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THIOPHENE CHEMISTRY—XIX*

ABOUT CHELATED 3-HYDROXYTHIOPHENES

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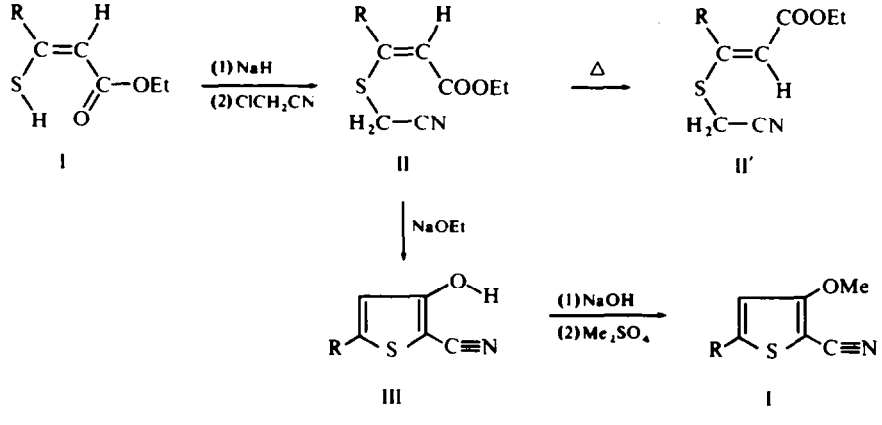
Abstract—Enethiols, prepared from β-ketoesters, have been S-cyanomethylated with chloroacetonitrile. Subsequent Dieckmann condensation produces 5-substituted 2-cyano-3-hydroxythiophenes. Spectroscopic studies have shown these to exist as intramolecularly H-bonded thiophenes. Also 3-hydroxy-5-methyl-2-phenylthiophene has been prepared and studied spectroscopically.

INTRODUCTION

IT IS well-known that 2-hydroxythiophene exclusively exists as 3-thiolene-2-one and is a stable and easily available compound.[1,2] On the other hand, 3-hydroxythiophene[3] is very unstable and exists as a mixture of 4-thiolene-3-one and 3-hydroxythiophene. Also some alkyl substituted 3-hydroxythiophenes have been studied.[4] All potential 2- or 3-hydroxythiophenes with an alkoxycarbonyl or acyl group in *ortho* position exist as true hydroxy heterocycles[5-7] and are stable compounds. As OH groups weakly chelate with π-electrons of multiple bonds or aromatic systems we have studied some potential 2-cyano-3-hydroxythiophenes and 3-hydroxy-2-phenylthiophene. The synthetic work is very much simplified by use of the now easily available enethiols.[8-11]

SCHEME I



I II II' III I

I, II, III, IVa: R = Me
b: R = *iso*-Pr
c: R = Z-Bu
d: R = Ph

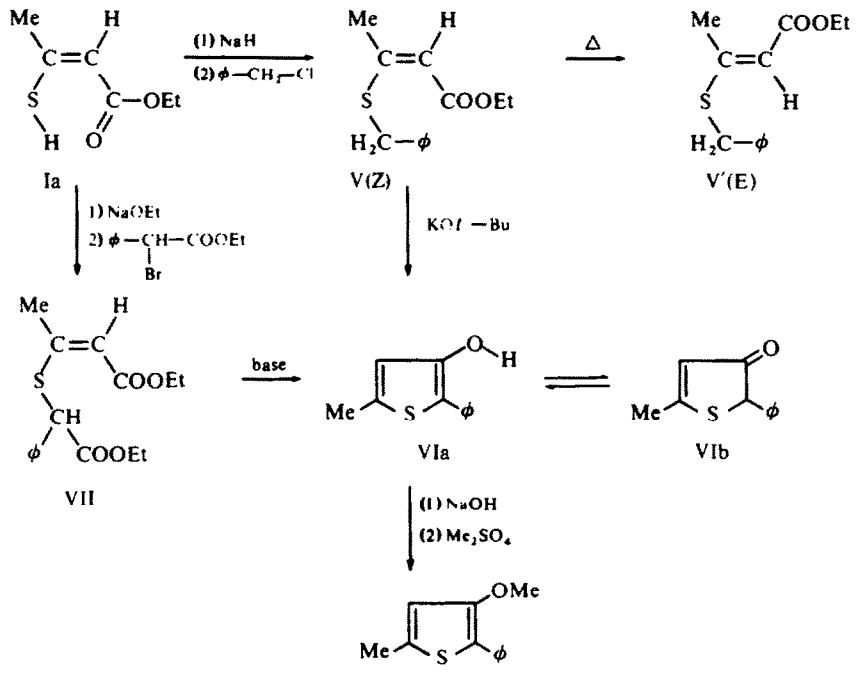
* Part XVIII. J. Z. Mortensen, B. Hedegaard and S. O. Lawesson., Tetrahedron 27,3839 (1971)

Synthesis

The sodium salts of the Z-enethiols, I, were alkylated with chloroacetonitrile to give the Z-isomer, II, as the main product (for the E and Z-nomeclature, see ref.[12]). In no case was the E-isomer observed by inspection of the NMR spectra. However, by heating II a Z→ E isomerization partly occurred. For this reason it is most convenient to perform the Dieckmann condensation on crude II to give the potential 2-cyano-3-hydroxythiophenes in high yields.

3-Hydroxy-5-methyl-2-phenylthiophene, VI, was prepared in two different ways (Scheme 2). Alkylation of Ia with benzyl chloride produced ethyl-3-benzylmercaptocrotonate (Z), V, and the subsequent treatment of V with a strong base, potassium t-butoxide, gave VI after a ring-closure reaction. Treatment of Ia as a sodium salt with ethyl-2-bromophenylacetate also gave an S-alkylated product, VII, (Z-isomer). The subsequent Dieckmann condensation of VII with sodium hydroxide produced VI after elimination of the ester group.

SCHEME 2



NMR, IR and UV studies

In Table 1 the NMR data of some known 3-hydroxythiophenes are collected. From the work of Hörnfeldt[4] it is seen that the shift of the non-chelated hydroxylic proton occurs at $\delta = 5{\cdot}6$–$6{\cdot}7$, whereas the intramolecularly chelated hydroxylic proton chemical shift occurs at a considerably lower field, $[\delta] \approx 9{\cdot}5$–$9{\cdot}6$.[5] From the spectroscopic data in Table 1 it is seen that the signals for hydroxylic protons of the 2-cyano-3-hydroxythiophenes appear at quite a low field, $\delta = 8{\cdot}1$–$8{\cdot}9$. This indicates that this class of compounds is intramolecularly chelated. Further support for this assumption is that

TABLE 1. OBSERVED PROTON CHEMICAL SHIFT (δ) OF 3-HYDROXYTHIOPHENES. THE SHIFT VALUES ARE GIVEN IN PPM RELATIVE TO TMS

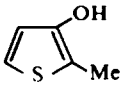
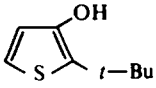
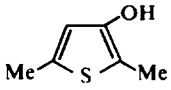
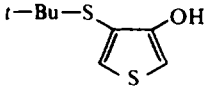
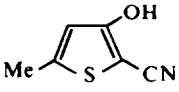
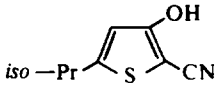
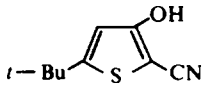
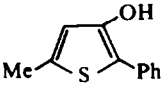
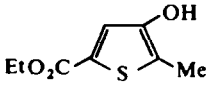
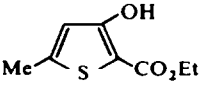
Compound	Solvent	δ_{OH}	Ref.
	CS_2	6·21	4
	CS_2	6·37	4
	CS_2	6·65	4
	CCl_4	5·57	13
	$(CD_3)_2CO$	8·88	this work
	$CDCl_3$	8·22	this work
	CS_2 $CDCl_3$	7·68 8·13	this work
	$CDCl_3$	5·52	this work
	$CDCl_3$	6·91	5
	$CDCl_3$ CCl_4	9·62 9·55	5

TABLE 2. IR AND UV SPECTRA OF SUBSTITUTED 3-HYDROXYTHIOPHENES

Compound	UV		IR
	Hexane λ nm (log ϵ)	EtOH λ nm (log ϵ)	CS_2 $\bar{\nu}_{OH}$ (cm^{-1})
IIIa	257 (4·08)	257 (4·04)	3580 (w), 3180 (s)
IVa	257 (4·04)	260 (4·11)	
IIIb	258 (4·08)	258 (4·07)	3580 (w), 3190 (s)
IVb	257 (4·07)	260 (4·11)	
IIIc	257 (4·09)	258 (4·08)	3570 (w), 3170 (s)
IVc	257 (4·06)	260 (4·12)	
IIId	283 (4·10)	283 (4·20)	3570 (w), 3130 (s)
IVd	284 (4·12)	285 (4·13)	
VIa	293 (4·12)	298 (4·18)	
VIII	299 (4·16)	300 (4·21)	

the chemical shift of the OH proton is almost unchanged when the concentration is varied.

Inspection of the IR data (Table 2) suggests that the weak OH absorption at 3570–3580 cm−1 is due to a non-chelated form of the hydroxythiophenes. The strong absorption at 3130–3180 cm^{-1}, unchanged by varying the concentration, also is a proof of a chelated form as the shift of hydroxylic bands in the IR spectra to lower frequencies is an indication of intramolecular H-bond.[14]

The UV spectra (Table *2*) also supports the chelated structures of the 2-cyano-3-hydroxythiophenes. Normally[15] a change of solvent from hexane to ethanol will cause no or a weak hypsochromic shift of compounds containing intramolecular H-bonds, while in compounds with intramolecular H-bonds, free OH groups or their ethers will cause a bathochromic shift. It is also demonstrated that, while *o*-hydroxy-carbonyl compounds undergo a hypsochromic shift on etherification, *m*-isomers show no difference.[15]

We have now found that 2-cyano-3-hydrocy-thiophenes undergo no or a very weak bathochromic shift on etherification. Further we find no shift at all when changing the solvent from hexane to ethanol while the 2-cyano-3-methoxythiophenes show a bathochromic effect.

3-Hydroxy-5-methyl-2-phenylthiophene (VIa) exists as a true hydroxy compound when freshly prepared. However, when kept for a month, the oxo-form, VIb, is generated, and 16% of VIb is present. The OH chemical shift of VIa appears at $\delta = 5{\cdot}52$, quite normal for an unchelated hydroxythiophene. However, in the IR spectrum, two OH absorptions are observed (Experimental).

DISCUSSION

Hörnfeldt[4] has shown that in 2-alkylsubstituted 3-hydroxythiophenes the conjugative effect of the substituents should determine the tautomeric equilibrium between the hydroxy and corresponding oxo forms.

IX

R = Me	80%	20%	R′ = H
R = *t*-Bu	55%	45%	

In our series of compounds, III, (IX, R = CN; R′ = different substituents) not a trace of the oxo form was detected, either by NMR spectroscopy or by TLC. The stability of the hydroxy form in these compounds is probably due to the -I,-R effect of the cyanogroup and to intra- and possibly intermolecular H-bonding in combination with the aromatic character of the thiophene nucleus. Our spectroscopical data lend support to the existence of both a chelated (conjugate chelation) and non-chelated forms of the 3-hydroxy-2-cyanothiophenes. Corresponding investigations[16–19] on 2-hydroxybenzonitriles have reached similar conclusions.

EXPERIMENTAL

NMR spectra were recorded at 60 Mc/s on a Varian A-60 spectrometer. TMS was used as internal reference standard and the chemical shifts are expressed in δ-values (ppm) downfield from TMS = O. (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet). The IR spectra were recorded as 5% solns in $CHCl_3$ or CS_2 on a Beckmann 18 IR spectrophotometer. UV spectra were measured on a Bausch and Lomb Spectronic 505 spectrophotometer. M.ps and b.ps are uncorrected. The microanalyses were performed by Novo Industri A/S, Copenhagen.

The β-mercapto acrylates were prepared according to known methods.[8, 11]

Ethyl 3-cyanomethylmercaptocrotonate (IIa). To NaH (6 g, 0·25 mole) in benzene (200 ml) were added ethyl 3-mercaptocrotonate (31·5 g, 0·21 mole) in benzene (50 ml) during $\frac{1}{4}$ hr and the mixture was refluxed for 1 hr. Chloroacetonitrile (23·0 g, 0·3 mole) in benzene (50 ml) was added dropwise during $\frac{1}{2}$ hr and refluxed for 5 hr. The mixture was poured into ice–water, acidified and washed with water, dried (Na_2SO_4), and the solvent stripped off. The remaining solid was recrystallized from low-boiling light petroleum, m.p. 60–61°; yield 24·5 g (84%). (Found: C, 51·71; H, 6·06; N, 7·48; S, 17·18; $C_8H_{11}NO_2S$ requires: C, 51·88; H, 5·99; N, 7·56; S, 17·28; NMR (IIa): 5·93 (1H, q, J = 1·2 cs), 4·18 (2H, q, J = 7 cs), 3·62 (2H, s), 2·36 (3H, d, J = 1·2 cs), and 1·26 (3H, t, J = 7 cs). IIa was heated for 16 hr at 160°; then 30% of the mixture consisted of the E-form (II′a); NMR (II′a): 5·62 (1H, q, J = 1·0 cs), 4·18 (2H, q, J = 7 cs), 3·63 (2H, s), 2·40 (3H, d, J = 1·0 cs), and 1·26 (3H, t, J = 7 cs).

Ethyl 3-i-propyl-3-cyanomethylmercaptoacrylate (IIb). The procedure was the same as above, starting from ethyl 3-*i*-propyl-3-mercaptoacrylate[10] (10·0 g, 0·606 mole), yield of crude product 14 g ≈ 100% (Z-form); NMR (IIb): 6·03 (1H, broad), 4·18 (2H, q, J = 7 cs), 3·63 (2H, s), 2·5–3·0 (1H, m), and 1·2–1·4 (9H, m).

IIc and IId were both prepared as above from the corresponding enethiols and in quantitative yields.

Ring closure of IIa-d

General procedure. To 50% excess of sodium ethoxide in EtOH IIa-d were added. After refluxing overnight the mixture was poured into water. After carefully acidifying and extraction with ether, the organic layer was washed with water, dried (Na_2SO_4) and the solvent stripped off. The residue was then further purified.

2-Cyano-3-hydroxy-5-methylthiophene (IIIa). IIa (11·1 g, 0·06 mole) gave IIIa (6·4 g, 78%) m.p. 137°, from CCl_4. (Found: C, 51·71; H, 3·68; N, 10·03; S, 23·32; C_6H_5NOS requires: C, 51·80; H, 3·62; N, 10·07; S, 23·00%).

2-Cyano-3-hydroxy-5-i-propylthiophene (IIb). IIb (4·8 g, 0·02 mole) gave IIIb (1·9 g, 57%) m.p. 67–68°, from $CHCl_3$. (Found: C, 57·44; H, 5·61; N, 8·40; S, 19·25; C_8H_9NOS requires: C, 57·48; H, 5·43; N, 8·38; S, 19·15%).

5-t-*butyl*-2-*cyano*-3-*hydroxythiophene* (IIIc). Crude Ic (11 g, ≈0·04 mole) gave 9 g crude product, which was sublimed (110°/0·2 torr) and recrystallized from CCl_4, yield 2·3 g (32%), m.p. 95–96°. (Found: C, 59·74; H, 6·22; N, 7·84; S, 17·84; $C_9H_{11}NOS$ requires: C, 59·66; H, 6·12; N, 7·73; S, 17·66%).

2-*Cyano*-3-*hydroxy*-5-*phenylthiophene* (IIId). Crude IId (11·7 g, ≈0·04 mole) gave after recrystallization from $CHCl_3$ 3·6 g (50%) of IIId, m.p. 182–184°. (Found: C, 65·44; H, 3·62; S, 15·96; N, 6·96; $C_{11}H_7NOS$ requires: C, 65·67; H, 3·57; S, 15·91; N, 6·96%).

Methylation of IIIa-d. IIIa-d, excess of NaOH (25%) and Me_2SO_4 (50%) in MeOH were refluxed for 16 hr. The mixture was washed with 2N NaOH and water, dried, and the solvent stripped off.

2-*Cyano*-3-*methoxy*-5-*methylthiophene* (IVa), yield 64%, m.p. 32–33°. (Found: C, 55·15; H, 4·61; N, 9·11; S, 21·01; C_7H_7NOS requires: C, 54·90; H, 4·61; N, 9·15; S, 20·90%); NMR ($CDCl_3$): 6·51 (1H, m, J = 1·2 cs), 3·95 (3H, s), 2·44 (3H, d, J = 1·2 cs).

2-*Cyano*-3-*methoxy*-5-*i*-*propylthiophene* (IVb), yield 65%. (Found: C, 59·76; H, 6·37; N, 7·87; $C_9H_{11}NOS$ requires: C, 59·66; H, 6·12; N, 7·73%); NMR ($CDCl_3$): 6·57 (1H, m, J = 1·2 cs), 3·97 (3H, s), 3·1 (1H, broad heptet), 1·30 (6H, d, J = 7 cs).

5-t-*Butyl*-2-*cyano*-3-*methoxythiophene* (IVc), yield 79%, liquid. (Found: C, 61·65; H, 6·98; N, 7·13; $C_{10}H_{13}NOS$ requires: C, 61·52; H, 6·71; N, 7·18%); NMR ($CDCl_3$): 6·56 (1H, s), 3·99 (3H, s), 1·35 (9H, s), 1·35 (9H, s).

2-*Cyano*-3-*methoxy*-5-*phenylthiophene* (IVd), yield 56% after sublimation (100°/0·1 torr), m.p. 129–130°. (Found: C, 66·89; H, 4·52; N, 6·48; S, 14·92; $C_{12}H_9NOS$ requires: C, 66·97; H, 4·22; N, 6·51; S, 14·87%); NMR ($CDCl_3$): 7·4 (5H, m), 6·93 (1H, s), 4·04 (3H, s).

Ethyl 3-*benzylmercaptocrotonate* (IV and V). Ethyl 3-mercaptocrotonate (3·9 g, 0·027 mole) was alkylated with benzylbromide (5·7 g, 0·033 mole) in the usual way. The crude product was distilled under reduced pressure (160–170°/10 torr) and fractional recrystallization from light petroleum (b.p. 40–60°) gave 4·6 g of the Z-form V, m.p. 62–63° and 1·5 g of the E-form V′, m.p. 34–35°.

V: (Found: C, 66·27; H, 6·56; S, 13·48; $C_{13}H_{16}O_2S$ requires: C, 66·08; H, 6·83; S, 13·55%); NMR ($CDCl_3$): 7·26 (5H, m), 5·72 (1H, q, J = 1·0 cs), 4·10 (2H, q, J = 7 cs), 4·02 (2H, s), 2·15 (3H, d, J = 1·0 cs), 1·20 (3H, t, J = 7 cs).

V′, (Found: C, 66·29; H, 6·76; S, 13·48; $C_{13}H_{16}O_2S$ requires: C, 66·08; H, 6·83; S, 13·55%); NMR ($CDCl_3$): 7·29 (5H, s), 5·61 (1H, broad), 4·11 (2H, q, J = 7 cs), 3·96 (2H, s), 2·39 (3H, d, J = 0·9 cs), 1·23 (3H, t, J = 7 cs).

3-*Hydroxy*-5-*methyl*-2-*phenylthiophene* VI).

Method 1. To $KOCMe_3$ (5·2 g, 0·051 mole) in ether (50 ml) were added V (8·1 g, 0·034 mole) during 10 min, and the mixture was then refluxed for 16 hr. After acidifying, the organic layer was extracted with ether and washed with water, dried, and sublimed (90°/0·5 torr) giving 3·1 g (50%) of VI, m.p. 72–73° (CCl_4). (Found: C, 69·34; H, 5·28; S, 16·70; $C_{11}H_{10}OS$ requires: C, 69·46; H, 5·30; S, 16·83%). After a month the NMR spectrum showed signals due to VIb; NMR ($CDCl_3$): 7·2–7·5 (5H, m), 5·90 (1H, broad), 4·76 (1H, broad), 2·30 (3H, d, J = 0·9 cs); IR ($CHCl_3$): 3600, 3290, 3000, 1660, 1590, 1560.

Method 2. Ethyl 3-mercaptocrotonate (31 g, 0·2 mole) was alkylated in the usual way with ethyl 2-bromo-2-phenylacetate (53 g, 0·21 mole). After a quick distillation (170–185°/0·5 torr) crude VII (48 g, 79%) was isolated. VII (23·8 g, 0·08 mole) and 100% excess of sodium alcoholate in EtOH were refluxed for 16 hr. The mixture was poured into water and extracted with ether. The ether-phase was dried, and the solvent stripped off. The residue was refluxed with 100 ml of 2N NaOH for 3 hr, then acidified, extracted with ether, and washed with water. The organic layer was dried and the solvent stripped off. Sublimation (90°/0·5 torr) twice and recrystallization from CCl_4 gave 1·6 g (12%) of VI, m.p. 72–73°, in all respects identical with compound VI by method 1.

3-*Methoxy*-5-*methyl*-2-*phenylthiophene* (VIII). VI was methylated in the usual way giving 92% VIII. (Found: C, 70·54; H, 5·90; $C_{12}H_{12}OS$ requires: C, 70·57; H, 5·92%); NMR ($CDCl_3$): 7·1–7·7 (5H, m), 6·52 (1H, q, J = 0·9 cs), 3·76 (3H, s), 2·35 (3H, d, J = 0·9 cs); IR ($CHCl_3$): 3000, 1590, 1560.

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