Tetrahedron. Vol. 27, pp. 3839 to 3851. Pergamon Press 1971. Printed in Great Britain

THIOPHENE CHEMISTRY—XVIII*

PREPARATION AND TAUTOMERIC STRUCTURES OF SOME POTENTIAL DIHYDROXYTHIOPHENES†

J. Z. MORTENSEN, B. HEDEGAARD and S.-O. LAWESSON
Department of Organic Chemistry, Chemical Institute, DK-8000 Aarhus C, Denmark

(*Received in the UK* 30 *September* 1970; *Accepted for publication* 8 *October* 1970)

Abstract—The four isomeric di-t-butoxythiophenes and also some substituted di-t-butoxythiophenes have been prepared via organometallic reagents. Acid-catalysed dealkylation gives the corresponding potential dihydroxthiophenes. Spectroscopic investigations of these by NMR, IR, and UV have proved their true structures.

INTRODUCTION

IN RECENT years many earlier unknown 2- and 3-hydroxythiophenes have been prepared (for simplicity the potential hydroxythiophenes and hydroxyfurans will be referred to as hydroxy compounds without prejudice to the final conclusions). Two different methods for the preparation of hydroxythiophenes are quite general. The oxidation of thienylboronic acids with hydrogen peroxide to give hydroxythiophenes,[1] is restricted in the sense that the preparation of substituted hydroxythiophenes is only possible for substituents that show no reactivity towards organometallic reagents. The other method, the acid-catalysed dealkylation of t-butylthienylethers,[2] avoids that limitation by making use of the t-Bu group as an OH protecting group: The t-butyl ether is first prepared, the other t-butoxy group and other different substituents are then introduced, and finally isobutylene is eliminated. The t-butoxy method should be the most suitable for the preparation of polyhydroxyheterocycles and in this paper problems in connection with dihydroxythiophenes are dealt with.

A literature search revealed‡ that the only two known 2,3-dihydroxythiophenes are: 2,3-dihydroxy-5-ethoxycarbonylthiophene,[2] and 2,3-dihydroxythiophene.[3] In the 2,4-dihydroxythiophene series only thiotetronic acids (4-hydroxy-3-thiolene-2-ones) are known.[4] Of the 2,5-dihydroxythiophenes, thiosuccinic anhydride has been prepared[5] and several 3,4-dihydroxythiophenes have been made,[6, 7] but no proof of their structure were given.[6-8]

Syntheses and spectroscopic studies

2,3-*Dihydroxythiophenes*. Different starting materials have been used for the preparation of the 2,3-dihydroxythiophenes. 2,3-Di-t-butoxythiophene (I), easily prepared from 3-bromothiophene,[2] was metallated with BuLi and subsequent treatment (of 2,3-di-t-

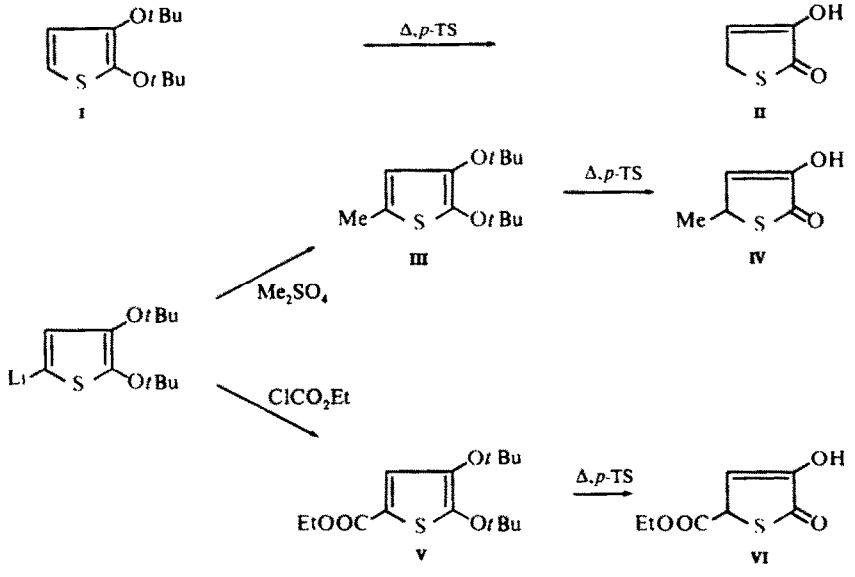
* Part XVIII, J. Z. Mortensen, B. Hedegaard and S.-O. Lawesson, *Tetrahedron*, 27, 3831 (1971)

† Presented in part at the 13 Nordic Chemical Meeting, Copenhagen, August 1968, and at the 2 International Congress of Heterocyclic Chemistry, Montpellier, France, July 1969.

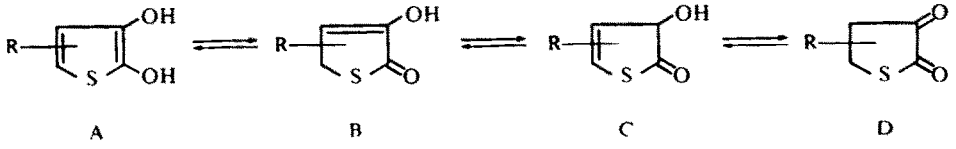
‡ After the completion of this manuscript a recent patent on 3,4-dihydroxythiophenes came to our attention (Dutch patent 6910103 (January 5, 1970).

butoxy-5-thienyllithium) with dimethyl sulphate and ethyl chloroformate gave III and V, respectively. Acid-catalysed dealkylation then produced IV and VI as in Scheme 1.

SCHEME 1

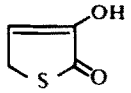
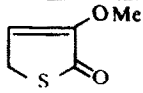
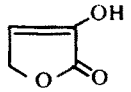
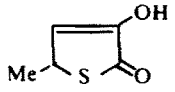
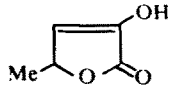
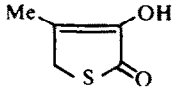
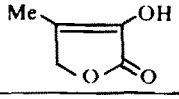
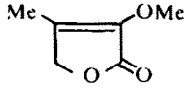
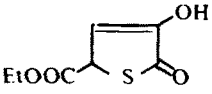
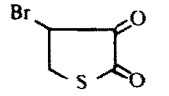
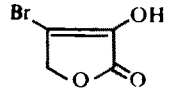
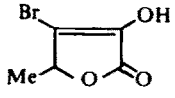


In the oxidation of 3-formyl-2-thiophene-boronic acid with hydrogen peroxide, Gronowitz and Bugge[3] isolated a very low yield of a compound, which they suggested to be II (only NMR data were given). We have dealkylated 2,3-di-t-butoxythiophene (I) and isolated II in 93% yield (Scheme 1).



Theoretically 2,3-dihydroxythiophenes can exist in four tautomeric forms (A–D), and we have now been able unequivocally to prove that II does exist as B (3-hydroxy-3-thiolene-2-one). The NMR spectrum (δ-values rel. TMS = 0, $CDCl_3$) shows peaks at 3·87 (d, CH_2 in 5-position) 6·52 (t, hydrogen 4), 6·40 (OH). $J_{4,5} = 3·3$ c/s. No peaks corresponding to other tautomers were observed. The IR spectrum in KBr shows two strong peaks at 1680 cm^{-1} and 1645 cm^{-1}, corresponding to >C=O and C=C, respectively, and a broad band with maximum at 3320 cm^{-1} (the O—H stretching vibration of the enol group). In Table 1 are spectroscopic data, and a comparison with already known data of 3-thiolene-2-ones[5, 9, 10] shows that the 3-OH or 3-OMe substituents do not have any marked influence on the CO stretching frequency, while the C=C frequency is about 40 cm^{-1} higher in the substituted compound. The UV spectrum of thiolene-2-ones usually shows one band at 220 nm and another at 265 nm.[11] OMe and OH substituents in the 3-position of 3-thiolene-2-one produce a hypsochromic shift of the 220 nm band, while the 265 nm band is unaffected by the substituents.

TABLE 1. SPECTROSCOPICAL DATA OF 2,3-DIHYDROXYTHIOPHENES AND SOME 2,3-DIHYDROXYFURANS

Compounds		IR, cm^{-1}	UV, nm (log ε) (EtOH)	NMR (δ, ppm)	ref.
	II	1645 1680 (KBr)	248 (3·9) 266 (sh.)	3·87 (2H) 6·40 (1H) ($CDCl_3$) 6·52 (1H)	3
		1645 1680 (KBr)	244 (3·9) 268 (3·3)		10
		1650 1750 (KBr)	*	4·72 (2H) 6·32 (1H) ($(CD_3)_2SO$)	16
	IV	1640 1690 (liquid)	247 (3·9) 264 (sh.)	1·55 (3H) 4·10 (1H) 6·1 (1H) ($CDCL_3$) 6·32 (1H)	
		1650 1750 (KBr)	230 (4·1)	1·42 (3H) 5·08 (1H) 6·30 (1H) ($CDCL_3$) 7·2 (1H)	16
	IX	1650 1680 (KBr)	249 (3·9) 266 (sh.)	2·10 (3H) 3·89 (2H) ($CDCl_3$) 6·2 (1H)	
			233 (4·1)		16
			230 (4·1)		16
	VI	1665 1695 (KBr) 1740		1·28 (3H) 4·10 (2H) 4·74 (1H) (CCl_4) 6·44 (1H) 6·5 (1H)	2
	XI	broad 1660–1700 (CCl_4)		† ABX-system	
		1700 1750 ($CHCl_3$)	237 (3·9)	4·75 (2H) 6·18 (1H) ($CDCl_3$)	16
		1670 1750 (KBr)	243 (4·0)	1·50 (3H) 5·00 (1H) ($CDCl_3$) 5·90 (1H)	16

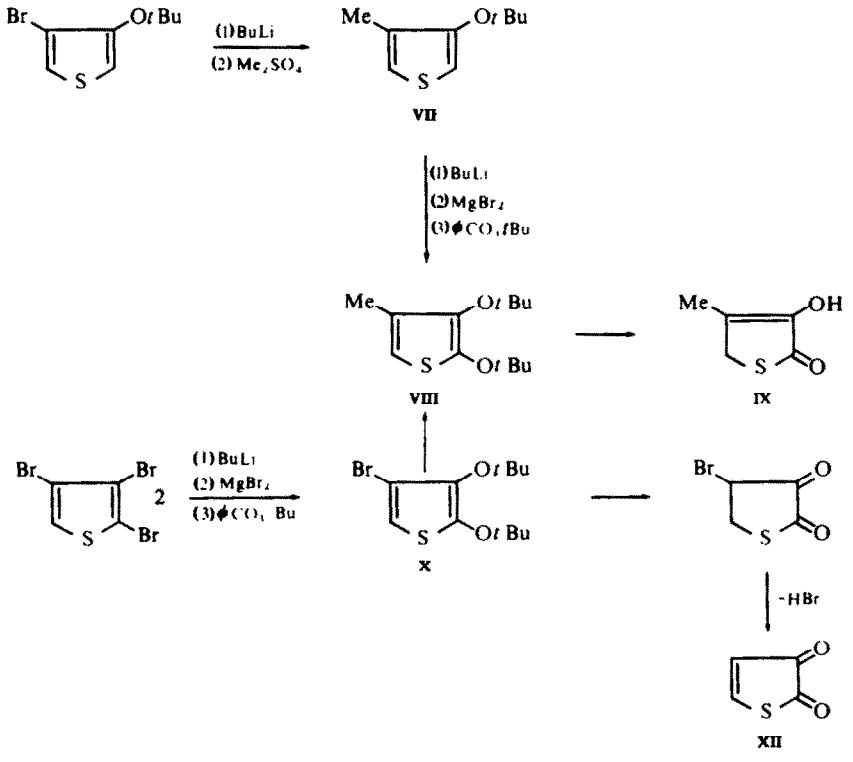
* This compound does not absorb within the range of our UV-spectrophotometer.
† See Experimental.

2,3-Dihydroxy-5-methylthiophene (IV) can also exist in the tautomeric forms A–D (R = 5-CH_3). The NMR spectrum in $CDCl_3$ shows a doublet at $\delta = 1{\cdot}55$, a double quartet at 4·10, a broad signal at 6·1, and a doublet at 6·32, with the relative intensities 3 : 1 : 1 : 1. No other peaks were observed and together with the IR and UV data (Table 1) the true structure of 2,3-dihydroxy-5-methylthiophene is 3-hydroxy-5-methyl-3-thiolene-2-one.

The structure of 2,3-dihydroxy-5-ethoxycarbonyl-thiophene, (IV), has been discussed,[2] but no definite conclusions could be drawn as to whether B or C (R = 5-COOEt) is the correct structure. It was assumed,[2] however, that it existed as a 4-thiolene-2-one (C). By inspection of the IR spectra of VI and related compounds (Table 1) it is now possible to distinguish between the two possibilities and show that VI is 3-hydroxy-5-ethoxycarbonyl-3-thiolene-2-one (B): The observed strong absorptions at 1695 and 1740 cm^{-1} in the CO frequency area only fit structure B. The band at 1695 cm^{-1} is assigned to the thiolactonecarbonyl group and is in good accordance with known data.[1, 11, 25] The unconjugated ester function also shows the characteristic absorption at 1740 cm^{-1}.

For the preparation of the 4-substituted 2,3-dihydroxythiophenes, two routes are used as seen in Scheme 2.

SCHEME 2



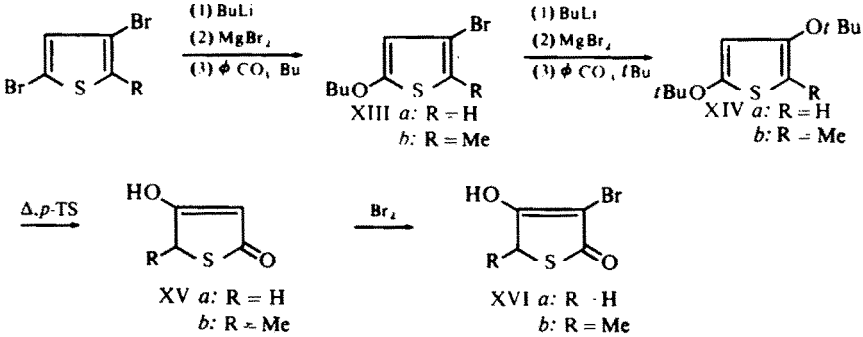
3-Bromo-4-t-butoxythiophene, after treatment with BuLi and the following reaction with dimethyl sulphate, produces 3-t-butoxy-4-methylthiophene (VII). Metallation (of VII) with BuLi introduces the Li in the 2-position *ortho* to the t-butoxy group, and the

subsequent reaction with anhydrous magnesium bromide and t-butyl perbenzoate gives 2,3-di-t-butoxy-4-methylthiophene (VIII). The same compound is also obtained from 2,3,4-tribromothiophene. The first t-butoxy group is introduced into the 2-position to give 3,4-di-bromo-2t-butoxythiophene, which, however, decomposed on attempted distillation. Also, 2,3-di-t-butoxy-4-bromothiophene could not be purified by distillation, but was methylated, via its lithium reagents, to give VIII. The 2,3-di-t-butoxy-4-methylthiophenes, prepared by two different routes were identical as judged from physical and spectroscopic data. This means that metallation of 3-t-butoxy-4-methylthiophene occurs exclusively in the 2-position, *ortho* to the t-butoxy substituent. Gronowitz[12] has shown that 3-t-butoxythiophene is metallated only in the 2-position (for a recent review on metallation by organo-lithium compounds, see Ref[13]). Dealkylation of VIII produces 4-methyl-2,3-dihydroxythiopnene (IX), the true structure of which is 4-methyl-3-hydroxy-3-thiolene-2-one. Quite unexpectedly, 4-bromo-2,3-dihydroxythiophene (XI) does exist in form D (R = 4-Br). From the spectroscopic data it is clear that it exists as 4-bromo-2,3-dioxy-4,5-dihydrothiophene, as the NMR spectrum shows an ABX system (Experimental). In the IR spectrum an absorption is observed at 3400 cm^{-1}, indicating traces of the hydroxy form B. Also 2,3-dioxo-dihydrothiophene (XII) formed from XI by HBr-elimination, could be present, as the NMR spectrum shows a singlet at 7·1 ppm, which could be the collapsed signal of the two H_3 and H_4-protons.

In Table 1 the spectroscopic data of both the potential 2,3-dihydroxythiophenes and the corresponding 2,3-di-hydroxyfurans[16] are collected. It is seen that in general they do exist in the same tautomeric form. Only one exception is observed among the compounds studied.

2,4-*Dihydroxythiophenes.* In this series of compounds, the ring-closure method of Benary[4] has been used for the preparation of ethoxycarbonyl substituted derivatives (XVIIa,b), and for the rest the t-butoxy method has been preferred as outlined below (Scheme 3):

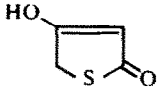
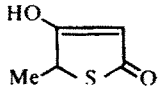
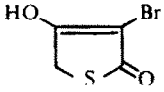
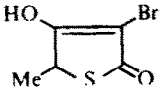
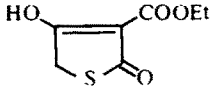
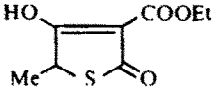
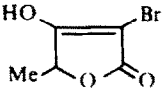
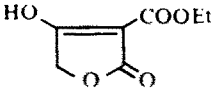
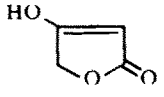
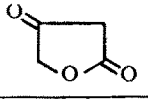
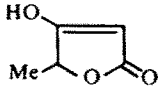
SCHEME 3



Unfortunately we were not able to isolate XIIIa in pure form as it decomposed on distillation.

Spectroscopic studies of compounds XV–XVII (Table 2) show that they all do exist as so-called thiotetronic acids (4-hydroxy-3-thiolene-2-ones). The structure of compound XVa, earlier prepared by Benary,[4] and believed to exist as thiotetronic acid (4-hydroxy-3-thiolene-2-one), was confirmed by our spectroscopical investigations. The

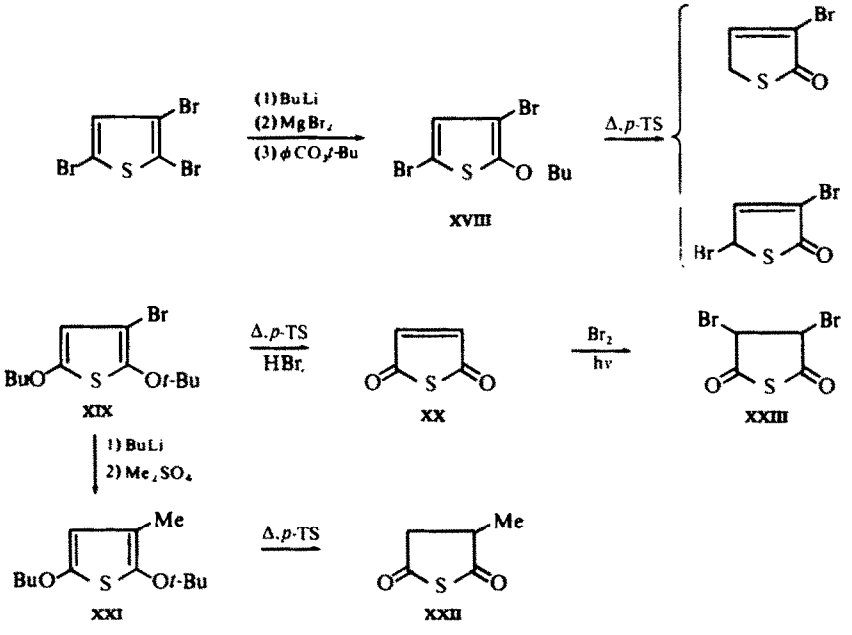
TABLE 2. SPECTROSCOPICAL DATA OF 2,4-DIHYDROXYTHIOPHENES AND SOME 2,4-DIHYDROXYFURANS

Compounds		IR, cm^{-1}	UV, nm (log ε) (EtOH)	NMR (δ, ppm)	ref.
	XVa	broad 1600–1700 (KBr)	232 (4·0) 263 (3·6) 284 (3·6) 350 (2·9)	4·00 (2H) 5·37 (1H) ($(CD_3)_2SO$) 9– (1H)	4
	XVb	broad 1600–1700 (liquid)	233 (4·0) 262 (3·4) 286 (3·4) 356 (2·9)	1·51 (3H) 4·29 (1H) 5·29 (1H) ($(CD_3)_2SO$) 7– (1H)	
	XVIa	broad ~1600 (KBr) ~1650		3·39 (2H) 8– (1H) ($(CD_3)_2SO$)	
	XVIb	broad ~1600 (liquid) ~1650		1·39 (3H) 3·63 (1H) ($(CD_3)_2SO$) 7·3 (1H)	
	XVIIa	1640 1675 ($CHCl_3$) 1680	232 (4·1) 245 (4·2) 267 (3·9)	1·39 (3H) 4·02 (2H) 4·42 (2H) 11– (1H)	4
	XVIIb	1645 1670 ($CHCl_3$) 1680	233 (4·2) 246 (4·1) 268 (3·8)	1·39 (3H) 1·70 (3H) 4·32 (1H) ($CDCl_3$) 4·43 (2H) 11– (1H)	
				0·70 (3H) 2·46 (1H) 3·8 (1H)	18
		1675 1705 ($CHCl_3$) 1772	230 (4·2) 265 (4·2)		17
		1632 1738 ($CHCl_3$)	224 (4·1)		17
		1765 (CCl_4)	219 (2·9)		17
		1634 1720 (KBr)	226 (4·1)	0·69 (3H) 2·38 (1H) 2·42 (1H) 3–6 (1H)	17, 18

NMR spectrum only shows peaks at 4·00 and 5·37 ppm (Table 2), a doublet and a triplet (resp.), with $J=0·9$ c/s for the long-range coupling between the hydrogen in the 3-position and the hydrogens in the 5-position. Table 2, where the spectroscopic data of the potential 2,4-dihydroxyfurans[17, 18] are collected, shows that the corresponding thiophene- and furan derivatives in all cases exist as 4-hydroxy-3-thiolene-2-ones and 4-hydroxy-3-furan-2-ones, respectively.

2,5-*Dihydroxythiophenes.* Thiosuccinic anhydride is easily prepared from 2,5-di-t-butoxythiophene by dealkylation and also a ring-closure reaction gives low yields of the same compound.[5] Other compounds in this series were prepared from 2,3,4-tribromothiophene, in which the first t-butoxy group was introduced into the 2-position[14] (Scheme 4).

SCHEME 4



Dealkylation of 2-t-butoxy-3,5-dibromothiophene (XVIII) at 120° in the presence of catalytic amounts of *p*-toluenesulphonic acid produced an unstable mixture of 3-bromo-3-thiolene-2-one and 3,5-dibromo-3-thiolene-2-one (ratio 1:4) in addition to a tarry residue (70%). The identification of 3-bromo-3-thiolene-2-one was somewhat anomalous, but similar results were recently obtained Jakobsen,[26] who isolated both 5-bromo-3-thiolene-2-one and 3-thiolene-2-one from dealkylation of 5-bromo-2-t-butoxythiophene. It was also found that 5-bromo-3-thiolene-2-one on standing for some time produces 3-thiolene-2-one and 3-bromo-3-thiolene-2-one.

2,5-Di-t-butoxy-3-bromothiophene (XIX) was prepared from 2-t-butoxy-3,5-dibromothiophene and other substituents can then be introduced into the 3-position of XIX via its lithium reagent. The subsequent treatment of XIX with acid at elevated temperature not only caused isobutylene elimination, but also HBr was eliminated to give fair yields of thiomaleic anhydride (XX)[14] after repeated distillation. However, inspection of the NMR spectrum of the crude product reveals that the mixture consists of

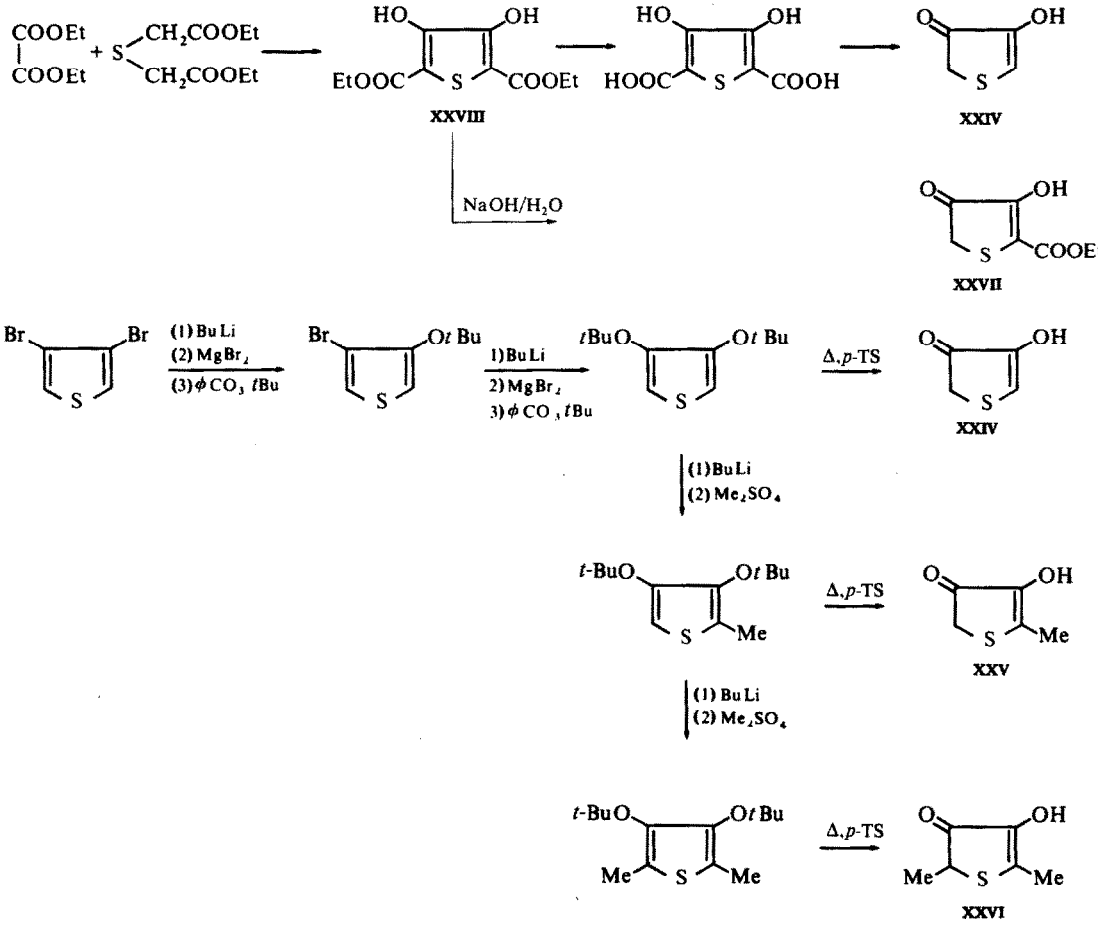
thiomaleic anhydride ($CDCl_3$: 7·13) and bromothiosuccinic anhydride ($CDCl_3$: 3·47) (1H, d, J=4·6 c/s); 3·63 (1H, d, J=7 c/s); 5·00 (1H, dd, J=7 c/s and 4·6 c/s)).

α,α′-Dibromothiosuccinic anhydride (XXIII) which also was needed for another purpose, was apparently impossible to prepare by dealkylation of 3,4-dibromo-2,5-di-t-butoxythiophene. We therefore added bromine to thiomaleic anhydride under irradiation and very small yields of α,α′-dibromothiosuccinic anhydride (XXIII) were isolated. Unfortunately, it decomposed on standing giving polymer-like products. Hydrolysis of XXIII gave α,α′-dibromosuccinic acid. In this connection it should be noted that earlier bromine was added to maleic anhydride in sunlight,[15] and after treatment with water α,α′-dibromosuccinic anhydride was said to be isolated. It has now been shown (Experimental) that the product isolated product was α,α′-dibromosuccinic acid.

From the spectroscopic investigations (Ref[14] and Experimental) it is concluded that all 2,5-dihydroxythiophenes exist as thiosuccinic anhydrides. The corresponding furan derivatives also exist as succinic anhydrides.

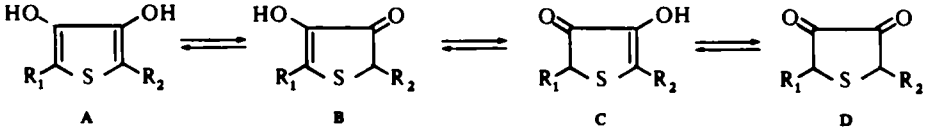
3,4-*Dihydroxythiophenes*. Two synthetic routes have been used and are shown in Scheme 5.

SCHEME 5



Earlier 3,4-dihydroxy-2,5-diethoxycarbonylthiophene (XXVIII) and 3,4-dihydroxythiophene (XXIV) were prepared by ring-closure reactions.[6-8] Compound XXIV has now also been prepared from 3-bromo-4-t-butoxythiophene[2] (Scheme 5).

This series of compounds may exist in four possible tautomeric forms (A–D).



A B C D

XXIV: $R_1, R_2 = H$ (B)
XXV: $R_1 = Me, R_2 = H$ (B)
XXVI: $R_1, R_2 = Me$ (B)
XXVII: $R_1 = COEt$, $R_2 = H$ (B)
XXVIII: $R_1, R_2 = COOEt$ (A)

The spectroscopical data (Table 3 and Experimental) shows that all compounds except 2,5-diethoxycarbonyl-3,4-dihydroxythiophene (XXVIII) exist in form B, which is not unexpectedly a true dihydroxythiophene. In Table 3 relevant spectroscopic data of potential 3,4-dihydroxyfurans [19-23] are collected and a comparison between the thiophene- and furan-series shows that they exist in the same tautomeric form with just one exception: 3,4-Dihydroxyfuran exists as 3,4-dioxotetrahydrofuran[23] (XXIX).

EXPERIMENTAL

NMR spectra were recorded at 60 Mc/s on a Varian A-60 spectrometer. The temps of the 15–20% solns (w/w) were 33° ± 1. TMS was used as internal reference standard and the chemical shifts are expressed in δ-values (ppm) downfield from TMS. The coupling constants, expressed numerically in c/s, were measured with an accuracy of ±0·1 c/s on the 50 c/s scale. The IR spectra were recorded as 5% solns on a Perkin–Elmer Infracord 137 and the UV spectra on a Bausch & Lomb Spectronic 505 spectrophotometer with EtOH as solvent. All syntheses were run in N_2 atmosphere. M.ps and b.ps are uncorrected. Analyses were made by The Analytical Laboratory, Løven A/S, Copenhagen and Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

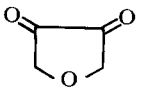
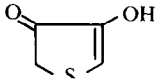
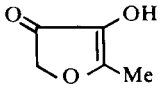
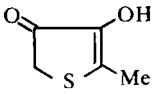
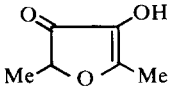
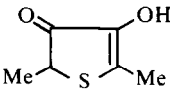
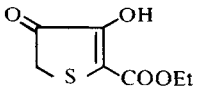
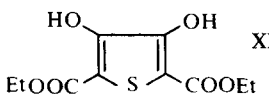
3-Hydroxy-3-thiolene-2-one. (II). Compound I[2] (3·5 g, 0·015 mole) was placed in a distillation flask with a few mg *p*-toluenesulphonic acid (*p*-TS) and heated to 160° in an oil-bath. After the evolution of gas had ceased the product was distilled immediately, $b.p._{12}$ 120–125°. The distillate solidified and recrystallisation (CCl_4) gave white crystals, m.p. 76° (lit[3] 73–74°), yield 1·65 g (93%) (Found: C, 40·96; H, 3·52; S, 27·41; $C_4H_4O_2S$ requires: C, 41·38; H, 3·44; S, 27·59%).

2,3-Di-t-butoxy-5-methylthiophene (III). To a stirred soln of 2,3-di-t-butoxythiophene (21·6 g, 0·095 mole) in ether (100ml) was added 1·9 Mn-BuLi (53ml, 0·1 mole) at 20°. After stirring for another 30 min at room temp the reaction flask was cooled to 0° and Me_2SO_4 (12·6 g, 0·1 mole) was added slowly during 30 min. After stirring overnight the mixture was poured into ice-water, the ether phase separated, the water phase extracted with ether, the combined ether phases washed neutral and dried (Na_2SO_4). The ether was stripped off and distillation gave the main fraction with $b.p._{0.15}$ 73–75°, $n_D^{20} = 1·4808$, yield 15·8 g (69%) (Found: C, 64·73; 9·15; S, 13·72; $C_{13}H_{22}O_2S$ requires: C, 64·44; H, 9·15; S, 13·71%); NMr (CCl_4): 6·42 (1H, s); 2·29 (3H, s); 1·30 (9H, s).

3-Hydroxy-5-methyl-3-thiolene-2-one (IV). Compound III. (5·0 g, 0·02 mole) was dealkylated at 140° as above, $b.p._{0.5}$ 80°, $n_D^{20} = 1·4895$, yield 2·5 g (90%) (Found: C, 46·06; H, 4·67; S, 24·71; $C_5H_6O_2S$ requires: C, 46·16; H, 4.65; S, 24·60). Probably due to its racemic properties IV would not solidify.

3-t-Butoxy-4-methylthiophene (VII). To -3-bromo-4-t-butoxythiophene[2] (30 g, 0·127 mole) in anhyd ether (100 ml) was added 2·8 M n-BuLi (46 ml, 0·127 mole) at −60°. After 30 min, Me_2SO_4, (16 g, 0·127

TABLE 3. SPECTROSCOPICAL DATA OF 3,4-DIHYDROXYTHIOPHENES AND 3,4-DIHYDROXYFURANS

Compounds		IR, cm^{-1}	UV, nm (log ε) (EtOH)	NMR (δ, ppm)	ref.
	XXIX	1780	520	4·5	23
	XXIV	3340 1665 1640 (sh)	335 (sh)	3·7 (2H) 5·5–5·9 (1H) 7·4 (1H)	
		3500 1690 1630	289 (4·0)	2·3 (3H) 4·4 (2H) 6·6 (1H)	19,20
	XXV	3300 1670 1645	255 (3·0) 343 (3·8)	2·1 (3H) 3·7 (2H) 5·9 (1H)	
		3500 1712 1618	289 (3·9)	1·4 (3H) 2·2 (3H) 4·4 (1H) 6·6 (1H)	21,22
	XXVI	3300 1670 1645	254 (3·0) 342 (3·8)	1·4 (3H) 2·1 (3H) 3·6 (1H) 5·9 (1H)	
	XXVII	3360 1680 1665 1650 (sh.)	290 (4·0) 297 (4·0) 328 (3·8) 342 (sh.)	1·4 (3H) 3·9 (2H) 4·4 (2H) 9·0 (1H)	24
	XXVIII	3310 1670 1650 (sh.)	287 (4·3) 295 (4·3) 326 (3·8)	1·4 (3H) 4·4 (2H) 9·3 (1H)	24

mole) in ether (100 ml) was added slowly. After stirring overnight the mixture was worked up in the usual way, $b.p._{.10}$ 76–78°, $n_D^{20} = 1.5034$, yield 19·5 g (90%) (Found: C, 63·44; H, 8·11; S, 18·91; $C_9H_{14}O_2$ requires: C, 63·51; H, 8·29; S, 18·80%).

2,3-*Di-t-butoxy-4-methylthiophene* (VIII). To a well-stirred soln of VII (21 g, 0·08 mole) in ether (200 ml) was added 1·5 M BuLi (54 ml, 0·08 mole) and the mixture refluxed for 30 min. The flask was cooled to −10° anhyd $MgBr_2$ (9·5 g, 0·090 mole) was added. After stirring for another 30 min, t-butyl perbenzoate (12·2 ml, 0·064 mole) in ether (50ml was added during 1 hr. After stirring overnight the mixture was worked up in the usual way, $b.p._{.2}$ 73–75°, $n_D^{20} = 1.4820$, yield 15·5 g (79%) (Found: C, 64·01; H, 9·09; S, 13·31; $C_{13}H_{22}O_2S$ requires: C, 64·44; H, 9·15; S, 13·21%).

Compound IV was also prepared in 40% yield from crude 2,3-di-t-butoxy-4-bromothiophene by treatment with n-BuLi at −60° and subsequent methylation with Me_2SO_4, $b.p._{.2}$ 73–75°, $n_D^{20} = 1.4820$. The IR and NMR spectra were identical with those of an authentical sample. NMR of X (CCl_4): 5·96 (1H, s) 1·33 (9H, s) 1·39 (9H, s).

4-*Methyl-3-hydroxy-3-thiolene-2-one* (IX). Dealkylation of VIII (3·2 g, 0·013 mole) (compare the preparation of II) gave, IX, $b.p._{.5}$ 85° m.p. 32°, yield 0·65 g (38%). (Found: C, 46·18; H, 4.10; S, 24·51; $C_5H_6O_2S$ requires: C, 46·16; H, 4·65; S, 24·60%).

4-*Bromo-2,3-dioxo-4,5-dihydrothiophene* (XI). To 2,3-4-tribromothiophene (80 g, 0·25 mole) in ether (200 ml) was added 1·9 M n-BuLi (135 ml, 0·25 mole) at −70°. After stirring for 30 min, $MgBr_2$ (0·3 mole) in ether (200 ml) was added at −40°. After another 30 min, t-butyl perbenzoate (37 ml, 0·2 mole) in ether (100 ml) was added during 20 min (reaction temp 0°). The mixture was stirred overnight and then worked up in the usual way, but was not fractionated by distillation; on attempted distillation complete decomposition occurred, yield of crude product: ≈70 g.

Similarly another t-butoxy group was introduced to give, $b.p._{.0.15}$; 110–112°, $n_D^{20} = 1.5135$, yield ≈59%, which partly decomposed on distillation to give the very unstable XI. This product was in all respect identical with the product obtained from 4-bromo-2,3-di-t-butoxythiophene, when decomposed in the presence of catalytic amounts of *p*-toluenesulphonic acid, $b.p._{.3}$ 80–81°; NMR (CCl_4): ABX system; A: 3·48; B: 3·58; X: 4·98; $J_{AX\ cis} = 7.05$ c/s; $J_{BX\ trans} = 4.25$ c/s; $J_{AB\ gem} = 18.5$ c/s.

2-*t-Butoxy-4-bromothiophene* (XIIIa). To 2,4-dibromothiophene (65g, 0·28 mole) in ether (150 ml) cooled to −70° were added 1·5 M n-BuLi (190 ml, 0·28 mole). After stirring for 30 min, anhyd $MgBr_2$ (0·34 mole) in ether (200 ml) was added and the soln was allowed to reach 0°. 52 g (0·27 mole) of t-Butyl perbenzoate (52 g, 0·27 mole) in ether (100 ml) was added during 2 hr. After stirring overnight the mixture was worked up in the usual way, but not distilled, crude product = 63 g.

2,4-*Di-t-butoxythiophene* (XIVa). To crude 2-t-butoxy-3-bromothiophene (63 g) was added 1·5 M BuLi (173 ml, 0·26 mole) at −70°. Subsequent treatment with $MgBr_2$ and t-butyl perbenzoate as above, and the usual work-up gave, after distillation, the main product with $b.p._{.1}$ 55–57°, $n_D^{20} = 1.5178$, yield 41 g (60% based on 2,4-dibromothiophene). (Found: C, 62·66; H, 8·68; S, 14·28; Calc. for $C_{12}H_{20}O_2S$: C, 63·12; H, 8·83; S, 14·02%), NMR (CCl_4): 6·52 (1H, d, $J = 1.4$ c/s), 6·21 (1H, d, $J = 1.4$ c/s), 1·31 (18H, s).

4-*Hydroxy-3-thiolene-2-one* (XVa). Compound XVIa (3·1 g, 0·013 mole) was dealkylated at 140° in the presence of catalytic amounts of *p*-toluenesulphonic acid, yield 1·1 g (77%), m.p. 115–116° (m.p.[4] 115–117°). Identical in all respect with an authentic sample.[4]

2-*Methyl-3-bromo-5-t-butoxythiophene* (XIIIb). As above from 2-methyl-3,5-dibromothiophene (63·1 g, 0·25 mole), $b.p._{.13}$ 59–63°, $n_D^{20} = 1.5206$, yield 36 g (67%). (Found: c, 40·98; H, 5·38; S, 13·45; Br, 33·38; Calc. for C_9H_{13} BrSO: C, 41·01; H, 5·44; S, 13·39; Br, 33·47%); NMR (CCl_4) 6·10 (1H, s), 2·23 (3H, s), 1·31 (9H, s).

2-*Methyl-3,5-di-t-butoxythiophene* (XIVb). Prepared as above from 2-methyl-3-bromo-5-t-butoxythiophene (9·3 g, 0·036 mole), $b.p._{.12}$ 57–58°, $n_D^{20} = 1.5202$, yield 6·7 g (92%). (Found: C, 64·28; H, 9·01; S, 13·29; Calc. for $C_{13}H_{22}O_2S$: C, 64·44; H, 9·15; S, 13·21%); NMR (CCl_4): 6·17 (1H, s); 2·25 (3H, s), 1·31 (18H, s).

4-*Hydroxy-5-methyl-3-thiolen-2-one* (XVb). Compound XIVb (4·1 g, 0·016 mole) was alkylated as above at 140°. Extraction of the mixture with hot water and then cooling gave a heavy brown oil, which was purified on a Sephadex LH20 ($CHCl_3$) column, yield 1·5 g (72%). (Found: C, 46·05; H, 5·08; S, 24·56; Calc. For $C_5H_6O_2S$: C, 46·16; H, 4·65; S, 24·60%). Probably due to its racemic properties XVb would not solidify.

3-*Ethoxycarbonyl-4-hydroxy-5-methyl-3-thiolen-2-one* (XVIIb). The title compound was prepared similarly to XVIIa (see Ref 4), starting with thiolactic acid. During the working-up procedure some of the compound spontaneously hydrolysed and decarboxylated. The product therefore contained small amounts

of XVb. It was not separated, but by hydrolysis of XVIIIb it decarboxylated giving pure XVb, identical in all respects with an authentic sample.

Preparation of XVIa *and* XVIb. Bromine was added dropwise to XVa and XVb (resp) in $CHCl_3$ solns. The solvent was stripped off and XVIa (m.p. 33°) and XVIb (brown oil) were isolated in quantitative yields.

2,5-*Di-t-butoxy*-3-*methylthiophene* (XXI). The procedure was the same as for VII, starting with 2,5-di-t-butoxy-3-bromothiophene[14] (17 g, 0·055 mole), $b.p._{10}$ 62–64°, yield 12·1 g (91%), $n_D^{20} = 1{\cdot}4862$. (Found: C, 64·44; H, 8·98; S, 13·25. Calc. for $C_{13}H_{22}O_2S$: C, 64.44; H, 9·15; S, 13·21%); NMR (CCl_4): 5·80 (1H, s), 1·91 (3H, s), 1·30 18H, s).

Methylthiosuccinic anhydride (XXII). Compound XXI 5·3 g, 0·022 mole) was dealkylated giving XXII (1·8 g, 63%), $b.p._{0.15}$ 55°, $n_D^{20} = 1{\cdot}5338$. (Found: C, 46·02; H, 5·06; S, 24·71. Calc. for $C_5H_6O_2S$: C, 46·16; H, 4·65; S, 24·60%). NMR (CCl_4): 1·41 (3H, $J = 6{\cdot}5$ c/s); 2·6–3.5 (3H, m)).

Bromine-addition to maleic anhydride. Maleic anhydride (16·4 g, 0.17 mole) Br_2 (27 g) in CCl_4 were irradiated for 48 hr with a Hanau Q81. The working-up procedure of Michael[15] was followed giving white crystals, m.p. 156°, identified as α,α′-dibromosuccinic acid. Equivalent wt: Found: 131; Calc.:138; NMR (CD_3)$_2$ SO: H 4·71 (2H), ≈10·7 (2H, broad), yield 19·1 g (98%).

Ring-closure of α,α′-*dibromosuccinic acid.* α,α′-Dibromosuccinic acid (17 g, 0·06 mole) and P_2O_5 (15 g) was heated for 1 hr at 180°. The mixture was dissolved in ether, dried, and evaporated; 8 g of the starting material precipitated and the remaining liquid was identified as a mixture of α,α′-dibromosuccinic anhydride and bromomaleic anhydride (3 : 1). α,α′-Dibromosuccinic anhydride hydrolyzed quickly (in contact with moisture) to the corresponding acid.

Bromine-addition to thiomaleic anhydride. Compound XX (15·0 g) and Br_2 (15·08) in CCl_4 were irradiated for 48 hr with a Hanau Q81 in N_2 atmosphere.

After evaporation of the solvent an oil separated, which decomposed very quickly. Due to the fast decompositions no further purification was made. The main product was identified as XXIII, NMR (CCl_4): 4·88 (s).

Compound XXIII (10·2 g) was hydrolysed with dil HCl. After salting out the product, α,α′-dibromosuccinic acid was isolated in poor yield: 1·3 g (13%), m.p. 156°, mixed m.p. 156°.

2-*t-Butoxy*-3,5-*dibromothiophene* (XVIII). 3,5-Dibromothienyllithium was prepared from 2,3,5-tribromothiophene (130 g; 0·41 mole) in ether (300 ml) and BuLi (168 ml, 0·42 mole). Then anhyd $MgBr_2$ (prepared from 16·4 g Mg and 80 g Br_2 in 200 ml ether, was added rapidly with stirring. After 75 min, when the temp was zero, t-butyl perbenzoate (65 g, 0·33 mole) in ether (100 ml) was added, during 30 min, to the soln kept at 0°. After stirring for another 4 hr the mixture was worked up in the usual way, $b.p._{0.3}$ 90–91°; $n_D^{20} = 1{\cdot}5620$; yield: 98 g (95%). (Found: C, 30·67; H, 3·35; Br, 50·94; S, 10·34. Calc. for $C_8H_{10}Br_2OS$; C, 30·57; H, 3·18; Br, 50·96; S, 10·19%).

2,5-*Di-t-butoxy*-3-*bromothiophene* (XIX). The title compound was prepared as above from XVIII (72 g, 0·25 mole) and worked up as usual, $b.p._{0.1}$ 62–64°; $n_D^{20} = 1{\cdot}5165$; yield: 59 g (90%). (Found: C, 47·35; H, 5·88; Br, 25·78. Calc. for $C_{12}H_{19}BrO_2S$: C, 46·97; H, 5·22; Br, 26·38%).

Thiomaleic anhydride (XX). Compound XIX (crude product from above) was placed in a Vigreux distillation set, heated with *p*-toluenesulphonic acid (5 mg) at 110–120° under vacuum. After isobutylene and HBr-elimination has ceased, the product was distilled immediately, $b.p._{10}$ 68–70°; m.p. ≈ 26° (lit.[27]: $b.p._{10}$ 72–74°; m.p. 28°); $n_D^{20} = 1{\cdot}5606$. (Found: C, 41·82; H, 1·83. Calc. for $C_4H_2O_2S$: C, 42·12; H, 1·77%); UV: (hexane) λ_{max} 230, 318 (ε 9220, 620); IR: (CCl_4) 1690 (s), 1730 (v); NMR: ($CDCl_3$) a single peak at 7·22.

3,4-*Di-t-butoxythiophene.* The normal method of introducing a t-butoxy group was used starting with 4-bromo-3-t-butoxythiophene[2] (29·0 g, 0·12 mole), $b.p._{0.2}$ 70–71°, $n_D^{20} = 1{\cdot}4875$, yield 18·0 g (66%). (Found: C, 63·10; H, 8·66; S, 14·17. $C_{12}H_{20}O_2S$ requires: C, 63·13; H, 8·83; S, 14·02; NMR (CCl_4): 6·36 (2H, s), 1·28 (18H, s).

4-*Hydroxy*-3-*oxo*-2,3-*dihydrothiophene* (XXIV). 3,4-Di-t-butoxythiophene (4·3 g, 0·019 mole) was dealkylated giving XXIV. Recrystallisation from benzene gave crystals very sensitive to moisture, m.p. 89–91°.

Decarboxylation of 2,5-dicarboxy-3,4-dihydroxythiophene also gave XXIV.[7]

3,4-*Di-t-butoxy*-5-*methylthiophene.* 3,4-Di-t-butoxythiophene (27·5 g, 0·12 mole) was methylated. The procedure used was the same as for III, $b.p._{0.14}$ 69–70°, $n_D^{20} = 1{\cdot}4870$, yield 26·6 g (91%). (Found: C, 64·31; H, 9·29; S, 13·32) $C_{13}H_{22}O_2S$ requires: C, 64·44; H, 9·15; S, 13·21%); NMR (CCl_4): 6·15 (1H, s), 2·24 (3H, s), 1·30 (18h, s).

4-Hydroxy-5-methyl-3-oxo-2,3-dihydrothiophene (XXV). The former (5·1 g, 0·021 mole) was dealkylated and recrystallised from benzene under N_2, as the compound immediately polymerises in contact with air, yield 1·9g (67%). Due to its instability towards moisture, we were not able to obtain satisfactory analysis.

3,4-Di-t-butoxy-2,5-dimethylthiophene. 3,4-Di-t-butoxy-5-methylthiophene (10·7 g, 0·044 mole) was methylated (see prep of III), b.p.$_{0.3}$ 90°, $n_D^{20} = 1{\cdot}4889$; yield 9·1 g (81%). (Found: C, 65·40; H, 9·29; S, 12·64. $C_{14}H_{24}O_2S$ requires: C, 65·59; H, 9·44; S, 12·50%; NMR (CCl_4): 2·19 (1H, s), 1·30 (3H, s).

4-Hydroxy-2,5-dimethyl-3-oxo-2,3-dihydroxythiophene (XXVI). The former (3·2 g, 0·0125 mole) was dealkylated, yield 0·9 g (50%). Due to instability, analyses could not be obtained.

4-Hydroxy-5-ethoxycarbonyl-3-oxo-2,3-dihydrothiophene. (XXVII). Compound XXVIII (5·2 g, 0·014 mole) was saponified with 50 ml 0·5 N NaOH (0·025 mole) After acidification it was extracted with $CHCl_3$, dried, and evaporated, m.p. 77–78° (lit.[24]: 76–78°).

4-Bromo-3-hydroxy-5-methyl-2,5-dihydrofuran-2-one. To a soln of 2,3-dihydroxy-5-methylfuran (3 g, 0·03 mole) in boiling $CHCl_3$ (125 ml) was added Br_2 (4·8 g) in $CHCl_3$ (25 ml). After evaporation of solvent the title compound was isolated, m.p. 100–102° (lit.[16]: 100–101°), yield 5 g (93%).

4-Bromo-3-hydroxy-2,3-dihydrofuran-2-one. The procedure was identical with the former, giving the title compound as a heavy oil, which slowly crystallised, m.p. 25–27°.

REFERENCES

[1] A.-B. Hörnfeldt, *Arkiv Kemi* **29**, 427 (1968), and refs cited
[2] H. J. Jakobsen and S.-O. Lawesson, *Tetrahedron* **21**, 3331 (1965)
[3] S. Gronowitz and A. Bugge, *Acta Chem. Scand.* **20**, 261 (1966)
[4] F. Benary, *Ber. Dtsch. Chem. Ges.* **46**, 2107 (1913)
[5] H. J. Jakobsen, E. H. Larsen and S.-O. Lawesson, *Tetrahedron* **19**, 1867 (1963)
[6] C. G. Overberger and L. Ioginder, *J. Am. Chem. Soc.* **73**, 2956 (1951)
[7] V. N. Gogte, L. G. Shah, B. D. Tilak, K. N. Gadekar and M. B. Sahasrabudhe, *Tetrahedron* **23**, 2437 (1967)
[8] H. von Euler and B. Eistert, *Chemie und Biochemie der Reduktone und Reduktonate.* Ferdinand Enke Verlag, Stuttgart (1957)
[9] S. Gronowitz and R. A. Hoffman, *Arkiv Kemi* **15**, 499 (1960)
[10] A.-B. Hörnfeldt and S. Gronowitz, *Ibid.* **21**, 239 (1967)
[11] A.-B. Hörnfeldt, *Tautomeric Properties and Some Reactions of the 2-Hydroxythiophene and 2-Hydroxyfuran Systems.* Dissertation (Stockholm 1968)
[12] S. Gronowitz, *Arkiv Kemi* **16**, 363 (1960)
[13] J. M. Mallan and R. L. Bebb, *Chem. Revs* **69**, 693 (1969)
[14] J. Z. Mortensen and S.-O. Lawesson, *Acta Chem. Scand.* **22**, 1056 (1968)
[15] A. Michael, *J. Pr.* [2] **52**, 289 (1895)
[16] F. Fleck, A. Rossi and H. Schinz, *Helv. Chim. acta* **32**, 998 (1949), and refs cited
[17] L. J. Haynes and I. R. Plimmer, *Quart. Rev.* **10**, 29 (1956), and refs cited
[18] P. M. Boll, E. Sørensen and E. Balieu, *Acta Chem. Scand.* **22**, 3251 (1968)
[19] Th. Severin and W. Seilmere, *A. Lebensm. Unt. Forsch.* **134**, 230 (1967)
[20] H. G. Peer, G. A. M. Van Den Ouweland and C. N. De Groot, *Rec. Trav. Chim.* **87**, 1011 and 1017 (1968)
[21] A. Hofmann and C. H. Eugster, *Helv. Chim. Acta* **49**, 53 (1966)
[22] D. W. Henry and R. M. Silverstein, *J. Org. Chem.* **31**, 2391 (1966)
[23] E. C. Kendall and Z. G. Hajas, *J. Am. Chem. Soc.* **82**, 3219 (1960)
[24] O. Hinsberg, *Ber. Dtsch. Chem. Ges.* **45**, 2413 (1912)
[25] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* Wiley, N.Y. (1958)
[26] H. J. Jakobsen, *Tetrahedron* **23**, 3737 (1967)
[27] H. D. Sharf and M. Verbeek, *Angew. Chem.* **79**, 870 (1967)