Preparation and some Reactions of Substituted Thieno[3,4-*b*]furans

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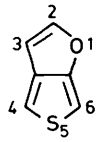
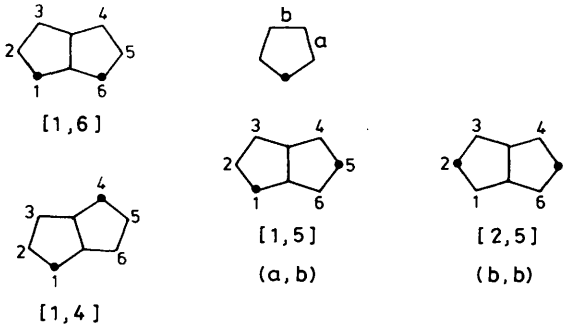
Treatment of a variety of 3-hydroxythiophenes with either an excess of methyl or ethyl bromoacetate and anhydrous potassium carbonate in acetonitrile under reflux, or in DMSO at room temperature, gave the 3-alkoxy derivatives in good to excellent yields. Utilization of the Dieckmann condensation, using either sodium alkoxide–alcohol or sodium hydride–benzene as base, afforded substituted thieno[3,4-*b*]furans in moderate to good yields. These compounds were found to exist predominantly in either the keto or enol form dependant upon the nature of substitution in the thiophene ring. Derivatives prepared from thieno[3,4-*b*]furan compounds showed that the system exhibited the chemical properties associated with ketones, enols, and β-keto esters. In addition the allyl ether was formed from 3-hydroxy-2,4-bismethoxycarbonylthieno[3,4-*b*]furan which underwent the Claisen rearrangement upon distillation.

The parent heterocycle thieno[3,4-*b*]furan (I) is not known in the literature. Indeed the annellation of two five-membered heterocyclic molecules each containing six π-electrons is of



(I)

interest both from a theoretical and a synthetic point of view. Milun and Trinajstić,[1] in their study of the aromatic stability of positional isomers,[2–4] using a novel aromaticity index called Topological Resonance Energy (TRE), compared the expected stability of some thirty positional isomers.[2] The systems studied were those obtained by annellation of two five-membered heterocycles each containing six π-electrons (furan, pyrrole, and thiophene). Positional isomers have an interesting feature: their stabilities and properties are related to the position of the heteroatoms. The molecules can be classified into three groups according to the annellation mode.

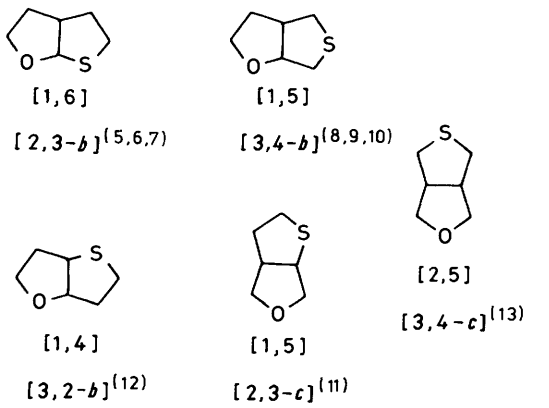


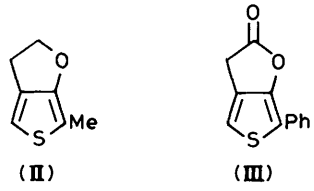
Experimental data and examination of TRE indices indicate that there is in general the following stability order among isomers of the same class.

$$[1,4] \sim [1,6] > [1,5] \gg [2,5]$$

There are five different modes of annellation possible for thienofurans and several examples are known in the literature.

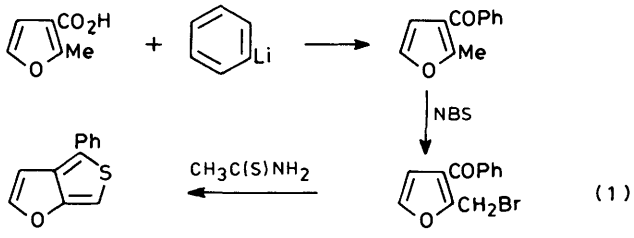
Since thieno[3,4-*b*]furan belongs to the [1,5] class it would be predicted to be of moderate stability and that stability should be enhanced by electron-withdrawing groups. Only a few examples of thieno[3,4-*b*]furan derivatives have been synthesized. To date two reduced thieno[3,4-*b*]furan systems have been prepared to test their value as food flavourings, *viz.* (II),[8] and as anti-inflammatory agents, (III).[9]





(II) (III)

In 1982 Shafiee and Sattari[10] prepared 4-phenylthieno[3,4-*b*]furan, which represented the first fully aromatic example of the [3,4-*b*] system, from 2-methyl-3-furoic acid in a three-step synthesis [equation (1)].



(1)

The aim of the present work was to prepare substituted thieno[3,4-*b*]furans and to study some aspects of the system's chemistry. The methodology employed was to prepare *O*-alkyl

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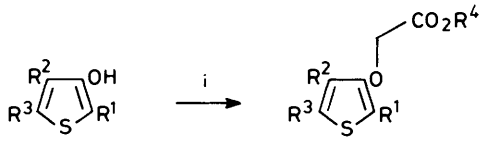
derivatives of substituted 3-hydroxythiophene compounds, followed by Dieckmann condensation to effect ring closure.

Results and Discussion

3-Hydroxythiophenes (**1**)—(**5**) employed in this study were alkylated by treatment of a suitable 3-hydroxythiophene (Scheme 1) with methyl or ethyl bromoacetate in the presence of



	R¹	R²	R³		R¹	R²	R³	R⁴
(1)	H	CO_2Et	Me	(6)	H	CO_2Et	Me	Et
(2)	H	CO_2Me	Me	(7)	H	CO_2Me	Me	Me
(3)	H	CO_2Et	H	(8)	H	CO_2Et	H	Et
(4)	H	CO_2Me	CO_2Me	(9)	H	CO_2Me	CO_2Me	Me
(5)	CO_2Et	CO_2Et	H	(10)	CO_2Et	CO_2Et	H	Et
				(11)	H	CO_2H	Me	H
				(12)	Cl	CO_2Et	Me	Et
				(13)	Br	CO_2Et	H	Et

Scheme 1. Alkylation of substituted 3-hydroxythiophenes. *Reagents*: i, $BrCH_2CO_2R^4$, K_2CO_3, MeCN or Me_2SO

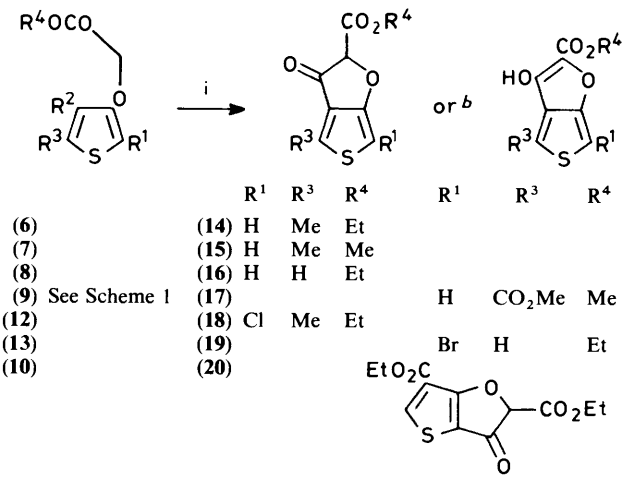
anhydrous potassium carbonate in either acetonitrile or dimethyl sulphoxide (DMSO). The reactions in acetonitrile were conducted under reflux, and those in DMSO at room temperature. (See Table 1 for ^{13}C n.m.r. data, Table 2 for preparative data, and Table 3 for physical, analytical, and spectral data.)

It is desirable to have bromoacetate present in a three-fold excess as the reaction was found to be rather sluggish with only equimolar amounts. During an initial optimization experiment an attempt to separate unchanged 3-ethoxycarbonyl-4-hydroxy-2-methylthiophene (**1**) from ethyl (4-ethoxycarbonyl-5-methyl-3-thienyloxy)acetate (**6**) with Claisen's alkali [14] led to the rapid hydrolysis of compound (**6**) to give (4-carboxy-5-methyl-3-thienyloxy)acetic acid (**11**). The yields of *O*-alkylated products were good (60—80%).

The structure of the alkylated products (**6**)—(**10**) was assigned on the basis of elemental analysis, ^1H n.m.r., and i.r. spectroscopy. The methylene ether group was found to resonate typically between δ_H 4.57—4.81 in the ^1H n.m.r. spectrum. The aromatic proton appears as a singlet in trisubstituted compounds (**6**), (**7**), (**9**), and (**11**) between δ_H 6.07—6.55, when adjacent to the ether group, and at low field when adjacent to an ester group, typically between δ_H 8.00—8.12 in compounds (**10**) and (**13**). In the disubstituted case (**8**) both types of proton are present and the chemical shifts for the pair of doublets are δ_H 6.44 (2-H) and 8.10 (5-H) with a coupling constant of 3 Hz (Table 3).

Examination of the i.r. spectra of the *O*-alkylated derivatives (**6**)—(**13**) reveals three main features. The aromatic ester carbonyl stretching frequency generally appears between 1 705—1 720 cm^{-1}, the aliphatic carbonyl stretching frequency is observed between 1 760—1 770 cm^{-1}, and the thiophene ring protons are seen as a medium sharp singlet between 3 100—3 129 cm^{-1}.

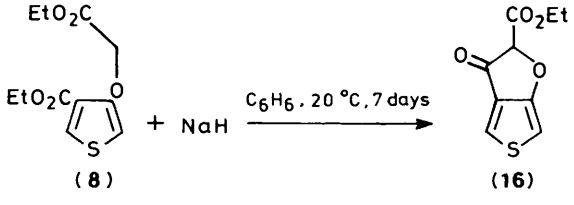
Cyclization of the *O*-alkylated compounds to yield thieno[3,4-*b*]furan derivatives was achieved by utilization of the Dieckmann condensation. Sodium hydride in benzene or sodium alkoxide in alcohol were the methods of choice. However, in some cases sodium alkoxide in alcohol was found to be very sensitive to both traces of moisture and excess of reagent (see Table 4 for preparative and analytical data). 2-Ethoxycarbonyl-4-methylthieno[3,4-*b*]furan-3(2*H*)-one (**14**) (see Scheme 2) was prepared in 60% yield by the action of sodium hydride in benzene, heated under reflux, on ethyl (4-ethoxycarbonyl-5-methyl-3-thienyloxy)acetate (**6**). Synthesis of 2-ethoxycarbonylthieno[3,4-*b*]furan-3(2*H*)-one (**16**) was unsatisfactory. The quoted yield of 36% was the best achieved and the problem seemed to be a question of thermal stability, since a crude yield of ~60% was obtained when diester (**8**) was treated with sodium hydride in benzene at 20 °C for 7 days [equation (2)]. However, after work-up the product decomposed when crystallization was attempted from hot ethanol.



	R¹	R³	R⁴		R¹	R³	R⁴
(6)		(14)	H	Me	Et		
(7)		(15)	H	Me	Me		
(8)		(16)	H	H	Et		
(9)	See Scheme 1	(17)			H	CO_2Me	Me
(12)		(18)	Cl	Me	Et		
(13)		(19)			Br	H	Et
(10)		(20)					

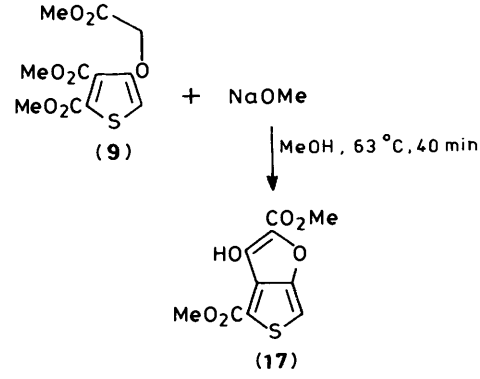
Scheme 2.[a] Cyclization of 3-*O*-alkylated substituted thiophenes. *Reagents*: i, NaH, C_6H_6 or NaOR, ROH

[a] See Table 3 for preparative and analytical data. [b] Predominant form at 25 °C in $CDCl_3$, thin film, and KBr disc.



(8) (16) (2)

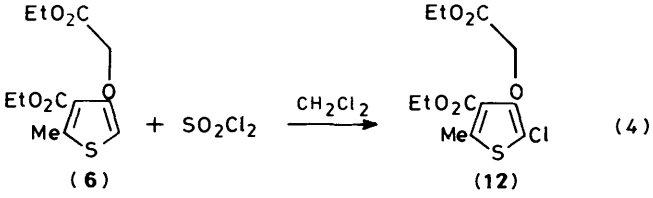
Cyclization of methyl (4,5-bismethoxycarbonyl-3-thienyloxy)acetate (**9**) was attempted using sodium hydride in benzene under reflux, but only starting material was recovered (in good yield). 3-Hydroxy-2,4-bismethoxycarbonylthieno[3,4-*b*]furan (**17**) was obtained in 87% yield by reaction of compound (**9**) with an equimolar amount of sodium methoxide [equation (3)].



(9) (17) (3)

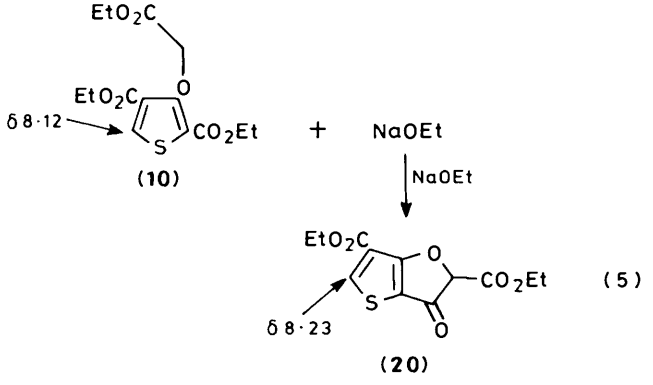
Ethyl (2-chloro-4-ethoxycarbonyl-5-methyl-3-thienyloxy)-acetate (**12**) [equation (4)] and ethyl (2-bromo-4-ethoxycarbonyl-3-thienyloxy)acetate (**13**) were prepared in good yield

by the action of sulphuryl chloride in dichloromethane on compound (**6**), and pyridinium bromide perbromide (PBB) in glacial acetic acid on compound (**8**), respectively. Although spectral data for these compounds were consistent with the proposed structures, satisfactory elemental analyses could not be obtained due to the air-sensitive nature of these compounds. Bromo compound (**13**) was cyclized with one equivalent of ethoxide to give 6-bromo-2-ethoxycarbonyl-3-hydroxythieno[3,4-*b*]furan (**19**) (Scheme 2) as an unstable purple solid in 49% yield. The same method was used to prepare the unstable 6-chloro-2-ethoxycarbonyl-4-methylthieno[3,4-*b*]furan-3(2*H*)-one (**18**).



(**6**) (**12**) (4)

It was noted in our laboratory[15] that attempted cyclization of methyl (2-methoxycarbonyl-3-thienyloxy)acetate with an equivalent of methoxide led to a complex mixture. When ethyl (2,4-bisethoxycarbonyl-3-thienyloxy)acetate (**10**) was subjected to the same reaction conditions the major product (75%) was 2,6-bisethoxycarbonylthieno[3,2-*b*]furan-3(2*H*)-one (**20**) [equation (5)].



(**10**) (**20**) (5)

The proposed structure was based on ^{1}H n.m.r. and i.r. data. The chemical shift of the thiophene proton was compared with the chemical shift in similar compounds, *e.g.* (**8**) and (**10**). Such protons are found typically between δ_H 7.9—8.2. If the product had been the [3,4-*b*] isomer the equivalent proton would be expected to resonate between δ_H 6.0—7.3 (see Table 3), *e.g.* (**6**)—(**9**), and (**11**).

It will be noted from Scheme 2 that the thienofuran system is shown as either the keto or the enol form and that no equilibrium has been indicated. Evidence for this convention comes from a variety of spectroscopic sources (^{1}H and ^{13}C n.m.r., and i.r.). For example, when the i.r. solution spectra of compounds (**14**) and (**17**) were run in solvents of differing dielectric constants (hexane, diethyl ether, chloroform, acetonitrile, and ethanol) no change was observed in either spectrum. There was no evidence in the i.r. spectra of compounds (**14**)—(**16**) and (**18**) for a hydroxy group. Indeed two carbonyl stretching bands were observed, one between 1 751—1 755 cm^{-1} and the other between 1 725—1 730 cm^{-1}. These values indicate that there is an aliphatic ester carbonyl group [*cf.* i.r. spectra of (**6**)—(**13**)] and a 5-membered-ring ketonic carbonyl function. The i.r. spectra of compounds (**17**) and (**19**) show a broad band centred on 3 350 cm^{-1} and sharp, unsaturated or aryl ester carbonyl groups at 1 710 and 1 705 cm^{-1} for (**17**), and 1 680 cm^{-1} for (**19**).

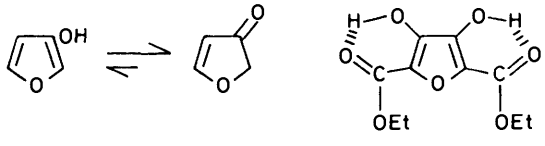
The ^{1}H n.m.r. spectrum of compounds such as (**14**)—(**16**) and (**18**) showed a resonance between δ_H 4.73—5.58 which integrates for one proton. These figures are consistent for an aliphatic proton flanked by an ester, a ketone, and an ether linkage; these figures are similar to those found for the methylene protons in compounds (**6**)—(**13**), *i.e.* δ_H 4.57—4.81 (Table 3).

On the other hand the ^{1}H n.m.r. spectrum of compound (**19**) showed no resonance between δ_H 4.73—5.58, but a broad resonance was observed at δ_H 8.25 which disappeared on treatment with D_2O. Compound (**17**) was found to be practically insoluble in common solvents and because of this it was not possible to obtain an n.m.r. spectrum. This behaviour was attributed to intramolecular hydrogen-bond formation because derivatization of the hydroxy group with tosyl chloride or acetic anhydride to produce 2,4-bismethoxycarbonyl-3-(4-tolylsulphonyloxy)- (**30**) and 3-acetoxy-2,4-bismethoxycarbonyl-thieno[3,4-*b*]furan (**27**) respectively (see later) gave compounds of normal solubility (see Scheme 3). A deep purple coloration was obtained on treatment of enol (**17**) with iron(III) chloride solution.

The ^{13}C n.m.r. spectra of 3-hydroxythiophenes (**1**) and (**4**), 3-*O*-alkyloxythiophenes (**6**) and (**9**), thieno[3,4-*b*]furan-3-ones (**14**), (**32**), (**33**), and (**34**), and thieno[3,4-*b*]furans (**22**), (**27**), and (**31**) were recorded in $CDCl_3$ at 25 °C with tetramethylsilane as internal standard. Resonances were observed between δ_C 90.8—100.0 and δ_C 185.1—188.1 in the keto compounds (**14**), (**32**), (**33**), and (**34**), which were assigned to the aliphatic carbon atom of the reduced furan ring (C-2 in Table 1) and the ketonic carbon atom (C-3). The C-2 resonance has moved downfield to the corresponding carbon atom (C-6) in precursors (**6**) and (**9**) by ~30 p.p.m. This was due to the adjacent ketonic function. On the other hand, resonances between δ_C 140.7—143.8 and δ_C 152.6—153.6 were attributed to C-2 and C-3 in aromatic thienofurans (**22**), (**27**), and (**31**).

In conclusion there is good spectroscopic evidence for both the keto and enol forms and the conclusion drawn is that one form is preferred over the other; which is the dominant seems to be dependent upon the nature of the thiophene ring substituents.

It is of interest that such a situation exists because although '3-hydroxyfuran' exists mainly in the keto form as furan-3(2*H*)-one, derivatives such as 2,5-diethoxycarbonyl-3,4-dihydroxyfuran appear to exist only in the enol form. Stabilization of the enol structure is thought possible through intramolecular hydrogen bonding. The thieno[3,4-*b*]furan systems studied all

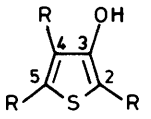


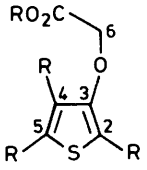
have potential for such enolic stabilization, yet only two, (**17**) and (**19**), showed such properties (Scheme 2).

Thieno[3,4-*b*]furans show a variety of chemical properties and these are now discussed. For example, thienofuranone (**14**) reacted as a ketone towards 2,4-dinitrophenylhydrazine to give 3-(2,4-dinitrophenylhydrazono)-2-ethoxycarbonyl-2,3-dihydro-4-methylthieno[3,4-*b*]furan (**21**) in 68% yield (see Scheme 3).

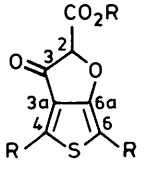
Although it was stated earlier that spectroscopic evidence suggested that one tautomeric form was preferred over the other in these systems, it was found possible to prepare enol derivatives of the predominantly keto compounds (**14**) and (**16**). On prolonged treatment with acetic anhydride and sodium

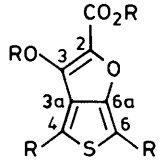
Table 1. ^{13}C N.m.r. data for substituted 3-hydroxythiophenes (**1**) and (**4**), 3-*O*-alkylthiophenes (**6**) and (**9**), thieno[3,4-*b*]furan-3-ones (**14**), (**32**), (**33**), and (**34**), and thieno[3,4-*b*]furans (**22**), (**27**), and (**31**)[a]





Compd.	C-2	C-3	C-4	C-5	C-2	C-3	C-4	C-5	C-6
(**1**)	95.2	155.8	115.8	147.9					
(**4**)	104.6	156.3	135.0	133.4					
(**6**)					96.4	155.0	120.7	147.8	67.9
(**9**)					106.6	160.9	130.6	130.5	67.8
(**14**)									
(**32**)									
(**33**)									
(**34**)									
(**22**)									
(**27**)									
(**31**)									





Compd.	C-2	C-3	C-3a	C-4	C-6	C-6a	C-2	C-3	C-3a	C-4	C-6	C-6a
(**1**)												
(**4**)												
(**6**)												
(**9**)												
(**14**)	92.8	184.7	124.8	145.3	92.8	164.4						
(**32**)	102.4	185.1		128.2	102.7	160.0						
(**33**)	99.5	187.3	125.1	145.1	92.3	164.3						
(**34**)	97.4	188.7	124.7	145.3	92.3	166.1						
(**22**)							140.7	152.7	127.1	136.4	93.9	159.1
(**27**)							143.8	153.1	136.1	131.8	105.5	158.9
(**31**)							143.4	153.6	132.0	130.9	105.1	159.5

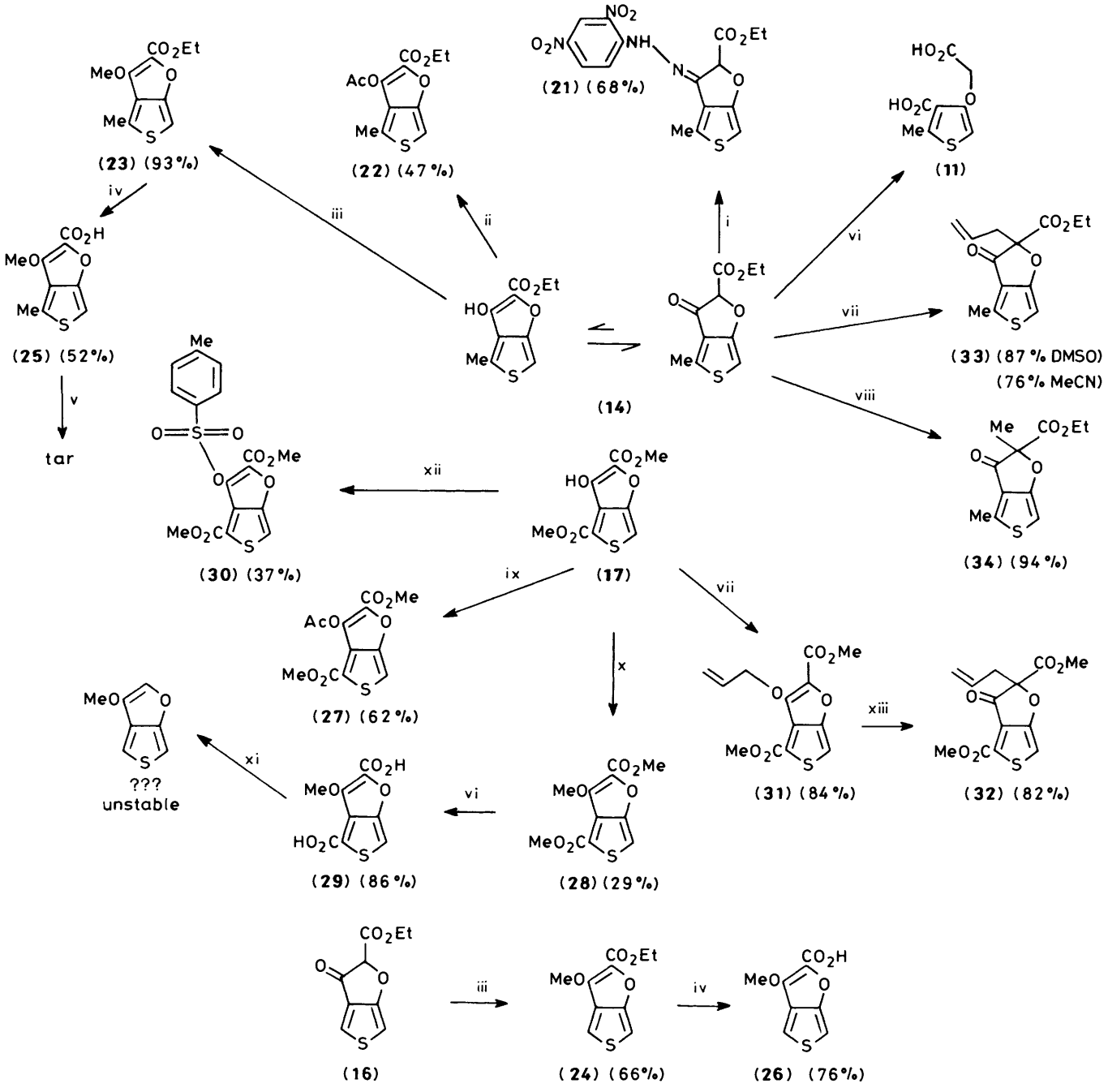
[a] All spectra were run on a JOEL PS100 n.m.r. spectrometer operating at 25.3 MHz. ^{13}C Shifts (δ_C) relative to internal Me_4Si at 25 °C in $CDCl_3$.

acetate, compound (**14**) gave 3-acetoxy-2-ethoxycarbonyl-4-methylthieno[3,4-*b*]furan (**22**) in 47% yield; also, prolonged treatment of both compounds (**14**) and (**16**) with an excess of diazomethane in diethyl ether produced 2-ethoxycarbonyl-3-methoxy-4-methylthieno[3,4-*b*]furan (**23**) and 2-ethoxycarbonyl-3-methoxythieno[3,4-*b*]furan (**24**) respectively. Compounds (**23**) and (**24**) underwent hydrolysis readily with 2M-sodium hydroxide to produce the corresponding carboxylic acid derivatives (**25**) and (**26**). Attempts to produce keto derivatives of the predominantly enolic compound (**17**) failed.

However, compound (**17**) readily formed enol derivatives such as the 3-acetoxy (**27**) and 3-(4-tolylsulphonyloxy) derivatives (**30**) upon treatment with the appropriate reagents. 3-Methoxy-2,4-bismethoxycarbonylthieno[3,4-*b*]furan (**28**) was prepared by reaction of compound (**17**) with iodomethane in dimethylformamide (DMF) in the presence of anhydrous potassium carbonate. Hydrolysis of compound (**28**) with 2M-sodium hydroxide afforded 2,4-biscarboxy-3-methoxythieno[3,4-*b*]furan (**29**). In a bid to produce 3-methoxy-4-methylthieno[3,4-*b*]furan the acid (**25**) was treated with pyridine in the presence of copper(I) oxide, but only a polymeric tar was obtained. Attempted decarboxylation of both the monoacid (**26**) and the diacid (**29**) was attempted using an intimate mixture of the acid and powdered glass in a cold-finger sublimation apparatus. In both cases a very unstable crystalline solid was obtained. It is possible that this compound was 3-methoxythieno[3,4-*b*]furan, which given the π-electron richness of the thieno[3,4-*b*]furan system and the π-electron-donating nature of the methoxy substituent would be expected to be unstable.

3-Allyloxy-2,4-bismethoxycarbonylthieno[3,4-*b*]furan (**31**) was produced in 84% yield by treatment of compound (**17**) with allyl bromide (3-bromoprop-1-ene) and anhydrous potassium carbonate in dry DMSO. Distillation of the crude reaction product gave the Claisen rearranged product 2-allyl-2,4-bismethoxycarbonylthieno[3,4-*b*]furan (**32**) in 82% yield.

The predominantly keto compound (**14**) was found to exhibit properties similar to β-keto esters. For example, treatment of compound (**14**) with 3-bromoprop-1-ene in acetonitrile under reflux, or in DMSO at 20 °C, in the presence of a relatively weak base, anhydrous potassium carbonate, produced 2-allyl-2-ethoxycarbonylthieno[3,4-*b*]furan-3(2*H*)-one (**33**). Similarly, treatment of compound (**14**) with iodomethane and anhydrous potassium carbonate in DMSO at 20 °C gave 2-ethoxycarbonyl-



Scheme 3. Various reactions of substituted thieno[3,4-*b*]furans. *Reagents and conditions*: i, 2,4-$(O_2N)_2C_6H_3NHNH_2$, 20 °C; ii, Ac_2O, NaOAc, reflux, 3 h; iii, CH_2N_2, Et_2O, 20 °C, 24 h; iv, 2M-NaOH, 100 °C, 2 h; v, pyridine, Cu_2O, 80 °C; vi, 2M-NaOH, 20 °C; vii, CH_2=$CHCH_2Br$, K_2CO_3, DMSO, 20 °C, 24 h *or* CH_2=$CHCH_2Br$, K_2CO_3, MeCN, 80 °C, 5 h; viii, MeI, K_2CO_3, DMSO, 20 °C; ix, Ac_2O, reflux, 1 h; MeI, K_2CO_3, DMF, 50 °C; xi, sublimation; xii, 4-$MeC_6H_4SO_2Cl$, pyridine, 80 °C, 2 h; xiii, 200 °C

2,4-dimethylthieno[3,4-*b*]furan-3(2*H*)-one (**34**) in 94% yield. There was no evidence in the ^1H n.m.r. spectrum of the crude reaction mixture for the *O*-methylated product (**23**).

Exploitation of the ease of decarboxylation of β-keto acids in a bid to form thieno[3,4-*b*]furan-3(2*H*)-ones was found to be futile. Treatment of compound (**14**) with cold 2M-sodium hydroxide led to the ring-opened diacid (**11**). Acid-catalysed hydrolysis was attempted with hydrochloric acid, but 90% starting material was recovered after 20 h at 20 °C, and polymeric tar was obtained after 2 h under reflux. In conclusion these observations would bear out Milun and Trinajstić's [1,2] predictions from TRE studies, namely that thieno[3,4-*b*]furans are moderately stable compounds and that stability is enhanced by electron-withdrawing substituents.

Experimental

Light petroleum refers to the fraction b.p. 40—60 °C, and ether refers to diethyl ether. M.p.s were determined on a Reichart hot stage apparatus and are uncorrected, and the internal standard for n.m.r. spectra was $SiMe_4$; spectra were run on a Hitachi Perkin-Elmer R24B n.m.r. spectrometer; i.r. spectra were run on a Perkin-Elmer 683 Infrared spectrophotometer.

Table 2. Preparative data for *O*-alkyl derivatives of 3-hydroxythiophenes

Compd.	S.M.[a] (g)	B[b] (g)	S[c] (ml)	K_2CO_3 (g)	*t*[d] (h)	*T*[e] (°C)	Yield (%)	Yield (g)
(**6**)	5	a, 14.33	c, 100	3.69	6	80	80	6.22
(**7**)	1	b, 2.66	c, 50	0.81	4	80	77	1.09
(**8**)	15.51	a, 45.20	d, 150	12.62	60	20	71	16.51
(**9**)	2	b, 4.25	c, 50	1.29	1.5	80	67	1.78
(**10**)	0.8	a, 1.64	d, 40	0.45	2	20	60	0.64

[a] Starting material = 3-hydroxythiophene derivative. [b] Bromoacetate, a ethyl, b methyl. [c] Solvent, c acetonitrile, d DMSO. [d] Reaction time. [e] Temperature.

A. Preparation of Substituted Hydroxythiophenes.—3-Ethoxycarbonyl-4-hydroxy-2-methylthiophene (**1**),[17,*] 4-hydroxy-3-methoxycarbonyl-2-methylthiophene (**2**),[17] 3-ethoxycarbonyl-4-hydroxythiophene (**3**),[18] 4-hydroxy-2,3-bismethoxycarbonylthiophene (**4**)[18,*] and 2,4-bisethoxycarbonyl-3-hydroxythiophene (**5**)[19] were all obtained by published methods.

B. Preparation of O*-Alkylated Thiophenes.*—The alkylations were effected by treatment of hydroxythiophene with a threefold excess of ethyl bromoacetate in the presence of anhydrous potassium carbonate in either acetonitrile or DMSO. The following procedures are typical (see Table 2 for preparative data, and Table 3 for appropriate analytical and spectral data).

Ethyl (4-[*ethoxycarbonyl-5-methyl-3-thienyloxy*)*acetate* (**6**). To a stirred solution of 3-ethoxycarbonyl-4-hydroxy-2-methylthiophene (**1**) (5 g, 28.6 mmol) in acetonitrile (100 ml) were added anhydrous potassium carbonate (3.69 g, 28.6 mmol) and 94% ethyl bromoacetate (14.33 g, 80.6 mmol) the mixture was heated under reflux for 6 h, treated with charcoal, cooled, and filtered, and the solvent and excess of bromoacetate were removed under reduced pressure. The brown oil obtained was purified by high-vacuum distillation (b.p. 146 °C/0.1 mmHg) to yield the *title acetate* as an oil (6.22 g, 80%) (Found: C, 52.6; H, 5.9. $C_{12}H_{16}O_5S$ requires C, 52.9; H, 5.9%); $\delta_H(CDCl_3)$ 1.27 (t, $OCH_2CO_2CH_2Me$, *J* 6 Hz), 1.36 (t, CO_2CH_2Me, *J* 6 Hz), 2.62 (s, 5-Me), 4.24 (q, $OCH_2CO_2CH_2Me$, *J* 6 Hz), 4.36 (q, CO_2CH_2Me, *J* 6 Hz), 4.61 (s, OCH_2CO_2Et), and 6.07 (s, 2-H); $\delta_C(CDCl_3)$ 14.2, 16.9, 60.3, 61.2, 67.9, 96.4, 120.7, 147.8, 155.0, 162.8, and 168.3; $\nu_{max.}$(thin film) 3 120w (2-H), 1 760s (aliphatic C=O), 1 705s (aromatic C=O), and 1 554s cm^{-1} (thiophene C=C).

This method was used to prepare *methyl* (4-*methoxycarbonyl-5-methyl-3-thienoxy*)*acetate* (**7**) and *methyl* (4,5-*bismethoxycarbonyl-3-thienyloxy*)*acetate* (**9**), $\delta_C(CDCl_3)$ 52.3, 52.6, 52.9, 67.8, 106.6, 130.5, 130.6, 160.9, 163.9, 168.3, and 169.0.

Ethyl (4-*ethoxycarbonyl-3-thienyloxy*)*acetate* (**8**). To a stirred solution of 3-ethoxycarbonyl-4-hydroxythiophene (**3**) (15.51 g, 90.1 mmol) in DMSO (150 ml) were added anhydrous potassium carbonate (12.62 g, 90.1 mmol) and 94% ethyl bromoacetate (45.20 g, 270 mmol), and the reaction mixture was stirred at room temperature for 60 h, filtered, and poured into water. The aqueous reaction mixture was extracted with ethyl acetate (×4). The extracts were combined, washed with water, dried ($MgSO_4$), treated with charcoal, and filtered, and solvent and excess of bromoacetate were removed under reduced pressure. The brown oil obtained was purified by high-vacuum distillation (b.p. 138—140 °C/0.15 mmHg) to yield the *title acetate* as an oil (16.51 g, 71%) (Found: C, 51.4; H, 5.7. $C_{11}H_{14}O_5S$ requires C, 51.2; H, 5.4%); $\delta_H(CDCl_3)$ 1.26 (t, $OCH_2CO_2CH_2Me$, *J* 8 Hz), 1.35 (t, CO_2CH_2Me, *J* 8 Hz), 4.30 (q, $OCH_2CO_2CH_2Me$, *J* 8 Hz), 4.37 (q, CO_2CH_2Me, *J* 8 Hz), 4.71 (s, OCH_2CO_2Et), 6.44 (d, 2-H, *J* 3 Hz), and 8.10 (d, 5-H, *J* 3 Hz); $\nu_{max.}$(thin film) 3 118m (thiophene proton), 1 760s (aliphatic C=O), 1 725s (aromatic C=O), and 1 545s cm^{-1} (thiophene C=C).

This method was also used to prepare *ethyl* (2,4-*bisethoxycarbonyl-3-thienyloxy*)*acetate* (**10**).

(4-*Carboxy-5-methyl-3-thienyloxy*)*acetic acid* (**11**). Ethyl (4-ethoxycarbonyl-5-methyl-3-thienyloxy)acetate (**6**) (1 g, 3.67 mmol) was stirred with 2M-sodium hydroxide (30 ml) for 1 h. The brown reaction mixture was extracted with ether (×2), chilled with crushed ice, acidified with 2M-hydrochloric acid, and extracted with dichloromethane (×4). The latter extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The product was recrystallized from chloroform to give a white solid (0.42 g, 59%), m.p. 149—150 °C (decomp.) (see Table 3 for analytical and spectral data).

Ethyl (2-*chloro*-4-*ethoxycarbonyl*-5-*methyl*-3-*thienyloxy*)*acetate* (**12**). To a stirred solution of ethyl (4-ethoxycarbonyl-5-methyl-3-thienyloxy)acetate (**6**) (2 g, 7.35 mmol) in dichloromethane (20 ml; dried over type 4A molecular sieves) was added dropwise a dichloromethane solution of sulphuryl chloride (0.99 g, 7.35 mmol in 10 ml). The reaction mixture was stirred for 1 h and poured into vigorously stirred water; the mixture was then stirred for a further 1 h. The two layers were separated and the aqueous fraction was extracted with dichloromethane. The dichloromethane fractions were combined and washed successively with water, saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), treated with charcoal, filtered, and evaporated under reduced pressure, and the residue was purified by high-vacuum distillation (b.p. 145 °C/0.8 mmHg) to give a yellow oil (1.43 g, 63%) (see Table 3).

Ethyl (2-*bromo*-4-*ethoxycarbonyl*-3-*thienyloxy*)*acetate* (**13**). To a stirred suspension of finely ground PBB (4.96 g, 15.2 mmol) in glacial acetic acid (20 ml) was added, in one portion, an acetic acid solution of ethyl (4-ethoxycarbonyl-3-thienyloxy)acetate (**8**) (4 g, 15.2 mmol in 20 ml). The reaction mixture was stirred for 15 min, and extracted with dichloromethane (×4). The extracts were combined and washed successively with water (×2), saturated aqueous sodium hydrogen carbonate (×1), and water (×1), dried ($MgSO_4$), treated with charcoal, filtered, and evaporated, and the remanent yellow oil was purified by high-vacuum distillation (b.p. 117 °C/0.05 mmHg) to yield an oil (3.17 g, 61%) (see Table 3).

C. Cyclization to Thieno[3,4-b]*furans.*—Treatment of *O*-alkylated thiophenes with either sodium hydride in benzene or sodium alkoxide in alcohol afforded substituted thieno[3,4-*b*]furans. The following procedures are typical. See Table 4 for preparative and analytical data.

* (**1**) $\delta_C(CDCl_3)$ 14.3, 17.3, 61.1, 95.2, 115.8, 147.9, 155.8, and 166.5. (**4**) $\delta_C(CDCl_3)$ 52.8, 53.3, 104.6, 133.4, 135.0, 156.3, 161.4, and 165.6.

Table 3. Physical, analytical, ^{1}H n.m.r. and i.r. data for 3-*O*-alkyl derivatives (**6**)—(**13**)

						δ_H[a]							$\nu_{max.}$[b] (cm^{-1})		
Compd.	M.p. (°C)	B.p. (°C/mmHg)	Empirical formula	Analysis Found (required) C	H	OCH_2	Ring proton(s)	2(5)-Me	$ArCO_2CH_2Me$	$ArCO_2Me$	$CH_2CO_2CH_2Me$	$-CH_2CO_2Me$	Ring proton(s)	Ar*C*OO	CH_2*C*OO
(**6**)		146/0.1	$C_{12}H_{16}O_5S$	52.6 (52.9)	5.9 (5.9)	4.61	6.07 2-H, s	2.65	1.36 t, *J* 6 Hz 4.36 q, *J* 6 Hz		1.27 t, *J* 6 Hz 4.24 q, *J* 6 Hz		3 120	1 705	1 760
(**7**)	43—45	114/0.04	$C_{10}H_{12}O_5S$	49.2 (48.9)	5.1 (5.1)	4.67	6.13 2-H, s	2.63		3.91		3.79	3 120	1 715	1 764
(**8**)		140/0.15	$C_{11}H_{14}O_5S$	51.4 (51.2)	5.7 (5.4)	4.71	6.44 2-H, d, *J* 3 Hz 8.10 5-H, d, *J* 3 Hz		1.35 t, *J* 6 Hz 4.37 q, *J* 6 Hz		1.26 t, *J* 6 Hz 4.30 q, *J* 6 Hz		3 118	1 725	1 760
(**9**)	59	89/0.07	$C_{11}H_{12}O_7S$	45.9 (45.8)	4.0 (4.2)	4.63	6.55 2-H, s			3.87 3.95		3.79	3 129	1 752 1 710	1 770
(**10**)		165/0.1	$C_{14}H_{18}O_7S$	50.7 (50.9)	5.6 (5.5)	4.81	8.12 5-H, s		1.31[c] 4.33				3 110	1 720	1 764
(**11**)	149—150 (decomp.)		$C_8H_8O_5S$	44.0 (44.4)	3.8 (3.7)	4.57	6.13 2-H, s	2.60						1 680	1 749
(**12**)		147/0.5	$C_{12}H_{15}ClO_5S$[d]			4.59		2.55	1.33 t, *J* 7 Hz 4.23 q, *J* 7 Hz		1.29 t, *J* 7 Hz 4.27 q, *J* 7 Hz			1 713	1 769
(**13**)		117/0.05	$C_{11}H_{13}BrO_5S$[d]	40.2 (39.7)	3.9 (4.1)	4.66	8.00 5-H, s		1.33 t, *J* 7 Hz 4.30 q, *J* 7 Hz		1.30 t, *J* 7 Hz 4.27 q, *J* 7 Hz		3 110	1 710	1 765

[a] 60 MHz (continuous wave) ^{1}H shifts relative to Me_4Si. [b] All i.r. spectra were run as thin films. [c] Three overlapping triplets and quartets. [d] Compounds (**12**) and (**13**) were air sensitive.

Table 4. Preparative and analytical data for thieno[3,4-*b*]furans (**14**)—(**19**) and thieno[3,2-*b*]furan (**20**)

Compd.	M[a]	T[b]	t[c]	Y[d]	M.p. (°C)	B.p. (°C/mmHg)	Empirical formula	Analysis (%) Found (required) C	H	S
(**14**)	a	80	3	60	80—81	164/0.25	$C_{10}H_{10}O_4S$	53.2 (53.1)	4.6 (4.4)	13.5 (14.1)
(**15**)	a	80	4	52		143/1.2	$C_9H_8O_4S$	51.0 (50.9)	4.0 (3.8)	15.0 (15.1)
(**16**)	a	80	2.5	36		115/0.35	$C_9H_5O_4S$	Unstable		
(**17**)	b	64	0.5	87	230—232		$C_{10}H_8O_6S$	46.5 (46.9)	2.8 (3.1)	12.3 (12.5)
(**18**)	b	78	2	40			$C_{10}H_9ClO_4S$	Unstable		
(**19**)	b	78	1.5	49	103—104 (decomp.)		$C_9H_7BrO_4S$	Unstable		
(**20**)	b	78	1	75	138—139		$C_{12}H_{12}O_6S{\cdot}H_2O$	47.5 (47.7)	4.5 (4.6)	10.7 (10.6)

[a] Method. a, NaH–benzene; b, alkoxide–alcohol. [b] Temperature (°C). [c] Reaction time (h). [d] Yield (%).

2-*Ethoxycarbonyl*-4-*methylthieno*[3,4-b]*furan*-3(2H)-*one* (**14**). Oil-free sodium hydride (0.66 g, 27.5 mmol) was added to a stirred solution of ethyl (4-ethoxycarbonyl-5-methyl-3-thienyloxy)acetate (**6**) (5 g, 18.3 mmol) in benzene (100 ml; dried over sodium wire), and the reaction mixture was heated under reflux for 3 h, cooled, and poured onto a vigorously stirred mixture of crushed ice and 2M-hydrochloric acid. The two layers were separated and the aqueous fraction was extracted with ether (× 2). The extracts were combined, washed with water (× 2), dried ($MgSO_4$), treated with charcoal, filtered, and evaporated. The product was purified by high-vacuum distillation (b.p. 164 °C/0.25 mmHg) to yield the *title compound* as an oil) 2.44 g, 60%) which solidified after a time (m.p. 80—81 °C) (Found: C, 53.2; H, 4.6; S, 13.5. $C_{10}H_{10}O_4S$ requires C, 53.1; H, 4.4; S, 14.15%); $\delta_H(CDCl_3)$ 1.31 (t, OCH_2Me, *J* 7 Hz), 2.50 (s, 4-Me), 4.27 (q, OCH_2Me, *J* 7 Hz), 5.32 (s, 2-H), and 6.09 (s, 6-H); $\delta_C(CDCl_3)$ 14.1, 14.4, 62.5, 90.8, 92.8, 124.8, 145.3, 164.4, 167.2, and 184.7; $\nu_{max.}$(KBr) 3 110s (thiophene proton), 1 751s (ester C=O), 1 725s (ketone C=O), and 1 589s cm^{-1} (thiophene C=C).

The following were similarly prepared. 2-*Methoxycarbonyl*-4-*methylthieno*[3,4-b-]*furan*-3(2H)-*one* (**15**), $\delta_H(CDCl_3)$ 2.65 (s, 4-Me), 3.90 (s, OMe), 5.45 (s, 2-H), and 6.23 (s, 6-H); $\nu_{max.}$ (thin film) 3 125m (thiophene proton), 1 755s (ester C=O), 1 727s (ketone C=O), and 1 586s cm^{-1} (thiophene C=C); and 2-ethoxycarbonylthieno[3,4-*b*]furan-3(2*H*)-one (**16**), $\delta_H(CDCl_3)$ 1.40 (t, OCH_2Me, *J* 7 Hz), 4.39 (q, OCH_2Me, *J* 7 Hz), 5.58 (s, 2-H), 6.60 (d, 4-H, *J* 3 Hz), and 7.98 (d, 6-H, *J* 3 Hz); $\nu_{max.}$ (thin film) 3 110m (thiophene protons), 1 755s (ester C=O), 1 730s (ketone C=O), and 1 573s cm^{-1} (thiophene C=C).

3-*Hydroxy*-2,4-*bismethoxycarbonylthieno*[3,4-b]*furan* (**17**). A solution of methyl 4,5-bismethoxycarbonyl-3-thienyloxy)-acetate (**9**) (2 g, 6.94 mmol) in dry methanol (type 4A molecular sieves) (20 ml) was added dropwise during 10 min to a refluxing solution of freshly prepared sodium methoxide (15 ml) [sodium (0.16 g, 6.94 mmol) in methanol]. The resulting bright orange suspension was heated under reflux for a further 30 min, cooled, and poured on to a vigorously stirred mixture of crushed ice and 2M-hydrochloric acid. The white solid (1.54 g, 87%) was filtered off and washed well with ice–water. A sample of the *title diester* was recrystallized from methanol for analysis (m.p. 230—232 °C) $\nu_{max.}$(KBr) 3 450br (hydrogen-bonded OH), 3 100m (thiophene proton), 1 714s (C=O), 1 710s (C=O), and 1 600m cm^{-1} (C=C) (analytical and other data are in Table 4).

Similarly were prepared 6-chloro-2-ethoxycarbonyl-4-methylthieno[3,4-*b*]furan-3(2*H*)-one (**18**), $\delta_H(CDCl_3)$ 1.36 (t, OCH_2Me, *J* 6 Hz), 2.55 (s, 4-Me), 4.30 (q, OCH_2Me, *J* 6 Hz), and 4.73 (s, 2-H); $\nu_{max.}$ (thin film) 1 756s (ester C=O), 1 724s (ketone C=O), and 1 580s cm^{-1} (thiophene C=C); 6-bromo-2-ethoxycarbonyl-3-hydroxythieno[3,4-*b*]furan (**19**), $\delta_H(CDCl_3)$ 1.43 (t, OCH_2Me, *J* 7 Hz), 4.45 (q, OCH_2Me, *J* 7 Hz), 7.30 (s, 4-H), and 8.25 (br, 3-OH); $\nu_{max.}$(Kbr) 3 310br (hydrogen-bonded OH), 3 111m (thiophene proton), 1 680s (ester C=O), 1 620s (C=C), and 1 580m cm^{-1} (C=C); and 2,6-*bisethoxycarbonylthieno*[3,4-b]*furan*-3(2H)-*one* (**20**), $\delta_H(CDCl_3)$ 1.38 (t, OCH_2Me, *J* 7 Hz), 1.39 (t, OCH_2Me, *J* 7 Hz), 4.42 (q, OCH_2Me, *J* 7 Hz), 4.44 (q, OCH_2Me, *J* 7 Hz), 4.89 (s, 2-H), and 8.23 (s, 5-H); $\nu_{max.}$(KBr) 1 760s (ester C=O), 1 721s, and 1 718s (C=O).

D. Derivatives of Thieno[3,4-b]*furan*-3-*ones.*—3-(2,4-*Dinitrophenylhydrazono*)-2-*ethoxycarbonyl*-2,3-*dihydro*-4-*methylthieno*[3,4-b]*furan* (**21**). A freshly prepared ethanolic solution of 2,4-dinitrophenylhydrazine (20 ml) was treated with an ethanolic solution of 2-ethoxycarbonyl-4-methylthieno[3,4-*b*]-furan-3(2*H*)-one (**14**) (1 g, 4.42 mmol in 10 ml) at 40 °C. The reaction mixture was rapidly stirred for 5 min, then kept in an ice–acetone bath for 30 min. The bright orange product was filtered off and washed well with ice-cold ethanol. The *title product* was obtained as red needles (1.22 g, 68%) by recrystallization from ethyl acetate [m.p. 210 °C (decomp.)] (Found: C, 47.2; H, 3.4; N, 13.8. $C_{16}H_{14}N_4O_7S$ requires C, 47.3; H, 3.4; N, 13.8%); $\nu_{max.}$(KBr) 3 239m (N–H), 3 120w (thiophene proton), 1 735s (ester C=O), 1 630m (hydrazone C=N), 1 609s (hydrazone N–H), 1 500s (NO_2), and 1 339s cm^{-1} (NO_2); *m/z* 406 (M^+, 27%); 371 (100%).

3-*Acetoxy*-2-*ethoxycarbonyl*-4-*methylthieno*[3,4-b]*furan* (**22**). 2-Ethoxycarbonyl-4-methylthieno[3,4-*b*]furan-3(2*H*)-one (**14**) (1 g, 4.42 mmol) was added to a solution of anhydrous sodium acetate (0.8 g, 9.8 mmol) in acetic anhydride (10 ml), and the mixture was heated under reflux for 3 h. The hot reaction mixture was poured carefully into vigorously stirred ice–water and then heated at 50 °C for 30 min. The aqueous solution was cooled and extracted with dichloromethane (× 3). The extracts were combined and washed successively with water (× 2), saturated aqueous sodium hydrogen carbonate (× 1), and water (× 1), dried ($MgSO_4$), treated with charcoal, filtered, and evaporated. The oil obtained was extracted with light petroleum (× 2) and the extracts were combined and evaporated under reduced pressure to yield an amber oil which was crystallized from aqueous ethanol to afford the *title acetate* as yellow needles (0.56 g, 47%), m.p. 76—77 °C (Found: C, 53.7; H, 4.4. $C_{12}H_{12}O_5S$ requires C, 53.7; H, 4.5%); $\delta_H(CDCl_3)$ 1.38 (t, OCH_2Me, *J* 7 Hz), 2.38 (s, OCOMe), 2.53 (s, 4-Me), 4.37 (q, OCH_2Me, *J* 7 Hz), and 6.56 (s, 6-H); $\delta_C(CDCl_3)$ 13.6, 14.3, 20.5, 61.3, 93.9, 127.1, 136.4, 140.7, 152.7, 159.1, and 167.6; $\nu_{max.}$(KBr)

3 140w (thiophene proton), 1 770s (acetate C=O), 1 710s (ester C=O), and 1 616s cm^{-1} (C=C).

Similarly was prepared 3-*acetoxy*-2,4-*bismethoxycarbonylthieno*[3,4-b]*furan* (**27**) in 62% yield (1 g scale) from diester (**17**), m.p. 168—169 °C (from methanol) (Found: C, 48.3; H, 3.4. $C_{12}H_{10}O_7S$ requires C, 48.3; H, 3.4%); $\delta_H(CDCl_3)$ 2.54 (s, OCOMe), 4.02 (s, OMe), 4.09 (s, OMe), and 7.40 (s, 6-H); $\delta_C(CDCl_3)$ 20.4, 52.4, 52.6, 105.5, 131.8, 136.1, 143.8, 153.1, 158.9, 161.2, 166.4, and 168.1; $\nu_{max.}$(KBr) 3 130m (thiophene proton), 1 775s (acetate C=O), 1 720s, 1 704s (ester C=O), 1 609m (C=C), and 1 593m cm^{-1} (C=C).

2-*Ethoxycarbonyl*-3-*methoxy*-4-*methylthieno*[3,4-b]*furan* (**23**). *N*-Methyl-*N*-nitrosotoluene-4-sulphonamide (2.14 g) was dissolved in ether (30 ml) and the solution was cooled in ice *in a scratch-free round-bottomed flask*. Potassium hydroxide (0.4 g) in 96% ethanol (10 ml) was added and the reaction mixture was kept for 10 min, after which diazomethane was distilled over as an ethereal solution.[20] The diazomethane solution (20 ml) was then added dropwise to a stirred solution of 2-ethoxycarbonyl-4-methylthieno[3,4-*b*]furan-3(2*H*)-one (**14**) (1 g, 44.2 mmol) in ether (30 ml; dried over sodium wire). Two further aliquots of diazomethane solution were prepared and added to the reaction mixture at intervals of 2 h. The reaction mixture was kept for 24 h, then glacial acetic acid was added dropwise until the yellow colour disappeared. The mixture was washed successively with water (× 2), saturated aqueous sodium hydrogen carbonate (× 1), and water (× 1), dried ($MgSO_4$), treated with charcoal, filtered, and evaporated. The *product* (**23**) was purified by high-vacuum distillation (b.p. 85 °C/0.1 mmHg) to afford an oil (0.98 g, 93%), which soon solidified (m.p. 73—75 °C) (Found: C, 55.0; H, 5.0. $C_{11}H_{12}O_4S$ requires C, 55.0; H, 5.0%); $\delta_H(CDCl_3)$ 1.37 (t, OCH_2Me, *J* 6 Hz), 2.62 (s, 4-Me), 4.11 (s, OMe), 4.41 (q, OCH_2Me), and 6.50 (s, 6-H); $\nu_{max.}$(KBr) 3 117m (thiophene proton), 1 705s (ester C=O), 1 608m (C=C), and 1 580m cm^{-1} (C=C).

Similarly was prepared 2-*ethoxycarbonyl*-3-*methoxythieno*[3,4-b]*furan* (**24**) in 66% yield (1 g scale) from compound (**16**), b.p. 100 °C/0.07 mmHg (Found: C, 53.2; H, 4.5. $C_{10}H_{10}O_4S$ requires C, 53.1; H, 4.4%); $\delta_H(CDCl_3)$ 1.39 (t, OCH_2Me, *J* 7 Hz), 4.28 (s, OMe), 4.37 (q, OCH_2Me, *J* 7 Hz), 6.84 (d, 4-H, *J* 2.7 Hz), and 7.51 (d, 6-H, *J* 2.7 Hz); $\nu_{max.}$(KBr) 3 110m (thiophene protons), 1 695s (ester C=O), 1 595s (C=C), and 1 570s cm^{-1} (C=C).

2-*Carboxy*-3-*methoxy*-4-*methylthieno*[3,4-b]*furan* (**25**). 2-Ethoxycarbonyl-3-methoxy-4-methylthieno[3,4-*b*]furan (**23**) (0.24 g, 1 mmol) was heated under reflux with 2M-sodium hydroxide (20 ml) for 2 h; the solution was then treated with charcoal, cooled, filtered, extracted with ether (× 2), cooled in ice, and acidified with 2M-hydrochloric acid. The aqueous mixture was extracted with ether (× 4). The latter extracts were combined, dried ($MgSO_4$), and evaporated to yield a cream-coloured solid which was recrystallized from ether to afford the *title carboxylic acid* (0.11 g, 52%), m.p. 152 °C (decomp.) (Found: C, 50.5; H, 4.0. $C_9H_8O_4S$ requires C, 50.9; H, 3.8%); $\delta_H(CDCl_3$–DMSO) 2.66 (s, 4-Me), 4.12 (s, OMe), 6.65 (s, 6-H), 7.00 (br, CO_2H, disappears on treatment with D_2O); $\nu_{max.}$(KBr) 3 430br (hydrogen-bonded acid OH), 1 650s (acid C=O), 1 592s (C=C), and 1 560m cm^{-1} (C=C).

Similarly was prepared, from the ester (**24**), 2-*carboxy*-3-*methoxythieno*[3,4-b]*furan* (**26**) in 76% yield (on 0.2 g scale), m.p. 172—174 °C (decomp.) (Found: C, 48.9; H, 3.6. $C_8H_6O_4S$ requires C, 48.5; H, 3.00%); $\delta_H(CDCl_3$–DMSO) 4.28 (s, OMe), 6.71 (d, 4-H, *J* 2.4 Hz), and 7.33 (d, 6-H, *J* 2.4 Hz); $\nu_{max.}$(KBr) 3 440br (hydrogen-bonded acid OH), 1 670s (acid C=O), 1 595s (C=C), and 1 567s cm^{-1} (C=C).

3-*Methoxy*-2,4-*bismethoxycarbonylthieno*[3,4-b]*furan* (**28**). To a stirred solution of 3-hydroxy-2,4-bismethoxycarbonylthieno[3,4-*b*]furan (**17**) (1 g, 3.77 mmol) in anhydrous DMF (50 ml; dried over type 4A molecular sieves) were added anhydrous potassium carbonate (0.54 g, 3.77 mmol) and iodomethane (22.80 g, 160.6 mmol), and the reaction mixture was heated at 50 °C for 2 h, poured onto crushed ice–2M-hydrochloric acid, and extracted with dichloromethane (× 4). The extracts were combined and washed with water (× 5), dried ($MgSO_4$), treated with charcoal, filtered, and evaporated to yield a brown oil, which was passed down a short neutral alumina column (dichloromethane as eluant). The yellow solid obtained was recrystallized from aqueous methanol to give the *title diester* as white needles (0.30 g, 29%), m.p. 155—156 °C (Found: C, 48.8; H, 3.8. $C_{11}H_{10}O_6S$ requires C, 48.9; H, 3.7%); $\delta_H(CDCl_3)$ 3.91, 3.95, and 4.05 (each s, 3 × OMe) and 7.08 (s, 6-H); $\nu_{max.}$(KBr) 3 103m (thiophene proton), 1 723s, 1 705s (2 × ester C=O), and 1 574s cm^{-1} (C=C).

2,4-*Dicarboxy*-3-*methoxythieno*[3,4-b]*furan* (**29**) was prepared from the above diester by the method described under compound (**25**) except that the reaction was carried out at 20 °C for 18 h to produce the diacid in 86% yield (on a 0.13 g scale), m.p. 240 °C (decomp.) (Found: C, 44.2; H, 2.3. $C_9H_6O_6S$ requires C, 44.6; H, 2.4%); δ_H(DMSO) 3.98 (s, OMe), 5.20 (br, 2 × CO_2H, disappears on treatment with D_2O), and 7.25 (s, 6-H).

2,4-*Bismethoxycarbonyl*-3-(4-*tolylsulphonyloxy*)*thieno*[3,4-b]-*furan* (**30**). A solution of 3-hydroxy-2,4-bismethoxycarbonylthieno[3,4-*b*]furan (**17**) (0.5 g, 1.95 mmol) in pyridine (20 ml; dried over type 4A molecular sieves) was treated with toluene-4-sulphonyl chloride (1 g, 5.24 mmol) and the mixture was heated under reflux for 30 min, then poured onto a vigorously stirred mixture of crushed ice and 2M-hydrochloric acid. The white precipitate was filtered off, washed well with ice-cold water, and recrystallized from aqueous methanol to afford the *title toluenesulphonate* (0.29 g, 37%), m.p. 136—137 °C (Found: C, 48.6; H, 3.3. $C_{17}H_{14}O_8S_2 \cdot \frac{1}{2}H_2O$ requires C, 48.7; H, 3.6%); $\delta_H(CDCl_3$–DMSO) 2.46 (s, MeC_6H_4), 3.50 (s, OMe), 3.80 (s, OMe), 7.35 (d, MeC_6H_4, *J* 8 Hz), 7.79 (d, MeC_6H_4, *J* 8 Hz), and 7.65 (s, 6-H); $\nu_{max.}$(KBr) 3 125w (thiophene proton), 3 085w (ArH) 1 729s, 1 710s (ester C=O), 1 610w (C=C), 1 593m (C=C), and 1 215s cm^{-1} (sulphonate OSO_2).

3-*Allyloxy*-2,4-*bismethoxycarbonylthieno*[3,4-b]*furan* (**31**). To a stirred suspension of 3-hydroxy-2,4-bismethoxycarbonylthieno[3,4-*b*]furan (**17**) (1 g, 3.90 mmol) in anhydrous DMSO (30 ml) were added anhydrous potassium carbonate (0.54 g, 3.90 mmol) and 3-bromoprop-1-ene (0.47 g, 3.90 mmol), and the reaction mixture was left for 24 h at room temperature, and then poured into water (100 ml) and extracted with ethyl acetate (× 3). The extracts were combined, washed with water, dried ($MgSO_4$), treated with charcoal, filtered, and evaporated to yield a bright yellow oil, which was purified by medium-pressure liquid chromatography [silica, *ex.* Merck, 230—400 mesh; eluant ether–chlorohexane (1:1)] for analysis. The product was a pale yellow oil (0.97 g, 84%) (Found: C, 52.6; H, 4.0; S, 10.7. $C_{13}H_{12}O_6S$ requires C, 52.7; H, 4.0; S, 10.8%); $\delta_H(CDCl_3)$ 3.84 (s, OMe), 4.00 (s, OMe), 4.20 (m, OCH_2), 5.10—5.80 (m, CH–CH_2), and 6.92 (s, 6-H); $\delta_C(CDCl_3)$ 41.0, 52.6, 52.8, 105.1, 118.2, 129.2, 130.9, 132.0, 143.4, 153.6, 159.5, 169.1, and 171.0; $\nu_{max.}$ (thin film) 3 125w (thiophene proton), 3 000w (allylic group, 1 740s (ester C=O), 1 660w (allyl C=C), and 1 595s cm^{-1} (C=C).

2-*Allyl*-2,4-*bismethoxycarbonylthieno*[3,4-b]*furan*-3(2H)-*one* (**32**). 3-Allyloxy-2,4-bismethoxycarbonylthieno[3,4-*b*]furan (**31**) (1 g, 3.90 mmol) was heated to 200 °C in a Kugelrohr oven at 0.1 mmHg. The *title product* distilled over as a bright yellow oil (0.82 g, 82%) (Found: C, 52.5; H, 3.9; S, 10.8. $C_{13}H_{12}O_6S$ requires C, 52.7; H, 4.0; S, 10.8%); $\delta_H(CDCl_3)$ 3.10 (m, CCH_2), 3.88 (s, OMe), 4.04 (s, OMe), 5.12—5.96 (m, CH=CH_2), and 6.86 (s, 6-H); $\delta_C(CDCl_3)$ 38.7, 52.6, 53.4, 102.4, 102.7, 121.1, 128.2, 129.2, 160.0, 165.7, 169.1, and 185.1; $\nu_{max.}$ (thin film) 3 100m

(thiophene proton), 1 760—1 710s (ketone and ester C=O), 1 640m (allyl C=C), and 1 570s cm^{-1} (C=C).

2-*Allyl*-2-*ethoxycarbonyl*-4-*methylthieno*[3,4-b]*furan*-3(2H)-*one* (**33**). (*a*) A stirred mixture of 3-bromoprop-1-ene (0.53 g, 4.42 mmol), anhydrous potassium carbonate (0.61 g, 4.42 mmol), and 2-ethoxycarbonyl-4-methylthieno[3,4-*b*]furan-3(2*H*)-one (**14**) (1 g, 4.42 mmol) in acetonitrile (20 ml) was heated under reflux for 5 h, treated with charcoal, filtered, and evaporated to yield the product as a brown oil (1.1 g). This was purified by high-vacuum distillation (b.p. 170 °C/0.15 mmHg) to give the *title product* as an oil (0.9 g, 76%) (Found: C, 58.9; H, 5.3; S, 12.0. $C_{13}H_{14}O_4S$ requires C, 58.7; H, 5.3; S, 12.0%); $\delta_H(CDCl_3)$ 1.10 (t, OCH_2Me, *J* 6 Hz), 2.67 (s, 4-Me), 2.96 (m, CCH_2), 4.30 (q, OCH_2Me, *J* 6 Hz), 5.08—6.00 (m, $CH{=}CH_2$), and 6.24 (s, 6-H); $\delta_C(CDCl_3)$ 14.1, 14.5, 38.7, 62.5, 92.3, 99.5, 120.5, 125.1, 129.8, 145.1, 164.3, 165.9, and 187.3; $\nu_{max.}$ (thin film) 3 110w (thiophene proton), 1 750s (ester C=O), 1 717s (keto C=C), 1 640m (allyl C=C), 1 584s cm^{-1} (C=C).

(*b*) A mixture of 3-bromoprop-1-ene (2.67 g, 22.1 mmol), anhydrous potassium carbonate (0.61 g, 4.42 mmol), and the thienofuran (**14**) (1 g, 4.42 mmol) in anhydrous DMSO (20 ml) was stirred for 18 h at ambient temperature. The reaction mixture was filtered into cold water (100 ml) and the aqueous mixture was extracted with ethyl acetate (×4). The extracts were combined, washed with water (×2), dried ($MgSO_4$), treated with charcoal, filtered, and evaporated to yield a brown oil (3.5 g), which was purified by high-vacuum distillation (b.p. 168—172 °C/0.15 mmHg). The title product was an oil (1.0 g, 87%).

2-*Ethoxycarbonyl*-2,4-*dimethylthieno*[3,4-*b*]*furan*-3(2H)-*one* (**34**). A mixture of 2-ethoxycarbonyl-4-methylthieno[3,4-*b*]-furan-3(2*H*)-one (**14**) (2.3 g, 10.2 mmol), iodomethane (1.45 g, 10.2 mmol), and anhydrous potassium carbonate (1.41 g, 10.2 mmol) in anhydrous DMSO (20 ml) was stirred at 20 °C for 18 h, then filtered into water (100 ml), and the aqueous fraction was extracted with ethyl acetate (×4). The extracts were combined and washed with water (×2), dried ($MgSO_4$), treated with charcoal, filtered, and evaporated to give a pale brown oil, which was purified for analysis by high-vacuum distillation (b.p. 150 °C/0.15 mmHg) (2.3 g, 94%). The *title compound* (Found: C, 55.0; H, 5.0; S, 13.3. $C_{11}H_{12}O_4S$ requires C, 55.0; H, 5.0; S, 13.3%) showed $\delta_H(CDCl_3)$ 1.30 (t, OCH_2Me, *J* 6 Hz), 1.78 (s, 2-Me), 2.70 (s, 4-Me), 4.20 (q, OCH_2Me, *J* 6 Hz), and 6.20 (s, 6-H); $\delta_C(CDCl_3)$ 14.0, 14.5, 20.1, 62.5, 92.3, 97.4, 124.7, 145.3, 166.1, 167.0, and 188.7; $\nu_{max.}$ (thin film) 3 110w (thiophene proton), 2 980m, 2 935w (aliphatic protons), 1 750s (ester C=O), 1 720s (keto C=O), and 1 585s cm^{-1} (C=C).

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