Reactions with Methyl 3-Hydroxythiophene-2-carboxylate. Part 2.[1] A New Route to Mono- and Di-alkyl Ethers of Thiotetronic and α-Halogenothiotetronic Acids

Carlos Corral* and Jaime Lissavetzky
Instituto de Química Médica (C.S.I.C.), Juan de la Cierva, 3. Madrid 28006, Spain

Methyl 2-chloro-3-oxo-2,3-dihydrothiophene-2-carboxylates (**2**), obtained from methyl 3-hydroxythiophene-2-carboxylate by straightforward halogenation, added alcohols and then lost hydrogen chloride at room temperature to yield thiophene-2,4-diols (**4**). Successive *O*-alkylation and alkaline hydrolysis of these compounds gave 3,5-dialkoxythiophene-2-carboxylic acids (**6**) in nearly quantitative yield. The latter could either be thermally decarboxylated or decarboxylated and partially dealkylated at room temperature by aqueous acid to the ethers of thiotetronic and α-halogenothiotetronic acids in high yield.

In contrast to the interest shown in the chemistry of tetronic acid, little attention has been paid to derivatives of thiotetronic acid since the initial work of Benary.[2,3] Some years ago, an I.C.I. research team reconsidered this work and claimed strong antiarthritic activity for some arylidene derivatives of α-acylthiotetronic acids.[4,5]

The easily available[6] methyl 3-hydroxythiophene-2-carboxylate (**1a**) appears to be a suitable starting material for the preparation of 3-hydroxythiophene derivatives; its use for the synthesis of the title compounds is considered in this paper.

A solution of (**1a**) and *N*-chlorosuccinimide when heated at 60 °C in acetic acid is reported to give (**2c**).[7] We have now found that treatment of (**1a**) and (**1b**) in chloroform at room temperature with sulphuryl chloride yields (**2a**) and (**2b**), respectively.

Compounds (**2**) are α,β-unsaturated cyclic ketones sensitive to base but capable of undergoing 1,4-addition of alcohols at room temperature in the absence of basic catalysts to give compounds (**3**). These compounds, which were not isolated, spontaneously lost hydrogen chloride by γ elimination to yield compounds (**4**) (see Scheme). Owing to the halogen inductive effect (**2b**) and (**2c**) were more reactive than (**2a**) to addition of alcohol as shown by shorter times of reaction with primary alcohols and by the fact that isopropyl alcohol added to (**2b**) and (**2c**), but not to (**2a**).

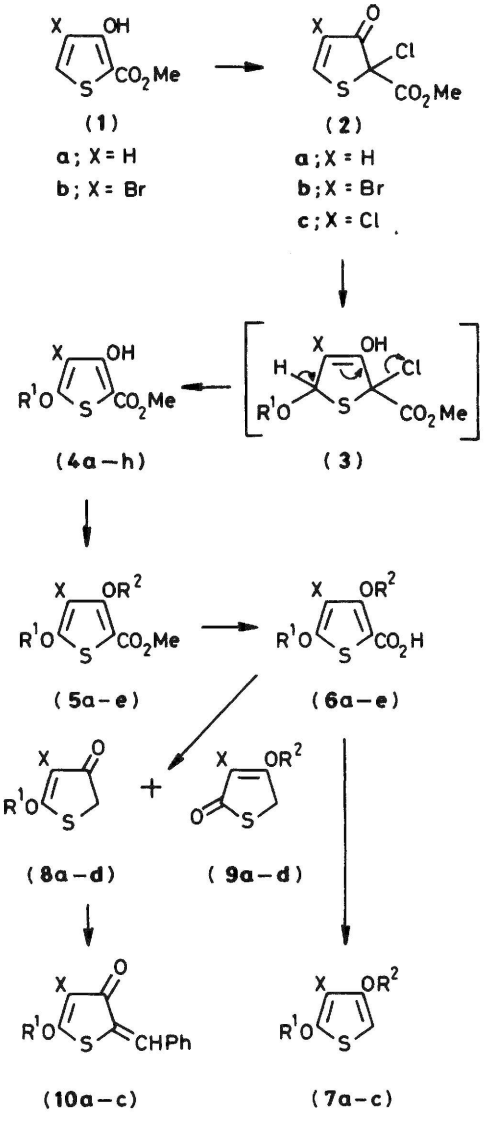
Compounds (**4**) could be methylated or ethylated in nearly quantitative yield by dimethyl or diethyl sulphate in boiling acetone in the presence of potassium carbonate. Thus, (**4a**), (**4b**), (**4c**), and (**4f**) were methylated to yield (**5a**), (**5b**), (**5c**), and (**5d**), and (**4a**) was ethylated to yield (**5e**).

Hydrolysis of compounds (**5**) to the corresponding compounds (**6**) was achieved in nearly quantitative yield by heating to reflux their suspensions in aqueous sodium hydroxide.

Compounds (**6**) could be decarboxylated in high yield by heating them above their melting points. Thus, (**7a**), (**7b**) and (**7c**), *i.e.* the dimethyl ethers of thiotetronic, α-bromothiotetronic and α-chlorothiotetronic acids, were obtained from (**6a**), (**6c**), and (**6d**), respectively.

When compounds (**6a—e**) were stirred in 3M-aqueous hydrochloric acid for *ca.* 5 h at room temperature they were simultaneously decarboxylated and partially dealkylated to give a mixture of the corresponding compounds (**8a—d**) and (**9a—d**). From the mixture, both types of compounds could be separated by column chromatography.

The assignment of structures (**8a**) and (**9a**) to the isomeric reaction products of (**6a**) was clear from the ^{1}H n.m.r. results, since the existence of an allylic coupling constant ($J_{3,5} \simeq 1$ Hz)



Scheme.

Table 1. Methyl 5-alkoxy-3-hydroxythiophene-2-carboxylates (**4a—h**)

Compound[a] (Formula)	X	R^1	Time of reaction (h)	Yield[b] (%)	M.p. (°C)[c]	Found (%) (Required) C	H	S
(4a) ($C_7H_8O_4S$)	H	Me	10	65	71—72[d]	44.5 (44.7)	4.3 (4.25)	16.8 (17.0)
(4b) ($C_8H_{10}O_4S$)	H	Et	72	57	52—53	47.3 (47.5)	5.1 (4.95)	16.1 (15.8)
(4c) ($C_7H_7BrO_4S$)	Br	Me	4	74	105—107	31.7 (31.5)	2.55 (2.6)	12.2 (12.0)
(4d) ($C_8H_9BrO_4S$)	Br	Et	4	87	156—158	33.9 (34.2)	3.25 (3.2)	11.7 (11.4)
(4e) ($C_9H_{11}BrO_4S$)	Br	Pr^i	120	50	70—71	36.7 (36.6)	3.85 (3.7)	10.95 (10.8)
(4f) ($C_7H_7ClO_4S$)	Cl	Me	4	58	79—80	37.9 (37.75)	3.3 (3.15)	14.6 (14.4)
(4g) ($C_8H_9ClO_4S$)	Cl	Et	4	54	160—162	40.8 (40.6)	3.95 (3.8)	15.1 (15.0)
(4h) ($C_9H_{11}ClO_4S$)	Cl	Pr^i	120	47	71—73	43.1 (43.1)	4.35 (4.4)	12.5 (12.8)

[a] All these compounds showed the following common ^1H n.m.r. spectroscopic data; δ_H ($CDCl_3$) 3.83—3.92 (3 H, s, CO_2Me); 10.05—10.15 (1 H, s, OH). They also showed the characteristic signals of methoxy, ethoxy, or isopropoxy groups and compounds (**4a**) and (**4b**) showed the signal of the thiophene proton in position 4 as a singlet at δ 5.96. Also they showed the following common i.r. spectroscopic data: $\nu_{max.}$ (Nujol) 3 300—3 280 (OH) and 1 670—1 655 cm^{-1} (CO). [b] Overall yield from (**1a**) and (**1b**). [c] Recrystallized from the corresponding alcohol (MeOH, EtOH, or Pr^iOH). [d] Lit.,[9] m.p. 72—73 °C.

points to structure (**9a**). Nevertheless, the structures were definitively established chemically since one of the products obtained from (**6b**) was identical with (**9a**) and one of the products obtained from (**6e**) was identical with (**8a**).

The structural assignment of the reaction products of (**6c**) and (**6d**) was made on the basis of i.r. spectra. In one of the series, corresponding to structure (**8**), the C=C stretching vibration appears at *ca.* 1 550 cm^{-1} whereas in the other one, corresponding to structure (**9**), it appears at *ca.* 1 600 cm^{-1}. Further chemical evidence which supports the assignment based on the i.r. data, was provided by compounds (**8**) which reacted with benzaldehyde in methanolic solution in the presence of catalytic amounts of piperidine to yield the corresponding yellow benzylidene derivative; compounds with structure (**9**) do not react in the same manner. Finally, the R_F values are in agreement with the proposed assignments, the higher value corresponding to structure (**9**) (4-alkoxy derivatives) and the lower to structure (**8**) (5-alkoxy derivatives).

Experimental

M.p.s were determined on a Büchi 510 melting point apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer. ^1H N.m.r. spectra were recorded on a Varian EM 390 90 MHz spectrometer (Me_4Si as an internal standard).

Compound (**2c**) was obtained according to the literature.[7]

Compound (**2b**) was obtained by bromination of (**1a**) in acetic acid at room temperature.[1]

Methyl 2-Chloro-3-oxo-2,3-dihydrothiophene-2-carboxylate (**2a**).—Sulphuryl chloride (8.9 mL, 0.11 mol) was added to a solution of compound (**1a**) (15.8 g, 0.1 mol) in anhydrous chloroform (50 ml). There was a rapid evolution of gases and the reaction mixture, protected from moisture, was left for 4 h at room temperature. The solution was evaporated to dryness and the solid residue was used as crude product for the subsequent reactions.

A sample (1.58 g) was crystallized from n-hexane (100 ml) to yield a colourless solid (1.31 g, 68%), m.p. 70.5—71 °C (Found: C, 37.7; H, 2.7; Cl, 18.7; S, 17.0. $C_6H_5ClO_3S$ requires C, 37.4; H, 2.6; Cl, 18.4; S, 16.6%); $\nu_{max.}$ (Nujol) 1 745 (CO) and 1 695 (CO); δ_H (CCl_4) 3.95 (3 H, s, Me), 6.26 (1 H, d, $J_{4,5}$ 6 Hz, thiophene 4-H), 8.44 (1 H, d, *J* 6 Hz, thiophene 5-H).

Methyl 4-Bromo-2-chloro-3-oxo-2,3-dihydrothiophene-2-carboxylate (**2b**).—This compound was obtained in the same manner as described above for (**2a**), except that the reaction time was 20 h. A sample (2.37 g) was crystallized from n-hexane (100 ml) to yield a colourless solid (1.98 g, 73%), m.p. 40—42 °C (Found: C 26.8; H, 1.4; S, 11.9. $C_6H_4BrO_3S$ requires C, 26.5; H, 1.5; S, 11.8%); $\nu_{max.}$ (Nujol) 1 750 (CO) and 1 705 (CO); δ_H (CCl_4) 3.91 (3 H, s, Me) and 8.38 (1 H, s, thiophene).

Methyl 5-Alkoxy-3-hydroxythiophene-2-carboxylates (**4a—h**): *General Procedure.*—The corresponding crude compound (**2a—c**) (0.01 mol) was dissolved in the suitable anhydrous alcohol (8—11 ml) and the reaction mixture was allowed to stand at room temperature for the time indicated in Table 1.

Compounds (**4c—h**) crystallized from the reaction mixture and were obtained as pure compounds by filtration and washing with further reaction solvent.

Compound (**4a**) crystallized only partially from the reaction mixture. A part of it was obtained by filtration and washing with methanol. The remainder was separated by elution of the evaporated reaction residue through a silica-gel column, using n-hexane–ethyl acetate (5:1) as eluant. Compound (**4b**) did not crystallize from the reaction mixture and was separated by elution of the evaporated reaction residue through a silica-gel column using n-hexane–ethyl acetate (5:1) as eluant.

The compounds obtained according to this procedure are shown in Table 1.

Methyl 3,5-Dialkoxythiophene-2-carboxylates (**5a—e**): *General Procedure.*—Potassium carbonate (0.01 mol) was added to a solution of the corresponding compound (**4a**), (**4b**), (**4c**), or (**4f**) in dry acetone (25 ml) and the mixture was stirred for 5—10 min; once the potassium salt was formed, the appropriate dialkyl sulphate (0.011 mol) was added. The reaction mixture was refluxed for 2—5 h (monitored by t.l.c. on silica gel with

Table 2. Methyl 3,5-dialkoxythiophene-2-carboxylates (**5a—e**)

Compound[a] (Formula)	X	R^1	R^2	M.p. °C	Found (%) (Required) C	H	S
(5a) ($C_8H_{10}O_4S$)	H	Me	Me	69—70[b]	47.4 (47.5)	5.1 (4.95)	15.95 (15.8)
(5b) ($C_9H_{12}O_4S$)	H	Et	Me	71—72[c]	50.2 (50.0)	5.6 (5.55)	15.0 (14.8)
(5c) ($C_8H_9BrO_4S$)	Br	Me	Me	78—79[b]	34.1 (34.2)	3.4 (3.2)	11.7 (11.4)
(5d) ($C_8H_9ClO_4S$)	Cl	Me	Me	82—84[d]	40.8 (40.6)	3.8 (3.8)	13.25 (13.5)
(5e) ($C_9H_{12}O_4S$)	H	H	Et	79—81[d]	50.1 (50.0)	5.65 (5.55)	15.1 (14.8)

[a] All these compounds showed the following common ^1H n.m.r. spectroscopic data: δ_H ($CDCl_3$) 3.80—3.82 (3 H, s, CO_2Me). They also showed the characteristic signals of methoxy or ethoxy groups and compounds (**5a**), (**5b**) and (**5e**) showed the signal of the thiophene proton in position 4 as a singlet at δ6.14. Also they showed the following common i.r. spectroscopic data: $\nu_{max.}$ (Nujol) 1 715—1 665 (CO). [b] Recrystallized from Pr^iOH; (**5a**) lit.,[9] m.p. 67—68 °C. [c] Recrystallized from n-hexane or n-hexane–ethyl acetate. [d] Recrystallized from MeOH.

Table 3. 3,5-Dialkoxythiophene-2-carboxylic acids (**6a—e**)

Compound[a] (Formula)	X	R^1	R^2	M.p. °C (decomp.)	Found (%) (Required) C	H	S
(6a) ($C_7H_8O_4S$)	H	Me	Me	108—110	44.9 (44.7)	4.3 (4.25)	17.2 (18.0)
(6b) ($C_8H_{10}O_4S$)	H	Et	Me	118—120	47.7 (47.5)	5.0 (4.95)	16.1 (15.8)
(6c) ($C_7H_7BrO_4S$)	Br	Me	Me	125	31.4 (31.5)	2.8 (2.6)	12.2 (12.0)
(6d) ($C_7H_7Cl_4S$)	Cl	Me	Me	125—126	37.9 (37.75)	3.3 (3.15)	14.5 (14.4)
(6e) ($C_8H_{10}O_4S$)	H	Me	Et	115—117	47.3 (47.5)	4.8 (4.95)	15.65 (15.08)

[a] All these compounds had the following ^1H n.m.r. signals in common: δ_H [$(CD_3)_2SO$] 3.2—3.8 (1 H, br s, OH); further, they showed the signals characteristic of methoxy or ethoxy groups. Compounds (**6a**), (**6b**), and (**6e**) showed the thiophene 4-H as a singlet at δ6.52. Also they had the following i.r. absorptions in common: $\nu_{max.}$ (Nujol) 3 500—3 000 (OH) and 1 670—1 640 (CO). [b] Recrystallized from ethyl acetate.

Table 4. 5-Alkoxythiophen-3(2*H*)-ones (**8a—d**) and 4-alkoxythiophen-2(5*H*)-ones (**9a—d**)

Starting material	Reaction products	Yield (%)	M.p. (°C)[a]	$\nu_{max.}$ (Nujol)	$\delta_H(CDCl_3)$	Found (%) (Required) C	H	S
(6a)	**(8a)** ($C_5H_6O_2S$)	56	84—85	1 655 (CO), 1 555 (C=C)	3.65 (2 H, s, CH_2), 4.07 (3 H, s, Me), 5.55 (1 H, s, CH)	46.0 (46.15)	4.75 (4.6)	24.8 (24.6)
	(9a) ($C_5H_6O_2S$)	34	85—86	1 665 (CO), 1 605 (C=C)	3.87 (2 H, d, $J_{3,5}$ 1 Hz, CH_2), 3.95 (3 H, s, Me), 5.50 (1 H, $J_{3,5}$ 1 Hz, CH)	46.2 (46.15)	4.7 (4.6)	24.9 (24.6)
(6b)	**(8b)** ($C_6H_8O_2S$)	48	57—58	1 670 (CO), 1 545 (C=C)	1.39—1.38 (3 H, t, Me), 3.72 (2 H, s, CH_2), 4.12—4.62 (2 H, q, Et), 5.50 (1 H, s, CH)	50.1 (50.0)	5.6 (5.55)	22.4 (22.2)
	(9a)	33						
(6c)	**(8c)** ($C_5H_5BrO_2S$)	63	140(decomp.)	1 675 (CO), 1 555 (C=C)	3.85 (2 H, s, CH_2), 4.25 (3 H, s, Me)	28.9 (28.7)	2.3 (2.4)	15.15 (15.3)
	(9b) ($C_5H_5BrO_2S$)	29	119—120	1 665 (CO), 1 600 (C=C)	4.04 (2 H, s, CH_2), 4.21 (3 H, s, Me)	28.5 (28.7)	2.4 (2.4)	15.2 (15.3)
(6d)	**(8d)** ($C_5H_5ClO_2S$)	37	118—120	1 660 (CO), 1 545 (C=C)	3.87 (2 H, s, CH_2), 4.28 (3 H, s, Me)	36.6 (36.45)	3.1 (3.0)	19.75 (19.45)
	(9c) ($C_5H_5ClO_2S$)	48	81—82	1 675 (CO), 1 605 (C=C)	4.06 (2 H, s, CH_2), 4.29 (3 H, s, Me)	36.7 (36.45)	3.2 (3.0)	19.7 (19.45)
	(8a)	38						
(6e)	**(9d)** ($C_6H_8O_2S$)	43	52—53	1 665 (CO), 1 600 (C=C)	1.37—1.62 (3 H, t, Me), 4.02 (2 H, d, $J_{3,5}$ 1 Hz, CH_2), 4.05—4.35 (2 H, q, CH_2, Et), 5.62 (1 H, t, $J_{3,5}$ 1 Hz, CH)	49.7 (50.0)	5.4 (5.55)	22.1 (22.2)

[a] Recrystallized from n-hexane.

ethyl acetate–n-hexane (1:5) as eluant and evaporated to dryness. The residue was treated with water and ether. The ethereal extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The solids thus obtained were practically pure compounds (t.l.c.) and were used without further purification in the following reactions.

The recrystallized compounds obtained according to this procedure are shown in Table 2.

3,5-*Dialkoxythiophene-2-carboxylic Acids* (**6a—e**).—A suspension of the appropriate compound (**5a—e**) (0.01 mol) in a 1M-sodium hydroxide solution (20 ml) was heated to reflux until the solid was dissolved (20—30 min). The reaction mixture, once cooled, was carefully neutralized with acid to yield compounds (**6a—e**) in nearly quantitative yield. These were used in the following reactions without any further purification. The recrystallized compounds obtained according to this procedure are shown in Table 3.

2,4-*Dimethoxythiophene* (**7a**).[8] 3,5-Dimethoxythiophene-2-carboxylic acid (**6a**) (0.01 mol) was distilled under reduced pressure to yield a colourless liquid (1.30 g, 90%), b.p. 115 °C (at 30 mmHg) (Found: C, 50.2; H, 5.4; S, 21.95. $C_6H_8O_2S$ requires C, 50.0; H, 5.55; S, 22.2); n_D^{20} 1.5262; δ_H (CCl_4) 3.73 (3 H, s, OMe), 3.84 (3 H, s, OMe), 5.37 (1 H, d, $J_{3,5}$ 2.4 Hz, thiophene 5-H), 5.87 (1 H, d, $J_{3,5}$ 2.4 Hz, thiophene 3-H).

3-*Bromo*-2,4-*dimethoxythiophene* (**7b**). 4-Bromo-3,5-dimethoxythiophene-2-carboxylic acid (**6c**) (0.01 mol) was suspended in xylene (25 ml) and the reaction mixture was refluxed for 15—20 min. The solvent was removed under reduced pressure and the residue crystallized from methanol (2.05 g, 92%), m.p. 98—100 °C (Found: C, 32.5; H, 3.1; S, 14.2. $C_6H_7BrO_2S$ requires C, 32.3; H, 3.1; S, 14.3); δ_H (CCl_4) 3.88 (3 H, s, OMe), 4.00 (3 H, s, OMe), and 5.61 (1 H, s, thiophene H).

3-*Chloro*-2,4-*dimethoxythiophene* (**7c**). This compound was obtained in the same manner as compound (**7b**) starting from compound (**6d**) (0.01 mol) to yield a colourless solid (1.39 g, 78%), m.p. 60—62 °C from n-hexane (15 ml) (Found: C, 40.2; H, 3.8; S, 17.6. $C_6H_7ClO_2S$ requires C, 40.3; H, 3.9; S, 17.9); δ_H (CCl_4) 3.83 (3 H, s, OMe), 3.96 (3 H, s, OMe), and 5.50 (1 H, s, thiophene H).

5-*Alkoxythiophen*-3(2H)-*ones* (**8a—d**) *and* 4-*Alkoxythiophen*-2(5H)-*ones* (**9a—d**).—The appropriate carboxylic acid (**6a—e**) was stirred for 5 h at room temperature with a large excess of 3M-hydrochloric acid and the reaction mixture or solution was then extracted with ethyl acetate [thoroughly in the case of (**6a**), (**6b**), and (**6c**)]. The organic extracts were evaporated to dryness and the residue, which showed two spots in t.l.c., was chromatographed on a silica-gel column using a mixture of n-hexane–ethyl acetate (2:1) as eluant except for compound (**6b**), in which the mixture used was 5:1, to yield compounds (**8a—d**) and (**9a—d**). The compounds obtained according to this procedure are shown in Table 4.

5-*Alkoxy*-2-*benzylidenethiophen*-3(2H)-*ones* (**10a—c**).—A solution of compound (**8a**), (**8c**), or (**8d**) (0.02 mol), benzaldehyde (0.015 mol), and a drop of piperidine in methanol (50 ml) was heated to reflux for the time required [monitored by t.l.c. on silica gel with n-hexane–ethyl acetate (2:1) as eluant]. The bright yellow solid that crystallized on cooling was filtered off and washed with methanol. Thus, the following compounds were obtained.

2-*Benzylidene*-5-*methoxythiophen*-3(2H)-*one* (**10a**) (1.96 g, 90%), m.p. 129.5—130.5 °C (methanol) (Found: C, 65.9; H, 4.4; S, 14.5. $C_{12}H_{10}O_2S$ requires C, 66.05; H, 4.6; S, 14.7). $\nu_{max.}$ (Nujol) 1 660 (CO); ν_H ($CDCl_3$) 4.09 (3 H, s, OMe), 5.75 (1 H, s, thiophene 4-H), 7.45—7.75 (5 H, m, Ph), and 7.94 (1 H, s, CH).

2-*Benzylidene*-4-*bromo*-5-*methoxythiophen*-3(2H)-*one* (**10b**) (2.08 g, 70%), m.p. 131—133 °C (methanol) (Found: C, 48.3; H, 3.1; S, 10.6. $C_{12}H_9BrO_2S$ requires C, 48.5; H, 3.0; S, 10.8); $\nu_{max.}$ (Nujol) 1 660 (CO); δ_H ($CDCl_3$) 4.28 (3 H, s, OMe), 7.50—7.75 (5 H, m, Ph H), and 8.12 (1 H, s, CH).

2-*Benzylidene*-4-*chloro*-5-*methoxythiophen*-3(2H)-*one* (**10c**) (1.84 g, 73%), m.p. 128—129 °C (methanol) (Found: C, 57.15; H, 3.6; S, 12.5. $C_{12}H_9ClO_2S$ requires C, 57.0; H, 3.6; S, 12.7). $\nu_{max.}$ (Nujol) 1 660 (CO); δ_H ($CDCl_3$) 4.25 (3 H, s, OMe), 7.45—7.75 (5 H, m, Ph H), and 8.09 (1 H, s, CH).

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