aqueous layer was neutralized with dilute hydrochloric acid to give 0.5 g (52%) of benzoic acid (**5**), mp 121–122 °C (mixture melting point). The chloroform extract was dried over anhydrous sodium sulfate and the solvent was removed under vacuum to give a viscous residue which was chromatographed over silica gel. Elution with benzene gave 0.12 g (19%) of *N*-cyclohexylbenzamide (**45**), mp 147 °C (mixture melting point).

Photolysis of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (42). A solution of **42** (1.0 g, 2 mmol) in benzene (600 mL) was flushed with oxygen-free nitrogen gas for 0.5 h and then it was irradiated for 2.5 h. Removal of the solvent under vacuum gave an oily residue which was chromatographed over silica gel. Elution with a mixture (4:1) of petroleum ether and benzene gave 0.41 g (65%) of 3,5,6-triphenyl-2*H*-pyran-2-one (**50**), mp 147–148 °C. There was no depression in the melting point of **50** when mixed with an authentic sample.[22]

Thermolysis of 4-Benzoyl-3-cyclohexyl-5-(*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (42). A solution of **42** (0.50 g, 1 mmol) in toluene (40 mL) was heated under reflux for 48 h. Removal of the solvent under vacuum gave a viscous material which on treatment with benzene gave 15 mg of a benzene-insoluble material, mp 282–284 °C, which has not been characterized.

The mother liquor, after concentration, was chromatographed over alumina. Elution with a mixture (1:1) of benzene and petroleum ether gave 30 mg of an unidentified product, mp 179–181 °C, after recrystallization from benzene.

Further elution of the column with benzene gave 20 mg (6%) of 3,5,6-triphenyl-2*H*-pyran-2-one (**50**), mp 147–148 °C, after recrystallization from methanol. There was no depression in the melting point of this product when mixed with an authentic sample of **50**.[22]

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Registry No. **5**, 65-85-0; **7**, 1981-53-9; **12**, 3593-38-2; **13**, 13591-60-1; **16**, 100-52-7; **19**, 55-21-0; **22**, 1489-06-1; **26**, 50609-88-6; **27**, 668-94-0; **32**, 965-04-8; **33a**, 573-33-1; **36**, 614-28-8; **40**, 37068-60-3; **42**, 21364-53-4; **45**, 1759-68-8; **50**, 70982-94-4.

Thiophene Systems. 2. Synthesis and Chemistry of Some 4-Alkoxy-3-substituted Thiophene Derivatives[1]

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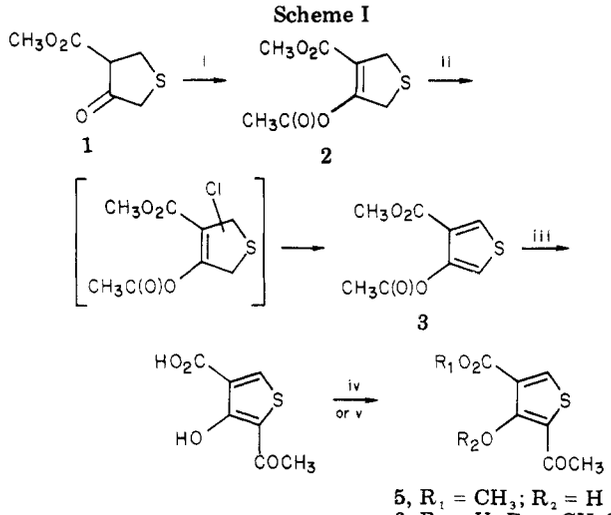
Several 4-alkoxy-, 4-hydroxy- and 3-amino-disubstituted thiophenes were prepared as potential intermediates for the preparation of novel thieno[3,4]tricyclic systems. The 4-alkoxy-3-substituted thiophenes **8a,b** were prepared by acid-catalyzed alcohol exchange of 4-hydroxythiophene **7**. Base stable thiophenes **8a,b** were converted to acids **10a,b**, amides **11a,b**, and hydrazide **12**. Electrophilic substitution reactions with **10b** occurred exclusively to give 5-substituted derivatives. Hydrazide **12** was converted via azide **17** to stable, electron-rich 4-ethoxy-3-thiopheneamine (**23**). 4-Alkoxythiophene derivatives **10a,b** and **19** were converted to 4-hydroxy derivatives with boron tribromide. Intermediate and final compounds were examined for potential tautomerism.

During the course of an investigation into the synthesis of thieno[3,4-*b*][1,5]benzodiazepines[1] and other novel thieno[3,4-*b*]-fused tricyclic compounds, it became necessary to synthesize 4-alkoxy- and 3-amino-substituted thiophenes as potential intermediates. Such thiophenes without substitution in the 2 and 5 positions are not well described in the literature and appear to be relatively unstable and/or difficult to prepare.[2,3]

The ready availability of methyl tetrahydro-4-oxo-3-thiophenecarboxylate[4] (**1**) allowed straightforward preparation of the thiophene system with the desired 3,4 substitution. Reaction of **1** with isopropenyl acetate led to enol acetate **2** which was oxidized by the action of sulfuryl chloride to acetoxy ester **3** via the unisolated chlorosulfide and thermal elimination of hydrogen chloride (Scheme I). The use of sulfuryl chloride for this type of

Scheme I



5, $R_1 = CH_3$; $R_2 = H$
6, $R_1 = H$; $R_2 = CH_3CO$

i. ⟩—OAc/*p*-TSA; ii. SO_2Cl_2 at −20 °C, then reflux; iii. LiI/NaCN/DMF; iv. CH_2N_2; v. Ac_2O/H_2SO_4

α chlorination of sulfides is extremely advantageous since the gaseous byproducts of this reaction are easily removed. Acetate **3** appeared to be an ideal precursor for the 4-hydroxy-3-carboxythiophenes of interest; however, at-

(1) For paper 1 in this series see: Press, J. B.; Hofmann, C. M.; Eudy, N. H.; Fanshawe, W. J.; Day, I. P.; Greenblatt, E. N.; Safir, S. R. *J. Med. Chem.* **1979**, *22*, 725.
(2) Hartough, H. D. "Thiophene and Its Derivatives"; Interscience: New York, 1952; and references contained therein.
(3) Elguero, J.; Marzin, C.; Katritsky, A. R.; Linda, P. "The Tautomerism of Heterocycles. Advances in Heterocyclic Chemistry"; Academic Press: New York, 1976; and references contained therein.
(4) (a) Woodward, R. B.; Eastman, R. N. *J. Am. Chem. Soc.* **1946**, *68*, 2232. (b) Hromatka, O.; Binder, D.; Eichinger, K. *Monatsh. Chem.* **1973**, *104*, 1520.

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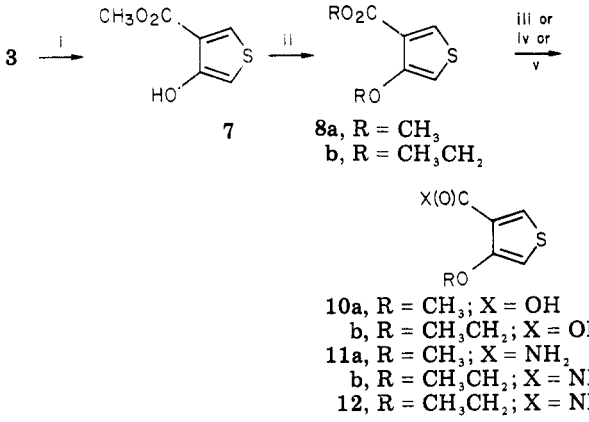
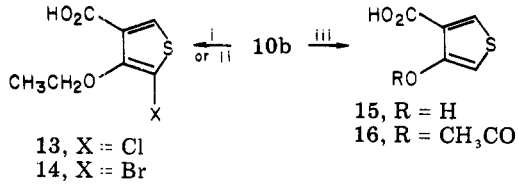
Scheme II



i. CH_3OH/p-TSA; ii. CH_3OH or CH_3CH_2OH/p-TSA/Δ; iii. KOH/H_2O then H_3O^+; iv. NH_4OH; v. NH_2NH_2

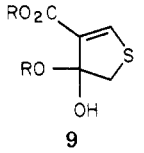
Scheme III



i. SO_2Cl_2; ii. Br_2; iii. BBr_3

tempted alkaline hydrolysis of **3** caused complete decomposition of the thiophene ring system. In fact, **3** decomposed in all the basic media employed with the exception of lithium iodide/sodium cyanide in DMF,[5] wherein acetyl-rearranged hydroxy acid **4** formed in good yield. This unique Fries-like rearrangement may be envisioned as a result of iodide-induced deacylation and subsequent C-acylation of the intermediate enolate anion. This appears to be the first example of a base-catalyzed acyl migration of an aromatic acetate. The structure of **4** was confirmed by conversion to ester **5** (an isomer of **3**) with diazomethane and to acetate **6** with acetic anhydride.

Thiophene ester **3** was found to be quite stable in acidic media. For example, treatment of **3** with *p*-toluenesulfonic acid in methanol resulted smoothly in transacetylation to **7** without significant decomposition (Scheme II). Unsurprisingly, **7** was also extremely base labile. When **3** or **7** was treated more vigorously in refluxing acidic methanol, methyl ether **8a** formed in high yield, identical with the reaction product of **7** and diazomethane. Similarly, reaction of **3** or **7** in refluxing acidic ethanol gave ethyl ether **8b**. Formation of **8** presumably arises from the acid labile enolic character of the 4-hydroxy substituent with intermediacy of hemiketal **9** and subsequent dehydration to



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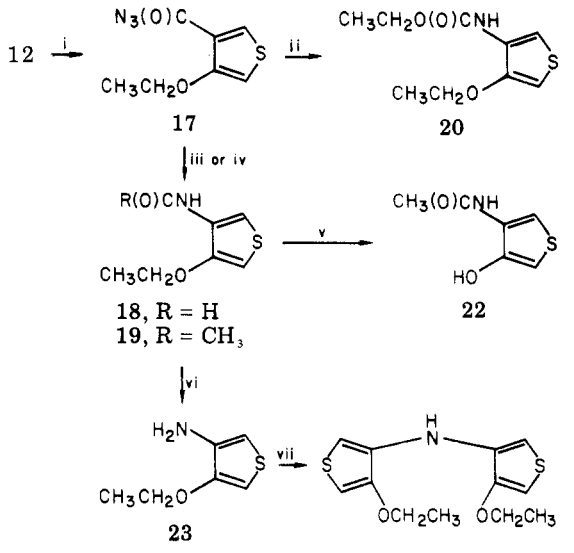
give the product. In contrast to the previous derivatives, thiophenes **8** were quite base stable as evidenced by conversion to alkoxy acids **10**, amides **11**, and hydrazide **12** under basic conditions.

Alkoxy acid **10b** reacted smoothly with halogenating agents, such as sulfuryl chloride or bromine, to form 5-chloro or bromo acids **13** and **14**, respectively (Scheme III).

(5) McMurray, J.; Wong, G. *Synth. Commun.* **1972**, *2*, 389.

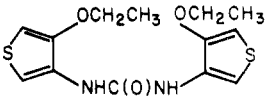
Scheme IV



i. $NaNO_2/HCl/AcOH$; ii. CH_3CH_2OH/Δ; iii. HCO_2H/Δ; iv. Ac_2O/Δ; v. BBr_3; vi. HCl/EtOH then OH^-; vii. Δ

Positional assignment of the halogens was determined by ^1H NMR analysis; both **13** and **14** exhibit a downfield resonance ($\delta \sim 8.0$) for the thiophene proton deshielded by the carboxylic acid moiety. Hydroxy acid **15** was prepared by boron tribromide cleavage[6] of methyl ether **10a** or (even better) ethyl ether **10b**. The superiority of boron tribromide cleavage of ethyl aryl ethers has previously been reported.[7] The structure of **15** was supported by conversion to acetate **16**.

In addition to the 4-alkoxy-3-carboxythiophene derivatives outlined above, 4-alkoxy-3-aminothiophene intermediates were also required as intermediates for fused thieno tricyclic systems. Hydrazide **12** was converted to stable azide **17** via carefully controlled diazotization (Scheme IV). Thermal decomposition of **17** in formic acid, acetic anhydride, or ethanol gave formamide **18**, acetamide **19**, or ethyl carbamate **20**, respectively, in excellent yield. When azide **17** was decomposed in glacial acetic acid, both **19** and urea **21** formed in nearly equal amounts; **21** pre-



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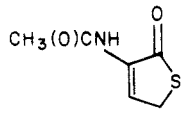
sumably arises from trace amounts of water present in the acetic acid. Urea **21** was prepared independently by decomposition of **17** in hot water. Acetamido ether **19** was cleaved with boron tribromide to give **22**.

Formamide **18** was deacylated with ethanolic hydrogen chloride with subsequent neutralization to give ethoxyamine **23**. Amine **23** was surprisingly stable[8] and was storable for months at 0 °C. However, self-condensation of **23** could be effected by prolonged heating to give bis(thiophene)amine **24** and ammonia. While such condensations have been noted for 3-aminothianaphthenes,[9] they have not been reported for the parent thiophene ring system. Amine **23** could be easily converted to amide **19** with acetic anhydride/pyridine.

(6) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289.
(7) Press, J. B. *Synth. Commun.* **1979**, *9*, 407.
(8) Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds", 3rd ed.; Wiley: New York, 1976; p 164.
(9) See Hartough, H. D.; Meisel, S. L., Ed. "Compounds with Condensed Thiophene Rings"; Interscience: New York, 1954; and references contained therein.

Potential tautomerization of the 4-hydroxy- or 3-aminothiophenes has been a subject of interest.[3] For example, recently, acetamide **25**,[10] an isomer of **22**, was



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reported to exist exclusively in the thiolactone form. However, all of the compounds prepared in this study, which had the potential of tautomerism, such as hydroxy derivatives **4**, **5**, **7**, **15**, and **22** as well as amine **23**, exist solely in the enol or enamine forms as evidenced by IR, UV, and ^{1}H NMR measurements. It is especially interesting that electron-rich systems such as **22**, **23**, and **24**, which might be expected to exist in the keto or imino form,[3] show no evidence of such tautomerism.

In summary, a number of 3- or 4-alkoxy- and aminobifunctional thiophene derivatives were prepared by the methods described herein. The utility of these intermediates for the preparation of novel thieno[3,4]-fused tricyclic compounds is the subject of future reports from these laboratories.[11]

Experimental Section

Melting points were determined on a Mel-Temp capillary block melting point apparatus and are uncorrected. All reported compounds are homogeneous by thin-layer chromatography analysis using Whatman K5F (5 × 10 cm) silica gel analytical plates. ^{1}H NMR measurements were obtained on a Varian Associates HA-100A spectrometer and shift values ($CDCl_3$) are reported in δ downfield from tetramethylsilane as the internal standard. Mass spectral measurements were made on a AEI MS-9 mass spectrometer. UV determinations were made in ethanol solvent with a Carey Model 14 recording spectrophotometer.

Methyl 2,5-Dihydro-4-acetoxy-3-thiophenecarboxylate (2). Methyl tetrahydro-4-oxo-3-thiophenecarboxylate[4] (160 g, 1 mol) and *p*-toluenesulfonic acid (1 g) were refluxed overnight in isopropenyl acetate (375 mL). Excess solvent was removed through a Vigreux column, and the residue was vacuum distilled: bp 94–96 °C (0.35 mmHg); 179.5 g (88%). The analytical sample from redistillation solidified and melted at 54–55 °C; the compound is unstable and easily hydrolyzes: IR 1775, 1730 cm^{-1}; ^{1}H NMR δ 3.95 (s, 4 H, CH_2), 3.80 (s, 3 H, CH_3O), 2.28 (s, 3 H, $CH_3C{=}O$). Anal. Calcd for $C_8H_{10}O_4S$: C, 47.51; H, 4.98; S, 15.86. Found: C, 47.25; H, 5.06; S, 16.02.

Methyl 4-Acetoxy-3-thiophenecarboxylate (3). Methyl 2,5-dihydro-4-acetoxy-3-thiophenecarboxylate (**2**, 179.5 g, 0.889 mol) in methylene chloride (375 mL) was cooled to −25 °C and treated with sulfuryl chloride (135 g, 80 mL, 1.0 mol) over a period of 1 h dropwise to maintain −25 °C. After the solution was stirred an additional 0.5 h at −25 °C, the black solution was allowed to stir at room temperature overnight. Excess reagent and solvent were removed through a Vigreux column, and the residue was vacuum distilled to give a water white solid: bp 104–106 °C (0.5 mmHg); mp 66.5–67.5 °C; 158.2 g (89%). Recrystallization from hexanes gave the analytical sample: IR 1755, 1720 cm^{-1}; UV 238, 205 nm; ^{1}H NMR δ 8.02 (d, 1 H), 6.94 (d, 1 H, both thiophene), 3.80 (s, 3 H, CH_3O), 2.30 (s, 3 H, $CH_3C{=}O$); M$^+$ 200. For preparative purposes, distillative isolation of **2** was unnecessary; in this case, the "one-pot" reaction sequence produced acetate **3** in 89% overall yield (179.8 g). Anal. Calcd for $C_8H_8O_4S$: C, 47.99; H, 4.03; S, 16.02. Found: C, 48.11; H, 4.09; S, 16.37.

5-Acetyl-4-hydroxy-3-thiophenecarboxylic Acid (4). Methyl 4-acetoxy-3-thiophenecarboxylate (**3**, 4.00 g, 0.02 mol) was added to a solution of lithium iodide (13.4 g, 0.10 mol) and sodium cyanide (0.98 g, 0.02 mol) in DMF (50 mL) and warmed overnight to 120 °C. After the mixture was cooled, it was poured into water (200 mL), acidified with 6 N hydrochloric acid, and extracted with ether (8×). The organic layer was washed with water and brine and treated with charcoal and sodium sulfate. Concentration gave the homogenous product as a tan solid which was purified by recrystallization from ethyl acetate: 2.60 g (70%); mp 256–258 °C; yellow crystals; IR 2850 (br), 1680 cm^{-1}; UV 305, 278, 240, 222 nm; ^{1}H NMR δ 10.5 (br s, 2 H, OH), 8.54 (s, 1 H, thiophene), 2.48 (CH_3); M$^+$ 186. Anal. Calcd for $C_7H_6O_4S$: C, 45.16; H, 3.25; S, 17.22. Found: C, 45.23; H, 3.08; S, 16.80.

Methyl 5-Acetyl-4-hydroxy-3-thiophenecarboxylate (5). 5-Acetyl-4-hydroxy-3-thiophenecarboxylic acid (**4**, 1.86 g, 0.01 mol) in ether (25 mL) was treated with ethereal diazomethane (0.3 M, 35 mL, 0.011 mol) and stirred at room temperature for 1 h. Formic acid was added dropwise until excess diazomethane was destroyed, and the reaction mixture was diluted with methylene chloride (50 mL) and washed with water and brine. After treating the mixture with charcoal and sodium sulfate, evaporation gave a yellow solid, 1.74 g (82%). Recrystallization from ethyl acetate–hexanes gave pure yellow crystals: mp 120–121 °C; IR 3300, 1690, 1640 cm^{-1}; UV 305, 278, 240, 225 nm; ^{1}H NMR δ 10.8 (s, 1 H, OH), 8.16 (s, 1 H, thiophene), 3.94 (s, 3 H, CH_3O), 2.54 (s, 3 H, CH_3); M$^+$ 200. Anal. Calcd for $C_8H_8O_4S$: C, 47.99; H, 4.03; S, 16.02. Found: C, 47.99; H, 3.90; S, 16.00.

5-Acetyl-4-acetoxy-3-thiophenecarboxylic Acid (6). 5-Acetyl-4-hydroxy-3-thiophenecarboxylic acid (**4**, 2.69 g, 0.015 mol) was treated with acetic anhydride (5 mL) and concentrated sulfuric acid (1 drop) and stirred at ambient temperature overnight. The reaction was poured into water (50 mL), warmed on a steam bath, and then cooled to 5 °C. The tan solid was collected by filtration, 2.91 g (85%). Decolorization with charcoal and recrystallization from ethyl acetate–hexanes provided the analytical sample: mp 179.5–181 °C, as yellow crystals; IR 3000, 1785, 1725, 1640 cm^{-1}; UV 267, 222 nm; ^{1}H NMR δ 8.58 (s, 1 H, thiophene), 2.48 (s, 3 H), and 2.34 (s, 3 H, both CH_3); M$^+$ 228. Anal. Calcd for $C_9H_8O_5S$: C, 47.36; H, 3.54; S, 14.05. Found: C, 47.72; H, 3.56; S, 13.69.

Methyl 4-Hydroxy-3-thiophenecarboxylate (7). Methyl 4-acetoxy-3-thiophenecarboxylate (**3**, 100 g, 0.50 mol) and *p*-toluenesulfonic acid (1 g) were stirred overnight in methanol (300 mL), and the solvents were removed through a Vigreux column. Distillation of the residue provided the product as a water white solid: bp 79 °C (0.35 mmHg); mp 48.5–49.5 °C; 71.32 g (91%), which was recrystallized from hexanes; IR 3300, 1700 cm^{-1}; UV 285, 240, 203 nm; ^{1}H NMR δ 8.68 (s, 1 H, OH), 7.86 (d, 1 H), 6.36 (d, 1 H, both thiophene), 3.89 (s, 3 H, CH_3O); M$^+$ 158. Anal. Calcd for $C_6H_6O_3S$: C, 45.58; H, 3.83; S, 20.28. Found: C, 45.25; H, 3.72; S, 20.11.

Ethyl 4-Ethoxy-3-thiophenecarboxylate (8b). Methyl 4-acetoxy-3-thiophenecarboxylate (**3**, 50.0 g, 0.25 mol) or methyl 4-hydroxy-3-thiophenecarboxylate (**7**, 39.5 g, 0.25 mol) and concentrated sulfuric acid (4 mL) were refluxed for 3 days in ethanol (750 mL). After concentration to 200 mL total volume, the mixture was diluted with water (200 mL) and extracted with ether (5×). The combined organic layer was washed with 1 N sodium hydroxide (3×) and dried with brine and sodium sulfate. Concentration and distillation gave the product as a pale yellow liquid: bp 92–98 °C (0.1 mmHg); 38.9 g (78%); IR 1725 cm^{-1}; UV 285, 240, 205 nm; ^{1}H NMR δ 7.96 (d, 1 H), 6.25 (d, 1 H, both thiophene), 4.20 (dq, 4 H, CH_2), 1.40 (dt, 6 H, CH_3); M$^+$ 200. Anal. Calcd for $C_9H_{12}O_3S$: C, 53.98; H, 6.04; S, 16.01. Found: C, 53.78; H, 6.28; S, 16.03.

Methyl 4-Methoxy-3-thiophenecarboxylate (8a). Methyl 4-hydroxy-3-thiophenecarboxylate (**7**, 4.74 g, 0.03 mol) in ether (50 mL) was treated with ethereal diazomethane (0.3 M, 100 mL, 0.03 mol) overnight at room temperature. The solution was concentrated and retreated with diazomethane twice. Finally, the organic solution was washed with 1 N sodium hydroxide, water, and brine, dried over sodium sulfate, and concentrated to a pale yellow solid, 1.62 g (32%). Recrystallization from hexanes gave the analytical sample: mp 68–70 °C; IR 1715 cm^{-1}; UV 285, 240, 205 nm; ^{1}H NMR δ 8.00 (d, 1 H), 6.30 (d, 1 H, both thiophene), 3.87 (d, 6 H CH_3O); M$^+$ 172. Anal. Calcd for $C_7H_8O_3S$: C, 48.78; H, 4.68; S, 18.62. Found: C, 48.95; H, 4.51; S, 18.27.

4-Methoxy-3-thiophenecarboxylic Acid (10a). Methyl 4-methoxy-3-thiophenecarboxylate (**8a**, 10.00 g, 0.058 mol) was treated with a solution of potassium hydroxide (10 g) in methanol (200 mL)–water (25 mL) and refluxed for 2 h. After the mixture was cooled, concentrated to a volume of 50 mL, and acidified with

(10) Spagnolo, P.; Zanirato, P. *J. Org. Chem.* **1978**, *43*, 3539.
(11) Press, J. B.; Eudy, N. H.; Safir, S. R. manuscript in preparation.

5 N sulfuric acid, the product was extracted with methylene chloride (5×). The organic extract was treated with charcoal and sodium sulfate, concentrated to a volume of 100 mL, and treated with petroleum ether (100 mL). The first crop was collected, 7.12 g, as white crystals. After several additional crops were collected, the combined yield was 9.07 g (98%). The analytical sample was prepared by recrystallization from methylene chloride–petroleum ether as white crystals: mp 106–107.5 °C; IR 2950, 1680 cm^{-1}; UV 282, 238, 205 nm; ^1H NMR δ 8.15 (d, 1 H), 6.38 (d, 1 H, both thiophene), 7.25 (s, 1 H, OH), 3.95 (s, 3 H, CH_3); M^+ 158. Anal. Calcd for $C_6H_6O_3S$: C, 45.56; H, 3.82; S, 20.27. Found: C, 45.13; H, 3.96; S, 19.81.

4-Ethoxy-3-thiophenecarboxylic Acid (10b). Ethyl 4-ethoxy-3-thiophenecarboxylate (**8b**, 20.00 g, 0.10 mol) was reacted as above using aqueous ethanol as solvent. The combined yield of white crystalline product was 16.16 g (94%). The analytical sample was prepared from methylene chloride–petroleum ether: mp 106–107.5 °C; IR 1660 cm^{-1}; UV 282, 240, 203, nm; ^1H NMR δ 10.38 (s, 1 H, OH), 8.12 (d, 1 H), 6.36 (d, 1 H, both thiophene), 4.17 (q, 2 H, CH_2), 1.48 (t, 3 H, CH_3); M^+ 172. Anal. Calcd for $C_7H_8O_3S$: C, 48.82; H, 4.68; S, 18.62. Found: C, 48.76; H, 4.73; S, 18.62.

4-Ethoxy-3-thiophenecarboxamide (11b). Ethyl 4-ethoxy-3-thiophenecarboxylate (**8b**, 15 g, 0.075 mol) was treated with concentrated ammonium hydroxide (150 mL) in a tightly sealed flask with stirring for 3 days. The reaction proceeded with the development and disappearance of a pasty gel-like material to give a crystalline precipitate which was collected by filtration and dried in a vacuum oven, 11.60 g (92%). Recrystallization of the white product from methylene chloride–hexanes gave the pure product: mp 170.5–171.5 °C; IR 3400, 3150, 1660 cm^{-1}; UV 275, 238 nm; ^1H NMR δ 8.15 (d, 1 H), 6.83 (d, 1 H, both thiophene), 4.26 (q, 2 H, CH_2), 1.53 (t, 3 H, CH_3); M^+ 171. Anal. Calcd for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18; S, 18.73. Found: C, 48.96; H, 5.30; N, 8.14; S, 18.72.

4-Methoxy-3-thiophenecarboxamide (11a). Methyl 4-methoxy-3-thiophenecarboxylate (**8a**, 3.44 g, 0.02 mol) was treated with concentrated ammonium hydroxide (50 mL) as above for 2 days. The crystalline precipitate (2.80 g, 89%) was recrystallized from methylene chloride for the analytical sample to give white crystals: mp 122.5–123 °C; IR 3450, 1670, 1655 cm^{-1}; UV 275, 237, 205 nm; ^1H NMR δ 8.10 (d, 1 H), 6.34 (d, 1 H, both thiophene), 7.20, 6.40 (br d, 2 H, NH_2), 3.92 (s, 3 H, CH_3); M^+ 157. Anal. Calcd for $C_6H_7NO_2S$: C, 45.84; H, 4.46; N, 8.91; S, 20.40. Found: C, 45.93; H, 4.33; N, 8.87; S, 20.54.

4-Ethoxy-3-thiophenecarboxylic Acid Hydrazide (12). Ethyl 4-ethoxy-3-thiophenecarboxylate (**8b**, 8.00 g, 0.04 mol) was refluxed with hydrazine hydrate (5 mL) in ethanol (25 mL) overnight; the reaction mixture was quenched with water (50 mL) and extracted with methylene chloride (5×). After drying the mixture with sodium sulfate, concentration gave a white solid product, 7.20 g (97%), which was recrystallized from methylene chloride–petroleum ether for the analytical sample: mp 104.5–105.5 °C; IR 3300, 1650 cm^{-1}; UV 275, 240 nm; ^1H NMR δ 8.49 (br s, 1 H, NH), 8.07 (d, 1 H), 6.30 (d, 1 H, both thiophene), 4.12 (q), 4.09 (s, 4 H, CH_2, NH_2), 1.47 (t, 3 H, CH_3); M^+ 186. Anal. Calcd for $C_7H_{10}N_2O_2S$: C, 45.14; H, 5.41; N, 15.04; S, 17.22. Found: C, 45.01; H, 5.40; N, 15.09; S, 17.08.

5-Chloro-4-ethoxy-3-thiophenecarboxylic Acid (13). 4-Ethoxy-3-thiophenecarboxylic acid (**10b**, 5.15 g, 0.03 mol) was dissolved in chloroform (10 mL) and treated with sulfuryl chloride (2.7 mL, 0.03 mol) cautiously. After the exothermic reaction subsided, the reaction mixture was allowed to stand at room temperature and was filtered to provide the white crystalline product, 5.02 g (81%). Recrystallization from methylene chloride–petroleum ether provided the analytical sample: mp 127.5–129 °C; IR 1685 cm^{-1}; UV 270, 242, 208 nm; ^1H NMR δ 11.80 (br s, 1 H, OH), 7.98 (s, 1 H, thiophene), 4.24 (q, 2 H, CH_2), 1.42 (t, 3 H, CH_3); M^+ 208, 206. Anal. Calcd for $C_7H_7ClO_3S$: C, 40.68; H, 3.41; Cl, 17.16; S, 15.52. Found: C, 40.79; H, 3.40; Cl, 17.12; S, 15.70.

5-Bromo-4-ethoxy-3-thiophenecarboxylic Acid (14). 4-Ethoxy-3-thiophenecarboxylic acid (**10b**, 5.15 g, 0.03 mol) in methylene chloride (50 mL) was cooled to 0 °C and treated with bromine (4.80 g, 0.03 mol) in methylene chloride (10 mL) over 0.5 h. The tan precipitate was collected (3.70 g, 49%), and the filtrate was diluted with petroleum ether to provide a second crop of crystals, 2.30 g, total yield 80%. The analytical sample was prepared by recrystallization from methylene chloride–petroleum ether: mp 137–139 °C; IR 1685 cm^{-1}; UV 270, 242, 209 nm; ^1H NMR δ 11.66 (br s, 1 H, OH), 8.03 (s, 1 H, thiophene), 4.16 (q, 2 H, CH_2), 1.40 (t, 3 H, CH_3); M^+ 252, 250. Anal. Calcd for $C_7H_7BrO_3S$: C, 33.48; H, 2.81; Br, 31.82; S, 12.77. Found: C, 33.71; H, 2.82; Br, 31.94; S, 12.82.

4-Hydroxy-3-thiophenecarboxylic Acid (15). 4-Ethoxy-3-thiophenecarboxylic acid (**10b**, 10.3 g, 0.06 mol) in methylene chloride (500 mL) was added to boron tribromide (30.0 g, 11.4 mL, 0.12 mol) in methylene chloride and allowed to stand overnight. The reaction mixture was treated with water (250 mL), stirred 0.5 h, and extracted with ether (3×). The combined organic layer was treated with charcoal and sodium sulfate and concentrated to provide the yellow crystalline product, 3.24 g (95%). If the reaction is run in an analogous manner on 4-methoxy-3-thiophenecarboxylic acid (**10a**), the product is obtained in 55% yield.

The analytical sample was prepared by crystallization from methylene chloride–petroleum ether: mp 145–145.5 °C; IR 3350, 1670 cm^{-1}; UV 295, 242, 205 nm; ^1H NMR δ 11.0 (br s, 1 H, OH), 9.25 (br s, 1 H, OH), 7.90 (d, 1 H), 6.34 (d, 1 H, both thiophene); M^+ 144. Anal. Calcd for $C_5H_4O_3S$: C, 41.66; H, 2.80; S, 22.24. Found: C, 41.50; H, 2.60; S, 22.47.

4-Acetoxy-3-thiophenecarboxylic Acid (16). 4-Hydroxy-3-thiophenecarboxylic acid (**15**, 5.03 g, 0.035 mol) was treated with acetic anhydride (15 mL) and concentrated sulfuric acid (1 drop). The mixture stood overnight, then was poured into water (150 mL) and warmed on a steam bath to decompose the excess anhydride. The aqueous layer was extracted with methylene chloride (3×); the combined organic layer was washed with water, treated with charcoal and sodium sulfate, and concentrated to give 5.03 g of a yellow gummy solid. Recrystallization from ethyl acetate–petroleum ether gave the yellow crystalline product: 2.44 g (38%); mp 173–175.5 °C; IR 1760, 1690 cm^{-1}; UV 235, 205 nm; ^1H NMR δ 8.09 (d, 1 H), 7.06 (d, 1 H, both thiophene), 2.22 (s, 3 H, CH_3); M^+ 186. Anal. Calcd for $C_7H_6O_4S$: C, 45.16; H, 3.25; S, 17.22. Found: C, 45.56; H, 3.42; S, 16.82.

4-Ethoxy-3-thiophenecarbonyl Azide (17). 4-Ethoxy-3-thiophenecarboxylic acid hydrazide (**12**, 7.42 g, 0.040 mol) was dissolved with difficulty in 3 N hydrochloric acid (100 mL) and acetic acid (150 mL), chloroform (150 mL) was added as a second layer, and the mixture was cooled to 5 °C. Sodium nitrite (2.79 g, 0.040 mol) in water (25 mL) was added dropwise maintaining the reaction temperaure below 8 °C. After warming the solution to ambient temperature, the organic layer was separated, washed with aqueous sodium bicarbonate (3×), dried over sodium sulfate, and concentrated without heat to give a yellow solid: 7.27 g (93%); mp 63–65 °C (gas evolution), which was storeable at 5 °C and was used for further reactions with no additional purification; IR 2170, 1695 cm^{-1}; ^1H NMR δ 8.20 (d, 1 H), 6.36 (d, 1 H, both thiophene), 4.15 (q, 2 H, CH_2), 1.50 (t, 3 H, CH_3).

***N*-(4-Ethoxy-3-thienyl)formamide (18).** 4-Ethoxy-3-thiophenecarbonyl azide (**17**, 1.97 g, 0.010 mol) was added portionwise to formic acid (97%, 5 mL) heated to boiling. Excess solvent was removed through a short-path still head, and the residue was distilled: 1.40 g (82%); bp 117 °C (0.08 mmHg); mp 105–108 °C. The distillate was recrystallized from hexanes to give a cream solid: mp 112–113 °C; IR 3300, 1660 cm^{-1}; UV 266, 210 nm; ^1H NMR δ 8.36 (s, 1 H, CHO), 7.70 (d, 2 H, thiophene and NH), 6.15 (d, 1 H, thiophene), 4.08 (q, 2 H, CH_2), 1.40 (t, 3 H, CH_3); M^+ 171. Anal. Calcd for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18; S, 18.73. Found: C, 49.00; H, 5.07; N, 8.08; S, 18.66.

***N*-(4-Ethoxy-3-thienyl)acetamide (19).** 4-Ethoxy-3-thiophenecarbonyl azide (**17**, 1.97 g, 0.010 mol) was refluxed in acetic anhydride (20 mL) for 3 h and cooled to 5 °C. Water was added (200 mL), and the mixture was warmed on a steam bath to decompose excess reagent. After being cooled the mixture was extracted with methylene chloride (3×), and the organic layer was washed with aqueous sodium bicarbonate, treated with charcoal and sodium sulfate, and concentrated to provide a brown solid residue (2.01 g) which was recrystallized from hexanes to give 1.00 g (55%) of pale yellow crystalline product: mp 104 °C; IR 3300, 1660 cm^{-1}; UV 263, 212 nm; ^1H NMR δ 7.70 (d, 1 H), 6.14 (d, 1 H, both thiophene), 7.56 (br s, 1 H, NH), 4.08 (q, 2 H, CH_2), 2.16

(s, 3 H, $CH_3C(O)$, 1.42 (t, 3 H, CH_3); M^+ 185. Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56; S, 17.31. Found: C, 51.88; H, 6.06; N, 7.35; S, 17.18.

Ethyl 4-Ethoxy-3-thiophenecarbamate (20). 4-Ethoxy-3-thiophenecarbonyl azide (**17**, 1.97 g, 0.010 mol) was refluxed overnight in ethanol (25 mL), filtered hot to remove a trace of insoluble material, and concentrated to dryness, and the residue was crystallized from petroleum ether at −78 °C to give the yellow crystalline product: 1.85 g, 86%; mp 62.5–63 °C; IR 3250, 1710 cm^{-1}; UV 260, 205 nm; ^1H NMR δ 7.32 (br s, 1 H), 6.14 (d, 1 H, both thiophene), 6.92 (br s, 1 H, NH), 4.10 (dq, 4 H, CH_2O), 1.35 (dt, 6 H, CH_3); M^+ 215. Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.21; H, 6.09; N, 6.51; S, 14.90. Found: C, 50.20; H, 5.92; N, 6.46; S, 15.18.

1,3-Bis(4-ethoxy-3-thienyl)urea (21). 4-Ethoxy-3-thiophenecarbonyl azide (**17**, 1.97 g, 0.010 mol) was refluxed in water (25 mL) for 1 h. After being cooled, the product was collected by filtration and dried in vacuo to give a yellow solid: 1.20 g (80%), which was purified by sublimation (bath 250 °C, pressure 0.05 mmHg); mp 298–299 °C; IR 3300, 1660 cm^{-1}; ^1H NMR δ 8.82 (s, 2 H, NH), 7.37 (d, 2 H), 6.54 (d, 2 H, all thiophene), 4.12 (q, 4 H, CH_2O), 1.40 (t, 6 H, CH_3). Anal. Calcd for $C_{13}H_{16}N_2O_3S_2$: C, 49.98; H, 5.16; N, 8.97; S, 20.53. Found: C, 50.03; H, 5.08; N, 8.63; S, 20.16.

***N*-(4-Hydroxy-3-thienyl)acetamide (22).** *N*-(4-Ethoxy-3-thienyl)acetamide (**19**, 2.96 g, 0.016 mol) in methylene chloride (75 mL) was added to boron tribromide (8.0 g, 3.1 mL, 0.032 mol) in methylene chloride (30 mL) and stirred overnight. After quenching the reaction with water (50 mL) for 0.5 h, the layers were separated, and the aqueous layer extracted with ether (2×). The organic layer was filtered through magnesium silicate and eluted with ethyl acetate which provided, after concentration, 1.03 g (41%) of a tan solid. The analytical sample was prepared by sublimation: mp 148.5–149 °C as a yellow crystalline solid; IR 3000, 1660 cm^{-1}; UV 266, 215 nm; ^1H NMR δ 9.70 (br s, 1 H, OH), 9.10 (br s, 1 H, NH), 7.31 (d, 1 H), 6.18 (d, 1 H, both thiophene), 2.11 (s, 3 H, CH_3); M^+ 157. Anal. Calcd for $C_6H_7NO_2S$: C, 45.54; H, 4.49; N, 8.91; S, 20.40. Found: C, 45.83; H, 4.52; N, 8.93; S, 19.92.

4-Ethoxy-3-thiopheneamine (23). A mixture of 15.4 g (0.09 mol) of *N*-(4-ethoxy-3-thienyl)formamide (**18**) in 50 mL of 2 N ethanolic hydrogen chloride and 90 mL of ethanol was refluxed for 2 h and filtered, and the filtrate was evaporated. Water was added to the residue, and the solution was cooled and made alkaline with 5 N sodium hydroxide. The mixture was extracted with methylene chloride, the extracts were dried ($MgSO_4$) and filtered, and the filtrate was evaporated to give 12.7 g (98%) of the product as a dark amber oil. A 1-g sample was distilled to give a colorless liquid: bp 69 °C (0.4 mmHg); IR 3400, 3330 cm^{-1}; UV 270, 213 nm; ^1H NMR δ 5.98 (dd, 2 H, thiophene H), 3.93 (q, 2 H, CH_2), 3.60 (br s, 2 H, NH_2), 1.32 (t, 3 H, CH_3); M^+ 143. Anal. Calcd for C_6H_9NOS: C, 50.34; H, 6.34, N, 9.79; S, 22.36. Found: C, 49.92; H, 6.49; N, 9.93; S, 22.39.

Bis(4-ethoxy-3-thienyl)amine (24). 4-Ethoxy-3-thiopheneamine (0.5 g, 0.0035 mol) was heated at 135–140 °C for 28 h, at which time no more starting amine was present by TLC analysis. The mass was cooled, dissolved in CH_2Cl_2, and filtered through a cake of magnesium silicate. The filtrate was evaporated to give 0.3 g (60%) of the solid product. The pure sample melted at 131–133 °C: IR 3350 cm^{-1}; UV 282, 215 nm; ^1H NMR δ 9.50 (br s, 1 H, NH), 6.51 (d, 2 H), 6.18 (d, 2 H, both thiophene), 4.08 (q, 4 H, CH_2), 1.35 (t, 6 H, CH_3); M^+ 269. Anal. Calcd for $C_{12}H_{15}NO_2S_2$: C, 53.50; H, 5.61; N, 5.20; S, 23.81. Found: C, 53.50; H, 5.55; N, 5.22; S, 23.17.

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Stereochemistry and Base-Catalyzed Rearrangement of 9-Phenylthioxanthene-*N*-(*p*-toluenesulfonyl)sulfilimine

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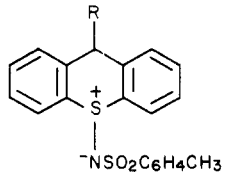
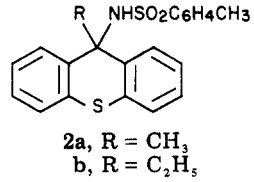
cis- and *trans*-9-phenylthioxanthene-*N*-(*p*-toluenesulfonyl)sulfilimines were synthesized. The stereochemical assignment was made by careful examination of the NMR spectra and thermodynamic considerations. The sulfilimines underwent base-catalyzed rearrangement to 9-(*N*-*p*-toluenesulfonamido)-9-phenylthioxanthene.

In a previous publication[1] we reported the base-catalyzed rearrangement of *cis*- and *trans*-9-alkylthioxanthene-*N*-(*p*-toluenesulfonyl)sulfilimines (**1**) to 9-alkyl-9-(*N*-*p*-toluenesulfonamido)thioxanthenes (**2**). The rate of the rearrangement was found to be markedly affected by the stereochemistry of the starting sulfilimines as well as by the steric bulk of the 9-alkyl group. It was of interest in this connection to synthesize *cis*- and *trans*-9-phenylthioxanthene-*N*-(*p*-toluenesulfonyl)sulfilimines in order to see the effect of the 9-phenyl substituent on the rate of the rearrangement as compared with the rate of the 9-alkyl derivatives **1**.



1a, R = CH_3
b, R = C_2H_5



2a, R = CH_3
b, R = C_2H_5

Results and Discussion

Reaction of 9-phenylthioxanthene (**3**) with *O*-mesitylenesulfonylhydroxylamine (MSH)[2] gave a mixture

(1) Tamura, Y.; Nishikawa, Y.; Muka, C.; Sumoto, K.; Ikeda, M.; Kise, M. *J. Org. Chem.* **1979**, *44*, 1684.

(2) Tamura, Y.; Matsuchima, H.; Minamikawa, J.; Ikeda, M.; Sumoto, K. *Tetrahedron* **1975**, *31*, 303.

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