

Synthesis of Substituted Thieno[2,3-*b*]pyrroles

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Received September 5, 1973

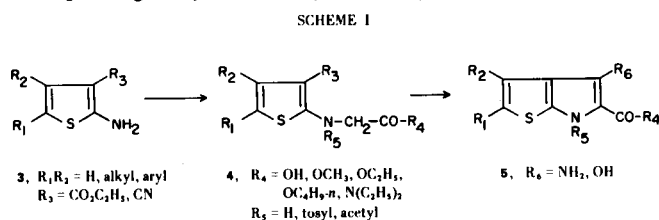
A relatively simple route for synthesis of substituted thieno[2,3-*b*]pyrroles from readily available starting material and data for structural assignment are reported.

In connection with the search for biologically active substances containing an indole nucleus, considerable interest has been given to synthesis of the isosteric thienopyrrole derivatives, particularly the thieno[3,2-*b*]pyrroles (1) (4). Less attention (5) has been given to the isomeric thieno[2,3-*b*]pyrrole (2), and most preparative procedures involve long reaction sequences from material which limit



the degree of structural variation for substituents. It is particularly desirable to have a reaction sequence which would facilitate introduction of substituents at position 4, the position corresponding to the seat of the side-chain in such naturally occurring 3-substituted indole derivatives as gramine, tryptamine and serotonin. The present paper describes results from a study to provide a relatively simple route for the production of functionalized thieno[2,3-*b*]pyrroles capable of being substituted for indole in biologically active compounds. The ready availability of starting materials should facilitate structure-activity studies.

The initial approach envisioned that readily available aminothiophenes (3) from Gewald procedure (6) would be amendable to suitable alkylation, and provide a side-chain which could undergo intramolecular Dieckmann or Thrope-Ziegler cyclization (Scheme I).



However, the aminothiophenes could not be directly alkylated with ethyl bromoacetate, chloro- or iodoacetonitrile, even in the presence of strong bases such as butyl lithium or sodium hydride. It was found more advantageous to prepare the tosylate, and alkylate the resulting sulfonamides (Table I). The low nucleophilicity of the amine function may result from their ability to act as enamines or dienamines (7,8). Alkylation of the tosylates of 3 was achieved without difficulty (Table II, 11-14) (Scheme II).

The tosylated diesters (11, 12) were subjected to conditions for Dieckmann condensation (9), employing a variety of bases (sodium hydroxide, sodium hydride, lithium triphenylmethane, sodium ethoxide, potassium *t*-butoxide, sodium diethylamide), but the only identifiable product isolated from the gums was either 3 or the tosylated material (7 or 9). Similar eliminations are reported (10) for analogous sulfonamides.

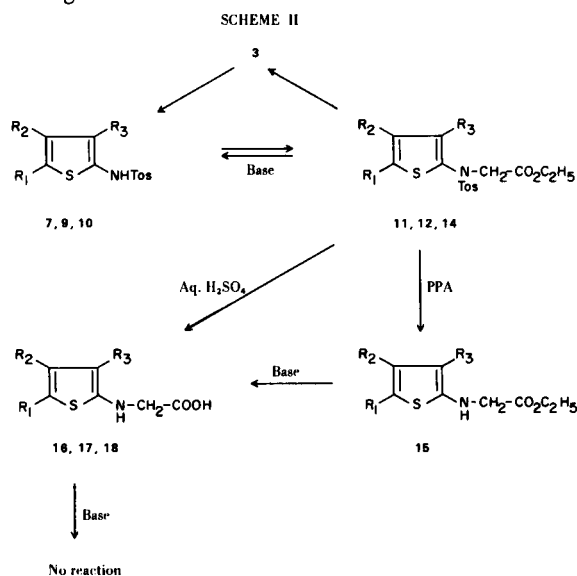


TABLE I
2-(*p*-Toluenesulfonamido)thiophenes

No.	R ₁	R ₂	R ₃	Yield (a) %	M.p., °C	Formula	Analysis					
							Calcd.			Found		
							C	H	N	C	H	N
6	CH ₃	CH ₃	CN	63	170-171	C ₁₄ H ₁₄ N ₂ O ₂ S ₂ (b)	54.90	4.58	9.15	54.98	4.61	9.19
7	CH ₃	CH ₃	CO ₂ C ₂ H ₅	88	91-93	C ₁₆ H ₁₉ NO ₄ S ₂	54.39	5.39	3.96	54.64	5.54	3.73
8	CH ₃	C ₂ H ₅	CO ₂ C ₂ H ₅	89	81-85	(c)						
9	H	C ₆ H ₅	CO ₂ C ₂ H ₅	64	97-99	C ₂₀ H ₁₉ NO ₄ S ₂ (d)	59.85	4.74	3.49	59.96	4.86	3.73
10	CH ₃	C ₆ H ₅	CO ₂ C ₂ H ₅	66	104-110°	(c)						

(a) Recrystallized from 95% ethanol. (b) *Anal.* Calcd. for S: 20.92. Found, 20.85. (c) Used directly without analysis. (d) *Anal.* Calcd. for S: 15.95. Found: 16.03.

Presence of a tosyl group probably facilitates the elimination reaction. Its removal with hot polyphosphoric or aqueous sulfuric acid-ethanol gave the diester (15). Detosylation in aqueous sulfuric acid gave the ester-acids (16-18). (It is assumed that the aliphatic ester has hydrolyzed. The aromatic ester group at position 3 exists in an intramolecular hydrogen bond (11) with the amino group, and apparently resisted hydrolysis.) Attempted cyclization of the diester (15) under various Dieckmann conditions gave only the ester-acid (16) upon workup. Similar attempts to cyclize the ester-acids (16-18) gave only recovered starting materials (Scheme II).

Since direct alkylation was not productive, reductive alkylation was attempted as an alternative procedure and found to be an effective method for *N*-alkylation of 3. Initially, the procedure of Taguchi and Westheimer (12), which employs molecular sieves as a dehydrating agent,

was utilized in the formation of various imines (Schiff bases) from *n*-butyl glyoxylate, methyl glyoxylate or glyoxylic acid hydrate. Reduction of the imine with sodium borohydride (or catalytically) resulted in monoalkylated derivatives (18-21) (Scheme III).

In addition, the monoalkylated ester-acid (18) obtained by this method confirmed the assumption for hydrolysis of the aliphatic ester noted above. The monoalkylated ester-acids (18, 21) could be obtained quite rapidly and in comparable yields by condensation of 3 and glyoxylic acid hydrate in the presence of sodium methoxide-methanol, followed by sodium borohydride reduction. These compounds (18, 21) were readily converted to the desired ester by the procedure of Harrison and coworkers (13).

It was not possible to isolate the *n*-butyl derivative (19) in a pure form, and reduction of the intermediate imine with excess sodium borohydride resulted in the production of 2-[*N*-(2-hydroxyethyl)amino]-3-cyano-4,5-dimethylthiophene (23). Brown and Rapoport (14) reported that aromatic and aliphatic esters can be reduced with excess sodium borohydride in methanol. Seki and coworkers (15) have also reported the synthesis of β -amino alcohols by the reduction of α -amino acid esters with sodium borohydride (16).

Attempts to cyclize the cyano-acid (21), or the cyano-esters (19, 20), by various conditions of the Dieckmann reaction gave results similar to those obtained with the ester-acids (16-18) or diester (15); i.e., recovery of starting material or hydrolysis of the aliphatic ester. Attempts to cyclize the *N*-acetyl derivative of 21 (25) met with similar failure, giving the starting material (25) or the deacetylated product (21).

Successful ring closure was, however, achieved when the cyano-ester (20), or the diester (26), was first acetylated and then subjected to the Dieckmann conditions. The cyclization proceeded quite satisfactorily to give 30 or 31; workup allowed recovery of any unreacted starting material. (As expected, the choice of solvent and reaction temp-

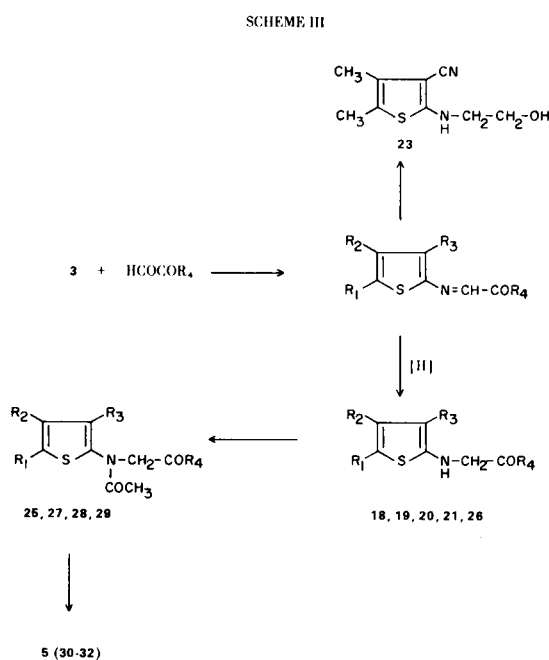
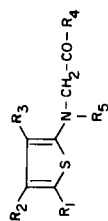


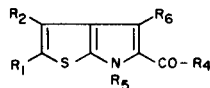
TABLE II
N-Alkylated 2-Aminothiophenes (4).



No.	R ₁	R ₂	R ₃	R ₄	R ₅	Yield %	M.p., °C	Recryst'd From (a)	Formula	Calcd.		Found			
										C	H	N	C	H	N
11	CH ₃	CH ₃	CO ₂ C ₂ H ₅	OC ₂ H ₅	Tosyl	91.5	89-96	A	C ₂₀ H ₂₅ NO ₆ S ₂ (b)	54.67	5.71	3.19	54.72	5.74	3.09
12	H	C ₆ H ₅	CO ₂ C ₂ H ₅	OC ₂ H ₅	Tosyl	81	82-85	A	C ₂₄ H ₂₅ NO ₆ S ₂	59.11	5.13	2.87	59.26	5.23	2.94
13	CH ₃	C ₂ H ₅	CO ₂ C ₂ H ₅	OC ₂ H ₅	Tosyl	68.4	86-89	A	C ₂₁ H ₂₇ NO ₆ S ₂	55.63	5.96	3.09	55.39	5.78	3.38
14	CH ₃	C ₆ H ₅	CO ₂ C ₂ H ₅	OC ₂ H ₅	Tosyl	56.2	110-112	A	C ₂₅ H ₂₇ NO ₆ S ₂	59.88	5.38	2.79	59.72	5.46	2.71
15	CH ₃	CH ₃	CO ₂ C ₂ H ₅	OC ₂ H ₅	H	86	62-64	A	C ₁₃ H ₁₉ NO ₄ S	54.74	6.67	4.91	54.76	6.86	4.70
16	CH ₃	CH ₃	CO ₂ C ₂ H ₅	OH	H	80	158-160	B	C ₁₁ H ₁₅ NO ₄ S (c)	51.36	5.84	5.45	51.55	5.89	5.41
17	H	C ₆ H ₅	CO ₂ C ₂ H ₅	OH	H	90	178-179.5	B	C ₁₅ H ₁₅ NO ₄ S (d)	59.00	4.92	4.59	59.11	4.87	4.57
18	CH ₃	C ₆ H ₅	CO ₂ C ₂ H ₅	OH	H	75-95	133-135	B or D	C ₁₆ H ₁₇ NO ₄ S	60.10	5.36	4.38	59.93	5.43	4.30
19	CH ₃	CH ₃	CN	OC ₄ H ₉	H	68									
20	CH ₃	CH ₃	CN	OCH ₃	H	59-87	84.5-85.5	C	C ₁₀ H ₁₂ N ₂ O ₂ S (e)	53.55	5.39	12.49	53.38	5.52	12.58
21	CH ₃	CH ₃	CN	OH	H	68-81	188-189	D	C ₉ H ₁₀ N ₂ O ₂ S	51.41	4.79	13.32	51.59	4.89	13.14
22	CH ₃	CH ₃	CONH ₂	OH	H	64	203-204	E	C ₉ H ₁₂ N ₂ O ₃ S	47.35	5.29	12.27	47.45	5.35	12.24
25	CH ₃	CH ₃	CN	OH	COCH ₃	67	153.5-154.5	C	C ₁₁ H ₁₂ N ₂ O ₃ S (f)	52.36	4.79	11.10	52.43	4.87	11.18
26	CH ₃	C ₆ H ₅	CO ₂ C ₂ H ₅	OC ₂ H ₅	H	(g)									
27	CH ₃	CH ₃	CN	OCH ₃	COCH ₃	69.5	111-112	C	C ₁₂ H ₁₄ N ₂ O ₃ S (h)	54.12	5.30	10.52	54.27	5.34	10.43
28	CH ₃	C ₆ H ₅	CO ₂ C ₂ H ₅	OC ₂ H ₅	COCH ₃	(g)									
29	CH ₃	CH ₃	CN	N(C ₂ H ₅) ₂	COCH ₃	67	68.5-69.5	E	C ₁₅ H ₂₁ N ₃ O ₂ S (i)	58.61	6.89	13.67	58.71	6.89	13.70

(a) A = 95% ethanol, B = acetone-water, C = benzene-cyclohexane, D = ethyl acetate-ligroine, E = methanol, F = ether. (b) *Anal.* Calcd. for S: 14.59. Found, 14.51. (c) *Anal.* Calcd. for S: 12.45. Found, 12.43. (d) *Anal.* Calcd. for S: 10.49. Found, 10.54; O, 21.07. (e) *Anal.* Calcd. for S: 14.29. Found, 14.45. (f) *Anal.* Calcd. for S: 12.70. Found, 12.81. (g) Used without isolation. (h) *Anal.* Calcd. for S: 12.04. Found, 12.13. (i) *Anal.* Calcd. for S: 10.43. Found, 10.55.

erature influenced yields.) Depending upon workup conditions, thieno[2,3-*b*]pyrroles could be obtained as the *N*-acylated or deacylated material. In one case, the cyano-diethylamide (**29**) was used for cyclization instead of the cyano-ester (**27**). Structural assignments were confirmed by elemental analysis, infrared, nmr and mass spectral data.



30. $R_1 = R_2 = \text{CH}_3$, $R_3 = \text{NH}_2$, $R_4 = \text{OCH}_3$, $R_5 = \text{CH}_2\text{CO}$
 31. $R_1 = \text{CH}_3$, $R_2 = \text{C}_6\text{H}_5$, $R_3 = \text{OH}$, $R_4 = \text{OC}_2\text{H}_5$, $R_5 = \text{H}$
 32. $R_1 = R_2 = \text{CH}_3$, $R_3 = \text{NH}_2$, $R_4 = \text{N}(\text{C}_2\text{H}_5)_2$, $R_5 = \text{CH}_2\text{CO}$

In summary, a relatively simple route has now been developed for synthesis of thieno[2,3-*b*]pyrroles from readily available starting materials, which facilitates considerable structural manipulation as required in structure activity relationship studies, and which possess functionality at position 4 to allow incorporation of the side-chains found in many biologically active indole derivatives. These studies will be the subject of future communications.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Hitachi Perkin-Elmer R-20A High Resolution nmr spectrometer using tetramethylsilane as internal reference. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia or by Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra were determined on a Perkin-Elmer 237B Grating Spectrophotometer using the potassium bromide technique. Mass spectra were determined by West Coast Technical Service, Inc., San Gabriel, California and the Mass Spectrometry Center, Department of Biochemistry, University of Georgia. Tlc were performed on Eastman chromatogram sheets, type 6060 (silica gel).

2-(*p*-Toluenesulfonamido)thiophenes (**6-10**, Table I).

The tosylated thiophenes were prepared by the routine procedure in pyridine solution (18). Physical data for new compounds given in Table I. In some cases (*e.g.*, **6**, **9**), it was necessary to maintain a reaction temperature below 10° to avoid formation of a ditosylated product.

3-Carboethoxy-2-[*N*-(carboethoxymethyl)-*p*-toluenesulfonamido]-4,5-dimethylthiophene (**11**, Table II).

Into a 2-l. three-necked round-bottomed flask, provided with a mechanical stirrer, a condenser, a nitrogen inlet tube and a separatory funnel was placed 12 g. (0.25 mole) of 50% sodium hydride-oil dispersion in 50-75 ml. benzene under nitrogen atmosphere. A benzene solution (800 ml.) of **6** (81 g., 0.023 mole) was added dropwise with stirring. After completion of the addition, the mixture was allowed to stir at room temperature for 2-3 hours, then at gentle reflux for 24 hours. The reaction mixture was chilled in an ice-bath and 200 ml. of ice water was added dropwise. After standing in the refrigerator, the resulting precipitate was filtered, washed with ice water and ether, and dried. The sulfonamido-salt was recrystallized from ethanol-water (2.5:1) in nearly quantitative yield; m.p. > 285° dec.

Into a 2-l. round-bottomed flask, provided with a condenser and a magnetic stirrer, was placed 45.6 g. (0.12 mole) of the sodium salt of **6**, 700 ml. of 95% ethanol and 120 ml. of water. The mixture was heated to dissolve the salt, cooled slightly, and treated with 23.4 g. (0.14 mole) of ethyl bromoacetate. The mixture was heated in an oil bath at 70-80° for 14 hours and filtered. The filtrate was diluted with 200 ml. of water, and the alcohol evaporated under reduced pressure, maintaining a bath temperature below 40-45°. The residue was chilled in an ice bath, filtered, washed with ice water and dried. Tlc (chloroform) of the analytical sample showed the product to be homogenous; ir (potassium bromide): 1754 (aliphatic ester), 1733 (aromatic ester), 1346 (tosyl), 1161 (tosyl) cm^{-1} .

3-Carboethoxy-2-[*N*-(carboethoxymethyl)-*p*-toluenesulfonamido]-4-phenylthiophene (**12**, Table II).

This compound was prepared by procedure given above. Recrystallization gave a homogenous material on tlc (chloroform); ir (potassium bromide): 1754, 1733, 1339, 1163 cm^{-1} .

3-Carboethoxy-2-[*N*-(carboethoxymethyl)-*p*-toluenesulfonamido]-4-ethyl-5-methylthiophene (**13**, Table II).

In a 1-l. round-bottomed flask was placed 0.1 mole of **8** (36.7 g.), 0.11 mole (5.94 g.) of sodium methoxide and 200 ml. of methanol. The stirred mixture was refluxed in an oil bath for 30 minutes. Ethyl bromoacetate (0.11 mole, 18.4 g.) in 50 ml. of methanol was added, and the solution refluxed for 18 hours. The reaction mixture was poured into 1.5 l. of cold water. Solvents were decanted from a gum which was covered with ether and filtered to remove some solid, m.p. 85-90°. After drying the ether filtrate (magnesium sulfate), it was concentrated to give an additional quantity of solid material, m.p. 76-83°. Recrystallization gave the analytical material; ir (potassium bromide): 1760, 1730, 1339, 1163 cm^{-1} .

3-Carboethoxy-2-[*N*-(carboethoxymethyl)-*p*-toluenesulfonamido]-5-methyl-4-phenylthiophene (**14**, Table II).

Prepared by procedure utilized for **13**; ir (potassium bromide): 1754, 1721, 1350, 1164 cm^{-1} .

3-Carboethoxy-2-[(carboethoxymethyl)amino]-4,5-dimethylthiophene (**15**, Table II).

Using the general detosylation procedure (18), 5 g. (0.0114 mole) of **11** was heated at 45-50° for 25 minutes in 10 ml. of ethanol-70% sulfuric acid (1:1). The mixture was cooled slightly and poured with vigorous stirring into 250 ml. of ice water. The resulting mixture was kept overnight in the refrigerator. The precipitate was collected and washed with cold water. Recrystallization gave the detosylated product; ir (potassium bromide): 1742 (aliphatic ester), 1653 (aromatic ester, hydrogen bonded) cm^{-1} .

3-Carboethoxy-2-[(carboxymethyl)amino]-4,5-dimethylthiophene (**16**, Table II).

In a 150 ml. Erlenmeyer flask, provided with a magnetic stirrer, 10 g. (0.022 mole) of **11** was suspended in 60 ml. of 75% sulfuric acid. This mixture was heated with stirring at 75-85° until starting material dissolved (2-4 hours), cooled and poured into 600 ml. of ice water. The precipitate was collected and dried in a desiccator to give 5.5 g. (95%). An analytical sample was recrystallized to give an 80% yield (homogenous on tlc, chloroform); ir (potassium bromide): 1736 (aliphatic acid), 1658 (aromatic ester, hydrogen bonded) cm^{-1} ; nmr (trifluoroacetic acid) (**16**): δ 1.48 (t, 3H, J = 7.0 Hz, CH₃ of ester), 1.85 (d, 3H, J = 7.5 Hz, CH₃ at C₅), 2.74 (s, 3H, CH₃ at C₄), 4.55 (q, 2H, J = 7.0 Hz, CH₂ of

ester), 4.60 (d, 2H, $J = 5.0$ Hz, $-CH_2-NH^\pm$), 4.90 (q, 1H, $J = 7.5$ Hz, H at C_5), 11.45 (broad, 1H, NH^+).

3-Carboethoxy-2-[(carboxymethyl)amino]-4-phenylthiophene (**17**, Table II).

Compound **17** was prepared (homogenous on tlc-chloroform) by the method given for **16**; ir (potassium bromide): 1724 (aliphatic acid), 1653 (aromatic ester, hydrogen bonded) cm^{-1} ; nmr (deuteriochloroform- $DMSO-d_6$) (**16**): δ 0.90 (t, 3H, $J = 7.0$ Hz, CH_3 of ester), 3.96 (d, 2H, $J = 6.0$ Hz, $-CH_2-CH_2-N$), 4.03 (q, 2H, $J = 7.0$ Hz, CH_2 of ester), 6.10 (s, 1H, H at C_5), 7.20 (s, 5H, phenyl at C_4), 8.07 (t, 1H, $J = 6.0$ Hz, NH), 10.66 (broad, 1H, COOH); nmr (trifluoroacetic acid) (**16**): δ 1.10 (t, 3H, $J = 7.0$ Hz, CH_3 of ester), 4.70 (d, 2H, $J = 5$ Hz, $-CH_2-NH^\pm$), 4.30 (q, 2H, $J = 7.0$ Hz, CH_2 of ester), 5.00 (s, 2H, H at C_5), 7.55 (s, 5H, phenyl at C_4).

3-Carboethoxy-2-[(carboxymethyl)amino]-5-methyl-4-phenylthiophene (**18**, Table II).

Obtained in quantitative yield from **14** by method given above; ir (potassium bromide): 1735 (aliphatic acid), 1660 (aromatic ester, hydrogen bonded) cm^{-1} ; nmr (trifluoroacetic acid) (**16**): δ 1.05 (t, 3H, $J = 7.0$ Hz, CH_3 of ester), 1.65 (d, 3H, $J = 7.5$ Hz, CH_3 at C_5), 4.30 (q, 2H, $J = 7.0$ Hz, CH_2 of ester), 4.75 (d, 2H, $J = 5$ Hz, $-CH_2-NH^\pm$), 5.40 (q, 1H, $J = 7.5$ Hz, H at C_5), 7.55 (m, 5H, phenyl at C_4).

Glyoxylate Esters.

Methyl glyoxylate and *n*-butyl glyoxylate were prepared according to the procedure of Wolf and Weijland (19) in near quantitative yields by oxidation of dimethyl and di-*n*-butyl *d*-tartrate, respectively, with lead tetracetate;

2-[(Carboxymethyl)amino]-3-cyano-4,5-dimethylthiophene (**21**, Table II).

Method A.

A solution of 2-amino-3-cyano-4,5-dimethylthiophene (**6**) (7.61 g., 0.05 mole), 12 g. 3A molecular sieves, glyoxylic acid hydrate (3.7 g., 0.05 mole), 5 drops of piperidine and 150 ml. of absolute ethanol was stirred overnight at room temperature. The system developed tan or orange coloration. The molecular sieves were removed by suction filtration and the filtrate collected. A 500 ml. pressure bottle was charged with the filtrate and 2.0 g. of 5% palladium on carbon. Reduction was achieved with 60 to 70 psi of hydrogen on a Parr low-pressure hydrogenation apparatus. Eighty percent (80%) of the theoretical amount of hydrogen was absorbed. The catalyst was removed by suction filtration and the ethanolic solution concentrated *in vacuo* to obtain the product. The crude product (7.15 g., 68%) was dissolved in 70 ml. of 10% sodium bicarbonate, reprecipitated with 5% hydrochloric acid and collected by suction filtration. The resultant crystals from recrystallization were homogenous on tlc with 95% ethanol ($R_f = 0.40$); ir (potassium bromide): 2205 (nitrile), 1710 (aliphatic acid) cm^{-1} ; nmr (deuteriochloroform): δ 2.0 (s, 3H, CH_3 at C_5), 2.1 (s, 3H, CH_3 at C_4), 3.85 (d, 2H, $J = 6.38$ Hz, $-NH-CH_2-$), 7.45 (t, 1H, $J = 6.38$ Hz, $-NH-CH_2-$), 12.5 (s, 1H, COOH).

Method B

A solution of 2-amino-3-cyano-4,5-dimethylthiophene (**6**) (1.52 g., 0.01 mole), glyoxylic acid hydrate (1.04 g., 0.015 mole) and sodium methoxide (0.81 g., 0.015 mole) in 100 ml. of absolute methanol was stirred at 65° for 30 minutes. After cooling to room temperature, the reaction was further cooled in an ice bath and the imine reduced with portionwise additions of sodium borohydride (0.56 g., 0.015 mole). (The color of the system changed from

a reddish-brown to a light yellow upon reduction.) Upon complete addition, the ice bath was removed and the mixture stirred for an additional 20 minutes. Methanol was removed *in vacuo*. The residue was dissolved in a saturated solution of sodium bicarbonate, filtered, and acidified with 18% hydrochloric acid. This method resulted in a yield of 1.70 g. (81%) and gave a product with an infrared spectrum and melting point identical to those of the product from Method A.

Compound **18** was also prepared by this method in 75% yield; ir (potassium bromide): 1735, 1660 cm^{-1} .

2-[(Carbomethoxymethyl)amino]-3-cyano-4,5-dimethylthiophene (**20**, Table II).

Method A.

The method of Taguchi and Westheimer (12) was utilized for imine (Schiff's base) formation. A mixture of 2-amino-3-cyano-4,5-dimethylthiophene (30.44 g., 0.20 mole), methyl glyoxylate (22.02 g., 0.25 mole) and 20 g. of 4A molecular sieves in anhydrous benzene was stirred at 35° for 15 minutes. Stirring was continued without heat for 14 hours resulting in a large amount of yellow precipitate. Benzene was removed *in vacuo* and the imine dissolved in absolute methanol (1200 ml). The mixture was stirred in an ice bath as sodium borohydride (9.25 g., 0.25 mole) was added over a 10 minute period. Upon complete addition, the ice bath was removed and the system was stirred for an additional 15 minutes. The molecular sieves were removed by filtration and the alcoholic solution poured onto 800 g. of ice. Precipitation occurred immediately. The crude product (26.7 g., 59.4%) was redissolved in hot methanol, treated with charcoal, and again poured onto ice (700 g.). The recrystallized product was homogenous on tlc (ethyl acetate, $R_f = 0.53$); ir (potassium bromide): 2200 (nitrile), 1740 (aliphatic ester) cm^{-1} , nmr (deuteriochloroform): δ 2.0 (s, 3H, CH_3 at C_5), 2.2 (s, 3H, CH_3 at C_4), 3.8 (s, 3H, CH_3O-), 4.0 (d, 2H, $J = 5.70$ Hz, $-NH-CH_2-$), 5.62 (t, 1H, $J = 5.70$ Hz, $-NH-CH_2-$).

Method B (13).

In a 500 ml. round-bottomed flask, a mixture of **21** (21.0 g., 0.10 mole), 350 ml. of methanol and 3 drops of concentrated sulfuric acid was refluxed for 22 hours with a Soxhlex extractor; thimble contained 70 g. of 3A molecular sieves. The methanol was concentrated *in vacuo*. This method resulted in a yield of 87%, and gave a product with infrared spectrum and melting point identical to those of **20** from Method A.

2-[(Carbobutoxymethyl)amino]-3-cyano-4,5-dimethylthiophene (**19**, Table II).

This ester was prepared from *n*-butyl glyoxylate and 2-amino-3-cyano-4,5-dimethylthiophene (**6**) by the same method as the methyl ester (**20**). The reddish-brown oil was not amenable to purification, even with column chromatography; ir (neat): 2200 (nitrile), 1735 (aliphatic ester).

2-[(2-Hydroxyethyl)amino]-3-cyano-4,5-dimethylthiophene (**23**).

The imine (Schiff's base) was prepared by the method of Taguchi and Westheimer (12) from *n*-butyl glyoxylate (19.25 g., 0.15 mole) and 2-amino-3-cyano-4,5-dimethylthiophene (15.22 g., 0.10 mole), which was reduced with sodium borohydride (12.95 g., 0.35 mole) in absolute methanol. Upon complete addition of the reducing agent (20 minutes), the mixture was stirred for an additional 30 minutes. The solution was poured over ice which resulted in the formation of a white precipitate. This precipitate was collected by suction filtration and air dried. The crude product (22.05 g., 90%) was recrystallized from benzene-cyclohexane

(homogenous on tlc, ethyl acetate, $R_f = 0.46$), m.p. 114-115°; ir (potassium bromide): 3365, 3205, 2890, 2180, 1550, 1070 cm^{-1} ; nmr (DMSO- d_6): δ 2.10 (s, 3H, CH_3 at C_5), 2.15 (s, 3H, CH_3 at C_4), 3.28 (t, 2H, $J = 5.48$ Hz, $-\text{NH}-\text{CH}_2-$), 3.67 (t, 2H, $J = 4.50$ Hz, $-\text{CH}_2-\text{CH}_2-\text{O}-$), 4.83 (broad s, 1H, OH), 7.15 (t, 1H, $J = 5.48$ Hz, $-\text{NH}-\text{CH}_2-$).

Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{OS}$: C, 55.10; H, 6.17; N, 14.28. Found: C, 55.28; H, 6.19; N, 14.43.

2-[*N*-(Carbomethoxymethyl)acetamido]-3-cyano-4,5-dimethylthiophene (**27**, Table II).

A solution of **20** (4.48 g., 0.02 mole) in 50 ml. of acetic anhydride was heated at 130-150° for 15 minutes, stirred at room temperature without heating for 2 hours, and poured into 500 ml. of ice and water. After 2 hours of stirring a light yellow oil was evident. The aqueous acid was extracted with ethyl acetate, the extracts dried, and the solvent removed *in vacuo*. The resulting crude precipitate (37 g., 69.5%) was recrystallized (homogenous on tlc, ethyl acetate, $R_f = 0.54$); ir (potassium bromide): 2240 (nitrile), 1745 (aliphatic ester), 1680 (amide carbonyl) cm^{-1} ; nmr (deuteriochloroform): δ 2.09 (s, 3H, acetyl CH_3), 2.28 (s, 3H, CH_3 at C_5), 2.39 (s, 3H, CH_3 at C_4), 3.80 (s, 3H, $\text{CH}_3\text{O}-$), 4.41 (s, 2H, $-\text{N}-\text{CH}_2-$).

2-[*N*-(Carboxymethyl)acetamido]-3-cyano-4,5-dimethylthiophene (**25**, Table II).

A suspension of **21** (16.8 g., 0.08 mole) in 250 ml. of acetic anhydride was heated on an oil bath at 135° for 15 minutes. (The system became quite dark.) The mixture was poured into water at room temperature and stirred for 4 hours. The yellow aqueous acid layer was decanted from a dark gummy residue which was also washed with 10% hydrochloric acid. The yellow aqueous layer from the reaction was combined with the 10% hydrochloric acid wash solution and extracted with diethyl ether and ethyl acetate. The extracts were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*, leaving an oily residue which smelled of acetic acid. The oily residue was dissolved in a saturated solution of sodium bicarbonate, filtered, acidified with 20% hydrochloric acid and extracted with ethyl acetate. After drying the extracts and concentrating *in vacuo*, the resulting viscous oil solidified on standing. The crude product (13.35 g., 67%) was recrystallized (homogenous on tlc, 95% ethanol, $R_f = 0.35$; ethyl acetate $R_f = 0.12$; chloroform, $R_f = 0.12$); ir (potassium bromide): 2225 (nitrile) 1725 (aliphatic acid), 1610 (amide carbonyl) cm^{-1} ; nmr (deuteriochloroform): δ 2.1 (s, 3H, acetyl CH_3), 2.25 (s, 3H, CH_3 at C_5), 2.40 (s, 3H, CH_3 at C_4), 4.40 (s, 2H, $-\text{N}-\text{CH}_2-$), 11.15 (s, 1H, $-\text{COOH}$).

3-Cyano-2-[*N*-(diethylaminocarbonylmethyl)acetamido]-4,5-dimethylthiophene (**29**, Table II).

A suspension of **25** (2.52 g., 0.01 mole) in 100 ml. of anhydrous benzene and thionyl chloride (1.80 g., 0.015 mole) was heated with stirring to 70° for one hour. After cooling the reaction mixture in an ice bath, diethylamine (2.2 g., 0.03 mole) in 10 ml. of anhydrous benzene was added dropwise to the system. Upon completion of the addition, the ice bath was removed and the viscous mixture was allowed to stir for 14 hours. A precipitate had formed (diethylamine hydrochloride), and was removed by suction filtration. The filtrate was washed with water, dried over magnesium sulfate, and the solvent removed *in vacuo*. A viscous, rust-colored oil resulted, which was purified by column chromatography using activated alumina. The light yellow oil was dried in vacuum desiccator over phosphorus pentoxide and solidified on standing. The solid (2.05 g., 67%) was washed with petroleum ether and recrystallized

from ethyl ether (homogenous on tlc, ethyl acetate, $R_f = 0.46$); ir (potassium bromide): 2220 (nitrile), 1680 and 1635 (amide carbonyls) cm^{-1} ; nmr (deuteriochloroform): δ 1.20 (t, 6H, $J = 6.76$ Hz, $\text{CH}_3\text{CH}_2\text{N}-$), 2.1 (s, 3H, acetyl CH_3), 2.25 (s, 3H, CH_3 at C_5) 2.36 (s, 3H, CH_3 at C_4), 3.49 (q, 4H, $J = 6.76$ Hz, $-\text{N}-\text{CH}_2-\text{CH}_3$), 4.48 (s, 2H, $-\text{N}-\text{CH}_2-\text{CO}-$).

3-Carbamyl-2-[(carboxymethyl)amino]-4,5-dimethylthiophene (**22**, Table II).

A solution of **21** (4.2 g., 0.02 mole) in 100 ml. of concentrated sulfuric acid was heated on a steam bath for 35 minutes with frequent shaking. The dark solution was allowed to stir without heating for 30 minutes and poured into 1-l. of ice water. No precipitate occurred and the mixture was extracted with ether and ethyl acetate. The extracts were dried (magnesium sulfate) and concentrated *in vacuo*, but failed to give any product. The aqueous acid layer was treated with 50% sodium hydroxide until precipitation was completed (about pH 3.5). This precipitate was dissolved in a saturated solution of sodium bicarbonate and acidified with 10% hydrochloric acid. The precipitate (2.70 g., 64%) was recrystallized (homogenous on tlc, methanol, $R_f = 0.12$), m.p. 203-204°; ir (potassium bromide): 1720 (aliphatic acid), 1635 (amide carbonyl) cm^{-1} ; nmr (DMSO- d_6): δ 2.14 (s, 6H, CH_3 at C_4 and C_5), 3.84 (s, 2H, $-\text{N}-\text{CH}_2-$), 6.73 (s, 2H, NH_2), 6.8-7.2 (broad s, 1H, $-\text{NH}-$), 11.7 (s, 1H, COOH).

6-*N*-Acetyl-4-amino-5-diethylcarbamyl-2,3-dimethylthieno[2,3-*b*]pyrrole (**32**).

Sodium hydride (2.11 g. of 57% oil dispersion, 0.05 mole) was washed with 100 ml. of anhydrous ethyl ether (2 x 50 ml.) while under nitrogen. Dry toluene (100 ml.) was added to the freshly washed sodium hydride followed by compound **29** (10.3 g., 0.0335 mole) in 50 ml. of toluene. The reaction was refluxed for 11 hours, after which it was stirred for 3 hours. The toluene solution was extracted with 150 ml. of 10% hydrochloric acid (6 x 25 ml.), dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give starting material (6.70 g.; 65%). The acid extract was made alkaline with 10% sodium hydroxide and produced a precipitate. The basic aqueous solution was extracted with ethyl acetate; the extract was then concentrated *in vacuo* producing more precipitate. The precipitate (2.30 g., 22.3%) was recrystallized from benzene-cyclohexane (homogenous on tlc, ethyl acetate $R_f = 0.55$), m.p. 258-259°; ir (potassium bromide): 3200 (broad), 2975, 2925, 1660, 1595, 1550, 1445, 1380, 1360, 1290, 1135, 1090, 760, 720, 650 cm^{-1} ; nmr (DMSO- d_6): δ 1.13 (t, 6H, $J = 7.13$ Hz, $\text{CH}_3-\text{CH}_2-\text{N}$), 2.06 (s, 3H, CH_3 at C_5), 2.13 (s, 3H, at C_4), 2.32 (s, 3H, acetyl CH_3), 2.4 (m, 4H, $J = 7.13$ Hz, $\text{CH}_3\text{CH}_2\text{N}$), 9.33 (broad s, 2H, NH_2); Mol. wt. (MS) Calcd. 307. Found 307.

Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$: C, 58.61; H, 6.86; N, 13.67; S, 10.43. Found: C, 58.86; H, 6.94; N, 13.49; S, 10.59.

6-*N*-Acetyl-4-amino-5-carbomethoxy-2,3-dimethylthieno[2,3-*b*]pyrrole (**30**).

The procedure used for the preparation of **32** was followed for production of **30**. The starting material (**27**) (0.6 g., 0.0023 mole) was refluxed for 12 hours in dry xylene in the presence of an excess of sodium hydride. The xylene was extracted with 10% hydrochloric acid, dried (magnesium sulfate), and removed *in vacuo*, resulting in starting material (0.14 g., 23.3%). The aqueous acid extract was made alkaline with 10% sodium hydroxide. The resulting precipitate (0.38 g., 63.4%) was recrystallized from benzene-cyclohexane (homogenous on tlc, ethyl acetate, $R_f = 0.49$), m.p. 150.5-151°; ir (potassium bromide): 3460, 3345, 2950, 1655, 1595, 1450, 1360, 1340, 1205, 1110, 1005, 756 cm^{-1} ; nmr

(deuteriochloroform): δ 2.32 (s, 6H, CH₃ at C₄ and C₅), 2.54 (s, 3H, acetyl CH₃), 3.39 (s, 3H, ester CH₃), 5.20-5.65 (broad s, 2H, NH₂); Mol. wt. (MS) Calcd. 266. Found 266.

Anal. Calcd. for C₁₂H₁₄N₂O₃S: C, 54.11; H, 5.30; N, 10.52; S, 12.04. Found: C, 54.19; H, 5.38; N, 10.45; S, 12.15.

5-Carboethoxy-4-hydroxy-2-methyl-3-phenylthieno[2,3-*b*]pyrrole (31).

In this procedure, **26** was prepared from **18** (10 g., 0.0313 mole) by the procedure given for **20**, Method B (13). The oily diester (**26**) was not isolated for characterization, but was acetylated directly by the procedure given for **27**. The crude acetylated diester (**28**), dissolved in 200 ml. of xylene, was placed in a 250 ml. three-necked round-bottomed flask, fitted with a dropping funnel, reflux condenser and nitrogen inlet. This solution was treated with 2 g. of 57% sodium hydride oil dispersion and heated under reflux and a nitrogen atmosphere for 18 hours. The dark solution, which contained a tan solid suspension, was treated dropwise with 50 ml. of 10 *N* sulfuric acid. After separation of the xylene layer, the aqueous phase was extracted with three 100 ml. portions of benzene, and the combined benzene-xylene extracts were dried (magnesium sulfate). Removal of the drying agent and concentration *in vacuo* gave 6.8 g. (72.2% from **18**). An analytical sample was prepared by recrystallization from chloroform-ligroine as tan flakes (homogenous on tlc, chloroform), m.p. 162-163°; ir (potassium bromide): 3310, 1650, 1525, 1510, 1410, 1345, 1250, 1175, 1125, 1025, 870 cm⁻¹; nmr (DMSO-*d*₆): δ 1.3 (t, 3H, J = 7.0 Hz, CH₃ of ester), 2.38 (s, 3H, CH₃ at C₅), 4.3 (q, 2H, J = 7.0 Hz, CH₂ of ester), 7.45 (m, 5H, phenyl at C₄), 8.4 (s, 1H, NH). 11.4 (s, 1H, OH); Mol. wt. (MS) Calcd. 301. Found: 301.

Anal. Calcd. for C₁₆H₁₅NO₃S: C, 63.77; H, 5.02; N, 4.56; S, 10.64. Found: C, 63.65, 63.72; H, 5.16, 5.12; N, 4.67, 4.66; S, 10.51.

Acknowledgement.

This work was supported by research grants MH-10673 and MH 16422 from the National Institutes of Health, U.S. Public Health Service, Bethesda, Maryland.

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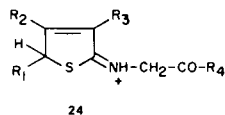
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amines of pK_a 1.0 to 3.5 most often exhibit this effect. This appears in agreement with our inability to achieve direct alkylation of the aminothiophenes (3). It should also be noted that the monoalkylated thiophenes still retain the ability to act as dienamines (24) in strongly acidic solvents (TFA) (7).



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