THIOPHENE AND ITS DERIVATIVES

Part Four

This is a part of the forty-fourth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

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THIOPHENE AND ITS DERIVATIVES

Part Four

Edited by

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The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of chemistry. The diversity of synthetic methods utilized in this field, coupled with the immense physiological and industrial significance of heterocycles, combine to make the general heterocyclic arena of central importance to organic chemistry.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extra ordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has dealt with syntheses, reactions, properties, structure, physical chemistry and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic and medicinal chemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry*, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocyclic compounds in organic synthesis, and the synthesis of heterocyclic compounds by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic and medicinal chemists, as well as to those whose particular concern is heterocyclic chemistry.

It has become increasingly clear that this arbitrary distinction created as many problems as it solves, and we have therefore elected to discontinue the more recently initiated series *General Heterocyclic Chemistry*, and to publish all forthcoming volumes in the general area of heterocyclic chemistry in *The Chemistry of Heterocyclic Compounds* series.

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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 up to the end of the 1980s. 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 systematically treat functionalized simple thiophenes, such as alkylthiophenes, halothiophenes, aminothiophenes, thiophenecarboxylic acids, and so on. The latter chapters, as is customary in the Taylor–Weissberger 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 uses of thiophene derivatives for the synthesis of aliphatic compounds by desulfurization follow. Two chapters treat thiophenes modified at 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 five-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.

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 thienyl derivatives.

In Part 4, an extensive treatment of physical properties of thiophenes is given. The second chapter deals with the important nucleophilic substitutions of thiophenes, and in the third chapter the many important results in the expanding field of biologically active thiophenes, obtained during 1983–1988, are summarized.

Finally, in Part 5, vinyl thiophenes and thienyl acetylenes will be treated. A second chapter will cover thienyllithium and other organometallic derivatives of thiophene, and in the last chapter, bithienyls will be covered.

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 chapters and those of some of the other authors whose native tongue is not English.

SALO GRONOWITZ

Lund, Sweden
January 1990

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THIOPHENE AND ITS DERIVATIVES

Part Four

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THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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CHAPTER I

Physical Properties of Thiophene Derivatives

Salo Gronowitz and Anna-Britta Hörnfeldt

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I. THERMODYNAMICS AND THERMOCHEMISTRY OF THIOPHENES

Vapor pressures and second virial coefficients for thiophene, 2- and 3-methylthiophene, 2,5-dimethylthiophene, 2-etylthiophene, and 2-chlorothiophene were measured by an isoteniscopic method in the temperature range 60–100°C.[1] The low vapor pressure of thiophene over solid thiophene at −80°C was measured with a special apparatus.[2,3] Vapor pressure–temperature relationships have been determined for thiophene and 2- and 3-methylthiophene.[4] The vapor pressure of 2-thiophenecarboxylic acid has been determined by a Knudsen effusion method over the temperature range 41.8–50°C. The lattice energy was 23.17 kcal/mol and the entropy of evaporation 48.71 cal/deg/mol.[5] The critical temperature of thiophene has been determined by the sealed-tube method to be 579.4 K.[6] Measurements have been reported on the interdiffusion coefficients of thiophene in binary systems with hydrogen, nitrogen, and oxygen. Collision diameters were evaluated from the viscosity of the vapors.[7] The variation of the coefficient of self-diffusion in thiophene with temperature was studied using a spin–echo spectrometer.[8]

The thermodynamic and thermochemical data of thiophene have been studied in great detail at the Thermodynamics Laboratory of the Bureau of Mines. The heat capacity of thiophene was measured over the temperature range 11–340 K. The solid had two λ-type transitions at approximately 112 and 138 K, an isothermal transition at 171.6 K, and a short region of anomalously high heat capacity on the high-temperature side of the latter transition. The heat of transition (152.4 cal/mol), heat of fusion (1215.5 cal/mol), and the triple point (234.95 K) were obtained. The vapor pressure of thiophene was measured over the temperature range 0–120°C, and the following equation was found to fit the data $\log_{10} P$ (mm) = 6.95926–1246.038/(221.354 + t). The normal boiling point was determined to be 84.16°C. The heat vaporization of thiophene was measured at three different temperatures, and the values found were 8032, 7808, and 7522 cal/mol at 45.36, 63.08, and 84.16°C, respectively. The heat capacity of

thiophene vapor was measured at five different temperatures in the range 343–472 K. The experimental values for C_p°, the heat capacity in the ideal-gas state, may be represented by equation $C_p^\circ = -7.017 + 0.10045T - 6.325 \times 10^{-5}T^2$. An equation for the second virial coefficient B in the equation of state $PV = RT + BP$, was obtained from thermal data. The equation is B (liters) $= -0.435\text{–}0.0172 \exp(1200/T)$. The entropy of liquid thiophene at 298.16 K is 43.30 ± 0.10 cal/deg/mol. The entropy of the ideal gas at the normal boiling point (357.32 K) and 1 atmosphere pressure is 70.04 ± 0.20 cal/deg/mol.[9]

The heat of combustion of thiophene was determined. For the reaction C_4H_4S (l) + $13/2O_2$ (g) + $0.7H_2O$ = $4CO_2$ (g) + H_2SO_4, $1.7H_2O$ at 298.16 K, $\Delta H_R = -667.19$ kcal/mol. The heat of formation of liquid thiophene is 19.52 kcal/mol, and the heat of formation of the gas is 27.82 kcal/mol, both at 298.16 K.[9] Later determinations of the heat of combustion gave -676.09 kcal/mol[10] and heat of formation of 19.13 ± 0.15 kcal/mol,[11] which was later corrected to 19.35 ± 0.15 kcal/mol at 25°C[10] and 19.20 ± 0.239 kcal/mol.[12] For some other determination of the heat of combustions, see Refs. 13 and 14.

From the heat combustion and from values of thermochemical bond energies a resonance energy of 20 kcal/mol was calculated for thiophene.[12]

Various thermodynamic properties of 3-methylthiophene in the solid, liquid, and vapor states have been determined between 12 and 473 K. The entropy of the liquid at 298.16 K, 52.18 ± 0.10 cal/deg/mol, was calculated from measured values of the heat capacity of the liquid and the heat of fusion (2518 cal/mol) at the triple point, 204.19 ± 0.05 K.

Experimental results obtained for the heat capacity of the liquid (C_{satd}), the heat of vaporization (ΔH_v), the heat capacity in the ideal gaseous state (C_p°), and the second virial coefficient [$B = (PV - RT/P)$] are represented by the empirical equations:

$$C_{satd}\,(\text{liq}) = 46.074 - 0.17610T + 6.8006 \times 10^{-4}T^2 - 6.8021 \times 10^{-7}T^3 \text{ cal/deg/mol (207–337 K)} \quad (1)$$

$$\Delta H_v = 13.593 - 13.913T \text{ cal/mol (329–389 K)} \quad (2)$$

$$C_p^\circ = -1.375 + 9.4508 \times 10^{-2}T - 4.2587 \times 10^{-4}T^2 \text{ cal/deg/mol (375–475 K)} \quad (3)$$

$$B = 75 - 94.56 \exp(1000/T) \text{ ml/mol (329–473 K)} \quad (4)$$

From determinations of the heat of combustion, the standard heat of formation [ΔH_f° (liq)] of 3-methylthiophene from graphite, hydrogen, and rhombic sulfur was found to be 10.49 ± 0.20 kcal/mol at 298.16 K. Calorimetic, spectroscopic, and molecular structure data were used to compute the functions $(F^\circ - H_0^\circ)/T$), $(H^\circ - H_0^\circ)$, S°, and C_p° at selected temperatures between 0 and 1000 K. The height of the barrier to internal rotation ($\sim$600 cal/mol) was evaluated from the experimental entropy and vapor heat capacity data. Values of ΔH_f°, ΔF_f°, and $\log_{10}K_f$ for the formation of 3-methylthiophene in the ideal-gas state from

graphite, hydrogen and gaseous diatomic sulfur were computed from the thermodynamic functions and appropriate calorimetric data.[16]

For 2-methylthiophene, the following thermodynamic data were obtained. Values of the heat capacity for the solid and liquid [$C_{satd} = 45.85 - 0.175^4T + 6.772 \times 10^{-4}T^2 - 6.771 \times 10^{-7}T^3$ cal/deg/mol (213–344 K)], and the vapor [$C_p^\circ = -1.745 + 9.562 \times 10^{-2}T^2 - 4.420 \times 10^{-5}T^2$ cal/deg/mol (375–473 K)]; the heat of fusion (2263 cal/mol) at the triple point (209.79 ± 0.05 K), the entropy in the liquid state at 298.16 K (52.22 cal/deg/mol); the heat of vaporization [$\Delta H_v = 11651 - 3.937T - 1.364 \times 10^{-2}T^2$ cal/mol (343–385 K)]; the second virial coefficient in the equation of state $PV = RT(1 + B/V)$ [$B = 114–127 \exp(900/T)$ ml/mol (343–473 K)]; and the standard heat of formation of the liquid from graphite, hydrogen, and rhombic sulfur [$\Delta H_{f,25^\circ C}^\circ = 10.86 \pm 0.21$ kcal/mol]. (10–340 K) were computed and the same chemical thermodynamic properties as for 3-methylthiophene were calculated.[17]

Conjugation energies in thiophene were estimated with the aid of bond energy terms and the calculated heats of formation of thiophene and 2- and 3-methylthiophene compared with the experimental values.[18]

The heat capacities of both the stable crystalline form ($T_m = 210.55$ K, $\Delta H_m = 1958$ cal/mol) and a metastable form ($T_M = 204.87$ K, $\Delta H_m = 1769$ cal/mol) of 2,5-dimethylthiophene were determined by adiabatic calorimetry. The derived thermodynamic properties of the liquid at 298.15 K are 42.62, 58.49, and 27.91 cal/mol K for the heat capacity (C_p), entropy (S°), and Gibbs energy function ($-[G^\circ - H_0^\circ]/T$), respectively.[19,20] The detailed trend of the heat capacity in the region of 2-methylthiophene has been delineated from 110 to 195 K by equilibrium adiabatic calorimetry. The temperature dependence is that of a glass-type transition with a continuously inflected curve without a local maximum.[21] Enthalpies of combustion for 2-isopropylthiophene have been measured by rotating-bomb combustion calorimetry.[22]

Tables containing chemical thermodynamic properties of some thiophenes are given in some other reports[23–26,28] and tabulated together with those of other sulfur-containing compounds.[29–31] Enthalpies of mixing of thiophene and cyclohexane at 45°C have been determined.[32] Thermodynamic functions of gaseous thiophene have been calculated from spectroscopic data and molecular structure.[33] Vapor-pressure measurements have been carried out at low temperatures with mixtures of silyl iodide and thiophene, and the stoichiometry and relative stability of the complex was inferred.[34] The saturated vapor pressures of chloro and chlorosilyl derivatives of thiophene have been determined.[35]

The wetting heat of thiophene on silica gel has been determined to 7.93 ± 0.03 cal/g by calorimetry.[37] The connection between molecular volume and critical pressure the number of atoms has been studied for thiophene.[38] The temperature dependence of the rate of sublimation of thiophene has been investigated.[39] The thermal conductivity of thiophene, which in the solid state undergoes continuous phase transitions, has been measured at 77–300 K.[40] The thermochemical behavior of thiophene under high pressure has been studied.[41]

II. PHASE EQUILIBRIA, CHEMICAL EQUILIBRIA, AND SOLUTIONS OF THIOPHENES

The liquid–vapor equilibrium of the binary systems ethanol–thiophene,[42,43] benzene–thiophene,[42,44–47] methanol–thiophene,[43,45] thiophene–fluorobenzene,[49] thiophene–heptane[48,50], thiophene–*N*,*N*-dimethylformamide,[47] thiophene–1-methylpyrrolidone,[47] thiophene–nitromethane,[48] and thiophene–methyl ethyl ketone[48] have been studied. In most cases these systems were characterized by positive deviations from Raoult's law. Azeotropes were observed for thiophene–nitromethane,[48] thiophene–heptane,[46] ethanol–thiophene[42] and methanol–thiophene.[45] Azeotropic characteristics of aqueous and alcoholic systems composed of alkenes and thiophenes have been obtained.[52] Azeotrope formation between various hydrocarbons and thiophene and 2- and 3-methylthiophene has also been observed.[53]

Several ternary systems have also been investigated. The systems benzene–thiophene–*N*,*N*-dimethylformamide and benzene–thiophene–1-methylpyrrolidone were studied under isobaric conditions (760 mm Hg) by the Gillespie method.[47] Isobaric studies have also been carried out on the binary system formed by thiophene and benzene with light alcohols.[54] A number of ternary systems containing thiophene has been investigated by Francis.[55,56,58–61] Calculation and study of vapor–liquid equilibria[57] in the benzene–thiophene–heptane[62] and ethanol–benzene–thiophene[63] ternary systems have been carried out. Phase equilibria for the ternary system *n*-heptane–thiophene–liquid ammonia have been determined at temperatures of 0 and 20°C. A new method has been proposed that correlates tie-line data in such a manner that a straight line is obtained for most systems, including solutropic systems.[64]

The relative volatilities of benzene–thiophene[65] and of toluene–methylthiophene mixtures[66] in the presence of polar solvents has been investigated. Critical properties and vapor pressure of thiophene have been determined.[67]

The liquid vapor equilibrium was studied by the distillation of dilute solutions of thiophene in carbon tetrachloride in trichloroethylene and benzene. For highly effective columns (~ 100 theoretical plates) the best testing solution was thiophene in carbon tetrachloride.[68] Other workers have suggested the use of dilute solutions of thiophene in benzene as test mixtures in fractional distillation[27] also (see Ref. 69). The vapor pressure and molar volume of thiophene as a function of temperature have been measured and the cohesion energy discussed.[51] The temperature–molar volume relationships for polar solvents and thiophene have been studied.[70] Distribution coefficients of dilute solutions of thiophene in trichloroethylene and benzene were determined using ^{35}S and ^{14}C as radioactive indicators. The distribution coefficients were constant and the solutions obeyed Henry's law.[50]

A study of the mutual solubility in the binary systems formed by thiophene with aliphatic glycols monoethanolamine and ethylenediamine at 20–80°C

showed that the Van Laar equation can be used for the calculation of the activity coefficient of these systems.[71] A comparative study of the solubility of thiophene and benzene in the dimethylsulfoxide–octane system has been undertaken.[72] The solubility of some thiophenes in 24 organic solvents was studied by determination of the critical dissolution temperatures.[73] The slightly mutual solubilities in water–benzene and water–thiophene systems at 30°C were investigated by measurements of differential refractive indexes.[74] The solubility of hydrogen chloride in thiophene has been measured.[75]

Freezing-point depressions have been measured for very dilute solutions of thiophene in benzene. Thiophene was found to pack in the benzene crystals with a small volume defect, as indicated by the collision areas (16.7×10^{-16} cm^2 obtained from viscosity of vapors) and parachor (187.4). The slightly larger volume occupied by thiophene (124.5×10^{-24} cm^3) than benzene (117.75×10^{-24} cm^3) in its own crystal lattice was attributed to differences of crystal structure.[76]

Solid–liquid-phase diagrams have been obtained for thiophene–fluorobenzene, giving a molecular compound at composition 1 : 1.[77] Phase equilibria have also been determined for the binary systems of thiophene with benzene,[78] *m*-xylene, ethylbenzene, cyclohexane, pyridine, and dioxane.[79] The solid-phase–melt distribution coefficient for a benzene–thiophene mixture in the low thiophene concentration region has been studied.[80] It has been shown that mixed melting-point determinations between isomeric thiophenes are not more unreliable than in other series, as stated previously.[81] The condensed-phase equilibrium for triphenylmethane and thiophene was studied, and a 1 : 1 complex, dissociated at 56°C, was observed.[82] Cryoscopic data have been presented for solutions of thiophene containing 0.5–18 mol% of *n*-, *iso*-, *sec*,- and *tert*-butanol.[83]

In connection with studies on the quasiracemate method, the melting-point diagrams for mixtures of the (+) and (−) forms of α-methoxypenylacetic acid, α-methoxy-2-thienylacetic acid, and α-methoxy-3-thienylacetic acid have been determined.[84] The formation and crystallization of thiophene as a glass have been studied.[85]

III. DIPOLE MOMENTS AND RELATED PROPERTIES OF THIOPHENES

1. Dipole Moments

Dipole moments of a large number of relatively simple thiophene derivatives have been measured, especially by Russian and French workers. The dipole moments were used in connection with estimations of electron- distribution and substituent effects in thiophenes, and for confirmation of molecular orbital (MO) calculations. However, their most important use has been in connection

with conformational analysis of carbonyl-substituted thiophenes and biheterocyclic derivatives.

Most of the electrical dipole moments were measured in benzene solution by using the well-known Debye refractivity method, and the method of Halverstadt and Kumler[86] was used to calculate the dipole moments. Dielectric constants were usually measured with a heterodyne beat apparatus.

The measured dipole moments of thiophene in different solvents are given in Table 1, and those of substituted derivatives are collected in Tables 1–9. Quite different values have been obtained for the same compound by different groups, which can be due only partly to variations in the method of calculation.

From the microwave spectra of thiophene and 3-methylthiophene, dipole moments of 0.533 ± 0.005 D[87,88] and ± 0.914 D were obtained.[89]

With regard to the direction of the dipole moment of thiophene, there has been some confusion, as some textbooks reported that the dipole moment of thiophene, as well as those of furan and pyrrole, is directed from the positive heteroatom toward the C(3)–C(4) bond.[90–92] However, Marino[93] and Lien and Kumler[94] presented evidence based on reactivity data, theoretical calculation, and dipole moment values of substituted thiophenes, that the dipole moments of both thiophene and furan are directed from the ring (positive pole) to the heteroatom (negative pole). This was confirmed by studying the orientational influence of dipolar solutes on the aromatic solvents benzene and hexafluorobenzene as reflected by NMR chemical shifts.[95] The same technique has also been used to show that the negative end of the dipoles of selenophene and tellurophene are directed toward the heteroatom.[96]

The experimental dipole moments of substituted thiophenes were compared with electric moment values calculated on the basis of vector addition using the group moment values obtained in the corresponding benzene derivatives, and

TABLE 1. Dipole Moments (in Debyes) for Thiophene

Solvent	Dipole Moment	Ref.
Carbon tetrachloride	0.562, 0.003	191
"	0.63	200
Benzene	0.54, 0.02	203
"	0.54	201
"	0.54, 0.02	101
"	0.53	204
"	0.52, 0.05	205
"	0.523, 0.002	199
Hexane	0.54, 0.002	201
Gas	0.58	202
"	0.55, 0.04	205
"	0.58	204
Cyclohexane	0.524, 0.002	199
"	0.53	156
Carbon disulfide	0.552, 0.01	199

TABLE 2. Dipole Moments (in Debyes) for 2-Substituted Thiophenes

n	R^2	Solvent	Dipole Moment	Ref.
4	Br	Dioxane	1.41, 0.03	94
		Benzene	1.35, 0.01	"
		"	1.36	102
		"	1.34, 0.01	191
		"	1.33	198
		"	1.39	100
		CCl_4	1.38, 0.01	191
	Cl	Dioxane	1.60, 0.01	94
		Benzene	1.48, 0.01	"
	I	Dioxane	0.83, 0.03	"
		Benzene	1.20, 0.01	"
		"	1.13	100
		"	1.08, 0.01	191
		CCl_4	1.12, 0.03	"
	NO_2	Dioxane	4.22, 0.05	101
	CHO	Dioxane	3.60	111
		Benzene	3.48	193
		"	3.55	98
		CCl_4	3.55	194
		"	3.45	111
	SH	Benzene	1.50	109
5	COCl	CCl_4	3.79	115
	COOH	Dioxane	1.96	196
		Benzene	1.26, 0.02	191
		CCl_4	1.30, 0.02	"
	CH_2Cl	Benzene	1.58	98
	$CSNH_2$	Benzene	4.23	117
	CH_3	"	0.67	98
	SCH_3	"	1.50	109
6	$COCH_3$	"	3.37	98
		"	3.40	195
		"	3.36, 0.01	191
		CCl_4	3.41, 0.01	"
7	COCCBr	Benzene	3.37	123
	$Cr(CO)_3$	"	5.98	128
	COCCH	"	3.49	123
	$COCH{=}CH_2$	"	3.28	120
	$CH{=}CHCOH$	Dioxane	4.00	119
	$CO_2C_2H_5$	"	2.09	196
		Benzene	1.91	98
8	$CH_3Cr(CO)_3$	"	6.23	128
	Hg-2-thienyl	Dioxane	1.15, 0.05	197
	2-thienyl	Dioxane	1.15, 0.02	94
		"	0.77	125
		Benzene	0.96, 0.02	94
		"	0.66, 0.05	101
	Te-2-thienyl	"	1.53	116

TABLE 2. (*Continued*)

n	R^2	Solvent	Dipole Moment	Ref.
	Te_2-2-thienyl	"	1.53	116
	2-Pyrrolyl	"	1.82	126
	$C(CH_3)_3$	Benzene	0.93	100
9	$COC(CH_3)_3$	"	3.09	112
10	C_6H_5	"	0.81	124
		"	1.04, 0.01	94
		"	0.58, 0.04	101
11	COCC-2-thienyl	"	4.14	123
	COCH=CH-2-thienyl	"	4.14	"
		"	3.37	120
	COC_6H_5	"	3.45	"
	$C(CH_3)_3Cr(CO)_3$	"	6.33	128
	$COCCC_4H_9$	"	4.33	123
	$CH=CHCOC(CH_3)_3$	Dioxane	3.40	119
12	$CH=CHC_6H_4$-2-Cl	Benzene	1.63	118
	$CH=CHC_6H_4$-3-Cl	"	1.73	"
	$CH=CHC_6H_4$-4-Cl	"	1.62	"
	$CH=CHC_6H_4$-2-NO_2	"	3.64	"
	$CH=CHC_6H_4$-3-NO_2	"	4.32	"
	$CH=CHC_6H_4$-4-NO_2	"	4.81	"
	$CH=CHC_6H_5$	"	0.53	"
13	$COCCC_6H_5$	"	4.30	123
	$CH=CHCOC_6H_4$-4-Cl	"	3.31	120
	$COCH=CHC_6H_4$-4-Cl	"	3.11	"
	$CH=CHCOC_6H_4$-4-NO_2	"	5.03	"
	$CH=CHCOC_6H_5$	Dioxane	3.27	119
		Benzene	3.11	120
	$COCH=CHC_6H_5$	"	3.43	"
		"	4.30	123
	CH=CHCOCH=CH-2-thienyl	"	3.19	120
	COCH=CHCH=CH-2-thienyl	"	3.44	"
14	$CH=CHCOC_6H_4$-4-CH_3	"	3.32	"
	$COCH=CHC_6H_4$-4-CH_3	"	3.75	"
	$CH=CHCOC_6H_4$-4-OCH_3	"	3.39	"
	$COCH=CHC_6H_4$-4-OCH_3	"	3.94	"
15	$CH=CHCH=CHCOC_6H_5$	"	3.25	"
	$COCH=CHCH=CHC_6H_5$	"	3.50	"
	$CH=CHCOCH=CHC_6H_5$	"	3.21	"
	$CH=CHCOC_6H_3$-2,4-OCH_3	"	3.91	"
	$COCH=CHC_6H_3$-2,4-OCH_3	"	4.64	"
	$CH=CHCOC_6H_4$-4-$N(CH_3)_2$	"	4.56	"
	$COCH=CHC_6H_4$-4-$N(CH_3)_2$	"	5.59	"
16	$CH=CHCOC_6H_2$-2,4,6-OCH_3	"	4.64	"
	$COCH=CHC_6H_2$-2,4,6-OCH_3	"	5.43	"

TABLE 2. (*Continued*)

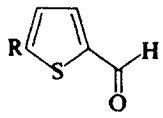
n	R^2	Solvent	Dipole Moment	Ref.
17	CH=CHCO-α-naphthyl		3.31	121
	CH=CHCO-β-naphthyl		3.62	"
	COCH=CH-α-naphthyl		3.20	"
	COCH=CH-β-naphthyl		3.62	"
19	$COCH{=}CHC_6H_5$	Benzene	3.67	120
	$CH{=}CHCOC_6H_4C_6H_5$	"	3.33	"

TABLE 3. Dipole Moments (in Debyes) for 3-Substituted Thiophenes

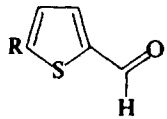
n	R^3	Solvent	Dipole Moment	Ref.
4	Br	Benzene	1.13	198
	NO_2	"	3.86, 0.04	101
	SH	"	1.07	100
5	CHO	Dioxane	2.94	111
		Benzene	2.82	"
		CCl_4	2.76	194
	CH_3	Benzene	0.82	98
8	$CH_3Cr(CO)_3$	"	6.24	128
	2-Thienyl	"	1.07	125
	3-Thienyl	"	0.75	"
	Te_2-3-thienyl	"	1.00	116
10	C_6H_5	"	0.81	124
		"	0.49, 0.05	101
11	$C(CH_3)_3Cr(CO)_3$	"	6.35	128

the results obtained were interpreted to indicate a greater importance of conjugation of the substituent with the thiophene than with the benzene ring.[97-104]

A study of the dipole moments of some 2-thiophene aldehydes over the temperature range 25–145°C showed on comparison with calculated data that the 5-bromo-2-thiophene aldehyde, as well as 2-thiophene aldehyde,[105,106] exist predominantly in the S,O-*cis* form **1**, in contrast to the corresponding furans. In 5-nitro-2-thiophene aldehyde, the two forms, **1** and **2**, are almost equally



S,O-*cis*
R = H, Br, NO_2
1



S,O-*trans*
R = H, Br, NO_2
2

TABLE 4. Dipole Moments (in Debyes) for 2,3-Disubstituted Thiophenes

n	R^2	R^3	Solvent	Dipole Moment	Ref.
4	Br	Br	Benzene	1.74	198
5	CHO	I	"	3.19	105
	I	CHO	"	2.61	"
	CHO	OH	"	2.86	112
6	CHO	CHO	"	3.39	111
			Dioxane	3.31	"
	CHO	$TeCH_3$	Benzene	3.50	116
	$TeCH_3$	CHO	"	2.84	"
7	$COCH_3$	$TeCH_3$	"	3.06	"
	$TeCH_3$	$COCH_3$	"	2.68	"
8	3-NO_2-2-thienyl	NO_2	"	5.55, 0.05	101
	CHO	COC_2H_5	"	4.84	111
9	CH_3	$CH_3Cr(CO)_3$	"	6.43	128
	CHO	$SC(CH_3)_3$	"	4.83	112
10	CO_2CH_3	$CH_3Cr(CO)_3$	"	5.32	128
	$COCH_3$	$SC(CH_3)_3$	"	4.73	112
11	C_6H_5	CH_3	"	1.10	124
16	C_6H_5	C_6H_5	"	0.86	"

TABLE 5. Dipole Moments (in Debyes) for 2,4-Disubstituted Thiophenes

n	R^2	R^4	Solvent	Dipole Moment	Ref.
5	CHO	I	Benzene	2.50	105
	I	CHO	"	2.51	"
6	CHO	CHO	"	2.22	111
			Dioxane	2.39	"
9	CH_3	$CH_3Cr(CO)_3$	Benzene	6.25	128
11	C_6H_5	CH_3	"	0.88	124
16	C_6H_5	C_6H_5	"	0.89	"

probable.[107] The position of the conformational equilibria for the 3-formyl group in 2-chloro-3-formylthiophene and 2-chloro-3-formyl derivatives of other heterocycles have been determined by dipole moment measurements.[108]

2-Acetylthiophene also appears to exist preferentially in the S,O-*cis* form.[106] This was elucidated from comparison of the dipole moment of 2-acetylthiophene with that of 7-oxo-4,5,6,7-tetrahydro-benzo[*b*]thiophene.[109] From the experimental dipole moments of 2-benzoylthiophene (3.45 D), 2-thiobenzoylthiophene (3.14 D), di-(2-thienyl)ketone (3.75 D) and di-(2-thienyl)thioketone (3.75 D), conclusions about their conformation in solution were obtained. It was claimed that while 2-benzoylthiophene exists in the S-*cis* conformation, the

TABLE 6. Dipole Moments (in Debyes) for 2,5-Disubstituted Thiophenes

n	R^2	R^5	Solvent	Dipole Moment	Ref.
4	Br	Br	Benzene	1.08	102
			"	1.13, 0.01	191
			CCl_4	1.08, 0.02	"
	Cl	Cl	Benzene	1.04, 0.01	"
			CCl_4	1.05, 0.01	"
5	CHO	Br	Decaline	3.31, 0.15	107
			CCl_4	3.28	194
	CHO	Cl	Benzene	3.24	111
			CCl_4	3.25	194
	CHO	I	Benzene	3.32	105
	CHO	NO_2	Decaline	3.30, 0.15	107
			CCl_4	3.56	194
	COOH	NO_2	Dioxane	4.43, 0.01	94
			Benzene	3.18, 0.02	"
6	CN	CN	"	2.36	113
	CHO	CHO	Benzene	4.18	193
			"	4.19	111
			Dioxane	4.41	"
	CO_2CH_3	NO_2	"	3.96, 0.01	94
			Benzene	3.74, 0.01	"
	CO_2CH_3	NH_2	"	3.35, 0.01	"
			Dioxane	3.94, 0.01	"
	CH_3	CH_3	Benzene	0.51	99
8	5-Br-2-thienyl	Br	"	1.73, 0.01	94
	2-Hg-5-I-2-thienyl	I	Dioxane	3.21, 0.1	197
	5-I-2-thienyl	I	"	1.87, 0.08	94
			Benzene	0.85, 0.04	"
	2-thienyl	I	"	1.28, 0.04	"
			Dioxane	1.79, 0.04	"
	$COCH_3$	$COCH_3$	Benzene	4.96	193
9	CH_3	$CH_3Cr(CO)_3$	"	6.39	128
12	$C(CH_3)_3$	$C(CH_3)_3$	"	0.55	100
16	C_6H_5	C_6H_5	"	0.92	124
17	CH=CHCO-α-naphthyl	NO_2		4.96	121
	CH=CHCO-β-naphthyl	NO_2		4.29	"
	COCH=CH-α-naphthyl	NO_2		4.70	"
	COCH=CH-β-naphthyl	NO_2		4.65	"
18	$CH{=}NC_6H_4$-4-NO_2	$CH{=}NC_6H_4$-4-NO_2	Benzene	5.28, 0.06	193
	$CH{=}NC_6H_4$-3-NO_2	$CH{=}NC_6H_4$-3-NO_2	"	5.49, 0.06	"
	$CH{=}NC_6H_5$	$CH{=}NC_6H_5$	"	2.93, 0.03	"
20	$CH{=}NC_6H_4$-3-CH_3	$CH{=}NC_6H_4$-3-CH_3	"	2.84, 0.03	"
	$CH{=}NC_6H_4$-4-CH_3	$CH{=}NC_6H_4$-4-CH_3	"	2.84, 0.03	"

TABLE 7. Dipole Moments (in Debyes) for 3,4-Disubstituted Thiophenes

n	R^3	R^4	Solvent	Dipole Moment	Ref.
4	Br	Br	Benzene	1.59	198
5	CHO	Br	"	2.86	112
	CHO	I	"	2.84	105
6	CHO	CHO	"	4.37	111
			Dioxane	4.41	"
	$TeCH_3$	CHO	Benzene	3.03	116
16	C_6H_5	C_6H_5	"	0.93	124

TABLE 8. Dipole Moments (in Debyes) for Trisubstituted Thiophenes

n	R^2	R^3	R^4	R^5	Solvent	Dipole Moment	Ref.
6	CHO	I		CHO	Benzene	3.80	105
	CH_3	SH		CH_3	"	1.44	109
7	CHO	CHO	CHO		"	3.61	112
	CHO	CHO		CHO	"	3.13	"
10	CH_3	CH_3	$CH_3Cr(CO)_3$		"	6.54	128
22	C_6H_5	C_6H_5		C_6H_5	"	1.03	124

TABLE 9. Dipole Moments (in Debyes) for Tetrasubstituted Thiophenes

n	R^2	R^3	R^4	R^5	Solvent	Dipole Moment	Ref.
4	Br	Br	Br	Br	Benzene	0.12	198
	Cl	Cl	Cl	Cl	"	0.93	99
11	CH_3	CH_3	CH_3	$CH_3Cr(CO)_3$	"	6.82	128
28	C_6H_5	C_6H_5	C_6H_5	C_6H_5	"	0.60	99
					"	1.04	124

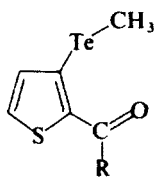
thioanalogue prefers the S-*trans* conformation.[110] 3-Thiophene aldehyde was estimated in this way to be 75% S,O-*cis* and 25% S,O-*trans*.[111]

In the same way, the preferential conformers of the various diformylthiophenes,[106,111] 2,5-diphenyliminomethylthiophenes,[106] and iodinated formyl thiophenes[105] were determined.

Dipole moments for hydroxythiophene systems, thiophenethiols, *ortho*-hydroxythiophene aldehydes, and formylthiophenes have been compared with those of the corresponding selenophene derivatives. The dipole moments were measured in order to obtain information about tautomeric structure and

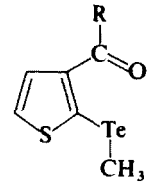
preferred conformations.[112] The dipole moments of bromo- and cyanoselenophenes have also been compared with those of the corresponding thiophenes.[113] The dipole moments for the 3-thiolene-2-one forms and 4-thiolene-2-one forms of the 5-alkyl-2-hydroxy-thiophene systems have been determined.[114]

Through a combined study of IR spectra, dipole moments, and Kerr constants, it was found that 2-thenoyl chloride existed only in the S,O-*cis* conformation and it was suggested that the energy barrier in the acid chlorides is higher than in the corresponding aldehydes.[115] The less hindred (Te,O)-*cis* conformations **3**, **4**, and **5** were preferred for some methyltelluro-, *ortho*-formyl-, or acetyl thiophenes.[116] In the Lumbroso–Liégeois paper[116] the rotational isomerism of bis(2-thienyl)- and bis(3-thienyl)ditelluride was also examined. In connection with an investigation of the dipole moments of various heterocyclic thiomides, 2-thiophene carbothioamide was estimated to be 73% S-*cis* and 27% S-*trans*, while both the 2-furan and 2-pyridine analogues were predominantly S-*trans* (64 and 83%, respectively).[117]



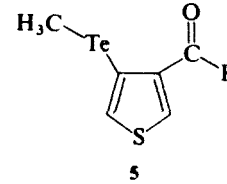
R = H, CH_3

3



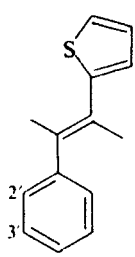
R = H, CH_3

4



5

Dipole moments have been extensively used in conformational studies of unsaturated thiophene derivatives. Thus, *trans* 2-styryl thiophenes substituted in the 2′- or 3′-position of the benzene ring can exist in four different coplanar forms, **6**–**9**.



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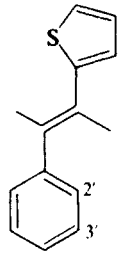

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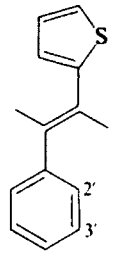

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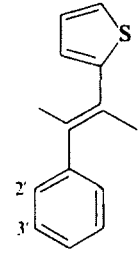
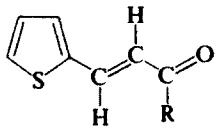


9

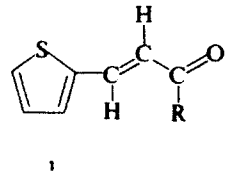
When the 2′-substituents are Cl or NO_2, the dipole moments indicate that for the former conformers **6** and **9** are equally probable, while in the nitro case **9** is the preferred conformer. For the 3′-NO_2-substituted case, **7** appears to be the most stable conformer.[118]

Trans-α,β-unsaturated thiophene aldehydes and ketones can theoretically exist in four different coplanar conformers: the S-*trans*–*anti* form **10**, the S-*trans*–*syn* **11**, the S-*cis*–*syn* **12**, and the S-*cis*–*anti* **13**.



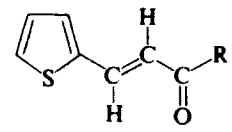
S-*trans*–*anti*

10



S-*trans*–*syn*

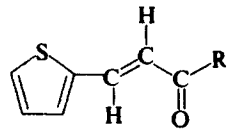
11



S-*cis*–*syn*

12

R = H, $C(CH_3)_3$, C_6H_5

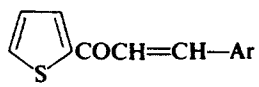


S-*cis*–*anti*

13

For the aldehyde, R = H, IR spectra indicate that the S-*trans* conformers are dominant, although C=C and C=O stretching bands assignable to the S-*cis*-isomers could be detected. From measurement of the dipole moment, and excluding the S-*cis*-isomers from the vector calculations, it was concluded that the aldehyde exists is the S-*trans*–*syn* form **11** (R = H). On the other hand, the two ketones exist according to IR preferentially in the S-*cis* forms (**12** and **13**). The mole fraction of **12** ($R = CH_3$) was 0.7, and for **12** ($R = C_6H_5$) it was 0.6.[119]

The dipole moments of a large number of chalcone derivatives of types **14** and **15**, in which Ar are phenyl and various substituted phenyl and naphthyl groups, have been measured.[120–122] In principle, **14** and **15** can exist in four coplanar conformers like **10**–**13**.



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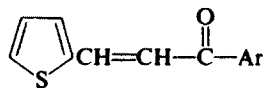

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These chalcones exist according to calculation as equal mixtures of the syn and anti forms of the S-*cis* conformer. By comparison of calculated and experimental dipole moments of ethynyl 2-thienyl ketones, it was shown that the S,O-*cis* conformation was the most probable one.[123] Dipole moments have also been used for conformational analysis of phenylthiophenes,[101,124,126] bithienyls,[94,101,125] and 2-(2-thienyl)pyrrole.[126] The interpretations of the dipole moment for 2,2'bithienyl vary in the literature from showing that the two rings are coplanar and cis,[94] perpendicular to each other,[125] and trans-gauche with an angle of about 40° between the rings.[101] In 3,3-dinitro-2,2'-bithienyl the two rings are perpendicular to each other.[101] From dipole moment measurements, He^I phototelectron spectra, and theroretical calculations, it was conclu-

ded that the most likely conformations for 2-(2-thienyl)pyrrole are the fully planar cis and trans, the former being more favorable.[126]

The dipole moments for tetraphenylthiophene[99] and its 1,1-dioxide[127] have been obtained.

The fact that thiophenethiols exist in the thiol form was confirmed by dipole moment measurements, and their confirmations as well as those of methylthiothiophenes were discussed.[109] An examination of the dipole moments of substituted benzene and thiophene chromium tricarbonyl compounds revealed that the arene-$Cr(CO)_3$ group moment depends upon the nature of the arene substituent. In spite of the lower π-basicity of thiophene, the dipole moment of tricarbonylthiophenechromium is 0.95 D higher than that of tricarbonylbenzenechromium. This was suggested to be due to the relatively high S—Cr bond moment.[128] The dipole moment of thiophene in the presence of tin tetrachloride was 1.7 D, indicating the formation of a donor–acceptor complex.[129] The complex between thiophene and iodine had a dipole moment of 0.42 D in benzene.[130,131] The dipole moment and heat of formation of the complex between iodine and thiophene were determined by dielectrometric titration and calorimetric titration methods.[132,133]

A dipole moment of 5.3 ± 0.1 D was found to tetraphenyl-thiophene-1,1-dioxide in dioxane.[127] In order to obtain some understanding of the electronic structure of some thieno[4,5-*c*]- and thieno[4,5-*b*]-tropones and some related compounds, their dipole moments were determined.[134]

Many calculations of the dipole moment of thiophene and some derivatives using various theoretical methods such as HMO, PPP, EHT, CNDO, and ab initio calculations (for review and list of references, see Ref.[135] and Part 1, Chapter II) have been carried out, which more or less satisfactorily reproduce the experimental results.

2. Various Dielectric Properties

The densities, d^{20}, refractive indices, dielectric constants, and viscosities of homologous esters of 2-thiophenecarboxylic acids, which remain liquid at 20°C, were determined and their variations were analyzed.[136] The refractive indices at 20°C, densities, and surface tensions over a range of temperature of thiophene, 2-alkyl-thiophenes (methyl to *n*-heptyl), *n*-alkyl thenoates (methyl to *n*-heptyl), and *n*-alkyl 2-thienyl ketones (methyl to *n*-hexyl) have been obtained. From these experimental data parachors, molecular refractions and molecular refraction coefficients for the 2-thienyl group have been evaluated.[137] Boiling point, freezing point, density at 20°C, and refractive index (sodium *D* and mercury *g* lines) at 20°C were determined for highly purified 3-ethyl- and 2,5-dimethylthiophene, and the refractivity intercept, specific dispersion, and molecular refraction were calculated.[138]

Some other thiophene derivatives have also been investigated.[139] General formulas were derived for determining the values of molecular refractions, R_D at

20° and 25°C for 2-alkyl- and 3-alkylthiophenes, 2-isoalkyl-, and 3-isoalkylthiophenes, with an accuracy of the order of 0.2–0.3%.[140] The molecular refractivities of thiophene, some halothiophenes, and alkylthiophenes have been estimated from valence refractivities.[141]

In connection with a study of the increment of sulfur on molecular refraction, a number of thiophene derivatives have been investigated.[142]

An empirical method for calculating average polarizabilities has been applied to thiophene.[143] Molar polarizabilities and diamagnetic susceptibilities have been determined for thiophene.[144] Polarizabilities of thiophene have been calculated for thiophene from the δ-function model of chemical binding.[145]

Thiophene has been used in studies of dielectric saturation in solutions of weakly dipolar substances and in nondipolar liquids.[146] Variations, $\Delta\varepsilon$, in the dielectric permittivity of solutions of thiophene in benzene and carbon tetrachloride were measured against an applied electric field. A positive variation was observed at all concentrations. The beat method was used with a pulsed external field.[147]

Theoretical calculations have been undertaken to relate dielectric relaxation time and the viscosity of thiophene.[148] Refractometric investigations on the binary systems between benzonitrile and thiophene[149] and nitrobenzene and thiophene[150] have been undertaken. The dielectric polarization of the binary thiophene–pyrrole system has been investigated.[151] Lippincott's δ-function model of chemical binding was applied to evaluate the main molecular polarizability of thiophene.[152]

The dielectric properties of thiophene were investigated at 68–200 K and 1–300 kC. The observed triple points and transition points almost agreed with those obtained from thermal studies. The dielectric constant just below the melting point is slightly smaller than that of the liquid, suggesting that molecules rotate at the lattice site.[153] Dielectric constants over large temperature intervals, have been determined in other investigations.[154,155] The dielectric relaxation time τ for thiophene in cyclohexane was determined to be $2.05 \cdot 10^{-12}$ sec.[156]

Electric double refraction, also called the *Kerr effect*, has been studied with thiophene and a few thiophene derivatives. For a definition of molecular Kerr constants of a solute $\infty (mK_2)$ and apparatus for their determination, see Ref.

TABLE 10. Kerr Constants of Some Thiophenes in Carbon Tetrachloride Solution

Compound	$\infty (mK_2) \times 10^{12}$	Ref.
Thiophene	11.19	157
2-Thiophene aldehyde	456.00	194
5-Chloro-2-thiophenealdehyde	252.00	"
5-Bromo-2-thiophenealdehyde	260.00	"
5-Nitro-2-thiophenealdehyde	401.00	"
3-Thiophenealdehyde	295.00	"
2-Thiophenecarbonylchloride	498.00	115

36. From $\propto (mK_2)$, estimates of molecular polarizability ellipsoids and of bond polarizability can be made and this has been done for thiophene and other fundamental heterocycles.[157] Russian workers have determined Kerr constants of thiophene aldehydes and 2-thiophene carbonyl chlorides in attempts to use it for conformational analysis. Kerr constant values are given in Table 10.

IV. GENERAL PHYSICAL CHEMISTRY OF THIOPHENES

The temperature dependence of the shear viscosity of thiophene has been determined in a broad temperature range.[158] The viscosity of thiophene has been approximately calculated from known physical constants.[159]

The changes in the contours of lines from anisotropic light scattering was investigated experimentally in order to study orientation interaction and rotational motion in thiophene at high temperature.[160] The connection between rotational mobility and the shape of molecules was studied.[161]

Extensive investigation on the interaction of thiophenes with ultrasound has been carried out. Correlations have been found between molecular structure and sound velocity, and adiabatic compressibility coefficients were calculated.[162–166] Sound velocity and density values have been determined in 3-methylthiophene at 5° intervals over the temperature range -10 to -50°C. These values were combined with data on the specific heat at constant pressure and used for the calculation of thermodynamic data.[167] The velocity and absorption coefficient of hypersound in thiophene were determined from the shift and intrinsic half-width of the Mandel'shtam–Brilloin component.[168]

The absorption coefficients of ultrasonic waves in the 8.5–30 MHz range in thiophene was 1570×10^{-17} sec^2/cm at 20°C. This value was considered abnormally high compared to theoretical values.[162] Absorptions for thiophene were also measured from 20 to 300 MHz at 7.5–60°C. The characteristic relaxation frequency determined from the decline in the ratio of the absorption coefficients to the square of the frequency ranged from 248 to 299 MHz for thiophene.[170] The absorption of ultrasound in thiophene has been measured in the 20–3000 MHz range.[173]

Hypersonic absorption measurements in thiophene have been carried out at 1–2 GHz,[174] at 2.8 GHz,[175] and at 0.3–3 GHz[176,177] frequencies. Acoustic dispersion was observed, which was ascribed to the vibration relaxation effect. The propagation rate and absorption of ultrasonic waves in thiophene vapors were measured by an acoustic interferometer in an investigation of vibrational relaxation.[178] Several other investigations treat the acoustical relaxation of thiophene by measuring ultrasonic wave propagation in thiophene.[179–182] In a more recent paper, the high-resolution Bragg reflection method was used for this purpose.[183] The ultrasonic and supersonic properties of thiophene have been studied. The sound absorption was measured at $\leq 2 \times 10^9$ Hz by using a pulse method. At $3–5 \times 10^9$ Hz the sound absorption and velocity were determined from the hyperfine structure of Rayleigh lines of scattered light by using the

optical method,[184] and the fine structure of the lines was studied.[185] The mechanism of acoustic relaxation in pure thiophene has been discussed.[186] The dispersion of ultrasound and hypersound in thiophene has been measured.[187]

Relaxation effects due to the lack of immediate response in the energy transfer process between the vibrational and translational degrees of freedom was investigated in thiophene by ultrasonic spectroscopy. The observed ultrasonic spectrum was analyzed to give the relaxation frequencies and strength, from which the rate of vibration to translation transfer and the vibrational modes involved in the process were determined.[188]

The rate of isomerization of the S,O-*trans* ↔ S,O-*cis* equilibrium in pure 2-thiophenecarboxaldehyde has been measured by using the ultrasonic pulse technique. From the Eyring rate equation and the temperature dependence of the exchange rate, the activation enthalpies for the S,O-*cis* → S,O-*trans* reaction was found to be of the order of 10–11 kcal/mol.[189,190]

V. ELECTROCHEMICAL PROPERTIES AND REACTIONS OF THIOPHENES

1. Introduction

In this section the extensive work on the polarography of thiophene derivatives, as well as electrochemical transformations of thiophenes for preparative purposes, will be discussed. Electrochemically generated radical anions and radical cations, which were studied by ESR, are treated in Section XII.

Thiophene itself is not reduced polarographically. Investigations were therefore carried out on thiophenes with reducible functions, such as halogens, nitro, and carbonyl groups, in order to compare the influence of the 2- and 3-thienyl group on the half-wave potential of those reducible groups, with other non-reducible rings such as phenyl or other heterocyclic rings. In addition, the effects of substituents in the thiophene ring on the half-wave potentials of reducible groups have been investigated.

2. Polarography

A. Halothiophenes

The half-wave potentials of all bromothiophenes have been determined in 91.1% ethanol and in 99.1% DMF, and are given in Table 11, together with the slopes of the semilogarithmic curves of the waves. The number of the reduction waves is equal to the number of bromine atoms in the molecule and independent of pH. The height of each wave was limited by diffusion and corresponds to the

TABLE 11. Values of Half-Wave Potentials (V) $E_{1/2}$ of bromothiophenes in 91% ethanol

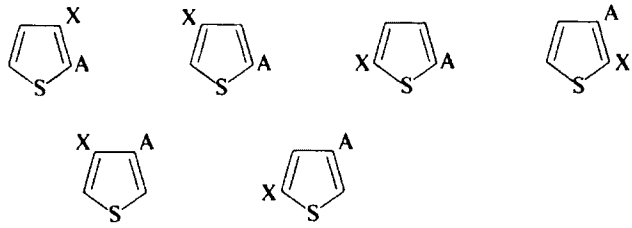
Substituents	1 Wave	2 Wave	3 Wave	4 Wave
2-Br	− 1.75			
3-Br	− 2.21			
2,3-Di-Br	− 1.41	− 2.20		
2,5-Di-Br	− 1.45	− 1.77		
3,4-Di-Br	− 1.80	− 2.18		
2,4-Di-Br	− 1.49	− 2.20		
2,3,5-Tri-Br	− 1.14	− 1.45	− 2.15	
2,3,4-Tri-Br	− 1.19	− 1.83	− 2.21	
2,3,4,5-Tetra-Br	− 0.93	− 1.20	− 1.83	− 2.20

transfer of two electrons. The electrochemical cleavage of the C Br bond is easier for an α-carbon than a β-carbon bond. With an increasing number of bromine atoms, the half-wave potential of the first wave becomes more positive. When the fraction of organic solvent was increased, the waves were shifted toward negative potentials.[208]

The polarographic reduction of all six isomeric bromoformylthiophenes have been studied both in a predominantly aqueous medium and in anhydrous ethanol. It was found that for 3-bromo-2-formyl-, 5-bromo-2-formyl-, and 2-bromo-3-formylthiophene the two-electron cleavage of the carbon–bromine bond preceded the reduction of the carbonyl group, while the three other isomers behaved as the bromobenzaldehydes, for which one observes one wave due to reduction of the carbonyl group, facilitated by the bromine.[209,210] The effect of pH on the half-wave potential was determined, and especially 5-bromo-2-formyl- and 5-bromo-2-acetylthiophene were studied in detail and compared with the corresponding furans.[209] Various aldehyde derivatives such as oximes and thiosemicarbazones were also investigated. Thus, the thiosemicarbazone of 5-bromo-2-thiophene aldehyde is reduced up to pH 3 in three stages corresponding to six electrons. The first wave was assigned to the rupture of the carbon–bromine bond, while the other two are also found in the polarogram of the thiosemicarbazone of 2-thiophene aldehyde.[169,210]

Various mono-, di-, and triiodothiophenes and tetraiodothiophenes were polarographically reduced in two different solvents, *N*,*N*-dimethylformamide and 2-ethoxyethanol, and the half-wave potential for each wave was calculated. The reduction of the iodothiophenes at the dropping mercury electrode was found to be the same as reduction of the iodothiophenes by chemical methods. Mixtures of iodothiophenes could be analyzed by polarography.[211]

The cleavage of the carbon–halogen bond was also studied for bromo- and iodothiophenes containing difficulty reducible groups such as the cyano, carboxylic, and carboxamide groups.[210,212] The half-wave potentials obtained in 10% ethyl alcohol in water are shown in Scheme 1.



X = Br, A = CN, $E_{1/2}$ = − 1.68
X = I, A = CN, $E_{1/2}$ = − 0.90
X = Br, A = COOH, $E_{1/2}$ = nr
X = I, A = COOH, $E_{1/2}$ = − 1.40
X = I, A = $CONH_2$, $E_{1/2}$ = − 0.90 (pH 12)

X = Br, A = CN, $E_{1/2}$ = nr
X = I, A = CN, $E_{1/2}$ = − 1.10
X = Br, A = COOH, $E_{1/2}$ = nr
X = I, A = COOH, $E_{1/2}$ = − 1.44
X = Br, A = $CONH_2$, $E_{1/2}$ = − 1.78

X = Br, A = CN, $E_{1/2}$ = − 1.25
X = I, A = CN, $E_{1/2}$ = − 0.70
X = Br, A = COOH, $E_{1/2}$ = − 1.70
X = I, A = COOH, $E_{1/2}$ = − 1.08
X = Br, A = $CONH_2$, $E_{1/2}$ = − 1.52
X = I, A = $CONH_2$, $E_{1/2}$ = − 0.80

X = Br, A = CN, $E_{1/2}$ = − 1.15
X = I, A = CN, $E_{1/2}$ = − 0.45
X = Br, A = COOH, $E_{1/2}$ = − 1.72
X = I, A = COOH, $E_{1/2}$ = − 1.08
X = Br, A = $CONH_2$, $E_{1/2}$ = − 1.16
X = I, A = $CONH_2$, $E_{1/2}$ = − 0.46

X = Br, A = CN, $E_{1/2}$ = − 1.75
X = I, A = CN, $E_{1/2}$ = − 1.02
X = Br, A = COOH, $E_{1/2}$ = nr
X = I, A = COOH, $E_{1/2}$ = − 1.44
X = Br, A = $CONH_2$, $E_{1/2}$ = − 1.63
X = I, A = $CONH_2$, $E_{1/2}$ = − 0.93

X = Br, A = CN, $E_{1/2}$ = − 1.44
X = I, A = CN, $E_{1/2}$ = − 0.62
X = Br, A = COOH, $E_{1/2}$ = nr
X = I, A = COOH, $E_{1/2}$ = − 1.10
X = Br, A = $CONH_2$, $E_{1/2}$ = − 1.59
X = I, A = $CONH_2$, $E_{1/2}$ = − 0.82

(nr = not reducible before discharge of the electrolyte support)

Scheme 1

For all six iodoformylthiophenes the first wave was assigned to the rapid cleavage of the carbon–iodine bond. The Hammett equation was successfully applied to the half-wave potentials of 5- and 4-substituted iodothiophenes and 5- and 4-substituted bromothiophenes. Use of σ_p and σ_m derived from benzene derivatives gave ρ' values of 0.6 and 0.80 V, respectively.[210,212]

The polarograms of 5-halo-2-thiophenecarboxaldehydes have been obtained at various pH values and in different solvents. The half-wave potentials for the reduction of the halogen are given in Table 12.[212]

The polarographic behavior of the methyl ester of 5-chloro-2-thiophenecarboxylic acid has been studied in detail in various solvents and with different buffers. The first wave on the polarogram corresponded to the detachment of the halide ion at $E_{1/2}$ = 1.68 V (in 99% DMF).[213]

As for diphenyliodonium salts, three waves were observed in the reduction of 2,2′-dithienyliodonium salts at −0.11, −0.86, and −1.13 V. The third is due to the reduction of 2-iodothiophene. The third wave of phenyl 2-thienyliodonium salt is divided into two waves at −1.14 and −1.65 V from 2-iodothiophene and iodobenzene, respectively, in the proportions 55:45, indicating almost

TABLE 12. Half-Wave Potentials of 5-Halo-2-thiophene Aldehydes

	Aqueous Alcohol pH		Ethanol pH	
X	3	12	5	14
I	− 0.67	− 0.72	− 0.62	− 0.95
Br	− 0.68	− 1.07	− 0.64	− 1.23
Cl	− 0.71	− 1.15		

random rupture of the bond to the iodine. From the half-wave potentials for 2-thienylmercuric chloride (−0.07, −0.81 V), it is probable that the reduction of the iodonium ion does not proceed via the mercury derivatives.[214]

B. Reduction of Thiophene Aldehydes and Ketones

The half-wave potential of 2-thiophene aldehyde at pH 7.1 in 50% aqueous methanol (−1.306 V) has been compared with those of 2-pyrrole aldehyde and furfural.[215,216-218] In connection with a systematic investigation of the polarography of heterocyclic aldehydes and other monosubstituted heterocycles, it was found that the half-wave potential of 2-thiophene aldehyde (−0.99 V) was smaller than that of 3-thiophene aldehyde (−1.06) at pH 2 in 10% aqueous ethanol.[219] The pyridine aldehydes,[219] as well as thiazole and imidazole aldehydes, and in contrast to the thiophene aldehydes, show some anomalies in their polarograms that were ascribed to pH-dependent hydratization of these heterocycles.[219,220] The cathodic reduction of 2-thiophene aldehyde was studied by rotating disk-ring electrode and triangular voltage pulse methods. The reduction gave two waves corresponding to $RCHO + e \rightarrow RCHO^-$; $RCHO^- + e \rightarrow RCHO^{2-}$. The doubly charged anion reacted with water to produce 2-thenyl alcohol, as well as with the original aldehyde according to $RCHO^{2-} - RCHO \rightarrow 2RCHO^-$.[221,222] The Hammett equation could be applied to the polarographic reduction of a large number of 5-substituted 2-thiophene aldehydes using σ_p values from the benzene series. The ρ' value obtained was 0.54 V. Thus a higher sensitivity than that in the benzene series ($\rho' = 9.33$ V) was observed.[210,212,223] The influence of hydration on polarography of 5-nitro-2-thiophene aldehyde has been investigated.[224]

The polarography and electrochemical reduction of 2-acetylthiophene in aqueous THF[225] and in acetonitrile[226] have been investigated. On polarography, 2-benzoylthiophene shows normal behavior in acidic media, giving two waves of about equal height at pH 3.2 and 4.1. The two waves are merged at pH 5.1 into the wave of full height, the half-wave potential of which becomes increasingly negative as the pH increases. In alkaline media this wave diminishes and a second wave appears with a half-wave potential of about 1.75 V.

2,2′-Dithienyl ketone shows similar polarographic behavior, forming double waves.[227]

The polarography and electrochemical reduction of 2-benzoylthiophene in acetonitrile,[228] di-(2-thenoyl)methane in 30% aqueous THF,[229] and 2-thenoylferrocene[230] have also been investigated.

The first waves of the polarograms of 5-formyl and 3-formyl-2-acetothienone in moderately acidic media correspond to reversible transfer of two electrons and two protons, one of each to each of the carbonyl groups. In strongly acidic or alkaline solutions, successive reduction of both carbonyl groups is observed.[231] By correlating the half-wave potentials and behavior of 2-thenoyltrifluoroacetone with those of thiophene, 2-acetylthiophene, 2-thenoylacetone, acetylacetone, and trifluoroacetylacetone, it was first concluded that the first wave results from the reduction of the carbonyl group, adjacent to the trifluoromethyl group, and is kinetically controlled, as a result of conversion of the hydrated 2-thenoyltrifluoroacetone to the reducible enolate form. The second wave is the result of a one-to-two electron diffusion-controlled process in which the thenoyl carbonyl group is reduced to the pinacol, the carbinol, or both as the pH varies.[232] In a later investigation no less than four polarographic waves were discovered, the presence and properties of which depend on the pH, the specific buffer used and the buffer component. An explanation for the complex polarographic behavior was based on spectrophotometric examination before and after controlled potential electrolysis and attributed to the various tautomeric and acid–base equilibria of 2-thenoylacetone.[233]

A polarographic investigation has been carried out on chalcone, *o*-hydroxychalcones, chromones, and chromanones derived from 2-thiophene aldehyde.[234]

The geometric isomers of 2-thiophene aldoximes have been studied by polarography. In tetramethylammonium bromide as buffer the syn isomer produced a one-step wave, while the anti isomer produced two-step waves. In general for aldoximes the reduction potential of a syn isomer was more negative than that of the trans isomer of the same oxime.[235,236] The half-wave potentials of the oximes from 3-thiophene aldehyde and 2-acetylthiophene have also been determined.[219]

Anomalies in the polarography of oximes, semicarbazones, thiosemicarbazones, and phenylhydrazones derived from 2-thiophene aldehyde have been discussed.[238] The polarographic behavior of Schiff bases derived from 2-thiophenealdehyde have been investigated in 50% dioxane–water medium in the pH range 4–10.[239] The polarographic behavior of *ortho*-mercapto- and alkylthio-substituted thiophene aldimines has been studied. As a result of hydrogen bonding the SH group considerably facilitates the electrochemical reduction of the aldimine functional group. In the presence of hydrogen chloride in 90% DMF a new more positive wave appears, corresponding to the reduction of the protonated form of the azomethine.[240] In connection with polarographic investigations of tetrazolium salts, the reduction of 2-(2-thienyl)tetrazolium was compared with that of the phenylhydrazone of

2-thiophene aldehyde.[241] The polarograms of some antibacterial hydrazones derived from 2-thiophenealdehyde have been obtained.[242] A polarographic investigation was carried out on 2-thiophenecarboxylic acid and its methyl, ethyl, and phenyl esters as well as on 2,5-thiophenedicarboxylic acid and on 5-bromo-2-thiophenecarboxylic acid and their methyl ester in 50% ethanol and compared with the polarographic behavior of the corresponding benzene and furan derivatives.[243] The half-wave potentials of methyl 2-thiophenedithiocarboxylate[244] and 2-thienylvinylenethioamide[245] have been determined.

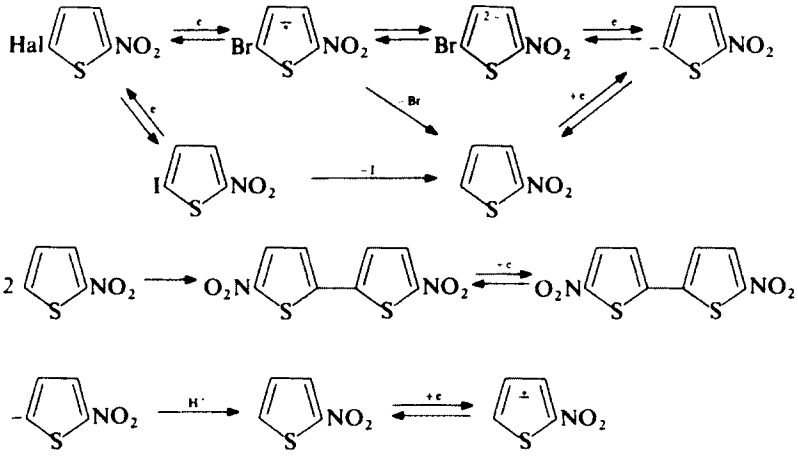
C. Polarography of Nitrothiophenes

The half-wave potentials of 2-nitrothiophene were -0.29, -0.48 and -0.63 V at pH 2.90, 4.97, and 7.55, respectively, in 50% ethanol.[216] Other values in the literature are -0.11 V at pH 0 and -0.25 at pH 2,[246] and in a buffer containing 10% ethanol at pH 2, the half-wave potential of 2-nitrothiophene is -0.23 V and that of 3-nitrothiophene is -0.32 V.[219]

Attempts were made to apply the Hammett equation to the half-wave potentials of some 5-substituted 2-nitrothiophenes. However, the limited number of substituents (Br, $COCH_3$, $CO_2C_2H_5$) makes it less feasible.[216] The increments in the half-wave potentials on introducing substituents such as CH_3, I, $CH(OCOCH_3)_2$, CH=NOH, $C(CH_3)$=NOH, COOH, $COCH_3$, CN, CHO, and $CO_2C_2H_5$ in the 5-position of 2-nitrothiophene, and some of these substituents in the 5-position of 3-nitrothiophenes, could be linearly correlated to results for *para*- and *meta*-substituted nitrobenzenes with a high correlation coefficient. From this result it was deduced that the Hammett equation was applicable in the thiophene series.[247]

The reduction of 2-bromo-5-nitrothiophene and 2-iodo-5-nitrothiophene in DMF has recently been studied with various polarographic techniques with preparative electrolysis and ESR spectroscopy. It was established that depending on the nature of halogen, their anion radicals may undergo further reduction to 2-nitrothiophene anion radicals or decomposition with splitting off of a halide ion and conversion to nitrothienyl radicals. The latter are capable of undergoing dimerization to 2,2'-dinitro-5,5'-dithienyl. The following mechanism has been proposed for the reduction of the 5-halo-2-nitrothiophenes.[248]

The polarography of 5-nitro-2-thiophenecarboxylic acid and 4-nitrothiophenecarboxylic acid has been compared with that of the *para*- and *meta*-nitrobenzoic acids, and the four-electron reduction in alkaline aqueous alcohol solution was discussed.[249,250] The polarography of methyl 4-nitro-2-thiophenecarboxylate and 5-bromo-4-nitro-2-thiophenecarboxylate has been studied.[243] Polarography was used as an analytical tool for the determination of thiophene as 2-nitrothiophene[251,252] and of the isomer distribution obtained on nitration of 2-substituted thiophenes such as 2-formyl-, 2-acetyl-, and 2-cyanothiophenes,[253] (for review, see Ref. 254). 2-Nitrothiophene, 2,4-dinitrothiophene, and 2,5-dinitrothiophene were among a number of heterocylic



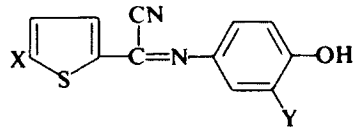
Scheme 2

nitro compounds for which electrochemical characteristics such as half-cell potential curves were obtained.[255]

A polarographic method for the determination of thiophene in liquid hydrocarbons is the reduction of thiophene-1,1-dioxide in DMF. The dioxide was formed by oxidation of thiophene with hydrogen peroxide.[256] Polarographic studies have been carried out on some antihistamine compounds containing a thiophene ring.[257]

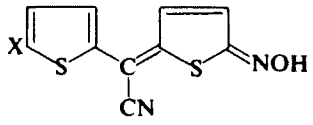
D. Miscellaneous Polarographic Work

Polarographic investigations have been carried out on the condensation products of 2-thienylacetonitrile and 5-chloro-2-thienylacetonitrile with nitrosophenols **16**[193,258] and on compounds **17**.[258,259]



X = H, Cl

16



X = H, Cl

17

The mechanism of polarographic reduction of 2,2'-dithienyl disulfide and 3,3'-dithienyl disulfide was studied in borate acetate buffer solutions in 50% ethanol, and a single reduction wave was observed.[260] A procedure has been developed for the estimation of thiophenes and aromatic sulfides in petroleum.[261] Dithienyl sulfide has been examined as an organic depolarizer. The autoinhibition phenomenon of 2-thienylmercuric chloride has been studied.[262]

The adsorption reaction of thiophene on mercury electrodes has been studied in different solvents.[263] The polarographic reduction of di-(2-thienylacetylene)mercury has been studied.[264]

In a review on electronic effects of the cyano group, its influence on the polarography of reducible thiophene derivatives such as 5- and 4-nitro-2-cyanothiophene was discussed.[265] In another review the influence of chemical structure on polarographic parameters in heterocyclic chemistry was discussed. The order of values of $E_{1/2}$ for reducible derivatives is 2-thiazolyl $\leq$ 4-pyridyl $\leq$ 2-pyridyl $<$ 3-pyridyl $<$ 2-thienyl $<$ 3-thienyl $\leq$ phenyl $<$ ferrocenyl $\leq$ 2-pyrrolyl.[266]

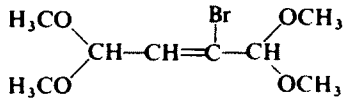
3. Anodic Oxidations of Thiophenes

The half-wave potential for the oxidation of thiophene in acetic acid -0.5 M sodium acetate at the rotating platinum electrode was 1.91 V.[267] Anodic voltograms to $+2.0$ V versus Ag/Ag^+ were obtained for thiophene in 0.5 M sodium perchlorate solutions of acetonitrile at a rotating platinum microelectrode. The anodic half-wave potential was found to be 1.60 V.[268] The irreversible oxidation potential of thiophene and 2-methylthiophene was found to be about $+0.41$ V.[269]

Electrochemical oxidations of 2,5-dimethylthiophene in methanol resulted in three types of reactions depending on the electrolytes used. The product was exclusively 3-bromo-2,5-dimethylthiophene with ammonium bromide as electrolyte. The formation of 2-methoxymethyl-5-methylthiophene was observed when ammonium nitrate, sodium acetate methoxide, and perchlorate were used as electrolytes. Finally, with sodium cyanide as electrolyte, the products were *cis* and *trans*-2-cyano-5-methoxy-2,5-dimethyldihydrothiophene (cis/trans = 2.3) together with comparable amounts of 3-cyano-2,5-dimethylthiophene and 2-methoxymethyl-5-methylthiophene.[270] The bromination involves discharge of the bromide ion at the anode. Electrochemical bromination has also been applied to 2-methylthiophene, which gave 5-bromo-2-methylthiophene as the main product, together with some 3,5-dibromo-2-methylthiophene and 1,1,1,4-tetramethoxy-2-pentene. From 3-methylthiophene, 2-bromo-3-methyl-, 2,5-dibromo-3-methylthiophene, and 1,1,4,4-tetramethoxy-2-methyl-2-butene were obtained.[271]

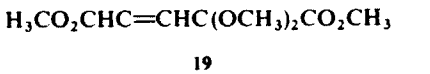
Recently, the kinetics, stoichiometry, and mechanism of the reaction of thiophene, pyrrole, and furan by electrogenerated bromine have been studied. While furan was oxidized to butenediol, thiophene under the same conditions was converted to 2-bromo- and 2,5-dibromothiophene. The reaction of pyrrole appeared to approach the encounter-controlled limit. Biomolecular rate constants $[k^{\circ}_{bc}/(dm^3/m\,sec)]$ for the transfer of Br^+ from Br_2 (water, 25°C) to the α-positions in these systems were as follows: pyrrole (10^8–10^{10}), furan ($2 \times 90 \times 10^4 \pm 5\%$), thiophene ($2 \times 5.2 \times 10^4 \pm 4\%$), and 2-bromothiophene ($2.65 \times 10^4 \pm 2\%$).[316] From the anodic oxidation of 2-methylthiophene in

methanol containing some concentrated sulfuric acid, a complex mixture containing methyl levulinate and the dimethyl acetal of α-methoxylevulinic aldehyde as main components was obtained. From 3-methylthiophene the methyl ester of 2-methyl-4,4-dimethoxybutanoic acid was the main product.[272] On electrolytic oxidation of 2,5-dibromothiophene, methyl fumarate was formed, while 3-bromothiophene afforded a mixture of compounds, among which **18** was the main product.[273]

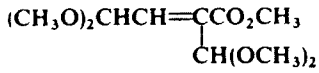


18

Electrochemical oxidation of methyl 2-thiophenecarboxylate and methyl 3-thiophenecarboxylate was carried out on a graphite anode in a methanolic solution of sulfuric acid. The 2-isomer yielded a mixture of the *cis*- and *trans*-isomers of **19**, while the 3-isomer gave **20** as the sole product.[274] Anodic acetoxylation of thiophene was not successful.[267] Electrochemical methoxylation of thiophene gave a complex product, probably by 1,4-addition of methoxy groups.[275] Electrochemical oxidation of **21** has been studied. While **21a** gave the tetramethoxylated product **22** in 70% yield, only the furan ring of **21b** was methoxylated, yielding **23** in 64% yield. The methoxylation of **21c** gave at least five compounds, of which two, 1,1-bis(2-thienyl)methyl ether and 2,2'-dithienyl ketone, formed via methoxylation at the CH_2 group, constituted 80% of that mixture.[276] The electrolysis of 2-thiophenecarboxylic acid in DMF on platinum electrodes gave **24**.[277,278] If the electrosynthesis was carried out in the presence of furan, 2,5-bis(2-thenoyloxy)2,5-dihydrofuran was obtained.[279]



19



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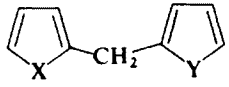
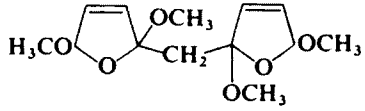
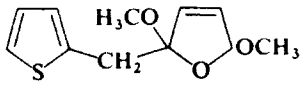


a X = Y = O
b X = S, Y = O
c X = Y = S

21



22



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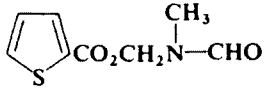
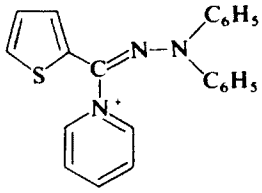


24

The anodic oxidation of the diphenylhydrazone of 2-thiophene aldehyde in the presence of a basic nucleophile such as pyridine gave **25**.[280] Thiophene-containing formazans **26** have been converted to tetrazolium salts **27** in good yields and purity by anodic oxidation.[281] The anodic oxidation of some thio derivatives of P(III) acids in the presence of thiophene led to *O,O*-dipropyl (2-thienyl)phosphonothioate in about 10% yield.[282] Voltametric data have been obtained for carbon complexes **28** and their electrochemical oxidation studied.[283]



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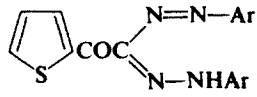
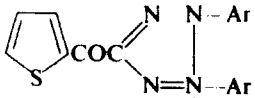


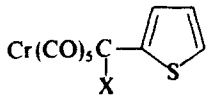
Ar = C_6H_5, *p*-$CH_3C_6H_4$

26



Ar = C_6H_5, *p*-$CH_3C_6H_4$

27



a X = OC_2H_5
b X = NH_2
X = $N(CH_2)_4$

28

4. Conducting Polymers from Thiophenes

The most important technical application of the anodic oxidation of thiophene is the preparation of conducting polythienyls with 10–100 monomer units. The electrochemical oxidation was carried out on a Pt electrode, with an electrolyte of acetonitrile and $Bu_4N^+BF_4^-$ or $Bu_4N^+ClO_4^-$. The polymer structures and charge distributions were determined by elemental analysis, IR and XPS[284–288] (see also Ref. 289]. In this connection, it should perhaps also be mentioned that (poly)thiophene has also been obtained through coupling of the Grignard reagent from 2,5-dibromo- or 2,5-diiodothiophene with nickel catalysts. From 2,5-diiodothiophene a crystalline polymer was recently obtained containing about 46 thiophene units. Physical studies indicated that the polymer is a semiconductor with a band gap of about 2 eV. The electrical conductivity could be enhanced by a factor of nearly 10^{10} (to values in excess of $10\,\Omega^{-1}\,cm^{-1}$) on partial oxidation with arsenic pentafluoride.[293] ESR studies of this doped poly(thiophene),[294] as well as X-ray scattering studies,[295] were carried out. Fourier transform IR spectra of electrochemically prepared poly(thiophene) films doped with various dopant species at varying doping

levels have been obtained.[296] Investigations of IR and Raman spectra are also reported.[297] The absorption spectra of *p*-type poly(thiophene) were in the region 20–1600 cm^{-1}. The results show intense polaron-induced vibrational absorption and an impurity-pinned polaron translational mode.[298] The IR and visible spectra of ClO_4^--doped poly(thiophene) and the ESR spectra and electric conductivity of BF_4^--doped poly(thiophene) have been studied.[299] ESR electrical conductivity and thermoelectric power were studied in electrochemically prepared and doped polythiophene films. The ESR spin density increased by two orders of magnitude up to dopant concentrations of approximately 3 mol%, and then decreased, while the conductivity increases drastically by more than 10 orders of magnitude up to this doping level, followed by a rather mild increase. The ESR linewidth decreased sharply from 9 to 0.4 G on slight doping, with a shape change from Gaussian to Lorentzian. These and other results were discussed in terms of shallow and deep polarons and the formation of bipolarons up to intermediate doping levels and the whole conduction at the metallic regime.[300] Studies on poly(thiophene) have been carried out in the 3-cm and 2-mm ESR ranges.[301] Infrared absorption and ESR were used to study photoexcitations in poly(thiophenes). The results indicate photoproduction of both charge- and spin-carrying species.[302] The relatively low temperature dependence of electric conductivity and dielectric permeability of poly(thiophene) prepared in glow discharge plasma was ascribed to its highly cross-linked structure.[303]

Because of its higher conductivity, poly(3-methylthiophene) has attracted special interest.[306] Electrochemical polymerization in propylene carbonate gave tough films with better conductivity. The conductivities of polythiophene, poly(3-methylthiophene), and poly(3-ethylthiophene) were 190, 510, and 270 S cm^{-1}, respectively.[304–306]

In situ Fourier-transform IR spectra of thin poly(3-methylthiophene) films electrochemically grafted onto a Pt electrode have been recorded. The doped conducting state showed a very large broad band in the near IR, associated with the creation of free carriers. The spectrum of the electrochemically undoped state reveals a structure corresponding to an α,α'-coupling of the thiophene units.[307] The IR spectroscopy-attenuated total reflection spectra of electrochemically prepared poly(thiophene), poly(bithiophene), and poly(3-methylthiophene) showed a α,α-, α,β-, and β,β-ring linkages.[308,309] An in situ spectroscopic study of poly(3-methylthiophene) electrochemically doped with BF_4^- showed that polarons are the primary elementary excitations in the dilute doping regime.[310]

Electron spin resonance spectra of poly(3-methylthiophene) and ClO_4^- and I_2-doped material resulted from defects in the π-conjugated system. Current carriers in the doped films are spinless, and a role of bipolarons in conduction was suggested.[311] Electrochemically generated poly(3-methylthiophene) and poly(3,4-dimethylthiophene) doped with $SO_3CF_3^-$ ions were studied by ESR. It was shown that these compounds exhibit quasimetallic behavior. Analysis of the *g* factor suggests that the electron transport occurs along the carbon skeleton of the polymeric chain for poly(3-methylthiophene).[312]

The ^{13}C NMR spectra of both doped and undoped electrochemically prepared poly(3-methylthiophene) films show two distinct absorption bands assigned to the methyl group and the thiophene ring.

Correlations between conductivity and ^{13}C NMR spectra were discussed.[313] Thick layers of heterocyclic aromatic polymers such as poly(thiophene) were ionized in the presence of pulsed high-power IR laser irradiation to yield ions in the high mass range, which were characterized by mass spectrometry.[314] Affinities of poly(thiophene) and poly(3-methylthiophene) toward electron acceptors such as iodine and sulfur trioxide and electric conductivities of the polymer–electron acceptor adducts have been investigated.[315]

The electrochemical inclusion of Cu^+ ions within a 5000-Å conducting poly(3-methylthiophene) electrochemically deposited on a Pt surface was studied by EXAFS and XANES spectra.[237]

A recent patent describes photoelectrochemical cells containing a blend of highly conducting polymers, including poly(thiophene), for conversion of solar energy to electricity.[317]

5. Cathodic Reduction of Thiophenes

Electrochemical reduction of 2,3,5-tribromothiophene to 3-bromothiophene has been carried out in good yield with a high current efficiency using a Pb, Hg, Zn, or graphite cathode in 70% dioxane–30% water containing sodium bromide. The electrolysis may be designed to form free bromine at the anode, or thiophene may be brominated in the anolyte.[318] The indirect electroreduction of thiophene in DMF solution, in the presence of biphenyl as the electron carrier, gives 2,5-dihydrothiophene and tetrahydrothiophene in high yields.[319]

2,5-Dihydro-2-thiophenecarboxylic acid has been prepared by electrochemical reduction of methyl 2-thiophenecarboxylate. The yields were dependent on the nature of the cation (Li, K, Na), the hydroxides of which were used as the inert electrolyte.[320] Electrolysis conditions have been found for the quantitative formation of 1,2-di(2-thienyl)ethane-1,2-diol from 2-thiophene aldehyde.[321]

The products from the electrochemical reduction of 2,5-diformylthiophene have been investigated.[322] Electrochemical reduction of cephalosporanic acids containing 2-thiopheneacetic acid as a side chain have been studied.[323] The electrochemical reduction of $(C_4H_3S)_2Fe_2(CO)_6$ has been investigated in connection with an investigation of a large number of iron–carbonyl complexes.[324] Electrochemical reduction of the thiophene analogue of TCNQ has been studied.

VI. STRUCTURE DETERMINATION OF THIOPHENES BY X-RAY CRYSTALLOGRAPHY

Structure determinations of thiophene derivatives by X-ray crystallography were first carried out in order to correlate experimental bond distances with

those calculated by various theoretical methods. Such investigations were also used to determine preferred conformations of bithienyl derivatives of various carbonyl derivatives and crowded thiophene derivatives. X-ray crystallography has also been used for structure determination of unusual or unexpected products of reactions of thiophenes when they were not known with certainty by other methods.

The crystal structure of thiophene itself was determined at − 55°C and was carried out on the highest-temperature form of the four crystalline modifications, just below the melting point. The closest intermolecular approach was found to be 1.7 Å.[325] Several publications concerning crystal structure of 2-thiophenecarboxylic acid have appeared.[326–328] The structure was solved by comparison with the isostructural 2-selenophenecarboxylic acid,[329,330] and the structure was refined at − 170°C.[328] Both 2-thiophenecarboxylic acid and 2-selenophenecarboxylic acid are planar, except that the sulfur and the selenium atoms are displaced by 0.03 and 0.06 Å, respectively, from the molecular plane. Both molecules are linked by hydrogen bonds forming centrosymmetrical dimers.[329] The planarity of the dicarboxylic acid dimer configuration of these acids has also been analyzed.[331] The bond lengths and angles obtained for 2-thiophenecarboxylic acid are given in Figure 1.

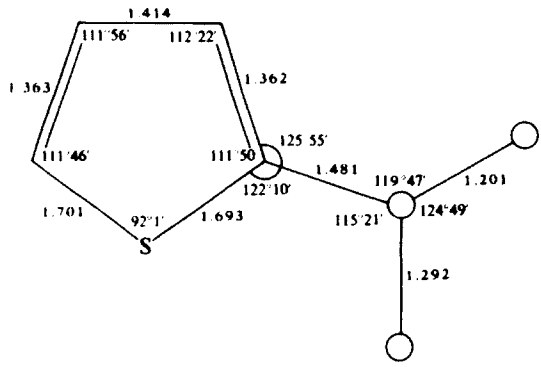


Figure 1. Bond lengths and angles obtained for 2-thiophenecarboxylic acid by X-ray crystallography.

The crystal and molecular structure of 3-thiophenecarboxylic acid has also been investigated. However, the results were unsatisfactory as, for instance, one of the formal C(2)–C(3) double bonds was found to be longer than the formal single bond.[332] Later investigations showed that this may be due to disorder in the crystals of 3-thiophenecarboxylic acid. Refinement of the structure changed the bond lengths significantly. However, the structure still appears to be inaccurate (see Figure 2).[333] Disorder in crystals of thiophene derivatives is a general phenomenon, and a very high refinement is necessary to obtain accurate

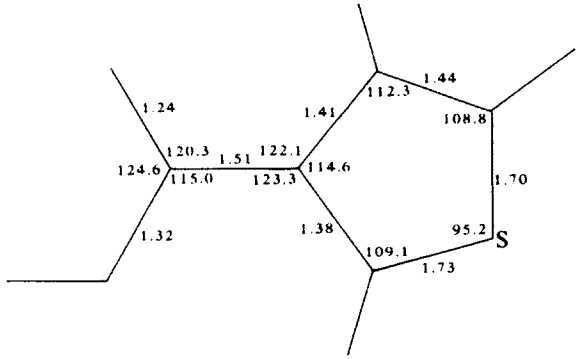


Figure 2. Bond lengths and angles obtained for 3-thiophenecarboxylic acid by X-ray crystallography.

bond lengths. The ab initio structure of 5-methyl-2-thiophenecarboxylic acid has been compared with the structure obtained by X-ray diffraction.[334]

The X-ray determination of the structure of 3,4-di-*t*-butylthiophene shows that the thiophene ring does not deviate significantly from planarity. The conformational arrangements C(3)–C(31) of the *t*-butyl groups were found to be such that the bond is nearly coplanar with the thiophene ring and in synclinal positions with the C(2)–C(1) bond. The bond angle C(3)–C(2)–C′(2), as well as the C(2)–C′(2) bond distance, were found to be extremely large (see Figure 3).[335,336]

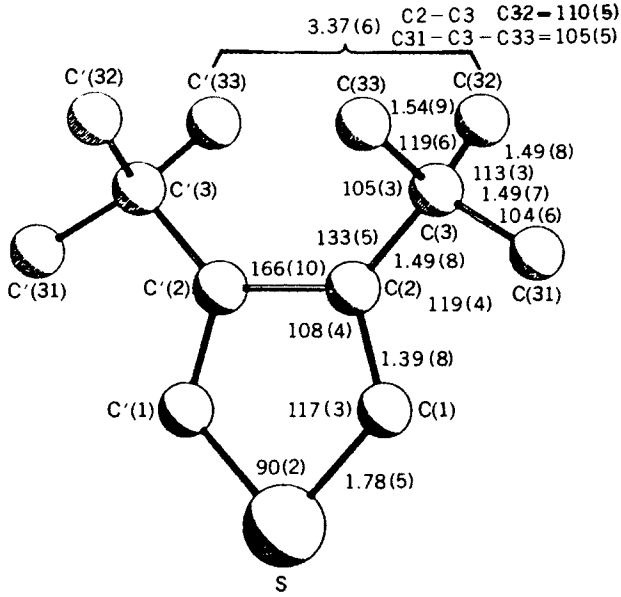


Figure 3. Bond lengths and angles obtained for 3,4-di-*tert*-butylthiophene by X-ray crystallography.

The structure of 3,3′-dithienyl ketone indicated that there was relatively limited π-delocalization between the C=O bond and thiophene π system and that of the thiophene rings was disordered.[337] X-ray crystallography showed that one in 2-pyrrolyl 2-thienyl ketone, the heterocyclic rings display an anti-twisted syn conformation with respect to the central ketone bridge. The molecules are linked into centrosymmetric dimers through two N—H · · · O hydrogen bonds.[338] The crystal structure of 2-acetyl-3-hydroxythiophene showed that there are four molecules in the unit cell and that the molecules are connected by hydrogen bonds to form chains.[339] The structure of 3-acetylamino-2-thiolanone was solved by direct methods. It was found that the ring was puckered and that the acetylamino group occupies a pseudoequatorial position.[340] The unit cell of 2-mercapto-3-thenylidene cyclohexylamine contains two identical molecules. The distribution of the bond lengths provided evidence for the contribution of two tautomeric forms, and for statistical delocalization of the H atom between the S and N atoms of the molecule.[341] The crystal and molecular structure of Co(II) and Ni(II) -chelates of (2-mercapto-5-ethyl-3-thenylidene)cyclohexylamine have been studied by X-ray crystallography.[342] In order to understand the peculiar reactivity of 2,5-dimethyl-3,4-dinitrothiophene, its structure was determined.[343] The structure of di-(2)-thienylmethane has been determined.[344,345] X-Ray crystallography showed that 4-(5-nitro-2-thienyl)-3-buten-2-one had the O,S-*trans* confirmation and a planar heterocyclic ring.[341] A thiophene derivative of Meldrum's acid, 2,2-dimethyl-5-(2-thienyl)-1,3-dioxane-4,6-dione, had a flattened boat confirmation in the dioxane dione ring.[346] The crystal structures of dibromo- and diiodomaleic acid thioanhydride have been determined.[347] The structures of thiophenium bismethoxycarbonylmethylide has been determined by X-ray analysis.[348] The structure of the complex between thiophene and triphenylmethane has been studied.[349]

X-Ray crystallographic investigations of tetracyanothiophene show that the molecule is planar and has C_{2v} symmetry. Bond lengths and angles are normal.[350]

The structure of 2,5-di-5-butylthiophene-1,1-dioxides show somewhat larger alternation in the C_2–C_3 and C_3–C_4 bond lengths than in thiophene, which was interpreted to indicate the absence of conjugation between the SO_2 group and the double bonds.[351]

An X-ray crystallographic investigation of 2-acetyl-5-bromothiophene showed that the conformation of the thiophene ring with respect to the carbonyl group is single-trans in the solid state, as it is in solution, as found by NMR investigations.[352]

The structures of all three ortho-acetylthiophenecarboxylic acids have been determined. In all the molecules the carbonyl group is in the same plan as the thiophene ring. Carboxylic and ketonic groups are linked together by intramolecular hydrogen bonds, and the position of the carboxylic hydrogen suggests enolic character.[353]

The structure of a number of compounds with thienylvinyl groupings have been determined with X-ray crystallography, such as *trans*-1,2-di-

(2-thienyl)ethene[354] and 1,4-bis(2-thienylvinyl)benzene, for which dihedral angles between the thiophene rings and the benzene ring of 5.7° and − 6.7° were found with a torsion angle of 7.0° between the two thiophene rings.[355] The crystal structures of 2,5-distyrylthiophene and 2,5-bis(2-thienylvinyl)thiophene were of interest in connection with their semiconducting properties.[356] The crystal structures of *trans*-1,4-di(2-thienyl)-1,3-butadiene (monoclinic) and *trans*-1,6-di(2-thienyl)1,3,5-hexatriene (triclinic) are two-layered and controlled by intermolecular electrostatic attraction between protons and delocalized π-electrons.[357,358] From a crystal structure determination of a mixed melt of 1-(2,6-dichlorophenyl)-4-phenyl-*trans*–*trans* 1,3-butadiene and 1-(2,6-dichlorophenyl)-4-(2-thienyl)-*trans*–*trans*-1,3-butadiene, the absolute configuration of the molecule was determined by anomalous scattering. The thienyl group of the guest showed conformational disorder between the syn and anti orientations.[359]

The bond lengths and conformation of the biologically inactive thiosemicarbazone of 2-thiophene aldehyde have been determined. The thiophene rings are planar but slightly distorted from *mm* symmetry, presumably owing to resonance interaction with the thiosemicarbazone side chain.[360,361]

The structures of simple thiophenes bound to some more unusual heteroatoms have been studied. Thus, the crystal structures of tetra(2-thienyl) derivatives of Ge, Sn, and Pb have been determined. All three compounds crystallize in space group $P42_{1c}$ and have crystallographically imposed 4 symmetry. The thienyl groups in each structure exhibit twofold orientational disorder.[362] Tetra(2-thienyl)silane belongs to the same space group. Each thienyl group has two conformations rotated 179° with respect to the Si—C bond.[363]

In the structure of tris(3-methyl-2-thienyl)phosphine, the thienyl groups are twisted, so that the molecule does not have threefold symmetry.[364] In the monocline tris(3-thienyl)phosphine the thienyl groups are disordered, so that for each ring there is another obtained by rotating about 180° about the P—C bond.[365] (2-Thienyl)bis(2,2′-biphenylene)phosphorane was found to adopt an almost regular trigonal bipyramidal geometry, in which the two biphenylene units span apical–equatorial positions and the 2-thienyl group occupies the remaining equational site. The 2-thienyl groups do not lie in the equatorial plane, and there is no indication of $C_{2\pi}$–$P_{3d\pi}$ interaction between the thienyl group and phosphorus.[366] Di(2-thienyl)mercury was found to be centrosymmetric with an Hg—C bond length of 2.061 Å.[367]

All three isomeric bithienyls appear to be planar in the solid state. As a result of disorder, there are rather large experimental errors in the bond lengths and angles obtained.[333] An investigation of 5,5′-dinitro-2,2′-bithienyl showed that the thiophene rings were in the trans conformation and nearly coplanar. The angle between the ring and NO_2 planes was 3.3°, and the bond between the ring had partial double-bond character.[368]

The crystal and molecular structures of 5,5′-bis[dimethyl(2-thienyl-silyl)]-2,2′-bithienyl have been determined. It was found that the bithienyl skeleton is planar with a transoid arrangement of the rings. The angles between the planes

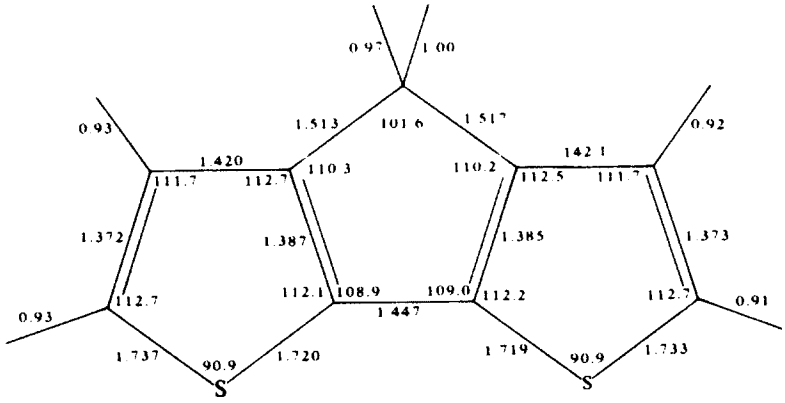


Figure 4. Bond lengths and angles obtained for the 4*H*-cyclopenta[2,1-*b*: 3,4-*b*']dithiophene molecule.

of the bithienyl and the outer thienyls were approximately 90°. The Si—C bonds to the thienyls (1.854 Å) were shorter than the Si—CH_3 bonds (1.881 Å).[369]

The absolute configuration of (+)-4,4'-dibromo-2,2'-dicarbomethoxy-3,3'-bithienyl was found to be (*R*) by X-ray crystallography. In two of the three different molecules the two bromine atoms and the two carbonyl carbons are in cisoid positions. The absolute configuration of (−)-2,2'-dibromo-4,4'-dicarbomethoxy-3,3'-bithienyl was found to be (*R*), and the conformation of the molecule in the crystal is cisoid.[371] The crystal structure of 4*H*-cyclopenta[2,1-*b*:3,4-*b*]dithiophene (Figure 4) shows that the molecule is approximately planar; the largest deviation from the least-squares plane is 0.035 Å for C and S.

There is much strain in the molecule, since the S—C—C and C—C—C angles range from 102° to 139°.[372]

In order to confirm that the high pK_{R^+} values of dithienotropylium ions were due to the absence of peri effects between the sulfur atoms and the central ring and the absence of ring-strain, allowing the rings to be almost coplanar,[373] X-ray crystallographic investigations were initiated to obtain detailed knowledge about the bonding distances and angles in the various molecules.

Two different phases of **29** have been investigated. The structures of **29** were essentially planar, and distances and angles are indicated in Figure 5.[374,375] The cation **30** is also almost planar. The angle between the planes of the two thiophene rings is 175.3°. The S—C bonds are equal and the BF_4^- ion disordered. For bond lengths and angles, see Figure 6.[376] The IR stretching frequency of the analogous tropone derivatives **31**–**33** also indicate that the system is highly conjugated and the three rings coplanar,[373] and X-ray crystallographic investigations were in accordance with these suggestions. Molecule **31** is almost planar; the planes of the two thiophene rings form an 171.6° angle. Conjugation is indicated by the short formal C—C single bonds and the long C—O bond distance (1.240 Å). The S—C bonds to the central ring are longer than the outer

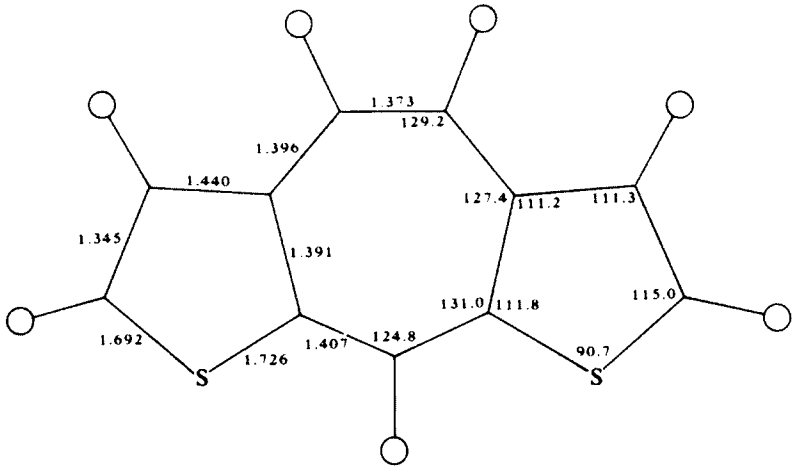


Figure 5. Bond lengths and angles obtained for the dithienotropylium cation **29**.

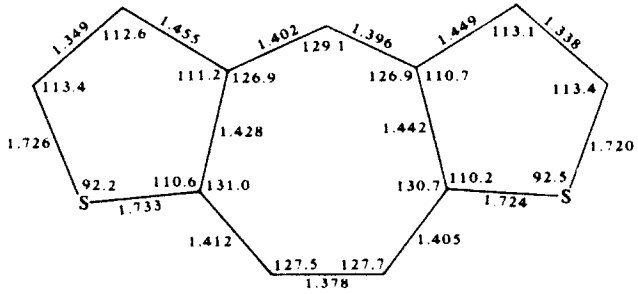
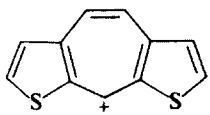


Figure 6. Bond lengths and angles obtained for the dithienotropylium cation **30**.

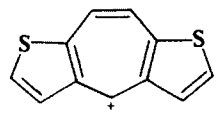
S—C bonds.[377] The central seven-membered ring of **32** is nearly planar, and the planes of the thiophene rings form an angle of 4.8°. The molecule has a shallow boat form;[378] **33** has a similar structure.[379]

It is interesting to compare the planar structure of **31** with that of its dihydro analog **34**, in which the central seven-membered ring deviates considerably from planarity and the planes of the two thiophene rings form an angle of 158°. The C—O bond length in **34** is 1.215 Å.[380]



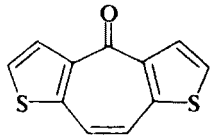
ClO_4^-

29



BF_4^-

30



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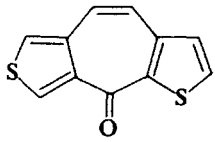

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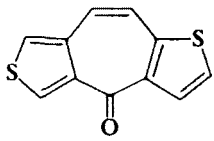

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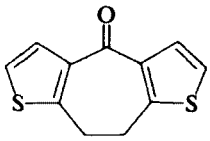
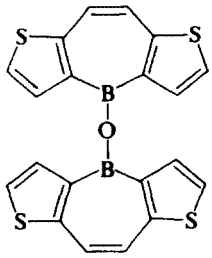


34

The structure of some dithienoborepins isoelectronic with the tropylium system discussed above have also been studied. Each tricyclic ring of **35** was essentially planar and showed rather large dihedral angles between the two rings and a large alternation of C—C bond length in the central borepin ring.[381] In **36**, the seven-membered ring has a boat conformation and the oxazaborilidine ring is a half-chair. The angle between the normals to the planes of the thiophene ring is 48°.[382] The structure of partly *C*-fused isomer **37** has also been determined.[383,384]



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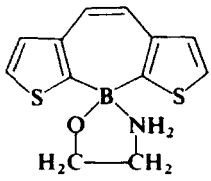

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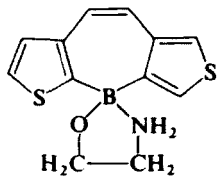
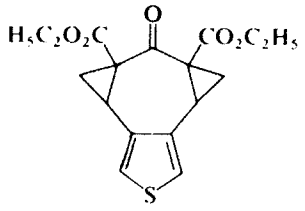


37

In order to determine the geometric arrangements of the cyclopropane ring in **38** and **39**, the crystal structures were solved.[385] The structure of the aromatic boron-containing fused-ring system **40** has also been determined. The fused rings were found to be approximately planar, and the B—N distance was found to be about the same as in hexachloroborazine.[386]

X-Ray crystallography has been used extensively as a final structure determination of pharmacologically active compounds. The detailed structures of the compounds were also used in connection with structure–activity discussions of receptor interactions. Thus, the structures of the cephalosporine **41**[387] and of the sodium salt of cephalotin[388] and other cephalosporins have been determined. Other examples are the antihypertensive drug tiamenidine **42**[389,390] diuretics such as **43**[391,392] and **44**,[393] the anticholenergic drugs quinuclidinyl di-α,α′-



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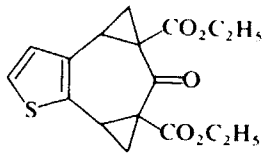

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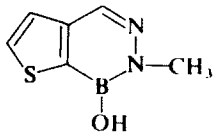
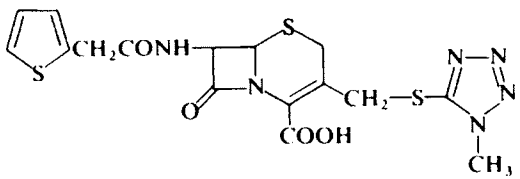


40

thienylglycollate,[394] penthienate bromide **45**,[415] and α-heteronium bromide **46**,[395] the carbonic and hydrase inhibitors 5-benzulphonyl 4-bromo-2-sulfamylthiophene[396] and 5-(2,5-dichloro)benzsulfonyl-2-sulfamylthiophene,[397] the analgesic active sulfentanil **47**,[398] the antihistamine 2-[(2)-dimethyl-aminoethyl-2-thenylamino]pyridine hydrochloride,[399] the antiinflammatory active α-methyl-4-(2-thienyl-carbonyl)-benzene acetic acid,[400] and the anti-anoxia active compound **48**.[401] X-Ray analysis is sometimes the only certain way to establish whether an *E*- or *Z*-isomer was obtained, and it was used to determine the correct structures of **49**[402] and **50**.[403] Attempts to determine the absolute configuration of optically active 3-*t*-butyl-3-(2-thienyl)propionic acid monohydrate failed.[404] X-ray crystallographic structure determination has also been carried out on an active tripeptide containing β-(2-thienyl)-L-alanine[405,406] and on thienyl-DL-serine monohydrate.[407]



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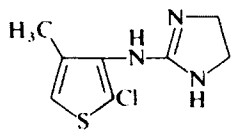

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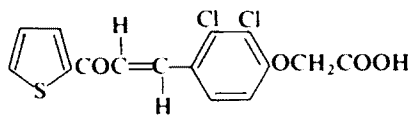

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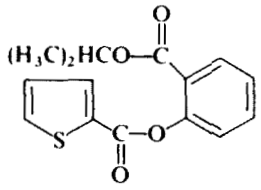

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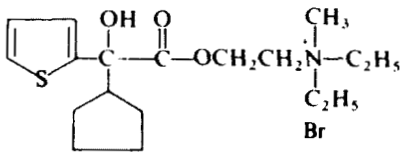

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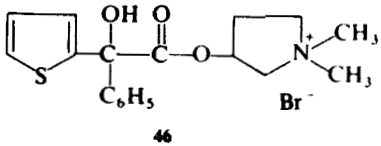

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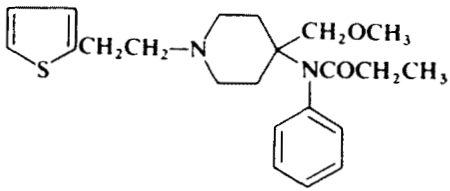

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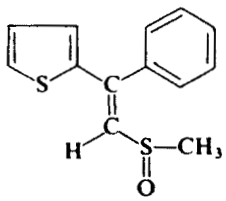

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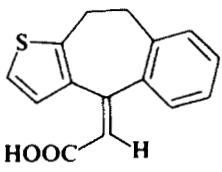

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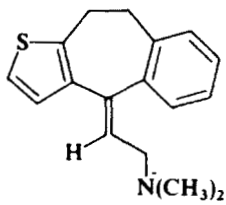
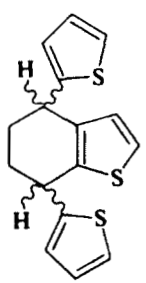


50

On acid-catalyzed polymerization of thiophene, a so-called pentamer was obtained, which by chemical and spectroscopical methods was shown to be **51**. However, it was not possible to distinguish between the two possible cis and trans isomers. X-Ray crystallography showed that the 2-thienyl groups had cis configuration and that the cyclohexane ring adopted the half-chair conformation.[408] X-Ray structure determination has, of course, been essential for determining the structure of unexpected products. Thus, X-Ray crystallography proved that the unexpected compound obtained in the reaction between 2,3,5-tribromothiophene and tetracyanoethylene oxide followed by debromination by hydrogen over palladium was **52**.[409]



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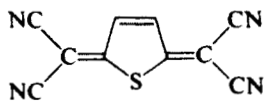
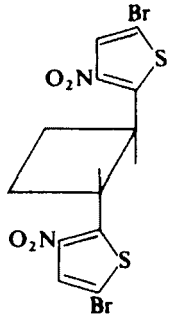


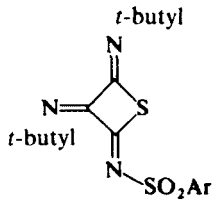
52

X-Ray crystallographic investigations were essential to show that a dimer obtained from 3-nitro-2-vinylthiophene, which was one of four possible cyclobutane derivatives, was the *trans*-1,2-bis compound. The X-ray investigation was carried out on the brominated derivative **53**.[605]



53

X-Ray structure determinations proved that reaction of trisiminothietanes **54** with *N*-diethylaminopropyne gave **55**.[410] From the reaction of **56** with sodium hydrogen selenite, X-ray crystallography showed the formation of the very unexpected compound **57**.[411] Crystal structure determination showed that the reaction of 2,5-diamino-3,4-dicyanothiophene with sulfur dichloride gave **58**.[412] Similarly, it was shown that lead tetraacetate induced ring contraction of **59** gave among other products **60**.[413]



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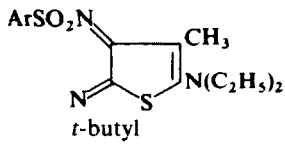

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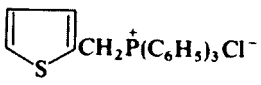

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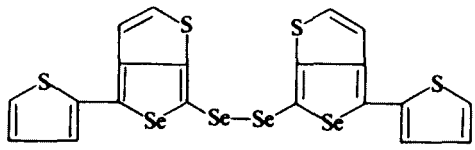

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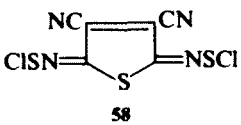

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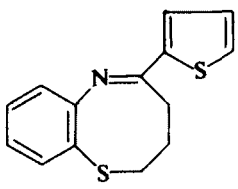

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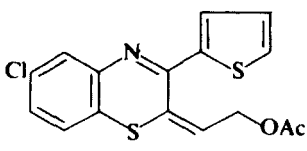
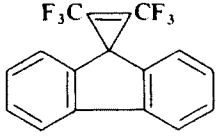


60

From the reaction of the spirocyclopropene **61** with carbon disulfide, 2 : 1 adducts with the complex structure **62** were formed.[414] Reacting **63** with dimethyl acetylenedicarboxylate followed by heating of the Diels–Alder adduct to 115° C gave **64**.[415] The reaction of **65** with sodium sulfide gave **66**.[416] Bis-(2,4-diphenyl-3-thienyl)disulfide was isolated from the thermal decomposition of 2,5-diphenyl-1,4-dithiin and its crystal structure determined.[417]



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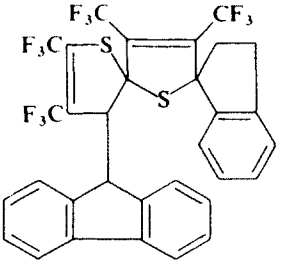

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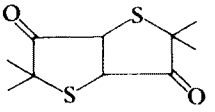

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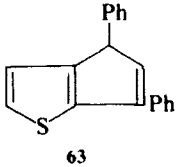

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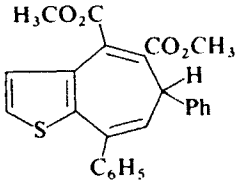

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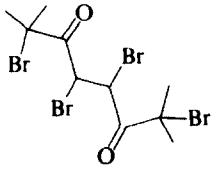
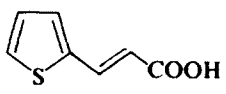


65

In fundamental work on solid-state photochemistry, the crystal structures of the two modifications of β-2-(thienyl)acrylic acid **67** were determined.[418] It was found that the *meta*-stable form gave the cyclobutane derivative **68** in high yields, whereas, the stable form polymerizes exclusively.[419] From 5-methyl-2-thienyl-acrylic acid oligomers were obtained.[419] (see also Ref. 359)

The reaction of 2,5-dimethyl-3,4-dinitrothiophene with morpholine led to 2,5-dimethyl-*trans*-2,3-dimorpholino-4-nitro-2,3-dihydrothiophene **69**, as proved by X-ray analysis. The dihydrothiophene ring is puckered, and the two C—S bonds are significantly different (1.89 and 1.73 Å, respectively).[420] Heating of **70** to 140° C gave a product, that by X-ray crystallography was shown to be **71**.[421] From the cycloaddition of phenyl azide to 3,6-dihydro-2*H*-thiopyran-3-one, compounds **72** and **73** were obtained, the structures of which were proven by X-ray crystallography.[422]



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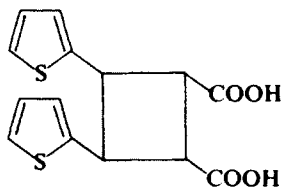

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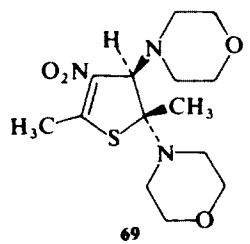

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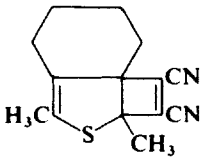

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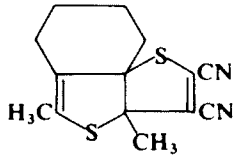

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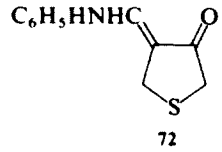

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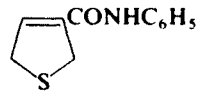

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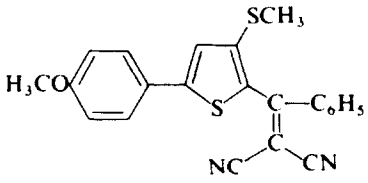
X-Ray crystallography was used for final structure determination of **74**, obtained from the reaction of methylthio-3-dithiole-1,2-ylium ions with arylidene dinitriles in the presence of triethyl amine in methylene chloride, followed by methylation.[423] In order to study the structures of dithiolium derivatives, some compounds, including **75**, were analyzed by X-ray crystallography.[424] The reversible isomerization of **76** to **77** was definitely proven by X-ray crystallography.[425] The two benzothiazolium derivatives **78** and **79** have been structure-determined in connection with investigations on their electrical properties.[426] The molecular structure of 1,1,4,4-tetramethyl-1*H*,4*H*-thieno[3,4-*c*]thiophene has been determined.[426]



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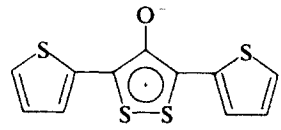

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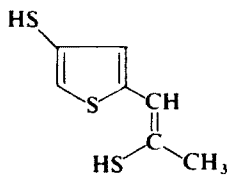

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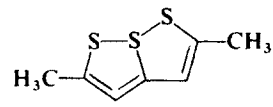

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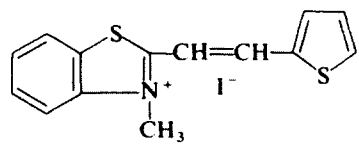

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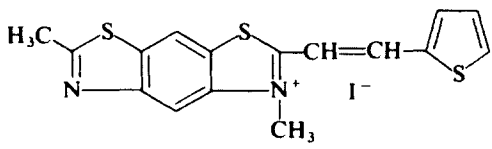

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In connection with studies of interesting thiophenes of more complex nature, X-ray crystallographic investigations have been carried out. For a study of charged-transfer interaction, the structure of the 1 : 1 complex of trithia(5)heterohelicene and 7,7,8,8-tetracyano-*p*-quinodimethane (TCNQ) was determined.[427] The crystal structure of the 1,2-di(thienyl)ethene and TCNQ complex has been elucidated.[428] The molecular structures of double- and triple-layered [2.2] paracyclophanes containing a thiophene ring have been determined. The thiophene ring has an envelope shape, the outer benzene ring is boat-shaped, and the inner benzene ring is twisted by the two upper and two lower methylene bridges.[429-431]

The crystal structure of a great number of metal chelates derived from 1-(2-thienyl)-4,4,4-trifluoro-1,3-butandione (TTA) have been determined, including the indium and iron(III) complexes,[432] the cesium salt,[433] the europium dihydrate,[434] and the copper(II) complex,[435] as well as the tetrameric di-μ-(ethoxo)-bis TTA dicopper(II) complex.[436,437] In the structure of tetrakis(TTA)-thorium(IV), the inner coordination polyhedron around thorium is a distorted dodecahedron. The four bidendate ligands span the legs of the two perpendicular trapezoids of the dodecahedron.[438] The crystal structures of *cis*-bis(TTA)bis(methanol) Co(II) and Zn(II) display *cis*-octahedral geometry. The chelate rings are puckered toward each other.[439] The crystal structure of TTA itself has been determined. The structural parameters do not indicate a tautomeric equilibrium, but a single enol form.[440] An unusual dodecahedral coordination was found in the structure of ammonium tetrakis(TTA)praseodymate(III)-monohydrate.[441] A structure determination of tetraethylammoniumtrichlorooxo(TTA)niobate(V) showed that the thenoyl group is trans with respect to the Nb=O bond.[442]

A number of complexes containing pyridine derivatives besides TTA have been studied. In the monoclinic crystal structures of *cis*-bis(TTA)bis-4-(methylpyridine)Co(II), Cu(II), and Zn(II), the metal ions occupy a special position that imposes symmetry 2 on the molecules with *cis*-octahedral conformation.[443] The crystal structures of the pyridine adducts of the Co(II), Ni(II), and Zn(II) complexes of TTA have been elucidated and their extraction properties studied.[444] The crystal structure of the 4-methylpyridine adducts of bis(TTA)Ni(II) shows that the molecule has a twofold axis and both enantiomers with cis configuration occurring in the crystal.[445] In tris(TTA)-1,2-di-(4-pyridyl)ethane–aquoneodymium(III), the neodymium atom is coordinated to six oxygen atoms of the three TTA groups, one oxygen atom of the water molecule, and one nitrogen atom of the 1,2-di(4-pyridyl)ethane molecule.[446]

In pyridiniumtetrakis(TTA)neodymium(III), the neodymium atom is coordinated to eight oxygen atoms of the four-TTA group in a geometric form described as a distorted square antiprism.[447] In the crystal structure of isoquinolinium tetrakis(TTA)cerium(III), a distorted dodecahedral arrangement around the cerium atom was found.[448]

The structures of TTA complexes with phosphorous compounds as additional ligands have also been determined. The structure determination of (TTA)

carbonyltriphenylphosphinerhodium(I) showed that the carbonyl group trans to the oxygen nearest to the thenoyl group was substituted by the phosphine group when the compound was prepared from Rh(TTA) $(CO)_2$.[449] The structure of (TTA)bis(triphenyl)phosphine oxide[neodymium(II)] was monomeric and the neodymium coordinates to six oxygen atoms from the three TTA groups and two from the triphenylphosphine oxide ligands to form a dodecahedron.[450] In tetrakis(TTA) (tri-*n*-octylphosphineoxide)thorium(IV), the thorium atom is coordinated to nine oxygens, eight from the four TTA groups and one from the phosphine oxide to a geometric form that could be best described as a distorted 4,4,4-tricapped trigonal prism.[451] The structure of di(TTA) (tri-*n*-octylphosphineoxide) UO_2 has been studied.[452]

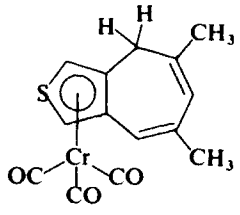
In an investigation of the crystal and molecular structures of a five-coordinated binuclear copper(II) complex, bis{TFA-[*N*-(2-methylethyl)-2-hydroxy-benzylideneaminato-μ-O]copper(II)} was studied.[453]

The 4-thio derivative of TTA has been used as a ligand in tetraethylammoniumpentacarbonyl[1,1,1-trifluoro-4-(2-thienyl)-4-thiooxobutan-2-onato-S]tungstate(0). A single-crystal X-ray structure analysis has shown that in this complex the S-bonded unidentate ligand was present in a hitherto unobserved trans configuration.[454]

The crystal structure of other chelates containing thiophene rings have also been elucidated. Examples are the bivalent platinum and palladium complexes of 2-(2′-thienyl)pyridine (TP) with a thienyl–metal bond; thus the complex has the composition Pt(TP) (TP-H)I. The platinum atom is coordinated by two pyridyl nitrogen trans to one another, a 2-thienyl carbon and an iodide, which lies slightly below the plane formed by the platinum and the other three coordinating atoms.[455] In a later study, the synthesis of complexes with the composition $M(TP)_2X_2$ ($X^- = Br^-$, Cl^-) has been described and the crystal structure of $Pd(TP)Br_2$ elucidated. The palladium atom is located on an inversion center and is coordinated to two nitrogen atoms and to bromine atoms in a typical square planar fashion. In addition, the two thiophene sulfur atoms are located above and below the palladium atom making the complex quasioctahedral.[456]

The structure of the complex between 2,2′-bithienyl and antimony trichloride has been determined.[457] The structures of various copper chelates have been studied. The structures of di-μ-chloro-bis[*N*-(2-aminoethyl)thiophene-2-aldimine]chlorocopper(II) and bis[*N*-(2-aminoethyl)thiophene-2-aldiminediperchloratocopper(II) show that the ligands are coordinated through nitrogen only, the thiophene sulfur remaining unattached.[458] The crystal structure of *N*,*N*′-bis[3-(2-thenylamino)propyl]piperazine $Cu(ClO_4)_2$ was elucidated, and the disposition of the thiophene-sulfur-atoms about the Cu ions was found to be indicative of an incipient CuN_4S_2 coordination.[459] The crystal structure of bis(2-mercapto-5-ethylthenylidene-α-aminopyridine)Co(II) has been elucidated.[460]

In the crystal structure of tetrakis(2-thienyldifluorophosphine)Ni no interaction between the sulfur atoms of the thiophene and the central nickel atoms was observed.[461] Two modifications of bis[(2-thienyl)methyldithiophosphi-



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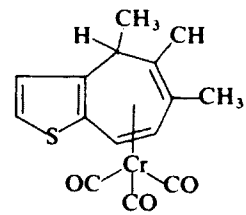


81

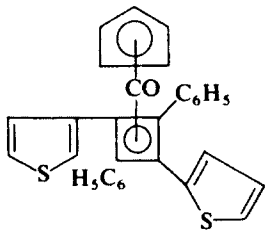
nato]Ni(II) have been studied by X-ray crystallography.[462] In the reaction of $MoCl_5$ with 2-(2′-thienyl)benzimidazole, a molybdenum complex was obtained, which surprisingly contained 2-(2′-thienyl)-1-(2′-thienylmethyl)benzimidazole.[463]

X-Ray crystallography is often the only way to determine the molecular structure of thiophene complexes with transition metals. The structure of thiophene chromium tricarbonyl, $(C_4H_4S)Cr(CO)_3$, was so disordered that a comparison of the dimensions of the metal-complexed thiophene with free thiophene could not be undertaken. However, the molecular configuration with the thiophene sulfur atom always trans to one of the three carbonyl groups was invariant to the crystalline disorder.[464] Other chromium tricarbonyl complexes that have been X-rayed were derived from 6*H*- and 4*H*-5,7-dimethylcyclohepta[*c*]thiophene, namely, (1–3, 3a, 8a-η) 5,7-dimethyl 4*H*-cyclohepta[*c*]thiophene)chromium tricarbonyl **80**,[464] in which the tricarbonylchromium group is fixed on the thiophene ring. However, in the two complexes derived from cyclohepta[*b*]thiophenes, (3a, 4–8, 8a-η)-(4,5,7-trimethyl-4*H*-cyclohepta[*b*]thiophene)tricarbonylchromium **81** and (3a, 4–8, 8a-η)-(5,7,8-trimethyl-8*H*-cyclohepta[*b*]thiophene)tricarbonylchromium, the tricarbonyl chromium group is fixed on the cycloheptatriene ring.[465]

In the crystal structure of tricarbonyl($\eta^4$3,4-dimethylthiophene-1,1-dioxide)iron, the iron is coordinated to the diene system and the sulfur atom is out of the diene plane by 26.9°.[466] In the crystal structure of 2,2′-bithienylbis(tricarbonyl)Fe there are two $Fe(CO)_3$ groups linked to 2,2′-bithienyl by only one of its thiophene rings, which is converted into a metallocycle by insertion of one iron atom.[467] Pentacarbonyl iron has been condensed with thiophene[*b*]- and thiophene[*c*]tropylidene to give $Fe(CO)_3$ complexes in which the $Fe(CO)_3$ group is fixed to the tropylidene moiety according to X-ray crystallography.[468] The molecular structure of (π-C_5H_5)-Fe(CO)-$P(C_6H_5)_3$ (σ-α-thienyl) has been elucidated.[469] An X-ray structural study of $C_5H_4CH_2C_4H_3SRu^+$ $(PPh_3)_2BF_4^-$ confirmed the structure of this η^1, S complex, showing that the sulfur is pyramidal.[470] The reaction of methyl 2-thiophenedithiocarboxylate with diiron nonacarbonyl gave a binuclear complex resulting from coordination of the carbon–sulfur double bond to the two iron atoms and donation of two electrons from the S-methyl group to one iron center.[471]

The reaction between η^5-cyclopentadienyldicarbonylcobalt and phenyl 2-thienylacetylene in refluxing xylene gave a 78% yield of (η-5-cyclopendienyl)

(η^4-diphenyldi-2-thienylcyclobutadiene)cobalt **82**) as proven by X-ray crystallography.[472] The reaction between hexafluoro 2-butyne with $[Mn(CO)_3(C_4F_6)_2 SC_6F_5]$ gave the organometallic derivative **83**.[473] Reaction of $Mn(CO)_5OSO_2CF_3$ with refluxing thiophene gave a high yield of $Mn(CO)_3$(thiophene)SO_3CF_3, which reacted with cyanide ion to give $Mn(CO)_3$(thiophene)CN. X-Ray crystallography showed that cyanide addition occurred at a carbon adjacent to sulfur.[474]



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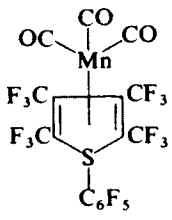

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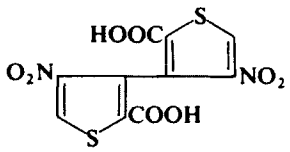
Several crystal structures of thiophene derivatives are described in Ph.D. theseses, including *p*-methoxyphenyl-2-thiophenecarboxylate and bis (*p*-methoxyphenyl)-2,4-thiophenedithiocarboxylate[468] and 3-(1)-naphthyl-4-thiophenecarboxylic acid[483] (see. also Ref. 484). X-Ray studies have been carried out on thiophene clathrates.[485,486] The sorption complexes on montmorillonite and thiophene have been studied by X-ray spacing measurements and one-dimensional Fourier synthesis.[487] The 2-bromothiopheneaflatoxin Gl complex was used for the direct determination of the structure of the latter compound by the method of isomorphous replacement.[464]

X-Ray powder photographs have been used for the detection of quasiracemates (1 : 1 molecular complexes of structurally similar compounds of opposite chirality), especially when the components are unstable at their melting points so that conventional detection of the quasiracemate by melting point diagrams is not feasible. Thus, powder photographs showed that 2-phenylsuccinic acid gave a true racemate, while optically inactive 2-thienylsuccinic acid was a solid solution of the enantiomers. The optically active phenylsuccinic acid and 2-thienylsuccinic acid with the opposite direction of rotation have been found to give a quasiracemate, and therefore have opposite configurations.[475] In a similar way, the configuration of optically active 3-thienylsuccinic acid was related to that of phenylsuccinic acid[476] 2- and 3-thenylsuccinic acids were related to benzylsuccinic acid[477,478] and 2-thenyl-2-thienylacetic acid to α-phenylhydrocinnamic acid.[479] Both optically active 2-thienylglycolic acid[480] and 3-thienylglycolic acid[481] could be related to mandelic acid in this way. Powder photographs have also confirmed the relative configurations of optically active atropisomeric 3,3′-bithienyls. Thus, the powder photographs derived from an equal mixture of (−)-**84** and (−)-**85** were similar to that of **84** while

those of an equimolar mixture of (+)-**85** were different from that of the active as well as of the inactive form, indicating it to be a quasiracemate.[459]



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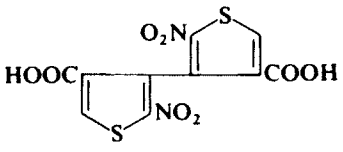

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VII. SURFACE CHEMISTRY OF THIOPHENES

The adsorption of thiophenes on zeolites has been studied extensively.[488-494] Thiophene is not adsorbed selectively by zeolites of types NaX, CaX, NaY, CaY, NaM, and KNaL in the cationic form. The same zeolites in the noncationic form adsorb thiophene effectively from benzene and at certain thiophene concentrations can remove it completely from solution. The ESR spectra of zeolites with adsorbed thiophene show that chemisorption proceeds with the formation of two types of ion radicals, differing in stability, and associated with two apparently different active sites on the surface of the zeolite lattice.[488] Thiophene complexes on montmorillonite saturated with different cations have been studied.[495] In another study X-ray spacing measurements and one-dimensional Fourier synthesis was used.[487] The effect of the degree of cation exchange in synthetic faujasite on the adsorption of thiophene from solutions has been investigated.[496]

The adsorption of thiophene by silica gel has been studied,[494,497-500] and quantum mechanical simulations of the adsorption have been carried out.[501] The adsorption of thiophene on nickel–alumina catalysts containing various proportions of nickel has been investigated. The sorption of thiophene on dispersed iron, cobalt, nickel, and copper increases with increasing temperature.[502,503] The magnetic moment[504] and the dielectric polarization[505] of clathrates of $Ni(CN)_2NH_3$ with thiophene have been determined.

The adsorption and decomposition of thiophene on nickel sulfide and molybdenum sulfide have been studied.[506,507] Low-pressure isotherms for thiophene on graphite are reported using an improved volumetric adsorption system based on a diaphragm, gauge-sensitive to 0.0001 torr.[508] Heats of adsorption of thiophene on graphitized and oxidized carbon black[509] and on carbon fibers[510] were determined by means of gas chromatography. The adsorption isotherms for thiophene of Graphon carbon black have been studied.[511] Thiophene self-hydrogenation on silver foil was established by SIMS cationization experiments.[512]

VIII. GAS CHROMATOGRAPHY OF THIOPHENES

The development of gas–liquid chromatography (GLC) is also reflected in the field of thiophene chemistry.[513–515] It was used for the identification of naturally occuring thiophenes in petroleum,[516–518,251] for the determination of thiophene in benzene,[519] in coke-oven gas,[502] and of silylated thiophenes.[521] GLC studies of sulfides of the thiophene series have been carried out for analysis and to study the thermodynamics of solution.[522,523] Activity coefficients and the determination of excess thermodynamic functions were used to interpret the retention of thiophene on Carbowax 400.[524] GLC was used for the determination of activity coefficients at infinite dilutions of a ternary system containing thiophenes, using the equations of Wohl and Wilson.[525,526] In order to check a theoretical treatment of the equilibria of complex formation in solution by GLC, an experimental study of the electron donor–acceptor interactions between dibutyl tetrachlorophthalate and volatile thiophenes has been undertaken.[527]

Paper chromatographic studies on various metal chelates of 2-thenoyl perfluorobutynyl methane have been described.[528]

IX. MICROWAVE SPECTROSCOPY OF THIOPHENES

The best determination of the geometry of thiophene was carried out by Bak et al. studying the microwave spectra of thiophene, deuterated thiophenes,[529] and 2- and 3-^{13}C enriched thiophene.[530,531] In addition, the lines from ^{34}S-thiophene were found and identified. From these data, an unambiguous calculation of the structure of thiophene could be made, and the following structural parameters were obtained: C—S = 1.714 Å; C=C = 1.370 Å; C—C = 1.423 Å; C(2)—H(2) = 1.078 Å; C(3)—H(3) = 1.081 Å; (angles) C(5)–S–C(2) = 92°10′; S–C(2)–C(3) = 111°28′; C(2)–C(3)–C(4) = 112°27′; S–C(2)–H(2) = 119°51′; C(4)–C(3)–H(3) = 124°16′.[530] The rotational constants, asymmetry parameter, and principal moment of inertia together with the inertial defect for thiophene and seven isotopic species were tabulated. The rotation constants for thiophene are in megahertz: A 8041.77; B 5418.12; C 3235.77[530] (see also Ref. 532). Almost identical rotational constants calculated from the microwave spectrum of thiophene[535,536] were later reported by Russian workers[87,88,553,554] (see also Refs. 535, 536). The charge distribution of thiophene as derived from microwave measurements has been discussed.[537] Measurements of dielectric constant and loss at wavelengths of 1.2, 3.22, 10.7, and 33.3 cm and 577 m have been carried out at temperatures from 1 to 60°C on thiophene in the pure liquid state, and molecular relaxation time was calculated.[538] An empirical method has been described by which the structure of thiophene was calculated from rotation spectra measurements, when the experimental data alone were insufficient to give a unique solution.[539]

From the microwave spectrum of thiophene and tetradeuteriothiophene, the centrifugal effect, rotational constants, and defects of inertia were obtained and compared with calculated data.[540,541] The dielectric absorption of thiophene at five microwave frequencies in carbon tetrachloride and in *p*-xylene has been investigated. The observed relaxation times are comparable to those of other rigid molecules of similar shape and size.[542] The Zeeman splitting of the microwave absorption of thiophene and other five-membered heterocycles has been used for the determination of magnetic susceptibility anisotropy, which has been proposed as a criterium for aromaticity.[543]

The microwave spectra of the ^{35}Cl and ^{37}Cl species of 2-chlorothiophene have been measured in the 26.5–40-GHz region. For both isotopic species, the rotational constants of the ground state and vibrationally excited states were determined, as well as the centrifugal distortion coefficients of the ground state. From the hyperfine splitting of the rotational lines, the nuclear quadrupole constants for ^{35}Cl and ^{37}Cl were calculated.[544] The molecular structure of 2-chlorothiophene was compared with those obtained by electron diffraction measurements (see Section X; also Ref. 545). Similarly, the microwave spectra of the ^{79}Br and ^{81}Br species of 2-bromothiophene were measured in the region of 18–40 GHz, and the rotational constants and quadropole coupling constants were determined.[546] The rotational spectrum of 3-bromothiophene has been investigated in the frequency range 8–18 GHz by the use of a microwave Fourier-transform spectrometer. Both a- and b-type spectra were assigned for the vibronic ground state. Rotational constants, quartic centrifugal constants and quadrupole coupling constants were obtained for the ^{79}Br and ^{81}Br isotopic species.[547] The rotational spectra of 3-bromothiophene in the excited states of two vibrational modes were observed, and the rotational constants, the centrifugal distortion constants, and the nuclear quadrupole coupling constants were determined. The wavenumbers of the two vibrational modes were evaluated to be 210 and 320 cm^{-1} by measuring relative intensities of the ground and excited vibrational transitions.[548]

The microwave spectra of 3-nitrothiophene has been studied in the 26, 5–40 GHz region. The rotational transitions of the ground state and of the first six torsionally excited states have been assigned. The ground state rotational constants were determined, and the planarity of the molecule was demonstrated. The first torsional frequency and the barrier to internal rotation of the nitro group were estimated at 60 cm^{-1} and 3.8 kcal/mol, respectively.[549] Similar investigations were carried out of 2-nitrothiophene, and the barrier to internal rotation of the nitro group was estimated to be 4.8 kcal/mol, which seems reasonable with regard to the more efficient conjugation in 2-nitro- than in 3-nitrothiophene. Both these investigations were carried out on commercial samples without purification and without giving any indications of the purity of the samples.[550] The microwave spectrum of 3-methylthiophene has been studied by Japanese[551] and Russian[89,552] workers. Rotational constants and moments of inertia were determined. The barrier to rotation of the methyl group was estimated to be 0.740 kcal/mol. Two measurements of the electric dipole moments of 3-methylthiophene gave values of 0.95 ± 0.06 D[551] and 0.914D.[89] The

microwave spectra of 2-methylthiophene in the torsional vibrational ground state[553,554] and in the first excited torsional state of A symmetry[555] have also been studied. From the microwave spectra of 2-thiophene aldehyde, rotational constants, the moment of inertia and the dipole moment have been determined.[556,557] The microwave spectra of 2,3-dihydrothiophene,[558] 2-oxotetrahydrothiophene,[559] 2,5-dihydrothiophene-1,1-dioxide,[560] thiacyclopentane-α-d_4,[561] and several dihydrothiophenes[562] have also been investigated. By combining high magnetic fields with high-resolution microwave spectroscopy it was possible to observe the high-field first- and second-order Zeeman effects of thiophene and obtain the molecular g values ($g_{aa} = -0.0862 \pm 0.0023$, $g_{bb} = -0.0662 \pm 0.0006$, $g_{cc} = 0.0501 \pm 0.0005$) and magnetic susceptibility anisotropies [$2\chi_{aa} - \chi_{bb} - \chi_{cc} = (49.6 \pm 1.1)\ 10^{-6}$ erg/G^2 mol and $2\chi_{bb} - \chi_{cc} - \chi_{aa} = (50.6 \pm 1.3\ 10^{-6}$ erg/G^2 mol). The molecular quadrupole moments were found to be $Q_{aa} = 1.7 \pm 1.6$, $Q_{bb} = 6.6 \pm 1.5$, and $Q_{cc} = -(8.3 \pm 2.2)$ in units of 10^{-26} electrostatic units (esu) per square centimeter. The second moment of the charge distribution of thiophene was also calculated.[563] In connection with studies of microwave absorption and molecular structure in liquids, dielectric constants and losses of thiophene have been measured at a wavelength of 2.2 mm at various temperatures between 20 and 55°C. The results have been used for the calculation of relaxation times, distribution parameters, and optical dielectric constants.[564] The dielectric relaxation time of rigid molecules such as thiophene in dilute solutions was shown to depend exponentially on an effective molecular radius that is independent of the solvent.[565]

X. ELECTRON DIFFRACTION OF THIOPHENES

The molecular structure of thiophene, which was previously[566] determined by electron diffraction was redetermined by more modern techniques.[567] In the latter work the following parameters were found for thiophene (distances: C—S = 1.717 ± 0.004 Å; C=C = 1.368 ± 0.004 Å; C—C = 1.424 ± 0.002 Å; C—H = 1.071 ± 0.015 Å; (angles) CSC = 91.9 ± 0.30°; SCC = 111.9 ± 0.03°; SCH = 121 ± 3°; C(3)–C(4)–H = 120 ± 6°. The structure was planar better than 0.1 Å. The dimensions are thus in good agreement with the parameters obtained by the microwave technique.[530] The structures of 2-chloro- and 2-bromothiophene were also determined, and are discussed in the Ph.D. thesis of Harshbarger.[568] However, there has been some controversy regarding this work in the literature,[569,570] regarding the conclusion that in these compounds the thiophene ring deviates from C_2 symmetry.

Electron diffraction studies based on the sector method have also been carried out on 2,2'-bithienyl. The structural parameters of the thiophene rings were in good agreement with the values obtained by microwave spectroscopy. The angle of twist between the rings was found to be 34°.[571] Electron diffraction studies of 2-thiophene sulfonyl chloride show a perpendicular arrangement of the plane of the five-membered ring and the CSCl plane.[572]

XI. NMR SPECTROSCOPY OF THIOPHENES

1. ^{1}H NMR Spectroscopy

A. Spectral Interpretation and Special Techniques

Thiophene derivatives have played an important role in the development of ^{1}H NMR spectroscopy, because of their easy availability and the fact that the ring hydrogens of di- and monosubstituted thiophenes constitute simple two- or three-spin systems suitable for the analysis of the ^{1}H NMR spectrum and for the development of special techniques.

Thus, the proton resonance of 2-bromo-5-chlorothiophene was already investigated in 1952 by studying the modulation of the spin echo,[573] and its proton ^{1}H NMR spectrum at 30.5 MHz was analyzed in 1956.[574] Nuclear resonance saturation effects and multiple quantum transitions were studied with 2-bromo-5-chlorothiophene.[575]

2-Bromo-5-chlorothiophene was also used in a method for the measurement of indirect coupling between nuclei in liquids in magnetic resonance by the transient method[576] and in connection with a compensating device for parasitic beat signals in ^{1}H NMR double-resonance experiments.[577]

Several groups have analyzed the A_2B_2 spectrum of thiophene itself,[578-582] although the first complete assignments of shifts and coupling constants in thiophene were obtained by an ^{1}H NMR study of the two monodeuterated and the four dideuterated thiophenes.[583] Imaginary solutions to three-spin spectra were studied with 2-chlorothiophene.[584] Table 13 lists ^{1}H-chemical shifts and coupling constants of thiophene in various solvents.

Thiophenes have played an important role in the development of nuclear magnetic double resonance. 2-Bromo-5-chlorothiophene[585,586] and 2,4-dibromothiophene[587] were used in studies of strongly coupled two-spin systems.

TABLE 13. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) for Thiophene

Solvent		∂_2, ∂_5	∂_3, ∂_4	J_{23}	J_{25}	J_{34}	J_{35}	Ref.
Ether		7.33	7.08					618
Cyclohexane		7.16	6.97					661
$CDCl_3$		7.36	7.13					665
"		7.34	7.12	4.95	2.85	3.50	1.05	716
TMS		7.16	6.98					648
$CDCl_3$		7.35	7.14	5.0	3.0	4.1	0.9	686
Acetone-d_6		7.46	7.14	4.6	3.6	2.8	1.1	"
Benzene-d_6		6.89	6.76					687
$CDCl_3$	$Cr(CO)_3$	5.37	5.61	2.8	0.9	2.2	1.2	686
Benzene-d_6	"	3.96	4.39					"
Acetone-d_6	"	5.93	5.93					"

The assignments of the appropriate energy-level diagram systems such as 2-chlorothiophene were also made by this technique.[588] The double-irradiation method has also been used to establish the correct level arrangement in the ABX spectrum of 5-methylthio-2-thiophenethiol.[589] The relative sign of the coupling constants of 2- and 3-bromothiophene and 2-thiophenecarboxylic acid have been determined by spectral analysis in conjunction with double irradiation or the interpretation of the double quantum spectrum.[590] The detection of very small ^{1}H NMR-spin coupling constants by resolution enhancement has been applied to 3-bromo-2-thiophene aldehyde.[591] Double-irradiation techniques have been used to detect NMR splittings that are so weak as to be obscured by the broadening due to spatial inhomogeneity of the applied magnetic field. In this way, the 0.05 Hz splitting in the 60-MHz ^{1}H NMR spectrum of 3-bromo-2-thiophene aldehyde was resolved.[592] Transfer of fine structure in nuclear magnetic double resonance has also been used to detect the very small long-range coupling in 3-bromo-2-thiophene aldehyde.[593] Signs of long-range proton spin coupling constants can be determined by nuclear magnetic triple resonance experiments, and in this way it was established that the long-range coupling to the aldehyde group of 3-bromo-2-thiophene aldehyde has the same sign as the vicinal coupling.[594]

The multiple transitory selective irradiation technique has been used to show that the sign of the long-range aldehyde coupling $J_{\text{CHO-5}}$ in 3-bromo-2-thiophene aldehyde is the same as that of the ring-coupling constants J_{45}.[595] The sign of the side-chain coupling $J_{\text{CHO-5}}$ relative to the ring coupling J_{45} in the ABX spectrum of 2-bromo-3-thiophene aldehyde has been found to be the same as that of J_{45} by the use of nuclear magnetic double resonance. From the ABX analysis of the single-resonance spectrum, it was found that $J_{\text{CHO-4}}$ is of opposite sign to $J_{\text{CHO-5}}$.[596]

Double and triple resonance techniques have also been used for the determination of the signs of the methyl couplings in 2-bromo-5-methylthiophene, 2-carbomethoxy-4-methylthiophene, and 4-methyl-3-thiophene aldehyde relative to those of the ring couplings. The couplings between the methyl groups and their ortho hydrogens were found to be of opposite sign to the ring coupling constant, while the methyl couplings to meta hydrogens carry the same sign as the ring coupling constants.[597] The same technique was also used for the determination of the side-chain spin couplings $J_{\text{CH}_3\text{-5}}$ in 3-nitro-2-methylthiophene, $J_{\text{CH}_3\text{-CH}_3}$ in 3-acetyl-2,5-dimethylthiophene,[598] and $J_{\text{CH}_3\text{-CH}_3}$ in 2,3-dimethylthiophene.[599] $J_{\text{CH}_3\text{-5}}$ coupling was found to be -0.15 Hz, while the $J_{(\text{CH}_3)2\text{-}(\text{CH}_3)5}$ coupling was 0.55 Hz, and both signs were related to the sign of the ring-proton couplings in thiophenes.[598] The signs and magnitudes were discussed in terms of σ- and π-electron contributions to the spin couplings.[598,599]

The signs of the side-chain spin couplings $J_{\text{SH-2}}$, $J_{\text{SH-4}}$, and $J_{\text{SH-5}}$ of 3-thiophenethiols, as well as those of the $J_{\text{SH-CH}_3}$ couplings between the side chains in the 2-methyl-, 4-methyl-, and 5-methyl-substituted 3-thiophenethiols, have been determined relative to those of the ring-proton couplings by selective double irradiation. The signs found were as follows: $J_{\text{SH-2}}$ (−), $J_{\text{SH-4}}$ (−), $J_{\text{SH-5}}$

(+), $J_{SH-(CH_3)2}$ (+), and $J_{SH-(CH_3)5}$ (−).[600] The same technique was used for the determination of the side-chain spin couplings in methyl 2-thiophenethiols. The signs found were (J_{SH-3} (−), J_{SH-4} (+), J_{SH-5} (−), $J_{SH-(CH_3)3}$ (+), $J_{SH-(CH_3)4}$ (−), and $J_{SH-(CH_3)5}$ (+).[601] The results support the interpretation of these couplings as being due to a π-electron contact mechanism.[600,601]

The double and triple quantum transitions of 2-chloro-, 2-bromo-, 2-iodo-3-bromo-, and 3-iodothiophene have been obtained and used in the assignments of the three-spin energy-level diagrams.[602,603] Localized saturation effects in nuclear magnetic double resonance have been studied for 2-chlorothiophene.[604] Some ^{1}H NMR coherence transfer experiments have been carried out with 2,3-dibromothiophene.[606]

2,3-Dibromothiophene has been used in a study of the simplification of ^{1}H NMR spectra by filtration through multiple quantum coherence,[607] in a study of pulsed field gradients in ^{1}H NMR,[608] and in improvements of pulse performance in ^{1}H NMR coherence transfer experiments.[609] 2,3-Dibromothiophene was also used as a component in pattern recognition in two-dimensional correlation spectra in attempts toward the automated assignment of nuclear resonance spectra.[610]

B. Coupling Constants of Thiophenes

During 1958 and 1959 scattered papers giving ^{1}H NMR spectra of simple mono- and disubstituted thiophenes started to appear.[611–614] An extensive and systematic investigation was carried out during 1959–1960 by Hoffman and Gronowitz. The ring-coupling constants in nineteen 2,5-, seventeen 2,3-, eighteen 2,4-, and eleven 3,4-disubstituted thiophenes were reported.[615,616] The following characteristic ranges of coupling constants were observed: J_{34} = 3.45–4.35 Hz, J_{45} = 4.90–5.80 Hz, J_{35} = 1.25–1.70 Hz, and J_{25} = 3.20–3.65 Hz.[616] The coupling constants in monosubstituted thiophenes also fell within these ranges.[617] These ranges were later somewhat expanded when strongly electropositive or electronegative substituents were present. Thus, in 2-thienyllithium J_{35}, J_{34}, and J_{45} were only 0.5, 2.8, and 4.3 Hz, respectively,[618] and in 2-fluorothiophene J_{35}, J_{34}, and J_{45} were 1.69, 3.89, and 6.02 Hz, respectively.[619] Abnormally high values of J_{34} of the order of 6.0 Hz have been found for 2-amino-5-nitrothiophene and some of its derivatives.[620] The following correlations between the coupling constants in 2-substituted thiophenes and substituent electronegativity were observed: $J_{35} = 0.44E_x + 0.00$, $J_{34} = 0.33E_x + 2.69$, $J_{45} = 0.58E_x + 3.75$, and $\Sigma J = 1.35E_x + 6.45$.[621]

The ring-proton–proton coupling constants of thiophene and 14 monosubstituted derivatives have been calculated using the perturbed SCF INDO method. The results satisfactorily reproduce signs, magnitudes, and some trends of the experimental values.[622] Subsequently, the nuclear spin constants of thiophene were calculated by finite perturbation theory in ZDO approximation.

Comparison of results of CNDO/2 and INDO calculation gave information about the relative importance of σ- and π-pathways for the various coupling constants.[623]

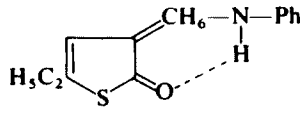
The characteristic coupling constants were of great importance for the structure determination of isomeric thiophenes obtained in substitution reactions, such as the nitration of 2-methyl-, 2-methoxy, 2-bromo-, 2-iodo-, and 3-methylthiophene;[624] the nitration of 2-thenyl acetate,[625,626] 2-thenyl chloride,[626] 2- and 3-thenyl alcohol,[627] 2- and 3-thiophene aldehyde, 2- and 3-thiophene nitrile, and 2- and 3-nitrothiophene;[628] as well as the acylation of 2- and 3-methylthiophene, 2- and 3-bromothiophene, 2- and 3-iodothiophene, and 2- and 3-methoxythiophene.[629] Other examples of the use of ^{1}H NMR spectroscopy for the determination of isomer distributions are a study of the nitration, acetylation, mercuration, and iodination of 3-iodothiophene[630] and the bromination of some carbamate derivatives of 3-aminothiophene.[631]

Characteristic coupling between the side-chain protons and ring protons were also discovered in methylthiophenes, thiophene aldehydes, and thiophenethiols.[616,632-634] These side-chain couplings have the values $J_{CH_3\cdot3} = 1.10$–1.15 Hz, $J_{CH_3\cdot4} = 0.2$–0.5 Hz, and $J_{CH_3\cdot5} < 0.4$ Hz in 2-methylthiophenes; $J_{CH_3\cdot2} = 0.9$–1.25 Hz, $J_{CH_3\cdot4} \sim J_{CH_3\cdot5} = 0.4$–$0.5$ Hz in 3-methylthiophenes; $J_{CHO\cdot5} = 1.05$–1.40 Hz in 2-thiophene aldehydes; $J_{CHO\cdot5} = (<0.4)$–0.8 Hz in 3-thiophene aldehydes; $J_{SH\cdot3} = 1.40$–1.60 Hz, $J_{SH\cdot5} = 0.9$–1.0 Hz in 2-thiophenethiols; $J_{SH\cdot2} = 0.65$–1.05 Hz; and $J_{SH\cdot5} \leq 0.3$ Hz in 3-thiophenethiols.[616,617] Couplings between protons of different side chains have been observed in the 3- and 5-methyl-2-thiophenethiols and in 2-methyl-3-thiophenethiol, but not in 3-methyl-4-thiophenethiol or any methyl-substituted thiophene aldehyde;[616] and also between methyl groups of 2,3-dimethylthiophenes[635] and 2,5-dimethylthiophenes.[598] The signs of these long-range couplings have been determined.[595-601,615] An attempt was made to account in a qualitative way for the observed methyl couplings by ascribing them largely to hyperconjugation between methyl group orbitals and π-electron orbitals.[636] The long-range couplings, especially those of the formyl group, were of great importance for conformational analysis (see Section XI.1.H).

Proton–fluorine coupling over six bonds has been observed between fluorine and the β-hydrogen of the thiophene ring in *ortho*-fluorophenyl derivatives of 4-phenylthienopyrimidines, 2-acetylamino-3-benzoylthiophene, and some bicyclic thiophene derivatives.[637,638] In 2-acetylamino-3-(*o*-fluorophenyl)-4-methylthiophene, a coupling of 0.5 Hz (over seven bonds) was observed between the fluorine and the methyl group.[639] These couplings were attributed to a through-space mechanism.[637-639] Cross-ring coupling constants over five and six bonds following a zigzag path have been observed.[64]

In early work satellite spectra in the ^{1}H NMR spectra were used to determine the ^{13}C–H coupling constants for thiophene,[641-643] methylthiophenes,[634,641,644] other alkylthiophenes,[645] and chlorothiophenes.[646] Using homonuclear double resonance, $J_{^{13}C-H}$ was determined for 2-bromothiophene.[647] An empirical method has been described for the estimation of

diamagnetic anisotropic effects in NMR based on a correlation between ^{13}C–H coupling constants and proton chemical shifts.[648] The magnitude and signs of the ^{15}N–H spin-coupling constants in **86** were found to be as follows: $J_{^{15}N-H(a)} = -93.0$ Hz, $J_{^{15}N-H(b)} = 0$ Hz, and $J_{H(a)-H(b)} = +13.0$ Hz.[649]



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C. Chemical Shifts of Thiophenes

In 1960 the proton magnetic resonance spectra of 36 monosubstituted thiophenes were reported at 40 MHz, and the chemical shifts were extrapolated to infinite dilution in cyclohexane.[617] In order to obtain the shifts from strongly coupled derivatives, deuterated compounds were used.[615] Attempts were made to estimate the influence of the anisotropic susceptibilities of the substituents on the chemical shift. It was found that they contribute to only a minor extent to the observed shifts, which therefore were considered to be directly related to the electron densities on the various hydrogens. The chemical shifts of twenty 2-substituted and sixteen 3-substituted thiophenes were discussed in terms of inductive effects and by using simple resonance theory. The smaller shifts in the 4-position compared to those in the 2-position in 3-substituted thiophenes, and the larger shifts of the 3-position in 2-substituted thiophenes were interpreted in these terms.[650]

In a later investigation, Gronowitz and coworkers compared the ^1H NMR shifts of 2-substituted thiophenes with those of the corresponding furans, selenophenes, and tellurophenes. Linear correlations between the shifts of the corresponding protons were observed (see Table 14), which can be used for predicting shifts of unknown selenophene and tellurophene derivatives when those of the corresponding thiophene are known.[651,652] Linear correlations between the electronegativity of the heteroatoms and several of the ^1H NMR parameters were also observed.[651] The proton chemical shifts of monosubstituted thiophenes were also correlated with reactivity parameters by the use of the two-parameter equation of Swain and Lupton[652,653] (see Tables 15–17; also Ref. 654).

Many other ^1H NMR investigations of special groups of thiophene derivatives have been carried out. Thus, the effect on methyl substitution on ring-proton chemical shifts in thiophene, furan, and pyrrole has been studied,[655] as well as the influence of substituents on the chemical shift of the methyl group protons in substituted methylthiophenes, which for 5-substituted 2-methylthiophenes was found to be approximately proportional to the shifts of the 2-ring hydrogen in 5-substituted thiophenes.[656]

TABLE 14. ^{1}H NMR Data for Some Furan, Thiophene, Selenophene, and Tellurophene Derivatives in Deuterioacetone Solution at 100 MHz Using TMS as Internal Standard[a]

Substituent	X	δ_3	δ_4	δ_5	δH_X	J_{34}	J_{35}	J_{45}
	O	7.45	6.74	7.94	7.72	3.45	0.83	1.73
	S	7.93	7.30	7.96	9.98	3.79	1.22	4.75
CHO	Se	8.17	7.54	8.68	9.86	3.90	1.22	5.44
	Te	8.62	8.05	9.56	9.58	4.10	1.32	6.77
	r					0.97	0.99	0.99
	O	7.32	6.65	7.81	2.41	3.58	0.76	1.74
	S	7.80	7.17	7.80	2.52	3.74	1.09	5.07
$COCH_3$	Se	8.02	7.43	8.52	2.51	3.96	1.14	5.54
	Te	8.44	8.00	9.41	2.52	4.22	1.16	6.78
	r					0.87	0.99	0.99
	O	7.24	6.59	7.76		3.53	0.88	1.72
	S	7.80	7.15	7.78	9.56	3.67	1.16	5.03
COOH	Se	8.03	7.37	8.42	10.53	3.90	1.26	5.50
	Te	8.53	7.93	9.40	10.81	4.20	1.34	6.76
	r					0.85	0.99	0.99
	O	7.23	6.61	7.79	3.86	3.50	0.83	1.74
	S	7.74	7.09	7.66	3.85	3.69	1.20	4.97
$COOCH_3$	Se	8.00	7.37	8.42	3.82	3.93	1.22	5.50
	Te	8.49	7.92	9.38	3.78	4.11	1.33	6.79
	r					0.90	0.99	0.99
	O	6.43	6.39	7.55	2.38	3.26	0.88	1.98
	S	7.07	6.96	7.40	2.45	3.60	1.26	5.36
SCH_3	Se	7.18	7.17	8.08	2.50	3.70	1.23	5.77
	Te	7.42	7.55	8.81	2.50	4.03	1.28	6.93
	r					0.94	0.97	0.99
	O	6.25	6.31	7.40	4.90	3.30	0.86	1.80
	S	6.91	6.88	7.21	4.67	3.40	1.11	5.14
CH_2OH	Se	7.05	7.11	7.90	4.82	3.50	1.18	5.59
	Te	7.41	7.64	8.77	4.74	3.88	1.25	6.83
	r					0.83	0.99	0.99

[a] X = heteroatom; and *r* = correlation coefficient for correlation with electronegativity.

The methyl substitution effect on the chemical shifts or ortho protons has been correlated with the π-bond order in thiophene.[657]

The ^{1}H spectra for a large number of fluorothiophenes have been analyzed[619,658–660] (for discussion, see Section XI.3.C). All bromothiophenes have been studied by ^{1}H NMR.[661] ^{1}H NMR data of 17 compounds, including all the iodosubstituted derivatives of 2-, 3- and 2,3-dimethylthiophene, have been reported.[662] An HMO–EIP treatment of the ^{1}H NMR shifts of monosubstituted thiophenes has been carried out.[663,664] Theoretical data obtained by simple HMO calculations of various methylthiophenes were correlated with ^{1}H NMR data.[634,665]

TABLE 15. $\mathcal{F}$ and $\mathcal{R}$ Constants for the Substituents Used in the Regression Analyses in This Chapter

Substituent	$\mathcal{F}$	$\mathcal{R}$
OMe	0.413	− 0.500
SMe	0.332	− 0.186
F	0.708	− 0.336
Cl	0.690	− 0.161
Br	0.727	− 0.176
I	0.672	− 0.197
CH_3	− 0.052	− 0.141
$COCH_3$	0.534	0.202
COOH	0.552	0.140
CN	0.847	0.184
NO_2	1.109	0.155

TABLE 16. Regression Equations Relating ^{13}C Chemical Shifts of Monosubstituted Thiophenes and Benzenes to Substituent Constants $\mathcal{F}$ and $\mathcal{R}$

Equation	σ^b	r^c	N[d]
$\Delta C_3^{2a} = 4.0 - 5.8\mathcal{F} + 46.7\mathcal{R}$	4.5	0.93	8
$\Delta C_4^2 = 1.1 - 0.9\mathcal{F} + 5.9\mathcal{R}$	0.6	0.93	8
$\Delta C_5^2 = 2.7 + 0.4\mathcal{F} + 33.5\mathcal{R}$	1.6	0.99	8
$\Delta C_2^3 = 2.9 - 5.2\mathcal{F} + 55.5\mathcal{R}$	3.3	0.97	8
$\Delta C_4^3 = 4.1 - 8.2\mathcal{F} + 15.1\mathcal{R}$	3.0	0.78	8
$\Delta C_5^3 = 0.7 + 1.9\mathcal{F} + 2.9\mathcal{R}$	0.4	0.93	8
$\Delta C_2^B = 2.9 - 8.0\mathcal{F} + 23.9\mathcal{R}$	4.1	0.80	8
$\Delta C_3^B = -0.4 + 1.5\mathcal{F} - 2.0\mathcal{R}$	2.0	0.94	8
$\Delta C_4^B = -0.1 + 2.3\mathcal{F} + 17.6\mathcal{R}$	1.0	0.98	8

[a] The shifts are given in ppm relative to those of thiophene. The notations ΔC_i^2, ΔC_j^3 denote the shifts of the i- and j-carbons of 2- and 3-substituted thiophenes, respectively, and ΔC_i^B, the shift of benzene.
[b] Standard deviation in ppm.
[c] Correlation coefficient.
[d] Number of substituents in the regression analysis.

The ^1H NMR data of various bromosubstituted thiophene aldehydes[666] and triformyl derivatives of thiophene[667,668] have been reported. Many other carbonyl derivatives, such as thieno-fused cycloalkanones,[669] thienyl phenyl ketones,[670–673] and thioketones,[670] have been studied in order to determine steric effects and effects of the torsional angle on chemical shifts of aryl thienyl ketones.[671,672] The transfer of substituent effects in thiophene analogues of

TABLE 17. Regression Equations Relating Proton and Fluorine Chemical Shifts[a] of Monosubstituted Thiophenes and Benzenes to Substituent Constants $\mathcal{F}$ and $\mathcal{R}$

Equation	σ^b	r^b	N^b
$\delta^2_{3H} = -0.04 + 0.34\,\mathcal{F} + 2.15\,\mathcal{R}$	0.12	0.98	9
$\delta^2_{4H} = -0.07 - 0.08\,\mathcal{F} + 0.73\,\mathcal{R}$	0.5	0.96	9
$\delta^2_{5H} = -0.83 + 0.05\,\mathcal{F} + 1.65\,\mathcal{R}$	0.10	0.97	9
$\delta^3_{2H} = -0.04 + 0.34\,\mathcal{F} + 2.42\,\mathcal{R}$	0.08	0.99	8
$\delta^3_{4H} = 0.00 + 0.12\,\mathcal{F} + 1.19\,\mathcal{R}$	0.12	0.88	8
$\delta^3_{5H} = 0.05 + 0.06\,\mathcal{F} + 0.40\,\mathcal{R}$	0.07	0.72	8
$\delta^2_{5F} = 3.8 + 7.5\,\mathcal{F} + 25.0\,\mathcal{R}$	2.2	0.96	12
$\delta^B_{4F} = -1.0 + 5.0\,\mathcal{F} + 22.5\,\mathcal{R}$	1.5	0.98	16

[a] The shifts are given in ppm relative to those of the α- or β-protons in thiophene. The notations δ^2_i and δ^3_j denote the shifts of the i- and j-nuclei in 2- and 3-substituted thiophenes, respectively, and δ^B the shift of benzene.

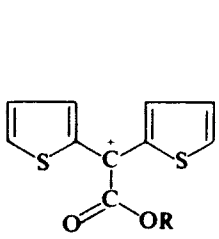
chalcones has been studied by ^{1}H NMR.[674] An additivity model study of EHT electron densities and ^{1}H NMR chemical shifts in some chlorothiophenes has been carried out.[675]

The ^{1}H NMR parameters for a large number of thenyl derivatives have been reported.[676] The ^{1}H NMR spectra of 38 chloromethylthiophenes and seven dithienylmethane derivatives have been studied. The chemical shifts of the methylene protons were 4.63 to 5.25 ppm for monosubstituted 2-chloromethylthiophenes and 4.37 to 4.56 ppm for 3-chloromethylthiophenes, with reference to TMS. The long range coupling constants observed for the methylene proton signals were useful for the determination of the positions of substituents.[667]

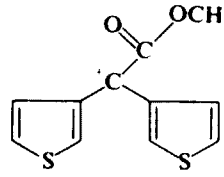
The ^{1}H NMR spectral of a number of methylthiophene sulfonyl chlorides have been reported.[678] ^{1}H NMR spectra parameters have been reported for the isomeric trithienyl carbonium ions. The low field shifts, relative to the corresponding carbinols, were discussed in relation to the delocalization of the positive charge into the thiophene ring bonded in the 2- or 3-position. A linear correlation was found between chemical shifts and π-charge densities.[679]

Treatment of methyl 2,2'-dithienyl glycolate with chlorosulfonic acid led at -50°C to the observation of the α-carboxylated carbonium ion **87**.[680] The analogs 3-isomer gave the carbonium ion **88** at -78°C, which already at -55°C started to rearrange to the α-protonated derivative **89**.[681]

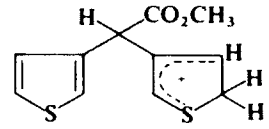
By means of ^{1}H NMR spectra it was shown that the order of variation in electron-withdrawing power of the substituent ($CHO > COCH_3 > CO_2CO_3$) was retained during the formation of the complex with aluminium chloride or protonation of the carbonyl group.[682] Within the framework of the CNDO/2 method, spin–spin coupling constants were calculated for 2-formylthiophene and its oxygen protonated form.[495]



87



88



89

The ^{1}H NMR spectra of mono- and diprotonated 2-thienylcarbonyl compounds in SO_2–SbF_5/$HFSO_3$ solution were investigated. The nature of the substituents in the thienyl ring and the configuration of the molecule, in the case of 2-thienyl phenyl ketones, were main factors in determining whether a proton is captured only by the carbonyl group, or by the thienyl ring as well.[683]

^{1}H NMR spectra showed that in the acylation of thiophene and its homologs, in addition to ketones, σ-complexes are formed, which arise as the result of the protonation of the α-position of the thiophene nucleus by the protons liberated on acylation.[684] Well-resolved ^{1}H NMR signals from the cations formed from chlorothiophenes were observed in the HSO_3F or $AlCl_3$–HCl–CH_2Cl_2 system. Chlorothiophenes were protonated exclusively at the position adjactent to sulfur, either with or without substituents. The protonation of 2-chloro-5-methylthiophene occurs in the 5-position, and in the HSO_3F system, the cation 5*H*-2-chloro-5-methylthiophenium ion thus formed undergoes an irreversible 2,5-hydrogen shift.[685]

Several thiophene-$Cr(CO)_3$ complexes have been studied by ^{1}H NMR spectroscopy. The more important shielding of the α-protons relative to the β-protons in all complexes was interpreted in terms of increased charge densities on α-carbon atoms. In contrast to the free thiophenes, the vicinal coupling constants are similar in the complexes and the importance of π-transmission was calculated from long-range coupling constants.[686,687]

^{1}H NMR spectra showed that the adduct formed between methoxide ion and 2-methoxy-3,5-dinitrothiophene was a Meisenheimer complex.[688] The ^{1}H NMR spectra of 2-thiophene thiocarboxamide with some metal chlorides and bromides [M = Ni(II), Zn(II), Cd(II), Hg(II), and Cu(I)] have been studied.[689] ^{1}H NMR spectra gave evidence for the coordination of the thiophenic sulfur atom in the Cu(II) complex of 2-thiophenecarboxylic acid.[690] An ^{1}H NMR method has been used to determine the association constants of thiophene with the electron acceptor 1,3,5-trinitrobenzene in chloroform solution.[691] The paramagnetic shift and width of the ^{1}H NMR lines of thiophene in the presence of oxygen have been measured.[692] The complex formation of benzoyl acetylene and phenyl acetylene with thiophene and a number of methylated thiophenes has been investigated using ^{1}H NMR techniques. Variable temperature studies on the benzoylacetylene-2-methylthiophene complex gave an estimate of the enthalpy of formation.[693] The ^{1}H chemical shifts and coupling constants of mono, di-, and trisubstituted thiophenes are collected in Tables 18–25.

TABLE 18. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 2-Substituted Thiophenes

C_n	Substituent	Solvent	δ_3	δ_4	δ_5	J_{34}	J_{35}	J_{45}	δ_R	Ref.
4	F	Cyclohexane	6.31	6.55	6.45	3.85	1.68	5.93		619
	Cl	$CDCl_3$	6.90	6.87	7.22	3.70	1.45	5.60		716
	Br	Cyclohexane	6.91	6.68	7.04	4.0	1.7	5.0		617
		"	6.90	6.69	7.03	3.6	1.4	5.3		661
		Neat	6.84	6.61	6.92	3.7	1.4	5.5		647
		Ether	7.04	6.83	7.26	3.7	1.7	5.5		618
		$CDCl_3$	7.04	6.86	7.22	3.70	1.35	5.60		716
	I	Cyclohexane	7.09	6.63	7.16	3.8	1.3	5.0		617
		$CDCl_3$	7.24	6.80	7.35	3.60	1.20	5.45		716
	Li	Ether	7.52	7.18	7.66	2.8	0.5	4.3		618
	NH_2	Cyclohexane	6.01	6.51	6.30	3.6	1.3	5.4		617
	NO_2	Cyclohexane	7.78	6.93	7.45	4.0	1.7	5.1		617
		$CDCl_3$	7.93	7.08	7.56	4.00	1.60	5.30		716
	SH	Cyclohexane	6.96	6.75	7.08	3.7	1.8	4.9		617
					$J_{3\text{-}SH} = 1.4$, $J_{5\text{-}SH} = 0.9$					
	SO_2Cl	Cyclohexane	7.69	7.02	7.60	3.8	1.4	5.1		617
5	CH_3	Neat	6.63	6.75	6.90	3.46	1.16	5.20	2.41	634
					$J_{CH_3\text{-}3} = 1.00$, $J_{CH_3\text{-}4} = 0.24$					
		Acetone-d_6	6.51	6.65	6.76	3.0	1.3	5.0	2.12	687
		$CDCl_3$	6.76	6.90	7.08					665
		TMS	6.63	6.75	6.89				2.38	655
		$CDCl_3$	6.79	6.91	7.08	3.4	1.4	5.3	2.46	686
		Acetone-d_6	6.80	6.91	7.16	3.1	1.2	4.8	2.45	"
		$CDCl_3$	6.75	6.89	7.07	3.35	1.20	5.15	2.50	716
			$J_{CH_3\text{-}3} = 1.10$, $J_{CH_3\text{-}4} = 0.30$, $J_{CH_3\text{-}5} = 0.15$							
	COCl	Cyclohexane	7.84	7.02	7.59	3.4	1.4	5.0		617
		CCl_4	7.87	7.17	7.84					673
	CN	Cyclohexane	7.43	6.96	7.43	4.5		4.5		617

TABLE 18. (*Continued*)

C_n	Substituent	Solvent	∂_3	∂_4	∂_5	J_{34}	J_{35}	J_{45}	∂_R	Ref.
	OCH_3	"	6.02	6.53	6.33	3.7	1.8	5.6	3.73	"
		$CDCl_3$	6.19	6.70	6.50	3.75	1.50	5.75	3.88	716
	CH_2OH	Acetone-d_6	6.91	6.88	7.21	3.40	1.11	5.14	4.67	651
	CHO	Cyclohexane	7.61	7.06	7.61	3.8		5.0	9.86	617
		CCl_4	7.70	7.17	7.68					673
		$CDCl_3$	7.79	7.22	7.77	3.75	1.15	4.90	9.95	716
						$J_{CHO-5} = 1.35$				
		Acetone-d_6	7.93	7.30	7.96	3.79	1.22	4.75	9.98	651
	COOH	"	7.80	7.15	7.78					651
		CCl_4	7.87	7.11	7.59					673
	SCN	Cyclohexane	7.26	6.91	7.43	3.7	1.4	5.2		617
	SCH_3	Acetone-d_6	7.07	6.96	7.40	3.60	1.26	5.36	2.45	651
	SO_2CH_3	Cyclohexane	7.78	7.16	7.78					613
6	CCH	"	7.11	6.80	7.03	3.5	1.4	5.1	3.03	617
	$COCH_3$	"	7.53	6.96	7.43	3.6	1.1	5.0	2.38	"
		CCl_4	7.61	7.06	7.56					673
		$CDCl_3$	7.70	7.13	7.63	3.80	1.20	4.90	2.57	716
		Acetone-d_6	7.80	7.17	7.80	3.74	1.09	5.07	2.52	651
	CO_2CH_3	"	7.74	7.09	7.66	3.69	1.20	4.97	3.85	"
		$CDCl_3$	7.80	7.10	7.55	3.70	1.30	5.00	3.89	716
		Cyclohexane	7.66	6.91	7.35	3.6	1.3	5.0	3.75	617
	OC_2H_5	"	6.04	6.53	6.34	3.6	1.7	5.8		"
	C_2H_5	C_6D_6	6.60	6.74	6.82	3.2	1.3	4.9	2.59	687
					$J_{CH_2-3} = 0.6$, $J_{CH_2-4} = 0.2$					
	$N(CH_3)_2$	CCl_4	5.75	6.62	6.33					694
		$CDCl_3$	5.87	6.76	6.44					"
7	COC_2H_6	Cyclohexane	7.52	6.95	7.43	3.6	1.2	5.0		617
	C_3H_7	C_6D_6	6.61	6.74	6.84	3.2	1.3	4.9	2.57	687
	COCHCH-pyrollidine	CCl_4	7.51	7.00	7.37					673

8	CH_3									
	$Cr(CO)_3$	$CDCl_3$	5.36	5.53	5.22	2.1		3.4	2.28	686
		Acetone-d_6	5.76	5.76	5.76				2.30	"
		C_6D_6	4.26	4.44	3.89				1.39	687
	2-thienyl	Cyclohexane	7.03	6.85	6.99	3.4	1.6	5.0		617
	Morpholine	$CDCl_3$	6.08	6.76	6.56					694
	Pyrollidine	"	5.71	6.76	6.33					"
		CCl_4	5.56	6.60	6.19					"
		DMSO-d_6	5.68	6.69	6.39					"
	$OC(CH_3)_3$	Cyclohexane	6.19	6.58	6.50	3.5	1.7	6.0	1.30	617
	$C(CH_3)_3$	C_6D_6	6.67	6.73	6.84	3.4	1.45	4.7	1.25	687
	$N(C_2H_5)_2$	$CDCl_3$	5.87	6.74	6.41					694
9	CO-2-thienyl	CCl_4	7.86	7.14	7.67					673
	CO-2-furyl	"	8.10	7.09	7.60					"
	CS-2-Thienyl	"	7.59	7.08	7.64					"
	$C_2H_5Cr(CO)_3$	C_6D_6	4.45	4.58	4.09				0.70	687
	CO-*t*-Bu	CCl_4	7.72	7.06	7.51					673
	CS-*t*-Bu	"	7.50	7.05	7.50					"
	Piperidine	$CDCl_3$	6.06	6.75	6.51					694
		CCl_4	5.95	6.63	6.40					"
		DMSO-d_6	7.07	6.72	6.61					"
10	Phenyl	C_6D_6	7.08	6.77	6.88	3.5	1.4	5.1		687
	C_3H_7									
	$Cr(CO)_3$	"	4.48	4.59	4.09				0.60	694
11	CO-2'-Br-phenyl	—	7.26	7.03	7.66					671
	CO-4'-Br-phenyl	CCl_4	7.56	7.09	7.62					673
	CS-4'-Br-phenyl	"	7.35	7.11	7.75					"
	CO-2'-Cl-phenyl	—	7.31	7.03	7.70					671
	CO-4'-Cl-phenyl	CCl_4	7.57	7.12	7.66					673
	CS-4'-Cl-phenyl	"	7.34	7.13	7.74					"
	CO-2'-F-phenyl		7.45	7.05	7.64					671
	CO-4'-F-phenyl	CCl_4	7.58	7.13	7.66					673

TABLE 18. (*Continued*)

C_n	Substituent	Solvent	∂_3	∂_4	∂_5	J_{34}	J_{35}	J_{45}	∂_R	Ref.
	CS-4′-F-phenyl	„	7.32	7.09	7.71					„
	CO-2′-I-phenyl	—	7.31	7.06	7.69					671
	CS-4′-I-phenyl	CCl_4	7.34	7.10	7.72					673
	CO-phenyl	„	7.56	7.07	7.69					671
	CS-phenyl	„	7.31	7.05	7.64					673
		„	7.32	6.99	7.61					670
	Benzyl	C_6D_6	6.60	6.70	6.80	3.4	1.3	5.50	3.86	687
	t-Bu-$Cr(CO)_3$	„	4.52	4.52	4.12				0.87	„
12	CO-4′-Me-phenyl	CCl_4	7.51	7.03	7.55					670
		„	7.51	7.04	7.57					673
	CO-2′-Me-phenyl	—	7.32	7.01	7.60					671
		CCl_4	7.30	6.99	7.58					670
	CS-4′-OMe-phenyl	„	7.37	7.10	7.69					673
	CO-4′-OMe-phenyl	„	7.53	7.04	7.57					„
	CO-2′-OMe-phenyl	—	7.32	6.98	7.57					671
	CS-2′-Me-phenyl	CCl_4	7.07	6.96	7.61					670
	CS-4′-Me-phenyl	„	7.32	7.06	7.64					„
	1′-Pyrazine-4′-2-thienyl	$CDCl_3$	6.19	6.80	6.63					694
13	Phenyl									
	$Cr(CO)_3$	C_6D_6	6.79	6.61	6.75					687
	CO-2′,4′-Me-phenyl	CCl_4	7.32	6.99	7.56					670
	CS-2′,4′-Me-phenyl	CCl_4	7.07	6.92	7.60					670
14	Benzyl-$Cr(CO)_3$	C_6D_6	6.54	6.66	6.79				3.35	687
	CO-2′,4′,6′-Me-phenyl	CCl_4	7.22	6.98	7.57					670
	CS-2′,4′,6′-Me-phenyl	„	7.07	6.96	7.58					„
17	CO-2′,6′-Me-4′-*t*-Bu-phenyl	„	7.23	6.97	7.57					„
	CO-2′,4′-Me-6′-*t*-Bu-phenyl	„	7.16	6.96	7.53					„

TABLE 19. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 3-Substituted Thiophenes

C_n	Substituent	Solvent	δ_2	δ_4	δ_5	J_{24}	J_{25}	J_{45}	δ_R	Ref.
4	F	Cyclohexane	6.50	6.68	7.00	1.50	3.46	5.36		619
	Cl	$CDCl_3$	7.10	6.96	7.27	1.35	3.30	5.10		716
	Br	Ether	7.32	7.01	7.32					618
		Cyclohexane	7.04	6.88	7.05	1.25	3.2	4.95		661
		$CDCl_3$	7.23	7.02	7.27	1.30	3.15	5.00		716
	I	"	7.40	7.10	7.19	1.20	3.05	5.00		716
		Cyclohexane	7.21	6.96	6.96	1.20	2.9	4.9		617
	NO_2	"	8.10	7.56	7.18	1.5	3.2	5.4		"
		$CDCl_3$	8.31	7.66	7.37	1.40	3.35	5.30		716
	SH	Cyclohexane	6.93	6.76	7.05	1.9	3.0	4.5		617
	NH_2	"	5.80	6.43	6.90	1.6	3.1	5.0		"
5	COCl	"	7.20	7.46	7.18	1.4	2.9	5.1		"
	CN	"	7.78	7.16	7.30	1.4	2.8	5.1		"
	SCN	"	7.40	7.00	7.20	1.5	3.0	5.0		"
	CHO	"	7.94	7.41	7.18	1.4	2.7	5.2		"
		$CDCl_3$	8.12	7.55	7.38	1.20	2.85	5.10	9.94	716
					$J_{4\text{-CHO}} = 0.36$, $J_{5\text{-CHO}} = 0.85$					
	OCH_3	"	6.24	6.74	7.17	1.60	3.10	5.20	3.81	"
		Cyclohexane	6.05	6.58	6.95	1.7	3.1	5.1	3.68	617
	SO_2CH_3	"	8.16	7.43	7.56					613
	CH_3	Neat	6.75	6.77	7.05	1.28	2.94	4.88	2.21	634
		TMS	6.71	6.75	7.03				2.17	655
		C_6D_6	6.54	6.62	6.86	1.4	2.6	4.6	1.98	687
							$J_{CH_3\text{-}2} = 1.10$, $J_{CH_3\text{-}4} =$		0.35	
		Acetone-d_6	7.01	6.93	7.31	0.9	3.1	4.8	2.24	686
		$CDCl_3$	6.91	6.91	7.22	1.2	3.4	4.8	2.27	"
		"	6.93	6.89	7.23					665
		"	6.88	6.89	7.20	1.25	2.85	4.90	2.27	716
						$J_{CH_3\text{-}2} = 1.05$, $J_{CH_3\text{-}4} = 0.40$, $J_{CH_3\text{-}5} = 0.40$				

TABLE 19. (*Continued*)

C_n	Substituent	Solvent	∂_2	∂_4	∂_5	J_{24}	J_{25}	J_{45}	∂_R	Ref.
6	$COCH_3$	Cyclohexane	7.83	7.43	7.13	1.3	2.8	5.1		617
		$CDCl_3$	8.04	7.54	7.31	1.25	2.90	5.00	2.54	716
	CO_2CH_3	Cyclohexane	7.94	7.43	7.10	1.3	2.9	5.1	3.73	617
		$CDCl_3$	8.10	7.53	7.30	1.15	3.05	5.05	3.87	716
7	COC_2H_5	Cyclohexane	7.85	7.43	7.12					617
8	CH_3									
	$Cr(CO)_3$	$CDCl_3$	5.12	5.56	5.40			3.8	2.27	686
		Acetone-d_6	5.76	5.76	5.92				2.32	"
		C_6D_6	4.02	4.54	4.22				1.61	687
	Morpholine	CCl_4	6.00	6.67	7.07					694
	Pyrollidine	$CDCl_3$	5.69	6.60	7.09					"
		CCl_4	5.55	6.49	7.00					"
	O-*t*-Bu	Cyclohexane	6.37	6.60	6.93	1.6	3.0	5.2	1.25	617
	t-Bu	C_6D_6	6.63	6.79	6.87	1.5	2.6	4.7	1.15	687
9	Piperidine	$CDCl_3$	6.10	6.79	7.13					694
		CCl_4	5.96	6.70	7.04					"
11	*t*-Bu									
	$Cr(CO)_3$	C_6D_6	4.05	4.70	3.98				0.97	687

TABLE 20. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 2,3-Disubstituted Thiophenes

C_n	R_2	R_3	Solvent	δ_4	δ_5	J_{45}	δ_{R_2}	δ_{R_3}	Ref.
4	D	Br	Cyclohexane	6.88	7.06	5.0			615
	Li	Br	Ether	7.04	7.59	4.4			618
	Br	Br	"	6.92	7.38	5.8			"
			Cyclohexane	6.73	7.03	5.70			616
			"	6.76	7.05	5.75			661
	D	D	"	6.94	7.10				583
	F	F	"	6.51	6.39	6.55			658
			C_6H_6	6.10	5.78	6.58			"
	NO_2	I	Acetone	7.39	7.92	5.6			630
	SH	Br	Cyclohexane	6.83	7.03	5.40			616
5	CHO	Br	"	7.23	7.83	5.10	9.93		606
				$J_{CHO-5} = 1.35$					
			$CDCl_3$	7.00	7.60	5.15	9.82		666
				$J_{CHO-5} = 1.4$					
	Br	CHO	Cyclohexane	7.23	7.13	5.75		9.83	616
				$J_{CHO-5} = 0.70$					
			$CDCl_3$	7.29	7.23	5.3		9.88	666
				$J_{CHO-5} = 0.9$					
	COOH	Br	Acetone	7.27	7.87	5.20		9.77	616
	CH_2Br	NO_2	Cyclohexane	7.52	7.21	5.5	4.97		676
	NO_2	CH_2Br	"	7.11	7.41	5.1		4.79	"
	Br	CH_3	"	6.53	6.91	5.6			611
			"	6.63	6.93	5.50		2.13	616
	CH_3	Br	"	6.73	6.83	5.45		2.23	"
	SCH_3	Br	"	6.83	7.03	5.55	2.33		"
	SO_2Cl	CH_3	"	7.03	7.73	5.5			611
			"	7.01	7.68	5.2		2.61	678
	CH_3	SO_2Cl	"	7.28	7.08	5.3	2.73		"
	CH_3	D	"	6.73	6.88	5.3	2.39		615

TABLE 20. (*Continued*)

C_n	R_2	R_3	Solvent	δ_4	δ_5	J_{45}	δ_{R_2}	δ_{R_3}	Ref.
	D	CH_3	„	6.74	7.01	4.9		2.20	„
			$CDCl_3$	6.93	7.22				686
	SCH_3	D	Cyclohexane	6.79	7.11	5.3	2.33		615
	I	CH_3	CCl_4	6.64	7.25	5.4		2.22	662
	CH_3	I	„	6.89	6.98	5.1	2.42		„
	CH_3	NO_2	*n*-Hexane	7.53	7.13	5.80	2.73		616
	CH_2OH	NO_2	„	7.56	7.36	5.4			676
	CH_3	OH	CS_2	6.43	6.72	5.5	2.15	6.21	701
	SH	CH_3	Cyclohexane	6.73	6.93	5.40	2.93	2.13	616
				$J_{SH-5} = 1.0$, $J_{CH_3-SH} = 1.30$					
	CH_3	SH	„	6.83	6.73	5.25			„
	SCH_3	SH	„	6.73	7.13	5.45	2.23	4.03	„
6	CN	CN		7.40	7.80	5.0			667
	NO_2	CH_2SCN	„	7.27	7.86	5.5		4.67	676
	CH_2SCN	NO_2	„	7.62	7.62		4.89		„
	COOH	CHO	Acetone	7.57	7.81	5.20	9.71	10.61	708
				$J_{CHO-4} = 0.30$, $J_{CHO-5} = 0.70$					
	CHO	COOH	„	7.63	7.97	5.10	10.61	10.29	„
				$J_{CHO-5} = 1.5$					
	Br	CO_2CH_3	$CDCl_3$	7.36	7.21	5.75		3.88	717
	CO_2CH_3	Br	„	7.09	7.45	5.25	3.90		716
	Cl	CO_2CH_3	„	7.35	7.05	5.85			717
	CO_2CH_3	Cl	„	7.01	7.46	5.25	3.90		716
	$COCH_3$	I	DMSO	7.05	7.56	5.0			630
	I	CO_2CH_3	$CDCl_3$	7.32	7.40	5.60		3.88	717
	CO_2CH_3	I	„	7.22	7.43	5.10	3.90		716
	NO_2	CO_2CH_3	„	7.18	7.50	5.45		3.96	717
	CO_2CH_3	NO_2	„	7.59	7.54	5.40	3.94		716

CH_3		CHO	Cyclohexane	7.23	6.93	5.40	2.63	9.93	616
				$J_{CHO-5} = 0.50$					
CHO		CH_3	„	6.83	7.53	4.90	9.93	2.53	„
				$J_{CHO-5} = 1.05$					
SCH_3		CHO	Acetone	7.47	7.47	5.43	2.67	10.07	„
				$J_{CHO-5} = 0.40$					
$COCH_3$		OH	$CDCl_3$	6.75	7.40	5.3		11.50	703
			CCl_4	6.66	7.30	5.3		11.37	„
CO_2CH_3		OH	$CDCl_3$	6.72	7.35	5.4		9.59	„
—CH_2SCH_2—			CCl_4	6.61	7.14				669
CH_3		CH_3	C_6D_6	6.53	6.69	5.0	2.02	1.87	687
				$J_{2-CH_3-5} = 1.5, J_{3-CH_3-4} = 0.35$					
			Cyclohexane	6.63	6.73	5.30	2.23	2.03	616
			„	6.51	6.71	5.2			611
			$CDCl_3$	6.77	6.97				665
			CCl_4	6.63	7.73				669
7	CHO		CO_2CH_3	$CDCl_3$	7.58	7.64	5.10	10.62	3.96	717
					$J_{CHO-5} = 1.15$					
CO_2CH_3		CHO	Acetone	7.53	7.78	5.25	3.95	10.55	707
			$CDCl_3$	7.60	7.48	5.20	3.97	10.65	716
				$J_{CHO-4} = 0.40, J_{CHO-5} = 0.80$					
CH_2OCOCH_3		NO_2	CCl_4	7.53	7.24	5.8			626
SCH_3		$COCH_3$	„	6.96	7.27	5.5	2.50	2.39	722
CO_2CH_3		CH_3	$CDCl_3$	6.90	7.36	5.00	3.85	2.55	716
				$J_{CH_3-4} = 0.40, J_{CH_3-5} = 0.40$					
CH_3		CO_2CH_3	„	7.37	6.97	5.40	2.74	3.84	717
OCH_3		$COCH_3$	CCl_4	7.08	6.40	6.0	4.04	2.05	722
CO_2CH_3		OCH_3	Cyclohexane	6.73	7.13	5.05			616
			$CDCl_3$	6.86	7.41	5.55	3.83	3.97	716
OCH_3		CO_2CH_3	„	7.18	6.48	6.00	4.06	3.83	717
$CO_2C_2H_5$		OH	„	6.71	7.34	5.3		9.65	703
—$(CH_2)_3$—			CCl_4	6.71	7.06				669
—$(CH_2)_2SCH_2$—			„	6.70	6.98				„

TABLE 20. (*Continued*)

C_n	R_2	R_3	Solvent	∂_4	∂_5	J_{45}	∂_{R_2}	∂_{R_3}	Ref.
8	D	CH_3							
	$Cr(CO)_3$		$CDCl_3$	5.56	5.40				686
	CO_2CH_3	$COCH_3$	„	7.47	7.14	5.10	3.90	2.59	716
	$COCH_3$	CO_2CH_3	„	7.35	7.46	5.10	2.61	3.91	717
	CO_2CH_3	CO_2CH_3	„	7.45	7.28	5.15	3.91	3.89	716
	$—CH_2CH(CH_3)CH_2—$		CCl_4	6.66	7.05				669
	$—CH_2CH(CH_3)SCH_2—$		„	6.65	6.90				„
	$C(CH_3)_3$	OH	CS_2	6.45	6.65	5.5	1.32	6.37	701
	CH_2SCH_3	CH_2SCH_3	CCl_4	6.86	7.01				669
9	CH_3	CH_3							
	$Cr(CO)_3$		C_6D_6	4.56	4.06	1.44	1.53		687
	$—(CH_2)_2S(CH_2)_2—$		CCl_4	6.66	6.83				669
	Br	$NHCO_2$-*t*-Bu	„	7.19	7.63	5.8		1.54	631
	CHO	$Se(CH_2)_3CH_3$	„	7.15	7.80	5.0	9.95	2.98	724
				$J_{CHO-5} = 1.1$					
	$—(CH_2)_5—$		„	6.68	6.80				669
	$—(CH_2)_2CH(CH_3)CH_2—$		„	6.58	6.90				„
	$—(CH_2)_2CH(CH_3)SCH_2—$		„	6.60	6.77				„
10	Br	$NHCO_2CH_2$-*t*-Bu	„	7.13	7.54	6.0		3.83	631
	Cl	„	„	6.99	7.57	6.0		3.84	„
	I	„	„	7.38	7.51	5.8		3.88	„
	NO_2	„	„	7.37	7.86	6.0		3.88	„
12	$COCH_3$	„	„	7.33	7.89	5.5	2.38	3.83	„
16	NN-*p*-NO_2Ph	„	„	7.50	7.85	6.0		3.94	„

TABLE 21. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 2,4-Disubstituted Thiophenes

C_n	R_2	R_4	Solvent	δ_3	δ_5	J_{35}	δ_{R_2}	δ_{R_4}	Ref.
4	D	Br	Cyclohexane	6.88	7.04	1.2			615
	F	Br	„	6.33	6.46	1.98			659
	Br	F	„	6.71	6.46	1.90			„
	Li	Br	Ether	7.27	7.56				618
	Br	Br	„	7.02	7.34	1.7			„
			Cyclohexane	6.83	6.93	1.65			616
			„	6.86	6.97	1.65			661
	Cl	F	„	6.59	6.31	1.99			659
	F	Cl	„	6.28	6.29	2.03			„
	SO_2Cl	NO_2	„	8.43	9.03	1.70			616
	SO_2Cl	SO_2Cl	„	8.08	8.46				611
	D	D	„	6.92	7.07				583
	F	I	„	6.37	6.63	1.85			„
	NO_2	F	„	7.86	7.44	2.28			„
	F	F	„	6.18	5.86	2.29			658
			Benzene	6.02	5.63	2.32			„
	NO_2	I	Acetone	8.03	8.08	1.7			630
	SH	Br	Cyclohexane	6.83	7.03	1.50	3.53		616
5	CN	F	Acetone	7.66	7.47	1.78			659
			Cyclohexane	7.22	6.90	1.72			„
	F	CN	„	6.65	7.34	1.85			„
	CN	NO_2	Acetone	8.47	8.97	1.55			616
	CHO	Br	$CDCl_3$	7.58	7.61	1.4	9.83		666
	Br	CHO	„	7.40	7.93	1.45		9.72	„
	COOH	Br	Acetone	7.77	7.77	1.55			616
	F	CHO	Cyclohexane	6.79	7.52	1.81		9.62	659
	CHO	F	„	7.44	7.11	1.73	9.75		„
	F	COOH	Acetone	6.92	7.70	1.88			„
	COOH	F	„	7.54	7.31	1.84			„
	CHO	NO_2	„	8.57	8.97	1.55	10.07		616
	NO_2	CHO	„	8.37	8.87	1.70	9.97		„

TABLE 21. (*Continued*)

C_n	R_2	R_4	Solvent	∂_3	∂_5	J_{35}	∂_{R_2}	∂_{R_4}	Ref.
	CHNOH (anti)	F	„	7.23	7.10	1.80	7.69		659
	F	CHNOH (syn)	„	6.82	7.02	1.88		7.99	„
		(anti)	„	7.11	7.51	1.88		7.25	„
	SO_2CH_3	Br	„	8.07	7.77	1.60	3.37		616
	SCH_3	Br	Cyclohexane	6.83	7.03	1.50	2.33		„
	SO_2Cl	CH_3	„	7.61	7.41	1.8	2.33		678
	CH_3	SO_2Cl	„	7.08	7.86	1.5	2.53		„
	SCH_3	D	„	6.93	7.09		2.33		615
	F	SO_2CH_3	Acetone	7.02	7.72	2.00		3.14	659
	SO_2CH_3	F	„	7.61	7.50	1.87	3.26		„
	CH_3	F	Cyclohexane	6.36	6.21	1.70	2.28		„
	F	CH_3	„	6.12	6.02	1.98		2.05	„
	SCH_3	F	„	6.70	6.48	1.75	2.36		„
	F	SCH_3	„	6.28	6.13	2.02			„
	I	CH_3	CCl_4	6.94	6.83	1.5		2.24	662
	CH_3	I	„	6.68	7.06	1.25	2.49		„
	SCH_3	SH	Cyclohexane	6.83	6.93	1.45	2.33	3.13	616
6	CN	CN		7.80	8.16	1.0			667
	COOH	CHO	Acetone	8.10	8.69	1.40	8.34	9.96	708
	CHO	COOH	„	8.29	8.66	1.40	10.02	6.51	„
	Br	CO_2CH_3	$CDCl_3$	7.47	7.98	1.55		3.85	717
	CO_2CH_3	Br	„	7.68	7.44	1.50	3.89		716
			Cyclohexane	7.43	7.23	1.40	3.83		616
	Cl	CO_2CH_3	$CDCl_3$	7.33	7.86	1.60		3.85	717
	CO_2CH_3	Cl	„	7.63	7.32	1.60	3.89		716
	$COCH_3$	F	Cyclohexane	7.33	6.97	1.69	2.41		659
	F	$COCH_3$	„	6.79	7.42	1.88		2.33	„
	F	CO_2CH_3	„	6.78	7.38	1.85			„
	CO_2CH_3	F	„	7.36	6.87	1.83			„
	$COCH_3$	I	DMSO	7.66	7.84	1.2			630

	I	CO_2CH_3	$CDCl_3$	7.65	8.08	1.40		3.85	717
	CO_2CH_3	I	„	7.76	7.59	1.40	3.89		716
	NO_2	CO_2CH_3	„	8.28	8.24	1.80		3.92	717
	CO_2CH_3	NO_2	„	8.26	8.45	1.60	3.95		716
			Acetone	8.17	8.87	1.70	3.97		616
	CHO	CH_3	Cyclohexane	7.53	7.43	1.45	9.93	2.23	
		$J_{CHO-5} = 1.25$, $J_{CH_3-5} = 1.00$, $J_{CH_3-4} = 0.50$							
	COOH	CH_3	Acetone	7.67	7.37	1.45	10.57	2.27	„
	SCH_3	CHO	Cyclohexane	7.33	7.83	1.25	2.43	9.73	„
	SCH_3	COOH	Acetone	7.47	8.27	1.35	2.57	10.27	„
	CH_3	CH_3	C_6D_6	6.34	6.42	1.5	2.16	1.99	687
			$J_{2-CH_3-3} = 1.0$, $J_{2-CH_3-5} = 0.2$						
	CH_3	CH_3	Cyclohexane	6.36	6.36				611
			$CDCl_3$	6.57	6.64				665
			C_6D_6	6.34	6.42	1.5	2.16	1.99	687
			$J_{2-CH_3-3} = 1.0$, $J_{2-CH_3-5} = 0.2$						
			$J_{4-CH_3-3} = 0.35$, $J_{4-CH_3-5} = 1.2$						
7	CHO	CO_2CH_3	C_6D_6	8.16	8.44	1.35	9.94	3.91	717
			$J_{CHO-3} = 0.20$, $J_{CHO-5} = 1.40$						
	CO_2CH_3	CHO	$CDCl_3$	8.17	8.27	1.40	3.92	9.91	716
	CH_2OCOCH_3	NO_2	CCl_4	7.56	8.21	1.6			626
	CO_2CH_3	CH_3	$CDCl_3$	7.60	7.12	1.55	3.86	2.27	716
	CH_3	CO_2CH_3	„	7.17	7.85	1.35	2.47	3.83	717
	SCH_3	CO_2CH_3	Cyclohexane	7.33	7.93	1.50	2.43	3.73	616
	CO_2CH_3	OCH_3	$CDCl_3$	7.42	6.50	1.85	3.86	3.80	716
	OCH_3	CO_2CH_3	„	6.59	7.37	1.65	3.88	3.83	717
8	CO_2CH_3	$COCH_3$	„	8.17	8.20	1.45	3.91	2.54	716
	$COCH_3$	CO_2CH_3	„	8.06	8.32	1.30	2.58	3.89	717
	CO_2CH_3	CO_2CH_3	„	8.16	8.25	1.40	3.90	3.88	716
9	CH_3	CH_3							
	CHO	$Se(CH_2)_3CH_3$	$CDCl_3$	7.68	7.62	1.4	9.82	2.53	724
10	F	C_6H_5	Cyclohexane	6.61	6.53	2.03			659
	C_6H_5	F	„	6.83	6.38	1.65			„

TABLE 22. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants of 2,5-Disubstituted Thiophenes

C_n	R_2	R_5	Solvent	∂_3	∂_4	∂_{34}	∂_{R_2}	∂_{R_5}	Ref.
4	Br	D	Cyclohexane	6.91	6.68	3.7			615
	F	Br	„	6.10	6.56	4.15			659
	Li	Br	Ether	7.29	7.06	2.6			618
	NO_2	Br	Cyclohexane	7.53	6.93	4.35			616
	Br	Br	„	6.61	6.61				612
			Ether	6.88	6.88				618
			Neat	6.69	6.69	3.7			661
	F	Cl	Cyclohexane	6.09	6.38	4.20			659
	NO_2	SO_2Cl	„	8.13	8.03	4.35			616
	SO_2Cl	SO_2Cl	„	7.88	7.88				611
	Cl	Cl	„	6.53	6.53				„
	D	D	„	6.80	6.80				583
			$CDCl_3$	7.10	7.10				686
	F	I	Cyclohexane	6.05	6.79	4.06			659
	F	NO_2	„	6.64	7.71	4.72			„
	F	F	„	5.91	5.91				658
			Benzene	5.58	5.58				„
	I	I	Cyclohexane	6.78	6.78				611
	NO_2	NO_2	„	8.36	8.36				„
	NH_2	NO_2	CD_3OD	6.05	7.75	6.0			620
5	COCl	NO_2	$CDCl_3$	8.0	8.0				„
	F	CN	Cyclohexane	6.52	7.28	4.30			659
	CON_3	NO_2	$CDCl_3$	7.75	7.95	5.0			620
	CHO	Br	„	7.48	7.15	4.0	9.75		666
			Cyclohexane	7.53	7.13	4.05	9.73		616
	COOH	Br	Acetone	7.67	7.27	3.95	9.67		„
	F	CHO	Cyclohexane	6.59	7.48	4.25	9.69		659
				$J_{CHO-3} = 0.21$, $J_{CHO-4} = -0.15$					
	F	COOH	Acetone	6.70	7.52	4.28			„

	CHO	NO_2	„	8.07	8.17	4.30	10.07		616
	COOH	NO_2	„	7.77	8.07	4.30	11.17		„
	CH_2Cl	Br	Cyclohexane	6.57	6.72	3.7	4.52		676
	CH_2Br	Br	„	6.68	6.68		4.49		„
	CH_2Cl	NO_2	„	7.08	7.73	4.15	4.84		„
	F	CHNOH syn	Acetone	6.52	6.91	4.11		8.15	659
	NHCHO	NO_2	CD_3OD	6.7	7.9	6.0			620
	Br	CH_3	Cyclohexane	6.63	6.33	3.70		2.23	616
	CH_3	SO_2Cl	„	6.83	7.61	4.1	2.58		678
	CH_3	Cl	„	6.34	6.51	3.65			656
	CH_3	D	„	6.59	6.71	3.5	2.40		615
	SCH_3	D	„	5.93	6.78	3.5	2.33		615
	F	OCH_3	„	5.89	5.61	4.26		3.67	659
	F	SO_2CH_3	Acetone	6.80	7.50	4.30		3.23	„
	F	CH_3	Cyclohexane	6.05	6.16	3.83		2.22	„
	F	SCH_3	„	6.19	6.67	4.02		2.32	„
	CH_3	I	„	6.34	6.85	3.60			656
			CCl_4	6.38	6.93	3.75	2.46		662
	NO_2	CH_3	Cyclohexane	7.73	6.83	3.90		2.53	616
	CH_2OH	NO_2	„	7.07	7.83	4.1	5.03		676
	SH	CH_3	„	6.73	6.43	3.50	3.43	2.23	616
		$J_{CH_3-4} = 1.05$, $J_{SH-3} = 1.60$, $J_{CH_3-SH} = 1.1$							
	SH	SCH_3	„	6.73	6.73	3.60	3.33	2.33	„
6	CN	CN	Neat	7.61	7.61				667
	CH_2NCS	Br	Cyclohexane	6.64	6.81	3.8	4.64		676
	CH_2CN	I	„	6.63	7.01	3.7	3.78		„
	CH_2SCN	NO_2	„	7.24	7.88	4.1	4.58		„
	CHO	COOH	Acetone	7.88	7.99	4.00	10.05	9.26	708
	CO_2CH_3	Br	$CDCl_3$	7.54	7.06	4.00	3.87		716
	CO_2CH_3	Cl	„	7.58	6.92	4.05	3.87		„
	F	$COCH_3$	Cyclohexane	6.50	7.40	4.29		2.39	659
	F	CO_2CH_3	„	6.40	7.34	4.23			„

TABLE 22. (*Continued*)

C_n	R_2	R_5	Solvent	∂_3	∂_4	∂_{34}	∂_{R_2}	∂_{R_5}	Ref.
	CO_2CH_3	I	$CDCl_3$	7.43	7.25	3.90	3.87		716
	CO_2CH_3	NO_2	„	7.70	7.87	4.30	3.95		„
	CH_3	CN	Cyclohexane	6.69	7.25	3.70			656
	CH_3	SCN	„	6.62	7.07	3.60			„
	$NHCOCH_3$	NO_2	CD_3OD	6.72	7.95	5.4			620
	CHO	CH_3	Cyclohexane	7.63	6.93	3.75	9.83	2.53	616
	CHO	$SeCH_3$	CCl_4	7.53	7.05	4.0	9.65	2.40	724
	CHO	OCH_3	Cyclohexane	7.53	6.33	4.25	9.63	3.93	616
	COOH	OCH_3	Acetone	7.57	6.47	4.15	7.97	4.07	„
	CH_2OCH_3	Br	Cyclohexane	6.53	6.76	3.7	4.36		676
	F	CH_2CH_3	„	6.06	6.20	3.86		2.61	659
	OCH_3	CH_3	„	5.83	6.23	3.70	3.63	2.23	616
			C_6D_6	5.83	6.19	3.7	3.32	2.07	687
	CH_3	CH_3	„	6.34	6.34		2.14	2.14	„
			Neat	6.39	6.39	3.46	2.32	2.32	634
			TMS	6.39	6.39		2.30	2.30	655
			$CDCl_3$	6.53	6.53				665
	SCH_3	CH_3	Cyclohexane	6.83	6.43	3.45	2.33	2.33	616
7	D	D							
	$Cr(CO)_3$		$CDCl_3$	5.59	5.59				686
	CO_2CH_3	CHO	„	7.83	7.73	3.90	3.94	9.97	716
	CH_2OCOCH_3	Br	Cyclohexane	6.71	6.83	3.9	5.06		676
	CH_2OCOCH_3	NO_2	„	6.96	7.67	3.9	5.14		„
			CCl_4	7.02	7.72	4.0			626
	CHO	$NHCOCH_3$	Acetone	7.77	6.87	4.25	9.87		616
	$CO_2C_2H_5$	NO_2	„	7.77	8.07	4.35			„
	CH_3	$COCH_3$	Cyclohexane	6.65	7.35	3.70			656
	$COCH_3$	$SeCH_3$	CCl_4	7.35	6.96	4.0	2.37	2.37	724
	SCH_3	$COCH_3$	„	7.38	6.80	4.2	2.52	2.36	722

	CH_3	CO_2CH_3	Cyclohexane	6.61	7.45	3.65			656
			$CDCl_3$	7.61	6.75	3.70	2.51	3.85	716
	OCH_3	$COCH_3$	CCl_4	7.33	6.16	4.5	3.91	2.32	722
	CO_2CH_3	OCH_3	$CDCl_3$	7.53	6.22	4.20	3.83	3.94	716
	F	C_3H_7	Cyclohexane	6.07	6.22	3.85			659
8	CH_2SCN	CH_2SCN	„	6.93	6.93		4.29	4.29	676
	CO_2CH_3	$COCH_3$	$CDCl_3$	7.76	7.63	4.00	3.92	2.59	716
	CO_2CH_3	CO_2CH_3	„	7.73	7.73		3.91	3.91	„
	$COCH_3$	C_2H_5	CCl_4	7.41	6.75			2.87	673
	F	C_4H_9	Cyclohexane	6.06	6.21	3.83			659
	F	$C(CH_3)_3$	„	6.05	6.27	3.94			„
	$N(CH_3)_2$	$COCH_3$	CCl_4	5.72	7.26	4.0	3.00	2.25	722
9	CH_3	CH_3							
	$Cr(CO)_3$		C_6D_6	4.42	4.42		1.49	1.49	687
	CH_3	OCH_3							
	$Cr(CO)_3$		„	4.31	4.24		1.38	2.89	„
	$NHCO_2C(CH_3)_3$	NO_2	$CDCl_3$	6.4	7.8	6.0			620
	COOH	$C(CH_3)_3$	Acetone	7.67	7.07	3.85	9.97	1.47	616
10	F	C_6H_5	Cyclohexane	6.25	6.69	4.09			659
11	$CO(CH_3)_3$	C_2H_5	CCl_4	7.52	6.72			2.86	673
	$CS(CH_3)_3$	C_2H_5	„	7.39	6.75			2.78	„
12	$C(CH_3)_3$	$C(CH_3)_3$	„	6.45	6.45		1.33	1.33	645
			C_6D_6	6.44	6.44		1.26	1.26	687
13	CO–*o*–Br–C_6H_4	C_2H_5	Neat	7.09	6.72				671
	CO–*p*–Br–C_6H_4	C_2H_5	CCl_4	7.33	6.80			2.90	673
	CS–*p*–Br–C_6H_4	C_2H_5	„	7.14	6.82			2.84	„
	CO–*o*–Cl–C_6H_4	C_2H_5	Neat	7.11	6.72				671
	CS–*p*–Cl–C_6H_4	C_2H_5	„	7.13	6.80			2.85	„
	CO–*o*–F–C_6H_4	C_2H_5	Neat	7.24	6.74				671
	CO–*p*–F–C_6H_4	C_2H_5	CCl_4	7.32	6.74			2.88	673
	CS–*p*–F–C_6H_4	C_2H_5	„	7.07	6.79			2.83	„

TABLE 22. (*Continued*)

C_n	R_2	R_5	Solvent	∂_3	∂_4	∂_{34}	∂_{R_2}	∂_{R_5}	Ref.
	CO–*o*-I–C_6H_4	C_2H_5	Neat	7.07	6.75				671
	CO–*p*-I–C_6H_4	C_2H_5	CCl_4	7.35	6.77			2.90	673
	COC_6H_5	C_2H_5	„	7.36	6.76			2.90	„
	CSC_6H_5	C_2H_5	„	7.10	6.77			2.82	„
14	CO–*p*-CH_3–C_6H_4	C_2H_5	„	7.33	6.73			2.88	„
	CO–*o*-CH_3–C_6H_4	C_2H_5	Neat	7.14	6.72				671
	CO–*o*-OCH_3–C_6H_4	C_2H_5	„	7.12	6.89				„
	CO–*p*-OCH_3–C_6H_4	C_2H_5	CCl_4	7.35	6.74			2.86	673
	CS–*p*-OCH_3–C_6H_4	C_2H_5	„	7.22	6.85			2.84	„
	CS–*p*-CH_3–C_6H_4	C_2H_5	„	7.14	6.77			2.82	„
	$C(CH_3)_3Cr(CO)_3$	$C(CH_3)_3$	C_6D_6	4.65	4.65		0.88	0.88	687

TABLE 23. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 3,4-Disubstituted Thiophenes

C_n	R_3	R_4	Solvent	δ_2	δ_5	J_{25}	δ_{R_3}	δ_{R_4}	Ref.
4	Br	D	Cyclohexane	7.05	7.05	—			615
	Li	Br	Ether	7.32	7.27	2.7			618
	Br	Br	Cyclohexane	6.98	6.98				612
			„	7.11	7.11				661
			Neat			3.45			„
			Ether	7.49	7.49				618
	D	D	Cyclohexane	7.04	7.04				583
	F	F	„	6.51	6.51	3.94			658
	SH	Br	„	7.03	7.13	3.40	3.43		616
					$J_{SH-2} = 0.65$				
5	CHO	Br	„	8.03	7.23	3.45	9.93		„
			$CDCl_3$	8.10	7.32	3.3	9.96		666
	COOH	Br	Acetone	8.47	7.67	3.50	9.67		616
	Br	CH_3	Cyclohexane	7.03	7.73	3.40		2.13	„
					$J_{CH_3-5} = 0.95$				
	CH_3	SO_2Cl	„	7.13	8.18	3.5	2.53		678
	CH_3	D	„	6.70	7.02	3.0	2.18		615
	SCH_3	D	„	6.82	7.12	3.0	2.31		„
	CH_3	I	CCl_4	6.84	7.31	3.4	2.25		662
	SH	CH_3	Cyclohexane	6.93	6.73	3.35	2.83	2.13	616
	SH	SCH_3	„	6.93	6.93	3.35	3.63	2.23	„
6	CN	CN		8.05	8.05				667
	CHO	COOH	Acetone	8.41	8.41		10.41	7.79	708
	CO_2CH_3	Br	Cyclohexane	7.93	7.13	3.65	3.73		616
			$CDCl_3$	8.11	7.31	3.60	3.88		717
	CO_2CH_3	Cl	„	8.12	7.18	3.70	3.88		„
	CO_2CH_3	I	„	8.07	7.50	3.45	3.88		„

TABLE 23. (*Continued*)

C_n	R_3	R_4	Solvent	∂_2	∂_5	J_{25}	∂_{R_3}	δ_{R_4}	Ref.
	CHO	CH_3	Cyclohexane	7.63	6.83	3.25	9.83	2.33	616
	CHO	$SeCH_3$	CCl_4	8.10	7.62	3.1	9.77	2.08	724
					$J_{Se-CH_3} = 12.8$, $J_{CHO-5} = 0.85$				
	CHO	SCH_3	Acetone	8.57	6.97	3.20	10.07	2.57	616
	OH	$COCH_3$	$CDCl_3$	6.33	7.90	3.30	9.80		703
			CCl_4	6.23	7.83		9.65		„
	COOH	SCH_3	Acetone	8.47	7.07	3.30			616
	$-CH_2SCH_2-$		CCl_4	6.98	6.98				669
	CH_3	CH_3	C_6D_6	6.49	6.49		1.86	1.86	687
			$CDCl_3$	6.88	6.88				665
7	CO_2CH_3	CHO	„	8.16	8.18	3.40	3.94	10.50	717
	CO_2CH_3	CH_3	„	8.06	6.91	3.40	3.84	2.46	„
	CO_2CH_3	OCH_3	„	8.01	6.28	3.60	3.85	3.89	„
	CO_2CH_3	SCH_3	Cyclohexane	8.03	6.53	3.45			616
	$-(CH_2)_3-$		CCl_4	6.65	6.65				669
8	CO_2CH_3	$COCH_3$	$CDCl_3$	7.89	7.68	3.20	3.88	2.53	717
	CO_2CH_3	CO_2CH_3	„	7.85	7.85	—	3.88	3.88	„

TABLE 24. ^{1}H NMR Chemical Shifts (ppm) of 2,3,4-Trisubstituted Thiophenes

C_n	R_2	R_3	R_4	Solvent	∂_5	∂_{R_2}	δ_{R_3}	∂_{R_4}	Ref.
4	Br	Br	Br	Cyclohexane	7.15				661
5	SO_2Cl	CH_3	SO_2Cl	„	8.63				611
	I	CH_3	I	CCl_4	7.52		2.33		662
	I	I	CH_3	„	7.12			2.36	„
	CH_3	I	I	„	7.32	2.56			„
6	CH_3	CH_3	I	„	7.09	2.42	2.13		„
7	CH_3	CH_3	CH_3	$CDCl_3$	6.65				665
8	CH_3	$CO_2C_2H_5$	OH	„	6.06			9.19	703
				CCl_4	5.92			8.90	„
10	$CH(CH_3)_2$	$CO_2C_2H_5$	OH	$CDCl_3$	6.13			9.32	„
11	$C(CH_3)_3$	$CO_2C_2H_5$	OH	„	6.12			9.47	„
13	C_6H_5	$CO_2C_2H_5$	OH	„	6.35			9.33	„

TABLE 25. ^{1}H NMR Chemical Shifts (ppm) of 2,3,5-Trisubstituted Thiophenes

C_n	R_2	R_3	R_5	Solvent	δ_4	δ_{R_2}	δ_{R_3}	δ_{R_5}	Ref.
4	Br	Br	Br	Cyclohexane	6.75				661
	F	Br	F	"	6.03				658
	F	F	Br	"	6.61				"
	F	F	F	Neat	6.13				"
5	Br	CHO	Br	$CDCl_3$	7.25		9.72		666
	CH_2Cl	NO_2	NO_2	Cyclohexane	8.43	5.42			676
	SO_2Cl	CH_3	SO_2Cl	"	7.86				611
	CH_3	D	D	$CDCl_3$	6.89				686
	CH_3	I	I	CCl_4	7.06	2.43			662
	I	I	CH_3	"	6.58			2.47	"
	I	CH_3	I	"	6.84		2.20		"
6	CH_3	CH_3	I	"	6.79	2.30	2.08		"
	CH_3	OH	CH_3	CS_2	6.15	2.09	6.65	2.25	701
7	$SeCH_3$	CHO	CH_3	"	6.93	2.30	9.82	2.40	724
	CO_2CH_3	OH	CH_3	$CDCl_3$	6.46		9.62		703
	CH_3	OCH_3	CH_3	"	6.43	2.14	3.70	2.30	705
	CH_3	CH_3	CH_3	"	6.43				665

8	CH_3	D	D						
	$Cr(CO)_3$			„	5.53				686
	CO_2CH_3	OH	CO_2CH_3	„	7.33		9.45		703
	CH_3	OH	$CO_2C_2H_5$	„	7.39		6.91		„
9	$COCH_3$	OH	$CCCH_3$	„	6.7				„
	SCH_3	$COCH_3$	$COCH_3$	„	7.88	2.57	2.51	2.51	722
	OCH_3	$COCH_3$	$COCH_3$	„	7.88	4.13	2.45	2.45	„
	$CO_2C_2H_5$	OH	$CH(CH_3)_2$	„	6.48		9.67		703
10	$C(CH_3)_3$	OCH_3	CH_3	„	6.51	1.34	3.74	2.34	705
11	$CO_2C_2H_5$	OH	$C(CH_3)_3$	„	6.53		9.63		703
12	CO_2CH_3	OH	C_6H_5	„	6.92		9.63		„
13	C_6H_5	$COCH_3$	CH_3	„	5.95			2.35	705
	CH_3	$COCH_3$	C_6H_5	„	7.04	2.22	2.24		„
14	$CO_2C_2H_5$	OH	1-Naphthyl	„	6.91		9.79		703

D. ^1H NMR Studies of Tautomeric Thiophene Derivatives

^1H NMR spectroscopy has been essential for determining the structure of tautomeric thiophenes, and clearly demonstrated that most aminothiophenes exist in the amino form.[617,694-696] It was found that the type of amino substituent (dialkylamino, pyrrolidino, piperidino) had a strong influence on the chemical shifts, which was ascribed to steric effects.[694] ^1H NMR also showed that the thiophenethiols exist in the thiol form,[617,697] while the simple 2-hydroxythiophene systems exist as unsaturated thiolactones.[698-702] For 3-hydroxythiophenes the hydroxy form can be detected in the tautomeric mixture.[703-705] For a detailed discussion of the tautomerism of the hydroxythiophene systems, see Part 3, Chapter 1. Chemical shifts and coupling constants of the 2- and 3-hydroxythiophene systems are given in Tables 26–28.

Recently a new antibacterial antibiotic, thiotetramycin, which is a derivative of the 2,4-dihydroxy system, has been isolated. Its structure was determined by ^1H NMR.[706]

^1H NMR investigations of the three *ortho* formyl-2-thiophenecarboxylic acids showed that they all existed in the open aldehydo-carboxylic acid form in contrast to phthalaldehydic acid.[707,708]

Other tautomeric systems that have been investigated by ^1H NMR are β-dicarbonyl derivatives, including 2-thenoyl trifluoracetone, 2-thenoyl perfluorobutyrylmethane, 1-(2-thienyl)-1,3-butanedione, and 1,3-di-(2-thienyl)propanedione.[709,710,858] Proton chemical shifts were measured and equilibrium constants (enol/keto) were determined. The ^1H NMR spectra of various metal chelates derived from these β-dicarbonyl derivatives have also been investigated[709-713] and used for the determination of thermodynamic formation constants.[709] ^1H NMR spectra revealed that β-(2-thienyl)-α-thiopyruvic acid exists predominantly in the *trans* form.[714]

E. ^1H NMR Studies of Various Substituted Thiophenes

2-(3-Bromo-2-thienyl)-1,3-dioxolane was an intermediate in the synthesis of 2-formyl-3-thiophenecarboxylic acid, and the A_2B_2 spectrum of its 1,3-dioxolane ring was analyzed.[715] The ^1H NMR spectra and the IR carbonyl stretching frequencies of methyl 3-, 4-, and 5-substituted 2-thiophenecarboxylates and of methyl 2-, 4-, and 5-substituted 3-thiophenecarboxylates have been measured, and good linear correlations between the chemical shifts of the proton in the methyl ester and those of the corresponding protons in substituted thiophenes were observed. The IR carbonyl stretching frequencies in methyl 5-substituted 2-thiophenecarboxylate were correlated reasonably well with the chemical shifts of 5-protons in 2-substituted thiophenes.[716,717] Similar investigations have also been carried out on substituted methyl β-(2-thienyl)acrylates[718] and β-(3-thienyl)acrylates.[719]

TABLE 26. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 3-Thiolene-2-ones

C_n	R_3	R_4	R_5	Solvent	δ_3	δ_4	δ_5	J_{34}	J_{35}	J_{45}	Ref.
4	Br	H	H	Cyclohexane		7.99	4.25			3.1	699
	H	Br	H	„	6.65		4.51		1.8		„
	H	H	Cl	Acetone	6.48	7.76	6.71	5.95	1.20	2.90	702
	H	H	F	„	6.45	7.71	7.17	6.14	0.80	2.77	„
	H	H	H	Cyclohexane	6.47	7.84	4.29	5.9	2.0	2.8	699
5	CH_3	H	H	„	1.93	7.30	3.97			3.0	„
	H	CH_3	H	„	6.11	2.23	4.02		1.5		„
	H	H	CH_3	„	6.34	7.67	4.69	6.0	1.9	2.6	700
					$\delta_{CH_3} = 1.65$						
				CCl_4	6.12	7.50	4.42	6.0	2.0	3.7	„
	OCH_3	H	H	Cyclohexane		6.59	3.94			3.4	699
6	H	H	C_2H_5	CCl_4	7.10	7.42	4.39	6.1	2.0	2.5	700
7	H	H	$CH(CH_3)_2$	„	6.29	7.52	4.42	6.3	2.1	2.6	„
	H	H	C_3H_7	„	6.10	7.40	4.43	6.0	2.0	2.7	„
8	H	H	$C(CH_3)_3$	„	6.15	7.43	4.27	6.1	2.1	2.5	„
	H	H	C_4H_9	„	6.21	7.50	4.42	6.3	2.0	2.8	„

TABLE 27. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 4-Thiolene-2-ones

C_n	R_3	R_4	R_5	Solvent	∂_3	∂_4	∂_5	J_{34}	J_{35}	J_{45}	Ref.
4	H	H	Cl	Acetone	2.03	6.02		2.90			702
	H	H	F	„	3.71	5.41		2.85			„
5	H	H	CH_3	Cyclohexane	3.35	5.53	2.05	2.5	2.5	1.5	698
				CCl_4	3.34	5.45		2.6	2.6	1.6	700
6	H	H	C_2H_5	„	3.27	5.43		2.5	2.5	1.5	„
7	H	H	$CH(CH_3)_2$	„	3.33	5.49		2.8	1.9	1.4	„
	H	H	C_3H_7	„	3.25	5.42		2.6	2.1	1.5	„
8	H	H	$C(CH_3)_3$	„	3.31	5.43		2.8			„
	H	H	C_4H_9	„	3.37	5.55		2.8	2.0	1.4	„

TABLE 28. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 4-Thiolene-3-ones

C_n	R_2	R_4	R_5	Solvent	δ_2		δ_4	δ_5	J_{45}	Ref.
5	H, CH_3	H	H	CS_2	3.53	1.46	6.07	8.28	6.0	701
6	H, CH_3	H	CH_3	„	3.68	1.44	5.85	2.33		„
7	CH_3, CH_3	H	CH_3	$CDCl_3$	1.43	1.43	5.72	2.28	1.0	705
8	H, $C(CH_3)_3$	H	H	CS_2	3.40	1.04	6.00	8.21	6.2	701

The stereochemistry of substituted 2-thienylethylene derivatives[720] and 1-dimethylamino-1(2-thienyl)ethene has been studied by ^{1}H NMR and quantum chemical calculations.[721]

^{1}H NMR studies have been carried out on thiophene derivatives containing thiophene–sulfur and thiophene–selenium bonds, as in connection with a study of the acetylation of 2-methylthiothiophene.[722] The ^{1}H NMR parameters of a number of thiophenethiocyanates and -selenocyanates have also been reported.[723] A study of the ^{1}H NMR spectra of a number of selenides of the thiophene series, with electron-attracting substituents, has been carried out and compared with the corresponding sulfides. Couplings between the ^{77}Se nucleus and the methyl protons of the order of 11.9–13.6 Hz were observed.[724]

In connection with work on atropisomeric bithienyls, their ^{1}H NMR parameters were determined.[725-744] From the ^{1}H NMR spectra of 62 methyl 3,3′-bithienyls, it was found that the 2-, 4-, and 5-methyl proton resonances occurred within three intervals that differed depending on the positions of the methyl groups. When the 3,3′-bithienyls were further substituted with bromine or methyl groups, the 2- or 2′-CH_3 resonance was found in the interval 2.05–2.36 δ, the 4- or 4′-CH_3 resonance in the interval 1.69–2.07 δ, and the 5- or 5′-CH_3 resonance in the interval 2.28–2.43 δ. Substitution of bromines by carboxyl groups in the 4- or 4′-positions caused a downfield shift of the 5-(5′-)methyl resonance, and substitution of bromines by carboxyl groups in the 5- or 5′-positions caused a downfield shift of the 4-(4′-)methyl resonance. In other cases, the effects of the carboxyl groups were small.[733] The OCH_3 resonance in 2- and 3-carbomethoxythiophenes and in various carbomethoxy-3,3′-bithienyl and dicarbomethoxy-3,3′-bithienyl fall in characteristic regions and are therefore useful for structure determination of 3,3′-bithienyls.[732,745]

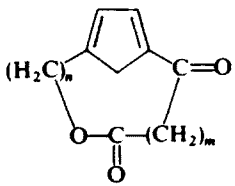
In connection with work on electrophilic substitution and metalation of 2- and 3-phenylthiophenes, ^{1}H NMR parameters were determined that were of great use for the structure determination of the products.[738,746-748,750]

^{1}H NMR parameters were also useful for studying the interaction between the rings in thiophene substituted with π-deficient heterocyclic rings, and for the structure determination of the products obtained on electrophilic substitution and metalation. Among the systems studied were the six isomeric thienylpyrimidines,[751-754] 1-(2′-thienyl)pyrazoles and 1(3′-thienyl)pyrazoles,[755,756] 4-(2′-

thienyl)pyrazoles and 4-(3′-thienyl)pyrazoles,[757] 3-(2′-thienyl)pyrazoles and 3-(3′-thienyl)pyrazoles,[752] and 3-(2′-thienyl)-1,2,4-oxadiazoles and 3-(3-thienyl)-1,2,4-oxadiazoles.[758] The ^{1}H NMR parameters of some thienylpyrroles have been reported.[759] The ^{1}H NMR spectra of thiophene analogs of indene[749,760–766] and fluorenes[767–771] have also been investigated.

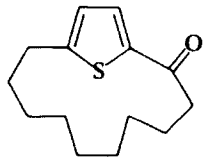
The 100-MHz ^{1}H NMR spectra of 4*H*-cyclopenta[c]thiophene and its 1,3-dichloro derivative were recorded, and the chemical shift and coupling parameters evaluated by the iterative computer program LAOCOON3. The small value for the 1,3-coupling constant in 4*H*-cyclopenta[c]thiophene was taken as evidence for partial bond fixation in this compound.[765] Another group of thiophene derivatives, the ^{1}H NMR spectra of which have been extensively been studied, are thieno- and dithieno-fused tropylium ions and tropones, and intermedates leading to such compounds.[772–781]

The ^{1}H NMR spectra of thiophenes connected to large rings, such as macrocyclic compounds **90** and **91**[859] and crown ether **92**[782] have been studied in order to obtain information about steric factors. ^{1}H NMR confirmed that the [18]annulene 1,4 : 7,10 : 13,16-trisulfide is a stable nonplanar aromatic system, in which the three thiophene rings are linked by three essentially olefinic vinylene groups.[783]

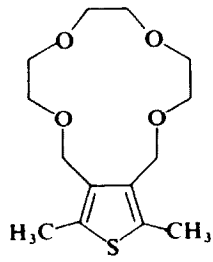


n = 5, *m* = 2
n = 4, *m* = 3
n = 3, *m* = 4
n = 2, *m* = 5

90



91



92

The ^{1}H NMR spectra of 2,3-dihalo-1,3-di(thienyl)propan-1-ones have been studied, and by the use of selected deuterated compounds the signals have been assigned to both the nonaromatic protons.[784,785] The chemical shift differences Δ of the diastereotopic thienyl protons of 1-phenyl (-d_5) ethyl 2,2′-dithienylglycolate have been measured for different solvents and at different temperatures. The solvent dependence of the Δs were interpreted as mainly due to solvent shifts of the diastereotopic protons.[786] Enantiomeric shift differences have been induced by achiral shift reagents in the ^{1}H NMR spectrum of partially resolved α-(2-thienyl)ethylamine.[787] Europium and praseodynium thenoyl trifluoracetonate have been used as shift reagents.[788] ^{1}H NMR spectra of 2-(2-nitrovinyl)thiophenes,[789] benzoylthiophenes, thienopyrimidines, and thienodiazepine derivatives have also been investigated.[790,791] The structure of the condensation product between 2-thenyl cyanide and quinone monoxime was determined by ^{1}H NMR.[792]

^{1}H NMR spectroscopy was of great importance for the structure elucidation of a great number of naturally occuring thiophenes.[671,793-807] For more details, see Part I, Chapter III of this treatise.

F. ^{1}H NMR Studies of Organometallic Thiophenes

The ^{1}H NMR parameters of thiophene–silicon-substituted derivatives have been studied by many workers, especially in the Soviet Union.[120,808-812] It was shown that the chemical shifts of the hydrogens atoms in the 3-position of 2-(organosilyl)thiophenes were linearly related to the Hammett σ_n-substituent were transmitted via inductive and conjugation (d_π–p_π interaction) mechanisms. The effect of d_π–p_π interaction was absent for $Si(OC_2H_5)_3$ and SiF_3 substituents,[808,811] however.

The ^{1}H NMR spectra of a number of phosphorylated derivatives of thiophene have been compared with those of the corresponding furans and pyrroles. The results indicate that some degree of d_π–p_π bonding is present. The chemical shifts and coupling constants were similar to those found in the corresponding derivatives.[813] The 60-MHz ^{1}H NMR spectra of tri-2-thienylphosphine and tri-3-thienylphosphine and some of their derivatives, such as the oxides, the sulfides, the selenides, and phosphonium salts, have been analyzed to obtain the magnitudes and relative signs of the ^{1}H–^{31}P spin coupling constants. In all cases, the ^{1}H–^{31}P, as well as the ^{1}H–^{1}H spin coupling constants, carried the same sign, presumably positive. For the tetracoordinated compound $^3J_{P-H}$ increased, whereas $^4J_{P-H}$ decreased in the order O, S, and Se.[814,815]

The ^{1}H NMR spectra of various organometallic derivatives of thiophene have been studied, such as lithium[618] and Grignard reagents, for which the exchange mechanism was studied, and the activation parameters for the rate-determining step of the formation and those for the Schlenk equilibrium were evaluated.[816] The ^{1}H NMR spectra of thienylmercury chloride[621] and of di(2-thienyl)mercury[817] have been studied, and the ^{199}Hg satellite bands of the latter and of di(2-furyl)mercury have been fully analyzed. By comparing experimental and simulated spectra, the relative signs of both J_{H-H} and J_{Hg-H} couplings were found to be alike. A linear relationship between J_{Hg-H} of the present compounds and the corresponding J_{H-H} of furan and thiophene has been established.[817] The ^{1}H NMR spectra of tetra(2-thienyl)lead[621,818] have been studied, and from the satellite spectrum, the $J(^{207}_{Pb-H})$ coupling constants were determined and compared with those of the corresponding J_{Hg-H} couplings.[818] The ^{1}H NMR spectrum of tetra(2-thienyl)tin has been reported.[621]

G. Miscellaneous ^{1}H NMR Investigations of Thiophenes

Solvent effects on the chemical shifts of thiophene were studied as early as in 1959.[819] Infinite dilution data for thiophene have been obtained from second-

order analysis of its ^{1}H NMR spectrum in CS_2, $CDCl_3$, CD_3COCD_3, and C_6D_6. Use of LAOCOON-3 led to accurate chemical shifts.[820] Evidence has been presented for specific association of chloroform[820-827] and 1,1,2,2-tetrachloroethane[821] with thiophene. The association constant with chloroform was obtained by the use of ^{1}H NMR over a temperature range from -50°C to $+50$°C.[495] The effect of various polar and nonpolar solvents (cyclohexane, CCl_4, C_6H_6, $CHCl_3$, CH_3OH, CH_3COCH_3, and CH_3CN) on the proton chemical shifts of thiophene, 2-iodothiophene, and 2-acetylthiophene have been investigated by ^{1}H NMR. The results were interpreted in terms of possible solute–solute, solute–solvent, and solvent–solvent interactions in these systems.[823] On the basis of a study of the ^{1}H NMR spectra of binary solutions of benzene and thiophene in polar substances, it was shown that at constant temperature the difference in the stabilities of the π-complexes of benzene and thiophene increases appreciably with increasing concentration of the polar substance, particularly in the system with 2-aminoethanol.[824] Thermodynamic parameters were calculated from the ^{1}H NMR spectra of the system thiophene-*N*,*N*-dimethylformamide.[825]

The effect of thiophene on the shifts of phenolic hydroxyl groups has been studied in connection with the determination of components in phenol mixtures[826] and in connection with studies on hydrogen bonding.[827,828] The effect of thiophene as solvent on the ^{1}H NMR parameters of α-chloroacrylonitrile has been studied.[829,830]

Attempts have been made to estimate aromaticity in thiophenes by ^{1}H NMR dilution shifts[831-833] in benzene or carbon tetrachloride. The ring-current effects in thiophene and furan were estimated to be $\sim 90\%$ of those in benzene, and attempts were made to correlate the ring-current effects in furan, thiophene, and pyrrole with the aromaticity of these five-membered heterocycles.[834,835]

From magnetic birefringence measurements, the molar Cotton–Mouton constants for pyridine, thiophene, furan, and pyrrole at infinite dilution in carbon tetrachloride were reported and the diamagnetic anisotropies were subsequently evaluated in conjunction with available polarizability and susceptibility data. Using known molecular dimensions, the π-electron ring currents appear (relative to benzene) to be 1.06 : 0.79 : 0.57 : 0.37 for pyridine, thiophene, furan, and pyrrole, respectively.[836] Other attempts have been made to estimate the aromaticity of the five-membered heteroaromatics from nonlocal contributions to molecular magnetic susceptibilities,[837,838] which can be obtained independently from ^{1}H NMR shifts by Zeeman microwave spectroscopy.[543] However, critical evaluations have shown that although ring currents are the most sensitive tests for the detection of aromatic character, it is not directly related to the resonance energy or reactivity of the molecule.[839] The ground state aromaticities of furan, thiophene, selenophene, and tellurophene have however been graded by using seven different criteria, several of them from ^{1}H NMR data:

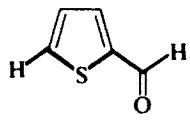
1. The ^{1}H NMR dilution shift
2. The difference in chemical shifts of the β- and α-protons
3. The effect of a 2-methyl substituent on the ring proton chemical shift
4. The diamagnetic susceptibility exaltation
5. The sum of the bond orders
6. The Julg parameter
7. The mesomeric dipole moment

The agreement among the results obtained using the various approaches was remarkably good. The following order of descreasing aromaticity was established: benzene > thiophene > selenophene > tellurophene > furan.[840]

Various correlations between ^{1}H NMR spectroscopic data and IR data have been reported.[841-843]

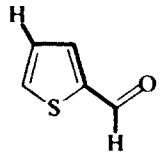
H. Conformational Studies of Thiophenes by ^{1}H NMR

The conformation of 2-thiophen aldehydes, which could exist in the planar, X = S,O-*cis* **93** and X = S,O-*trans* **94** forms have been extensively studied by various ^{1}H NMR techniques.[673,844-850]



S,O-*cis*

93



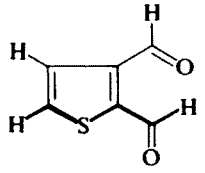
S,O-*trans*

94

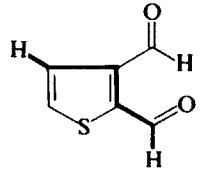
For 2-furan aldehyde, both conformers could be detected. The proportion of the O,O-*cis* form to the O,O-*trans* form was about 1 : 9 at low temperature[851] and at room temperature, about 35 : 65,[852] as judged from the magnitude of the specific coupling constants. The barrier to internal rotation was determined by dynamic ^{1}H NMR.[851,853,854] For 2-thiophene aldehyde, on the other hand, only the S,O-*cis* form **93** has been detected,[845,848] and thus no rotational barrier could be measured. The long-range couplings are stereospecific, following a W-path (zigzag path). In the O,O-*cis* isomer the strongest coupling is to the 5-hydrogen, while that to the 4-hydrogen is less than 0.2 Hz. In the O,O-*trans* isomer the sterospecific coupling is to the 4-hydrogen.[855] An especially interesting case is 3-hydroxy-2-thiophene aldehyde. In nonpolar solvents (CCl_4), the formyl group is locked into the S,O-*trans* configuration, owing to hydrogen bonding, and a J_{CHO-4} coupling of 0.65 Hz was observed, while in DMSO, in the absence of the hydrogen bond, a J_{CHO-5} coupling of 1.2 Hz was observed.[852] It was also shown by X-ray crystallography that 4-bromo-2-thiophene aldehyde exists in the S,O-*cis* form in the solid state, and in solution at low temperature

only this isomer, with J_{CHO-5} = 1.4 Hz, could be observed.[852] Several substituted 2-thiophene aldehydes were also studied, and from the magnitude of the long-range coupling constants it was concluded that they exist almost exclusively in the S,O-*cis* conformation while in analogous furan derivatives the O,O-*cis* isomer constituted 60–90%.[845] In addition, investigations of ^{1}H NMR solvent shifts, the temperature dependence of ^{1}H NMR spectra and nuclear Overhauser effects confirm that compounds like 4-bromo-2-thiophene aldehyde and 2-acetyl-4,5-dibromothiophene,[856] and some other thienyl ketones,[848] exists as the S,O-*cis* isomer. Later investigation at 220 MHz, including studies of benzene solvent shifts, induced chemical shifts by Eu(FOD)$_3$ and nuclear Overhauser effects confirm the favored S,O-*cis* form of 2-thiophene aldehydes. Semiempirical calculations indicate that this might be due to sulfur 3*d*-orbital participation.[857]

The small ^4J coupling constants between the formyl and 3-hydrogens in 2-thiophene aldehydes and in 2,3-thiophene dialdehyde have been studied. The preferential conformation of these molecules was established by using the "zigzag" route for the ^5J coupling constant. This allowed an analysis of the ^4J coupling pathways.[847] From an analysis of the long-range couplings of 2,3-thiophene dialdehyde, it was concluded that the equilibrium mixture contained approximately 66% **95** and 34% **96**.[855]



95

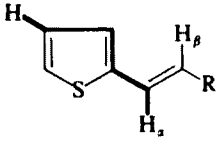


96

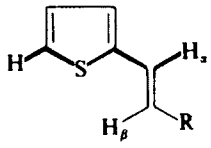
Attempts have also been made to use the magnitude of J_{CHO-5} of 3-thiophene aldehyde for conformational analysis,[852] assuming that it is largest in chelated 3-hydroxy-4-formylthiophene.[856]

Rotational isomers in 2-thiophenecarbonyl chlorides have been studied by ^{1}H NMR spectroscopy.[857] The conformation of the —CO—CO— grouping in 2-thienylglyoxylic acid and its *N*,*N*-diethylamide has been investigated.[704]

Characteristic long-range couplings have also been used to determine the conformation of *trans*-2-(2-thienyl)ethylenes **97** and **98**.



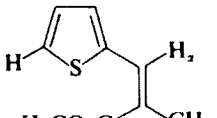
97



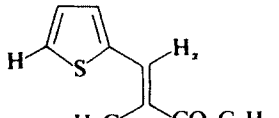
98

R = NO_2, COOH, $COCH_3$

In all three compounds, it was found that $^5J_{4\alpha}$ was either very small or nonobservable, while $^5J_{5\alpha}$ was of the order of 0.7–0.9 Hz, thus indicating that **98** is the stable conformation.[860] Later this study was extended to other types of thienylethylene derivatives, and both *Z* and *E* isomers **99** and **100**, respectively, were concluded to exist in the *Z*-S-*trans* and *E*-S-*trans* conformation on the basis of $^5J_{5\alpha}$ values of 0.6 and 0.5 Hz, respectively.[861] Furthermore, α-nitro-β-(2-thienyl)ethylenes exist only in the S-*trans* forms, as shown by variable-temperature spectra and the presence of $^5J_{5\alpha} = 0.6$ Hz.[862] It should be pointed out that in the analogous furan and pyrrole derivatives different conformation preferences were observed.[860-862]

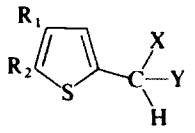


99



100

The ^{1}H NMR spectra of 2-thienylmethylene derivatives of type **101** have been used to deduce the average conformation by studying the long-range benzylic coupling constants. Conformations in which the benzylic hydrogen is in or near the plane of the ring and anti to the sulfur were preferred. The signs of the long-range couplings relative to J_{34} were determined.[863]



101

R_1, R_2 = H or NO_2
X, Y = OAc or CMe_2NO_2

The position of the gem-vinyl protons in the ^{1}HNMR spectrum of 1-(2-thienyl)-1-phenylethylene shows that the phenyl ring is twisted out of the plane defined by the coplanar thiophene ring and ethylenic bond.[864]

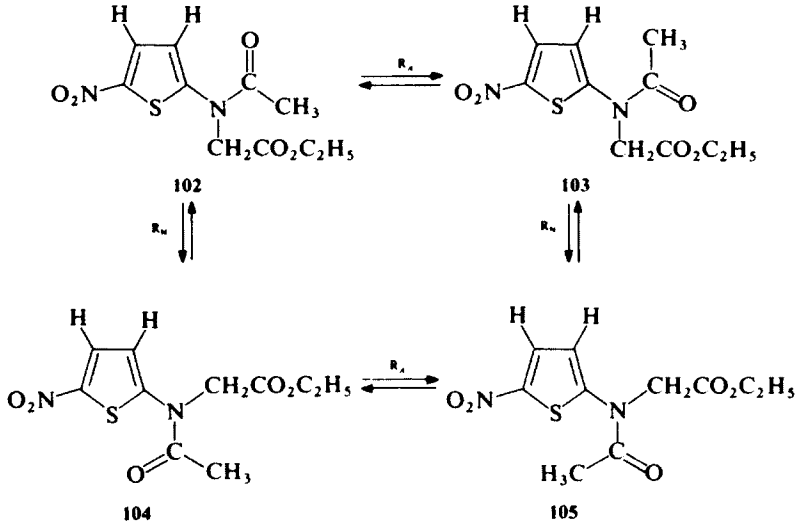
I. Dynamic ^{1}H NMR Investigations of Thiophenes

Dynamic ^{1}H NMR has been used for determination of the rotational barriers in 2- and 3-thiophene-*N*,*N*-dimethylcarboxamide.[865,866] Free-energy (Gibbs) $\Delta G\ddagger$ values of 14.5 ± 0.2 kcal/mol ($CDCl_3$),[865] 12.83 ± 0.04 kcal/mol (CS_2), and 13.8 kcal/mol ($CDCl_3$)[866] were obtained for the 2-isomer and 13.64 ± 0.02 kcal/mol, for the 3-isomer.[866] For 2-thiophene-*N*,*N*-dimethylthiocarboxamide, a $\Delta G\ddagger$ value of 14.14 ± 0.05 kcal/mol was obtained.[866] Lanthanide-induced shifts indicated that the S-*cis* conformation was preferred (~73%) in 3-thiophene-*N*,*N*-dimethylcarboxamide.[866] A computer method to simulate the observed

lanthanide-induced shifts and its application to the study of conformational equilibria has been described.[867] The ^{1}H NMR spectra of some 3- and 5-substituted 2-thiophenecarboxamides in $CDCl_3$ have been studied, and intramolecular hydrogen bonds between the NH and the 3-substituent were observed. The activation energies for rotation of the 3-substituted amides are higher than those of the corresponding 5-substituted derivatives, for which they depend on the electronic nature of the substituents.[868] Barrier heights in 2-thiophene-*N*,*N*-diethylcarboxamide and 2,5-thiophenedi-*N*,*N*-diethylcarboxamides have been measured in the presence and absence of $Eu(fod)_3$.[514]

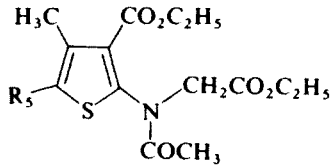
The rotational barriers about the carbon–nitrogen bond in a number of 2-dimethylamino-3-nitrothiophenes were found to be between 6.1 and 9.3 kcal/mol by dynamic ^{1}H NMR. Band coalescence temperatures were between -90 and -143°C.[869]

Four conformers are possible for *N*-acetyl-*N*-ethoxycarbonylmethyl-2-amino-5-nitrothiophene, **102–105**. Two stereoisomers were observed by ^{1}H NMR at 10°C. Their spectra coalesce at higher temperatures (10–90°C). The equilibrium and rate constants were strongly dependent on the solvent used. The two isomers were shown to be **102** and **104** and resulted from hindered rotation around the thienyl–nitrogen bond, presumably owing to a direct resonance effect between the amide and nitro groups. The more abundant isomer **104** was assigned a planar structure, in which the oxygen atom of the amide group is close to the thiophenic sulfur, probably owing to an electrostatic interaction between these two atoms, which bear partial charges of opposite sign.[870]



In 3-substituted *N*-acetyl-*N*-ethoxycarbonylmethyl-2-amino thiophenes **106**, the geminal methylene protons were nonequivalent, in contrast to **102–105** compound **106** was shown to exist in the endo (the amide carbonyl cis to the

thiophene ring) and exo forms, with the latter predominating (92–98%). The proton nonequivalence indicates that the thiophene and amide planes are not coplanar and indicates the presence of two atropisomeric enantiomers. The barrier to rotation about the amide bond and the thiophene–nitrogen bond had $\Delta G\ddagger$ (25°C) values of 71 and 54 kJ/mol, respectively.[871]



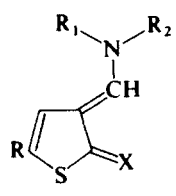
$R_5 = COCH_3, CO_2C_2H_5$

106

The restricted rotation about the C—N bond of the amino group in 2-bromo-5-nitro-3-thiophenecarboxamide ($\Delta G\ddagger$ = 68.8 kJ/mol), 2-bromo-4-methyl-5-nitro-2-thiophenecarboxamide ($\Delta G\ddagger$ = 76.2 kJ/mol), and the analogous dimethylamides ($\Delta G\ddagger$ = 76.2 and 87.3 kJ/mol, respectively) have been determined by dynamic ^{1}H NMR.[872]

The conformation and dynamic processes in [2] (2,5)thiophene paracyclophane have been analyzed. The temperature dependence of the ^{1}H NMR spectra at low temperature was ascribed to two types of dynamic processes—the torsional motion about the sp^3–sp^3 C—C bonds in the bridges and the rotation around the sp^2–sp^3 C—C bonds adjacent to the aromatic rings.[873] The conformation of ansa compounds of the thiophene series has been studied with ^{1}H and ^{13}C NMR spectroscopy using paramagnetic displacing reagents.[874]

Protonation of 2,2′-bithienyl in superacid media occurred at the 5-position to give the 2-(2-thienyl)-5-thiophenium ion. The energy barrier to rotation about the bond connecting the two rings was determined to be $\Delta G\ddagger$ = 11.4 kcal/mol by dynamic ^{1}H NMR spectroscopy. Substituent effects on the rate of rotation were correlated by σ_p^+ constants with a ρ-value of 4.8.[875] ^{1}H NMR spectra indicated that *N*,*N*-disubstituted 3-aminomethylene-4-thiolene-2-thiones and 3-aminomethylene-4-thiolene-2-ones prefer the conformation indicated in **107**, as a result of steric hindrance. The barriers to rotation around the C—N bond were determined by dynamic ^{1}H NMR, and $\Delta G\ddagger$ was found to be about 3 kcal lower for the thiolene-ones than for the corresponding thiolene-thiones.[876]



X = O, S

107

J. ^1H NMR Spectra of Thiophenes in Nematic Solvents and in Adsorbed States

Several groups have studied the ^1H NMR spectrum of thiophene in nematic solvents.[877-880] The proton spectrum of the oriented 4-spin system with C_{2v} symmetry of the type (*AABB'*), as exemplified by thiophene, was analyzed in the nematic phase of *p,p'*-di-*n*-hexyloxyazoxybenzene, and the ratio of the various interproton distances were determined.[880] The structural parameters calculated agreed well with microwave geometries.[878,879] The r_z-structure determinations (corrected for harmonic vibrations) of thiophene included ^{13}C satellites at natural abundance. The importance of vibrational corrections was demonstrated.[879] The influence of an electric field applied in a direction perpendicular to the magnetic field on the ^1H NMR spectrum of thiophene oriented in the nematic phase of a liquid crystal has been studied.[881] From the precise internuclear distances obtained for five-membered heterocycles, a relationship between the ratio of the distance between the two α- to the two β-protons and the covalent radii of the heteroatom has been given.[882]

The r_α-structure of thiophene has been studied in thermotropic liquid crystals and their mixtures. In each case, ^{13}C-enriched methane was added to the sample to serve as an internal deformation reference.[883]

The ^1H NMR spectra with the ^{13}C satellites and the ^{13}C spectra of 2-chloro- and 2-bromothiophene in nematic Merck ZLI-1167 and ZLI-1132 crystal solutions were analyzed. The ^1H spectra and three of the four ^{13}C satellite spectra appeared to be deceptively simple and prevented the determination of certain individual coupling constants. However, the use of two liquid crystal solvents and the assumption of unchanged structures in the solutions made it possible to determine the complete *r*-structures. The structures did not agree well with those obtained by electron diffraction.[884]

The ^1H NMR spectrum of 2-thiophene aldehyde oriented in the nematic phase of a liquid crystalline solvent confirmed that also in this case the aldehyde exists only in the SO-*cis*-conformation, which was found to be planar or very nearly so; and the orientational parameters of the molecule with respect to the magnetic field have been determined.[885] ^1H NMR investigation in a nematic phase was also used for the conformation analysis of 2,5-thiophenedialdehyde.[886,887] It was concluded that the molecule exists in the O-*cis*–*cis* (70–80%) and O-*cis*–*trans* (20–30%) conformations.[887]

The temperature dependence of the ^1H NMR spectrum of thiophene trapped in the cage of dicyanoamine–nickel clathrate has been studied.[888-890] Some other types of clathrates[891] have been investigated to obtain information about the motion of the guest molecules. Thiophene clathrate exhibited no change in the linewidth.[891] Molecular reorientation processes in crystalline thiophene and furan have been studied using pulse ^1H NMR techniques over a range of temperatures.[892,893] Molecular motion persists in solid thiophene well below its lowest temperature phase transition. ^1H NMR second-moment studies show

that thiophene as well as benzene reorient about axes perpendicular to their molecular planes in these solids. Solid solutions of thiophene in benzene were also investigated.[892]

The ^{1}H NMR spectra of a number of azomethines and vinylenes containing the 2,2′-bithienyl 5,5-diyl unit as mesogenic group were studied in relation to their liquid crystalline properties.[894]

2. Various Magnetic Investigations of Thiophenes

Proton spin relaxation and molecular motion in liquid thiophene were studied in the temperature range 200–550 K by measuring the spin–lattice relaxation time T_1 and the coefficient of self-diffusion D, using the spin–echo technique. The value of T_1 varied from 24.0 sec at 300 K to 72.0 sec at 550 K, with a maximum of 94.0 sec at 490 K. The value of D varied from 2.4×10^{-5} cm^2/sec at 300 K to 38.0×10^{-5} cm^2/sec at 550 K. The results were analyzed in terms of three relaxation mechanisms: inter- and intramolecular dipolar interaction and spin–rotation interaction.[895,896] In a later paper only the first two mechanisms were observed for thiophene.[897] A high-resolution study of ^{1}H NMR spin echoes has been carried out on 3-bromo-2-thiophene aldehyde[898] and 2-bromo-5-chlorothiophene.[899]

High-resolution ^{1}H NMR studies of relaxation mechanisms in two-spin systems have been performed for 2,3-dibromothiophene and for 3-bromo-2-thiophene aldehyde. Assuming an interproton distance equal to that in thiophene, the direct dipole–dipole contribution to the relaxation has been used to estimate the rotational correlation times $r_c = 4.4 \times 10^{-12}$ sec for the dibromothiophene, and $r_c = 5.2 \times 10^{-12}$ sec for the bromothiophene aldehyde.[900] Averaging the transverse relaxation times of scalar coupled nuclei under spin–lock conditions has been studied for 2,3-dibromothiophene[901] as well as spin–lattice relaxation times by progressive saturation.[902] Proton spin relaxation has been studied in 2- and 3-bromothiophene,[903,904] in 2,5-dimethylthiophene,[905] and in 2,4-dibromothiophene.[906] Rotational correlation times for thiophene in carbon tetrachloride were determined by proton spin lattice relaxation and compared with calculated theoretical values.[907] When an electrical field was applied to thiophene, the spin–lattice relaxation time was reduced by a factor of 2.[908] The magnetic susceptibility of thiophene was found to be $-X_M \times 10^6 = 56.37$,[909] 57.20,[910] and 57.7.[911] The magnetic susceptibility of Co(II) and Ni(II) chelates of 2-mercapto-5-ethyl-3-thenylidene)-α-aminopiperidine have been determined.[912]

The variation of permitivity, caused by a strong magnetic field, was observed for thiophene.[913] Mössbauer spectra of μ-oxo-bis(α,β,γ,δ-tetrakis-2-thienyl)-phosphinatoiron(III) complexes have been measured.[914] The rotativity of thiophene has been determined.[915]

3. NMR Investigations of Other Magnetically Active Nuclei in Thiophenes

A. ^{13}C NMR Spectroscopy of Thiophenes

The first papers on ^{13}C NMR spectra of thiophenes started to appear in 1965–1970.[916–920] Chemical shifts and coupling constants of the thiophene, mono-, and disubstituted thiophenes are given in Tables 29–33.

TABLE 29. ^{13}C NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of Thiophene

Solvent	C_2	C_3	$J_{C_2-H_2}$	$J_{C_3-H_3}$	Ref.
Acetone-d_6	125.6	127.3	185	168	653
$CDCl_3$	124.9	126.4			925
CS_2^a	68.1	66.3			919
			187.0	180.0	648
			189	168	916

	$J_{C_2-H_3}$	$J_{C_2-H_4}$	$J_{C_2-H_5}$	$J_{C_3-H_2}$	$J_{C_3-H_4}$	$J_{C_3-H_5}$	
Acetone	7.35	10.0	5.15	4.7	5.9	9.5	918

[a] Relative to CS_2.

In a systematic investigation, the ^{13}C parameters for a series of 2- and 3-substituted thiophenes, such as methoxy-, methyl-, and the four halothiophenes, as well as a number of –I–M-substituted compounds, were determined. Unequivocal shift assignments were in some cases obtained from deuterated derivatives. Both the direct and long-range coupling constants fall in well-defined intervals. The larger direct C—H coupling of the α-carbon than the β-carbon has been useful, especially for the structure determination of trisubstituted thiophenes. The shifts due to the substituents (Table 34) were compared with those in benzenes, and also with ^1H and ^{19}F shifts of thiophenes. Shift correlations with several types of reactivity parameters were attempted. The greatest success was achieved with the use of the two-parameter equation of Swain and Lupton (see Table 35).[653] The substituent-caused chemical shifts of thiophenes were compared with those of the corresponding furans, selenophenes and tellurophenes. Linear correlations were observed, which give information about the transmission of substituent effects in the five-membered chalcogen heterocycles. Linear correlations between the electronegativity of the heteroatoms and several of the ^{13}C NMR parameters were also observed.[652,921,922] The ^{13}C chemical shift data for the five-membered heterocycles were later used in an attempted unified correlation of substituent effects with carbon, proton, and fluorine chemical shifts in aromatic and olefinic systems, in which the Swain

TABLE 30. ^{13}C NMR Chemical Shifts (ppm) and Coupling Constants (Hz) for 2-Substituted Thiophenes

C_n	R	Solvent	C_2	C_3	C_4	C_5	$J_{C_3-H_4}$	$J_{C_4-H_4}$	$J_{C_5-H_5}$	$J_{C_3-H_4}$	$J_{C_3-H_5}$	$J_{C_4-H_3}$	$J_{C_4-H_5}$	$J_{C_5-H_3}$	$J_{C_5-H_4}$	C_R	Ref.
4	Br	Acetone-d_6	112.0	130.7	128.4	128.2	172	171	190	5.6	8.5	4.7	3.3	10.3	6.5		653
		Neat					172.7	170.1	188.3	5.6	8.0	4.2	3.4	11.0	5.6		647
		CS_2[a]	79.9	62.5	64.8	65.4											919
	Cl	Acetone-d_6	129.7	127.4	129.6	125.3	172	171	190	5.5	8.2	4.5	3.1	10.5	6.4		653
	F[b]	„	166.5	108.0	124.7	114.9	171	172	192								„
	I	„	73.6	137.6	129.7	132.5	173	170	189	5.6	9.0	5.0	3.5	10.0	6.7		„
		CS_2[a]	117.7	54.8	62.8	60.2											919
	NO_2	Acetone-d_6	151.2	129.9	128.4	134.7	177	176	191	4.7	8.6	4.0	3.5	11.3	6.8		653
5	CN	„	110.0	138.6	128.7	134.2	174	173	192	5.8	9.0	4.5	3.8	10.8	7.1	114.5	„
																183.4	„
	CHO	„	144.9	137.4	129.2	135.6	168	170	185	5.3	9.4	4.4	3.8	10.6	7.0	190.4	
		CS_2[a]	49.1	56.1	64.4	57.9										163.4	919
	COOH	Acetone-d_6	134.7	134.2	128.5	133.5	170	171	187	5.3	9.3	4.7	3.5	10.7	7.1	162.9	653
	CH_2OH	„	146.0	125.1	127.2	125.3	165	167	186	5.5	9.0	5.2	3.7	10.0	6.7		„
	OCH_3	„	167.4	104.2	125.5	112.4	167	168	189	5.3	7.5	4.0	2.8	10.6	5.9	60.5	„
		CS_2[a]	25.8	88.9	68.0	81.1											919
	CH_3	Acetone-d_6	139.8	125.9	127.5	123.7	164	165	186	5.2	9.0	5.3	3.5	10.0	6.8	14.9	653
																	919
		CS_2[a]	53.5	67.8	66.1	69.9	163.56	165.50	184.92								634
																	916
		Neat[c]					164	170	186	5.8	8.2	5.55	3.8	6.8	9.8		918
	SCH_3	Acetone-d_6	137.6	131.5	128.1	128.6	169	168	188	5.7	8.5	4.8	3.5	10.3	6.7	22.0	653
6	$COCH_3$	„	145.5	133.4	128.9	134.4	168	170	186	5.0	9.5	4.7	3.6	10.5	7.0	26.7	„
	CO_2CH_3	„	134.4	134.2	128.8	133.6	170	171	187	5.3	9.3	4.6	3.7	11.0	7.3	52.3	„
		CS_2[a]	59.3	59.7	65.4	60.6											919

[a] Relative CS_2.
[b] $J_{C_2-F} = 283$; $J_{C_3-F} = 10$; $J_{C_4-F} = 8$; $J_{C_5-F} = 2$.
[c] $J_{C_2-CH_3} = 128.26$.

TABLE 31. ^{13}C NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 3-Substituted Thiophenes

C_n	R	Solvent	C_2	C_3	C_4	C_5	$J_{C_2-H_2}$	$J_{C_4-H_4}$	$J_{C_5-H_5}$	$J_{C_2-H_4}$	$J_{C_2-H_5}$	$J_{C_4-H_2}$	$J_{C_4-H_5}$	$J_{C_5-H_2}$	$J_{C_5-H_4}$	C_X	Ref.
4	Br	Acetone-d_6	123.4	110.0	130.1	127.6	191	174	189	7.5	4.0	7.4	4.7	5.0	6.4		653
		CS_2[a]	65.6	82.1	62.4	69.5											919
	Cl	Acetone-d_6	120.9	125.7	128.1	127.5	191	173	189	6.9	3.7	7.2	4.4	5.5	6.0		653
	F[b]	„	104.2	159.2	117.8	126.4	189	172	189	6.0	2.8	6.5	3.8	5.7	4.8		„
	I	„	129.9	80.8	135.5	128.7	193	174	189	8.1	4.5	8.0	4.8	4.5	6.8		„
		CS_2[a]	64.4	113.8	57.3	63.3											919
	NO_2	Acetone-d_6	129.2	149.7	123.1	128.9	199	177	194	7.0	4.7	7.3	4.5	6.0	6.4		653
5	CN	„	137.1	111.4	129.6	129.1	192	174	191	7.7	5.0	7.8	4.8	6.2	6.5		„
	CHO	„	138.0	144.1	125.6	128.5	187	171	189	8.0	5.0	8.0	4.7	5.3	6.9		„
		CS_2[a]	55.4	49.9	67.6	65.2										7.8	919
	COOH	Acetone-d_6	133.9	134.8	128.7	127.3	189	170	188	7.8	5.2	8.1	4.8	5.5	7.0	163.9	653
	OCH_3	„	97.3	159.8	119.9	125.6	184	168	187	6.5	3.3	7.0	4.2	5.5	5.5	57.6	„
		CS_2[a]	95.8	33.6	73.3	68.0											919
	CH_3	Acetone-d_6	121.3	138.2	130.1	126.1	184	165	185	7.9	4.9	8.2	4.8	5.4	7.2	15.5	653
		CS_2[a]	72.4	55.7	63.7	67.8											919
		Neat[c]					182.36	164.48	184.92								634
										8.95	4.3	7.2	5.5	4.3	8.95		918
6	$COCH_3$	Acetone-d_6	133.5	143.7	127.4	127.6	187	170	189	7.8	5.4	8.0	4.9	5.5	7.0		653
	CO_2CH_3	CS_2[a]	60.6	59.6	65.4	67.1										30.6	919
	SCH_3	Acetone-d_6	119.3	135.0	128.4	127.1	187	169	189	8.1	4.0	7.8	4.4	5.1	6.5		653

[a] Relative CS_2.
[b] $J_{C_2-F} = 22$; $J_{C_3-F} = 255$; $J_{C_4-F} = 27$; $J_{C_5-F} = 10$.
[c] $J_{CH_3-F} = 217.10$.

TABLE 32. ^{13}C NMR Chemical Shifts (ppm) of Disubstituted Thiophenes

C_N	R_2	R_3	R_4	R_5	Solvent	C_2	C_3	C_4	C_5	C_R	Ref.
4	Br	H	H	D	Acetone-d_6	112.1	138.8	128.4	128.0		653
	H	Br	D	H	„	123.6	110.0	130.3	127.8		„
	D	Br	H	H	„	123.5	110.1	130.4	127.9		„
5	SCH_3	D	H	H	„	137.7	131.3	128.1	128.6	22.0	„

and Lupton parameters and the semiempirical parameter R was used for the linear multiple regression analysis.[923]

Recently, ^{13}C NMR data of fourteen 2-substituted thiophenes have been obtained in $CDCl_3$. The correlation between the carbon chemical shift and the Hammett constants was poor. The charge densities of typical compounds were calculated by the CNDO/2 method and discussed in connection with the observed chemical shifts.[924] The ^{13}C and ^{1}H NMR spectra of thiophene-1,1-dioxide reveal its nature as a cyclic diene.[925]

The effect of carbonyl substitution in the 2-position of furan and thiophene on ^{13}C NMR chemical shifts has been reported in connection with studies on the transmission of substituent effects.[926] In another study on the transmission of substituent effects, the ^{13}C NMR spectra and the IR carbonyl stretching frequencies of 4-(substituted methyl)-2-thiophenecarboxylic acids and 2-(substituted methyl) 4-thiophenecarboxylic acids were determined. Lanthanide shift reagents were used to support assignments. Unequal transmission of substituent effects was observed. All the data, pK_a, IR, and ^{13}C NMR for transmission of substituent effects, were explained in terms of differences in the relative coplanarity of the two systems.[927] The relation between ^{13}C NMR chemical shifts and electronic states and IR, absorption band intensity of some thiophene derivatives has been studied.[928]

The effect of vacant d^{π}-orbital on the charge distribution on thiophenes containing halogens has been discussed. From an appropriate estimation of the Coulomb and resonance integrals associated with the vacant d^{π}-orbitals, a linear relationship between the charge density and ^{13}C chemical shifts was obtained.[929] From ^{13}C NMR and UV investigations, as well as SCF-π-MO calculations, it was concluded that the π-electron structure of amino- or carbonyl-substituted thiophenes is strongly affected, especially if both groupings are present simultaneously.[930]

Carbon–hydrogen coupling constants, together with standard errors, have been given for thiophene and furan via an iterative spectral fitting procedure from undecoupled 20 MHz ^{13}C NMR spectra. Carbon chemical shifts and carbon–hydrogen coupling constants for carbonyl derivatives were discussed. It was concluded that long-range carbon–hydrogen couplings in these systems are not as valuable for conformational assignments as the analogous proton–proton interactions.[931]

TABLE 33. ^{13}C NMR Coupling Constants (Hz) of Disubstituted Thiophenes

Compound	R_2	R_3	R_4	R_5	Solvent	$J_{C_2H_2}$	$J_{C_3H_3}$	$J_{C_4H_4}$	$J_{C_5H_5}$	Ref.
A	Br	H	H	D	Acetone-d_6		170		20[a]	653
B	D	Br	H	H	„	29[a]		174	189	„
C	Br	Br			Neat			176.5	190.5	661
D	Br	H	Br	H	„			178.5	195.0	„
E	Br	H	H	Br	„		174.5			„
							172.0			648
F	Cl	H	H	Cl			174.3			„
G	SCH_3	D	H	H	Acetone-d_6			168		653
H	CH_3	H	H	CH_3[b]			161.24			634
							162			916
							162			648

Long-Range Couplings (Hz)

Compound	$J_{C_2H_4}$	$J_{C_2H_5}$	$J_{C_3H_4}$	$J_{C_3H_5}$	$J_{C_4H_2}$	$J_{C_4H_3}$	$J_{C_4H_5}$	$J_{C_5H_2}$	$J_{C_5H_3}$	$J_{C_5H_4}$
A			5.7	1.2[a]		4.8	0.5[a]		10.3	6.5
B	7.7	4.3			1.0[a]		4.5	6.5		1.0[a]
G						0.15[a]	3.5		1.5[a]	6.5

[a] Deuterium coupling.

[b] $J_{C_2-CH_3} = J_{C_5-CH_3} = 218.20$.

TABLE 34. Chemical Shifts (ppm)[a] of the Carbons of 2- and 3-Substituted Thiophenes Relative to the α- and β-Carbons of Thiophene in Deuterioacetone Solution

	2-Substituted				3-Substituted			
Substitutent	ΔC_2	ΔC_3	ΔC_4	ΔC_5	ΔC_2	ΔC_3	ΔC_4	ΔC_5
OMe	41.8	− 23.1	− 1.8	− 13.2	− 28.3	32.5	− 7.4	0.0
SMe	12.0	4.2	0.8	3.0	− 6.3	7.8	1.1	1.5
F	40.9	− 19.3	− 2.6	− 10.7	− 21.4	31.9	− 9.5	0.8
Cl	4.1	− 0.4	0.1	− 0.3	− 4.7	− 1.6	0.8	1.9
Br	− 18.1	3.4	1.2	2.5	− 2.2	− 17.3	2.9	1.9
I	− 52.0	10.3	2.4	6.9	4.3	− 46.5	8.2	3.1
CH_3	14.2	− 1.4	0.2	− 1.9	− 4.3	10.9	2.8	0.5
CH_2OH	20.4	− 2.2	− 0.1	− 0.3	—	—	—	—
CHO	19.3	10.1	1.9	10.0	12.4	16.8	− 1.7	2.9
$COCH_3$	19.8	6.2	1.6	8.8	7.9	16.4	0.2	1.9
COOH	9.1	7.0	1.3	7.9	8.3	7.6	1.5	1.7
COOMe	8.8	6.9	1.5	8.0	—	—	—	—
CN	− 15.6	11.3	1.5	8.6	11.5	− 15.9	2.3	3.5
NO_2	25.6	2.6	1.1	9.1	3.6	22.5	− 4.2	3.3

[a] ΔC = C (substrate) − C (reference); positive values are downfield.

TABLE 35. Regression Equations Relating ^{13}C Chemical Shifts of Monosubstituted Thiophenes and Benzenes to Substituent Constants $\mathcal{F}$ and $\mathcal{R}$

Equation	σ^b	r^c	N^d
$\Delta C_3^{2a} = 4.0 - 5.8\mathcal{F} + 46.7\mathcal{R}$	4.5	0.93	8
$\Delta C_4^2 = 1.1 - 0.9\mathcal{F} + 5.9\mathcal{R}$	0.6	0.93	8
$\Delta C_5^2 = 2.7 + 0.4\mathcal{F} + 33.5\mathcal{R}$	1.6	0.99	8
$\Delta C_2^3 = 2.9 - 5.2\mathcal{F} + 55.5\mathcal{R}$	3.3	0.97	8
$\Delta C_4^3 = 4.1 - 8.2\mathcal{F} + 15.1\mathcal{R}$	3.0	0.78	8
$\Delta C_5^3 = 0.7 + 1.9\mathcal{F} + 2.9\mathcal{R}$	0.4	0.93	8
$\Delta C_2^B = 2.9 - 8.0\mathcal{F} + 23.9\mathcal{R}$	4.1	0.80	8
$\Delta C_3^B = -0.4 + 1.5\mathcal{F} - 2.0\mathcal{R}$	2.0	0.94	8
$\Delta C_4^B = -0.1 + 2.3\mathcal{F} + 17.6\mathcal{R}$	1.0	0.98	8

[a] The shifts are given in ppm relative to those of thiophene (see Table 34). The notations ΔC_i^2, ΔC_j^3 denote the shifts of the *i*- and *j*-carbons of 2- and 3-substituted thiophenes, respectively, and ΔC_i^B the shift of benzene[1753].

[b] Standard deviation in ppm.

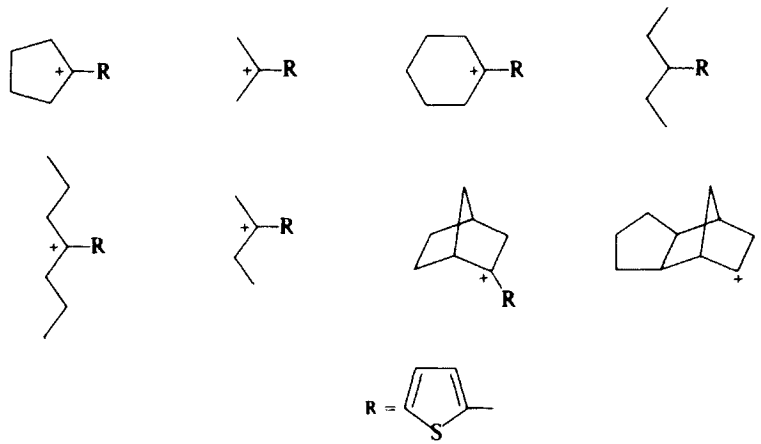
[c] Correlation coefficient.

[d] Number of substituents in the regression analysis.

The assignment of *E*- or *Z*-configuration thiophenic oximes and oxime ethers has been made from their ^{13}C NMR spectra.[932]

The ^{13}C NMR spectra of all bromosubstituted thiophenes have been studied. The ^{13}C signal assignments for monobromothiophenes have been confirmed with the spectra of their partially deuterated derivatives.[933,934]

^{13}C NMR data for mono-, di-, tri- and tetraiodothiophene have been discussed.[935] The ^{13}C NMR shifts of 2- and 3-allylthiophene have been reported.[936] The ^{13}C spectra of 2-thiophene aldehyde, 2-acetylthiophene, and their complexes with one and two moles of $AlCl_3$, as well as a 1 : 1 complex of ethyl 2-thiophenecarboxylate with $AlCl_3$, have been studied. As a result of complex formation, the C_3 and C_5 resonances are shifted markedly downfield, while C_4 is only slightly shifted downfield, and the 2-carbon is shifted upfield.[937] The response of ^{13}C chemical shifts at the ring position of various 2-thienylcarbenium ions to changes in substituents at the carbenium center have been compared to the corresponding changes in phenyl- and furylcarbenium ions. The unusually high sensitivity of the C_5-position was discussed in relation to calculated charges.[938] These studies were later expanded to thienylcarbonium ions such as those shown in Scheme 3.[939]



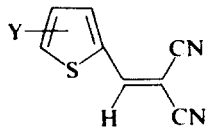
Scheme 3

Carbon-13 chemical shifts of 2-methoxy-3-nitro-5-substituted thiophenes and the Meisenheimer adducts with a gem-dimethoxy group have been determined. The ^{13}C chemical data suggest that most of the substituents in the 5-position favor the formation of the adducts mainly by stabilizing a fractional negative charge on C-5 of the ring.[940] The ^{13}C shifts of carbene complexes of the type $(CO)_5MXY$, where M = Cr or W; X = OR or NR_1R_2, and Y = 2-thienyl, have been studied. The 2-thienyl group was found to be less effective in shielding the carbene carbon than the 2-furyl group.[941] The ^{13}C NMR of bithienyls, terthienyls, and related compounds have been assigned on the basis of literature

data and by relaxation measurements, from which qualitative information about the conformational equilibria of these compounds was obtained.[942] The ^{13}C data for iron carbonyl derivatives of 2,2′-bithienyl have been reported.[943] The ^{13}C NMR spectrum analysis of electrochemically prepared poly(3-methylthienylene) films has been investigated. Both a film doped with ClO_4^- and an undoped film gave only two distinct absorption bands through the electrochemical reduction of the chlorate doped polythiophene.

The ^{13}C and ^{1}H NMR spectra of substituted 2-thienylethenes have been obtained.[944] In connection with a study of the ^{1}H and ^{13}C NMR spectra of 1-(5-nitro-2-furyl)-2-X-2-Y-ethylenes, some of their thiophene analogs were also investigated. All thiophene derivatives were found to have the S-*trans* conformation.[945] The ^{13}C NMR spectra of poly(2-vinylthiophene) and poly(3-vinyl-thiophene) have been studied.[946] ^{13}C NMR spectroscopy has been utilized for the identification of thiophene-substituted *E*- and *Z*-, α,β-unsaturated esters, ketones, and nitriles.[947]

Detailed investigations of ^{13}C NMR spectra of a large number of thiophene and furan chalcone analogues have been carried out. The effect of substituents on the ^{13}C chemical shifts in the phenyl and five-membered rings were discussed and were correlated with Hammett parameters.[948] These and other chalcone shifts were later analyzed by the application of principal component analysis, which was shown to be a useful tool for shift assignment and for the study of substituent effects.[949] The ^{13}C NMR shifts and direct CH coupling constants for some 2-thienylpropane dinitriles **108** have been reported. Linear correlations between the substituent chemical shifts for the β-carbons with those of the corresponding chalcones were found. The CN shifts were assigned from their J_{CCCH} long-range coupling constants.[950] The ^{13}C-substituent effects in the related 3-(2-tienyl)acrylamides **109** have been examined by multiple linear regression analysis using standard field parameters together with various resonance parameters.[951]



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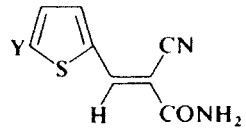

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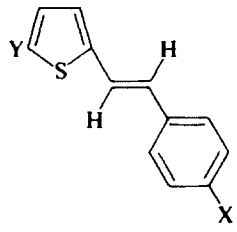
^{13}C NMR shifts for 15 compounds of type **110** have been reported. Substituent chemical shift considerations allow the assignment of disubstituted aromatic ring carbons. The effect of X- and Y-substituents on aromatic and ethylenic carbon shifts were discussed. The J_{CCCH} long-range coupling constants gave evidence for the *Z*-configuration of **110**.[952] ^{13}C NMR spectra for thienylpyrylium cations,[953] thienylselenediazoles,[954] thieno-[2,3-*b*]-[1,5]benzodiazepines,[955] 2-(2-thenyliden-3(2*H*)benzofuranones[1027] and 1,6-dithiaindan-4-one and -4-ols[956] have been reported. The ^{13}C NMR spectra of thiophene fused to



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four-, six-, and eight-membered rings have been studied and show that annelation by small rings results in an upfield chemical shift of the α-carbon atoms.[957]

The C-3 resonance of 2-thiophene aldehyde broadens to a maximum value at − 75°C and then sharpens to resume its original height at − 90°C. It was concluded that this shows that although 2-thiophene aldehyde exists as the *syn*-conformer over the whole temperature range, the ^{13}C results still demonstrate the occurrence of rotational isomerism.[958] In a later investigation, the low-temperature ^{13}C NMR spectra of 2- and 3-thiophenecarboxaldehyde were studied. They displayed line-broadening effects due to exchange between their S,O-*syn*- and S,O-*anti*-conformers. The free energy of activation for rotation of the CHO moiety was measured to be 10.15 and 8.5 kcal/mol for the 2- and 3-isomers, respectively. In the case of 3-thiophene aldehyde, the signals of both conformers were detected, and the ratios were 97 : 3 at − 140°C and 93 : 7 at − 100°C in favor of the S,O-*anti*-conformer. In 2-thiophene aldehyde the minor conformer (S,O-*anti*) was present in too small an amount to be unambiguously detected by a conventional spectrometer, but spectra taken with a superconducting instrument (75.48 MHz) revealed approximately 1.5% of this conformer at − 100°C.[959]

The adaption of a rigorous analysis of the lanthanide induced shifts allowed the nonpseudocontact components of the $Yb(fod)_3$-induced shifts in 2-thiophene aldehyde to be isolated. They are largest at the carbonyl carbon and at the 3- and 5-carbons, and appear to be due to complexation (diamagnetic) shifts.[960] This technique was also applied to 3-thiophene aldehyde, and from the pseudocontact shifts, it was concluded that this aldehyde exists to 80% in the S,O-*anti* form.[961]

In contrast to 2-acylfurans, separate ^{13}C signals for the *anti*- and *syn*-conformers could not be observed in the low-temperature spectra for 2-acylthiophenes. However, line-broadening effects allowed measurements of interconversion barriers. Lanthanide-induced shift experiments showed that in all the 2-acylthiophenes investigated, the S,O-*syn* rotamers are predominant.[962] ^{13}C NMR spectra have been utilized to compare protonation sites of aminothiophenes with those of other heterocyclic amines.[963] The pK_a values of 13 heterocyclic aromatic compounds, including thiophene, have been measured in THF using ^{13}C NMR spectroscopy.[964]

The one-bond carbon–carbon coupling $J_{C(2)-C(3)}$ of thiophene was found to be 64.2 Hz.[965] The magnitudes of the $^{13}C-^{31}P$ spin–spin coupling constants for tri-(2-thienyl)phosphine and tri-(3-thienyl)phosphine oxide have been obtained

from natural abundance noise-modulated proton-decoupled ^{13}C spectra. The assignment of ^{13}C chemical shifts, and thus the ^{13}C–^{31}P coupling constants, were based on established relationships and additivity rules of ^{13}C chemical shifts of thiophenes, on the nuclear Overhauser effect, and for the two tetracoordinated compounds on single frequency of resonance proton decoupling experiments. The one-bond ^{13}C–^{31}P coupling constants in the phosphines were much smaller than in the tetracoordinated compound, owing to the changes in phosphorus hybridization. Furthermore, in the phosphines the magnitude of this coupling constant was smaller than the two-bond ^{13}C–C–^{31}P coupling.[966] The assignment and relative signs of the ^{13}C–^{1}H coupling constants of 2,3-dibromothiophene[967,968] and the ^{13}C–^{31}P coupling constants of tri-(3-bromo-2-thienyl)phosphine were determined from selective population transfer.[967]

The ^{13}C NMR spectra of boron-substituted thiophenes have been studied. Low-temperature ^{13}C NMR and/or $^{13}C(^{11}B,^{1}H)$ heteronuclear triple resonance experiments were used to obtain ^{13}C shifts of the boron-bonded carbon atoms.[969] The ^{13}C NMR spectra of some selenium-substituted thiophenes have been studied.[970]

Electron–nuclear spin–lattice relaxation times for ^{13}C in natural abundance were determined for thiophene in the presence of metal chelates such as Gd 2,2,6,6-tetramethylheptane-3,5-dionate. The T_{1P} values for a 1-mol/cm^3 solution containing 5×10^{-4} mol/dm^3 of the metal chelate were 22 sec and 27 sec for C_α and C_β of thiophene, respectively.[971] The spin–lattice relaxation times for ^{13}C in 2-acetylthiophene[972] and 2-bromthiophene[904] have been determined. In a study of 30 solvents, the effect of thiophene on the chemical shift and ^{13}C–H coupling of bromoform was determined.[973]

B. ^{33}S NMR Spectroscopy of Thiophenes

Because of the low natural abundance of the ^{33}S isotope, its spin of 3/2, and its large quadropole moment, ^{33}S NMR spectra have been difficult to study. The chemical shifts of thiophene[974,975] 2- and 3-methylthiophene and 3-bromothiophene[975] relative to CS_2 were -220 ± 6 ppm, -178 ± 9 ppm, -197 ± 26 ppm, and 134 ppm, respectively.

A chemical shift of neat thiophene of -119 ppm to external 2-mol/cm^3 aqueous cesium sulfate and a linewidth of 1450 Hz have recently been obtained.[976] In another investigation of thiophene, a chemical shift of -138 ppm relative to sulfolane was reported for the neat compound, and -151 ppm in CS_2 solution corresponding to shifts of 223 and 220 ppm relative to CS_2.[977] ^{33}S NMR spectra have been obtained for 2-ethylthiophene-1,1-dioxide and 2,5-dimethylthiophene-1,1-dioxide, with chemical shifts of 31 and 26 ppm relative to sulfate ion.[978] The ^{33}S spectra of tetrahydro- and dihydrothiophene-1,1-dioxides have been carefully investigated.[979–981]

It was possible to study the influence of substituent on the thiophenic sulfur indirectly by investigating the ^{77}Se shifts of selenophenes. Linear correlations were observed between the substituent-caused ^{77}Se shifts of 2-substituted

selenophenes and similarly ortho-positioned ^{13}C shifts, when carbonyl-containing derivatives and 2-nitroselenophene were excluded. The substituent-caused shift in the 3-substituted derivatives indicate that electronically the heteroatom and the substituents are para- and not meta-related.[982]

C. ^{19}F NMR Spectroscopy of Thiophenes

Detailed investigation of substituent effects on the chemical shifts and coupling constants of fluorinated thiophenes have been carried out.[619,658-660,683,684] 2-Fluorothiophene showed a chemical shift of 28.30 ppm downfield from hexafluorobenzene, and proton couplings $J_{F-3} = 1.62$, $J_{F-4} = 3.07$, and $J_{F-5} = 3.10$ Hz, all having the same sign as the H–H spin coupling constants. The ^{13}C–^{19}F coupling constant was 285 Hz. An isotope shift of 0.014 ppm of the fluorine resonance of 2-fluorothiophene due to ^{34}S was observed. The chemical shift for 3-fluorothiophene was 32.05 ppm, and $J_{F-2} = 1.08$ Hz, $J_{F-4} = -0.81$ Hz, and $J_{F-5} = 3.3$ Hz were obtained. The ^{13}C–^{19}F coupling constant was 256 Hz for 3-fluorothiophene.[619]

Analyses of the ^{19}F spectra of the four difluorothiophenes, 5-bromo-2,3-difluorothiophene, 3-bromo-2,5-difluorothiophene, and 2,3,5-trifluorothiophene, gave the following H–F spin couplings (in Hz): $J_{2F-3} = 1.29$–3.40; $J_{3F-2} = 1.23$–2.92; $J_{3F-4} = -0.33$– $+0.88$; $J_{2F-3F} = 3.08$–3.66; $J_{3F-5} = 3.17$–4.61; and $J_{2F-5} = 3.40$–4.47. The magnitudes of the different F–F spin couplings were $J_{2F-3F} = 0.22$–4.85 Hz, $J_{2F-4F} = 9.23$–15.26 Hz, $J_{3F-4F} = 12.88$ Hz, and $J_{2F-5F} = 22.91$–27.76 Hz.[658] Large J_{2F-5F} (26–31 Hz) coupling were also observed in 2,5-difluoro-3-methoxythiophene, 2,3,5-trifluoro-4-methoxythiophene, and tetrafluorothiophene, while this large coupling was absent in 2,3,4-trifluoro-5-methoxythiophene.[985] The J_{3F-4F} coupling was found to be of opposite sign to the proton–proton spin coupling J_{25}. In the polyfluorothiophenes with a fluorine atom in both the 2- and 3-positions, a considerable increase in the fluorine chemical shifts compared to those in 2- and 3-fluorothiophene was observed. In 2,3-difluorothiophene, this upfield shift was 21.87 ppm for the 2-fluorine and 18.68 ppm for the 3-fluorine. In 3,4-difluorothiophene, there is also an increase in the shielding of the fluorine nuclei by 8.08 ppm compared to that of 3-fluorothiophene. In 2,5-difluorothiophene, the fluorine chemical shift is 1.80 ppm upfield from that of 2-fluorothiophene, whereas in 2,4-difluorothiophene the 2-fluorine resonance is shifted 8.97 ppm and the 4-fluorine resonance 7.73 ppm downfield from the fluorine resonance in 2- and 3-fluorothiophene, respectively.[658] The ^{1}H and ^{19}F NMR spectra of nineteen 5-substituted 2-fluorothiophenes (type I), thirteen 4-substituted 2-fluorothiophenes (type II), and fourteen 5-substituted 3-fluorothiophenes (type III) have been analyzed, and the results are collected in Tables 36 and 37.[659]

The chemical shifts of these three series have been correlated with the reactivity constants $\mathcal{F}$ and $\mathcal{R}$ of Swain and Lupton by means of linear two-parameter equations. However, certain substituents had to be excluded from

TABLE 36. ^{19}F NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 2-Fluorothiophenes in Cyclohexane Solution with Hexafluorobenzene as in Ref 659.

R_3	R_4	R_5	δF	J_{F-3}	J_{F-4}	J_{F-5}	J_{F-R}
	Br		34.60	0.78		3.32	
		Br	36.17	2.39	3.43		
	Cl		35.36	0.95		3.40	
		Cl	34.51	2.76	3.49		
	I		33.25	0.61	3.13		
		I	38.75	2.22	3.22		
		NO_2	46.31	2.06	4.29		
	F		37.27	1.29		3.40[a]	
			37.25	1.35		3.45[b]	
F			6.31		3.08	4.28[a]	
			6.31		3.12	4.47[b]	
		F	26.50	0.5	2.86[a]		
			26.53	3.26	3.66[b]		
			28.28[c]				
	CHO		35.38	1.37		3.63	3.29
	CN		34.49	1.18		3.55	
		CN	40.74	1.82	3.74		
		CHO	45.73	1.17	3.66		4.20
		COOH	41.17	1.76	3.89[d]		
	COOH		33.00	1.56	3.92[d]		
	Anti	CHNOH	33.98	2.23	4.01		3.76[d]
	Syn	"	34.14	1.98	3.77		3.42[d]
Anti	CHNOH		29.56	2.04	3.97		1.07[d]
Syn	"		32.39	1.98	3.78		2.27[d]
		OCH_3	23.62	3.46	3.02		
	SO_2CH_3		36.72	1.12		3.82[d]	
		SO_2CH_3	42.65	1.47	3.75		0.32[d]
	CH_3		30.61	1.55		3.55	0.11
		CH_3	29.60	2.03	3.20		2.77
	SCH_3		33.24	1.34		3.44	
		SCH_3	39.07	2.52	3.49		0.30
	$COCH_3$		33.40	1.53		3.55	
		$COCH_3$	43.14	1.45	3.52		0.44
	CO_2CH_3		32.98	1.36	3.86		
		CO_2CH_3	40.82	1.50	3.85		
		C_2H_5	29.21	1.95	3.20		2.66
		C_3H_7	29.39	1.85	3.17		2.74
		C_4H_9	29.30	1.90	3.14		2.75
		t-C_4H_9	28.57	1.75	3.19		
	C_6H_5		31.99	1.74		3.54	
		C_6H_5	31.83	1.92	3.48		

[a] Ref. = 658.
[b] In benzene.
[c] Ref. 619.
[d] In acetone.

TABLE 37. ^{19}F NMR Chemical Shifts (ppm) and Coupling Constants (Hz) of 3-Fluorothiophenes in Cyclohexane with Hexafluorobenzene as in Ref. 659

R_2	R_4	R_5	δ_F	J_{3F-2}	J_{3F-4}	J_{3F-5}	J_{3F-R}
		Br	37.76	1.88	− 0.96		
		Cl	38.40	2.00	− 0.80		
		I	36.58	1.54	− 1.16		
		NO_2	41.02	1.55	− 0.89		
F			13.34		− 0.09	4.41[a]	
			13.71		− 0.12	4.61[b]	
		F	39.85	2.81	− 0.33[a]		
			39.83	2.92	− 0.27[b]		
	F		23.80	1.23		3.17[a]	
			23.68	1.35		3.26[b]	
			32.04[c]				
		CN	36.35	1.08	− 0.86		
			36.10	1.45	− 0.67[d]		
		CHO	36.97	0.58	− 0.99		0.57
		Anti-CHNOH	31.72	1.61	− 0.55[d]		
		COOH	36.88	1.15	− 0.80[d]		
		SO_2CH_3	38.21	0.87	− 1.09[d]		
		CH_3	34.65	1.45	− 0.69		− 0.22
		SCH_3	36.59	1.75	− 0.90		0.11
		$COCH_3$	37.22	0.78	− 0.96		0.57
		CO_2CH_3	36.48	0.87	− 0.87		
		C_6H_5	36.05	1.21	− 0.54		

[a] Ref. 658.
[b] In benzene.
[c] Ref. 619.
[d] In acetone.

these correlations, and the reason for this was discussed. No good correlations were obtained for J_{2F-3} and J_{2F-5} in 4-substituted 2-fluorothiophenes and J_{3F-4} in 5-substituted 3-fluorothiophenes. The observed regression equations are given in Table 38.[660] Molecular orbital calculations of ^{19}F chemical shifts in fluorothiophenes have been carried out.[986]

The possible occurrence of rotational isomerism in 2-thiophenecarbonyl fluoride[857,987] and some bromosubstituted thiophenecarbonyl fluorides[857] has been studied with ^{19}F NMR. As the temperature was lowered, the signals gradually broadened and at certain temperatures became so broad that they were no longer visible. With all of the thiophenecarbonyl fluorides, except for 2,4-dibromothiophenecarbonyl fluoride, a further decrease in temperature resulted in the appearance of two ^{19}F signals. However, the energy barrier to rotation in the fluorides must be low.[857] The coupling constants of 2-thiophenecarbonyl fluoride were calculated in the CNDO/2 and INDO approximations. The correlations were discussed in terms of model geometries.[988,989]

TABLE 38. Regression Equations Relating Proton Chemical Shifts[a] of Fluorothiophenes to Substituent Constants $\mathcal{F}$ and $\mathcal{R}$, and Linear Relations between Some of the Shifts

Equation	σ	C	N
$\delta^{I}_{3} = 0.07 \pm 0.06 - (0.11 \pm 0.08)\mathcal{F} - (1.05 \pm 0.13)\mathcal{R}$	0.09	0.95	9
$\delta^{I}_{4} = 0.01 \pm 0.10 - (0.52 \pm 0.14)\mathcal{F} - (2.65 \pm 0.22)\mathcal{R}$	0.15	0.98	9
$\delta^{II}_{3} = -0.02 \pm 0.05 - (0.24 \pm 0.09)\mathcal{F} - (1.06 \pm 0.15)\mathcal{R}$	0.08	0.94	8
$\delta^{II}_{5} = -0.02 \pm 0.06 - (0.51 \pm 0.10)\mathcal{F} - (2.86 \pm 0.18)\mathcal{R}$	0.09	0.99	8
$\delta^{III}_{2} = 0.06 \pm 0.13 - (0.35 \pm 0.18)\mathcal{F} - (2.11 \pm 0.37)\mathcal{R}$	0.19	0.92	8
$\delta^{III}_{4} = 0.05 \pm 0.12 - (0.52 \pm 0.18)\mathcal{F} - (2.21 \pm 0.36)\mathcal{R}$	0.18	0.94	8
$\delta^{I}_{4} = 0.01 \pm 0.02 + (0.89 \pm 0.03)\delta^{II}_{5}$	0.06	0.99	11
$\delta^{III}_{4} = -0.01 \pm 0.02 + (0.87 \pm 0.03)\delta^{I}_{4}$	0.07	0.99	16
$\delta^{III}_{2} = 0.10 \pm 0.03 + (0.88 \pm 0.05)\delta^{III}_{4}$	0.08	0.98	13
$\delta^{II}_{3} = -0.22 \pm 0.03 + (0.99 \pm 0.12)\delta^{I}_{3}$	0.11	0.92	13

[a] The shifts in the regression analyses are given in ppm relative to those of the unsubstituted fluorothiophenes. The notation δ^{I}_{i} denotes the shift of the i-proton in compounds of type I.

The nonequivalence of the enantiomers of 2,2,2-trifluoro-1-(2-thienyl)ethanol in optically active α-(1-naphthyl)ethylamine has been observed with ^{19}F NMR spectroscopy.[990] The ^{19}F- and ^{29}Si-NMR parameters have been determined for 2-thenoylmethyl trifluorosilane.[991]

D. NMR Spectra of Thiophenes Bound to Other Magnetically Active Nuclei

a. ^{11}B-Substituted Thiophenes

The ^{11}B-chemical shifts of tri-(2-thienyl)borane, di-(2-thienyl)methylborane, di(dimethylamino)-2-thienylborane, 2-thienylboron dichloride, and some other 2-thienylboron derivatives have been reported.[969]

b. ^{27}Al-Substituted Thiophenes

The complex between thiophene and triethylaluminium has been studied with ^{27}Al NMR.[993]

c. ^{31}P-Substituted Thiophenes

^{31}P chemical shifts have been measured for tri-(2-thienyl)methylphosphonium iodide, tri-(2-thienyl)-benzylphosphonium bromide, and diethyl 2-thienylposphonate and compared with those of the corresponding benzene and furan derivatives. A trend toward a greater shielding of the phosphorous on going from phenyl to 2-thienyl to 2-furyl substituents was observed. This is due to the increasing electron-withdrawing character of the heteroaryl ring as the electronegativity of the heteroatom increases. The equilibria between the

phosphonium salts and methoxide ion, in absolute methanol, to form the methoxyphosphoranes, has been studied by ^{31}P NMR. The position of the equilibrium was shown to depend on the electron-withdrawing character of the group attached to phosphorous.[994] The ^{31}P NMR spectra of a number of acylmethylene phosphoranes, also containing thienyl substituents, have been measured and the chemical shifts interpreted in terms of steric interactions and resonance stabilization of the ylides.[995] Atomic orbital exponents have been regarded as dependent on the electronegativity difference between directly bonded atoms in the molecule. A simple relationship was introduced, which led to good agreement between calculated and experimental shifts or magnetic anisotropies for both ^{31}P and ^{13}C atoms.[996]

d. ^{77}Se-Substituted Thiophenes

^{77}Se shifts have been reported for alkyl seleno- and selenocyano-substituted thiopenes.[970]

e. ^{119}Sn-Substituted Thiophenes

^{119}Sn chemical shifts have been reported for 2- and 3-thienyltrimethylstannane and tetra-(2-thienyl)- and tetra-(3-thienyl)stannane. The assignments of some ^{13}C chemical shifts in 2-thienylstannanes were reversed. Proton coupled ^{119}Sn NMR spectra were shown to be useful for the detection of long-range Sn–H couplings not readily obtained from the complex ^{1}H NMR spectra.[998] ^{119}Sn NMR investigations and Mössbauer studies of 2- and 3-thienylthin halides $(C_4H_3S)_nSnX_{4-n}$ $n = 2,3$ have been reported.[883,999] Mössbauer spectroscopy indicated that the halides have an associated tetrahedral structure.[883]

4. Nuclear Quadropole Resonance Spectra (NQR) of Thiophenes

A. ^{35}Cl Spectra

Measurements of ^{35}Cl NQR spectra of 2-chloro-, 2,5-dichloro-, and tetrachlorothiophene[992,997,1000] and of a series of 5-substituted 2-chlorothiophenes[1001] have been reported and correlated with Hammett's σ-constants.[1001] The NQR frequency of 2-thiophenesulfonyl chloride was found to be 33.1507 MC/sec at liquid nitrogen temperature.[1002]

B. ^{77}Br Spectra

^{77}Br NQR frequencies of 37 bromothiophenes (Table 39) have been measured at 77 K. The frequencies correlate with Hammett's σ-values, and this correlation demonstrated the importance of the inductive effect. The influence

TABLE 39. ^{79}Br NQR Frequencies of Bromothiophene Derivatives

R_2	R_3	R_4	R_5	F (MHz)	S/N
Br				290.9	10
Br			Br	291.68	5
				291.98	10
				292.73	10
				293.07	10
				293.86	8
				294.47	3
				295.09	2
Br			Cl	291.91	2
				292.67	2
				292.96	2
				293.54	2
				293.58	2
				293.77	2
				293.94	2
Br			I	290.08	5
				290.17	3
				292.45	1.5
				292.67	1.5
				298.5	2
Br	Cl	Cl	Br	297.36	2
				297.71	2
				298.24	3
				298.42	3
Cl	Br	Br	Cl	297.24	25
				297.72–298.98	5
Br	Br	Cl	Cl	297.04–299.15	5.5
				305.83–306.51	2.5
H	Br	Br	H	285.15	10
				288.40	5
				289.46	5
				292.44	10
H	Br	H	H	277.4–279.8	4
Br	Br	Br	Cl	296.25–298.14	4
Br	Br	Br	Br	296.62	20
				296.89	20
				305.51	20
				305.94	20
Br	Br	Br	C_2H_5	291.87	3
				291.99	3
				297.40	4
				297.53	4
Br	Br	H	Br	289.01–291.84	4
				296.06–299.52	4
				300.84–304.32	4
Br	Br	Br	H	294.63–297.12	4
				297.36–298.54	2.5

TABLE 39. (*Continued*)

R_2	R_3	R_4	R_5	*F* (MHz)	S/N
Br	H	Br	COOH	295.36	2
Br	H	H	COCOOH	297.06	3
Br	H	H	$COCHCl_2$	294.87	2.5
Br	H	H	$COCCl_3$	297.35 297.56	12 12
Br	H	H	$CH(OCOCH_3)CCl_3$	295.74	7
Br	H	H	$COCH_3$	299.58	16
Br	Br	Br	$COCOOCH_3$	299.64 305.76 306.90	10 10 10
Br	Br	Br	$COCOOC_2H_5$	297.11 306.80 307.52	10 10 15
Br	Br	Br	$COCOOC_3H_7$	301.31 302.08 309.63	2 2 3
Br	Br	Br	$COCOOCH(CH_3)_2$	300.10 300.99 304.52	6 5 5
Br	Br	Br	$COCOOC_4H_9$	296.94 305.48 305.93	20 20 20
C_2H_5	Br	H	COOH	280.70	3.5
C_2H_5	Br	H	COCOOH	281.95–283.3	2
CH_3	Br	H	$COCOOCO(CH_3)_2$	283.30	6
H	Br	Br	$COCOOCH_3$	294.87	2
H	Br	Br	$COCOOC_2H_5$	293.82 297.94	4 5
Br	H	Br	COCOOH	294.35 299.64	2 2
Br	H	Br	$COCOOC_2H_5$	297.97 300.13	6 5
Cl	Br	Cl	$COCOOC_2H_5$	308.08–308.36	2.5
Br	Cl	Cl	$COCOOC_3H_7$	307.22	4.5
Br	H	H	5-Bromo-2-thienyl	292.00	6
Br	H	H	$CH[CH(CH_3)_2]$-5-Bromo-2-thienyl	294.47 296.09	6 6
Br	H	H	CH_2-5-Bromo-2-thienyl	290.70 291.35	4 5

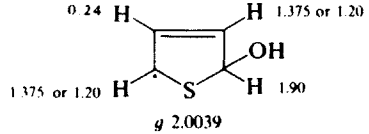
[a] Signal/noise ratio.

of more than one substituent on the thiophene ring was found to be additive.[1003,1004] The ^{35}Cl, ^{79}Br, and ^{127}I NQR frequencies of a number of halothiophenes have been determined in terms of the Kaplansky–Whitehead theory with the INDO-MO approximations, using a consistent set of atomic parameters derived from SCF Hartree–Fock calculations.[1005]

XII. ELECTRON SPIN RESONANCE SPECTROSCOPY OF THIOPHENES

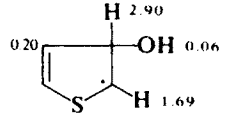
1. Radicals Derived from Thiophenes

Electron spin resonance spectroscopy has been used to identify the radicals formed at different pH values in the reaction of thiophenes with a variety of radical species, such as ·OH, Cl_2^-·, NH_3^+· and SO_4^-·. When thiophene was oxidized by ·OH at pH 6, the radicals **111** and **112** were detected. The g values and splittings observed are indicated in the formulas. The relative concentrations of **111** and **112** remained about 4 : 1 in the pH range 4.5–6. As the pH was lowered below 4.5, the signal due to **111** increased in intensity, and that of **112** decreased; below pH 2.5 only **111** was observed.



g 2.0039

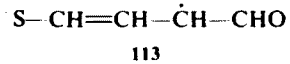
111



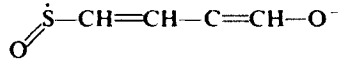
g 2.0038

112

When thiophene was oxidized by ·OH at pH higher than 6, two new species, **113** and **114**, formed by ring opening were observed, in addition to **111** and **112**. The radicals **113** and **114** were formed at the expense of **111**, and at pH 8.5 signals from **111** had disappeared completely.



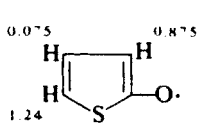
113



114

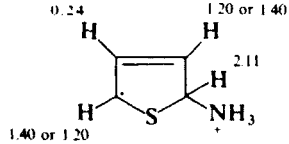
The major species detected when thiophene was oxidized by Cl_2^-· below pH 2.5 was also **111**; in addition, a signal assigned to **115** was observed. Reaction of thiophene with NH_3^+· at low pH led to the formation of **116** and **117** in a 4 : 1 ratio, which did not change with pH.

On oxidation with ·OH in the pH range 2–7, 2-methylthiophene gave **118** and **119** in a ratio of about 4 : 1. In addition, at pH > 4, traces of **120** were observed. When the pH was lowered to 1.5, signals from **119** disappeared and the signal of the thenyl radical **121** appeared, which on further lowering of the



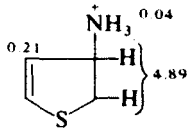
g 2.0037

115



g 2.0038

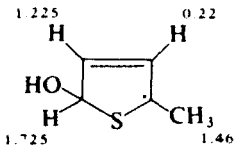
116



g 2.0039

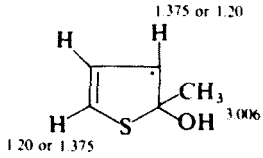
117

pH increased at the expense of the signal due to **118**. Furthermore, a weak signal attributed to the thenoxyl radical **122** was observed. Reaction with $Cl_2^-\cdot$ in the pH range 0–2 resulted in the formation of **118**, **121**, and **122**.



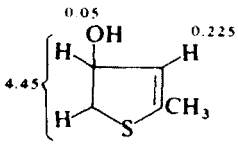
g 2.0037

118



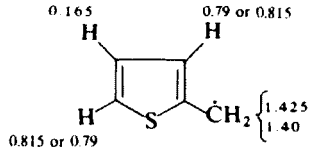
g 2.0039

119



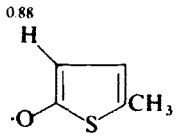
g 2.0039

120



g 2.0032

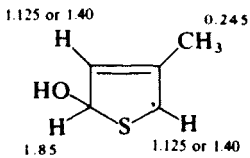
121



g 2.0036

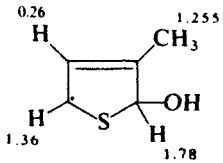
122

In the reaction of 3-methylthiophene with ·OH, signals from all three adducts, **123**, **124**, and **125**, were observed, with **125** present in much lower concentration than the other two.



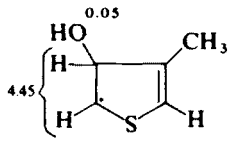
g 2.0040

123



g 2.0039

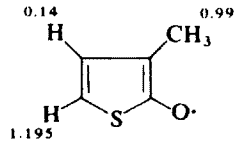
124



g 2.0040

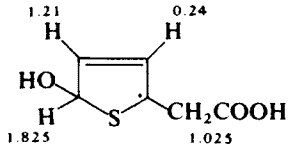
125

In addition, at pH lower than 0.5 a weak background signal from **126** was detected. On reaction with $Cl_2^-\cdot$, **124** and **126** were observed. No 3-thenyl radical was detected, reflecting the greater stability of **121** due to more extensive conjugation. Reaction of 2-thienylacetic acid with ·OH at pH < 3 led to the thenyl radicals **121** and **127**. With $Cl_2^-\cdot$, only **121**, and with $NH_3^+\cdot$, only **128**, was obtained.



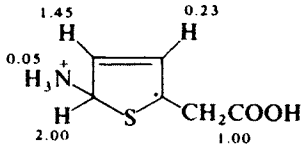
g 2.0036

126



g 2.0038

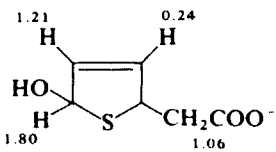
127



g 2.0036

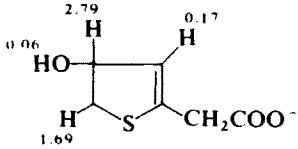
128

Oxidation of the anion of 2-thienylacetic acid at pH values greater than 4 gave a more complex product mixture, and besides **121** the three hydroxylated species **129–131** were also observed. Their proportions varied considerably with pH.



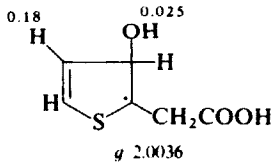
g 2.0036

129



g 2.0038

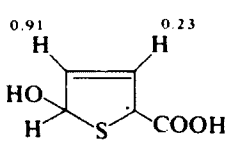
130



g 2.0036

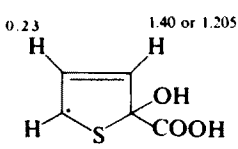
131

2-Thiophenecarboxylic acid gave a more complex product mixture than 2-thienylacetic acid on oxidation with ·OH, and signals due to **132–135** were observed. In alkaline media the anions corresponding to **132–134** were observed, in addition to **136**.



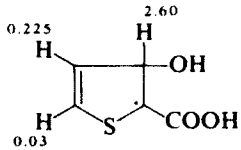
g 2.0048

132



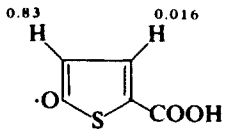
g 2.0038

133



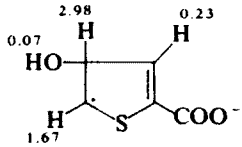
g 2.0051

134



g 2.0043

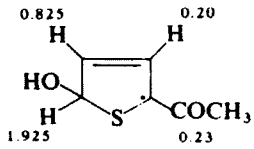
135



g 2.0038

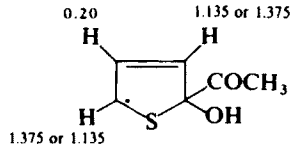
136

The reaction of 2-acetylthiophene with ·OH in the pH range 0–2 led to the detection of a complex spectrum, in which signals attributed to **137** and **138** could be discerned. At pH > 2, signals assigned to **139** appeared, and at pH > 7 **137** and **138** disappeared, and signals due to the ring-opened species **140** were observed.[1006] Thenyl radicals have also been generated by the reaction of tert-butoxy radicals with methylthiophenes. The hyperfine coupling constants are given in Table 40. The nonequivalence of the two methylene protons, which show different hyperfine coupling constants, was discussed and the spin distributions in the radicals were compared with the results of semiempirical molecular orbital calculations.[1007,1008]



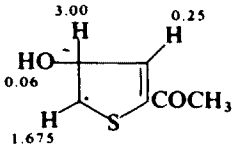
g 2.0051

137



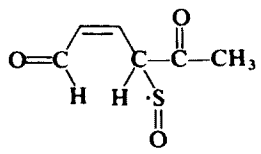
g 2.0038

138



g 2.0039

139



140

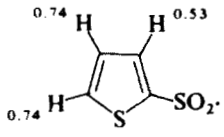
TABLE 40. Hyperfine Coupling Constants of Some Thiophene Radicals

Radical	a_2	a_3	a_4	a_5	a_{CH}
2-Thenyl		8.26	1.62	7.89	13.97, 14.22
3-Thenyl	8.94		0.74	1.86	16.39, 16.89
5-Methyl-2-thenyl		8.52	1.36	8.28[a]	13.56, 13.23

[a] Quartet from three equivalent protons.

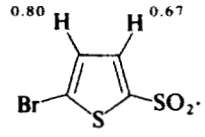
The ESR spectra of a variety of photochemically generated thiophene-2-sulfonyl radicals have been described (**141–148**). Their spin distribution was typical of σ-radicals. Radicals without substituents at position 3 exhibit relat-

ively rapid rotation about the C—S bond at all accessible temperatures, while the 3-bromo substituted ones demonstrate a marked conformational preference, which was interpreted in terms of a π-type conjugated structure.[1009]



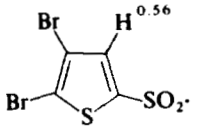
g 2.0042

141



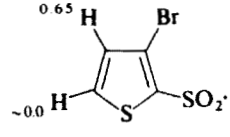
g 2.0047

142



g 2.0048

143



g 2.0054

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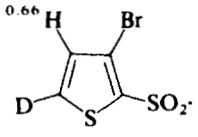
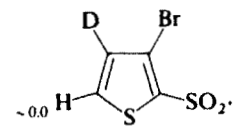


g 2.0054

145



g 2.0053

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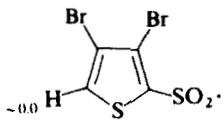
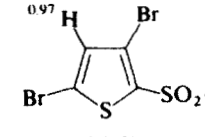


g 2.0057

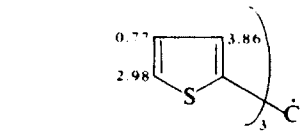
147



g 2.0058

148

In the reaction of solid 3-methylthiophene with hydrogen atoms at low temperature, the 3-thenyl radical was formed by stripping a hydrogen atom from the CH_3 group, while 2-methylthiophene, as well as 2-thiophene aldehyde and 2-acetylthiophene, added the hydrogen atom to the ring to form radicals with an unpaired electron at the carbon atom. In the gas phase reaction at room temperature with hydrogen atoms, 2- and 3-methylthiophene gave the 2- and 3-thenyl radicals, respectively.[1010] The ESR spectra of thienylphenyl- and trithienylmethyl radicals have been analyzed. These radicals (**149–154**) can conveniently be generated by heating an oxygen-free mixture of the corresponding perchlorates with zinc powder in dimethoxyethane. The hyperfine splittings observed are indicated in the formulas.[1011–1013]



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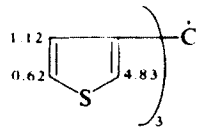

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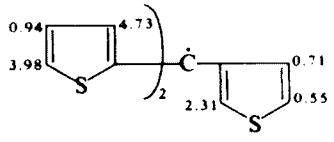

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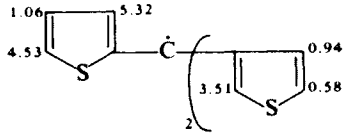

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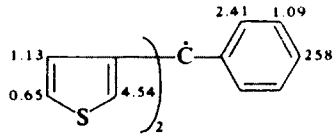

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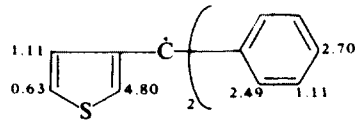


154

It is apparent from the experimental hyperfine coupling constants that the 2-thienyl group is much more efficient than the phenyl groups in the delocalization of the odd electron, while the 3-thienyl group behaves approximately as a phenyl group. The hyperfine splitting constants of a variety of thiophene radicals have been calculated by the INDO SCF-MO method and found to be in quite satisfactory overall agreement with experiment.[1014]

An INDO study showed that the tris-(2-thienyl)methyl radical exists in two diastereomeric propeller-like conformations. The cis form (C_3 symmetry) is more stable by 0.75 kcal/mol than the trans form (C_1 symmetry). The two forms undergo readily conformational interconversions by the two-ring flip mechanism, with activation energies of about 6 kcal/mol.[1015] Radicals have also been generated during the oxidation of 4,5-diphenyl-2-(2′-thienyl)imidazole, but their weak ESR spectra were not analyzed.[1016]

The ESR spectra of the paramagnetic species produced by the photoreaction of benzo[2,1-*b*; 3,4-*b*′]dithiophene-4,5-dione with a number of organomercurials have been recorded. The spectral parameters and the temperature dependence of the ^{199}Hg coupling constants were consistent with a structure of the adducts in which the Hg atom was bound to both carbonyl oxygens.[1017]

2-Thienyl and 3-thienyl radicals have been suggested as intermediates in various reactions, but they have not yet been fully characterized by their ESR spectra[1018,1019] (see also this series, Part 1, Chapter IX).

The products formed on radiolysis (5–50 Mrad) of thiophene[730,1020,1021] and some substituted derivatives, such as 2-chloro-, 3-bromo-, 2-t-butyl-, and 2-carboxythiophene,[1022,1023] were analyzed by ESR. The radicals formed from thiophene, alkylthiophenes, and thiophenecarboxylic acid arose in a primary radiation–chemical event with splitting of the C—H bond in both ring and side

chain. Characteristic of the radiolysis of these compounds was the formation of secondary radicals by the addition of hydrogen atoms to the double bond of the heteroaromatic ring. In the radiolysis of 2-chloro and 3-bromothiophene, the main products were radicals with the unpaired electron localized on the sulfur atom.[1022] In the ESR spectrum, γ-irradiated 2-thiophenecarboxylic acid showed two large couplings that were nearly isotropic, but always different from each other. These couplings (78 and 90 MHz) were attributed to two hydrogens attached to the 5-position, which was proved by studying the 5-deuteriated derivative, and suggests that the ring is buckled.[1023,1024] The substitution of 2-thenoyl-, 5-methyl-2-thenoyl-, 2-thiopheneacryloyl-, 5-bromo-2-thenoyl-, and 5-bromo-2-thiopheneacryloyl groups on fibrous cotton cellulose increased the radiation resistance of cellulose at high dosages of γ-radiation.[1025] In connection with the recent interest in polythiophenes as conducting polymers, studies of the ESR spectra of doped polythiophenes have been carried out.[293,294,300,301,311,312,315,1026]

2. Radical Anions Derived from Thiophene Derivatives

A. Carbonyl Derivatives

Extensive investigations of the radical anions of thienyl carbonyl derivatives have been carried out.[1007,1011,1028–1031] When the anion radical of 2-acetylthiophene was generated by electrolysis in DME or DMF, only one isomer was observed.[1031] On the other hand, generating the radical anion by photolysis in 10^{-2} M solutions and sodium methoxide in methanol gave two overlapping spectra, present in unequal amounts, which were assigned to the O-*cis* and O-*trans* isomers, respectively.[1007,1011] The relative strengths of the overlapping spectra were temperature-dependent, as expected for two species in thermal equilibrium. Similar results were obtained for 2-thiophene aldehyde. Based on theoretical considerations, the major rotameter, with larger couplings to the proton in position 3, was assigned to be the O-*cis* form. The signals from the 3-thiophene aldehyde ketyl were rather weak and poorly resolved, and only one single isomer was observed[1007] (see Table 41). The role of solvation and surface factors in the electrochemical hydrodimerization of the radical anion derived from 2-thiophenecarboxaldehyde in DMF[321] has been studied.

The room-temperature ESR spectrum of the photolytically generated anion of 2,5-thiophenedicarboxaldehyde showed the existence of two of the three possible rotational isomers. The less stable one could easily be identified as the O-*cis*–*trans* isomer because of the nonequivalence of the thiophene proton splittings. The ESR spectrum of 2,5-diacetylthiophene also showed two rotational isomers and a definite increase of the asymmetric species from 8% in the dialdehyde to 25%. This supports the conclusion that the major rotamer is the O-*cis*–*cis* isomer, as bulkier substituents at the carbonyl group are expected

TABLE 41. Hyperfine Splitting Constants of Radical Anions Derived from

R	R_3	R_4	R_5	Solvent	R	Splitting Constants (G) a_3	a_4	a_5	Ref.
CH_3	H	H	H	DMF	6.15	6.68	1.50	6.38	1031
CH_3	H	H	H	DMF	6.38	6.68	1.38	6.38	"
CH_3	H	H	$C(CH_3)_3$	DMF	6.13	6.63	1.50	—	"
CH_3	H	$C(CH_3)_3$	H	DMF	6.25	6.25	—	6.25	"
CH_3	$C(CH_3)_3$	H	$C(CH_3)_3$	DMF	5.06	- -	1.50	-	"
CH_3	$C(CH_3)_3$	H	$C(CH_3)_3$	CH_3CN	5.38	—	1.52	—	"
$C(CH_3)_3$	H	H	H	DMF	0.17	6.40	1.27	6.03	"
H(O-*cis*)	H	H	H		11.24	7.42	1.73	7.29	1007
H(O-*trans*)	H	H	H		11.87	7.29	1.67	6.43	"
CH_3(O-*cis*)	H	H	H	9.75	7.40	1.73	7.16	"	"
CH_3(O-*trans*)	H	H	H	10.12	7.65	1.73	6.91	"	"

to reduce the stability of the three conformers in the order O-*cis*–*cis* > O-*cis*–*trans* > O-*trans*–*trans*. On the other hand, in 3,4-dimethyl-2,5-thiophenedicarboxaldehyde the stability of the O-*cis*–*cis* isomer should be enhanced because of the greater methyl–oxygen repulsion, and indeed only the symmetric rotamer could be detected. Also for 2,5-bis-trifluoroacetylthiophene only the symmetric O-*cis*–*cis* form was detected.[1029] The ESR spectrum of the radical anion of 2,5-thiophenedicarboxaldehyde was also produced by metal reduction in ethereal solvents. It showed a marked linewidth alternation that was attributed to the migration of the counterion between two equivalent carbonyl groups. A kinetic study of this process in dimethoxymethane and THF using sodium or potassium as reducing agent was also undertaken.[1030] The hyperfine splitting constants are given in Table 42.

The radical anions of a number of dithienyl ketones and arylthienyl ketones have been generated by electrolysis and their ESR spectra interpreted.[1007,1011,1028,1032] The hyperfine coupling constants are indicated in the formulas in Table 43. By the use of deuterated derivatives, it was determined that the coupling to the 3-hydrogen was larger than that to the 5-hydrogen.[1028]

TABLE 42. Hyperfine Splitting Constants (in Gauss) of the Radical Anions of Some Dicarbonyl Derivatives

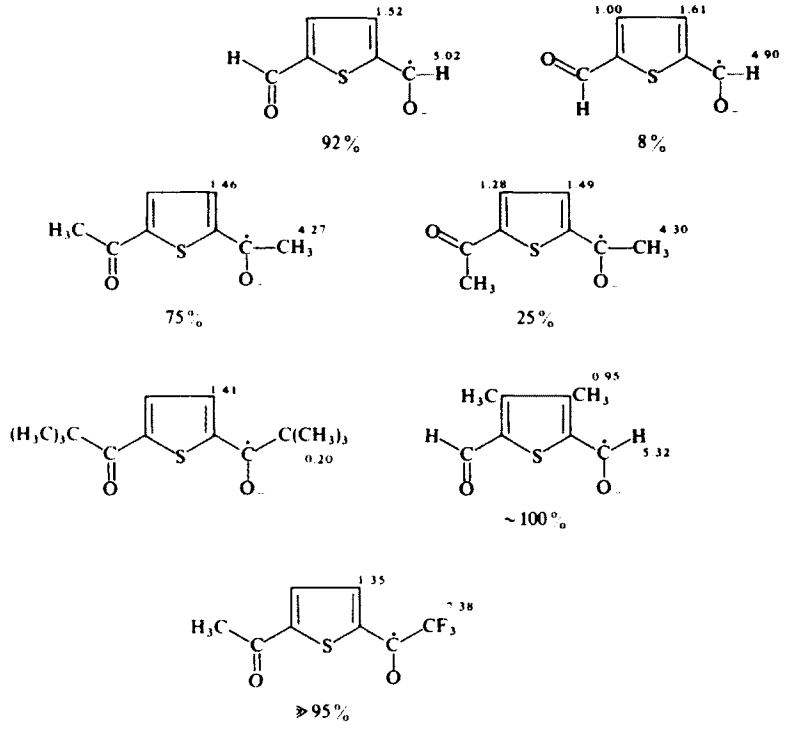
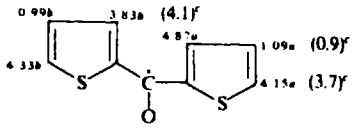
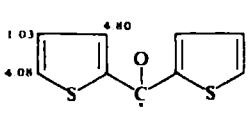
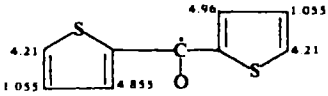


TABLE 43. Hyperfine Coupling Constants (in Gauss) of the Radical Anions of Some Dithienyl and Arylthienyl Ketones

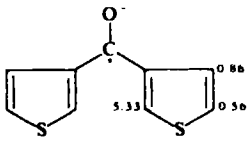




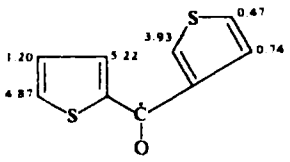
trans-trans
Solvent MeOH-DMe



cis-trans
Solvent MeOH-DMe



Ref. 1028



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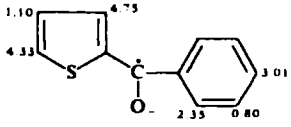

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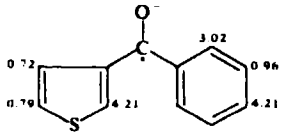

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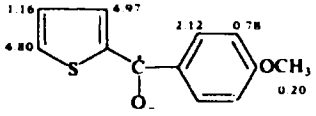
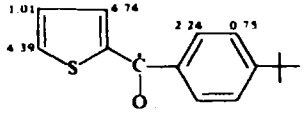
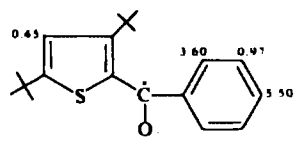


Ref. 1031



Ref. 1031



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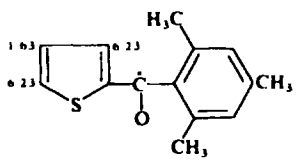

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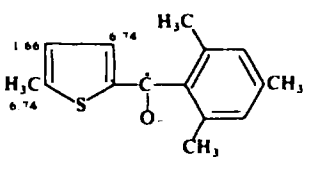
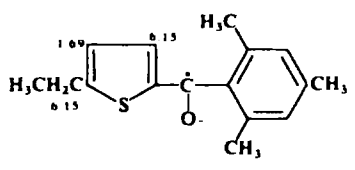
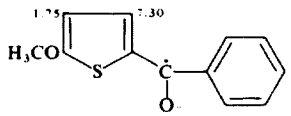


Ref. 1031

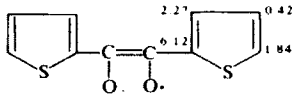


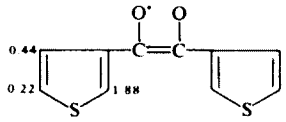
Ref. 1031

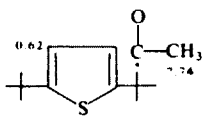
TABLE 43. (*Continued*)



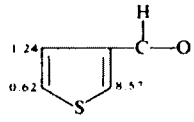
Ref. 1031







Ref. 1031



Ref. 1007

[a] Ref. 1007, photolytic.
[b] Ref. 1028, electrolytic.
[c] Ref. 1033.

The values of the coupling constants show that the efficiency in the delocalization follows the order 2-thienyl, phenyl, 3-thienyl.[1028] At room temperature only one rotamer was observed, owing to rapid rotation of the thienyl rings. At $-70°C$, however, both rotamers were observed in the spectrum of the radical anion from 2,2′-dithienyl ketone.[1011] The configurational isomers of the radical anions generated photochemically from di-(2-thienyl)ketone were subsequently studied in detail by ESR. Of the three possible rotational isomers, it was found that the cis–trans and trans–trans were the preferred ones. The ratio at $-50°C$ was 1.30 : 1. The assignment of the cis trans rotamer was based on the different hyperfine splittings of the non equivalent 3- and 3′-protons. The strong electrostatic interaction between the negative oxygen and the adjacent ring atom is assumed to cause the smaller splitting of 3-H in the ring with sulfur trans to the oxygen. A study of the lineshape variations of the ESR spectra with temperature allowed the determination of the activation parameters for the rotations of the aromatic ring. The activation energy of 31.30 kJ/mol was compared with those of the corresponding radical anions derived from bis-2-thieno[3,2-*b*]thienyl ketone, bis-2-thieno[2,3-*b*]thienyl ketone, and benzophenone, which were 37.95, 35.73, and 26.57 kJ mol, and apparently follow the same order as the electron-delocalizing power of the nuclei.[1032]

When conjugation of the phenyl ring is inhibited in the radical anions of arylthienyl ketones, as in 2-thienyl mesityl ketones, the electron spin is distributed mainly over the thiophene ring, and hyperfine splitting constants greater than $6g$ are observed. On the other hand, when the thienyl conjugation is inhibited by 3-*t*-butyl-substitution, the electron spin is mainly distributed over the phenyl ring.[1031]

The radical anion of 2,2′-dithienylketone was also produced oxidation of 2,2′-dithienylmethane with oxygen in basic solution.[1033] These authors also studied the radical ions derived from 2,2′-thenil and 3,3′-thenil obtained on treatment of

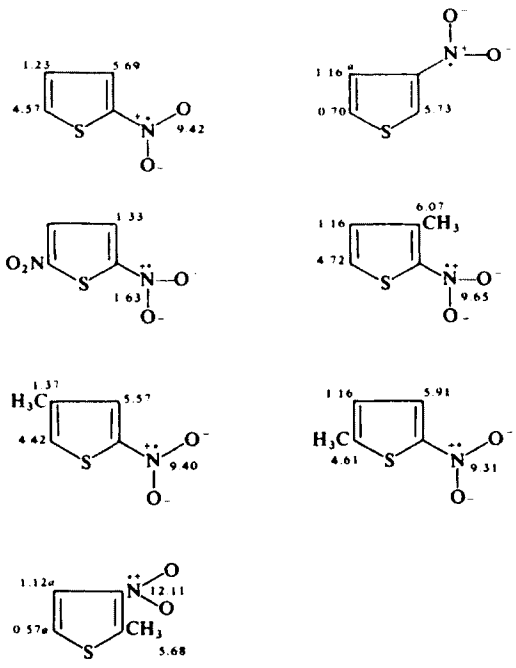
2,2′-thenoin with insufficient quantities of oxygen in alkaline ethanol solution, and 3,3′-thenil with the anion of propiophenone. Probable assignments of the coupling constants are indicated in Table 43.[1033]

In a comparative investigation of the ESR spectra of electrochemically generated anion radicals of 5-nitro-2-furfural, 5-nitro-2-thiophenecarboxaldehyde, and 5-nitro-2-acetylthiophene, the first-mentioned compound showed two rotamers in a 10 : 1 ratio, while only one conformation was detected for the thiophene derivative. Hyperfine splitting constants were solvent dependent, due to the association of the solvents with the nitro group[1034] (see also a recent extensive investigation reported in Ref. 1035).

B. Nitro Derivatives

The radical anions of a number of nitrothiophenes generated by electrolysis of their solutions in both acetonitrile and DMF have been studied by ESR and their hyperfine splitting constants are collected in Table 44. Assignments of the parent nitrothiophenes were based on methylated derivatives. Spin densities

TABLE 44. Hyperfine Splitting Constants (in Gauss) of the Radical Anions of Nitrothiophenes in Acetonitrile



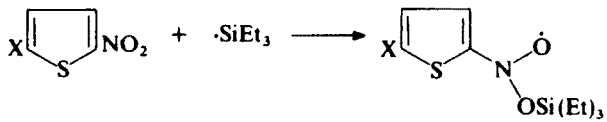
[a] These assignments might be reversed.

have been calculated by McLachlan's extension of the Hückel molecular orbital method. Both the *p*-model and the *d*-model gave fairly adequate predictions of the experimental results.[1036] Later an investigation by the same technique of a large number of the radical anions, derived from many 5-substituted 2-nitrothiophenes, was undertaken in order to determine the effective substituent delocalising power with respect to an unpaired electron in the thiophene series.

Attempts were also made to generate these radical anions by use of the DMSO–potassium *tert*-butoxide method. Even if good results were obtained in some cases, spectra were less intense and sometimes mixtures of radicals were observed. In the case of 2-nitro-5-methyl- and 2-nitro-5-ethylthiophene, the spectra of the radical anions of 2-nitro-5-formyl- and 2-nitro-5-acetylthiophene were formed.

The nitrogen splitting constants of the radical ions correlate well with Bower's σ-constants [slope -0.30; mean-square error (mse) 0.012 in acetonitrile]. Bower's σ-constants were especially chosen to fit hyperfine splittings in arene nitro anions. Hyperfine splitting constants calculated by the INDO method using an *s,p* basis set for the sulfur atom are in good agreement with the experimental values. The experimental hyperfine splitting constants are given in Table 45.[1037]

5-Substituted 2-thienyl nitroxides **156** were generated by scavenging triethylsilyl radicals generated by hydrogen abstraction from triethylsilane with substituted nitrothiophenes **155**.



155 **156**

The hyperfine splitting constants of **156** are given in Table 46. The nitrogen hyperfine coupling constants were plotted against the Hammett σ-constants. Least-squares analysis yields a slope of -0.077 (mse 0.0008); thus, electron-donating groups increase and electron-withdrawing substituents decrease the nitrogen splitting.[1037]

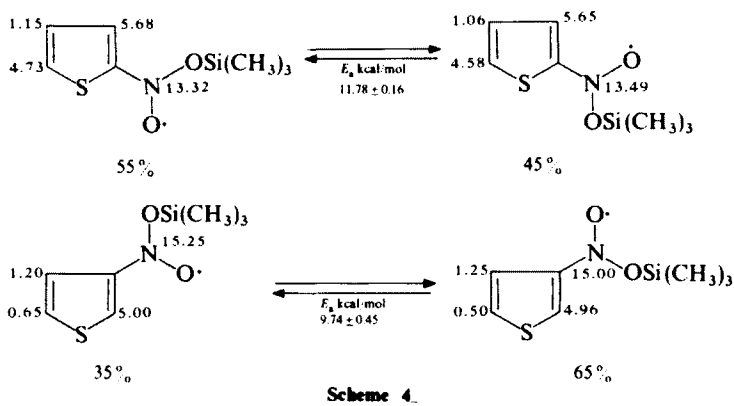
The ESR spectra of both 2- and 3-triethylsilyloxynitroxides at low temperatures show the existence of two conformers, due to hindered rotation (Scheme 4).

On lowering the temperature some peaks begin to broaden, and then split into new lines. These lines sharpen again until at approximately $-40°C$ the spectra of the cis and trans isomers, which have similar couplings and slightly different *g* values, are distinguishable. The kinetics of the interconversion could be followed by examining variation in the lineshape with temperature. The activation parameters were determined, and the rotational barrier is larger for the 2-thienyl- than the 3-thienylsilyloxynitroxide (see Scheme 4).[1038]

TABLE 45. Hyperfine Splitting Constants in 5-X-2-Nitrothiophene Radical Ions

	Splitting (G)			
X	3*H*	4*H*	X	NO_2
H	5.70[b]	1.25	4.75	9.15
H	5.80[c]	1.25	4.75	10.10
CH_3	6.00	1.20	4.90	9.60
	6.10	1.30	4.80	10.80
C_2H_5	6.00	1.20	4.15	9.50
	6.15	1.20	4.25	11.0
C_6H_5	5.50	1.30	1.30 (3*H*)	7.85
			0.45 (2*H*)	
	5.30	1.30	1.30 (3*H*)	8.20
			0.50 (2*H*)	
SCH_3	5.50	1.25	0	8.00
	5.60	1.30	0	8.75
Cl	6.20	1.50	0	8.65
	6.00	2.00	0	9.80
CO_2Me	4.23	0.98	0.43 (OMe)	6.00
	4.50	1.10	0.40	6.75
SO_2Me	4.70	0.95	0.95 (Me)	6.55
	4.70	0.95	0.95	7.00
$COCH_3$	3.75	0.75	1.35 (Me)	5.15
	4.10	1.15	1.15	6.50
CHO[a]	2.00	0.55	3.50 (CHO)	4.50
	1.75	0.80	3.85	5.70
CN	4.55	1.00	1.00 (CN)	6.00
	4.70	1.05	1.05	6.60
NO_2	1.20	1.20	1.54	1.54
	1.25	1.25	1.63	1.63

[a] Tentative assignment.
[b] DMF as solvent.
[c] Acetonitrile as solvent.



Scheme 4

TABLE 46. Hyperfine Splitting Constants of 5-X-2-Thienyl-nitroxides in Triethylsilane[1037]

X	Splitting (G) 3H	4H	X	$N^0_{OSiEt_3}$
H[a]	5.60	1.07	4.65	13.40
CH_3	6.00	0.70	4.30	14.50
C_2H_5	5.80	1.00	4.20	13.85
C_6H_5	5.60	1.35	1.00 (3H) 0.35 (2H)	12.50
SCH_3	5.60	1.20	0	12.95
Cl	5.85	1.20	0.4	13.25
CO_2Me	5.00	1.35	0.21	12.05
SO_2Me	5.05	1.30	0.75	11.75
$COCH_3$	4.95	1.35	0.45	11.45
CHO	4.90	1.40[b]	0.65[b]	11.30
CN	5.10	1.40	0.70	11.70
NO_2	5.00	1.45	1.10	10.85

[a] Coupling constants recorded at 30 C. Two conformers present at lower temperature.
[b] Tentative assignment.

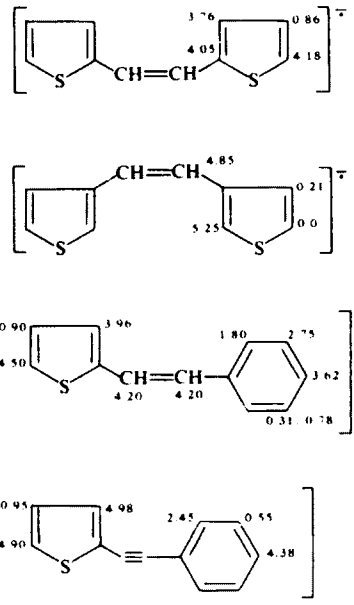
The ESR data indicated that the reaction of 2-bromo- or 2-iodo-5-nitrothiophene with tetrabutylammonium hydroxide in DMF produced the anion radical of the starting materials, together with 2-nitrothiophene and 5,5′-dinitro-2,2′-bithienyl.[1039] From the electrochemical reduction of 2-bromo- and 2-iodo-5-nitrothiophene it was not possible to observe their radical anion spectra. Instead, the spectra of the anion radicals from 2,2′-dinitro-5,5′-bithienyl or 2-nitrothiophene were obtained, depending on the cathode potential.[248]

C. Miscellaneous Derivatives

Trimethylsilyl- and cyanosubstituted thiophenes have been reduced in THF using potassium, and the resulting radical anions were characterized by their ESR spectra.[1040]

Alkali-metal reduction of some thienylethylene derivatives at $-80^{\circ}C$ gave the corresponding radical anions, whose ESR spectra were interpreted by the use of deuteriated derivatives. The assignments are given in Table 47. The ESR spectrum of 1-(2-thienyl)-2-(3-thienyl) ethene has also been interpreted. The measured hyperfine splittings were 0.13, 0.31, 0.79, 3.52, 3.68, 4.50, 4.96, and 5.27 *g*. Definite assignments could not be made, as no deuteriated derivatives were examined. The results of this investigation indicate that the phenyl and thienyl groups are locked in a definite position on the ESR time scale, and rotational isomers were detected in the case of 1,2-di(2-thienyl)ethylene. The

TABLE 47. Hyperfine Splitting Constants (in Gauss) of Some 1,2-Di(thienyl)Ethenes and 1-Phenyl-2-thienyl)Ethenes

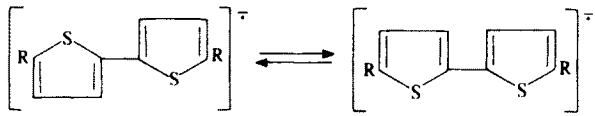


experimental hyperfine splittings were reproduced satisfactorily by molecular orbital calculations in the *p*-model framework, assuming twisting angles of 40° for the 3-thienyl and 0° for the 2-thienyl and phenyl groups.[1041]

Electron spin resonance spectroscopy has proved very useful for the study of rotational isomerism in the radical anions of bi- and teraryls containing thiophene rings. When an oxygen-free solution of 2,2′-bithienyl in DME was reacted at − 80°C with potassium, a green color developed and a well-resolved ESR spectrum was recorded, which was more complicated than that theoretically expected for the radical anion of 2,2′-bithienyl. It was in effect the result of the superimposition of the spectra of two very similar radicals with an intensity ratio of 4 : 1 and with their centres 0.29 G apart. On the other hand, for the anion radical of 2-phenylthiophene, for which only one rigid conformation is possible, only one set of lines was observed, and the ortho and meta protons were nonequivalent. The assignment of the hyperfine splitting constant of the 2,2′-bithienyl radical anion was made by using deuteriated derivatives.[1042] Since in neutral 2,2′-bithienyl the S-*trans* isomer is the only observable species in the solid state,[1043,1044] it was assumed that the same conformation is the preferred one for the corresponding radical anion.[1045] It was not possible to measure the barrier to internal rotation, since no lineshape variation could be detected up to − 40°C, and at higher temperatures the radical anion rapidly decays. A series of

5,5′-disubstituted 2,2′-bithienyls containing electron-withdrawing groups, which should give more stable radical anions, was therefore studied, and in every case both conformers were detected by ESR (see Table 48, where the hyperfine splitting constants are given). However, in no case could exchange broadening be observed, even at temperatures as high as 100°C, indicating that the isomerization process in the negatively charged 2,2-bithienyl has a high activation energy; its lower limit was estimated to be approximately 15 kcal/mol, assuming that the presence of the substituent does not have much effect on the height of the barrier. These findings contrast with the behavior of neutral 2,2-bithienyl, for which the barrier to S-*cis* ⇔ S-*trans* interconversion has been calculated to be only 4 kcal/mol.[1044,1046,1047]

TABLE 48. Hyperfine Splitting Constants of the Radical Anions of Substituted Bithienyls and Differences $\Delta B_0 = B_0(trans)\text{-}B_0(cis)$ of the Resonance Fields of the Spectral Centers of the Two Isomers



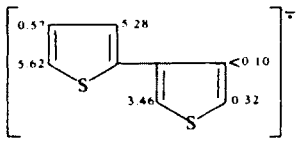
S-*trans* S-*cis*

R	Solvent	Relative Concentration (%)	Splitting Constants (G) a_3	a_4	a_5	ΔB_0
H-*trans*	DME	78	4.01	0.75	4.76	0.27
H-*cis*		22	3.97	0.70	4.80	
CN-*trans*	DME–THF	55	2.38	0.15	0.99(N)	− 0.02
CN-*cis*		45	2.50	0.04	0.97(N)	
CHO-*trans*	DMSO	62	0.87	1.36	2.65(CHO)	− 0.085
CHO-*cis*		38	0.66	1.42	2.64(CHO)	
NO_2-*trans*	DMSO	66	0.49	1.34	1.65(N)	− 0.02
NO_2-*cis*		34	0.51	1.15	1.75(N)	

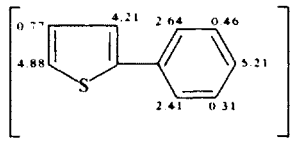
It is interesting to note that the attempts to record the ESR spectrum of the radical anion of 3,3′-bithienyl were unsuccessful under all conditions, since its reduction with alkali metals gave an ESR spectrum consisting of a single broad line, which in a few minutes evolves to the spectrum of the radical anion of 2,2′-bithienyl. An interesting rearrangement thus occurs. The rearrangement also occurs with 2,3′-bithienyl. However, by using dilute samples at − 90°C, it was possible to record the ESR spectrum of the radical of 2,3′-bithienyl. The hyperfine splitting constants of this radical ion, those of 2-phenylthiophene, 4-(2-thienyl)pyridine and 2,5-diphenylthiophene, and of some *p*-di(2-thienyl)

benzenes, are collected in Table 49.[1048] The properties of the radical anion of 2-(2-thienyl)thiazole have been compared with those of 2,2'-bithiazole, which, in contrast to 2,2'-bithienyl, is very stable, lasting for several days at room temperature, and showing only one rotamer. For the radical anion of 2-(2-thienyl)thiazole, only one rotamer was also found, which was assumed to have the sulfur atoms trans, as in 2,2'-bithienyl. The hyperfine coupling constants (given in Table 50), and indicate that the 2-thiazolyl group delocalises the unpaired electron much less than the 2-thienyl group, or even the phenyl group.[1049]

TABLE 49. Hyperfine Splitting Constants (in Gauss) of the Radical Anions of Some Di- and Triaryl Derivatives



In DME



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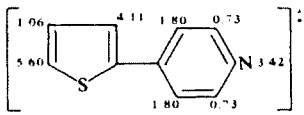
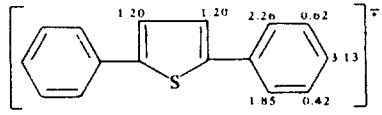
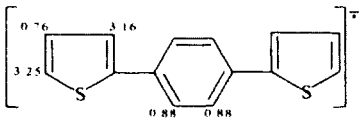


In HMPA



In DME



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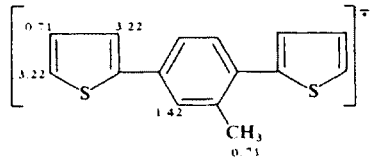
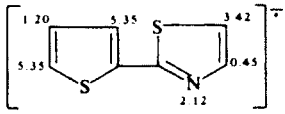


In DME

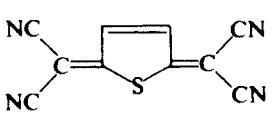


THF/Li⁺

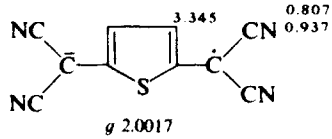
TABLE 50. Hyperfine Splitting Constants (in Gauss) for the Radical Anions of Thiazole Derivatives

Compound	Solvent/ Counterion	Thiazole-2-yl			2-Thienyl		
		a_N	a_4	a_5	a_3	a_4	a_5
2,2'-Bithiazole	THF/K^+	2.91	0.66	4.04			
2-(2-Thienyl)thiazole	THF/Li^+	2.12	0.45	3.42	5.35	1.20	5.35

The radical anion **158** was obtained from **157** by reduction with lithium iodide in methylene chloride,[1050] acetonitrile, or propylene carbonate.[1051] The observed hyperfine splitting constants are indicated in the formulas.[1051]



157



g 2.0017

158

Electron spin resonance spectra of both anion radicals and cation radicals were observed from tetracyanothiophene. The former was obtained on reduction by potassium metal at $-80°C$ in dimethoxyethane, while the latter was obtained on oxidation with fuming sulfuric acid. A large g value (2.0123) was observed for the radical cation, while the radical anion showed a g value of 2.0020 and a hyperfine splitting of the cyano nitrogen of 1.10 G.[1052]

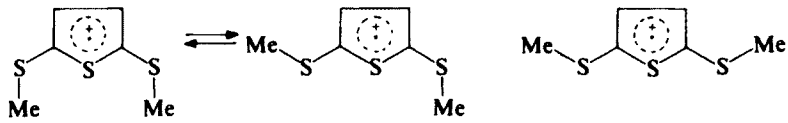
The adsorption of thiophene and its derivatives on H-mordenite provides individual ESR signals with hyperfine structure. A comparison of the experimental ESR spectra with the calculated magnetic resonance parameters suggest that during absorption, anion radicals of thiophene are formed.[1053]

3. Radical Cations Derived from Thiophenes

Radical cations of thiophene, 2- and 3-methylthiophene, and some furan and pyrrole analogues have been detected and identified by ESR studies on solid solutions of the parent molecules in various fluorinated matrices on γ-irridation. The spin density distribution obtained by ESR analysis suggests that the unpaired electron resides in the $1a_2$ π-orbital for all the radical cations. This is consistent with photoelectron spectra of the parent molecules, and with INDO calculations for the respective cations. Using $c\text{-}C_6F_{11}CF_3$ as a matrix, well-observed and well-resolved ESR spectra were obtained for 2- and 3-methyl thiophene cation radicals.[1054] Similar conclusions were drawn from exposure of thiophene and 2,5-dimethylthiophene in Freon at 77 K to ^{60}Co-X-rays, which gave the corresponding cation radicals. In all cases, analyses of their ESR spectra established that the unpaired electron occupied the $1a_2$ (π_3) orbital with a node through the sulfur.[1055]

Attempts to oxidize thiophenes with low first ionization potentials to their radical cations using the $AlCl_3/H_2CCl_2$ oxidizing system failed, except for dithienyl disulfide, the radical cation of which rearranges under the reaction conditions to that of dithieno-[2,3-*b*, 2′,3′-*c*]-*p*-dithiin.[1040] Radical cations were prepared from 2,5-bisalkylthiothiophenes by reaction with aluminum trichloride in nitromethane and their ESR spectra interpreted. The ESR spectrum of 2,5-dimethylthiophene shows two superimposed groups of signals, which have been interpreted as due to two of the three possible rotational isomers, S,-*cis*–*cis*

159, S-*cis*–*trans* **160**, and S-*trans*–*trans* **161**. The less intense signal (~25%) was unambiguously assigned to the asymmetric conformer because of the different hyperfine splittings. Assignment of the cis–cis conformation was based on the fact that for 2,5-diisopropylthiothiophene only the symmetric radical cation was detected, as it would be unrealistic to consider the S-*trans*–*trans* conformer the more stable, when R is the bulky isopropyl group. Furthermore, 3,4-dimethyl- and 2,5-dimethylthiothiophene gave only the symmetric cation, which leaves little doubt that the more stable of the two symmetric structures in S-*cis*–*cis*. The hyperfine splitting constants are given in Table 51.

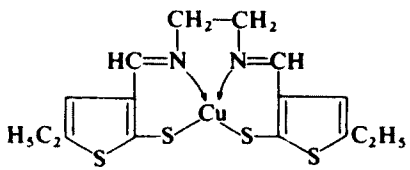


159 160 161

The radical cation from tetraphenylthiophene has also been obtained, but the lack of appreciable fine structure made definite identification by ESR difficult.[1056] However, on electrochemical oxidation of tetraphenylthiophene at a controlled potential of 1.70 V in nitromethane, an ESR spectrum of the cation radical with a g value of 2.0024 was obtained in which the couplings to the *o*-, *m*- and *p*-hydrogens could be resolved.[1057]

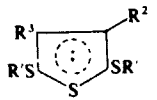
4. Miscellaneous ESR Work on Thiophenes

The ESR spectrum of the copper complex **162** has been studied. A supplementary hyperfine structure of 11 lines was obtained in solution, and it was shown that this was due to the interaction of the spin of the unpaired electron with the spins of the ^{14}N nuclei and protons of the CH groups equivalent in pairs. The distribution of spin density on the nitrogen atom and copper atoms was estimated.[1058,1059] Other types of copper complexes containing thiophene rings as ligands have also been studied.[1060–1062] Reversible ESR photosignals in charge-transfer complexes of *p*-chloranil in thiophene have been studied.[1063] The adsorption of thiophene on the intracrystal surface of Fe(III) and VO^{2+} exchange forms of a larger lattice silicate (heetorite) has been studied by ESR.[1064] The isotropic hyperfine splitting constants of NO_2 in various media, including thiophene, have been determined.[1065]



162

TABLE 51. Hyperfine Splitting Constants of Radical Cations of Some 2,5-Dialkylthiothiophenes



Per cent Conformer	Conformer	R'	R²	R³	Hyperfine Splitting Constants (G)					
					3*H*	4*H*	*syn*-SR'	*anti*-SR'	3-Me	4-Me
75	*cis–cis*	CH_3	H	H	2.60	2.60	4.30			
25	*cis–trans*	CH_3	H	H	3.48	2.16	4.40	3.82		
80	*cis–cis*	C_2H_5	H	H	2.625	2.625	3.485			
20	*cis–trans*	C_2H_5	H	H	2.95	2.30	3.70	3.125		
~100	*cis–cis*	$CH(CH_3)_2^a$	H	H	2.625	2.625	2.50			
100	*cis–cis*	CH_3	CH_3	CH_3			3.90		2.25	2.25
80	*cis–cis*	CH_3	CH_3	H		1.96	3.94		2.74	
							4.20			
20	*cis–trans*	CH_3	CH_3	H		1.60	4.30	3.70 or 3.60	3.60 or 3.70	

[a] An additional splitting (0.13 G) corresponding to the 12 protons of the two isopropyl groups was also detected.

XIII. VIBRATIONAL SPECTRA OF THIOPHENES

1. Introduction

Since the introduction of IR spectroscopy at the beginning of the 1950s as a routine physical tool in organic chemistry, such a large number of applications to thiophene chemistry can be found that it is not feasible to cover them all. It will therefore not be possible to discuss in detail all the cases where IR spectroscopy has been used to determine isomeric purity of thiophene derivatives, or in connection with the structure determination of complicated thiophene derivatives. The stress in this chapter will be on the detailed vibrational analysis of thiophene itself and its simple derivatives by IR and Raman spectroscopy and the use of these spectroscopic techniques for the study of conjugation, especially in carbonyl-substituted derivatives, and for the conformational analysis of thiophene derivatives.

2. Vibrational Spectra of Thiophenes and Deuterated Thiophenes

Through a very extensive investigation of the IR spectra of thiophene itself, and of all deuterated thiophenes except 2,4-dideuteriothiophene, Orza and coworkers in 1965 made assignments of all fundamental frequencies, fitting conveniently all the available criteria. The assignments were checked by using the complete isotopic rule,[1066,1067] and values of some thermodynamic functions for thiophene at several temperatures were calculated.[1068-1072] In previous investigations, the resolution was not sufficient to allow a complete study of the band contours.[9,1073-1077] Several Russian groups have also studied the vibrational spectra of thiophene and deuteriated thiophenes,[1078,1079] and comparisons have also been made with selenophene and deuteriated selenophenes,[1080-1082] and with furan.[1083] These authors confirmed the interpretation of the IR spectrum of thiophene given in Ref. 1069.

The 21 fundamental vibrations of C_{2v} symmetric thiophenes are distributed in the four symmetry species in the following way:

$$8A_1 + 7B_1 + 3A_2 + 3b_2$$

They are indicated in Figure 7.

The fundamental frequencies, their approximate description, and symmetry species for thiophene and deuteriated thiophenes as obtained in Ref. 1069 are given in Tables 52 and 53.

Based on the observed vibrational frequencies, a complete set of harmonic symmetry force constants has been developed for thiophene, leading to calculated frequencies for thiophene, tetradeuteriothiophene, and 2,5- and 3,4-dideuteriothiophene.[1084]

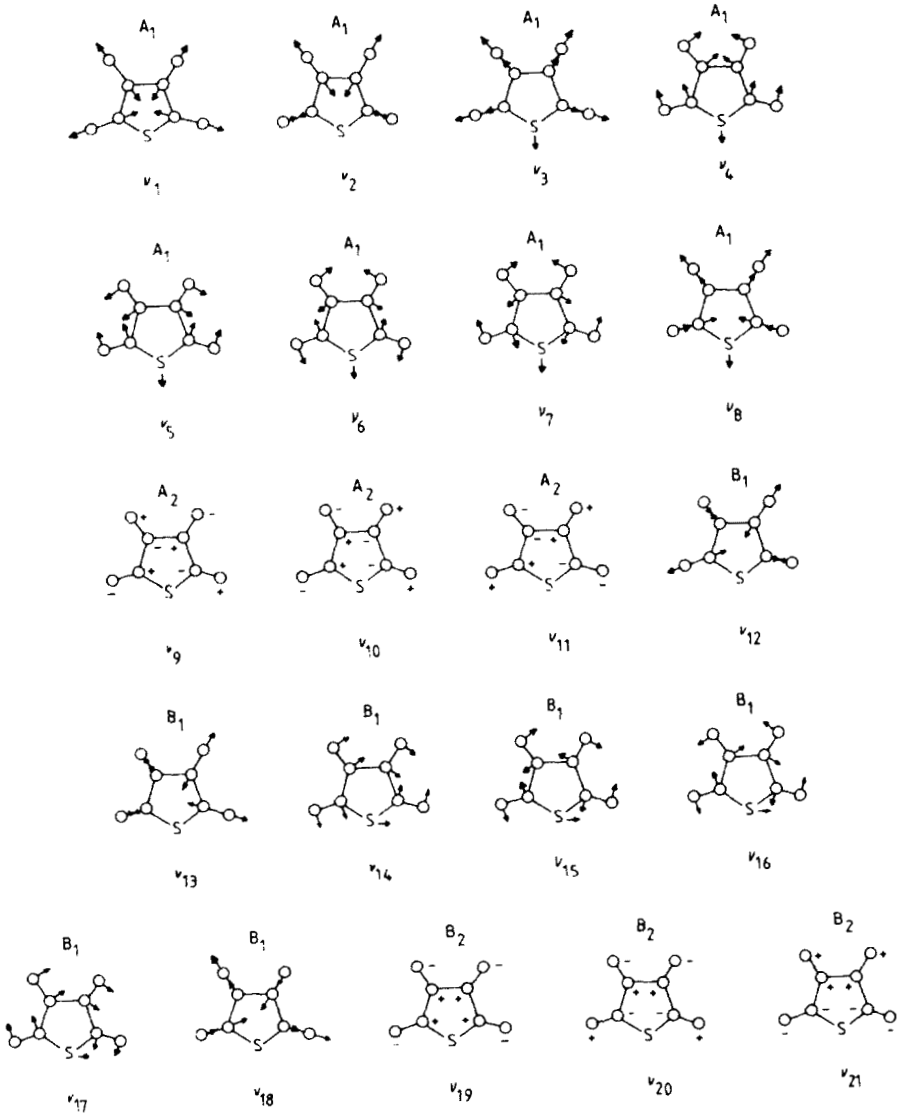


Figure 7. Fundamental vibrations of C_{2v} symmetric thiophenes.

The harmonic force fields for thiophene and tetradeuteriothiophene were also used for the calculation of mean amplitudes of vibration, perpendicular amplitude correction coefficients, and atomic vibration mean-square amplitudes. The calculated mean amplitudes of thiophene were compared with electron diffraction data.[1085] Absolute band intensities for the out-of-plane fundamental vibrations and their combinations were measured for thiophene and its deuterium and methyl derivatives and were successfully interpreted by introducing

TABLE 52. Fundamental Frequencies of Thiophene, 2,5-, 3,4-Dideuteriothiophene, and Tetradeuteriothiophene in the Gas Phase

Vibration (cm^{-1})	Approximate description	Symmetry species	Thiophene	2,5-D_2	3,4-D_2	D_4
ν_1	CH-stretching	A_1	3126	3101	3123	2343
ν_2	CH-stretching		3098	2336	2314	2306
ν_5	Ring stretching		1409	1398	1389	1376
ν_4	Ring stretching		1360	1310	1322	1248
ν_6	CH deformation in plane		1083	1046	1034	896
ν_7	CH deformation in plane		1036	884	876	785
ν_3	Ring stretching		839	754	750	731
ν_8	Ring deformation in plane		608	(590)[b]	593	585
ν_9	CH deformation out of plane	A_2	898[a]	(887)[b]	(775)[b]	750[a]
ν_{10}	CH deformation out of plane		683[a]	(566)[b]	(671)	531[a]
ν_{11}	Ring deformation out of plane		565[a]	(528)[b]	(488)	(484)[b]
ν_{12}	CH stretching	B_1	(3125)[b]	3088	(3120)	(2340)[b]
ν_{13}	CH stretching		3098	(2326)[b]	(2317)	2290
ν_{14}	Ring stretching		1507	1490	1480	1459
ν_{15}	CH deformation in plane		1256	1218	1178	1034
ν_{16}	CH deformation in plane		(1085)[b]	918	918	846
ν_{17}	Ring deformation + stretching		872	(770)	849	752
ν_{18}	Ring deformation in plane		751	(740)	713	711
ν_{20}	CH deformation out of plane	B_2	867	819	811	684
ν_{19}	CH deformation out of plane		712	584	587	531
ν_{21}	Ring deformation out of plane		452	419	442	414

[a] Corrected Raman values.
[b] Nonobserved Frequencies.

TABLE 53. Fundamental Frequencies of 2- and 3-D-Deuteriothiophene, 2,3-Dideuteriothiophene and 2,3,5- and 2,3,4-Dideuteriothiophene in the Gas Phase

Vibration	Symmetry Species	2-D	3-D	2,3-D_2	2,3,5-D_3	2,3,4-D_3
ν_1	A′	3125	3126	3124	3093	3121
ν_2		3099	(3122)	3091	2344	2340
ν_{12}		3087	3093	2345	(2330)	2315
ν_{13}		2331	2315	2302	2301	2298
ν_3		1501	1485	1478	1469	1476
ν_4		1404	1400	1387	1386	1380
ν_5		1342	1352	1322	1293	(1290)
ν_6		1230	1215	1152	1152	1116
ν_7		1081	1080	1078	951	963
ν_8		1042	1040	(932)	888	880
ν_{14}		906	891	863	820	849
ν_{15}		851	862	808	(760)	775
ν_{16}		760	799	756	750	738
ν_{17}		745	728	727	722	(711)
ν_{18}		601	606	598	585	(593)
ν_9	A″	896	882	882	860	788
ν_{10}		839	800	744	711	738
ν_{11}		701	685	668	579	614
ν_{19}		567	645	553	531	531
ν_{20}		553	516	511	504	486
ν_{21}		433	446	(427)	416	427

several bond-moment parameters, and then combined with normal coordinate calculations.[1086] In order to obtain reliable vibrational assignments for use in statistical thermodynamic calculations, a valence force field was derived from 300 observed vibrations of thiophene, eight deuterium derivatives, and six methyl derivatives.[1087] These elaborate calculations confirmed the vibrational assignments proposed by Orza et al.[1069] for thiophene and gave reliable vibrational assignments for the two monomethyl- and four dimethylthiophenes.[1087] Force-field calculations of the vibrational spectra of thiophene, furan, and cyclopentadiene have been compared with those of benzene.[1088] By means of the force field and mean amplitudes of vibration of thiophene, furan, selenophene, and tellurophene, it was concluded that the ground-state aromaticity order in the series is thiophene > tellurophene > selenophene > furan.[1089]

Out-of-plane force constants have been calculated for the thiophene molecule using complete deuterium isotopic data and the most general quadratic symmetry potential function. The 12 force constants initially obtained by solving the secular equation of the symmetrical derivatives were afterwards refined by a least-squares method to fit the 60 observed frequencies of thiophene and all its deuteriated derivatives.[1090] The inverse kinetic energy matrix elements for the torsional vibrations, out-of-plane bending vibrations, and the IR interactions

were derived for thiophene using the vector expression given by Malhiot and Ferigle.[1091] Compliance constant matrix C of the thiophene molecule has been determined on the basis of the experimental frequencies of thiophene and tetradeuteriothiophene.[1092] Unresolved type B infrared bands of asymmetric top molecules, such as thiophene often exhibit PQQR structure; therefore a formula for the separation of the Q-branches was developed.[1093] Proton resonance separations of band envelopes produced by prolate and oblate top molecules such as thiophene have been carried out.[1094] Calculation of IR band contours of planar asymmetric top molecules such as thiophene has been carried out.[1095]

Far-IR absorption bands have been measured for thiophene in liquid and glassy decalin. The results were interpreted in terms of a general relationship between the volume of molecular rotation and the mean-square torque.[1096] The temperature dependence of Raman spectra in the premelting region of thiophene has been investigated. Normal-mode calculations were performed using atom–atom potentials. Complete disappearance of the phonon spectrum of thiophene was observed near the melting point. This was related to disorder all molecular orientations in the crystal.[1097] The ring-puckering vibration in the far-IR spectrum of 2,5-dihydrothiophene has been studied.[1098] Shifts of low frequencies between liquid and vapor states were observed in the far-IR spectra of some methylthiophenes.[1099]

MINDO/3 calculations of molecular vibration frequencies have been reported for thiophene and compared with experimental data.[1100]

Theoretical and experimental studies of absolute intensities in the IR and Raman spectra of thiophene have been carried out.[1101] A comparison of the width of liquid-phase IR absorption bands and of the corresponding Raman bands has been made.[1102] The IR spectra of 2-D-thiophene and thiophene have been compared with the Raman spectrum of thiophene.[1103] The IR absorption spectra of liquid thiophene and thiophane have been measured over the range 400–4000 cm^{-1}. The vibrational assignments of the observed frequencies were discussed.[1104] Hydrogen bonding between thiophene and thiophane with proton donors such as alcohols, carboxylic acids, water, and chloroform was studied by IR spectroscopy. Thiophane was a stronger proton acceptor than thiophene.[1105] The absolute intensities of bands in the IR absorption and Raman spectra were used for the determination of electrooptical parameters of thiophene, and for a discussion of the aromaticity of thiophene.[1106] Integral intensities of the background and wing of a Rayleigh line for thiophene were compared with those of some benzene derivatives.[1107] The anisotropic component of the Rayleigh scattering of thiophene has been studied.[1108]

The intensities of the CH vibrations of the five-membered heterocycles are considerably smaller than those of benzene and diminish in the series thiophene > pyrrole > furan. Attempts were made to explain the result through changes in the hybridization of the CH orbitals, as well as by the relative electronegativities of the heteroatoms.[1109]

Solvent effects on the CH vibrations of thiophene and furan have been investigated. While the CH out-of-plane bending vibrations show an increase in frequency in polar solvents, the band arising from CH stretching vibrations shows a strong enhancement of their intensity. In DMSO and triethylamine new bands were also detected.[1110] The influence of solvents on the band at 712 cm^{-1} in the spectrum of thiophene, corresponding to nonplanar vibrations of the CH bonds, has been studied. Frequency, width, and even central moments (μ_c) of the line increased with increasing electron-donor ability of the solvents.[1111] The influence of solvent concentration of IR and Raman band intensities was measured in mixtures of thiophene and chloroform.[1112] The intensities were used for the discussion of the structure of chloroform complexes. A comparative investigation of the CH stretching region of thiophene, selenophene, tellurophene, pyrrole, and furan has been carried out. Spectra were obtained for gas, liquid, solution (CCl_4), and crystalline samples. Polarized IR radiations was employed for crystalline oriented films.[1113] The fifth overtones of the CH stretching vibrations of thiophene, 3-methylthiophene, and some other aromatic heterocycles in the liquid state have been observed by a thermal bandwidth technique. It was found that their frequency shifts from that of benzene was proportional to the decrease in the relevant C—H bond length.[1114] The variation with temperature of the width of 10 fundamental vibration bands of thiophene was studied. In combination with Raman diffusion measurements at room temperature, it was possible to give a more accurate evaluation of the vibrational and rotational contributions to the widths of the bands.[1115] Later, the same research group studied IR absorption and Raman scattering bandwidths of some fundamental modes of A_1, B_1, and B_2 species of both thiophene and furan and their temperature dependence. In this way, rotational A_1 fundamental modes of both thiophene and furan and their temperature dependence were studied in the liquid phase. The vectorial and tensorial rotational correlation times and correlation functions were derived by deconvolution.[1117] Widths and shapes of [$V_3(A_1)$] IR and Raman bands of thiophene at 834 cm^{-1} have been studied in liquid and plastic phases. The results obtained allowed accurate determination of vibrational and rotational correlation functions and correlation times for different temperatures.[1118]

The far-IR absorption spectrum of thiophene has been studied in the 10–200-cm^{-1} spectral region in the liquid state at 303 and 208 K, and in the plastic phase at 223 K. The frequencies of the absorption peaks represented the molecular vibration frequency.[1119]

Many investigations have been carried out on the IR and Raman spectra of crystalline thiophene at low temperature.[1120–1125] Four crystalline modifications were observed,[1123,1126] with the transition temperatures of 171.6, 138, and 112 K. The structures of two phases observed at 70 K have been discussed.[1126] A quadratic structure was suggested to account for a crystalline cell.[1122] Polarization measurements carried out on the phase at 112 K allowed a tentative determination of the crystal structure at 108 K.[1127] The IR absorption spectra of

crystalline thiophene were also compared with those of furan and pyrrole. In all three cases, it was possible to experimentally observe the A_2 class vibrations forbidden in the IR spectrum by the selection rules of the C_{2v} group of the isolated molecule, and also other vibrations theoretically active but not found in the liquid state.[1121] Davidov splitting of absorption bands in the intramolecular vibrational region of crystalline thiophene were observed in polarized light.[1123] Infrared spectra of oriented single crystal films of thiophene and its deuteriated derivatives were obtained by using polarized light at -40 to -100°C. From the polarization measurements, the space group of thiophene and its deuterio derivatives was found to be $D^{18}{}_{2h}$–*Cmca*.[1128] Phase transformations in thiophene crystals were studied by temperature changes in the Raman spectra within the range of frequencies of lattice vibrations. All phase transformations were accompanied by a change in the orientation ordering of molecular mobility in the crystal, mainly around an axis normal to the molecular plane.[1129]

The infrared spectra of complexes of thiophene with bromine, chlorine, BCl_3, and TCNQ were examined to study the effect of complexing on the aromaticity of five-membered heterocycles.[1130] The laser-stimulated (carbon dioxide laser beam) IR *emission* spectrum of thiophene has been measured.[1131]

Thiophene has been used extensively in different types of Raman spectroscopical investigations. Thus, the intensities of some totally symmetric Raman lines of thiophene, furan, and pyrrole have been measured with 5145- and 3371-Å excitations. The Raman lines due to the stretching vibrations of two equivalent C—C bonds of the ring with greater double-bond character showed a greater wavelength dependence of the intensities.[1132] Thiophene has also been used in an investigation of polarized Raman spectra as a function of the exciting light frequency.[1133] The Raman spectra of thiophene and other heterocycles in different phase states have been investigated.[1134] The effect of temperature on the low-frequency Raman spectrum (30–85 cm^{-1}) of thiophene has been elucidated.[1135,1136] The laser Raman spectrum of thiophene adsorbed on silica has been reported. The observed changes in Raman line intensity and half-bandwidth were attributed to hydrogen bonding interaction via the π-electron system of the aromatic adsorbate.[1137] The shape and length of the laser pulse and the components of the stimulated Raman scattering in thiophene and other compounds have been studied. The data are in accordance with a stepwise mechanism for the production of the stimulated Raman compounds.[1138] Rayleigh and Raman light scattering of thiophene have been extensively studied to obtain information about thermal motion and intermolecular interactions.[1139,1141] New methods for exciting stimulated Raman spectra of thiophene have been developed,[1142] and experimental and theoretical determinations of its stimulated Raman spectra parameters have been carried out.[1143–1145]

The vibrational relaxation functions associated with the $\nu_6(A_1)$-vibration of thiophene were obtained from the lineshape analysis of isotropic Raman lines. Data on intermolecular interactions and motional characteristics of thiophene in 19 different solvents have been obtained.[1146] Another group carried out

similar investigations of various A_1 totally symmetric bands.[1147] Several other aspects of the Raman spectra of thiophene have been studied.[1148-1156]

3. Vibrational Spectra of Substituted Thiophenes

The fundamental vibrations of only a few thiophene derivatives have been completely determined. The vibrational spectra of 2,5- and 3,4-dimethylthiophene and 2,3,4,5-tetramethylthiophene have been interpreted by use of the force field of thiophene. Substitution with the methyl groups considerably lowers the frequencies of both the symmetric and antisymmetric C—S vibrations of 2,5-dimethylthiophene, compared with those of thiophene, while in the other two derivatives the frequencies of the antisymmetric C—S vibrations are higher than those of thiophene.[1157] An assignment of the vibrational spectra of 2-chloro, 2-bromo-, and 2-iodothiophene has been made using IR gas-phase data and Raman polarization data.[1158] The IR (3650–50 cm^{-1}) and Raman spectra of 2-chloro- and 2-bromothiophene, 2,5-dimethyl-, 2,5-dibromo-, and 2,5-dichlorothiophene in the liquid state have been measured and interpreted. The spectroscopic thermodynamic parameters were calculated, and the values for 298 K were reported.[1159,1160]

The IR spectra of 2,3-dibromothiophene and 2,3,5-tribromothiophene have been studied from 4000 to 200 cm^{-1}. The laser Raman spectra have also been recorded, and depolarization values have been measured. An assignment of the 21 fundamental vibrations was proposed based on group frequency correlations, Raman polarization data, and comparison with the spectra of the parent and some halogen-substituted molecules.[999]

The IR and Raman spectra of 4-chloro-, 4-bromo-, 4-iodo, and 4-cyano-2-fluorothiophene were studied in the region 5000–40 cm^{-1}. The fundamental frequencies were assigned and normal coordinate calculations were performed. The force constants were adjusted to accurately reproduce the fundamental frequencies. Thermodynamic functions and mean amplitudes of vibration were also calculated.[1161] The IR and Raman spectra of sodium 2-thiophenecarboxylate have been measured, and almost all the fundamental vibrations have been assigned.[1162] The Raman spectrum of 2-thiophene aldehyde has been studied.[1163]

Great efforts were made in connection with the introduction of commercial IR spectrometers to find characteristic absorptions for 2- and 3-substituted thiophenes and various disubstituted thiophenes. Much of this work became obsolete when NMR spectrometers became available. The IR spectra of 24 alkylthiophenes were carefully analyzed.[1164] In an investigation of thirteen 2-substituted thiophenes, characteristic regions were assigned for ring stretching at 100–1300 cm^{-1}, hydrogen in-plane deformations at 1250–1000 cm^{-1}, hydrogen out-of-plane deformations below 1000 cm^{-1}, and ring-breathing frequencies at 831–790 cm^{-1}.[1165] A similar investigation was also carried out of eighteen 3-substituted thiophenes.[1166] An investigation of the IR spectra of

2- and 3-monosubstituted and 2-nitro-5-disubstituted thiophenes showed that the absorption pattern in the region between 900 and 750 cm^{-1} seemed to be significantly different enough for 2- and 3-substituted derivatives to allow the identification of the position of substitution, even in the presence of substituted benzene rings. All compounds showed at least one or two bands at $721 \pm 25\ cm^{-1}$ and $680 \pm 20\ cm^{-1}$.[1167] The IR spectra of 2,5-dialkylthiophenes and 2,2'-bithienyl and terthienyl have been analyzed in the 4000–670-cm^{-1} region and showed a strong absorption band at $800 \pm 15\ cm^{-1}$.[1168] The main absorption frequencies of the thienyl and furyl groups of 2- and 3-thiophenecarboxamides and the corresponding furancarboxamides have been investigated.[1169] In a later study of twenty 2-substituted thiophenes over the range 200–1700 cm^{-1} and around 3000 cm^{-1}, an assignment of the fundamental vibrations of the thiophene ring was proposed. Some assignments for substituents were also discussed.[1170,1171] The vibrational spectra of 2- and 3-substituted thiophenes containing Br, CH_3, R—S, and CN as substituents were compared with those of the corresponding furans and selenophenes. It was found that the intensities of the symmetric and asymmetric C=C vibrations in the Raman spectra were increased, when the ring was conjugated with the substituent. It was shown that the position of a substituent in the ring can be determined from the Raman spectrum in the C—H vibration region.[1172] The spectra of 2,5-disubstituted thiophenes have been analyzed over the range 200–170 cm^{-1}. An assignment of the fundamental vibrations was proposed, and coupling between thiophenic skeletal vibrations and substituent vibrations was discussed.[1173]

Correlations between the intensities of the CH vibrations of 2-substituted thiophenes and Taft's substituent constants have been observed,[1174] and the IR intensities of ring-stretching bands of 2-substituted thiophenes and furans have been correlated with σ_R. For carbonyl substituents, the results were influenced by the conformation of the carbonyl group relative to the ring.[1175] The influence of solvents on the CH deformation vibrations of 2-substituted thiophenes has been studied. Correlation between the IR band intensity of the C=N stretching vibration and the ^{13}C NMR chemical shifts of cyanothiophenes and other aromatic nitriles has been attempted.[1176] The substituent effect on the maximum extinction coefficient (ε) of the CH stretching vibrations and rate constants (k) of deuterium exchange of protons in substituted acylmethanes, including thienyl methines, has been studied.[1177] The Raman spectra of various 2-substituted thiophenes, selenophenes, and furans have been reported.[1178]

4. Influence of the Thiophene Ring on the Vibrational Frequencies of Side Chains

The most widely studied vibration is the C=O stretching frequency of thiophene aldehydes, thiophene ketones, thiophene carboxylic acids, and their

derivatives. Investigations were carried out to study the electronic interaction of the carbonyl group with the ring, and later also to determine the conformation of the carbonyl group relative to the ring. Thus, in a very early investigation, it was demonstrated that the carbonyl group in 2-formylthiophene was more efficiently conjugated with the ring than in 3-formylthiophene, since the C=O frequencies were 1673 and 1691 cm^{-1}, respectively, and similar effects were found in 2- and 3-thiophenecarboxylic acid.[1179] High-resolution IR spectra of the carbonyl region showed the multiple absorptions,[1180-1183] the interpretation of which caused some problems. The Raman spectrum of neat 2-formylthiophene also showed twin carbonyl bands, which were ascribed to intermolecular association,[1184] whereas the results of ultrasonic studies were interpreted in terms of an equilibrium between rotational isomers.[1185] Multiple bands were also observed for 5-methyl-, 5-chloro-, and 5-bromothiophene aldehyde.[1180] It was first suggested that this was due to the existence of rotational isomers.[1186] However, from examinations of 2-deuterio- and ^{18}O-aldehydes, it was concluded that the multiple arises from the operation of Fermi resonance.[1182,1187,1188] The same conclusions were drawn from an investigation of the C=O region of a large number of substituted 2-formylthiophenes.[1180,1189] Bromination was often effective in diagnosing the occurrence of Fermi resonance.[1189] The claim that the existence of two bands in the C=O region of 2,5-diformyl- and 2,5-diacetylthiophene is due to the equilibrium of two conformers must therefore be taken with some reservation.[1190] The conformational equilibria in the β-formyl group of 2-chloro-3-formylthiophene and other five-membered heterocycles have been studied by IR spectroscopy. It was shown that the α-chloro-β-aldehydes of furan, pyrrole, oxazole, and imidazoles have the Cl,O-*trans* structure, whereas thiophene, thiazole, and pyrazole also shown minor amounts of the Cl,O-*cis* isomer.[108]

The question of conformational equilibria in carbonyl derivatives of thiophene has best been studied by ^1H NMR spectroscopy (see Section XI.1.H).

The shoulders and/or splittings of the carbonyl band of 5-substituted 2-acetylthiophenes were interpreted as a Fermi resonance by means of the solvent variation method. The unperturbed carbonyl frequencies were calculated by the intensity method and checked by correlation analysis of solvent and substitutent effects. Infrared spectroscopy also shows that the acetyl group is more sensitive to substituent effects in acetylthiophenes than in acetophenones.[1191]

The frequencies and total absolute intensities of the IR absorption band of the C=O group have been determined for a number of mono- and diacetylated thiophenes, as well as for esters of thiophene mono- and dicarboxylic acids.[1192]

Spectra of thiophene ketones, together with spectra of many other ketones, have been analyzed in the range 700–350 cm^{-1} to obtain spectra-structure correlations.[1193] The IR spectra of cyclic thiophene ketones have been studied to determine the influence of the size of the annelated ring.[669] The IR spectra of some 5-substituted 2-thenoylacetylenes have been analyzed.[1194,1195] The

change in the carbonyl stretching frequency in 2-acetylthiophene on hydrogen bond formation with phenol and pentachlorophenol has been compared with the corresponding changes in acetophenones, 2-acetylfurans, and 2-acetylselenophenes, and correlation analyses of the C=O frequencies were carried out using the Hammett and related equations.[1196,1197] Hammett correlations between the C=O stretching frequencies and substituent constants were also studied for a series of 5-phenyl-2-thiophenecarboxaldehydes and 2-(5-phenyl-2-thenylidene)-1,3-indandiones.[1198,1199] In the IR spectrum of the solid molecular complex of 2-acetylthiophene with $AlCl_3$, the C=O stretching frequency is shifted $-70\ cm^{-1}$.[1200]

The IR spectra of a number of 2-aroylthiophenes have been compared with those of the corresponding thioketones, in which the C=S stretching vibration is between 1186 and 1195 cm^{-1}.[230] From the intensities and dipole moments, the conformation of the 2-aroylthiophenes were determined.[1201]

Russian researchers have intensively studied the infrared spectra of chalcone analogs of thiophene.[121,351,1202-1208] Frequency assignments were made from a study of the 1700–650-cm^{-1} region of the IR spectra of 45 thiophene analogs of chalcones and vinylogs of 2-thienyl phenyl ketone. It was confirmed that the carbonyl group and aliphatic double bond are situated cis with respect to one another, so there is an approximation to the S-*cis* form. It was also confirmed from the C=O stretching frequencies that the 2-thienyl group has a larger electron-donating effect than the 2-furyl group, and for the 1-(2-thienyl)-3-arylpropen-1-ones, correlations between Hammett's σ-values and the C=O stretching frequencies were observed.[121,351] In a later investigation, the C=O stretching frequencies of 145 conformers of aromatic α,β-unsaturated carbonyl and arylfurancarbonyl compounds were correlated by the Yukawa–Tsuno structure reactivity equation.[1210] Theoretical calculations of the relation between the frequencies of the characteristic carbonyl vibrations and the basicities of the ketones as well as the mobile C=O bond orders have been carried out.[1212] The S-*cis* and S-*trans* carbonyl stretching frequencies of a series of *trans*-1-phenyl-3(5-aryl-2-thienyl)propenones and the analogous furyl derivatives have been measured. Statistically significant linear free-energy relationships were obtained between the C=O frequencies and σ^+. Poorer correlations were obtained with σ-values or with the Swain–Lupton two-parameter equation. Using the slopes of the ν(C=O) versus σ^+ correlations, the transmitive factors for the thiophene and furan rings were calculated. The determined order of transmission was furan > thiophene > benzene.[1211] Changes of the C=O stretching frequencies in chalcones on protonation have been measured.[1203,1205,1206]

On the basis of investigations of the IR spectra of the hydrogen-bonded complexes of 2-thenylideneacetone and the analogous benzene and furan derivatives with phenol, it was suggested that the S-*trans* conformers of the α,β-unsaturated ketones possess considerably greater proton-accepting capacity than their S-*cis* forms.[1208] This type of investigation was also carried out on the thiophene, selenophene, and furan ananlogs of chalcone.[1204,1205]

Infrared spectroscopy, together with UV and NMR, has been used for the conformational analysis of 2- and 3-thienylglyoxylic acid and some of their derivatives. The carbonyl group appears strongly conjugated, and thus coplanar with the thiophene ring. It was concluded that the 2-isomer exists in two forms, one open and one chelated. The latter exists mainly in the S-*cis–trans* conformer.[704] The IR spectra of 15 esters of α-2-thienylglyoxylic acid have been studied in the 3200–1100-cm^{-1} region. The effects of substituents on the frequencies of the skeletal vibrations of the ring and the stretching vibrations of the CO group have been discussed.[1213] The IR spectra of different hydrazides were also studied.[1214]

Infrared spectroscopy was used early for the study of keto enol tautomeric systems, such as 1,3-dicarbonyl derivatives, including 2-thenoyltrifluoroacetone, which was found to exist as the chelated enol.[1209] This was also found to be the case with di-(2-thenoyl)methane.[1215,1216] The IR spectra of the Co(II), Cu, Cd, Al, Fe(III), In, and Zr complexes of 2-thenoyltrifluoroacetone have been investigated,[1217] as have the spectra of thio derivatives of 2-thenoyltrifluoroacetone and its metal chelates.[1218]

The IR spectra of the potentially tautomeric hydroxythiophene systems indicated their thiolacetone structure, as the 3-thiolene-2-one forms showed C=O stretching frequencies in the interval 1695–1670 cm^{-1}, and 4-thiolene-2-one in the interval between 1750 and 1730 cm^{-1}.[699,700,1219,1220] (For more details, see. Part 3, Chapter I.) The IR, UV, and NMR spectra of the thiophene analogues of phthalaldehydic acid and their esters clearly showed that these compounds existed as the three ortho formylthiophene carboxylic acids and their esters, and not as cyclic tautomers.[707,708]

Two bands were observed for 2-thiophene carboxylic acid in the C=O stretching region in dilute carbon tetrachloride. The more intense band at lower frequency was ascribed to a dimer, while the other was assigned to the monomer.[1221] Similarly, esters of 2-thiophene carboxylic acids show two C=O stretching bands, which have tentatively been assigned to the syn S-*trans* and anti S-*trans* conformations.[1222,1223] This assignment was supported by the fact that deuteriated analogs had similar doublets, thus eliminating the possibility that the splitting was due to Fermi resonance.[1223] A study of the temperature variation of the carbonyl bands of the rotamers gave reliable enthalpy differences.[1223]

The carbonyl stretching frequencies of methyl (3-, 4-, and 5-substituted 2-thiophene carboxylates) and of methyl (2-, 4-, and 5-substituted 3-thiophene carboxylates) have been correlated with ^1H NMR spectra.[716,717] Thus, good linear correlations between the IR carbonyl stretching frequencies in methyl (5-substituted 2-thiophenecarboxylates) and the chemical shifts of the 5-protons in 2-substituted thiophenes were observed.[716] Some methyl ortho-substituted 3-thiophene carboxylates showed two C=O stretching bands, which were assigned to anti S-trans and syn S-*trans* forms.[717]

The C=O stretching frequency region of solutions of 38 alkyl thiophene 2-carboxylates have been analyzed in detail. In carbon tetrachloride, 11 esters

showed single bands, one showed three bands (Fermi resonance) and 26 showed doublets. It was shown that the doublets were caused by rotational isomerism between the syn S-*trans* and anti S-*trans* forms. The high wavenumber components of the doublets observed with 3- and 5-bromo-2-thiophenecarboxylates arise from the forms with the lower dipole moments and higher enthalpies, and are probably due to the anti S-*trans* rotamers.[1224] The IR spectra of the anhydrides of the thiophene dicarboxylic acids have been discussed.[1225]

An extensive review of correlations between IR spectra and NMR data, also covering some thiophene derivatives, has been published.[1226] The C=O stretching frequency of a series of derivatives of 5-methyl-2-thiophene carboxylic acids substituted in the methyl group and their furan analogues have been studied, and the inductive effect of the substituents influenced this stretching frequency.[1227]

A detailed investigation of rotational isomerism in thirty-five 2-thiophene carbonyl halides and 2-furan carbonyl halides have been undertaken using IR and ^{1}H NMR spectroscopy. At room temperature, solutions of the fluorides contain appreciable amounts of the syn and anti rotamers.[857] In another IR investigation of 40 aromatic acid chlorides, including thiophenecarbonyl chloride, the stretching frequencies, and integrated intensities of the bands in the regions around 1770 and 870 cm^{-1} were tabulated.[1228]

The IR spectra of 2- and 3-thiophene carboxamides have been analyzed, and especially the NH and CO stretching and NH deformation bands were discussed.[1169,1229] The IR spectra of ortho-aminothiophenecarboxylates and related carbonyl derivatives were analyzed, and gave evidence for the through-conjugation in such systems.[1230] In an investigation of the IR spectra of malonate esters, a thiophene derivative was also studied.[1231] Infrared spectra were used in connection with studies on the dissociation and association of 2- and 3-thiophenecarboxylic acids and the rate of saponification of their ethyl esters.[1232] Similar investigations were also carried out on thiophenedicarboxylic acids and their esters.[1233] Infrared spectra of carboxylic acid derivatives such as anilides and substituted anilides,[1234] *p*-phenylphenacyl esters, and *p*-nitrobenzyl esters,[1235] and *p*-bromophenacyl esters[130] have been studied. The IR spectra of 2-thienylglyoxylic and 2-thienylbutylglycolic acid tosylhydrazides[1236,1237] were obtained. The hydrogen bond conditions in some anticholinergetic esters of glycolic acids containing thiophene rings have been studied by IR investigation of the OH and C=O stretching regions.[1238] The yttrium(III) salt of 2-thiophenecarboxylate has also been studied.[1239] The IR spectral characteristics of the dimethylhydrazones of various aldehydes, including 2-thiophenecarboxaldehyde, have been analyzed.[1240] As the only geometric isomer of 2-thiophenecarboxaldehyde only shows one band at 2.054 μm, the β-configuration was assigned to it, since from a study of five pairs of geometrically isomeric aldoximes it appeared that α-oximes exhibit two absorption peaks at 2.010–2.030 μm and at 2.065–2.085 μm, while β-oximes exhibit only one, at 2.045–2.060 μm.[1241]

5. Various IR Spectroscopic Investigations

The IR spectra of 10 substituted thiophenethiols show SH stretching frequencies between 2538 and 2506 cm^{-1}.[1242] The IR spectra of di(thienyl) sulfides were studied in connection with investigations of the transmission of the electronic effects through the sulfide bond.[1243,1244] In KBr disks, only one N—H stretching absorption band was observed in 2-thiophenesulfonamides, while in CCl_4 two bands, due to free and associated NH groups, were present. Good correlations were found between the NH frequencies and Hammett substituent constants.[1245,1246] An IR spectroscopic study of 2-thiophenesulfonyl urea and thiourea derivatives has been carried out.[1247] Hydrogen bonds in β-hydroxysulfides of the thiophene series have been studied by IR.[1248]

The frequencies and apparent extinction constants for bands in the 1550-, 1350-, 1300-, and 850-cm^{-1} regions have been determined for 2-nitrothiophene in connection with an investigation of a large number of aromatic nitro compounds.[1249]

The IR spectra of a large number of thienylsilanes have been studied in detail. The σ^* inductive constants of substituted thienyl groups were calculated from the experimental (Si—Cl) values.[1250] The IR spectrum of 2-thienylphosphorous dichloride has been investigated.[1251] The IR spectra of some pairs cis and trans isomers of 2'- and 3'-substituted 2-styrylthiophenes have been analyzed. The spectra of the stereoisomers were sufficiently different to assign the configurations.[1252] The IR spectra of thienylacetylene[1253] and of 1-thenoyl-2-arylacetylenes have been studied,[1254] in the latter case in order to obtain information about interactions between the aromatic rings. To obtain information about rotational isomers, the IR spectra of a large number of *N*-mono- and *N,N'*-disubstituted amidines, some of which contained thiophene rings, have been investigated.[1255] Infrared spectra of indigoid derivatives of the thiophene series have been studied,[1256] as have condensation products between 2-thiophenecarboxaldehyde and azulene.[1257] Infrared spectra of thiophene-1,1-dioxides have been studied to obtain information about conjugation in this type of compound.[1258,1259]

Infrared spectroscopy has been used in the study of electrochemically generated polythiophenes[307,308] by using in situ IR attenuated total reflection spectroscopy of electrode surfaces.[1260] Infrared absorption has been used for the study of the photoexcitation of polythiophene.[302] Many other publications concerned with the IR and Raman spectra of conducting doped polythiophene films have recently appeared.[296,298,299,302,314]

The IR spectra of transition-metal complexes containing thiophene as ligand, such as thiophene–$Cr(CO)_3$[1261] and thiophene–$W(CO)_5$,[1262] have been studied. The IR spectra of nickel cyanide–ammonia clathrates containing thiophene have attracted the interest of several research groups.[1263–1265] The IR spectra of transition-metal complexes of 2-thiophene carboxaldehyde thiocarbohydraz-

ones[1266] and some aldimines[1267] have been studied. The IR spectrum of thiophene adsorbed on laminar silicates,[1268] silica-supported nickel,[1269] ultramarine,[1270] montmorillonites,[1271] and cobalt molybdate[1272] have been studied in connection with investigation of hydrogenation catalysts.[1272] The IR spectrum of the complex between thiophene and tetrahydrothiophene and $SnCl_4$ has been studied.[1273]

Infrared spectra in the solid state have been used on optically active and racemic thiophene derivatives to determine whether the compound is a true racemate or a eutectic mixture, and also for the detection of quasi-racemates.[459,1274,1275]

Coordination and intermolecular hydrogen bond formation of thiophenes with phenols has also been investigated by studying the $\Delta\nu$(OH) shifts. Derivatives that have been studied were 2-methyl- and 2,5-dimethylthiophene,[1276] 2-acetylthiophene,[1196] 2-thienylphenyl ketones,[1197] 2-thenylideneacetone,[1208] and thiophene analogs of chalcone,[1269,1205] as well as organosilicon derivatives of thiophene.[1277,1278] The interaction of thiophene with the hydroxyl groups of silica gel[1279] and hydroxylated Silochrome[1277] has also been studied.

At the beginning of the 1950s IR spectroscopy was the major tool for determining the isomeric purity of thiophene derivatives. Characteristic bands were found for 2- and 3-bromothiophene.[1280] The band at 834 cm^{-1} in 2-nitrothiophene indicated the presence of small amounts of the 3-isomer.[1281] Infrared spectroscopy was used to ascertain the isomeric purity of chlorothiophenes[1282] and for analysis of mixtures of 4- and 5-bromo-2-acetylthiophene, obtained on bromination of 2-acetylthiophene.[1283] Infrared spectroscopy was also used for following the reaction between organometallic thiophene derivatives and phenylthiocyanate,[1284] to determine the kinetics of the reaction of thiophenecarboxylic acids with diphenyl phosphorazidate,[1285] and for the identification of thiophenes in petroleum, tar, and bitumen.[516,1286–1288] In the 1950s and early 1960s it was quite common to publish the full IR spectra for characterization of the products, and such spectra of thiophene derivatives can for instance be found in Refs. 728, 731, 793, 794, 1225, and 1289–1297. Near-IR atomic emission lines of carbon and sulfur from a helium microwave induced plasma have been used for element ratio determination in thiophene.[1009]

XIV. ELECTRONIC SPECTRA OF THIOPHENES

1. UV Spectra of Thiophenes

The vapor-phase UV spectrum of thiophene has been studied with more and more advanced equipment over the past 50 years.[1298–1301] Milazzo[1299] inferred the existence of two overlapping bands at 263–222 and 244–222 nm, and a third band at 222–204 nm. He estimated the position of the 0—0 transitions of the overlapping band to be at 240 and 233 nm. However, later investigations of the

electronic absorption spectra of thiophene and of 2-deuterio-, 2,5-dideuterio-, and tetradeuteriothiophene in the range of 250–140 nm led to three electronic transitions with origins at 240, 207, and 188 nm in thiophene itself. Two Rydberg series leading to the 140-nm limit were also analyzed. The broadness of the bands prevented the identification of the symmetry of the upper states by analysis of band contours.[1301] The absorption bands at 240, 207, and 188 nm have been assigned as $\bar{A}$—$\tilde{X}$, $\bar{B}$—$\tilde{X}$, and $\bar{C}$—$\tilde{X}$, respectively. The A and B systems have been classified as π–π^* transitions, but there is disagreement in the assignment of the symmetry of the two excited states. The $\bar{C}$ system has been interpreted as a π–π^* transition[1301] or as a Rydberg transition.[1302] On the other hand, investigations of the magnetic circular dichroism (MCD) spectra of thiophenes showed the existence of two transitions in the region 263–222 nm with opposite signs, indicating two adjacent bands as suggested by Milazzo.[1299] The B term for the lowest transition is negative, while it is positive for the higher one. Quantum-mechanical calculations in the π-electron approximation resulted in energies, oscillator strengths, and MCS terms in good agreement with the observed spectra.[1303–1305] Recently, the UV spectrum of single crystals of thiophene has been recorded in the spectral region 263–200 nm for temperatures down to 12 K.[1306] From these measurements and theoretical calculations, a new assignment of the UV spectrum of thiophene has been made. The two intense electronic transitions are assigned to π–π^* states of A_1 and B_2 symmetry, and the intermediate absorption in the vapor spectrum is attributed to a Rydberg state. For earlier interpretations of the UV spectrum of thiophene, see Refs. 1307–1309.

Weak peaks in the spectrum of thiophene, previously reported at 261 and 268.5 nm, have been shown to be due to impurities from benzene and toluene.[1310,1311] However, the presence of a very weak absorption between 4 and 5 eV was not excluded by the Hungarian authors. This very weak band, as well as the very weak bands ($\varepsilon_{max} = 0.048$) at 313 and 318 nm for a 2 N solution of thiophene in hexane,[1312] tentatively assigned to forbidden singlet–triplet transitions, might be real. (For a recent discussion, see Ref. 1313.)

The electronic spectrum of thiophene continues to attract attention. Thus, high resolution and temperature-dependence measurements have been recorded for the lowest energy UV transition of thiophene. Based on the new observations of the hot bands, the vibronic fine structure has been reassigned. The new assignments can be fitted well to the spectra of deuteriated derivatives. The first band system of the UV spectrum was assigned to the ψ_4–$\psi_3(B_2)$ transition.[1314] The new assignement was also confirmed by studying the UV spectrum of thiophene between 225 and 246 nm at elevated temperatures. Vibrational structure was lost as the temperature approached 773 K.[1315]

Many quantum-mechanical calculations of the electronic transitions of thiophene have been carried out,[135,192,1316–1318] and the conjugation and UV bands of the five-membered aromatic heterocycles and cyclopentadiene were compared.[1316] Thiophene, furan, and pyrrole, as well as their benzo and dibenzo derivatives, have been studied by INDO/S and CINDO/SHIFT/UV

methods in order to rationalize their electronic structure and UV spectra, and to calculate the excited state dipole moments.[1319] For additional information, see Part 1, Chapter II of this treatise.

The effect of substituents on the UV bands of thiophene at 215 nm and 235 nm were discussed in a semiquantitative manner, even before definite assignments of the transitions had been made.[1320,1321] The spectra were interpreted in analogy with the discussion by Doub and Vandenbelt[1322] of the effect of substituents on the 203- and 254-nm transitions of benzene. The UV spectra of 2-substituted thiophenes with -I-M-substituents show two high-intensity bands, both of which were displaced toward longer wavelengths with increasing conjugating power of the substituents. The extinction increased in the same order as in the benzene series (NO_2 > CHO > COOH > CN > SO_2CH_3), and the displacements of the low wavelength (primary band) of thiophenes are of the same order of magnitude as those in the corresponding benzenoid compounds. The ratio of the wavelengths of the secondary band to the primary bands is constant, as is the case in the benzene series.[1323] These shifts in -I-M-substituted furans are even larger.[1321] In thiophenes containing a -I-M-substituent in the 3-position, only one band is observed, and the bathochromic shifts are smaller than in the 2-substituted derivatives, indicating better conjugation in the latter.[1321,1323,1324] The λ_{max} values of the first absorption bands of 2-monosubstituted thiophenes show linear relationships with the λ_{max} values of the first primary bands of the corresponding monosubstituted benzenes, while the band of 3-substituted thiophenes does not show such a relationship.[1324] Thiophene substituted with groups such as alkyl, halogens, OCH_3, and SCH_3 show small but characteristic differences between the 2- and 3-substituted derivatives. In these cases, however, it is the 2-substituted derivative that shows the simpler spectrum and also a considerably larger extinction.[1323] These differences are also present in the spectra of 2,5- and 3,4-dihalo-substituted compounds.[1325] It is also interesting to note that in 2-substituted thiophenes the intensity of the band varies inversely as the electronegativity of the halogen substituent. This is opposite from the effect observed in the corresponding benzene derivatives and in the 3-substituted thiophenes.[1325,1326] A good correlation was obtained between the algebraic sums of the shift of the first absorption band of monosubstituted thiophenes with the shift of the first absorption band of the corresponding 2,3-disubstituted thiophenes, although the calculated values are slightly greater than the measured values. In the case of 2,5-disubstituted compounds, the calculated shifts were smaller than the measured ones.[1324] The intensities of the first absorption band of some 2,5-disubstituted thiophenes have been calculated[1324] from the spectroscopic moments of the substituents.[1327] The UV absorption of thiophene was displaced toward lower frequencies on methyl substitution, and the oscillator strength has been calculated for several methyl thiophenes.[1326]

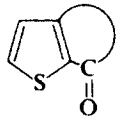
The UV spectra of a number of 2-alkylthiophenes and 2-*n*-alkyl thenoates have been obtained.[137]

Vapor and condensed-phase spectra of 18 thiophene derivatives and of the parent molecule have been investigated in the near-UV region. Based on the spectra and CNDO/S calculations, it was pointed out that although two bands can be observed in the vapor-phase spectra of thiophene and most of its derivatives, the near-UV spectrum contains three singlet transitions. These are the following (with increasing energies):[1328]

$$\pi 4^* \leftarrow \pi 3(B_2 \rightarrow A_1), \qquad \pi 4 \leftarrow \pi 2(A_1 \leftarrow A_1), \qquad R_S \leftarrow \pi 3.$$

The effect of the ring size of annelated saturated rings on the UV spectrum has been studied. Comparison with the spectra of 2,3- and 3,4-dimethylthiophene indicated that the effects were small. Only when the annelated ring was five-membered was a hypsochromic shift observed.[669] A large number of investigations have been concerned with the UV spectra of various carbonyl-substituted thiophenes[645,669,1212,1329–1335] and some derivatives such as hydrazones and azines.[1334,1329]

The electronic spectra of 2-thienylarylketones show three absorption bands. The one at the lowest wavelength was attributed to a π–π^* transition in the thienyl ring, in aroyl compounds mixed with a contribution from an aroyl carbonyl band. This band is not disturbed by *ortho*-disubstitution in the phenyl ring of 2-benzoylthiophenes. The second absorption band has been assigned to a π–π^* transition of the thienyl–carbonyl chromophore and the third one of low or medium intensity above 310 nm is the usual n–π^* transition of carbonyl compounds.[1335] From an investigation of a number of phenyl 2-thienylketones, *ortho*-alkyl-substituted in the benzene ring, it was found that this substitution had no influence on the electronic spectra, and no difference in the ε_{max} was found between these compounds and the parent compound. It was therefore concluded that in 2-thienyl phenyl ketone, the phenyl ring is turned out of the plane defined by the coplanar thiophene ring and the carbonyl group.[1332,1335,1336] On substitution with electron-donating substituents in the 5-position of 2-acetylthiophenes, the band at lowest wavelength is not affected, while the second band, assigned to a transition in the thienylcarbonyl chromophore, undergoes a bathochromic shift, which was ascribed to increased conjugation between the thienyl ring and the carbonyl group.[1332] A detailed study of thienocyclanones of types **163**–**165**, and analogous compounds with sulfur in the side chain, has been carried out. Characteristic differences were found, which allowed the identification of the position of the carbonyl group.[1337] The ring size, on the other hand, did not influence the UV spectrum very much.



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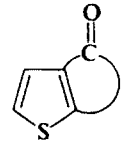

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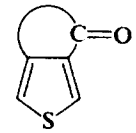

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The UV absorption and phosphorescence emission spectra of 2- and 3-benzoylthiophene and their *p*-cyano and *p*-methoxy derivatives have been analyzed in detail, and partial state diagrams were given.[1338] The lowest energy absorption was in all cases assigned to the carbonyl $n \rightarrow \pi^*$ transition. The π–π^* transition with the 2-thenoyl chromophore was again found at considerably longer wavelengths than the corresponding transition of the 3-thenoyl chromophore. This was ascribed to a greater contribution of charge separated structures to the excited state of the former. The emission from the 2-benzoylthiophenes is structured, with a prominent vibrational separation of 600 cm^{-1}. Based on triplet lifetimes, it was assigned as a π,π^* triplet. On the other hand, the shape of the emission from the 3-benzoylthiophenes was typical of an n,π^* showing the characteristic five-fingered pattern of vibrational structure separated by the carbonyl stretching frequency (1700 cm^{-1}).[1338] In 2,5-diacetyl- and 2,5-diaroylthiophenes, greater thienyl–carbonyl interaction is observed, resulting in red-shifts and increased intensity of the related absorption band.[1335] In 2-acetyl- and 2,5-diacetylthiophene, methyl substitution, both in the 3- and 4-positions, does not influence the UV spectrum, while, as mentioned previously, ortho-substitution in the phenyl ring of 2-benzoyl- and 2,5-dibenzoylthiophene disturbs the interaction between the phenyl and the carbonyl groups.[1335] In connection with an investigation of the electronic spectra of phenyl aryl ketones, their protonation and their charge-transfer π-complexes with tetracyanoethylene and 2- and 3-benzoylthiophene were also studied, and HMO calculations were carried out.[1212]

The UV spectra of *ortho*-formylthiophenecarboxylic acids and their methyl esters were investigated in connection with a study of ring-chain tautomerism in these acids. It was found that in all cases the spectra of the acids were identical with those of the esters, thus giving no evidence for the existence of cyclic lactol forms in dilute alcoholic solution.[708] The UV spectra of the esters, amides, and azomethine dyes from 2- and 3-thenoyl acetic acid have been studied.[1340] The UV spectra of 5-methyl-2-thiophenecarboxylic acid derivatives containing polar substituents in the methyl group have been studied, and the effect on the UV spectra of these changes were compared with those of the corresponding furan derivatives.[1227]

The UV spectra of the thiophene analogs of mandelic acid have been obtained in connection with a comparative investigation of their CD spectra.[1341]

A comparative investigation of the electronic spectra of thienylphenyl thioketones and thienyl phenyl ketones indicates that steric effects manifest themselves more strongly in the spectra of the thioketones.[1336] The UV spectra of other compounds containing the carbonyl–sulfur double bond, such as esters of thienyldithiocarboxylic acids, have also been studied, and calculations by the HMO method carried out.[1342]

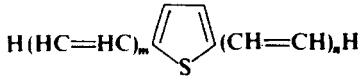
Ultraviolet spectra of other simple thiophenes, such as halothiophenes[1343] and nitrothiophenes,[1281,1343,1344] aminothiophenes,[1215,1290,1245,1246] and methoxythiophene[1347] have been obtained, in most cases only for the character-

ization of the compounds. The unstable 2-thienyldiazomethane shows absorption in the visible region λ_{max} = 504 nm [ether, ε 30].[1348]

The UV spectra of compounds containing thiophene–sulfur bonds have attracted special interest. The electronic spectra of thiophenethiols were studied and their ionization constants determined by the dependence of the optical density of their alcoholic solutions on pH.[1339] The UV spectra of isomeric dithienyl sulfides and alkyl thienyl sulfides have been studied by several groups.[1243,1244,1349,1350] On measuring the UV spectra down to 190 nm, a sharp intense band was observed at 200 nm for 2-thienyl sulfides and at 212 nm for 3-thienyl sulfides.[1244] The absorption band in the 260–275-nm region is common to both the sulfides and the corresponding sulfones, and is probably due to interaction of the substituent with the thiophene ring.[1244] It is also claimed that the UV spectra show that no interaction occurs between thiophene rings separated by a sulfur atom.[1243]

A comparative investigation of ethers, sulfides, and selenides of the thiophene series showed an increasing bathochromic shift in the series OR < SR < SeR.[1351] The long-wavelength band of the selenide showed lower intensity than that of the sulfide, which was taken as evidence for less conjugation between the ring and the substituent in the selenide.[1351] The UV spectra of thirty-one 2-thiophenesulfonamides have been measured, and the spectral changes were correlated with substituent effects.[1245]

The electronic spectra of a number of polyenyl-substituted furans and thiophenes (**166**) have been compared with those of the corresponding polyenes having the same number of double bonds, and it was found that the net contribution of the heterocyclic ring is roughly equivalent to that of a butadiene unit.[1352,1353] This was also confirmed by LCI/SCF/MO calculations on furans and thiophenes with ethylene, butadiene, or hexatriene groups at the 2- and 5-positions. The calculated excitation energies were almost independent of the presence or the nature of the heteroatom.[1354] Spectroscopic data, including UV data for **167**, showed this compound to be a stable nonplanar, nonaromatic system, in which the three olefinic rings are linked by three essentially olefinic vinyl groups.[783]



X = O, S
$m = 0, n = 1$ $m = n = 1$
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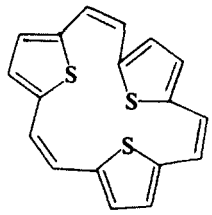

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Ultraviolet spectra of polyunsaturated naturally occurring thiophene derivatives have also been very useful for the structure determination of these

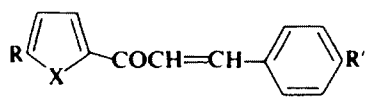
compounds[756,793,797,800,804,805,1355–1360] (for additional discussion, see also Part 1, Chapter III).

The electronic spectra of 2-thiophenecarbonyl derivatives, such as carboxylic acids, esters, aldehydes, and methyl ketones, have been compared with those of the corresponding 2-thienylacrylic acid derivatives. Interposing the CH=CH group led to a bathochromic shift of about 25 nm for the primary band and about 40 nm for the secondary band. The change was smaller than that for the corresponding furans.[1361] The effect on the spectra of a bromine or nitro group in the 5-position of both types of compounds has also been investigated.[1361,1362] Ultraviolet spectra and halochromism of the thiophene analogues of dibenzylidene cycloalkanones have been studied.[1363]

The UV spectra of some 4′-substituted *cis*- and *trans*-2-styrylthiophenes show two main absorption bands: one at 230 nm, which is in the same spectral region as the corresponding stilbenes, and a second band that is shifted toward longer wavelength, compared to that of the corresponding stilbenes. This band can be used for cis–trans assignment, since in the *cis*-isomer it occurs at about 290 nm, and in the *trans*-isomer around 325 nm in most cases. The band for the *cis*-isomer also shows lower intensity. An exception is the 4-nitro derivative, for which these bands occur at 354 and 372 nm, respectively.[1364] Similar results have been obtained for the *cis*- and *trans*-isomers of 2′- and 3′-substituted 2-styrylthiophenes. The spectra of the stereoisomers are sufficiently different to allow assignment of the configuration. The effect of substituents on the long-wavelength band was discussed and the absence of this absorption in *cis*-2-(2′-nitrostyryl)thiophene was taken as evidence for steric hindrance to coplanarity.[1252] The UV absorption spectra of *trans*-2-(styryl)thiophene and α-cyanostylthiophene have recently been interpreted.[1365]

A subsequent UV study of 2-styrylfurans and thiophenes indicated that the S-*trans* conformation was the preferred one for the 2-isomer (*cis*-isomer). A correlation between the frequency shifts ($\nu_Z - \nu_E$) and Hammett's σ-constants showed a greater sensitivity of the thiophene ring than the furan ring to substituent effects.[1366] The UV spectra of vinylthiophenes and *trans*-1,2-di(thienyl)ethenes substituted at the vinylic group have been compared with the corresponding parent compounds.[1367]

Analogs of chalcones of types **168–171** have attracted the interest of several groups.[122,1203,1204,1252,1330,1324,1368–1373]



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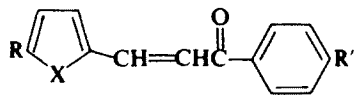

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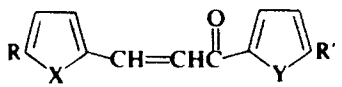

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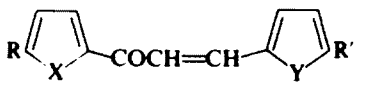

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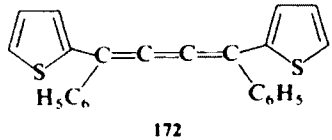
In both types of thiophene analogs of chalcones such as **168** (R = H, X = S) and **169** (R = H, X = S) the 2-thienyl group causes a bathochromic shift, indicating that it is both a better electron-releasing and a better electron-donating group than is the phenyl group.[1330,1371] Later, the UV spectra of a series of compounds of types **168** and **169** in which R = H, CH_3, OMe, and Br and R′ = NH_2, and X = S were also studied in dioxane and the long-wave band assigned to the different chromophores, by comparison with the UV spectra of simpler compounds, such as aminoacetophenone, aminobenzalacetone, and acetothienone.[1372] The basicity constants of **168** (R = R′ = H, X = S), **169** (R = R′ = H, X = S), and **170** (R = R′ = H, X = S) have been determined in sulfuric acid solutions by UV spectroscopy. It was found that the replacement of a benzene ring by thiophene in chalcone leads to increased basicity, which is largest when the carbonyl group is remote from the thiophene ring (in **169**).[1203] These investigations were later extended to compounds of type **168–171** containing furan and selenophene rings.[1204,122] Alcohols corresponding to **168** and **169** in which X = S and R = H, have been studied and the long-wave absorption maximum correlated with the chemical shift of the OH proton and Hammett's σ-constants.[1374] The UV spectra of some polyenic bis-ω,ω'- and mono-ω-dimethylamino thienyl ketones have also been investigated.[1375] As mentioned previously, the replacement of a benzene ring by a thiophene ring in compounds containing other chromophores causes bathochromic shifts, as a result of the superior electron-releasing power of the 2-thienyl group. These effects have been noticed in cumulenes, such as **172**,[1376] in thiophene analogs of malachite green **173**,[1377,1378] and in simple carbonium ions derived from thiophene analogs of triphenyl and divinylcarbinols.[1379]



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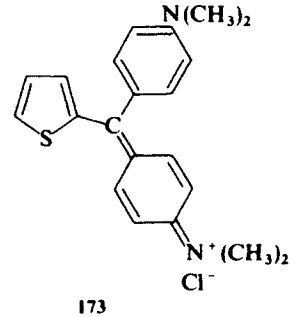

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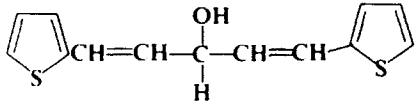
The protolytic equilibria and the rate constants of **173** have been investigated spectroscopically in aqueous solution. Similarities to the *o*- and *p*-hydroxy and methoxy derivatives of malachite green were observed.[1377]

The spectra of vinologs of 1-thienylphenyl- and bis-(2-thienyl)-carbinols, such as **174** and **175** and the carbonium ions derived from them, have been investigated. A linear dependence between the absorption maxima of the polymethine salt and the number of methine groups in the cation were established.[1380] The thienyl-substituted diformazane **176** is blue, in contrast to the red phenyl analog, owing to this bathochromic effect.[1381]



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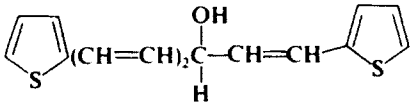

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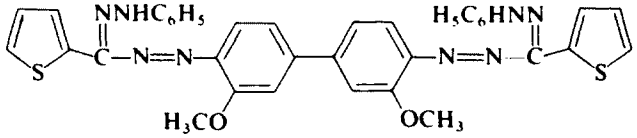

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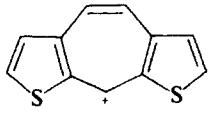
The UV spectra of some other types of azo dyes containing thiophene rings have been obtained.[1054,1382,1383] The electronic spectra of a number of thiophene- and furan-annelaed tropylium cations, such as **177–179**, and tropones, derived from them, as well as the *c,c*-fused ketone were measured. Theoretical spectra calculated within the PPP approximation were in good agreement with the experimental ones.[1384] The UV spectra of some thieno[2,3-*d*]tropolone derivatives, such as **180** and **181**, have also been studied.[1385] The electronic spectra of acenaphto[1,2-*b*]thiophene and acenaphto[1,2-*c*]thiophene have been studied and compared with fluranthene and assignments discussed.[1386]



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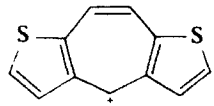

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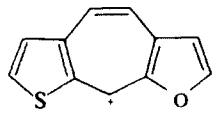

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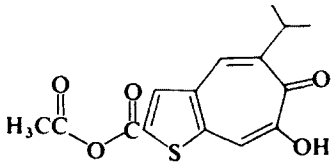

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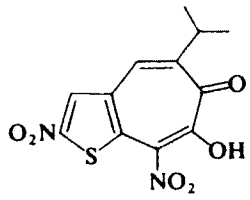


181

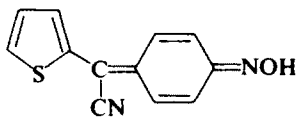
In connection with investigations on conformation of and conjugation in aryl thiophenes the UV spectra of 2- and 3-phenylthiophene,[1387–1390] 3,4- and 2,5-diphenylthiophene,[1391,1392] and tetraphenylthiophene,[1393–1395] as well as of some thienyltetrazoles,[1387] thienylpyrazoles,[1396] and thienyl anthracenes[1397]

have been discussed. The experimental spectrum of 2-phenylthiophene has been compared with the calculated one.[1398] The UV spectra of resolvable 2,2',4,4'-tetrasubstitued 3,3'-bithienyls and 3-phenylthiophenes indicated that conjugation between the two rings is negligible,[1390,1399] and the UV spectra of a large number of this type of compounds have been obtained in connection with investigations of their ORD and CD spectra[459,1400–1407] (see Section XVI.7).

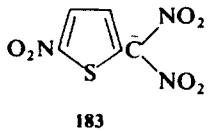
The UV absorption spectra of 5- and 5,5'-disubstituted 2,2'-bithienyls show three absorption bands. The absorption band at 207 ± 3nm was assigned to n–σ^* transition of the electrons of the heteroatom to the antibonding σ-orbital. The second band at 240–250 nm, (ε_{max} 5000–9000) does not change much with substitution and was assigned to a π–π^* transition of the thiophene ring. The strong broad band in the 300–360-nm region ($\varepsilon_{max} \sim 20{,}000$), characteristic of 2,2'-bithienyls, was considered to be an electron-transfer transition. Auxochromic substituents in the 2- and 2,5-positions cause a bathochromic shift in the order of 6–14 nm relative to 2,2'-bithienyl $\lambda_{max} = 301$ nm ($I > Br > Cl > CH_3$). Carbonyl-containing substituents shift this band bathochromically about 50 nm.[1408] The effect of UV light on the toxicity of some naturally occurring phenylthiophene toward the eggs of Drosophila melanogaster has been studied.[1409–1411]

The UV spectra of 2,2'-bithienyl, 3,3'-bithienyl, 5,5'-dimethyl-3,3-bithienyl, and hexamethyl-3,3'bithienyl have been obtained as solution spectra in cyclohexane and as polarized spectra in oriented polyethylene films. By comparing the experimentally obtained directions for the π–π^* transitions with those obtained from MO calculations using semiempirical parameters, conclusions about the predominating conformations could be made.[1412] The experimental data and calculated electronic singlet transitions are given in Table 54.

The electronic spectra of many other types of thiophene derivatives, such as **182**[792] and **183**,[1291] have been studied in connection with structure determinations and to evaluate the conjugation between ring and substituent. The electronic spectrum of **184** exhibits a broad absorption band with charge-transfer character.[1413]



182



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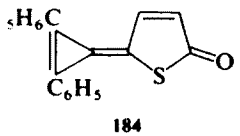

184

The UV spectra of **185** and of the indanones derived from it have been discussed,[1414] as well as thiophene derivatives with indigoid structure[1256,1415] and thiophene-manganese tricarbonyl complexes.[1416]

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TABLE 54. UV Absorption Spectra and MO Calculations for the π–π^* Transition for Some Bithienyls

Compound	Condition	Position of Bands (Wavelengths in nm) and Polarizations	$\varepsilon \times 10^{-4}$ ($M^{-1}\,cm^{-1}$)	Symmetry	(nm)
2,2′-Bithienyl	Cyclohexane	335[a] 327[b] 317[c]		(Planar *cis*)	
		311[d] 302[e] 290[f]		B_2	290
		275[g] 254[h] 247[i]		„	246
		207[j] 192[k]		A_1	241
		302	1.23	„	215
		247	0.71	B_2	183
		192	1.60		
				(Planar *trans*)	
	Film	306 x ($\alpha = 0°$)		B_u	289
		247 x and y ($\alpha = 46°$)		„	250
				A_g	245
				„	215
				B_u	176
3,3′-Bithienyl	−190°	309.0[a] 296.0[b] 282.5[c]		(Planar *cis*)	
	film	278.0[d] 272.5[e] 270.0[f]		B_2	259
		266.5[g] 262.0[h] 252.5[i]		A_1	250
		247.0[j] 232.5[k] 220.0[l]		B_2	243
				A_1	223
		216.0[m] 211.5[n]		B_2	196

	Cyclohexane	261	1.33	(Planar *trans*)	
		211	2.51	B_u	261
				A_g	250
	Chloroform	263	1.17	B_u	236
	film	260*x* ($\alpha = 20^\circ$)		A_g	234
		210*x* ($\alpha = 0^\circ$)		B_u	194
5,5′-Dimethyl-3,3′-bithienyl	Cyclohexane	330[a] 277[b] 265[c]		(Planar *cis*)	
		255[d] 240[e] 220[f]		B_2	255
		265	1.24	A_1	246
		220	2.50	B_2	241
	Film	265*x* ($\alpha = 40^\circ$)		A_1	228
		255*x*		B_2	203
		220*x*		(Planar *trans*)	
				B_u	252
				A_g	246
				B_u	239
				A_g	238
				B_u	199
Hexamethyl-3,3′-bithienyl	Cyclohexane film	244 (242)	1.63		
		195	2.73		
		244, 197*x*			

Dissociation constants of Ni^{2+} and Co^{2+} complexes of di-(2-thenoyl)-methane have been determined by UV spectroscopy.[1417] Ultraviolet data are collected in Tables 55–63.

2. UV Spectra of Charge-Transfer Complexes of Thiophenes

The charge-transfer complexes of thiophene and some other five-membered heterocycles with tetracyanoethylene,[1418–1421] chloranil, and maleic anhydride have been investigated by electron spectroscopy.[1422] The following CT bands were observed: λ_{max}, ε: with TCNE [445 nm(shoulder) 2000; 390 nm, 2750]; with chloranil (348 nm, 2360); and with maleic anhydride (270 nm, 10,300).[1422] With iodine thiophene gives a CT band at 295 nm.[131,1423–1425] The temperature dependence of the formation constant, extinction coefficient, and total absorption intensity of the thiophene–iodine complex has been determined.[1427] The existence of a π-complex during the bromination of thiophene was confirmed spectrophotometrically. The formation constant and molar extinction coefficient of the complex between 2-bromthiophene and bromine were determined.[1428]

The association constants K (in liters mole) of the charge-transfer complex of thiophene with TNCE was 0.53 ± 0.02, with chloranil 0.22 ± 0.02, with maleic anhydride 0.02 ± 0.01,[1422] and with iodine 0.59.[1424] These association constants were compared with that for the formation of a bond between thiophene and phenol.[1422] The charge-transfer band of 2-benzoylthiophene with TCNE has been measured and correlated with the highest occupied molecular orbital of the ketone.[1212]

The charge-transfer complexes of 2,2′-bithienyl, 5,5′-dimethyl-2,2′-bithienyl, and 2-methyl-, 2-bromo-, 2-chloro-, and 2-iodothiophene as donors with tetracyanoethylene as an acceptor have been studied spectrophotometrically. In addition, complexes of 2,2′-bithienyl with chloranil and iodine have also been investigated. The ionization potentials of the donors were obtained from the energies of the charge-transfer transitions.[1429] The absorption maxima in the charge-transfer complexes of thiophenes with TCNE were compared with those of the corresponding furans, selenophenes, and tellurophenes; most complexes displayed split bands. The ionization potentials of the donors were calculated and agreed with published values from photoelectron spectra.[1420] The charge-transfer energy on formation of molecular complexes between thiophene and 2-chlorothiophene with various acceptors has been related to the energy of the highest occupied molecular orbital of the donors.[1430] The charge-transfer bands in the complexes between 1,3,5-trinitrobenzene and thiophene and between 1,3,5-trinitrobenzene and 3-methylthiophene have been studied.[1305] The spectrophotometric properties of charge-transfer complexes between 2-thiophene aldehyde azine and both TCNE and 2,3-dichloro-5,6-dicyanobenzoquinone in methylene chloride were discussed.[1441]

TABLE 55. UV-Spectral Data for Thiophene and 2-Substituted Thiophenes

C_n	R_2	Solvent	λ (nm)	log ε	Ref.
4	H	Hexane	235	3.65	1324
		Heptane	236	2.78	1351
	Br	Ethanol	237	3.96	1361
			236	3.90	1323
		Hexane	228(sh)	3.82	1325
			236	3.89	
			237	3.99	1361
	Cl	Hexane	236	3.80	1325
		Hexane	228	3.68	
			243	3.95	
			250	3.90	
			280	2.40	
	NO_2	Ethanol	280	3.75	1362
			308.5	3.80	
			270	3.80	1323
			296	3.78	
		Hexane	270.5	3.80	1362
			297	3.80	
			253(sh)	3.68	1325
			270	3.79	
			298	3.76	
		Isooctane	298	3.85	1281
	SH	Ethanol	219	3.52	1339
			255	3.88	
			295	3.71	
			305	3.62	
			317	3.56	
	SO_2NH_2	„	238	3.86	1245
		„	250(sh)	3.73	

TABLE 55. (*Continued*)

C_n	R_2	Solvent	λ (nm)	log ε	Ref.
5	CN		243	3.97	1323
			258	3.80	
	CHO	Ethanol	260	4.02	1361
			285	3.85	
			260	4.04	1321, 1323
			286	3.86	
		Hexane	265	4.02	1361
			278.5	3.84	
			257.5	3.93	1324
			279	3.78	
		Heptane	255	3.93	1351
			275	3.78	
	CO_2H	Ethanol	246	3.93	1361, 1321
			264	3.76	
			246	3.96	1323
			260	3.84	
		Hexane	249	4.06	1361
			268.5	3.91	
			248	3.96	1324
			270	3.86	
	$CONH_2$	Ethanol	248	3.78	1321, 1361
			272	3.87	
	CH_3	"	232	3.87	1333
		Hexane	248	4.06	
			275	4.05	
	OCH_3	Hexane	228(sh)	3.57	1325
			244	3.66	
	SO_2CH_3	Ethanol	233	3.89	1323
			252	3.77	

	$SeCH_3$	Ethanol	236	3.91	1351
			284	3.40	
		Heptane	236	3.88	
			284	3.40	
	SCH_3	Ethanol	236	3.72	
			273	3.59	
			236	3.76	1323
			273	3.58	
		Heptane	236	3.79	1243, 1351
			273	3.58	
	SO_2NHCH_3	Ethanol	239	3.92	1245
			250(sh)	3.84	
6	$COCH_3$	Dioxane	260	3.88	1332
			285	3.76	
		Ethanol	260	4.01	1333
			283	3.87	
			260	3.89	1330
			285	3.75	
			260	3.89	1361
			282	3.84	
			260	3.97	1332
			283	3.84	
			260	3.98	1321
			282	3.84	
			260	4.01	1323
			283	3.87	
			260	4.01	
		Hexane	257	3.97	1335
			270–275	3.85	
			325–332	1.86	
			252	4.02	1361
			273	3.86	
	CH_2CHO	Ether	282	4.12	796

TABLE 55. *(Continued)*

C_n	R_2	Solvent	λ (nm)	log ε	Ref.
	CO_2CH_3	Ethanol	248	3.97	1321
			268	3.68	
			248	3.97	1361
			268	3.86	
		Hexane	245.5	4.04	
			266	3.84	
	CH_2CO_2H		235	3.59	1324
	$CH{=}CH_2$	Cyclohexane	275	4.00	1353
	CS_2CH_3	Ethanol	296	3.78	1342
			342	4.24	
			507	1.98	
		Cyclohexane	295	3.79	
			340	4.24	
			513	1.96	
	$NHCOCH_3$	Ethanol	264	4.01	1324
	SC_2H_5	Heptane	236	3.86	1243
			273	3.51	
7	$CH{=}CHCO_2H$	Ethanol	272	4.29	1361
			297	4.27	
		Ethanol	260	3.99	1333
			282	3.88	
	$CH{=}CHOCH_3$	Ether	231	3.91	796
	$CO_2C_2H_5$	Ethanol	249	3.95	1321, 1361
			269	3.89	
		Hexane	245	4.05	1361
			265	3.86	
	C_3H_7	Ethanol	234	3.88	1333

8	SO_2-2-Th	„	204	3.67	1244
			244	3.89	
			276	3.83	
	SO_2-3-Th	„	206	3.76	
			245	4.04	
			264	3.98	
	2-Th	„	206	3.62	1408
			246	3.81	
			301	4.11	
	S-2-Th	Heptane	237	4.09	1243
			263	3.91	
		Hexane	200	3.90	1244
			238	4.06	
			264	3.88	
	S-3-Th	„	204	4.08	
			235	4.02	
			268(sh)	3.93	
	S_2-2-Th	Heptane	251	4.08	1243
			275	4.00	
	$CH{=}CHCOCH_3$	Dioxane	213	3.49	1372
			323	3.80	
		Ethanol	276	3.84	1361
			321.5	4.29	
		Hexane	271	3.88	
			312	4.28	
	$CH{=}CHCO_2CH_3$	Ethanol	278	3.98	
			311	4.26	
		Hexane	275	3.99	
			304.5	4.27	
	$CH{=}CHCH{=}CH_2$	Cyclohexane	216	4.15	1353
			304	4.36	
	30% *cis*		217	4.13	
			204	4.31	

TABLE 55. (*Continued*)

C_n	R_2	Solvent	λ (nm)	log ε	Ref.
	$CO(CH_2)_2CH_3$	Ethanol	260	4.07	1333
			282	3.95	
	$(CH_2)_3CO_2H$	"	234	3.81	
	S-C_4H_9	Hexane	204	3.59	1244
			238	3.77	
			272	3.52	
	S-CH_2-*i*-Pr	Heptane	236	3.87	1243
			273	3.57	
9	SO_2NH-4-Py	Ethanol	251	4.09	1245
			294	4.18	
	SO_2NH-3-Py	"	247	4.10	
			305(sh)	2.20	
	SO_2NH-2-Py	"	243	4.18	
			318	3.77	
	CH_2-2-Th	Heptane	208	4.00	1243
			236	4.16	
	$CH{=}CHCO_2C_2H_5$	Ethanol	279	3.98	1361
			311	4.26	
		Hexane	274	3.99	
			303.5	4.27	
	$COCH_2CO_2C_2H_5$	Ethanol	260	3.97	1333
			282	3.86	
	SO_2-*N*-Pip	"	241	3.96	1245
			255	3.87	
10	$SO_2NHC_6H_4$-4-Cl	"	233	4.19	
			255	3.98	
	$SO_2NHC_6H_4$-3-Cl	"	233	4.21	
			255	3.99	

$SO_2NHC_6H_4$-2-Cl	"	227(sh)	4.05	
		240(sh)	3.97	
$SO_2NHC_6H_5$	"	227(sh)	4.08	
		250(sh)	3.92	
$SO_2NHC_6H_4$-4-NO_2	"	231	4.10	
		255(sh)	3.91	
		313	4.01	
		375	3.60	
$SO_2NHC_6H_4$-3-NO_2	"	226	4.25	
		255(sh)	4.16	
		320(sh)	3.20	
$SO_2NHC_6H_4$-2-NO_2	"	223	4.23	
		240(sh)	4.19	
		342	3.43	
$SO_2NHC_6H_4$-4-OH	"	232	4.18	
		252(sh)	3.87	
		280(sh)	3.52	
$SO_2NHC_6H_4$-3-OH	"	227	4.07	
		250(sh)	3.87	
		280(sh)	3.57	
$SO_2NHC_6H_4$-2-OH	"	227	4.05	
		250(sh)	3.87	
		283	3.61	
$(CH_2)_5CH_2$	Cyclohexane	245	4.17	1353
		318	4.45	
		330	4.55	
		345	4.45	
$S(CH)_2$S-2-Th	Heptane	237	4.18	1243
		272	3.86	
$CO(CH)_4CH_3$	Ethanol	260	3.99	1333
		283	3.88	
$CH_2CH(OC_2H_5)_2$	Ether	232	3.92	796
C_6H_{13}	Ethanol	234	3.91	1333

TABLE 55. (*Continued*)

C_n	R_2	Solvent	λ (nm)	log ε	Ref.
11	COC_6H_2-2,4,6-Br	Hexane	267	4.01	1335
			285	4.02	
			326(sh)	2.20	
			335(sh)	2.08	
	COC_6H_5	Hexane	256	4.07	
			286	4.04	
			332(sh)	2.28	
			336–340	2.25	
			353(sh)	2.10	
		Ethanol	263	4.11	1330
			293	4.12	
		Methanol	222(sh)	3.84	1212
			260	4.11	
			292	4.11	
			354(sh)	2.35	
	CH=CHCO-2-Th	Ethanol	285	3.93	1371
			354	4.57	
	COCH=CH-2-Fu	"	243	3.75	1330
			353	4.39	
	CH=CHCO-2-Fu	"	298(sh)	4.00	
			355	4.68	
	$C(NNH_2)C_6H_5$	"	255	4.11	1334
			275	4.08	
	$SO_2NHC_6H_4$-4-CH_3	"	229	4.13	1245
			250(sh)	3.90	
	$SO_2NHC_6H_4$-3-CH_3	"	229	4.07	
	$SO_2NHC_6H_4$-2-CH_3	"	227	3.92	
			244	3.92	
	$SO_2NHC_6H_4$-4-OCH_3	"	232	4.22	
			250(sh)	3.90	

	$SO_2NHC_6H_4$-3-OCH_3	"	227	4.10	
			250(sh)	3.90	
			280	3.60	
	$SO_2NHC_6H_4$-2-OCH_3	"	228	4.09	
			250(sh)	3.85	
			285	3.56	
	$CH_2(CH)_4CO_2CH_3$	Ether	255.5	4.41	796
12	$CH{=}CHC_6H_4$-4-Cl-*trans*	Ethanol	234	3.95	1252, 1364
			240	3.96	
			328	4.27	
	" -*cis*	"	240	4.12	
			292	4.02	
	$CH{=}CHC_6H_4$-3-Cl-*trans*	"	236	3.87	
			327	4.40	
	" -*cis*	"	234	3.95	
			295	3.87	
	$CH{=}CHC_6H_4$-2-Cl-*trans*	"	239	3.88	
			326	4.34	
	" -*cis*	"	235	3.92	
			289	3.95	
	$CH{=}CHC_6H_4$-4-NO_2-*trans*	"	272	4.09	1364
			372	4.21	
	" -*cis*	"	269	4.20	
			354	3.88	
	$CH{=}CHC_6H_4$-3-NO_2-*trans*	"	216	4.07	
			279	4.06	
			324	4.43	
	" -*cis*	"	221	4.14	
			270	4.14	
			300(sh)	3.92	
	$CH{=}CHC_6H_4$-3-NO_2-*trans*	"	281	4.09	
			315	4.23	
			365(sh)	3.87	
	" -*cis*	"	268	4.06	

TABLE 55. (*Continued*)

C_n	R_2	Solvent	λ (nm)	log ε	Ref.
	COC_6H_4-4-CH_3	"	268	4.13	1332
			292	4.16	
	COC_6H_4-2-CH_3	"	264	4.03	
			292	4.03	
	COC_6H_4-4-OCH_3	Cyclohexane	224	3.96	
			264(sh)	4.02	
			294	4.28	
	$CH{=}CHC_6H_5$-*trans*	Ethanol	230	3.98	1252, 1364
			270(sh)	3.71	
			325	4.42	
	" -*cis*	"	233	4.01	
			290	3.99	
	$CC(CH)_5{=}CH_2$	Ether	257	3.96	1360
			332	4.56	
			355	4.52	
			372	3.93	
	$SO_2NHC_6H_3$-2,6-CH_3	Ethanol	245	3.95	1245
			255(sh)	3.91	
	$SO_2NHC_6H_4$-4-C_2H_5	"	229	4.19	
			250(sh)	3.97	
	$SO_2NHC_6H_4$-2-C_2H_5	"	243	3.92	
			255(sh)	3.88	
	$C(CH_3)C_2H_5$-2-Th	Heptane	235	4.15	1243
13	$COCH{=}CHC_6H_3$-3,4-Cl	Ethanol	245	3.99	1330
			322	4.32	
	$COCH{=}CHC_6H_3$-2,4-Cl	"	245	3.92	
			321	4.26	
	$COCH{=}CHC_6H_4$-4-Cl	"	245	3.85	
			328	4.41	

$CH{=}C(CN)C_6H_5$	"	230	3.91	1365
		275.5	3.68	
		344	4.40	
$COCH_2CONHC_6H_4$-4-Cl	"	255	4.70	1340
$COCH_2CONHC_6H_4$-3-Cl	"	255	4.11	
$COCH_2CONHC_6H_4$-2-Cl	"	255	3.98	
$COCH_2CONHC_6H_4$-4-NO_2	"	220	4.24	
		265	4.11	
		305	4.28	
$COCH_2CONHC_6H_4$-3-NO_2	"	250	4.24	
$COCH_2CONHC_6H_4$-2-NO_2	"	235	4.32	
		260	4.27	
$COCH{=}CHC_6H_5$	"	320	4.29	1330, 1371
$CH{=}CHCOC_6H_5$	"	275	4.00	
		345	4.28	
$COCH{=}CHC_6H_5$-4-NH_2	Dioxane	250	4.20	1372
		270	4.00	
		300	3.85	
$CH{=}CHCOC_6H_4$-4-NH_2	"	307	4.03	
		357	4.12	
$COCH_2CONHC_6H_5$	Ethanol	250	4.48	1340
COC_6H_3-2,4-CH_3	"	267	4.06	1332
		292–293	4.09, 4.01	
$CH{=}CHC_6H_4$-4-CH_3-*trans*	"	232	3.99	1252, 1364
		327	4.45	
" -*cis*	"	237	4.08	
		294	3.99	
$CH{=}CHC_6H_4$-3-CH_3-*trans*	"	238	4.01	
		244(sh)	3.91	
		330	4.45	
" -*cis*	"	236	3.85	
		294	3.50	

TABLE 55. (*Continued*)

C_n	R_2	Solvent	λ (nm)	log ε	Ref.
	$CH{=}CHC_6H_4$-2-CH_3-*trans*	"	237	3.78	
			254(sh)	3.16	
			262	3.25	
			329	4.30	
	" -*cis*	"	238	3.79	
			288	3.94	
	$SO_2NHC_6H_4$-4-$CH(CH_3)_2$	"	229	4.15	1245
			250(sh)	3.92	
	$SO_2NHC_6H_4$-2-$CH(CH_3)_3$	"	243	3.95	
			253(sh)	3.90	
	COC_8H_{17}	Heptane	258	3.97	1754
			275	3.86	
	C_9H_{19}	"	234	3.92	
14	$COCH{=}CHC_6H_4$-3-CF_3		230	3.81	1330
			314	4.36	
	SO_2NH-1-naphthyl	Ethanol	223	4.80	1245
			260(sh)	3.85	
			285	3.84	
	SO_2NH-2-naphthyl	"	280(sh)	3.89	
			290(sh)	3.74	
			350(sh)	3.16	
	$COCH_2CONHC_6H_4$-4-CO_2H	"	270	4.49	1340
	$COCH_2CONHC_6H_4$-3-CO_2H	"	225	4.47	
			255	4.38	
			390	4.15	
	$COCH_2CONHC_6H_4$-2-CO_2H	"	220	4.32	
			255	4.21	
			295	4.00	
	$COCH_2CONHC_6H_4$-4-OCH_3	"	265	4.60	

	$COCH_2CONHC_6H_4$-3-OCH_3	"	255	4.45	
			299	4.29	
	$COCH_2CONHC_6H_4$-2-OCH_3	"	255	4.34	
			290	4.26	
		Hexane	261	4.04	1335
			284	4.00	
			333–337	2.16	
			341(sh)	2.14	
			359	1.99	
	$SO_2NHC_6H_3$-2,6-C_2H_5	Ethanol	243	3.93	1245
			255(sh)	3.89	
	$CH{=}CHCH_2CH{=}CHCONHCH_2CH(CH_3)_2$	Ether	272	4.31	796
	$(CH)_4CH_2CONHCH_2CH(CH_3)_2$	"	306	4.46	
	$CH_2(CH)_4CONHCH_2CH(CH_3)_2$	"	252	4.48	
	$CO(CH_2)_2CH{=}CHCONHCH_2CH(CH_3)_2$	Ether	257	4.37	
			271	4.33	
	$CH(OH)(CH_2)_2CH{=}CHCONHCH_2CH(CH_3)_2$	Ether	230.5	3.91	
15	$CH_2(CH)_4C_6H_5$	"	306	4.67	
	$CC(CH)_4(CH_2)_3O_2CCH_3$	"	315	4.42	1360
			336	4.36	
	$SO_2NHC_6H_3$-2,4-$CH(CH_3)_2$	"	244	3.93	1245
			255(sh)	3.89	
17	COC_6H_2-2,6-CH_3-4-$C(CH_3)_3$	"	266	3.98	1332
			292	3.98	
	COC_6H_2-2,4-CH_3-6-$C(CH_3)_3$	"	264	4.02	
			292	4.01	
	$C_{13}H_{27}$	Heptane	234	3.91	1754
	$COC_{12}H_{25}$	"	258	4.04	
			274	3.89	
18	$CH_2CONHCH_2CH(CH_3)_3$	Ether	233	3.94	796

TABLE 55. (*Continued*)

C_n	R_2	Solvent	λ (nm)	log ε	Ref.
19	$COCH_2CH(C_6H_4\text{-}4\text{-}Cl)CH_2CO\text{-}2\text{-}Th$	Ethanol	263	4.16	1330
			285	4.06	
	$COC_{14}H_{29}$	Heptane	258	3.98	1754
			275	3.88	
	$C_{15}H_{31}$	"	234	3.87	
			258	3.98	
21	$COC_{16}H_{33}$	"	275	3.87	
	$C_{17}H_{35}$	"	235	3.87	
22	$C(C_6H_5)=NN=C(C_6H_5)\text{-}2\text{-}Th$	Ethanol	276–278	4.31	1334
			355	4.11	
23	$COC_{18}H_{37}$	Heptane	258	3.98	1754
			275	3.87	
	$C_{19}H_{39}$	"	235	3.90	
24	$COC_{19}H_{39}$	"	258	3.97	
			275	3.87	
	$C_{20}H_{41}$	"	234	3.87	

TABLE 56. UV Spectroscopic Data for 3-Substituted Thiophenes

C_n	Substituent	Solvent	λ (nm)	log ε	Ref.
4	Br	Ethanol	232	3.61	1323
			241	3.65	
		Hexane	231(sh)	3.59	1325
			243	3.63	
			253(sh)	3.41	
		"	243	3.54	1324
	I	"	238(sh)	3.57	1325
			248	3.67	
			267(sh)	2.50	
	NO_2	"	260	3.94	
			285(sh)	3.75	
			355(sh)	2.20	
		Isooctane	Figure		1281
	SH	Hexane	218	3.72	1339
			256	4.06	
			296	3.78	
			305	3.74	
			317	3.76	
5	CN	"	225	3.03	1324
			236	3.04	
	CHO	Ethanol	251	4.12	1323
	CO_2H	"	241	3.92	
			239	3.79	1321
	$CONH_2$	"	241	3.89	
	OCH_3	"	221	3.59	1323
			253	3.59	
		Hexane	221	3.59	1325
			253	3.59	
	SO_2CH_3	Ethanol	232	3.72	1323
	$SeCH_3$	"	235	3.43	1351
			275	3.30	
		Heptane	231	3.60	
			278	3.48	
	SCH_3	Ethanol	216	3.70	1323
			269	3.56	
6	$COCH_3$	"	250	4.08	1755
			300	1.75	
		"	239.5	3.80	1321
		Hexane	221	3.04	1324
			227	3.03	
	CO_2CH_3	Ethanol	240.5	3.95	1321
	CH_2CO_2H	Hexane	234	3.53	1324
	$NHCOCH_3$	Ethanol	257.5	3.77	
7	$CH{=}CHOCH_3$	Ether	219	4.25	796
			248	4.08	
	$CO_2C_2H_5$		240	3.95	1321
8	SO_2-3-Th	Ethanol	208	4.15	1244
			245	4.21	

TABLE 56. (*Continued*)

C_n	Substituent	Solvent	λ (nm)	log ε	Ref.
	S-3-Th	Hexane	212	4.13	
			272	3.77	
	N-Morfoline	Cyclohexane	272	3.62	1290
	N-Pyrrolidine	"	291	3.56	
	S-C_4H_9	Hexane	212	3.92	1244
			268	3.45	
9	N-Piperidine	Cyclohexane	274	3.57	1290
11	COC_6H_5	Ethanol/hexane			1338
		Methanol	257	4.21	1212
			282(sh)	3.33	
			329	2.32	
13	$COCH_2CONHC_6H_4$-4-Cl	Ethanol	255	4.56	1340
	$COCH_2CONHC_6H_4$-3-Cl	"	255	4.41	
	$COCH_2CONHC_6H_4$-2-Cl	"	255	4.36	
	$COCH_2CONHC_6H_4$-4-NO_2	"	255	4.23	
			315	4.40	
	$COCH_2CONHC_6H_4$-3-NO_2	"	255	4.19	
	$COCH_2CONHC_6H_4$-2-NO_2	"	215	4.09	
			255	4.13	
	$COCH_2CONHC_6H_5$	"	250	4.42	
14	$COCH_2CONHC_6H_4$-4-CO_2H	"	265	4.39	
	$COCH_2CONHC_6H_4$-3-CO_2H	"	220	4.35	
			250	4.30	
			305	3.98	
	$COCH_2CONHC_6H_4$-2-CO_2H	"	215	4.40	
			255	4.26	
			300	3.88	
	$COCH_2CONHC_6H_4$-4-OCH_3	"	255	4.09	
	$COCH_2CONHC_6H_4$-3-OCH_3	"	255	3.87	
	$COCH_2CONHC_6H_4$-2-OCH_3	"	255	3.82	

TABLE 57. UV Spectroscopic Data for 2,3-Disubstituted Thiophenes

C_n	2-Substituent	3-Substituent	Solvent	λ (nm)	log ε	Ref.
5	CN	NO_2	Hexane	222	4.04	1324
				265	3.96	
	NO_2	CN	„	286	3.95	
				292	3.95	
6	CHO	CO_2	Ethanol	274	3.91	708
				295	3.79	
	CO_2H	CHO	„	266	4.00	
				295(sh)	3.63	
	CO_2H	CO_2H	„	258	3.99	
				282(sh)	3.68	

TABLE 57. (*Continued*)

C_n	2-Substituent	3-Substituent	Solvent	λ (nm)	log ε	Ref.
	NO_2	$NHCOCH_3$	Hexane	252	4.10	1324
				322	3.98	
		CH_2SCH_2	Ethanol	235	3.72	669
7		$COCH_2CH_2$	„	261	4.18	1755
		$COCH_2SCH_2$	„	275–278	3.93	
				340(sh)	2.58	
	CHO	CO_2CH_3	„	273	3.92	708
				295	3.75	
	CO_2CH_3	CHO	„	266	4.00	
				295(sh)	3.62	
	$COCH_3$	CH_3	„	273–274	4.10	1330
		$CH_2CH_2CH_2$	„	226	3.66	669
				241(sh)	3.60	
		$CH_2CH_2SCH_2$	„	236–238	3.73	
8		$CH_2CH_2CH_2CO$	„	216	4.18	1755
				220	4.16	
				253	4.09	
				278	3.45	
		$COCH_2CH_2CH_2$	„	272	4.09	
		$COCH(CH_3)SCH_2$	„	275–278	3.91	
				340	2.63	
		$COCH_2CH_2SCH_2$	„	272–275	3.95	
		$COCH_2SCH_2CH_2$	„	268–283	3.98–3.95	
		$CH_2CH_2SCH_2CO$	„	216–219	4.07	
				253	3.93	
				278	3.53	
		$CO_2CH_3CO_2CH_3$	„	256	3.93	708
		$-(CH_2)_4-$	„	235	3.72	669
		$CH_2CH(CH_3)CH_2$	„	228	3.58	
				245	3.48	
		$CH_2CH_2SCH_2CH_2$	„	240	3.73	
		$CH_2CH(CH_3)SCH_2$	„	235–237	3.73	
9		$CH_2CH_2CH(CH_3)CO$	„	218–222	4.13	1755
				253	4.06	
				278	3.53	
		$COCH_2CH(CH_3)CH_2$	„	272	4.13	
		$COCH_2CH_2CH_2CH_2$	„	274	4.05	
		$CH_2CH_2SCH(CH_3)CO$	„	216	4.11	
				251	3.95	
				278	3.60	
		$COCH(CH_3)SCH_2CH_2$	„	268–285	3.99–3.93	
		$COCH_2CH(CH_3)SCH_2$	„	275	3.93	
	CHO	SeC_4H_9	Heptane	284	3.79	1351
				341	3.49	
		$CH_2CH_2CH(CH_3)CH_2$	Ethanol	234	3.72	669
		$-(CH_2)_5$	„	234	3.80	
		$CH_2CH_2CH(CH_3)SCH_2$	„	234	3.72	

TABLE 57. (*Continued*)

C_n	2-Substituent	3-Substitutent	Solvent	λ (nm)	log ε	Ref.
10	CH=CH-2-Fu	NO_2	Hexane	248	4.23	1324
				287	3.99	
14	$COCH=CHC_6H_5$	CH_3	Ethanol	232	3.94	1330
				321	4.42	
18	$C_{13}H_{27}$	CH_3	Heptane	236	3.81	1754
20	$C_{15}H_{31}$	CH_3	"	236	3.80	
22	$C_{17}H_{35}$	CH_3	"	236	3.79	
24	$C_{19}H_{39}$	CH_3	"	234	3.81	

TABLE 58. UV Spectroscopic Data for 2,4-Disubstituted Thiophenes

C_n	2-Substituent	4-Substituent	Solvent	λ (nm)	log ε	Ref.
5	CO_2H	Br	Ethanol	245	3.90	1324
				279	3.62	
	CO_2H	NO_2	"	238	4.09	
				267	3.68	
6	CO_2H	CHO	"	233	4.36	708
				250(sh)	3.95	
	CHO	CO_2H	"	223	4.18	
				261	3.91	
				280	3.71	
	CO_2H	CO_2H	"	251	3.83	
	$COCH_3$	NO_2	Hexane	248	4.35	1324
				273	3.89	
7	CHO	CO_2CH_3	Ethanol	226	4.31	708
				261	3.88	
				275(sh)	3.74	
	$COCH_3$	CH_3	"	261	4.00	1330
				295–297	3.80	
8	CO_2CH_3	CO_2CH_3	"	250	3.80	708
	CO_2H	$CH(CH_3)_2$	"	247	3.93	1324
				278	3.79	
9	CHO	SeC_4H_9	Heptane	261	4.07	1351
				332	3.08	
14	$COCH=CHC_6H_5$	CH_3	"	245	3.82	1330
				326	4.25	

TABLE 59. UV Spectroscopic Data for 3,4-Disubstituted Thiophenes

C_n	3-Substituent	4-Substituent	Solvent	λ (nm)	log ε	Ref.
4	Br	Br	Hexane	235	3.60	1325
				240	3.63	
				247	3.69	
				252	3.73	
				256	3.62	
	Cl	Cl	"	232	3.50	
				238	3.56	
				244	3.64	
				250	3.67	
				255	3.53	
	I	I	"	244	3.64	
				250	3.74	
				253	3.79	
				259	3.82	
				264	3.66	
				274(sh)	2.95	
6	CHO	CO_2H	Ethanol	224	4.26	708
				255	3.70	
	CO_2H	CO_2H	"	237(sh)	3.72	
	CH_2 S CH_2		"	232	3.78	669
7	$COCH_2CH_2$		"	259	4.11	1755
	CHO	CO_2CH_3	"	225	4.40	708
				251	3.74	
	$CH_2CH_2CH_2$		"	244	3.87	669
8	CO_2CH_3	CO_2CH_3	"	235(sh)	3.79	708
12	SO_2-3-Th	SO_2-3-Th	"	209	4.40	1756
				245	4.28	
	SO_2-2-Th	SO_2-2-Th	"	209	4.03	
				242	4.15	
				268	4.10	
	S-3-Th	S-3-Th	Hexane	208	4.65	
				274	4.00	
	S-2-Th	S-2-Th	"	206	4.55	
				237	4.30	
				276	3.91	

TABLE 60. UV-Spectroscopical Data for 2,5-Disubstituted Thiophenes

C_n	2-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
4	Br	Br	Hexane	245(sh)	3.91	1325
				254	3.93	
	Cl	Cl	"	242(sh)	3.79	
				253	3.82	
	I	NO_2	"	327	4.13	1324
	I	I	"	248(sh)	3.91	1325
				267	4.10	
	Cl	SH	"	206	3.61	1339
				258	3.80	
				310	3.68	
5	Br	CHO	"	265	3.91	1361
				291	4.09	
			Ethanol	267	3.91	
				295.5	4.07	
	Br	CO_2H	Hexane	251(sh)	3.89	1324
				261(sh)	3.97	
				276	4.07	
			"	260	3.90	1361
				281	4.09	
			Ethanol	257	3.94	
				269	4.00	
	Cl	CO_2H	Hexane	256	4.01	1324
				280	4.14	
	I	CO_2H	"	267	3.86	
				293	4.10	
	NO_2	CHO	"	231	3.79	1362
				301	4.07	
			Ethanol	236	3.90	1362
				316.5	4.24	

		NO_2	CO_2H	"	322.5	3.99	
				"	250	3.41	1324
				"	312.5	3.95	
		Br	$CONH_2$	"	226	3.54	1361
					276	4.06	
		NH_2	CHNOH	Water	345	4.29	1346
		CH_2SH	CO_2H	Ethanol	276	4.03	1227
	6	CHO	CO_2H	"	281	4.13	708
		CO_2H	CO_2H	"	273	4.13	
		Br	$COCH_3$	"	268	3.92	1361
					293	4.09	
				Hexane	265	3.91	
					288.5	4.09	
				Ethanol	268	3.91	1333
					294	4.08	
				"	267	3.91	1332
					294	4.08	
		Br	CO_2CH_3	"	259	3.93	1361
					279	4.09	
				Hexane	259	3.96	
					277	4.10	
		Cl	$COCH_3$	Ethanol	264.5	3.94	1330
				"	292	4.05	
				"	265	3.93	1332
					291	4.04	
		F	$COCH_3$	"	252	3.85	
					284	3.93	
		I	$COCH_3$	"	271	3.83	
					304	4.13	
		NO_2	$COCH_3$	"	228	3.72	1362
					309	4.05	
				Hexane	228	3.74	
					301	4.07	

TABLE 60. (*Continued*)

C_n	2-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
	NO_2	CO_2CH_3	Hexane	223	3.85	
				294.5	4.04	
			Ethanol	222	3.82	
				300.5	4.04	
	$SeCH_3$	CHO	"	265	3.72	1351
				348	4.08	
			Heptane	263	3.81	
				340	4.06	
	SCH_3	CHO	"	265	3.73	
				329	4.06	
	CH_3	CO_2H	Ethanol	253	4.08	1227
				274	4.11	
			"	252	3.98	1399
				273	3.95	
	OCH_3	CHO	"	256	3.61	1351
				329	4.15	
	SCH_3	CO_2H	"	255	3.65	
				317	4.04	
	$SeCH_3$	CO_2H	"	256	3.85	
				328	3.90	
	CH_2OH	CO_2H	"	251	3.98	1227
				272	3.91	
	OCH_3	CO_2H	Water	243	3.54	1351
				287	3.94	
	CH_3	OCH_3	Pentane	249	3.70	1758
	$SeCH_3$	SCH_3	Heptane	245	3.70	1351
				304	3.65	
			Ethanol	239	3.72	
				298	3.87	

7	I	CCCHO		264	3.88	1356
				324	4.31	
				331	4.32	
	Br	$CHCHCO_2H$	Ethanol	243.5	3.79	1361
				308	4.30	
	NO_2	$CHCHCO_2H$	"	245	4.01	1362
				365	4.23	
	CHO	CO_2CH_3	"	281	4.16	708
	Br	$CO_2C_2H_5$	"	259	3.95	1361
				278.5	4.11	
			Hexane	258	4.00	
				276.5	4.12	
	NO_2	$CO_2C_2H_5$	"	223.5	3.82	1362
				296	4.04	
			Ethanol	222	3.80	
				301	4.03	
	CH_3	$COCH_3$	"	264	3.96	1333
				295	4.05	
			"	263–264	3.97	1330
				294	4.06	
			"	263	3.92	1332
				294	4.02	
	OCH_3	$COCH_3$	"	256	3.61	1758
				314	4.15	
			"	256	3.60	1332
				315	4.16	
	C_2H_5	CO_2H	"	253	3.97	1227
				274	4.00	
	CH_2OCH_3	CO_2H	"	253	4.00	
				269	3.92	
8	Br	5-Br-2-Th	"	208	3.80	1408
				255	3.84	
				318	4.18	

TABLE 60. (*Continued*)

C_n	2-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
	Cl	5-Cl-2-Th	"	206	3.70	
				250	3.80	
				318	4.22	
	I	5-I-2-Th	"	209	3.98	
				246	3.83	
				324	4.30	
			"	246	3.83	1358
				324	4.30	
	Br	2-Th	"	209	3.75	1408
				249	3.73	
				311	4.14	
	Cl	2-Th	"	207	3.86	
				247	3.77	
				311	4.14	
	I	5-CO_2H-2-Th	"	249	3.77	1358
				339	4.33	
	I	2-Th	"	248	3.73	
				314	4.20	
			"	210	3.82	1408
				248	3.75	
				314	4.20	
	Br	$CHCHCOCH_3$	"	222	3.65	1361
				272	3.54	
				330	4.26	
			Hexane	222	3.85	
				242	3.69	
				322.5	4.36	
	Br	$CHCHCCCO_2CH_3$	"	244	3.67	
				314.5	4.35	

			Ethanol	266	3.67	
				319.5	4.36	
	NO_2	$CHCHCOCH_3$	"	268.5	3.96	1362
				356	4.17	
			Hexane	247	3.88	
				347	4.05	
	NO_2	$CHCHCO_2CH_3$	"	243	4.00	
				345	4.24	
			Ethanol	257	3.84	
				352.5	4.25	
	NH_2	CHNN <				
		$-CONHCOCH_2-$	50% "	348	4.32	1346
	$COCH_3$	$COCH_3$	Isooctane	221–222	3.57	1335
				283–287	2.48	
				330	2.48	
	CO_2CH_3	CO_2CH_3	Ethanol	274	4.08	708
	$CHCH_2$	$CHCH_2$	Cyclohexane	212	4.17	1353
				217	4.15	
				316	4.23	
	C_2H_5	$COCH_3$	Ethanol	264	3.92	1332
				294	4.02	
	CO_2H	$N(CH_3)_3{}^+Cl^-$	"	254	3.99	1227
9	Br	5-CO_2H-2-Th	"	239	3.74	1358
				335	4.25	
	Cl	5-CO_2H-2-Th	"	244	3.14	
				337	4.30	
	I	5-CHO-2-Th	"	210	4.08	1408
				258	4.05	
				357	4.40	
	$CHCl_2$	2-Th	"	210	4.00	
				248.5	3.91	
				342	4.31	
			"	250	3.90	1355
				344	4.35	

TABLE 60. *(Continued)*

C_n	2-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
	CHO	2-Th	"	207	3.90	1408
				244	3.86	
				350.5	4.35	
			Heptane	265	3.73	1243
				329	4.06	
	CHO	S-2-Th	"	233	4.01	
				270(sh)	3.81	
				325	4.12	
	CH_3	5-I-2-Th	Ethanol	204	3.97	1408
				239.5	3.83	
				320	4.23	
	CH_3	2-Th	"	210	3.75	
				245	3.76	
				308	4.12	
	Br	$CHCHCO_2C_2H_5$	"	264	3.68	1361
				319	4.32	
			Hexane	243	3.66	
				314.5	4.32	
	NO_2	$CHCHCO_2C_2H_5$	"	243	4.00	1362
				345	4.27	
			Ethanol	245	4.00	
				352.5	4.27	
	$Si(CH_3)_3$	$COCH_3$	"	270	4.07	1332
				290	4.03	
10	CHO	5-CHO-2-Th	"	207	4.05	1408
				260	3.80	
				336	4.41	
				358	4.38	

	CHO	S-5-CHO-2-Th	Heptane	267	4.14	1243
				318	4.20	
	HCC	2-Th	Hexane	248		1355
				326		
				331		
	CO_2CH_3	5-Br-2-Th	Ethanol	210	3.93	
				245	3.77	
				339	4.35	
	CO_2CH_3	5-Cl-2-Th	"	207	4.07	
				245	3.89	
				339	4.27	
	CO_2CH_3	5-I-2-Th	"	210	4.02	
				251	3.83	
				344	4.36	
	NO_2	CHCH-2-Fu	Hexane	288	4.13	1324
	CCl_2CH_3	2-Th	Ethanol	249	4.07	1355
				345	4.35	
	$COCH_3$	2-Th	"	207	3.99	1408
				245	3.94	
				348	4.34	
	CO_2CH_3	2-Th	"	206	3.94	
				257	3.75	
				332	4.29	
	$COCH_3$	$C(CH_3)_3$	"	265	3.92	1332
				295	4.05	
11	CO_2H	SO_2Ph	"	216	3.87	1227
				265	3.96	
				274	3.93	
	$CO_2C_2H_5$	5-Cl-2-Th	"	245	3.89	1358
				339	4.27	
	$CO_2C_2H_5$	5-Br-2-Th	"	245	3.77	
				339	4.35	

TABLE 60. (*Continued*)

C_n	2-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
12	CCCHO	$CCCCCH_3$	Ether	342	4.51	805
				364	4.56	
	SO_2-3-Th	SO_2-3-Th	Ethanol	206	3.98	1756
				231	3.95	
				277	4.14	
	SO_2-2-Th	SO_2-2-Th	"	255	4.04	
				295	4.11	
	$CCCHCH_2$	2-Th	"	210	4.10	1408
				249	3.95	
				341	4.36	
				249	3.95	1355
				341	4.36	
	2-Th	2-Th	"	252	3.96	
				350	4.35	
			"	210	4.09	1408
				252	3.96	
				350	4.36	
	S-2-Th	S-2-Th	Heptane	238	4.26	1243
				282	4.05	
			Hexane	205	4.55	1756
				240	4.27	
				274	4.07	
	S-3-Th	S-3-Th	"	206	4.57	
	$CCCH(OH)CH_2Cl$	2-Th	Ethanol	214	3.98	1408
				245	3.96	
				331	4.40	
	CCC_2H_4OH	2-Th		242	3.82	1359
				328	4.34	
				334	4.35	

		Ethanol	242	3.82	1355
			328	4.34	
			334	4.35	
		"	207	3.92	1408
			242	3.82	
			328	4.34	
			334	4.35	
OCH_3	COPh	"	254	3.92	1332
			329	4.23	
$COCH_3$	5-$COCH_3$-2-Th	"	208	4.11	1408
			260	3.87	
			357	4.47	
$CCCH(OH)CH_2OH$	2-Th	Ether	238	3.81	805
			325	4.34	
			332	4.34	
CHO	SC_2H_4S-2-Th-5-CHO	Heptane	267	4.06	1243
			323	4.21	
CO_2H	CH_2OPh	Ethanol	215	3.98	1227
			254	4.04	
			270	4.04	
$CHCHC_2H_4OH$	2-Th	Ether	243	3.97	1355
			333–337	4.32	
" *-trans*		Ethanol	210	3.99	1408
			245	3.94	
			339–341	4.31	
" *-cis*		"	207	4.10	
			243	3.97	
			333–337	4.32	
$CHCHCHCH_2$	$CHCHCHCH_2$	Cyclohexane	215	4.28	1353
			258	4.33	
			350(sh)	4.29	
			364	4.36	
			381(sh)	4.22	

TABLE 60. (*Continued*)

C_n	2-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
	CH_3	$COCHCHCHCHN(CH_3)_2$	Ethanol	312(sh)	4.01	1375
				438	4.73	
	$C(CH_3)_3$	$C(CH_3)_3$	Cyclohexane	237	3.97	645
			Methanol	237	3.98	
13	CC-epoxide	$CCCCCH_3$	Ether	208.5	4.42	805
				234	3.89	
				246	4.05	
				319.5	4.50	
				341	4.47	
	$CCCH_3$	$CCCCCHCH_2$	"	258	4.17	1360
				264	4.16	
				274	4.22	
				324(sh)	4.43	
				338	4.50	
				357.5	4.35	
	$CCCHCH_2$	$CCCCCH_3$	"	253	3.98	805
				332	4.48	
				357	4.42	
	Cl	COCHCHPh	Ethanol	260	3.99	
				328	4.32	
	Br	$COCHCHC_6H_4$-4-NH_2	Dioxane	260	4.30	1372
				275	4.10	
				305	4.15	
				394	4.40	
	Br	$CHCHCOC_6H_4$-4-NH_2	"	260	4.25	
				364	4.40	
	CH_2OH	2-Th-5-$CCCHCH_2$	Ethanol	207	4.08	1408
				252	3.72	
				348	4.39	

	$CCCH(OH)CH_2OH$	$CCCCCH_3$	Ether	208	4.45	805
				233	3.92	
				246	4.07	
				318.5	4.50	
				340	4.49	
	$CCCH_3$	$CCCHCHCHCH_2$		264	3.88	1356
				324	4.31	
				331	4.32	
			Ether	253	4.05	1360
				334	4.48	
				357.5	4.42	
	$CCCHCH_2$	$CCCHCHCH_3$ *-trans*	"	268	3.97	
				360.5	4.56	
				380(sh)	4.53	
		" *-cis*	"	333.5	4.51	
				355(sh)	4.31	
	$CCCH_3$	Ph		310	4.4	1757
	$CCCHCH_2$	2-Th-5-CH_3	Ether	250	3.97	756
				349	4.46	
			Ethanol	207	4.17	1408
				252	3.96	
				350	4.44	
	$CHCHCH_3$-*trans*	2-Th-5-$CHCH_2$	Ether	254	3.99	800
				262	4.00	
				366	4.46	
14	$CCCHCH_2$	2-Th-5-CO_2CH_3	Ethanol	207	4.19	1408
				263	3.95	
				358	4.38	
	$CCCOCH_2OCOCH_3$	2-Th	Ether	258	3.79	805
				362	4.38	
	CH_3	COCHCHPh	Ethanol	252	3.85	1330
				326	4.24	

TABLE 60. (*Continued*)

C_n	2-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
	$CCCHCHCH_3$	$CCCHCHCH_3$		334	4.51	1356
				354(sh)	4.31	
	CH_3	$CHCHCOC_6H_4$-4-NH_2	Dioxane	256	4.05	1372
				363	4.50	
	CH_3	$COCHCHC_6H_4$-4-NH_2	"	250	4.20	
				270	4.10	
				308	4.00	
				390	4.35	
	OCH_3	$COCHCHC_6H_4$-4-NH_2	"	250	3.85	
				270	4.15	
				320	3.85	
				384	4.50	
	OCH_3	$CHCHCOC_6H_4$-4-NH_2	"	254	3.85	
				375	4.50	
15	$CCCCCH_3$	$CCCH(Cl)CH_2OCOCH_3$	"	207.5	4.41	805
				233	3.89	
				245	4.04	
				320	4.51	
				364	4.49	
	$CCCHCH_2$	2-Th-5-CH_2OCOCH_3	Ethanol	208	4.22	1408
				252	3.99	
				348	4.45	
	$CH_2CO_2CH_3$	CCCHCHFu	Ether	344	4.35	804
				363	4.27	
	OCH_3	COC_6H_2-2,4,6-CH_3	Ethanol	259	3.61	1332
				324	4.23	
	C_9H_{19}	CO_2CH_3	"	254	3.91	1754
				275	4.03	

16	COPh	COPh	Isooctane	260(sh)	4.06	1335
				304	4.32	
				350(sh)	2.86	
				365(sh)	2.65	
	2-Th	$CCCH(OCOCH_3)CH_2OCOCH_3$	Ether	239	3.81	805
				325	4.36	
				332	4.36	
17	$CO(CH)_4N(CH_3)_2$	$(CH)_4N(CH_3)_2$	Ethanol	400(sh)	4.10	1375
				500	4.79	
18	COC_6H_2-2,4,6-Br	COC_6H_2-2,4,6-Br	Isooctane	306	4.37	1335
				350(sh)	2.65	
				355	2.57	
	$C_{13}H_{27}$	CO_2H	Heptane	254	2.24	1754
				274	4.03	
19	$C_{13}H_{27}$	CO_2CH_3	"	254	3.89	
				275	4.06	
21	$C_{15}H_{31}$	CO_2CH_3	"	254	3.97	
				275	4.05	
22	$C_{17}H_{35}$	CO_2H	"	254	4.27	
				275	4.00	
23	$C_{17}H_{35}$	CO_2CH_3	"	254	3.95	
				275	4.06	
24	COC_6H_2-2,4,6-CH_3	COC_6H_2-2,4,6-CH_3	Isooctane	305	4.32	1335
				366(sh)	2.55	
				270(sh)	2.44	
	$C_{19}H_{39}$	CO_2H	Heptane	254	4.31	1754
				274	4.00	
25	$C_{19}H_{39}$	CO_2CH_3	"	254	3.97	
				275	4.04	

TABLE 61. UV-Spectroscopic Data for 2,3,4-Trisubstituted Thiophenes

C_n	2-Substituent	3-Substituent	4-Substituent	Solvent	λ (nm)	log ε	Ref.
5	CHO	Br	Br	Hexane	254 283	4.34 3.91	1324
6	NH_2	CN	CH_3	Methanol	219 287	4.62 3.93	1345
7	CH_3	NO_2	CO_2CH_3	Hexane	246 270	4.52 4.11	1324
8	$COCH_3$	CH_3	CH_3	Ethanol	268 278	3.97 3.85	1755
				Hexane	268 277(sh) 322–323(sh)	4.08 4.00 2.00	1335
10	CH_3	Br	(2-CH_3-3-Br)-3-Th	Ethanol	253 274	4.14 4.05	1399
11	NH_2	C_6H_4-4-NO_2	CH_3	Methanol	219 272 381	4.09 4.03 3.51	1345
13	COC_6H_2-2,4,6-Br	CH_3	CH_3	Hexane	278 287–290(sh) 347	4.17 4.08 1.98	1335
	COC_6H_5	CH_3	CH_3	"	248 278 288 332–335(sh)	3.94 4.04 4.03 2.40	
16	COC_6H_2-2,4,6-CH_3	CH_3	CH_3	"	273 282(sh) 340(sh)	4.16 4.07 1.97	

TABLE 62. UV Spectroscopic Data for 2,3,5-Trisubstituted Thiophenes

C_n	2-Substituent	3-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
5	Cl	NO_2	CHO	Hexane	251	4.43	1324
6	Br	NO_2	$COCH_3$	"	253	4.33	
					282.5	3.98	
	Br	NO_2	CO_2CH_3	"	244	4.28	
					270	3.94	
	Cl	NO_2	$COCH_3$	"	250	4.35	
					282	3.96	
	CH_3	Br	CO_2H	Ethanol	246	3.91	1399
					280	3.75	
7	$SeCH_3$	CHO	CH_3	Heptane	260	4.08	1351
	CH_3	CO_2H	CH_3	Water	245	3.88	1758
					275	3.20	
	OCH_3	CO_2H	CH_3	"	238(sh)	3.68	
					279	3.58	
	CH_3	CO_2H	OCH_3	"	234	3.80	
					275	3.41	
9	$COCH_3$	OCH_3	CO_2CH_3	Ether	279.5	4.04	793
					321	4.02	
	CO_2CH_3	OCH_3	CO_2CH_3	"	268.5	4.08	
					316	3.95	
10	CHCHFu	NO_2	Br	Hexane	286	4.11	1324
	CHCHFu	NO_2	NO_2	"	264	4.17	
	$COCH_3$	OCH_3	$CCCH_3$	Ether	300	4.23	793
					317	4.28	
12	CO_2H	3-Th-2-CO_2H-5-CH_3	CH_3	Ethanol	262	4.23	1399
					276	4.19	

TABLE 62. (*Continued*)

C_n	2-Substituent	3-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
14	$C(CH_3)_3$	$COCH_3$	$C(CH_3)_3$	Methanol	225	4.16	645
					258	3.57	
					284(sh)	3.86	
16	C_9H_{19}	CH_2Cl	CO_2CH_3	Heptane	255	3.93	1754
					277	3.97	
	C_9H_{19}	CH_3	CO_2CH_3	"	254	3.94	
					284	3.96	
19	$C_{19}H_{27}$	CH_3	CO_2H	Ethanol	253	3.93	
					283	3.98	
20	$C_{13}H_{27}$	CH_2Cl	CO_2CH_3	Heptane	255	3.92	
					278	3.97	
	$C_{13}H_{27}$	CH_3	CO_2CH_3	"	254	3.93	
					284	3.96	
21	$C_{15}H_{31}$	CH_3	CO_2H	"	252	3.92	
					284	3.99	
22	$C_{15}H_{31}$	CH_2Cl	CO_2CH_3	"	256	3.93	
					2.78	3.98	
	$C_{15}H_{31}$	CH_3	CO_2CH_3	"	254	3.94	
23	$C_{17}H_{35}$	CH_3	CO_2H	"	283	3.96	
					253	3.92	
					284	3.96	
24	$C_{17}H_{35}$	CH_2Cl	CO_2CH_3	"	256	3.93	
					278	3.98	
	$C_{17}H_{35}$	CH_3	CO_2CH_3	"	254	3.93	
					284	3.99	

25	$C_{19}H_{39}$	CH_3	CO_2H	"	253	3.94
					285	3.99
26	$C_{19}H_{39}$	CH_2Cl	CO_2CH_3	"	256	3.93
					278	3.98
	$C_{13}H_{27}$	CH_3	COC_7H_{15}	"	264	3.91
					298	4.01
	$C_{19}H_{39}$	CH_3	CO_2CH_3	"	254	3.91
					285	4.00
29	$C_{13}H_{27}$	CH_3	$CH_2CH(CH_3)C_8H_{17}$	"	241	3.90
30	$C_{13}H_{27}$	CH_3	$COC_{11}H_{23}$	"	264	3.91
					298	4.02
33	$C_{33}H_{27}$	CH_3	$COCH(CH_3)C_{12}H_{25}$	"	257	3.89
					298	4.01
	$C_{13}H_{27}$	CH_3	$CH_2CH(CH_3)C_{12}H_{25}$	"	241	3.89
34	$C_{13}H_{27}$	CH_3	$COC_{15}H_{31}$	"	263	3.92
					297	4.02
36	$C_{15}H_{31}$	CH_3	$COC_{15}H_{31}$	"	264	3.90
					298	3.96
	$C_{13}H_{27}$	CH_3	$COC_{17}H_{35}$	"	265	3.92
					298	4.02
	$C_{13}H_{27}$	CH_3	$C_{18}H_{37}$	"	241	3.90
	$C_{15}H_{31}$	CH_3	$C_{16}H_{33}$	"	241	3.90
37	$C_{13}H_{27}$	CH_3	$COCH(CH_3)C_{16}H_{33}$	"	257	3.91
					297	4.00
	$C_{13}H_{27}$	CH_3	$CH_2CH(CH_3)C_{16}H_{33}$	"	242	3.90

TABLE 62. (*Continued*)

C_n	2-Substituent	3-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
38	$C_{15}H_{31}$	CH_3	$C_{18}H_{37}$	"	241	3.89	
	$C_{17}H_{35}$	CH_3	$C_{16}H_{33}$	"	241	3.89	
	$C_{13}H_{27}$	CH_3	$C_{20}H_{41}$	"	241	3.89	
	$C_{15}H_{31}$	CH_3	$COC_{17}H_{35}$	"	263	3.89	
					297	4.00	
	$C_{17}H_{35}$	CH_3	$C_{15}H_{31}$	"	264	3.90	
					296	4.01	
	$C_{19}H_{39}$	CH_3	$COC_{13}H_{27}$	"	264	3.91	
					298	4.00	
39	$C_{19}H_{39}$	CH_3	$COCH(CH_3)C_{12}H_{25}$	"	257	3.91	
					298	3.99	
	$C_{13}H_{27}$	CH_3	$COCH(CH_3)C_{18}H_{37}$	"	251	3.90	
					298	4.01	

TABLE 63. UV Spectroscopic Data for Tetrasubstituted Thiophenes

C_n	2-Substituent	3-Substituent	4-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
4	Br	Br	Br	Br	Hexane	260	3.98	1325
						290	2.75	
	Cl	Cl	Cl	Cl	"	245	3.91	
						248	3.92	
	I	I	I	I	"	244	3.75	
						275	4.05	
						315–375	2.26	
7	Cl	—$COCH_2CH_2$—		Cl	Ethanol	219	4.08	1755
						263	4.01	
						304	3.54	
9	CH_3	—$COCH_2CH_2$—		CH_3	"	213		
						267		
						300		
	CH_3	—$COCH_2SCH_2$—		CH_3	"	225	4.16	
						265	3.95	
						302	3.07	
	CH_3	—$CH_2SCH_2CH_2$—		CH_3	"	228	3.98	669
						244	3.88	
	NH_2	$CO_2C_2H_5CH_3$		CH_3	Methanol	227	4.47	1345
						309	3.75	
10	CH_3	—$CO(CH_2)_3$—		CH_3	Ethanol	219	4.11	1755
						265	4.04	
						297	3.29	
	CH_3	—$COCH(CH_3)SCH_2$—		CH_3	"	228	4.15	
						265	3.95	
						300	3.40	
	$COCH_3$	CH_3	CH_3	$COCH_3$	Isooctane	228	3.80	1355
						290	4.26	
						340	2.50	
						360	2.10	

TABLE 63. (*Continued*)

C_n	2-Substituent	3-Substituent	4-Substituent	5-Substituent	Solvent	λ (nm)	log ε	Ref.
	CH_3	—$CH_2CH(CH_3)SCH_2$—		CH_3	Ethanol	240	3.89	669
11		—$COCH_2CH(CH_3)CH_2$—			"	220	4.14	1755
						2.65	4.07	
						300	3.39	
	CH_3	—$CO(CH_2)_4$—		CH_3	"	222	4.11	
						261	3.98	
						295(sh)	3.30	
	CH_3	—$COCH_2CH(CH_3)SCH_2$—		CH_3	"	225	4.11	
						255	3.80	
	NH_2	$CO_2C_2H_5$	—$(CH_2)_4$—		Methanol	230	4.49	1345
						312	3.98	
12	CH_3	—$CO(CH_2)_5$—		CH_3	Ethanol	222	4.17	1755
						261	3.92	
						297	3.32	
20	CO-2,4,6-Br-phenyl	CH_3	CH_3	CO-2,4,6-Br-phenyl	Isooctane	238(sh)	4.25	1335
						310	4.37	
						368(sh)	2.27	
	CO-phenyl	CH_3	CH_3	CO-phenyl	"	253–255	4.22	
						299–302	4.25	
					"	340(sh)	3.15	
					"	374(sh)	2.63	
26	CO-2,4,6-CH_3-phenyl	CH_3	CH_3	CO-2,4,6-CH_3-phenyl		237(sh)	3.97	
						300	4.32	
						358(sh)	2.58	

The charge-transfer complexes of a large number of organosilicon derivates of thiophene with TCNE have been studied in order to compare the effects of d_π–p_π interaction and p,π conjugation in the excited states of silicon-substituted thiophenes.[1442,1443] Correlations between the frequencies of the charge-transfer complex and the maximum chemical shifts of the ring protons in the ^{1}H NMR spectra, which were assumed to give information about the influence of substituents on the distribution of electron density in the ground state of the ring, were attempted. It was found that in the formation of donor–acceptor complexes of thiophene derivatives with TCNE, and also in their formation of hydrogen bonds with phenols, the predominant intermolecular interactions are specific. On the other hand, in the adsorption of thiophenes on hydroxylated Silichrome both specific and nonspecific interactions with the adsorbent surface occur, as shown by GLC investigations measuring the differential molar changes in internal energy in adsorption on hydroxylated Silichrome.[1277] The frequencies of the CT bands of thiophenes with TCNE are given in Table 64.

The protonation of some 5-X-substituted 2-thiophenecarboxamides (X = CH_3O, CH_3, H, Cl, Br, I, and NO_2) in aqueous sulfuric acid at 25°C has been studied by UV spectroscopy.[1444] The UV spectrum of the solid molecular compound from 2-acetylthiophene and aluminium trichloride, which easily dissociated in dilute chloroform solution, was shifted 100 nm toward longer wavelengths compared to the spectrum of 2-acetylthiophene.[1200] The UV spectra of the complexes of thiophene and tetrahydrothiophene with $SnCl_4$ have been investigated.[1273]

3. Fluorescence Spectra of Thiophenes

The fluorescence spectra of some thiophene derivatives, such as 4,5-di-(2-thienyl)glyoxalone, and 5-halo-2-acetylthiophenes, were compared with those of the corresponding benzene derivatives.[1445,1446] The absorption and fluorescence spectra and the scintillation properties of 1,4-bis-(2-vinylthienyl)benzene have been studied.[1447]

Derivatives of 2,2′-bithienyl with carbonyl-containing substituents are highly fluorescent in hydrogen-bonding solvents. 2-(2′-Furyl)thiophene, with a formyl group in the 5-position of the thiophene ring, was also fluorescent, whereas the derivative with the formyl group in the furan ring was not. This is also the case with carbonyl derivatives of 2,2′-bifuryl.[1448]

The photophysical and photochemical properties of thiophene derivatives have been studied by fluorescence and by 253-nm laser flash spectroscopy. α-Terthienyl and its derivatives show a moderate fluorescence quantum yield ($1 < 0.1$). An additional thiophene ring increases this value to 0.2 in ethanol and in micelles. The transient triplet state of six terheterocycles and related derivatives is characterized by strong absorption ($\varepsilon \approx 50{,}000\ M^{-1}\ cm^{-1}$) in the visible region.[1426]

TABLE 64. Charge-Transfer (CT) Complexes of Thiophenes with Tetracyanoethylene (TCNE) in Methylene Chloride

R_2	R_3	R_4	R_5	ν_{CT} (cm^{-1})			Ref.
H	H	H	H	24,400	(6,604)		
CH_3	H	H	H	24,400	19,600	19,600 (6604)	1443
Cl	H	H	H	29,940	22,050	24,400 (6604)	"
$Si(CH_3)_3$	H	H	H	24,750	20,400	21,700 (6604)	"
SiH_2CH_3	H	H	H	24,800	21,300		"
SiH_3	H	H	H	24,950	21,750		"
$SiCl_2CH_3$	H	H	H	30,200	26,300		"
H	CH_3	H	H	23,350	20,200	19,900 (6604)	"
$SiCl(CH_3)_2$	CH_3	H	H	23,500	20,400		"
$SiCl_2C_2H_5$	CH_3	H	H	23,900	21,300		"
$SiCl_2CH_3$	CH_3	H	H	23,800	2,100		"
$SiCl_3$	CH_3	H	H	28,600	25,000		"
CH_3	H	H	$SiCl_3$	25,000	20,000		"
CH_3	H	H	$SiCl(CH_3)_2$	24,400	19,600		"
CH_3	H	H	$SiClH_2$	24,750	20,400		"
Cl	H	H	CH_3	26,000	19,300	19,300 (6604)	"
Cl	H	H	SiH_3	28,400	21,650		"
Cl	H	H	$SiCl(CH_3)_2$	28,250	2,100		"
Cl	H	H	$SiCl_3$	28,600	22,300		"
CH_3O	H	H	H	17,500			1442
CH_3	H	H	$SiCl_2CH_3$	21,300			"
Cl	H	H	$SiCl_2H$	22,000			"
Br	H	H	$SiCl_3$	23,400			"
Br	H	H	$SiCl_2CH_3$	22,700			"
Cl	H	H	$SiCl_2CH_3$	22,200			"

$SiOH(CH_3)_2$	H	H	$SiOH(CH_3)_2$	23,600	
SiH_3	H	H	$SiBrH_2$	23,100	
$SiCl_2(CH_3)$	H	H	$SiCl_2CH_3$	25,000	(8020)
$SiCl_3$	H	H	$SiCl_3$	27,800	(8020)
CH_3	H	H	S-2-Th-5-CH_3	16,200	(8020)
$SiCl(CH_3)_2$	H	H	S-2-Th	17,400	(8020)
$SiCl_2CH_3$	H	H	S-2-Th	17,500	(8020)
$SiCl(CH_3)_2$	H	H	S-2-Th-Cl	17,400	(8020)
$SiCl_2CH_3$	H	H	S-2-Th-Cl	17,900	(8020)
Cl	H	H	SiF_3	24,100	(8020)
$SiCl(CH_3)_2$	H	H	H	24,600	(8020)
$SiHClCH_3$	H	H	H	25,000	(8020)
$SiHBrCH_3$	H	H	H	25,600	(8020)
SiH_2Br	H	H	H	26,300	(8020)
$SiClH_2$	H	H	H	25,600	(8020)
$SiCl_3$	H	H	H	28,200	(8020)
SiF_3	H	H	H	28,850	(8020)
Cl	H	H	Cl	21,600	(6604)
Cl	Cl	H	Cl	22,500	(6604)
Br	H	H	Cl	21,300	(6604)
Br	H	H	Br	21,000	(6604)
S-2-Th	H	H	H	17,800	(6604)
S-2-Th-5-CH_3	H	H	CH_3	16,200	(6604)
$Si(CH_3)_2$-2-Th	H	H	H	21,000	(6604)
$SiH(C_6H_5)$-2-Th	H	H	H	24,800	(6604)
$Si(CH_3)$ (2-Th)	H	H	H	24,200	(6604)
Si-(2-Th)$_3$	H	H	H	21,500	(6604)

The influence of solvent on the fluorescence of 5-acyl-2,2′-bithienyl has been examined in detail, and indications were found that the fluorescence arises from a charge-transfer excited state. Relative fluorescence efficiency also showed a pronounced dependence on the hydrogen bonding properties of the solvent These investigations were extended to 2-(2-quinolinyl)thiophenes, and these compounds normally show fluorescence from an excited state that is mainly π–π^* in character.[1431] This investigation was further extended to include 2-benzoxazolyl-, 2-benzothiazolyl-, 2-benzimidazolyl-, and 2-indolyl-substituted 2,2′-bithienyls.[1431] Solvent effects on the electronic absorption and fluorescence spectra of 2-thiophene aldehyde 2-quinolyl hydrazone have been studied. The ground- and excited-state dissociation constants reveal that the compound has an increased basicity in the excited state and undergoes intermolecular charge transfer from the secondary amine nitrogen atom to the heterocyclic nitrogen atom on excitation.[1432]

The fluorescent exciplexes between aromatic hydrocarbons, such as 1-cyanonaphtalene and 9-cyanoanthracene, in their excited singlet states with thiophene, 2,5-dimethylthiophene, and other heterocycles have been studied. If fluorescent exciplex formation was not observed, quenching rates were measured.[1433]

A large number of papers treat fluorescence and phosphorescence spectra of rare-earth-metal complexes with 2-thenoyltrifluoroacetonate, especially europium and terbium complexes.[233,1434–1440,1449,1450] Thus, measurements of absorption and emission spectra, fluorescence lifetimes, and relative quantum yields have been made on solutions of europium thenoyltrifluoroacetonate in acetone, toluene, and ethanol, and laser threshold parameters were calculated.[1434] Fluorescence spectroscopy has been used for the analysis of antihistamines containing a thiophene ring.[1452]

4. Magnetic Circular Dichroism Spectra of Thiophenes

The magnetic circular dichroism (MCD) spectrum of thiophene has been compared with those of furan, pyrrole, selenophene, and tellurophene[1304] (see also Ref. 1453). The effect of substituents on the MCD spectra was elucidated by a study of 3-methyl- and 3-bromothiophene, 2,4- and 2,5-dimethylthiophene, 2,5-dibromothiophene, 3-brom-2,5-diformylthiophene, and 2-thiophenecarboxylic acid. The MCD spectra confirmed the presence of at least two electronic transitions of the π–π^* type in thiophene and showed that this was also the case for selenophene and tellurophene. The MCD spectrum of thiophene was only slightly perturbed by the substituents mentioned above, and thus can be classified as a "hard" chromophore. On the other hand, pyrrole and furan have different and much weaker MCD spectra, which change shape considerably when substituents are introduced. The MCD spectra of 3,3′-bithienyls in liquid solution and in the crystal state have been compared to obtain information

about conformations.[1454] The longest wavelength absorption and the MCD bands of the thiophene analogs of quinocycloheptatriene and quinocyclopropene were interpreted in terms of intramolecular charge-transfer transitions.[1455] The linear dichroism spectra of a number of 3,3'-bithienyls, 2,5-dimethylthiophene, and a few other thiophene derivatives in polyethylene matrices have been studied. For the twisted substituted bithienyls, it was suggested that the two lowest π–π^* transitions with mutually orthogonal polarization in thiophene may be recognized at longer wavelengths. It was further suggested that the polarizations as obtained in 2,5-dimethylthiophene may be utilized to predict the optical activity in the bithienyls.[1456]

5. Photoelectron Spectra and ESCA Spectra of Thiophenes

The photoelectron spectra (PES) of thiophene have been studied experimentally by a large number of authors.[1457–1467] The two lowest ionization bands have been assigned to the $1a_2$ (π_3) and $2b_1$ (π_2) orbitals,[1462,1463,1465,1466] depending on calculations and on the intensities in the X-ray photoelectron spectrum. A study of the Penning electron spectra indicated that the assignments given in Refs. 1466 and 1467 should be the correct ones. There are a number of semiempirical and ab initio calculations on the PES spectra of thiophene.[1046,1470–1487]

The valence ionization potentials (IP) of thiophene and furan were studied by an ab initio multibody approach, which included the effects of electron correlation and reorganization beyond the Hartree-Fock approximation.[1451] The intensity of the shake-up lines of thiophene has been computed by the PPP method, including single excitation CI in the final state.[1488]

Relative photoionization cross sections of 2,5-dimethylthiophene computed by a theoretical method were compared with experimental photoelectron band intensities obtained by integrating the band areas in HeI and HeII photoelectron spectra.[1489] The results were compared with those for furan.[1490]

Recently, a theoretical study of photoionization cross sections, as well as electron affinities and ionization potentials of thiophene, furan, selenophene, and tellurophene, was carried out.[1491] The threshold photoelectron spectrum (TPES) of thiophene was obtained and gave the same ionization energy (8.87 $\pm$ 0.01 eV). [1492], as previously determined from the HeI photoelectron spectrum.[1457,1462] Photoionization efficiency curves for $C_4H_4S^+$, $C_4H_3S^+$, C_3HS^+, $C_2H_2S^+$, CHS^-, and $C_3H_3^+$ from thiophene were measured in the 8–14-eV photoenergy range.[1492]

Penning ionization electron spectroscopy and CNDO/S calculations have been successfully applied to the analysis of the UV photoelectron spectra of 2- and 2,5-bistrimethylsilylthiophene and 2-*t*-butylthiophene. The relative intensities of the π-type bands were greatly enhanced in the Penning spectra compared with those of the UV photoelectron spectra.[1493]

It has been shown that photoelectron spectroscopy is of considerable value in the interpretation of Raman and IR spectra, and the assignment of the symmetric "double-bond stretching" vibration of thiophene was confirmed.[1494] Very early the photoelectron spectra of thiophene and simple substituted derivatives, such as 2- and 3-bromothiophene, 2-chloro- and 2-iodothiophene, and 2,5-dichlorothiophene, were studied in connection with attempts to apply PES to pesticide analysis.[1495] A comparative study of the photoelectron spectra of a number of 2-substituted derivatives of thiophene, furan, selenophene, and tellurophene has been undertaken. The substituent effects confirmed the reversal in the energy sequence of the two highest occupied π-MOs of tellurophene with respect to the other five-membered heterocycles. The effect of the ring on the orbitals mainly localized on the substituents was also discussed.[1496] Highly resolved HeI photoelectron spectra of 2-chloro-, 2-bromo-, and 2-iodothiophene have been recorded. On the basis of comparison with the spectra of thiophene and the corresponding 2-haloselenophenes, assignments have been made for all the electronic bands. Vibrational structure was observed and analyzed in the band corresponding to the $1a_2$ (π) and $4a_1$ bands of thiophene, as well as the bands arising from the halogen lone pairs.[1497] The HeI photoelectron spectra of 2- and 3-methoxythiophene and 2,4- and 2,5-dinitrothiophene have been recorded, and their electronic structures were discussed in terms of inductive and mesomeric effects.[1498]

The HeI and HeII photoelectron spectra of styrylthiophene and α-cyanostyrylthiophene have been reported. The assignments and the interpretation of the spectra were made by comparison with the spectra of related molecules and with the aid of INDO/S-CI calculations.[1365]

The photoelectron spectra of 2,5-di-*t*-butylthiophene and of its 1,1-dioxide were studied and interpreted to indicate an unexpected extraordinarily strong through-conjugation involving the sulfone moiety.[1499] The photoelectron spectra of thienothiophenes[1500] and selenolo- and pyrrolothiophenes[1501] have been compared with those of the parent compounds.

Photoelectron spectroscopy has also been used as a tool in conformational studies of 2,2′-dithienylsulfide and 3,3′-dithienylsulfide,[1502] of 2- (2-thienyl)pyrrole,[126] and of dithieno[*c*,*e*]-dihydroazepines–oxepines and thienopines.[1503] The PES in the latter case indicated a twisted conformation in the gas phase.[1503]

The ESCA spectra of thiophene have been obtained in the gas phase[1463] and on a film on gold.[1485] Through the development of high-resolution ESCA instruments with X-ray monochromators for gases and solids, high-resolution spectra of the $2P_{1/2}$, 3/2 sulfur doublets with a spin–orbit splitting of 1.20 eV was obtained. The narrow lines allowed the line position to be determined within better than 0.05 eV. The chemical shift between the two S 2*p* lines of thiophene and carbonyl sulfide was 0.70 eV.[1504] The intensity and energy of satellite peaks in the ESCA spectra of gaseous thiophene, furan, and pyrrole have been measured.[1467] The ESCA chemical shifts of inner-core binding energies of thiophene were calculated by the semipirical SCCMO method, and the result

agreed with the experimental shifts.[1505] For some other papers concerned with ESCA of thiophenes, see Refs. 1506 and 1507.

It is known that the wavelength, the relative intensity, and the peak shape of characteristic X-ray lines emitted by elements depend to some extent on the chemical bond or the valence state of the elements. In these connections the S K_a doublet of thiophene and 2-thiophenecarboxylic acid has been measured in an investigation of 50 sulfur compounds using rhombic sulfur as standard.[1508] The S K_b X-ray photoemission spectra of thiophene has also been studied.[1509,1510] Both these types of spectra were used for the estimation of chemical forms of sulfur in petroleum pitches, which contain thiophenes.[1511] The fluorescent sulfur $L_{II,III}$ emission spectrum of thiophene has been investigated.[1507,1512]

6. Miscellaneous Reactions of Thiophenes with Radiation

The γ-radiolysis of thiophene has been studied.[1513–1516] In a matrix at 77 K a cation could be stabilized, and its spectrum showed maxima at 830 and 320 nm.[1515] Thiophene showed greater stability to radiation than did pyrrole.[1516] Spectroscopic studies of some transient species formed on flash photolysis of thiophene and selenophene have been carried out.[1517,1518] Q-Switched laser-induced reactions of thiophene with oxygen have been studied.[1519]

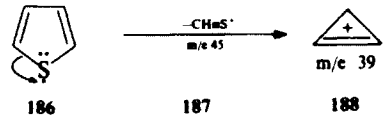
The emission bands obtained. in the region 390–450 nm by a radiofrequency discharge in thiophene have been studied. They were assigned to the HCCS transient species, whose absorption spectrum has been observed.[1520] The triplet-state photophysical behavior of *trans*-1-(2-anthryl)-2-(2-thienyl)ethylene has been studied by laser flash photolysis and pulse radiolysis. The absorption spectrum of the triplet was sharp, intense, and well resolved and displayed two major band systems at 400–500 and 550–650 nm. The observed triplet lifetimes (t_T) were 25–22 msec.[1521] Thiophene has been photoionized with UV lasers.[1522]

XV. MASS SPECTRA OF THIOPHENES

1. Fragmentation Patterns

Early in the development of mass spectrometry, before it came into general use in organic chemistry laboratories, the mass spectra of thiophenes were obtained in the laboratories of the petrochemical industry. For an early review, see Hartough's monograph.[1523] Interest in the mass spectra of thiophene derivatives in petroleum is continuing.[1524–1526]

Two main fragmentation patterns were found for thiophene, as schematically visualized in Scheme 5.[1527]



186 187 188

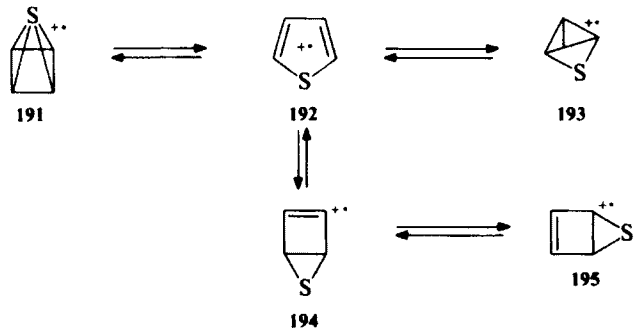
189 190

Scheme 5

The detailed structure of the fragments was determined only quite recently. However, detailed investigations by different groups of 2,3-D_2,2,5-D_2,3,4-D_2, and 2,3,5,-D_3, as well as 2-^{13}C- and 2,5-$^{13}C_2$-labeled thiophenes, showed that appreciable hydrogen and carbon scrambling occurs on electron impact on thiophene.[1528–1533] The mass spectra of the labeled thiophenes obtained at 70 eV show that about 40–50% of the CHS^+ arises by paths in which both hydrogen and carbon scrambling occur;[1531,1532] carbon scrambling is the more important.[1528,1530] The amount of scrambling in the formation of CHS^+ was different in 2,5-D_2-thiophene and 3,4-D_2-thiophene and increases sharply when the beam energy is reduced to 27 eV. It reaches a maximum of 80% at 13 eV for 2,5-D-thiophene, and 88% for 3,4-D-thiophene at the appearance potential for CHS^+.[1532]

It was suggested that hydrogen scrambling predominates over carbon scrambling in the loss of acetylene.[1530] It was also suggested that the carbon scrambling occurred through a "Ladenburg" thiophene structure **191**.[1492,1528,1530,1534] The fragmentation of thiophene has recently been re-investigated, using all four isomeric di-^{13}C-thiophenes and the 2,5- and 3,4-dideuterio derivatives to determine whether carbon and hydrogen scrambling are coupled or occur separately, and to determine through which intermediates rearrangement and dissociation occur.[1535] From this detailed study it emerges that the unimolecular loss of acetylene directly from the metastable thiophene cation radical **192** amounts to less than 5.3%, 1.2% involves C_α–C_β and 4.1% C_β–C_β, and the lifetime t is $\cong 10^{-5.5}$ sec. More than 94% of the long-lived molecular ion rearranged prior to dissociation and the majority of **192** (64.5%) undergoes complete carbon atom scrambling, presumably via **193**, while 30.2% of **192** suffers a degenerate isomerization involving either the pyramidal cation **191**, or the bicyclic cation radicals **194** and **195**. The latter are proposed to a "merry-go-round" rearrangement. It was also shown by collisional activation mass spectrometry and MINDO/3 calculations that the structure of the $H_2C_2S^+$ ion generated from **192** is best described as the thioketene cation radical **196**, and not as the isomeric **197**, or, as previously suggested, the symetrica thiirene.[1527] This investigation confirmed the previous results of Williams et al.,[1533] that complete hydrogen scrambling occurs, and from

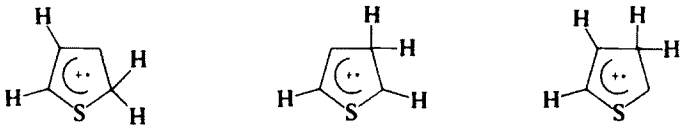
MINDO/3 calculations this is suggested to take place via intermediates of type **198–200**.



191 **192** **193** **194** **195**

$H_2C{=}C{=}S^{+\cdot}$ $HC{\equiv}C{-}SH^{+\cdot}$

196 **197**

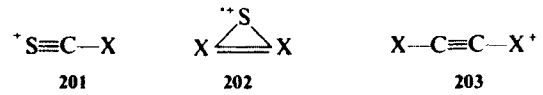


198 **199** **200**

Investigations of scrambling in substituted thiophenes became of interest in connection with the discovery of the photochemical rearrangements of phenylthiophenes.[1535,1536] The mass spectra of 2- and 3-phenylthiophenes and their phenyl d_5 derivatives revealed that the thiophene ring is markedly more reactive than the phenyl ring under electron impact.[1537] Recently, the mass spectra of a large number of 2,5-(bis-R-phenyl)thiophenes have been discussed.[1538] However, an investigation of the mass spectra of ^{13}C-labeled 3-phenylthiophene, as well as its 2-bromo and 5-bromo derivatives, showed that carbon–hydrogen, carbon–bromine and carbon–phenyl bond cleavages and substituent migration occurred. The extent to which substituent isomerization was reversible was not clear, but in the brominated compounds scrambling by the bond cleavage process seems to be essentially complete. By contrast, no proof of the occurrence of ring-carbon scrambling, as in thiophene itself, was found. All fragmentation reactions in this investigation were substantiated by the observation of the corresponding metastable decomposition ions, and exact mass measurements were employed to establish the assigned ionic compositions.[1539] These results indicate that the scrambling observed in tetraarylthiophenes is, at least in part, due to aryl scrambling by the substituent cleavage mechanism. Similar results were obtained in an investigation on partially deuterated 2- and 3-phenylthiophene. It was shown that the main reaction was a 3- to 2-phenyl migration. The reactions on electron impact therefore differ from the photochemical reactions, in which 2-phenylthiophene irreversibly rearranges to

3-phenylthiophene.[1534,1540] On electron impact, tetraphenylthiophene-1,1-dioxide loses SO_2, and it was suggested that a tetrahedral $C_4R_4^+$ species was formed.[1541]

A detailed study of the mass spectra of 26 halothiophenes, including all the theoretically possible isomeric bromo- and iodothiophenes, was reported.[1542] The intensity of ions **187** and **188** (Scheme 5) was lower in the 3-substituted derivatives, from which they are formed by rearrangement, than in the 2-substituted derivatives. Otherwise, the spectra of 2- and 3-monosubstituted isomers were very similar. The $[M—S]^+$ ion is very intense for the iodo derivatives, and this fragmentation was also very important in the bromo compounds, but was almost absent in the fluoro derivatives, in which loss of HF is of greater importance. Ion **201**, which can be formed in two ways from 2,5-disubstituted compounds, but only in one way from the 2,3- and 2,4-isomers, was appreciably more abundant in the former case. In the 3,4-series, this ion was almost absent in the bromine and iodine isomers. Ion **202** was only found in 2,3-disubstituted isomers, except for 2,4-and 3,4-difluoro isomers, which gave this ion in low intensity. No proof of the structure of ion **202** was given, and considering the recent results of Francke et al.,[1543] it could also be a dihalothioketene ion. However, the weak ion **203** is very characteristic for 2,3-disubstituted isomers, and was not observed in intensities exceeding 0.01% in any other dihalothiophene. Other differences in the mass spectra of positional disubstituted thiophenes were also observed. If we compare the effect of different halogens in the disubstituted isomers, we observe that the fluorine derivatives behave differently than other halogen derivatives. While the $[M—X]^+$ and $[M—2X]^+$ ions are of high intensity in the diiodo- and dibromothiophene spectra, and of intermediate intensity in that of 2,5-dichlorothiophene, they are almost absent in the spectra of the four difluorothiophenes. The main feature of the mass spectra of the tribromo- and triidodothiophenes is the consecutive loss of halogen atoms. Characteristic differences between the 2,3,4- and 2,3,5-isomers were also observed.[1542]

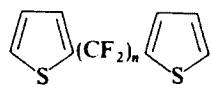


201 **202** **203**

The mass spectra of alkylthiophenes differ considerably from that of thiophene. The base peak is often due to the $C_5H_5S^+$ ion (m/e 97), formed by the breaking of a β-bond of an alkyl group attached to the thiophene ring.[1099,1544] In analogy with the corresponding benzene derivatives, it was suggested that the $C_5H_5S^+$ ion had a thiopyrylium structure.[1544] The mass spectra of alkylthiophenes have been studied for many years in detail at the Bureau of Mines of the US Department of the Interior in connection with the identification of thiophenes in petroleum. From a study of twenty-three 2-alkyl- and 2,5-dialkylthiophenes the following conclusions were drawn.

1. The ratio of the m/e 85/84 peaks is less than 1 for 2-*n*-alkylthiophenes and greater than 1 for 2,5-di-*n*-alkylthiophenes, if a methyl or ethyl is one of the groups. The size of the m/e 85 peak depends on the availability of hydrogen atoms for rearrangement from the β-carbon atom position.
2. Monosubstituted compounds have higher m/e 45 peaks than do 2,5-disubstituted compounds of the same molecular weight for compounds containing a total of 10 or less carbons in the substituent groups.
3. The base-minus-2 peak will be from 3 to 6% if one of the alkyl groups in the 2,5-position of a dialkyl-substituted thiophene is an ethyl group. If no ethyl group is present in a 2,5-dialkylthiophene and one of the groups is *n*-propyl, the base-minus-2 peak will be 1–3%. For other 2,5-disubstituted thiophenes with C_4 and larger groups, and also if only the 2-position is occupied by an ethyl group or larger, the base-minus-2 peak will be less than 1%.
4. The base peak is formed for most alkylthiophenes by breaking a β-bond in an alkyl chain attached to the thiophene ring. For the 2,5-dialkyl-substituted compounds with ethyl or larger groups, the β-bond of the longest alkyl group fragments to form the base peak. The β-bond cleavage for groups, such as isopropyl or *t*-butyl, does not lead directly to the m/e 97 ion, which consists of the thiophene ring plus the α-methylene group.
5. The $(M + 1)$ peak (above the isotopic contribution) is due to a rearrangement ion, whose intensity increases as the chain lengthens for the 2-*n*-alkyl compounds. For the 2-ethyl-5-*n*-alkylsubstituted compounds, this peak is small in the case of C_1–C_3 alkyl substituents, and increases to a maximum of 4% as the *n*-alkyl group chain lengthens. The excess for the 2,5-dialkylthiophenes is less than 1% when an isobutyl group is present. If isobutyl is absent but an isoamyl group is present, the excess is relatively large, more than 10%.[1545] Other systematic observations were described in Refs. 1546–1548 In connection with the above-mentioned work, 2-hexyl-1-^{13}C-thiophene was synthesized in order to secure evidence for α,β-bond fission on electron impact.[1549] The mass spectrum of *n*-decylthiophene has been analyzed.[1550]

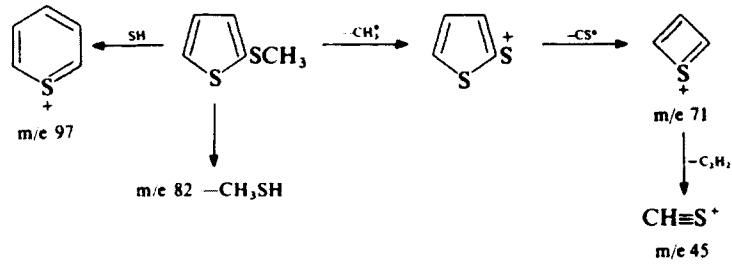
Electron impact and thermal fragmentation patterns of some perfluoroalkylene-linked thiophenes **204** have been studied. The spectra of **204** were dominated by peaks at m/e 133, corresponding to ions formed by cleavage β to the thiophene. The immediate precursor of the ion at m/e 45 is the ion at m/e 133. Precise mass measurement established the composition of the ion at m/e 75 as



$n = 3, 5$

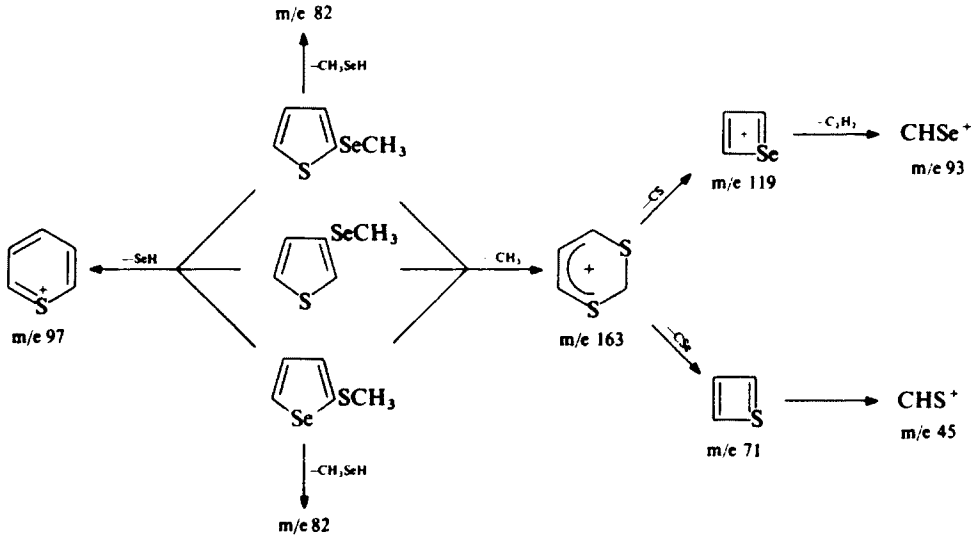
204

C_3HF_2.[1551] The mass spectra of some sulfides, selenides, and ethers of furan, thiophene, and selenophene have been analyzed and compared.[1552] The fragmentation of 2-methylthiothiophene is indicated in Scheme 6.



Scheme 6

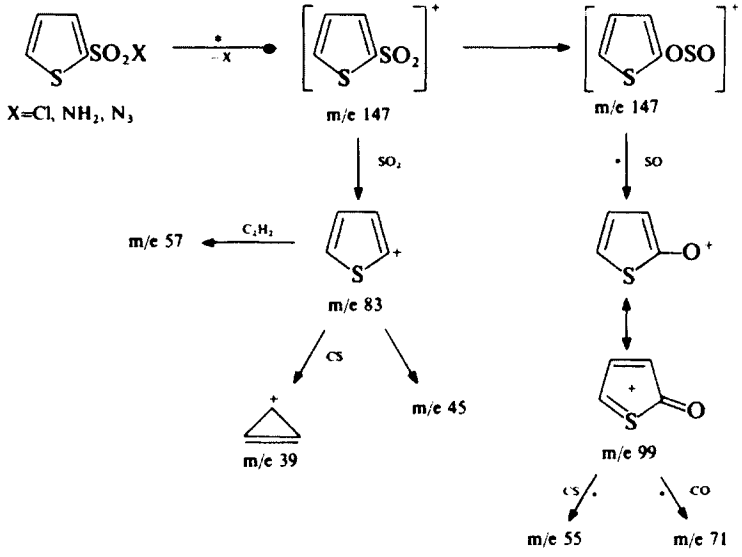
2-Methylselenoselenophene shows a similar fragmentation pattern. A new pattern was discovered when the very similar mass spectra of 2-methylselenothiophene, 3-methylselenothiophene, and 2-methylthioselenophene (Scheme 7) were compared.



Scheme 7

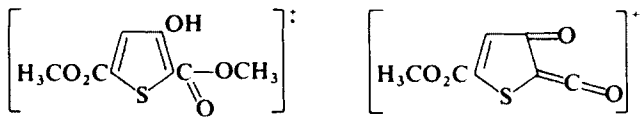
In these cases, after CH_3 loss alternative splitting off of CS or CSe takes place; loss of CS is predominant for the thiophene derivatives. It appears that the CX group with the more electronegative X is preferentially split off, as shown by comparison of the mass spectra of 2-methyl-5-methoxythiophene and 2-methyl-5-methylselenothiophene. The mass spectra of longer alkyl selenothiophenes

and 2-alkylthio-5-alkylselenothiophenes were also analyzed in this paper.[1552] The mass spectra of various carbonyl-substituted alkylthiothiophenes have also been elucidated.[1553] A detailed study of fifteen 1-(5-ethyl-2-thienyl)-1-thiaalkanes that occur in fossil fuels has been carried out. Prominent ions due to β-cleavage of the molecular ion were observed at m/e 144 ($C_8H_8S_2^{+}\cdot$) and at m/e 129 ($C_5H_5S_2^{+}$) due to β,β'-cleavage.[1554] The mass spectral fragmentation of dithienylsulfones has been studied, and a 1,2-migration of a thienyl group from sulfur to oxygen was observed.[1555] The fragmentation of some thiophenesulfonyl derivatives has been studied, and the suggested routes are indicated in Scheme 8.[1556,1558]

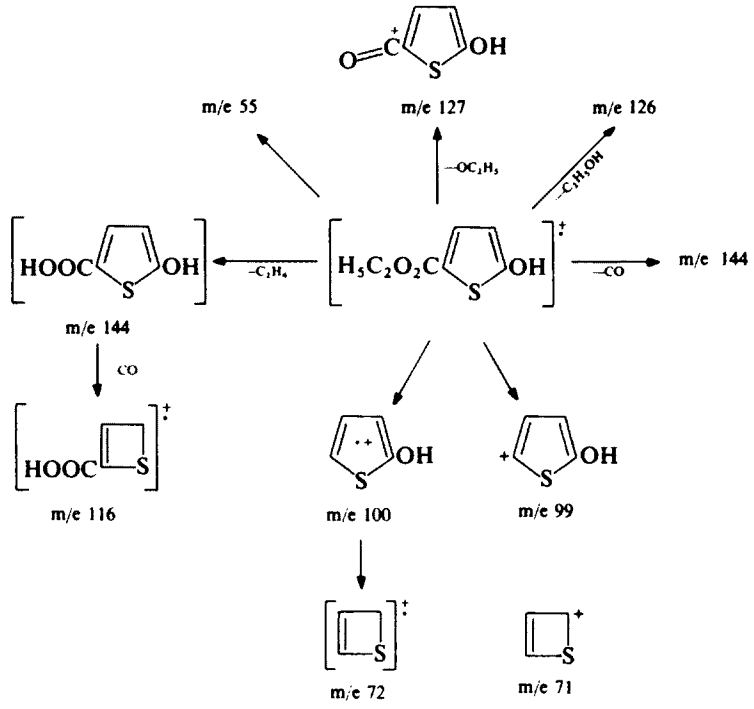


Scheme 8

The mass spectra of 17 potentially tautomeric hydroxythiophenes have been analyzed. An ortho effect between adjacent OH and CO_2R substituents was observed as indicated by the formation of **206** from **205**, which is useful for substituent location on the thiophene nucleus. If the groups are not ortho related, fragmentation is often more complex, as indicated in Scheme 9.



205 **206**



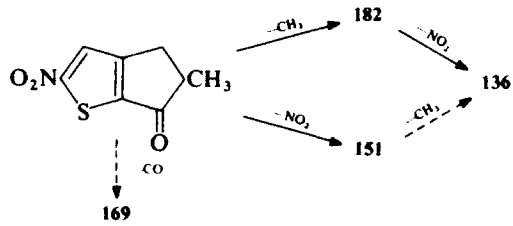
Scheme 9

The mass spectra of the simple 5-alkyl-2-hydroxythiophenes, which exist as 3-thiolene-2-one and 4-thiolene-2-one forms (see Part 3, Chapter I) fragment to an appreciable extent by loss of carbon monoxide from the molecular ion, by loss of the alkyl substituent, or by a combined loss of both.[1559] The mass spectra of 2-*t*- and 3-*t*-butoxythiophenes are similar; both contain few abundant ions, the molecular ions are weak, and the base peaks in both instances occur at M-56, which corresponds to the loss of isobutylene with concurrent transfer of a hydrogen atom to the oxygen. Further fragmentation is similar to that of the hydroxy thiophene system (see Scheme 9).[1560] The major fragmentation paths of 1-(2-thienyl)alkylalkanones have been elucidated by means of isotopically labeled molecules, metastable ion peaks and low ionization voltage data. The prominent processes were cleavage of the bond β to the carbonyl group with the concurrent rearrangement of a hydrogen atom and cleavage α to the carbonyl group to produce a thenoylium ion.[1561] The mass spectra of 3-thienylcyclohexyl ketone and the carbinol derived from it have been compared with those of the corresponding furyl derivatives.[1562]

The fragmentation of the isomeric substituted nitrothiophenes has been analyzed. It was found that the NO^+ fragment was relatively more abundant for the 2,3- and the 3,4-isomers than for the 2,4- and 2,5-isomers.[1563] Fragmentation patterns in the mass spectra of nitrothiophenes and bromonitrothiophenes

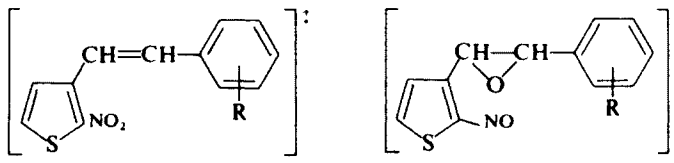
showed that, except for 3-nitrothiophene, the $[M—NO]^+$ fragment formed by rearrangement was more predominant than the $[M-NO_2]^+$ fragment formed by simple cleavage.[1564] Derivatives of 2-cyclopropyl-3-nitrothiophene under electron impact and under conditions of chemical ionization do not show isomerization characteristic of the *o*-nitrophenylcyclopropanes.[1565] The fragmentation of cyclopropylthiophene and of its methyl and acetyl derivatives, with substituents in the 1- and 2-positions of the three-membered ring, begins with the cleavage of the H, CH_3, or $COCH_3$ radicals. The further decomposition of the resulting ions is limited to the cleavage of the H_2, C_2H_2, and CH_3CCH molecules and the SX atoms.[1566]

An interesting difference in the fragmentation pattern between two nitrated cyclopenta[*b*]thiophenes has been found, as indicated in Scheme 10.[760]



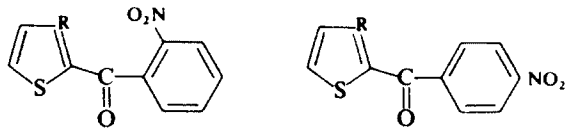
Scheme 10

Solid arrows indicate processes whose occurrence is supported by metastable peaks. The different fragmentation of the 3-nitro isomer was ascribed to an ortho effect similar to that in *o*-nitrotoluene. Other examples of ortho effects in nitro derivatives have been found in styrylnitrothiophenes **207** in which oxygen transfer from the nitro group to the olefinic double bond to give **208** was suggested to be the primary step before further fragmentation.[1567]



207 **208**

The fragmentation patterns of **209** and **210** have been compared and large ortho effects on the fragmentation pattern of **209** were observed.[1568] The



$R = H, CH_3$ $R = H, CH_3$

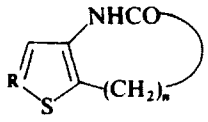
209 **210**

fragmentation of some 2- and 4-substituted 3-thiophenecarboxylic acids[1569] has been compared with those of the corresponding 3-substituted 2-thiophenecarboxylic acids.[1570]

The mass spectra of some substituted 2- and 3-thiophenecarboxanalides show cleavage of the amide bond followed by CO elimination as an important fragmentation pattern.[1071,1072] A comparative study of 5- and 3-substituted thiophene-2-carboxamide showed a strong "ortho effect," which activates NH_3 elimination. In the ortho cases, the most important fragmentation is NH_2 loss, followed by CO elimination.[1573] The mass spectra of some thiophene chalcone analogs are characterized by $[M - 1]^+$ ions of rather high intensity.[1574]

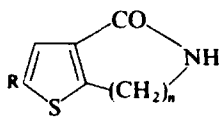
The structure of the minor isomers obtained in the nitration of 2- and 3-nitrothiophene, 2- and 3-formylthiophene, and 2- and 3-cyanothiophene was partly determined by mass spectrometry, and certain characteristic fragmentation patterns were pointed out.[1563]

The fragmentation pattern of cyclic compounds of types **211** and **212** has been investigated. This allowed the determination of the dimensions of the lactam ring and the relative positions of the carbonyl and imino group.[1576]



R = CH_3, $n = 3$
R = H, $n = 4$
R = CH_3, $n = 4$

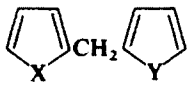
211



R = CH_3, $n = 3$
R = H, $n = 4$
R = CH_3, $n = 4$

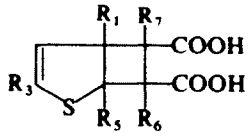
212

The mass spectra of heterocyclic diaryl methanes of type **213** have been investigated. The intensity of the molecular ion peak in the mass spectrum decreases in the following order of X, Y: S, O > Se, O > Se, S.[1577] The mass spectra of 1,2-cycloaddition products **214**, obtained from the benzophenone photosensitized irradiation of 2,3-dimethylmaleic and citraconic anhydride in the presence of thiophene derivatives, were discussed.[1578] The mass spectrum of

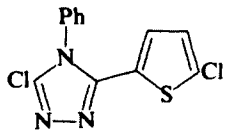


X, Y = O, S, Se

213



214



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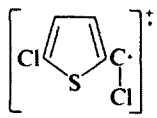
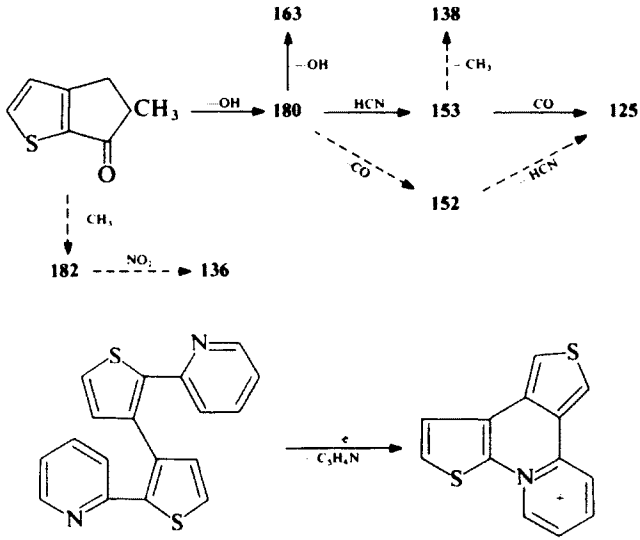


216

215 revealed a rearrangement involving the migration of the 3-chlorine to the C-5 carbon of the triazol ring, followed by a concerted loss of nitrogen and benzonitrile to give ion **216**.[1579]

The mass spectra of polyheteroaromatics usually do not show ions due to the elimination of a heterocyclic ring, except when one of the middle rings is *o,o*-disubstituted, in which case a very strong $[M—Ar]^+$ peak is obtained (Scheme 11).[1580]



Scheme 11

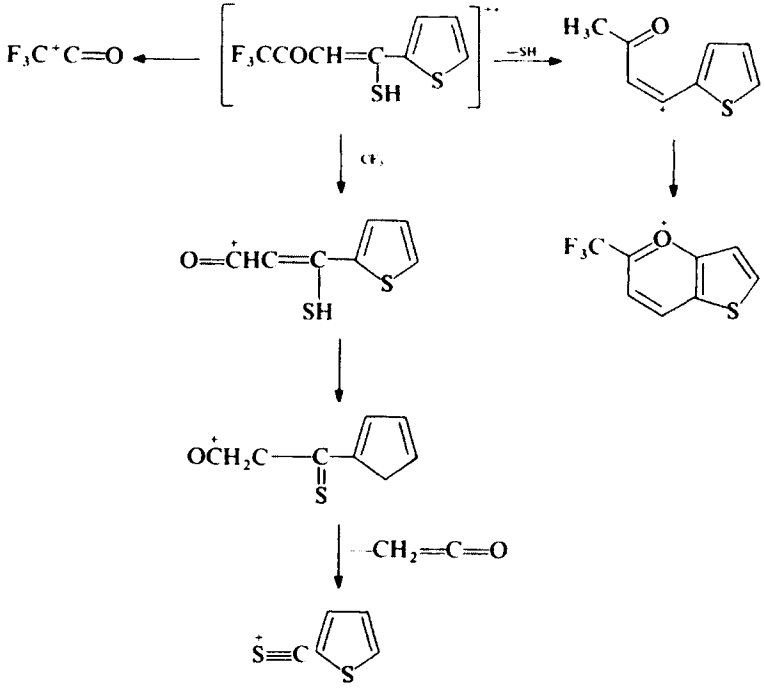
The fragmentation pattern of 2,2′-5,2′-terthiophene has been discussed.[1581] The mass spectra of naturally occurring nematodicidal bithienyl derivatives have been elucidated.[797] The stability of bithienyls and terthienyls to electron bombardment and radiation has been investigated.[1582]

Mass spectral fragmentation studies have been carried out on thiophene, tropone, and thiophenetropylidene derivatives and their metal tricarbonyl complexes,[1583] as well as on other transition-metal complexes, such as *p*-thiophene chromium tricarbonyl complexes[1581,1584,1585] and π-butadienyldicarbonyl (ethoxythienyl-carben) iron complexes.[1586]

The fragmentation pattern shown in Scheme 12 has been suggested for 1,1,1-trifluoro-4-(2-thienyl)-4-mercaptobut-3-en-2-one.[1218]

The fragmentation of 2,4-diphenyl 3,5-di-(*p*-fluorophenyl)thiophene-1,1-dioxide has been used in a study of unimolecular and collisionally activated decompositions of fluorine-substituted tetraphenyltetrahedrane ions on the microsecond time scale.[1587]

Direct analysis by mass spectrometry of heavy cuts of petroleum containing thiophenes has been described.[1588] The analysis of complex mixtures of hydrocarbons and organic sulfur compounds, including thiophenes, was carried out



Scheme 12

by a combination of gas chromatography and spectrometry, with electron impact ionization, with pulse recording of positive and negative ions.[1589] Thiophenes were studied as model compounds by pyrolysis-gas chromatography–mass spectrometry in a study of coal hydrogenates.[1590] Other special mass spectrometric techniques applied to thiophene derivatives have been described.[1591–1593]

2. Appearance and Ionization Potentials of Thiophenes

The ionization potential of thiophene and some substituted derivatives, and the appearance potential of several fragment ions, have been determined by mass spectral techniques[1575,1594–1599] and compared with those of the other five-membered heterocycles. The ionization potentials have also been correlated with the relative rates of electrophilic substitution in five-membered heteroaromatic rings.

The potentials obtained are given in Table 65. Ionization potentials have also been obtained by photoelectron spectroscopy (see Section XIV.5).

The ionization potentials by photoionization obtained for thiophene and 2-chloro- and 2-bromothiophene were 8.860 ± 0.005, 8.68 ± 0.01, and 8.63

TABLE 65. Ionization Potentials of Monosubstituted Thiophenes, Selenophenes, Furans, and Pyrroles

Substituent	Ionization Potentials (eV)			
	Thiophenes	Selenophenes	Furans	Pyrroles
2-OCH_3	8.30			
2-SCH_3	8.10			
2-CH_3	8.63	—	8.47	8.01
2-C_2H_5	8.67		8.45	7.97
2-C_4H_9-*trans*	8.54			7.95
2-Br	8.93			
3-Br	9.02			
2-Cl	9.06			
H	9.12	9.01	8.99	8.40
2-$COCH_3$	9.20	9.30	9.27	8.72
3-$COCH_3$	9.32			
2-CO_2CH_3	9.22		9.32	8.65
2-CHO	9.55	9.47	9.50	8.93
2-$COCF_3$	9.70	9.64	9.77	9.18
3-$COCF_3$	9.63			
2-CN	9.83		9.77	
2-NO_2	9.77		10.04	9.30

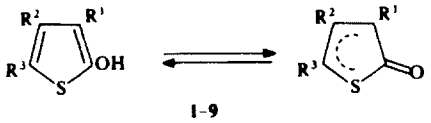
$\pm$ 0.01 eV, respectively.[1600-1602] Inductive effects on the ionization potentials of alkylthiophenes have been studied.[1603]

The ionization potentials of the substituted heterocycles could be reasonably well correlated with σ_p^+-constants. The ρ-value for this reaction, however, was more negative than that for the most selective electrophilic substitutions. The sensitivity to substituent effects appears to vary in reverse order to that of the "ground-state" aromaticity of the rings (furan > pyrrole > thiophene).[1604]

The absolute charge-exchange cross sections Q in the gas phase between thiophene, furan, and pyrrole and 48 primary positive ions of known ionization potential has been determined. A plot of Q against the ionization potential for a particular product ion constitutes the charge-exchange mass spectrum of that ion from which appearance potential of the ion is directly obtained. Appearance potentials obtained in this way agreed well with those obtained previously by other methods.[1596]

The ionization potentials for tautomeric 2-hydroxythiophenes, -selenophenes, and -furans have been analyzed by comparison with ionization potentials of locked compounds derived from either tautomeric form. The enol form was not observed. Of the two possible thiolactone forms, 3-thiolene-2-one and 4-thiolene-2-one, the former one was the major isomer. However, the ratios depend on the position of the alkyl group and on the heteroatom. The ionization potentials obtained are given in Table 66.[1604]

TABLE 66. Ionization Potentials for 2-Hydroxythiophenes and Derivatives



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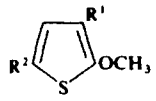

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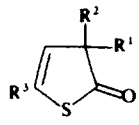


15-17

Compound	R^1	R^2	R^3	IP ± 0.05 (eV)
1	H	H	H	9.78
2	CH_3	H	H	9.60
3	$C(CH_3)_3$	H	H	9.25
4	H	H	CH_3	9.16
5	H	H	C_2H_5	9.08
6	CH_3	H	CH_3	9.35
7	CH_3	CH_3	H	9.44
8	H	CH_3	CH_3	9.13
9	$C(CH_3)_3$	H	CH_3	9.07
10	H	H	—	8.14
11	CH_3	H	—	8.05
12	$C(CH_3)_3$	H		7.67
13	H	CH_3	—	8.01
14	CH_3	CH_3	—	7.78
15	CH_3	CH_3	H	8.77
16	CH_3	$C(CH_3)_3$	H	8.38
17	CH_3	CH_3	CH_3	8.53

Similar investigations on 3-hydroxy-2,5-dialkylthiophenes, -selenophenes, and -furans showed that both the ketone and enol forms were important. The ratio varied from almost pure ketone to considerable amounts of the enol. The isomer ratios depended on the substituents the nature of the heteroatom, and the relative evaporation rates from rapidly equilibrating samples. The resulting ionization potentials are given in Table 67.[1605]

Ionization potential measurements on the potentially tautomeric 2- and 3-thiophenethiols and analogous selenophene and furan derivatives showed that they exist as thiols mainly in the gas phase. The ionization potentials obtained are given in Table 68.[1606]

For additional discussions of ionization potentials, see section on photoelectron spectroscopy and charge-transfer complexes (XIV.5).

TABLE 67. Ionization Potentials of 2,5-Dialkyl-3-Hydroxythiophenes

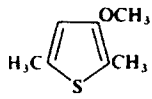
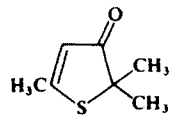
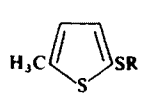
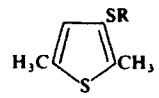
R^1	R^2	IP ± 0.05 eV
CH_3	CH_3	8.56
CH_3	C_2H_5	8.34
CH_3	$CH(CH_3)_2$	8.21
CH_3	$C(CH_3)_3$	8.10
C_2H_5	CH_3	8.22
$C(CH_3)_3$	CH_3	8.09
		
7.89 ± 0.05 eV		8.49

TABLE 68. Ionization Potentials of Some Thiophenethiols



1-2



3-4

Compound	R	IP ± 0.05 eV
1	H	8.48
2	CH_3	8.13
3	H	8.22
4	CH_3	7.96

3. Negative Ion Mass Spectra

The formation of negative ions on electron impact of thiophene, 2-ethyl-, 2-propyl-, and 2-butylthiophene has been studied.[1594,1607] The ions S^-, SH^-, CHS^-, and $C_4H_4S^-$ were observed in the spectrum from thiophene. The lifetime of the M ion was determined.[1608] Deuterium isotope effects were found to be largest in ions of the type $(M—H)^-$.[1609] In a later investigation on 2-substituted

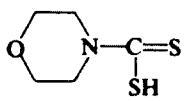
thiophenes (R = CH_3, C_2H_5, C_6H_5, COOH, COC_6H_5, Br), only pronounced molecular anions were observed, and no fragment ions were produced, except for 2-bromothiophene, in which case the Br^- ions were observed and no molecular ion. Negative ion mass spectra of dihydrothiophene-1,1-dioxide have been studied.[1610]

4. Various Mass Spectral Aspects

The transmission coefficient for monoenergetic electrons (0.04 eV FWHM) passing through a thin film (~100 Å) of solid thiophene was measured as a function of electron energy in the range 0–15 eV. The visibility of sharp maxima in the transmission spectra was enhanced by measuring the second energy derivative of the transmitted current with respect to electron energy. In thiophene, only four structures were resolved.[1611] Low energy (0–3 above threshold) variable-angle electron impact excitation spectra and transmission spectra for thiophene, furan, and pyrrole were compared by two different groups.[1612–1614] For each molecule, two low-lying triplet states were reported. An additional new transition at 6.5 eV was observed for thiophene.[1614] In the wavelength region of 200–600 nm, photoemissions from electronically excited H, CH, C_2, and CS were observed, when thiophene was excited by electron impact.[1615]

The molecular stopping cross sections for thiophene have been measured for 0.3–2.0 M eV He^+ ions.[1616] Ion–molecule reactions have been carried out between thiophene and 2,5-dimethylthiophene and CH_3OD in the gas phase. No exchange was observed in the latter case, while thiophene exchanged two deuterium atoms. It was therefore concluded that protonation of thiophene in the gas phase occurs preferentially in the α-positions, as is the case in acid-catalyzed hydrogen–deuterium exchange in solution.[1617]

Glow-discharge reactions of thiophene have been investigated. The major solid product were polymers, whereas the volatile products were identified as S, H_2S, and CS. When morpholine and thiophene together (ratio 5 : 1) were fed into the glow-discharge zone, the morpholine salts of **217–219** were formed. This indicates that carbon monosulfide and thioketene are the initial products from thiophene.[1618] Resistance against electron impact and radiation have been studied for thiophene and some bithienyls and terthienyls.[1619] The collision of field ionized molecular ions of thiophene of high kinetic energy (8 keV) with neutral target atoms (helium) gives rise to a large variety of fragments.[1620]



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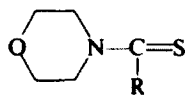


218 R = H
219 R = CH_3

XVI. OPTICALLY ACTIVE THIOPHENE DERIVATIVES

1. Introduction

Thiophene derivatives have been resolved into enantiomers, mainly in connection with investigations on their ability to form quasiracemates with each other and with their analogous benzene derivatives. The quasiracemate method developed by Fredga (for review, see Refs. 1621 and 1622) allows the determination of the relative configurations of thiophenes to benzenes. Combination of the quasiracemate method with Raney-nickel desulfurization thus allows the steric correlation of aromatic and aliphatic compounds.[1623]

Raney-nickel desulfurization of optically active thiophene derivatives has also been used for the synthesis of otherwise difficulty available aliphatic compounds. Other reasons for the resolution of thiophene derivatives are related to interest in biologically and pharmacologically active compounds. Optically active thiophenes have also been obtained by asymmetric organic synthesis (see Chapters V and VI in Part 1 of this series).

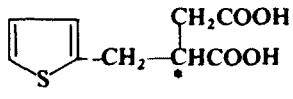
A large number of atropisomeric bithienyls and some 3-phenylthiophenes have been prepared and resolved. ORD and CD spectra of these compounds have been studied to determine configurations and conformations. The racemization of some of these 3,3'-bithienyls has also been investigated.

2. Optically Active Thienyl- and Thenyl-Substituted Acids

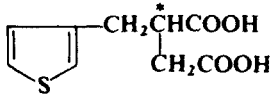
Compounds such as 2- and 3-thenylsuccinic acid **220**[477] **221**,[478] 2- and 3-thienylsuccinic acid **222**[1624] **223**,[476] α-2-thienylhydrocinnamic acid **224**,[1625] 2-thenylphenylacetic acid **225**,[1625] 2-thenyl-2-thienylacetic acid **226**,[479] α-phenyl-2-thienylglycolic acid **227**,[1626] 2- and 3-thienylglycolic acid **228a**[480] **229a**,[481] 2- and 3-α-methoxythienylacetic acid **228b**, **229b**,[1627] and α-amino-3-thienyl acetic acid **231a** and α-azido-3-thienylacetic acid **231b**[1274] were resolved by conventional resolution by recrystallization of the diastereomeric salts with alkaloids and other optically active bases. An exception is **231a**, which was resolved by salt formation with optically active sulfonic acids. The dextrorotatory substituted α-methoxyl-3-thienylacetic acids **230** were obtained by recrystallization of their (−)-phenylethylamine salts.[1628] The enantiomers of **232** were obtained by resolution with (+)- and (−)-ephedrine and by asymmetric synthesis. Comparison of CD spectra with that of the phenyl analog, and also the quasiracemate method, showed that (+)-**232** has the *S*-configuration.[1629]

Brucine was the only base that could be successfully used for the resolution of 2,5-dimethyl-3-(2,2,6-trimethyl-6-cyclohexenyl)-4-thiophenecarboxylic acid **233**. The opticall activity is due to hindered rotation about the thiophene–cyclohexene ring, as in the atropisomeric biphenyls. Attempt to racemize (−)-**233** in diglyme at 190°C failed. The methyl ester of (−)-**233** was

also prepared, and it was also reduced to the optically active (+), 3-(2,6,6-trimethylcyclohexenyl)-2,4,5-trimethylthiophene.[1630] The bases used and the rotations obtained are given in Table 69. Melting-point diagrams showed that both **220** and **221** were true racemates, as is also the case with benzylsuccinic acid.[477,478]



220



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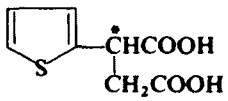
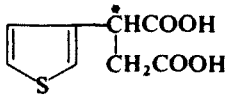


222



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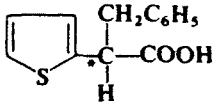

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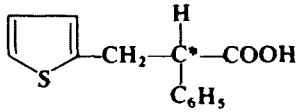

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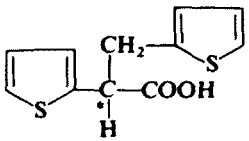

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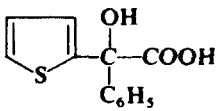
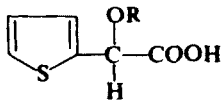
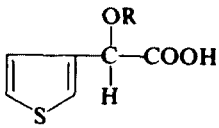


227



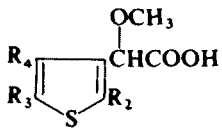
a R = H
b R = CH_3

228



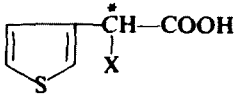
a R = H
b R = CH_3

229



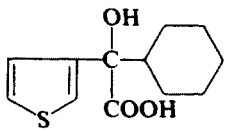
a $R_2 = R_3 = CH_3$; $R_4 = H$
b $R_2 = R_3 = CH_3$; $R_4 = Br$
c $R_2 = R_3 = Cl$; $R_4 = H$

230



a $X = NH_2$
b $X = N_3$

231



232

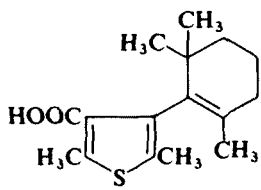


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TABLE 69. Bases Used for Resolution of Compounds **220–231** and Their Rotation

Compound	Resolving Base (solvent)	$[\alpha]_D^{25}$ (solvent)
(−)-**220**	(+)-α-Phenylethylamine (ethyl acetate)	− 14.8° (acetone)
(+)-**220**	Strychnine (35% C_2H_5OH)	+ 14.7° (acetone)
(+)-**221**	Strychnine	+ 20.0° (acetone)
(−)-**221**	(+)-α-Phenylethylamine	− 20.0° (acetone)
(+)-**222**	Cinchonidine (50% C_2H_5OH)	+ 103.5° (C_2H_5OH)
(−)-**222**	(−)-α-Phenylethylamine (ethyl acetate–CH_3OH 6 : 1)	− 103.9° (C_2H_5OH)
(+)-**223**	Cinchonidine (50% C_2H_5OH)	+ 102.3° (C_2H_5OH)
(−)-**223**	(−)-α-Phenylethylamine (ethyl acetate–CH_3OH)	− 102.5° (C_2H_5OH)
(+)-**224**	Cinchonidine (C_2H_5OH–H_2O)	+ 88.3° (acetone)
(−)-**224**	l-Ephedrine dihydrate (C_2H_5OH–H_2O)	− 87.7° (acetate)
(+)-**225**	(+)-Benzedrine (50% C_2H_5OH)	+ 126.9° (acetone)
(−)-**225**	(+)-α-Phenylethylamine	− 127.9° (acetone)
(−)-**226**	l-Ephedrine dihydrate (benzene)	− 95.9° (acetone)
(+)-**226**	Quinine	Incomplete resolution
(−)-**227**	(+)-Phenylethylamine (H_2O–CH_3OH 1 : 1)	− 28° (ethyl acetate)
(+)-**227**	(−)-Phenylethylamine (H_2O–CH_3OH)	− 25° (ethyl acetate)
(−)-**228a**	Cinchonidine (H_2O–C_2H_5OH 4.5 : 1)	− 98.3° (H_2O)
(+)-**228a**	(−)-α-Phenylethylamine (ethyl acetate)	+ 99.6° (H_2O)
(+)-**228b**	Quinine (CH_3OH)	+ 83.2° (acetone)
(−)-**228b**	Cinchonidine (10% acetone)	+ 83.1° (acetone)
(−)-**229a**	(+)-α-Phenylethylamine (ethyl acetate–methanol 2 : 1)	− 102.1° (C_2H_5OH)
(+)-**229a**	Strychnine (H_2O)	+ 102.5° (C_2H_5OH)
(+)-**229b**	Quinine (CH_3OH)	+ 94.6° (acetone)
(−)-**229b**	Strychnine (H_2O–acetone 1 : 1)	− 95.0° (acetone)
(+)-**230a**	(−)-Phenylethylamine	+ 186° (ethanol)
(+)-**230b**	(−)-Phenylethylamine	+ 144° (ethanol)
(+)-**230c**	(−)-Phenylethylamine	+ 151° (ethanol)
(+)-**231a**	α-Bromo-*d*-camphor-α-sulfonic acid (ethyl acetate)	+ 100° (H_2O)
(−)-**231a**	*d*-Camphor-10-sulfonic acid (isobutanol)	− 100° (H_2O)
(−)-**231b**	Cinchonine (ethyl acetate)	− 180° (acetone)
(+)-**231b**	(−)-Ephedrine (ethyl acetate)	+ 107° (acetone)

Both (+)-**221** and (+)-**222** gave a quasiracemate with (−)-benzylsuccinic acid, and **221** and **222** of opposite rotation also gave a quasiracemate with each other. X-Ray powder photographs indicated that these quasiracemates were isomorphic with the corresponding racemates.[478] The enantiomers with the same mode of rotation formed solid solutions. It is thus obvious that **221**, **222**, and benzylsuccinic acid with the same mode of rotation have the same configuration. Great parallelism in the rotation values in different solvents was also observed for these three acids.[478] Raney-nickel desulfurization of (−)-**220** gave (−)-pentylsuccinic acid almost without racemization. As the absolute configuration of alkylsuccinic acids was known, this connects (−)-**220** and (−)-benzylsuccinic acid to the glyceraldehyde system.[1623,1631]

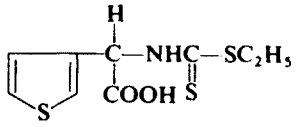
In a similar way, (+)-**222** was desulfurized to (+)-*n*-butylsuccinic acid, thereby establishing its absolute configuration.[1624] A study of the phase diagrams of phenylsuccinic acid and **222** by X-ray powder photographs showed that both acids were dimorphic, probably even trimorphic. While the optically inactive phenylsuccinic acid is a true racemate, inactive **222** is most probably a solid solution of the enantiomers. However, the optically active phenylsuccinic acid and **222** with opposite direction of rotation have been found to give a quasiracemate and therefore have opposite configurations.[475] The configuration of **223** relative to phenylsuccinic acid was determined by the study of X-ray powder photographs and of IR spectra in the solid state. While **222** and phenylsuccinic acid with the same mode of rotation probably form a solid solution, those of opposite mode of rotation gave a quasiracemate, thus establishing the absolute configuration of **233**.[476] It is interesting to note that **222** and **223** have almost the same rotation in several solvents.[476] The different effects of the various rings on the acidity of the benzylic position was reflected in the rate of racemization. While optically active phenylsuccinic acid is not racemized on refluxing for 2 hr with 2 N sodium hydroxide, optically active **222** is completely racemized, and optically active **223** is racemized by about 20%.[476,1624] Eight of the sixteen possible two-component systems of the enantiomers of α-phenylhydrocinnamic acid and the thiophene derivates **224**–**226** have been analyzed by a study of melting-point diagrams. From the occurrence of quasiracemates it was concluded that α-phenylhydrocinnamic acid, **224**, and **225** with the same direction of rotation have the same configuration. It was also noticed that the 2-thiophene compounds had a markedly lower tendency toward racemate formation than their phenyl analogs.[1632]

X-Ray powder photographs of an equimolar mixture of mandelic acid and **228a** of opposite modes of rotation showed the formation of a quasiracemate, while the powder photograph of an equimolar mixture of these acids with the same mode of rotation was additively composed of the lines of the components. Furthermore, IR spectra in the solid state indicated the formation of a quasiracemate. When Raney-nickel desulfurization of (+)-**228a** was carried out at room temperature, racemization was avoided and the levorotatory salt of α-hydroxycaproic acid was obtained. This shows that (+)-**228a** belongs to the L-series of α-hydroxy acids, and confirms the previous assignment of (+)-mandelic

acid to the same series.[480] The greater stability of 3-thienylglycolic acid **229a** than the 2-isomer allowed for the determination of the relative configuration of **229a** relative to mandelic acid, and a quasiracemate was observed for an equimolar mixture of **229a** and mandelic acid with opposite rotation, while those with the same mode of rotation gave a solid solution. Powder photographs and IR spectra led to the conclusion that **229a** and mandelic acid with the same mode of rotation have the same configuration. The rate of racemization of optically active mandelic acid, **228a** and **229a** were measured at 90°C in 0.2 N sodium hydroxide solution. It was found that **228a** was racemized 33 times faster than mandelic acid and 20 times faster than the 3-isomer **229a**.[481] While inactive α-methoxyphenylacetic acid is a true racemate, both inactive **228a** and **229a** constitute the rather rare case of conglomerates, which made possible spontaneous resolution of **228a** by picking crystals. The six-component systems, which these three acids give, are all of the eutectic type. However, it is noteworthy that those systems in which the components have opposite configurations give the lower eutectic temperatures.[84] The absolute configurations of **228b** and **229b** were determined by relating them to **228a** and **229a**, which by aluminum *tert*-butoxide catalyzed methylation with diazomethane were converted to the methyl ester of **228b** and **229b**.[1633]

The absolute configuration of **231a** was obtained by desulfurization of (−)-**231a** to a mixture of about equal amounts of levorotatory isoleucine and alloisoleucine,[1274] in contrast to previous claims that only isoleucine was formed on desulfurization of inactive α-amino-3-thienylacetic acid.[1752] Active **231a** could also be related to the phenyl analog phenylglycine by studying the ORD spectra of their dithiocarbamates **234** and **235**. This type of compound shows anomalous Cotton effect curves at 330 nm, and according to Sjöberg et al.,[1634] dithiocarbamates derived from α-amino acids of the L-series show a positive Cotton effect. It was found that **234** and **235**, derived from (−)-**231a** and (−)-phenylglycine, gave curves with a negative Cotton effect, confiming that both acids belong to the D-series.[1274] Hydrogenation of (+)-**231b** over palladium gave the amino acid with the same mode of rotation, thus relating the acids to each other. The azido acid **231b** was also related to α-azidophenylacetic acid by the quasiracemate method, as equimolar mixtures of these acids with opposite modes of rotation gave a very pronounced quasiracemate, while the enantiomers with the same mode of rotation gave a melting-point curve of the eutectic type.[1274] Both optically active **231b** and optically active α-azidophenylacetic acid are easily racemized, and at 24.7°C in 1.00 N sodium hydroxide solution half-times of 40.5 and 90 min, respectively, were observed.[1274] Both 2- and 3-thienylglycine have also been resolved via salt formation of their *N*-formyl derivatives with dehydroabietylamine.[1635] β-2-Thienylalanine was resolved by salt formation of its *N*-formyl derivative with brucine.[1636] Esters of 2-thienylglycine were also selectively resolved by reaction with tartaric acid or dibenzoyltartaric acid and aldehydes or ketones, such as cyclohexanone in a solvent to form the insoluble salt of the desired enantiomer, with simultaneous continuous racemization of the Schiff base, formed from the undesired enantiomer.[1637] The

(−)-form of 2-thienylmethyl carbinol has been obtained by crystallization of the brucine salt of its hydrogen phthalate.[1638,1639]



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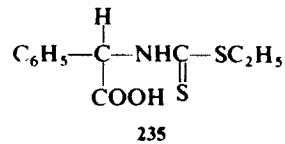
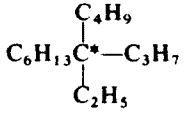


235

The racemic forms of the hydrochlorides and hydrobromides of the analgesically active 3-piperidino-1,1-di(2-thienyl)-1-butene exist as conglomerates, and could be resolved by preferential recrystallization on inoculation with one enantiomer.[1640]

3. Optically Active Thiophenes as Intermediates for Chiral Quaternary Hydrocarbons

An interesting theoretical question in the field of optical activity is a study of quaternary hydrocarbons, such as **236** and the even simpler **237**. For the synthesis of such chiral compounds, Raney-nickel desulfurization of optically active thiophenes proved very useful. Compound **236** was obtained by the condensation of thiophene with 3-hexanone in the presence of sulfuric acid to give **238**, which was monoacetylated and then reduced according to Wolff-Kishner to give **239**. Vilsmeyer formylation followed by oxidation with silver oxide gave the acid **240**. Crystallization of the cinchonine salt of **240** gave the (−)-form of **240** ($[M]_{575} = -3.6°$). Decarboxylation of **240** by heating it with copper in quinoline at 213°C gave dextrorotatory **241** ($[M]_{578} = +0.36°$). It was checked that no racemization occurred during this vigorous decarboxylation by reconverting **241** to optically active **240**.



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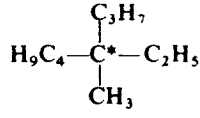

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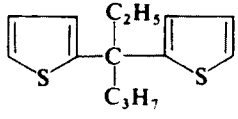

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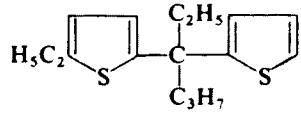

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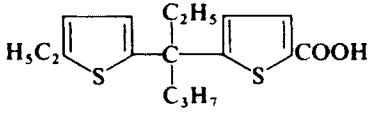

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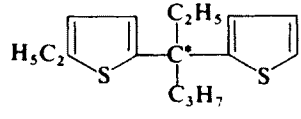
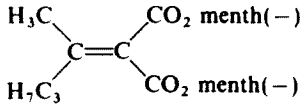


241

Raney-nickel desulfurization then gave achiral **236**, which exhibited no rotation of plane-polarized light between 280 and 580 nm. This finding was considered to be in accordance with predictions based on empirical calculations.[1462] However, it was assumed that no racemization could occur during Raney-nickel desulfurization. In order to eliminate the possibility of complete racemization during Raney-nickel desulfurization, chiral **237** was prepared in two different ways, one involving thiophene derivatives. Thus, the addition of 2-thiophene magnesium bromide to the α,β-unsaturated di(−)-menthyl ester **242** in the presence of catalytic amounts of CuCl, gave the diastereomeric adducts **243**, which were readily separated by crystallization. Hydrolysis of the major crystalline diastereomer of **243** gave the acid **244** ($[I\alpha]_{578} = -20.3°$, enantiomeric excess 95 ± 5%). Raney-nickel desulfurization of **244** gave levorotatory **245**, which on reduction with lithium aluminum hydride, tosylate formation, and reduction gave optically active **237** ($[M]_{578} = 0.309°$). The second route to **237** consisted of the resolution of **246** with cinchonidine, followed by decarboxylation and Raney-nickel desulfurization to **245**, which then gave optically active **237** ($[M]_{578} + 0.209°$). Thus, no evidence for racemization could be found when thiophene derivatives with the 2-thienyl unit directly attached to an asymmetric quaternary carbon atom are desulfurized.[1641]



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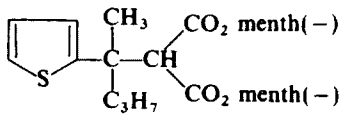

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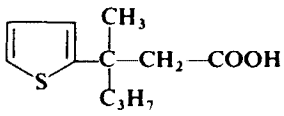

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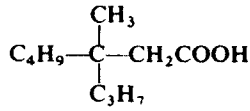

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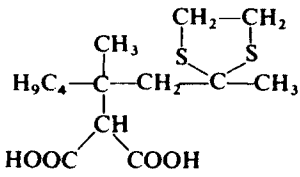
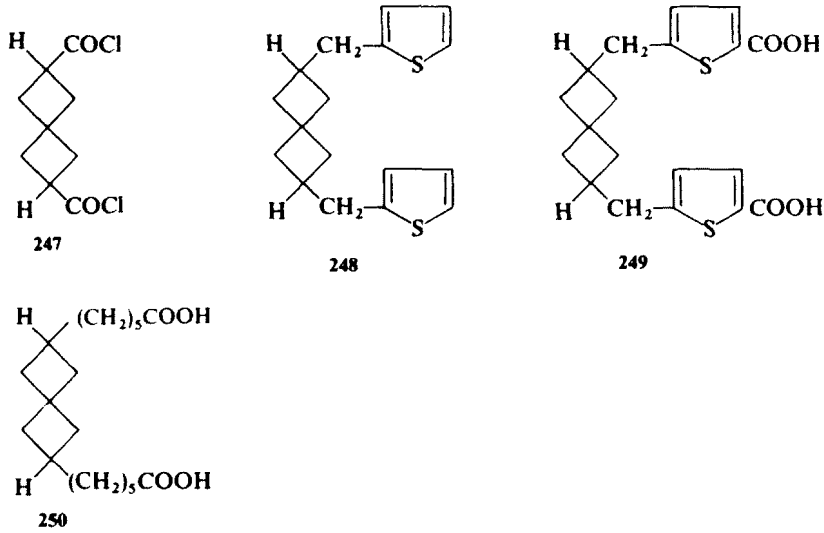


246

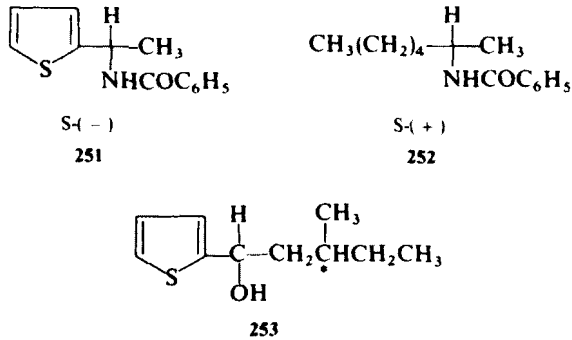
4. Preparation of Optically Active Thiophenes from Chiral Precursors

Another example of the use of Raney-nickel desulfurization for the preparation of aliphatic optically active compounds, in connection with attempts to assign the absolute configuration of Fecht's acid, is shown in Scheme 13.



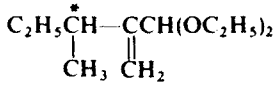
Scheme 13

The optically active acid chloride **247**, derived from Fecht's acid, was used for acylating thiophene, and the resulting ketone was reduced to **248**. Formylation, followed by oxidation, yielded optically active **249**, which was desulfurized to optically active **250**.[1642] The absolute configuration of *S*(−)-methyl 2-thienylmethylamine, prepared by asymmetric synthesis, has been established by desulfurization of its benzoyl derivative **251** to **252**.[1643] Optically active **253** was prepared through the reaction of 2-thiophene aldehyde with the Grignard reagent derived form 1-iodo-2-methylbutane. Treatment of **253** with 47% HBr gave the bromine derivative, which still showed optical activity, and on Raney-nickel desulfurization it was converted to partially racemized 3-methylnonane.

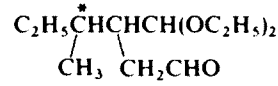


It is not clear whether racemization occurred during the formation of the bromine derivative, or on Raney-nickel desulfurization.[1644] Hydroformylation of optically active **254** gave exclusively **255**, which, on ring closure with

hydrogen sulfide in methanolic hydrogen chloride, gave the optically active 3-substituted thiophene **256**. Compound **255** could also be oxidized to a mixture of (*R,S*)- and *S,S*-*sec*-butylsuccinic acid, the sodium salt of which was ring-closed to (+)-**256** on treatment with P_4S_{10}. Finally, (+)-**256** was also obtained by the reaction of **257** with hydrogen sulfide in barium hydroxide.[1645] Ozonization of **256** gave (+)-*S*-2-methylbutanoic acid of 65% purity, and evidence was given that the racemization occurred in the ring closure of **255** to **256**.



254



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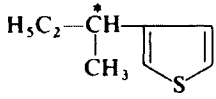

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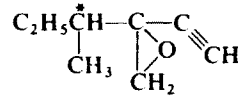
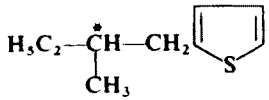


257

Even lower optical yields were obtained in the other two ring-closure reactions.[1645] The most convenient method for the synthesis of optically active **258** was the nickel-catalyzed cross-coupling of 2-chlorothiophene with the Grignard reagent derived from **259**. The optical purity obtained was 82%.[1646] Ethyl β-dimethylaminobutyrate derived from L-(+)-alanine gave compound **260** on reaction with 2-thienyllithium. Compound **260** was dehydrated by dry hydrogen chloride to (−)-**261a**. The analgesically active (+)-isomer is therefore related to D-(−)-alanine. Ethyl β-dietylaminobutyrate derived from D-(−)alanine was similarly transformed to the analgesically active (+)-**261b**.[1647] Other thiophene derivatives of pharmacologic interest, which have been obtained in optically active forms, are **262**, prepared from 2-thiophene carboxaldehyde and *d*-1-phenyl-2-aminopropane[1648] and **263**.[1649]



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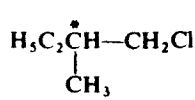

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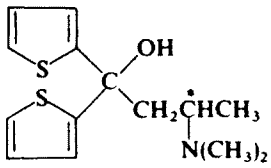

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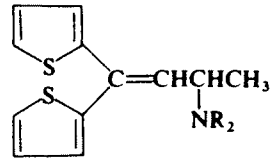
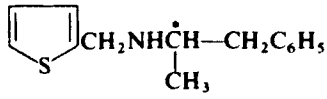


a R = CH_3
b C_2H_5

261



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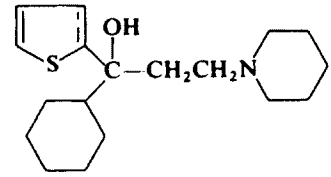
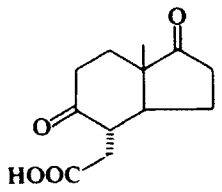


263

The reaction of 2- and 3-thiophene magnesium bromide with optically active **264** gave the chiral thienyllactones **265**. They were converted through multistep reactions to modified steroids in which the A ring is thiophene.[1650] From 2,5-dimethyl-3-thienyllithium and (−)-menthone, dextrorotatory **266** (X = H) was obtained. In a similar way, dextrorotatory **266** (X = Br) was obtained from 2,5-dimethyl-3,4-dibromothiophene, which on halogen–metal exchange, followed by reaction with carbon dioxide, gave dextrorotatory **266** (X = COOH). (+)-3-(1-Menthene)-thiophene was similarly prepared from 3-bromothiophene.[1651] Halogen–metal exchange of **266** (X = Br) with butyllithium at room temperature leads to ring opening of the 4-lithio derivative, and optically active **267** was obtained.[1652]



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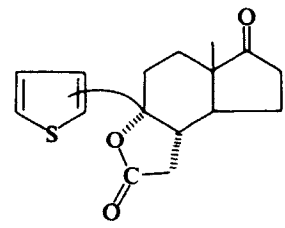

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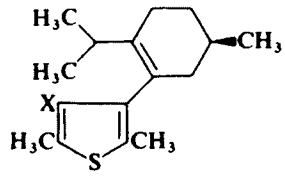
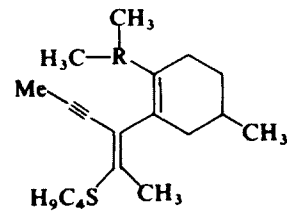


X = H, Br, COOH

266



R = CH_3; R = $CH(CH_3)_2$

267

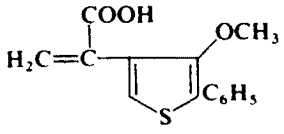
5. Enzymatic Resolution of Thiophene Derivatives

β-2-Thienylalanine has been resolved by beef pancreatic carboxypeptidase on the chloroacetylated derivative[1653,1654] and on carbobenzyloxyglycyl-β-2-thienyl-L-alanine. Both β-2-thienyl-L-alanine and β-2-thienyl-D-alanine have

been obtained by the action of papaine of *N*-acetyl-β-2-thienylalanine *p*-toluidide.[1655] A detailed description is given in Biochemical Preparations.[1656] *S*(−)-β-(2-Thienyl)ethanol amine has been synthesized by the D-hydroxynitrile-lyase-catalyzed addition of hydrogen cyanide to 2-thiophenecarboxaldehyde, followed by reduction of the hydroxy nitrile with lithium aluminum hydride.[1658,1659]

6. Optically Active Thiophenes by Asymmetric Syntheses

Early work on asymmetric synthesis was carried out by Červinka and coworkers, who, by using lithium aluminum hydride (−)-quinine or lithium aluminum deuteride quinine, reduced 2-acetylthiophene to optically active methyl 2-thienylcarbinol. However, the optical purity was only 16%.[1633,1643] Catalytic hydrogenation of **268**, using a chiral rhodium catalyst (DIOP) (Kagan's catalyst), gave (+)-**269** in an optical purity of 88% in almost quantitative yield.[1660] Compound **269** could also be resolved into its enantiomers in conventional ways using salt formation with cinchonidine for obtaining the (−)-form and (−)-α-phenylethylamine for obtaining the (+)-form. The same chiral rhodium catalyst was also used for the hydrogenation of the *Z*-form **270** to give **271** in up to 78% enantiomeric excess. Using (+)- and (−)-DIOP, both enantiomers were obtained.[1661] Better enantiomeric excess was obtained with acetamido than with benzamido derivatives. The 3-thienyl analog of **271** has also been prepared by catalytic hydrogenation with DIOP, albeit with low enantiomeric excess.[1662]



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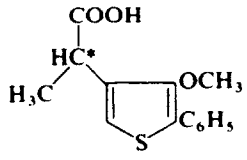

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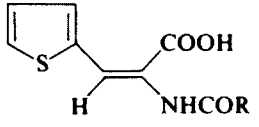
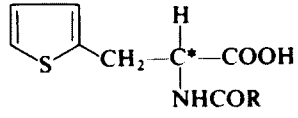


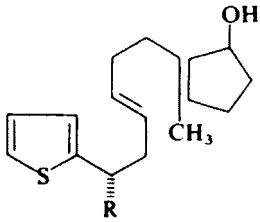
R = C_6H_5, CH_3

270



271

High asymmetric induction has been observed in the synthesis of thiophene-containing steroid-like molecules via olefinic cyclizations catalyzed by $SnCl_4$, as in the formation of **273** from **272**.[1633–1665]



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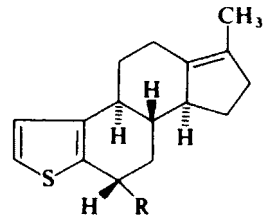


273

7. ORD and CD Spectra of Thiophenes

In early work on the dependence of optical rotatory power on chemical constitution, Kenyon and coworkers studied the ORD curve of (−)-2-thienylmethylcarbinol.[1638] After the introduction of modern equipment for ORD measurements, thienyl-substituted mono and dicarboxylic acids, such as **220–226**, were investigated. They all showed plain dispersion curves, which could be used for establishing configurational relationships.[1666] Compounds that gave plain curves, such as (−)-thienylglycine and (−)-phenylglycine, were converted to dithiocarbamates, which showed anomalous Cotton effects at 330 nm, indicating that both acids belong to the D-series.[1274] The ORD spectra of (−)-β-(2-thienyl)ethanolamine and (−)-β-(2-furyl)ethanolamine have been compared. The former shows a positive Cotton effect around 235 nm; the latter, at 220 nm. The negative ORD curves in the near-UV and visible region indicate the presence of strong negative Cotton effects below 190 nm.[1659]

The CD spectra of (−)-**229a** and (−)-**231a** have been compared with that of (−)-mandelic acid. The CD spectra of the acidic forms of all three acids exhibit two negative effects, or a negative band with a shoulder, between 200 and 250 nm, and a positive band is situated at shorter wavelengths. Compound **231a** and mandelic acid have in addition positive bands at longer wavelengths. The spectra of the anions were different from those of the corresponding acids. The origin of the different Cotton effects has been discussed in some detail.[1341] The CD spectra of 2- and 3-α-methoxythienylacetic acids are very similar to those of the corresponding hydroxy acids. Substitution of both *ortho*-positions of the aromatic ring in α-methoxy-3-thienylacetic acid **230c** significantly influenced the CD spectrum.[1667] In order to determine the absolute configuration of especially **230c**, the CD spectra of the complexes of the α-methoxy-3-thienylacetic acids with $Mo_2(CH_3CO_2)_4$ were studied. They were all found to possess the *S*-configuration.[1668]

Great similarities between the CD spectra of α-methoxy-3-thienylacetic acids and those of comparable 3-cyclohexenylthiophenes and 3,3′-bithienyls were observed.[1667] The CD spectra of optically active 3-(1-cyclohexenyl)thiophenes, such as **233** and **266**, have been discussed in detail.[1630,1651]

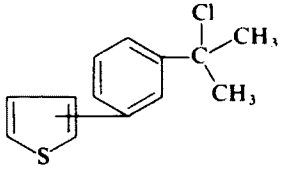
XVII. FREE-ENERGY RELATIONSHIPS IN THE THIOPHENE SERIES

1. Introduction

Over the years, there have been many attempts to correlate chemical equilibria, chemical reactivity, and physical properties, such as NMR parameters and IR data, with one-parameter equations of the Hammett type or by using several-parameter equations of the Yukawa–Tsuno or Swain–Lupton type. The application of the Hammett and related equations to thiophenes and other heterocyclic systems has been reviewed several times, most recently in 1976.[1669-1673] In the following the effect of the thienyl groups as substituents on benzene will be discussed. Subsequently different treatments of side-chain reactivity and substitution reactions in thiophenes will be dealt with. Finally, various correlations of physical properties will be discussed.

2. Thienyl as Substituent on Benzenes

The ionization constants of *p*- and *m*-2- and 3-thienylbenzoic acids and phenols have been determined in aqueous ethanol at 25°C[1674]. The substituent constants σ_p and σ_m were obtained from the former class of compounds, and σ_p^- and σ_m^- from the phenols. The σ-values are given in Table 70. In order to obtain σ_p^+ and σ_m^+-values for the 2-thienyl and 3-thienyl groups as substituents on benzene, the rates of solvolysis in 90% aqueous acetone of 2-chloro-2-[*m*](or *p*)-2- (or 3)-thienylphenylpropanes, **274** and **275**,[1675] and the solvolyses of **276** and **277** in 30% aqueous ethanol[1676] were measured. The σ_p^+ and σ_m^+ constants were calculated by use of the Brown–Okamoto equation. However, it was found that



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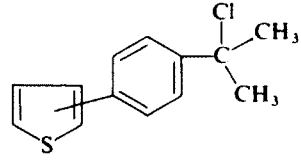

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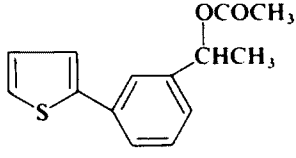

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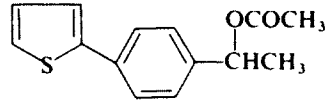

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TABLE 70. σ-Values for 2- and 3-Thienyl Groups

σ-Values	2-Thienyl	3-Thienyl	Reaction
σ_m	0.09	0.03	Ionization of benzoic acids
σ_p	0.05	− 0.02	
σ_m^-	0.11	0.07	Ionization of phenols
σ_p^-	0.19	0.13	
σ_m^+	0.16	0.08	Solvolysis of phenyldimethyl carbonyl chlorides
σ_p^+	− 0.43	− 0.38	
σ_m^+	0.15		Solvolysis of 1-arylethylacetate
σ_p^+	− 0.33	—	
σ_m^+	0.15	—	IR carbonyl stretching frequencies
σ_p^+	− 0.38	-	of substituted acetophenones

the σ_p^+-value for the 2-thienyl group obtained from these two types of reactions was not constant. Furthermore, the σ_p^+-values calculated for the 2-thienyl group from the carbonyl stretching frequencies of thienyl-substituted acetones by applying the Traylor–Ware correlation were different. This behavior is analogous to that of other polarizable groups, especially other aromatic substituents. However, in the 2-thienyl case, contrary to what has been observed for other related groups, the σ_p^+-value does not become increasingly negative as ρ becomes larger. It was suggested that this anomaly would probably disappear if the Yukawa–Tsuno equation were used. It is also clear from the various σ-constants that the thienyl groups fall in the small category of substituents that can both accept and donate electrons according to the demands of the reaction.[1674-1676]

3. Hammett-Type Correlations in Substituted Thiophenes

In the 1950s, especially Imoto and coworkers applied the Hammett equation to acid constants of 5-substituted 2-thiophenecarboxylic acids and 2-thiopheneacetic acids, the rates of esterification, and the hydrolysis of 5-substituted methyl and ethyl thenoates.[223,1678-1685] From these studies it was concluded that the same substituent constants (σ_p) and reaction constants (ρ) could be used. Similar conclusions were also drawn from the measured rates of side-chain bromination of 5-substituted 2-acetylthiophenes[1686] and from the acetoxymercuration of 2-substituted thiophenes,[1687] the decomposition of 5,5′-substituted bis(2-thenoyl)peroxides,[1688] and the polarographic reduction of substituted nitrothiophenes and thiophene aldehydes.[1689-1694]

In the same way, the reactivities of 4-substituted 2-thiophenecarboxylic acids and their esters were correlated, using the same σ_m-values and ρ as in the

benzene series, while this attempt failed with 5-substituted 3-thiophenecarboxylic acids.[1685,1695] However, only a very limited number of substituents, such as alkyl groups, halogens, and electron-attracting groups, such as nitro and formyl, were used. It was pointed out as early as 1963[1669] that these investigations do not prove the general applicability of the Hammett equation using σ- and ρ-constants of the benzene series. Large deviations could be expected for strongly electron-donating groups, such as OCH_3 and NH_2, as was observed on attempted Hammett correlation of 5-proton shifts in 2-substituted thiophenes.[1696]

In later investigations, two different approaches have been made. One uses the σ-constants from the benzene series, and the resulting ρ-values, which differ from those for the corresponding benzenoid side-chain reactions, are then discussed in terms of the intensity of transmission of substituent effects. In the other approach, the same ρ-values as in the benzene series are used, and σ-values for the thiophene series are calculated. Finally, attempts have also been made to build up independent ρ- and σ-values in the thiophene series, in analogy with the benzene series, starting with the dissociation constants of thiophenecarboxylic acids. Thus, from the dissociation constants of a series of 4- and 5-substituted 2-thiophenecarboxylic acids, the σ-values given in Table 71 were calculated, using the same ρ-values as in the benzene series in the same solvents.[1697]

TABLE 71. Experimental σ-Values from 5- and 4-Substituted 2-Thiophenecarboxylic Acids[1697,1700]

Substituent	Calculated	$\sigma_{\text{Ref. 9939}}$	$\sigma_{\text{Ref. 9616}}$	$\sigma_{\text{Ref. 127}}$	σ	$\sigma_{\text{Ref. 1698}}$ Calculated
5-OCH_3	− 0.24	− 0.225	− 0.27			
5-CH_3	− 0.17	− 0.167	− 0.15	− 0.09		
5-C_2H_5			− 0.16			
5-t-C_4H_9			− 0.17			
5-C_6H_5			0.02			
2-CO_2^-			0.02			
2-F		0.187				
2-Br	0.28		0.30	0.36		
2-Cl	0.27	0.276	0.30	0.33		
2-CH_3CO			0.55			
2-COOH			0.59			
2-NO_2	0.85	0.997	0.81	0.72		
4-$COCH_3$	0.12					
4-CH_3	− 0.07				− 0.07	
4-Br					0.38	
4-NO_2					0.66	
3-Cl						0.40
3-Br						0.41

It is rather surprising that only small deviations from the corresponding σ_p and σ_m of the benzene series were obtained. The values were also in good agreement with those obtained by the method of Dewar and Grisdale,[1677]

according to which $\sigma = (F/r) + M_q$, where F and M are found for a given substituent by interpolation in the benzenoid system, r is the distance between substituent and reaction site, and q is a quantum-mechanical parameter, defining the propagation of the resonance effect.

The transmission of substituent effects through the thiophene and furan rings has been evaluated through a study of the rate of reduction of 2-benzoylthiophenes and 2-benzoylfurans. Variation of the 5-substituent (OCH_3, CH_3, Br, NO_2) in the thiophene gave a very good plot of log rate against σ_p. The correlation was not improved using the Yukawa–Tsuno equation. It was also clear from the results that 4- or 5-substituents in the heterocyclic rings have substantially greater effects on the rate than do the corresponding meta or para substituents in the benzene rings and, thus, that the transmission of substituent effects through the thiophene and furan rings is indeed greater than through the benzene ring.[1698] Application of the Dewar–Grisdale equation leads to the calculated values given in Table 71.[1698] The rate of reaction of 5-methoxy-, 5-methyl, 5-chloro-, and 5-nitro-2-thenoyl chloride with aniline was measured in benzene at different temperatures. Use of the Hammett equation, using σ_p-values, gave a ρ-value of 1.79, much greater than for the benzoylation of aniline (ρ = 1.219, 1.42), which was taken as evidence for the more efficient relay of electronic effects from the substituent to the reaction center through the thiophene ring than the benzene ring.[1699] On the other hand, it was stated from a study of the rates of alkaline hydrolysis of substituted 2-thiophenecarboxylic esters (methyl, chloro, bromo, and nitro) that they could be adequately related by a set of substituent constants σ_{th}, which were rather similar to σ_m in the benzene series.[1700] However, it is obvious that the differences between σ_m and σ_p are not very pronounced for these substituents. In any case, both the acidic hydrolysis of the same esters and the chemical shifts of the methyl protons of 5-substituted 2-methylthiophenes showed large deviations from the relation.[1700] Another set of σ_{th} values has been determined from dissociation constants in water at 49.5°C.[1701] From the deviations it was concluded that there cannot be a simple accurate relationship between substituent effects in benzene vis à vis substituent effects in 5-substituted 2-thiophenes, especially those with electron-withdrawing groups.[1702] The deviation in the Hammett plot, caused by halo substituents in the thenilic acid rearrangement, could be understood on this basis.[1701] In most cases, however, σ-values for the 2- and 3-thienyl groups, as well as substituted thienyl groups, have been determined by establishing a Hammett-type relationship in the benzene series for a certain reaction, equilibrium, or physical property, and then measuring the same with the thiophene derivative. The reactions include the protonation of 5-substituted 2-thiophenecarboxamides,[1444,1675] the acid dissociation of arenesulfonamides,[1703,1704] hydrogen exchange,[1705] the reaction of 2-thenoyl chlorides with anilines,[1706,1707] the reaction of β-2-thienylacryloyl chlorides with anilines,[1708] E2 eliminations from 2-thienylethyl bromides promoted by sodium ethoxide in ethanol,[1709] the solvolysis[1710,1711] and pyrolysis[1712] of 1-aryletylacetates, the solvolytic rearrangement of 2-arylethyl tosylates,[1713] the

solvolysis of 1-(thienyl)-*p*-nitrobenzoates,[1714,1715] the base-catalyzed reaction of 2-thiophenecarboxaldehydes with acetonitriles,[1716] and acid- and base-catalyzed hydrolysis rates of ethyl 2- and 3-thiophenecarboxylates.[1700] Especially Marino and coworkers have carried out extensive and important work on the correlation of electrophilic aromatic reactivity.[1716-1720]

Isomer distributions were determined for bromination by Br_2 and Br^+, chlorination, tin tetrachloride or iodine-catalyzed acetylation by acetic anhydride, trifluoroacetylation with acetyl trifluoroacetate, and Vilsmeyer formylation. From the α : β ratios and other data from the literature it was possible to test the applicability of linear free-energy treatments at the α- and β-positions of thiophene. Plots of log α_f and log β_f against ρ for nine reactions were linear, and from the slopes values of $\sigma_\alpha^+ = -0.79$ and $\sigma_\beta^+ = -0.52$ were obtained. The linearity was used as an argument for the similar characters of the transition states for substitution at thiophene and benzene rings.[1717] However, certain electrophilic substitutions, such as nitration, mercuration, and protodimercuriation, do not correlate well with these σ_α and σ_β values. Reasons for this have been discussed[1714] (see also Table 72).

TABLE 72. σ^+-Values for the 2- and 3-Positions of Thiophene Evaluated for Different Reactions

Reaction	$\sigma_{2\text{-Th}^+}$	$\sigma_{3\text{-Th}^+}$	Ref.
Thermolysis of 1-arylethyl acetates	− 0.68	− 0.24	1721
	− 0.79	− 0.38	1722
Various electrophilic substitutions	− 0.79	− 0.52	1714
Photodesilylation	− 0.79	− 0.60	1723
Iododebromination	− 0.84	− 0.60	1724
Bromination	0.80		1725
Protodetritiation	− 0.87	− 0.50	1726
Solvolysis of 1-arylethyl acetates	− 0.84	− 0.47	1710
Solvolysis of 1-arylethyl *p*-nitrobenzoates	− 0.80	− 0.47	1714
Isomerization of *cis*-1-aryl-2-phenylethene	− 0.80	− 0.47	"
Protodebromination	− 1.20	− 0.78	1727

4. Ortho Correlations in the Thiophene Series

The larger angles between ortho-related substituents in thiophenes make steric factors less important and therefore allow for linear free-energy ortho-correlations in the thiophene series. Thus, the acid dissociation constants of 10 or more 3-substituted 2-thiophenecarboxylic acids[1667] and 2-substituted 3-thiophenecarboxylic acids[1722] have been measured in water at 25°C, and correlated with the acid dissociation constants of other substituted thiophenecarboxylic acids and *para*-substituted benzoic acids. The best correlations were obtained with the Yukawa–Tsuno-type equation. The following correlations

were observed for the two 2,3-series of *ortho*-substituted thiophenecarboxylic acids.

$$(-\Delta pK_a)_{3\text{-X-2-COOH}} = 1.34(\sigma^n + 0.57\,\Delta\sigma_R^+) \qquad (R = 0.996)$$

$$(-\Delta pK_a)_{2\text{-X-3-COOH}} = 1.80(\sigma_n + 0.32\,\Delta\sigma_R^+) \qquad (R = 0.996)$$

The dissociation constants of some 4-substituted 3-thiophenecarboxylic acids were also obtained under the same conditions and tentatively correlated with various kinds of substituent constants. The best correlations were observed with σ_m values, specifically, with substituent constants that include a low, but significant, resonance effect ($\sigma_m = \sigma_I + 1/3\sigma_R$).[1728] Linear correlations of the pK_a values in the three different *o*-substituted thiophenecarboxylic acid series and with 5-substituted 2-thiophenecarboxylic acid clearly showed the greater transmittance of the substitutent effect in the 3-substituted 2-thiophenecarboxylic acids (1.72 times) and 2-substituted 3-thiophenecarboxylic acids (1.82 times; hyperortho relation) than in the 4-substituted 3-thiophenecarboxylic acids (hypoortho relation). The transmittance in the latter series was approximately the same (1.10 times) as for 5-substituted 2-thiophenecarboxylic acids.[1728]

The rate constants for alkaline hydrolysis of some methyl 3-substituted 2-thiophenecarboxylates in methanol–water (80% v/v) have been determined. The logarithms of the rate constants gave an excellent straight line when plotted against the pK_a values of the corresponding acids (slope 1.91), and in contrast to the hydrolysis of *ortho*-substituted methyl benzoates, obeyed an equation of the Yukawa–Tsuno type (ρ + 2.77, r^+ 0.44, $R = 0.996$).[1729]

Similarly, when the logarithms of the rate constants for the alkaline hydrolysis of 11 methyl esters of 2-substituted 3-thiophenecarboxylic acids (X = OCH_3, CH_3, SCH_3, H, F, Cl, Br, I, $SOCH_3$, CN, SO_2CH_3) were plotted against σ^H and $-\Delta pK_a$, linear free-energy ortho-correlations were obtained, thus giving additional evidence for the much smaller steric effects in ortho-like substituted thiophenes than benzenes.[1730] On the other hand, somewhat unexpectedly, the logarithms of the rate constants ($\log k$) of the alkaline hydrolysis of methyl esters of 4-substituted 3-thiophenecarboxylic acid gave only fair correlations with σ_p, σ_m, or σ^n, and an unsatisfactory correlation with σ_I. The best linear free-energy correlation was observed by plotting $-\log k$ against—ΔpK_a of the corresponding 4-substituted 3-thiophenecarboxylic acids. Better correlations were obtained when bulky substituents, such as SO_2CH_3, were excluded, indicating that in the 3,4-substituted case steric factors play a role, in spite of the fact that the distances between the substituent and the reaction centre in the 3,4-substituted case is larger than in the 2,3-substituted case, where no steric effects were observed. This was ascribed to through-conjugation in the latter case. However, the ρ-values obtained further confirmed the hypoortho character of the 3,4-relation.[1731]

Another reaction for which linear free-energy ortho-correlations were observed was the esterification of 3-substituted 2-thiophenecarboxylic acids[1732]

and of 2- and 4-substituted 3-thiophenecarboxylic acids[1733] with diazodiphenylmethane. Again, linear correlations were obtained with σ^H in the 2,3-related series, giving ρ-values of 1.31 and 1.38, respectively, while deviations were observed for the 3,4-related series, giving correlation with σ^n and a ρ-value of 1.10. The weaker transmittance of substituent effects in the 3,4-series compared to the 2,3-series was again evident from the correlation between the log of the rates:

$$\log\left[\frac{k}{k_H}\right]_{4-X} = 0.70 \log\left[\frac{k}{k_H}\right]_{2-X}$$

5. Linear Free-Energy Correlations in Nucleophilic Substitution of Thiophenes

Linear free-energy correlations have been extensively studied in nucleophilic aromatic substitution of thiophenes. A good fit for the Hammett equation was found for the reaction between piperidine and several 2-bromo-3-nitro-5-X-thiophenes (X = H, Br, $CO_2C_2H_5$, $CONH_2$, SO_2CH_3, CN, $SO_2OC_6H_5$, NO_2) in ethanol. A highly positive ρ-value (+3.21) was obtained.[1734] The rates of nucleophilic substitution of bromine on 3-bromo-2-nitrothiophene and 2-bromo-3-nitrothiophene by *ortho*-, *meta*-, and *para*-substituted thiophene-oxide ions were measured in methanol. Plots of log k against σ^--constants have ρ-values of -0.78 and -0.76, respectively.[1735] The rate constants of debromination of 2-bromo-3,5-dinitrothiophene by various *meta*- and *para*-substituted anilines in methanol were analyzed by the Yukawa–Tsuno equation:

$$\log\frac{k}{k_H} = r(\sigma^n + r^+\Delta\sigma_R^+ + r^-\Delta\sigma_R^-)$$

where r (-3.00), r^- (0.99), and r^+ (0.38) values were obtained and discussed.[1736] Also the rates of anilinodebromination of 2-bromo-3,5-dinitrothiophene by some *ortho*-substituted anilines have been measured in methanol.[1737] The kinetic results were treated according to the multiparameter analysis of ortho effects proposed by Fujita and Nishoka.

The absence of significant steric effects in ortho-substituted thiophenes made it possible to obtain linear free-energy ortho-correlations in aromatic nucleophilic substitution. Thus, the logarithm of the rate constants of the piperidino-debromination of some 2-bromo-3-X-5-nitrothiophenes (X = Me, H, Br, $CONH_2$, CO_2Me, SO_2Me, CN, NO_2) could be correlated against σ_p^- and against the logarithm of the rate constant of piperidino-debromination for the corresponding 2-bromo-3-nitro-5-X-thiophenes. The $\rho_{2,3}$ value (+4.02) and the ratio $\rho_{2,3}/\rho_{2,5}$ (1.18) gave evidence for the larger transmission of electronic effects between the 2- and 3-positions, than between the 2- and 5-positions of

the thiophene ring.[1751] In order to obtain information on the transmission of substituent effects through the 2,3-position compared to the 3,4-positions, the rates of the reactions of some 3-bromo-2-nitro-4-X-thiophenes and 3-bromo-4-nitro-2-X-thiophenes with sodium benzenethiolate were measured. The correlation of the log k values of the first series with σ^- constants and of the second series with σ_p^- constants, together with the ρ-values obtained (+3.95 and 8.18, respectively), confirm the low conjugative effect from position 2 on position 3 of the thiophene ring.[1738] The rates of piperidinodebromination of some 2-bromo-3-nitro-5-X-substituted thiophenes and 2-bromo-4-methyl-3-nitro-5-X-substituted thiophenes in methanol have been measured. The results showed that the Hammett equation could also be applied to tetrasubstituted thiophenes.[1739] In a recent paper, the rate of piperidino-debromination of 2-bromo-3-X-4-methyl-5-nitrothiophenes (X = Me, H, Br, $CONH_2$, CO_2Me, SO_2Ne, CN, NO_2) have been measured in methanol. The logarithm of the rate constants gave excellent correlations against ρ^- (except for X = Br and $CONH_2$), again confirming the applicability of Hammett-type relationships to fully ortho tetrasubstituted thiophene derivatives.[1740]

The rates and equilibrium constants for the formation of the Meisenheimer-type adducts from some 2-methoxy-3-nitro-5-X-thiophenes and sodium methoxide in methanol have been measured at various temperatures. The absence of linear correlations between log K_c or log k_1 and σ_p^- interpreted as an effect of the hyperortho relation in the thiophene ring.[1741]

6. Various Correlations

A correlation between the logarithms of the protophilic deuterium exchange rate constants in the 3-position of the thiophene ring and its methyl derivatives and Hammett's σ-constants has been established. A correlation between Taft's σ^*-constants and the kinetic data for deuterium exchange in the 2-position of thiophene and its methyl and methoxy derivatives was also obtained.[1742] The logarithms of the rate constants of the hydroxide-catalyzed detritiation of 4- and 5-substituted 2-(^{3}H-acetyl)thiophenes could be correlated with Hammett's σ-values. However, the reaction constant ρ (1.61) was considerably higher than the value (1.03) obtained for the corresponding acetophenones.[1743] The apparent pK_a values of 4-methyl-2-thiophenecarboxylic acids and 5-methyl-3-thiophenecarboxylic acids substituted in the side chain in 80% methyl cellosolve have been correlated with σ_I-constants, using the Hammett equation. Then ρ-values of -0.772 and -0.499, respectively, were obtained.[1744] They were also compared with the corresponding pK_a values obtained for the 5-methyl-2-thiophenecarboxylic acids substituted in the methyl group.[1745]

The aromatic 2-thenoyloxylation with 2-thenoyl peroxide in the presence of cupric chloride followed the Hammett equation. A plot of the partial rate factors of meta- and para-positions versus σ^- constants gave a ρ-value of -1.96.[1746]

7. Linear Correlations between Physical Properties and Substituent Constants

A. IR Stretching Frequencies

Several groups have found various correlations with IR frequencies, especially C=O stretching frequencies. Statistically significant correlations were obtained between σ^+ and the C=O stretching frequency of 1-phenyl-3-(5-aryl-2-thienyl)propenones.[1747] Hammett correlations between the C=O stretching frequencies and substituent constants for a series of 5-phenyl-2-thiophenecarboxaldehydes, 2-(5-phenyl-2-thenylidene)-1,3-indandiones,[1198] and 2-(5-phenyl-2-thenylidene)-4,7-dithia-4,5,6,7-tetrahydro-1,3-indandione[1199] have been found, and the transmission of substituent effects through the thiophene ring was compared with that of the benzene and furan rings. Hammett relations were also observed for the C=O and C—Br frequencies of 2,3-dibromo-1-aryl-3-(2-thienyl)propanone-1-enes and 2,3-dibromo-1-(2-thienyl)-3-arylpropanone-1-ene.[784] Wavenumbers of the C=O stretching fundamentals in a series of 145 conformers of aromatic α,β-unsaturated carbonyl and arylfurancarbonyl compounds, including thiophene derivatives, were investigated with the Yukawa–Tsuno structure–reactivity equation.[1210] The C=O stretching frequency data for (4-substituted methyl)-2-thiophenecarboxylic acids and (2-substituted methyl)-4-thiophenecarboxylic acids correlated reasonably well with σ_I-values.[927]

Infrared intensities of ring stretching bands for 2-substituted thiophenes have been correlated with σ_R°-constants, and provide evidence for the electronic interactions within these compounds.[1175,1748] The σ^*-inductive constants of 5-substituted 2-thienyl groups have been calculated from experimental Si—Cl stretching frequencies.[1250] The shifts in the frequencies of the stretching vibrations of the hydroxyl group of phenol and pentachlorophenol that arise during the formation of hydrogen bonds with a number of 2-acetylthiophenes[1197] and 2-thenylideneacetone[1209] were subjected to correlation analysis, using Hammett, Brown, Taft, Yukawa, and Swain–Lupton equations.

B. NMR Chemical Shifts

Various one- and two-parameter correlations of proton, ^{13}C-, and ^{19}F-chemical shifts with substituent constants have been carried out.[135,651–654,660,808,811,875,923,927,929,938,950,951,1001] Especially successful was the application of the Swain–Lupton equation. For more details, see Section XI.3.

C. Various Correlations

The molecular ionization potentials of a number of substituted thiophenes and other five-membered heterocycles have been determined by the electron-impact technique. The ρ-values for this reaction was more negative than that for the most selective electrophilic substitutions.[1595] Linear correlation between Taft's σ^* and the limiting activity coefficients of thiophene and benzene has been observed in a study of the effect of the structure of polar solvents on their selectivity in the system thiophene–benzene.[1749] A log P value of $+1.81$ has been obtained for thiophene in a study of substituent constants for aliphatic functions obtained from partition coefficients.[1750]

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CHAPTER II

Nucleophilic Substitution of Thiophene Derivatives

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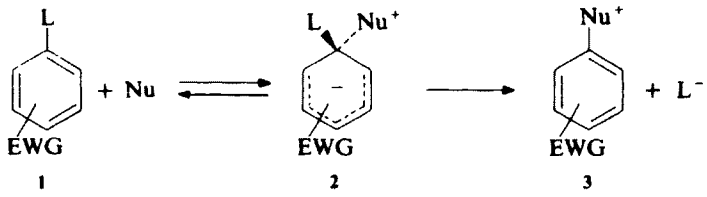
I. INTRODUCTION

1. The Mechanisms of Nucleophilic Substitutions

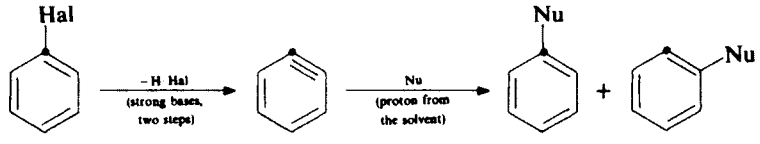
It has been shown that the nucleophilic substitutions of aromatic and heteroaromatic compounds proceed mainly through the following reaction pathways*: (1) the attachment–detachment mechanism (S_NAr mechanism; Scheme 1),[21–28] (2) the elimination–addition mechanism occurring via aryne or hetaryne (Schemes 2 and 3),[11,29–34] and (3) the reductively activated nucleophilic substitution mechanism ($S_{RN}1$ mechanism, Scheme 4).[35–39]



1 2 3

L = leaving group
EWG = electron-withdrawing group
Nu = nucleophile

Scheme 1

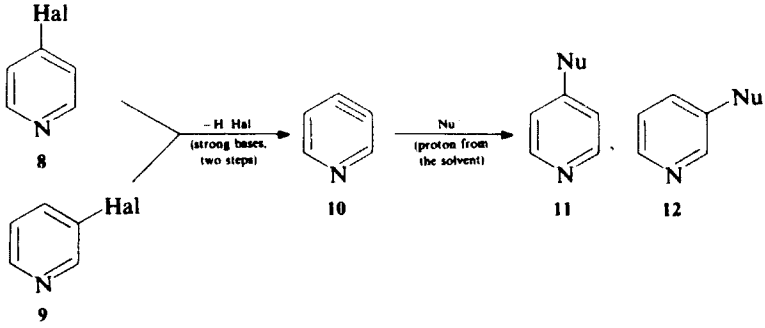


4 5 6 7

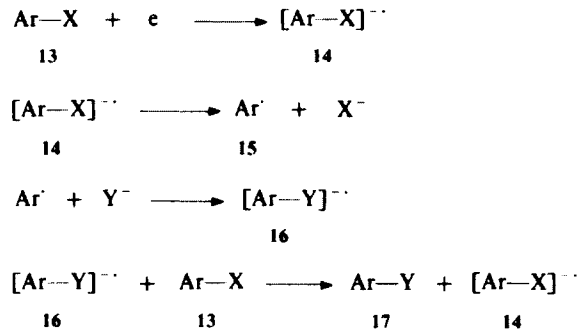
Hal = halogen

Scheme 2

* Other mechanisms are possible for nucleophilic substitution reactions in carbocyclic and heterocyclic compounds, e.g., the S_N1 mechanism (peculiar to diazonium cations),[1–3] the BCHD (*b*ase-*c*atalyzed *h*alogen *d*ance) mechanism (a reaction pathway involving a series of positive halogen transfers to aryl anions),[4] the AE_a (*a*bnormal *a*ddition–*e*limination) mechanism,[5–10] the ASE (*a*ddition–*s*ubstitution–*e*limination) mechanism (observed in five- and six-membered heterocycles able to give products of covalent addition with nucleophiles),[11–18] and the ANRORC (*a*ddition of *n*ucleophile followed by *r*ing *o*pening and *r*ing *c*losure) mechanism[19,20] (proposed for reactions of nitrogen containing six-membered ring heterocycles).



Scheme 3



Scheme 4

Concerning the nature of the substitution products obtained, three different situations can be observed: (a) *ipso*-substitution (i.e., the nucleophile forms a bond with the atom previously linked to the leaving group), (b) *cine*-substitution (i.e., the nucleophile attacks an atom near to that which bears the leaving group), and (c) *tele*-substitution (i.e., the nucleophile attacks an atom far from that which bears the leaving group).

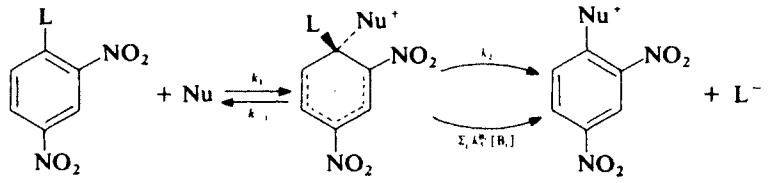
The nucleophilic substitutions of thiophene compounds include many examples of S_NAr and a few cases of $S_{RN}1$ reactions: on the other hand, evidence for reactions occurring via thiophyne intermediate (presumably 2,3-didehydrothiophene) have been obtained only through flash vacuum thermolysis (FVT) studies and plasmolysis experiments on the anhydride of 2,3-thiophenedicarboxylic acid.[40] This kind of reaction mechanism is well documented by the review by M. G. Reinecke.[34] There are also some reports concerning reactions that probably occur through the ASE mechanism (see also Section III.2.E.a.).[41]

Reaction products of *ipso*-, *cine*-, and *tele*-substitution have all been observed in thiophene series. The relevant reaction mechanisms will be discussed later.

2. The Mechanism of S_NAr Reactions

The review by Bunnett and Zahler[21] on nucleophilic substitution reactions formed the basis of the present knowledge by replacing the aromatic S_N2 mechanism put forward by Chapman et al.[22,23] The most important contributions in this field have to be ascribed to Bunnett, Bernasconi, and their coworkers.

The S_NAr mechanism consists of many steps and can be sketched as shown in Scheme 5.



18 19 20

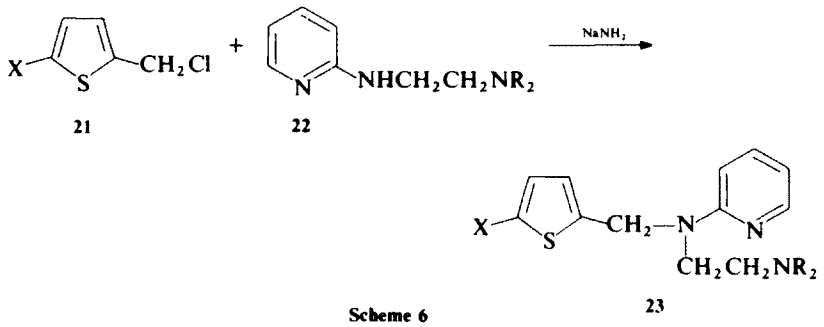
Scheme 5

The first step usually is rate-determining but the evolution of σ-complex in the reactions involving neutral nucleophiles can be a multistep base-catalyzed pathway (see Section II.4). The mechanism first proposed by Bunnett and Zahler recalls in some respects the arenium ion mechanism of aromatic electrophilic substitutions (S_EAr), and much information collected for S_EAr[42–44] have been used to study S_NAr reactions. Among the numerous pieces of evidence for the S_NAr mechanism, the leaving-group effect on the reaction rate,[45–47] the isolation of Meisenheimer adducts that resemble the intermediate σ-complexes,[21,24,48–56] the pattern of base catalysis in reactions involving amines as nucleophiles,[28,57,58] and the substituent effects represent compelling proofs.[59–63]

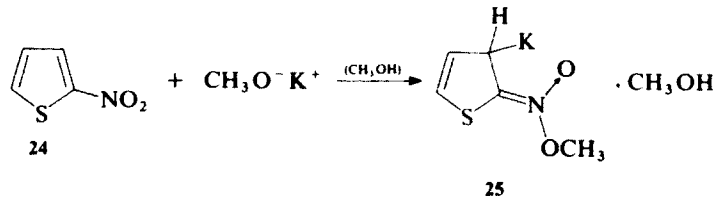
3. Early Studies on S_NAr Reactions in Thiophene Series

The excellent books on thiophene and its derivatives by Steinkopf in 1941[64] and Hartough in 1952[65] did not give any example of nucleophilic substitution reactions on thiophene ring, although reporting the synthesis of some thenylamines (**23**) of pharmaceutical interest by nucleophilic substitution on a side chain[66] (Scheme 6).

On the other hand, some information about the behavior of nitrothiophenes with alkali (hydroxide or alkoxide ions) have been reported[67] as in Scheme 7. Of course, later reviews give detailed information on the aromatic nucleophilic reactivity of thiophene compounds (see also Part 2, Chapter III, Section II.2 and Chapter IV, Section II.2).[68–82] Moreover, two important recent reviews[55,56] on



Scheme 6



Scheme 7

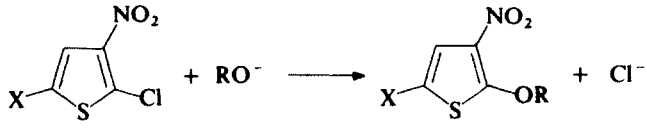
Meisenheimer adducts give a full picture of this field (see also Part 2, Chapter IV, Section II.2.A).

The first information on S_NAr and the first examples of S_NAr in the thiophene series come from studies concerning the synthesis of thiophene derivatives. For instance, Hurd and Kreuz,[83] looking for convenient methods for the preparation of nitrothienols, observed the higher nucleophilic reactivity of halogenonitrothiophenes compared to the corresponding benzene derivatives. Moreover, they synthesized some thiophene compounds (**27**, **29**, **31**) (Scheme 8) by nucleophilic substitution of chloronitroderivatives (**26**, **28**, **30**) with alkaline methoxide, ethoxide, phenoxide, and some amines (aniline, *p*-toluidine, *p*-nitroaniline, and *n*-butylamine).

Blatt and coworkers,[84] by applying to thiophene derivatives the replacement reaction of halogen with hydrogen peculiar to nitroaryl halides, synthesised some bromo-polynitrothiophenes and observed the high reactivity of 2-bromo-3,4,5-trinitrothiophene (**32**) with aniline (Scheme 9).

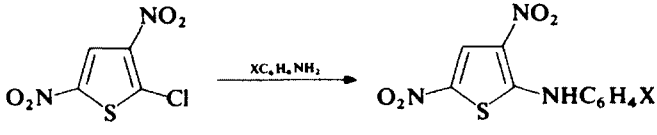
Later Towne et al.,[85] in a patent directed to the preparation of some azothiophene compounds, reported examples of aminodechlorination reactions concerning 5-substituted 2-chloro-3-nitrothiophenes (**34**) (Scheme 10).

In the 1960s, our group began research concerning aromatic nucleophilic substitutions in the thiophene series. The first papers[86–88] were devoted to the qualitative study of nucleophilic exchange reactions, followed by kinetic investigations whose findings will form the subject of the following sections. In Schemes 11–15 are summarized the results obtained in our earlier researches on the reactivity of 2,5-dibromo-3,4-dinitrothiophene (**36**), 3,4-dibromo-2,5-dinitrothiophene (**43**), 3,4-dinitro-2,5-diphenylsulfonylthiophene (**37**), 2,4-dibromo-3,5-



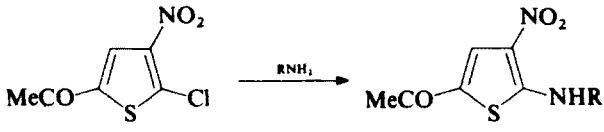
26 27

X = H, COMe, NO_2
R = Me, Et, Ph



28 29

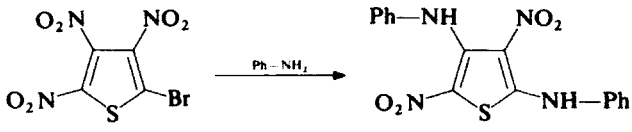
X = H, *p*-Me, *p*-NO_2



30 31

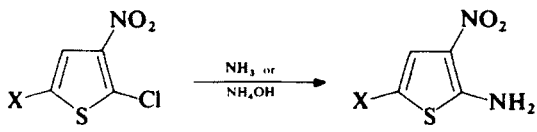
R = H, *n*-C_4H_9, C_6H_5

Scheme 8



32 33

Scheme 9

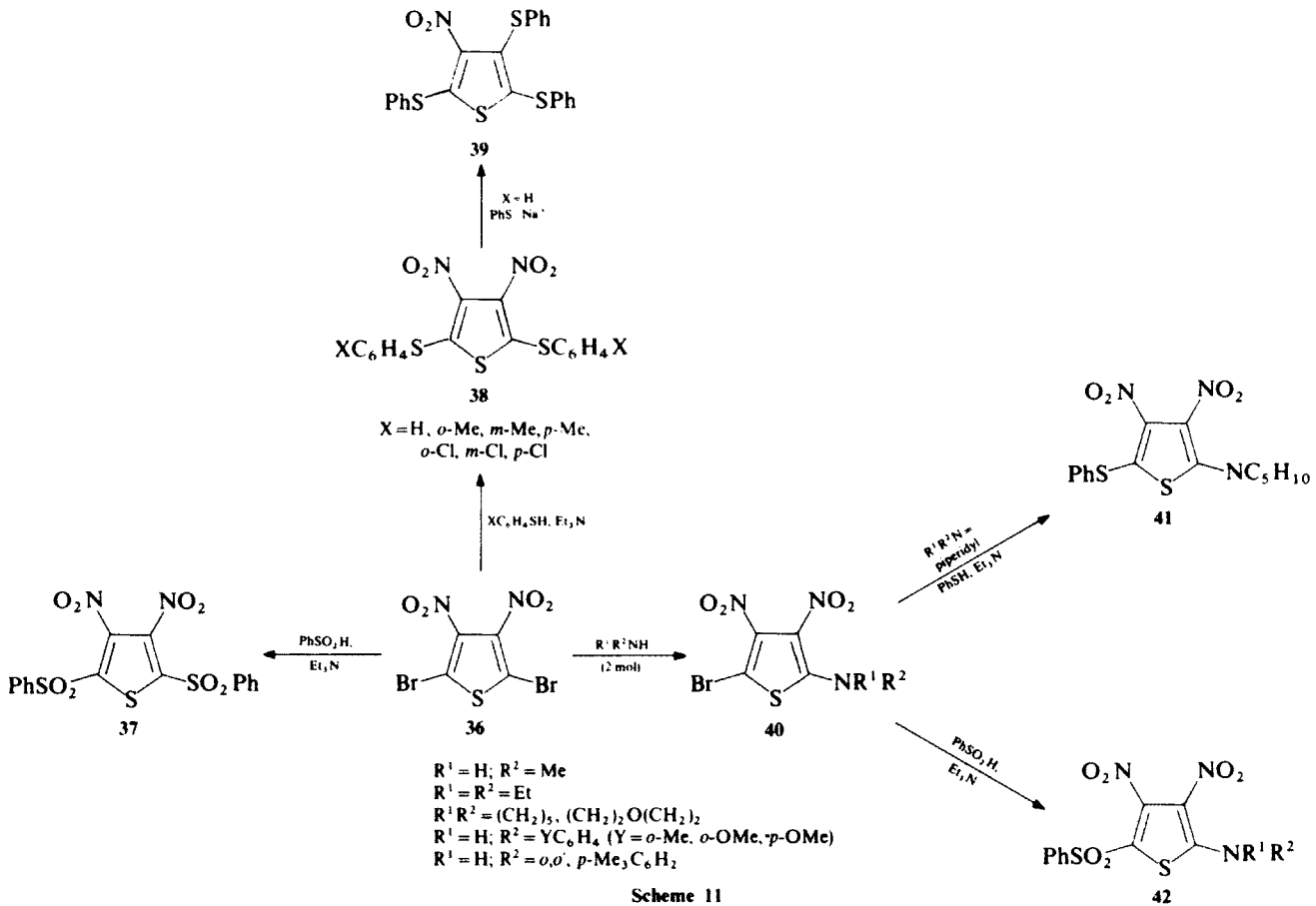


34 35

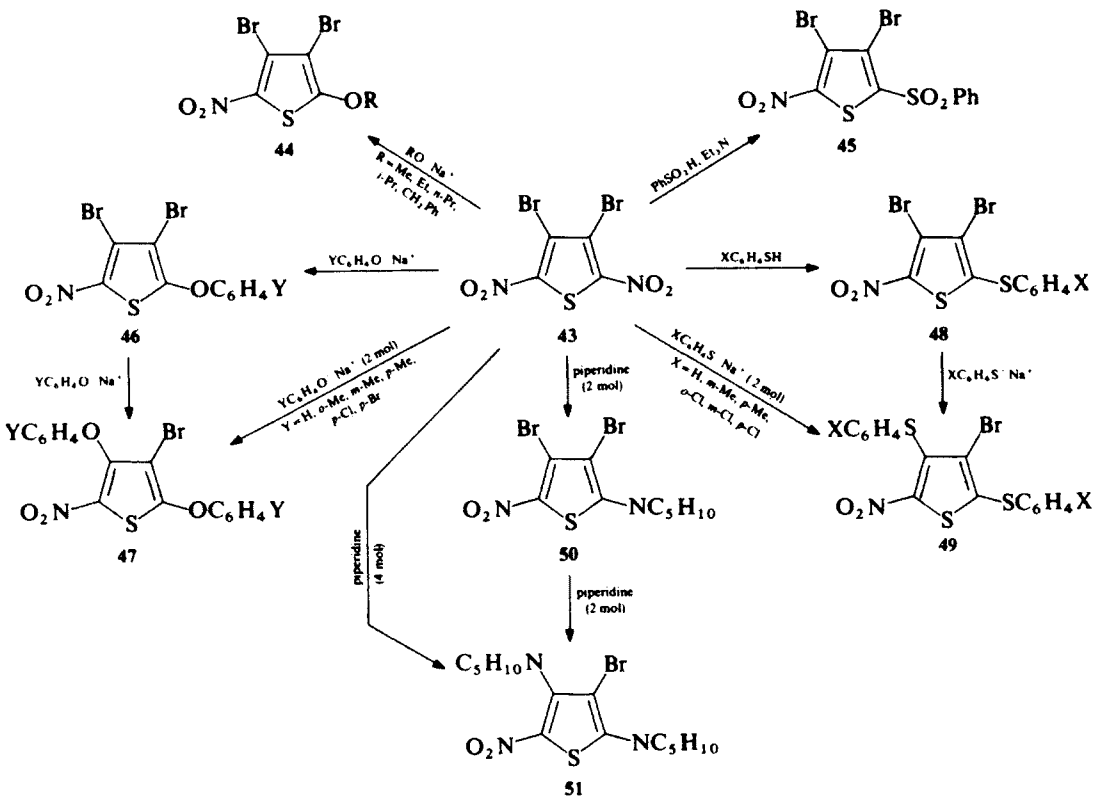
X = SO_2Me, SO_2NHR (R = Me, Et, Pr, Bu)

Scheme 10

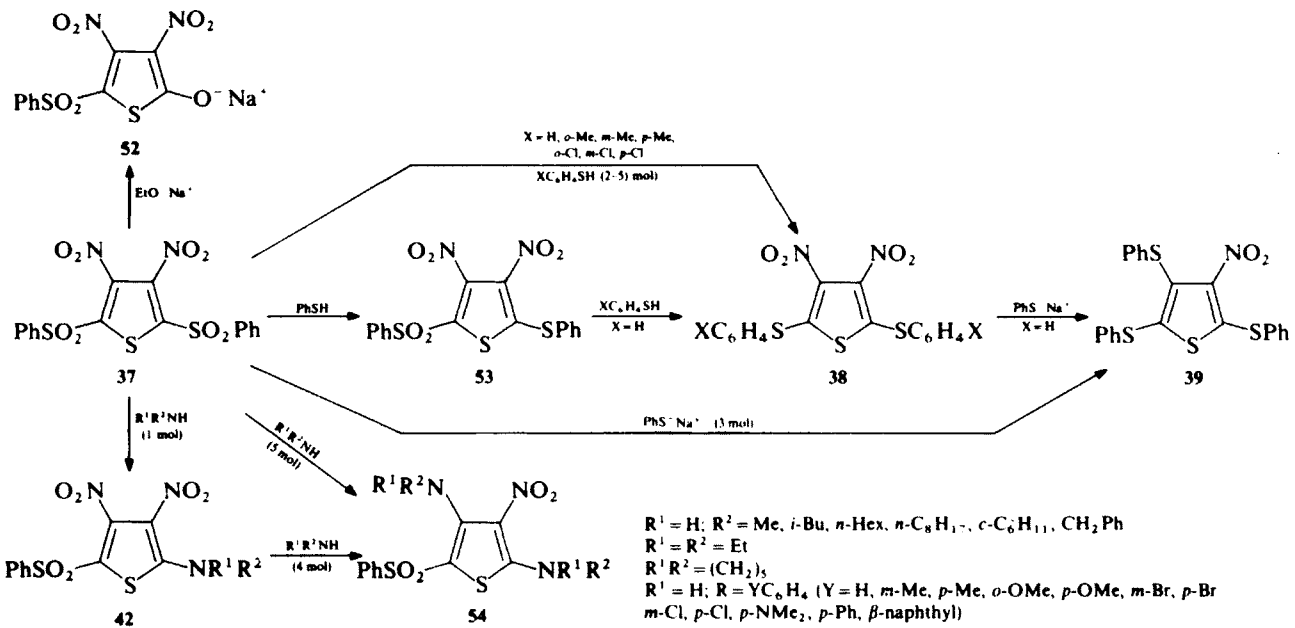
dinitrothiophene (**55**), and 2-bromo-3,4,5-trinitrothiophene (**32**) with various nucleophiles such as primary and secondary aliphatic amines, aromatic amines, thiophenols, thiophenoxides, benzenesulphinic acid, benzenesulfinate, and phenoxides.


O2N
SPh
PhS
SPh
S
39
X = H
PhS⁻ Na⁺
O2N
NO2
XC6H4S
SC6H4X
S
38
X = H, o-Me, m-Me, p-Me,
o-Cl, m-Cl, p-Cl
XC6H4SH, Et3N
PhSO2H,
Et3N
R1R2NH
(2 mol)
Br
NR1R2
37
36
40
R1R2N =
piperidyl
PhSH, Et3N
PhSO2
SO2Ph
NC5H10
41
42
R1 = H; R2 = Me
R1 = R2 = Et
R1R2 = (CH2)5, (CH2)2O(CH2)2
R1 = H; R2 = YC6H4 (Y = o-Me, o-OMe, p-OMe)
R1 = H; R2 = o,o', p-Me3C6H2

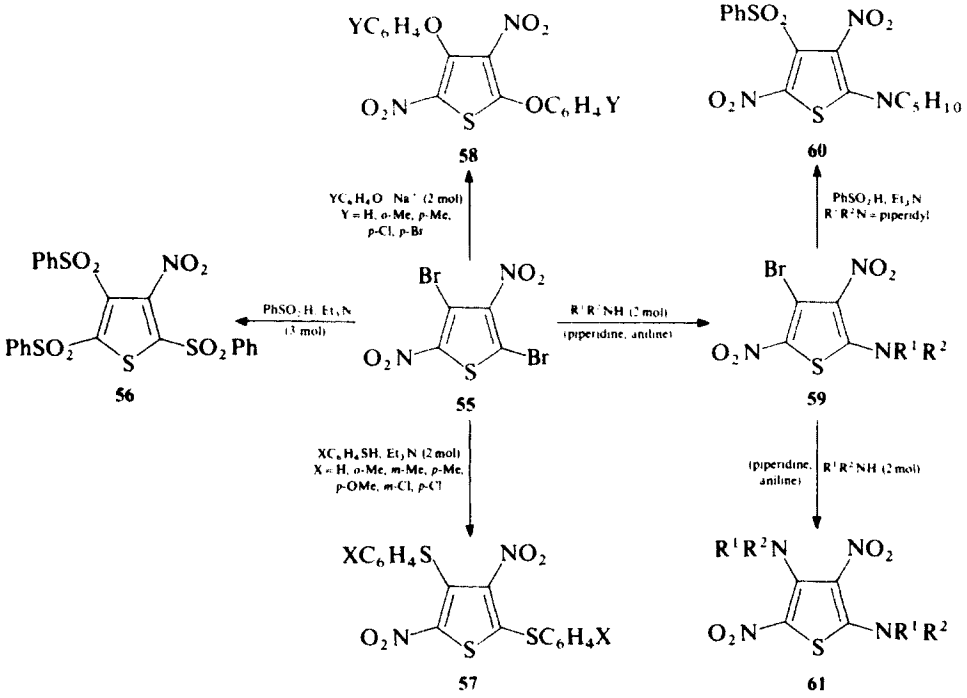
Scheme 11


44
45
46
43
48
47
50
49
51
piperidine (2 mol)
piperidine (4 mol)
piperidine (2 mol)

Scheme 12


52
EtO Na⁺
37
X = H, o-Me, m-Me, p-Me, o-Cl, m-Cl, p-Cl
XC6H4SH (2-5 mol)
PhSH
53
XC6H4SH
X = H
38
PhS⁻ Na⁺
X = H
39
PhS⁻ Na⁺ (3 mol)
R1R2NH (1 mol)
R1R2NH (5 mol)
42
R1R2NH (4 mol)
54
R1 = H; R2 = Me
R1 = R2 = Et
R1R2 = (CH2)5, (CH2)2O(CH2)2
R1 = H; R2 = YC6H4 (Y = H, o-Me, o-OMe, p-OMe, o-Cl, p-Br, o-Ph, m-NO2, p-NO2),
R1 = H; R2 = o, p-Cl2C6H3, o,o', p-Me3C6H2, 2-pyridyl
R1 = H; R2 = Me, i-Bu, n-Hex, n-C8H17, c-C6H11, CH2Ph
R1 = R2 = Et
R1R2 = (CH2)5
R1 = H; R = YC6H4 (Y = H, m-Me, p-Me, o-OMe, p-OMe, m-Br, p-Br m-Cl, p-Cl, p-NMe2, p-Ph, β-naphthyl)

Scheme 13

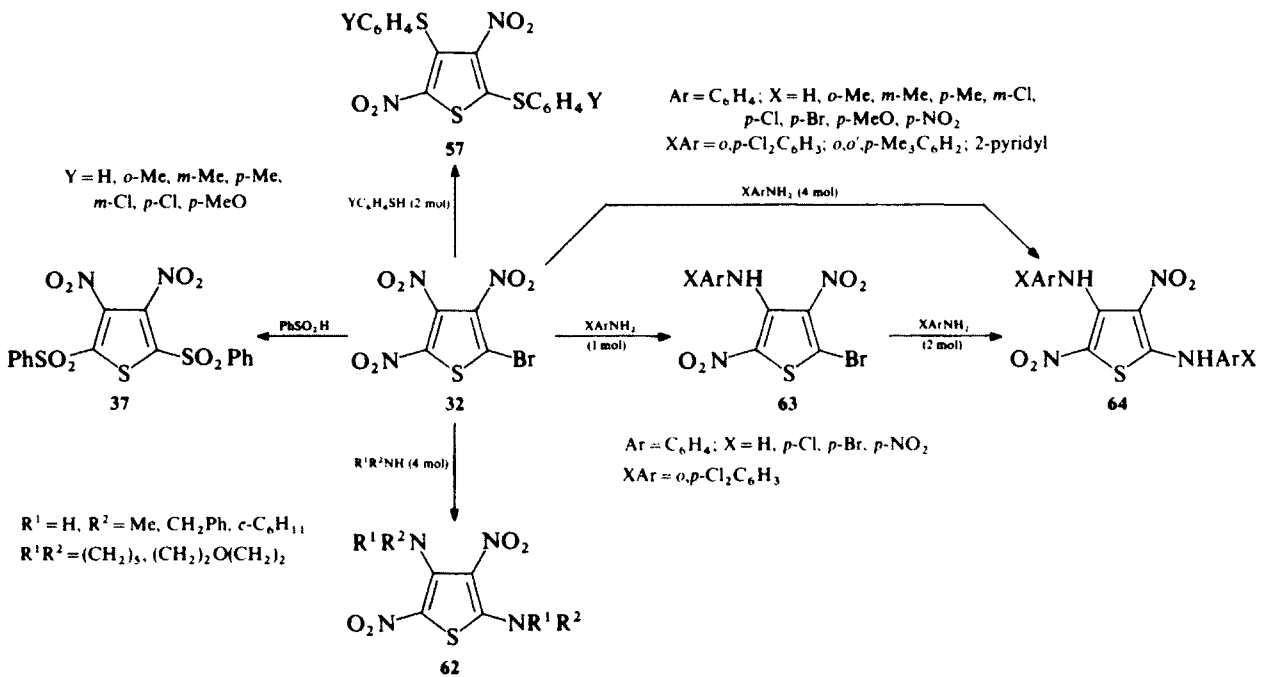


Scheme 14

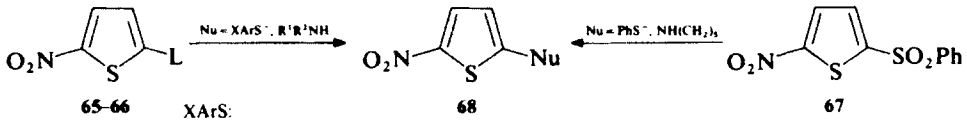
Of interest is also the behavior of some nitrothiophenes, dinitrothiophenes, and nitrophenylsulfonylthiophenes. The reactivity of 2- and 3-nitrothiophene, 3,4-dinitrothiophene and its alkyl derivatives, and 3-nitro-4-(phenylsulfonyl) thiophene will be discussed in Section III.2.

Some pieces of information concerning the 2,5-*para*-like and the 2,3-*ortho*-like isomers will be given herein. The 2,5-dinitrothiophene (**65**) reacts[89] with nucleophiles (either aliphatic, cyclic, or aromatic amines, or sodium arenethiolates) to give *ipso*-substitution products (**68**) via the usual S_NAr mechanism: the same compounds can be obtained from both 2-nitro-5-(phenylsulfonyl)thiophene (**67**)[90,91] and 2-bromo-5-nitrothiophene (**66**)[89,92,93] (Scheme 16).

A somehow similar reactivity with nucleophiles (piperidine, aniline, or sodium methoxide, benzenethiolate, or benzeneselenate) is shown also by 2,3-dinitrothiophene (**69**)[94,95] where either nitro groups can be replaced, the ratios of substitution products at C(2) (**74**) or at C(3) (**75**) depending on the nucleophile and the experimental conditions. In contrast, 3-nitro-2-(phenylsulfonyl) thiophene (**70**) and 2-nitro-3-(phenylsulfonyl)thiophene (**72**) behave[90,96] as 2-bromo-3-nitrothiophene (**71**)[92,93,97–99] and 3-bromo-2-nitrothiophene (**73**),[90,97,100] giving a regiospecific substitution of phenylsulfonyl group or bromine, respectively (Scheme 17).


YC6H4S NO2
O2N SC6H4Y
S
57
Ar = C6H4; X = H, o-Me, m-Me, p-Me, m-Cl, p-Cl, p-Br, p-MeO, p-NO2
XAr = o,p-Cl2C6H3; o,o',p-Me3C6H2; 2-pyridyl
Y = H, o-Me, m-Me, p-Me, m-Cl, p-Cl, p-MeO
YC6H4SH (2 mol)
XArNH2 (4 mol)
PhSO2H
XArNH2 (1 mol)
XArNH2 (2 mol)
PhSO2 SO2Ph
37
Br
32
XArNH
63
64
NHArX
R1R2NH (4 mol)
R1 = H, R2 = Me, CH2Ph, c-C6H11
R1R2 = (CH2)5, (CH2)2O(CH2)2
NR1R2
62
Ar = C6H4; X = H, p-Cl, p-Br, p-NO2
XAr = o,p-Cl2C6H3

Scheme 15

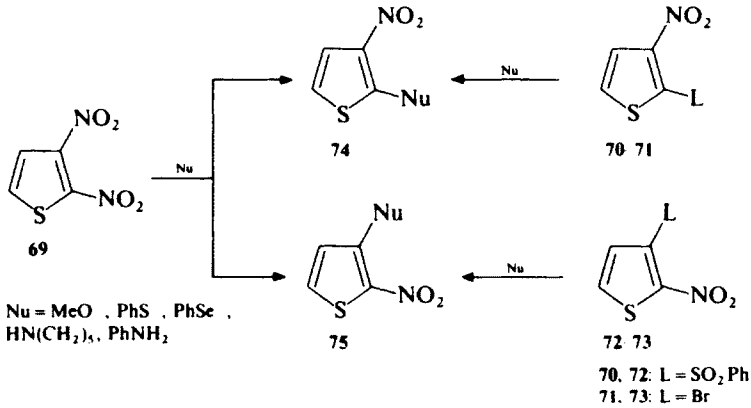


65: L = NO_2
66: L = Br

XArS:
Ar = C_6H_4; X = H, *o*-Me, *p*-Me, *o*-OMe, *o*-Cl
X-Ar = *o*,*o*',*p*-$Me_3C_6H_2$

R^1R^2NH:
$R^1 = R^2 = C_2H_5$
$R^1R^2 = (CH_2)_5$, $(CH_2)_2O(CH_2)_2$
R^1 = H; R^2 = Ph, *p*-MeC_6H_4

Scheme 16



Nu = MeO , PhS , PhSe , $HN(CH_2)_5$, $PhNH_2$

70, 72: L = SO_2Ph
71, 73: L = Br

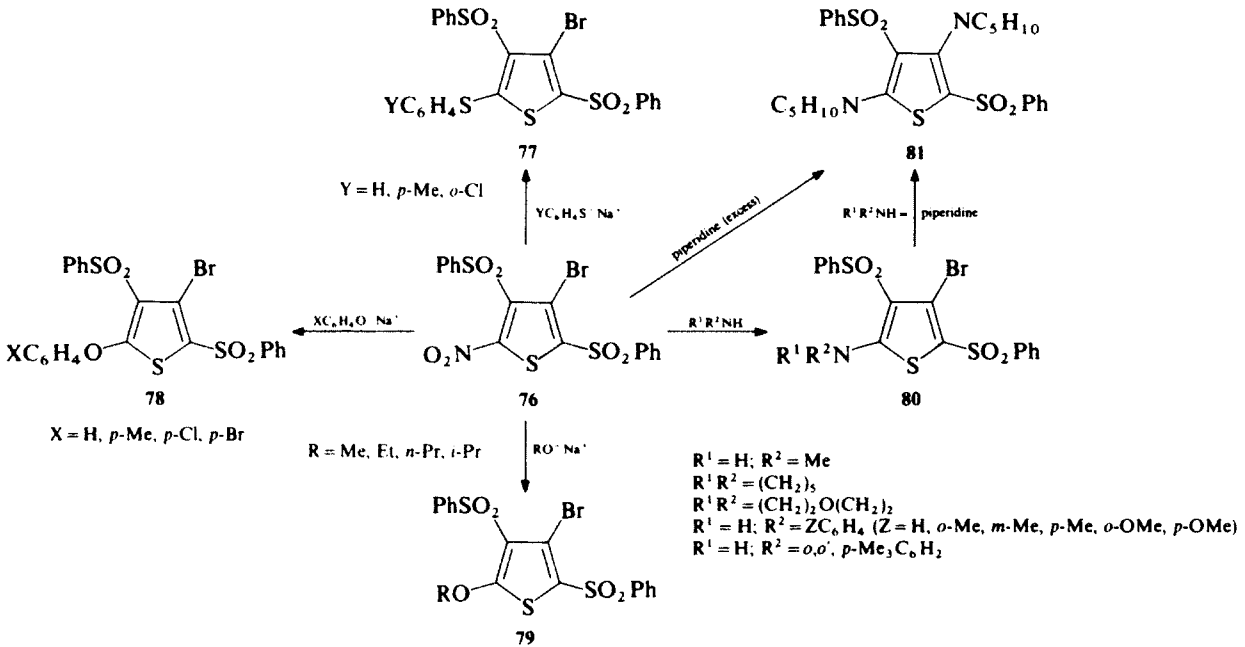
Scheme 17

Many other (unpublished) data[101] concerning the reactivity with nucleophiles of a number of halogeno- or phenylsulfonylnitrothiophenes have been collected by us. Some relevant results are summarized in Schemes 18–19.

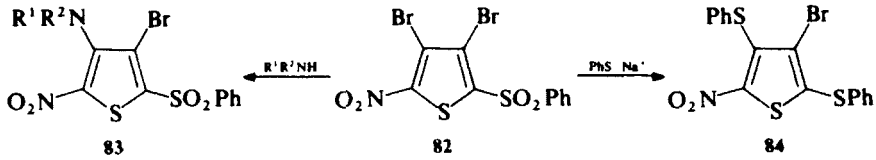
In recent years many reports have been published on S_NAr reactions in the thiophene series; many of them have also been quoted in the recent reviews on thiophene. We would like to mention only some significant examples.

Nucleophilic substitution can also occur with compounds containing activating groups other than nitrogroups; a typical example is 2,3,4,5-tetrafluorothiophene (**85**).[102] In contrast to 2,3,4,5-tetrafluorofuran,[103] this compound neither polymerizes at room temperature nor adds bromine, but it reacts slowly with sodium methoxide in methanol to yield 5-methoxy-2,3,4-trifluorothiophene (**86**), which is relatively unstable and therefore polymerizes at room temperature[102] (Scheme 20).

Of interest are some papers referring on the synthesis of the three isomeric thieno[1,4]benzodiazepinones (**92**)[104] through the reactions of the three corresponding *ortho*-bromonitrothiophenes (**71**, **73**, **88**; Scheme 21) with anthranilic acid (**87**) in boiling alcohol and in the presence of bases (potassium hydrogen carbonate or triethylamine).


PhSO2
Br
YC6H4S
SO2Ph
77
Y = H, p-Me, o-Cl
YC6H4S⁻ Na⁺
PhSO2
NC5H10
C5H10N
SO2Ph
81
R1R2NH = piperidine
piperidine (excess)
PhSO2
Br
XC6H4O
SO2Ph
78
X = H, p-Me, p-Cl, p-Br
XC6H4O⁻ Na⁺
PhSO2
Br
O2N
SO2Ph
76
R1R2NH
PhSO2
Br
R1R2N
SO2Ph
80
R = Me, Et, n-Pr, i-Pr
RO⁻ Na⁺
PhSO2
Br
RO
SO2Ph
79
R1 = H; R2 = Me
R1R2 = (CH2)5
R1R2 = (CH2)2O(CH2)2
R1 = H; R2 = ZC6H4 (Z = H, o-Me, m-Me, p-Me, o-OMe, p-OMe)
R1 = H; R2 = o,o', p-Me3C6H2

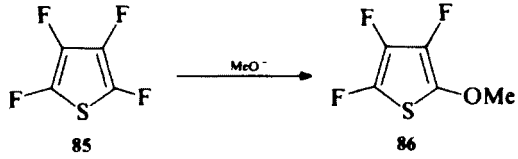
Scheme 18



83 82 84

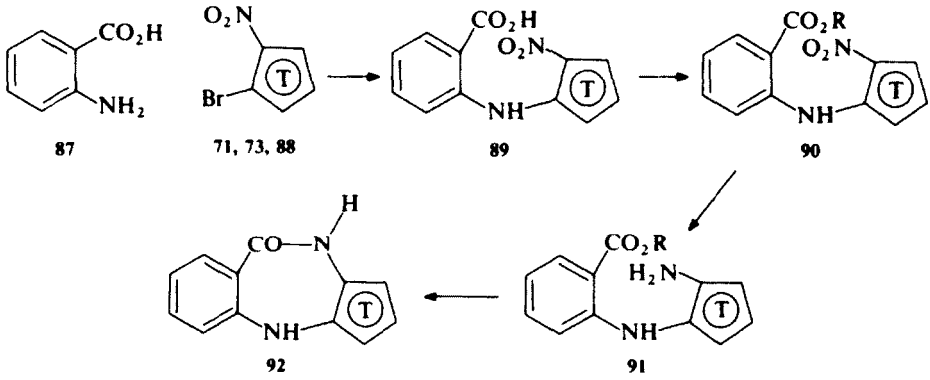
R^1R^2NH = piperidine, aniline

Scheme 19

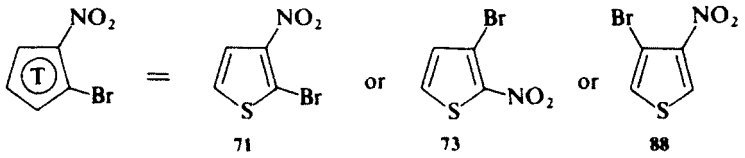


85 86

Scheme 20



87 71, 73, 88 89 90 91 92

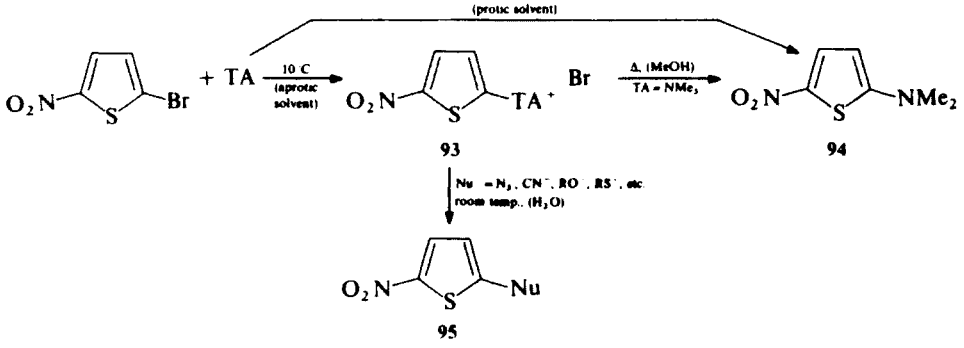


71 73 88

Scheme 21

In these reactions the *ortho*-carboxylate group of the nucleophile probably plays a peculiar role.

Moreover, the activated S_NAr reactions of quaternary *N*-thienylammonium salts (**93**),[105,106] with the neutral amines as leaving groups, are very promising from a synthetic point of view. These ammonium salts can be obtained in good yields from the corresponding halogenoderivatives and a tertiary amine (TA in Scheme 22) in an aprotic solvent where the reaction products are almost insoluble.

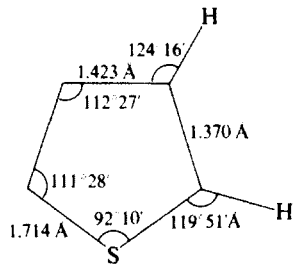


Scheme 22

Considering the reaction of 2-bromo-5-nitrothiophene (**66**) with trimethylamine, the rate of formation of the salt is higher in acetone than in (other) aprotic solvents with a lower dielectric constant (tetrahydrofuran, dimethoxyethane, ethyl ether, ethyl acetate, benzene, or hexane). In protic solvents such as ethanol, however, this salt is soluble and it decomposes rapidly to 2-*N*,*N*-dimethylamino-5-nitrothiophene (**94**) by transalkylation. The same kind of decomposition is also observed when (**93**) is heated. The quaternary salts offer many possibilities for the synthesis in that they react straightforwardly with many nucleophiles and sometimes such a S_NAr reaction represents the only practicable route to the desired substituted compound.

4. Geometric Structure of Thiophene

Different physical methods[107] (X-rays, electron diffraction and microwave studies, etc.) give consistent data on the structure of thiophene and its derivatives; all the results obtained reveal a high double-bond character of the carbon–sulfur bond. The question of sulfur *d*-orbital participation in the structure of thiophene and its relevance to the reactivity of thiophene derivatives has been widely debated, but a definitive verdict has not been achieved.[107] On the other hand, the C(2)—C(3) and C(3)—C(4) bonds are, respectively, shorter and longer than a C—C bond in benzene and therefore have a correspondingly higher and lower bond order (**96**).



96

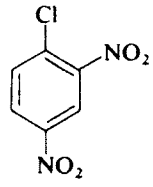
This fact causes the occurrence of different *ortho*-relations concerning 2,3- and 3,4-disubstituted thiophenes: many kinetic, spectroscopic, and reactivity data support this difference and lead to distinguish the two relations[108-118] as hyper-*ortho* and hypo-*ortho*, respectively. Moreover, in the five-membered ring of thiophene the values of internal angles [S–C(2)–C(3) and C(2)–C(3)–C(4)] are not far from those of sp^3-hybridized carbon atoms such as those that represent the reaction centre in the σ-complexes for both S_NAr and S_EAr: at the same time, the high values of external angles make the distance between two *ortho*-like substituents larger than in benzene derivatives, thus affecting both the interactions between these substituents and their geometry with respect to the ring.

Theoretical and experimental criteria used to evaluate the aromaticity (see also Part 2, Chapter 1, Section 1) indicate that thiophene is less aromatic than benzene but more aromatic than the other five-membered rings containing one heteroatom (selenophene, tellurophene, furan, and pyrrole).[107,119-121] The geometric structure and the aromaticity are factors that surely affect the reactivity of thiophene derivatives with nucleophiles.

II. KINETIC STUDIES

1. Reactivity of Thiophene Derivatives with Nucleophiles

Aromatic five-membered ring derivatives containing one heteroatom of the fifth (nitrogen) or of the sixth (oxygen, sulfur, or selenium) group give S_EAr and S_NAr reactions very easily. Taking into account only thiophene and its derivatives, it has to be pointed out that, under analogous experimental conditions, their reactivity is higher than that of the corresponding benzene derivatives; for example, the nitration and acetoxymercuration of thiophene are faster,[122-124] respectively, by a factor 850 (at 10°C) and 10^5 (at 25°C) than those of benzene, and the piperidinodechlorination in ethanol at 20°C of 2-chloro-3,5-dinitrothiophene (**28**) is faster[92] by a factor 500 than that of 2,4-dinitrochlorobenzene (**97**).[125]



97

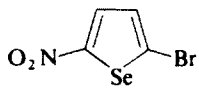
This last experimental datum is in contrast with early comments on nucleophilic substitution in thiophenes occurring through the attachment–detachment mechanism. Indeed, J. Miller in his book on aromatic nucleophilic substitution, referring to heteroaromatic systems such as thiophene,[126] stated

that "in π-excessive heteroaromatics which contain a five-membered ring and only one heteroatom, electron density is high on ring carbon atoms, and for nucleophilic substitution the negative charge of the hetarenide system cannot be placed on the heteroatom. This implies low reactivity toward nucleophiles" and again, "Similarly Motoyama[127] et al. have shown that 2-bromo-5-nitrothiophene is a little more reactive than *p*-bromonitrobenzene."

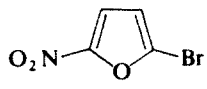
As a matter of fact, Motoyama observed,[127] on the contrary, a relative benzene : thiophene rate of 1 : 154 for *para*-isomer and 1 : 390, 1 : 1540, and not measurable, for the three possible thiophene *ortho*-isomers, 3-bromo-4-nitro-, 3-bromo-2-nitro, and 2-bromo-3-mitrothiophene, respectively. These relative rates cannot be regarded as an indication of only a little difference in reactivity. Also the semiquantitative data of Hurd and Kreuz[83] and the qualitative data of Blatt et al.[84] not quoted by Miller, show clearly the higher nucleophilic reactivity of halogenonitrothiophenes compared to the corresponding benzene compounds. Moreover, at that time, some papers concerning the kinetics of piperidino-[92] and benzenethiolate-dehalogenation[93] of thiophene compounds had already been published and the higher reactivity of thiophene[92] with respect to benzene derivatives had already been discussed on the grounds of the different ability of the π-orbitals of the aromatic systems to interact with (activating) electron-withdrawing substituents.

As far as the similar behavior in S_EAr and in S_NAr of thiophene is concerned, at least two factors, operating in both reactions, control the energy difference in going from the starting substrates to the relevant transition states:

1. The low resonance stabilization energy of thiophene[119-121] with respect to benzene, which causes a lower loss of stabilization energy on going from starting products to transition states.[92] The importance of this factor can be brought to evidence by an examination of the nucleophilic reactivity of the iso-π-electronic cogeners 2-bromo-5-nitro-thiophene (**66**),[128] -selenophene (**98**),[129] and -furan (**99**).[130]



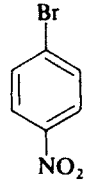
98



99

Indeed, a large increase in the rate of piperidinodebromination is observed as the aromaticity of the heterocycle decreases[119-121] (in benzene, at 20°C, the following rate ratios have been calculated: 1 : 8.5 : 300). A similar trend has also been observed for benzenethiolate debromination.[93,129,130] In view of the higher reactivity with piperidine of 2-bromo-5-nitrothiophene (**66**)[92,128] with respect to *p*-bromonitrobenzene[22] [see above, the comparison between the reactivities with piperidine of 2-chloro-3,5-dinitrothiophene (**28**) and of 2,4-dinitrochlorobenzene

(97)], one can calculate that 2-bromo-5-nitrofuran (**99**) is at least 10^5 times more reactive than *p*-bromonitrobenzene (**100**);*



100

2. The internal bond angles along the ring carbon atoms,[107] which are about 111–112°, thus, very similar to the figure corresponding to sp^3-hybridized carbon atoms such as the carbon atom of the reaction centre in the σ-complex, which factor implies a lower energy, with respect to benzene, for the reorganization of the ring skeleton in the formation of the transition state.[131] Other factors, such as the lower F-strain to the approach of the reagent to the aromatic compound, also play a role.[132]

On the other hand, many other factors affect in different ways S_EAr and S_NAr reactions in thiophene with respect to benzene; for instance, the high electron density on ring carbon atoms, characteristic of π-excessive heteroaromatics, causes a stabilization of the transition states for S_EAr reactions in thiophene, whereas the high electron delocalization ability of the electron-withdrawing aromatic residue favors the course of S_NAr reactions in thiophene derivatives. Concerning the latter effect, two factors have to be considered: (1) the intrinsic ability of the thiophene ring to transmit the electronic effects of substituents more efficiently than in benzene—this factor can also be enhanced by the hyper-*ortho*[108–114,116,117] relation or by the quasi-*para* relation[133] (involving the transmission of electronic effects also through the sulfur heteroatom); (2) the different geometry of substituted thiophene with respect to benzene compounds, as shown by molecular models and by X-ray structure determinations,[107,134] which suggests, also on the basis of the reactivity observed in hindered compounds, that in nitrosubstituted thiophene derivatives the nitrogroups are nearer to the coplanarity with the aromatic ring than in nitrosubstituted benzenes. This factor could be important in determining the electronic activation of S_NAr reactions because the nitrogroup should be more able to exert its electronic activating effect than in benzene.

The ability of a nitrogroup to give through-conjugation with electron-donor substituents in neutral benzene compounds has been recently questioned by Lipkowitz[135] on the basis of ^{17}O NMR and NQDR data, and of ab initio molecular orbital calculations.

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* In the light of these experimental results Miller's statement[126] that five-membered π-excessive heteroaromatics are not prone to give S_NAr reactions does not appear quite right.

More recent studies have corrected this conclusion. In fact, Fraser and coworkers[136] have studied some 10 *para*-substituted nitrobenzenes covering a wide range of σ or σ^+ values and using such experimental conditions as to warrant a great precision in the measurements. Their ^{17}O NMR data strongly support the occurrence of a through-conjugation between nitrogroup and electron-donating substituents. Craik and coworkers[137] measured ^{15}N and ^{17}O NMR spectra for a series of *para*- and *meta*-substituted nitrobenzenes and obtained a good correlation of the chemical shifts by a dual-substituent parameter equation; the results confirmed that both polar and resonance substituent effects operate. Moreover, they showed that the π-electron densities calculated ab initio agree with the observed trends of ^{15}N and ^{17}O chemical shifts. Whatever the real situation is, no doubt many kinetic results indicate that the ability of a nitrogroup to exert its electron-withdrawing effect is an inverse function of the dihedral angle between the plane of the nitrogroup and that of the aromatic or heteroaromatic ring. On the other hand, it is also possible that in polar transition states the nitrogroup exerts its electron-withdrawing effect in a different way with respect to the neutral compounds.

The X-ray determination of the structure of 2-chloro-3,5-dinitrothiophene (**28**) has shown[134] that the nitrogroups at C(5) and at C(3) are practically coplanar with the aromatic ring, with only the second being a little twisted (twist angle $\simeq 20°$). In contrast, in the corresponding benzene compound [2,4-dinitrochlorobenzene (**97**)] both *ortho*- and *para*-nitrogroups are rotated with respect to the plane of the aromatic ring, by about 40° and 15°, respectively.[138,139]

In the thiophene ring, the peculiar geometry and the greater bond fixation with respect to benzene give rise to C(2)—C(3) and C(3)—C(4) bonds, respectively, with a higher and a lower π-bond order than carbon–carbon bonds in benzene.[107] This affects the reactivity of thiophene compounds.

In fact, if one compares the reactivity in methanol of the three possible ortho-like substituted isomeric bromonitrothiophenes with sodium benzenethiolate,[93,100,109] the two hyper-*ortho* isomers (**71**, **73**) appear much more reactive than does the hypo-*ortho* isomer (**88**) (ratios $>10^5$; see data in Table 1)* in accordance with the previsions based on the different transmission of electronic effects through bonds of different π-bond order.[100,109] On the other hand, the two hyper-*ortho* (**71**, **73**) isomers $[(k)_{73}/(k)_{71} = 2.0]$ show much the same reactivity irrespective of the position (α or β) of the leaving group. This suggests that the stability of the intermediates does not significantly depend on the

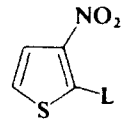
* Evidence for the hyper- and the hypo-*ortho* relations have also been obtained from studies concerning the transmission of substituent effects in nucleophilic substitutions[109] as well as from measurements of pK_A[111,113,115] and of the reactivities with diazodiphenylmethane[116,117] of 2- and 4-substituted 3-thiophenecarboxylic acids and of 3-, 4-, and 5-substituted 2-thiophenecarboxylic acids, and from studies of alkaline hydrolysis of the corresponding methyl esters.[112,114,117] Also, ^{13}C NMR chemical shifts measurements of some 2- and 3-substituted thiophenes have given similar information.[110]

TABLE 1. Reactivity of Some Bromonitrothiophenes with Sodium Benzenethiolate (PhS^-) or Benzeneselenate ($PhSe^-$) in Methanol at 20°C

Substrate	Nucleophile	k (liters mol^{-1} sec^{-1})	Ref.
2-Bromo-3-nitrothiophene (**71**)	PhS^-	0.116	93
3-Bromo-2-nitrothiophene (**73**)	PhS^-	0.234	100
3-Bromo-4-nitrothiophene (**88**)	PhS^-	$< 10^{-6}$[a]	100
2-Bromo-5-nitrothiophene (**66**)	PhS^-	0.136	93
2-Bromo-3-nitrothiophene (**71**)	$PhSe^-$	0.535	97
3-Bromo-2-nitrothiophene (**73**)	$PhSe^-$	1.52	97
2-Bromo-5-nitrothiophene (**66**)	$PhSe^-$	0.633	97

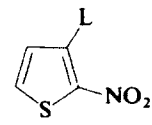
[a] The value calculated by extrapolation from reactivity data of some 3-bromo-4-nitro-2-X-thiophenes for X = H is $\sim 10^{-8}$ liters mol^{-1} sec^{-1} (see Ref. 109).

relative position of the heteroatom and of the reaction center; the only significant factor is the size of the leaving group. In fact, it has been observed[90] that on changing the leaving group in a series of 2-L-3-nitro (**70**, **71**, **101**, **102**) and 3-L-2-nitrothiophenes (**72**, **73**, **103**, **104**) the k_{3-L}/k_{2-L} ratios show a regular trend increasing from 0.5 to ~10 in going from *p*-nitrophenoxy to phenylsulphonyl, indicating that the endocyclic sulfur behaves as an *ortho*-substituent, which causes a primary steric effect in the presence of the bulky phenylsulfonyl leaving group.



$L = OC_6H_4NO_2$-*p*.Cl

101–102

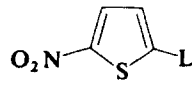


$L = OC_6H_4NO_2$-*p*, Cl

103–104

Moreover, whereas the *ortho*-like isomer 2-bromo-3-nitrothiophene (**71**) is only a little less reactive than the *para*-like isomer (**66**) (e.g., at 20°C, in methanol:[93] k_o/k_p 0.85)* in the "truly aromatic" six-membered ring derivatives; for example, in benzene derivatives,[61,140] the *ortho/para* ratios are low (~0.2). Also in this case the bond fixation plays an important role by favoring the *ortho*-like isomer with respect to the *para*-like isomer. Similar results have been obtained studying the reactivity of hyper-*ortho* and *para*-like isomers with sodium benzeneselenate (Table 1).[97]

* Similar k_o/k_p ratios (0.73, 0.56, and 0.32) have been measured comparing the reactivities of 2-chloro-3-nitrothiophene[90] (**102**), 4-nitrophenyl 2-(3-nitro)thienyl ether[90] (**101**), and phenyl 2-(3-nitro)thienyl sulfone[90] (**70**) and of 2-chloro-5-nitrothiophene[93] (**106**), 4-nitrophenyl 2-(5-nitro)thienyl ether[90] (**105**), and phenyl 2-(5-nitro)thienyl sulfone[90] (**67**) with sodium benzenethiolate at 20°C. The unique exception is offered by (**65**) and (**69**), which show a k_o/k_p ratio higher than unity (1.3 at 20°C),[95] thus duplicating the situation observed in benzene series.[95]



L = $OC_6H_4NO_2$-*p*, Cl

105–106

The previous interpretation concerning the anionic nucleophiles (sodium benzenethiolate and benzeneselenate) has been confirmed by the results obtained with piperidine, a neutral nucleophile, in various solvents (dioxane–water, ethanol, methanol, and benzene).[92,128] It is well known that the reactivity of *ortho*-halogenonitrobenzenes with neutral nucleophiles (e.g., piperidine) is affected by the "built-in solvation"[141] that enhances and levels off the reactivity in solvents with different polarities. In contrast, the reactivity of *para*-halogenonitrobenzenes is strongly dependent on the nature of the solvent (see data in Table 2). In benzene series, as determined by the built-in solvation, the *ortho*/*para* ratios range from 1.4 in dioxane/water (1/99) to 46 in benzene.

The *ortho*/*para* ratios calculated by studying the reactivities of 2-bromo-3-nitrothiophene (**71**) and of 2-bromo-5-nitrothiophene (**66**) range from ~4.1 in dioxane : water (60 : 40) to ~440 in benzene[92,128] (Table 2). This trend is similar to that observed for benzene series but the ratios are expectedly higher in thiophene than in benzene series on account of the bond fixation factor. The reactivity with piperidine of the *para*-like isomer strongly decreases on going from dioxane–water (at 20°C, k 1.76 × 10^{-4} liters mol^{-1} sec^{-1}) to benzene (at 20°C, k 0.97 × 10^{-6} liters mol^{-1} sec^{-1}); on the contrary, owing to the levelling effect of the built-in solvation, which in turn is caused by a compensation between activation enthalpy and entropy variations, the reactivity of the *ortho*-like isomer smoothly decreases on going from dioxane/water (at 20°C, k 7.3 × 10^{-4} liters mol^{-1} sec^{-1}) to benzene (at 20°C, k 4.25 × 10^{-4} liters mol^{-1} sec^{-1}). Indeed, an examination of the activation parameters shows that the variations of activation enthalpy with changing solvent are similar for the two isomers, whereas the corresponding variations of activation entropy are higher for the *para*-like than for the *ortho*-like isomer.

Also the kinetic behavior of 2,3-dinitrothiophene[95] (**69**) and 2,5-dinitrothiophene[142–144] (**65**) deserves some comments.

The reactivity of (**65**) with piperidine (in acetonitrile[142] and benzene[144]) and with aniline,[144] sodium benzenethiolate,[144] and toluene-*p*-thiolate[143] (in methanol) has been studied. Substrate (**65**) gives a second-order piperidinosubstitution in acetonitrile (at 25°C, k 1.06 × 10^{-3} liters mol^{-1} sec^{-1}) and a catalyzed substitution in benzene (at 20°C, k_0 1.1 × 10^{-6} liters mol^{-1} sec^{-1}, k_{PIP}/k_0 38), showing that the change from a dipolar solvent (acetonitrile) to a nonpolar solvent (benzene) can reduce the k_2/k_{-1} ratio to such an extent as to make the piperidine catalysis detectable[144] (see Section II.4). On the other hand, **65** follows a clean second-order reaction (at 20°C, k 3.58 × 10^{-5} liters mol^{-1} sec^{-1}) with aniline in methanol. The reaction of phenylthio- (at 20°C, k 130 liters mol^{-1} sec^{-1}) and *p*-tolylthio-denitration (at 25°C, k 420 liters mol^{-1} sec^{-1}) of

TABLE 2. Reactivity of Some Halogenonitro Compounds with Sodium Benzenethiolate (PhS^-) or Piperidine (PIP)

Substrate	Nucleophile	Solvent	k (liters mol^{-1} sec^{-1}) (°C)	k_o/k_p	Ref.
2-Bromo-3-nitrothiophene (**71**)	PhS^-	Methanol	0.116 (20)	0.85	93
2-Bromo-5-nitrothiophene (**66**)	PhS^-	Methanol	0.136 (20)		93
2-Bromo-3-nitrothiophene (**71**)	PhS^-	Dioxane 60%	4.00 (20)	0.60	93
2-Bromo-5-nitrothiophene (**66**)	PhS^-	Dioxane 60%	6.64 (20)		93
1-Chloro-2-nitrobenzene	PhS^-	Dioxane 60%	0.0046 (25)	0.16	61
1-Chloro-4-nitrobenzene	PhS^-	Dioxane 60%	0.0295 (25)		61
2-Bromo-3-nitrothiophene (**71**)	PIP	Dioxane 60%	7.30×10^{-4} (20)	4.15	128
2-Bromo-5-nitrothiophene (**66**)	PIP	Dioxane 60%	1.76×10^{-4} (20)		128
2-Bromo-3-nitrothiophene (**71**)	PIP	Ethanol 95%	1.29×10^{-4} (20)	5.0	92
2-Bromo-5-nitrothiophene (**66**)	PIP	Ethanol 95%	0.258×10^{-4} (20)		92
2-Bromo-3-nitrothiophene (**71**)	PIP	Methanol	1.12×10^{-4} (20)	6.9	128
2-Bromo-5-nitrothiophene (**66**)	PIP	Methanol	0.163×10^{-4} (20)		128
2-Bromo-3-nitrothiophene (**71**)	PIP	Benzene	4.25×10^{-4} (20)	438.00	128
2-Bromo-5-nitrothiophene (**66**)	PIP	Benzene	0.0097×10^{-4} (20)		128
1-Chloro-2-nitrobenzene	PIP	Dioxane 1%	44.0×10^{-3} (102)	1.35	141
1-Chloro-4-nitrobenzene	PIP	Dioxane 1%	32.5×10^{-3} (102)		141
1-Chloro-2-nitrobenzene	PIP	Methanol 75%	5.20×10^{-3} (102)	1.7	141
1-Chloro-4-nitrobenzene	PIP	Methanol 75%	2.98×10^{-3} (102)		141
1-Chloro-2-nitrobenzene	PIP	Ethanol 93%	4.02×10^{-3} (102)	2.3	141
1-Chloro-4-nitrobenzene	PIP	Ethanol 93%	1.72×10^{-3} (102)		141
1-Chloro-2-nitrobenzene	PIP	Benzene	5.14×10^{-3} (102)	47.	*a*
1-Chloro-4-nitrobenzene	PIP	Benzene	0.11×10^{-3} (102)		*a*

[a] Data from J. A. Brieux and V. Deulofeu, *Anales Assoc. Quim. Argentina*, **9**, 189 (1951).

65 confirm the high reactivity of nitrocompounds (e.g., see dinitrobenzenes reactivity[95,143]) with anionic sulfur nucleophiles.

A comparison of the reactivity of **65** and **66** with the same nucleophile shows, interestingly, that the relative nucleofugality of the two leaving groups (nitrogroup and bromine) depends on the used nucleophile: with piperidine in benzene and with aniline in methanol similar reactivities have been observed[144] (at 20°C, $k_{L=NO_2}/k_{L=Br} \sim 1.2$ and 0.7, respectively); in contrast with sodium benzenethiolate in methanol, the nitrogroup is much more nucleofugal than bromine[144] (at 20°C, $k_{L=NO_2}/k_{L=Br} \sim 10^3$), showing that different factors (e.g., the electron density on the carbon atom seat of the nucleophilic attack, the F-strain on the approach of the nucleophile, the Bunnett–Reinheimer effect, etc.) can affect the reactivity ratios depending on the position of the rate-determining transition state in the reaction coordinates.

The reactivity of **69** has been studied with piperidine in benzene and with aniline and sodium benzenethiolate* in methanol. In the two first reactions clean second-order kinetics have been observed. The nucleophilic substitution reactions of **69** are not regiospecific (see Section I.3) and a mixture of substitution products at C(2) and at C(3) was obtained:[94,95] with piperidine and aniline the attack at C(3) prevails[95] [$k_{C(3)}/k_{C(2)}$ 2.1 and 3.9, respectively] whereas with sodium benzenethiolate similar amounts of the two substitution products were obtained[95] ($k_{C(3)}/k_{C(2)}$ 0.93); probably this indicates that the endocyclic sulfur atom behaves as an *ortho*-substituent, which disfavors the reactions with nucleophiles having high steric requirements.

At variance with that observed before[144] on comparing the reactivities of **65** and **66**, in the instance of **69** a higher nucleofugality of nitrogroup with respect to bromine in **71** or **73** has always been observed[95] (at 20°C, $k_{L=NO_2}/k_{L=Br}$ $44 - 2 \times 10^3$).

2. The S_NAr Mechanism in the Thiophene Series

Most of the evidence for the S_NAr mechanism in the benzene series apply also to the thiophene series. Since the evidence based on the isolation, the structure, and the reactivity of Meisenheimer-type adducts formed from thiophene compounds have been thoroughly discussed in the recent literature (see also Part 2, Chapter IV, Section II.2.A),[55,56] only a brief account of this subject will be given here.

In the next sections two points will be discussed in some detail: the element effect (Section II.3) and the base catalysis (Section II.4). The substituent effects on the reaction rate will form the subject of a following section (II.5).

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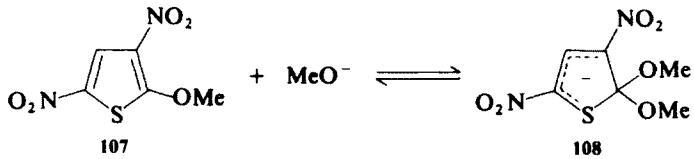
* Both **69**[95] and **65**[144] show some kinetic complications with this reagent: an increase of kinetic constants can be observed with increasing the nucleophile concentration. The reported kinetic data for phenylthiodenitration represent values extrapolated at $[PhS^-] = 0$.

Meisenheimer adducts are considered[21-28,48-56] to be a good model for intermediates in S_NAr because their structure closely resembles that of the σ-complexes assumed to be the intermediates of nucleophilic substitution. This fact stimulated the study of these compounds in both aromatic and heteroaromatic series.

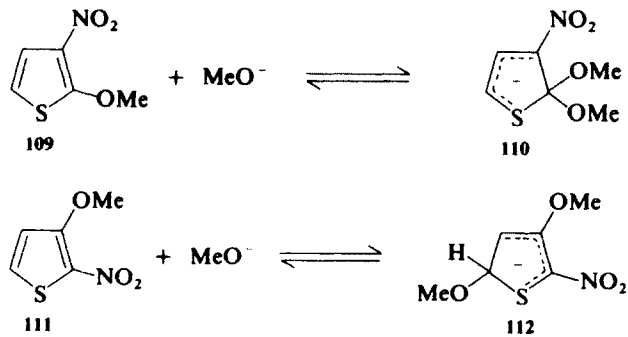
The first Meisenheimer-type adduct, formed from a five-membered ring derivative, specifically, 2-methoxy-3,5-dinitrothiophene (**107**) (Scheme 23), was described in 1969.[145]



107 **108**

Scheme 23

Soon after, the formation of the Meisenheimer adducts from mononitromethoxythiophenes (**109**, **111**) (Scheme 24) was also put forward.[146]



109 **110**

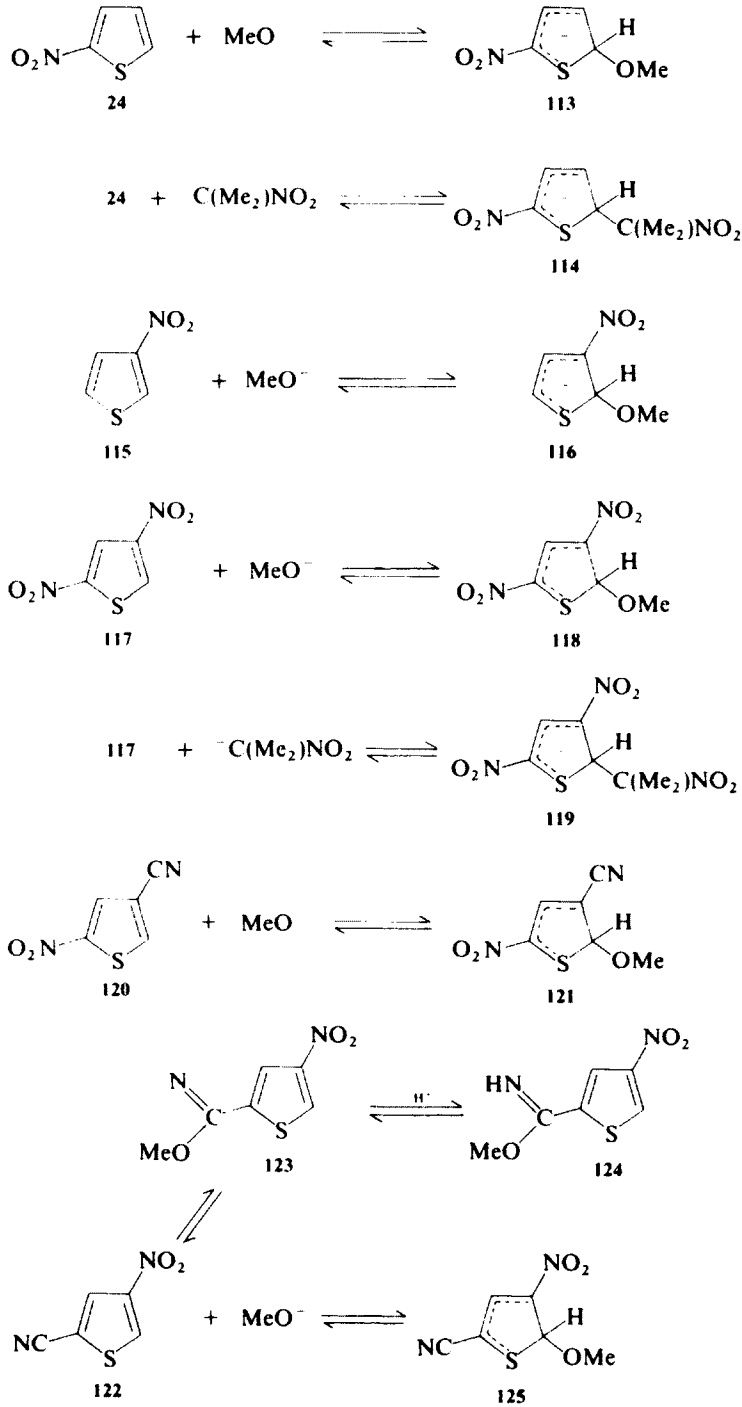
111 **112**

Scheme 24

Characterization of the σ-adducts generally was realized by spectroscopic (^1H and ^{13}C NMR, UV–visible, and IR) techniques. The seat of nucleophilic attack is an α-position as pointed out by the study of the reaction of 3-methoxy-2-nitrothiophene (**111**) with sodium methoxide,[146] which gives the nongeminal adduct in spite of the usual higher stability of a geminal with respect to a nongeminal adduct.

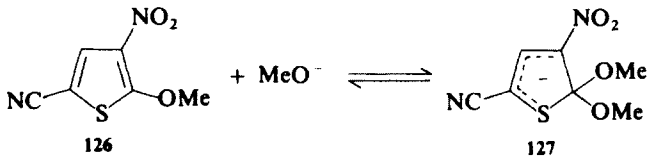
Some adducts have also been obtained from nitro- (**24**, **115**), dinitro- (**117**), and cyanonitrothiophenes (**120**, **122**) (Scheme 25).[132,148-154]

The study of the behavior of 2-cyano-4-nitrothiophene (**122**) and 5-cyano-2-methoxy-3-nitrothiophene (**126**) with methoxide enables an interesting comparison between geminal and nongeminal adducts. In dimethylsulfoxide (DMSO) 2-cyano-4-nitrothiophene (**122**) gives the expected σ-adduct



Scheme 25

(**125**),[147] but in methanol it undergoes an attack at the cyanogroup, yielding an anion (**123**) by acidification of which the corresponding carboxyimidate (**124**) can be obtained.[148] An accurate examination of the course of the reaction in methanol by using the stopped-flow technique[149] has shown that initially the σ-adduct (**125**) is formed (kinetic control) but it can give the more stable carboxyimidate (**123**) (thermodynamic control). On the contrary, 5-cyano-2-methoxy-3-nitrothiophene (**126**), where the α-carbon atom bears a methoxyl and not a hydrogen, gives the usual geminal σ-adduct (**127**) (Scheme 26).[132]

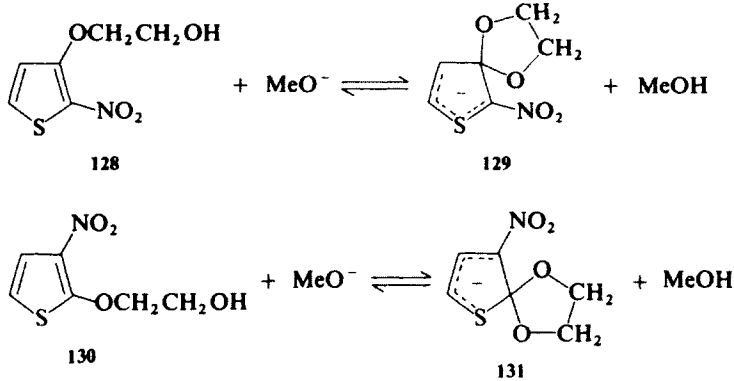


126 **127**

Scheme 26

On the other hand, 4-cyano-2-nitrothiophene (**120**) gives the expected σ-adduct (**121**) in both DMSO[147] and methanol.[148] This peculiar behavior has no comparable situation in benzenoid compounds.[154]

The unique example of a β-adduct in thiophene series is represented by the spiro-adduct formed from 3-(2-hydroxyethoxy)-2-nitrothiophene (**128**) by ring closure at the β-position (**129**), analogously to what happens with the isomeric 2-(2-hydroxyethoxy)-3-nitrothiophene (**130**) (Scheme 27).[155] The driving force for the β-adduct formation clearly comes from the intramolecular cyclization.

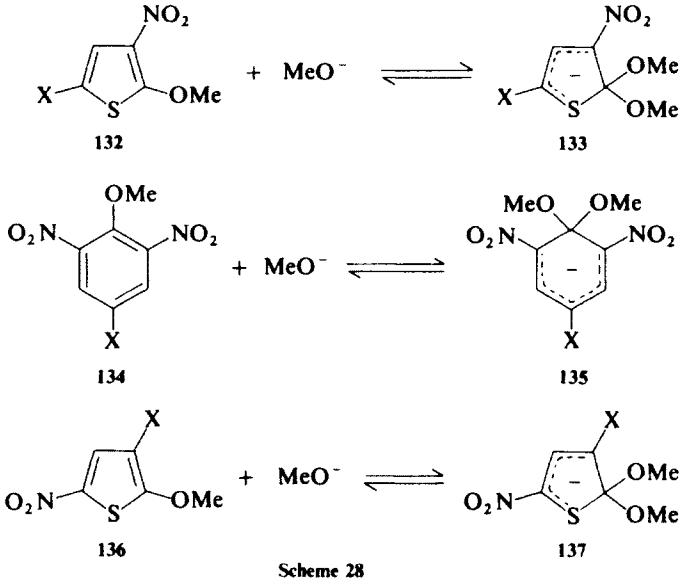


128 **129**

130 **131**

Scheme 27

Evidence for the formation of a series of adducts (**133**) from 2-methoxy-3-nitro-5-X-thiophenes (**132**) have been reported:[131,132,145,146,156,157] rate and equilibrium constants for the formation of the Meisenheimer adducts (Scheme 28) as well as ^{13}C NMR chemical shifts for the substrates (X = H, $CONH_2$, CO_2Me, Ac, SO_2Me, CN, or NO_2) and the corresponding geminal adducts, have been determined.



Scheme 28

Although both kinetic and equilibrium constants increase with increasing the electron-withdrawing ability of X (see data in Table 3), the correlation of logarithmic equilibrium ($\log K_e$) or kinetic ($\log k_1$) constants with σ_p^- is not linear, nor is the "direct" correlation between $\log K_e$ and $\log k_1$, in contrast with the situation observed for "analogous" benzene compounds such as the 2,6-dinitro-4-X-anisoles (**134**).[158] This has been interpreted on grounds of the hyper-*ortho* relation occurring in thiophene derivatives.[108-114,116,117] In fact, it has been proposed[157] that when X is a "mild" electron-withdrawing substituent, there is a preferential through-conjugation between the 2- and 3-positions, whereas there is no such preference with "strong" electron-withdrawing substituents. As a consequence, in the first situation the substituent shows a reduced conjugative ability and practically behaves as having only an inductive effect; in the second case the substituent can affect the electronic density of the ring by both the inductive and the conjugative effect. Because the greater the negative charge of the adduct, the more it is stabilized by the electron-withdrawing substituent, the relation (Figure 1) of $\log K_e$ or $\log k_1$ with σ_p^- is not linear and $\log K_e$ increases more "rapidly" than $\log k_1$ with increasing σ_p^-.[157]

Quite interestingly, the results of ^{13}C NMR studied suggest that most substituents increase the stability of σ-adducts not so much by assuming part of their negative charge but mainly by stabilizing the negative fractional charges on ring carbons.[157] It should be pointed out that the adducts derived from 2-methoxy-3-nitro-5-X-thiophenes (**132**), which contain only *one* nitrogroup, show formation rates close to those of the adducts (**135**) derived from 2,6-dinitro-4-X-anisoles[158] (Table 3), which contain *two* nitrogroups. Since the decomposition rates are much lower for thiophene than for benzene adducts, the first are much more stable than the latter ones.

TABLE 3. Kinetic and Equilibrium Constants for Reactions of Some Methoxynitrocompounds with Sodium Methoxide in Methanol at 20°C

2-Methoxy-3-nitro-5-X-thiophenes (**132**) X =	K_e (liters mol^{-1})	k_1 (liters mol^{-1} sec^{-1})	2,6-Dinitro-4-X-anisoles (**134**) X =	K_e (liters mol^{-1})	k_1 (liters mol^{-1} sec^{-1})
H[a]	6.0	1.3×10^{-3}	H[b]	$7.5–9 \times 10^{-5}$	1.5×10^{-3}
$CONH_2$[c]	34.2	2.78×10^{-2}	F[b]	8.5×10^{-5}	2.5×10^{-3}
CO_2Me[c]	109	0.116	Cl[b]	2.5×10^{-3}	1.2×10^{-2}
Ac[c]	152	0.301	CF_3[b]	5	0.4
SO_2Me[c]	3.13×10^{3}	0.769	SO_2Me[b]	1.01×10^{2}	1.75
CN[c]	7.65×10^{3}	1.30	CN[b]	1.68×10^{2}	2.82
NO_2[d]	3.50×10^{5}	27.2	NO_2[b]	1.95×10^{4}	1.18×10
			SO_2CF_3[b]	1.2×10^{6}	1.41×10^{2}

[a] Ref. 156.
[b] Ref. 158.
[c] Ref. 157.
[d] Ref. 132.

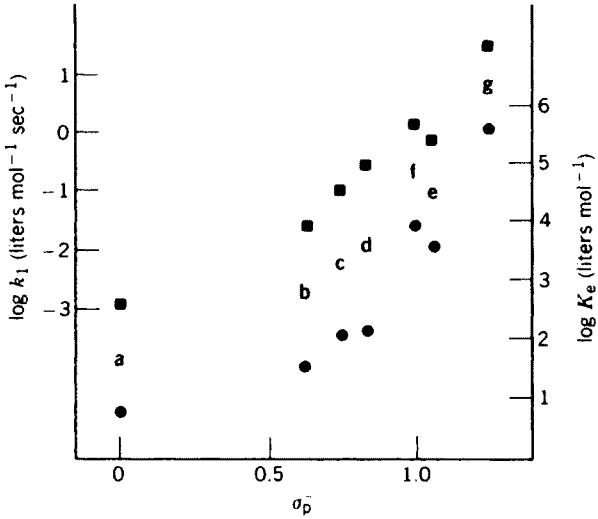


Figure 1. Plot of log k_1 (■) or log K_e (●) for the reaction of some 2-methoxy-3-nitro-5-X-thiophenes (**132**; **a**: X = H, **b**: X = $CONH_2$, **c**: X = CO_2Me; **d**: X = Ac, **e**: X = SO_2Me, **f**: X = CN, **g**: X = NO_2) with sodium methoxide in methanol at 20°C versus σ_p^- constants.

Similar results have been obtained studying the formation of a series of Meisenheimer adducts (**137**) from some 2-methoxy-5-nitro-3-X-thiophenes (**136**).[159] The observed stability-reactivity patterns for the two series of reactions have been interpreted on the basis of a major role played by the hyper-*ortho* relation in the 3-nitro-substituted substrates (**132**), at variance with (**136**); thus, the greater stability and rate of formation of adducts (**137**) with respect to the corresponding adducts (**133**) would result from the preferential conjugative interaction between the 2 and 3 positions which renders substrates (**132**) more stable than substrates (**136**).

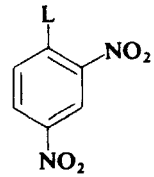
Many interlocking factors influence the formation and the stability of thiophene and benzene adducts: the more favorable geometry (especially the values of the angles at the carbon of the reaction centre) together with the lower aromaticity and the presence of the sulfur (the *d*-orbitals of which are available to accommodate part of the negative charge in the adducts) would render the thiophene substrates more reactive than the analogous benzene compounds. On the contrary, the hyper-*ortho* relation lowers and levels the reactivity of thiophene compounds. A comparison with data concerning furan,[150,160] selenophene,[147,161] and pyrrole[162,163] σ-adducts supports this viewpoint.

3. Element Effect

The leaving group effect on the reaction rate represents a useful tool for investigating the nature of the mechanism of nucleophilic substitution. In fact,

in a S_N2-like mechanism the rate-determining transition state involves the fission of the carbon–leaving-group bond;[164] on the other hand, in the attachment–detachment mechanism,[21–28] which implies the formation of two transition states and of a σ-complex, the fission of the carbon–leaving-group bond, in principle, could be or not to be rate-determining, in much the same way as what happens for S_EAr reactions.[165–168]

This proof, first proposed by J. F. Bunnett and his coworkers[45] in the study of aromatic nucleophilic substitution reactions, has been named "element effect" and used to establish which is the rate-determining transition state. Data obtained by J. F. Bunnett and his coworkers for piperidino-[45] and benzenethiolate-substitution[140] in the benzene series are collected in Table 4. The results obtained in the reaction of some nine 1-L-2,4-dinitrobenzenes (**138**: L = F, NO_2, $OSO_2C_6H_4CH_3$-*p*, SOPh, Br, Cl, SO_2Ph, $OC_6H_4NO_2$-*p*, I) with piperidine in methanol are particularly meaningful.



L = F, NO_2, $OSO_2C_6H_4CH_3$-*p*, SOPh, Br, Cl, SO_2Ph, $OC_6H_4NO_2$-*p*, I

138

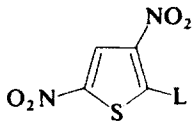
TABLE 4. Reactivity of Some 1-L-2,4-Dinitrobenzenes (**138**) with Sodium Benzenethiolate (PhS^-) or Piperidine (PIP) in Methanol at 0°C

L =	k (liters mol^{-1} sec^{-1})[a] (PIP)	k (liters mol^{-1} sec^{-1})[b] (PhS^-)
F	90	103.4
NO_2	24.2	—
$OSO_2C_6H_4CH_3$-*p*	2.72	—
SOC_6H_5	0.129	—
Br	0.118	6.68
Cl	0.117	3.89
$SO_2C_6H_5$	0.0860	—
$OC_6H_4NO_2$-*p*	0.0812	1.66
I	0.0272	5.17

[a] Ref. 45.
[b] Ref. 140.

In fact, both the enthalpy and the entropy of activation were constant for six substrates (L = SOPh, Br, Cl, SO_2Ph, $OC_6H_4NO_2$-*p*, I); indeed, these substrates react with a common nucleophile at nearly the same rate irrespective of the nature of the first atom of the leaving group. This indicates that the fission of the

carbon–leaving-group bond does not occur in the rate-determining step. Later on, as a consequence of a criticism by Lamm and Lammert,[46] Rappoport and Bunnett[47] indicated some limitations for this criterion; however, it has been used largely in the study of nucleophilic substitution, especially S_NAr, to gain mechanistic information. Similar results have been obtained in the study of piperidino- and benzenethiolate-substitution of thiophene derivatives. For example, a study of the reactions of five 2-L-3,5-dinitrothiophenes [**28** and **139** (L = Cl, Br, I, SO_2Ph, $OC_6H_4NO_2$-*p*); see data in Table 5] with piperidine in ethanol[92] showed a little variation in reactivity for four leaving groups; the exception was 2-iodo-3,5-dinitrothiophene, which, on account of the low electronegativity of the leaving group, was rather less reactive than the other compounds.



L = Br, I, SO_2Ph, $OC_6H_4NO_2$-*p*

139

TABLE 5. Reactivity of Some Thiophene Derivatives with Piperidine (PIP) or Sodium Benzenethiolate (PhS^-) at 20°C

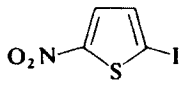
2-L-3,5-Dinitrothiophenes L =	*k* (liters mol^{-1} sec^{-1})[a] (PIP, Ethanol)	*k* (liters mol^{-1} sec^{-1})[b] (PIP, Methanol)
I (**139**)	0.178	0.176
Br (**139**)	2.27	1.98
Cl (**28**)	4.73	3.74
$SO_2C_6H_5$ (**139**)	11.6	6.80
$OC_6H_4NO_2$-*p* (**139**)	20.1	15.5
2-L-3-Nitrothiophenes L =	***k* (liters mol^{-1} sec^{-1}) (PhS^-, Methanol)**	
Br (**71**)	0.116[c]	
Cl (**102**)	0.092[d]	
$SO_2C_6H_5$ (**70**)	4.40[d]	
$OC_6H_4NO_2$-*p* (**101**)	0.460[d]	
3-L-2-Nitrothiophenes L =	***k* (liters mol^{-1} sec^{-1}) (PhS^-, Methanol)**	
I (**141**)	0.169[d]	
Br (**73**)	0.234[e]	
Cl (**104**)	0.136[d]	
$SO_2C_6H_5$ (**72**)	43.4[d]	
$OC_6H_4NO_2$-*p* (**103**)	0.238[d]	

TABLE 5. (*Contd.*)

2-L-3,5-Dinitrothiophenes L =	k (liters mol^{-1} sec^{-1})[a] (PIP, Ethanol)	k (liters mol^{-1} sec^{-1})[b] (PIP, Methanol)
2-L-5-Nitrothiophenes L =	k (liters mol^{-1} sec^{-1}) (PhS^-, Methanol)	
I (**140**)	0.088[c]	
Br (**66**)	0.136[c]	
Cl (**106**)	0.126[c]	
$SO_2C_6H_5$ (**67**)	13.9[d]	
$OC_6H_4NO_2$-*p* (**105**)	0.826[d]	

[a] Ref. 92.
[b] Ref. 96 and references cited therein.
[c] Ref. 93.
[d] Ref. 90.
[e] Ref. 100.

A similar range of reactivities has been observed in benzenethiolate-substitutions of some 2-L-5-nitrothiophenes (**66**, **67**, **105**, **106**, **140**), 2-L-3-nitrothiophenes (**70**, **71**, **101**, **102**), and 3-L-2-nitrothiophenes (**72**, **73**, **103**, **104**, **141**) (L = Cl, Br, I, SO_2Ph, $OC_6H_4NO_2$-*p*) in methanol (Table 5);[90] in this case there is such a balance between electronegativity and polarizability for the various leaving groups that very close reaction rates can be observed for the three halogens and *p*-nitrophenoxy.



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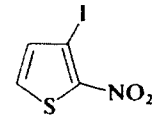
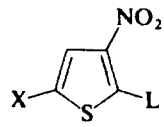


141

More recently the leaving-group variation has been studied in the case of the piperidinosubstitution in methanol of seven series of 2-L-3-nitro-5-X-thiophenes (**142**) (L = Cl, Br, I, SO_2Ph, $OC_6H_4NO_2$-*p*, OPh, OCH_2CF_3) and the results obtained[96,169] deserve some comments. Indeed, whereas a relatively small range of reactivities with changing leaving group has been observed for X = NO_2 (reactivity range less than 90 for all the seven or 10 for six leaving groups, except L = I), in the series of 2-L-3-nitrothiophenes (X = H), the



L = Cl, Br, I, SO_2Ph, $OC_6H_4NO_2$-*p*, OPh, OCH_2CF_3

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variation in reactivity with changing leaving group is much more pronounced (reactivity range ~600 without any possible grouping of leaving groups). The logarithmic plots of the rate constants of 2-L-3-nitro-5-X-thiophenes versus σ_p or σ_p^- values show many intersections between the straight lines (Figure 2). As a consequence of the different ρ-values calculated, the element-effect criterion gives different results as a function of the 5-X-substituted 2-L-3-nitrothiophene considered. Whatever that may be, the enlargement of the reactivity range cannot be understood only on the basis of the variations in the electronegativity of the leaving group.

On the basis of the results concerning the substituent effects in S_NAr reactions of thiophene derivatives, the element-effect criterion should be used with caution and suitable leaving groups should be carefully chosen. Among the leaving groups usually used for the study of the element there are *p*-nitrophenoxy, halogens (chlorine, bromine, and iodine) and phenylsulfonyl, but the relevant susceptibility constants fall in a rather wide range: $\rho \sim 2.7$ for *p*-nitrophenoxy, 3.3 for halogens, and 4.0 for phenylsulfonyl.[96] Both phenoxy and trifluoroethoxy leaving groups display[169] susceptibility constants (2.5) similar to that of *p*-nitrophenoxy.[96] In fact, Figure 2 shows that there is a lower dependence of reaction rates on the nature of the leaving groups in the right side than in the left side of the plot. In fact, there is a range of strong electron-withdrawing substituents (large positive σ_p^- values) where the reaction rates for six out of the

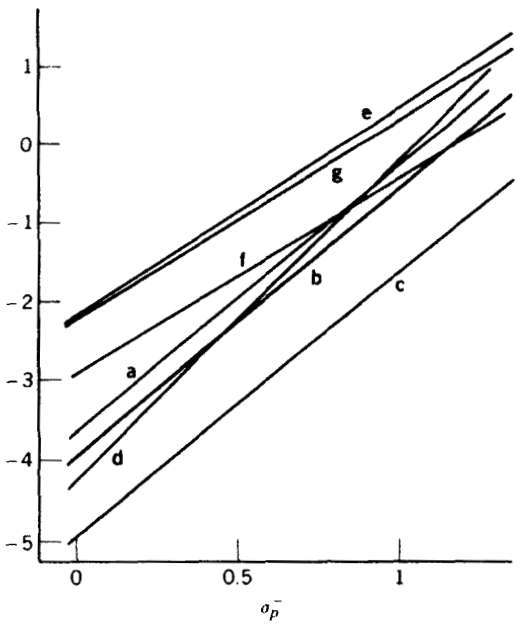

Figure 2. Hammett plot for the piperidinosubstitution of some 2-L-3-nitro-5-X-thiophenes (**142**; **a**: L = Cl; **b**: L = Br, **c**: L = I, **d**: L = SO_2Ph, **e**: L = $OC_6H_4NO_2$-*p*, **f**: L = OPh, **g**: L = OCH_2CF_3).

seven leaving groups are only slightly dependent on the nature of the leaving group but the dependence increases with decreasing σ_p^- or σ_p values. As a consequence, it is evident that one can obtain opposite information from studies of element effect, depending on the substituents present in the series studied. In conclusion, a correct use of the element effect as a tool for investigating aromatic nucleophilic substitutions should limit the leaving groups to halogens that show much the same susceptibility constants* and would give the same response, as to the element effect, whatever the substituent present.

4. Base Catalysis

In contrast to the situation where the nucleophile is an anion, the S_NAr reactions involving primary and secondary amines as nucleophiles can be catalyzed.[28] With reference to Scheme 5, this is expressed by Eq. 1, which is obtained by applying the usual 'steady-state' approximation to the intermediate of the attachment–detachment mechanism.[26] In Eq. 1 k_A is the apparent second-order kinetic constant, obtained by dividing the pseudo-first-order rate constant by amine concentration:

$$k_A = \frac{k_1 k_2 + k_1 k_3^B[B]}{k_{-1} + k_2 + k_3^B[B]} \tag{1}$$

According to Eq. (1), absence of base catalysis can mean that $(k_2 + k_3^B[B]) \gg k_{-1}$ or that $k_{-1} > k_2$ but $k_2 \gg k_3^B[B]$. Apart from the rare situation where, as a result of large steric effects, the k_3^B coefficient could become very small, generally the insensitivity to base catalysis indicates that the overall reaction rate is controlled by the formation of the reaction intermediate: $k_A = k_1$.

When $(k_2 + k_3^B[B]) \ll k_{-1}$, the reaction responds linearly to base catalysis and Eq. 1 is converted into Eq. 2:

$$k_A = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3^B[B]}{k_{-1}} \tag{2}$$

If k_2 is relatively small and $k_{-1} \simeq k_3^B[B]$ within the experimental range of base concentrations, k_A depends on [B] in a curvilinear fashion.

Depending on the aromatic substrate, the amine, the nucleofugal group, the base, and the solvent, different catalysis laws can be, and are, observed.[28]

Thus, the reactions of some 2-L-3-nitrothiophenes (**70**, **71**, **101**, **102**, **143**, **145**) and 2-L-5-nitrothiophenes (**66**, **67**, **105**, **106**, **140**, **144**) (L = F, Cl, Br, I, $OC_6H_4NO_2$-*p*, SO_2Ph) with piperidine in methanol or ethanol are bimolecular, first-order in both substrate and piperidine, and they proceed through a rate-determining formation of the intermediate:[170, 171]

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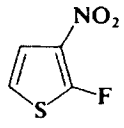
* Comparing the behavior of halogens as leaving groups the observed reactivity variations can be discussed with respect to their electronegativities and polarizabilities.



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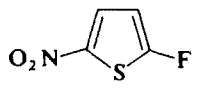

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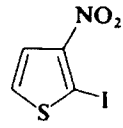

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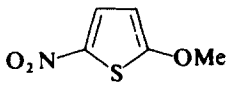
The variation of the solvent, from methanol to benzene, has very different effects with respect to each series of compounds. The reactivity of *ortho*-nitrosubstituted compounds does not change (L = $OC_6H_4NO_2$-*p*)[170] or increases only slightly (L = Cl, Br, SO_2Ph, NO_2)[95, 170, 171] with increasing piperidine concentration, probably owing to a "medium" effect similar to that observed for benzene derivatives.[172] The apparent kinetic constant of 2-iodo-3-nitrothiophene (**145**) decreases as the piperidine concentration is increased:[170] this behavior seems to depend on some effect of complexing between the two reagents. The reactivity of all the *para*-nitrosubstituted compounds increases linearly with increasing piperidine concentration; however, whereas three halogen derivatives (L = Cl, Br, I) show low k_3^B/k_2 ratios (1–8),[170, 171] the reactivity in the case of L = F, $OC_6H_4NO_2$-*p*, SO_2Ph, NO_2 indicates a high sensitivity to base concentration.[144, 170, 171]

According to Bunnett's classification,[57] based on k_3^B/k_2 values, only the piperidinosubstitutions of 2-L-5-nitrothiophenes with L = F, $OC_6H_4NO_2$-*p*, SO_2Ph, NO_2 are genuinely base-catalyzed, and this agrees with the low nucleofugality of fluoro, *p*-nitrophenoxy, phenylsulfonyl, and nitrogroups in benzene.[28, 173]

The absence of base catalysis in the case of *ortho*-nitrosubstituted compounds in both methanol and benzene can be explained on grounds of the "built-in solvation"[141] by which the *ortho*-nitrogroup promotes the elimination of the proton and of the leaving group from the reaction intermediate (see Section II.1); on the other hand, the reactions of 2-L-5-nitrothiophenes where the activating nitrogroup is in *para*-position are assisted by the solvent when it is methanol[28] but certainly not by benzene.

According to the general behavior of 2-L-5-nitrothiophenes,[170, 171] 2-methoxy-5-nitrothiophene (**146**) reacts with piperidine in methanol giving second-order kinetics.[174]



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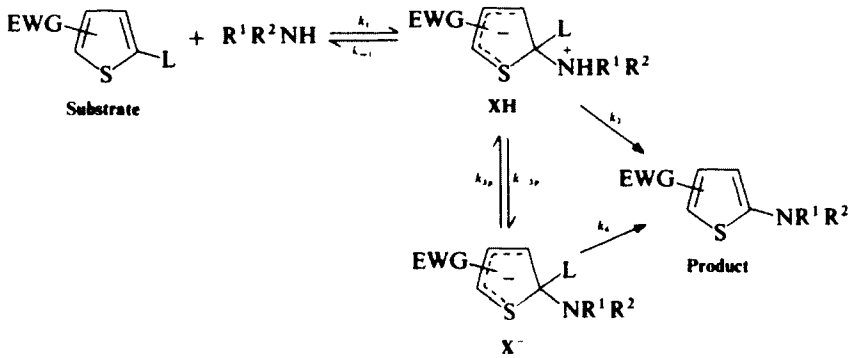
Quite surprisingly k_A for the piperidinosubstitution of 2-methoxy-3-nitrothiophen (**109**) in methanol increases with increasing piperidine concentration in a curvilinear fashion.[174] Experiments carried out in the presence of piperidine hydrochloride allowed to conclude that the catalysis is due mainly to the methoxide ion deriving from the basic ionization of piperidine in methanol.

Owing to the dominance of catalysis by methoxide ion, catalysis by piperidine was not detectable. Also the piperidinosubstitutions of some 2-methoxy-3-nitro-5-X-thiophenes (**132**) (X = COOMe, COMe) in methanol are strongly accelerated by MeO^- with a curvilinear plot of k_A versus $[MeO^-]$.[175] The reactions are also catalyzed by piperidine with k_A increasing somewhat less than linearly with piperidine concentration.[175] With reference to Scheme 29, the general expression for k_A, in terms of rate coefficients for specific steps, is Eq. 3.



Scheme 29

Equations 3–6 apply where k_{3p}^{MeO} and k_{3p}^{PIP} refer to deprotonation of **XH** by MeO^- and by piperidine, respectively, k_{-3p}^{MeO}, and k_{-3p}^{PIP} refer to the protonation of X^- by the solvent and by $PIPH^+$, respectively, and k_4^{MeO} refers to uncatalyzed or solvent-assisted leaving-group expulsion whereas k_4^{PIP} allows for the possibility of general-acid-catalyzed leaving-group departure by the protonated amine.

$$k_A = \frac{k_1 k_2 (k_{-3p} + k_4) + k_1 k_{3p} k_4}{(k_{-1} + k_2)(k_{-3p} + k_4) + k_{3p} k_4} \tag{3}$$

$$k_{3p} = k_{3p}^{MeO}[MeO^-] + k_{3p}^{PIP}[PIP] \tag{4}$$

$$k_{-3p} = k_{-3p}^{MeO} + k_{-3p}^{PIPH}[PIPH^+] \tag{5}$$

$$k_4 = k_4^{MeO} + k_4^{PIPH}[PIPH^+] \tag{6}$$

The three principal mechanisms[176] of base catalysis, which involves the removal of the ammonium proton from the intermediate (**XH**), are (a) rate-limiting proton abstraction by the base to form deprotonated intermediate, followed by rapid leaving-group expulsion (proton transfer mechanism); (b) rapid equilibrium deprotonation followed by rate-limiting general-acid-catalyzed detachment of the nucleofugal group (SB–GA mechanism); or (c) concerted proton transfer and leaving-group detachment with bifunctional catalysis by the amine. Assuming either $k_4 \gg k_{-3p}$ (proton transfer mechanism) or $k_4 \ll k_{-3p}$ (SB–GA mechanism) leads to the same formal dependence of k_A on $[MeO^-]$

and [PIP]:

$$k_A = \frac{a(b + cx_1 + dx_2)}{1 + b + cx_1 + dx_2} \tag{7}$$

where $x_1 = [PIP]$ and $x_2 = [MeO^-]$

The fitting of kinetic data to equation (7) by a least-squares method gives results pointing out that there is no significant contribution to k_A from the solvent-assisted pathway for the decomposition of the intermediate.

An upper limit of k_4 can be estimated from k_r values for the decomposition of Meisenheimer-type adducts deriving from 2-methoxy-3-nitro-5-X-thiophenes (**132**)[157] to be 0.5 and 0.7 for X = CO_2Me and X = Ac, respectively. Since

$$k_{-3p} = \frac{k_{3p}^{MeO} K_s}{K_a^{XH}} \left(1 + \frac{k_{3p}^{PIP}[PIPH^+]}{k_{3p}^{MeO} K_b^{PIP}}\right) \tag{8}$$

where K_s is the autoprotolysis constant of methanol, K_b^{PIP} is the basic ionization constant of piperidine in methanol, and K_a^{XH} is the acid dissociation constant of **XH**, by suitable estimates of the unknown constants, one obtains as a lower limit $k_{-3p} = 1.4 \times 10^{-9} k_{3p}^{MeO}$. Since the deprotonation of **XH** by MeO^- is diffusion-controlled or nearly so, it is clear that k_4 values can never approach k_{3p} values, as the real situation is $k_4 \ll k_{3p}$; thus, the catalysis observed occurs through the SB–GA mechanism.[28] This happens because the pK difference between the methoxy leaving group and the acid catalyst ($PIPH^+$) is large enough to balance the increase in entropy of including another molecule into the transition state. Assuming the SB–GA mechanism for base catalysis and $k_2 = 0$ (see above) leads to the following simplification of Eq. 3:

$$k_A = \frac{k_1 K_3 k_4}{k_{-1} + K_3 k_4} \tag{9}$$

where

$$K_3 = \frac{k_{3p}^{MeO}[MeO^-]}{k_{-3p}^{MeO}} = \frac{k_{3p}^{PIP}[PIP]}{k_{-3p}^{PIPH}[PIPH^+]} = \frac{K_a^{XH}}{[MeOH_2^+]} \tag{10}$$

Base catalysis in the piperidinosubstitutions of 2-methoxy-3-nitro-5-X-thiophenes (**132**) (X = H, COOMe, COMe)[174,175] is observable as long as k_{-1} is larger than or similar to $K_3 k_4$. Since the piperidinosubstitutions of 2-L-3-nitrothiophenes (L = Cl, Br, I, $OC_6H_4NO_2$-*p*, SO_2Ph, OPh, OCH_2CF_3) in methanol are not catalyzed,[169,170] base assistance in the substitution of a methoxy leaving group could be, in principle, needed because of a larger k_{-1} and/or a lower $K_3 k_4$ for methoxy than for the other leaving groups studied. The hyper-*ortho* relation[108–114,116,117] between 2-methoxy and 3-nitro groups makes the first transition state for piperidinosubstitution closely resemble the reaction intermediate (high k_{-1} value); on the other hand, k_4 refers to a bond-breaking process, and it is likely to be quite low with the very sluggish methoxy

leaving group. As 2-methoxy-5-nitrothiophene (**146**) lacks the above through-conjugation factor, the absence of catalysis in methanol is accordingly accounted for.[174]

Since the reversion of the reaction intermediate (Scheme 29) to reactants leads to charge neutralization, k_{-1} is expected to increase strongly on going from methanol to benzene, thus reducing the k_2/k_{-1} ratio. The piperidinosubstitution reactions of 2-methoxy-3-nitrothiophene (**109**) in benzene[177] show a more than linear increase of k_A with increasing piperidine concentration, with the relevant curve going through the origin. In fact, the reaction is wholly piperidine-catalyzed and the slight upward curvature can be attributed to a medium effect.* The piperidinosubstitution reactions of 2-methoxy-3-nitro-5-X-thiophenes (**132**) (X = H, $CONH_2$, COOMe, COMe, CN) respond *linearly* to catalysis by piperidine and the kinetic data obey Equation 11:[182]

$$k_A = k'[\text{PIP}] = \frac{k_1 k_3^{\text{PIP}}[\text{PIP}]}{k_{-1}} \tag{11}$$

With reference to Scheme 29, Eq. 11 implies that $k_2 = 0$ and $k_{-1} \gg k_3^{\text{PIP}}[\text{PIP}]$ for all the compounds studied. The "catalytic" constant k' increases with increasing the electron-withdrawing power of the 5-substituent, but there is no linear correlation between log k' values and the substituent constants, σ_p^-[183]. Since the reactions of the same 2-methoxy-3-nitro-5-X-thiophenes (**132**) with *n*-butylamine in benzene are not base-catalyzed and then $k_A = k_1$, the plot (Figure 3) of $\log[k'/(k')_H]$ (piperidine reaction) versus $\log[k_1/(k_1)_H]$ (*n*-butylamine reaction) represents with a good approximation the variation of $\log(k_3^{\text{PIP}}/k_{-1})$ as the 5-substituent is changed. We have already shown that the substitutions of 2-methoxy-3-nitro-5-X-thiophenes (**132**) (X = H, COOMe, COMe) by piperidine in methanol are catalyzed by the SB–GA mechanism. It is conceivable that the corresponding reactions in benzene are catalyzed by the same mechanism. In fact, the points relative to 2-methoxy-3-nitro-5-X-thiophenes (**132**) (X = H, $CONH_2$, COOMe, COMe) show a good adherence to the solid line of slope 1.1 and indicate that in this range of electron activation k_3^{PIP}/k_{-1} is nearly independ-

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* Recently Sbarbati and Palleros have suggested a "dimer" mechanism for the catalysed pathways,[178–180] on grounds of the quadratic dependence on base concentration of the observed second-order rate coefficient, k_A. In our opinion this new formulation of base catalysis does not give a deeper insight into the base-catalyzed mechanism, compared to the current classical approach. In fact, the hypothesis that the catalyzed pathway proceeds only through a stepwise addition of molecules of the monomer nucleophile and/or of an added base catalyst or also through a pathway involving the dimer of the nucleophile and/or a complex nucleophile-added base removes the attention from the focal point which is the understanding of the various factors involved (the nature of the solvent, the base, and/or the nucleophile; the kind of the nucleofugality of the leaving group; etc.). On the other hand, the validity of the "dimer" mechanism has been questioned by Banjoko and Ezeani[181] on account of the different response to base catalysis, as a function of the substituted phenoxy leaving group, of the reactions involving X-phenyl 2,4,6-trinitrophenyl ethers and aniline in benzene. The results were interpreted in terms of a cyclic mechanism much similar to bifunctional catalysis.[176,181]

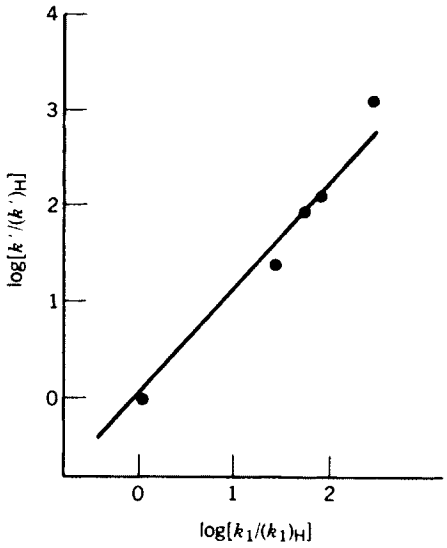


Figure 3. Plot of $\log[k'/(k')_H]$ (piperidine reaction) versus $\log[k_1/(k_1)_H]$ (*n*-butylamine reaction) in benzene at 20°C of some 2-methoxy-3-nitro-5-X-thiophenes (**132**).

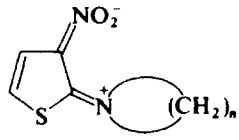
ent of the 5-substituent and that the Hammett absolute ρ-value for k_3^{PIP} is nearly the same as that for k_{-1}. Bearing in mind the above mentioned mechanism for base catalysis, the similar sensitivities of k_3^{PIP} and k_{-1} to the acidifying effect of the electron-withdrawing 5-substituent suggest that the intermediate (Scheme 29) is deprotonated in an equilibrium reaction (SB–GA) mechanism where the variable substituent exerts its full electronic effects in contrast with the situation in the other two mechanisms where the proton is only partially transferred in the transition state.[176]

The pyrrolidinosubstitution of 2-methoxy-3-nitrothiophene (**109**) in methanol at 20°C is second-order overall, first-order in both substrate and nucleophile.[184] The change from piperidine to pyrrolidine therefore causes the spectacular variation from $k_2/k_{-1} \ll 1$ to $k_2/k_{-1} \gg 1$.[174,184] In principle, the smaller k_2/k_{-1} ratio for piperidine could be a consequence of a smaller k_2, a larger k_{-1}, or a combination of both. If the k_{-1} values for the two amines are about the same, the cause of the different response to catalysis should be the k_2 parameter.

A possible factor of steric nature that has the effect of reducing k_2 is the hindrance, by an *ortho*-substituent, of the developing resonance in the structure (**147**), a canonical form of the product of reaction.

On changing from methanol to benzene[184] there is an increase in k_{-1} comparatively greater than in k_2 and the relation $k_2 \gg k_{-1}$ is reversed for pyrrolidine (PYR).

The reaction of 2-methoxy-3-nitrothiophene (**109**) with piperidine (PIP) and with perhydroazepine (PHA) in benzene are also catalyzed by the amine.[177,182]



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On the assumption[185] that $k_{-1}^{PYR} \simeq k_{-1}^{PIP} \simeq k_{-1}^{PHA}$ and by estimating the reactivity ratios in nucleophilic attack, expressed as k_1, for each pair of cyclic amines,[184] one calculates $k_3^{PYR} : k_3^{PIP} : k_3^{PHA} = 40 : 3.4 : 1$. These results suggest that the base-catalyzed product-forming step ($k_3^{B_i}$) is controlled by the ring size of the cyclic amine, in accordance with the above interpretation concerning k_2.

In the SB–GA mechanism $k_3^{B_i}$ represents the product of the equilibrium constant between **XH** and each base B_i by $k_4^{BH_i}$, namely, $k_3^{B_i} = K_{3p}^{B_i} k_4^{BH_i}$. Since the $K_{3p}^{B_i}$ constants for the reaction between **XH** and the corresponding amines are expected to be independent of the nature of the amines, because $K_{3p}^{B_i} = K_a^{XH}/K_a^{B_i}$ and both electronic and steric effects are essentially constant for each **XH** intermediate, the difference in the $k_3^{B_i}$ parameter must stem from a difference in $k_4^{B_i}$ values.

The reaction of 2-methoxy-3-nitrothiophene (**109**) with the three cyclic amines are also catalyzed by DABCO. The relative catalytic efficiency, as measured by $k_4^{B_i}/k_4^{DABCO}$, varies with changing amine size, showing a different steric hindrance for the three amines, by the carbon-bound amino-moiety to the approach of DABCO · H^+. This and the preceding results can be explained in terms of conformational differences that produce additional steric compression in the reaction area.

5. The Substituent Effects

In the attachment–detachment mechanism the formation of the first transition state, with a negative charge developing in the aromatic or heteroaromatic ring, usually is rate-determining, and thus electron-withdrawing and -repelling substituents increase and decrease the reaction rate, respectively.[59–63] As in benzene compounds, the effect of substituents in the thiophene ring can be correlated with the S_NAr reaction rates by the Hammett equation, using σ_m, σ_p, and σ_p^- constants for *meta*-like substituents, electron-repelling and electron-withdrawing *para*-like substituents, respectively.

The reactions studied are concerned with substitution at C(2) or at C(3), that is, at an α- or a β-carbon atom of the thiophene ring and with both anionic (sodium arenethiolates and lithium chloride-36) and neutral (piperidine, aniline and substituted anilines, and *n*-butylamine) nucleophiles in various solvents (ethanol, methanol, benzene, and sulfolane). The relevant reaction constants are presented in Tables 6 and 7.

TABLE 6. Linear Free-Energy Relationships for Some Nucleophilic Substitutions of Thiophene Derivatives

Reaction No.	Substrate	Nucleophile (Solvent, °C)	Susceptibility Constant	Statistical Data[a]	Ref.
1	2-Bromo-3-nitro-5-X-thiophenes (**142**, L = Br)	Piperidine (ethanol, 20)	3.21	8, 0.995	133
2	2-Bromo-3-nitro-5-X-thiophenes (**142**, L = Br)	Piperidine (methanol, 20)	3.18	7, 0.995	186
3	2-Bromo-3-nitro-5-X-thiophenes (**142**, L = Br)	Piperidine (methanol, 20)	3.31	8, 0.9998	96
4	2-Bromo-4-methyl-3-nitro-5-X-thiophenes (**148**)	Piperidine (methanol, 20)	3.24	7, 0.995	186
5	2-Chloro-3-nitro-5-X-thiophenes (**142**, L = Cl)	Piperidine (methanol, 20)	3.42	7, 0.9998	96
6	2-Iodo-3-nitro-5-X-thiophenes (**142**, L = I)	Piperidine (methanol, 20)	3.26	7, 0.9990	96
7	2-*p*-Nitrophenoxy-3-nitro-5-X-thiophenes (**142**, L = $OC_6H_4NO_2$-*p*)	Piperidine (methanol, 20)	2.65	7, 0.9983	96
8	2-Phenylsulfonyl-3-nitro-5-X-thiophenes (**142**, L = $SO_2C_6H_5$)	Piperidine (methanol, 20)	4.02	8, 0.9993	96
9	2-Bromo-3-nitro-5-X-thiophenes (**142**, L = Br)	*p*-Anisidine (methanol, 20)	3.66	8, 0.9999	99
10	2-Bromo-3-nitro-5-X-thiophenes (**142**, L = Br)	*p*-Toluidine (methanol, 20)	3.66	8, 0.9998	99
11	2-Bromo-3-nitro-5-X-thiophenes (**142**, L = Br)	Aniline (methanol, 20)	3.64	8, 0.9999	99
12	2-Bromo-3-nitro-5-X-thiophenes (**142**, L = Br)	*m*-Cloroaniline (methanol, 20)	3.53	8, 0.9997	99
13	2-Bromo-3-nitro-5-X-thiophenes (**142**, L = Br)	*p*-Carbomethoxyaniline (methanol, 20)	3.48	8, 0.9996	99
14	2-Chloro-3-nitro-5-X-thiophenes (**142**, L = Cl)	Lithium chloride (sulfolane, 50)	5.55	7, 0.996	187
15	2-Chloro-3-nitro-5-X-thiophenes (**142**, L = Cl)	Lithium chloride (sulfolane, 100)	4.68	7, 0.993	187
16	2-Chloro-3-nitro-5-X-thiophenes (**142**, L = Cl)	Sodium benzenethiolate (methanol, 20)	3.97	8, 0.990	*b*
17	3-Bromo-2-nitro-5-X-thiophenes (**154**)	Sodium benzenethiolate (methanol, 20)	4.51	7, 0.989	188
18	3-Bromo-2-nitro-4-X-thiophenes (**150**)	Sodium benzenethiolate (methanol, 20)	3.96	6, 0.993	109
19	3-Bromo-4-nitro-2-X-thiophenes (**151**)	Sodium benzenethiolate (methanol, 20)	8.18	4, 0.998	109
20	2-Bromo-5-nitro-3-X-thiophenes (**152**)	Piperidine (methanol, 20)	4.02	7, 0.998	190
21	2-Bromo-4-methyl-5-nitro-3-X-thiophenes (**149**)	Piperidine (methanol, 20)	3.77	6, 0.996	189
22	2-Phenylsulfonyl-5-nitro-3-X-thiophenes (**153**)	Piperidine (methanol, 20)	4.60	5, 0.995	91

[a] Number of points and correlation coefficient.

[b] D. Spinelli, R. Noto, and G. Consiglio, unpublished results.

TABLE 7. Linear free-Energy Relationships for Some Nucleophilic Substitutions of Thiophene Derivatives in Methanol at 20°C

Reaction No.	Substrate	Nucleophile	Susceptibility Constant	Statistical Data[a]	Ref.
1	2-Bromo-3-nitrothiophene (**71**)[b]	*m*-Substituted sodium arenethiolates	− 0.76	6, 0.996	191
2	3-Bromo-2-nitrothiophene (**73**)[b]	*m*-Substituted sodium arenethiolates	− 0.78	6, 0.995	191
3	2-Bromo-3,5-dinitrothiophene (**142**, L = Br, X = NO_2)[c]	*m*-,*p*-Substituted anilines	− 3.00	14, 0.9983	192
4	2-Bromo-3,5-dinitrothiophene (**142**, L = Br, X = NO_2)[d]	*o*-Substituted anilines	− 2.75	7, 0.9984	193
5	2-Bromo-3,5-dinitrothiophene (**142**, L = Br, X = NO_2)[e]	*o*-,*m*-,*p*-Substituted anilines	− 2.96	20, 0.9980	193

[a] Number of points and correlation coefficient.

[b] The rates of the nucleophilic substitution of (**71**) and (**73**) with 10 *p*-substituted sodium arenethiolates have also been measured, but they do not give good Hammett correlations. Vice versa an excellent free-energy relationship (*n* 16, slope 1.06, *r* 0.999) has been obtained by plotting the kinetic data referring to **73** against those of **71** for the reactions with *m*- and *p*-substituted sodium arenethiolates.

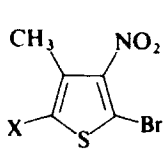
[c] Susceptibility constant and statistical data refer to the Ingold–Yukawa–Tsuno relationship: $\log k/k_H = \rho\sigma^n + 0.38\,\Delta\sigma_R^+ + 0.99\,\Delta\sigma_R^-$).

[d] Susceptibility constant and statistical data refer to the Fujita-Nishioka relationship: $\log k_o/k_H = \rho\sigma_o + 1.27E_S - 1.91F$.

[e] Susceptibility constant and statistical data refer to the Fujita-Nishioka relationship: $\log k_{o,m,p}/k_H = \rho\sigma_{o,m,p} + 1.31E_S - 1.83F$.

The whole of results lead to the following conclusions:

1. The 2,5- and the 2,4-relation, where there is no steric interaction between substituent and reaction center, can be regarded as *para*-like[96,99,133,186,187] and *meta*-like[188] relations as also indicated by the kind of substituent constants used for calculations (σ_p and σ_p^- in the first case and σ_m in the second); moreover, on account of the favorable geometry of thiophene ring, also 2,3- and 3,4-*ortho*-like[109] substituted compounds can give good linear free-energy relationships (LFERs).
2. The nature of the substituent constants used for electron-withdrawing *para*-like substituents[96,99,133,186,187] and the susceptibility constants calculated[96,99,133,186,187] similar to those observed for the analogous benzene derivatives[59-63] represent strong evidence for the occurrence of an attachment–detachment (S_NAr) mechanism.
3. Good LFERs can also be observed for tetrasubstituted, that is, wholly *ortho*-substituted thiophene derivatives[186,189] (see reactions 4 and 21 in Table 6 and formulas **148**, **149** here).



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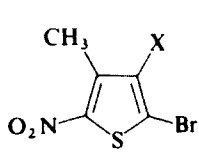
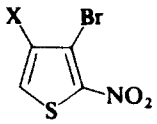


149

4. Also when the variable substituent is adjacent (*ortho*-like) to the reaction center, good linear free-energy *ortho*-correlations can be observed (see reactions 18–22 in Table 6) and the relevant susceptibility constants are higher than the corresponding values for *para*-correlations,[91,189,190] showing that an *ortho*-substituent affects the position of the rate-determining transition state along the reaction coordinate more than a *para*-substituent (see formulas **150–153**).



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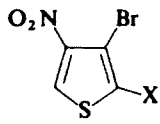

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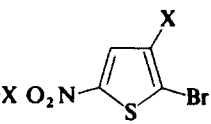

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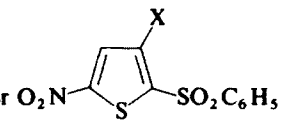

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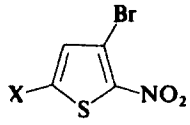
5. The transmission of substituent effects through the C(2)–C(3) bond[109] of the thiophene ring is very different from that through the C(3)–C(4) bond[109] (cf. reactions 19 and 18 in Table 6). This has to be attributed[109] to the different bond orders of the two bonds[107] and supports the hyper-*ortho* and the hypo-*ortho* character, respectively, of the two relationships.[108-118] As a consequence, different kinds of substituent constants have to be used (σ_p^- and σ_p, respectively) and very different susceptibility

constants are calculated.[109] For the benzenethiolate-debromination at C(3) (reactions nn.17–19 in Table 6) the following order of susceptibility constants has been observed for hyper-*ortho*, *meta*-like, and hypo-*ortho* relations,[109,188] respectively:

$$\rho_{C(2)-C(3)} > \rho_{C(2)-C(4)} > \rho_{C(3)-C(4)}$$



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6. The substituent effect on the reactions of 2-methoxy-3-nitro-5-X-thiophenes (**132**) with *n*-butylamine or piperidine in benzene gives a curvilinear plot of log *k* versus σ_p^-.[182] The curvature of the plot is more pronounced in the second case, a base-catalysed reaction, and this result is consistent with the SB–GA mechanism for base catalysis (see Section II.4). A similar curvilinear plot has been observed in the formation of Meisenheimer-type adducts (**133**) of 2-methoxy-3-nitro-5-X-thiophenes in methanol[157] (see Section II.2).
7. The study of effects of the substituents present in benzenethiolate nucleophile has pointed out[191] the following facts: (a) the reactions with 2-bromo-3-nitrothiophene (**71**) and 3-bromo-2-nitrothiophene (**73**) (see reactions 1 and 2 in Table 7, respectively) show the same susceptibility constants, suggesting that the changes in the electronic interactions between the sulfur atom and the substituents in the benzenethiolate ions are almost independent of the position of the reaction center with respect to the heteroatom of the thiophene ring, (b) in the corresponding Hammett plots the effects of electron-withdrawing and -repelling *para*-substituents in the benzenethiolate are lower and higher, respectively, than those expected on the basis of the effects exerted by *meta*-substituents, indicating the occurrence of through-conjugation with both classes of substituents (see paragraph 8).[191]
8. The effect of substituents present in the aniline as nucleophile in the reaction with 2-bromo-3,5-dinitrothiophene (see reaction 3 in Table 7) has pointed out[192] the necessity of using an Ingold–Yukawa–Tsuno relationship, which indicates that both electron-withdrawing and -repelling *para*-substituents give rise to through-conjugation with the reaction center in S_NAr reactions. Also the corresponding reaction of ortho-substituted anilines has been correlated[193] with substituent effects by means of the multiparameter Fujita–Nishioka equation (see reactions 4 and 5 in Table 7), which takes into account both the electronic and the steric effects of substituents.

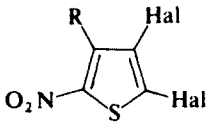
The effect of a substituent at C(5) in the thiophene substrate has also been studied[96] in methanol as a function of the leaving group in the piperidinosubstitution reaction to gain information about the position of the rate-determining transition state along the reaction coordinate (see reactions 3 and 5–8 in Table 6). When the leaving group was a halogen (chlorine, bromine, or iodine), the ρ-values calculated were nearly equal (~ 3.3), whereas when the leaving group was *p*-nitrophenoxy or phenylsulfonyl, the susceptibility constants were smaller (2.7) and larger (4.0), respectively. Bearing in mind that the absolute ρ value is an index of the change of position of the rate-determining transition state along the reaction coordinate as a function of the substituent present, the different ρ-values calculated clearly indicate a strong influence by the nature of the leaving group. The similar ρ-values obtained with the three halogens as leaving groups in spite of the large variations of absolute reactivity point out that the selectivity–reactivity relationship does not apply and suggest that the effectiveness of the halogen in controlling the position of the rate-determining transition state depends on factors that balance with each other. Both steric and electronic factors play a role in the interaction of the leaving group with the ring and its substituents in the starting substrate as well as in the transition state: thus, the *p*-nitrophenoxy group behaves as an electron donor and has a levelling effect on the electronic effects of the present substituents. Moreover, the head-atom of this leaving group is small, and therefore electronic interactions between nucleophile and reaction center are possible when the old bond is not much distorted and the new bond is only minimally formed: since in this case the 5-substituent scarcely affects the structure of the rate-determining transition state, a low susceptibility constant is observed. On the other hand, the phenylsulfonyl leaving group is a strong electron-attracting group and, by lowering the electronic density in the thiophene ring, enhances the substituent effects. Moreover, owing to its bulkiness, the electronic interactions between nucleophile and reaction center are possible only when the old bond is strongly deformed and the new bond largely formed; in this case the 5-substituent largely affects the structure of the rate-determining transition state and a high susceptibility constant is observed.

By studying the reactions of a series of 2-bromo-3-nitro-5-X-thiophenes with a number of *meta*- and *para*-substituted anilines,[99] it has been possible to get a deeper insight into the applicability of the reactivity–selectivity principle. Both the susceptibility parameters, the ρ-value for a given substituent in the nucleophile (see reactions 9–13 in Table 6) and the β-value for a given substituent in the thiophene substrates (ranging between 0.95 and 1.06) are practically invariant, and this is in contrast with the background of the Hammond postulate.[196,197] The apparent failure of the reactivity–selectivity principle depends on the various possible interactions between aromatic substrate and nucleophile, including the formation of intramolecular and intermolecular hydrogen bonds. The structure–reactivity relationships can be visualized by the More O'Ferrall–Jencks diagrams,[196,197] which show how both the

"Hammond" and "anti-Hammond" effects can operate, causing the invariance of ρ- and β-values.

It is customary to consider the methyl group as an electron-repelling substituent relative to hydrogen. Such a + I effect generally lowers the mobility of a leaving nitro-activated halogen in S_NAr reactions.[26]

A study[198] of piperidino- and benzenethiolate-debromination of 2,3-dibromo-5-nitrothiophene (in **155a**: Hal = Br) and 2,3-dibromo-4-methyl-5-nitrothiophene (in **155b**: Hal = Br), in methanol, brought to light an unusual example of rate enhancement by a methyl group located in a *meta*-position with respect to the reaction center (see data in Table 8). This peculiar behavior was tentatively related to the Reinheimer–Bunnett effect[199] of the 3-bromine on the 2-bromine "augmented" by the 4-methyl group.



a: R = H
b: R = CH_3

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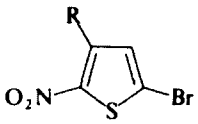
The subsequent study[200] designed to ascertain whether the weak activation by the *meta*-methyl group was dependent on the halogen as both leaving group and *ortho*-substituent showed (see data in Table 8) much the same increase in reactivity with both piperidine and benzenethiolate, on changing from any **155a** to any **155b**, whatever halogen (chlorine, bromine, or iodine).

However, also in the reactions, with piperidine and sodium benzenethiolate in methanol, of some 3-alkyl-5-bromo-2-nitrothiophenes (**156a–f**) where there is *no halogen* in the 3-position, the *meta*-alkyl group determines a weak acceleration with respect to the parent compound (**66**).[201]



a: R = CH_3; **b**: R = C_2H_5; **c**: R = *n*-C_3H_7;
d: R = *n*-C_6H_{13}; **e**: R = *i*-C_3H_7; **f**: R = *t*-C_4H_9

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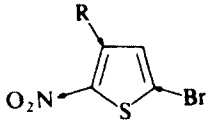
An examination of k_R/k_H ratios revealed that *meta*-alkyl substitution increases the reactivity of 2-bromo-5-nitrothiophene (**66**) with both nucleophiles to an extent that is practically independent of nucleophile and of alkyl group, the average value of k_R/k_H being 2.1 ± 0.5 (see data in Table 8). Changing hydrogen for alkyl group in an *ortho*-like position with respect to the nitrogroup might hinder the orientation of solvent molecules in this region and then cause

TABLE 8. Reactivity Ratios (k_R/k_H) for Some Nucleophilic Substitutions of Thiophene Derivatives in Methanol at 20°C

Reactivity Ratio No.	Substrates	Nucleophile[a]	k_R/k_H	Ref.
1	2,3-Dichloro-4-methyl-5-nitrothiophene (**155b**)/2,3-dichloro-5-nitrothiophene (**155a**)	PIP	1.4	200
2	2,3-Dibromo-4-methyl-5-nitrothiophene (**155b**)/2,3-dibromo-5-nitrothiophene (**155a**)	PIP	1.4	198
3	2,3-Diiodo-4-methyl-5-nitrothiophene (**155b**)/2,3-diiodo-5-nitrothiophene (**155a**)	PIP	1.4	200
4	2,3-Dichloro-4-methyl-5-nitrothiophene (**155b**)/2,3-dichloro-5-nitrothiophene (**155a**)	PhS^-	1.7	200
5	2,3-Dibromo-4-methyl-5-nitrothiophene (**155b**)/2,3-dibromo-5-nitrothiophene (**155a**)	PhS^-	1.2	198
6	2,3-Diiodo-4-methyl-5-nitrothiophene (**155b**)/2,3-diiodo-5-nitrothiophene (**155a**)	PhS^-	1.7	200
7	2-Bromo-4-methyl-5-nitrothiophene (**156a**)/2-bromo-5-nitrothiophene (**66**)	PIP	1.8	201
8	2-Bromo-4-ethyl-5-nitrothiophene (**156b**)/2-bromo-5-nitrothiophene (**66**)	PIP	2.0	201
9	2-Bromo-5-nitro-4-*n*-propylthiophene (**156c**)/2-bromo-5-nitrothiophene (**66**)	PIP	1.7	201
10	2-Bromo-4-*n*-hexyl-5-nitrothiophene (**156d**)/2-bromo-5-nitrothiophene (**66**)	PIP	1.8	201
11	2-Bromo-5-nitro-4-*i*-propylthiophene (**156e**)/2-bromo-5-nitrothiophene (**66**)	PIP	2.1	201
12	2-Bromo-4-*t*-butyl-5-nitrothiophene (**156f**)/2-bromo-5-nitrothiophene (**66**)	PIP	4.8	201
13	2-Bromo-4-methyl-5-nitrothiophene (**156a**)/2-bromo-5-nitrothiophene (**66**)	PhS^-	2.0	201
14	2-Bromo-4-ethyl-5-nitrothiophene (**156b**)/2-bromo-5-nitrothiophene (**66**)	PhS^-	2.2	201
15	2-Bromo-5-nitro-4-*n*-propylthiophene (**156c**)/2-bromo-5-nitrothiophene (**66**)	PhS^-	1.6	201
16	2-Bromo-4-*n*-hexyl-5-nitrothiophene (**156d**)/2-bromo-5-nitrothiophene (**66**)	PhS^-	1.8	201
17	2-Bromo-5-nitro-4-*i*-propylthiophene (**156e**)/2-bromo-5-nitrothiophene (**66**)	PhS^-	1.2	201
18	2-Bromo-4-*t*-butyl-5-nitrothiophene (**156f**)/2-bromo-5-nitrothiophene (**66**)	PhS^-	1.9	201
19	3,4-Dibromo-2-methyl-5-nitrothiophene (**159b**)/3,4-dibromo-2-nitrothiophene (**159a**)	AN	2.8	201
20	3-Bromo-5-methyl-2-nitrothiophene (**160**)/3-bromo-2-nitrothiophene (**73**)	AN	3.2	201
21	3-Bromo-5-methyl-2-nitrothiophene (**160**)/3-bromo-2-nitrothiophene (**73**)	PhS^-	2.5	201
22	2-Bromo-5-methyl-3-nitrothiophene (**161**)/2-bromo-3-nitrothiophene (**71**)	PIP	1.0	201
23	2-Bromo-5-methyl-3-nitrothiophene (**161**)/2-bromo-3-nitrothiophene (**71**)	PhS^-	1.8	201

[a] Nucleophiles: piperidine (PIP), sodium benzenethiolate (PhS^-), aniline (AN).

some reduction in solvation, this effect should act mainly in the initial state than in the transition state. As far as the ground states of substrates under investigation are concerned, the polarity features of the molecules are dependent principally on the polar interactions with the ring, as sketched in **157**. In the formation of the rate-determining transition state **158** in the reaction with both nucleophiles, it is necessary that the nitrogroup is in conjugation with the ring so that the negative charge arising from nucleophilic attack can be delocalized. The alkyl substituents might determine a different solvation of the initial state compared to the transition state, and the observed acceleration could be accounted for on these grounds.



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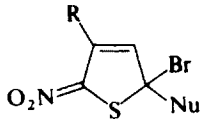

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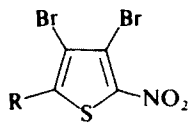
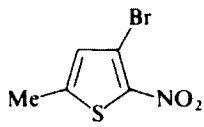
Surprisingly, the S_NAr reactivity pattern of some model thiophene compounds (**159b**, **160**, **161**), where both the leaving group (bromine) and the kind of activation (conjugated *ortho*- or *para*-like nitrogroup) remained the same, whereas the relative positions of alkyl groups and nitrogroups were changed, shows that pairs **159a** and **159b** and **73** and **160** behave (see data in Table 8) in the same way as 2,3-dibromo-4-R-5-nitrothiophenes (**155a–b**: Hal = Br) and the pair **66** and **156a**, respectively. Moreover, the introduction of a methyl group in the *para*-like 5-position of 2-bromo-3-nitro-thiophene **71** had no effect or once again a weakly activating effect in the reactions of **161** with piperidine or sodium benzenethiolate (see data in Table 8). These findings constitute compelling evidence *against* the differential solvation hypothesis.



a: R = H
b: R = CH_3

159



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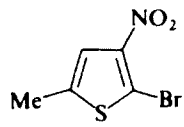

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In principle, alkyl groups are able to both donate and accept electrons as the charged site demands, resulting in the stabilization of both positive and negative charge through a polarization-type process. Traditionally, a methyl group is considered to be electron-releasing in that it stabilizes cations and destabilizes anions. However, there are exceptions to this generalization.[202,203]

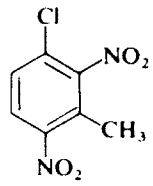
As far as the S_NAr reactions are concerned, there is no example of alkyl activation in the benzene series.[204] Nevertheless, we consider the stabilization of the transition state through electron polarization by alkyl groups as a plausible hypothesis.

6. Steric Effects in S_NAr Reactions of Thiophene Derivatives

It is well known that the S_NAr reactivity of six-membered ring compounds is influenced by both secondary and primary steric effects.[199,204-208] Both effects influence S_EAr reactions, too.[42,209,210] In view of the different geometry of the five-membered ring compounds,[107,134,211] which presumably affects the distance and therefore the interactions (steric and/or electronic) between adjacent groups, which is the situation as to steric effects?

A. Secondary Steric Effects

The formation of the first transition state of the attachment–detachment mechanism, which often is the rate-determining step, is strongly influenced by the electronic effects exerted by the substituents present in the aromatic substrate: the electron-withdrawing substituents, able to exert mesomeric and through-resonance effects from positions conjugated with the reaction centre, are particularly effective in favoring the S_NAr reaction. Considering the structure of the rate-determining transition state, as exemplified by **19** for a substitution in a nitro activated benzene compound, it is evident that the condition for a high effectiveness of an electron-withdrawing substituent is its coplanarity (or quasi-coplanarity) with the aromatic ring. On the other hand, each additional substituent that prevents the electron-withdrawing substituent to be coplanar, or nearly so, with the aromatic ring, causes a strong decrease in the reactivity in S_NAr reactions. For example, the insertion of a methyl group [which because of its electronic effect would cause only a slight decrease of reactivity (a factor of ~ 2)] between the two nitrogroups of 2,4-dinitrochlorobenzene **97** in 3-chloro-2,6-dinitrotoluene **162** strongly lowers the piperidino-dechlorination rate in ethanol (k_H/k_{Me} in ethanol ~ 960 at 20°C).[204] This represents a good example of kinetic secondary steric effect as determined by the steric inhibition of resonance of the activating nitrogroups. Indeed, the intervening methyl group causes the torsion and/or the out-of-plane bending of nitrogroups.

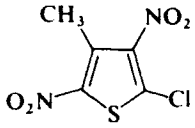


162

A strong support to this interpretation comes from the recent structure determination,[212] by X-rays, of 3-chloro-2,6-dinitrotoluene **162**, as compared with that of 2,4-dinitrochlorobenzene **97**, already known.[138,139] The positions of the two nitrogroups with respect to the plane of the benzene ring are very

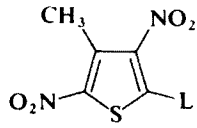
different; in fact, in **97** the *ortho*- and the *para*-nitrogroups are rotated by about 40° and 15°, respectively, whereas in **162** they are rotated by about 81° and 30°, respectively. Thus, the crystal structures of **97** and **162** are in agreement with the kinetic data: the presence of the methyl group in **162** allows the *ortho*-nitrogroup to exert, practically, only its inductive effect, whereas the *para*-nitrogroup can still exert its mesomeric and through-resonance effects, even though with a lower effectiveness than in **97**.

On going from six-membered to five-membered ring derivatives, the kinetic secondary steric effects become less considerable. In fact, 2-chloro-3,5-dinitro-4-methylthiophene **163** is only a little less reactive than 2-chloro-3,5-dinitrothiophene **28** in piperidinodechlorination reaction ($k_H/k_{Me} \sim 2$ at 20°C in methanol; see data in Table 9).[213]



163

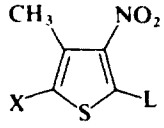
Similar results have been obtained by a comparison of the reactivities in methanol at 20°C of the other halogenoderivatives **164**: L = Br, I; see data in Table 9.[213,214] Only when the leaving group is the phenylsulfonyl group (in **164**: L = $SO_2C_6H_5$) there is a little secondary effect ($k_H/k_{Me} \sim 8$, see data in Table 9).[213] In this case the methyl group seems to exert a buttressing effect that increases the steric interactions between the phenylsulfonyl and the adjacent nitrogroup.[213]



L = Br, I, $SO_2C_6H_5$

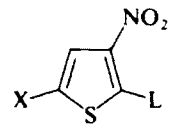
164

These interactions appear to be limited to the groups present at C(2), C(3), and C(4) of the thiophene ring; in fact, independently of the substituent present at C(5) (hydrogen, bromine, or nitrogroup) similar rate ratios (k_H/k_{Me}) are observed in some 2-L-3-nitro-4-R-5-X-thiophenes (**70**, **71**, **139**, **164**–**166**) with



L = Br, $SO_2C_6H_5$
X = H, Br

165



L = Br, $SO_2C_6H_5$
X = H, Br

166

TABLE 9. Reactivity Ratios (k_H/k_R) for Some Nucleophilic Substitutions of Thiophene Derivatives at 20°C

Reactivity Ratio No.	Substrates	Nucleophile, Solvent[a]	k_H/k_R	Ref.
1	2-Chloro-3,5-dinitrothiophene (**28**)/2-chloro-3,5-dinitro-4-methylthiophene (**163**)	PIP, MeOH	1.9	213
2	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-methylthiophene (**164**)	PIP, MeOH	1.9	214
3	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-methylthiophene (**164**)	PIP, EtOH	2.3	214
4	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-methylthiophene (**164**)	PIP, PhH	1.6	214
5	2-Iodo-3,5-dinitrothiophene (**139**)/2-iodo-3,5-dinitro-4-methylthiophene (**164**)	PIP, MeOH	1.7	213
6	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-phenylsulfonyl-3,5-dinitro-4-methylthiophene (**164**)	PIP, MeOH	7.8	213
7	2-Bromo-3-nitrothiophene (**71**)/2-bromo-4-methyl-3-nitrothiophene (**165**)	PIP, MeOH	2.0	213
8	2-Phenylsulfonyl-3-nitrothiophene (**70**)/2-phenylsulfonyl-4-methyl-3-nitrothiophene (**165**)	PIP, MeOH	7.7	213
9	2,5-Dibromo-3-nitrothiophene (**166**)/2,5-dibromo-4-methyl-3-nitrothiophene (**165**)	PIP, MeOH	2.7	213
10	2-Phenylsulfonyl-5-bromo-3-nitrothiophene (**166**)/2-phenylsulfonyl-5-bromo-4-methyl-3-nitrothiophene (**165**)	PIP, MeOH	8.9	213
11	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-methylthiophene (**164**)	*p*-TOL, MeOH	1.2	215
12	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-phenylsulfonyl-3,5-dinitro-4-methylthiophene (**164**)	*p*-TOL, MeOH	5.6	215
13	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-methylthiophene (**164**)	AN, MeOH	1.2	215
14	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-phenylsulfonyl-3,5-dinitro-4-methylthiophene (**164**)	AN, MeOH	5.7	215
15	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-methylthiophene (**164**)	DEA, MeOH	1.9	215
16	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-phenylsulfonyl-3,5-dinitro-4-methylthiophene (**164**)	DEA, MeOH	7.4	215
17	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-methylthiophene (**164**)	MAN, MeOH	1.1	215
18	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-phenylsulfonyl-3,5-dinitro-4-methylthiophene (**164**)	MAN, MeOH	16	215
19	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-methylthiophene (**164**)	*o*-TOL, MeOH	1.4	215

TABLE 9. (*Contd.*)

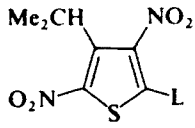
Reactivity Ratio No.	Substrates	Nuceophile, Solvent[a]	k_H/k_R	Ref.
20	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-phenylsulfonyl-3,5-dinitro-4-methylthiophene (**164**)	*o*-TOL, MeOH	5.9	215
21	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-methylthiophene (**164**)	DMA, MeOH	1.6	215
22	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-phenylsulfonyl-3,5-dinitro-4-methylthiophene (**164**)	DMA, MeOH	5.8	215
23	2-Bromo-3-nitrothiophene (**71**)/2-bromo-4-methyl-3-nitrothiophene (**165**)	PhS^-, MeOH	2.5	215
24	2-Phenylsulfonyl-3-nitrothiophene (**70**)/2-phenylsulfonyl-4-methyl-3-nitrothiophene (**165**)	PhS^-, MeOH	6.4	215
25	2-Bromo-3-nitrothiophene (**71**)/2-bromo-4-methyl-3-nitrothiophene (**165**)	MeO^-, MeOH	3.3	215
26	2-Phenylsulfonyl-3-nitrothiophene (**70**)/2-phenylsulfonyl-4-methyl-3-nitrothiophene (**165**)	MeO^-, MeOH	17	215
27	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-*i*-propylthiophene (**167**)	AN, MeOH	7.4	216
28	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-phenylsulfonyl-3,5-dinitro-4-*i*-propylthiophene (**167**)	AN, MeOH	60	216
29	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-*i*-propylthiophene (**167**)	PIP, MeOH	6.9	216
30	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-Phenylsulfonyl-3,5-dinitro-4-*i*-propylthiophene (**167**)	PIP, MeOH	96	216
31	2-Bromo-3,5-dinitrothiophene (**139**)/2-bromo-3,5-dinitro-4-*i*-propylthiophene (**167**)	MAN, MeOH	7.4	216
32	2-Phenylsulfonyl-3,5-dinitrothiophene (**139**)/2-phenylsulfonyl-3,5-dinitro-4-*i*-propylthiophene (**167**)	MAN, MeOH	110	216

[a] Nucleophiles: piperidine (PIP), *p*-toluidine (*p*-TOL), aniline (AN), diethylamine (DEA), *N*-methylaniline (MAN), *o*-toluidine (*o*-TOL), 2,6-dimethylaniline (DMA), sodium benzenethiolate (PhS^-), sodium methoxide (MeO^-). Solvents: methanol (MeOH), ethanol (EtOH), benzene (PhH).

both bromine and phenylsulfonyl leaving groups in methanol at 20°C (see data in Table 9).[213]

The pattern observed in piperidinosubstitution holds also for the substitution reactions with other nucleophiles (2,6-dimethylaniline, *o*- and *p*-toluidine, aniline, *N*-methylaniline, diethylamine, sodium benzenethiolate, and sodium methoxide). The slight scattering of rate ratios (see data in Table 9) depends on the steric requirements of the nucleophile in that it can increase the steric inhibition of resonance of the 3-nitrogroup and then can render the kinetic secondary effect more pronounced.[215]

The size of the alkyl group inserted between the two activating nitrogroups could be a critical factor in determining the steric interactions in the reaction area. Thus, the behavior of 2-L-3,5-dinitro-4-isopropylthiophenes **167** with some nucleophiles (aniline, piperidine, and *N*-methylaniline) in methanol has been studied.[216]



L = Br, $SO_2C_6H_5$

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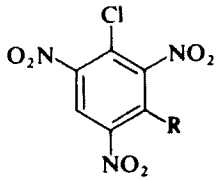
The kinetic data in Table 10 show that the k_H/k_R ratios at 20°C increase to approximately 7 with bromine as leaving group and to 60–110 with phenylsulfonyl, and that significant steric interactions occur when a highly branched alkyl group is inserted between the two nitrogroups.

In fact, the secondary steric effects are much lower in five-membered than in six-membered ring derivatives. Consistently a study of the radioactive chlorine exchange reactions in some 3-R-2,4,6-trinitrochlorobenzenes **168** has shown[217] a strong dependence of secondary steric effects on the bulkiness of the alkyl substituent inserted between the two nitrogroups (k_H/k_R increases from 190 and 140 with methyl and ethyl to 4700 and 82,000 with isopropyl and *t*-butyl, respectively).



R = H, CH_3, C_2H_5, *i*-C_3H_7, *t*-C_4H_9

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Therefore, in benzene series taking into account the different influence of steric effects in piperidinodechlorination and in radioactive chlorine exchange, the piperidinodehalogenation reaction would show a $k_H/k_{i\text{-}Pr}$ ratio of ~20,000;

TABLE 10. Reactivity Ratios (k_H/k_R) for Some Nucleophilic Substitutions of 2-L-5-Nitro-3-R-thiophenes in Methanol at 20°C

Reactivity Ratio No.	Substrates	k_H/k_R PIP[a]	k_H/k_R PhS^-[b]	Ref.
1	2-Chloro-5-nitrothiophene (**106**)/2-chloro-3-methyl-5-nitrothiophene (**172**)	3.0	0.38	219
2	2-Bromo-5-nitrothiophene (**66**)/2-bromo-3-methyl-5-nitrothiophene (**173**)	3.9	0.40	219
3	2-Iodo-5-nitrothiophene (**140**)/2-iodo-3-methyl-5-nitrothiophene (**174**)	3.8	—	219
4	2-Phenylsulfonyl-5-nitrothiophene (**67**)/2-phenylsulfonyl-3-methyl-5-nitrothiophene (**175**)	17	1.3	219
5	2-Bromo-5-nitrothiophene (**66**)/2-bromo-3-ethyl-5-nitrothiophene (**176a**)	5.0	0.60	220
6	2-Bromo-5-nitrothiophene (**66**)/2-bromo-5-nitro-3-*n*-propylthiophene (**176b**)	3.9	0.83	220
7	2-Bromo-5-nitrothiophene (**66**)/2-bromo-3-*n*-hexyl-5-nitrothiophene (**176c**)	5.1	0.73	220
8	2-Bromo-5-nitrothiophene (**66**)/2-bromo-5-nitro-3-*i*-propylthiophene (**176d**)	15	2.0	220
9	2-Bromo-5-nitrothiophene (**66**)/2-bromo-3-*t*-buthyl-5-nitrothiophene (**176e**)	110	9.5	220
10	2-Phenylsulfonyl-5-nitrothiophene (**67**)/2-phenylsulfonyl-3-ethyl-5-nitrothiophene (**177a**)	—	2.5	220
11	2-Phenylsulfonyl-5-nitrothiophene (**67**)/2-phenylsulfonyl-5-nitro-3-*n*-propylthiophene (**177b**)	—	3.2	220
12	2-Phenylsulfonyl-5-nitrothiophene (**67**)/2-phenylsulfonyl-3-*n*-hexyl-5-nitrothiophene (**177c**)	—	3.7	220
13	2-Phenylsulfonyl-5-nitrothiophene (**67**)/2-phenylsulfonyl-5-nitro-3-*i*-propylthiophene (**177d**)	—	22	220
14	2-Phenylsulfonyl-5-nitrothiophene (**67**)/2-phenylsulfonyl-3-*t*-buthyl-5-nitrothiophene (**177e**)	—	120	220

[a] Piperidine.
[b] Sodium benzenethiolate.

on the other hand, in thiophene series the piperidino-debromination reaction shows a ratio of only ~7. Moreover, although phenylsulphonyl is a leaving group much more steric demanding than bromine, $k_H/k_{i\text{-}Pr}$ for piperidinodephenylsulfonylation is only ~100.

The previsions of low interactions between adjacent substituents in five-membered ring derivatives, based on the geometric structure of thiophene* (see Section I.4) and on the kinetic data obtained in the study of secondary steric effects, have been strongly supported by X-ray crystal structure determinations. Crystal structures of 3,5-dinitro-2-iodothiophene (**139**: L = I) and 3,5-dinitro-2-iodo-4-methylthiophene (**164**: L = I) have been determined:[134] iododerivatives should show the highest steric interactions among the halogenoderivatives. However, the crystal structure of (**164**:L = I) confirms the previsions based on kinetic data; in spite of the presence of the methyl between the two nitrogroups and the large atomic radius of iodine [which could exert a buttressing effect on the substituents at C(3), C(4), and C(5)], the torsion and/or the out of plane bending of the nitrogroup is relatively small. Indeed, while the nitrogroup at C(5) practically is coplanar with the ring both in (**139**: L = I) and in (**164**: L = I) the nitrogroup at C(3) in (**164**: L = I) is rotated of about 44° out of plane. This shows as far as the activation by the nitrogroups is concerned, that the steric situation is really more favorable, than that observed in 3-chloro-2,6-dinitrotoluene (**162**).[204,211]

B. Primary Steric Effects

Unlike the secondary steric effect, which is an electronic effect determined by steric interactions (steric inhibition of resonance), the primary steric effect is essentially a straightforward steric effect exerted by a substituent near to the reaction site and disfavors the approach of the nucleophile. For example, the electronic effect exerted by an *ortho*-alkyl group in a benzene compound such as **169**, which can be estimated to cause a two- to sixfold decrease in the reaction rate, is largely exceeded by the primary steric effect, especially if a bulky nucleophile is used. In fact, by comparing the reactivities in methanol at 46°C of **170** and **169** in piperidinodefluorination, one can observe a primary steric effect that strongly lowers the reactivity (k_H/k_{Me} ~45).[199] On the other hand, because of the dominance of the Reinheimer–Bunnett factor,[199] no such effect is observed in the parallel reaction of benzenethiolate-defluorination (k_H/k_{Me} ~0.96).[199] Parallel results have been obtained with chlorine or bromine as leaving groups.

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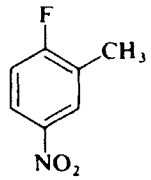
* It is well known that small changes in steric compression can cause large differences in kinetic effects.[218] A comparison of scalar molecular models of a five-membered (e.g., **163**) and a six-membered (e.g., **162**) ring derivative shows that there is a significant difference in steric interactions between methyl and nitrogroups in the two aromatic systems, which depends on the greater bond length and the larger external angles in thiophene than in benzene.



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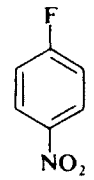

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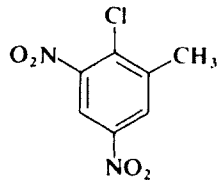
Higher primary kinetic effects have been observed[204] in dinitrobenzene derivatives; for example, 2-chloro-3,5-dinitrotoluene **171** is strongly less reactive than 2,4-dinitrochlorobenzene **97** (k_H/k_{Me} at 20°C with piperidine or aniline in ethanol, and sodium methoxide in methanol is 276, 22, and 13.5, respectively).



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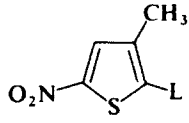
On going from six-membered to five-membered ring derivatives the kinetic primary steric effects are strongly reduced (see the case for kinetic secondary steric effects discussed in Section II.6.A). In fact, the 2-halogeno-3-methyl-5-nitrothiophenes (**172–174**) are only a little less reactive than the 2-halogeno-5-nitrothiophenes (**66**, **106**, **140**) in the piperidinodehalogenation reactions (k_H/k_{Me} at 20°C in methanol ~3–4; see data in Table 10),[219] as expected on grounds of the electron-donating effects of the methyl group. On the other hand, when the leaving group is the phenylsulfonyl group (compounds **175** and **67**, respectively), a significant primary steric effect (k_H/k_{Me} 17)[219] occurs.



172–175

172: L = Cl; 173: L = Br;
174: L = I; 175: L = $SO_2C_6H_5$

As a result of the Reinheimer–Bunnett effect,[199] however, the k_H/k_{Me} ratios for benzenethiolate-substitution (see data in Table 10) are lower than unity (k_H/k_{Me} ~0.4) for halogen as leaving groups and just greater than unity (k_H/k_{Me} 1.3) for phenylsulfonyl.[219]

Clearly, both the k_H/k_{Me} ratios observed in piperidino- and in benzenethiolate-substitution reactions arise from a balancing of at least three effects: (1) the electron-repelling effect of the methyl group, which reduces the reactivity of

172–175 with respect to **66–67**, **106**, **140**; (2) the accelerating Reinheimer–Bunnett effect;[199] and (3) the extent of the steric interactions between the entering and leaving groups and the methyl group.[219]

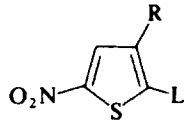
The second and third effects are strongly dependent on the nature of the nucleophiles and of the leaving groups that affect the reactivity of compounds **172–175** because of their dimensions and polarizabilities. The rate ratios (k_S/k_P; see data in Table 11) make allowance for substituent electronic effects and reflect differences in only the inherent nucleophilicities of reagents and in local (steric and electronic) interactions of *ortho*-substituents with entering and leaving groups. Additional information concerning the sensitivity of leaving groups to the polarizability effects of the different nucleophiles are given by the adjusted rate ratios.[219]

TABLE 11. Rate Ratios and Adjusted Rate Ratios for Some Nucleophilic Substitutions[a] of 2-L-5-Nitro-3-R-thiophenes in Methanol at 20°C

L =	$(k_S/k_P)_H$[b,c]	$(k_S/k_P)_{CH_3}$[b,d]	$(k_S/k_P)_{CH_3}/(k_S/k_P)_H$
Cl	5.0×10^3	4.0×10^4	8.0
Br	8.6×10^3	8.2×10^4	9.5
I	3.5×10^4	—	—
SO_2Ph	2.1×10^6	2.8×10^7	13

[a] Data from Ref. 219.
[b] k_S and k_P, reactivity rates toward sodium benzenethiolate and piperidine, respectively.
[c] Rate ratios concerning 2-L-5-nitrothiophenes.
[d] Rate ratios concerning 2-L-3-methyl-5-nitrothiophenes.

The influence of the structure of the alkyl groups on the steric effects has been studied [220] by measuring the reactivity with piperidine and sodium benzenethiolate of some 2-L-3-R-5-nitrothiophenes (**176** and **177**) (see data in Table 10) where the size of the 3-alkyl group was increased by chain lengthening (Me, Et, *n*-Pr, and *n*-hexyl) or by branching at the α-carbon atom (Me, Et, *i*-Pr, and *t*-butyl).

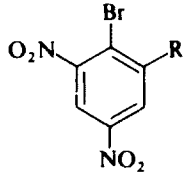


176–177

176: L = Br; **177**: L = $SO_2C_6H_5$
a: R = C_2H_5; **b**: R = *n*-C_3H_7; **c**: R = *n*-C_6H_{13};
d: R = *i*-C_3H_7; **e**: R = *t*-C_4H_9

The results of piperidinodebromination reactions of compounds **176a–c** ($k_H/k_R \sim 4$–5) are very similar to those relative to **173** and confirm the absence of primary steric effects also when the straight chain of the 3-alkyl group has been

significantly lengthened by ω-methylation. On the contrary, the α-branching causes a strong increase in the k_H/k_R ratios ($k_H/k_{i\text{-Pr}}$ 15 and $k_H/k_{t\text{-But}}$ 110): indeed, an examination of molecular models indicates that the primary steric effects can operate in piperidinodebromination provided the *ortho*-alkyl group is bulky enough to give rise to strong steric interactions. A similar situation can be depicted for S_NAr reactions of benzene derivatives bearing bulky alkyl groups in ortho position with respect to the reaction center, but the reactivity ratios k_H/k_R would be expectedly much higher in six-membered than in five-membered ring derivatives* (e.g., formula **178**).

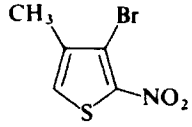


R = H, CH_3, C_2H_5, i-C_3H_7, t-C_4H_9

178

The results of phenylthio-dehalogenation of compounds **172–174** and **176a–e** clearly indicate the intervention of the accelerating Reinheimer–Bunnett effect.[199] In fact, compounds **172–174** or **176a–c** and **176d–e** give k_H/k_R ratios respectively lower (k_H/k_R 0.4–0.8) and a little higher ($k_H/k_{i\text{-Pr}}$ 2.0 and $k_H/k_{t\text{-But}}$ 9.5) than unity, confirming the progressive importance of α-methylation in determining the occurrence of primary steric effects (see data in Table 10). These effects become more evident in phenylthio-dephenylsulfonylation of compounds **175** and **177a–e**, where the balancing between the various steric and electronic effects is quite different. In fact, the bulky phenylsulfonyl leaving group enhances the steric interactions and then causes an increase of all the k_H/k_R ratios, especially with α-branched alkyl groups ($k_H/k_{i\text{-Pr}}$ 22 and $k_H/k_{t\text{-But}}$ 120).

Parallel results have been obtained in the study of the reactions of **73** and **179** with sodium methoxide and benzenethiolate in methanol.



179

* The effect of α-branching on the primary steric effects in six-membered derivatives has been extensively studied[205] in the case of the reaction of some 1-alkyl-2-bromo-3,5-dinitrobenzenes (**178**) with iodide in dry acetone at 80°C, a reaction that is less sensible than the piperidinodehalogenation to steric effects. However, the k_H/k_R ratios range from k_H/k_{Me} 4.5 to $k_H/k_{t\text{-But}}$ 583. Therefore, one can expect that $k_H/k_{t\text{-But}}$ in piperidinodehalogenation of 1-alkyl-2-bromo-3,5-dinitrobenzenes should be as high as 10^5. From a comparison of the kinetic primary steric effects in mono- and dinitrobenzenes one can suggest $k_H/k_{t\text{-But}}$ 10,000 in 1-alkyl-2-halogeno-5-nitrobenzenes.

In **179** the β-carbon atom of the ring is the reaction centre, and the leaving group (bromine) is flanked by the activating nitrogroup and by a group (methyl) able to exert the primary steric effect*: in fact, the two nucleophiles give in methanol at 20°C k_H/k_{Me} ratios (2.2 and 0.7, respectively) according to the previous analysis of electronic and steric effects in the substrate and in the nucleophile.

III. 2,3-DIDEHYDROTHIOPHENE AND NONBENZENOID REACTIONS

1. 2,3-Didehydrothiophene

While it is well known that nucleophilic substitutions on benzene derivatives can proceed via benzyne [elimination–addition (EA) mechanism], no experimental evidence has been produced to the present in support of the fact that nucleophilic substitutions on either α- or β-substituted thiophenes could involve 2,3-didehydro- (**180**) or 3,4-didehydrothiophene (**181–182**) as intermediates.[32,34]

180

181

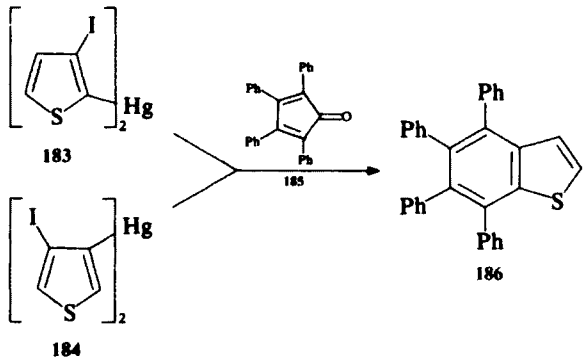
182

Indeed, since they were first postulated, the existence of five-membered hetarynes has been subjected to many argumentations. Actually, several methods employed with success to generate six-membered carbocyclic and heterocyclic arynes proved abortive in the five-membered heterocyclic series as shown by the lack of formation of expected *cine*-substitution and cycloaddition products. On the other hand, even in the cases where such products were isolated, it has been demonstrated that they were formed via nonaryne pathways. For instance, Wittig originally proposed[222,223] that iodomercury thiophenes **183** and **184** gave, by thermolysis in the presence of tetraphenylcyclopentadienone (**185**), the cycloadduct (**186**) through the intermediate didehydrothiophene (**180**).* Soon after the author himself questioned this interpretation[224,225] suggesting that **186** arised from an addition–elimination reaction of **185** with 3-iodothiophene, the product of the decomposition of **183** and **184**.

---

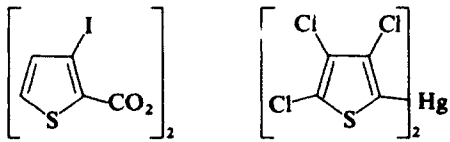
* It must be mentioned that on comparing the reactivities of 2,4-dinitrochlorobenzene (**97**) and 2-chloro-3,5-dinitrotoluene (**171**) in piperidino- and methoxydechlorination, the k_H/k_{Me} ratios observed were 276 and 13.5, respectively.[204]

* In the case of **184** it was postulated[223] that the initially formed 3,4-didehydrothiophene (**181–182**) rearranged to the supposed more stable 2,3-isomer (**180**).

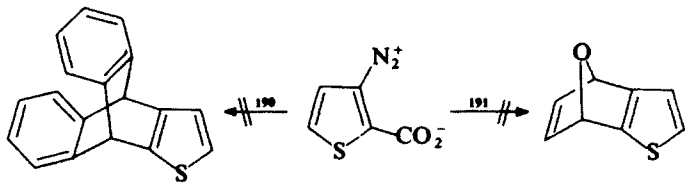


Scheme 30

Similar results were observed and similar conclusions can be advanced for the thermal decomposition of the iodoperoxide (**187**)[225] and of the perchloromercury (**188**)[226] in the presence of **185** as well as for the photolysis of **183**.[227]



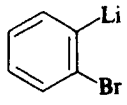
Even the diazonium carboxylate (**189**), whose benzene analog easily furnishes benzyne,[228] is not prone to give aryne reactions. In fact, decomposition of **189** in the presence of anthracene (**190**) or furan (**191**) as potential aryne-trapping agents gave coupling and substitution products in low yield but no trace of the corresponding aryne adducts **192** or **193**.[229,230]



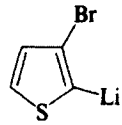
Scheme 31

As advanced by Reinecke,[32,34] the observed difficulty in generating five-membered hetarynes can be due to two interdependent reasons: (a) the noticeable reactivity of the potential precursors of five-membered hetarynes toward nonaryne pathways, which conversely are hindered for the six-membered carbocyclic and heterocyclic analogs; (b) the sluggish tendency of the same precursors, owing to their greater intrinsic stability, to generate five-membered

hetarynes. The former pattern is, of course, enhanced by the latter. The remarkable increase in stability observed on passing from six-membered heterocyclic precursors to five-membered ones is well documented by the difference in stability of the relative *ortho*-metallohalogeno compounds. Thus, while **194** eliminates LiBr even at $-100°C$ to furnish benzyne,[231] also because of the difficulty in generating **180**, **195** is stable in ether up to 100°C and has been carboxylated in yields ranging from 70 to 90%.[227,232,233] On the other hand, attempts to increase the severity of the reaction conditions leads either to substantial decomposition of the molecule or to intervention of nonaryne reactions.



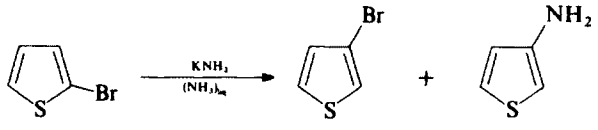
194



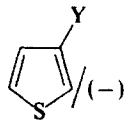
195

The different behavior of **194** and **195** can also be related to a greater stability of benzyne with respect to thiophyne (**180**). Actually, because of the difference in the ring geometries, the stabilizing interaction between the two carbon orbitals containing two electrons and coplanar with the ring is expected to be greater in the six-membered than in the five-membered aromatic system.

The effective competition of nonaryne pathways for potential precursor of **180** is well exemplified by the results[234] obtained from reaction of 2-bromothiophene (**196**) with potassium amide in liquid ammonia. This reaction, carried out under the same conditions used by Roberts in his classic studies establishing the intermediacy of benzyne in the amination of chlorobenzene,[30] yielded a mixture of 3-bromo- (**197**) and 3-aminothiophene (**198**). At this first sight, these results could be consistent with a regiospecific addition of Br^- and NH_2^- to C(3) of the thiophyne (**180**) to give the more stable[235] carbanions (**199**) with the negative charge adjacent to the sulfur atom.



196 **197** **198**

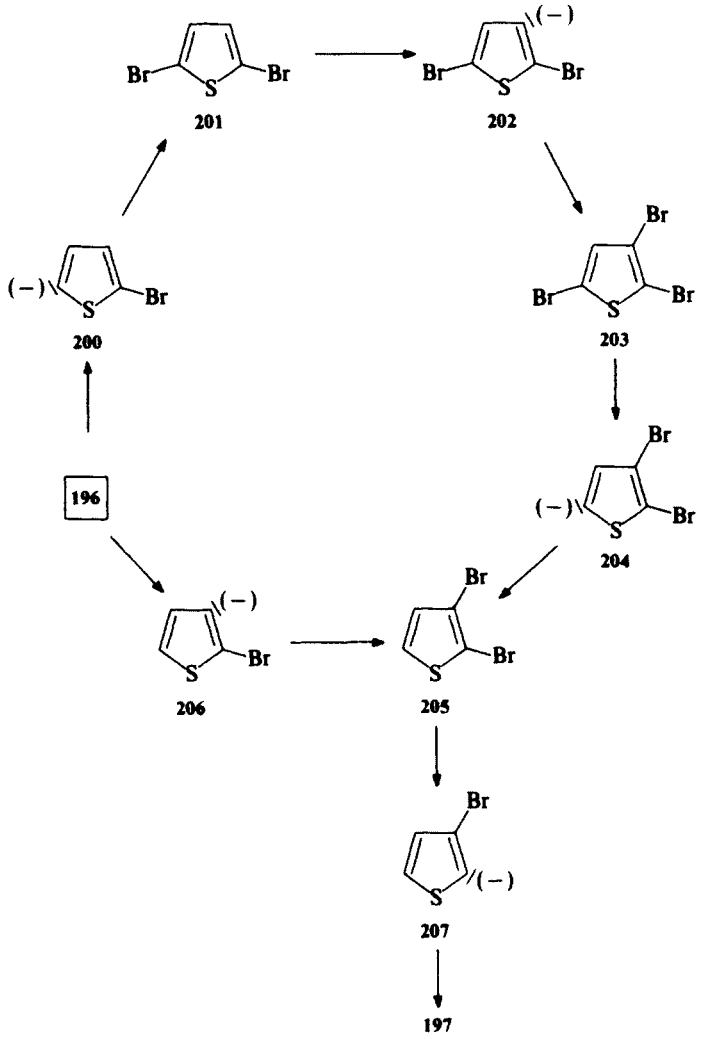


199

Y = Br, NH_2

Further investigations on this reaction,[234, 236–240] however, showed that by changing the experimental conditions (shorter reaction times and lower temperatures) it was possible to isolate polybromo- and/or aminobromothiophenes,

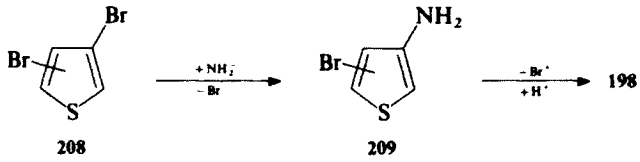
which could be transformed into **197** and **198** under the original reaction conditions.[234] These results, together with the very low formation of 3-amino-derivatives in 4- and 5-methyl-substituted 2-bromothiophenes[237] and the failure to detect any cyclo-adduct in the presence of tetraphenylcyclopentadienone,[240] were best interpreted[234,236,239] on the basis of a "base-catalyzed halogen dance" (BCHD) mechanism.[4] According to this mechanism, two pathways (among the possible ones) leading to **197** from **196** are sketched in Scheme 32.



Scheme 32

As illustrated in Scheme 33, moreover, the formation of 3-aminothiophene (**198**) is believed to occur[32,34] from the 2,3-, 2,4,- and 3,4-dibromothiophenes

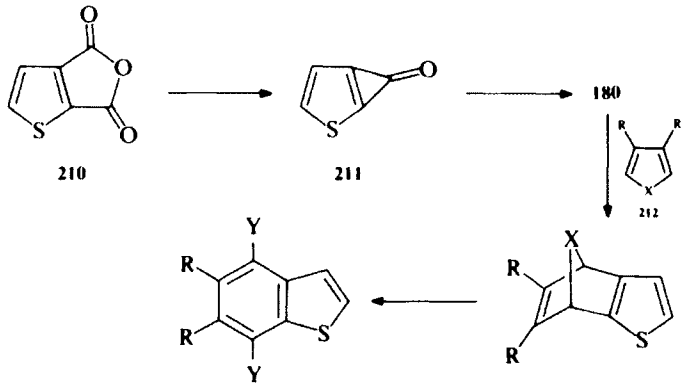
(**208**) via substitution of the β-bromine by the amide anion (AE or $S_{RN}1$[314] mechanism) followed by debromination of the resulting aminobromo derivatives (**209**).



208 **209**

Scheme 33

The only unambiguous evidence to date for the generation of 2,3-didehydrothiophene (**180**) comes from the study of the flash-vacuum thermolysis of thiophene-2,3-dicarboxylic acid anhydride (**210**) carried out in the presence of several diene-trapping agents.[241-243] The results are well interpreted by admitting that the formation of the isolated products arises from aromatization of the initially formed [4 + 2] and/or [2 + 2] Diels–Alder adducts of the hetaryne (**180**). Some examples are reported in Scheme 34.



X =	R =	Y =
CH_2CH_2	H	H
S	H	H
CH=CH	H	H
CH_2	H	H, CH_3
H, H	CH_3	H
O	H	H, OH

Scheme 34

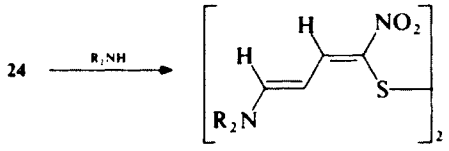
2. Nitrothiophenes

Owing to the peculiar nature of the thiophene ring, some nitrothiophene derivatives react with various nucleophiles in an unexpected way, which,

according to Gronowitz,[244] can be regarded as representative of a non-benzenoid behavior.

A. Nonbenzenoid Behavior of 2-Nitrothiophene

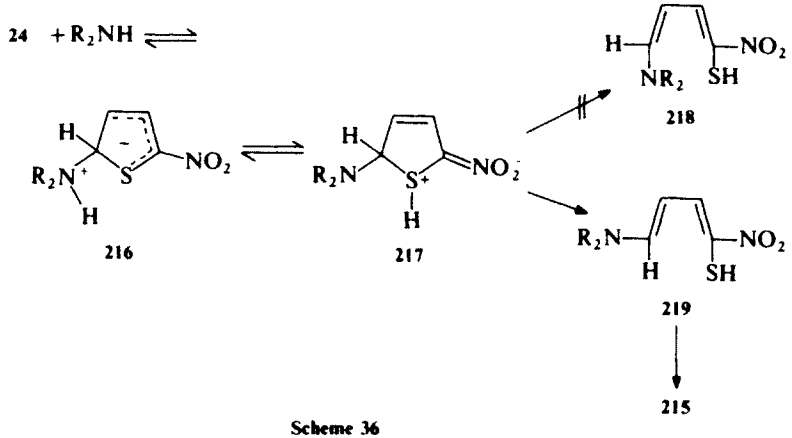
Aliphatic secondary amines react readily with 2-nitrothiophene (**24**; Scheme 35) in ethanol at room temperature to yield bis(4-dialkylamino-1-nitrobuta-1,3-dienyl)disulfides (**215**) via an interesting ring-opening process.[245]



215

Scheme 35

It has been demonstrated that disulfides (**215**) arise from oxidation of the actual reaction products, specifically, the corresponding thiols (**219**). The proposed mechanism (Scheme 36) involves nucleophilic attack by the amine on the favored 5-position of **24**. Rapid proton transfer from the positivised nitrogen to the sulfur atom, to give the sulfonium-type intermediate (**217**), followed by ring-opening reaction, eventually furnishes thiols (**219**).



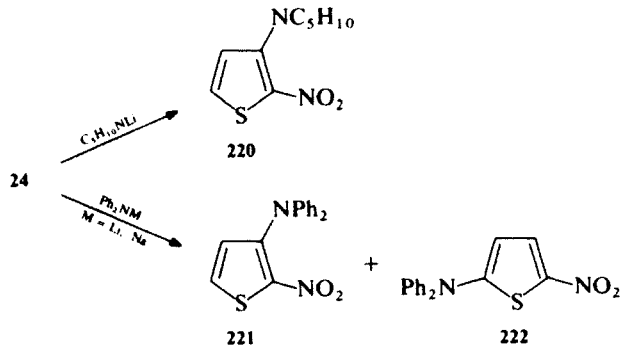
Scheme 36

It is interesting to note that ring opening of the intermediate (**217**) can yield in principle both the (*Z*,*E*)-buta-1,3-diene derivative (**219**) and its (*Z*,*Z*)-isomer (**218**). The observed stereospecificity (exclusive formation of the former) has been rationalized by supposing greater steric interactions in the transition state

leading from **217** to **218** than in passing from **217** to **219**. This is not unreasonable since, during the C—S bond breaking, outward rotations of the NR_2 group should be sterically favored.

B. Benzenoid Behavior of 2-Nitro- and 3-Nitrothiophene

In opposition to the above behavior, 2-nitrothiophene (**24**), when reacted with N-lithium or N-sodium amines,[151] manifests a behavior comparable to that of nitrobenzene.[246–248] Thus, the reaction of **24** with N-lithium piperidine in ether or in toluene furnishes 3-piperidyl-2-nitrothiophene (**220**). With N-lithium and N-sodium diphenylamine in ether a mixture of the amination products **221** and **222** is obtained, where the former is the main component (Scheme 37).

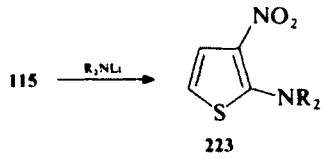


Scheme 37

The nature of the counterion and of the solvent plays a role in the product distribution of these aminations: the use of lithium salts in aprotic solvents (poor solvating media) always favors attack at C(3), whereas with N-sodium diphenylamine in liquid ammonia (able to solvate ionic species) prevalent formation of **222** [attack at C(5)] is observed. In agreement with these findings, the calculated[249,250] electronic densities in **24** indicate that this nitroderivative can receive nucleophilic attack at C(3) and/or C(5), and therefore it is not surprising that the nature of reagents and solvents can affect the nature of the reaction products. In particular, the high extent of solvation of the reagent in liquid ammonia is expected to hinder, for sterical reasons, attack at C(3) of **24**, hence favoring, indirectly, attack at C(5). In a highly polar solvent (DMSO/MeOH) favoring charge dispersion, **24** undergoes with sodium methoxide unique attack at C(5), giving the Meisenheimer-type adduct (**113**) (see Scheme 25 in Section II.2).[151]

A similar benzenoid behavior toward the same reagents is shown by the 3-nitro isomer (**115**) (see also Scheme 25 in Section II.2), which, according to the

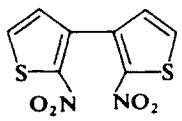
calculated electronic densities,[249, 250] gives only products deriving from attack at C(2) (Scheme 38). Formation of amination products such as **223** is observed with N-lithium amines in ether, wheras with N-sodium diphenylamine in liquid ammonia no detectable reaction occurs. The latter result has been attributed to the fact that, for highly solvated reagents, the C(2)-position of **115** is hindered by both the nitrogroup and the annular sulfur.



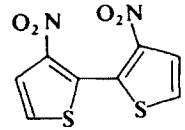
223

Scheme 38

It is interesting to remark that the reactions of **24** and **115** with N-lithium piperidine also give moderate yields of dimerization products such as **224** and **225**, which, for instance, are absent in the corresponding reactions with nitrobenzene.[248]



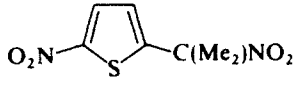
224



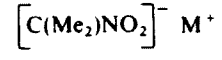
225

C. Reaction of 2-Nitrothiophene with the 2-Nitropropan-2-ide Ion

In the attempt to prepare 2-(1-methyl-1-nitroethyl)-5-nitrothiophene (**226**), Newcombe and Norris[153] studied the reaction of 2-nitrothiophene (**24**) with lithium (**227a**) or tetra-*n*-butylammonium (**227b**) 2-nitropropan-2-ide. The preparation of **226** in this way failed and could be better accomplished by reaction of 2,5-dinitrothiophene (**65**) with **227a** in DMSO or with (**227b**) in benzene or in benzene–water under phase-transfer conditions (see Section V.2).



226

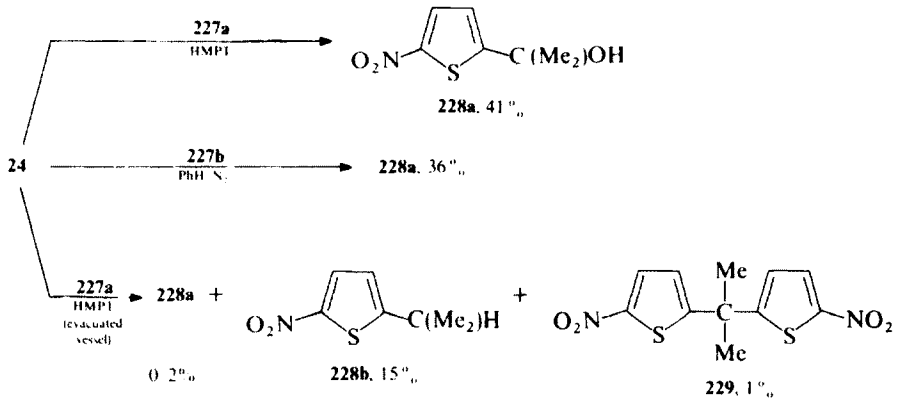


227a–c

a: M = Li
b: M = NBu_4
c: M = NMe_4

The study of the reaction of **24** with the 2-nitropropan-2-ide ion gave interesting results, anyway. For instance, it has been shown by ^1H NMR that

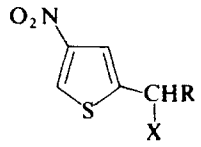
treatment of **24** with the tetramethylammonium salt (**227c**) in CD_3SOCD_3 results in more than 95% conversion into the corresponding Meisenheimer adduct (**114**), which represents one of the few examples of adduct of an aci-nitro anion with a thiophene (see Scheme 25 in Section II.2). The products isolated from the reaction of **24** with **227a** in hexamethylphosphoramide (HMPT) or with **227b** in benzene (Scheme 39) appear to form from adduct **114** via intricate pathways whose real nature has not been yet completely elucidated.



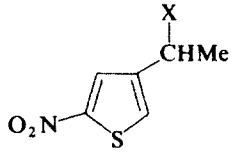
Scheme 39

D. Nonbenzenoid Behavior of 4-Nitro-2-thenyl and 2-Nitro-4-thenyl Derivatives

The 4-nitro-2-thenyl and 2-nitro-4-thenyl derivatives (**230–235**) react with lithium 2-nitropropan-2-ide, in dimethyl sulfoxide or dimethylformamide, to give good yields of the C-alkylates **236–238**.[251,252]



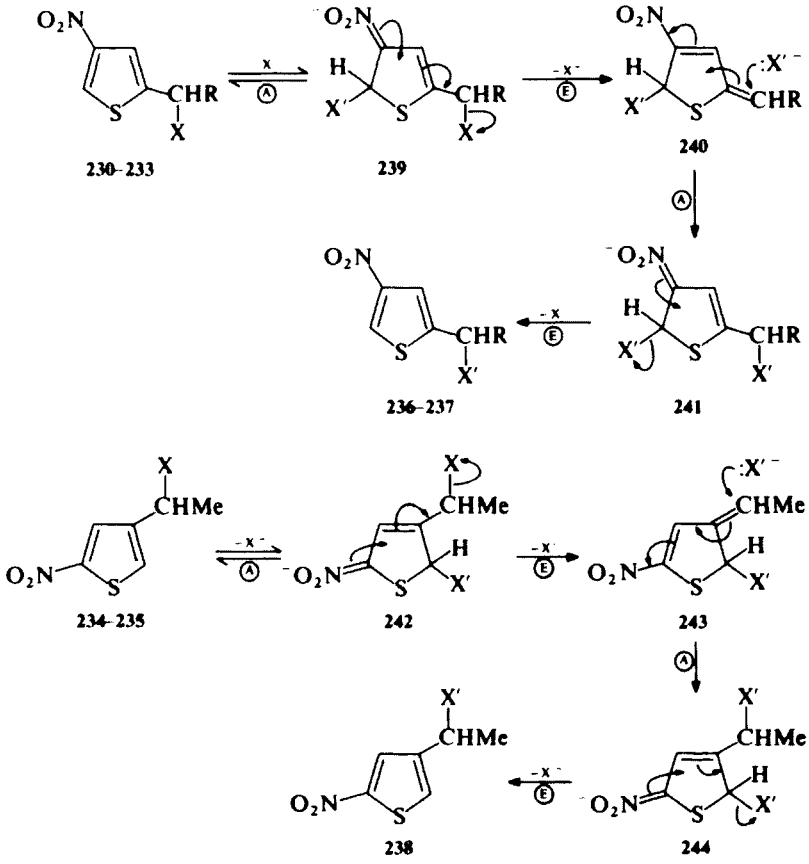
230: X = Cl; R = H
231: X = AcO; R = H
232: X = Cl; R = Me
233: X = AcO; R = Me
236: X = $C(Me_2)NO_2$; R = H
237: X = $C(Me_2)NO_2$; R = Me



234: X = Cl
235: X = AcO
238: X = $C(Me_2)NO_2$

Unlike the case of *m*-nitrobenzylic and *m*-nitrocumylic[253–255] derivatives and of the same 5-nitrothenyl isomers,[251] however, these substitutions in the *meta*-like thiophene series take place by an interesting ionic process [S_N(AEAE)],[252]

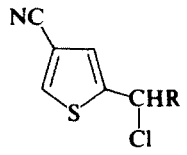
which involves initial attack of the nucleophile at the free α-ring position of the substrate (Scheme 40).



X = Cl, AcO; X′⁻ = $C(Me_2)NO_2^-$; R = H, Me
Ⓐ= addition step; Ⓔ= elimination step

Scheme 40

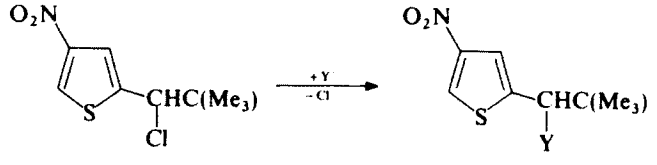
Indirect evidence for the formation of the Meisenheimer adduct (**239**), which is supposed to be the rate-controlling step, comes from the fact that when the nitrogroup in **230** and **232** is substituted for the less activating cyanogroup, as in **245** and **246**, the nucleophilic attack on the thiophene ring is disfavored and only



245: R = H
246: R = Me

O-alkylation products by an S_N2 mechanism were obtained from the reactions with lithium 2-nitropropan-2-ide.[252]

The occurrence of an S_N(AEAE) process has also been proved for the reactions of (4-nitro-2-thienyl)neopentyl chloride (**247**) with various nucleophiles.[256,257] Compound **247**, in fact, reacts smoothly with *p*-toluenesulfinate, azide, and *p*-toluenethiolate ions to give high yield (70–95%) of the corresponding substitution products (**248–250**) (Scheme 41).

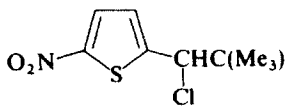


247

248: Y = *p*-$MeC_6H_4SO_2$
249: Y = N_3
250: Y = *p*-MeC_6H_4S

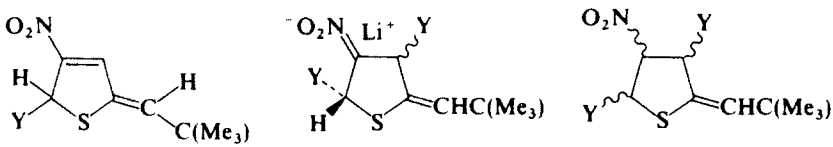
Scheme 41

As expected for an ionic nonchain mechanism as the S_N(AEAE) and unlike the reactions on the 5-nitro-isomer (**251**),[257] where conversely an $S_{RN}1$ mechanism is operative (see Section V.2), no substantial influence on the rate and on the yields of the reactions of (**247**) was observed by oxygen, lack of irradiation, or by the presence of di-tert-butyl nitroxide.



251

Moreover, an overwhelming support to the proposed S_N(AEAE) mechanism came from the isolation[256] of compound **252** (corresponding to intermediate **240** of Scheme 40) and products **253** and **254** derived from it, when the chloride (**247**) is treated with lithium 2-nitropropan-2-ide. Finally the observation that **252**, on treatment with *p*-toluenesulfinate[256] or azide[276] ions, gave the final substitution products **248** and **249** led further independent support to the proposed mechanism.



252 **253** **254**

In **252**–**254**: Y = $C(Me_2)NO_2$

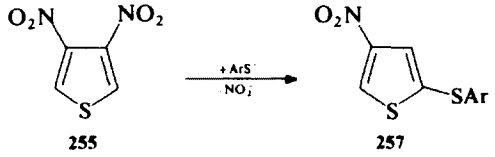
E. Nonbenzenoid Behavior of 3,4-Dinitro- and 3-Nitro-4-(phenylsulfonyl) thiophene

As reported in previous sections, the behavior of nitro-activated thiophene derivatives can be somehow benzene-like. For instance, the *o*-nitro derivatives **69**[94,95], **70**, and **72**[90] react with nucleophiles to give *ipso*-substitution products, in analogy with similar benzene derivatives, via the common S_NAr mechanism (see Sections I.3 and II.1). In the case of **69** substitution of the nitro group in either 3- or 2-position occurs, while in the other two cases only products derived from substitution of the phenylsulfonyl group are isolated.

In the case of other "ortho-like" disubstituted thiophenes such as 3,4-dinitro- (**255**) and 3-nitro-4-(phenylsulfonyl)thiophene (**256**), a completely different (non-benzenoid) behavior has been observed using sodium arenethiolates[258–260] or amines[89,261] as nucleophiles.

a. Reactions with Sodium Arenethiolates

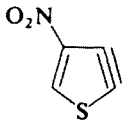
The dinitroderivative (**255**; Scheme 42) reacts with ArSNa/ArSH in methanol to give 2-arylthio-4-nitrothiophenes (**257**) through a *cine*-substitution process.[258,259]



255 **257**

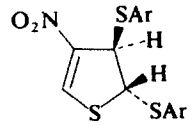
Scheme 42

The presence of free arenethiol is essential to improve the yield. A mechanistic pathway involving 4-nitro-2,3-didehydrothiophene (**258**) as intermediate (EA mechanism) was confidently rejected on the following grounds: (a) the nitro-group is not a good leaving group for aryne formation;[262,263] (b) both methanol and free arenethiol are expected[264,265] to inhibit an EA pathway by fast protonation of the carbanionic precursor of **258**; (c) no methoxy-derivative, which could arise from attack of methanol on (**258**), is formed.



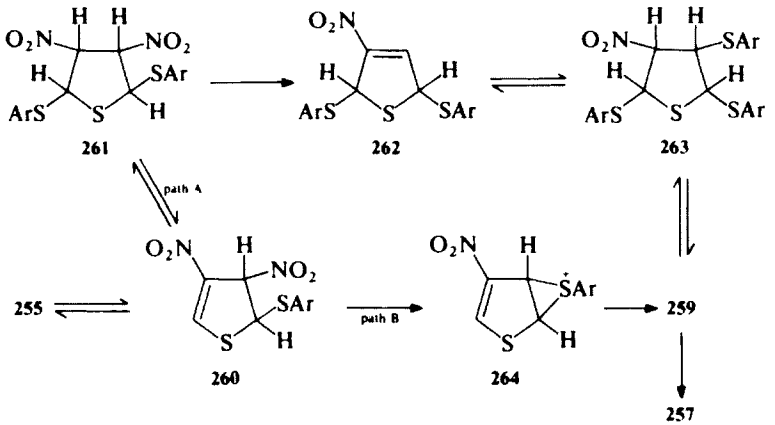
258

Conversely, an addition–substitution–elimination (ASE)[32,34] mechanism for the above *cine*-substitution is supported by the isolation of compound **259**, which can be converted into the final product (**257**) in a variety of base–solvent systems.



259

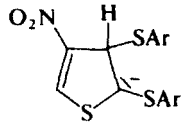
The results are well interpreted[258,259,266,267] by admitting that the reaction initially proceeds through a reversible base-promoted Michael addition of a thiol molecule to a double bond of **255** to give intermediate **260**. In principle, this addition product can evolve into the final *cine*-substitution product via either path A[259] or path B[266,267] of Scheme 43.



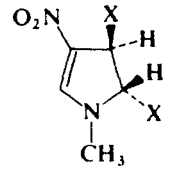
Scheme 43

According to path A, the two diastereomeric tetrahydrothiophenes (**263**), likewise isolated in the course of the reaction, would be precursors of **259**, whereas according to path B they would be side products arising, as independently ascertained, from reversible addition of another thiol molecule to the residual double bond of **259**. The fact that, under appropriate conditions and at short times, **259** is the only reaction product appears in favor of the latter possibility, which, on the other hand, would better justify the exclusive trans configuration ascertained for **259**.[266,267]

Structural parameters obtained through a crystal structure determination of **259** (Ar = 2,4,6-$Me_3C_6H_2$) substantiate the regiospecificity of the base-induced *syn*-elimination of thiol from **259** in toluene, for which a carbanionic stepwise pathway via ion pairs has been postulated on grounds of kinetic evidence.[266,267] The abstraction of the proton from C(2) of **259** is favored by the presence of two α-sulfur atoms that increase its acidity by stabilization of the corresponding carbanion (**265**),[268-270] which is nothing but a dithioacetal anion. It is possible that this particular acidity of the H(2) in **259** is a rationale also for the opposite regiospecificity observed[16-18,271] in similar systems such as pyrrolines (**266**), which undergo base-promoted HX elimination to 3-X derivatives.



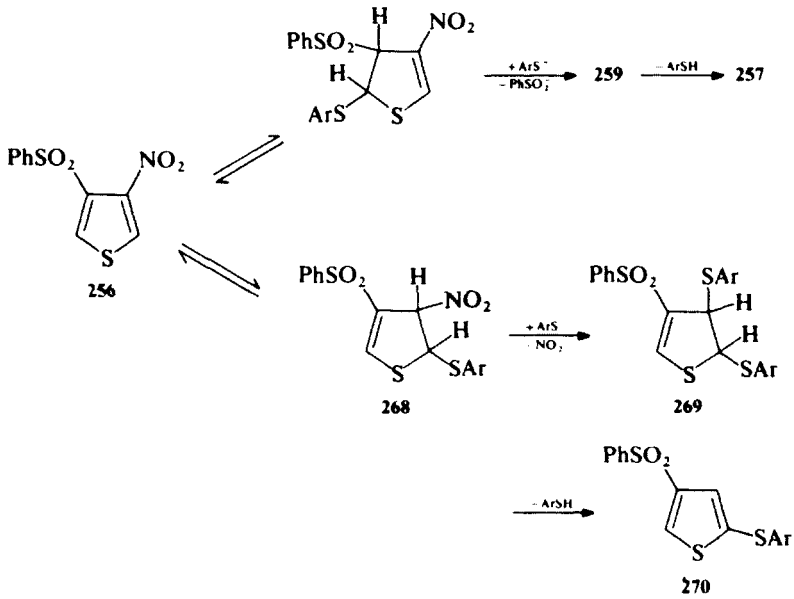
265



X = MeO, piperidino, morfolino

266

The behavior of 3-nitro-4-(phenylsulphonyl)thiophene (**256**) toward sodium arenethiolates in methanol is similar to that observed for **255**. Accordingly, a mixture of the two possible *cine*-substitution products **257** and **270** is obtained (Scheme 44).[260]



Scheme 44

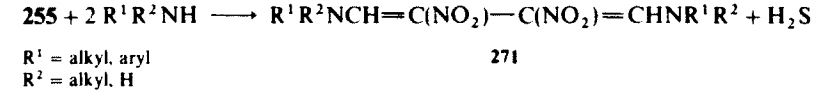
The values of the **270** : **257** molar ratios (ranging between 6 and 14 as a function of the arenethiolate employed) indicate that in this *cine*-substitution the nitrogroup is the preferred leaving group. In the light of an ASE process operating also in this case, the higher yield of **270** can be rationalized by considering that in the transition states, relative to the two competing initial steps, the nitrogroup delocalizes the negative charge better than does the phenylsulfonyl group, thus favoring attack at C(2) rather than at C(5) of **256**.

b. Reactions with Amines

Another interesting aspect of the nonbenzenoid behavior of 3,4-dinitrothiophene (**255**) is represented by the ring-opening reaction occurring by treat-

ment with primary and secondary amines, which furnishes good yields of 1,4-diamino-2,3-dinitrobuta-1,3-dienes (**271**).[89,261]

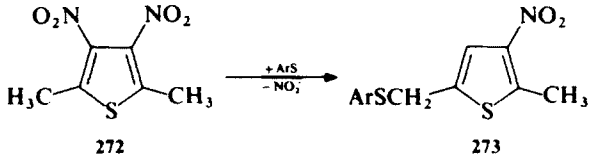
While other ring-opening reactions in the thiophene series require severe conditions,[68,272–274] the reaction on **255** (see Scheme 45), as that on 2-nitrothiophene (**24**) (see Section III.2.A), occurs smoothly in methanol at room temperature with evolution of hydrogen sulfide.



Scheme 45

F. Nonbenzoid Behavior of 2,5-Dialkyl-3,4-dinitrothiophenes

The tendency of the 3,4-dinitrothiophene system toward a nonbenzenoid behavior[89,258,259,261] is further evidenced by the reactivity of its 2,5-dialkyl derivatives. Thus 2,5-dimethyl-3,4-dinitrothiophene (**272**) reacts with sodium arenethiolates in methanol to give 5-[(arylthio)methyl]-2-methyl-3-nitro-thiophene (**273**) in 70–80% yield (Scheme 46).[275]



272 **273**

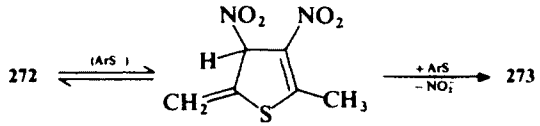
Scheme 46

It is interesting to note that even blocking the α-positions of the ring by substitution of two methyl groups for the two replaceable (*cine*-substitution) hydrogens of 3,4-dinitrothiophene (**255**), the *ipso*-substitution of a nitrogroup does not take place. Conversely an unusual nucleophilic substitution occurs that involves attack of the nucleophile on a side-chain carbon atom with departure of the nearest nitrogroup from the ring (*tele*-substitution).

A substantial improvement both in rate and yield can be achieved by the use of polar aprotic solvents such as DMSO and dimethylformamide.[276,277] For instance, the reaction of **272** with sodium benzenethiolate in DMSO goes to completion in 30 min at room temperature while in methanol, at the same concentration of reagents, 17 hr at reflux are necessary, the yields of isolated *tele*-substitution product are 96 and 70%, respectively.

A radical or radical-anion chain mechanism has been excluded as no significant effect on the yield and on the rate of formation of sulfides (**273**) is observed when the reaction is carried out under photostimulation or in the presence of di-*tert*-butylnitroxide.[278] Therefore, to explain the formation of **273**

from **272** (Scheme 47), it has been assumed[279] that, under the basic reaction conditions, **272** partially tautomerises into **274**. This tautomeric form then furnishes the *tele*-substitution product via displacement involving a three carbon anionotropic rearrangement that recalls the S_N2' or S_N2'-like processes occurring on allylic derivatives.[280]



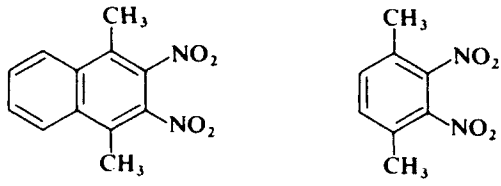
274

Scheme 47

A result that can be somehow indicative about this last step is the fact that the rate of *tele*-substitution increases as the nucleophilicity of the arenethiolate is enhanced. Thus a competitive reaction between 4-methyl- and 3-chlorobenzenethiolate toward **272** gives **273** (Ar = 4-MeC_6H_4) and **273** (Ar = 3-ClC_6H_4) in approximately 3 : 1 ratio.[277]

The accelerative effect found on going from MeOH to DMSO can be related not only to the well-known property of the latter medium of enhancing basicity and nucleophilicity of anionic reagents[281–284] but also to its greater activity in promoting isomerization of α,β-unsaturated nitroolefins (to which **272** can be structurally related) into the β,γ-unsaturated isomers.[285,286]

As advanced to explain the reactivity pattern of 3,4-dinitrothiophene (**255**) with the same reagents,[258,259] the behavior of **272** can be rationalized by the dienic character of the thiophene ring.[287,288] Accordingly, the reactions with sodium arenethiolates of the analogous naphthalene (**275**) and benzene (**276**) derivatives show[279] that while (**276**) exclusively furnishes the expected *ipso*-substitution products (most likely via an S_NAr process), a competition between *ipso*- and *tele*-substitution is observed for **275**. This indicates that for the three aromatic substrates **272**, **275**, and **276** the order of reactivity toward the two possible competing processes (S_NAr and *tele*-substitution) varies in function of the dienic character of the ring as shown in Scheme 48.



275 **276**

Scheme 48

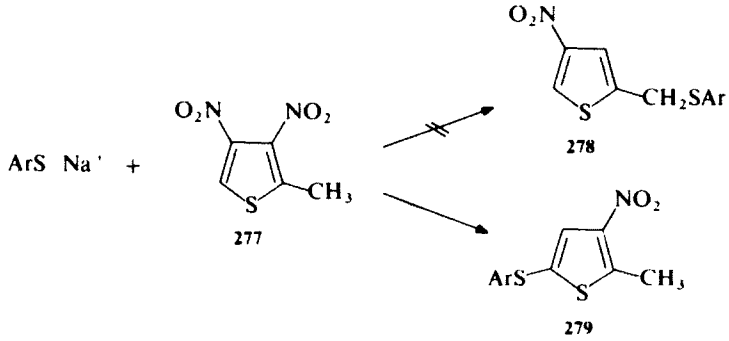
Increase in S_NAr reactivity

Thiophene (**272**) Naphthalene (**275**) Benzene (**276**)

Increase in dienic character and in *tele*-substitution reactivity

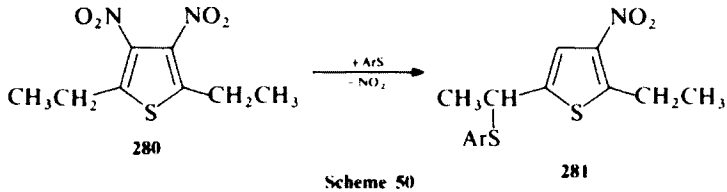
Besides the localization of the π-electrons in the ring, which is the main factor, another factor possibly contributing to the *tele*-substitution process is the steric compression present in these molecules. It is reasonable, in fact, to suppose that tautomerization of the "aromatic" substrate be promoted, inter alia, by formation of a sterically less congested molecule like the "nonaromatic" tautomer itself. As a matter of fact a crystal structure analysis of **272** showed[289] an overcrowding due to the four vicinal substituents, which gives rise both to a rotation of the nitrogroups and an out-of-plane bending of the C(3)—N and C(4)—N bonds in opposite directions referring to the thiophene ring.

It is interesting to note in this regard that in the reaction[277] of 2-methyl-3,4-dinitrothiophene (**277**) with arenethiolates (Scheme 49) the *tele*-substitution does not succeed in competing efficiently with the alternative *cine*-substitution process.



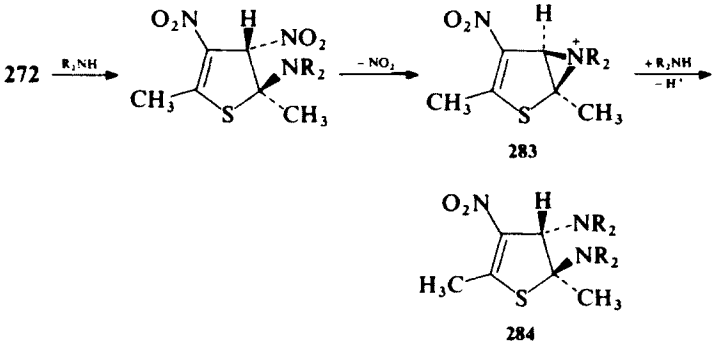
Scheme 49

In analogy with **272** the diethyl derivative (**280**) reacts with arenethiolates in DMSO to give quantitatively the *tele*-substitution products (**281**).[276] In agreement with the proposed mechanism, competitive experiments show that (**280**) is remarkably more reactive than (**272**): thus when equimolar amounts of (**272**) and (**280**) are allowed to compete for a single molar equivalent of sodium benzenethiolate in DMSO, only (**281**, Ar = Ph) is obtained with quantitative recovery of unreacted **272** (see Scheme 50).



Scheme 50

The last aspect worth mentioning regarding the behavior of the dimethyldinitrothiophene (**272**) is that, unlike the case of the naphthalene derivative (**275**),[290] in the reaction with **272** the nature of the products seems to depend on the nature of the nucleophile employed. In fact, the reaction of **272** with excess secondary amines gives quantitatively *trans*-2,3-diamino-2,5-dimethyl-4-nitro-2,3-dihydrothiophene (**284**; Scheme 51).[291]



Scheme 51

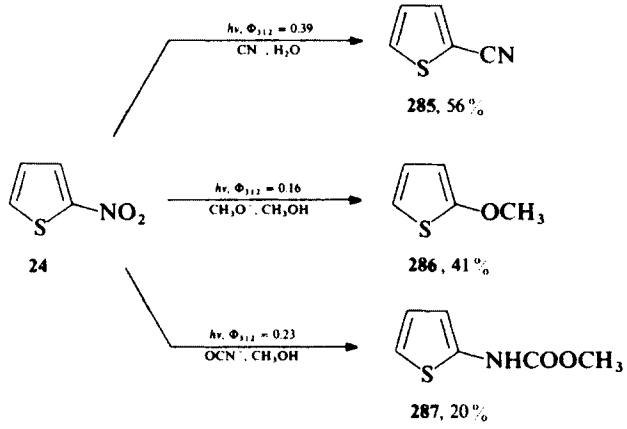
There is an obvious analogy between compound **284** and the dihydrothiophene (**259**), isolated as an intermediate in the *cine*-substitution reactions of 3,4-dinitrothiophene (**255**) with sodium arenethiolates. Unlike the case of **259**, however, some attempts of acid-catalyzed rearomatization of **284** proved futile, leading to tarry material.[277]

IV. PHOTONUCLEOPHILIC AROMATIC SUBSTITUTIONS IN THIOPHENE DERIVATIVES

Unlike the usual S_NAr processes occurring on ground-state molecules, which have been widely investigated, and in spite of numerous studies carried out on other aromatic systems, the photoactivated nucleophilic substitutions[292-296] in the thiophene series have received little attention.

Relevant results have been reported by Groen and Havinga,[297] who showed that 2-nitrothiophene (**24**) on irradiation in water or methanol undergoes substitution of the nitrogroup by nucleophiles such as CN^-, MeO^-, or OCN^- as shown in Scheme 52.

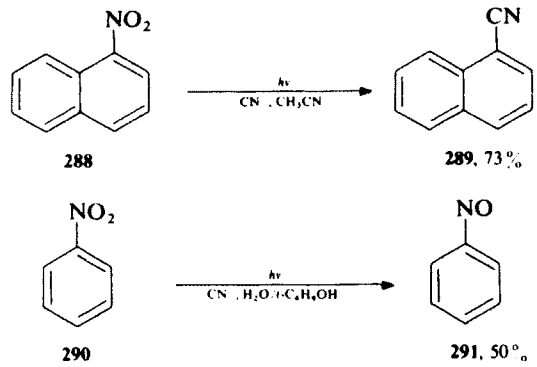
Triplet sensitization (acetone) and quenching (sodium sorbate) experiments suggest that the first reaction proceeds mainly, if not entirely, via a triplet state (calculated lifetime $\sim 5 \times 10^{-7}$ sec in pure water and $\sim 10^{-8}$ sec in 0.01 M KCN). The preceding photonucleophilic substitutions are initiated by complex formation between the nucelophile and the aromatic substrate in its lowest π,π^* triplet (exciplex, excited π, or σ complex?). The complex may then



Scheme 52

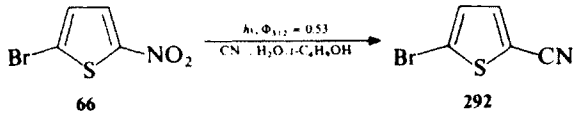
either dissociate into starting compounds back again or transform into the substitution product.

The observed behavior of **24** with cyanide is similar to that of 1-nitronaphthalene (**288**),[298] and unlike that of nitrobenzene (**290**)[299,300] (Scheme 53), the difference in behavior between the latter compounds is ascribed[299,300] to a difference in triplet state character: it appears that a low-lying n,π^* state (e.g., in **290**) undergoes reduction, whereas a low-lying π,π^* excited state (as in **288** and **24**) undergoes substitution with cyanide.The lower quantum yield observed in the reaction of **24** with the methoxide ion has been attributed to an unfavorable decay ratio of the intermediate complex.



Scheme 53

The substitution[297] of bromine for the hydrogen atom in the 5-position of **24**, most likely by enhancing the probability of radiationless processes such as $S_1 \rightarrow T_1$ (heavy atom effect on ISC[301,302]), results in a considerable increase in the quantum yield of the reaction with cyanide (Scheme 54).

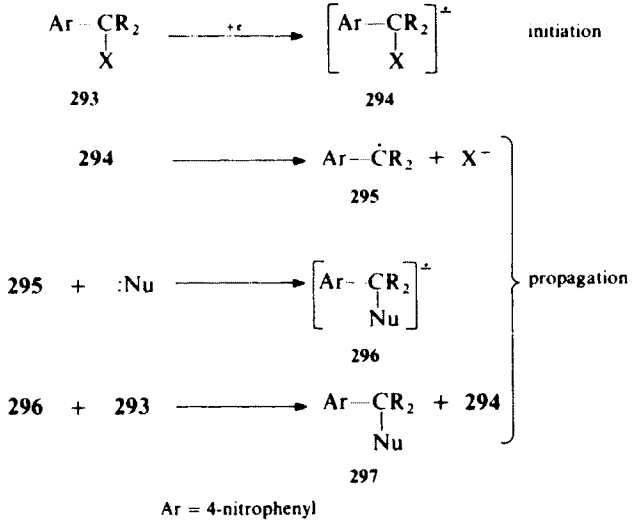


Scheme 54

Unlike the 2-nitroisomer (**24**), nucleophilic photosubstitutions on 3-nitrothiophene (**115**) could not be observed,[297] most likely owing to concomitant disruptive ring-opening reactions that were not investigated.

V. REDUCTIVELY ACTIVATED NUCLEOPHILIC SUBSTITUTIONS ($S_{RN}1$ MECHANISM) IN THIOPHENE DERIVATIVES

The chain character of electron-transfer substitutions at saturated carbons of nitrobenzyl systems was simultaneously and independently recognized by Kornblum et al.[303] and Russell and Danen[304] in 1966 (Scheme 55).



Scheme 55

Four years later, in 1970, Kim and Bunnett[35] extended the above mechanism to unactivated aryl compounds (Scheme 56) and proposed the term $S_{RN}1$, which recalls that "the mechanism is unimolecular in the same sense as S_N1, except that unimolecular bond fission occurs in a radical anion instead of in a neutral molecule."[35] Since then the wide scope and the obvious value in synthesis of this mechanism have been demonstrated in several studies, and the topic has been reviewed several times.[37-39,278,305-313]

$$\underset{\mathbf{298}}{Ar{-}X} \xrightarrow{+e} \underset{\mathbf{299}}{[Ax{-}X]^{\cdot}}$$

$$\mathbf{299} \longrightarrow \underset{\mathbf{300}}{Ar^{\cdot}} + X^{-}$$

$$\mathbf{300} + :Nu^{-} \longrightarrow \underset{\mathbf{301}}{[Ar{-}Nu]^{\cdot}}$$

$$\mathbf{301} + \mathbf{298} \longrightarrow \underset{\mathbf{302}}{Ar{-}Nu} + \mathbf{299}$$

Scheme 56

A brief survey of $S_{RN}1$ reactions occurring in the thiophene series will be reported in this chapter beginning with those processes involving thiophene ring carbons. The behavior of some nitrothenylic systems, where substitution occurs on a side-chain carbon atom, will then be summarized.

1. Substitution on a Thiophene Ring Carbon

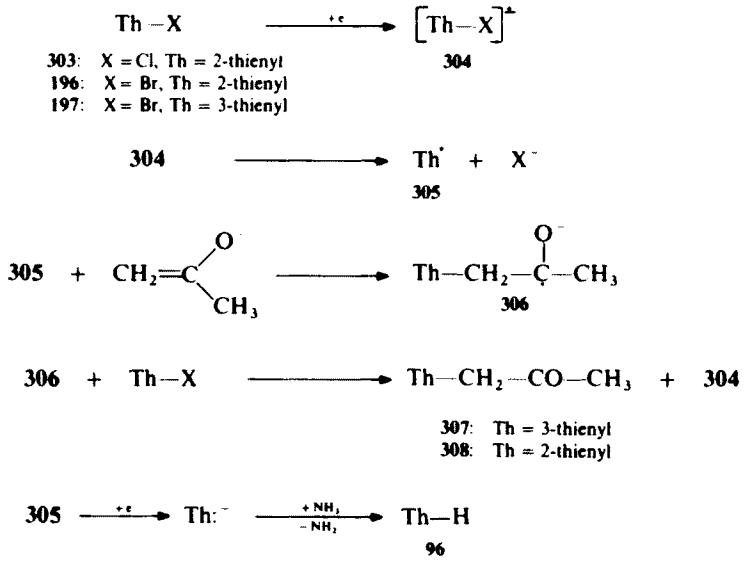
A. Photostimulated Reactions

The photostimulated reactions of 2-chloro- (**303**), 2-bromo- (**196**), and 3-bromothiophene (**197**) with acetone enolate anion in liquid ammonia was investigated by Bunnett and Gloor in 1976.[314]

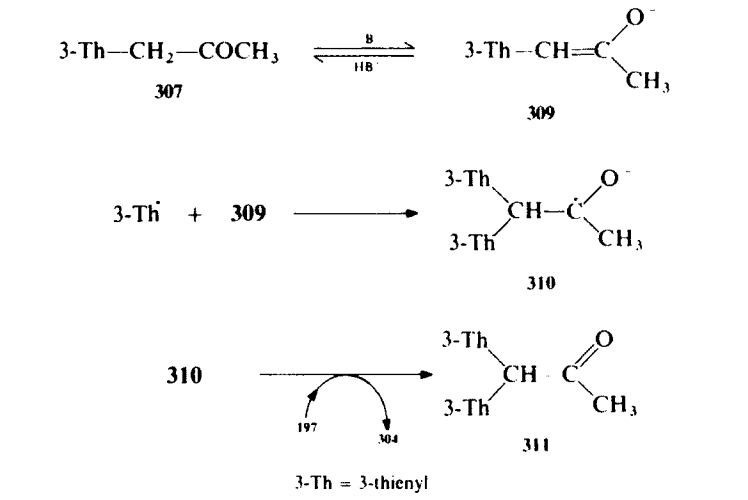
After 60 min of irradiation by Pyrex filtered light, the more reactive substrate (**197**) gave the monothienylation product (**307**) in 51% yield and dithienylation product (**311**) in 25% yield. Small amounts (~7%) of (**197**) were recovered, and 2% of debromination to thiophene (**96**) occurred (Schemes 57 and 58).

The diarylation product (**311**) is supposed to be formed from **307** by trapping of a thienyl radical from the corresponding enolate (Scheme 58) as in the analogous reactions carried out on bromobenzene,[315-317] a point of difference being that relatively more diarylation occurs with **197** than with bromobenzene.

Under conditions similar to those employed for **197**, the 2-halothiophenes (**196** and **303**) showed to be much less reactive. Actually, after the same irradiation time, very low yields of the substitution product (**308**) and a substantial recovery of the starting material was observed: 44% with **196** and 83% with **303**. While the lower reactivity of **303** with respect to **196** has been attributed[314] to the difference in fragmentation rate of the corresponding radical anions (which reflects the order of leaving-group ability of the relative halide ions Br > Cl[318-324]), it has not been clearly shown which part of the mechanistic sequence of the $S_{RN}1$ process has to be considered responsible for the lesser



Scheme 57

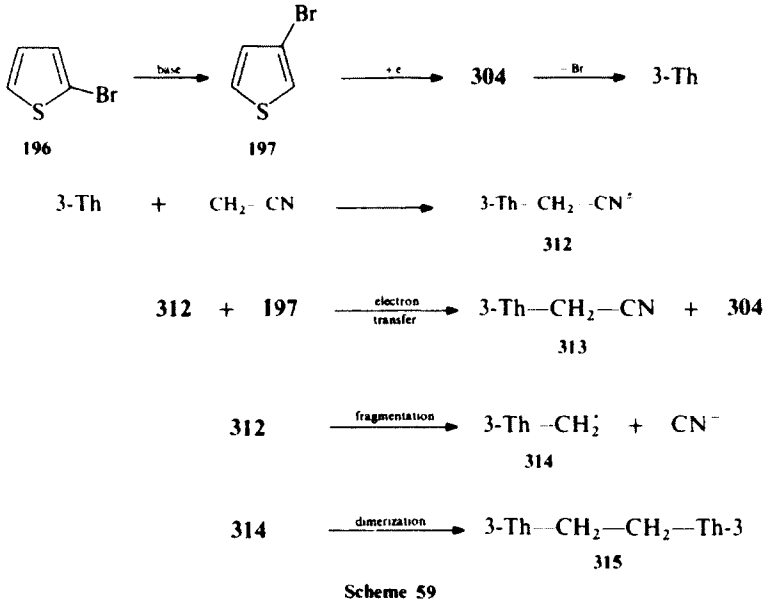


Scheme 58

reactivity of **196** as compared with the 3-isomer **197**.[319–324] An explanation of this reactivity pattern was advanced later by Rossi,[325] who attributed it to the lower electrophilicity of the 2-thienyl as compared to the 3-thienyl radical.

The photostimulated reaction of 3-bromothiophene (**197**) with cyanomethyl anion in liquid ammonia[326] afforded 3-cyanomethylthiophene (**313**) (37.5%) and 3,3′-(1,2-ethanediyl)bisthiophene (**315**) (6.5%) via the $S_{RN}1$ process. The

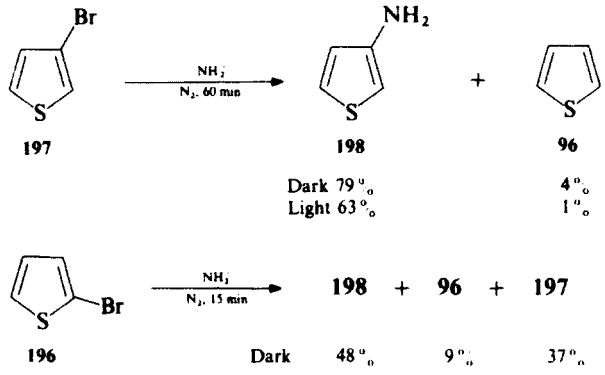
analogous reaction carried out on the 2-isomer[196-326] gave comparable yields of the same products (**313** and **315**). Most likely they arise from a preliminar base-catalyzed isomerization of **196** to **197**, which is a well-recognized reaction[234,239] and is a prominent example of the base-catalyzed halogen dance (BCHD) (see Section III.1).[4] As for the case of benzene derivatives,[327] these results can be explained by the reactions of Scheme 59, where the formation of **313** and **315** is believed to occur respectively via electron transfer and fragmentation of the radical anion intermediate (**312**).[328] As sketched in Scheme 59, the formed thenyl radical dimerizes giving the observed bisthienylethane (**315**).



Scheme 59

Results consistent with an $S_{RN}1$ mechanism have been obtained also from the study[314] of the spontaneous reactions of **196** and **197** with amide ions in liquid ammonia (Scheme 60). While the latter substrate gave 79% yield of 3-aminothiophene (**198**), the 2-isomer (**196**) furnished a mixture of **197** and **198**, presumably by way of **197**. Thiophene (**96**) was present as by-product in both cases. It is interesting to note that the first reaction of Scheme 60 is faster in the dark than under illumination. It was suggested[314] that in this case the effective initiation process is unsensitive to photostimulation, but light produces a few poorly defined radicals deactivating the chain process.

In spite of the presence of a good nucleofugal group in the substrate and the use of very reactive nucleophiles, the photoinduced reactions of 2-iodothiophene with ammonium benzenethiolate or with potassium diethyl phosphite failed to give any substitution product.[314] Mostly unreacted substrate was recovered with ammonium benzenethiolate, while in the reaction with potassium diethyl phosphite the only detectable volatile product was thiophene (**96**) in spite of

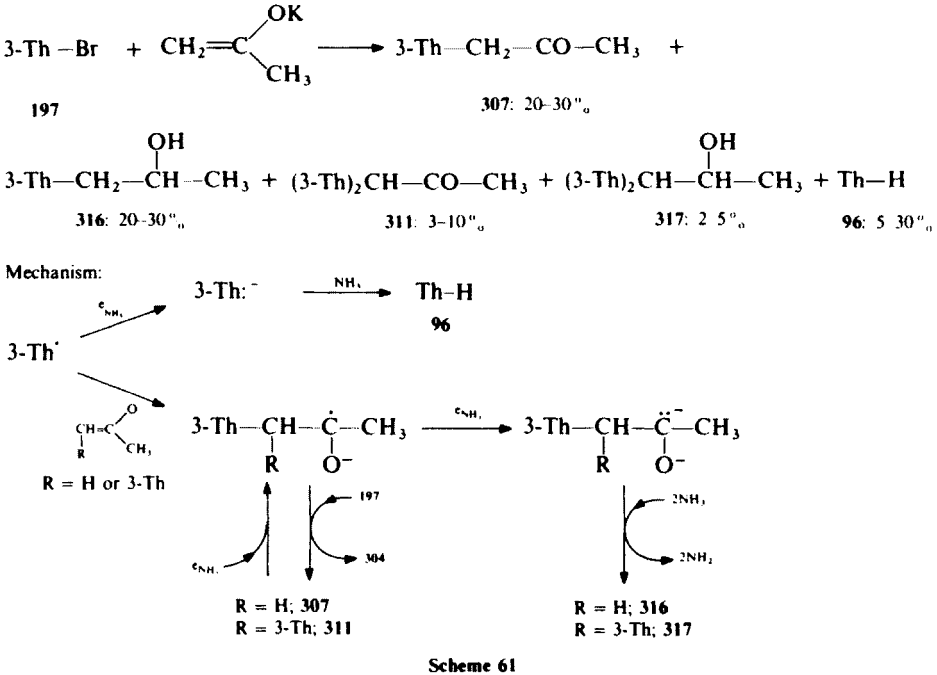


Scheme 60

91% iodide release. The analogous reactions of iodobenzene with the preceding nucleophiles gave practically quantitative yields of substitution products.[329,330]

B. Reactions Stimulated by Solvated Electrons

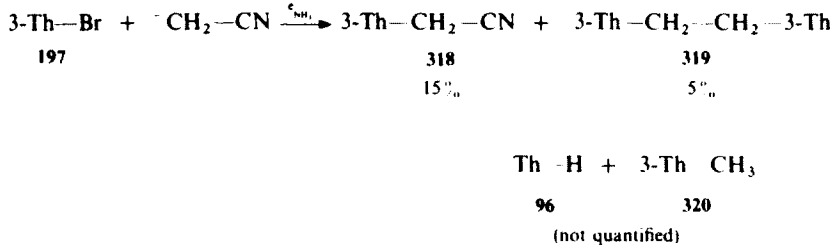
The reductive activation of an appropriate substrate molecule, in the initiation step of $S_{RN}1$ processes, can be well accomplished by solvated electrons obtained by dissolution of alkali metals (usually K or Na) in liquid ammonia.



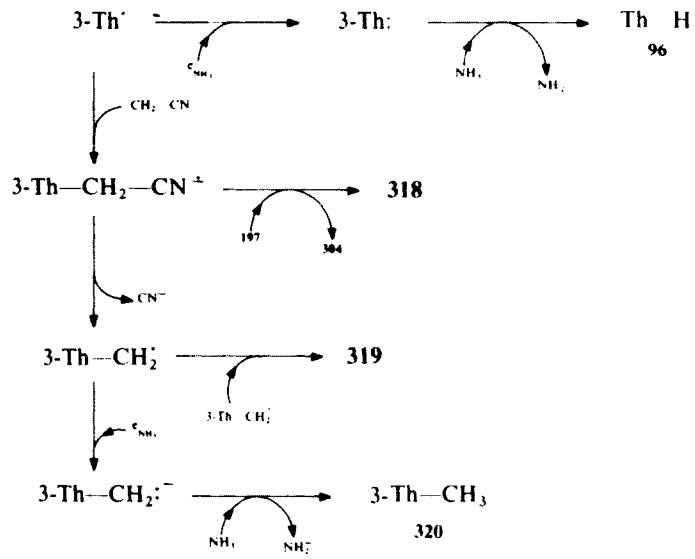
Scheme 61

The reactions of the thiophene derivatives **196**, **197**, and **303** with acetone enolate anion stimulated by solvated electrons have also been studied[314] in liquid ammonia at $-78°C$, and, similarly, the behavior of **197** with cyanomethyl anion at $-68°C$ has been investigated.[326]

The results show that these reactions proceed similarly to the photostimulated ones with the difference that (owing to the easy availability of electrons in the proximity of the dissolving metal) larger amounts of products deriving from competitive reduction of the neutral radical intermediates and, possibly, of the substitution products were obtained. Some prominent examples and the mechanistic paths accounting for the formation of the various products (some of which not observed in the photostimulated reactions) are illustrated in Schemes 61 and 62 (see also Schemes 57–59).



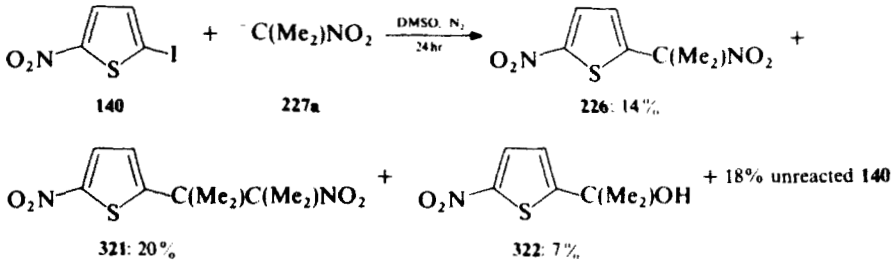
Mechanism (see also Scheme 59):



Scheme 62

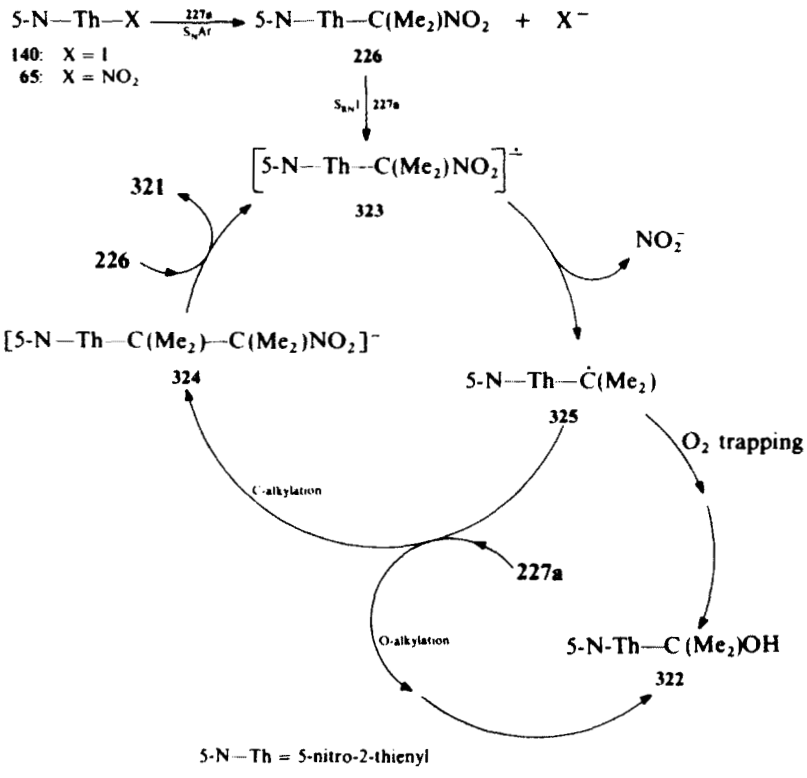
2. Substitution on a Side-Chain α-Carbon of Thiophene Derivatives

The reaction of 2-iodo-5-nitrothiophene (**140**) with the lithium salt of 2-nitropropane (**227a**) in DMSO[153] gives 2-(1-methyl-1-nitroethyl)-5-nitrothiophene (**226**) (via the usual S_NAr process) together with products **321** and **322** deriving from the $S_{RN}1$ reaction of **226** with **227a** (Scheme 63).



140 **227a** **226**: 14% **321**: 20% **322**: 7%

Scheme 63



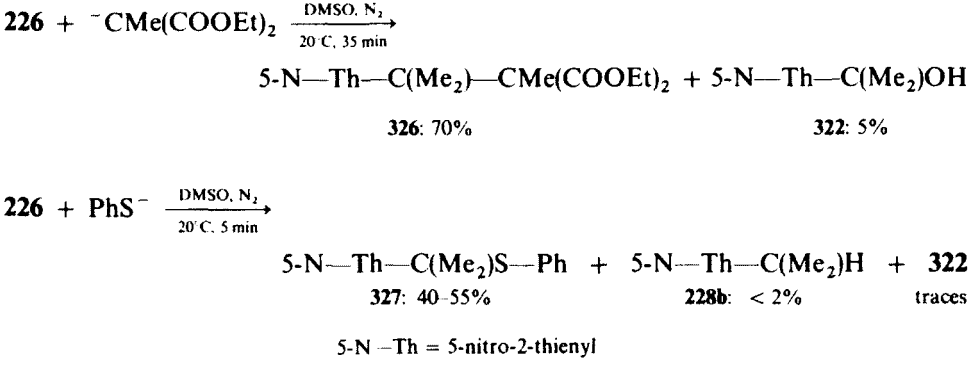
Scheme 64

When 2,5-dinitrothiophene (**65**) was used[153] as substrate, only substitution product (**226**) (69%) was formed. This constitutes an indirect piece of evidence for the $S_{RN}1$ character of the pathway leading to the C-alkylate **321** from **226**.

The starting material, in fact, being a dinitro compound, can act as an electron scavenger and hence an $S_{RN}1$ inhibitor.

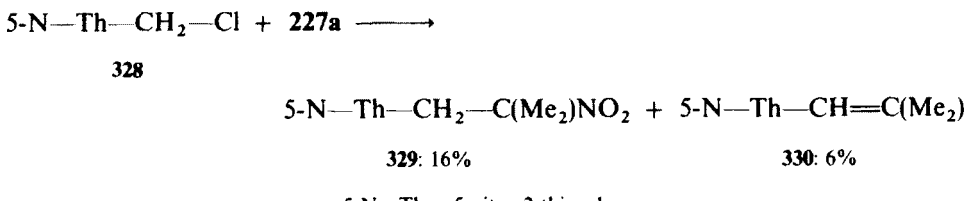
The reaction of **226** with **227a** was then studied,[153] and further confirmation of the $S_{RN}1$ nature of the process was achieved from the analysis of the change in the C-alkylated versus O-alkylated product ratio when the nitrogen atmosphere was changed to oxygen and also from the inhibition of the reaction by oxygen. The mechanisms proposed for the reactions of compounds **140**, **65**, and **226** with **227a** are summarized in Scheme 64.

The $S_{RN}1$ reactions of the nitrocompound (**226**) with the sodium salt of diethyl 2-methylmalonate and sodium benzenethiolate in DMSO were also investigated.[153] Satisfactory yields of the corresponding substitution products (**326** and **327**) could be obtained in both cases (Scheme 65).



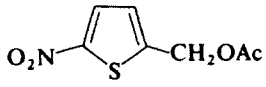
Scheme 65

The reaction[251] of 5-nitro-2-thienylmethyl chloride (**328**) with lithium 2-nitropropan-2-ide (**227a**) in DMSO gives poor yield of the C-alkylated product (**329**) via an $S_{RN}1$ process. Minor amounts of the alkenyl-derivative (**330**), deriving from elimination of the elements of nitrous acid from **329**, were also detected (Scheme 66).



Scheme 66

The analogous reactions[251] carried out on **331** and **332** gave a complex mixture of products arising from $S_{RN}1$, S_N2 O-alkylation, elimination, electron transfer, and radical coupling processes. See, for instance, Scheme 67 for the case of (**332**).



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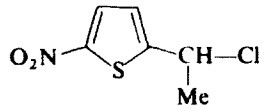


332

5-N—Th—CH(Me)—C(Me$_2$)—NO$_2$

333: 35%

5-N—Th—C(Me)=C(Me$_2$)

334: 17%

332 —(227a, DMSO, N$_2$, 20°C)→ 5-N—Th—C(Me)=O

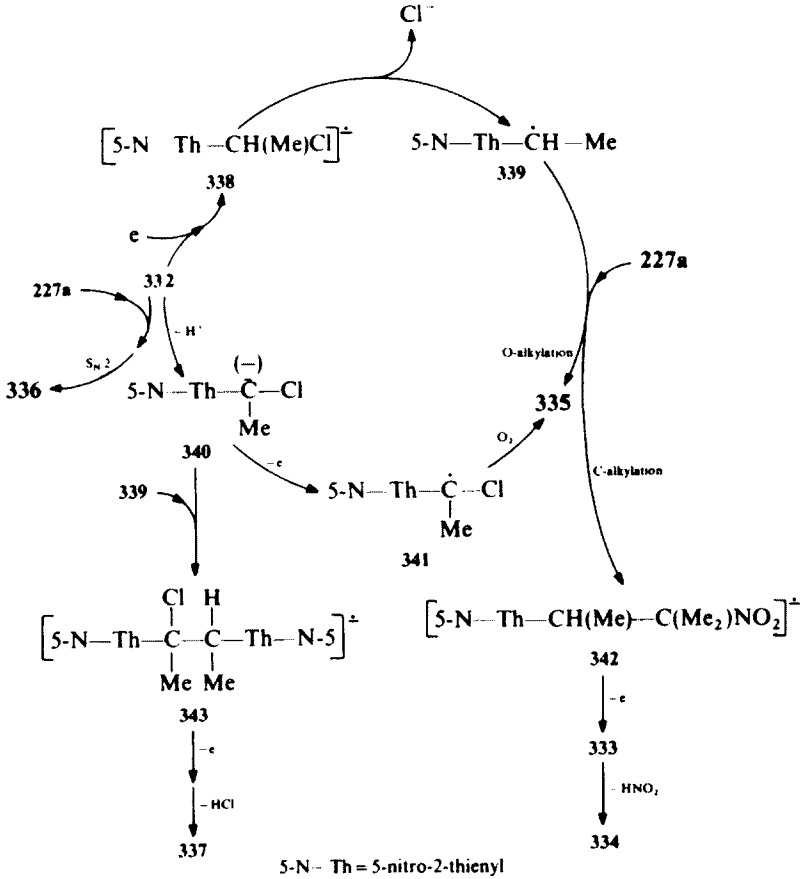
335: 12%

5-N—Th—CH(Me)OH

336: 3%

5-N—Th—C(Me)=C(Me)—Th—N-5

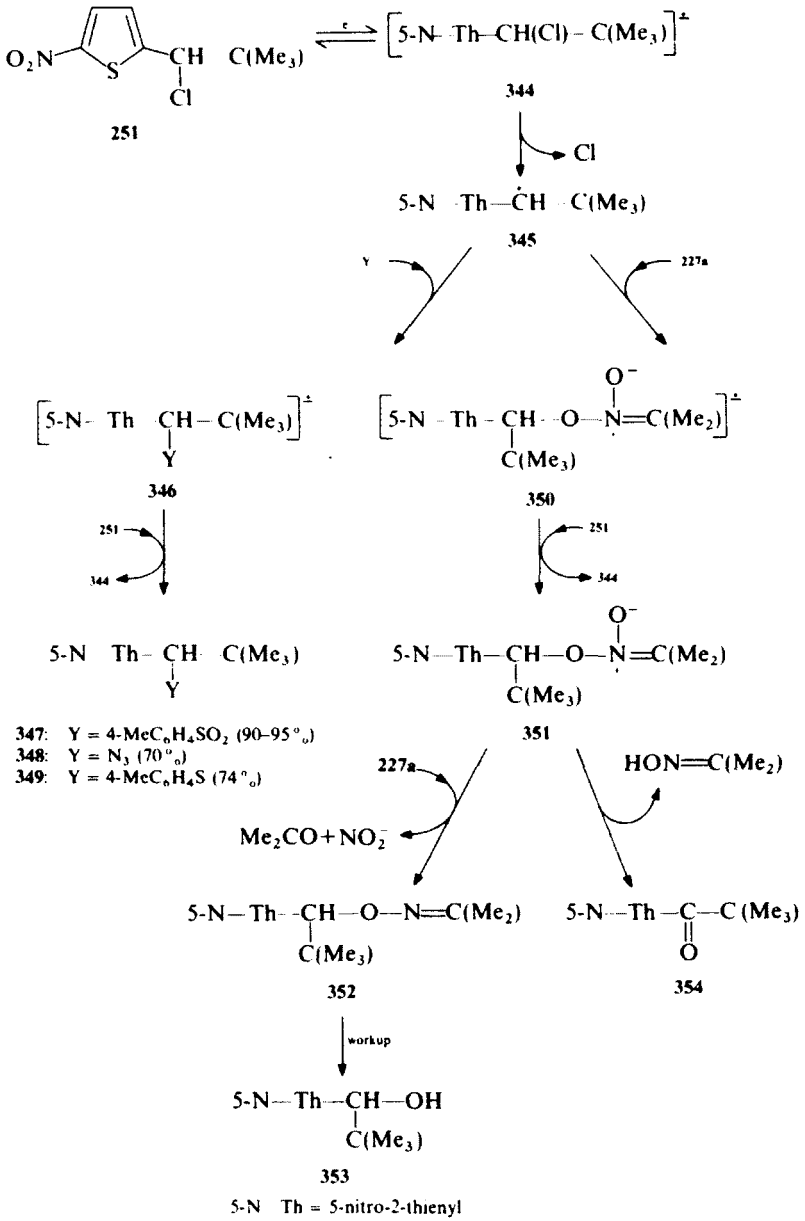
337: 20%



5-N— Th = 5-nitro-2-thienyl

Scheme 67

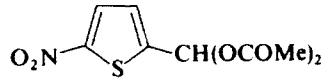
In analogy with the *p*-nitrophenyl analog,[331,332] the (5-nitro-2-thienyl)-neopentyl chloride (**251**) reacts,[257] smoothly and in high yield, with *p*-toluenesulfinate, azide, and *p*-toluenethiolate to give the substitution products **347**–**349** via an $S_{RN}1$ process. Interestingly, with the lithium salt of 2-nitropropane, exclusive sterically induced O-alkylation,[331–334] which eventually leads to **353** and **354**, was observed (Scheme 68).



Scheme 68

It is worth noting that, while several examples of $S_{RN}1$ processes occurring on 5-nitro-2-thenylic derivatives have been observed, the analogous reactions carried out on the "meta-like" isomers **230–235** and **247** proceed through an alternative nonchain mechanism [S_N(AEAE) and similar processes] involving initial attack of a nucleophile at the free α-position of the thiophene ring.[251,252,256] This reactivity pattern represents a prominent example of nonbenzenoid behavior of nitrothiophene derivatives and has been summarized previously (see Section III.2.C).

Pieces of evidence against the $S_{RN}1$ mechanism but in favor of an interesting alternative ionic chain mechanism have likewise been reported by the same research group[335] for the reaction of 5-nitro-2-thienylmethylene diacetate (**355**) with lithium 2-nitropropan-2-ide (**227a**) in DMSO.



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ADDENDUM

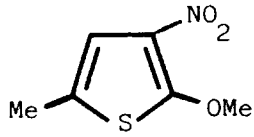
Since the submission of the manuscript to the Editor (march 1987) some papers on nucleophilic substitution of thiophene derivatives have been published. For this reason this short addendum, containing a review of the most significant contributions, has been appended to the chapter.

Section II.1.

The close correlation existing between geometry and reactivity is confirmed by a comparison of the crystal structure of 2-chloro- (**28**) and 2-phenylsulphonyl-3,5-dinitrothiophene (**139**: L = SO_2Ph) and that of the analogous benzene derivatives.[336] In the thiophene derivatives, more reactive than the corresponding benzene compounds, the rotation angles of nitro groups are lower than those measured for 2,4-dinitrochlorobenzene (**97**).

Section II.2.

A kinetic and thermodynamic study of the reaction of 2-methoxy-5-methyl-3-nitrothiophene (**356**) with sodium methoxide in methanol has shown[337] that a methyl group can help delocalization of a negative charge. This effect, made possible by the polarizability of C—H bonds, depends on the electronic request from the aromatic ring to which the methyl group is bonded and accounts for the weak activation by this group in S_NAr reactions.



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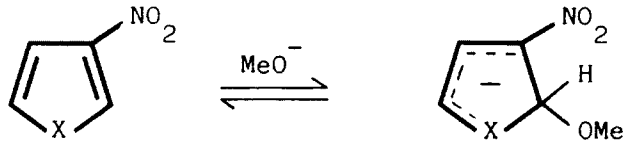
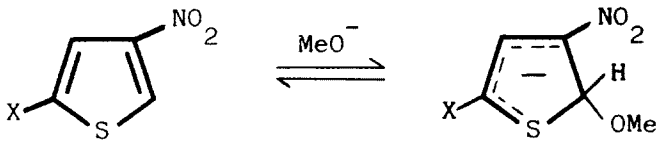
An analysis of ^{13}C nuclear magnetic resonance spectra of 3-nitrofuran (**357**), 3-nitrothiophene (**115**), and 3-nitroselenophene (**358**) and the corresponding Meisenheimer-type adducts at C-(2) (**359–361**) formed by reaction with sodium methoxide, in DMSO-d_6, has shown[338] that the electronic density at C-(5), in the adducts, follows the order (**359**) < (**360**) < (**361**). This result, together with other data on some competitive reactions, has been interpreted on the grounds of the low aromatic character of the furan ring and the different aptitude of sulphur and selenium to delocalize a negative charge.



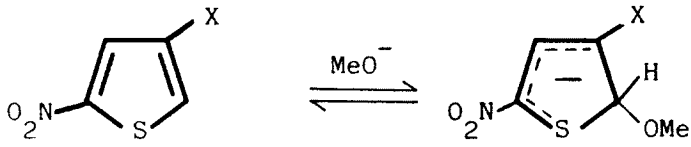
357: X = O
115: X = S
358: X = Se

359: X = O
360: X = S
361: X = Se

Scheme 69



362 **364**



363 **365**

Scheme 70

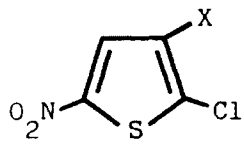
The results obtained from a kinetic and thermodynamic study of the formation of the Meisenheimer-type adducts from some 4-nitro-2-X-thiophenes (**362**) or 2-nitro-4-X-thiophenes (**363**) and sodium methoxide in methanol or methanol-dimethylsulphoxide mixtures have shown[339] that when there is no methoxy group at the reactive site and the starting compound is consequently not stabilized by through-conjugation with the nitro group, the Meisenheimer adducts are formed faster than the corresponding *gem*-adducts. On the other hand, the attack of methoxide ion at C-(2) is faster and the Meisenheimer adduct is less stabilized when the nitro group is at C-(3) and the X-substituent is at C-(5) than *vice versa*. These findings confirm the role of the hyper-*ortho* relation in the thiophene compounds.

Section II.4.

The reaction of 2-methoxy-3-nitrothiophene (**109**) with N-benzylmethylamine (BMA) in methanol has been studied[340] as a function of amine and/or methoxide ion concentration. The rate coefficients obtained have shown that the reaction is catalysed by methoxide ion through a specific base catalysis mechanism.

Section II.5.

A further example of *ortho*-Hammett relationship has been reported.[341] A kinetic study of chlorine-isotopic exchange between lithium chloride and some 2-chloro-5-nitro-3-X-thiophenes (**366**) in sulpholane has shown that the substituent effects give a satisfactory *ortho*-like l.f.e.r. (n 7, r 0,987, C.L. > 99%) with a high susceptibility constant (at 75°C, $\rho + 4.56 \pm 0.33$).



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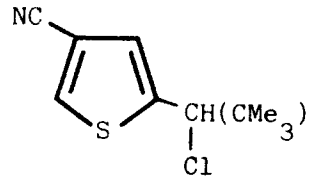
Sect. III.1.

Through an *ab initio* molecular orbital approach,[342] carried out at the CASSCF/3-21G level, 2,3-didehydrothiophene (**180**) was calculated to lie just 1 KJ mol^{-1} lower in energy with respect to the 3,4-didehydro isomer (**181**). With such a low difference in energy, the results obtained with the iodomercury thiophene (**184**) may be interpreted by admitting a much faster trapping of (**180**), with respect to (**181**), by tetraphenylcyclopentadienone.

Sect. III.2.D.

In analogy with the behaviour of the analogous 4-nitroderivative (**247**), (4-cyano-2-thienyl)neopentyl chloride (**367**) has been shown[343] to undergo, by action of p-toluenethiolate in dipolar aprotic solvents, substitution of the chlorine via an S_N (AEAE) process similar to that shown in Scheme **40**.



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Sect. III.2.E.2.

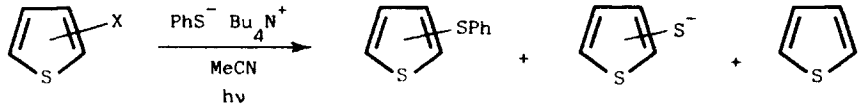
Recently, the ring opening reactions of 3,4-dinitrothiophene (**255**) with primary and secondary amines[89,261] in various solvents has been deeper investigated[344] and dinitrobutadienes (**271**, $R^1 = R^2$ = alkyl; R^1 = H, R^2 = alkyl or aryl) have been obtained in yields ranging between 45 and 90%. In analogy with the case of simple mononitroenamines,[345–347] by ^{1}H and ^{13}C NMR compounds (**271**, $R^1 = R^2$ = alkyl) were found to consist only of (E,E) isomers. Conversely, the ring opening products (**271**, R^1 = H, R^2 = alkyl or aryl) obtained from the reactions with primary amines appear as mixtures of (E,E), (E,Z), and (Z,Z) forms whose compositions are strongly dependent on the polarity of the solvent used: whereas the (Z,Z) isomers predominate in $CDCl_3$, due to their increased stability by intramolecular hydrogen bond between the NH and the adjacent nitro group, the (E,E) form is favoured in strong hydrogen-bond-accepting solvents like CD_3SOCD_3.

Sect. V.

For reviews on $S_{RN}1$ reactions see also references 348–356.

Sect. V.1.A.

The photoinduced $S_{RN}1$ reactions of 2-bromo- (**196**), 3-bromo- (**197**), 2-chloro- (**303**), and 2-iodo-thiophene (**368**) with tetrabutylammonium benzenethiolate have been investigated in acetonitrile.[357] As shown in the scheme 71, such reactions yield 2- or 3-phenylthiothiophenes (**369**) and (**370**) accompanied by thiophene (**96**) and 2- or 3-thiophenethiolate (**371**) or (**372**) as side products.



303: X = 2-Cl
196: X = 2-Br
368: X = 2-I
197: X = 3-Br

369: 2-PhS
370: 3-PhS

371: 2-S⁻
372: 3-S⁻

96

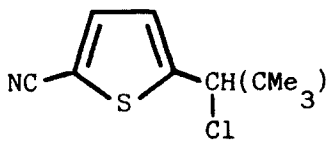
Scheme 71

The proportions of the above by-products increase as the reduction potential of the starting halothiophene is more negative (see Part 2, Chapter III, Section II.6.C) and as the conversion percentage of the reaction increases. On this regard, as to the obtainable yield of phenyl thienyl sulfides, the main drawback is represented by the competitive[328] fragmentation into 2- or 3-thiophenethiolate and phenyl radical of the radical anions of the substitution products (**369**) or (**370**), formed along the $S_{RN}1$ propagation cycle or by single-electron reduction of the same sulfides. By addition of suitable electron acceptors to the reaction mixture the above fragmentation, which for diaryl sulfide radical anions is a well documented process,[315,316,358–368] could be limited and the yields of (**369**) or (**370**) improved although at the expense of the overall reaction rate.[357]

As regards the overall reactivity order found in the reactions of halothiophenes with benzenethiolate,[357] while the order 2-I > 2-Br > 2-Cl matches that commonly found for other haloarenes in similar processes,[318–324] the reactivity order 2-Br > 3-Br is in agreement with the easier reducibility of the former as shown by both competitive experiments[357] and electrochemical studies: $E_{1/2}$ being −1.75 and −2.14 V vs. SCE in DMF for (**196**) and (**197**), respectively.[369] The reactivity order 2-Br > 3-Br however results to be the reverse of the order found, e.g., in the photon or solvated-electron stimulated reactions with acetone enolate in liquid ammonia.[314] Differences in the reaction conditions between the two cited systems are anyway so substantial that any attempt of comparison would be rather unwarranted.

Sect.V.2.

(5-Cyano-2-thienyl)neopentyl chloride (**373**) has been shown[343] to react in DMF or DMSO with p-toluenethiolate to give (5-cyano-2-thienyl)neopentyl



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p-tolyl sulfide via an $S_{RN}1$ process. Such reactivity matches that of the 5-nitro analogue (**251**) and it is different, on a mechanistic point of view, from the behaviour of the 4-cyano isomer (**367**) which undergoes substitution via an S_N (AEAE) process.

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CHAPTER III

Biologically Active Thiophene Derivatives Revisited: 1983–1988

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I. INTRODUCTION

The incorporation of the thiophene moiety into biologically active derivatives has continued unabated during the past 5 years since our last major review of this class of compounds.[1] The discovery and development of pharmacologically active molecules has been guided not only by classical medicinal chemistry but also by the use of sophisticated mechanistic approaches and new biochemical assays. New concepts of therapy such as the use of enzyme inhibitors to control disease states [such as angiotensin-converting enzyme (ACE) or 3-hydroxy-3-methylglutaryl coenzyme A (HMG–CoA) inhibition for cardiovascular diseases] has increased the scope of medicinal chemical research. The continued need to develop agents with increased potency and activity as well as greater specificity and reduced toxicity has driven medicinal and agricultural chemical research in the 1980s. As the scope of this research has increased, so has the use of thiophene in these studies.

Several reviews of biologically significant thiophene derivatives have been published. A review by Drehsen and Engel provides some detailed insights into the structure–activity relationships that have been developed for various thiophene series.[2] Compounds active as chemotherapeutics, in the central nervous system (CNS), and in the cardiovascular system as well as other miscellaneous derivatives were discussed. Böhm updated his previous excellent review of the synthetic and pharmacological aspects of thiophene structures.[3] Reviews of limited scope on thieno[2,3-*d*]pyrimidines[4] and thienopyridines[5] were also reported in the Russian literature during the past 5 years.

The reasons for investigations into thiophene derivatives as possible pharmacologic agents are numerous. Certainly, the need to develop complete structure–activity relationships in any series requires investigation into the steric and electronic requirements of aromatic moieties in such molecules. The electron-rich properties as well as the slightly smaller steric volume of thiophene (6π-electron heteroaromatic system) as compared to benzene may play an important role in fitting the necessary biological receptor sites. Generally, thiophene analogs (isosteres) of benzene systems are also patentably novel systems and thus may allow the economical development and commercialization of drugs related to those of competing drug companies. The concept of bioisosterism was initially proposed by Erlenmeyer[6] and was further elaborated recently by both Thornber[7] and Böhm.[8]

The thiophene moiety has been incorporated into biologically active molecules in two manners. The most chemically interesting of these is the synthesis of molecules containing thiophene as part of the central ring. In such systems, synthesis of the three possible 2,3-, 3,4-, and 3,2-isomeric substitution patterns may be difficult at best. Such synthesis targets provide the greatest insight into

the effect of thiophene on biological activity. There are examples of these types of compounds wherein the thiophene derivative was designed as the isostere of an active benzene molecule. In other cases, a thiophene derivative was prepared de novo and not as an isostere. The thiophene moiety has also been incorporated as a pendent aromatic ring on biologically active series aiding in the development of aromatic substitution patterns to improve activity and potency.

This chapter will review biologically active thiophene derivatives as well as isosteres of known active systems reported in the literature between early 1983 and the end of 1988. Several of the major journals have been reviewed into mid-1989. As was the case for our earlier review,[1] benzothiophene derivatives have been ignored, except for those cases where a logical development requires their mention. The use of computer-aided searching has significantly eased the task of writing such a review, but the scope of a chapter attempting to review all such thiophene derivatives is overwhelming. Computer searches in CAS on-line and Derwent led to lists of well over 1500 references. Obviously from this scope, some references most likely have been overlooked and this author regrets any oversights. As a consequence of the lack of consistent, scientifically meaningful data in the patent literature, only compounds described in the scientific literature are covered in this review.

The topic areas discussed and their ordering follows the format of the previous review.[1] Some areas of biological research overlap and their order of appearance is at the choice of this author. When agents have more than one mode of action, they will be included in the topic area that appears to be most important in the development of the compound in question.

The incorporation of thiophene in pharmacologically active molecules continues to give unpredictable results. Numerous attempts to generalize the best activity to the 2- or the 3-thienyl derivatives has repeatedly failed. As is evident throughout this review, different molecule types developed for different biological activities require unpredictable thiophene substitution. There are numerous examples of the 2-thienyl derivatives having superior properties and vice versa. All possible isomeric thiophene derivatives must be prepared to discover the best substitution pattern. There are examples where a thiophene-containing molecule is significantly less active than its benzene isostere and vice versa, so that generalizations here are nearly impossible. The thiophene moiety (as compared to its benzene counterpart) changes physical chemical properties such as solubility, bioavailability, and metabolic fate as well as synthesis approaches in biologically driven research projects. As was the case in the previous review,[1] research of thiophene compounds leads to unexpected and sometimes quite superior results in the development of pharmacologic agents.

II. CENTRAL NERVOUS SYSTEM THERAPY

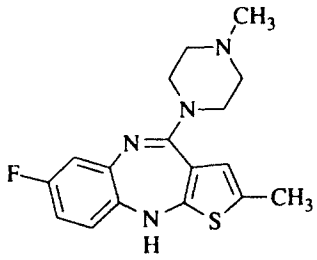
Central nervous system drugs had worldwide sales of close to $12 billion in 1988. In addition to the relatively mature areas of antipsychotic, antidepressant, and antianxiety therapy, newer areas of research have focused on nootropic

agents, which might treat memory loss in Alzheimer's disease, and selective serotoninergic agents. The issues of specificity of drug action are particularly acute in CNS research since mood alteration and involuntary muscle action are especially pertinent to patients already suffering from diseases of the CNS.

1. Antipsychotic Agents

Research in this area continues to be directed toward the development of an antipsychotic agent without extrapyramidal side effect (EPS) liabilities typical of classic neuroleptic drugs such as chlorpromazine or haloperidol. The only compound without EPS liability that has reached clinical trials is clozapine, which has failed to reach the market because it causes agranulocytosis. Efforts to find agents effective as D_2 dopamine antagonists specific to the mesolimbic system (thus avoiding EPS) continue. The role of serotonin in psychosis is also under study.

Flumzaepine (**1**, LY 120363) has been developed as a neuroleptic agent with few side effects. The compound is a potent antagonist of the dopamine D_2 receptor, which also has some serotonin effects.[9] The compound is metabolized by the replacement of the fluorine with a thiomethyl moiety,[10] and blockade of serotonin may play a role in reduction of extrapyramidal side effects of this agent.[11] Several comprehensive reviews of the status of this potential drug have appeared.[12] Studies of the Free–Wilson structure–activity correlation for this series of compounds have also been reported.[13]



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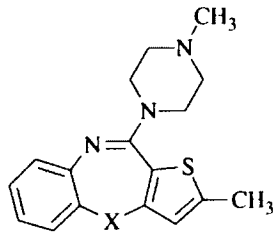
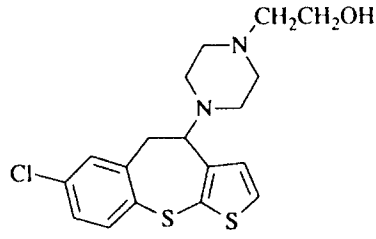
Syntheses of the isosteric sulfur[14] (**2**) and oxygen[15] (**3**) thieno[3,2-*b*] systems have been studied further since the last review. The noncataleptic neuroleptic properties of thieno[2,3-*b*]benzothiepin **4** suggest that this compound may have interesting development possibilities. The compound was inactive toward apomorphine-induced stereotypies in rats.[16]

Some interesting polycyclic thiophene derivatives have also been reported to be neuroleptic agents. QM 7184 (**5**), the thiophene isostere of taclamine, was compared to haloperidol and butaclamol. In addition to its neuroleptic profile, which was somewhat less potent than the standards, compound **5** had high



2, X = S
3, X = O



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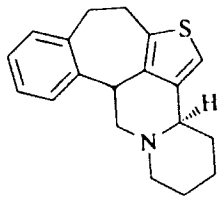
affinity for rat cortical and striatal α-adrenergic receptors. These affinities may play a role in the drug's use in treatment of schizophrenia.[17] The compound's properties have been summarized.[18] The syntheses of QM 7184[19a] and the intermediate lactam **6**[19b] were reported in detail.



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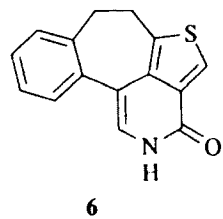
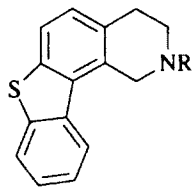


6

The thiophene analogs (**7**) of apomorphine have been prepared and are dopamine antagonists.[20] These rigid compounds tethered by a sulfur bridge are dopamine receptor antagonists in vitro but have no antipsychotic activity in vivo. Tienocarbine (**8**) and related compounds altered dopamine turnover in striata but had no effect on other biogenic amines. Compound **8** displaced ^{3}H-dopamine and ^{3}H-spiperone in calf brain caudate,[21] and the pharmacokinetics of **8** have been reported.[22]



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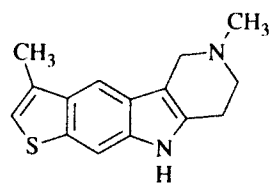

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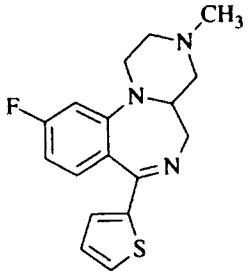
Timelotem (**9**, KC 7507) is an outgrowth of ongoing research programs investigating structure–activity modifications of anxiolytic benzodiazepine (BDZ) systems. The antipsychotic activity of **9** is not linked solely to D_2 receptor activity. The compound has no in vitro binding affinity for BDZ receptors

but has in vivo activity predictive of antipsychotic and anxiolytic agents with potency comparable to haloperidol.[23a] Only the (+)-enantiomer has D_2 receptor affinity.[23b] Citizolam (**10**, WE 973) is a neuroleptic agent more potent than brotizolam.[24]



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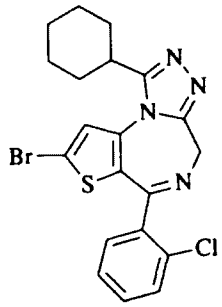
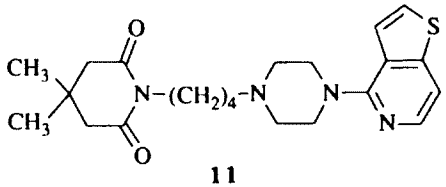


10

The best derivative out of a series of thieno[3,2-*c*]- and furo[3,2-*c*]pyridine derivatives is thiophene **11**.[25] The compound had significant activity in the blockade of apomorphine stereotypy and apomorphine-induced climbing as well as the conditioned avoidance test. The compound also had potent affinity for the serotonin 5-HT_1 and 5-HT_2 receptor. Interestingly, it is likely that **11** has a mechanism of action different from that of the isosteric furan derivative. The thiophene isosteres (**12**) of haloperidol have been prepared, but no biologic data were reported.[26]



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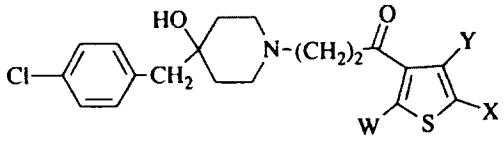
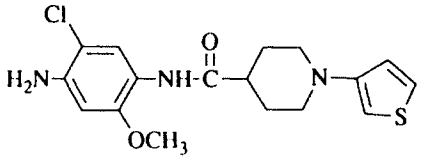


12

A series of substituted benzamides related to clebopride, including **13**, was prepared.[27] The compounds were tested against apomorphine-induced climbing. While the 3-thienyl derivative **13** had an ED_{50} of 3.4 mg/kg, the isomeric 2-thienyl derivative had only marginal activity at 10 mg/kg. Lipophilic binding sites play a major role in this activity. A series of aminopyrazoles was reported to cause marked CNS depression with no anticonvulsant activity. Ketone **14** was a potent lead in this class of antipsychotic agents.[28] Subsequent work led to the development of the imine analogs **15**, which were tested for effects on

spontaneous motor activity and D_2 dopamine receptor binding, and compared to clozapine and thioridazine.[29] In this latter series, **15** was not one of the better compounds. The tetrahydrothiophene and thiophenium isosteres of sulpiride were made to investigate the relationship of ionic charge to D_2 binding activity. Only the tetrahydrothiophenium analog displaced ^{3}H-spiperone.[30]



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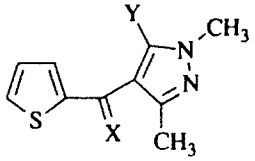
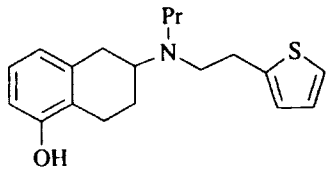


14, X = O, Y = NH_2
15, X = NH, Y = OH

The selective D_2 dopamine agonist N-0437 (**16**) has received significant attention in the past 5 years.[31] The compound was more potent than apomorphine in reversing increased γ-butyrolactone-induced central DOPA synthesis in rat.[32] The compound displaced ^{3}H-spiperone from D_2 receptors in rat brain. This type of compound fit a two-site receptor model.[33] Additional radioreceptor data has been reported[34] and autoreceptor selectivity is dependent on the position of the aromatic hydroxyl substituent.[35] Metabolic pathways of the racemic material were studied and glucuronidation appears to be the major pathway.[36] The compound might be useful in the treatment of glaucoma.



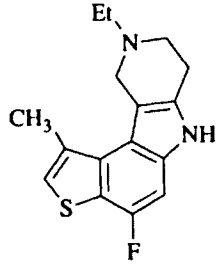
16

2. Antidepressant Agents

Research in this area in the last decade continues to focus on the selective inhibition of serotonin reuptake in CNS transmission sites. The problem with current therapies lies both in drug-induced cardiac toxicity observed for both the tricyclics and MAO inhibitors as well as the slow onset of drug action. It is difficult to convince depressive patients, many of whom have suicidal tendencies, to wait 1–3 weeks for their treatment to take effect.

Tiflucarbine (**17**, TVX P 4495) is a fluorinated analog of the neuroleptic tienocarbine (**8**).[37] The compound potentiated amphetamine stimulation in rats and reversed tetrabenazine- or reserpine-induced ptosis in mice.[38] The compound down-regulates β-adrenergic receptors in the brain. Compound **17** had

moderate affinity exclusively for the 5-HT_2 receptor and blocked serotonin reuptake.[39]



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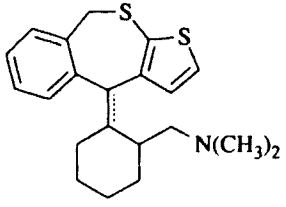
Thiophene derivatives with more classical tricyclic structures also have been reported. The semirigid analogue of dithiadene **18** had both antidepressant and antihistaminic activity. Compound **18** had the most interesting antidepressant profile.[40] Related thienothiepin **19** also had antireserpine effects but, interestingly, did not affect ^{3}H-imipramine binding.[41] The amine analogs **20** were synthesized as isosteres of desimipramine. They were 10-fold less potent than desimipramine in blockade of imipramine receptors.[42] Compound **21** was prepared as an extension of the prothiadine series and was a selective 5-HT uptake inhibitor. The *Z*-isomer in the series had the more interesting antidepressant profile of action with antireserpine activity in vivo.[43] Synthesis and activity of pizotifen as an antiserotonin agent was reported.[44]



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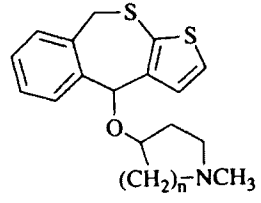

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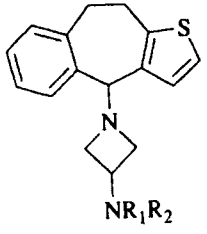

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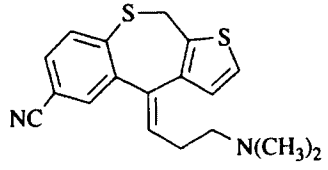
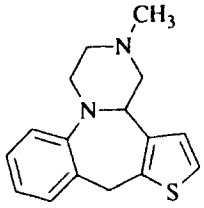


21

The thiophene analog of the novel antidepressant mianserin was prepared. CGS 11049A (**22**) had a profile similar to that of mianserin in receptor binding

profile (^{3}H-clonidine, ^{3}H-prazosin, ^{3}H-serotonin, ^{3}H-rauwolscine) and was active in the behavioral despair assay. Compound **22** bound more tightly to central presynaptic α-adrenergic receptors.[45] The *N*-methylthienopyridine analog (**23**) of nomifensine was found to inhibit norepinephrine and serotonin uptake in rat brain synaptosomes as well as to antagonize tetrabenazine-induced ptosis in mice.[46] Very closely related dihydroxyphenyl analogs of **23** had selective affinity for dopamine D_1 receptors.[47] Full structure–activity studies were published.[47] Some differences between the thieno[2,3-*c*] and thieno[3,2-*c*] systems were noted.[49]



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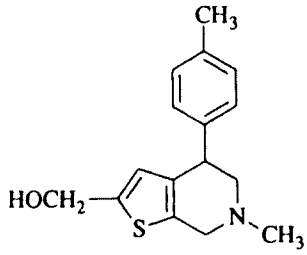

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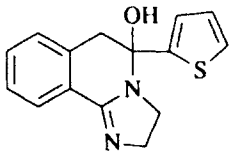
In a series of aryl-substituted imidazo[2,1-*a*]isoquinolin-5-ols, thiophene derivative **24** was slightly less active than the 4-chlorophenyl derivative to antagonize reserpine-induced hypothermia.[50] A series of spiropiperidine derivatives dramatically potentiated serotonin-induced behavior effects in rats. Compound **25** was more active than chlorimipramine and fluoxetine.[51] The thiophene analog of trazodone was prepared as part of a series of 1,2,3-triazin-4-ones. Compound **26** was among the best compounds in the study and was more effective than trazodone in potentiating serotonin-induced stereotypy in mice.[52] A series of quinoline derivatives was found to have in vitro affinity for 5-HT_1 and 5-HT_2 receptors. 3-Thienyl derivative **27** was the most potent of the heterocyclic analogs but was less interesting that the phenyl derivative.[53] Sulfoxazine (**28**, Y-8894) had antidepressant and nootropic properties.[54] A



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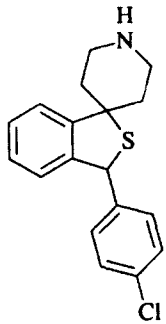

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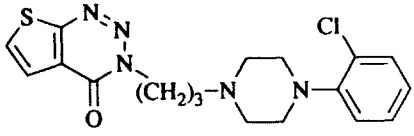

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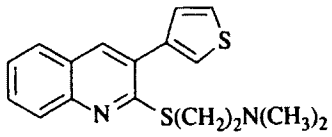
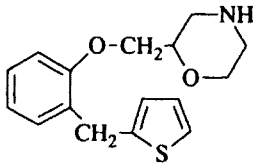


27

number of reviews on this compound that summarize its antidepressant properties have appeared.[55] A series of carbonates of thienylpropanols (**29**) was reported to have reserpine-antagonist activity. The thiophene compounds generally had lower toxicity than their benzene isosteres.[56] LY 227942 (**30**) inhibits serotonin and norepinephrine uptake. Compound **30** has an antidepressant profile in vivo.[57] In an interesting digression from active thiophene derivatives, **31** was inactive while the diphenyl isostere was one of the most potent antagonists of tetrabenazine-induced ptosis and motor depression.[58] Some thiophene isosteres of amphetamines (**32**) were shown to have antidepressant effects but were less potent than imipramine.[59] Thiophene effectively replaced benzene in a series of antidepressant aminopyridazines (**33**).[60]



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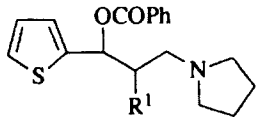

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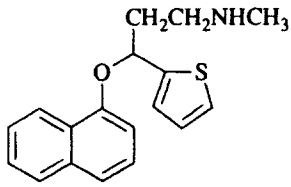

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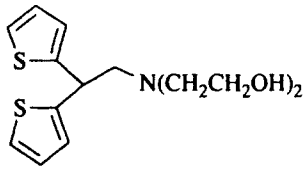

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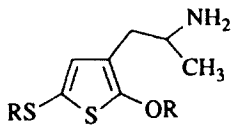

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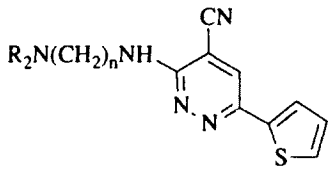
3. Antianxiety Agents and Anticonvulsants

Benzodiazepine derivatives such as valium and lorazepam revolutionized the treatment of health-impairing anxiety. While everyone suffers mild anxiety that is probably a condition of life, debilitating anxiety interferes with normal function in society. Reports of alcohol–benzodiazepine interactions have intensified the search for better forms of treatment. In addition to the role of

γ-aminobutyric acid (GABA) in anxiety, several laboratories are investigating serotonin agonists and antagonists as possible methods of treatment.

In the continuing development of benzodiazepine analogs, etizolam (**34**) was reported to have antimetrazol effects and to prevent electroshock convulsions.[61] The closely related compound, brotizolam (**35**), has been marketed as an anxiolytic and hypnotic. The detailed synthesis of **35** and its metabolites has been published.[62] Drug distribution, metabolite patterns in varying species,[63] and the metabolic fate of **35** have also been studied.[64] The haptan **36** of brotizolam was prepared for a radioimmune assay of **35** in clinical studies.[65] KW 1937, the *p*-chlorophenyl analog of **35**, had high affinity to peripheral-type benzodiazepine receptors. This compound caused convulsions.[66]



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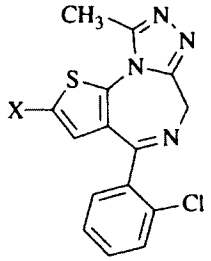
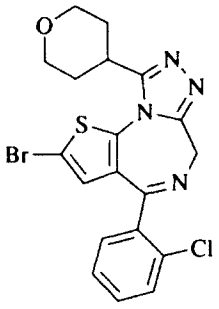


34, X = CH_2CH_3
35, X = Br
36, X = $CH_2CH_2CO_2H$

The binding potencies of ciclotizolam and its 4-tetrahydropyranyl analog **37** (WE 1008) on the benzodiazepine receptor were unaffected by GABA. Both had no hypnotic activity in rats but prevented pentylenetetrazole-induced seizures. These results suggest that a GABA shift may not distinguish benzodiazepines in vitro.[67] Several thieno[2,3-*e*][1,4]diazepine thiones have been reported to have anxiolytic activity. TDT (**38**), TDO (**39**), and BrTDO (**40**) have been studied using a variety of instrumental techniques.[68–71]



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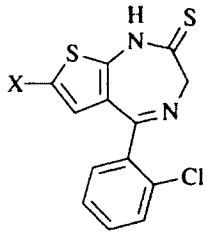
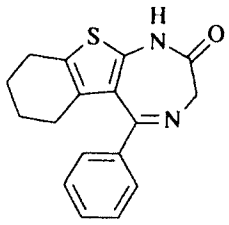


38, X = Cl
39, X = H
40, X = Br

Tiadipone (**41**, QM 6008) has been reported to have psychotropic activity in humans. The compound had anxiolytic, tranquilizing, and anticonvulsant effects in animal screens.[72] A series of inverse agonists to the benzodiazepine receptors culminated in the synthesis of **42** (S-135). While **42** was a proconvulsant when administered with pentylenetetrazole, the isomeric **43** prevented seizures under the same conditions.[73] Further studies have shown the 2-thienyl derivatives are benzodiazepine agonists with less potency than diazepam while the 3-thienyl compounds are more potent as benzodiazepine inverse agonsits than the phenyl isosteres.[74] Structure–activity studies have defined a continuous shift from agonist to inverse agonist activity with increasing bulk of the alkyl-substituent on thiophene.[75]



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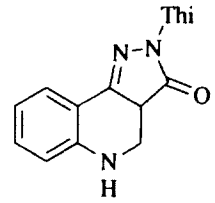
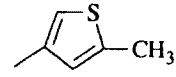
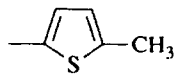
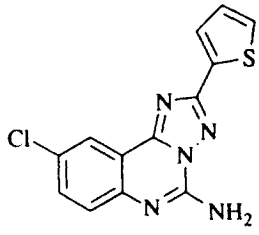


42, Thi = 

43, Thi = 

A related furan analog, CGS 15943, was found to be a novel adenosine antagonist that also modulated the benzodiazepine receptor. In this case, the thiophene **44** was essentially devoid of activity.[76] Pyrrolo[1,2-*c*]thieno[3,2-*e*]-pyrimidine **45** is another nonbenzodiazepine antianxiety agent. The compound has potent affinity for the receptor albeit slightly less than half that of diazepam.[77] The thiophene derivative of the 1,2,4-triazolo[4,3-*b*]pyridazine series of anxiolytics was prepared (**46**), but no activity was reported.[78] A novel series of thienopyridines (**47**) also has anticonvulsant properties.[79]



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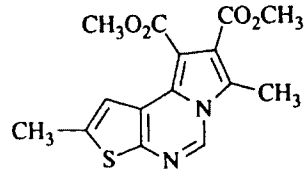

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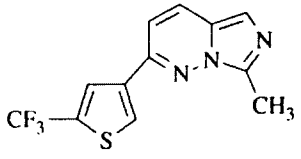

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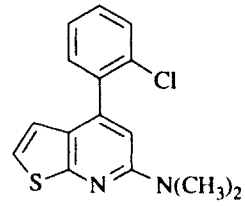
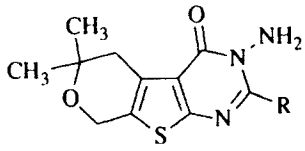


47

Two closely related thienopyrimidine series of compounds (**48** and **49**) had anticonvulsant activity. Compound **48** prevented corazol-induced convulsions but had no effect in the electroshock test.[80,81] The 2-isopropyl derivative caused interference with maze-learning in rats.[82] The related tetrahydrobenzothiophene derivative **49** has pronounced anticonvulsant activity. An electron-donor substituent at the 2-position (R_1) is critical to activity.[83]



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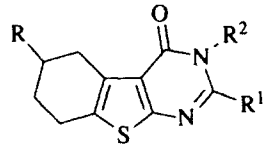
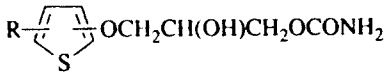


49

The thiophene isosteres of mephensin were prepared as possible skeletal muscle relaxants. While the 3,4-isomer **50** had a similar biological profile to that of mephensin, albeit with less potency and less toxicity, the other isomers were essentially inactive.[84] A series of thiobutyrolactones (**51**) were potent anticonvulsants with activity and toxicity comparable to valproic acid.[85] The thiophene isostere (**52**) of the anticonvulsant AD 810 had no activity against pentylenetetrazole or electroshock convulsions.[86] A series of pyrrolidiones (**53**) was found to have anticonvulsant activity.[87] The (−)-enantiomers showed greater inhibition of butyrylcholinesterase than did the (+)-enantiomers.[88]



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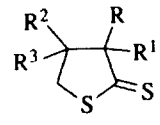

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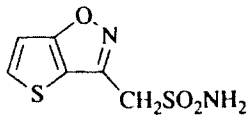

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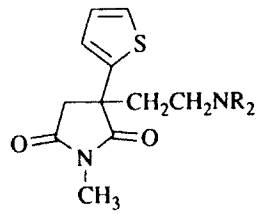
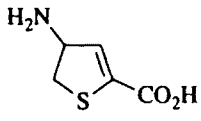


53

Compound **54** was designed as a mechanism-based inhibitor of GABA- T.[89] Compound **55** is an aminopyridazine derivative of GABA-A that antagonized GABA-induced ^3H diazepam indicative of a receptor antagonist.[90] Baclofen analog **56** was surprisingly inactive in binding at the GABA receptor.[91] SKF 100604 (**57**) was prepared as a part of a series of nipecotic acid derivatives and was as potent as the parent compound in GABA uptake and in muscimol binding.[92] A series of 6-arylpyridazines including **58** was similar in activity to phenobarbital. Interestingly, the 2- and 3-thiophene derivatives were significantly less active than the substituted-phenyl derivatives.[93]



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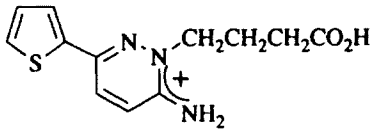

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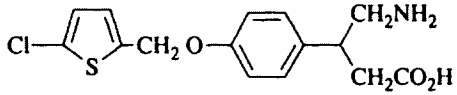

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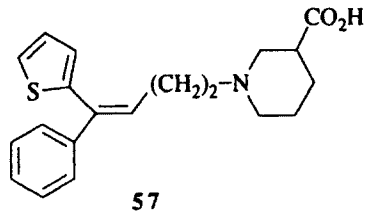

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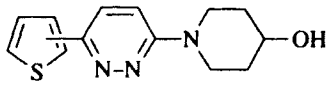


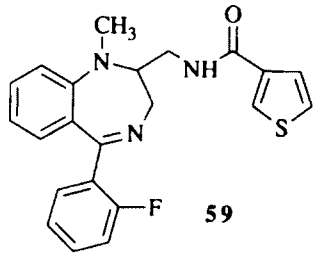
58

4. Analgesic Agents

Analgesics represent the largest single market for CNS agents, with worldwide sales of over $3 billion in 1988. The group includes the relatively weak drugs such as aspirin and acetaminophen as well as the centrally acting agents which have strong pain-relieving properties but have strong sedative and addictive side effects. Research in this latter area is directed to structure–activity studies of morphans and related centrally active drugs that might lead to reduced addiction potential.

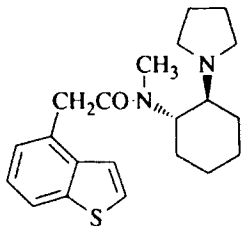
Tifluadom (**59**) represents an unique benzodiazepine with 25-fold greater affinity for the opiate receptor than morphine. While it binds to the μ- and κ-receptors and its analgesic effects are reversed by naloxone, the compound is not a minor tranquilizer.[94] Other workers report that there is a reverse

stereoselectivity for tifluadom for the opiate and benzodiazepine receptor.[95] The (+)-enantiomer but not the (−)-enantiomer of **59** induces κ-receptor-mediated EEG power spectra changes.[95] The 4-methyl quaternary salt of 59 was used to determine ability to cross the blood–brain barrier.[96]



59

PD 117302 (**60**) is a selective κ-opioid agonist with activity attenuated by naloxone.[97] By comparing its activity in vivo with morphine and ethylketocyclazocine, it was found to have a pharmacologic profile characteristic of κ-agonists and some μ- partial agonists.[98] Compound **60** had low- and high-affinity binding sites heterogeneously distributed in guinea pigs.[99] A monograph has been published on sufentanil (**61**), a Schedule II controlled-drug substance of the morphine type.[100] The compound has high affinity for the μ-receptor (10 × fentanyl) and has profound analgesic and anesthetic effects. A method to analyze **61** and two metabolites has been developed[101] as well as determination of its metabolic pathways.[102]



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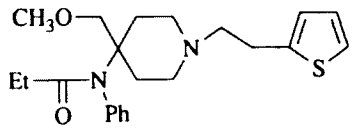
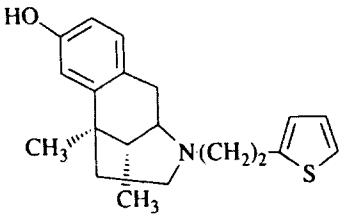


61

A series of nonnarcotic benzazocine analgesic agents was reported. Compounds in the series were compared to pentazocine and morphine, and **62** was one of the most potent in the benzomorphan series.[103] Some thiamorphinan derivatives (**63**) were prepared by several groups as potential analgesic agents, but no biologic activity was reported.[104] Thiophene-containing thebaine alkaloids were also described to have analgesic activity.[105] Some rigid analogs of **60** were prepared in order to investigate the structural requirements of the κ-receptor, but the activity of **64** was not reported.[106] Some thienoquinolines were also prepared as analogs of analgesics.[107]



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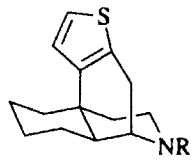

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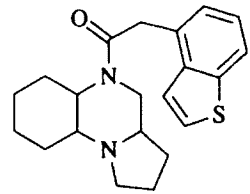
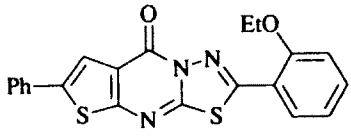


64

A series of thienothiazolopyrimidines, including **65**, were found to be non-narcotic analgesics without gastrointestinal (GI) liability. Compound **65** was the most active against phenylquinone-induced writhing.[108] The 2,3-dihydrobenzothiophene **66** was among the most potent of a series with activity similar to that of zomepirac. The furan isosteres were the best inhibitors of prostaglandin synthesis.[109] The 2- and 3-thienyl derivatives **67** in the glafenine series had similar activities.[110] A number of pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine Schiff bases (**68**) were found to have interesting analgesic activity without GI complications even at doses of 200 mg/kg.[111]



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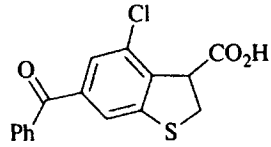

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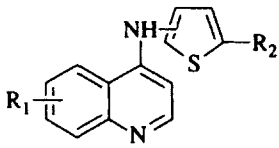

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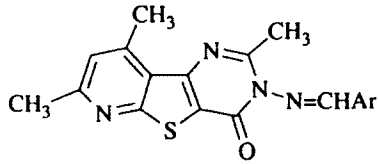
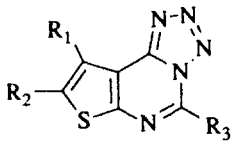


68

Compounds with the general structure **69** were found to have both analgesic and antiinflammatory activities and also inhibited acetic acid-induced writhing.[112] Studies on the deamination of the analgesic agent tinoridine led to **70**, which also has analgesic activity.[113] Some 2-aryl-4-(3-thienyl)imidazole derivatives (**71**) were prepared as analogs of the related oxazoles and thiazoles and also had analgesic activity.[114] Indene derivatives **72** had analgesic and myorelaxant activity in mice.[115]

Other thiophene derivatives with pain-relieving activity included **73**, **74** and **75**.[116–118] Aminothiophene derivatives **76** had central opiate activity.[119]



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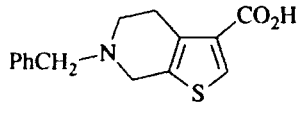

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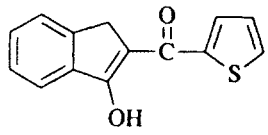

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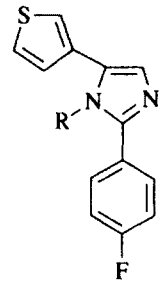

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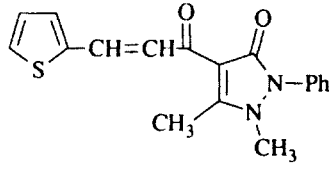

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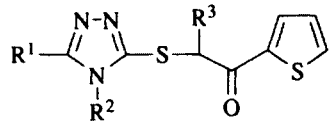

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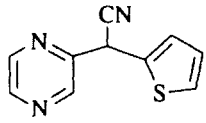

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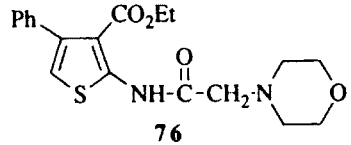
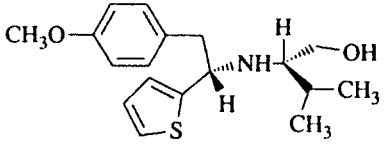


76

Some phenethylamines were prepared in optically pure forms and found to have opioid activity. Compound **77** was equipotent to pentazocine in the acetic acid-induced writhing test but was less active than morphine. The 3-thienyl isomer had similar activity.[120] Several reports of syntheses and analgesic activity of enkephalin analogs containing the thienyl moiety have been published (**78**).[121-122]



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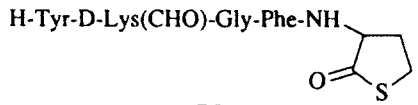


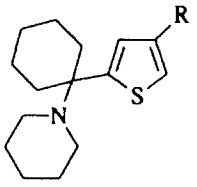
78

5. Mood-Altering Drugs

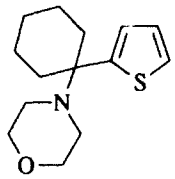
Drug abuse has plagued civilization for centuries. Increased drug usage in the late 1960s and beyond has heightened awareness of stimulants and other illicit

drugs. Some work in legitimate laboratories has been directed at understanding addiction potential and modes of action of these agents. Many illicit drugs are related to opiate analgesics. The thiophenes reported in this area in the past 5 years are either phencyclidine (PCP) or fentanyl analogs.

TCP (**79**), the thiophene analog of PCP, inhibited NMDA-associated excitory effects.[123] The thiocyano derivative (**80**) was an irreversible inhibitor of the PCP receptor.[124] The pyrrolidine analog (THP) as well as PCP and TCP were found to cause spasms of canine cerebral arteries suggestive of the presence of a P receptor on the cerebral vessels.[125] TCP was found to readily substitute for PCP in habituated monkeys with similar pharmacologic effects.[126] The conformation equilibria of TCP and PCP were different for the two molecules, which might account for observed differences in their pharmacology.[127] The morpholine analog (TM, **81**) was found to have analgesic and anesthetic activity.[128] A comparison of the ^{3}H PCP and ^{3}H TCP binding sites in rat brain showed that the compounds labeled the same sites.[129] The compounds interact with dopamine uptake system in the brain.[130]

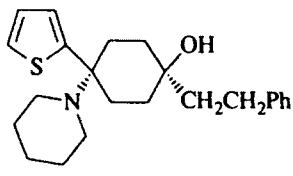


79, R = H
80, R = SCN



81

The *trans*- and *cis*-isomers of **82** were prepared as part of a structure–activity study of PCP. While neither isomer has affinity for the ^{3}H phencyclidine receptor, the *trans*-isomer displaces ^{3}H morphine with an IC_{50} of 0.73 μM. Both isomers had some affinity for the muscarinic receptor.[131] The 2-thienyl (2-MTTP) and 3-thienyl (3-MTTP) **83** both inhibited monoamine oxidase. 2-MTTP, but not 3-MTTP, induced dopamine depletion in mouse striatum and nucleus accumbens. While 2-MTTP oxidized by mitochondria more slowly than the phenyl isostere, 3-MTTP oxidized the slowest.[132]



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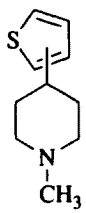
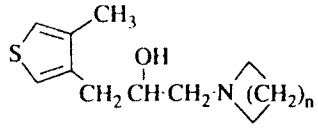


83

6. Local Anesthetic Agents

Local anesthetic agent research is limited to a few laboratories. Studies are directed at increasing duration of action of such agents so that they might be more useful in surgery and thus avoid the need for general anesthesia and at improving their therapeutic index by reducing their toxicity.

Thiophene isosteres of lotucaine were reported to have local anesthetic and platelet aggregation inhibitory activity. The piperidine **84** was more potent as a local anesthetic than the pyrrolidine analogues.[133] The 3,4-thiophene derivative had duration of action similar to that of propranolol. All compounds prepared inhibited platelet aggregation induced by adrenaline.

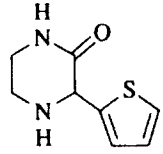


84

7. Nootropic Agents

With the aging populations of the industrialized countries, efforts at reducing memory deficits brought on by natural aging or by premature aging (Alzheimer's disease) have intensified. Approaches to cognition activation include increasing blood circulation as well as increasing acetylcholine turnover in the brain.

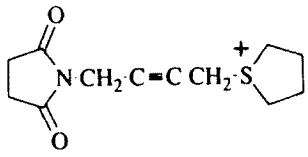
Tenilsetam (**85**) has been reviewed as a potent antihypoxic–nootropic agent that improves cognitive function in animal models.[134] The compounds are ring-extended nitrogen analogs of piracetam. Compound **85** reversed learning deficit in forebrain ischemic gerbils.[135] In clinical trials, the compound improved information processing, problem solving, and memory.



85

Thiolonium analog **86** of the muscarinic agent oxotremorine was synthesized and had potent in vitro activity relative to carbachol. Compound **86** displaced ^{3}H *N*-methylscopolamine from cerebral cortex and was a potent nicotinic acid agonist.[136] It was also evaluated in guinea pig ileum and found to be a muscarinic agonist.[137] A modified tripeptide portion of the *C*-terminal portion

of oxytocin was found to be a possible cognition activator. While **87** reversed electroconvulsant shock, it did not enhance memory in rats or aged monkeys.[138]



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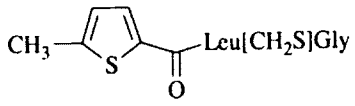
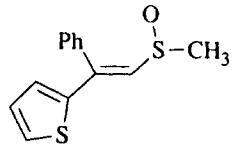


87

A series of thiophene-substituted vinyl sulfoxides (**88**) was synthesized and studied for antianoxic effects.[139] Telenzepine was found to have muscarinic antagonist activity with M_1 selectivity comparable to pirenzepine. The agent might have utility to enhance cognitive function.[140]



88

III. PHARMACODYNAMIC AGENTS

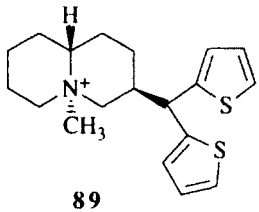
Cardiovascular drugs represent the single largest class of drugs with worldwide sales of more than $19 billion in 1988. New modes of treating hypertension (ACE inhibitors and calcium channel blockers) have led to strong growth in this drug category. One extremely promising new drug therapy for the treatment of congestive heart failure uses cardiotonic (positive inotrope) activity based on inhibition of phosphodiesterase (PDE) in cardiac muscle. The role of cholesterol control in prevention of arteriosclerosis is deferred in this review to Section IV. Treatment of ulcers using H_2-antagonists such as cimetidine and rantidine have led this $4 + billion market. Clearly, pharmacodynamic agents play a major role in drug marketing and there are numerous efforts at developing agents that are more selective as well as investigating compounds with novel mechanisms of action.

1. Antiulcer–Antispasmodic Agents

Classical treatment of gastrointestinal disease has focused on antispasmodic agents such as anticholinergic drugs to control and heal ulcers. A major breakthrough in the treatment of ulcers was the introduction of histamine H_2-antagonists, which have become the treatment of choice. Current research in this

area centers on the development of K^+/H^+ ATPase (proton pump) inhibitors. The latter two therapies prevent acid secretion in the stomach, which is the cause of most ulcers.

HSR 902 (**89**) was found to be a new antispasmodic agent that increased bloodflow in the gastric mucosa in rabbits. Data suggest that **89** might be effective in repairing ischemia due to gastric ulcer.[141] The very closely related antispasmodic agent tiquizium bromide (**90**) was marketed to treat gastritis, duodenal ulcer, and colitis. The compound had slight α-adrenergic blocking properties. A monograph has reviewed the properties of **90**.[142] The pharmacokinetic profile of **90** has also been reported.[143]



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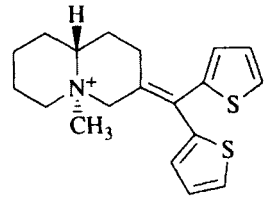
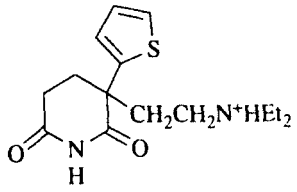


90

Other quaternary ammonium compounds reported to be antispasmodic agents include **91**. Only the (+)-enantiomer was found to have anticholinergic effects in isolated rat ileum. The phenyl isostere of **91** was the most potent in the series.[144] Compound **92** was among the most potent in a series of piperidines studied as spasmolytic agents. This compound was at least as active as atropine in the isolated guinea pig ileum.[145] The *trans*-isomers were more active than the *cis*-isomers in the series.[146] Quinuclidine derivatives, including **93**, inhibited gastric secretion in pylorus-ligated rats. The antisecretory activity of **93** was greater than that of cimetidine. The furan isosteres had significantly less activity in this study.[147] The optical resolution of some 3-thienyl-2-hydroxy acetic acid quinuclidinyl esters was accomplished to study their anticholinergic properties.[148]



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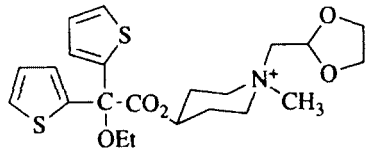

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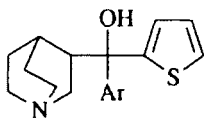
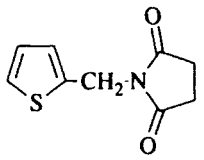


93

Some thienyl alkyl succinimide derivatives protected against aspirin-induced ulcer formation in rats. Compound **94** was the best compound in the series.[149] Subsequent reports showed that cyclic carbamate **95** had superior activity in this assay.[150] The 2,4-oxazolidinedione derivative **96** had the best ulcer protective properties of all of these compounds.[151] The related pyrimidinone **97**, which is the thiophene isostere of tolimidon, had no notable antiulcerogenic activity.[152]



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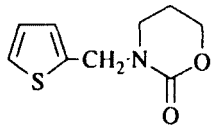

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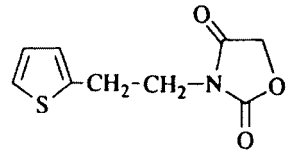

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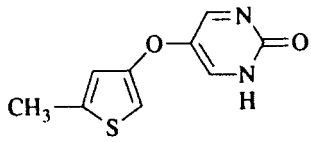
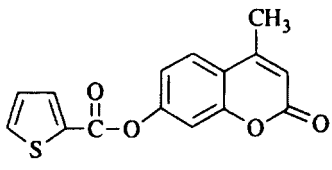


97

Among some 4-methylumbelliferone aroyl derivatives prepared as potential spasmolytic agents, thienyl derivative **98** had good activity and was more potent than papaverine. The pyridine isostere was the best compound in the series, while the furan analog was inactive.[153] Naphthyridines, including **99**, had cholinomimetic-like activity as determined by stimulation of ileum muscles.[154] Spasmolytic activity of a series of thienylaminobutyronitriles (**100**) was determined and used for QSAR predictions.[155] Guanidine derivatives, including **101**, were also studied for antisecretory activity. Compound **101** had weak antisecretory activity unrelated to H_2-antagonism.[156] While the thiophene derivatives **102** had interesting spasmolytic activity in electrically stimulated guinea pig ileum, the benzoisothiazole analogs were the most interesting in the study.[157] A series of furyl- and thienylvinyl- (**103**) substituted imidazol[1,2-*a*]imidazoles had spasmolytic, among other, pharmacologic activities.[158]



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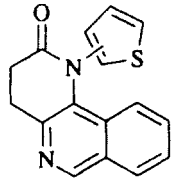

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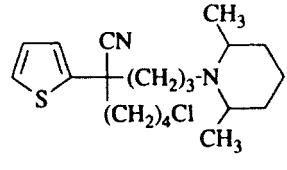

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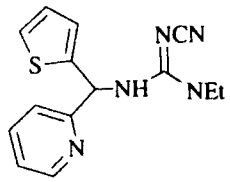

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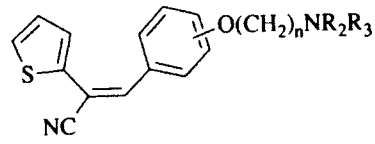

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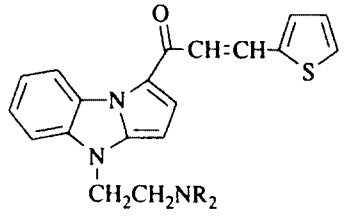
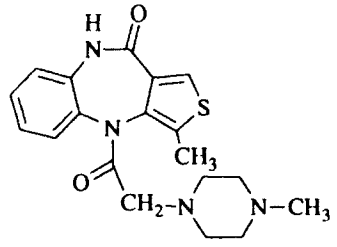


103

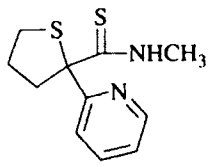
Telenzepine (**104**), already mentioned to have nootropic activity, is under development as an antimuscarinic agent for use in treating peptic ulcer disease and went into Phase I clinical study in 1985. The compound is a selective, potent antagonist of muscarinic receptors and is active as an antispasmodic in smooth-muscle preparations.[159] A detailed summary of the synthesis, pharmacology, and early clinical studies has appeared.[160]



104

Picartamide (RP 40749, **105**) is undergoing clinical trials to treat ulcers. The compound was found to inhibit the H^+/K^+ ATPase enzyme in vitro and to effectively heal 100% of duodenal ulcers with no side effects.[161] The structure–activity study leading to the development of **105** showed the compound to be antisecretory against histamine-induced gastric secretion in Shay rats.[162] Among other antisecretory agents that were studied in the clinic, **106** was the most active in a large series of orally active compounds in dogs. The agent also had comparable potency as a cytoprotective agent. While the 3-thienyl derivative **106** was extremely interesting, the 2-isomer as well as other heteroaromatic derivatives were less active.[163] In an attempt to improve the absorption of drug, the cyanomethyl moiety of **106** was replaced by an amine;

activities of the 2- and 3-thienyl derivatives were similar to that of the phenyl isostere, while the pyridyl derivative was even less interesting.[164] Completion of these studies led to the development of the nonthiophene containing agent, Sch 32651.[165]



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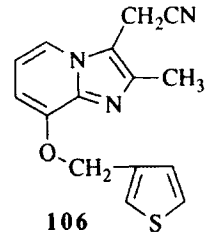
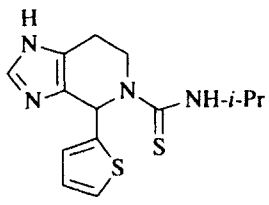


106

The antiulcer and antisecretory activity of some imidazopiperidines showed that aryl-substitution at the 4-position (such as **107**) reduces antiulcerative effects.[166] While the pyridyl-substituted benzimidazolinones had interesting antisecretory activity in dogs, the phenyl and thienyl (**108**) analogs had no useful effects.[167]



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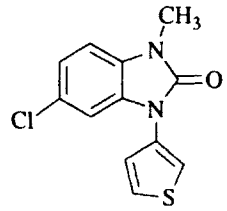
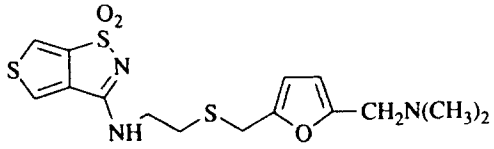


108

The use of histamine H_2-antagonists as a method of treatment for ulcers has exploded with the marketing of cimetidine and ranitidine. Wy 45727 (**109**) has good antisecretory activity. The potency of **109** is 10-fold greater than ranitidine without excessive duration of action.[168] Compound **109** antagonizes histamine-induced chronotropic effects in isolated guinea pig atria and ^{14}C aminopyrine uptake in gastric mucosa. The compound has been tested clinically.[169] Another series of H_2-antagonists from the same laboratories studies both the thieno[2,3-*d*]- (**110**) as well as thieno[3,4-*d*]-isomer. Both isomers have better potency than ranitidine as H_2-antagonists in both rats and dogs. Wy 45662 (**110**) was selected for further evaluation.[169] The detailed antisecretory activity of **110** in rats and



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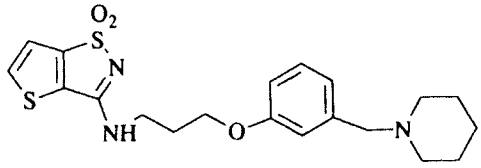
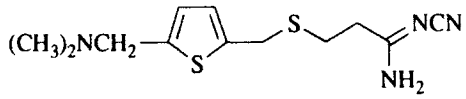


110

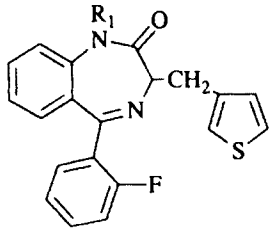
dogs using carbachol, histamine, aminopyrine, forskolin, and dibutyryl cyclic AMP agonists was reported.[170] N-Benzylation of **110** altered the subcellular site of action and reduced of H_2 antagonist activity but maintained modest antisecretory effects.[171]

N-Cyano and N-carbamoyl amidines have also been developed as H_2 receptor antagonists. Of these compounds, **111** had weak antisecretory activity, the benzene isostere was better, and the furan isostere was most interesting and comparable to cimetidine.[172] When the amidine moiety was replaced by an aminothiadiazole, the compounds also had potent antisecretory effects. In this case the thiophene and furan derivatives were equipotent when tested against histamine-induced acid secretion.[173]



111

Cholecystokinin antagonists may have some role in the treatment of gastrointestinal disease. Novel benzodiazepines have been developed based in part on the structural requirements of naturally occurring antagonists. Compound **112** has good binding affinity and inhibits gastrin in guinea pig gastric glands. The phenyl isostere of **112** is less active, while the indole derivative is the lead in the series.[174] A report of the replacement of the imidazole ring of the GI peptide secretin by a thiophene gave molecules of similar shape and aromatic properties. The [D-Thi][1]-secretin was more potent than the [L-Thi][1] analog.[175]

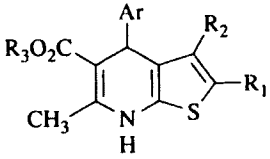


112

2. Antihypertensive–Diuretic Agents

There are numerous treatment regimens for hypertension. Classically, first-line therapy utilizes diuretic agents that reduce extracellular volume and thus decrease load on the heart. Diuretic agents act at various sites in the kidney and cause ion imbalances that must be treated. β-Adrenergic blocking agents are used routinely as part of second-line therapy and reduce cardiac energy requirements. α-Adrenergic blocking agents dramatically lower blood pressure, but their potent peripheral vasodilation frequently causes postural hypotension, which is an undesired side effect. Calcium channel blockers have gained a significant place in the treatment of angina by their ability to dilate the coronary vasculature. Most recently, angiotensin-converting enzyme inhibitors (ACEI) have shown dramatic control of elevated blood pressure and are proposed as a possible first-line treatment. Control of blood clotting, to prevent second heart attacks and arteriosclerotic plaque formation, is also an area of intense research.

Calcium channel blockers have utility both to treat angina pectoris as well as hypertension. Thieno[2,3-*b*]pyridine derivatives **113** were prepared as part of an on-going structure–activity study focused on dihydropyridines. A number of **113**, wherein Ar = 2- or 3-nitrophenyl, had good vasodilating and hypotensive activity.[176] S-312 (**114**) was selected as a promising calcium channel blocking agent for further development. A correlation between absolute configuration and biologic activity was established.[177] Thiophene has been used to replace the aryl substituent in other dihydropyridines such as in **115**.[178]



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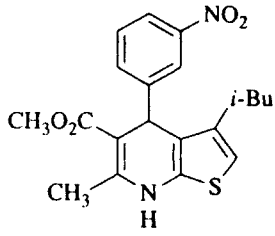

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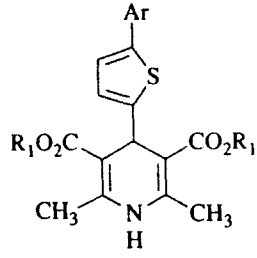
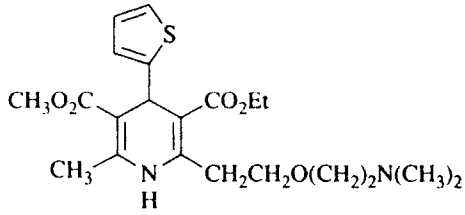


115

Some long-acting antihypertensive agents were prepared by substitution of a basic side chain on the dihydropyridine. Unfortunately, the thienyl substituent in **116** was part of the general conclusion that replacement of nitrophenyl by heteroaryl moieties was adverse to good activity.[179] A series of pyrazolopyridines were found to be potent antihypertensive and coronary vasodilatory agents with long duration of action. Even though it had good activity, **117** was not one of the five derivatives chosen for further study.[180]

Although not related to dihydropyridines, N-benzhydrylpiperazine derivatives also have calcium channel blocking activity. Some phenyl isosteres were more potent that cinnarizine or flunarizine but **118** was inactive.[181]



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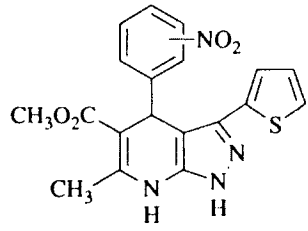
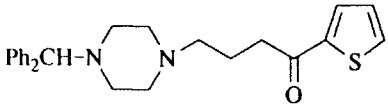


117

A number of angiotensin converting enzyme inhibitors (ACEI) have been prepared since the pioneering discovery of captopril. CS 622 (**119**) is the most advanced among thiophene-containing ACEI. The compound is the prodrug of the active diacid principal which is more potent than enalapril after oral administration.[182] The synthesis, structure activity relationship and conformational studies of **119** have been reported.[183] The diacid inhibited pressor response to angiotensin I when administered intravenously or orally.[184] Compound **119** decreases cardiac load which decreases plasma levels of ANF.[185]



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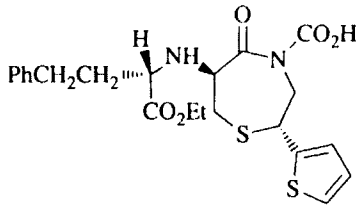

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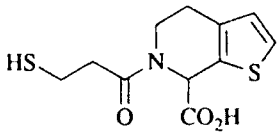
A series of isoquinoline derivatives had ACE inhibitory and antihypertensive activity. The thiophene isostere **120** as well as the indole isostere had reduced potency but retained good activity.[186] A series of mercaptans modeled on captopril led to the development of REV 3659 as an ACEI. While thiophene **121** had the greatest potency of heteroaryl derivatives, it was not better than simple glycine analogs.[187]



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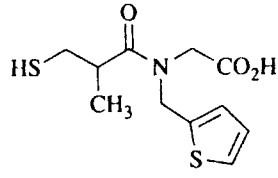
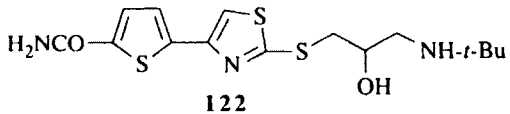


121

In work prompted by the ACEI, research on kinins and bradykinins has also been active in recent years. The incorporation to thienylalanine in bradykinin analogs has been accomplished, and stability and structural effects have been studied.[188] The ability for labeled kinins to bind to pig renal angiotensin I was

studied.[189] Thienylalanine has been incorporated into bradykinin antagonists[190] as well as into molecules used to map bradykinin receptors.[191] Replacement of alanine by β-(2-thienyl)-L-alanine in bradykinin analogs antagonizes the action of bradykinin on rabbit vasculature.[192] [Thi^{5,8}-D-Phe^{7}] bradykinin prevented hydrolysis by carboxypeptidase into active β_1-receptor agonists.[193] Compounds of this type prevented bradykinin arteriole dilation and might be useful in examining the role of bradykinin in cerebral circulation.[194] Thienylglycine was incorporated into pepstatin analogs that were potent renin inhibitors.[195]

The role of β-adrenergic blockers in the treatment of hypertension is well documented and thiophene isosteres have been reviewed.[196] Arotinolol (**122**) has been in clinical use as a treatment of essential hypertension, angina pectoris and tachyarrhythamias since 1986. The compound has weak α-adrenergic antagonist properties. The enantiomers of **122** have been separated.[197,198] The isosteres of tolamol were prepared and the 2,3-isomer **123** had hypotensive activity similar to that of metoprolol, while the 3,4-isomer was essentially devoid of activity.[199] Toliprol and bevantolol isosteres **124** showed β-sympatholytic activity in isoprenaline treated rats and directly decreased heart rate and blood pressure.[200] L 643717 (**125**) is an orally active, long acting β_1-selective adrenergic blocker.[201] The extraordinary β_2/β_1 selectivity of **125** was 100 times that of atenolol.[202] The phenyl isostere was less selective.[203]



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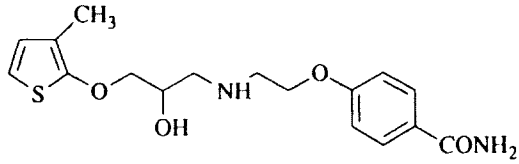

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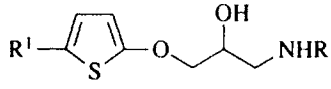

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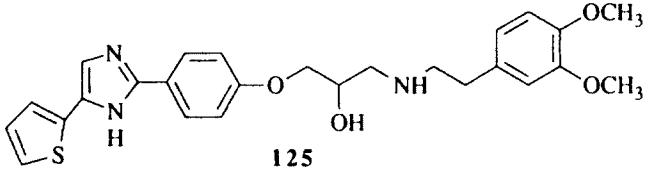
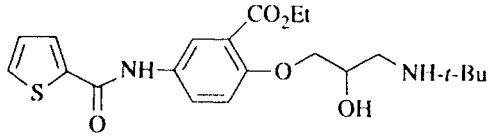


125

The compound UP 788-42 (**126**) had slightly less β-blocking potency than propranolol but had moderate potassium sparing diuretic activity in rats and monkeys.[204] The 2- and 3-thienyl derivatives were equivalent as cardioselective β-blockers but the 3-thienyl derivative was a less efficacious diuretic agent.[205] Compound **127** was among the most cardioselective β-blockers in a series but was less potent that practolol.[206]



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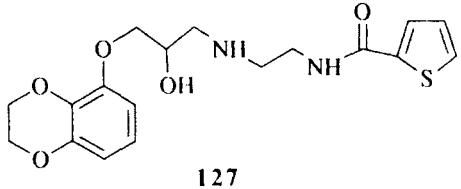
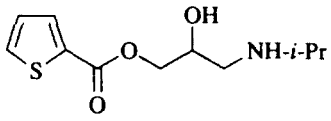


127

In a series of acyloxy derivatives, **128** was the most selective β-adrenergic antagonist studied except for butoxamine.[207] The thiophene isostere of practolol could not be prepared and was deduced to be unstable.[208] The thiophene isostere of metoprolol was prepared; **129** was found to have a similar pharmacologic profile to the model.[209] Several substituted oximes (**130**) had β-blocking activity in guinea pig cardiac and tracheal preparations.[210] Derivatives **131** were prepared as potential α- and β-adrenergic agents.[211] Several benzothiophenes had partial agonist and antagonist activities (**132**).[212] In another series, S 596 (**133**) had the highest β-blocking potency in radioligand binding and in pharmacologic assays.[213]



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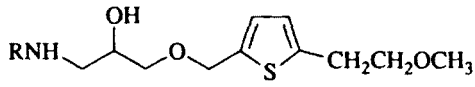

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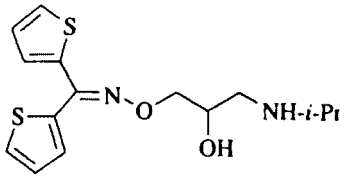

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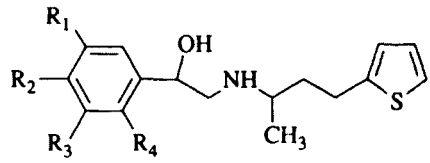

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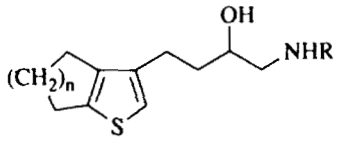

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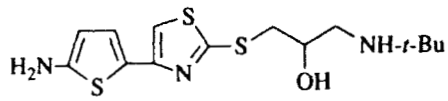
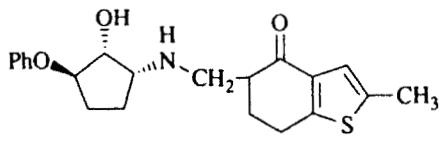


133

MDL 197449 (**134**) has many structural features in common with β-blockers but has α_1-adrenergic receptor antagonist activity instead. Compound **134** produced dose-dependent increases in renal blood flow and increased Na^+ excretion in normotensive dogs. It was devoid of β-adrenergic effects.[214] Thieno[2,3-*h*]cinnoline hydrazine **135** and its derivatives, which are related to the α-blocker hydralazine, were found to have dose-dependent antihypertensive activity of long duration.[215] Clonidine analog **136** was the most potent antihypertensive of a series with duration of action of 1 hr. The compound is a pre- and postsynaptic α_2-agonist that also lowers heart rate and *dP/dt* in normotensive dogs. Replacement of thiophene in **136** considerably weakens biologic effects.[216] The centrally acting clonidine analog tiamenidine was marketed in 1988.[217]



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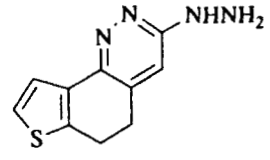

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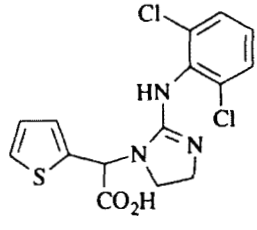
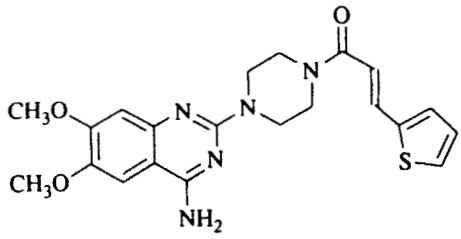


136

Continued work on prazosin α-blocking structure–activity relationships led to vinylogous isostere **137**. Of these compounds, 2- and 3-thienyl derivatives as well as furyl and phenyl were all potent with activity similar to prazosin.[218a] A QSAR was reported for this series.[218b] Some related quinazolinine derivatives also had good antihypertensive effects.[219] A series of piperazine analogs of prazosin included **138**, which was 10 times less potent than the furan isostere.[220] Some thienopyrimidinedione isosteres of the potent α-blocker SGB 1534 were prepared. The thieno[3,4-*d*] (**139**) and thieno[3,2-*d*] systems were more potent than the thieno[2,3-*d*]-isomer and prazosin.[221]



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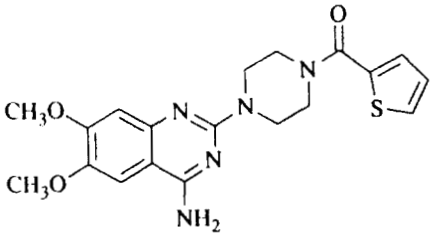

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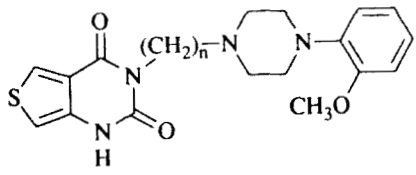
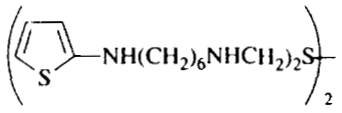


139

A series of di- and tetraamine disulfides, including **140**, had greater potency that benextramine. While the pyrrole and furan derivatives have this activity, **140** had little α-sympatholytic activity.[222] Tibalosine (**141**) was reported to be an α_1-adrenoceptor antagonist as well as a slow Ca^{2+} channel inhibitor. While the (+)-enantiomer was essential for good adrenoceptor activity, stereochemistry was unimportant for calcium channel activity.[223] Compound **141** reduced blood pressure in clinical trials.[224] Quaternary salt **142** dilated coronary artery and antagonized morphine-induced contractions.[225] A series of α_2-adrenoceptor antagonists included **143**, which binds at all subtypes of α-receptor.[226]



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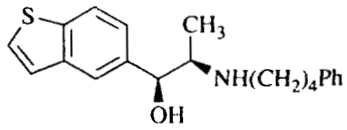

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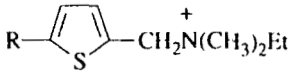

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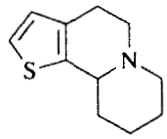
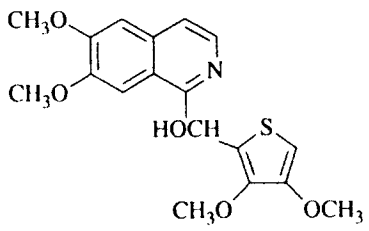


143

Thiophene analogs of papaverine (**144**)[227] and protoberberine (**145**)[228] have been reported. Other thiophene analogs of antihypertensive alkaloids include **146**, which was found to have no interesting activity in anesthetized cats.[229]

No activity was reported for **147**, which are isosteres of 4-quinolone alkaloid antihypertensives,[230] and thieno[3,2-*a*]quinolizidine **148**, an isostere of the hypotensive agent indoramine, also had no interesting pharmacologic activity.[231] Thienoquinuclidine **149** had antihypertensive activity similar to that of temechin in rats. Other compounds in the series had antihistamine and anti-inflammatory activity.[232] Thienylallylamine **150** was 1,000-fold more active than the phenyl isostere.[233]



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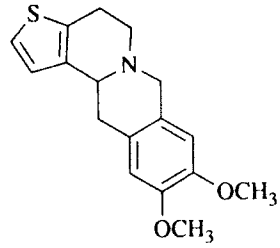

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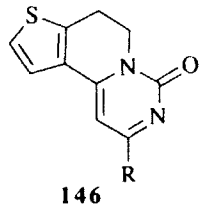

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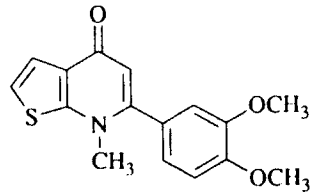

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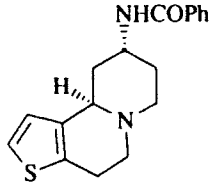

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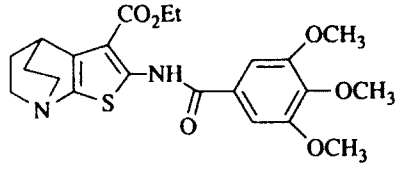

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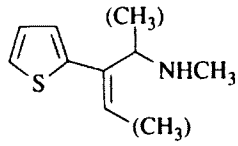
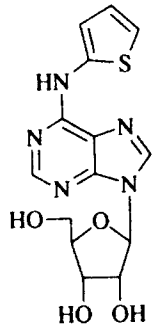


150

A series of compounds, including **151**, were prepared as coronary artery adenosine receptor binding agents. Thiophene **151** as well as the 3-pyridine isostere were the most interesting compounds.[234] The heterocycles with no sugar substitution were studied in A_1 brain receptors and compared to A_2

coronary receptors.[235] Compound **152** was prepared in a potent series of A_1- and A_2-adenosine receptor antagonists. Since thiophene **152** has high receptor affinity and is easily iodinated, the compound has potential as a receptor probe.[236] 8-(2-Thienyl)theophylline was part of a study of A_2 receptors labeled by ^3H NECA[237], as was 2-(2-thienethyl)-adenosine in a study of A_1 brain receptors.[238]



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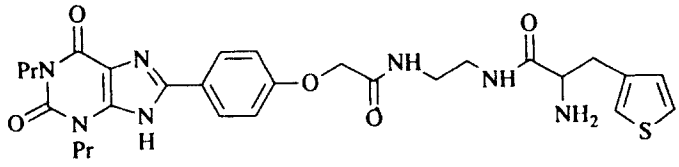
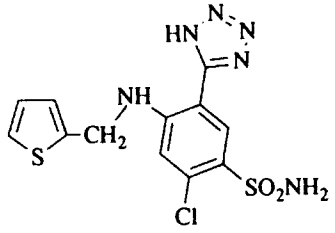


152

Azosemide (**153**) was brought to the market as a diuretic agent, and a monograph was published on the compound.[239] Several reports have appeared on the discontinued diuretic agent tienilic acid.[240,241] Several studies of diuretic agents under development used tienilic acid as a standard for comparison.[242,243] Tienilic acid is metabolically hydroxylated in the 5-position of thiophene.[244] Compound **154** had good activity in spontaneously hypertensive rats as well as saline-loaded mice, water-loaded dogs, and renal hypertensive rats. Maximal activity was achieved in **154**, which is a candidate for further development.[245] An annulated derivative of tienilic acid was prepared and had 80% of the activity of the drug.[246] Thienothiopyran sulfonamides were reported as a novel class of carbonic anhydrase inhibitors. While this activity might be useful in promoting diuresis, compound **155** has greater potential for treatment of glaucoma.[247]

A group of sulfonamides had salidiuretic activity; **156** was considerably less active than the furan isostere.[248] Among some sulfonamides that were carbonic anhydrase inhibitors, **157** was the most interesting. This series increases cerebral blood flow and has anticonvulsant properties in mice.[249] Some calculations of drug–receptor interactions of thiophene-containing anhydrase inhibitors were



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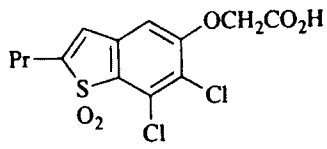

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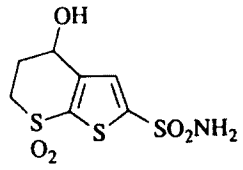
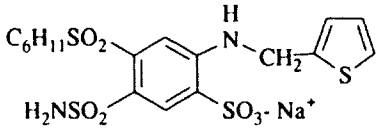


155

published.[250–252] β-Lactamase renel dipeptidase inhibitors containing thiophene such as **158** have been reported.[253] Some thienopyrans (**159**) were found to have modest diuretic activity.[254]



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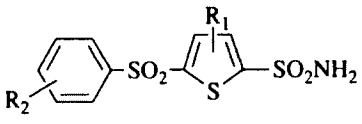

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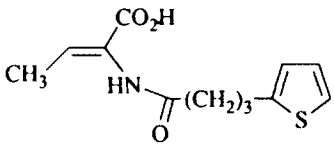

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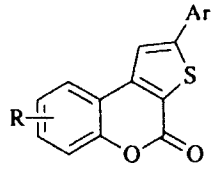


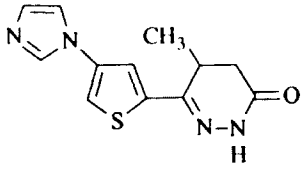
159

3. Cardiotonic (Positive Inotropic) Agents

Digitalis and the cardiac glycosides have been the only drugs used to treat congestive heart failure (CHF) for the last century. Drawbacks to their use include high levels of cardiac toxicity as well as low levels of efficacy. The concept of improving heart-pump function by inhibition of cardiac phosophodiesterase (PDE) has led to the development of a number of novel drug candidates that are beginning to reach the market.

Motapizone (**160**) inhibited phosphodiesterase and had antihypertensive and platelet antiaggregatory effects.[255] The compound had a direct cardiotonic action.[256] Some imidazolones, including **161**, led to the development of enoximone. While thiophene **161** was not the clinical agent, the thienyl moiety was found to enhance potency and selectivity, while furyl did not.[257] Ring-annelated

analogs of the potent inotrope isomazole were reported. Compound **162** was the most potent cardiotonic tested in the series.[258]



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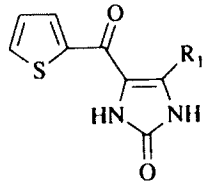

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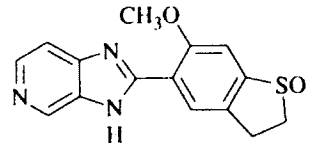
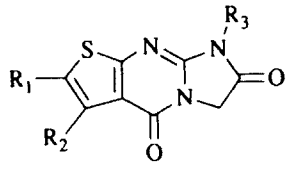


162

A series of thienopyrimidinones **163** cause phosphodiesterase inhibition. Both the [2,3-*d*] and [3,2-*d*] systems inhibited platelet aggregation.[259] Related fused thienopyridines **164** also had potent phosphodiesterase activity.[260] The three possible isomeric thienopyridinols **165** were reported to have good cardiotonic activity similar to the benzo isosteres.[261]



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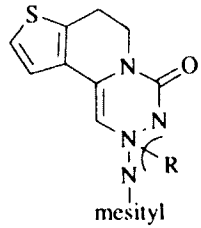

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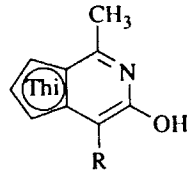


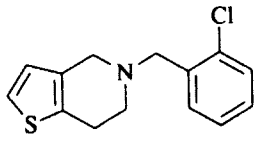
165

4. Antithrombotic Agents

The role of platelet aggregation in a number of cardiovascular disease states has been actively pursued in the past decade. Thromboxane A_2 (TXA_2) antagonists have been reported from numerous laboratories. Agents that non-specifically prevent platelet aggregation induced by a number of agonists have been marketed and continue to be developed. The issue of platelet adhesion causing platelet thrombi that result in stroke and heart attack is a subject of increasing interest. The platelet antiaggregatory action of thiophene derivatives has been reviewed.[262]

The development of the very interesting platelet aggregation inhibitor ticlopidine (**166**) has continued. Ticlopidine and its analogs appear to interfere with the energy-conserving mechanisms of mitochondria.[263] Other studies for a physicochemical model of activity have been reported.[264] The carboxylated analog of ticlopidine, PCR 4099 (**167**), inhibits platelet aggregation.[265] The metabolite of ticlopidine, PCR 3787 (**168**), is also active.[266] Thienoazepine **169** was prepared as a ticlopidine analog but had little antiaggregatory effects in animal tests.[267]

Fused pyrimidine derivatives **170** have also been prepared.[268] Other thienopyrimidines have been reported to be platelet aggregation inhibitors.[269,270]



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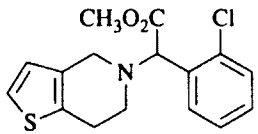

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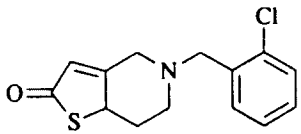

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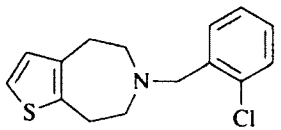

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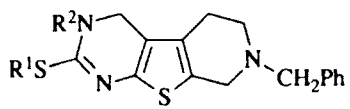
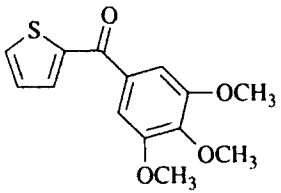


170

Thienyl aryl ketones have interesting antiaggregation properties, and **171** is 25 times more potent than aspirin against arachadonic acid- and collagen-induced aggregation.[271] Some phenacyl piperazines, including **172**, had some modest platelet effects.[272] Some thiophene derivatives related to β-adrenergic blockers were reported (**173**); R^1 = carboxyl were considerably less active.[273] Thromboxane synthetase inhibitor **174** was among the most interesting of a series of heterocyclic derivatives, all of which were at least as active as the phenyl isostere. Compound **174** was 10-fold more potent than the benzene analog but was not as interesting as the indole derivative.[274]



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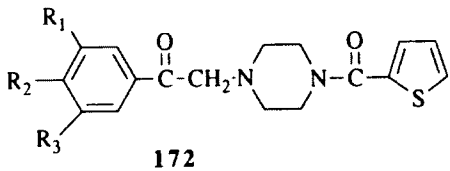

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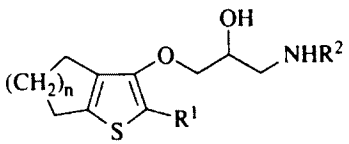

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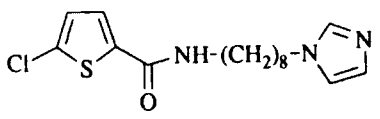
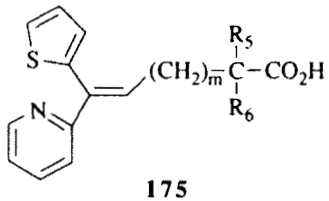


174

A series of aryl pyridyl alkenoic acids were prepared wherein the phenyl and thienyl (**175**) were equiactive and believed to bind at a lipophilic region of the enzyme.[275] The thiophene isostere (**176**) of dazoxiben was prepared and had similar potency in vitro as a specific TX synthetase inhibitor in human platelets.[276] The compound did not cause vasoconstriction. The 4-chloro analog was also reported.[277] The thienyl derivative **177** had high potency as a selective TX synthetase inhibitor but was not as potent as the phenyl isostere.[278] TS 5186 (**178**) effected myocardial salvage in the canine occlusion–reperfusion paradigm, and compound **178** decreased infarct size, gross myocardial hemorrhage, and polymorphonuclear (PMN)-infiltration into the infarcted area.[279,280]



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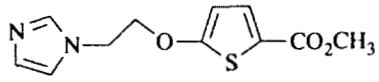

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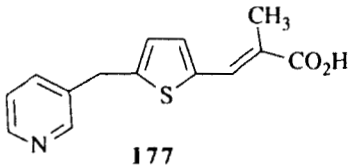

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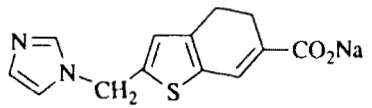
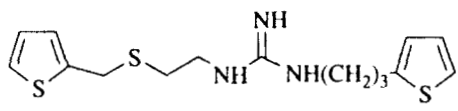


178

A series of guanidines was prepared, and the thioether **179** was a potent H_2-agonist and a moderately potent H_1-antagonist. The compound was compared to impromidine.[281] The structurally related oligoamines have anticoagulant activity, and **180** had interesting, but not the best, activity.[282] The monothiophene derivative had both anticoaggulant and antiplatelet effects in the same molecule.[283] A series of spirothienopyridines (**181**) inhibited platelet aggregation induced by ADP, collagen, and arachadonic acid.[284] Some bisaryl thiadiazoles, including **182**, inhibited collagen-induced platelet aggregation. Most interestingly, **182** was 100 times more potent than the aryl transposed isomer.[285] The closely related oxazole **183** inhibited platelet aggregation induced by collagen and ADP, while the furan isostere was not active.[286] The heparinoid **184** activated antithrombin III but had little effect on overall clotting. Compound **184** might be useful as a prophylactic antithrombotic agent.[287]



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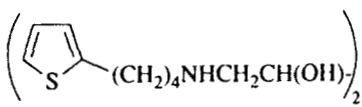

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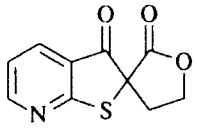

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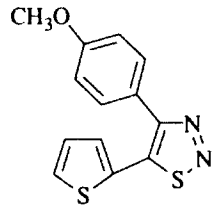

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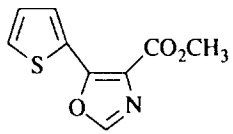

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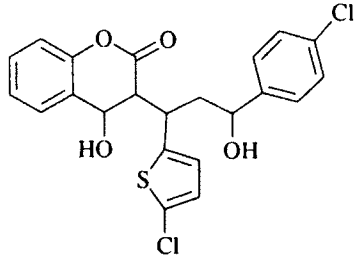


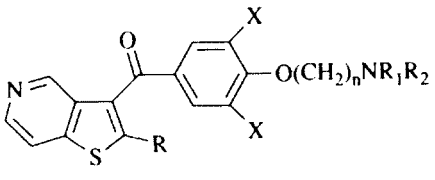
184

5. Antiarrythmic Agents

Antiarrythmics currently on the market are based on local anesthetic molecules and for the most part are Class I agents. As such, they lack specificity and have side-effect liabilities. β-Adrenergic blocking agents also have some utility as antiarrythmic agents but, because of decreased cardiac output, are unsuitable for congestive heart failure (CHF) patients. Current research interest in this area is directed as Class III agents that may have greater specificity and utility in the treatment of the ventricular arrythmias that are risk factors in sudden death.

The thiophene isosteres of amiodarone and butoprozine (**185**) were synthesized and found to have antianginal and antiarrythmic acitivity.[288] The thiophene isosteres of lotucaine were reported, and the 3,4-substituted compound **186** was the most interesting but was less active than lotucaine. The other isomers were less active either as antiarrythmic or as platelet antiaggregatory agents.[289] LG 84-6-10 (**187**) had antiarrythmic effects, increased effective refractory period, and decreased contractile force in papillary muscles.[290] A series of compounds, including **188**, were reported to have antiarrythmic and parasympatholytic properties. It was noted in this report that thiophene readily substituted for phenyl substitution. The compound acts as a Class I type antiarrythmic agent.[291]

Some tetramethylpyrrolidine derivatives had interesting antiarrythmic activity. Only thiophene derivatives were active among the heteroaryl substitutions in this study; the 3-thienyl derivative **189** was more active and more toxic than the 2-thienyl derivative, which had the best therapeutic index.[292] Aminopyrroline derivatives also had antiarrythmic effects. Thiophene **190** had some activity, but benzofuran derivatives were the best.[293]



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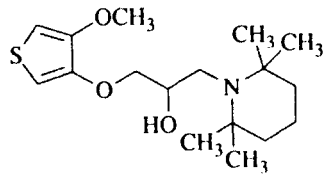

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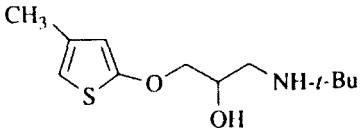

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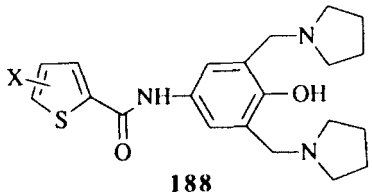

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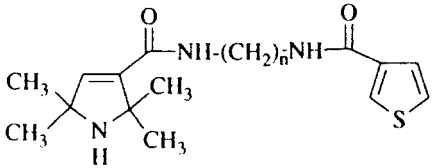

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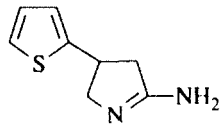


190

IV. METABOLIC DISEASE THERAPY

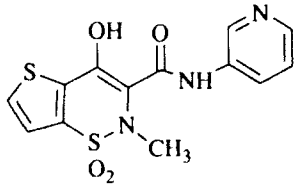
Treatment of inflammation has been a long-term goal in the history of humankind. In the recent past, such treatment involved the use of aspirin and other nonsteroidal antinflammatory drugs (NSAIDs) or corticosteroids. Such therapy accounted for more than $4 billion sales worldwide in 1988. Asthma and allergy are major contributors to pulmonary disease and had more than $1 billion worldwide sales in 1988. Significant progress has been made in the definition and treatment of other metabolic processes such as hypercholestermia, which has been identified as a major risk factor for heart attack. Reduction of elevated levels of blood cholesterol has become a major research focus. Another chronic disease, osteoporosis, is caused by an age-related metabolic imbalance between bone formation and resorption. Laboratories have begun to investigate methods to control such bone loss.

1. Antiinflammatory Agents

Nonsteroidal antiinflammatory drugs control inflammation by inhibition of the cyclooxygenase enzyme in the arachadonic acid cascade, which reduces the synthesis of prostaglandins (PGs). PGs are mediators in the inflammation process. While steroids provide more central control of inflammation, serious

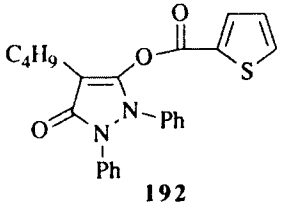
side effects limit their utility. Both types of agents cause gastrointestinal problems and ulcer formation. Current research is examining other mediators of inflammation such as platelet activating factor (PAF), lipoxygenase (LO) inhibition, leukotriene antagonists, and superoxide inhibitors.

Some additional studies on the clinical NSAID suprofen have been reported on metabolites,[294] absorption,[295] X-ray structure,[296] and prodrugs.[297] Several additional reports on tiaprofenic acid have also appeared.[298] A substantial number of studies have been published on tenoxicam (**191**), which is an important clinical antiinflammatory agent with indications for rheumatoid, osteoarthritis and nonarticular arthritis, as well as ankylosing spondylitis and gout.[299] Chlortenoxicam has a shorter half-life of action than **191**.[300] The metabolism of **191** has been studied.[301–304] Some analogs wherein the *N*-methyl and pyridyl moieties of **191** have been altered has shown that the *N*-substituent has significant effect on the pharmacologic profile of this series.[305]



191

Several new phenylbutazone esters have been synthesized with the goal of reducing the toxic effects of phenylbutazone. SP 124 (**192**) is active in the carragheenin rat hind paw edema assay and has significantly reduced ulcerogenic effects.[306] S 6907 (**193**) is a potent agent against adjuvant arthritis and inhibits carragheenin-induced edema. Compound **193** inhibits prostaglandin release.[307] Aroyl acid **194a** is equipotent with zomepirac as an antiinflammatory and analgesic agent.[308] The dihydro analog (**194b**) also has these activities but the benzofuran isosteres are more active.[309]



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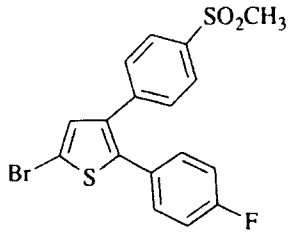

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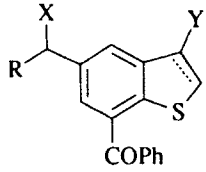
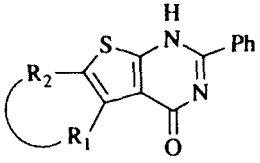


194a, X = H, Y = CO_2H
194b, X = CO_2H, Y = H

The antiinflammatory activity of a series of thienopyrimidinones **195** shows them to be equal or superior to aspirin.[310] Several aminothiophenes (**196**) have anticarragheenan effects.[311] Thienoisochoman derivatives **197** had weak antiinflammatory activity.[312] Aryl acrylonitrile derivatives interfered with prosta-

glandin synthesis; thienyl and phenyl derivatives were essentially equivalent.[313] Some thienothiadiazolopyrimidines such as **198** had greater antiinflammatory effects than did phenylbutazone, as well as analgesic effects similar to those of indomethacin.[314]



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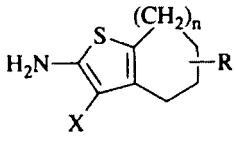

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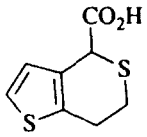

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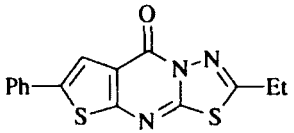
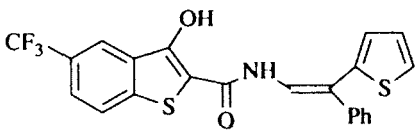


198

The compound L 652343 (**199**) was reported as a novel lipoxygenase-cyclooxygenase inhibitor. The compound inhibited LTC_4, TXA_2, CO, and LO in vitro and had antiarthritic activity in vivo.[315] Compound **199** had a favorable therapeutic ratio as an antiinflammatory and analgesic agent.[316] The compound has clinical potential in the treatment of psoriasis.[317] L 653150 (**200**) is a dual inhibitor of 5-lipoxygenase and platelet activiating factor. The furan isostere of **200** lacks the 5-LO inhibitory effects.[318]



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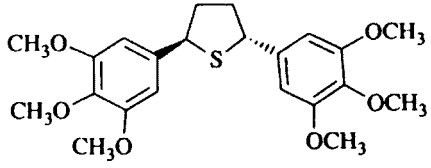
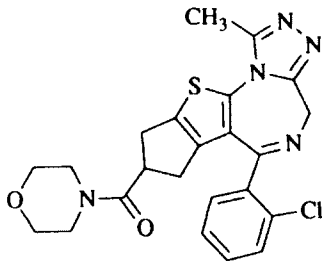


200

Etizolam, discussed previously, also reverses PAF-induced hypotension in rats and is thus a PAF antagonist.[319] WEB 2086, to be discussed later in the section on antihistamines, is currently one of the best PAF antagonists under development. WEB 2086 was discovered as part of the structure–activity study of brotizolam.[320] Modifications led to the related thienothiazepine derivatives WEB 2170 (**201**) and STY 2108, which are also potent PAF antagonists.[321] Clinical studies of WEB 2086 have shown it to produce long-lasting inhibition of platelet aggregation when administered orally or intravenously.[322,323] The leukotriene (LTD_4) antagonist **202** was also active against ovalbumin-induced bronchospasm in guinea pigs. The thienyl derivative was equiactive with the phenyl isostere.[324]



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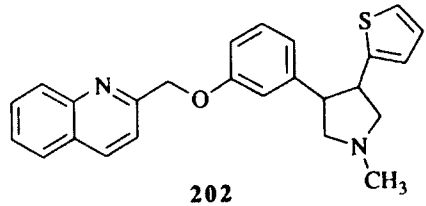
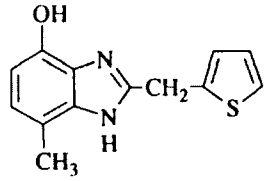


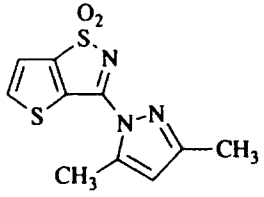
202

Compound **203** was equiactive with the phenyl and pyridyl isosteres as a 5-LO inhibitor. In contrast to standard agents such as phenidone, **203** did not inhibit release of SRS-A in rats with peritoneal anaphylaxis.[325] Dithienyl iodonium inhibited superoxide anion and inactivated the enzyme system of this inflammation process.[326]



203

A series of thienoisothiazoles was prepared and the [2,3-*d*] compound (**204**) had the best activity and was 6 times better than aspirin as an analgesic.[327] The [3,4-*d*]-isomers were less active as antiinflammatory agents. Thieno[2,3-*c*]-azepines (**205**) were active in the carragheenin hind paw assay.[328]



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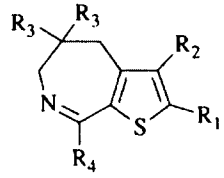

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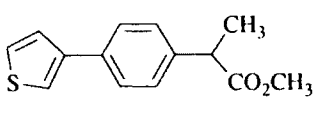
Other research on NSAIDs includes the development of IDPH 8261 (**206**). It was potent in the carragheenan hind paw ($\approx 5 \times$ ibuprofen) as well as in established adjuvant arthritis ($> 20 \times$ ibuprofen) with less ulcerogenicity. The major metabolite is the acid.[329] Compound **207** is an NSAID with greater analgesic activity than indomethacin; the pyrrole moiety significantly enhances antiinflammatory activity.[330] 5-Acylbenzofurans such as **208** reduced adjuvant arthritis in rats presumably by cyclooxygenase inhibition; most of the compounds prepared in this study were 5-thenoyl derivatives.[331] R 830 (**209**) was an

antiinflammatory with antioxidant properties. Compound **209** was comparable to indomethacin and ibuprofen in animal models.[332] Oximes **210** had moderate antiinflammatory properties with mild CNS depression.[333]



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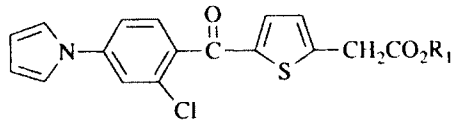

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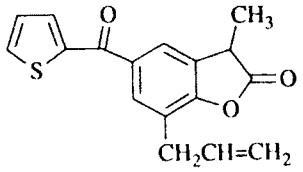

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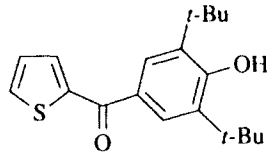

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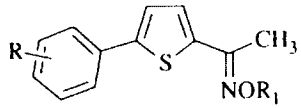
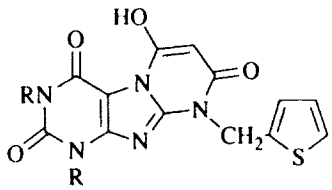


210

Substituted pyrimidopurines had activity against adjuvant and Type II collagen arthritis. Surprisingly, thienyl derivative **211** had low activity as compared to the very interesting phenyl isosteres.[334] Pyridothienopyrimidinones **212** were evaluated for analgesic, antiinflammatory, and antipyretic effects and compared to indomethacin.[335] Several 2-mercaptoimidazoles, including **213a**, were screened against carragheenan edema in rats and toxicity in mice. Compound **213a** had the best therapeutic ratio in the study comparable to mefenamic acid and was at least 2 times better than the 2-thienyl isomer.[336] Structure–activity studies led to the preparation of **213b**, which had strong activity comparable to ibuprofen with low acute toxicity or ulcerogenicity.[114] Some 1-arylpyrrole derivatives (**214**) were tested for effects against carragheenin edema and granuloma in rats.[337]



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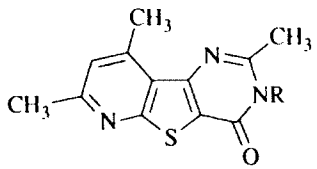

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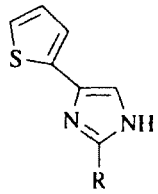
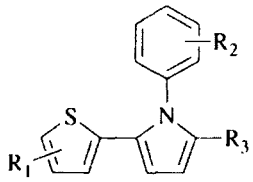
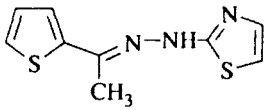


213a, R = SH
213b, R = *p*-FPh



214

A series of hydrazones represents a new class of antiinflammatory agents with CBS 1108 (**215**) as the best of the series. The compounds had a wider spectrum of activity than did standard NSAIDs, which was in part the result of LO/CO inhibition.[338] Compound **215** affected leukocyte migration in vivo[339] and was selected for further study.[340] Pyrimidine **216** was less active[341] than the imidazole analog.[342] Thienyl derivative **217** had antiinflammatory and analgesic effects similar to those of the phenyl compound, and the bioisosterism was noted.[343] Thienopyrimidines (**218**) were active against carragheenain hind paw edema in rats.[344,345] Several aryl malonate derivatives (**219**) had similar activity.[346] Thienocycloheptane **220** had antiinflammatory effects,[347] but the thienooxetane HP 573 (**221**) was much more interesting.[348] The antiinflammatory effects of **221** were about half those of indomethacin with very low ulcerogenicity; the compound was studied in the clinic. The butanol side chain is a prodrug for an acetic acid moiety.[349–351]



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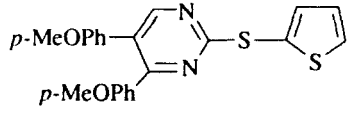

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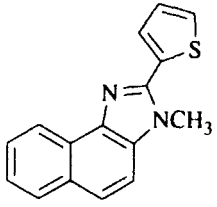

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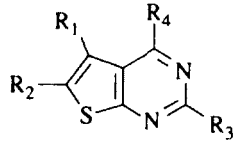

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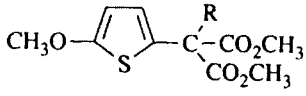

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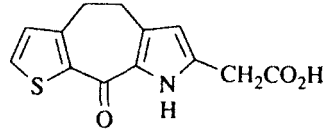

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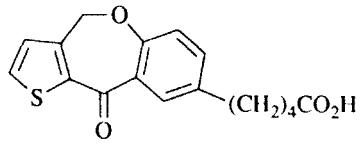
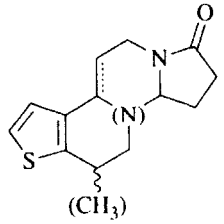


221

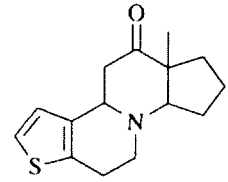
2. Prostaglandin and Steroid Analogs

During the investigation of prostaglandin and steroid pharmacology, a wide spectrum of pharmacologic properties was discovered. Prostaglandins (PGs) have activities in many biologic processes, including the cardiovascular system and the inflammation process. Steroids have activity in the endocrine system and in inflammation processes, among others. Synthetic analogs of these naturally occurring compounds have been and continue to be prepared in the hope of reducing side effects and increasing specificity.

Synthesis of 13-aza-3-thiaestradiene **222a**[352a] and its dehydro analog **222b** have been reported.[352b] Diaza-3-thianorgonadieneone **222c** was reported to show antiviral, local anesthetic, analgesic, and antiinflammatory effects.[353] β-Aza-3-thianorestradienone **223** had similar biologic activity.[354] 6,9-Epithiotachysterol (**224**) and other thiophene-des-A-steroids were prepared in vitamin D_3 synthetic studies.[355]



222 a,b,c



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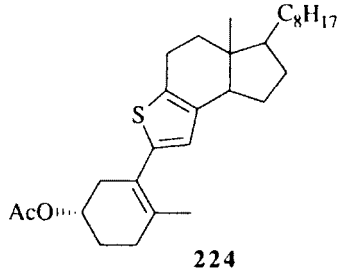

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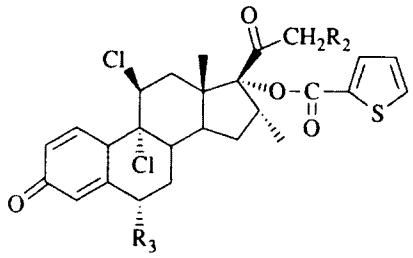
Acyl esters of antiinflammatory corticosteroids, including **225**, were prepared; the furan isostere had the best activity with 8 times the potency of betamethasone. Compound **225** was more potent than the 3-thienyl isomer.[356]

Hexestol-like steroidal hydrazone derivatives such as **226** were prepared as potential anticancer agents but to have little antileukemic activity.[357]



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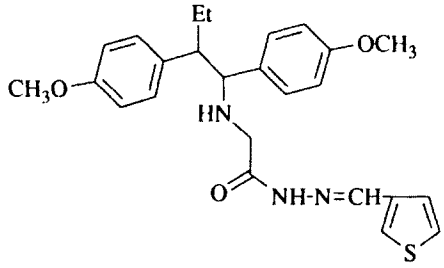

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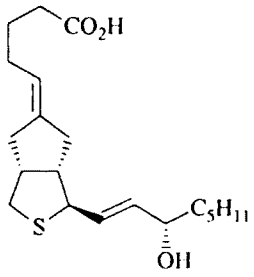
Carbaprostacyclin analog **227** was prepared to test if replacement of the CHOH moiety by S would affect antihypertensive activity.[358a] The compound had platelet aggregation inhibiting properties.[358b] A review of prostacyclin derivatives showed that compounds such as **228** were more stable chemically and metabolically than the natural product.[359]



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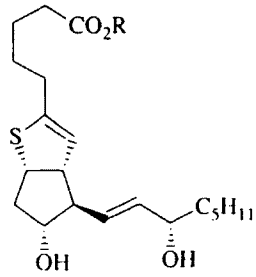

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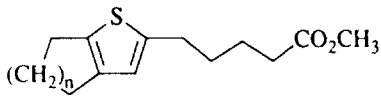
The heterocyclic prostaglandin analog **229** as well as the pyrrole and furan isosteres were prepared but no biologic activity was reported.[360] The prostaglandin endoperoxide analog **230** was found to be less active than the natural product; the acetylenes such as **230** in the series were more active than the ethylene analogs against platelet aggregation.[361] The synthetic PG analog tiaprost (**231**) is a luteolytic more potent than $PGF_{2\alpha}$ and was marketed for use in farm animals. Compound **231** also has a better therapeutic ratio between leuteolytic and spasmogenic activity than does $PGF_{2\alpha}$.[362]



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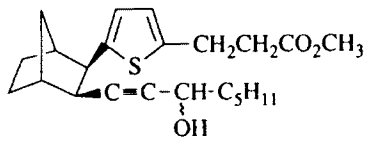

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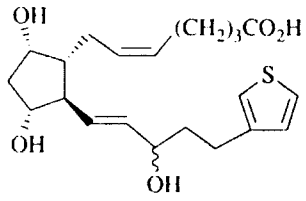
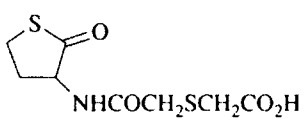


231

3. Antiallergic Agents and Antiasthmatics

Bronchodilators such as xanthines and β-adrenergic agonists are used as symptomatic treatment of early phases of asthma. Tricyclic antiasthma agents have begun to gain usage. Late-phase asthma is most effectively treated with steroids. Allergies are effectively treated with a variety of antihistamines that have been marketed for decades. Current research is directed toward drugs with far less sedative effects.

While not specifically antiallergic or antihistaminic, mucolytic agents play a role in the treatment of bronchial disease. Dithiosteine (RV 144, **232**) was the most promising candidate in a series of mucolytic agents. Compound **232** was active in experimentally induced bronchitis in rabbits after oral administration.[363] Bronchoplus (**233**) was tested in thoracic surgery patients and produced a greater respiratory function than standards.[364]



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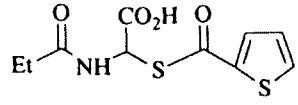

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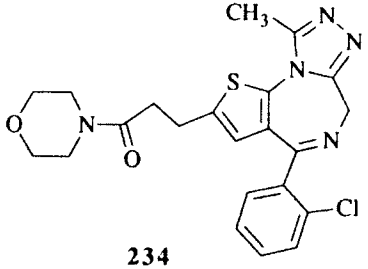
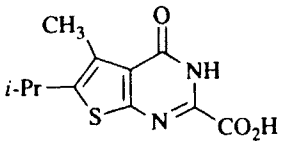
The known anxiolytic agent etizolam (**34**) also has PAF antagonist activity and has effects against bronchoconstriction in guinea pigs.[365] The related PAF inhibitor WEB 2086 (**234**) prevents PAF acether-induced decrease in respiratory flow and blood pressure but has no CNS effects.[366] Compound **234** also has effects against bronchoconstriction in rats[367] but not anaphylactic responses to



234

antigen.[368] The compound also prevented *Escherichia coli* endotoxin lethal response in rats and dogs.[369] The role of PAF in asthma and adult respiratory diseases as well as other allergic conditions has been reviewed with reference to **234**.[370] The compound also prevents PAF-induced platelet aggregation.[371] L 653150 (**200**) was the most potent binding agent to PAF receptors in human lung tissue.[372]

Tiprinast (MJ 12175, **235**) is an NSAID with a pharmacology similar to that of disodium cromoglycate but with greater potency and duration of action.[373] The antiallergic effects of **235** have been established clinically against hay-fever,[374] and a practical synthesis of **235** has been published.[375] The related thienothiazinones **236** have weak antiallergic effects against rat active cutaneous anaphylaxis and inhibited histamine release in rat peritoneal mast cells.[376] Thieno[3,2-*d*] derivative **237** was prepared as a standard antiallergy agent in a study of thiazoloquinazolines, and the isomeric thieno[2,3-*d*] has similar activity.[377] Interestingly, the dihydro-[3,4-*d*] derivative **238** had maximal activity in the rat passive cutaneous anaphylaxis (PCA) assay.[378] A continued study of this system showed the tetrazole analog **239** to be 10 times more potent in the PCA assay than doxantrazole.[379]



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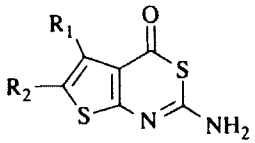

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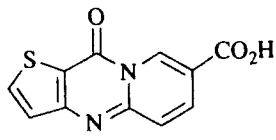

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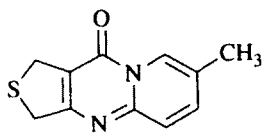

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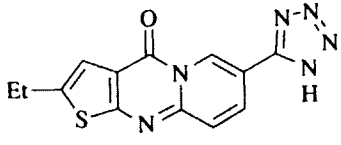
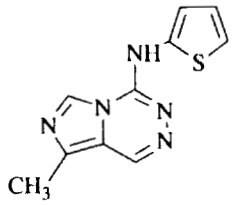


239

Among a large series of imidazotriazines, **240** was inactive as an antiallergy agent. Only the aminopyrazole isosteres had in vitro (but not oral in vivo) activity.[380] Related compounds (**241**) that were prepared as xanthine analogs were as active as theophylline in the prevention of acetylcholine and histamine-induced bronchospasm.[381] In a study of orally active antiallergic agents, **242a** was 60 times better than disodium cromoglycate and the most potent for inhibiting histamine release from passively sensitized rat mast cells.[382] The methyl derivative **242b** was studied in further detail.[383] The 2-thienyl derivative **243** had greater antiallergic potency than the 3-thienyl compound, but both the phenyl and furyl isosteres had more interesting activity. The clinical agent tioxamast was developed from the study in this report.[384] The antianaphylactic effects of **244** were notable among a large series. Compound **244** was more interesting than the 3-thienyl or halogenated thienyl derivatives.[385]



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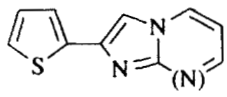

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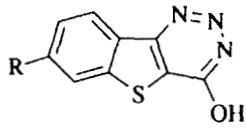
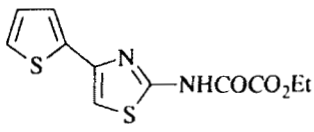


242a, R = Ph
242b, R = Me



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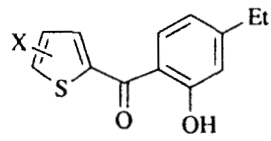

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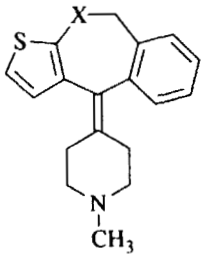
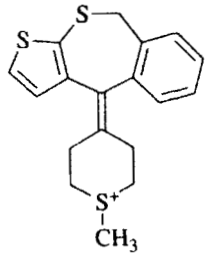
Studies of the tricyclic antihistaminic agent ketotifen (**245a**)[386] led to development of pipethiadene (**245b**)[387a] and pizotifen (**245c**)[388] as potential antimigraine drugs. The piperazine analogs of **245b** had little activity in the rat PCA test.[387b] The thiopyranium iodide analog (**246**) of pipethiadene had antihistaminic as well as antitussive effects.[389] The metabolism of ketotifen has been studied.[390] An isomer of ketotifen (**247**) was prepared to study antiasthmatic action.[391]



245a, X = CO
245b, X = S
245c, X = CH_2



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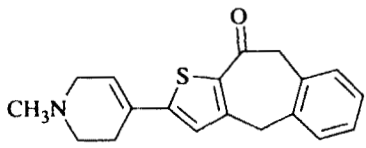
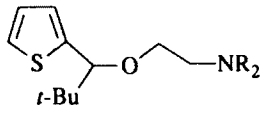


247

2-Thienylethylamine was found to have antihistamine activity.[392] A series of thienyl ethers (**248**) were prepared as potential antihistaminic agents, but none had notable activity.[393] The piperidine derivative **249** was extremely potent as an antihistamic but was 3 times less potent than the best compounds in the series.[394] Continued study in this area identified the clinical antiallergic agent astemizole.[395] Related imidazopyridines were less active and the thiophene derivative had no oral activity.[396] Astemizole analogue **250** was poorly active in the gastric lesion test and against 48/80 lethality.[397] Thiophene **251** had antihistaminic effects identical to the furan isostere, both of which were more interesting than the phenyl, imidazole, and pyridine isosteres.[398]



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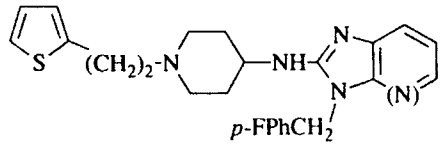

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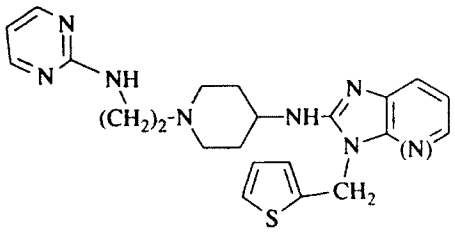

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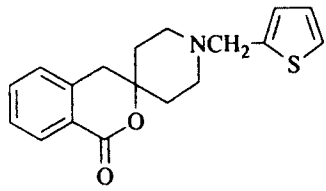
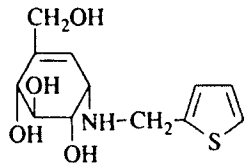


251

4. Metabolism Modifiers

Since epidemiologic studies have demonstrated a high risk factor for heart attacks, reduction of circulating levels of cholesterol has become a major goal of Western countries. In addition to HMG–CoA enzyme inhibition, agents that sequester dietary cholesterol in the gastrointestinal tract as well as other methods to inhibit cholesterol synthesis at other points in the synthesis pathway are under study. Similar approaches are under study for the treatment of metabolic diseases such as osteoporosis and diabetes. Attempts to control obesity by modifying metabolism is another area of intense research interest.

Treatment of diabetes involves both dietary control and drug treatment. Valiolamine derivatives including **252** inhibit α-D-glucosidase as well as porcine sucrase and maltase. Preliminary testing showed the compound to be similar in activity to the phenyl and pyridyl isosteres and has oral hypoglycemic activity in rats.[399] The related valienamines had similar α-D-glucosidase and α-glucoamylase inhibiting properties; in this study, the thiophene derivatives had only modest activity.[400] Additional study of the thiophene isostere of saccharin (**253**) was reported,[401] and a detailed structure–activity–taste relationship was developed.[402]



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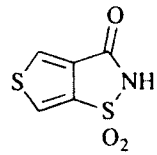
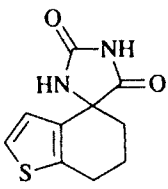


253

Aldose reductase inhibitors have been developed for the treatment of diabetes and include spirohydantoin **254**, which was prepared as part of the research

leading to sorbinol.[403] A series of thiazolidinediones were aldose reductase inhibitors; thiophene isostere **255** was not as interesting as the 3,4-dimethoxyphenyl analog.[404] The related oxazoline **256** was an inactive member of a series of hypoglycemic agents.[405]



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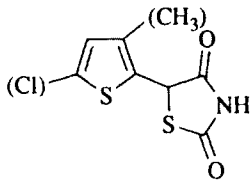

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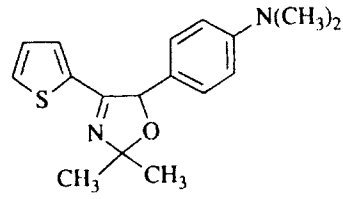
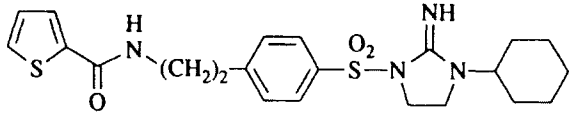


256

While **257** and the phenyl isostere were potent agents for lowering blood glucose in nondiabetic rats, they had no effect on blood glucose in diabetic animals; interestingly, the furan isostere was active in both animal models.[406] Arylidene derivatives **258** were prepared as part of a study of hypoglycemic agents.[407]



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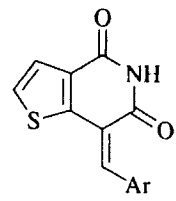
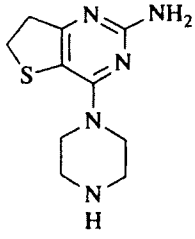


258

Dihydrothienopyrimidine **259** had hypoglycemic activity but was less interesting than the homologous thiopyran analogs.[408] The thienopyrimidine **260** was reported to have antidiabetic activity and to increase plasma insulin levels. Compound **260** was 3–19 times more potent than tolbutamide in reducing blood sugar levels in rats but not in guinea pigs.[409]



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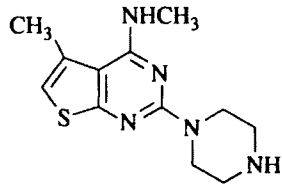
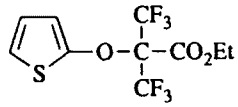


260

Some analogs of clofibrate were prepared and had hypolipidemic activity and reduced plasma cholesterol. Compound **261** was too unstable to test in the series.[410] Thienopyrimidine **262** was more effective than clofibrate in reducing serum triglycerides and cholesterol.[411]



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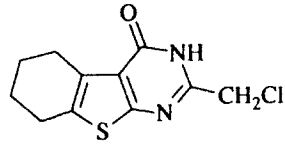
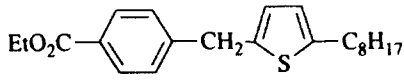


262

A series of antiatherosclerotic agents designed to inhibit acyl–CoA cholesterol acyl transferase (ACAT) led to the identification of cetaben sodium as a development candidate. Of the heterocyclic derivatives in the study, thiophene analogs such as **263** most consistently exhibited hypolipidemic activity in vitro as ACAT inhibitors and in vivo as hypolipidemic agents.[412] Of the related alkylamino acid derivatives, only **264** showed significantly more activity than cetaben.[413] While 3-thienyl derivative (**265**) was the most potent oxazole in a series of hypolidemic agents and was 4 times more active than clofibrate in hereditary hyperlipidemic rats, the 2-thienyl isomer was less interesting.[414] The 2-furyl isostere was reported to have the best activity and is the subject of further development.[415]



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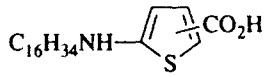

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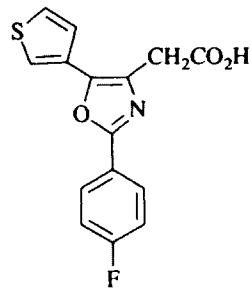
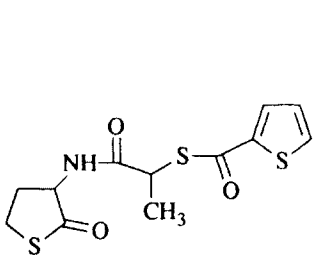


265

It has been shown that MR 889 (**266**) inhibits hydroxymethylglutaryl–CoA (HMG) reductase which is a viable method to control hypercholesteremia. This sulfhydryl reagent has low toxicity and may have potential as an anticholesterolemic drug.[416] As part of a thorough study, a series of reports of HMG–CoA reductase inhibitors showed the compactin analog **267** had identical activity to the furyl but was less interesting than the phenyl isostere.[417] In another approach to control of cholesterol, the antiobesity activity of Ro 22-0654 (**268**) has been the subject of several reports.[418] Compound **268** is a hepatic fatty-acid synthesis inhibitor that causes weight loss in rats without reducing food intake.[419] The compound may increase fat oxidation.[420] The tissue distribution[421] and metabolism[422,423] have been reported as part of the development of **268**.



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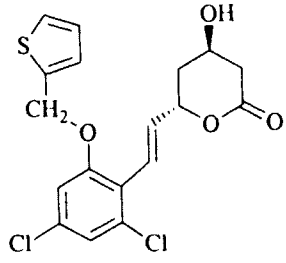

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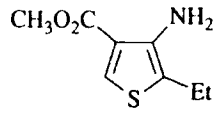


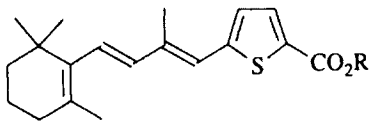
268

Several reports have appeared on the role of thiophene carboxylic acid derivatives in the treatment of osteoporosis. Benzothiophene-2-carboxylic acid produced a more prolonged decrease in serum calcium concentration than did 2-thiophenecarboxylic acid.[424] A review of osteoporosis and treatment using 2-thiophenecarboxylic acids among other agents has appeared.[425]

5. Dermatologic Agents and Retinoids

The use of Retin-A to treat wrinkles and certain types of precancerous skin lesions in addition to the treatment of acne has led to an explosion of interest in this type of drug. Tetracycline antibiotic drugs have also been used in the treatment of acne.

A series of analogs of aromatic retinoids include **269** (R = CH_2CH_3), which was an active inhibitor of ornithine decarboxylase (ODC). The compound has potential keratolytic activity.[426] The acid analog **269** (3920-59, R = H) was one of three derivatives with 90–100% of the binding efficiency of retinoic acid; this binding activity correlated well with keratolytic activity.[427] SRI 5447-28 is a benzothiophene analog with interesting cell nonproliferative properties.[428] Ro 1907224 (**270**) had intermediate activity in a series of immunomodulators with antiinflammatory effects.[429a] The naphthalene analog of **270** has good enzyme-inhibiting activity.[429b] CBS-211A (**271**) was prepared as a retinoic acid analog in an attempt to improve solubility. Compound **271** significantly reduced ^{3}H-thymidine incorporation into the DNA of corneal endothelial cells and may be useful in the treatment of psoriasis.[430]



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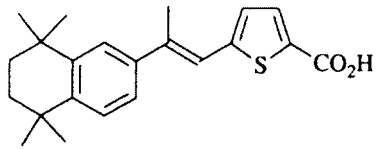

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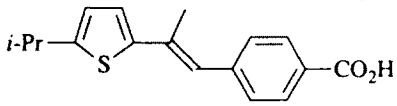
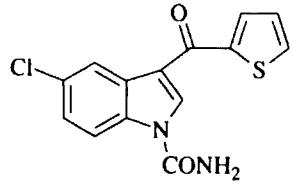


271

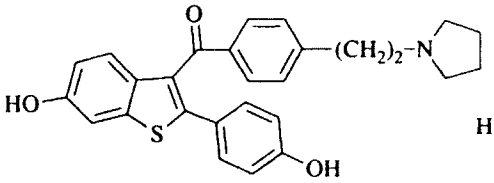
The 3-thienyl analog of retinoic acid reverses keratinization in vitamin A-deficient hamsters.[431] Several thiophene-containing retinoid derivatives have potential anticancer effects.[432,433] Unrelated to retinoids, **272** has IL-1 inhibitory properties that might be useful in the treatment of psoriasis.[434,435]



272

6. Endocrine Function Modulators

A number of derivatives have interesting estrogenic and antiestrogenic effects and should be mentioned despite their benzo[*b*]thiophene structures. LY 117018 (**273**) was the most effective antiestrogen in the series with modest uterotropic activity. Compound **273** inhibited estradiol with greater potency than did tamoxifen and inhibited the growth of DMBA-induced mammory tumors.[436] It was less estrogenic than tamoxifen.[437] The closely related LY 139481 was also quite interesting as an antiestrogen.[438] Among a group of boar sperm inhibitors, **274** had no effect on fertilization.[439]



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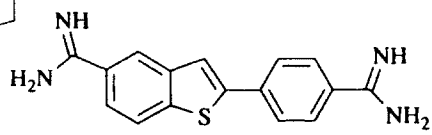
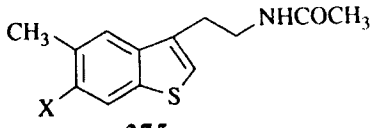


274

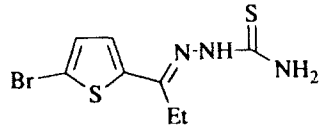
The N-protected analog of melatonin (**275**) had comparable activity to melatonin with the fluoro derivative the best in prevention of ovulation in rats.[440] Peptide **276** was a gonadotropin-releasing hormone agonist and was part of a structure–activity study of ovarian estrogen production modulators.[441] Thiosemicarbazone **277** suppressed progesterone, which adversely affected pregnancy in rats.[442]



275

Ac-D-ALA,D-PHE,D-TRY,D-Thienyl-ALA-GnRH

276



277

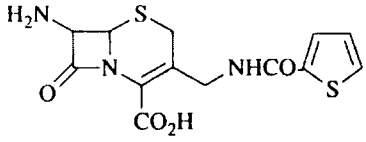
V. INFECTIOUS DISEASE THERAPY

The concept of chemotherapy to treat diseases was postulated by Ehrlich around the turn of the century. Antiinfective therapies that were used in the 1980s involve the use of antibiotics (naturally derived materials) and antibacterial agents (synthetic materials). These agents are used to treat bacterial, fungal, and helminthic infections. Chemotherapeutic principles from these drugs have been extended to the treatment of virus infections and cancer.

1. β-Lactam Antibiotics

The special role that penicillins and cephalosporins have played in the treatment of bacterial infections has continued with the combined sales of β-lactum antibiotics of greater than $8 billion. The main issues of current antibiotic research are bacterial resistance, β-lactamase stability, and increased spectrum of action. Synthetic β-lactam antibacterials include carbapenems, penems, and monobactams.

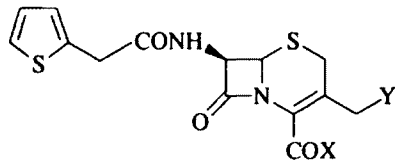
In the field of cephalosporins, a series of 7β-3-substituted cephems **278** were prepared to investigate 3-substitutent effects on the activity of cephalosporins.[443]



278

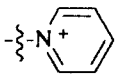
A series of cephalothin analogs **279a** were prepared as possible prodrugs with increased bioavailability but were inactive.[444] A comparison of the diffusion of cephaloridine **279b** and cefoxitin **279c** suggested that zwitterions diffuse through porin channels more rapidly than do noncharged species.[445] Hydrolysis of 3-substituents proceeds by a nonconcerted mechanism[446] that is important[447a] but not essential[447b] for β-lactamase inactivation. Tetrazole derivatives **279d** have excellent antibacterial activity, better than that of cefotaxine against some organisms.[448] Pivaloylmethyl esters **279e**, part of a design of β-lactam prodrugs, have increased lipophilicity and bioavailability.[449] The sugar derivatives of

cephalothin **279f** are not active against *Staphylococcus* strains under test conditions; this is presumably due to β-lactamase inactivation.[450] Cephalosporin **279g** with an antibiotic peptide ester side chain was prepared as a prodrug and had good antimicrobial activity.[451] Conformational flexibility of **279h** was studied to investigate binding at the active site.[452] A three-dimensional model for recognition sites has been proposed that might lead to improved antibacterial properties of these compounds.[453] The electronic effects of the 3-substituent (Y) have been studied against selected organisms for QSAR studies.[454] No direct correlation between the NMR chemical shift of the amide

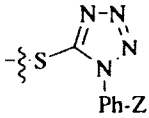


279

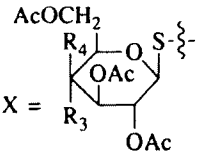
a, Y = OAc, X = amino acids-OH

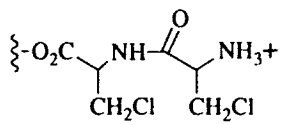
b, Y =  , X = OH

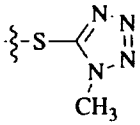
c, Y = ONH_2, X = OH

d, Y=  , X = OH

e, Y = OAc, X = OCH_2OCO-*t*-Bu

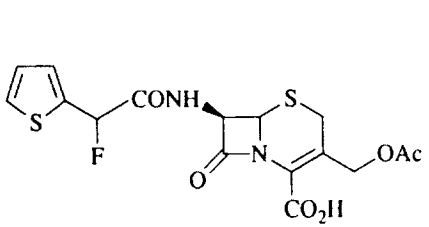
f, Y = OAc, X = 

g, Y =  , X = OH

h, Y =  , X = OH

carbon in **279** and antibacterial activity was found.[455] The sulfone derivatives of cephalothin were inhibitors of mammalian serine proteases rather than antibacterial agents.[456]

The compound L 14655 (**280**) is the fluorinated analog of cephalothin with similar antimicrobial activity. The compound is 325-fold more stable to β-lactamase but not to LTEM enzyme.[457] ICI 194008 (**281a**) has in vitro activity similar to that of ceftazidine and is relatively stable to β-lactamase-producing bacteria such as Enterobacteriacae.[458] The related cephalosporin **281b** has an activity profile similar to that of cefpiramide against gram positive and negative organisms except *Pseudomonas aeruginosa*.[459] The related oxime ethers **282a**[460] and **282b**[461] were less interesting than ceftizoxime.



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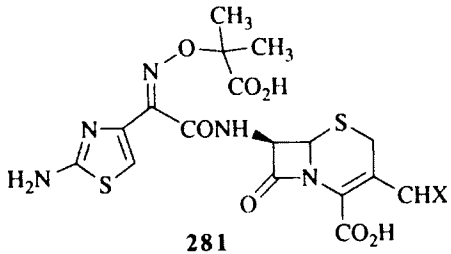

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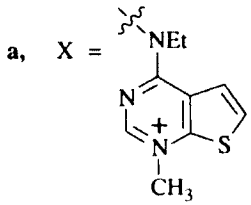
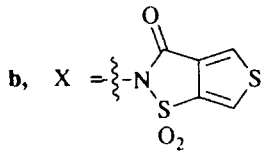
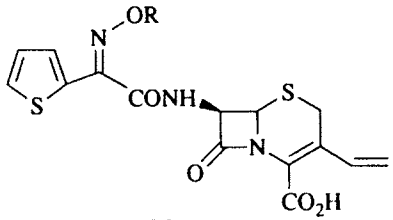


a, X =



b, X =

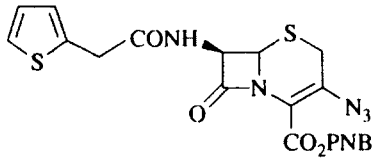


282

a, R = CH_3
b, R = CH_2CO_2H

The azidocephem **283** was prepared and ring-expanded, but none of the derivatives had good antimicrobial activity compared to cephalothin.[462] The C-3 thiadiazole **284** had gram-positive activity comparable to cephalothin, but other heterocycles such as pyrazole caused significant reduction in antimicrobial activity.[463] Compound **285** had good antimicrobial activity in the screens.[464]

Thienopyrimidine derivatives **286** were active only against gram-positive organisms, and no structure–activity profile was formulated in the report.[465]



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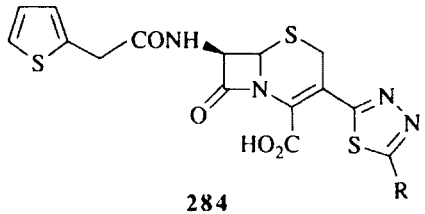

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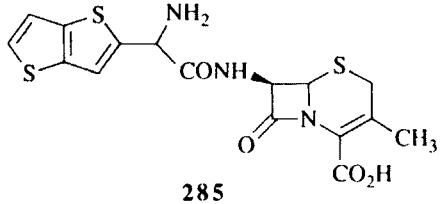

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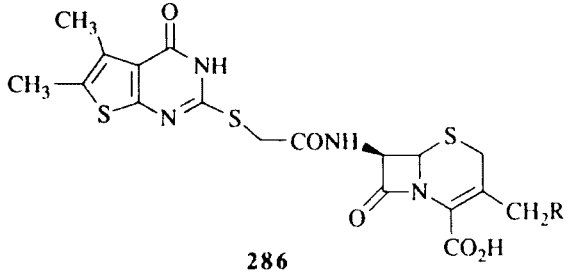
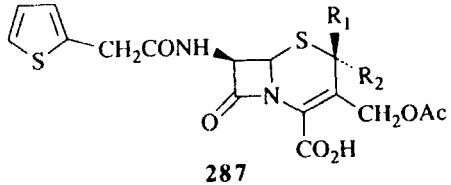


286

The 2-β-substituted cephalosporin **287a** was somewhat more active than the 2-α-isomer against a variety of microbial strains.[466] The *cis*-isomer of **287b** had good activity against both gram-negative and gram-positive bacteria.[467]

7-α-Substituents increase β-lactamase stability of cephalosporins. The 7α-methoxy analog of cephalothin is a highly active compound of great interest.[468] The 7-α-methoxy group of **288a** and **288b** has a substantial effect on the acylated

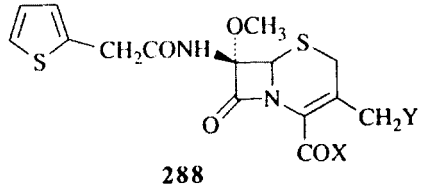


287

a, $R_1 = CH_3$ $R_2 = H$

b, $R_1, R_2 =$ $=CHCO_2CH_3$

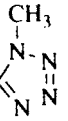
β-lactamase configuration and possibly accounts for the increased stability of such derivatives.[469] Synthesis of useful intermediates for the preparation of **288c** has been reported.[470]



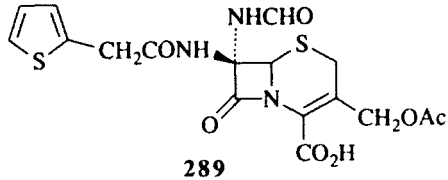
288

a, X = OH, Y = $OCONH_2$

b, X = OH, Y = OAc

c, X = OH, Y = 

Related compounds where the methoxy has been replaced by thiomethyl or cyano also have increased stability to enzymatic hydrolysis but have reduced antibacterial effects.[471] Methyl replacement of the methoxy does not give increased stability,[472] while hydroxymethyl does.[473] The 7α-formamido group in **289** also increases β-lactamase stability; **289** has a broad spectrum of antibacterial action.[474] Other compounds of interest include SQ 14359 (**290**), which has marked enzyme stability with antibacterial activity comparable to latamoxef and ceftazidime,[475] a related thienyl urea derivative.[476]



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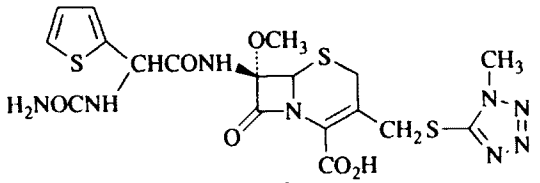
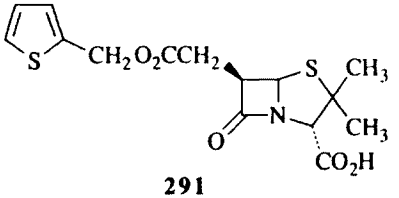


290

In the field of penicillin research, the 6-carbon isosteric derivative **291** was only active against gram-positive organisms and was less potent than the amide isostere.[477] Compound **292** was less interesting than other derivatives in the series of vinyl derivatives.[478]



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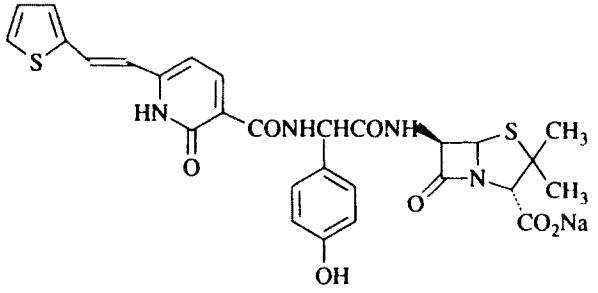
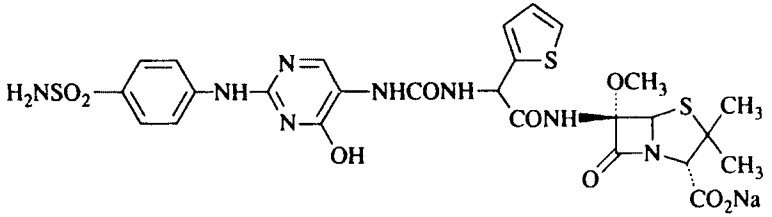


292

D-Penicillin **293** was stable to β-lactamase and had good gram-negative activity and moderate activity against *Staphyloccocus aureus*.[479] Thienyl isoxazole **294** was significantly less interesting than other members of the arylisoxazole analogs of ampicillin.[480] While **295** had similar activity, the phenyl isostere was best.[481] A review of ticaricillin (BRL 14151, **296**) describes the broad spectrum of antibacterial activity, the mechanism of action via cell wall disruption, and the use of clavulanic acid to retard β-lactamase inactivation of this drug.[482] The metabolites of **296** have been reported.[483]



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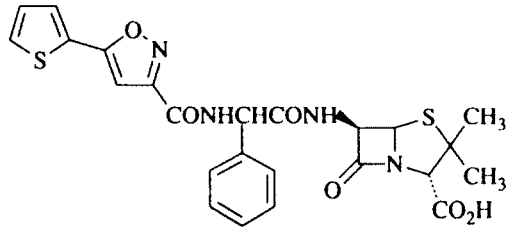

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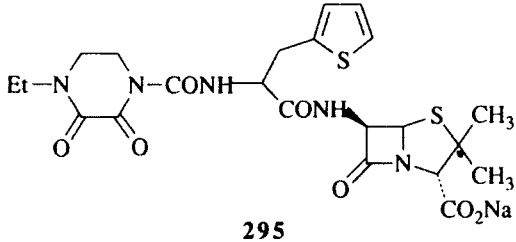

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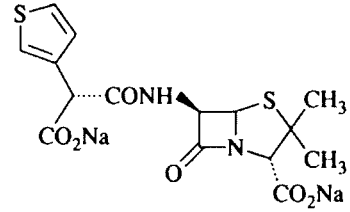
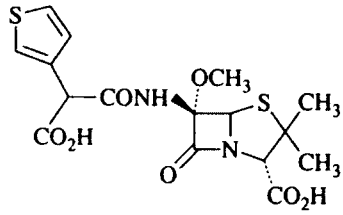


296

Temocillin (BRL 17421, **297**) was reported to have good gram-negative activity and was stable to β-lactamase.[484,485] The drug was active against Enterobactericae-resistant third-generation cephalosporins.[486] Degradation of **297**[487] as well as ^{3}H-labeling studies[488] have been published. BRL 203030 (**298**) is an orally active prodrug of **297** with the highest bioavailability of esters studied[489] and was well absorbed after oral administration in humans.[490]



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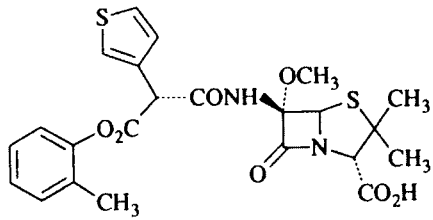
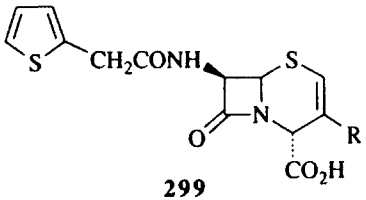


298

Additional studies on "newer-generation" β-lactams include work on 3-alkyl cephems **299** wherein the lipophilic character at C-3 enhances gram-positive and decreases gram-negative activity.[491] 2-Thienyl oxacephalosporin **300a** has

stability to penicillinases and inactivates cephalosporinases of gram-negative bacteria.[492] 3-Thienyl derivative **300b** was prepared as a moxalactam analog; the thienyl derivatives epimerized the fastest among the compounds prepared in the study.[493] A review of this and related compounds has appeared in the literature.[494]



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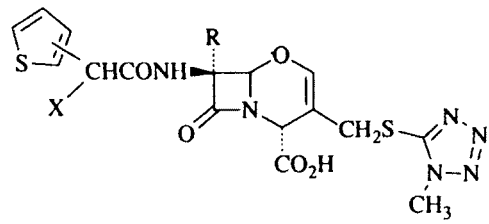
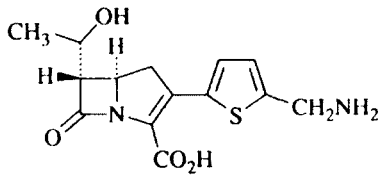


300

a, X = $NHCONHCH_3$, R = NHCHO

b, X = CO_2H, R = OCH_3

Thienamycin analog **301** was less potent than thienamycin but was active against *Pseudomonas* and was stable to DHP-1.[495] Analog **302** had antimicrobial activity superior or comparable to that of thienamycin.[496] Compound **303** was highly stable in vitro to kidney renal dehydropeptidase and had good antibacterial and β-lactamase properties. The compound had good protective effects in mice infected with *E. coli*.[497] Clavulanic acid analog **304** had no microbiologic activity, presumably as a result of the thiazolidine ring.[498]



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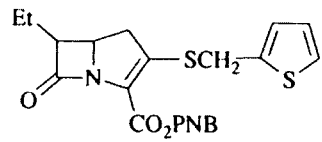

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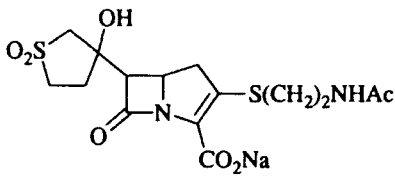

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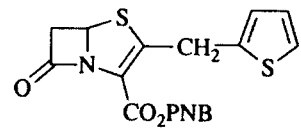
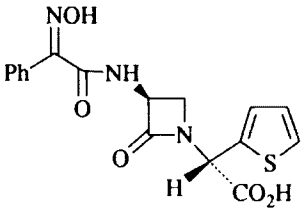


304

The field of monobactam research has produced some interesting compounds, including the norcardacin A analog **305**. Compound **305** was selected as the best in a series with good activity against *Pseudomonas aeriginosa*, *Bacillus*

subtillus, and *Staphylococcus aureus*.[499] Monosulfactam SQ 81387 (**306**) was among the best in the series of antibacterial agents.[500] The side chain was noted as that common to penicillins,[501] and another group has reported similar results.[502] The 3-α-methoxy derivative **307** had improved activity against β-lactamase producing strains of *E. coli*.[503] Thiophene **308** was less interesting than the phenyl and furyl isosteres.[504]



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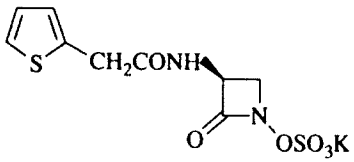

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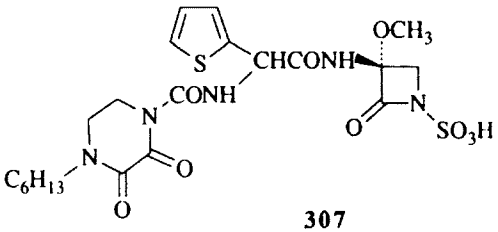

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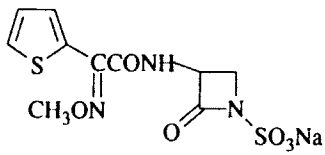
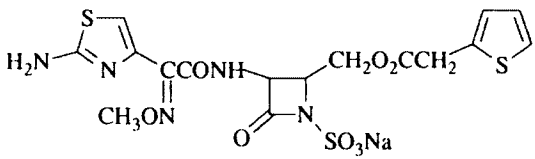


308

β-Lactam **309** was prepared as part of a series of compounds leading to AMA 1080, which was selected for clinical trials.[505] Derivative **310** and others in its series were uninteresting.[506] Thienopyridines, including **311**, were prepared, but no testing data were reported.[507]



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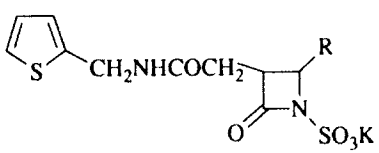

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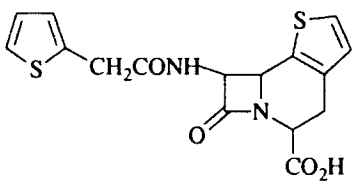
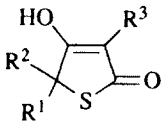


311

2. Antibacterial Agents

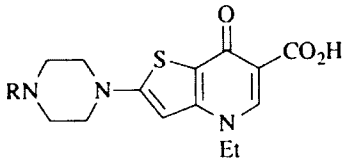
In addition to β-lactam antibiotics, tetracyclines, aminoglycosides, and macrolide antibiotics have significant efficacy in the treatment of bacterial infections. Recently, quinolones have become significant antibacterial agents. They have an especially wide spectrum of activity and are active against the chronic phases of bacterial infections. Quinolones also have good oral efficacy, which is advantageous as compared to β-lactams.

Thiotetramycin (**312a**) was isolated from a culture of Streptomyces and was active against *Bacteriocides fragilis*.[508] The structure was ascertained by NMR spectral analysis,[509] and structure–activity relationships were reported.[510] The related derivative U 68,204 (**312b**) was also isolated from a Streptomyces and was as active as **312a**. The compound protected mice infected with *Haemophilus influenzae* but had no effect against *S. aureus*.[511,512] The related derivative **312c** as well as the other compounds have been synthesized.[513]



	R^1	R^2	R^3
312a	Et	CH_2=CHC(Me)=CH-	Et
312b	Et	CH_2=CHC(Me)=CH-	CH_2CONH_2
312c	Me	CH_2=CHC(Me)=CH-	Me

Quinolone antibiotics, which developed from studies of nalidixic acid, have several thiophene analogs. Derivative **313** and other thienopyridines had weak antibacterial activity.[514] A diverse series of quinolones, including **314**, were used to establish a QSAR for quinolones.[515] Several reports of *N*-aryl pyridones, including **315**, have appeared. Compounds in these studies had low urinary concentrations, presumably as a consequence of poor intestinal absorption.[516] Thieno[3,2-*g*]quinoline carboxylic acid **316** was the best antibacterial agent and was more effective than norfloxacin against gram-positive bacteria.[517] Tetrazole **317** and other analogs showed no antibacterial activity, indicating that tetrazole is not a bioisostere of carboxyl groups in this class of drugs.[518] Several analogs of **318a** were as effective as nalidixic acid as antibacterial agents. T 14097 (**318b**) was interesting against a broad spectrum of microbes.[519] The closely related diazaborine derivatives had very interesting activity as lipopolysaccharide biosynthesis inhibitors.[520] Among the series of thieno[3,2-*d*] and thieno[2,3-*d*] derivatives, **319** had remarkably good activity in vitro and in vivo and was selected for further study.[521]



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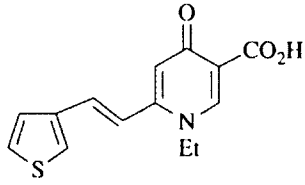

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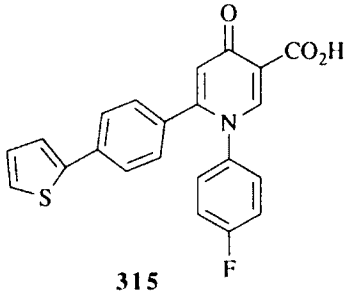

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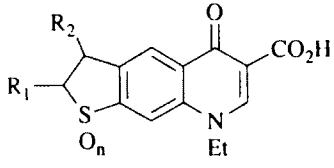

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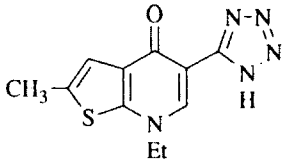

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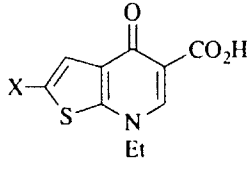
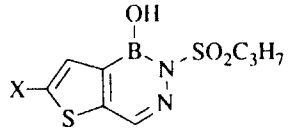


318a, X = H
318b, X = Cl



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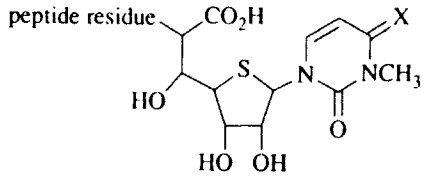
The peptide-like antibiotic albomycin (**320**)[522] as well as the macrolide oleandomycin (**321**)[523] have been described in the literature. Macrolide **321** was chosen for further study and found to be more active than erythromycin against *S. aureus* and *S. epidermis*.[524] Erthyromycin ester (**322**) was prepared as a possible prodrug for improved bioavailability but was less bioavailable than the succinate ester.[525] Synthetic analogs of chryscandin, including **323**, had activity in vitro against *Candida albicans* but were inactive against *E. coli* or *S. aureus*.[526] Benzothiazine **324** had some antibiotic activity,[527] while tricyclic **325** had low activity against *S. aureus*.[528] Some bis(thienyl) hydrazones **326** had modest antibacterial activity.[529] Cyanopyridone **327** and other analogs had antimicrobial activity against several microorganisms.[530] Imidazole derivatives, including **328**, are active against *E. coli* and *C. albicans*. Nitro-substitution substantially increased potency.[531]

While **329** had good activity against *B. megaterium* and *Proteus vulgaris*, the pyridyl isostere was the most interesting.[532] Azepinone **330** had antimicrobial activity.[533] Thiazole **331** was among the most active of bacteriocides, with better activity than the phenyl or nitrophenyl isosteres.[534] Thienyl substitution in



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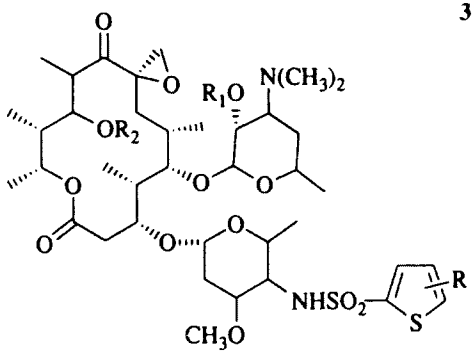

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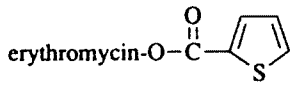

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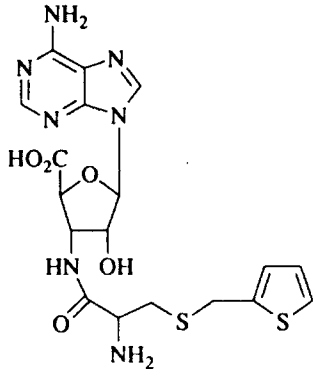

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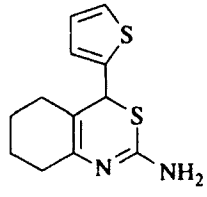

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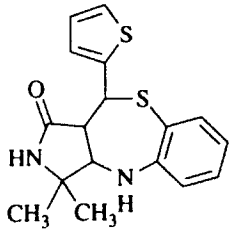

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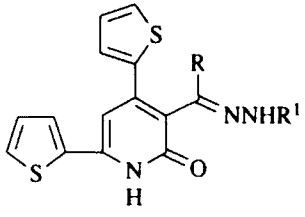

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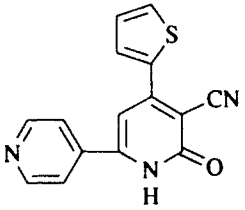

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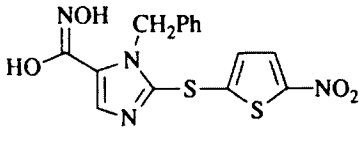
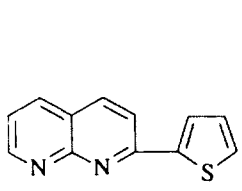


328

analogs of trimethoprim (**332**) reduced in vitro antibacterial activity.[535] Thiophene **333** and the phenyl isostere were inactive.[536] Thieno[3,2-*b*]indole **334** was active as an antibacterial, tuberculostat, and virucide.[537] Pyrazole **335** had broad-spectrum activity against a variety of microorganisms.[538] Some thenoyl coupled dipeptides were found to have in vitro activity against *B. subtilis*, *B. myocides*, and *B. cereus*, and pharmacologic studies were initiated.[539] Thienyl β-diketones with fluorine substitution had interesting activity against *P. aeruginosa* and *S. aureus*.[540]



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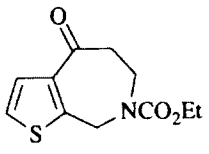

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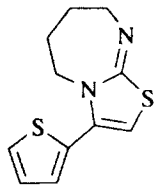

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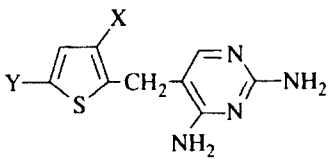

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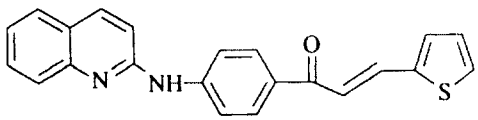

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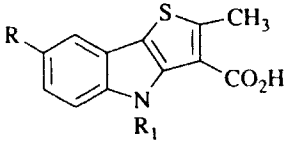

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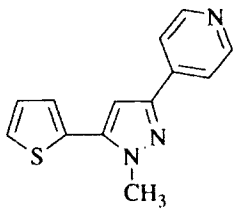

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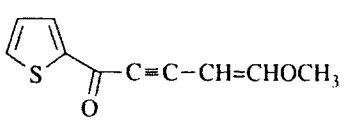
Acetylene **336** was part of a study of new bacteriostats,[541] as was **337**.[542] Benzoylaminothiophenes, including **338**, also had bacteriocidal activity.[543] All isocyanides were antibacterial, and **339** had striking antifungal properties.[544] Extension of this work led to the synthesis of A 32390A (**340**) with good activity against *B. subtilis*, *E. coli*, and several infective fungi.[545] Sulfonamides **341** were found to have bacteriostatic properties.[546] Some thienyl hydrazones,[547] pyrazoles,[548] acylhydrazones,[549] and 1,2,3-triazolines[550] all had bacteriostatic properties. Thienyl-substituted α-enones,[551] unsaturated ketones,[552] and thienylidine hydrazides[553] had similar bacteriostatic effects. Triazolones **342** had antibacterial activity against gram-positive and gram-negative organisms as well as bacteriostatic activity, especially against gram-positives,[554a] as did related thiobarbituric acid thiophenylidene derivatives.[554b] Dinitrothienylsulfides were less active than the phenyl isosteres.[555] While the phenyl isosteres were inactive, compounds such as **343** were highly active against *B. megaterium*, *E. coli*, *M. luteus*, and *S. aureus*.[556]



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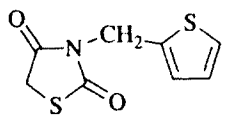

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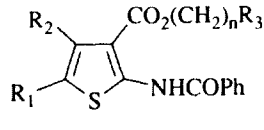

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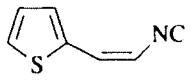

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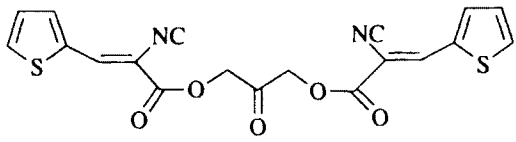

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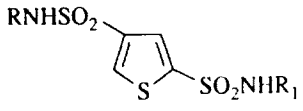

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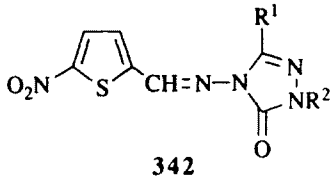

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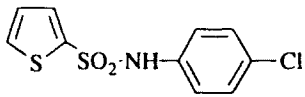
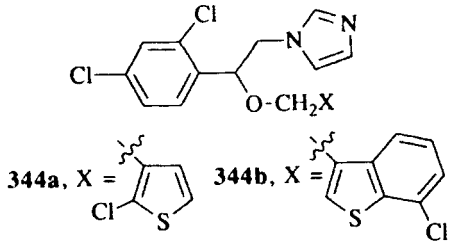


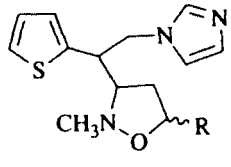
343

3. Antiparasitic and Antifungal Agents

Fungus and protozoal infections are serious diseases in many third-world countries. Schistosomiasis and malaria are the most common cause of mortality in the world. While much research in the antifungal area is directed with the rationale of structure–activity development, many compounds reported to have antiparasitic activity are discovered by random screening. A review of chemotherapy of tropical diseases discusses the use of various drug treatments.[557]

Tioconazole (**344a**) is a broad-spectrum antifungal agent with a low rate of resistance. Clinical results correlate with in vitro screening data.[558a] An HPLC method of analysis has been reported as part of the studies to support the drug.[558b] Seraconazole (**344b**) is also a broad-spectrum antifungal active against yeasts, dermatophytes, and aspergilli.[559] The novel antifungal agents **345** had moderate to potent activity against *Trichophyton rubrum*, *Aspergillis fumigatus*, and *Candida albicans*.[560] The activity of **346** is comparable to miconazole against *C. albicans* and is fungistatic at low concentrations. Topically, **346** is comparable to clotrimazole.[561] Novel azolylpropanolone derivatives, including **347**, had antifungal activity comparable to ketoconazole,[562] as did related dehydrated compounds.[563]





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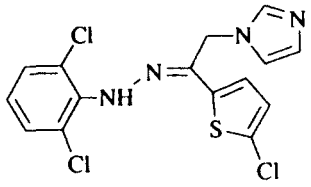

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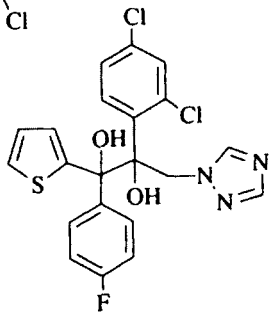
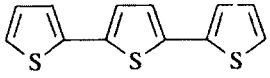


347

α-Terthienyl (**348**) and related compounds such as thiophene A (**349**) had nematocidal and antifungal activity.[564] Some thiosemicarbazones **350**,[565] and related derivatives[566–569] had antitubercular activity. Aryl furans and related thiophenes (**351**) were tubercularstats.[570] Nitrothiophenes **352** were antiamebic and antiparasitic agents,[571] as were other nitrothiophene derivatives.[572] Thienylbenzoxazines had no noteworthy antiparasitic activity.[573] In another report, thienylvinyl derivative **353** had the highest activity against both dermatophytes and systemic fungi, as well as promising antiamebic effects.[574a] Further studies showed that nitroimidazole analogs of **353** gave little improvement in activity.[574b] Acetamide **354** had antimalarial activity,[575] as did related compounds.[576]



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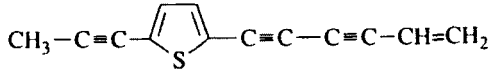

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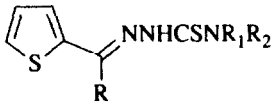

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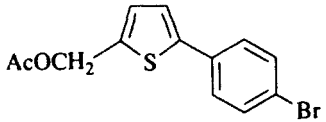

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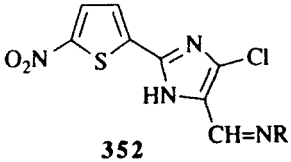

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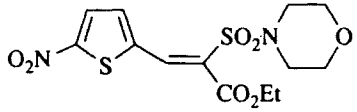

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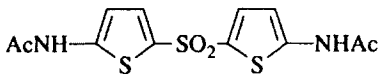

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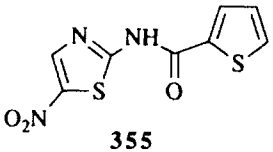
Atrican (**355**) has been reported to have activity against *Trichomonas vaginalis* and antimycotic activity with prolonged duration of action. X-Ray structure determination of **355** was published.[577] Protiofate (BT 799, **356**) is an antimycotic and antiprotozoal agent.[578] Benzylidine thiophenones (**357**) as well as the pyrrole and furan isosteres all had antifungal activity against *Candida albicans* lower than that of ketoconazole.[579] Schiff's bases of 2-thiophenecarboxaldehyde have in vitro anthelmintic and antifungal activity.[580] 2-Thienylidene derivative **358** had activity against schistosomiasis,[581] while related compounds inhibited the growth of yeast and gram-negative bacteria.[582]



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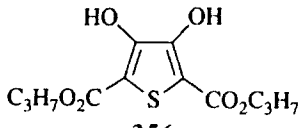

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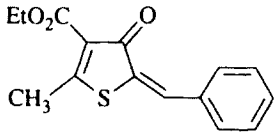

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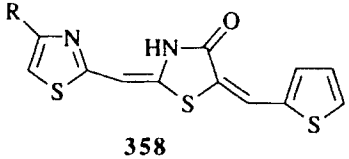

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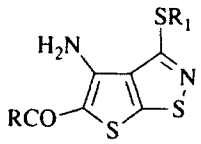
Thieno[3,2-*d*]isothiazoles **359** were 30 times less potent antifungal than miconazole against Dermatophytes, while the thieno[2,3-*d*] isomers were inactive.[583] A series of spiroarsorans, including **360**, had in vitro filaricidal activity against *Molinem dessetae*.[584] The naftifine analog **361** had good antimycotic activity against *Trichophyton mentagrophytes* and was comparable to the phenyl isostere and better than the furyl derivative. The 3-thienyl **361** was slightly more active than the 2-isomer.[585] A series of thienohexanones and thienothiapyrans **362** were very active against both bacterial and *Candida* fungal infections with the sulfur analogs much more active than the carbon isosteres.[586]



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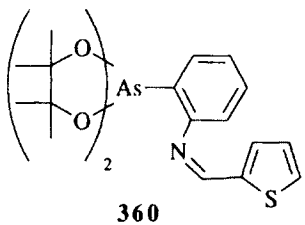

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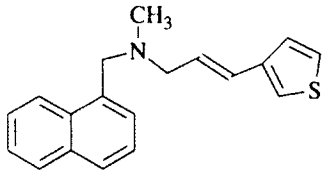

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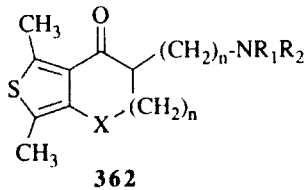
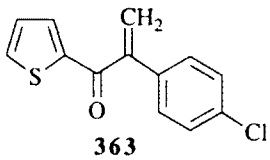


362

The thienyl derivative **363** was among the most interesting of a series of propenones with activity comparable to that of miconazole. The 2-thienyl **363** had better activity than the 3-thienyl isomer against *Candida albicans, Aspergillus fumigatus and Trichophyton asteroides.*[587] 1,2-Dithiole 3-thione **364** had no antifungal properties, in contrast to the phenyl isostere,[588a] and had little schistosomicide activity, in contrast to the pyridyl isosteres.[588b] Compound **365** was a fungistatic agent as were a number of analogs in the study.[589] Pyrazoline **366** had good broad-spectrum antifungal activity.[590]



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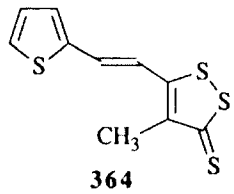

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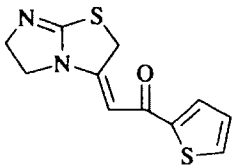

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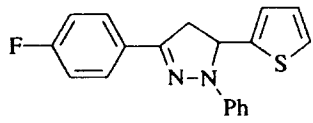
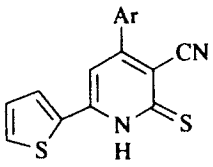


366

A series of 2-thienyl-substituted 3-cyanopyridine 2-thiones (**367**) had moderate to satisfactory fungicidal acitivity.[591] While the quinazolinone had remarkable antifungal activity, **368** was uninteresting.[592] Compound **369** had modest fungicidal properties.[593]



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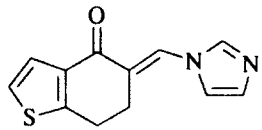

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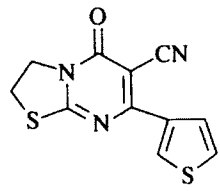
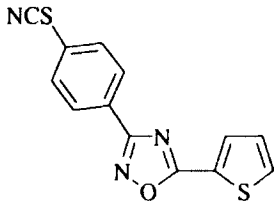


369

Thiophene **370** was less active than the benzene isostere, while the furan had good nematocidal activity.[594] Tetracyclic thiophene derivatives with bridgehead nitrogen such as **371** had fungicidal and fungistatic activity[595a] wherein the

thiophene seemed to enhance activity,[595b] while related tricyclics had no reported activity.[595c] 7,9-Dideaza-7-thiaadenosine (DI, **372**) could be incorporated into the nucleotide pool of *Schistostoma mansoni*, which suggests that possible selective toxicity against schistosomiasis might be achievable.[596]



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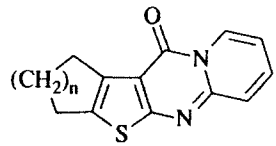

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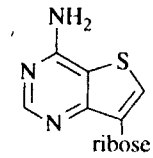
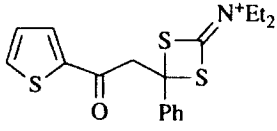


372

Compound **373** and other analogs had tuberculostatic activity.[597] Quinoline **374** had antimalarial activity,[598] while acridine **375** had activity against *C. albicans*, *T. gypseum*, and *T. rubrum*, among others.[599] The thiophene isostere of petrocarpan, **376**, had moderate antifungal activity against *F. annosus*.[600] Alkylated papulacandin B (**377**) as well as other ether derivatives had good in vitro antifungal activity.[601]



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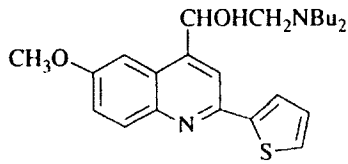

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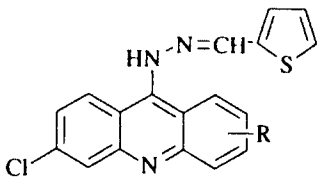

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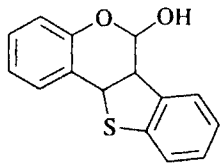

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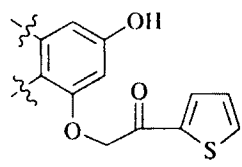


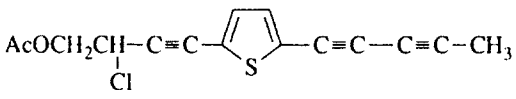
377

4. Antiviral and Cancer Chemotherapy

Chemotherapeutic treatment of cancer is part of an aggressive regimen for treatment that also includes surgery and radiation. Drugs that are used to treat cancer include DNA intercalators (of both the major and minor groove), nonspecific cytostatic agents such as alkylating agents, antimetabolites, and antitumor antibiotics, as well as many other such agents. All such agents are targeted toward the interruption of the replication of DNA in the most

metabolically active cells, specifically, uncontrollable cancer cells. Inevitably normal cells with high growth rates such as bone marrow, hair follicles, and gastrointestinal epithelium are adversely affected by such treatments. Antiviral therapies are also targeted to interfere with viral DNA and RNA synthesis. Immunoregulatory drugs, including cytostatic immunomodulators, immunostimulants, and immunosuppressive agents, have diverse therapeutic targets. These agents have been used in the treatment of autoimmune diseases such as rheumatoid arthritis and organ transplant rejection.

In addition to α-terthienyl (**348**), thiophene **378**,[602a] among other analogs,[602b] has Sindbus virus inactivating effects when used with UV-A irradiation; thiophene A (**349**) was essentially inactive.[602] Several thiophene analogs of antiviral flavans were prepared. Compound **379** was less active against rhinovirus but retained flavan serotype specificity,[603] while **380** was barely active.[604] The drug stepronin (**381**) had clinical utility in the treatment of viral hepatitis.[605] Several aminothiophene derivatives have activity against Herpes simplex Types I and II.[606]



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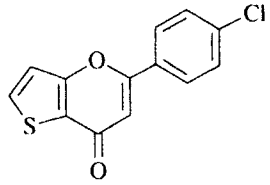

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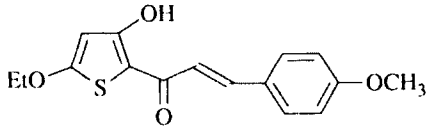

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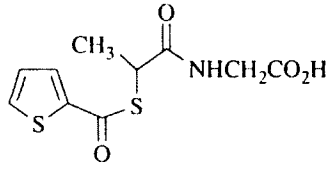

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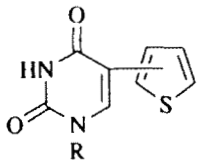
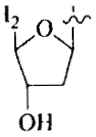
Thienyl- (**382a**) and selenylpyrimidines were prepared as potential antiviral agents,[607] while the nucleotides **382b** are potential thyidylate synthetase inhibitors that might be useful to control growth of virus and cancer.[608] The thiosugar analogs **383a**[609] and **383b**[610] as well as the sulfoxide and sulfone derivatives caused the highest inhibition of L 1210 cells in vitro.

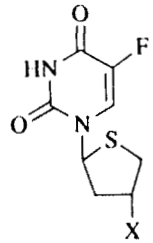
Thieno[3,2-*d*]pyrimidines **384**[611] as well as several thieno[2,3-*d*]pyrimidines **385** were prepared; **385** inhibited Herpes virus but not influenza A.[612] Thieno[2,3-*d*]imidazoles including **386** were less active than the benzimidazole isostere enviroxime against Rhino-type, Polio myelitis, and Coxsackie virus strains.[613] Among pyrimidine derivatives, **387** had noteworthy activity against Picona and Herpes simplex virus.[614]

The C-nucleoside thieno[3,4-*d*]pyrimidine analog of inosine (**388**)[615] and 7-thia-7,9-dideazinosine have been prepared;[616] the latter derivative had high

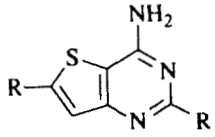


382a, R = H
382b, R = $H_2O_3POCH_2$





383a, X = $NHCOCF_3$
383b, X = H



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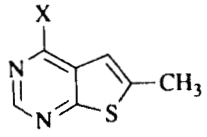

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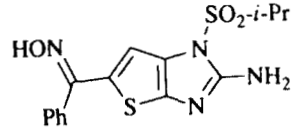

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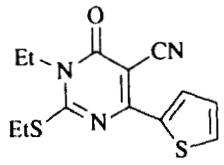
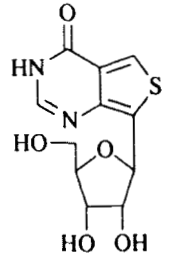


387

toxicity and was not a subject for further development. The thieno[3,2-*d*]-isomer of **388** had significant inhibiting activity against P-815 and L-1210 leukemia in mouse cell lines.[617] The adenosine analog had less interesting activity.[618] The thiophene analog of pyrazfurin **389** had no significant activity against a variety of virus and cancer lines.[619] Thienylmethylguanine PD 119229 (**390**) was 20 times more potent than 8-aminoguanosine in inhibiting RBC purine nucleoside phosporylase in vitro and was selective for T-cells in vivo.[620] The compound might have utility in tissue transplant, arthritis, and T-cell cancer.[621]



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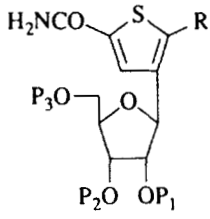

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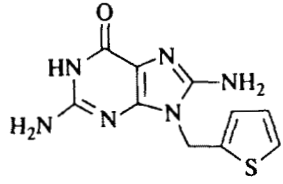
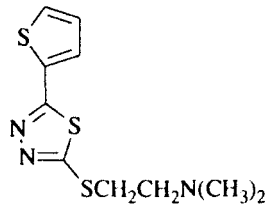


390

Thiadiazole **391** had intermediate activity as an amplifier of phleomycin.[622] The thienyl-substituted pyrimidine **392** is a significantly better DNA binding agent than the amine analog as a phleomycin amplifier.[623] The compound had unusually strong interaction with DNA base pairs and was a nonclassical intercalating agent model for bleomycin amplifiers.[624] Other analogs have been studied.[625] Polyamine **393** contains both the bleomycin amplifier moiety of **392** as well as a polyamine moiety that enhances bleomycin degradation of DNA.[626] An extension of this work has led to **394**, which was the best in vitro amplifier of bleomycin reported to date.[627]



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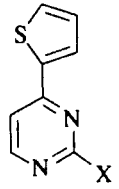
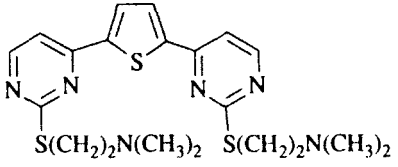
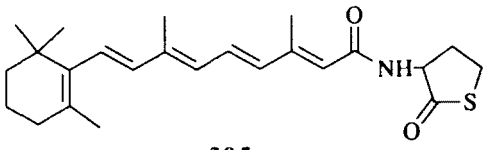


392, X = $S(CH_2)_2N(CH_3)_2$
393, X = $NH(CH_2)_3N(CH_3)(CH_2)_3NH_2$



394

Thiolactonyl retinamide **395** reduced lung tumor growth induced by ethyl carbamate, while *trans*-retinoic acid was inactive.[628] Other cytotoxic agents include **396**[629] and mitomycin analog **397**.[630] Angelicin analog **398** inhibited DNA synthesis in murine Ehrlich ascites tumor cells and also had photobiologic properties.[631] Dihydropyridine **399** inhibited neoplasms.[632]



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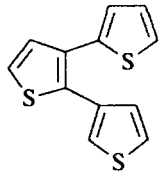

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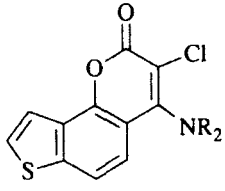

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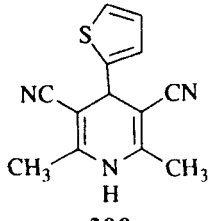
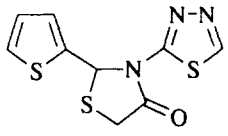


399

Thiadiazole **400** was selected from a series for further study as a result of its good activity against P-388 leukemia in mice.[633] Further studies showed slight activity against L-1210 leukemia but not against B16 melanoma.[634] Thiophene **401** had no significant antitumor activity,[635] while **402** had activity related to the PDE inhibitor CC-1065.[636] Some thienyl substituted triazines also had no activity.[637] The heterocyclic analogs (**403**) of the anticancer agent bisantrene were prepared.[638] Some disodium salts of thiophene carboxylates have potential as slow-acting anticancer agents.[639]



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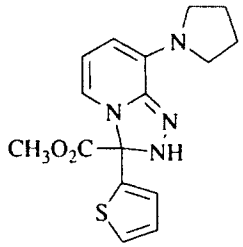

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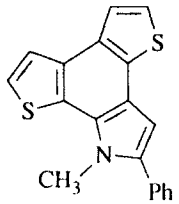

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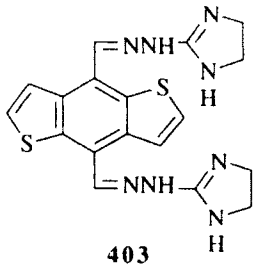
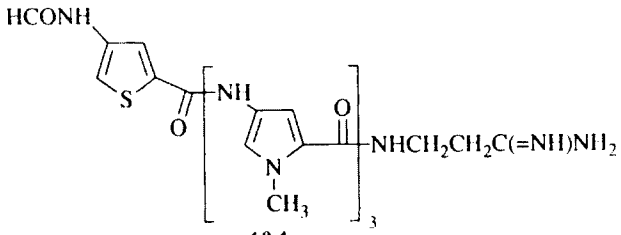


403

Distamycin derivatives **404** all complexed with calf thymous DNA and were cytostatic against human and murine tumor cells.[640a] Synthesis and binding activity of other distamycin analogs (**405**) have been reported.[640b] These compounds also had antitumor activity.[641] Compound **406** was 20–30 times more active than hydroxyguanidine as an inhibitor of ribonucleotide reductase.[642] In a subsequent study, **406** was of intermediate activity with the best compounds having the greatest lipophilicity.[643] Quinoline **407** was prepared as part of a study that produced inactive compounds against P-388 leukemia.[644] In an ongoing study of antitumor tropolone derivatives, the thienyl, furyl, and phenyl derivatives were essentially equiactive.[645] This research led to **408**, which has better antitumor activity at low concentrations; this activity might result by iron chelation and subsequent inhibition of ribonucleoside diphosphate reductase.[646] Compound **408** had weak potency against P-388 leukemia.[647] A series of metal complexes of aryl-substituted ethylenediamines included **409**, which was relatively inactive as a inhibitor of cell proliferation and of ^{3}H-thymidine incorporation in carcinoma cells.[648] Other thiophene-containing metal complexes have reported antitumor activity.[649]



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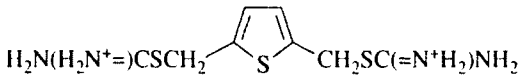

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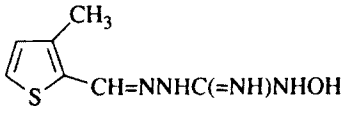

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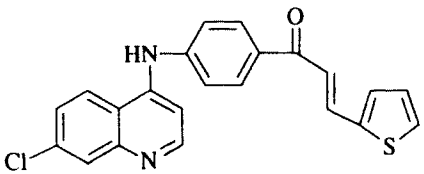

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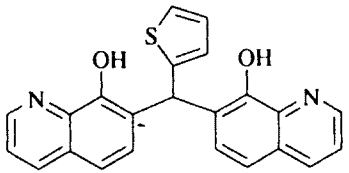

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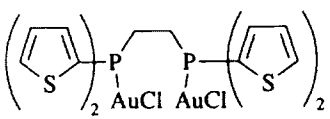
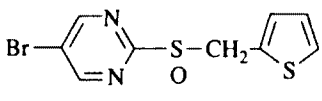


409

The compound NY 4138 (**410**) is an antineoplastic agent that inhibits mitosis and arrests metaphase activity in membranes. The compound is less effective on a molar basis than vincristine.[650] The compound reduced survival of human cancer cell lines,[651] and a closely related compound has also been studied.[652] Oncadazole (**411**) and some analogs have been reported to have high tubulin binding affinity, with some analogs having enhanced antitumor activity compared to oncadazole.[653] A photoaffinity labeled oncadazole derivative has been prepared.[654] Aziridine **412** was part of a study of potential DNA alkylating agents related to mitomycin.[655] The isosteric analogs of PDE I and PDE II inhibitors (**413**) based on CC 1065 have been reported to have enzyme-inhibiting and antitumor activity.[656]



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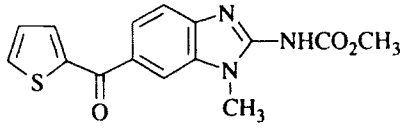

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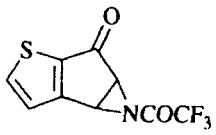

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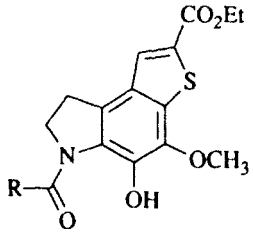
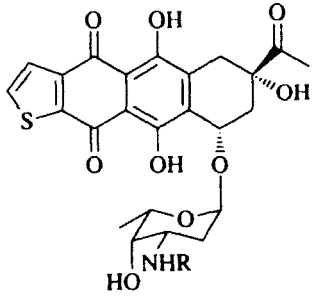


413

Thiophene D-ring isosteres of daunomycin (**414**) inhibit L-1210 cell growth comparable to adriamycin.[657] The adriamycin isosteres have also been reported.[658] Teniposide (**415**) is a nonintercalative antitumor agent that inhibits DNA topoisomerase and creates lethal DNA strand breaks.[659] Glycosidic derivatives of **415** have been compared.[660] The steganol series analog of **415** is inactive against P-388 leukemia.[661] The C-4 ester of **415** did not show increased cross-resistance in hamster ovary cells.[662] Other analogs of **415** have been prepared that might avoid delayed toxicity of **415**.[663] The 4′-OH group of **415** is unnecessary for cytotoxic activity.[664] Esperamicins (**416**) are of high interest as antitumor antibiotics.[665] Prianosins (**417**) are also thiophene-containing antineoplastic natural products.[666]



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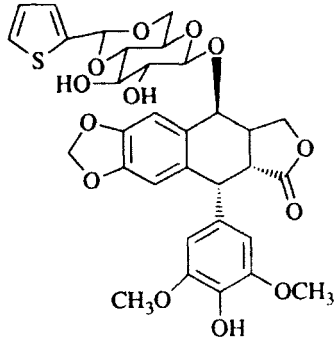

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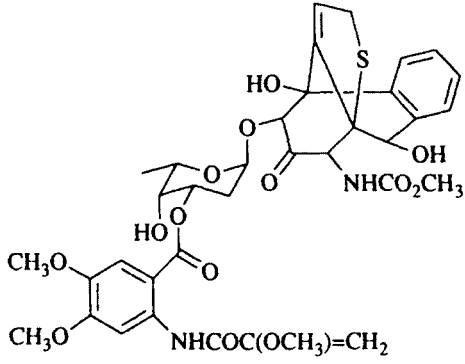

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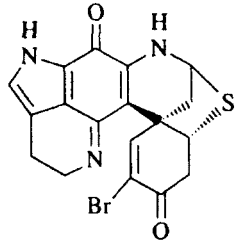
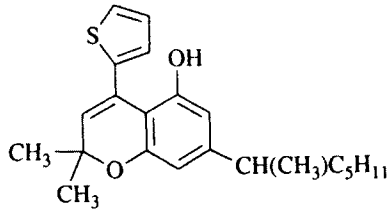


417

Analogs of the cannabinoid-like antiemetic agent nonabine have been prepared. Thienyl analogs **418** are compounds of the most interest with a similar profile of activity to the nonabine. These agents have been used to reduce the nausea that results from chemotherapy.[667]



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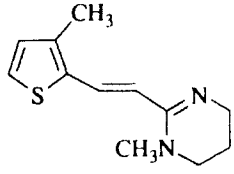
VI. VETERINARY AND AGRICULTURAL AGENTS

Nematode infections continue to be a major problem for the livestock industry. Morantel (**419**), which has been used to treat a variety of infections, has been registered for use in lactating dairy cattle. The tritium-labeled material was examined in the same report.[668] A series of hydroxy-, aza-, and deaza- derivatives of pyrantel (**420**) were prepared in an attempt to improve the activity of this commercially used anthelminth, but all the new compounds were inactive against *Necator americanus* in neonatal hamsters.[669] Thiophene isosteres **421** of the antischistomicide praziquantel have been prepared.[670]



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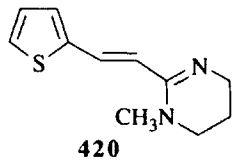

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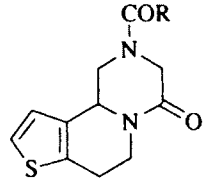
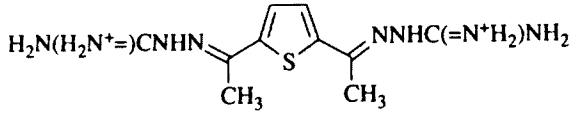


421

Trypanocidal activity was found for bisguanylhydrazone **422**, although it was considerably less active than the phenyl or pyridyl isostere.[671] The related bisamidine **423** had human activity, while other related compounds were active in bovine trypanoside infections.[672] Insects continue to plague agriculture as well as spread airborne disease. Pest control and plant growth regulation are important practices that enable agriculture to feed the world's expanding



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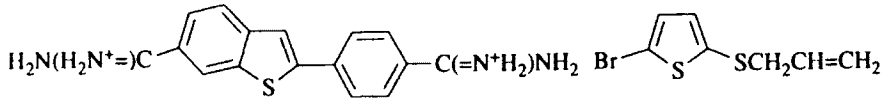
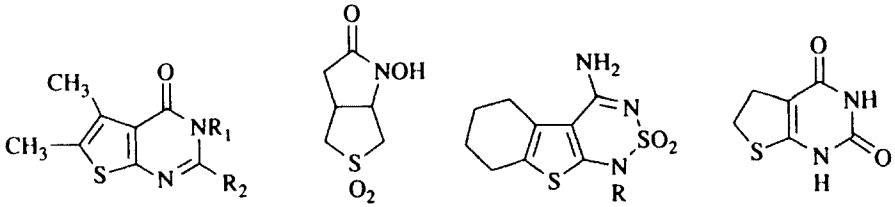


423 424

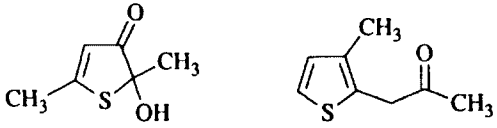
population. A series of relatively simple thiophene derivatives has insecticidal activity, with the bromo analog **424** having the best activity against houseflies.[673]

Thienopyrimidinones **425** are reported to have pesticidal activity.[674] QSAR techniques were applied to a series of DDT derivatives.[675] Sulfone derivatives were found to be effective plant growth regulators, with **426** having potent growth-inhibiting properties. Closely related acid analogs altered the profile of the compounds to that of growth stimulators.[676] Thieno[2,3-*c*]thiadiazines **427** have herbicidal activity,[677] as do uracil derivatives **428**.[678]



425 426 427 428

The use of thiophene derivatives as flavoring agents in the food industry has been reported. The 3-thienone **429**[679] and propanone **430**[680] have been prepared in these studies.



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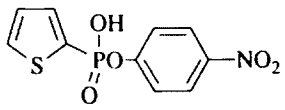
VII. MISCELLANEOUS PROPERTIES OF THIOPHENE DERIVATIVES

A series of reports on the toxicity of cholinesterase inhibitors have been published. Compound **431** and isosteres were prepared to examine hydrolysis rates versus cholinesterase activity, but no correlations was found.[681] Oxime **432** was part of a series of cholinesterase reactivators that might have use in cases of poisoning, but the thiophene was relatively uninteresting.[682] 4-Nitro-di-2-thienylphosphinate was the most potent inhibitor of porcine liver carboxylester hydrolysis.[683]



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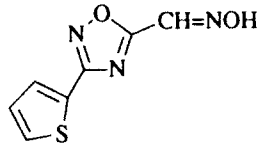
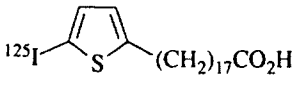


432

The use of thiophene as a substrate for the synthetic introduction of iodine radiolabels in drugs has been reported. Thienyl fatty-acid iodide **433** was easily prepared and showed significant myocardial uptake. Compound **433** appears to be an attractive alternative to iodophenyl isosteres for diagnostic myocardial imaging.[684] Iodination to produce **434** was equally facile, and **434** gave useful tissue distributions for imaging work.[685]



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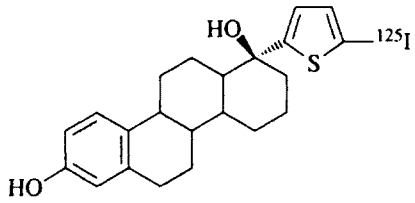
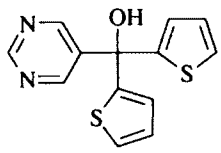


434

Some thienyl derivatives of an antimutagen furanone series were inactive.[686] Compound **435** had modest activity in a series of compounds that inhibited the aromatase enzyme essential for estrogen synthesis. Such compounds might be useful in the treatment of breast cancer.[687] Sulfoxide **436** is a liver alcohol dihydrogenase inhibitor that might have use to prevent methanol or ethylene glycol poisoning.[688]



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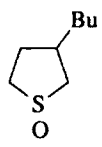
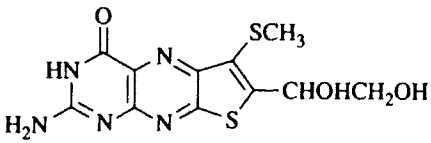


436

Urithione (**437**) is a urinary metabolite of molybdenum cofactor and has recently been synthesized.[689] The thiophene models of NADH were prepared and **438** was less water-sensitive than the standard nicotinamide derivatives.[690a] The thieno[2,3-*b*] **438** had different Mg^{2+} chelating properties than the [3,2-*b*]-isomer.[690b] Improved enantioselective hydrogen transfer in reactions with **438** was achieved by replacing the 1° amide moiety with a chiral aminoalcohol auxiliary.[691] Compound **439** has been prepared as the thiophene isostere of the fish toxin ichthyothereol.[692] α-Terthienyl (**348**) was effective in the photo-inactivation of yeast alcohol dehydrogenase.[693]



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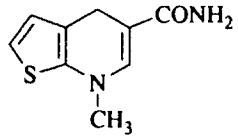

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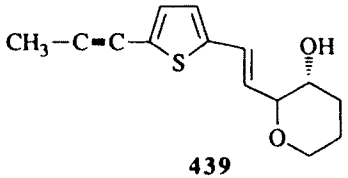

439

The metabolic fate of 2-thienylallylamine has been studied; the compound rapidly inactivates dopamine-β-hydroxylase.[694] Thienylphenols have been reported to have mutagenic activity.[695] A thienopyridine derivative was used as a basis for an indicator of toxicity.[696] The metabolism of methapyrilene has been studied intensively since the commonly used antihistaminic agent was found to be carcinogenic. The deuterium labeled compound[697] and the N-oxide[698] have been studied. The compound is carcinogenic in rats but does not bind to DNA. The metabolites might play a role in carcinogenisis.[699]

VIII. CONCLUSIONS

There are more references in this review of biologically active thiophenes reported during the past 5 years than were included in the previous review that covered three decades.[1] As the number of sensitive biologic probes expands in connection with the increasing sophistication of medical and biochemical research, there are more opportunities to incorporate thiophene with its unique physicochemical properties into potential drug candidates. As is evident scanning the contents of this review, each biologic application requires different chemical properties; 2-thienyl and 3-thienyl derivatives each may have superior properties depending on their use. Thieno[2,3]-, [3,4]- and [3,2]-fused molecules all have good activities, and the issue of which isomeric system will have superior properties is unpredictable. Clearly, the preparation of thiophene-containing biologically active molecules, either as isosteres or as compounds interesting in their own right, continues to be an area of active research.

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