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THIOPHENE CHEMISTRY—XII*

SYNTHESIS AND TAUTOMERIC STRUCTURE OF ACETYL AND CARBETHOXY CHELATED 2-HYDROXYTHIOPHENES†

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Abstract—3-Acetyl-2-hydroxythiophene and 3-carbethoxy-2-hydroxythiophene have been prepared by acid-catalysed dealkylation of the corresponding t-butyl ethers at 160°. The t-butyl ethers were prepared via organometallic reagents derived from 3-bromo-2-t-butoxythiophene by metal-halogen interconversion with n-butyllithium at $-70°$. Investigations by NMR and IR spectroscopy show that these 2-hydroxythiophenes exist in the tautomeric hydroxy form in the pure liquid state and in solution. Evidence for the presence of the tautomeric α,β-unsaturated γ-thiolactone form in minute quantities is obtained from the formation of a dimer in the case of 3-carbethoxy-2-hydroxythiophene.

INTRODUCTION

IN A recent paper,[1] the preparation of acetyl and carbethoxy substituted 3-hydroxythiophenes was described. By spectroscopic methods it was shown[1] that these compounds exist exclusively in the hydroxyaromatic form. Simultaneously the synthesis of formyl chelated 3-hydroxythiophenes was achieved[2] and these compounds were also shown to exist solely in the enol form. Alkyl-substituted 3-hydroxythiophenes have recently been shown to exist as mixtures of the keto- and enol tautomers.[3]

2-Hydroxythiophenes show interesting tautomeric behaviour as most of the compounds that have been prepared exist as $\alpha\beta$- and β,γ-unsaturated γ-thiolactones.‡ The only exception so far, is 5-carbethoxy-2-hydroxythiophene which in the crystalline state exists in the hydroxyaromatic form;[4] this has been ascribed to an extended conjugated system and to intermolecular hydrogen bonding.

The study of the potentially tautomeric 2-hydroxythiophenes has been extended to 3-acetyl- and 3-carbalkoxy-substituted 2-hydroxythiophenes which are the isomers of the compounds described in our previous papers (e.g. thioisomaltol).[1] Attempted preparation of 3-formyl-2-hydroxythiophene[2] yielded 3-hydroxy-3-thiolene-2-one probably according to the Dakin reaction.

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* Part XI. R. Grigg, H. J. Jakobsen, S.-O. Lawesson, M. V. Sargent, G. Schroll and D. H. Williams, *J. Chem. Soc.* (B) 331 (1966).

† Presented at *The Second Organic Sulphur Symposium*. May 9–12, Groningen, Holland (1966).

‡ For Refs, see Ref. 1.

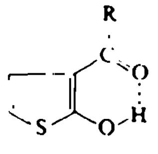
[1] H. J. Jakobsen and S.-O. Lawesson, *Tetrahedron* **21**, 3331 (1965).

[2] S. Gronowitz and A. Bugge, *Acta Chem. Scand.* **20**, 261 (1966).

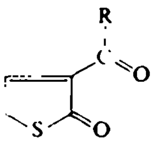
[3] A.-B. Hörnfeldt, *Acta Chem. Scand.* **19**, 1249 (1965).

[4] H. J. Jakobsen, E. H. Larsen, and S.-O. Lawesson, *Tetrahedron* **19**, 1867 (1963).

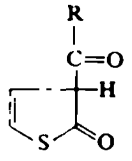
The new compounds should exist in the chelated hydroxy form (I) or in the α,β-unsaturated γ-thiolactone form (II). Structure I could be expected from the stabilization due to the intramolecular hydrogen bonding, the extended conjugation, and the electron withdrawing effect of the substitutent in position 3. The possible existence of structure II is justified by the fact that all 3-substituted 2-hydroxythiophenes previously studied[5] exist exclusively as α,β-unsaturated γ-thiolactones and that 2,4-dihydroxy-3-carbethoxythiophene exist almost exclusively as IV (α-carbethoxythiotetronic acid).[6] The structure III is not very probable as the tautomeric β,γ-unsaturated γ-thiolactone form is only found in 5-substituted 2-hydroxythiophenes;[4,7] furthermore, conjugation is lost in structure III.



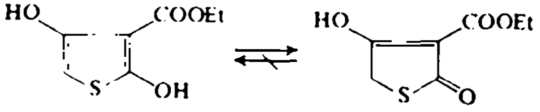
I



II



III



IV

Syntheses

The key material for the synthesis of 3-acetyl- and 3-carbethoxy-2-hydroxythiophene was 3-bromo-2-t-butoxythiophene (V). It was prepared in the ordinary way[1] as illustrated in Scheme 1. The isolated product may contain some unchanged t-butyl perbenzoate because of the use of nearly equivalent amounts of Grignard reagent and t-butyl perbenzoate; this may be judged from the IR spectrum which then shows a characteristic absorption near 1760 cm^{-1} due to the carbonyl stretching frequency in t-butyl perbenzoate. The perbenzoate is, however, easily removed by treating the product at 0° with an ethereal solution of ethylmagnesium bromide which converts the unreacted t-butyl perbenzoate to ethyl t-butyl ether and benzoic acid. The separation of 3-bromo-2-t-butoxythiophene from these compounds is straight-forward (Experimental).

Metal-halogen interconversion of 3-bromo-2-t-butoxythiophene (V), with n-butyllithium gives 3-lithium-2-t-butoxythiophene (VI) which may be converted to the corresponding Grignard reagent (VII) by treatment with an ethereal solution of anhydrous magnesium bromide. Via these reagents, VII and VI, 3-acetyl-2-t-butoxythiophene (VIII) and 3-carbethoxy-2-t-butoxythiophene (IX) were prepared in high yields by reaction with acetic anhydride and ethyl chloroformate, respectively. The

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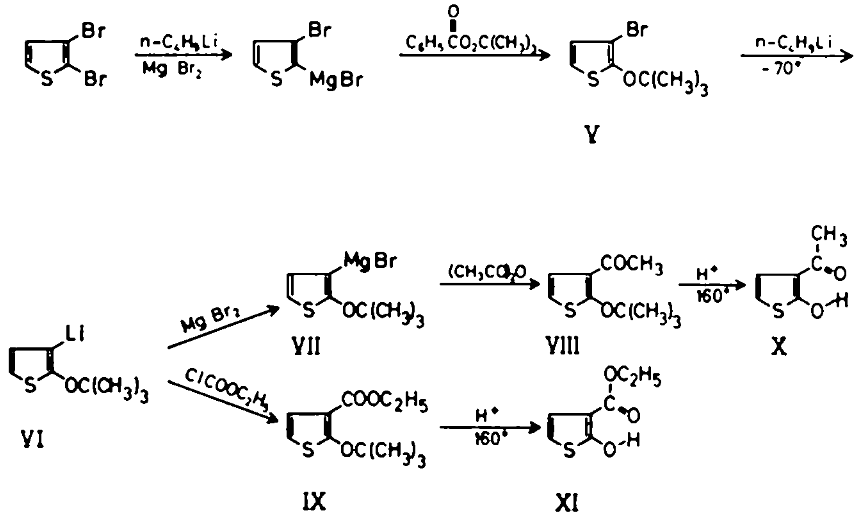
[5] A.-B. Hörnfeldt and S. Gronowitz, *Arkiv Kemi* **21**, 239 (1963).

[6] E. Benary, *Ber. Dtsch. Chem Ges.* **46**, 2103 (1913).

[7] A.-B. Hörnfeldt, *Arkiv Kemi* **22**, 211 (1964).

pyrolysis of the t-butyl ethers VIII and IX in the presence of a trace of *p*-toluenesulphonic acid gave 3-acetyl-2-hydroxythiophene (X) and 3-carbethoxy-2-hydroxythiophene (XI) but the dealkylations in these cases were not so easy as in the case of the isomeric 3-t-butoxythiophenes where nearly quantitative yields of the chelated



Scheme 1

3-hydroxythiophenes were obtained.[1] The hydroxythiophenes X and XI should be distilled from the acidic medium immediately after the evolution of isobutylene has ceased; otherwise, only undistillable tars are formed. Dealkylation with trifluoroacetic acid[8] at room temperature was investigated in the case of the t-butyl ether IX, but the only product obtained after removal of trifluoroacetic acid was a light brown, viscous oil which decomposed on attempted distillation *in vacuo* (0·05 mm Hg). This oil was shown to be identical with a dimer formed from 3-carbethoxy-2-hydroxythiophene on standing for a few days at room temperature; the probable structure and formation of the dimer is discussed in the spectroscopic part. 3-Acetyl-2-hydroxythiophene (X), a light-yellow liquid which colours the skin an intense blue, is unchanged after storage in the crystalline state at −20° for a year, Similarly 3-carbethoxy-2-hydroxythiophene (XI), which is a colourless liquid, should be stored in the crystalline state at −20° in a quartz flask in order to avoid dimerization.

NMR and IR spectra

The NMR spectrum of 3-bromo-2-t-butoxythiophene was expected to show an AB pair of doublets for the H_4 and H_5 protons. However, in $CDCl_3$ and in CCl_4 solutions only one single peak was observed in the aromatic region ($\delta = 6\cdot75$ ppm and $\delta = 6\cdot68$ ppm, respectively) and it proved impossible to resolve this peak into an AB system even on a 100 Mc/s instrument. However, by using C_6H_6 as solvent a pair of doublets appeared at $\delta_A = 6\cdot57$ ppm and $\delta_B = 6\cdot30$ ppm with $J_{AB} = 6\cdot1$ c/s. Fig. 1 shows the aromatic region recorded using $CDCl_3$ (A) and a 1 : 1 mixture of C_6H_6 and $CDCl_3$ (B) as solvents.

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[8] H. C. Beyerman and J. S. Bontekoe, *Rec. Trav. Chim.* **81**, 691 (1962).

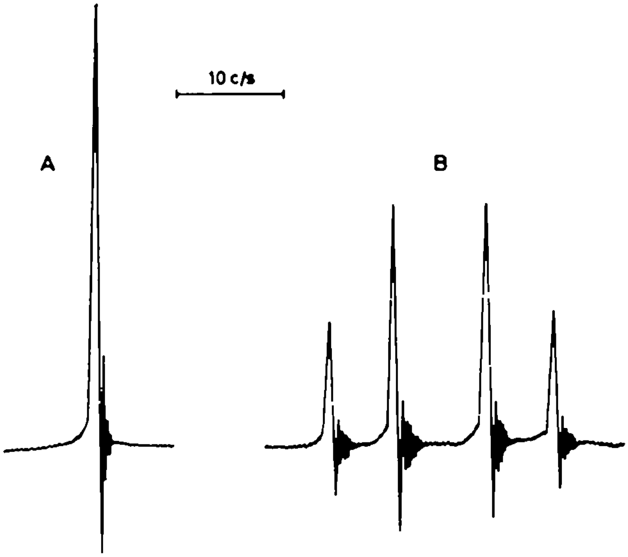
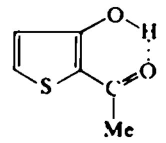
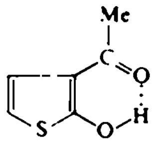
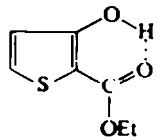
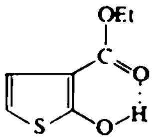


Fig. 1. 100 Mc/s NMR spectrum of the aromatic protons of 3-bromo-2-t-butoxythiophene. A: CDCl$_3$ as solvent. B: C$_6$H$_6$/CDCl$_3$ (50/50) as solvent.

Table 1. NMR and IR data for isomeric 2,3-carbonyl-chelated hydroxythiophenes. Solvents: CDCl$_3$ (NMR) and CCl$_4$ (IR).

	δ_{OH}	$\Delta\delta_{OH}$	$\nu_{C=O}$	ν_{OH}
	11·50[*]	2·13	1618[*]	3100[*]
	13·63		1624	2900–3000
	9·65[*]	0·97	1652[*]	3250[*]
	10·62		1654	3000–3100

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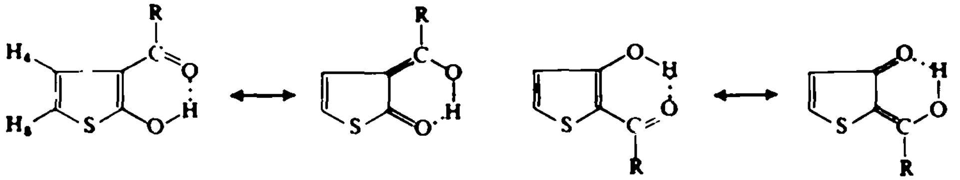
[*] Ref. 1.

The NMR and IR spectra of 3-acetyl-2-hydroxythiophene (X) and 3-carbethoxy-2-hydroxythiophene (XI) show that in the pure liquid state and in solutions of $CDCl_3$ and CCl_4 they exist in the enol form; the keto tautomers were not present in sufficient quantities to be detected. As in our studies on carbonyl chelated 3-hydroxythiophenes[1] the δ_{OH} values in the NMR spectra and the ν_{OH} and $\nu_{C=O}$ values in the IR spectra have received special attention. From the spectroscopic data in Table 1 it is seen that the resonance fields for hydroxylic protons in the chelated 2-hydroxythiophense appear at a considerably lower field as compared with the isomeric 2-carbonyl chelated 3-hydroxythiophenes. This difference is particularly conspicuous for the acetyl chelated hydroxythiophenes where a difference in resonance position ($\Delta\delta_{OH}$) in more than 2 ppm is observed. However, as the IR carbonyl stretching frequencies are nearly constant for each pair of isomers (Table 1) the spectroscopic values for the carbonyl chelated 2-hydroxythiophenes X and XI will not fit the earlier obtained linear correlations for the chelated 3-hydroxythiophenes.[1] The OH stretching frequencies show up as very broad, overlapped bands with the maximum intensities occurring in the regions given in Table 1.

The differences in OH resonance position $\Delta\delta_{OH}$ for the isomeric chelated hydroxythiophenes in Table 1 may result from a much larger contribution of the quinoid resonance (XIIb) to the true structure of the chelated 2-hydroxythiophenes as compared with the contribution of the quinoid structure (XIIIb) to the structure of the 2-carbonyl chelated 3-hydroxythiophenes. This assumption is supported by comparison of the chemical shifts of the protons 4 and 5 in the chelated hydroxythiophenes with the chemical shifts in the corresponding t-butyl ethers (Table 2). The excellent agreements in the case of 2-carbonyl-3-hydroxythiophenes suggest that they should be formulated as thiophenes (XIIIa) while the much larger deviations for the 2-hydroxy-chelated isomers suggest a considerable contribution of the quinoid structure (XIIb) in these compounds; it has recently been shown[9] that 2-acetyl-3-hydroxyfuran (isomaltol) should be formulated analogously to XIIIa. Furthermore, as the coupling constant J_{45} in thiophenes so far only have been observed in the range 4·9–5·9 c/s,[10] the value 6·7 c/s for 3-acetyl-2-hydroxythiophene (Table 2) may indicate delocalization of the π-electrons (XIIa ↔ XIIb) for this compound in accordance with the assumption drawn from the large chemical shift difference $\Delta\delta_{OH} = 2{\cdot}13$ ppm (Table 1).



XIIa XIIb XIIIa XIIIb

A recent NMR investigation indicates that chelated phenols are better formulated

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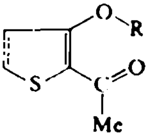
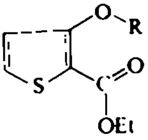
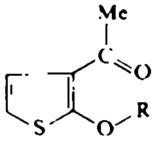
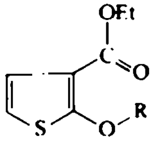
[9] A. Hofmann, W. v. Philipsborn and C. H. Eugster, *Helv. Chim. Acta* **48**, 1322 (1965).

[10] S. Gronowitz in A. R. Katritzky: *Advances in Heterocyclic Chemistry* Vol. 2; p. 8. Academic Press (1963).

TABLE 2. PROTON CHEMICAL SHIFTS, $\delta_{H(5)}$ AND $\delta_{H(4)}$, AND RING COUPLING CONSTANTS, J_{45}, OF 2,3-CARBONYL CHELATED HYDROXYTHIOPHENES AND THEIR CORRESPONDING t-BUTYL ETHERS IN SOLUTIONS OF CCl_4

	R	H_5	H_4	J_{45}
	t-Bu	7·38	6·87	5·5
	H	7·34	6·70	5·3
	t-Bu	7·25	6·73	5·3
	H	7·27	6·67	5·3
	t-Bu	6·51	7·09	6·2
	H	6·25	6·65	6·7
	t-Bu	6.55	7.10	6.1
	H	6·24	6·85	6·0

as quinoids than as benzene derivatives.[11] X-ray crystallographic analysis of salicylic acid are in accordance with these findings.[12,13]

As mentioned above 3-carbethoxy-2-hydroxythiophene is converted into a colourless, very viscous dimer on standing at room temperature; the same dimer was formed on attempted dealkylation of 3-carbethoxy-2-t-butoxythiophene with trifluoroacetic acid at room temperature. This was inferred from the NMR spectra obtained from CCl_4 solutions of the oils; following signals were observed: a singlet at 10·50 ppm (1 H) for a chelated hydroxylic proton; a singlet at 6·77 ppm (1 H) for an aromatic proton; a quintet (1:4:6:4:1) at 4·27 ppm (4 H) due to two superimposed quartets at 4·33 ppm and 4·21 ppm for the methylene protons in two different carbethoxy groups; the matching methyl triplets are found at 1·37 ppm (3 H) and 1·28 ppm (3 H); finally, a complex pattern is found in the region 3–4 ppm (4 H). These NMR data are in accordance with the structure XVI for the dimer and it could be formed by internal Michael addition of the conjugated thiolactone form XIV which may be present in minute quantities. Enolization of the addition product XV gives the supposed structure XVI. The α,β-unsaturated γ-thiolactone, 3-thiolene-2-one has earlier been shown to undergo Michael addition with active methylene compounds.[14]

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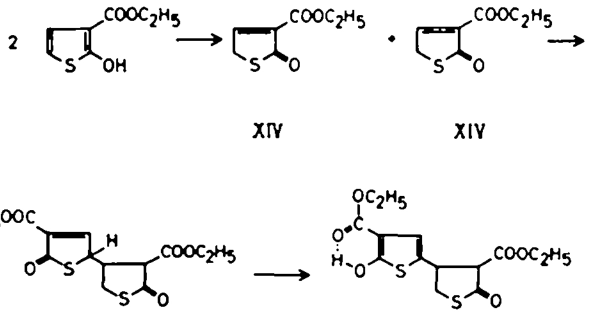
[11] G. O. Dudek and E. P. Dudek, *Chem. Commun.* 464 (1965).

[12] W. Cochran, *Acta Cryst.* 6, 260 (1953).

[13] M. Sundaralingam and L. H. Jensen, *Acta Cryst.* 18, 1053 (1965).

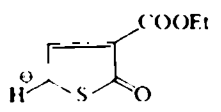
[14] H. J. Jakobsen, E. H. Larsen and S.-O. Lawesson, *Rec. Trav. Chim.* 82, 791 (1963).



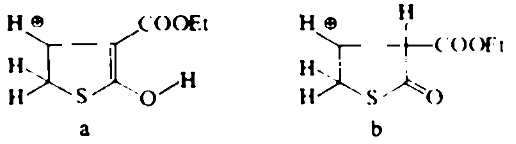
XIV XIV

XV XVI

The formation of the dimer following the base-catalysed (alkali from the glass) Michael addition is understood from the fact that the methylene protons in the 5



XVII



XVIII

position of 3-thiolene-2-ones show acidic behaviour (e.g. condensations with aromatic aldehydes[6]); the formation of the carbanion XVII would then account for the mechanism for the addition reaction. The acid-catalysed (trifluoroacetic acid) dimerization probably involves the formation of the carbonium ion XVIII (a or b) followed by electrophilic attack at the methylene group of XIV (similar to the mechanism for the acid catalysed condensation of benzaldehyde with 3-thiolene-2-ones).

EXPERIMENTAL

NMR spectra were recorded at 60 Mc/s on a Varian A-60 spectrometer. The temp of the 14–16% (w/w) sols was 34° ± 1. TMS was used as internal reference standard and the chemical shifts are expressed in ppm from TMS taken as 0·00 (δ units) and are believed to be correct within ±0·02 ppm. The coupling constants were measured with an accuracy of ±0·2 c/s on the 50 c/s scale. IR spectra were recorded as 1% solns in CCl_4 on a Perkin–Elmer model 221 spectrophotometer and on a Beckmann IR10. Analyses were made by Dr. I. Beetz, Kronach, Germany, and by the analytical laboratory at this institute. B. ps and m. ps are uncorrected.

3-*Bromo*-2-t-*butoxythiophene* (V). 3-Bromo-2-thienyllithium was prepared[18] from 2,3-dibromothiophene[19] (80·0 g, 0·33 mole) and n-BuLi (295 ml, 1·20 N; 0·35 mole) at −70°. The cold Li-reagent (−70°) was added rapidly under N_2 to an ethereal soln of anhydrous $MgBr_2$ [prepared by dropping 60 g (19·2 ml, 0·38 mole) Br_2 to 10 g (0·42 g-atoms) Mg in 200 ml anhydrous ether; excess of Mg was removed by filtration under N_2] and the red–brown soln was allowed to warm up to room temp. After stirring for ½ hr, 0·33 mole (66 ml) t-butyl perbenzoate in 100 ml anhydrous ether was added dropwise to the Grignard reagent at 0° and stirred for 2 hr. It was then poured into ice water and the complex dissolved by adding dil. HCl. The acidic water phase was extracted with ether, the combined ether phases extracted with 2N NaOH to remove benzoic acid and finally washed neutral with water and dried (Na_2SO_4). The ether was removed and careful distillation *in vacuo* gave a light yellow liquid with b.p. 55–58°/0·1 mm. In some experiments this fraction contained unreacted t-butyl perbenzoate; this was, however, easily removed by adding the fraction to an ethereal solution of EtMgBr (0·1 mole) at 0° and stirring for 1 hr. The work-up was done as described above. Distillation

[18] P. Moses and S. Gronowitz, *Arkiv Kemi* **18**, 119 (1961).

[19] S.-O. Lawesson, *Arkiv Kemi* **11**, 373 (1957).

then gave 3-bromo-2-t-butoxythiophene as a colourless liquid with b.p. 50–52°/0·1 mm; n_D^{20} = 1·5320; yield 49·4 g (64%). (Found: C, 41·52; H, 4·83; Calc: C, 40·88; H, 4·72%.)

3-*Acetyl*-2-t-*butoxythiophene* (VIII). 3-Bromo-2-t-butoxythiophene (43·3 g, 0·185 mole) in 100 ml dry ether was added to n-BuLi (160 ml, 1·33 N; 0·21 mole) at −70°. After stirring for 15 min the Li-reagent, which is partly precipitated, was converted to the corresponding Grignard reagent by adding it (−70°) rapidly under N_2 to 0·24 mole anhydrous $MgBr_2$ in 150 ml ether (prepared as described above) at 0°. The mixture was allowed to warm up to room temp, concentrated by removal of some ether under N_2 and transferred to a dropping funnel under N_2. The organometallic reagent was added to a vigorously stirred soln of 80 g Ac_2O in 250 ml dry ether at −70° during 1 hr. A very efficient mechanical stirrer is recommended because after addition of about ½ of the Grignard reagent the separating complex becomes very pasty and the stirrer may stop; if so, the Grignard reagent may be added in small portions while the reaction flask is shaken in the dry ice-Et-OH bath (−70). After addition of about ¾ of the Grignard reagent the complex becomes more mobile and mechanical stirring may be resumed. Stirring was continued for 1 hr at −70° after the addition was complete. The mixture was then allowed to warm up to −10° − 0° and the complex was hydrolysed by adding 2N NH_4Cl. The complex dissolved in a few min and the phases were separated. The water phase was extracted with ether and the combined ether phases extracted with 2N NaOH under cooling with ice (removal of AcOH) until the water phase was strongly alkaline. The organic layer was finally washed with water until neutral and dried (Na_2SO_4). The ether was removed and distillation gave a main fraction of 3-acetyl-2-t-butoxythiophene as a light yellow liquid with b.p. 82–85°/0·1 mm; redistillation gave an almost colourless liquid b.p. 75–77°/0·05 mm; n_D^{20} – 1·5285; yield 26·9 g (74%). (Found: C, 60·62; H, 7·01; Calc.: C, 60·59; H, 7·12%.)

3-*Acetyl*-2-*hydroxythiophene* (X). 3-Acetyl-2-t-butoxythiophene (18·8 g, 0·095 mole) in a 25 ml distillation flask was placed in an oil bath at 160° and 0·1 g *p*-toluenesulphonic acid was added. After the evolution of isobutylene had ceased (5 min) the product was *immediately* distilled *in vacuo* (N_2 was drawn through the capillary) giving a fraction of 3-acetyl-2-hydroxythiophene with b.p. 55–65°/0·2 mm (avoid contact with the skin); a tarry, undistillable residue was left in the flask. Redistillation gave pure 3-acetyl-2-hydroxythiophene as a light yellow-green liquid with b.p. 46–48°/0·2 mm; n_D^{20} = 1·5926; yield 9·5 g (71%). When stored at −20° the compound crystallizes. (Found: C, 50·74; H, 4·29; Calc.: C, 50·71; H, 4·26%.)

3-*Carbethoxy*-2-*t*-*butoxythiophene* (IX). 3-Bromo-2-t-butoxythiophene (43·3 g, 0·185 mole) in dry ether was converted to 3-lithium-2-t-butoxythiophene at −70° as described above. The organolithium reagent (kept at −70°) was added in portions under N_2 to a stirred soln of ethyl chloroformate (70 g, 0·65 mole) in 100 ml dry ether at 0° (ice-water bath) during ½ hr. The light yellow mixture was stirred overnight at room temp and then worked up by adding water (300 ml) saturated with Na_2CO_3 under cooling in ice-water. After stirring for 1 hr the phases were separated, the water phase extracted with ether and the combined organic layers finally washed with water and dried (Na_2SO_4). Distillation gave a light yellow, pleasant smelling fraction of 3-carbethoxy-2-t-butoxy-thiophene with b.p. 80–83°/0·1 mm. Redistillation gave an almost colourless liquid with b.p. 75–77°/0·08 mm; n_D^{20} = 1·5062; yield 34·3 g (81%). (Found: C, 57·82; H, 7·02; Calc.: C, 57·88; H, 7·07%.)

3-*Carbethoxy*-2-*hydroxythiophene* (XI). 3-Carbethoxy-2-t-butoxythiophene (16·5 g; 0·072 mole) was dealkylated at 160° in the presence of 0·1 g *p*-toluenesulphonic acid. When the evolution of isobutylene had ceased (10 min) the product was *immediately* distilled *in vacuo* giving 3-carbethoxy-2-hydroxytiophene as a colourless liquid with b.p. 58–62°/0·2 mm. A tarry residue decomposes on attempted distillation. Redistillation of 3-carbethoxy-2-hydroxythiophene gives b.p. 44–46°/0·08; n_D^{20} = 1·5288 (slowly increasing); yield 9·1 g (73%). (Found: C, 49·08; H, 4·60; Calc.: C, 48·84; H, 4·68%.) The compound should be stored in the crystalline state at −20° in order to avoid dimerization; it is rapidly converted to the crystalline state by keeping it at −70° (dry ice-alcohol bath) for a few min and then placing it in a refrigerator at once.

Acknowledgements—Our thanks are due to Professor Hakon Lund for his interest in this work and for the facilities put at our disposal. NMR spectra were kinldy recorded by Mrs. B. Bock and IR spectra by Mrs. S. Andersen and Mrs. L. Nielsen at this institute. Thanks are also due to Dr. J. Feeney, Varian Associates, for recording the 100 Mc/s spectra.