Pyridine-Substituted Hydroxythiophenes. I. Preparation of o-(2-, 3- and 4-pyridyl)-3-hydroxythiophenes

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2-(2-, 3- and 4-pyridyl)-3-hydroxythiophenes and 4-(2-, 3- and 4-pyridyl)-3-hydroxy-thiophenes† have been prepared by hydrogen peroxide oxidation of the corresponding boronic esters. In the former case the boronic esters were obtained in three steps from 2,3-dibromothiophene via the corresponding 3-bromo-2-pyridylthiophenes synthesized by Pd(0)-catalyzed coupling between 3-bromo-2-trimethylstannylthiophene and the corresponding bromopyridines. In the latter case the known isomeric pyridylthiophenes were converted into the corresponding boronic esters in three steps via tribromo- and 3-bromo-4-pyridylthiophenes successively. 4-(3- and 4-pyridyl)thiophen-2(5H)-ones were also obtained in the syntheses of 4-(3- and 4-pyridyl)-3-hydroxythiophene. They are suggested to arise from rearrangement during the halogen–metal exchange. Spectroscopic investigations by ¹H NMR and IR show that these hydroxythiophene systems exist exclusively as enol forms.

Dedicated to Professor Lars Skattebøl on the occasion of his 65th birthday.

Compounds containing pyridine and thiophene residues have been found to be of biological interest.[1] A number of aryl-3-hydroxythiophenes have recently been investigated as potential 5-lipoxygenase inhibitors, for the treatment of inflammations and other leukotriene-mediated diseases, with encouraging results.[2] Our interest in substituted hydroxythiophenes, which dates back to the 1960s,[3–8] has been renewed owing to potential biological applications.

It is well known that 3-hydroxythiophene is very unstable and exists as a mixture of thiophen-3(2H)-one and 3-hydroxythiophene.[9–11] In order to obtain more stable derivatives of this system, both α-positions were substituted with alkyl groups.[7] The compounds so obtained exist in a tautomeric equilibrium, where the oxo form predominates. However, when one of the two substituents is changed to a phenyl group, the enol form becomes the major component.[8] The enol form is stabilized by the extended conjugation with the phenyl group.

Further support for this assumption is that the ¹H NMR spectrum of the 2-methyl-3-hydroxythiophene system shows that it exists as a tautomeric mixture with 80 % of the enol form and 20 % of the keto form. When the 2-substituent is changed to t-butyl the amount of enol form is

reduced to 55 %.[10] This variation of the proportions of the tautomeric mixture is in agreement with the expected hyperconjugative effect of the substituents. It is also reported that all potential 2- and 3-hydroxythiophenes with an alkoxycarbonyl or acyl group in the *ortho* positions exist in their hydroxy form.[12,13] In these compounds the stabilization is probably due to the -I, -M effect of the substituents and to intra- and possibly inter-molecular hydrogen bonding in combination with sufficient aromatic character of the thiophene nucleus. It therefore seemed probable that o-pyridyl-substituted 3-hydroxythiophenes would exist in their hydroxy forms.

Results and discussion

Syntheses. The key intermediates for the synthesis of 2-(2-, 3- and 4-pyridyl)-3-hydroxythiophene (1–3) and 4-(2-, 3- and 4-pyridyl)-3-hydroxythiophenes (4–6) were considered to be the analogous bromo derivatives (7–12), which are

1   2   3

4   5   6

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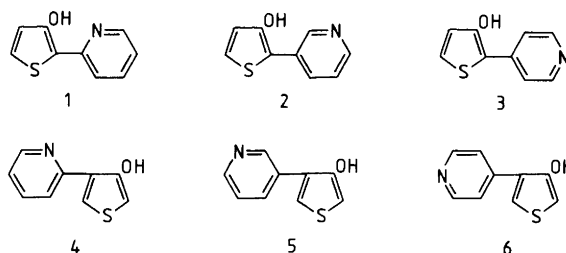
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† According to usual nomenclature rules thienylpyridine should be the correct name because pyridine has priority over thiophene. In order to emphasize that substitution occurs on the thiophene ring we prefer to use the name pyridylthiophene.
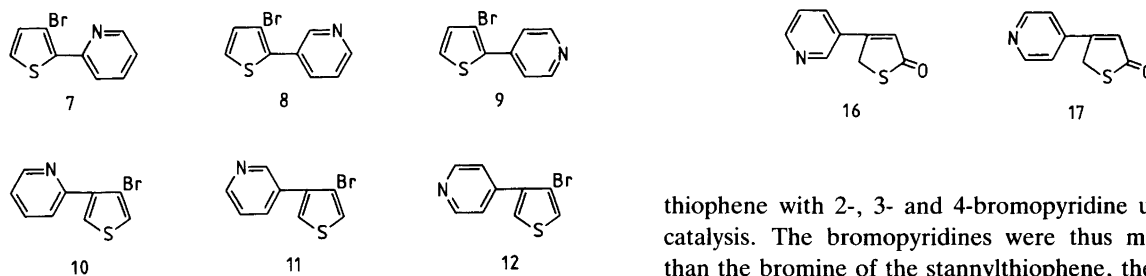
convertible, via boronic acids[3,8] or *t*-butoxy derivatives[14,15] into the hydroxy systems.

Preparation of **7** by the coupling of 3-bromothiophene-2-boronic acid with 2-bromopyridine in the presence of a catalytic amount of Pd(PPh₃)₄ in aqueous sodium carbonate–dimethoxyethane[16] yielded only 8 %, probably due to deboronation. A similar attempt to couple 3-bromo-2-thienylmagnesium bromide with 2-bromopyridine in the presence of a catalytic amount of Ni[Ph₂P(CH₂)₃PPh₂]Cl₂ was less successful. Preparation of **7** by addition of 3-bromo-2-thienyllithium from butyllithium and 2,3-dibromothiophene to the azomethine bond of pyridine failed; only 3-bromo-2-butylthiophene was formed. The reaction also failed when 3-bromo-2-thienyllithium was prepared from 3-bromothiophene and LDA.

In another attempt to prepare **1**, 3-*t*-butoxythiophene was stannylated to 3-*t*-butoxy-2-trimethylstannylthiophene, which was coupled under Pd(0)catalysis with 2-bromopyridine, to give 2-(2-pyridyl)-3-*t*-butoxythiophene in only 13 % yield. Dealkylation was therefore not attempted.

Finally, more satisfactory yields (28–35 %) of **7–9** were obtained by the coupling of 3-bromo-2-trimethylstannyl-thiophene with 2-, 3- and 4-bromopyridine under Pd(0)-catalysis. The bromopyridines were thus more reactive than the bromine of the stannylthiophene, the reaction of which would lead to polymers (Scheme 1).

In order to prepare 3-bromo-4-(2-, 3- and 4-pyridyl)thio-phenes (**10–12**), the strategy of perbromination followed by removal of the α-bromines was used.[17,18] Polybromination of the three 3-pyridylthiophenes could only be achieved by use of an excess of bromine as the solvent, as in the preparation of 2,4,5-tribromo-3-thiophenecarboxylic acid.[19] The tribromo compounds (**13–15**) were obtained in 70 % yield and were debrominated by treatment with butyl-lithium at −100 °C followed by water (Scheme 2).

In order to convert the six bromo(pyridyl)thiophenes into the hydroxy(pyridyl)thiophenes, we used the method previously developed by us,[4,6,7,16,18] halogen–metal exchange (at −100 °C in THF, in order to avoid addition to the azomethine bond), followed by reaction with triethyl borate. The crude boronic ester product was directly oxidized to the hydroxy systems in 30–40 % yield (cf. Schemes 1 and 2). Complications were only observed in the halogen–metal exchange of **11** and **12** where competing rearrangement occurred. Besides the desired compounds **5** and **6** 4-(3-pyridyl)thiophen-2(5*H*)-one (**16**) and 4-(4-pyridyl)thiophen-2(5*H*)-one (**17**) were also obtained in low yields upon treatment with triethyl borate followed by oxidation. The mass spectra of these compounds indicated

Scheme 1.

Scheme 2.

18   19
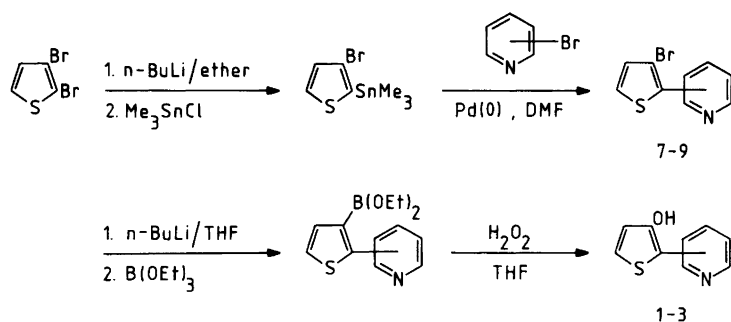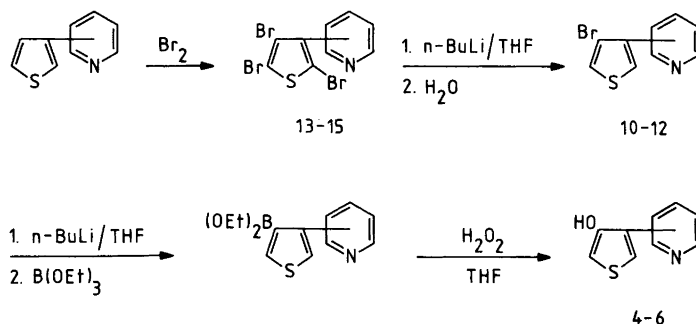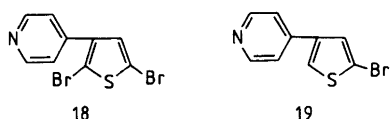
that they were isomeric with **5** and **6**. The carbonyl stretching band found at 1665 cm^{-1} is compatible with a thiophen-2(5H)-one and not with a thiophen-2(3H)-one form (1730–1750 cm^{-1}).[3] Definite proof that the by-products were **16** and **17** and not the corresponding 3-pyridylthiophen-2(5H)-ones came from their NMR spectra, where a coupling of 1.75 Hz was observed between the CH- and CH$_2$-groups. For the 3-pyridylthiophen-2(5H)-ones a coupling of over 3 Hz is expected for the CH–CH$_2$ grouping.[3] Finally an unambiguous synthesis of **17** was carried out as follows. 3-(4-Pyridyl)thiophene was brominated to 2,5-dibromo-3-(4-pyridyl)thiophene (**18**) which upon treatment with one equivalent of butyllithium followed by water gave 2-bromo-4-(4-pyridyl)thiophene (**19**). Its structure followed from its characteristic thiophenic J_{35}-coupling of 1.75 Hz. Upon halogen–metal exchange followed by reaction with triethyl borate and hydrogen peroxide, compound **17** was obtained in 41 % yield, having the same properties as the by-product described above.

Rearrangements of thermodynamically unstable thienyllithium derivatives via transmetalation are well known[20] and were first observed with 3-thienyllithium and 4-bromo-3-thienyllithium in 1961.[21] It is, however, somewhat unexpected that the rearrangement of the 3-lithio-4-pyridyl-

thiophenes occurs at the 2-position and not at the more acidic 5-position. Attempts to suppress the formation of **17** in the synthesis of **6**, by reversing the mode of addition, led to a reduction in the amount of **17** formed from 8 to 4 %.

^{1}H NMR and IR studies. Compounds **4–6** and **10–12** show doublets at δ 6.43–7.40 and δ 7.42–8.22 for the 2- and 5-protons, respectively, with the characteristic J_{25}-coupling of 3.45–3.65 Hz.[22] The assignments are based on chemical-shift considerations, regarding the pyridyl groups as electron-withdrawing causing larger downfield shifts than the hydroxy or bromine group. All 2,3-disubstituted thiophenes **1–3** and **7–9** (Tables 1 and 2) show doublets at δ 6.75–7.11 and δ 7.17–7.40 with the characteristic coupling constants J_{45} of 5.25–5.45 Hz.[22] As the chemical shift differences are too small to allow definite assignments of the protons based on substituent effects, HETCOR experiments were carried out on compounds **7–9**. Compound **7** shows ^{13}C shifts at δ 132.6 and 127.4 interacting with the proton shifts at δ 7.07 and 7.36. In the ^{13}C-coupled spectrum the carbon absorption at δ 132.6 shows a J_{C-H} splitting of 172.6 Hz and that at δ 127.4 a J_{C-H} splitting of 188.8 Hz, which fall in the characteristic regions for β-CH and α-CH coupling constants in thiophene.[23] Consequently the band at δ 7.36 in the proton spectrum is due to the proton in the 5-position. Similarly for compound **8**, the shifts at δ 7.11 and 7.37 were assigned to the 4- and 5-protons, respectively, as the doublet at δ 7.37 was connected to the carbon having its shift at δ 126.1 and a J_{C-H} coupling constant of

Table 1. ^{1}H NMR chemical shifts for some pyridyl-substituted thiophenes.

Comp.	Solv.	H$_2$	H$_3$	H$_4$	H$_5$	H$_2$	H$_3$	H$_4$	H$_5$	H$_6$	OH
1	CDCl$_3$			6.80	7.17		7.28	7.69	7.08	8.42	12.77
	DMSO			6.81	7.72		7.43	7.78	7.17	8.49	11.54
2	(CD$_3$)$_2$CO			6.86	7.35	8.99		8.12	7.36	8.39	9.30^a
	DMSO			6.81	7.43						10.36
3	CD$_3$OD			6.75	7.36	8.39	7.80		7.80	8.39	
	DMSO			6.80	7.50						10.72
4	CDCl$_3$	6.43			7.66		7.72	7.79	7.23	8.50	12.42
	DMSO	6.52			8.22		8.06	7.96	7.39	8.58	12.02
5	DMSO	6.46			7.71	8.90		8.08	7.41	8.47	10.10
6	DMSO	6.47			7.88	8.56	7.75		7.75	8.56	10.25
7	CDCl$_3$			7.07	7.36		8.29	7.75	7.22	8.61	
8	CDCl$_3$			7.11	7.37	8.88		7.98	7.35	8.62	
9	CDCl$_3$			7.11	7.40	8.67	7.62		7.62	8.67	
10	CDCl$_3$	7.39			7.71		7.77	7.48	7.27	8.68	
11	CDCl$_3$	7.35			7.42	8.74		7.86	7.37	8.62	
12	CDCl$_3$	7.40			7.43	8.67	7.46		7.46	8.67	
13	CDCl$_3$						7.42	7.82	7.35	8.76	
14	CDCl$_3$					8.67		7.68	7.41	8.61	
15	CDCl$_3$					8.74	7.28		7.28	8.74	
16	CDCl$_3$		6.77		4.47^b	8.88		7.89	7.43	8.71	
17	CDCl$_3$		6.84		4.44^b	8.76	7.44		7.44	8.76	
18	CDCl$_3$			7.06		8.67	7.44		7.44	8.67	
19	CDCl$_3$		7.40		7.54	8.63	7.41		7.41	8.63	

^{a}Broad. ^{b}Intensity of two protons.

189.9 Hz, while the doublet at δ 7.11 was connected to a carbon shift at δ 131.9 having a splitting of 176.0 Hz. For compound 9 it was found that the proton resonances at δ 7.11 and 7.40 could be assigned to the 4- and 5-protons, respectively, as the corresponding ^{13}C-shifts occurred at δ 132.5 and 126.7 giving splittings of 171.1 and 190.2 Hz, respectively. As the hydroxy group generally causes higher upfield shifts than bromine, the shift assignment for the protons in compounds 1–3 could be based on substituent effects. The shifts and coupling constants of the pyridyl hydrogens of all 12 compounds are of expected magnitudes.[24]

The chemical shifts of all six hydroxy derivatives were compared with those arising from a sample in DMSO solution. The shifts of 2, 3, 5 and 6 fall between δ 10.10 and 10.72, while the shifts for 1 and 4 are δ 11.54 and 12.02, respectively. Also, the IR spectra of 1 and 4 and the four other isomers show different patterns. Compounds 1 and 4 give bands at 3400–2200 cm^{-1} with maximum intensity at 2900 cm^{-1} while 2, 3, 5 and 6 give bands at 3200–2000 cm^{-1} with maximum intensity at 2500 cm^{-1}. Thus both NMR and IR clearly indicate the existence of intramolecular hydrogen bonds in the two 2-pyridyl-substituted derivatives 1 and 4.

Both NMR and IR show that compounds 1–6 all exist in their hydroxy forms. The stabilization of the enol forms is most probably due to the electron-withdrawing nature of the pyridyl groups and the formation of intramolecular (1, 4) and intermolecular (2, 3, 5, 6) hydrogen bonds.

Experimental

3-Thiopheneboronic acid,[14] 3-(2-pyridyl)thiophene,[16] 3-(3-pyridyl)thiophene[16] and 3-(4-pyridyl)thiophene[16] were prepared according to the literature. 2-,3- and 4-bromopyridines are commercially available.

2,3-Dibromothiophene. A 500 ml three-necked flask, equipped with stirrer, dropping funnel and condenser with gas outlet, was charged with 3-bromothiophene (81.5 g, 0.50 mol) in acetic acid (100 ml). Bromine (27.0 ml, 0.50 mol) in acetic acid (50 ml) was added dropwise with stirring. The reaction mixture was left overnight and then poured onto ice. The product was extracted with ether and the combined ether phases were washed with sodium hydroxide (2 M) solution and dried over calcium chloride. Evaporation and distillation gave 107.6 g (89 %), b.p. 88.0–90.0 °C/1.33 kPa. Literature value:[15] b.p. 89–91 °C/ 1.73 kPa.

3-Bromo-2-trimethylstannylthiophene. To a stirred solution of 2,3-dibromothiophene (24.2 g, 0.10 mol) in anhydrous ether (100 ml) at −70 °C under nitrogen, butyllithium (53.4 ml, 2.06 M in hexane) was added dropwise at such a rate

Table 2. ^{1}H NMR coupling constants for some pyridyl-substituted thiophenes.

Comp.	Solv.	J_{25}	J_{35}	J_{45}	J_{23}	J_{24}	J_{25}	J_{34}	J_{35}	J_{36}	J_{45}	J_{46}	J_{56}
1	CDCl₃			5.40				8.10	1.05	1.05	7.55	1.80	5.05
	DMSO			5.45				8.05	1.10	1.00	7.55	1.75	4.90
2	(CD₃)₂CO			5.45		2.40	0.85				8.05	1.60	4.75
	DMSO			5.25									
3	CD₃OD			5.45	4.80		1.65			1.65			4.80
	DMSO			5.45									
4	CDCl₃	3.50						8.20	1.20	1.20	7.30	1.80	5.10
	DMSO	3.45						8.05	1.10	1.00	7.40	1.80	5.05
5	DMSO	3.50				2.25	0.70				7.95	1.65	4.70
6	DMSO	3.55			4.60		1.45			1.45			4.60
7	CDCl₃			5.35				8.10	1.05	1.00	7.55	1.80	4.85
8	CDCl₃			5.35		2.05	0.85				7.95	1.60	4.80
9	CDCl₃			5.30	4.50		1.65			1.65			4.50
10	CDCl₃	3.65						7.85	1.40	1.20	7.85	1.75	4.90
11	CDCl₃	3.50				2.30	0.85				7.90	1.70	4.90
12	CDCl₃	3.55			4.45		1.65			1.65			4.45
13	CDCl₃							7.75	1.10	1.00	7.75	1.80	4.75
14	CDCl₃					2.25	0.80				7.85	1.70	4.85
15	CDCl₃				4.40		1.65			1.65			4.40
16	CDCl₃		1.65			2.40	0.75				8.10	1.60	4.85
17	CDCl₃		1.75		4.50		1.70			1.70			4.50
18	CDCl₃				4.50		1.65			1.65			4.50
19	CDCl₃		1.75		4.65		1.55			1.55			4.65

that the temperature did not exceed −70 °C. The solution was stirred for 10 min at −70 °C, whereupon trimethyl-stannyl chloride (19.9 g, 0.10 ml) dissolved in anhydrous THF (30 ml) was added dropwise at such a rate that the temperature did not exceed −70 °C. The mixture was stirred for 4 h at the same temperature and then allowed to reach ambient temperature. Water was added to the mixture, the phases were separated, the aqueous phase was extracted with diethyl ether and the combined organic phases were dried over magnesium sulphate and evaporated. Distillation of the residue under reduced pressure gave 21.8 g (67 %), b.p. 71–73 °C/0.11 kPa. Anal. $C_7H_{11}BrSSn$: C, H, S. ^1H NMR ($CDCl_3$): δ 0.45 [s, 9 H, $Sn(CH_3)_3$], 7.13 (d, 1 H, H_4, J 4.75 Hz), 7.51 (d, 1 H, H_5, J 4.75 Hz).

3-t-Butoxy-2-trimethylstannylthiophene. To a solution of 3-*t*-butoxythiophene[25] (7.81 g, 0.050 mol) in anhydrous diethyl ether (40 ml) was added dropwise butyllithium (26.7 ml, 2.06 M in hexane) under nitrogen at ambient temperature. The reaction mixture was refluxed for 10 min and then cooled to −70 °C. A solution of trimethylstannyl chloride (9.96 g, 0.050 mol) in anhydrous diethyl ether (40 ml) was added dropwise at −70 °C. When the addition was complete, the mixture was allowed to warm to ambient temperature. The precipitate was filtered off. The filtrate was dried over magnesium sulphate and evaporated. The residue was distilled at reduced pressure, to yield 9.1 g (57 %) of the title compound b.p. 73–74 °C/0.053 kPa. Anal. $C_{12}H_{20}OSSn$: C, H, S, M. ^1H NMR ($CDCl_3$): δ 0.38 [s, 9 H, $Sn(CH_3)_3$], δ 1.39 [s, 9 H, $OC(CH_3)_3$], δ 7.05 (d, 1 H, H_4, J 5.5 Hz), δ 7.46 (d, 1 H, H_5, J 5.5 Hz).

3-t-Butoxy-2-(2-pyridyl)thiophene. A 100 ml three-necked flask was charged with 3-*t*-butoxy-2-trimethylstannylthio-phene (3.83 g, 0.012 mol), 2-bromopyridine (1.58 g, 0.010 mol), tetrakis(triphenylphosphine)palladium(0)[26] (0.35 g, 0.30 mmol) and DMF (60 ml). The reaction mixture was stirred under nitrogen at 100 °C for 48 h and then cooled to ambient temperature and evaporated. To the residue was added diethyl ether (100 ml) and the precipitate was filtered off. The ethereal solution was dried over magnesium sulphate and evaporated. The residue was chromatographed using silica gel 60 and hexane–ethyl acetate (8:3) as the eluent, to yield 0.32 g (13.7 %) of the title compound as an oil. Anal. $C_{13}H_{15}NOS$: C, H, N, M. ^1H NMR ($CDCl_3$): δ 6.89 (d, 1 H, H_4, J 5.5 Hz), δ 7.07 (octet, 1 H, H_5, J 7.5, 4.9 and 1.1 Hz), δ 7.23 (d, 1 H, H_5, J 5.5 Hz), δ 7.65 (octet, 1 H, H_4, J 8.1, 7.5 and 1.9 Hz), δ 8.23 (sextet, 1 H, H_3, J 8.12, 1.1 and 1.0 Hz), δ 8.53 (octet, 1 H, H_6, J 4.9, 1.9 and 1.0 Hz).

General procedure for the preparation of 3-bromo-2-(pyridyl)thiophenes. A 100 ml three-necked flask, equipped with condenser, magnetic stirring bar and nitrogen inlet, was charged with 3-bromo-2-trimethylstannylthiophene (3.91 g, 12 mmol), 2-, 3- or 4-bromopyridine (1.58 g, 10

mmol), tetrakis(triphenylphosphine)palladium(0)[26] (0.35 g, 0.30 mmol) and DMF (60 ml). The mixture was vigorously stirred under nitrogen at 100 °C for 24–65 h and monitored by GLC. After being cooled to ambient temperature, the mixture was evaporated, and diethyl ether (100 ml) was added to the residue. The precipitate was filtered off and the filtrate was washed with water and dried over magnesium sulphate. After evaporation, the residue was purified by column chromatography using silica gel 60.

3-Bromo-2-(2-pyridyl)thiophene (7) was obtained as an oil, by using dichloromethane–heptane (4:1) as the eluent, to give 792 mg (33 %). Anal. C_9H_6BrNS: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

3-Bromo-2-(3-pyridyl)thiophene (8) was obtained by using ethyl acetate–cyclohexane (3:2) as the eluent and after recrystallization from petroleum ether to give 672 mg (28 %), m.p. 43.0–44.0 °C. Anal. C_9H_6BrNS: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

3-Bromo-2-(4-pyridyl)thiophene (9) was purified as described for 8 to give 840 mg (35 %), m.p. 88.5–89.5 °C. Anal. C_9H_6BrNS: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

General procedure for the preparation of 2,4,5-tribromo-3-pyridylthiophenes. A 25 ml two-necked flask, equipped with a condenser connected to a gas trap and a magnetic stirring bar, was charged with bromine (2.0 ml), and 3-(2-,3- or 4-pyridyl)thiophene (0.80 g, 5.0 mmol) was carefully added in small portions. When the addition was complete, the mixture was refluxed for 1–3 h and monitored by GLC. After removal of unchanged bromine, 5 ml of water were added with stirring, and the mixture was warmed to 50–60 °C, whereupon 5 ml of 2 M sodium hydroxide solution were added dropwise with vigorous stirring. The alkaline mixture was extracted with dichloromethane. The combined dichloromethane phases were washed with saturated sodium chloride solution, dried over magnesium sulphate and evaporated.

2,4,5-Tribromo-3-(2-pyridyl)thiophene (13) was obtained, when the residue after evaporation was recrystallized from toluene, yielding 1.52 g (77 %), m.p. 136.0–138.0 °C. Anal. $C_9H_4Br_3NS$: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

2,4,5-Tribromo-3-(3-pyridyl)thiophene (14) was obtained, when the residue after evaporation was recrystallized from petroleum ether, yielding 1.41 g (71 %), m.p. 109.0–110.0 °C. Anal. $C_9H_4Br_3NS$: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

2,4,5-Tribromo-3-(4-pyridyl)thiophene (15) was obtained, when the residue after evaporation was recrystallized from ethanol, yielding 1.39 g (70 %), m.p. 108.0–109.0 °C. Anal.

$C_9H_4Br_3NS$: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

General procedure for the preparation of 3-bromo-4-pyridylthiophenes. To a stirred solution of 3-(2-,3- or 4-pyridyl)-2,4,5- tribromothiophene (1.0 g, 2.5 mmol) in anhydrous THF (20 ml) at −100 °C under nitrogen, butyllithium (2.7 ml, 2.05 M in hexane) was added dropwise at such a rate that the temperature did not exceed −100 °C. When the addition was complete, the reaction mixture was stirred at the same temperature and followed by GLC. After 30 min the solution was allowed to warm to ambient temperature and then poured into cold water with stirring. The THF layer was separated, and the water phase was extracted with ether. The combined organic phases were washed with saturated sodium chloride solution and dried over magnesium sulphate. After evaporation, the residue was purified by column chromatography using silica gel 60.

3-Bromo-4-(2-pyridyl)thiophene (10) was obtained as an oil by using hexane–ethyl acetate (3:2) as the eluent, in a yield of 516 mg (86 %). Anal. C_9H_6BrNS: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

3-Bromo-4-(3-pyridyl)thiophene (11) was obtained as an oil by using dichloromethane–acetone (4:1) as the eluent in a yield of 450 mg (75 %). Peak matching on M^+. Calc. for C_9H_6BrNS: 238.9404. Found: 238.9397. For ^1H NMR data see Tables 1 and 2.

3-Bromo-4-(4-pyridyl)thiophene (12) was obtained by using dichloromethane–acetone (7:3) as the eluent in a yield of 462 mg (77 %), m.p. 49.0–50.0 °C. Anal. C_9H_6BrNS: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

General procedure for the preparation of o-pyridyl-3-hydroxythiophenes. To a stirred solution of 3-bromo-o-(2-,3- or 4-pyridyl)thiophene (1.20 g, 5.0 mmol) in anhydrous THF (24 ml) at −100 °C under nitrogen, butyllithium (2.70 ml, 2.05 M in hexane) was added dropwise at such a rate that the temperature did not exceed −100 °C. The reaction mixture was stirred at −100 °C for 30 min, and then treated with triethyl borate (0.80 g, 5.50 mmol) in anhydrous THF (5.0 ml). After stirring at −100 °C for 4 h, the reaction mixture was allowed to reach ambient temperature and then treated with 30 % hydrogen peroxide solution (1.5 ml). The mixture was vigorously stirred at 50 °C for 2–3 h and then cooled, cold water (20 ml) was added and the layers were separated. The aqueous phase was extracted with diethyl ether. The combined organic phases were washed with cold water until the separated water did not oxidize ferrous ammonium sulphate and then dried over magnesium sulphate. After evaporation, the crude product was purified by column chromatography using silica gel 60.

3-Hydroxy-2-(2-pyridyl)thiophene (1). Dichloromethane–heptane (4:1) was used as the eluent and the material so obtained was recrystallized from petroleum ether to give a yield of 389 mg (44 %), m.p. 46.0–48.0 °C. Anal. C_9H_7NOS: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

3-Hydroxy-2-(3-pyridyl)thiophene (2). Dichloromethane–acetone (7:3) was used as the eluent and the material so obtained was recrystallized from methanol to give a yield of 416 mg (47 %), m.p. 167.0–168.0 °C. Peak matching on M^+. Calc. for C_9H_7NOS: 177.0248. Found 177.0244. For ^1H NMR data see Tables 1 and 2.

3-Hydroxy-2-(4-pyridyl)thiophene (3). Ethyl acetate was used as the eluent and the material so obtained was recrystallized from methanol to give a yield of 301 mg (34 %), m.p. 216.0–218.0 °C. Peak matching on M^+. Calc. for C_9H_7NOS: 177.0248. Found: 177.0243. For ^1H NMR data see Tables 1 and 2.

3-Hydroxy-4-(2-pyridyl)thiophene (4). Dichloromethane–heptane (4:1) was used as the eluent and the material so obtained was recrystallized from petroleum ether to give a yield of 301 mg (34 %), m.p. 50.0–52.0 °C. Anal. C_9H_7NOS: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

3-Hydroxy-4-(3-pyridyl)thiophene (5). Dichloromethane–acetone (4:1) was used as the eluent and the material so obtained was recrystallized from methanol to give a yield of 266 mg (30 %), m.p. 150.0–153.0 °C. Peak matching on M^+. Calc. for C_9H_7NOS: 177.0248. Found: 177.0251. For ^1H NMR data see Tables 1 and 2.

3-Hydroxy-4-(4-pyridyl)thiophene (6). Dichloromethane–methanol (92:8) was used as the eluent and the material so obtained was recrystallized from methanol to give a yield of 301 mg (34 %), m.p. 168.0–171.0 °C. Peak matching on M^+. Calc. for C_9H_7NOS: 177.0248. Found: 177.0247. For ^1H NMR data see Tables 1 and 2.

4-(3-Pyridyl)thiophene-2(5H)-one (16) was obtained in the preparation of 3-hydroxy-4-(3-pyridyl)thiophene (5). The fraction containing 16 was evaporated and the residue was recrystallized from ethanol to give a yield of 53 mg (6 %), m.p. 151.0–151.5 °C. IR spectrum (KBr): 1665 cm^{-1} (C=O). Anal. C_9H_7NOS: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

4-(4-Pyridyl)thiophene-2(5H)-one (17) was obtained in the preparation of 3-hydroxy-4-(4-pyridyl)thiophene (6). The fraction containing 17 was evaporated and the residue was rechromatographed using ethyl acetate as the eluent to give a yield of 71 mg (8 %), m.p. 156.0–158.0 °C. For an authentic preparation see below.

2,5-Dibromo-3-(4-pyridyl)thiophene (18). To a stirred solution of 3-(4-pyridyl)thiophene (1.0 g, 6.2 mmol) in acetic

acid (5 ml), bromine (2.5 g, 15.6 mmol) in acetic acid (2.5 ml) was added dropwise. When the addition was complete, the mixture was refluxed for 1 h and monitored by GLC. The solution was cooled to ambient temperature and poured into cold water. After neutralization with 2 M sodium hydroxide solution, the mixture was extracted with THF, the combined THF phases were washed with saturated sodium chloride solution, dried over magnesium sulphate and then evaporated. The residue was recrystallized from petroleum ether to give a yield of 1.47 g (74 %), m.p. 113.0–113.5 °C. Anal. $C_9H_5Br_2NS$: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

2-Bromo-4-(4-pyridyl)thiophene (**19**) was prepared similarly to 3-bromo-4-(4-pyridyl)thiophene from 2,5-dibromo-3-(4-pyridyl)thiophene (**18**) (1.0 g, 3.1 mmol), except that one equivalent of butyllithium was used instead of two equivalents. The product was purified by sublimation followed by recrystallization from petroleum ether to give a yield of 0.43 g (57 %), m.p. 62.0–64.0 °C. Anal. C_9H_6BrNS: C, H, N, M. For ^1H NMR data see Tables 1 and 2.

4-(4-Pyridyl)thiophene-2(5H)-one (**17**). To a stirred solution of 2-bromo-4-(4-pyridyl)thiophene (**19**) (1.0 g, 4.17 mmol) in anhydrous THF (20 ml) at −100 °C under nitrogen, butyllithium (2.2 ml, 2.05 M in hexane) was added dropwise at such a rate that the temperature did not exceed −100 °C. The reaction mixture was stirred at −100 °C for 30 min, and then treated with triethyl borate (0.73 g, 5.0 mmol) in anhydrous THF (5 ml). After stirring at −100 °C for 4 h, the reaction mixture was allowed to reach ambient temperature and then treated with 30 % hydrogen peroxide solution (1.3 ml). The mixture was vigorously stirred at 50 °C for 2 h and then cooled, 20 ml of cold water was added and the layers were separated, the aqueous phase was extracted with ether. The combined organic phases were washed with cold water until the separated water did not oxidize ferrous ammonium sulphate and then dried over magnesium sulphate. After evaporation, the residue was purified by column chromatography using silica gel 60 and ethyl acetate as the eluent followed by sublimation to give a yield of 0.30 g (41 %), m.p. 156.0–158.0 °C. Anal. C_9H_7NOS: C, H, N, M. IR spectrum (KBr): 1665 cm^{-1} (C=O). For ^1H NMR data see Tables 1 and 2.

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