reduction and at 0° for the acrylate reduction. Electrolyses in which [olefin] ≠ 0 were run to less than 20% conversion of the initial activated olefin charged to the catholyte so as not to significantly lower the olefin concentration below its desired initial concentration in the cell. A constant-current power supply was employed for these electrolyses.

Bisactivated Olefins. A solution of the olefin (0.015 mol) in acetonitrile was gradually added to the catholyte while potentiostating at −2.2 V (sce). The electrolyses were discontinued when the final current had decayed to the background current observed for carbon dioxide reduction.

Work-Up and Analysis of Catholyte. The products of electrocarboxylation were converted to their methyl esters by treatment with excess methyl iodide (*cf.* footnote *b* of Table II). The acetonitrile and excess methyl iodide were removed and the organic products were separated from the electrolyte by benzene–water extraction. If authentic samples were available, analyses were done directly on the benzene-soluble material by glc (internal standards or known addition methods) using either a 6 ft × 0.125 in. S.S. 3% OV-101 on Chromosorb W (80–100 mesh) or 8 ft × 0.125 in. S.S. 3% OV-17 on Gas-Chrom Q (60–80 mesh) column. Products for which authentic samples were not available were isolated and characterized as described below. Products so obtained were subsequently used for yield determinations by glc.

Isolation and Identification of Products. The relevant analytical data for new compounds obtained during this study are shown in Table V.

Hexamethyl 1,1,2,3,4,4-Butanehexacarboxylate (2). The residue from the benzene extract of the dimethyl maleate electrolysis was taken up in hot methanol; **2** (mp 136–137°) precipitated upon cooling.

Dimethyl [2,3-bis(methoxycarbonyl)cyclopentyl]malonate (9) was isolated by column chromatography (neutral Al_2O_3–benzene) of the benzene-soluble products obtained from the electrolysis of dimethyl 2,6-octadiene-1,8-dioate (**8**, n = 2). Attempts to distil the viscous product resulted in decomposition.

Tetramethyl 1,2-cyclopentylenedimalonate (10) was separated from the starting material by column chromatography (neutral Al_2O_3–benzene) of the benzene-soluble residue obtained from the electrolysis of dimethyl 2,7-nonadiene-1,9-dioate (**8**, n = 3). Attempts to distil the viscous product resulted in decomposition.

Hexamethyl 1,1,2,7,8,8-octanehexacarboxylate (12) was isolated as a solid by treating the benzene-soluble residue from the electrolysis of dimethyl 2,8-decadiene-1,10-dioate (**8**, n = 4) with ice-cold ether (mp 136–137° from methanol).

Tetramethyl 1,1,2,8-Octene-7-tetracarboxylate (11). The ether-soluble residue remaining after precipitation of **12** was adsorbed onto a column of neutral Al_2O_3. Benzene elution gave unreduced **8**, (n = 4) and **11**, respectively; **11** is a viscous liquid which decomposed upon attempted distillation.

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Registry No.—**2**, 40853-30-3; **8** (n = 2), 4756-84-7; **8** (n = 3), 52002-95-6; **8** (n = 4), 52002-96-7; **9**, 52002-97-8; **10**, 52002-98-9; **11**, 52002-99-0; **12**, 52003-00-6; dimethyl maleate, 624-48-6; methyl acrylate, 96-33-3; tetramethyl 1,1,3,4-butanetetracarboxylate, 52003-01-7.

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Reactivity of Benzo[*b*]thiophene in Electrophilic Reactions as Determined from Solvolysis Rates[1]

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Electrophilic replacement constants, σ_{Ar}^+, have been obtained for all positions of benzo[*b*]thiophene. The σ_{Ar}^+ values were defined from rate constants for the solvolysis of the six isomeric 1-(benzo[*b*]thienyl)ethyl chlorides in 80% ethanol–water. The positional order of reactivity in the benzo[*b*]thiophene ring was determined to be 3 > 2 > 6 > 5 > 4 > 7. All positions are more reactive than benzene.

Recent studies in these laboratories have determined relative reactivities of several heteroaromatic systems in an "electrophilic side-chain reaction," [3] the solvolysis of 1-arylethyl derivatives.[4–7] A correspondence between solvolytic reactivity and reactivity in electrophilic aromatic substitutions is expected because of the similar electron deficiency developed in the aromatic system in the two types of reactions. In this paper we extend our studies of side-chain reactivity to the benzo[*b*]thiophene ring system and compare the results to literature data concerning the reactivity of benzo[*b*]thiophene in electrophilic reactions.

Aromatic reactivity data can be conveniently generalized by defining σ_{Ar}^+ values for use in the modified Hammett equation introduced by Brown.[8] For the particular electrophilic reaction being considered, a ρ value for the reaction is established from the rate data for substituted benzenes and then σ_{Ar}^+ constants are defined for aromatic systems from rate data obtained under the same conditions. We refer to σ_{Ar}^+ values as "replacement σ^+ values" [9] or "electrophilic replacement constants," rather than "substituent constants," because they signify replacement of the entire benzene ring by another aromatic system instead of the substitution of the aromatic system for one of the phenyl hydrogens. In addition to our studies,[4–7] this approach has been applied to aromatic hydrocarbons by Streitwieser,[10] and to heteroaromatic systems by Hill, *et al.*,[11] by Taylor,[12] by Marino,[13] and by Baker, Eaborn, and Taylor.[14]

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EXPERIMENTAL SECTION[29]

5-(2'-Methylbenzylidene)rhodanine.- o-Methylbenzaldehyde and rhodanine were combined according to the procedure of Chakrabarti, Chapman, and Clarke[30] to give a 94% yield of 5-(2'-methylbenzylidene)rhodanine: mp 202.5-203.5°; nmr (acetone) δ 7.42 (s [broadened at base], 4, ArH), and 7.86 (s, 1, ArCH) (the peak due to $ArCH_3$ is obscured by the acetone peak and its sidebands, and the NH peak could not be detected); UV (95% ethanol) λ_{max} mμ/ε: 373/25,800; 274/6200; and 235(sh)/7250.

Anal. Calcd for $C_{11}H_9NOS_2$: C, 56.14; H, 3.86; N, 5.95; S, 27.25. Found: C, 55.97; H, 3.70; N, 5.88; S, 27.04.

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α-(2-Methylphenyl)-α-mercaptoacrylic Acid.- This procedure is that used by Julian and Sturgis for similar compounds.[31] A suspension of 5-(2'-methylbenzylidene)rhodanine (43.95 g, 0.187 mol) in aqueous sodium hydroxide (10% w/w, 300 ml) was heated on the steam bath for 30 min. The solution was cooled to 10° and was acidified rapidly by the addition of cold 3 N hydrochloric acid (250 ml). The odor of hydrogen sulfide was apparent after acidification. The creamy white precipitate was filtered, washed with water, and dried to give 29.51 g (81%) α-(2-methylphenyl)-α-mercaptoacrylic acid: mp 115-124° (the broad mp range is probably the result of the product existing as a mixture of the cis and trans isomers[32]); nmr ($CDCl_3$) approximate peak areas are given relative to the area of 3 assigned to the CH_3 peak; exact assignments were not made for all peaks because the product was probably a mixture of isomers) δ 2.33 (s [with broad base and shoulder due possibly to a second peak], 3, CH_3), 4.23 (b, 1, SH), 7.22 (m, 3.5), 7.56 (m, 1), 7.97 (s, 1, α-H), and 9.97 (b, 1, CO_2H).

The product was used without further purification in the preparation of 4-methylbenzo[b]thiophene-2-carboxylic acid.

4-Methylbenzo[b]thiophene-2-carboxylic Acid.- This procedure is patterned after the synthesis of Campaigne and Cline of benzo[b]thiophene-2-carboxylic acid.[33] Crude α-(2-methylphenyl)-α-mercaptoacrylic acid (28.00 g, 0.144 mol) was added to a solution of iodine (146 g, 0.576 mol) in nitrobenzene (500 ml) at 190°. The mixture was stirred vigorously for one min, and then was quickly cooled in an ice bath. The product was extracted with dilute sodium hydroxide, sodium bisulfite (110 g) was added, and the alkaline solution was acidified with hydrochloric acid. The precipitated product was filtered, washed with water, and dried to give as a gray powder 17.45 g (63%) of 4-methylbenzo[b]thiophene-2-carboxylic acid: mp 198-200°. The product was purified by sublimation (150°, 0.1 mm) and separately by crystallization from dichloromethane: mp 204-205° [lit.[34] mp 197-198°], nmr (acetone) δ 7.20 (broad d, 1, [overlapping with H-C_6], H-C_5), 7.37 (t, 1, $J_{5,6} \approx J_{6,7} \approx$ 7 Hz, H-C_6), 7.69 (dd, 1, $J_{6,7}$ = 7 Hz and $J_{5,7}$ = 1.5 Hz, H-C_7), 8.15 (s, 1, H-C_3), and 8.43 (b, 1, CO_2H)); nmr (nitrobenzene) δ 2.69 (s, CH_3).

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In view of the similarity between the impurities and the product, the separation of the naphthalene material from the benzo[b]thiophene material was delayed until a later step in the synthetic scheme where separation would be easier (benzo[b]thiophene-4-carboxaldehyde was purified).

5-Methylbenzo[b]thiophene (1).- (p-Tolylthio)acetaldehyde diethyl acetal was prepared from p-thiocresol and bromoacetaldehyde diethyl acetal in 80% yield, following the procedure of Elvidge and Foster:[35] bp 120-123°/1.0 mm [lit.[35] bp 168-169°/15 mm].

This cyclization procedure is based on the method of Bhattacharjee, et al.[36]

(p-Tolylthio)acetaldehyde diethyl acetal (20.00 g, 0.0833 mol) in dry chlorobenzene (150 ml) was heated to reflux. While stirring moderately, polyphosphoric acid (160 ml), maintained at 120-150°, was dripped in over 1 hr. The reaction mixture was cooled to 100°, and the chlorobenzene layer was decanted and saved. Water (150 ml) was dripped slowly into the hot acid layer while stirring vigorously. After cooling to 70°, benzene (80 ml) was added. The mixture was stirred vigorously to mix the layers. The benzene layer was decanted, and the extraction was repeated in a separatory funnel. The chlorobenzene and benzene layers were combined, dried ($MgSO_4$), filtered, and the solvents were evaporated under reduced pressure. The residue was distilled to give 9.53 g (77%) 5-methylbenzo[b]thiophene: bp 66-67°/0.6 mm; mp 35-36° [lit.[37] mp 37-38°].

6-Methylbenzo[b]thiophene.- (m-Tolylthio)acetaldehyde acetal was prepared from m-thiocresol and bromoacetaldehyde diethyl acetal in 90% yield, following the procedure of Elvidge and Foster:[35] bp 115-118°/0.8 mm [lit.[35] bp 164-166°/13 mm].

(m-Tolylthio)acetaldehyde diethyl acetal was used in the cyclization procedure described for 1, resulting in an 87% yield of a mixture of the 6- and 4-methylbenzo[b]thiophenes: bp 79-81°/0.8 mm. Nmr analysis showed two methyl peaks, at δ 2.35 and 2.49, indicating a product mixture of 68% 6-methylbenzo[b]thiophene and 32% 4-methylbenzo[b]thiophene, respectively. After one crystalli-

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zation from petroleum ether, the mixture was enriched to 97% 6-methylbenzo[b]thiophene. A number of successive recrystallizations, and reworkings of the filtrates, gave pure 6-methylbenzo[b]thiophene: mp 43.2-44° [lit.[35] mp 42-43°].

7-Methylbenzo[b]thiophene.- (o-Tolylthio)acetaldehyde dimethyl acetal was prepared from o-thiocresol and bromoacetaldehyde dimethyl acetal in 91% yield, following the procedure of Elvidge and Foster:[35] bp 109-111°/0.5 mm [lit.[38] bp 155-160° (bath temp.)/6 mm].

(o-Tolylthio)acetaldehyde was used in the cyclization procedure described for 1, resulting in a 75% yield of 7-methylbenzo[b]thiophene: bp 56-57°/0.6 mm [lit.[35,38] bp 112°/6 mm].

Benzo[b]thiophene-5-carboxaldehyde (2).- The bromination step of this synthesis follows the method of Chapman, et al.[39] A solution of benzoyl peroxide (0.20 g) and 5-methylbenzo[b]thiophene (3.30 g, 0.0223 mol) in dry carbon tetrachloride (70 ml) was heated to reflux while being irradiated by a 250-W electric lamp. N-Bromosuccinimide (3.96 g, 0.0223 mol) was added to the boiling mixture in small portions during 20 min. The mixture was heated under reflux for an additional 90 min, cooled, and filtered from succinimide. The carbon tetrachloride was evaporated under reduced pressure. The crude 5-bromomethylbenzo[b]thiophene was crystallized once from mixed hexanes, yielding 3.60 g (71%).

A solution of the crude 5-bromomethylbenzo[b]thiophene (3.60 g, 0.0158 mole) in dioxane (40 ml) was heated under reflux with 2 N NaOH (40 ml) for 16 hr. After cooling, the solution was extracted with ether, and the combined ether extracts were washed with water three times, washed with 10% aqueous sodium chloride, dried ($MgSO_4$), and filtered. The ether was evaporated under reduced pressure to give 2.12 g (81%) of crude 5-hydroxymethylbenzo[b]thiophene.

A suspension of MnO_2/C[40] (22 g) in benzene (150 ml) was refluxed in an apparatus fitted with a Dean-Stark trap for 30 min to remove water. A solution of the crude 5-hydroxymethylbenzo[b]thiophene (2.12 g, 0.0128 mol) in benzene (30 ml) was added and the

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refluxing was continued for 2 hr. The mixture was then cooled and filtered. The solid residue was shaken with benzene and refiltered. The combined benzene solutions were washed with water, washed with 10% aqueous sodium chloride, dried ($MgSO_4$), and filtered. Evaporation of the benzene under reduced pressure gave 1.85 g (88%) of benzo[b]thiophene-5-carboxaldehyde. From the crude product by column chromatography on silica gel, using 5% benzene-hexanes as the eluent, a pure sample (1.34 g) of benzo[b]thiophene-5-carboxaldehyde was obtained: mp 56-57° [lit.[41] mp 57°] (from hexane).

Benzo[b]thiophene-6-carboxaldehyde.- 6-Methylbenzo[b]thiophene was used in the procedures described for the synthesis of 2, first producing 6-bromomethylbenzo[b]thiophene (71% crude yield), then 6-hydroxymethylbenzo[b]thiophene (80% crude yield), and finally benzo[b]thiophene-6-carboxaldehyde (82% crude yield). Treatment of the crude aldehyde by column chromatography on silica gel, first using 5% benzene-hexanes as the eluent and then 10% benzene-hexanes, gave a colorless product which was crystallized from mixed hexanes to yield a pure sample of benzo[b]thiophene-6-carboxaldehyde: mp 42.5-44° [lit.[41] mp 43°].

Benzo[b]thiophene-7-carboxaldehyde.- 7-Methylbenzo[b]thiophene was used in the sequence described for the synthesis of 2, first producing 7-bromomethylbenzo[b]thiophene (69% crude yield), then 7-hydroxymethylbenzo[b]thiophene (85% crude yield), and finally benzo[b]thiophene-7-carboxaldehyde (86% crude yield). Treatment of the crude aldehyde by column chromatography on silica gel, using 5% benzene-hexanes as the eluent, gave a colorless product which was crystallized from mixed hexanes to yield a pure sample of benzo[b]thiophene-7-carboxaldehyde as white crystals: mp 42-43.5° [lit.[41] mp 42-43°].

Benzo[b]-thiophene-4-carboxaldehyde.- The mixture of 4-methylbenzo[b]thiophene and methylnaphthalenes was oxidized by the procedure described for the synthesis of 2. Two recrystallizations of the aldehyde product mixture from mixed hexanes afforded a pure sample of benzo[b]thiophene-4-carboxaldehyde as yellow crystals: mp 33-34° [lit.[42] mp 34°].

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1-(2-Benzo[b]thienyl)ethanol.- A solution of 1.6 N n-butyllithium in hexane (46.6 ml, 0.0746 mol, Foote Mineral Co.) was added to a solution of benzo[b]thiophene (10.0 g, 0.0746 mol) in anhydrous ether (150 ml) at 0° under a nitrogen atmosphere in a flame-dried flask. The mixture was stirred at 0° for 6 hr, at which time the solution was cloudy and yellow. Acetaldehyde (4.18 ml, 0.0746 mole) in dry ether (30 ml) at 0° was rapidly injected into the reaction mixture, and stirring was continued for 1 hr without further cooling. Water (100 ml) containing NH_4Cl (10 g) was added, the mixture was shaken, the ether layer was removed, and the water layer was extracted three times with 50-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and the ether was evaporated under reduced pressure to give an orange-red oil. The oil was taken up in hot n-hexane, from which crystallized 1-(2-benzo[b]thienyl)ethanol (5.91 g, 44%) as yellow crystals: mp 55-58° [lit.[42] mp 58-58.3°].

1-(3-Benzo[b]thienyl)ethanol.- The procedure of Szmuszkovicz and Modest[43] was used to synthesize 3-bromobenzo[b]thiophene in 72% yield: bp 115-117° (5 mm) [lit.[38] bp 95° (1.5 mm)]. A solution of 1.6 N n-butyllithium in hexane (62 ml, 0.10 mol, Foote Mineral Co.), which had been precooled in a dry ice-acetone bath, was slowly added to a solution of 3-bromobenzo[b]thiophene (21.3 g, 0.10 mol) in anhydrous ether (200 ml), which was cooled by a dry ice-acetone bath around the flame-dried flask protected from moisture by a nitrogen atmosphere. After stirring the cooled solution for 20 min, acetaldehyde (6.9 ml, 0.20 mol) was injected by precooled syringe into the reaction mixture. Stirring was continued for 1 hr while the temperature was controlled by a dry ice-acetone bath. The reaction mixture was quenched with dilute ammonium chloride solution (100 ml). The aqueous and organic phases were separated and the aqueous layer was extracted with 50 ml of ether. The organic layers were combined, dried (Na_2SO_4), and the solvents were removed on the rotary evaporator. Distillation gave 1-(3-benzo[b]thienyl)ethanol as a pale yellow oil: bp 142-144° (2.0 mm); crystallization from mixed hexanes gave white crystals: mp 53.5-55° [lit.[21] mp 43-45°]; nmr ($CDCl_3$) δ 1.57 (d, 3, J = 6 Hz, $CHCH_3$), 2.43 (b, 1, OH), 5.10 (q, 1, J = 6 Hz, $CHCH_3$), 7.15-7.41 (m, 3, H-C_2, H-C_5, and H-C_6), and 7.62-7.87 (m, 2, H-C_4 and H-C_7).

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Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.19; H, 5.55; S, 17.78.

1-(5-Benzo[b]thienyl)ethanol (3).- A solution of 3 M methylmagnesium bromide in ether (5.11 ml, 0.014 mol, ALFA Inorganics) was rapidly syringed into a stirred solution of benzo[b]thiophene-5-carboxaldehyde (1.24 g, 0.0077 mol) in 15 ml of dry ether at 0° under a nitrogen atmosphere in a flame-dried flask. A white precipitate formed immediately. Stirring was continued for 2 hr without further cooling. Aqueous ammonium chloride was added, the mixture was shaken in a separatory funnel, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed with water, washed with aqueous sodium chloride, dried ($MgSO_4$), and filtered. Evaporation of the ether under reduced pressure gave 1.36 g (99%) of 1-(5-benzo[b]thienyl)ethanol. Nmr analysis indicated complete conversion to the alcohol, with no residual aldehyde or other products present: mp 72.5-74° (mixed hexanes); nmr ($CDCl_3$) δ 1.52 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.18 (b, 1, OH), 4.89 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.10-7.38 (m, 3, H-C_2, H-C_3, and H-C_6), 7.65 (H-C_4 peak overlapping upfield half of H-C_7 doublet), and 7.71 (d, 1, $J_{6,7} \approx$ 7 Hz, H-C_7).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.24; H, 5.89; S, 17.82.

The following alcohols were prepared from the corresponding aldehydes by the procedure described for 3:

1-(4-Benzo[b]thienyl)ethanol.- Yield 89%; mp 37-39° (mixed hexanes); nmr ($CDCl_3$) δ 1.48 (d, 3, J = 6 Hz, $CHCH_3$), 2.68 (b, 1, OH), 5.13 (q, 1, J = 6 Hz, $CHCH_3$), 6.98-7.40 (m, 4, H-C_2, H-C_3, and H-C_5), and 7.64 (dd, 1, $J_{6,7}$ = 6.5 Hz and $J_{5,7}$ = 2.5 Hz, H-C_7).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.18; H, 5.73; S, 17.72.

1-(6-Benzo[b]thienyl)ethanol.- Yield 100%; mp 35-36.5°

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(mixed hexanes); nmr ($CDCl_3$) δ 1.53 (d, 3, J = 6 Hz, $CHCH_3$), 1.93 (b, 1, OH), 4.95 (q, 1, J = 6 Hz, $CHCH_3$), 7.16-7.43 (m, 3, H-C_2, H-C_3, and H-C_5), 7.73 (d, 1, $J_{4,5} \approx$ 8-9 Hz [downfield half obscured by H-C_7 peak], H-C_4), and 7.82 (s, 1, H-C_7).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.11; H, 5.49; S, 17.98.

1-(7-Benzo[b]thienyl)ethanol.- Yield 100%; mp 67-68° (mixed hexanes); nmr ($CDCl_3$) δ 1.62 (d, 3, J = 6 Hz, $CHCH_3$), 2.17 (b, 1, OH), 5.19 (q, 1, J = 6 Hz, $CHCH_3$), 7.16-7.43 (m, 4, H-C_2, H-C_3, H-C_5, and H-C_6), and 7.63 (m, 1, H-C_4).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.31; H, 5.45; S, 18.12

1-(Benzo[b]thienyl)ethyl Chlorides.- The six isomeric 1-(benzo[b]thienyl)ethanols were converted to the chlorides for use in the solvolysis studies. The crude products were used without further purification to avoid possible decomposition in workup procedures. The following procedure for 1-(2-benzo[b]thienyl)ethyl chloride was typical.

Thionyl chloride (1.12 g, 0.0094 mol) in 5 ml of dichloromethane was added to a solution of 1-(2-benzo[b]thienyl)ethanol (1.39 g, 0.0078 mol) in dichloromethane (35 ml). The mixture was heated under reflux for 1 hr, and then cooled to room temperature. Sodium carbonate (1.0 g) and water (0.5 ml) were added, and stirring was continued for 10 min. Magnesium sulfate (ca. 1 g) was added for drying, the mixture was filtered, and the dichloromethane was removed on the rotary evaporator to yield 1.44 g of the crude product. Nmr analysis indicated that 75-80% of the alcohol had been converted to 1-(2-benzo[b]thienyl)ethyl chloride. New peaks in the nmr spectrum were assigned to the aliphatic protons of the chloride (peaks for the aromatic protons overlap inseparable with those from the unreacted alcohol): nmr ($CDCl_3$) δ 1.88 (d, 3, J = 6.5 Hz, $CHCH_3$) and 5.23 (q, 1, J = 6.5 Hz, $CHCH_3$).

Kinetic Procedures.- Solvolysis rates in 80% ethanol-20% water were measured in the static pH method described previously.[6] The first-order rate constants for the solvolyses are listed in Table II, with standard deviations for each kinetic run.

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Table II
Rate Constants for the Solvolysis in 80% Ethanol of 1-(x-Benzo[b]thienyl)ethyl Chlorides

Compd Solvolyzed	T,°C	10^4k, sec^{-1}
2-Benzo[b]thienyl	0.0	4.20±0.01; 4.23±0.01
	25.0	90.4±0.2; 90.5±0.2; 91.6±0.2
3-Benzo[b]thienyl	0.0	12.0±0.0; 12.2±0.0
	25.0	238±0; 240±1; 237±1; 238±1
4-Benzo[b]thienyl	25.0	3.29±0.03; 3.61±0.02; 3.58±0.02
	45.0	31.9±0.2; 32.1±0.3; 33.2±0.2
5-Benzo[b]thienyl	25.0	11.2±0.0
	25.1	12.3±0.0
	44.9	90.6±0.3
	45.0	91.9±0.2; 90.8±0.3
6-Benzo[b]thienyl	0.0	1.43±0.00; 1.39±0.01
	25.0	33.6±0.1; 33.4±0.1
7-Benzo[b]thienyl	25.0	0.513±0.0006; 0.494±0.0006
	44.9	5.03±0.03; 5.06±0.05

Table I
Solvolyses of 1-(Benzo[b]thienyl)ethyl Chlorides in 80% Ethanol–Water at 25°

Aryl group	k, sec^{-1}	σ_{Ar}^+	Registry no.
2-Benzo[b]thienyl	9.11×10^{-3}	−0.49	51830-42-3
3-Benzo[b]thienyl	2.37×10^{-2}	−0.56	51830-43-4
4-Benzo[b]thienyl	3.50×10^{-4}	−0.25	51830-44-5
5-Benzo[b]thienyl	1.12×10^{-3}	−0.34	51830-45-6
6-Benzo[b]thienyl	3.37×10^{-3}	−0.42	51830-46-7
7-Benzo[b]thienyl	5.06×10^{-5}	−0.11	51830-47-8

Table I presents the electrophilic replacement constants determined in the present study for all six of the benzo[b]thiophene positions to which a side chain may be attached. These constants were established from titrimetric rate measurements of the solvolysis in 80% ethanol–water of the six isomeric 1-(benzo[b]thienyl)ethyl chlorides. The first-order rate constants for the solvolyses at 25° are also listed in Table I. The defining ρ value for the reaction was −6.05.[15]

The negative values of the σ_{Ar}^+ constants in Table I indicate that all positions of the benzo[b]thiophene ring are more reactive than a single benzene position in this electrophilic reaction. The positional order of reactivity is 3 > 2 > 6 > 5 > 4 > 7.

Previous kinetic studies of benzo[b]thiophene in electrophilic reactions have been confined to the 2 and 3 positions. Very similar results to those reported here were found by Hill for the solvolysis of 1-(benzo[b]thienyl)ethyl acetates: σ_{Ar}^+ values of −0.46 and −0.54 for the 2 and 3 positions, respectively.[11] Eaborn found that acid cleavage of the 2- and 3-trimethylsilylbenzo[b]thiophenes proceeded at nearly the same rate, with the 3 position reacting 1.15 times faster than the 2 position; these rate measurements give σ_{Ar}^+ values of −0.33 and −0.34 for the 2 and 3 positions.[16] Similarly, the protodetritiation rates showed very little difference between the two positions, although the σ_{Ar}^+ constants are much more similar to those found here than are the protodetrimethylsilylation values; protodetritiation σ_{Ar}^+ constants are −0.61 and −0.62 for the 2 and 3 positions, respectively.[14] A Russian study of protodedeuteration also found little difference in reactivity of the two positions, with the 3 position the faster of the two.[17] A result at variance with the general rule of greater reactivity of the 3 position is the report of σ_{Ar}^+ values from the gas-phase thermolysis of 1-(benzo[b]thienyl)ethyl acetates as being −0.53 for the 2 position and −0.46 for the 3 position.[18] The only other report of greater reactivity of the 2 position over the 3 position concerns Friedel–Crafts isopropylation,[19] for which the anomalous order of reactivity may be explained in terms of rearrangement of the product.[20]

Electrophilic aromatic substitution reactions with benzo[b]thiophene occur predominantly at the 3 position.[20,21] The 3 position has often been reported to be the only position attacked in electrophilic reactions, but careful studies usually reveal the presence of other isomeric products in most reactions. The literature data are not entirely consistent in regard to the relative reactivities of the other positions in benzo[b]thiophene. A review of the literature by Chalvet, Royer, and Dermerseman[22] led them to conclude that the order of reactivity toward electrophiles was 3 ≥ 2 > 6 ≥ 5 ≫ (4,7), which is precisely the order determined from the solvolysis of 1-(benzo[b]thienyl)ethyl chlorides. In a comprehensive review of the literature of benzo[b]thiophene chemistry, Iddon and Scrowston stated that halogenation and acylation reactions usually give a mixture of the 2 and 3 isomers, with the 3 isomer predominating.[20] Nitration also gives the 3 isomer as the major product; however, nitration has been reported to occur at all the ring positions with the relative proportions of the products varying widely in different studies.[20,23-26] The most recent research, by Martin-Smith, *et al.*, indicated that separation of isomeric nitration products of benzo[b]thiophenes by chromatographic methods was incomplete;[26] such difficulties may have contributed to the inconsistencies in the literature.

In summary, the bulk of the data available in the literature agree on a qualitative level with the findings reported in Table I, that the 3 position is more reactive than the 2 position, and that the 3 position is the most reactive site in the benzo[b]thiophene ring. On a quantitative level, there is insufficient information to test the validity of the σ_{Ar}^+ values in linear free-energy relationships. Although Hill[11] concluded that there was no correlation between isomer ratios from electrophilic substitutions and the ratios expected from considering the ρ values for the reactions and the σ_{Ar}^+ values for the 2 and 3 positions of benzothiophene, more recent studies have indicated that the Extended Selectivity Treatment[27] may be profitably applied to thiophenes.[4,13] More recent discussion of the 2 and 3 positions of benzothiophene in this regard[28] indicate some nonlinearity, and therefore a lack of constancy in σ_{Ar}^+ values.

Registry No.—1, 14315-14-1; **2,** 10133-30-9; **3,** 51830-48-9; 5-(2′-methylbenzylidene)rhodanine, 50459-52-4; *cis*-β-(2-methylphenyl)-α-mercaptoacrylic acid, 7575-67-9; *trans*-β-(2-methylphenyl)-α-mercaptoacrylic acid, 51830-49-0; 4-methylbenzo[b]thiophene-2-carboxylic acid, 1735-13-3; 4-methylbenzo[b]thiophene, 14315-11-8; (*p*-tolylthio)acetaldehyde diethyl acetal, 51830-50-3; 6-methylbenzo[b]thiophene, 16587-47-6; (*m*-tolylthio)acetaldehyde diethyl acetal, 51830-51-4; 3-bromobenzo[b]thiophene, 7342-82-7; 7-methylbenzo[b]thiophene, 14315-15-2; (*o*-tolylthio)acetaldehyde dimethyl acetal, 51830-52-5; 5-bromobenzo[b]thiophene, 10133-22-9; 5-hydroxymethylbenzo[b]thiophene, 20532-34-7; benzo[b]thiophene-6-carboxaldehyde, 6386-80-7; 6-bromomethylbenzo[b]thiophene, 6179-30-2; 6-hydroxymethylbenzo[b]thiophene, 6179-28-8; benzo[b]thiophene-7-carboxaldehyde, 10134-91-5; 7-bromomethylbenzo[b]thiophene, 10133-24-1; 7-hydroxymethylbenzo[b]thiophene, 51830-53-6; benzo[b]thiophene-4-carboxaldehyde, 10133-25-2; 4-bromomethylbenzo[b]thiophene, 10133-19-4; 4-hydroxymethylbenzo[b]thiophene, 51830-54-7; 1-(2-benzo[b]thienyl)ethanol, 51868-95-2; benzo[b]thiophene, 95-15-8; acetaldehyde, 75-07-0; 1-(3-benzo[b]thienyl)ethanol, 20896-18-8; 1-(4-benzo[b]thienyl)ethanol, 51830-55-8; 1-(6-benzo[b]thienyl)ethanol, 51830-56-9; 1-(7-benzo[b]thienyl)ethanol, 51830-57-0.

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Nucleophilic Reactivity of Peptides toward 2-Acyloxy-*N*-ethylbenzamides. The Utility of Free Peptides as Nucleophiles in Amide Bond Forming Reactions

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The free peptides (Gly-L-Leu-Gly)$_n$, n = 1, 2, 4, and 8, have been found to react slowly but cleanly with DMSO solutions of the *N*-ethylsalicylamide esters of Z(Gly-L-Leu-Gly)$_n$, n = 1, 2, and 4, to yield the sequence polymers, Z(Gly-L-Leu-Gly)$_n$OH, n = 2, 4, 8 and 16. The virtues and limitations of peptide synthesis using suspensions of peptides as nucleophiles are described.

The most commonly encountered amide-forming process in peptide synthesis involves reaction of an activated acyl derivative with a peptide derivative bearing a free N terminus and a blocked C terminus. In certain circumstances, it has been possible to obtain reasonable yields of clean products for coupling reactions in which the C-terminal blocking group of the nucleophilic component is reduced to a simple salt,[1] although difficulties can arise from insolubility and the necessary high basicity of the reaction medium. The simplest possible coupling situation would combine an N-blocked, C-activated peptide with a free, unblocked peptide as nucleophile. In this paper, we demonstrate that high yields of pure products can indeed be obtained with this procedure, provided that certain key conditions are met.

Two serious problems arise if one attempts to employ an amino acid or a free peptide as a reactive amine nucleophile. For all solvents of the aprotic type, the solubility of

$$\underset{\text{crystal}}{\underset{1}{NH_3^+\!\!-\!\!-\!\!-CO_2^-}} \overset{K_1}{\rightleftharpoons} \underset{\text{solution}}{\underset{2}{NH_3^+\!\!-\!\!-\!\!-CO_2^-}} \overset{K_2}{\rightleftharpoons} \underset{\text{solution}}{\underset{3}{NH_2\!\!-\!\!-\!\!-CO_2H}}$$

amino acids and peptides is low, presumably because the strong crystal lattice forces can be compensated for only by a solvent of high dielectric constant which can serve as both hydrogen bond donor and acceptor; on the other hand, in protic solvents, solvated material is present essentially exclusively as the zwitterion **2**, and the magnitude of this effect is essentially independent of chain length.[2]

We were led to attempt the present study through the conjecture that solubility in dipolar aprotic solvents should be lowest for amino acids and should converge to a value characteristic of the particular amide backbone as the peptide size is increased, and through the further conjecture that species larger than dipeptides should be present in solution in dipolar aprotic solvents as the neutral species **3** and not as the zwitterion **2**. If these conjectures are correct, then aminolysis of reactive acyl species should be possible using suspensions of free peptides in solvents such as DMF or DMSO and should occur with increasing ease as one changes the peptide size from small to medium. Should such a procedure be realizable, its mildness and simplicity might prove important advantages when designing coupling reactions between fragments in the 6–12 size range.

1. Results with Gly-L-Leu-Gly Peptides. Since we had previously prepared the peptide Z(Gly-L-Leu-Gly)$_2$OH and found this substance to be readily characterizable,[3] the coupling, Z-Gly-L-Leu-Gly-X with Gly-L-Leu-Gly, seemed an appropriate initial experiment. The active acyl derivative was chosen to be an *N*-ethylsalicylamide ester, despite