TRANSFER OF INDUCTIVE EFFECT IN THIOPHENE SERIES*

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Apparent dissociation constants of 4-methyl-2-thiophenecarboxylic acids (*I*) and 5-methyl-3-thiophenecarboxylic acids (*II*), substituted in the side chain, have been determined in 80% Methyl Cellosolve and compared with pK values of analogously substituted 5-methyl-2-thiophenecarboxylic acids *III*. The pK values have been correlated with σ_I constants using Hammett equation, the slope ϱ being $-0{\cdot}772$ for the acids *I* and $\varrho = -0{\cdot}499$ for the acids *II*. The interpretation of transfer of the inductive effect across the thiophene nucleus involves participation of π-electrons.

In a previous paper[1] we described methods which enabled synthesis of compounds needed for an investigation of inductive effect transfer in mutually reverse directions in structurally similar thiophene derivatives *I* and *II*.

A model in which steric and mesomeric effects are eliminated by insertion of methylene group was used for the first time by Exner[2]. In the case of *p*-toluic acids, substituted in the methyl group[2], the results of the study of the inductive effect transfer were in accord with other methods, *e.g.* with the approach using substituted bicyclo[2,2,2]octane-1-carboxylic acids[3] for the elimination of steric and mesomeric effects. The relative pK value, determined in 50% aqueous ethanol and 80% Methyl Cellosolve, was considered to be a measure of the inductive effect in the mentioned derivatives of *p*-toluic acids. On the basis of comparison of ϱ constant for this series with ϱ constant for dissociation of substituted benzoic acids, the authors calculated the transmission coefficient $\varepsilon = 0{\cdot}59$ which represents the decrease in the inductive effect due to the introduction of methylene group. An analogous study compared *para* and *meta* substituted benzoic acids with CH_2—X, CF_3 and CCl_3 groups as substituents. It was found[4] that the substitution effect in *para*-derivatives is stronger than in *meta*-isomers by the ratio $\lambda = 1{\cdot}14$. The transfer of the inductive effect itself was deduced from the linear relationship. Benzylic derivatives were used in the study of the inductive effect transfer also in the furan and thiophene series[5,6], in the case of substituted 5-X-methyl-2-furancarboxylic and 5-X-methyl-2-thiophene-

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carboxylic acids. The plots of pK values of acids belonging to one series against the values of analogously substituted acids of other series were linear and the acid strength of the series increased in the order benzene, thiophene, furan. The acidity of thiophene and furan derivatives is higher than the corresponding benzoic acids by 0·7 and 1·1 pK units, respectively. The sensitivity towards the substituent effect in the particular series increases in the order benzene, thiophene, furan in the ratio 1 : 1·17 : 1·31.

TABLE I

Dissociation Constants (pK) of the Acids *I*, *II* and *III* and the Corresponding σ_I Constants

Substituent X	*I*	*II*	*III*	σ_I[b]
H	6·08	6·58	6·16	0·00
Br	5·68	5·75[c]	—	0·50
OH	5·87	6·48	5·95	0·31
OCH_3	5·84	6·41	5·85	0·33
OC_6H_5	5·70	6·37	5·79	0·42
SH	5·90	6·47	5·89	0·28
SC_2H_5	5·92	6·49	—	0·22[d]
$SO_2C_6H_5$	5·64	6·28	5·63	0·62
COOH pK_1	5·83	5·95[b]	—	0·34
pK_2	6·95	6·99	—	—
COOH[e]	5·54[c] 5·76[f]	7·30[b,g]	—	—

[a] The values are taken from ref.[6]; [b] the values are taken from ref.[4]; [c] the values were not included into the correlation; [d] value for SCH_3; [e] substituent on the nucleus; [f] the value was calculated using the transmission coefficient $\varepsilon = 0{\cdot}59$; [g] the actual substituent in this case is $COO^{(-)}$

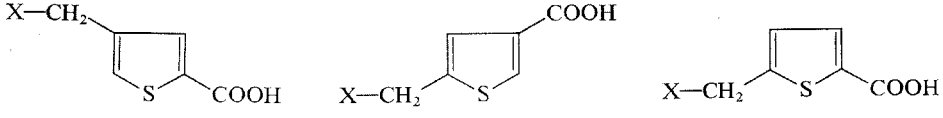
TABLE II

Statistical Characteristics of Plots of pK against σ_I for the Acids *I*, *II* and *III*

Characteristics	*I*	*II*	*III*
pK_0 orig.	6·087	6·596	6·159
s_{pK}[a]	0·026	0·018	0·029
ϱ	−0·772	−0·499	−0·858
s_ϱ[a]	0·068	0·050	0·077
r[b]	0·977	0·975	0·984

[a] Standard deviation; [b] correlation coefficient.

In order to study the extent of inductive effect transfer in the compounds *I* and *II* we measured the dissociation constants in 80% Methyl Cellosolve at 25°C. The results are given in Table I together with analogous values for 5-substituted 2-thiophenecarboxylic acids *III*, included for comparison, and σ_I constants. The ϱ constants and pK values for the single series were calculated using the least squares method. The dependence of pK on the σ_I constant of a given substituent for single series of acids is expressed by the equation $pK = \varrho \,.\, \sigma_I + pK_0$. The calculated values for the series of acids *I*, *II* and *III* are given in Table II and the correlations are depicted graphically in Figures 1, 2 and 3. Besides these correlations we correlated also the pK values of the acids *I* with that of the acids *II* (Fig. 4). This correlation can be expressed by the equation $pK_{II} = 0{\cdot}6468 \,.\, pK_I + 2{\cdot}6563$, the correlation coefficient being 0·9755.



I *II* *III*

All these correlations are linear and are of a relatively high accuracy as seen from the values of correlation coefficients. The transfer of inductive effect is proportional in all the three series and its magnitude decreases in the following order: *III* (5-substituted 2-thiophenecarboxylic acids), *II* (4-substituted 2-thiophenecarboxylic acids), *II* (5-substituted 3-thiophenecarboxylic acids) in the ratio 1 : 0·90 : 0·58. This decrease is thus in accord with the decrease in the mobility of π-electrons. The ratio

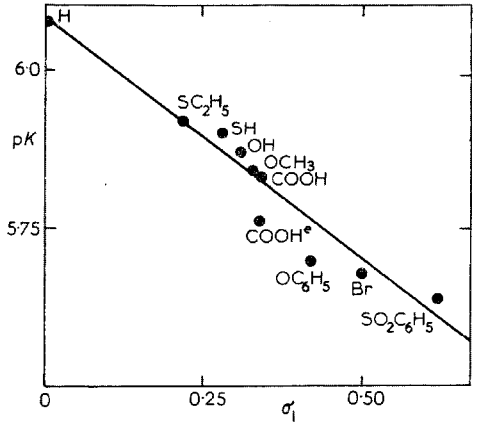


FIG. 1

Dependence of pK on σ_I for the Acids *I*

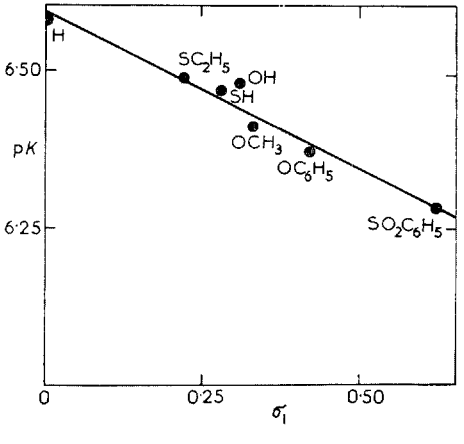


FIG. 2

Dependence of pK on σ_I for the Acids *II*

of transfer of the inductive effect in series *III* (from position 5 to position 2) to that in series *I* (from position 4 to position 2), $\varrho_{III} : \varrho_I = 1{\cdot}11$, agrees very well with a similar ratio found by Exner[4,7] in the benzene series for *para* (*p*) and *meta* (*m*) positions, $\varrho_p : \varrho_m = 1{\cdot}14$. From this point of view the comparison of 2,5-substitution and 2,4-substitution in the thiophene series with the respective *para*- and *meta*-substitution in the benzene series is justified. In our opinion, the found difference in the extent of the inductive effect operation in both directions ($\varrho_I : \varrho_{II} = 1{\cdot}55$) between the positions 2 and 4 of the thiophene nucleus is a proof of the mechanism of the inductive effect transfer along σ-bonds with participation of π-electrons.

EXPERIMENTAL

The temperature data are uncorrected. ^{1}H-NMR spectra were measured on a Varian XL 100 (100 MHz) instrument in hexadeuterioacetone using tetramethylsilane as internal standard. Mass spectra were taken on an LKB 9000 spectrometer. Dissociation constants were determined potentiometrically in 80% aqueous Methyl Cellosolve at 25°C. The elemental analyses of the acids *I* and *II* are listed in Table III and ^{1}H-NMR spectra of the acids *I* and *II* in Table IV and Table V, respectively. Mass spectra of the acids *I* and *II* are shown in Table VI.

4-Hydroxymethyl-2-thiophenecarboxylic Acid (*Ic*)

A mixture of the bromomethyl acid *Ib* (2·2 g; 0·01 mol, ref.[1]) and a solution of sodium hydroxide (1·0 g; 0·025 mol) in water (10 ml) was refluxed for 6 hours, filtered, acidified with concentrated hydrochloric acid and extracted with ether. The extract was taken down, affording 1·2 g of the acid *Ic*, which upon crystallisation from water melted at 114°C.

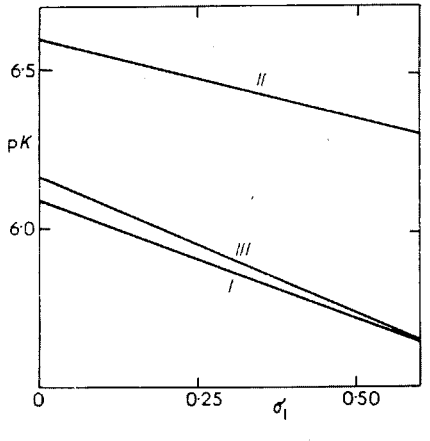


FIG. 3

Hammett Relationship for p*K* Values of the Acids *I*, *II* and *III*

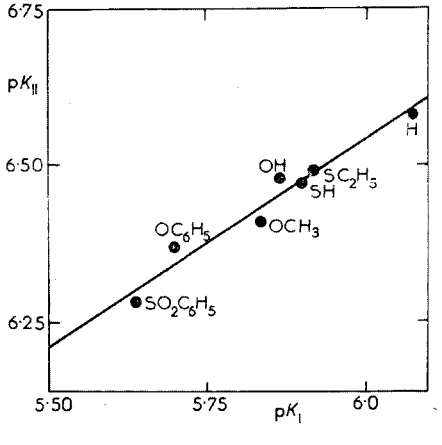


FIG. 4

Plot of p*K* Values of the Acids *I* (abscissa) against p*K* Values of the Acids *II* (ordinate axis)

TABLE III

Elemental Analyses of the Acids[a] *I* and *II*

Compound	Formula (mol.w.)	Calculated/Found		
		% C	% H	% S
Ib	$C_6H_5BrO_2S$	32·60	2·28	14·50
	(221·1)	32·63	2·50	15·31
IIb	$C_6H_5BrO_2S$	32·60	2·28	14·50
	(221·1)	32·13	2·61	14·25
Ic	$C_6H_6O_3S$	45·56	3·82	20·27
	(158·2)	45·37	3·91	20·10
IIc	$C_6H_6O_3S$	45·56	3·82	20·27
	(158·2)	45·79	3·90	20·25
Id	$C_7H_8O_3S$	48·83	4·68	18·62
	(172·2)	48·82	4·69	19·07
IId	$C_7H_8O_3S$	48·83	4·68	18·62
	(172·2)	48·68	4·77	18·65
Ie	$C_{12}H_{10}O_3S$	61·52	4·30	13·69
	(234·3)	61·18	4·47	13·74
IIe	$C_{12}H_{10}O_3S$	61·52	4·30	13·69
	(234·3)	62·34	4·63	13·55
If	$C_6H_6O_2S_2$	41·36	3·47	36·80
	(174·2)	41·59	3·62	37·38
IIf	$C_6H_6O_2S_2$	41·36	3·47	36·80
	(174·2)	41·28	3·56	36·10
Ig	$C_8H_{10}O_2S_2$	47·50	4·98	31·70
	(202·3)	47·83	5·01	30·92
IIg	$C_8H_{10}O_2S_2$	47·50	4·98	31·70
	(202·3)	47·11	4·80	31·15
Ih	$C_{12}H_{10}O_4S_2$	51·05	3·57	22·71
	(282·3)	51·07	3·66	23·54
IIh	$C_{12}H_{10}O_4S_2$	51·05	3·57	22·71
	(282·3)	51·05	3·70	23·01
Ii	$C_7H_6O_4S$	45·16	3·25	17·22
	(186·2)	45·19	3·37	17·70
IIi	$C_7H_6O_4S$	45·16	3·25	17·22
	(186·2)	45·18	3·39	17·76

[a] See note added in proof.

TABLE IV

^{1}H-NMR Spectra of the Acids *I*

Compound	H_5[a]	H_3[a]	CH_2	Other signals
Ia	7·60	7·36	—	2·28 (CH_3)
Ib	7·83	7·83	4·66	
Ib[b]	7·90	7·60	4·50	
Ic	7·76	7·61	4·66	
Id	7·73	7·64	4·45	3·34 (OCH_3)
Ie	7·85	7·80	5·14	6·84—7·40 (m, OC_6H_5)
If	7·78	7·60	3·81	2·29 (SH), J_{CH_2SH} = 8·0 Hz
Ig	7·75	7·58	3·78	1·20 (t, 3, CH_3), 2·46 (q, 2, CH_2)[3], J_{HH} = 7·5 Hz
Ih	7·50—7·80	7·50—7·80	4·60	7·50—7·80 (m, C_6H_5)
Ii	7·78	7·62	3·73	
Ij	8·48	8·06	—	

[a] $J_{3,5}$ = 1·4—1·6 Hz; [b] measured in deuteriochloroform.

TABLE V

^{1}H-NMR Spectra of the Acids *II*

Compound	H_2[a]	H_4[a]	CH_2	Other signals
IIa	7·96	7·16	—	2·48 (CH_3)
IIb	8·26	7·58	4·94	
IIc	8·10	7·33	4·80	
IId	8·16	7·38	4·61	3·34 (OCH_3)
IIe	8·20	7·54	5·32	6·84—7·40 (m, C_6H_5)
IIf	8·08	7·36	4·02	2·50 (SH), $J1_{H_2SH}$ = 8·0 Hz
IIg	8·11	7·35	4·00	1·23 (t, 3, CH_3), 2·54 (q, 2, CH_2)[3], J_{HH} = 7·5 Hz
IIh	8·17	7·28	4·82	7·50—7·86 (m, C_6H_5)
IIi	8·11	7·36	3·92	

[a] J_{24} = 1·4—1·6 Hz.

4-Phenoxymethyl-2-thiophenecarboxylic Acid (*Ie*)

A solution of 4-chloromethyl-2-thiophenealdehyde[1] (6·4 g; 0·04 mol) and sodium phenoxide (4·6 g; 0·04 mol) in methanol (100 ml) was refluxed for 1 h and then concentrated *in vacuo*. Water was added to the residue and the mixture was three times extracted with ether. The ethereal extract was dried over magnesium sulphate and taken down under diminished pressure. The residue (8·0 g) was dissolved in methanol (120 ml) and the solution treated with silver nitrate (21 g) in water (150 ml) and with 1M-NaOH (126 ml). The mixture was set aside for 2 days, filtered and the filtrate was concentrated *in vacuo*. Acidification with concentrated nitric acid afforded 1·5 g of the acid *Ie* which was twice crystallised from heptane, m.p. 134—136°C.

4-Mercaptomethyl-2-thiophenecarboxylic Acid (*If*)

A solution of methyl 4-bromomethyl-2-thiophenecarboxylate[1] (4·7 g; 0·02 mol) and thiourea (1·56 g; 0·02 mol) in methanol (6 ml) was refluxed for 2 h. The solvent was distilled off and the residue (7·2 g) was boiled with benzene and ethyl acetate (100 ml). Upon cooling the crystalline portion was filtered, yielding 6·0 g of the thiuronium salt. This was refluxed with 50% potassium

TABLE VI

Mass Spectra of the Acids *I* and *II*

Compound	*m* (e/rel. intensity, %)
Ia	142 (100), 141 (33), 125 (65), 97 (80), 53 (24), 45 (37)
IIa	142 (100), 141 (38), 125 (48), 97 (77), 53 (19), 45 (30)
Ib	222 (4), 220 (4), 141 (100), 97 (10), 45 (25)
IIb	222 (4), 220 (4), 141 (100), 95 (8), 45 (18)
Ic	158 (85), 141 (100), 113 (50), 97 (30), 85 (75), 45 (95)
IIc	158 (100), 141 (49), 129 (58), 95 (9), 85 (69), 45 (74)
Id	172 (35), 142 (86), 141 (100), 111 (54), 97 (55), 45 (85)
IId	172 (40), 142 (18), 141 (100), 97 (15), 45 (34)
Ie	234 (10), 141 (100), 97 (8), 45 (12)
IIe	234 (6), 141 (100), 95 (10), 45 (20)
If	174 (28), 141 (100), 97 (7), 45 (29)
IIf	174 (16), 141 (100), 97 (22), 45 (45)
Ig	202 (22), 141 (100), 97 (7), 45 (23)
IIg	202 (22), 141 (100), 95 (5), 45 (15)
Ih	282 (3), 141 (100), 97 (9), 45 (14)
IIh	282 (2), 141 (100), 95 (5), 45 (10)
Ii	186 (38), 141 (100), 97 (14), 45 (26)
IIi	186 (34), 141 (100), 97 (10), 45 (21)
Ij	172 (88), 155 (100), 82 (13), 69 (12), 45 (25)

hydroxide for 2 h, the solution was filtered with charcoal and made acid by addition of hydrochloric acid (1 : 1). The obtained acid *If* (3·8 g) was crystallised from water, m.p. 128—130°C.

4-Ethylthiomethyl-2-thiophenecarboxylic Acid (*Ig*)

Ethyl mercaptane (1·55 g; 25 mmol) was added at 5°C to a solution of sodium (0·55 g; 25 mgat) in methanol (30 ml). A solution of methyl 4-bromomethyl-2-thiophenecarboxylate (4·7 g; 20 mmol) in benzene (40 ml) was then added dropwise at 5°C to the above mixture in the course of 1 h. The reaction mixture was stirred for 2 h, concentrated to one third of its original volume on a rotatory evaporator, poured into water, extracted with dichloromethane and the extract was dried over magnesium sulphate. Distillation afforded 3·0 g (70%) of methyl 4-ethylthiomethyl-2-thiophenecarboxylate, b.p. 115—120°C/0·4 Torr. This ester was saponified by 2·5 hours' boiling with 10% potassium hydroxide solution (20 ml). Acidification with concentrated hydrochloric acid gave the acid *Ig* which after two crystallisations from aqueous ethanol melted at 80°C.

4-Phenylsulphonylmethyl-2-thiophenecarboxylic Acid (*Ih*)

A solution of methyl 4-bromomethyl-2-thiophenecarboxylate[1] (4·7 g; 20 mmol) and sodium benzenesulphinate (4·0 g; 20 mmol) in methanol (40 ml) and benzene (6 ml) was heated under reflux for 4 h, concentrated on an evaporator, poured into water and extracted with chloroform. The chloroform was distilled off and the residue (6·3 g) was boiled with a 10% sodium hydroxide solution (30 ml) for 4 h. The solution was filtered with charcoal and upon acidification with hydrochloric acid it afforded 4·6 g (81%) of the acid *Ih* which was crystallised from aqueous ethanol, m.p. 188—190°C.

4-Carboxymethyl-2-thiophenecarboxylic Acid (*Ii*)

Methyl 4-bromomethyl-2-thiophenecarboxylate[1] (4·7 g; 20 mmol) was added dropwise at room temperature to a stirred suspension of sodium cyanide (1·2 g; 24 mmol) in dimethyl sulphoxide (10 ml). The mixture was stirred for 5 hours and poured into water. The aqueous solution was extracted five times with chloroform, the extract was washed with water and dried over magnesium sulphate. Distillation afforded 2·7 g (75%) of methyl 4-cyanomethyl-2-thiophenecarboxylate, b.p. 110°C/0·2 Torr. ^{1}H-NMR spectrum: 3·75 (s, 2 H, CH_2), 3·89 (s, 3 H, OCH_3), 7·48 (m, 1 H, H-3), 7·69 (d, 1 H, H-5), $J_{3,5} = 1·6$ Hz. This nitrile was boiled with 10% potassium hydroxide (50 ml) for 20 hours, the solution was filtered with charcoal and acidified with hydrochloric acid. The obtained acid *Ii* (2·0 g) was crystallised from water and melted at 208—210°C.

2,4-Thiophenedicarboxylic Acid (*Ij*)

The acid *Ij* was prepared by hydrolysis of dimethyl 2,4-thiophenedicarboxylate[8] and purified by crystallisation from water, m.p. 280°C (reported[9] m.p. 280°C).

5-Methyl-3-thiophenecarboxylic Acid (*IIa*)

Zinc powder (20 g) was added portionwise in the course of 10 min to a stirred mixture of ethyl 5-chloromethyl-3-thiophenecarboxylate[10] (20 g; 0·1 mol) and acetic acid (58 ml) and dry hydrogen chloride was introduced into the mixture for 4 h. The mixture was stirred for 30 min at 55 to 60°C on a water bath, cooled and poured into an ice–water mixture (150 ml). The product was

taken into ether, the combined ethereal extracts were washed with water, sodium hydrogen carbonate solution and dried over magnesium sulphate. Distillation afforded 8·0 g (49%) of ethyl 5-methyl-3-thiophenecarboxylate, b.p. 105–107°C/15 Torr. The acid *IIa* was prepared by hydrolysis of the ester and upon crystallisation from water it melted at 128–130°C (reported[9] m.p. 131–132°C).

5-Bromomethyl-3-thiophenecarboxylic Acid (*IIb*)

The acid *IId* (3·0 g; 17·5 mmol) was treated as described for the preparation of the acid *Ib*, yield 3·9 g (100%) of the acid *IIb* which was sublimed at 130°C/0·06 Torr; m.p. 170–173°C.

5-Hydroxymethyl-3-thiophenecarboxylic Acid (*IIc*)

A stirred mixture of ethyl 5-chloromethyl-3-thiophenecarboxylate[10] (4·0 g; 20 mmol), fused sodium acetate (4·1 g; 50 mmol) and glacial acetic acid (40 ml) was refluxed for 6 h, cooled, poured into ice-cold water (60 ml) and extracted with ether. The ethereal extract was washed with water and sodium hydrogen carbonate solution and taken down. The residue was refluxed with 10% sodium hydroxide for 3 h, acidified with concentrated hydrochloric acid and the product was taken up into ether. The obtained acid *IIc* was crystallised from water, m.p. 135 to 136°C.

5-Methoxymethyl-3-thiophenecarboxylic Acid (*IId*)

A solution of ethyl 5-chloromethyl-3-thiophenecarboxylate[10] (10 g; 0·05 mol) and sodium methoxide (2·7 g; 0·05 mol) in methanol (80 ml) was refluxed for 6 h, concentrated to half of its volume, poured into water and extracted with ether. The extract was dried over magnesium sulphate, taken down and distilled, affording 6·1 g of ethyl 5-methoxymethyl-3-thiophenecarboxylate. This ester was boiled for 4 h with a 10% potassium hydroxide solution (40 ml), the mixture filtered with charcoal and the filtrate acidified with concentrated hydrochloric acid. The obtained acid *IId* (4·0 g) was crystallised from water, m.p. 73–74°C.

5-Phenoxymethyl-3-thiophenecarboxylic Acid (*IIe*)

A solution of ethyl 5-chloromethyl-3-thiophenecarboxylate[10] (4·0 g; 20 mmol) and sodium phenoxide (2·3 g; 20 mmol) in methanol (50 ml) was refluxed for 1 hour. The methanol was removed on an evaporator, the residue poured into water and extracted with ether. The ethereal solution was washed with 5% sodium hydroxide and water, taken down and the residue boiled with 10% sodium hydroxide and then acidified with concentrated hydrochloric acid. The obtained acid was crystallised from heptane, m.p. 124°C.

5-Mercaptomethyl-3-thiophenecarboxylic Acid (*IIf*)

The acid *IIf* was prepared from ethyl 5-chloromethyl-3-thiophenecarboxylate[10] in the same manner as described for the acid *If*. It was crystallised from water, m.p. 106–107°C.

5-Ethylthiomethyl-3-thiophenecarboxylic Acid (*IIg*)

The acid *IIg* was prepared from ethyl 5-chloromethyl-3-thiophenecarboxylate using the procedure described for the preparation of the acid *Ig*; m.p. 99–101°C (water).

5-Phenylsulphonylmethyl-3-thiophenecarboxylic Acid (*IIh*)

The acid *IIh* was prepared from ethyl 5-chloromethyl-3-thiophenecarboxylate similarly as described for the preparation of the acid *Ih*. It was crystallised from aqueous ethanol, m.p. 197 to 199°C.

5-Carboxymethyl-3-thiophenecarboxylic Acid (*IIi*)

Preparation of the acid *IIi* from ethyl 5-chloromethyl-3-thiophenecarboxylate was similar to the preparation of the acid *Ii*. On crystallisation from water the acid melted at 210°C.

Note added in proof: Acid *Ia* (X = H) was prepared using method described earlier[1].

REFERENCES

1. Němec M., Janda M., Šrogl J., Stibor I.: This Journal *39*, 3527 (1974).
2. Exner O., Jonáš J.: This Journal *27*, 2296 (1962).
3. Roberts J. D., Moreland W. T.: J. Amer. Chem. Soc. *75*, 2167 (1953).
4. Exner O.: This Journal *31*, 65 (1966).
5. Janda M., Dvořák F., Exner O.: This Journal *27*, 1191 (1962).
6. Exner O., Simon W.: This Journal *29*, 2016 (1964).
7. Exner O.: Tetrahedron Lett. *1963*, 815.
8. Janda M., Šrogl J., Němec M., Stibor I.: Org. Prep. Proc. Int. *3*, 295 (1971).
9. Hartough H. D.: *Thiophene and Its Derivatives*, p. 199. Interscience, New York 1952.
10. Sojka J.: *Thesis*. Prague Institute of Chemical Technology, Prague 1969.

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