Electrophilic Aromatic Substitution. Part 32.[1] Partial Rate Factors for Detritiation of Dithieno[2,3-*b*:3',2'-*d*]thiophen, Dithieno[3,2-*b*:2',3'-*d*]-thiophen, and Dithieno[2,3-*b*:2',3'-*d*]thiophen

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Dithieno[2,3-*b*:3',2'-*d*]thiophen (I), dithieno[3,2-*b*:2',3'-*d*]thiophen (II), and dithieno[2,3-*b*:2',3'-*d*]thiophen (III), specifically labelled with tritium in each position have been prepared, and their rates of detritiation measured either in pure trifluoroacetic acid, or mixtures of acetic and trifluroacetic acids, at 70 °C. The variation in rate with acidity shows that these compounds are more strongly hydrogen bonded in trifluoroacetic acid than are the thienothiophens (which are in turn more strongly bonded than thiophen); the overall extent of bonding appears to be greater than in anisole. Partial rate factors (corrected for hydrogen bonding) are calculated as (position and compound in parentheses): 3.8×10^9 [2-(I)]; 3.63×10^6 [3-(I)]; 2.07×10^9 [2-(II)]; 1.94×10^6 [3-(II)]; 2.67×10^9 [2-(III)]; 6.31×10^6 [3-(III)]; 1.62×10^9 [5-(III)]; 3.41×10^6 [6-(III)], the corresponding σ^+-values being −1.095, −0.75, −1.065, −0.72, −1.08, −0.78, −1.05, and −0.75. These compounds are thus very reactive towards electrophilic substitution and the reactivity of each position is increased by 0.05—0.1 σ units compared to the corresponding position in the thienothiophens, *i.e.* slightly less than the amount by which the latter are more reactive than the corresponding positions in thiophen. The reactivities of the α-positions of a given ring are increased more by addition of a thiophen ring which has sulphur on the same side of the molecule as in the ring undergoing substitution; this was true also for the thiophen to thienothiophen transformation. The converse is true for the β-position reactivities and this is the reverse of the observation for the thiophen to thienothiophen transformation. Hückel localization energies correctly predict the relative order of reactivities of the α-positions, and are only marginally incorrect for the β-positions despite the fact that the *d*-orbital electrons are not taken into account.

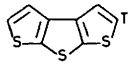
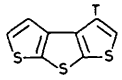
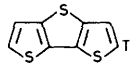
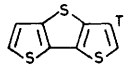
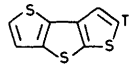
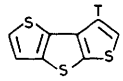
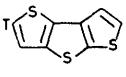
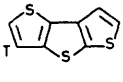
In the accompanying paper we described the quantitative electrophilic aromatic reactivities of the thienothiophens, determined *via* acid-catalysed hydrogen exchange, and compared the results with those obtained in preparative electrophilic substitutions. As our extension of this work we have investigated the reactivities of all positions in the dithienothiophens, molecules for which no other reactivity data exist. For carbocyclic aromatics, Hückel localization energy calculations are very successful in predicting the relative positional reactivities, but these are less good for heterocyclics and they do not for example correctly predict the reactivity of thiophen relative to the thienothiophens. An additional reason for carrying out this work was to provide a more extensive data set for future testing and refining of theoretical methods of calculating heteroaromatic reactivities, as they become available.

RESULTS AND DISCUSSION

The kinetic data are given in Table 1. The difference in rates observed in 100% CF_3CO_2H and 35% CF_3CO_2H–65% HOAc is 550-fold which may be compared with previously observed values of 5 230 (mesitylene), 2 420 (thiophen), 950 (thienothiophens), and 717 (anisole). The differences in these values is accounted for by hydrogen bonding which thus appears to be more severe for the dithienothiophens and this is reasonable since there are three sulphur atoms present. Indeed it is interesting to note that the difference in rates approximately halves with the addition of each sulphur atom. Because of this hydrogen bonding, the exchange rates observed in 100% CF_3CO_2H do not represent the true electrophilic reactivities of these compounds, and it is

Table 1

Rate coefficients (10^7 k/s^{-1}) for detritiation in CF_3CO_2H–HOAc mixtures [a]

No.	Aromatic	CF_3CO_2H in HOAc (v/v) 100	35	15
(1)			15 900	1 50
(2)		8 100	15	*1.77*
(3)			8 400	1 010
(4)		4 500	8	*0.946*
(5)			11 000	*1,300*
(6)			26	*3.07*
(7)			6 700	*792*
(8)			14	*1.66*

[a] Italicised values are calculated from data obtained at higher acidities, using the rate–acidity profiles for compounds (1) and (3).

necessary to calculate these from data obtained at lower acidities. As with the thienothiophens we have chosen 15% CF_3CO_2H (v/v) in HOAc as the medium for which we assume that hydrogen bonding is no longer significant. For the dithienothiophens this may not be entirely true because the fall-off in rates between 35% CF_3CO_2H (v/v) in HOAc and 15% CF_3CO_2H (v/v) in HOAc is 8.45 fold, compared with values of 12.5, 16.4, 19, and 36 for anisole, thienothiophens, thiophen, and mesitylene. [The spread of these values is smaller than noted between 100% and 35% CF_3CO_2H (v/v) in HOAc, as expected since the extent of hydrogen bonding is smaller.] There is then a smaller fall off in rates compared to mesitylene by a factor of 4 which would represent the maximum error in the rate coefficients (which would lead to an error in the derived σ^+-value of <0.07). In the 15% CF_3CO_2H (v/v) in HOAc acid the error must of course be less than this because it is the weakest acid in the range, so that we can use the data derived from this acid with some confidence. The rate coefficients in this medium have therefore been multiplied by 195 000, the difference in exchange rate for mesitylene in 100% and 15% CF_3CO_2H (v/v) in HOAc, to obtain the rate coefficients which would obtain in the former medium in the absence of hydrogen bonding. Division of these rate coefficients by 0.095×10^{-7} s^{-1}, the exchange rate coefficient for benzene [2] gives the partial rate factors in Figure 1, and hence the σ^+-constants in Figure 2 (ρ -8.75).

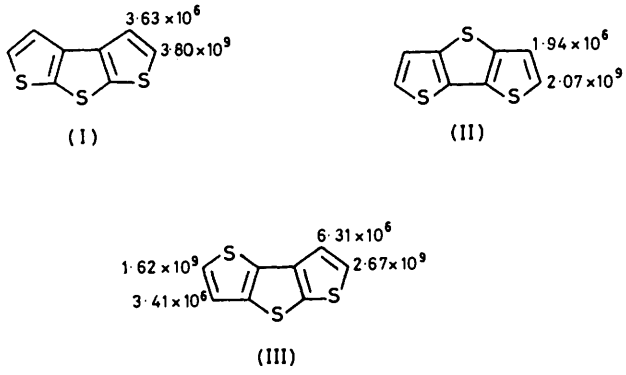
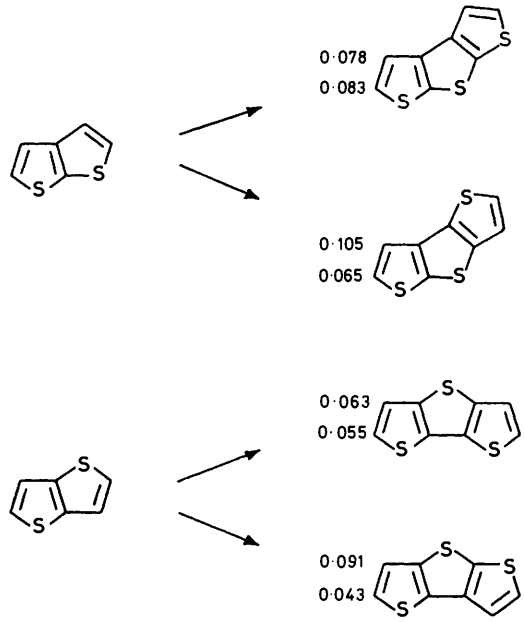


FIGURE 1 Partial rate factors for detritiation

The main features of these results are as follows. (i) The dithienothiophens are very reactive toward electrophilic substitution and indeed are amongst the most reactive aromatics known being comparable in reactivity to phenol.

(ii) The reactivities of the α-positions on one hand and the β-positions on the other, are almost independent of structure. Scheme 1 shows the increment in σ^+-values



SCHEME 1 Increase in σ^+-value produced by annelation

on going from the thienothiophens to the dithienothiophens, from which two facts are evident. (a) The reactivity of the α-position increases most when an annelating sulphur-containing ring has sulphur on the same side of the molecule as the sulphur in the ring undergoing substitution, and the same was true on going from thiophen to thienothiophens.[1] (b) On the whole, annelation increases the β-reactivities more than the α-reactivities. For the thiophen to thienothiophen transformation, one β-position increased in reactivity more than the corresponding α-position, whereas the other pair of α- and β-positions shared a common increase in reactivity.

(iii) The positional reactivity order is quite well predicted by Hückel calculations using $\beta_{CS} = 0.6$ and $\alpha_S = 1.0$ as parameters;[3] the localization energies are given in Table 2. The order of reactivity observed is $1 > 5 > 3 > 7 > 6 > 2 > 8 > 4$ compared with $1 >$

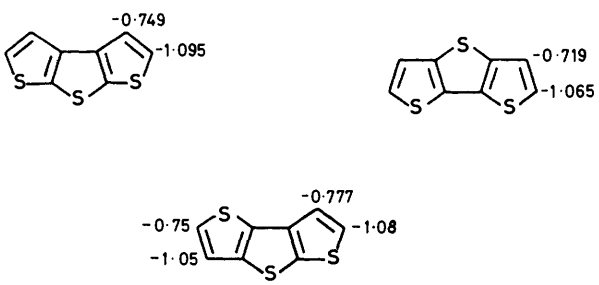


FIGURE 2 σ^+-Values

TABLE 2

Hückel localization energies for dithienothiophens

Compound	Position	No.	$\Delta L_r^+/-\beta$
(I)	2	1	1.6044
	3	2	1.8173
(II)	2	3	1.6445
	3	4	1.8100
(III)	2	5	1.6097
	3	6	1.8030
	5	7	1.6464
	6	8	1.8153

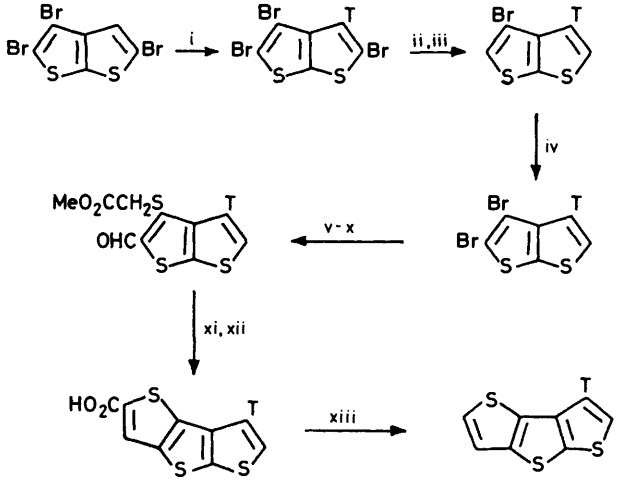
5 > 3 > 7 > 6 > 4 > 8 > 2 predicted which is remarkably good in view of these small differences in reactivity for like positions. Small differences in polarisability of the molecules could cause slight changes in the order in other electrophilic substitutions.

EXPERIMENTAL

[2,3,4,5-$^3H_4$]*Dithieno*[2,3-b:3′,2′-d]*thiophen*.—Dithieno[2,3-*b*:2′,3′-*d*]thiophen (0.01 g, 0.000 05 mol) (kindly donated by Professor M. H. Janssen, University of Groningen, The Netherlands) was heated under reflux with trifluoroacetic acid (1 g) and tritiated water (10 ml; 500 mCi g^{-1} activity) during 1 h. The mixture was then poured into sodium hydroxide solution, extracted with ether, and worked up in the usual way, followed by column chromatography (neutral alumina, activity grade 1) using 1 : 1 ether–pentane as eluant to give [2,3,4,5-$^3H_4$]dithieno[2,3-*b*:3′,2′-*d*]thiophen (74%), m.p. 53.5—54.5 °C, specific activity 8 mCi g^{-1}, *cf.* 10 mCi g^{-1} calculated.

[2,3,5,6-$^3H_4$]*Dithieno*[3,2-b:2′,3′-d]*thiophen*.—*3,3′-Dithienyl sulphide*. 3-Bromothiophen (prepared as previously described) was reacted according to the literature method with bis(phenylsulphonyl) sulphide [prepared in 71% yield, m.p. 131—134 °C (lit.,[4] 128—133 °C)] to give 3,3′-dithienyl sulphide (35%), b.p. 132—135 °C at 1 mmHg, n_D^{20} 1.6689 (lit.,[4] n_D^{20} 1.6720). Ring closure of 3,3-dithienyl sulphide according to the literature method [4] gave dithieno[3,2-*b*:2′,3′-*d*]thiophen (44%), m.p. 65.5—67.5 °C (lit.,[4] 66—67 °C), τ($CDCl_3$) 2.48 and 2.66 (4 H, m). Tritium was incorporated as described above to give [2,3,5,6-$^3H_4$]dithieno[3,2-*b*:2′,3-*d*′]thiophen, specific activity 1.4 mCi g^{-1}, *cf.* 1.7 mCi g^{-1} calculated.

[7-^{3}H]*Dithieno*[2,3-b:2′,3′-d]*thiophen*.—This was prepared according to the route shown in Scheme 2.



SCHEME 2 *Reagents*: i, CF_3CO_2H–T_2O; ii, Mg–Et_2O; iii, H^+; iv, NBS–HOAc; v, Bu^nLi; vi, DMF; vii, Bu^nLi; viii, S; ix, $ClCH_2CO_2Me$; x, H^+; xi, NaOEt; xii, H^+; xiii, heat, Cu

[4-^{3}H]-2,3,5-*Tribromothieno*[2,3-b]*thiophen*. Thieno[2,3-*b*]thiophen was brominated according to the literature method [5] to give 2,3,5-tribromothieno[2,3-*b*]thiophen (76%), m.p. 121—123.5 °C (lit.,[5] 122—124 °C). This compound (3.80 g, 0.01 mol) was heated under reflux with trifluoroacetic acid (14.6 g, 0.01 mol) and tritiated water (50 ml of 500 mCi g^{-1} activity) during 1 h. Normal work-up gave [4-^{3}H]-2,3,5-tribromothieno[2,3-*b*]thiophen (92%), specific activity 2.1 mCi g^{-1}, *cf.* 2.57 mCi g^{-1} calculated.

[4-^{3}H]-3-*Bromo*[2,3-b]*thiophen*. The Grignard reagent formed from [4-^{3}H]-2,3,5-tribromothieno[2,3-*b*]thiophen (3.5 g, 0.0093 mol) and magnesium (0.5 g, 0.021 mol) in ether (10 ml) was hydrolysed followed by normal work-up including recrystallisation from light petroleum (b.p. 80—100 °C), to give [4-^{3}H]-3-bromo[2,3-*b*]thiophen (1.8 g. 88%), m.p. 35.5—37 °C (lit.,[5] 36.5—37 °C for the inactive compound).

[4-^{3}H]-2,3-*Dibromo*[2,3-b]*thiophen*. [4-^{3}H]-3-Bromothieno[2,3-*b*]thiophen was brominated according to the literature method [6] to give [4-^{3}H]-2,3-*dibromo*[2,3-b]*thiophen* (58%), m.p. 62—65 °C (lit.,[6] 63—65 °C).

[7-^{3}H]-*Dithieno*[2,3-b:2′,3′-d]*thiophen*-2-*carboxylic acid*. n-Butyl-lithium (3.2 ml of a 1.6N solution in hexane, 0.005 mol) was added to a stirred solution of [4-^{3}H]-2,3-dibromodithieno[2,3-*b*]thiophen (1.4 g, 0.0047 mol) in THF (5 ml) under nitrogen at −78 °C. After 10 min, dry dimethylformamide (0.37 g, 0.005 mol) was added and the mixture stirred during 15 min. The same quantity of n-butyllithium was then added with stirring during 15 min, sulphur (0.16 g, 0.005 mol) was added, the mixture allowed to attain room temperature, and then heated under reflux during 30 min. It was then cooled, methyl chloroacetate (0.55 g, 0.005 mol) was added, the mixture was stirred overnight at room temperature, then acidified and extracted with ether (three times). The dried ether extracts were added dropwise to sodium ethoxide (0.68 g, 0.01 mol) in ethanol (5 ml) and the mixture heated under reflux during 8 h. The ether was then removed, the residue acidified with concentrated hydrochloric acid, and extracted with ethyl acetate. The dried extracts were concentrated to a crude semi-crystalline oil (26%) which was added to a stirred suspension of copper powder (300 mg) in freshly distilled quinoline (5 ml) and heated at 180—190 °C during 12 h and then 240 °C during 20 h. The cooled mixture was filtered through a plug of Celite 554, the filtrate poured into water, acidified with concentrated HCl and extracted with ether (three times). The combined extracts were washed with sodium hydrogencarbonate solution, dried, concentrated under vacuum, and chromatographed [pentane–ether (2 : 1) as eluant] to give [7-^{3}H]dithieno[2,3-*b*:2′,3′-*d*]thiophen (24%), m.p. 52—53 °C (lit.,[4] 53—54 °C) (Found: C, 48.9; H, 2.05. Calc. for $C_8H_4S_3$: C, 49.0; H, 2.05%).

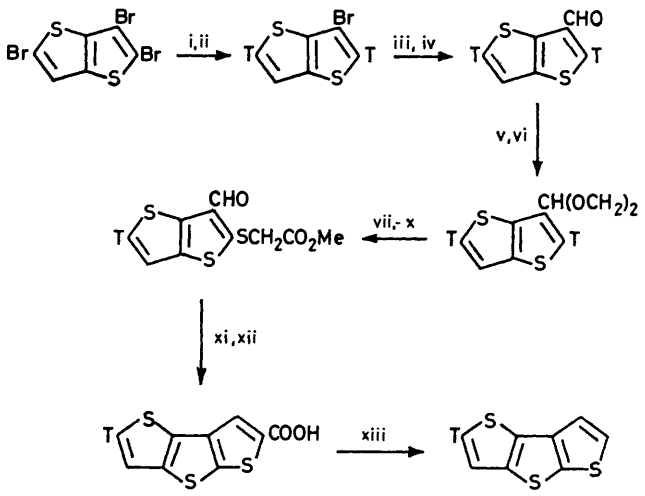
[2-^{3}H]*Dithieno*[2,3-b:2′,3′-d]*thiophen*.—This was prepared according to the route shown in Scheme 3.

2,3,5-*Tribromothieno*[3,2-b]*thiophen*. Bromine (10.5 g, 0.13 mol) was added during 1 h to a cooled (0 °C) and stirred solution of thieno[3,2-*b*]thiophen [1] in chloroform (10 ml), which was then allowed to stand overnight. After washing with sodium hydroxide solution (50 ml; 2N) the organic layer was separated and heated under reflux during 2 h with a solution of potassium hydroxide (3 g, 0.054 mol) in aqueous 95% ethanol (10 ml). Normal work-up followed by two recrystallisations from ethanol gave 2,3,5-tribromothieno[3,2-*b*]thiophen (72%), m.p. 141—142.5 °C (lit.,[5] 141—142 °C).

[2,5-$^3H_2$]-3-*Bromothieno*[3,2-b]*thiophen*. The Grignard reagent formed from 2,3,5-tribromothieno[3,2-*b*]thiophen (11 g, 0.029 mol) and magnesium (1.6 g, 0.066 mol) in THF (30 ml) was hydrolysed with tritiated water followed by

excess of water. Normal work up gave [2,5-$^3H_2$]-3-bromothieno[3,2-*b*]thiophen (72%) as a crude oil indicated by g.l.c. to be 95% pure.

[2,5-$^3H_2$]-3-*Formylthieno*[3,2-b]*thiophen*. Crude [2,5-$^3H_2$]-3-bromothiophen (4.5 g, 0.021 mol) in THF (10 ml) was added dropwise to a stirred solution of n-butyl-lithium (14.5 ml of a 1.6N solution in hexane) in THF (15 ml) at −78 °C under nitrogen. After the mixture had warmed to room temperature it was poured into water, acidified with 2N-hydrochloric acid, and worked up in the normal way to give an oily solid. Two recrystallisations from light



SCHEME 3 *Reagents*: i, Mg–Et_2O; ii, T_2O; iii, Bu^nLi; iv, DMF; v, $HO(CH_2)_2OH$; vi, H^+; vii, Bu^nLi; viii, S; ix, $ClCH_2CO_2Me$; x, H^+; xi, NaOEt; xii, H^+; xiii, heat, Cu

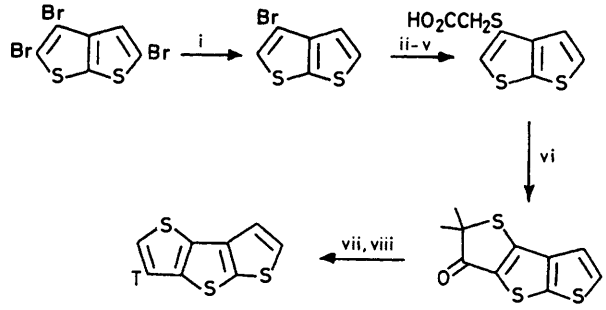
petroleum (b.p. 60—80 °C) gave crystals of [2,5-$^3H_2$]-3-formylthieno[3,2-*b*]thiophen (79%), m.p. 68.5—69.5 °C (lit.,[7] 68—69.5 °C), τ($CDCl_3$) −0.11 (1 H, s, CHO), 1.30 (1 H, s, ArH), 2.19—2.46 (2 H, m, ArH).

[2,5-$^3H_2$]*Thieno*[3,2-b]*thiophen-3-carbaldehyde ethylene acetal*. The above aldehyde (3.0 g, 0.016 mol), benzene (15 ml), ethylene glycol (1 g, 0.16 mol), and a few crystals of toluene-*p*-sulphonic acid were heated during 6 h in a Dean and Stark apparatus. The product was worked up in the usual way to give crude [2,5-$^3H_2$]*thieno*[3,2-b]*thiophen-3-carbaldehyde ethylene acetal* as a brown oil, indicated by g.l.c. analysis to be *ca.* 95% pure, τ($CDCl_3$) 1.59 (1 H, s, ArH), 2.18—2.54 (2 H, m, ArH), 4.20 (1 H, s, CH), and 6.19 [4 H, d, $(CH_2)_2$].

[2-^{3}H]*Dithieno*[2,3-b:2′,3′-d]*thiophen-6-carboxylic acid*. n-Butyl-lithium (10 ml of a 1.6N solution in hexane) was added dropwise to a stirred, cooled (0 °C) solution of the crude acetal (3.2 g, 0.015 mol) in THF (10 ml) under nitrogen. The mixture was heated under reflux during 1 h then cooled to 0 °C. Sulphur (0.5 g, 0.0156 mol) was added in portions and the mixture heated under reflux during 1 h. Methyl chloroacetate (1.15 g, 0.16 mol) in THF (5 ml) was added to the cooled solution which was then stood overnight. Normal work-up gave an ethereal solution of crude *methyl* [5-^{3}H]-3-*formylthieno*[3,2-b]*thiophen-2-thioacetate*. This was heated under reflux during 7 h with sodium ethoxide (4.4 g, 0.065 mol) in ethanol, then acidified to give a crude yellow-orange [2-^{3}H]dithieno[2,3-*b*:2′,3′-*d*]thiophen-6-carboxylic acid.

The crude acid was heated at 190 °C during 2 h and then at *ca.* 230 °C during 40 h with copper powder (3 g) and freshly distilled quinoline (60 ml). Most of the quinoline was removed by distillation and the remainder poured into 2N-hydrochloric acid (100 ml). Normal work-up followed by column chromatography [pentane–ether (2 : 1) as eluant] gave [2-^{3}H]dithieno[2,3-*b*:2′,3′-*d*]thiophen (26%), m.p. 52.5—53.5 °C (lit.,[4] 53—54 °C).

[3-^{3}H]*Dithieno*[2,3-b:2′,3′-d]*thiophen*.—This was prepared according to the route shown in Scheme 4.



SCHEME 4 *Reagents*: i, Zn–HOAc; ii, Bu^nLi; iii, S; iv, $ClCH_2CO_2K$; v, H^+; vi H^+; vii, $NaBT_4$; viii, H^+

3-*Bromothieno*[2,3-b]*thiophen*. This was prepared in 60% yield from 2,3,5-tribromothieno[2,3-*b*]thiophen according to the literature method.[5]

Thieno[2,3-b]*thiophen-3-thioacetic acid*. n-Butyl-lithium (10 ml of a 2N solution in hexane) was added to a stirred solution of 3-bromothieno[2,3-*b*]thiophen under nitrogen, and the mixture heated under reflux during 1 h. It was then cooled to 0 °C, sulphur (0.64 g, 0.02 mol) was added, and the mixture heated under reflux for a further 3 h. The cooled mixture was poured into a neutral solution of potassium carbonate (1.36 g) and chloroacetic acid (1.86 g) in water (40 ml), and stirred during 30 h. The product was ether extracted, and the aqueous phase acidified with concentrated HCl to give a red-brown oil. This was ether extracted and worked up in the normal way, but could not be crystallised. The yield of crude product was 76%.

2,3-*Dihydro-3-oxodithieno*[2,3-b:2′,3′-d]*thiophen*. The above crude acid (3 g, 0.0138 mol) was added to concentrated sulphuric acid (50 ml) with stirring. The mixture was heated on a steam-bath during 45 min, cooled, and poured onto ice. Normal work-up gave a semi-crystalline oil (3%) as a crude product.

The crude ketone (100 mg, 0.005 mol) was dissolved in absolute ethanol (1.5 ml) and a solution of sodium borotriti-ide (5 mCi) in aqueous 95% ethanol (1 ml) was added. The mixture was stirred during 30 min, sodium borohydride (20 mg, 0.0005 mol) was added and the total heated at 50 °C during 2 h. The alcohol was removed by distillation, and the residue treated with water and dilute HCl. Normal work-up followed by column chromatography [pentane–ether (2 : 1) as eluant] gave [3-^{3}H]dithieno[2,3-*b*:2′3′-*d*]-thiophen (40%), m.p. 52.5—54 (lit.,[4] 53—54 °C).

[2,3,6,7-$^3H_4$]*Dithieno*[2,3-b:2′,3′-d]*thiophen*.—A sample of the inactive compound, kindly supplied by Professor M. J. Janssen, University of Groningen, The Netherlands, was totally tritiated as described above for the [2,3-*b*:3′,2′-*d*]-isomer to give a product with 7.4 mCi g^{-1} specific activity, *cf.* 10 mCi g^{-1} calculated.

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