Pyridine-substituted Hydroxythiophenes. II. Alkylation of *o*-(2-, 3- and 4-Pyridyl)-3-hydroxythiophenes: Regiospecific Formation of *o*-Pyridyl-3-alkoxythiophenes

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Dedicated to the memory of Roland K. Robins

The alkylation of *o*-(2-, 3- and 4-pyridyl)-3-hydroxythiophenes has been investigated. In the case of 4-(2-, 3- and 4-pyridyl)-3-hydroxythiophene systems, the soft alkylating reagent, methyl iodide, using sodium hydride as the base and dimethylimidazolidinone as the solvent, gave rise to a mixture of *O*-alkylated and *O,C*-dialkylated products in the proportions of 4.6-6.5 to 1. However, in the case of 2-(2-, 3- and 4-pyridyl)-3-hydroxythiophene systems, the same reaction conditions brought about exclusively *O*-alkylated compounds in yields of 45-53%. In both cases, the hard alkylating reagent, methyl *p*-toluenesulfonate, with the same base and solvent, only give *O*-alkylated compounds in yields of 51-77%. These latter conditions resulted in a good preparative route for the regiospecific formation of *o*-pyridyl-3-alkoxythiophenes by using ethyl 2-bromopropionate as well as methyl *p*-toluenesulfonate as alkylating reagents. The hydrolysis of the esters, derived from alkylation with ethyl 2-bromopropionate, has also been investigated.

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Introduction.

In the preceding paper [1], we described the preparation of *o*-(2-, 3- and 4-pyridyl)-3-hydroxythiophenes **1-6** by hydrogen peroxide oxidation of the corresponding boronic esters and spectroscopic investigations by ^{1}H nmr and ir which showed that these potentially tautomeric hydroxythiophenes exist exclusively as enol forms.

In this paper, we will focus on the investigation of the alkylation of these pyridine-substituted hydroxythiophenes. It has previously been shown that the alkylation of dialkyl-substituted 3-hydroxythiophene gave both *O*- and *C*-alkylated products. The soft alkylating reagent, methyl iodide, predominantly afforded *C*-alkylation while the hard alkylating reagent, dimethyl sulfate, preferentially resulted in *O*-alkylation [2] (Table 1).

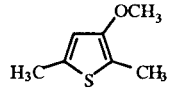
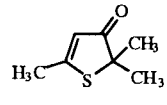
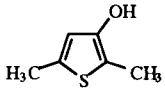
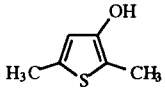
Results.

For the methylation of 4-(4-pyridyl)-3-hydroxythiophene (**6**), we employed the ion-pair extraction method, which was developed by Brändström and coworkers [3-5] and later successfully applied to the alkylation of 2-hydroxythiophene and alkyl-substituted 3-hydroxythiophene systems [2,6-10]. We used methyl iodide as the alkylating reagent, tetrabutyl ammonium hydrogen sulfate (TBAHS) as the phase transfer catalyst and chloroform as the solvent.

The amount of methyl iodide varied from 1 to 3 equivalents. Unfortunately these conditions only gave a mixture (6-8% yield) consisting of *O*-alkylated compound **12** and *O,C*-dialkylated compound **15** in the proportions of 2.6-3.8 to 1 as shown by ^{1}H nmr spectra. The products could not be separated either by column chromatography on silica gel or by distillation. The low yield can presumably be attributed to the low acidity of **6**. Thus, an insufficient amount of the *O*-anion was formed to attack methyl iodide in the presence of sodium hydroxide. Therefore, water-soluble products resulting from *N*-alkylation of **6**, and also **12** or **15**, may be formed to some extent. However, treatment

Table 1

Alkylation of 2,5-Dimethyl-3-hydroxythiophene

Substrate	Reagent	Yield	Product and relative yield	
				
	CH_3I	66%	35%	65%
	$(CH_3O)_2SO_2$	91%	90%	10%

of the same substrate and reagent with a stronger base, sodium hydride, in aprotic solvents, dimethyl sulfoxide (DMSO) or dimethylimidazolidinone (DMI), a highly polar solvent recommended as a replacement for hexamethylphosphoramide (HMPA) [11], resulted in higher yields with larger proportions of *O*-alkylated products of 50% (3.9 to 1) and 66% (4.8 to 1), respectively. When alkylation was carried out with methyl *p*-toluenesulfonate as the reagent, sodium hydride as the base and dimethyl sulfoxide as the solvent, the *O*-alkylated product **12** was exclusively formed in 43% yield. Moreover, by the use of the more polar aprotic solvent, dimethylimidazolidinone, the *O*-alkylation yield was improved to 75% (Table 2). This is quite compatible with the results obtained in the regiospecific formation of 3-alkoxypyrroles [12].

Table 2

Methylation of 4-(4-Pyridyl)-3-hydroxythiophene (6)

Solvent	Reagent (molar equivalents)	Base	Product (yield %) **12**	Mixture of **12** and **15**
$CDCl_3$ [a]	MeI (3.0)	MaOH	2.6:1	(7)
$CDCl_3$ [a]	MeI (2.3)	NaOH	2.7:1	(6)
$CDCl_3$ [a]	MeI (1.0)	NaOH	3.8:1	(8)
DMSO	MeI (2.3)	NaH	2.9:1	(47)
DMSO	MeI (1.0)	NaH	3.9:1	(50)
DMI	MeI (2.3)	NaH	3.7:1	(52)
DMI	MeI (1.0)	NaH	4.8:1	(66)
DMSO	TsOMe [b] (1.0)	NaH	(43)	(0)
DMI	TsOMe [b] (1.0)	NaH	(75)	(0)

[a] For solubility reasons the substrate was first dissolved in a small amount of dimethyl sulfoxide and then chloroform was added. [b] Methyl *p*-toluenesulfonate.

In order to investigate the influence of the pyridinic nitrogen on the ratio of *O*- to *O,C*-alkylation both in the 4-pyridyl-3-hydroxythiophene and in the 2-pyridyl-3-hydroxythiophene series, the methylation of the other five *o*-pyridyl-3-hydroxythiophenes **1-5** was carried out with methyl iodide as the reagent, sodium hydride as the base and dimethylimidazolidinone as the solvent. It is interesting to find that 4-(2- and 3-pyridyl)-3-hydroxythiophenes **4** and **5**, in the same way as compound **6**, also provided an inseparable mixture of *O*-alkylated and *O,C*-dialkylated compounds **10, 11, 13** and **14** in the proportions of 4.6 to 1 and 6.5 to 1, respectively, while 2-(2-, 3- and 4-pyridyl)-3-hydroxythiophenes **1-3** only gave *O*-alkylated compounds (**7-9**) in yields of 45-53%. Neither *C*-alkylation nor *O,C*-dialkylation was observed (Table 3). Since methyl *p*-toluenesulfonate in the methylation of **6** gave exclusively *O*-alkylated compound **12** in a yield up to 75%, methylation of compounds **1-5** under the same reaction conditions was next performed. Thus the alkylation of **4** and **5** gave 3-methoxy-4-(2- and 3-pyridyl)thiophenes **10** and **11** were formed in yields of 64% and 66% respectively. The alkylation of **1-3** afforded 3-methoxy-2-(2-, 3- and 4-pyridyl)thiophenes **7-9** in yields of 77%, 51% and 52% respectively (Table 3). These reactions show that the combination of methyl *p*-toluenesulfonate, sodium hydride and DMI represents the best available route to *o*-pyridyl-3-methoxythiophenes.

From the results of the methylation of **4-6** with sodium hydride as the base and DMI as the solvent, it can be seen that the hard alkylating reagent, methyl *p*-toluenesulfonate, caused exclusive *O*-alkylation, which is expected according to the HSAB theory [13]. However, the soft reagent, methyl iodide, resulted in a mixture of *O*-alkylated and *O,C*-dialkylated compounds in which the former compounds predominate. In view of the stable and exclusive enol forms in *o*-pyridyl-3-hydroxythiophene systems [1], a possible mechanism for the formation of *O*-alkylated and *O,C*-dialkylated compounds **10-15** is suggested as follows (Scheme 1).

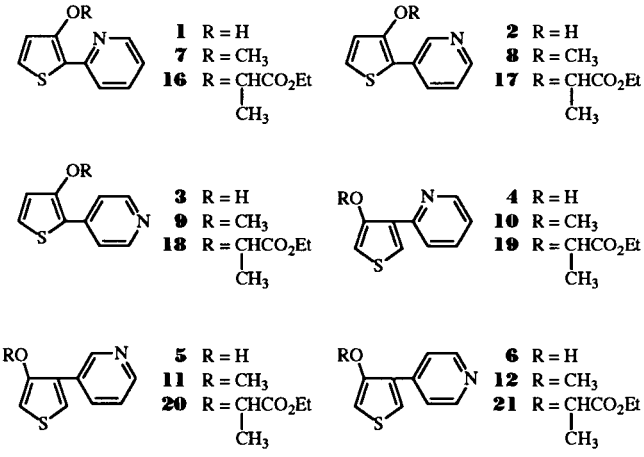


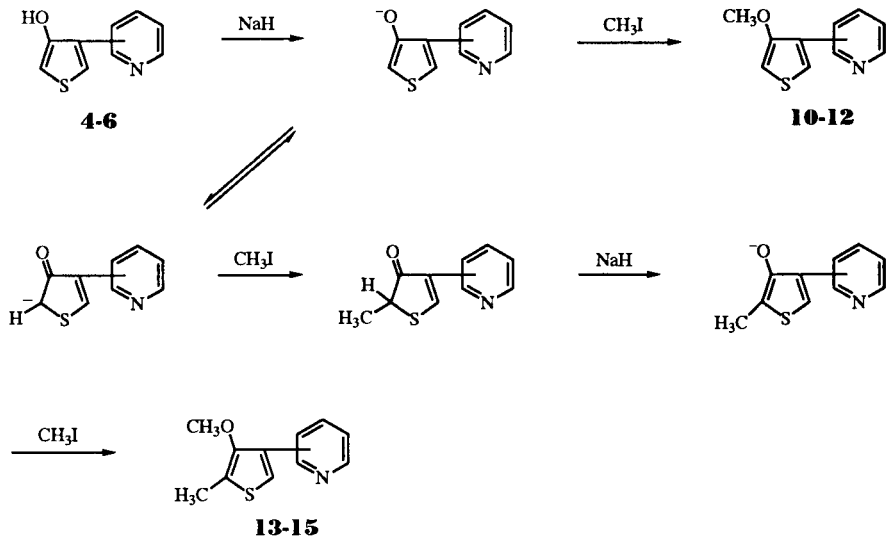
Table 3

Alkylation of *o*-Pyridyl-3-hydroxythiophenes with Sodium Hydride as the Base and Dimethylimidazolidinone as the Solvent

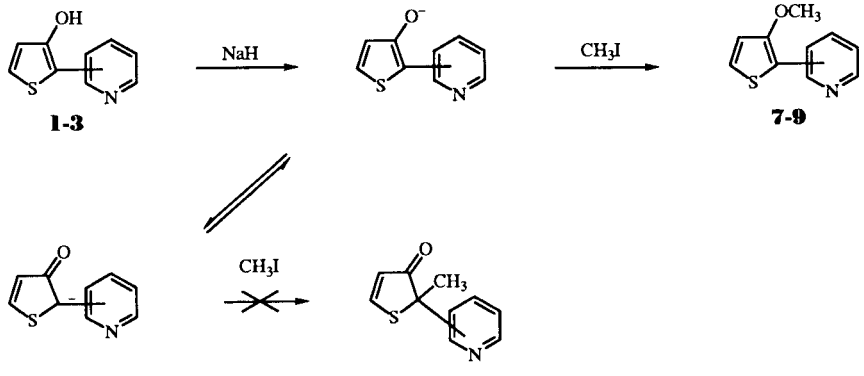
Compound	Reagent	Product (yield %)	
1	MeI	7	(53)
	TsOMe [a]	7	(77)
	EBP [b]	16	(68)
2	MeI	8	(45)
	TsOMe	8	(51)
	EBP	17	(66)
3	MeI	9	(51)
	TsOMe	9	(52)
	EBP	18	(68)
4	MeI	10/13, 4.6:1	(47)
	TsOMe	10	(64)
	EBP	19	(70)
5	MeI	11/14, 6.5:1	(46)
	TsOMe	11	(66)
	EBP	20	(63)
6	MeI	12/15, 4.8:1	(66)
	TsOMe	12	(75)
	EBP	21	(75)

[a] Methyl *p*-toluenesulfonate. [b] Ethyl 2-bromopropionate.

Scheme 1



Scheme 2



It is obvious that the formation of *O,C*-dialkylated compounds stems only from the intermediate, *C*-alkylated compounds. In the alkylation of **1-3** with methyl iodide using the same base and solvent as mentioned above, on the other hand, steric hindrance from the pyridine ring probably blocked *C*-alkylation. Therefore, both methyl *p*-toluenesulfonate and methyl iodide always gave *O*-alkylated products with compounds **1-3** (Scheme 2).

As expected, alkylation of **6** with ethyl 2-bromopropionate as the reagent, sodium hydride as the base, dimethyl sulfoxide or dimethylimidazolidinone as the solvent resulted exclusively in *O*-alkylated compound **21** in yields of 32% and 75%, respectively. It is clear that dimethylimidazolidinone is particularly effective in promoting *O*-alkylation of pyridine substituted 3-hydroxythiophenes. Thus, treatment of **4** and **5** with dimethylimidazolidinone as the solvent produced ethyl 2-[4-(2- and 3-pyridyl)-3-thienyloxy]propionates **19** and **20** were formed in yields of 70% and 63%, respectively. Similarly, **1-3** gave ethyl 2-[2-(2-, 3- and 4-pyridyl)-3-thienyloxy]propionates **16-18** in yields of 68%, 66% and 68% respectively (Table 3).

The *o*-pyridyl-3-alkoxythiophenes prepared above are normally oils or low-melting solids and are readily purified by column chromatography on silica gel. Complications were observed upon attempted hydrolysis of esters **16-21**. In the first procedure [14] (I) 1 *M* aqueous sodium hydroxide was used to hydrolyse the esters. Then 0.5 *M* aqueous hydrochloric acid was added to acidify the alkaline solution in order to precipitate the acids. In the case of ester

Table 4

Hydrolysis of Ethyl 2-[*o*-(2-,3- and 4-Pyridyl)-3-thienyloxy]propionates

Ester	Procedure	Product	Yield (%)
16	II	22	65
17	II	23	72
18	I	24	75
19	II	25	60
20	II	26	63
21	I	27	65

Table 5

^{1}H NMR Chemical Shifts for some *o*-Pyridyl-3-alkoxythiophenes

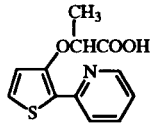
Compounsd	Solvent	H_2	H_4	H_5	H_2	H_3	H_4	H_5	H_6	OCH_3	OCH	$CH_3(CH)$	OCH_2	$CH_3(CH_2)$
7	$CDCl_3$		6.94	7.28		8.07	7.66	7.06	8.52	3.99				
8	$CDCl_3$		6.95	7.24	8.97		8.03	7.28	8.43	3.94				
9	$CDCl_3$		6.95	7.29	8.53	7.64		7.64	8.53	3.98				
10	$CDCl_3$	6.37		7.94		7.95	7.70	7.17	8.62	3.93				
11	$CDCl_3$	6.39		7.36	8.86		7.96	7.31	8.53	3.89				
12	$CDCl_3$	6.37		7.46	8.58	7.57		7.57	8.58	3.89				
16	$CDCl_3$		6.80	7.25		8.23	7.68	7.08	8.52		4.82	1.69	4.23	1.24
17	$CDCl_3$		6.81	7.20	9.01		8.12	7.29	8.46		4.74	1.63	4.20	1.23
18	$CDCl_3$		6.80	7.26	8.55	7.71		7.71	8.55		4.79	1.67	4.22	1.24
19	$CDCl_3$	6.32		7.95		8.10	7.71	7.17	8.60		4.75	1.67	4.24	1.26
20	$CDCl_3$	6.34		7.34	8.91		8.04	7.32	8.54		4.71	1.62	4.23	1.26
21	$CDCl_3$	6.34		7.45	8.62	7.65		7.65	8.62		4.72	1.64	4.23	1.26
22	DMSO		6.99	7.52		8.16	7.81	7.19	8.48		5.0	1.58		
23	DMSO		7.04	7.55	8.96		8.12	7.43	8.43		4.94	1.52		
24	DMSO		7.06	7.64	[a]	[b]		[b]	[a]		5.02	1.57		
24	CD_3OD		7.00	7.59	8.50	8.02		8.02	8.50		4.91	1.67		
25	DMSO	6.55		8.01		8.12	7.84	7.29	8.60		4.79	1.54		
26	DMSO	6.72		7.81	8.93		8.11	7.45	8.61		4.85	1.52		
27	DMSO	6.71		7.97	8.58	7.77		7.77	8.58		4.82	1.54		

[a] 8.35-8.70. [b] 7.65-7.82.

Table 6

^{1}H NMR Coupling Constants for some o-Pyridyl-3-alkoxythiophenes

Compound	Solvent	J_{25}	J_{45}	J_{23}	J_{24}	J_{25}	J_{34}	J_{35}	J_{36}	J_{45}	J_{46}	J_{56}	$J_{CH\text{-}CH_3}$	$J_{CH_2\text{-}CH_3}$
7	$CDCl_3$		5.55				8.10	1.10	1.00	7.50	1.80	5.10		
8	$CDCl_3$		5.60		2.30					8.05	1.65	4.85		
9	$CDCl_3$		5.60	5.15		1.60			1.60			5.15		
10	$CDCl_3$	3.60					8.00	1.10	1.00	7.50	1.90	4.85		
11	$CDCl_3$	3.35			1.85	0.85				8.00	1.85	4.85		
12	$CDCl_3$	3.40		5.90		1.40			1.40			5.90		
16	$CDCl_3$		5.55				8.05	1.05	0.95	7.60	1.80	4.70	6.80	7.15
17	$CDCl_3$		5.60		2.30	0.75				8.05	1.65	4.80	6.85	7.15
18	$CDCl_3$		5.60	4.65		1.65			1.65			4.65	6.85	7.15
19	$CDCl_3$	3.55					8.05	1.10	1.00	7.55	1.90	4.85	6.75	7.10
20	$CDCl_3$	3.30			1.95	0.75				7.85	1.80	4.80	6.80	7.10
21	$CDCl_3$	3.40		6.00		1.35			1.35			6.00	6.80	7.10
22	DMSO		5.65				7.95	1.00	0.85	7.60	1.70	4.90	6.80	
23	DMSO		5.65		1.95					7.90	1.95	4.65	6.75	
24	DMSO		5.60										6.70	
24	CD_3OD		5.65	5.15								5.15	6.80	
25	DMSO	3.50					7.90	1.10	0.85	7.60	1.80	4.85	6.75	
26	DMSO	3.25			1.85					8.00	1.85	4.70	6.75	
27	DMSO	3.35		5.30		1.75			1.75			5.30	6.55	



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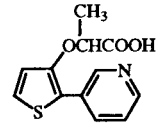

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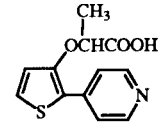

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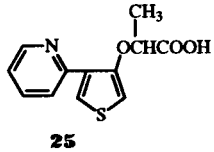

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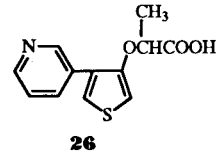

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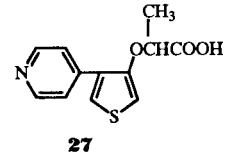

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18, after acidification (*p*H 3-4) in an ice-bath, acid **24** was precipitated. Acid **27** was also generated after ester **21** was hydrolysed and then acidified to *p*H 4-5. However, in the cases of esters **16, 17, 19** and **20** no precipitation took place after acidification (*p*H 5-6, 4-5, 3-4, 2-3, 1-2), even when the acidic solution was kept in a refrigerator for one week. An attempt to acidify with acetic acid, which was effective in precipitating 2-(2-pyridyl)benzoic acid [15], was unsuccessful. Finally, we succeeded with the following procedure (II). After acidification with more than two equivalents of 0.5 *M* hydrochloric acid, the resulting acidic solution was freeze-dried and purified by reversed phase hplc with water-acetonitrile (80:20) as the eluent. The white acids **22, 23, 25,** and **26** were obtained after removal of the solvent by freeze-drying. Elemental analyses and ^{1}H nmr spectra (see Tables 5 and 6) showed that the free acids and not their hydrochlorides had been obtained. In this way, 2-[2-(2- and 3-pyridyl)-3-thienyloxy]propionic acids **22** and **23** were formed in yields of 65% and 72%, respectively, and 2-[4-(2- and 3-pyridyl)-3-thienyloxy]propionic acids **25** and **26** were obtained in yields of 60% and 63%, respectively (Table 4).

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a Finnigan 4021 and a JEOL JMS-SX102 spectrometer. The glc analyses were carried out on a Varian 1400 gas chromatograph using an OV-17 (3%, 2 m) column. *o*-(2-, 3- and 4-Pyridyl)-3-hydroxythiophenes **1-6** were prepared according to the literature [1].

Alkylation of 4-(4-Pyridyl)-3-hydroxythiophene (**6**) with Methyl Iodide.

Method A.

A freshly prepared solution of 37.4 mg (1.10 mmoles) of tetrabutylammonium hydrogen sulfate and 92.4 mg (2.30 mmoles) of sodium hydroxide in 1.0 ml of water was added dropwise with stirring to a solution of 177 mg (1.00 mmole) of compound **6** and an appropriate amount of methyl iodide in 1.0 ml of DMSO and 5.0 ml of chloroform. The mixture was stirred for an additional 10 minutes and monitored by glc and tlc, and then poured into water. The chloroform phase was separated and the water phase was extracted with chloroform. The combined chloroform phases were washed with water and dried over sodium sulfate. After evaporation the residue was purified by column chromatography using silica gel 60 and dichloromethane/methanol (92:8) as the eluent.

Methyl iodide (1.0 mmole) gave 15.3 mg (8.0% yield) of a mixture as an oil consisting of 79% 3-methoxy-4-(4-pyridyl)thiophene (**12**) (see below) and 21% 3-methoxy-2-methyl-4-(4-pyridyl)thiophene (**15**); ^{1}H nmr (deuteriochloroform): 2.41 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 7.21 (s, 1H, 5-H), 7.59 [dd, 2H, 3(5)-H, J = 5.90 and 1.39 Hz], 8.58 [dd, 2H, 2(6)-H, J = 5.90 and 1.39 Hz]. Methyl iodide (2.3 mmoles) gave 11.5 mg (6.0% yield) of a mixture consisting of 73% **12** and 27% **15**. Methyl iodide (3.0 mmoles) gave 13.4 mg (7.0% yield) of a mixture consisting of 72% **12** and 28% **15**.

Method B.

A solution of 177 mg (1.00 mmole) of **6** in 4.0 ml of DMSO was added dropwise to a suspension of sodium hydride (80% dispersion in oil, 36 mg, *ca* 1.2 mmoles, previously washed twice with anhydrous ether) in 2.0 ml of DMSO at ambient temperature. After stirring for 10 minutes, a solution of an appropriate amount of methyl iodide in 4.0 ml of DMSO was added dropwise, and the reaction mixture was stirred for one hour more. Methanol (1.0 ml) and water (20 ml) were added dropwise successively. The aqueous solution was extracted with ether. The combined organic phases were then washed with water, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using silica gel 60 with ethyl acetate as the eluent. Methyl iodide (1.0 mmole) gave 96.0 mg (50% yield) of a mixture composed of 80% **12** and 20% **15**. Methyl iodide (2.3 mmoles) gave 89.8 mg (47% yield) of a mixture composed of 74% **12** and 26% **15**.

Method C.

The same procedure as described in method B was carried out using dimethylimidazolidinone (DMI) as the solvent.

Methyl iodide (1.0 mmole) gave 126.1 mg (66% yield) of a mixture containing 83% **12** and 17% **15**. Methyl iodide (2.3 mmoles) gave 99.4 mg (52% yield) of a mixture containing 79% **12** and 21% **15**.

Alkylation of 4-(4-Pyridyl)-3-hydroxythiophene (**6**) with Methyl *p*-Toluenesulfonate.

Method D.

A solution of 177 mg (1.00 mmole) of **6** in 4 ml of DMSO was added dropwise to a suspension of sodium hydride (80% dispersion in oil, 36 mg, *ca.* 1.2 mmoles, previously washed twice with anhydrous ether) in 2.0 ml of DMSO at ambient temperature. After stirring for 10 minutes, a solution of 186 mg (1.00 mmole) of methyl *p*-toluenesulfonate in 4 ml of DMSO was added dropwise, and the reaction mixture was stirred for an additional hour. Methanol (1.0 ml) and water (20 ml) were added dropwise successively. The aqueous solution was extracted with ether, the combined organic phases were then washed with water, dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using silica gel 60 and ethyl acetate as the eluent, yielding 82.5 mg (43%) of **12**, mp 54.5-56.5°; for ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.69; H, 4.80; N, 7.33.

Method E.

The same procedure as described in method D was used, using DMI as solvent giving 142.5 mg (75%) of **12**.

Alkylation of 4-(2- and 3-Pyridyl)-3-hydroxythiophenes **4** and **5** with Methyl Iodide.

The same procedure as described in method C was used, with 1.0 mmole of methyl iodide.

A mixture consisting of 82% of 3-methoxy-4-(2-pyridyl)thiophene (**10**) (see below) and 18% of 3-methoxy-2-methyl-4-(2-pyridyl)thiophene (**13**) (90 mg, 47% yield) was obtained from **4** using dichloromethane/methanol (98:2) as the eluent; ^{1}H nmr of **13** (deuteriochloroform): 2.41 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 7.19

(octet, 1H, 5-H, J = 7.4, 4.8 and 1.2 Hz), 7.61 (s, 1H, 5-H), 7.71 (octet, 1H, 4-H, J = 8.0, 7.4 and 1.8 Hz), 7.87 (sextet, 1H, 3-H, J = 8.0, 1.2 and 1.2 Hz), 8.62 (octet, 1H, 6-H, J = 4.8, 1.8 and 1.2 Hz).

A mixture consisting of 87% of 3-methoxy-4-(3-pyridyl)thiophene (**11**) (see below) and 13% of 3-methoxy-2-methyl-4-(3-pyridyl)thiophene (**14**) (88 mg, 46% yield) was obtained from **5** using dichloromethane/methanol (96:4) as the eluent; ^{1}H nmr of **14** (deuteriochloroform): 2.42 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 7.09 (s, 1H, 5-H), 7.31 (octet, 1H, 5-H, J = 8.0, 4.9 and 0.9 Hz), 7.96 (sextet, 1H, 4-H, J = 8.0, 1.8 and 1.8 Hz), 8.53 (dd, 1H, 6-H, J = 4.9 and 1.8 Hz), 8.86 (dd, 1H, 2-H, J = 1.8 and 0.9 Hz).

3-Methoxy-2-(2-pyridyl)thiophene (**7**).

This compound was prepared from **1** according to either method C using 1.0 mmole of methyl iodide or method E using dichloromethane/petroleum ether (9:1) as the eluent to give 102 mg (53%) of oil and 147.2 mg (77%) of oil, respectively. For ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.82; H, 4.92; N, 7.39.

3-Methoxy-2-(3-pyridyl)thiophene (**8**).

This compound was prepared from **2** according to either method C using 1.0 mmole of methyl iodide or method E using dichloromethane/methanol (97:3) as the eluent to give 85 mg (45%) of oil and 98.2 mg (51%) of oil, respectively. For ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.66; H, 4.80; N, 7.22.

3-Methoxy-2-(4-pyridyl)thiophene (**9**).

This compound was prepared from **3** according to either method C using 1.0 mmole of methyl iodide or method E using dichloromethane/methanol (95:5) as the eluent to yield 97 mg (51%) and 100 mg (52%), respectively, mp 39.5-41.5°; for ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.48; H, 4.79; N, 7.38.

3-Methoxy-4-(2-pyridyl)thiophene (**10**).

This compound was prepared from **4** according to method E using dichloromethane/methanol (98:2) as the eluent to yield 122.5 mg (64%), mp 62-63°; for ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.66; H, 4.78; N, 7.26.

3-Methoxy-4-(3-pyridyl)thiophene (**11**).

This compound was prepared from **5** according to method E using dichloromethane/methanol (96:4) as the eluent to yield 126 mg (66%) of oil. For ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.68; H, 4.82; N, 7.20.

Ethyl 2-[4-(4-Pyridyl)-3-thienyloxy]propionate (**21**).

Method F.

The same procedure as described in method B was carried out, but ethyl 2-bromopropionate was used as the reagent and ethyl acetate/dichloromethane (9:1) as the eluent to give 90 mg (32%), mp 44-46°; for ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.76; H, 5.55; N, 5.12.

Method G.

The same procedure as described in method F was used, except that the solvent was DMI, to give 210 mg (75%), mp 44-46°.

Ethyl 2-[2-(2-Pyridyl)-3-thienyloxy]propionate (**16**).

This compound was obtained as an oil from **1** according to method G using dichloromethane/methanol (99.5:0.5) as the eluent, yielding 188 mg (68%). For ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.48; H, 5.38; N, 5.02.

Ethyl 2-[2-(3-Pyridyl)-3-thienyloxy]propionate (**17**).

This compound was obtained as an oil from **2** according to method G using dichloromethane/methanol (97:3) as the eluent yielding 183 mg (66%). For ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.55; H, 5.37; N, 4.98.

Ethyl 2-[2-(4-Pyridyl)-3-thienyloxy]propionate (**18**).

This compound was obtained from **3** according to method G using dichloromethane/methanol (95:5) as the eluent, yielding 188 mg (68%), mp 76-78°; for ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.72; H, 5.49; N, 5.21.

Ethyl 2-[4-(2-Pyridyl)-3-thienyloxy]propionate (**19**).

This compound was obtained as an oil from **4** according to method G using dichloromethane/methanol (92:8) as the eluent, yielding 193 mg (70%). For ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.54; H, 5.56; N, 5.15.

Ethyl 2-[4-(3-Pyridyl)-3-thienyloxy]propionate (**20**).

This compound was obtained as an oil from **5** according to method G using dichloromethane/methanol (96:4) as the eluent, yielding 174 mg (63%). For ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.51; H, 5.38; N, 5.02.

General Procedure for the Preparation of 2-[*o*-(4-Pyridyl)-3-thienyloxy]propionic Acid.

A suspension of 100 mg (0.36 mmole) of ethyl 2-[*o*-(4-pyridyl)-3-thienyloxy]propionate in 0.83 ml of 1 *M* aqueous sodium hydroxide was refluxed with stirring for 1 hour. The mixture was then cooled and acidified with 0.5 *M* aqueous hydrochloric acid in an ice-bath. The precipitate thus formed was filtered off and purified by crystallization.

2-[2-(4-Pyridyl)-3-thienyloxy]propionic Acid (**24**).

This compound was obtained from **18** after acidification (*p*H 3-4) and crystallization from methanol to yield 67.4 mg (75%), mp 185-186°; ir (potassium bromide): ν 3400, 1710 cm^{-1} (COOH); for ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.85; H, 4.62; N, 5.68.

2-[4-(4-Pyridyl)-3-thienyloxy]propionic Acid (**27**).

This compound was obtained from **21** after acidification (*p*H 4-5) and crystallization from ethanol to yield 62.9 mg (70%), mp 184.5-185.5° dec; ir (potassium bromide): ν 3450, 1715 cm^{-1} (COOH); for ^{1}H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.74; H, 4.43; N, 5.57.

General Procedure for the Preparation of 2-[*o*-(2- and 3-Pyridyl)-3-thienyloxy]propionic Acids.

A mixture of 100 mg (0.36 mmole) of ethyl 2-[*o*-(2- or 3-pyridyl)-3-thienyloxy]propionate in 0.83 ml of 1 *M* aqueous sodium hydroxide was refluxed for 1 hour. The mixture was then cooled and acidified with 2.5 ml of 0.5 *M* aqueous hydrochloric acid. The resulting acidic solution was freeze-dried and purified by reverse phase hplc using water/acetonitrile (80:20) as the eluent. The white acid was formed after removal of the solvent at high vacuum (below 0.06 mm Hg) again by freeze-drying.

2-[2-(2-Pyridyl)-3-thienyloxy]propionic Acid (**22**).

This compound was obtained from **16** in a yield of 58.4 mg (65%), mp 53-55°; ir (potassium bromide): ν 3420, 1735 cm^{-1} (COOH); for ^1H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.85; H, 4.57; N, 5.84.

2-[2-(3-Pyridyl)-3-thienyloxy]propionic Acid (**23**).

This compound was obtained from **17** in a yield of 64.7 mg (72%), mp 149-151.5°; ir (potassium bromide): ν 3410, 1715 cm^{-1} (COOH); for ^1H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.80; H, 4.37; N, 5.63.

2-[4-(2-Pyridyl)-3-thienyloxy]propionic Acid (**25**).

This compound was obtained from **19** in a yield of 53.9 mg (60%), mp 56-58°; ir (potassium bromide): ν 3420, 1725 cm^{-1} (COOH); for ^1H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.91; H, 4.52; N, 5.83.

2-[4-(3-Pyridyl)-3-thienyloxy]propionic Acid (**26**).

This compound was obtained from **20** in a yield of 56.6 mg (63%), mp 172-174.5°; ir (potassium bromide): ν 3420, 1725 cm^{-1} (COOH); for ^1H nmr data see Tables 5 and 6.

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.96; H, 4.55; N, 5.87.

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