Tetrahedron, 1965, Vol. 21, pp. 3331 to 3349. Pergamon Press Ltd. Printed in Northern Ireland

THIOPHENE CHEMISTRY—X*

PREPARATION, TAUTOMERIC STRUCTURE AND HYDROGEN BONDING STUDIES OF THIOISOMALTOL (2-ACETYL-3-HYDROXY-THIOPHENE)† AND SOME RELATED 3-HYDROXYTHIOPHENES

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(*Received* 8 *June* 1965)

Abstract—Different acetyl- and carbethoxysubstituted 3-t-butoxythiophenes have been prepared via organometallic reagents. Dealkylation of these t-butyl ethers in the presence of a catalytic amount of *p*-toluenesulphonic acid at 150° gives the corresponding 3-hydroxythiophenes in almost quantitative yields. Spectroscopic investigations by NMR and IR show that carbonyl (acetyl or carbalkoxy)-substituted 3-hydroxythiophenes exist exclusively in the hydroxyaromatic form in polar and non-polar media and in the pure (solid or liquid) state. The only exception is 5-carbethoxy-2,3-dihydroxythiophene which is shown to exist in one of its two possible unsaturated γ-thiolactone forms. The NMR and IR-spectra show the presence of hydrogen bonding and when intramolecular hydrogen bonding is sterically possible its strength, as measured by the chemical shift of the enolic proton (NMR) and shifts to lower wave numbers for both the hydroxyl and carbonyl frequencies (IR), is discussed along with observations for compounds with similar structures. Long-range spin coupling between the aromatic C-5 proton and the OH proton is observed in one case.

INTRODUCTION

DURING the last few years many of the earlier unknown or not easily available tautomeric 2-hydroxythiophenes (2-thienols) have been obtained by two different methods of preparation. One of these, the hydrogen peroxide oxidation of thiophene boronic acids, as studied by Hörnfeldt and Gronowitz,[2-4] is restricted in the sense that the preparation of substituted 2-thienols is only possible for substituents that show no reactivity toward organometallic reagents. The other method, the acid-catalysed dealkylation of t-butyl 2-thienyl ethers, which has been studied by the present authors,[5-7] avoids this limitation by making use of the t-butyl group as a hydroxyl protecting group. First the unsubstituted t-butyl ether is prepared, then the different substituents are introduced and finally isobutylene is eliminated; the synthesis of 5-carbethoxy-2-hydroxythiophene[7] is an excellent example of the general application

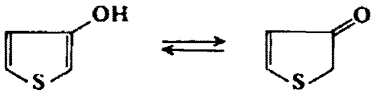
* Part IX. H. J. Jakobsen, E. H. Larsen and S.-O. Lawesson, *Tetrahedron* **19**, 1867 (1963).

† We suggest the name thioisomaltol for the hitherto unknown compound 2-acetyl-3-hydroxythiophene by analogy with the recently studied compound 2-acetyl-3-hydroxyfuran which has been given the name isomaltol.[1]

[1] B. E. Fischer and J. E. Hodge, *J. Org. Chem.* **29**, 776 (1964) and Refs. cited therein.
[2] A.-B. Hörnfeldt and S. Gronowitz, *Acta Chem. Scand.* **16**, 789 (1962).
[3] A.-B. Hörnfeldt and S. Gronowitz, *Arkiv Kemi* **21**, 239 (1963).
[4] A.-B. Hörnfeldt, *Arkiv Kemi* **22**, 211 (1964).
[5] S.-O. Lawesson and C. Frisell, *Arkiv Kemi* **17**, 393 (1961).
[6] C. Frisell and S.-O. Lawesson, *Org. Syntheses* **43**, 55 (1963).
[7] H. J. Jakobsen, E. H. Larsen and S.-O. Lawesson, *Tetrahedron* **19**, 1867 (1963).

of this method. The present paper is an extension of our general studies of the scope and usefulness of t-butyl aryl (heterocyclic) ethers in organic synthesis as well as constitutional investigations of hydroxyheterocycles.

Concerning the 3-hydroxythiophenes, only a few simple compounds are known. The very unstable 3-hydroxythiophene has been prepared in poor yield by oxidation of 3-thienylmagnesium bromide,[8] and by decarboxylation of 2-carboxy-3-hydroxythiophene.[9] It was stated from IR spectra[8] that 3-hydroxythiophene in the pure liquid state and in solutions of carbon tetrachloride exists as a mixture of the enolic form (I) and the keto form (II) with the former predominating in concentrated solutions.



I II

5-Phenyl-3-hydroxythiophene[10,11] has been prepared by a four-step ring-closure synthesis and was shown by UV spectroscopy to exist in the enolic form in alcoholic solution while the keto tautomer is predominant in solutions of chloroform.

The success in the syntheses of simple 2-hydroxythiophenes via the corresponding t-butyl ethers[7] prompted the preparation of the difficultly accessible 3-isomers by the same method; it was found that by dealkylation of 3-t-butoxythiophene, following the usual procedure, only resinous material and no 3-hydroxythiophene was obtained. The hydrogen peroxide cleavage of 3-thiopheneboronic acid in the presence of acetic anhydride gave the acetate of 3-hydroxythiophene, but the compound itself could not be obtained.[2] However, the literature indicates that 2- and 4-carbalkoxysubstituted 3-hydroxythiophenes are stable compounds, as a series of such compounds have been synthesized through ring-closure reactions by different research groups.* Furthermore, quite recently the occurrence of 5-propyn(-1)-2-acetyl-3-hydroxythiophene in nature (*Artemisia arborescens* L.)[15] and its synthesis[16] have been described; it is the first acetyl substituted 3-hydroxythiophene given in the literature.

These facts indicate that at least carbonyl substituted 3-hydroxythiophenes should be available via the corresponding t-butyl ethers obtained by directly introducing the different groups into the thiophene nucleus, and this paper bears out the assumption. Furthermore, structure determination (tautomerism) of this class of compounds by

* For pertinent Refs., see the review in *Organic Reactions*,[12] the review by Gronowitz[13] and Ref. 14.

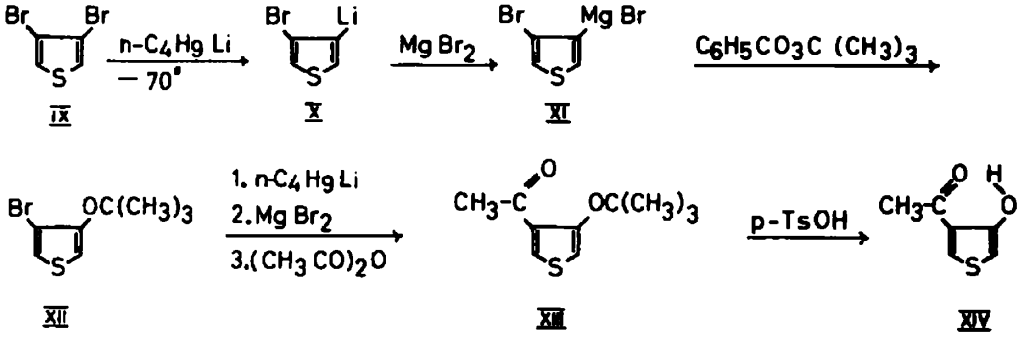
[8] M. C. Ford and D. Mackay, *J. Chem. Soc.* 4985 (1956).
[9] H. Fiesselmann, P. Schipprack and L. Zeitler, *Chem. Ber.* **87**, 841 (1954).
[10] P. Friedländer and S. Kielbasinski, *Ber. Dtsch. Chem. Ges.* **45**, 3389 (1912).
[11] A. I. Kosak, R. J. F. Palchak, W. A. Steele and C. M. Schirtz, *J. Amer. Chem. Soc.* **76**, 4450 (1953).
[12] D. E. Wolf and K. Folkers, *Organic Reactions* **6**, 410 (1951).
[13] S. Gronowitz in A. R. Katritzky: *Advances in Heterocyclic Chemistry* Vol. 1; p. 29. Academic Press (1963).
[14] A. Courtin, E. Class and H. Erlenmeyer, *Helv. Chim. Acta* **47**, 1748 (1964).
[15] F. Bohlmann, K.-M. Kleine and H. Bornowski, *Chem. Ber.* **95**, 2934 (1962).
[16] F. Bohlmann, H. Bornowski and D. Kramer, *Chem. Ber.* **96**, 584 (1963).

spectroscopic methods (NMR and IR) is missing in the literature as mentioned by Rosenkranz *et al.*,[17] and such an investigation is included in the present paper.

The synthetic methods of preparation

3-t-Butoxythiophene (III) is easily prepared from 3-thienylmagnesium bromide and t-butyl perbenzoate,[18] and metallation of it with n-butyllithium has been shown to occur exclusively in the sterically hindered 2-position[18] giving 3-t-butoxy-2-thienyllithium (IV). Via this lithium reagent (IV) and the corresponding Grignard reagent the carbethoxy and acetyl group were introduced into the 2-position by treating IV with ethyl chloroformate and acetic anhydride respectively; thus 2-carbethoxy-3-t-butoxythiophene (V) and 2-acetyl-3-t-butoxythiophene (VI) were both obtained in a yield of 75% (Scheme 1). Pyrolysis of the t-butyl ethers V and VI in the presence of catalytic amounts of *p*-toluenesulphonic acid (*p*-TsOH) at about 150° causes dealkylation and the corresponding hydroxythiophenes, 2-carbethoxy-3-hydroxythiophene (VII) and 2-acetyl-3-hydroxythiophene (thioisomaltol; VIII), were produced in excellent yields.

Similarly, 3,4-dibromothiophene gave 4-acetyl-3-hydroxythiophene (XIV) as illustrated below (IX–XIV):



2-Methyl-5-carbethoxy-3-hydroxythiophene (XVII) and 5-carbethoxy-2,3-dihydroxythiophene (XX) were prepared from 3-t-butoxythiophene by first introducing the methyl and t-butoxy group, respectively, into the 2-position, followed by introducing the carbethoxy group into the 5-position (Scheme 1). Finally, dealkylation gave the desired hydroxythiophenes. 2,3-Di-t-butoxythiophene (XVIII) being an intermediate in one of the named synthesis is, as far as we know, the first known example of an aromatic *ortho* di-t-butoxy compound.

All the t-butyl thienyl ethers are stable compounds and the same is valid for the hydroxythiophenes, except 5-carbethoxy-2,3-dihydroxythiophene which quite rapidly deteriorates when exposed to air and for that reason should be kept under nitrogen and at a low temperature (−20°).

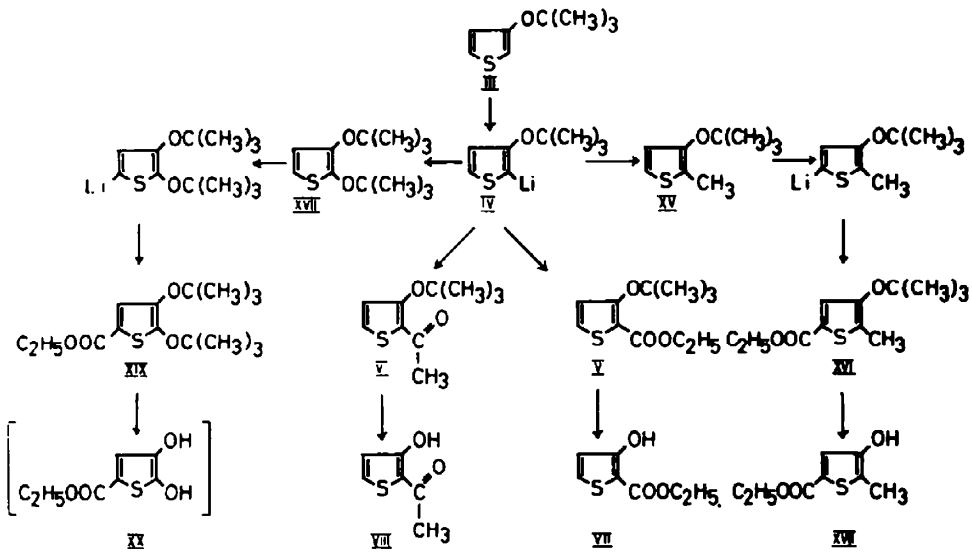
NMR, IR and hydrogen bonding studies

3-t-Butyl thienyl ethers. That metallation of 3-t-butoxythiophene with n-butyllithium occurs exclusively in position 2[18] has been further substantiated by running

[17] R. E. Rosenkranz, K. Allner, R. Good, W. v. Philipsborn and C. H. Eugster, *Helv. Chim. Acta* **46**, 1259 (1963).

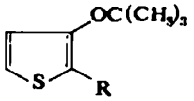
[18] S. Gronowitz, *Arkiv Kemi* **16**, 363 (1960).

Scheme 1



the NMR spectra of some new compounds prepared via this organolithium reagent. The NMR data of these compounds (Table 1) show that the coupling constants of the AB systems in these spectra fall within the range characteristic of 2,3-disubstituted thiophenes (J_{45} = 4·90–5·80 c/s)[19] except in one case to be discussed below. Table 1 also includes the IR stretching frequencies of the carbonyl group in the carbalkoxy- and acetylsubstituted 3-t-butoxythiophenes. It is to be noted that 2-carbethoxy-3-t-butoxythiophene shows two bands of nearly equal intensities in the carbonyl region in the pure liquid state as well as in carbon tetrachloride solution.

TABLE 1. OBSERVED PROTON CHEMICAL SHIFTS (δ), RING-COUPLING CONSTANTS (J) AND CARBONYL STRETCHING FREQUENCIES ($\bar{\nu}$) OF SOME 2-SUBSTITUTED 3-t-BUTOXYTHIOPHENES IN SOLUTIONS OF CCl_4. THE SHIFT VALUES ARE GIVEN IN PPM RELATIVE TO TETRAMETHYLSILANE, THE SPIN COUPLING CONSTANTS ARE IN C/S AND THE STRETCHING FREQUENCIES IN CM^{-1}

	R	$\delta_{H(4)}$ and $\delta_{H(5)}$*		J_{45}	$\bar{\nu}$
	Carbethoxy	6·73	7·25	5·3	1713; 1683
	Acetyl	6·87	7·38	5·5	1645
	t-Butoxy†	6·52	6·56	6·0	—
	Methyl	6·59	6·78	5·5	—

* No attempts have been made to assign the peaks of the AB system to H(4) or H(5).

† This spectrum was run using $CDCl_3$ as solvent and the data given here are those obtained from the 100 Mc/s spectrum.

In the NMR spectrum of 4-acetyl-3-t-butoxythiophene (CCl_4-solution) the aromatic protons appear as doublets at 6·43 ppm and 7·79 ppm with a coupling

[19] Ref. 13, p. 8.

constant equal to about 3·4 c/s characteristic for 3,4-disubstituted thiophenes (J_{25} = 3·20–3·65 c/s).[19] In the IR spectrum, of the same compound, the carbonyl stretching frequency occurs at 1670 cm^{-1}.

The NMR spectrum of 2,3-di-t-butoxythiophene in deuterochloroform solution is of particular interest and a few words should be said about this special case. When recorded on the A-60 spectrometer (sweep width: 500 c/s) the region of aromatic hydrogens shows only a singlet peak at δ = 6·54 ppm and no indication of an AB system is present. However, by working at the optimum resolution power of the A-60 spectrometer and running the aromatic peak region using a sweep width of 50 c/s the peak was split into a doublet with a separation of only about 0·35 c/s and, furthermore, two weak peaks, one on each side of the resolved peak, appeared.* It is thus evident that the signal is due to an AB system with two nearly magnetic equivalent protons; from the 60 Mc spectrum (Fig. 1) the coupling constant J_{45} was found to be 6·1 c/s which is about 0·3 c/s above the upper limit previously determined for 2,3-disubstituted thiophenes.[19] It is interesting to note that when recorded under these conditions (A-60 spectrometer) the intensities of the inner lines of the AB system are dependent upon the magnetic sweep direction. Sweeping from lower to higher magnetic field, the inner line at lowest field is the more intense while the reverse is true when the sweep is from higher to lower field (Fig. 1).

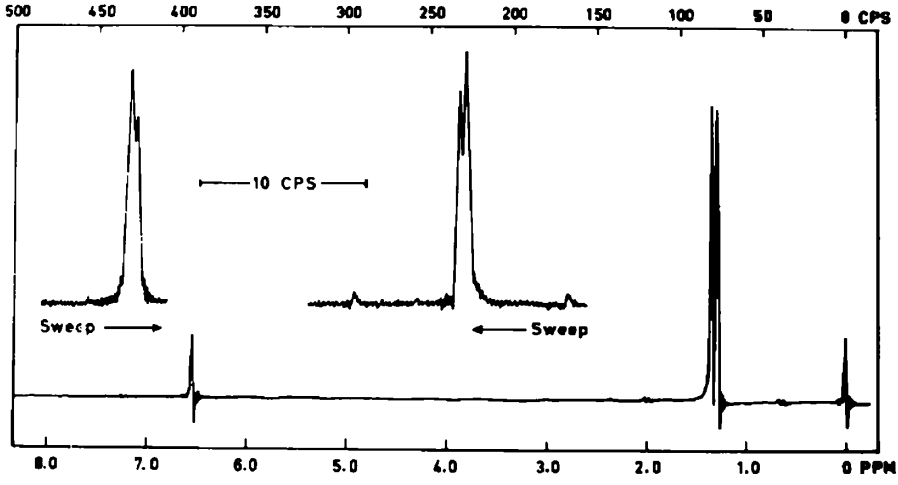


FIG. 1 60 Mc/s spectrum of 2,3-di-t-butoxythiophene in deuterochloroform solution.

When recorded on a 100 Mc/s spectrometer the aromatic part of the spectrum clearly shows up as an AB system even at first sight (sweep width: 1000 c/s; Fig. 2). Expansion to a larger scale (sweep width: 100 c/s) gives a fully resolved AB system from which the ratio of intensities of the inner and outer lines was found by planimetry:

$$\frac{I_{in}}{I_{out}} = \frac{74}{8} = 9{\cdot}3$$

Analysis of the AB system gives the following data for the chemical shift difference and the spin coupling constant: $|\nu_0(\delta_{H(5)} - \delta_{H(4)})| = 4{\cdot}3$ c/s and $J_{45} = 6{\cdot}0$ c/s. Using

* The authors wish to thank Dr. K. Schaumburg at the Chemical Laboratory V, University of Copenhagen, for performing this delicate operation.

these parameters, the ratio of the intensities of the inner and outer lines is calculated[20] to be 9·6, which is in good agreement with the experimental value. The theoretical spectrum is shown in Fig. 2 below the experimental one.

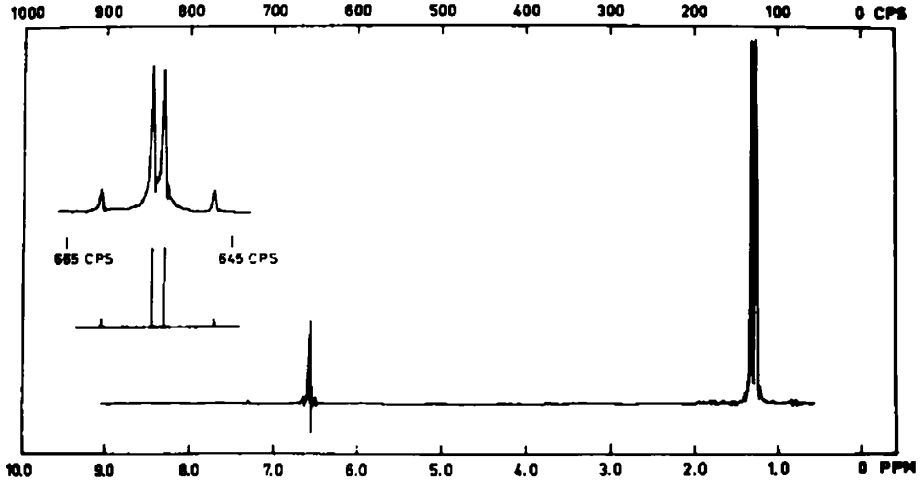


FIG. 2 100 Mc/s NMR spectrum of 2,3-di-t-butoxythiophene in deuterochloroform solution.

Carbalkoxy- and acetylsubstituted 3-hydroxythiophenes

Concerning the possibility of keto-enol tautomerism in carbalkoxy- and acetyl-substituted 3-hydroxythiophenes it has been shown by NMR and IR spectroscopy that all the hydroxy compounds studied in this work exist exclusively in their enol form. The only exception found is the dihydroxythiophene, 5-carbethoxy-2,3-dihydroxythiophene, which exists in one of its two tautomeric unsaturated γ-thiolactone forms. The stabilization of the aromatic enol form in these mono-hydroxy compounds is probably due to the —I, —R effect of the carbalkoxy- and acetyl groups and to intra- (conjugate chelation) and intermolecular hydrogen bonding in combination with an adequate aromatic character of the thiophene nucleus. The stabilization of the enolic aromatic form by the carbethoxy group, in thiophene chemistry, has earlier been demonstrated in the series of potentially tautomeric 2-hydroxythiophenes by the enolic structure of 5-carbethoxy-2-hydroxythiophene;[7] a similar stabilization is also found in the case of potential 2-hydroxypyrroles.[21]

Spectra of the compounds were recorded in solutions of carbon tetrachloride and deuterochloroform. The resonance field for the hydroxylic protons (NMR) and the stretching frequencies (IR) of the carbonyl and hydroxyl groups in compounds with geometric requirements (2- and 4-carbalkoxy- or acetylsubstituted 3-hydroxythiophenes) for intramolecular hydrogen bonding have received special attention as these quantities are closely related to the strength of the hydrogen bonded chelate rings. Hydrogen bonding causes displacement of the hydroxyl proton resonance signal

[20] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* Chap 6; Sec. 5. McGraw-Hill, New York (1959).

[21] H. Plieninger, H. Bauer and A. R. Katritzky, *Liebigs Ann.* **654**, 165 (1962).

towards lower field[22] and this displacement may be used for comparing the strengths of the hydrogen bonds. Furthermore, the shifts of the hydroxyl and carbonyl bands in the IR spectra to lower frequencies are also related to the strength of the intramolecular hydrogen bond.[23] Correlations between the NMR and IR data have earlier been noted in certain enols[24] and in *o*-hydroxy-esters, ketones and aldehydes of the benzene series.[25–27] The NMR and IR data for the compounds investigated in this work are summarized in Table 2.

The NMR spectra of the un- and 5-substituted 2-carbalkoxy-3-hydroxythiophenes in deuterochloroform show signals for the hydroxyl protons in the range $\delta = 9{\cdot}45 - 9{\cdot}79$ ppm while the carbonyl bands in the IR spectra appear at 1652–1664 cm^{-1}. The hydroxyl stretching frequencies show up as broad, merged and strongly shifted bands at 3500–3050 cm^{-1} with the maximum intensities occurring at the values given in Table 2; this indicates that the hydroxyl group is not free. It is further noted that the IR spectra of these compounds all show a rather broad shoulder on the hydroxyl band at 3440–3460 cm^{-1} and a second band of weak intensity in the carbonyl region at 1710–1725 cm^{-1}; one of the two carbonyl bands of equal intensity for 2,5-dicarbmethoxy-3-hydroxythiophene falls in this last region (Table 2).

In the NMR spectrum of the acetyl analog, 2-acetyl-3-hydroxythiophene (thioisomaltol), the resonance of the hydroxylic proton occurs at a considerably lower field, $\delta_{OH} = 11{\cdot}50$ ppm ($CDCl_3$); the NMR spectrum of thioisomaltol in carbon tetrachloride is shown in Fig. 3. The hydroxyl band of the title compound in carbon tetrachloride is very broad, 3500–2600 cm^{-1}, with the maximum intensity occurring near 3100 cm^{-1}; the carbonyl band is shifted down to 1618 cm^{-1}. The IR spectrum of the compound in the pure liquid state (before crystallization; Fig. 4) is identical to the spectrum discussed above with no frequency shifts of the bands mentioned; in

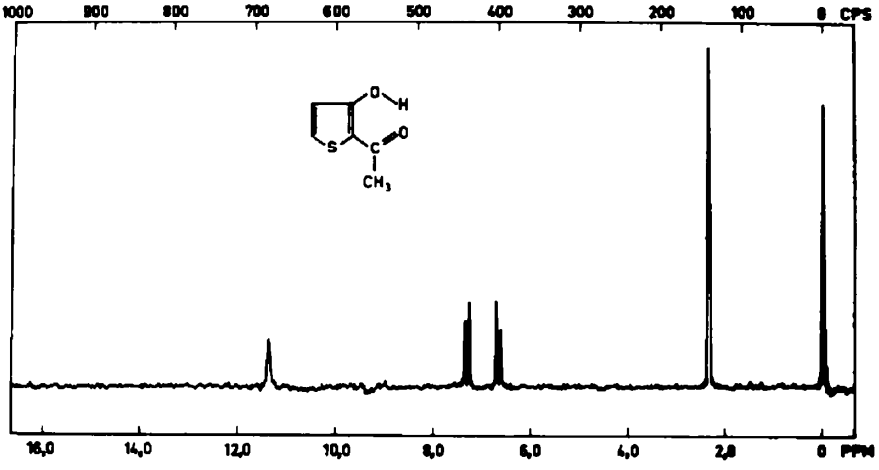


FIG. 3 NMR spectrum of thioisomaltol in carbon tetrachloride.

[22] Ref. 20. Chap. 15.
[23] G. C. Pimentel and A. L. McClellan, *The Hydrogen Bond*. W. H. Freeman, San Francisco (1960).
[24] S. Forsén, F. Merényi and M. Nilsson, *Acta Chem. Scand.* **18**, 1208 (1964) (and Refs. cited therein).
[25] A. L. Porte, H. S. Gutowsky and I. M. Hunsberger, *J. Amer. Chem. Soc.* **82**, 5057 (1960).
[26] S. Forsén and B. Åkermark, *Acta Chem. Scand.* **17**, 1907 (1963).
[27] R. W. Hay and P. P. Williams, *J. Chem. Soc.* 2270 (1964).

TABLE 2. OBSERVED PROTON CHEMICAL SHIFTS (δ), RING COUPLING CONSTANTS (J) AND CARBONYL AND HYDROXYL STRETCHING FREQUENCIES ($\tilde{\nu}$) OF CARBALKOXY AND ACETYLSUBSTITUTED 3-HYDROXYTHIOPHENES IN SOLUTIONS OF $CDCl_3$ OR CCl_4 (INDICATED BY *). THE SHIFT VALUES ARE GIVEN IN PPM RELATIVE TO TETRAMETHYLSILANE, THE SPIN COUPLING CONSTANTS ARE IN C/S AND THE STRETCHING FREQUENCIES IN CM^{-1}

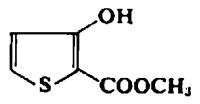
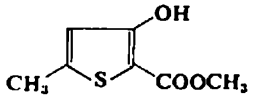
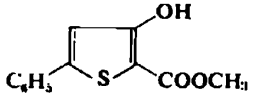
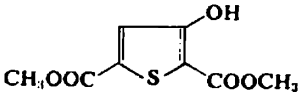
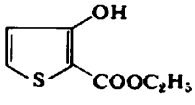
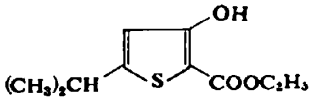
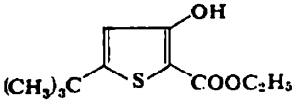
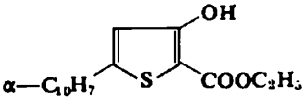
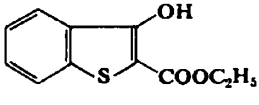
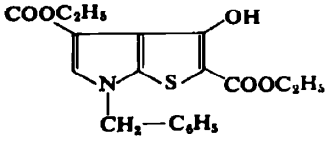
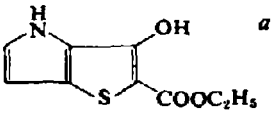
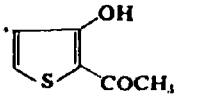
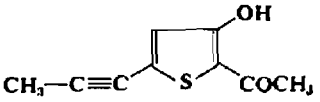
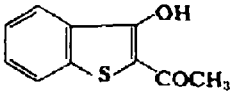
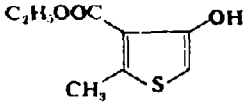
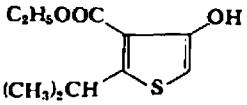
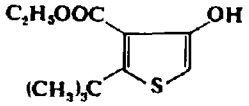
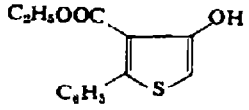
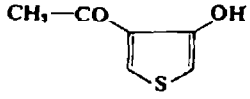
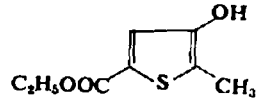
	Compound		δ_{OH}	$\delta_{H(2)}$	$\delta_{H(4)}$	$\delta_{H(5)}$	J	$\tilde{\nu}_{C=O}$	$\tilde{\nu}_{OH}$
1		*c*	9·59	—	6·72	7·35	$J_{45} = 5{\cdot}4$		
			9·52*		6·64*	7·28*		1660*	3260*
2		*c*	9·62	—	6·46	—	$J_{CH_3,H(5)} = 1{\cdot}0$		
			9·55*		6·38*			1653*	3250*
3		*c*	9·63	—	6·92	—	—	1654*	3260*
4		*c*	9·45	—	7·33	—	—	1664* 1718*	3270*
5			9·65	—	6·71	7·34	$J_{45} = 5{\cdot}3$	1652*	3250*
			9·60*		6·67*	7·27*	$J_{OH,H(5)} = 0{\cdot}45$		
6			9·67	—	6·48	—	$J_{CH,H(4)} = 0{\cdot}9$	1655*	3240*
7			9·63	—	6·53	—	—	1656*	3245*
8			9·79	—	6·91	—	—	1654* 1660†	3260* 3250†
9			10·19 10·47*	—	—	—	—	1655*	3210*
10		*a*	10·43*	—	—	—	—	1652* 1695*	3200*

TABLE 2 (cont.)

	Compound	δ_{OH}	$\delta_{(2)H}$	$\delta_{H(4)}$	$\delta_{H(5)}$	J	$\tilde{\nu}_{C=O}$	$\tilde{\nu}_{OH}$
11		10·77[a]	—	—	—	—	1642[a]	
12		11·50 11·37*	—	6·75 6·66*	7·40 7·30*	J_{45} = 5·3	1618* 1582†	~3100* 3300–2000†
13		—	—	6·7[b]	—	—	1630[b]	
14		12·12 12·38*	—	—	—	—	1618*	~3025*
15		9·19 8·90*	6·06 5·92*	—	—	—	1668*	3295*
16		9·32	6·13	—	—	—	1670*	3290*
17		9·47	6·12	—	—	—	1665*	3250*
18		9·33	6·35	—	—	—	1670* 1658†	3290* 3275†
19		9·80 9·65*	6·33 6·23*	—	7·90 7·83*	J_{34} = 3·3	1650* 1638†	3250* 3160†
20		6·91	—	7·39	—	—	1700* 1672*	3610* 3400*

[a] Ref. 29. [b] Ref. 15. * Kindly supplied by Professor H. Fiesselmann.
† In KBr.

the crystalline state (KBr disk) the hydroxyl band is especially broad (3300–2000 cm^{-1}) and the carbonyl band occurs near 1580 cm^{-1}.

In this connection it should be mentioned that from the close resemblance of the hydroxyl and carbonyl bands in the IR spectrum of isomaltol (2-acetyl-3-hydroxyfuran) in the crystalline state, and the similar bands of carboxylic acid dimers, Fisher and Hodge[1] conclude that these bands should not be interpreted as representing a chelated structure (similar to XXI↔ XXII), but that isomaltol is probably a strongly hydrogen bonded dimer in the crystalline state. The possible existence of isomaltol as a dimer in organic solvents is also considered by Fisher and Hodge[1] in analogy to the dimeric structure found by Carpenter and Snyder[28] for 2-carbethoxy-3-hydroxythieno-[3,2-b]-pyrrole by mol. wt. determination in boiling methyl ethyl ketone. Quite recently Olsen and Snyder[29] have shown that a related compound exists in solution as the monomer. In our work on 2-carbonylsubstituted 3-hydroxythiophenes no indication of the existence of a dimeric structure for these compounds have been met;

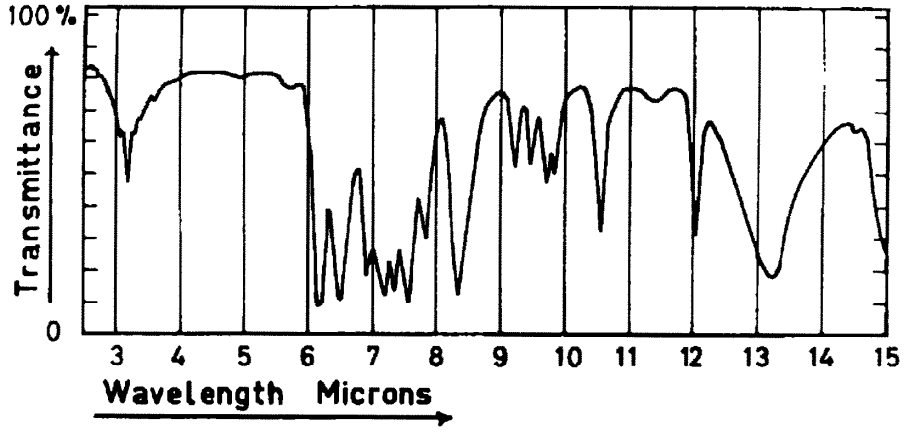
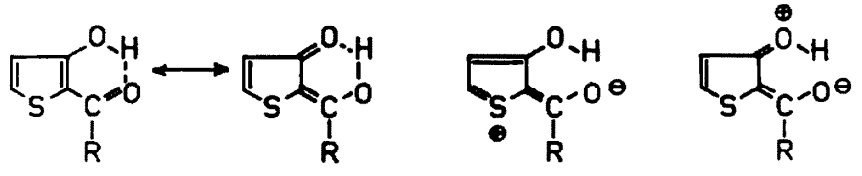


FIG. 4 IR spectrum of thioisomaltol (liquid film).

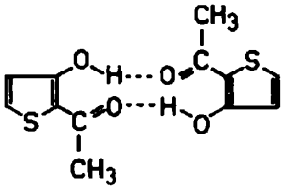
on the contrary, the low b.ps of thioisomaltol (40°/0·1 mm Hg) and 2-carbethoxy-3-hydroxythiophene (63–65°/0·4 mm Hg) compared with the higher b.ps of the corresponding t-butyl ethers and 5-carbethoxy-2-methyl-3-hydroxythiophene (131–133°/0·4 mm Hg) (no intramolecular hydrogen bonding) suggest a monomeric structure with intramolecular hydrogen bonding of a conjugate chelate type, XXI↔ XXII ("internal tautomerism"[24]) at least for the compounds in the pure liquid state. Concerning a possible dimeric structure, as e.g. XXV, for thioisomaltol



XXI XXII XXIII XXIV

[28] W. Carpenter and H. R. Snyder, *J. Amer. Chem. Soc.* **82**, 2592 (1960).
[29] R. K. Olsen and H. R. Snyder, *J. Org. Chem.* **30**, 184 (1965).

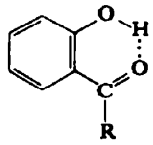
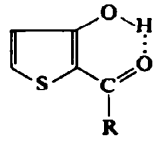
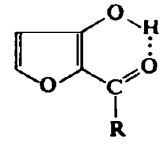
in the crystalline state, an X-ray investigation is planned to settle this problem. Finally, it should be added that polar structures such as XXIII and XXIV (and others) probably also make some contribution to the resonance hybrid for 2-carbonyl-substituted 3-hydroxythiophenes.



XXV

The NMR and IR data for thioisomaltol indicate a stronger hydrogen bonding in this compound than in 2-carbalkoxy-3-hydroxythiophenes. This is probably caused by the difference in electron-releasing power of the methyl and alkoxy groups, increasing the negative charge on the carbonyl oxygen atom more in the former case, which again should strengthen the hydrogen bonding.[25] This result is in good agreement with the results for *o*-hydroxyacetophenone and methyl salicylate; the difference in chemical shift for the hydroxylic protons (1·29 ppm) and the difference in carbonyl stretching frequencies ($-26\ cm^{-1}$) for these two compounds may be compared with the corresponding differences for the analogous thiophene compounds (1·85 ppm and $-42\ cm^{-1}$). The hydroxylic proton chemical shifts (δ in ppm) and carbonyl stretching frequencies ($\tilde{\nu}$ in cm^{-1}) for some analogous hydrogen bonded chelate rings in the benzene, thiophene and furan series are given in Table 3. Comparisons of hydrogen bond strengths in the benzene, thiophene and furan series from NMR and IR data should be made with caution as the aromatic rings are directly involved in the conjugate chelate rings. Thus differences in the hydroxylic proton chemical shifts may be partly due to differences in induced ring-currents in the aromatic rings, and further, the carbonyl stretching frequencies may be influenced by various degrees of contributions from the resonance structures (i.e. XXI–XXIV and others) to the resonance hybrid for the different aromatic systems.

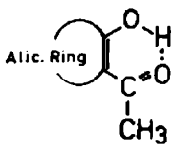
TABLE 3

			
δ_{OH}	R = CH_3: 12·06[a] R = OCH_3: 10·77[b]	R = CH_3: 11·37[b] R = OCH_3: 9·52[b]	R = CH_3: 8·95[d]
$\tilde{\nu}_{C=O}$	R = CH_3: 1645[a,c] R = OCH_3: 1671[c]	R = CH_3: 1618[b] R = OCH_3: 1660[b]	R = CH_3: 1637[d]

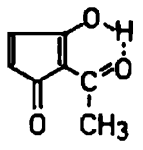
[a] Ref. 26; [b] this work (CCl_4 solution); [c] Ref. 27; [d] Ref. 17.

It has recently been shown[24] that the hydrogen bond strength in enols of the general type XXVI, where the chelate ring is attached to an alicyclic ring, is first of all dependent upon the size (the molecular geometry) of the aliphatic ring: A more

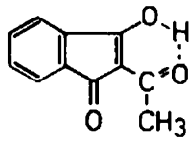
"contracted" ring (the two chelate oxygen atoms are moved apart) gives weaker hydrogen bonding than that resulting from a more "enlarged" ring. From the NMR data of Table 3 it seems as if this rule is further borne out in the aromatic series of the



XXVI



XXVII

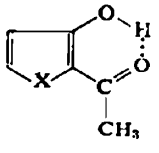


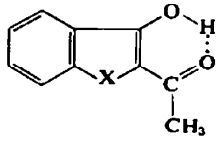
XXVIII

three rings furan, thiophene and benzene. Furthermore, as a weaker hydrogen bonding should make the enolic proton more acidic,[24] the effect of ring size is also demonstrated by the pk_a-values of isomaltol, thioisomaltol and *o*-hydroxyacetophenone which are 5·7[1], 6·8 (spectrophotometric determination) and 10·82,[30] respectively. Among the examples used for illustrating the above mentioned rule, Forsén *et al.*[24] investigated the effect on hydrogen bonding strength in going from 2-acetylcyclopent-4-ene-1,3-dione (XXVII) to 2-acetylindane-1,3-dione (XXVIII) and found that the decrease in bond order of the 4-5 double bond (enlargement of the ring attached to the chelate ring) resulted in an increase in hydrogen bond strength in accordance with the rule (Table 4; ring current effects from the benzene ring were estimated to displace the signal of the enolic proton about 0·1 ppm towards lower field). In this work a corresponding effect upon the hydrogen bond strength was noted in going from thioisomaltol and isomaltol to the analogous benzothiophen and benzofuran compounds (NMR data in Table 4); it is noted that the differences in chemical shift for the hydroxylic protons, $\Delta\delta_{OH}$, are all of the same magnitude and that the displacements are about ten times those estimated due to ring current effects from the benzene ring only.[31]

Turning to the 4-carbethoxy- and 4-acetylsubstituted 3-hydroxythiophenes, the NMR and IR spectra show that these compounds exist exclusively in the enol form;

TABLE 4. PROTON CHEMICAL SHIFTS (δ IN PPM) OF THE HYDROXYLIC PROTON IN A CONJUGATE CHELATE RING ATTACHED TO 5-MEMBERED RINGS AND TO THEIR 4,5-BENZODERIVATIVES. ALL SPECTRA ARE OBTAINED IN SOLUTIONS OF CCl_4





			X	$\Delta\delta_{OH}$
δ_{OH}	12·10[a]	13·13[a]	C=O	1·03
δ_{OH}	11·37[b]	12·38[b]	S	1·01
δ_{OH}	8·95[c]	9·65[b]	O	0·70

[a] Ref. 24; [b] this work; [c] Ref. 17.

[30] A. Ågren, *Acta Chem. Scand.* **9**, 49 (1955).
[31] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.* **29**, 1012 (1958).

the NMR spectra showed no evidence for the presence of the tautomeric keto form. In Fig. 5 the NMR spectrum of 5-methyl-4-carbethoxy-3-hydroxythiophene (XXIX) in carbon tetrachloride is depicted as a typical example of this class of compounds. These findings are in contrast with the results obtained in the furane and pyrrole

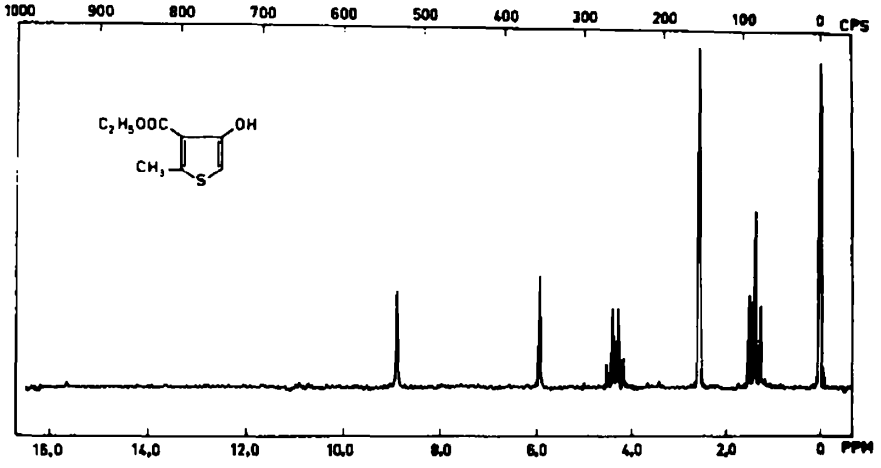
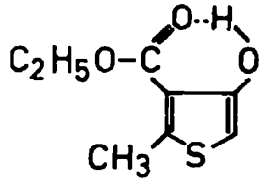


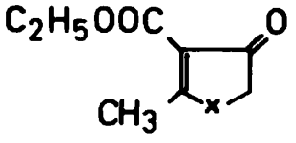
FIG. 5. NMR spectrum of XXIX in carbon tetrachloride.

series, as it has been shown (NMR- and IR spectroscopy) that the quite analogous furane and pyrrole compound (XXX and XXXI) exist exclusively in their α,β-unsaturated keto form[17,32] (vinylogous lactone and lactam), even though the possibility for stabilization of the enol form by intramolecular hydrogen bonding is present.

The NMR spectra of the 4-carbalkoxy-3-hydroxythiophenes in deuterochloroform solution show signals for the hydroxylic protons at a somewhat higher field than the isomeric 2-carbalkoxy compounds; the same is valid for the acetylsubstituted 3-hydroxythiophenes. Furthermore, the carbonyl stretching frequency occurs at a higher frequency (1665–1670 cm^{-1}); a second band of weak intensity at 1710–1730



XXIX



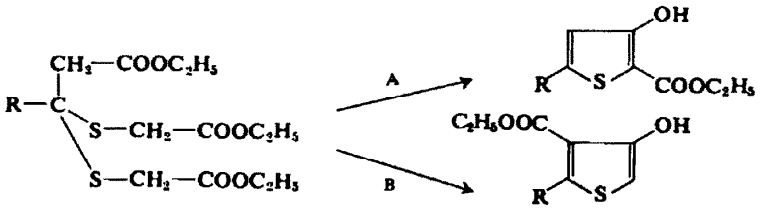
x = O XXX

x = NH XXXI

cm^{-1} is also observed for this class of compounds in carbon tetrachloride solution. These findings indicate a somewhat weaker hydrogen bond strength in the 4-carbalkoxy- and 4-acetylsubstituted compounds than in the corresponding 2-isomers. This is probably due to a lesser degree of bond order in the 3,4-bond than in the 2,3-bond in thiophene; 1,2- and 2,3 chelated derivatives of naphthalene behaves similarly.[25]

[25] R. S. Atkinson and E. Bullock, *Canad. J. Chem.* **41**, 625 (1963).

From the NMR spectra of 5-isopropyl- and 5-t-butyl-2-carbethoxy-3-hydroxythiophene, prepared according to Erlenmeyer *et al.*,[14,*] it was found that these compounds contain 36–37% and 38–39% of the isomeric compounds 5-isopropyl and 5-t-butyl-4-carbethoxy-3-hydroxythiophene, respectively. The isomeric compounds show well-separated bands in the NMR spectra (data are given in Table 2). This means that the Dieckmann ring-closure condensation of the intermediate XXXII[13] in these cases follows both of the routes A and B, contrary to earlier findings with other substituents, R, where only condensation following path A, has been observed.[9]



XXXII

R = $(CH_3)_2CH$ and $(CH_3)_3C$

Earlier papers on intramolecular hydrogen bonding studies by spectroscopic methods have demonstrated a good correlation between the chemical shift of the hydroxylic protons (δ_{OH}) and the chelate carbonyl and hydroxyl stretching frequencies for certain enols and *o*-hydroxy-ketones, aldehydes and esters in the benzene series.[24,26,27] Plots of the data listed in Table 2 of the δ_{OH}-values and carbonyl and hydroxyl stretching frequencies for 2- and 4-carbalkoxy- and acetylsubstituted 3-hydroxythiophenes and some analogous benzothiophene and thienopyrrole compounds are shown in Figs. 6 and 7. The plot of δ_{OH} against $\bar{\nu}_{C=O}$ (Fig. 6) seems to make up two distinct, almost parallel lines: one containing the ordinary substituted thiophene derivatives, and the other containing the condensed thiophene compounds, whereas the plot of δ_{OH} against $\bar{\nu}_{OH}$ seems to make up only one line. Fig. 6 also contains the linear plots obtained by Forsén *et al.*[26] and by Hay and Williams.[27] The fairly good correlation in Figs. 6 and 7 justifies the use of the hydroxyl proton chemical shift and the stretching frequencies of the hydroxyl and carbonyl groups as reflecting the strength of the hydrogen bond in intramolecular hydrogen bonded 3-hydroxythiophenes.

Spectroscopic investigations on 5-carbethoxy-2-methyl-3-hydroxythiophene (XXXIII) show it to exist exclusively in the hydroxyaromatic form, even though the possibility of intramolecular hydrogen bonding is lost; the NMR spectrum which fully supports this structure is shown in Fig. 8. The IR spectrum of a 1% solution of XXXIII in carbon tetrachloride shows two bands in the hydroxylic region: a narrow band at 3610 cm^{-1} is due to "free" hydroxyl groups and a broad band (3550–3100 cm^{-1}) with maximum at 3400 cm^{-1} for intermolecular hydrogen bonded hydroxyl groups. In the carbonyl region two bands with nearly equal intensities appear at 1700 and 1672 cm^{-1} due to "free" and intermolecular hydrogen bonded carbonyl groups. From the conclusions of Rosenkranz *et al.*[17] it is interesting to note

* The authors wish to thank Professor H. Erlenmeyer for kindly delivering samples of these and some other 3-hydroxythiophenes.

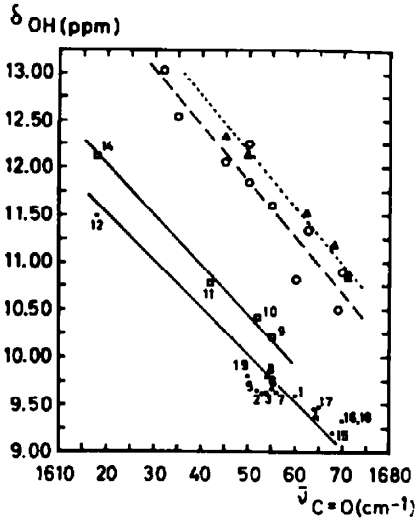


FIG. 6

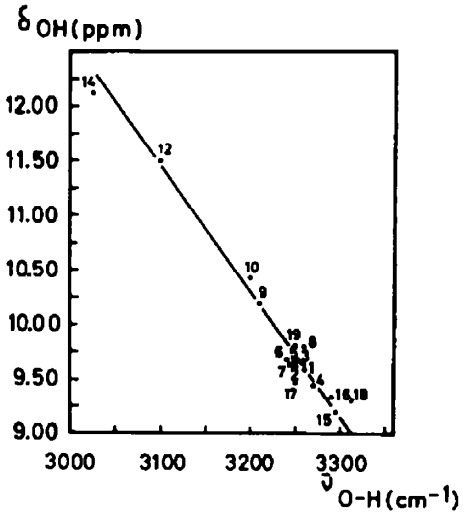


FIG. 7

Correlation of NMR and IR data ($CDCl_3$ and CCl_4 solution, respectively) for the intramolecular hydrogen bonded 3-hydroxythiophenes listed in Table 2. The numbers refer to the compounds in Table 2. In Fig. 6 the symbols ○ and △ are for the data from the works of Forsén *et al.*[24] and Hay and Williams,[37] respectively.

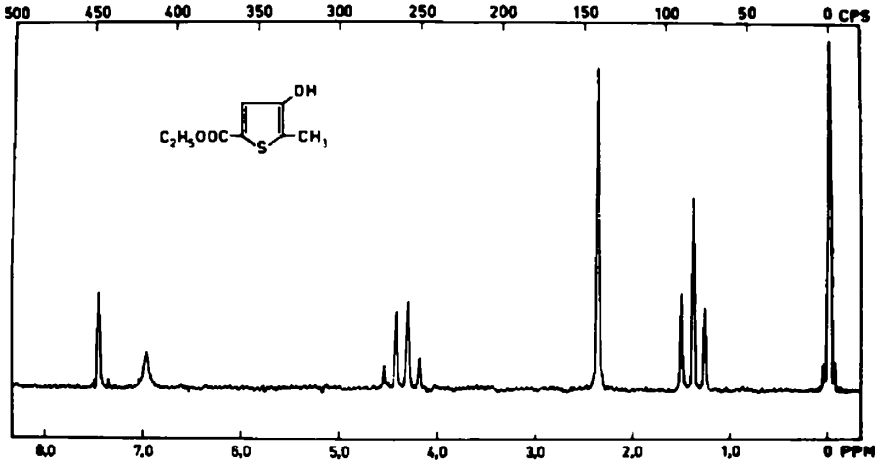
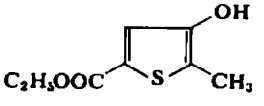
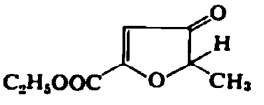


FIG. 8. NMR spectrum of XXXIII in deuterochloroform solution.

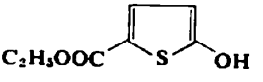
that the analogous 3-hydroxyfuran presumably exists as the α,β-unsaturated ketone (vinylog lactone) XXXIV.



XXXIII

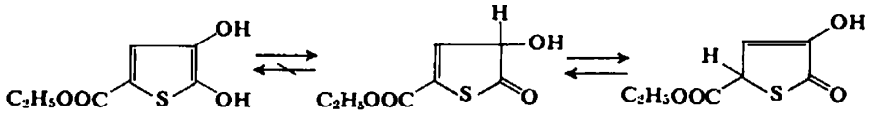


XXXIV



XXXV

From the enolic structures of XXXIII and XXXV one would perhaps expect a hydroxyaromatic structure for 5-carbethoxy-2,3-dihydroxythiophene (XXXVI). However, from its NMR spectrum (Fig. 9) it is concluded that it exists in one of the unsaturated γ-thiolactone forms XXXVII or XXXVIII. From the features of the



XXXVI XXXVII XXXVIII

NMR spectrum, which shows the presence of an AB system (J_{AB} = 3·0–3·2 c/s), the existence of all other possible tautomers may be refuted. The IR spectrum of a 1% solution of the compound in carbon tetrachloride shows the presence of "free" and intra- and/or intermolecular hydrogen bonded hydroxyl groups (3485 and 3385 cm^{-1}) and three bands in the carbonyl region (1740, 1695 and 1665 cm^{-1}) for hydrogen bonded and non-bonded carbonyl groups, but no conclusion from these data can be drawn as to which structure is the true one. However, based on earlier investigations on the stability of substituted unsaturated γ-thiolactones,[3,4,7] it is our opinion that the structure XXXVII is the most stable one.

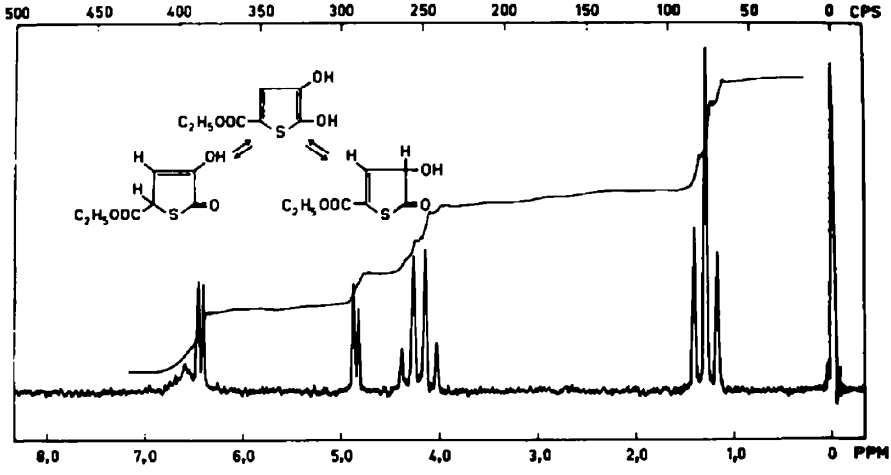


FIG. 9. NMR spectrum of XXXVII or XXXVIII in carbon tetrachloride solution.

In our NMR work on 2- and 4-carbalkoxy- and acetylsubstituted 3-hydroxythiophenes a long-range spin coupling of the phenolic hydroxyl proton with the ring proton in position 5 has been observed in 2-carbethoxy-3-hydroxythiophene, $J_{OH,H(5)}$ = 0·45 c/s, and only in this case. Similar long-range couplings have quite recently been observed in salicylaldehydes,[33] *o*-hydroxyacetophenones[33] and methyl salicylate[34] and couplings have only been observed from the hydroxyl group to the

[33] S. Forsén, B. Åkermark and T. Alm, *Acta Chem. Scand.* **18**, 2313 (1964).
[34] R. Freeman, N. S. Bhacca and C. A. Reilly, *J. Chem. Phys.* **38**, 293 (1963).

proton in the *meta* position (J = 0·33–0·65 c/s).[33] This stereospecificity for the long-range coupling is also followed in our observation. As pointed out by Forsén *et al.*,[33] this coupling is only observed using extremely pure samples and freshly distilled solvents, and further experimental efforts to meet these claims in order to observe the expected long-range coupling in 2-carbmethoxy-3-hydroxythiophene and thioisomaltol have not been made.

Work is in progress on preparation and hydrogen bonding studies of carbonyl chelated 2-hydroxythiophenes and related compounds.

EXPERIMENTAL

The NMR spectra were recorded at 60 Mc/s on a Varian Associates A-60 spectrometer except in one case where a Varian model HA-100 spectrometer (100 Mc/s) was used. The temp of the 16–20% solutions was 33 ± 1°. Tetramethylsilane (TMS) was used as internal standard and the chemical shifts are expressed in ppm (δ units) from TMS taken as 0·00. The IR spectra were recorded on a Perkin–Elmer model 221 spectrophotometer and on a Perkin–Elmer Infracord. Analyses were made by Dr. I. Beetz, Kronach, Germany, and by Dr. A. Bernhardt, Mülheim (Ruhr), Germany. B.ps and m.ps are uncorrected.

2-*Carbethoxy*-3-t-*butoxythiophene* (V). Ethereral 1·55 N n-butyllithium (135 ml) was added without cooling to a solution of 33·0 g (0·21 mole) 3-t-butoxythiophene[18] in 100 ml dry ether during 20 min. The mixture which turned yellow-orange was gently refluxed for about 2 hr until evolution of butane had ceased. The organolithium reagent was transferred to a dropping funnel by the use of N_2 and added dropwise to 60 g (0·55 mole) ethyl chloroformate in 100 ml ether under cooling in an ice-water bath and stirred overnight at room temp. Water (100 ml) saturated with Na_2CO_3 was added, and after stirring for 1 hr the mixture was worked up by extracting the water phase with ether. The combined ether extracts were washed until neutral and dried (Na_2SO_4). Distillation gave the main fraction of 2-carbethoxy-3-t-butoxythiophene with b.p. 96–98°/0·3 mm, n_D^{20} = 1·5131, yield 36·0 g (75%). (Found: C, 57·81; H, 6·91; Calc.: C, 57·88; H, 7·07%.)

2-*Carbethoxy*-3-*hydroxythiophene* (VII). 2-Carbethoxy-3-t-butoxythiophene (17·3 g, 0·076 mole) in a 25 ml distillation flask was placed in an oil bath at 155° and 0·1 g *p*-toluenesulphonic acid was added. After 5–10 min the evolution of isobutylene had ceased and the product was distilled at once while N_2 was drawn through the capillary. 2-Carbethoxy-3-hydroxythiophene had b.p. 63–65°/0·4 mm; (lit.:[9] b.p. 109°/16 mm); n_D^{20} = 1·5399; yield 11·8 g (90%). (Found: C, 49·06; H, 4·63; Calc.: C, 48·84; H, 4·68%.)

2-*Acetyl*-3-*t-butoxythiophene* (VI). 3-t-Butoxythiophene (39·0 g, 0·25 mole) was metallated with 168 ml 1·55 N (0·26 mole) n-butyllithium as described above. To the Li-reagent an ethereal solution of anhydrous $MgBr_2$ [prepared by dropping 50·0 g (15·7 ml, 0·31 mole) Br_2 to 9·5 g (0·40 g-atoms) Mg in 175 ml anhydrous ether] was added rapidly under cooling in ice-water. The Grignard reagent was concentrated by removal of some ether under N_2 and then transferred to a dropping funnel by means of N_2. It was now added dropwise to a stirred solution of 80 g acetic anhydride in 250 ml dry ether at −70° during 1–2 hr. After stirring for 1 hr at −70° the mixture was allowed to warm up to −10–0° and the white complex was hydrolysed by adding 2 N 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 2 N NaOH under cooling with ice (removal of acetic acid) 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 2-acetyl-3-t-butoxythiophene as a light yellow liquid with b.p. 94–96°/0·1 mm; redistillation gave an almost colourless liquid b.p. 86–88°/0·07 mm; n_D^{20} = 1·5388, yield 36·9 g (75%). (Found: C, 60·41; H, 7·00; Calc.: C, 60·59; H, 7·12%.)

2-*Acetyl*-3-*hydroxythiophene* (*thioisomaltol*) (VIII). 2-Acetyl-3-t-butoxythiophene (15·5 g, 0·078 mole) was pyrolysed in the usual way at 160°. The dark product was immediately distilled giving thioisomaltol as a colourless liquid with b.p. 47–49°/0·2 mm; n_D^{20} = 1·5795; yield 10·2 g (92%). On standing overnight in a refrigerator the fraction crystallized; sublimation at 40°/0·1 mm, gave fine white crystals with m.p. 51·5–52·5°. (Found: C, 50·62; H, 4·30; Calc.: C, 50·71; H, 4·26%.)

2-*Methyl*-3-*t-butoxythiophene* (XV). 3-t-Butoxythiophene (39·0 g, 0·25 mole) was metallated with 0·25 mole n-butyllithium in ether in the usual way. The organolithium reagent was cooled in

ice-water and 32 g (0·25 mole) dimethyl sulphate in 100 ml ether were added dropwise. After stirring overnight the mixture was poured into ice-water and the phases separated. The water phase was extracted with ether, the combined ether phases washed with water until neutral and dried (Na_2SO_4). Distillation gave 2-methyl-3-t-butoxythiophene as a colourless liquid with b.p. 77–78°/10 mm; $n_D^{20} = 1·4975$; yield 36·9 g (87%). (Found: C, 63·67; H, 7·90; Calc.: C, 63·51; H, 8·29%.)

5-Carbethoxy-2-methyl-3-t-butoxythiophene (XVI). 2-Methyl-3-t-butoxythiophene (36·5 g, 0·21 mole) in 75 ml ether was metallated with 200 ml 1·26 N (0·25 mole) n-butyl-lithium in the usual way; during the metallation the Li-reagent precipitated. The organometallic reagent was transferred to a dropping funnel and added dropwise to an ice cooled solution of 70 g ethyl chloroformate in 100 ml ether. The mixture, which turned green, was stirred overnight at room temp and then worked up following the procedure described for the preparation of 2-carbethoxy-3-t-butoxythiophene. The ether was removed and distillation gave a light yellow main fraction of 5-carbethoxy-2-methyl-3-t-butoxythiophene with b.p. 100–103°/0·4 mm; redistillation gave a colourless liquid with b.p. 96–97°/0·3 mm; $n_D^{20} = 1·5092$, yield 34·0 g (66%). (Found: C, 59·69; H, 7·24; Calc.: C, 59·49; H, 7·49%.)

5-Carbethoxy-2-methyl-3-hydroxythiophene (XVII). 5-Carbethoxy-2-methyl-3-t-butoxythiophene (13·0 g, 0·054 mole) was dealkylated as usual in the presence of catalytic amounts (0·1 g) *p*-toluenesulphonic acid. The product was distilled at once under N_2 giving a fraction, b.p. 131–133°/0·4 mm, which crystallized in the condenser. Recrystallization from pet. ether (b.p. 60–80°) gave colourless crystals, m.p. 80–82°, yield 8·7 g (87%). (Found: C, 51·84; H, 5·37; Calc.: C, 51·61; H, 5·41%.)

4-Bromo-3-t-butoxythiophene (XII). 4-Bromo-3-thienyllithium was prepared in the usual way from 3,4-dibromothiophene (80·0 g; 0·33 mole) and n-butyllithium (225 ml, 1·56 N; 0·35 mole) at −70°. An ethereal solution of 0·38 mole anhydrous $MgBr_2$ in 200 ml ether (prepared as described for 2-acetyl-3-t-butoxythiophene) was added rapidly to the Li-reagent at −70°. The organometallic reagent was allowed to warm up to room temp. After stirring for ½ hr, 0·21 mole (42 ml) t-butyl perbenzoate in 50 ml ether was added dropwise to the Grignard reagent at 0° and stirred overnight. 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 2 N NaOH to remove benzoic acid and finally washed neutral with water and dried (Na_2SO_4). The ether was removed and crystals of 4,4′-dibromo-3,3′-bithienyl (15·5 g) were filtered off and washed with cold pet. ether (m.p. 125–127°, lit.[35] m.p. 124·5–126·5; mixed m.p. 125–127°; identical in all respects with an authentical sample). The combined filtrate and washings were concentrated and fractionated. The main fraction had b.p. 58–62°/0·2 mm, (redistillation gave the product as an almost colourless liquid with b.p. 49–50°/0·1 mm); $n_D^{20} = 1·5365$; yield 31·0 g (63%). (Found: C, 41·62; H, 4·98; Calc.: C, 40·88; H, 4·72%.)

4-Acetyl-3-t-butoxythiophene (XIII). 4-Bromo-3-t-butoxythiophene (24·1 g, 0·10 mole) was added to n-butyllithium (80 ml, 1·30 N; 0·10 mole) at −70°. An ethereal solution of 0·15 mole anhydrous $MgBr_2$ (prepared as usual) was added rapidly to the Li-reagent at the same temp. 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 dropwise to a stirred solution of 50 g acetic anhydride in 150 ml dry ether at −70° during 1 hr. The procedure described for the preparation of 2-acetyl-3-t-butoxythiophene was now followed. Fractionation gave the product as a colourless liquid with b.p. 78–80°/0·2 mm; $n_D^{20} = 1·5260$; yield 14·7 g (70%). (Found; C, 60·24; H, 7·02; Calc.: C, 60·59; H, 7·12%.)

4-Acetyl-3-hydroxythiophene (XIV). 4-Acetyl-3-t-butoxythiophene (7·5 g, 0·038 mole) was dealkylated in the usual way at 160°. Distillation under N_2 gave 4-acetyl-3-hydroxythiophene as a light yellow liquid, b.p. 63–65°/0·2 mm, which soon crystallized; yield 4·9 g (91%). Recrystallization from pet. ether at −15° gave light yellow crystals with m.p. 51–53°. (Found: C, 50·19; H, 4·44; Calc.: C, 50·71; H, 4·26%.)

2,3-Di-t-butoxythiophene (XVIII). 3-t-Butoxythiophene (25·5 g, 0·16 mole) was metallated with 0·17 mole n-butyllithium (125 ml 1·38 N) and then converted to the Grignard reagent by adding an etheral solution of 0·22 mole anhydrous $MgBr_2$ at 0°. After stirring for ½ hr, 0·12 mole (24 ml) t-butyl perbenzoate in 50 ml dry ether was added dropwise to the Grignard reagent at 0° and stirred overnight. The complex was worked up following the usual procedure for t-butyl ethers (e.g. 4-bromo-3-t-butoxythiophene). Distillation gave 2,3-di-t-butoxythiophene as a colourless liquid with

[35] S. Gronowitz, *Acta Chem. Scand.* **15**, 1393 (1961).

b.p. 51–53°/0·1 mm; $n_D^{20} = 1{\cdot}4820$; yield 19·2 g (70%). (Found: C, 62·56; H, 8·64; Calc.: C, 63·13; H, 8·83%.)

5-*Carbethoxy*-2,3-*di-t-butoxythiophene* (XIX). 2,3-Di-t-butoxythiophene (16·0 g, 0·070 mole) was metallated by adding 0·10 mole (80 ml 1·30 N) n-butyllithium at room temp and refluxing for 1½ hr. The organolithium reagent (some of which had separated during the reflux) was transferred to a dropping funnel under N_2 and added dropwise to a stirred solution of 30 g ethyl chloroformate in 40 ml dry ether under cooling in ice-water. The mixture, which turned yellow–orange, was stirred overnight at room temp and worked up following the usual procedure (2-Carbethoxy-3-t-butoxythiophene). Distillation gave a yellow main fraction, b.p. 115–125°/0·3 mm, which crystallized on standing overnight in a refrigerator; yield 10·7 g (51%). Recrystallization from ethanol gave beautiful, colourless crystals with m.p. 39–40°. (Found: C, 60·05; H, 7·96; Calc.: C, 59·98; H, 8·05%.)

5-*Carbethoxy*-2,3-*dihydroxythiophene* (XX). 5-Carbethoxy-2,3-t-butoxythiophene (6·75 g; 0·023 mole) was dealkylated as usual in the presence of a trace of *p*-toluenesulphonic acid at 160°. Distillation under N_2 gave a main fraction, b.p. 95–110°/0·1 mm, which crystallized on standing in a refrigerator; yield 3·5 g (83%). Recrystallization from toluene at −15° gave light green crystals, m.p. 45–47°, which are unstable and should be kept under N_2 and at a temp of −20° or lower. The crystals deteriorate rapidly in contact with air. (Found: C, 44·49; H, 4·62; Calc.: C, 44·69; H, 4·29%.)

5-*Methyl*-4-*carbethoxy*-3-*hydroxythiophene* was prepared according to Benary *et al.*;[36] m.p. 66–68° (lit.[36] m.p. 64·5–66°). 2-*Carbethoxy*-3-*hydroxybenzothiophene* and 2-*acetyl*-3-*hydroxybenzothiophene* were prepared via the corresponding t-butylethers.[37] 2-*Acetyl*-3-*hydroxybenzofuran* were prepared according to Geissmann and Armen[38] and purified by sublimation at 0·1 mm; yellow crystals with m.p. 90–92° (lit.[38] m.p. 90–91°).

Acknowledgements—Our thanks are due to Professor Hakon Lund for his interest in this work and to Dr. K. Schaumburg (University of Copenhagen) for many helpful discussions in the field of NMR. NMR spectra were kindly recorded by Miss E. Cruse (University of Copenhagen) and IR spectra by Mrs. S. Andersen (this institute). Acknowledgements are also expressed to Dr. U. Scheidegger, Varian Associates of Zürich, Switzerland, for recording the 100 Mc/s spectrum and to Lucidol Division, Wallace and Tiernan Inc., Buffalo, N.Y., U.S.A., for financial support.

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[38] T. A. Geissmann and A. Armen, *J. Amer. Chem. Soc.* **77**, 1623 (1955).