ring systems. It is followed by a chapter on theoretical calculations. Then, in two chapters, naturally occurring thiophenes in plants and in petroleum, shale oil, and coals are treated. The topic of the next chapter is the important field of pharmacologically active compounds. The synthetic use of thiophene derivatives for the synthesis of aliphatic compounds by desulfurization follows. Two chapters treat thiophenes modified at the sulfur, namely thiophene-1,1-dioxides and thiophene-1-oxides, and S-alkylation of thiophenes. In the last three chapters, the discussion on different reactivities of thiophenes starts with radical reactions of thiophenes, cycloaddition reactions, and photochemical reactions.

Part 2 of this four-part volume begins with a treatment of the important field of electrophilic aromatic substitution of thiophenes, followed by systematic treatment of four classes of functionalized thiophenes, namely the alkyl-, halo-, nitro- and aminothiophenes.
Preface

The first two chapters of Part 3 of this volume treat the chemistry of thiophene derivatives containing thiophene-to-oxygen bonds and thiophene-to-sulfur bonds, respectively, and the remaining chapters cover formyl and acyl derivatives of thiophene, thiophenecarboxylic acids, and thenyl derivatives.

In part 4, nucleophilic aromatic substitution of thiophenes, physical properties of thiophenes, metal derivatives of thiophenes as well as thienyl ethenes, thienyl acetylenes and aryl- and heteroarylthiophenes will be examined.

I wish to thank all the distinguished scientists who contributed chapters to these volumes for their splendid cooperation and my secretary Ann Nordlund for her invaluable help. I am also indebted to Dr. Robert E. Carter for correcting my chapter and those of some of the other authors whose native tongue is not English.

SALO GRONOWITZ

Lund, Sweden
January 1986
Contents

I SYNTHESSES, PHYSICAL PROPERTIES, AND REACTIONS OF COMPOUNDS CONTAINING THIOPHENE–OXYGEN BONDS 1
SALO GRONOWITZ and ANNA-BRITTA HÖRFELDT

II SYNTHESIS, PHYSICAL PROPERTIES, AND REACTIONS OF COMPOUNDS CONTAINING THIOPHENE–SULFUR BONDS 135
SALO GRONOWITZ AND ANNA-BRITTA HÖRFELDT

III FORMYL AND ACYL DERIVATIVES OF THIOPHENES AND THEIR REACTIONS 309
RICHARD M. SCROWSTON

IV THIOPHENECARBOXYLIC ACIDS AND THEIR DERIVATIVES 565
JOHN M. BARKER and PATRICK R. HUDDLESTON

V SIDE-CHAIN REACTIVITY OF THIOPHENES. THENYL DERIVATIVES 975
GIUSEPPE MUSUMARRA

AUTHOR INDEX 1155
SUBJECT INDEX 1245
THIOPHENE AND ITS DERIVATIVES

Part Three

This is the Forty-Fourth Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS
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CHAPTER I

Syntheses, Physical Properties, and Reactions of Compounds Containing Thiophene—Oxygen Bonds

SALO GRONOWITZ and ANNA-BRITTA HORNFELDT

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I. Introduction .................................................. 2
II. Preparation of Hydroxythiophenes .................................. 3
   1. Preparation of 2-Hydroxythiophenes through Ring-Closure Reactions .... 3
      A. C₆ + S Methods ........................................ 3
      B. C₅S + C Methods ..................................... 4
      C. Other Ring Systems ................................... 4
   2. Preparation of 3-Hydroxythiophenes through Ring-Closure Reactions .... 5
      A. C₆ + S Methods ........................................ 5
      B. C₃ + CSC Methods .................................... 7
      C. C₅S + C₅ Methods .................................... 9
      D. C₅S + C Methods ..................................... 10
      E. C₅ + CS Methods ..................................... 14
      F. 3-Hydroxythiophenes through Ring Closure of C₅S Componds .......... 20
      G. 3-Hydroxythiophenes through Ring Closure of C₅SC Componds .......... 20
      H. 3-Hydroxythiophenes from 3-Oxotetrahydrothiophenes .......... 21
      I. 3-Hydroxythiophenes from Other Heterocyclic Compounds .......... 22
   3. Hydroxythiophenes by Way of Thiophene Metal Derivatives .......... 23
      A. Hydroxythiophenes from Grignard and Thiencyllithium Reagents .... 23
      B. Hydroxythiophenes from Thiopheneboronic Acids .................. 24
      C. Hydroxythiophenes from t-Butoxythiophenes .................... 25
      D. Hydroxythiophenes from Other Alkoxythiophenes ............ 33
      F. Various Methods for the Preparation of Hydroxythiophenes .......... 38
III. Tautomerism of Hydroxythiophenes .......................... 40
   1. Alkyl-, Aryl-, and Halo-Substituted 2-Hydroxythiophenes .......... 40
   2. Carbonyl-Substituted 2-Hydroxythiophenes .......................... 57
   3. Alkyl-Substituted 3-Hydroxythiophenes .......................... 58
   4. Carbonyl-Substituted 3-Hydroxythiophenes .......................... 59
   5. Dihydroxythiophenes .................................... 60
IV. Physical Properties of the Hydroxythiophene Systems ............ 60
   1. Ultraviolet Spectra of the Hydroxythiophene Systems ............ 60
   2. Infrared Spectra of the Hydroxythiophene Systems ............ 63
   3. NMR Spectra of the Hydroxythiophene Systems ............ 64
   4. Mass Spectra of the Hydroxythiophene Systems ............ 70
   5. Acid Dissociation Constants of Hydroxythiophenes ............ 70
This chapter treats the 2- and 3-hydroxythiophenes, their alkyl and aryl ethers, their esters, the acyloxythiophenes, as well as other thiophene derivatives containing thiophene-oxygen bonds.

The chemistry of the hydroxythiophene systems, which only recently has been studied in detail, differs very much from that of the analogous phenols. Hydroxythiophenes are often very unstable air-sensitive, and acid-sensitive compounds, which decompose easily. They also show characteristic tautomeric properties. Thus 2-hydroxythiophene could in principle exist in the three tautomeric forms 1 to 3 (Scheme 1). The unsaturated thiolactone forms 2 and 3 are also called 3-thiolen-2-one and 4-thiolen-2-one, respectively. In another nomenclature, which has been used in the literature, 2 and 3 are called 2,5-dihydro-2-oxothiophene and 2,3-dihydro-5-oxothiophene. In Chemical Abstracts they are found under 2(5H)-thiophenone and 2(3H)-thiophenone, respectively. In analogy with the corresponding furan derivatives they have also been called $\alpha,\beta$-thiobutenolide (2) and
β,γ-thiobutenolide (3). In substituted derivatives, depending on the nature and position of the substituents, the form 1, 2, or 3 can be the most stable. 3-Hydroxythiophene (4) can also exist in the keto form (5), which is called 4-thiolen-3-one, or 3(2H)-thiophenone. The position of the tautomeric equilibrium is greatly influenced by solvent effects.

II. PREPARATION OF HYDROXYTHIOPHENES

1. Preparation of 2-Hydroxythiophenes through Ring-Closure Reactions

In this section on synthesis the compounds are called 2-hydroxythiophenes regardless of their true tautomeric structure. Only a few ring-closure reactions leading to 2-hydroxythiophenes are known.

A. \( C_4 + S \) Methods

5-Methyl-2-hydroxythiophene was prepared as early as 1886 by Kues and Paal through the reaction of levulinic acid with \( P_4S_{10} \). Steinkopf and Thormann realized that two tautomeric forms of 5-methyl-2-hydroxythiophenes could be obtained, but made an erroneous structure assignment. Correct structure assignments were made in 1960 by the use of NMR. 5-Aryl-2-hydroxythiophenes have also been prepared by this method. The reaction of aliphatic \( \gamma \)-oxo esters with \( H_2S/HCl \) gave a mixture of tautomers of the 5-alkyl-2-hydroxythiophene system and 5-alkyl-5-mercapto-thiolan-2-ones, which upon refluxing in pyridine could be transformed to the tautomers of 5-alkyl-2-hydroxythiophenes (cf. Part 1, Chapter I, Section II.E). 5-Methyl-2-hydroxythiophene has also been prepared in low yield through the reaction of the acid chloride of pentyne-4-carboxylic acid with KSH and \( H_2S \) in pyridine. The reaction of 6 with \( H_2S/HCl \) gives the 2-hydroxy-4-carbethoxy-5-methylthiophene (7) in 54% yield (see also Part 1, Chapter I, Section II.3) (Scheme 2). The reaction of 3-bromomethyl-3-(2-furyl)-2-propenoic acid with thiourea gave 4-(2-furyl)-3-thiolen-2-one.
B. \( C_3S + C \) Methods

Condensation of crude carbonyl sulfide with malonitrile and alkylation of the intermediate (8) with phenacyl bromide gives 4-amino-2-hydroxothiophene (9) in 64\% yield\(^9\) (Scheme 3).

\[
\begin{align*}
\text{NC} & \quad \text{C} = \text{C} & \quad \text{O}^-\text{Na}^+ \\
\text{NC} & \quad \text{C} = \text{C} & \quad \text{S}^-\text{Na}^+ \\
\end{align*}
\]

Scheme 3

C. Other Ring Systems

The reaction of bromocysteine thiolactone hydrochloride with pyridoxal in ethanol gave the 3-amino-2-hydroxothiophene derivative 10\(^10\) (Scheme 4). Bromination of the thiolactones (11), followed by dehydrobromination with triethylamine, was used for the preparation of 2-hydroxythiophene and 3-ethyl-2-hydroxythiophene (12).\(^11\) The reaction of 13 with NaSH and hydrogen chloride, followed by an aromatic aldehyde, gave 14 directly,\(^12\) which can also be prepared by the acid-catalyzed condensation of 2-hydroxythiophenes with aldehydes (Scheme 5). Compound 13 was prepared by the treatment of 4-aryl-4-oxybutanoic acids with acetic anhydride and sulfuric acid.

Treatment of dichloromaleic thioanhydride with acetic anhydride, followed by
heating with powdered zinc, gave the acetoxy derivatives of 2,5-dihydroxythiophene (15).13 The reaction of 4-chloromethyl-4-methyl-azetidin-2-one with sodium hydrogen sulfide gave 4-methyl-2-hydroxythiophene in 4% yield.14 The azetidinone was obtained through the cycloaddition of methallyl chloride to chlorosulfonyl isocyanate, followed by splitting off the sulfonyl chloride group. The reaction of 16 with sodium ethoxide in refluxing ethanol gave the 3-cyano-2-hydroxythiophenes (17)15 (Scheme 6).

\[
\begin{align*}
\text{Ar} = & \text{C}_6\text{H}_5, & \text{Ar'} = & 4-\text{ClC}_6\text{H}_4 \\
\text{Ar} = & 3,4-(\text{CH}_3)_2-\text{C}_6\text{H}_3, & \text{Ar'} = & 2,4-\text{Cl}_2\text{C}_6\text{H}_3
\end{align*}
\]

Scheme 5

2. Preparation of 3-Hydroxythiophenes through Ring-Closure Reactions

In this section on synthesis the compounds are called 3-hydroxythiophenes, regardless of their true tautomeric structure, although the most stable tautomeric forms are usually indicated in the formulas. Ring-closure reactions are in many cases the best routes for the preparation of mono- or disubstituted 3-hydroxythiophenes.

A. \(C_4 + S\) Methods

This approach has been used for the preparation of some 2-amino-4-hydroxythiophenes (19) through the reaction of 18 with NaSH16 (Scheme 7). Another example is the reaction of \(\alpha,\alpha'-\text{dibromo-1,2-diketones}\) (20) with sodium sulfide to give the 3,4-dihydroxythiophene (21)17 (Scheme 8). A somewhat modified approach starts
from the ditosylate of 3-hexyne-2,5-diol, which was oxidized with potassium permanganate to hexane-3,4-dione-2,5-diol ditosylate, which upon reaction with sodium sulfide gave 21.18

The classical Benary reaction,19 which consists of the reaction of 22 with sodium hydrogen sulfide in ethanol, has been used repeatedly for the preparation of 5-substituted 3-hydroxy-4-thiophenecarboxylic acid derivatives (23)20–24 (Scheme 9).

The reaction of tetraketones (24) with sulfur dichloride gave 2,5-diacyl-3,4-hydroxythiophenes (25)25 (Scheme 10).

The reaction of the diacetylenic ketones (26) with thiourea gave by way of 27 the condensation product of 2-phenyl-4-hydroxythiophene with benzaldehyde (28), which was also prepared from 2-phenyl-4-hydroxythiophene and benzaldehyde26 (Scheme 11). Michael addition of ethyl acetoacetate to 28 led to thiophene (29). In acidified methanol 28 gave most probably 30, which might have been formed by reverse aldol condensation to give 2-phenyl-4-hydroxythiophene, which then condensed with 28 to give 30.26,27

\[
R - C = C = CO_2C_2H_5 \\
\text{NH}_2 \quad \text{COCH}_2\text{Cl}
\]

\[
H_5C_2O_2C \quad \text{OH}
\]

\[
\text{R} = \text{H, CH}_3, \text{C}_6\text{H}_5
\]

Scheme 9
Preparation of Hydroxythiophenes

\[ R\text{CH}_2\text{COCH}_2\text{COR'} \xrightarrow{\text{ScI}_\text{2}} \]

\[ \text{R} = \text{R'} = \text{C}_6\text{H}_5\text{CO} \quad 33\% \\
\text{R} = \text{COCH}_3, \quad \text{R'} = \text{C}_6\text{H}_5\text{CO} \quad 33\% \\
\text{R} = \text{R'} = \text{COCH}_3 \quad 26\% \\
\text{R} = \text{R'} = \text{isovaleryl} \quad 20\% \\
\text{R} = \text{R'} = \text{pivaloyl} \quad 40\% \\

Scheme 10

\((\text{C}_6\text{H}_5\text{C}═\text{C})_2\text{CO} \xrightarrow{(\text{NH}_2)_2\text{C}═\text{S}} \)

\[ \text{H}_5\text{C}_6\text{C}═\text{CHC}═\text{CHC}_6\text{H}_5 \]

\[ \xrightarrow{150\°} \]

\[ \text{H}_5\text{C}_6\text{SCHCH}_2\text{COCH}_3 \]

\[ \xrightarrow{\text{NaOH}} \]

\[ \text{H}_5\text{C}_6\text{SCHCH}_2\text{COCH}_3\text{C}_2\text{H}_5 \]

Scheme 11

B. \( \text{C}_2 + \text{CSC Methods} \)

The Hinsberg reaction\(^2^8\) has been extensively used for the preparation of 3-hydroxythiophenes (31), and especially 3,4-dihydroxythiophenes through the reaction of diethylthiodiacetate with \(\alpha\)-keto esters\(^2^9\) and diethyl oxalate\(^2^6,3^0-3^6\),
respectively (Scheme 12). It has been claimed that 3,4-dihydroxythiophene is obtained as yellow needles in 82% yield upon heating 3,4-dihydroxy-2,5-thiophenedicarboxylic acid at 120°C/3 mm Hg. In these cases the mechanism is most probably a normal Dieckman reaction, since 2,5-diesters are obtained. In the reaction with α-diketones, monoesters of the 2,5-thiophenedicarboxylic acids and a Stobbe-type mechanism are indicated (cf. Part 1, Chapter I, Section 11.2).

The reaction of the diketo sulfide (33) with butyl glyoxylate, diethyl mesoxalate, and dibutyl oxalate gave (R = H), (R = OH), and (R = CO₂C₂H₅) in 50%, 36%, and 25% yields (Scheme 13).

Mixed sulfides such as 35 have been reacted with glyoxylates, mesoxalates, and oxalates to give 3-hydroxythiophenes and 3,4-dihydroxythiophenes. The reaction is regiospecific, and 35 (R = C₆H₅) gave only 36 (R = H) and 36 (R = CH₃) with butyl glyoxylate and ethyl pyruvate, respectively. Similarly, 35 (R = CH₃) gave only 37. The reaction of 35 (R = (H₃C)₃CH₂C) with diethyl oxalate gave 38. The complex sulfide 39 gave 40 with butyl glyoxalate (Scheme 14). For additional details about the Hinsberg reaction, see Part 1, Chapter I, Section II.A and Table I-15 in that chapter, and the four dissertations from the University of Erlangen.
There are only a few examples of this approach to the synthesis of 3-hydroxythiophenes. Thus a Russian patent describes the preparation of 2-amino-4-hydroxythiophenes (42) through the reaction of an arylacetonitrile (41) with esters of thioglycolic acid in a refluxing organic solvent such as pyridine or t-butyl alcohol in the presence of an alkali metal alkoxide (Scheme 15).

The reaction of 2,3-dienonitriles (43) with mercaptoacetates (44) gave 4-cyano-3-hydroxythiophenes in 65 to 90% yield (Scheme 16).
The Gompper reaction (see Part 1, Chapter I, Section II.4.A), which consists of the condensation of active methylene compounds with carbon disulfide, followed by alkylation of the intermediate enethiolates (47) with α-halogenacetic acid to 48 and ring closure, leads to 3-hydroxythiophenes (49) when malonate (46) is used as the active methylene compound\(^{39,40}\) (Scheme 17).

If cyanoacetate is used as active methylene compound, both 3-αmido- and 3-hydroxythiophenes can be formed, as observed in the reaction of 50 with methyl iodide and sodium methoxide, which gave a mixture of 51 and 52\(^{41}\) (Scheme 18).

S-Alkylation of dimethyl monothione malonate (53) with α-haloesters or α-haloketones to give 54, followed by base treatment, leads to 5-methoxy-3-hydroxythiophenes (55)\(^{42}\) (Scheme 19). Treatment of 53 with morpholine gave the corresponding thioamide, which was alkylated with ethyl chloroacetate and then ring closed to 56. Etheniols prepared from β-ketoesters (57) have been S-methylated to give 58, which upon treatment with sodium ethoxide ring closed to the 3-hydroxy-2-cyanothiophenes (59). Alkylation of 57 with benzyl chloride followed
Scheme 18

Scheme 19
by treatment with potassium \( t \)-butoxide, or alternatively with ethyl 2-bromophenylacetate and treatment with aqueous sodium hydroxide, gave 2-phenyl-5-methyl-3-hydroxythiophene.\(^4^3\)

The condensation of malonic acid derivatives with esters of thione or dithio acids in the presence of potassium alkoxides gave 60, which upon reaction with 61 gave the 3-hydroxy-2-thiophene ester 62\(^4^4\) (Scheme 20).

\[
\begin{align*}
60 & \quad \text{R'} = \text{C}_6\text{H}_5, \text{CH}_3 \\
61 & \quad \text{R''} = \text{C}_6\text{H}_5, \text{CH}_3 \\
62 & \quad \text{R'} = \text{C}_6\text{H}_5, \text{CH}_3
\end{align*}
\]

Scheme 20

Condensation of ethyl cyanoacetate with ethyl dithioacetate or thione acetate, followed by alkylation with ethyl \( \alpha \)-haloacetate or \( \alpha \)-haloacetonitrile, gives 63, which is in equilibrium with 64. Upon treatment with base 65 and 66 were formed. The proportions of 65 and 66 depended both on the nature of the substituent R and on the base and were independent of the proportions of 63 and 64 in equilibrium. Thus for \( R = \text{CO}_2\text{C}_6\text{H}_5 \) the E to Z ratio, 64 to 63, was 8:92, and cyclization with sodium hydride in benzene gave 80% of 65 and 13% of 66. On the other hand, triethylamine in benzene gave 32% of 65 and 35% of 66. 2,3,4,6,7,8-Hexahydropyrrole[1,2-a]pyrimidine(HHP) in benzene, which is a system not prone to cause rearrangement, also gives 82% of 65 derived from the predominant Z-isomer and 10% of 66. When \( R = \text{CN} \), only the Z-isomer 63 can be observed with NMR. In spite of this, 95% of 66 (\( R = \text{CN} \)) is obtained on treatment with triethylamine, and 3% of 65 (\( R = \text{CN} \)). Thus the nondetectable E-isomer (64) ring-closes much faster than the Z-isomer, and isomerization of 63 to 64 must be very fast. When HPP in

\[
\begin{align*}
63 & \quad \text{Z-isomer} \\
64 & \quad \text{E-isomer} \\
\end{align*}
\]

\[ R = \text{CO}_2\text{C}_6\text{H}_5, \text{CN} \]

Scheme 21
benzene was used, 33% of \textbf{65} and 36% of \textbf{66} was obtained. The hydroxythiophenes were easily separated from the aminothiophenes by extraction of the benzene phase with water followed by acidification\textsuperscript{45} (Scheme 21).

The $C_3S + C$ modification of the Fiesselmann reaction is a useful method for the preparation of 3-hydroxy-2-carbonyl-substituted thiophenes. Thus the sodium salt of thiocyclopentanonecarboxylic acid (\textbf{67}) prepared from the $\beta$-ketoester, hydrogen chloride, and hydrogen sulfide were reacted with various $\alpha$-halocarbonyl derivatives to yield sulfides (\textbf{68}), which, in most cases without isolation, ring closed to the hydroxythiophene (\textbf{69}) on treatment with alkoxides\textsuperscript{275}. It was shown that the product from the reaction with ethyl chloroacetate has the structure \textbf{69} ($R = \text{OC}_2\text{H}_5$) and not \textbf{70}, as previously claimed\textsuperscript{222} (Scheme 22). In the same way,

\begin{align*}
\textbf{67} & \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\textbf{68} & \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\textbf{69} & \quad \text{CO}_2\text{C}_2\text{H}_5
\end{align*}

$$R = \text{OC}_2\text{H}_5, \text{C}_6\text{H}_5, \text{CH}_3$$

\begin{align*}
\textbf{70} & \quad \text{OH} \\
\textbf{71} & \quad \text{R} = \text{CH}_3, \text{C}_6\text{H}_5 \\
\textbf{72} & \quad \text{R} = \text{CH}_3, \text{C}_6\text{H}_5
\end{align*}

\begin{align*}
\textbf{73} & \quad \text{R} = \text{OC}_2\text{H}_5, \text{CH}_3, \text{C}_6\text{H}_5 \\
\textbf{74} & \quad \text{R} = \text{OCH}_3, \text{C}_6\text{H}_5, \text{CH}_3 \\
\textbf{75} & \quad \text{R} = \text{CH}_3, \text{C}_6\text{H}_5
\end{align*}

\begin{align*}
\textbf{76} & \quad \text{R} = \text{OC}_2\text{H}_5, \text{CH}_3, \text{C}_6\text{H}_5
\end{align*}

\textbf{Scheme 22}
71 and 72 were alkylated with α-halocarbonyl compounds and the intermediate sulfides ring closed to 73 and 74.

The analogous reaction of 75 gave 76. Thiolates such as 67, 71, and 72 were also reacted with α,α-dichloroacetone and upon treatment with ethoxide gave 77, 78, and 79 (Scheme 23). For more details see Part 1, Chapter I, Section 4.C and Table 1-26 of that chapter.

Scheme 23

E. \( C_3 + CS \) Methods

The most important method for the preparation of 3-hydroxy-2-carbonyl-substituted thiophene derivatives is due to Fiesselmann, and consists of the reaction of \( \beta \)-keto-esters 80 with 2 eq. of anhydrous or 80% thioglycolic acid in the presence of hydrogen chloride, which quantitatively gives the thioacetals (81), which are esterified in high yield to 82. On treatment of 82 with alcoholic potassium hydroxide or alcoholate, 5-, as well as 4,5-substituted 3-hydroxy-2-thiophene-carboxylates are obtained (Scheme 24).

Many \( \beta \)-ketoesters functionalized in the 3-(\( \alpha \))-position with an acetoxy alkylthio, arylthio, or phenacylamino group can be transformed to thioacetals by the foregoing methodology, and with alkoxides ring closed to 3,4-dihydroxy-2-thiophene-carboxylates, 4-alkylthio- and 4-arylthio-3-hydroxy-2-thiophene-carboxylates, and 4-amino-3-hydroxy-2-thiophene-carboxylates. An alternative to the Hinsberg synthesis of diethyl 3,4-dihydroxy-2,5-thiophenedicarboxylate is the reaction of diethyl chlorooxaloacetate (84) with ethyl thioglycolate in pyridine to give 85, which on treatment with sodium ethoxide in ethanol gave 86 in 33% yield (Scheme 25). For more details, see Part 1, Chapter I, Section 5.A.c, and especially Table 1-29 in that chapter. Much of this work has only been published in dissertations at the University of Erlangen.

In another version of the Fiesselmann synthesis, esters of \( \alpha,\beta \)-dihalocarboxylic