Synthesis and examination of transmission of the substituent effect in dimethyl 4-X-2,3-thiophenedicarboxylates

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Dimethyl 4-X-2,3-thiophenedicarboxylates (X = NH$_2$, NHCOCH$_3$, H, Cl, Br, I, CN, NO$_2$) were synthesized and their i.r. and ^{1}H-n.m.r. spectra were measured. The correlations between the respective $\nu(C=O)_I$, $\nu(C=O)_{II}$ and chemical shift (p.p.m.) of the proton at C-5, and constants of substituents were studied. Best correlativities for transmission in *ortho* position 3—4 with σ_m^+ constants and in *ortho* position 2—3 with σ_p constants were ascertained.

Осуществлен синтез диметиловых эфиров 4-X-2,3-тиофендикарбоксильных кислот (X = NH$_2$, NHCOCH$_3$, H, Cl, Br, I, CN, NO$_2$). Измерены их ИК спектры и спектры ЯМР ^{1}H. Были получены отдельные корреляции между $\nu(C=O)_I$ и $\nu(C=O)_{II}$ и константами заместителей, химическим сдвигом (млн. д.) протона в положении 5 и константами заместителей. Самая хорошая корреляция была обнаружена между переносом в орто-положении 3—4 и константами σ_m^+ и также в орто-положении 2—3 и σ_p константами.

The preparation of dimethyl 2,3-thiophenedicarboxylate according to [1] proceeds through dimethyl 4-amino-2,3-thiophenedicarboxylate. Synthesis of this ester stimulated us to utilize this compound for preparation of further 4-substituted dimethyl 2,3-thiophenedicarboxylates *via* the appropriate diazonium salts. Although analogous preparations have been well elaborated with various benzene derivatives, no detailed study appeared with thiophene ring compounds and nothing has been reported with this type of substances. In addition to the preparation of the hitherto unpublished dimethyl 4-X-2,3-thiophenedicarboxylates by this procedure, transmission of substituent effects through thiophene backbone was studied. Only recently several authors *e.g.* [2—10] paid attention to this problem. The majority of papers, concerning these problems, stated that the substituent effects were transmitted through the 2—3 positions differently from the 3—4 position. Some papers reported (*e.g.* [4]) that electronic effects were transmitted through the 2—3 position (hyper-*ortho* position) by 100% better than through the 3—4 position (hypo-*ortho* position), which is surely due to certain

localization of the π bond between carbons 2—3, or 4—5. On the other hand, effects of substituents more considerably influenced the pK_a value of 4-X-3-thiophenecarboxylic acids, than that of 3-X-2-thiophenecarboxylic, or 2-X-3-thiophenecarboxylic acids [9]. The question of using linear relationships for correlations in *ortho* positions has been discussed in detail [9]; the successful application of the *ortho* correlation in a 5-membered ring in contrast to a 6-membered one was evidenced. The use of substituent constants remained an open question, since σ_p^- [4], σ_p [9], and also σ_m [9] constants were employed. The study of transmission of substituent effects through thiophene ring was complicated by a rather tedious preparation of greater series of thiophene derivatives, so that conclusions were made from a small number of compounds only. The aim of this paper was to contribute to the solution of these questions.

Experimental

Infrared spectra of CCl_4 solutions were taken with a Perkin—Elmer, model 567 apparatus. The spectrometer was calibrated against a polystyrene foil in the region of the carbonyl group vibration with respect to the band at 1603 cm^{-1}. The ^{1}H-n.m.r. spectra (p.p.m., δ scale) were recorded with a Tesla 80 instrument operating at 80 MHz ($CDCl_3$ solutions containing tetramethylsilane as an internal reference).

Dimethyl 4-amino-2,3-thiophenedicarboxylate (*I*), dimethyl 4-acetamido-2,3-thiophenedicarboxylate (*II*), and dimethyl 2,3-thiophenedicarboxylate (*III*) were prepared according to [1].

Dimethyl 4-chloro-2,3-thiophenedicarboxylate (IV)

To a solution of *I* (3.5 g; 16 mmol) in concentrated HCl (6.5 ml) sodium nitrite (1.13 g) in water (6.5 ml) was added at 0°C with stirring; this diazonium salt was poured into a fresh prepared solution of Cu_2Cl_2 (22 mmol) in concentrated HCl (8.8 ml). The reaction mixture was heated on a steam bath till the evolution of nitrogen ceased. The crude product was extracted with diethyl ethher, washed with a 10% solution of $NaHCO_3$, water and dried. The solvent being removed, the residue was separated on a silica gel-packed column (Silica gel L 100/250) with benzene—ethyl acetate (5:1) as an eluent. Dimethyl 4-chloro--2,3-thiophenedicarboxylate was eluted as first.

Dimethyl 5-(2,3-dimethoxycarbonyl-4-thiopheneazo)-4-hydroxy-2,3-thiophenedicarboxylate (*IX*) was present in the next chromatographic band. M.p. 216—217°C, yield 0.56 g (8%). For $C_{16}H_{14}N_2O_9S_2$ (442) calculated: 43.44% C, 3.17% H, 6.33% N, 14.48% S; found: 43.44% C, 3.05% H, 6.32% N, 14.47% S. ^{1}H-NMR spectrum (p.p.m., δ scale): 3.85 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 4.00 (s, 3H, CH_3), 7.48 (s, 1H, 5-H), 14.20 (s, 1H, OH).

Dimethyl 5-(2,3-dimethoxycarbonyl-4-thiophenazo)-4-amino-2,3-thiophenedicarboxylate (*X*) was isolated from the third band. M.p. 166—167°C, yield 0.35 g (5%). For $C_{16}H_{15}N_3O_8S_2$ (441) calculated: 43.54% C, 3.40% H, 9.52% N, 14.51% S; found: 43.41% C, 3.34% H, 9.62% N, 14.53% S. ^{1}H-NMR spectrum: 3.88 (s, 9H, CH$_3$), 3.93 (s, 3H, CH$_3$), 6.12 (s, 2H, NH$_2$), 7.81 (s, 1H, 5-H).

Dimethyl 4-bromo-2,3-thiophenedicarboxylate (V)

Sodium nitrite (1.13 g) in water (6.5 ml) was added to *I* (3.5 g) suspended in concentrated HBr (4.0 ml) at 0°C; the diazonium salt was added to a fresh prepared Cu_2Br_2 (22 mmol) in concentrated HBr (12.8 ml) at the same temperature and further proceeded as with preparation of *IV*.

Dimethyl 4-iodo-2,3-thiophenedicarboxylate (VI)

A solution of sodium nitrite (1.13 g) in water (3.5 ml) was added under stirring to *I* (3.5 g) dissolved in concentrated HCl (16 ml) at 0°C. The homogeneous paste thus formed was added to potassium iodide (2.6 g) dissolved in water (3 ml) with stirring at 0°C and further proceeded as with *IV*.

Dimethyl 4-cyano-2,3-thiophenedicarboxylate (VII)

Compound *I* (3.5 g) was dissolved in 65% sulfuric acid (15 ml) and stirred with a finely crushed ice till a homogeneous paste was formed. A solution of sodium nitrite (1.13 g) in water (2 ml) was added during 10 min to the paste cooled to 0°C. Fresh prepared solution containing CuCN (20 mmol) and KCN (50 mmol) in water (15 ml) was added to the diazonium salt at 0°C and proceeded as given with *IV*.

Dimethyl 4-nitro-2,3-thiophenedicarboxylate (VIII)

A solution of sodium nitrite (1.22 g) in water (1.5 ml) was poured with stirring to *I* (3.5 g) dissolved in concentrated HCl (8.1 ml) and cooled to − 5°C. Fluoroboric acid (40%, 4.40 g) was added to the solution of diazonium salt and stirred for 20 min. The tetrafluoroborate was filtered off with suction, washed with water (1 ml), methanol and diethyl ether. 2,3-Dimethoxycarbonyl-4-thiophenediazonium tetrafluoroborate formed was first dried in air, and then in a desiccator over calcium chloride *in vacuo* for 2 days. Yield 4.31 g (85%). This product (4.3 g) was added at room temperature to a solution of sodium nitrite (8.6 g) in water (17.5 ml) in which powdered copper (2.15 g) was suspended. The end of this reaction was indicated with a drop of alkaline solution of 2-naphthol. The work-up was the same as with *IV*.

Yields, melting points, and analytical data of compounds *I—VIII* are listed in Table 1, their spectral data in Table 2.

Table 1

Dimethyl 4-X-2,3-thiophenedicarboxylates

| Compound	Formula	M_r	Calculated/found				Yield		M.p., °C
			% C	% H	% S	% N	g	%	
I	$C_8H_9NO_4S$	215.1	44.64	4.18	14.91	6.51	49.3	68	60—61
			44.64	4.17	14.97	6.48			
II	$C_{10}H_{11}NO_5S$	257.0	46.69	4.28	12.48	5.45	3.24	76	99—100
			46.98	4.37	12.72	5.46			
III	$C_8H_8O_4S$	200.2	47.95	4.00	15.98		3.36	52	33—34
			47.86	3.95	16.07				
IV	$C_8H_7ClO_4S$	234.7	40.90	2.98	13.66		1.22	32	65—67
			40.47	2.88	13.16				
V	$C_8H_7BrO_4S$	297.0	34.41	2.51	11.49		1.28	29	77—78
			34.30	2.63	11.47				
VI	$C_8H_7IO_4S$	326.0	29.45	2.15	9.84		0.73	15	63—64
			30.13	2.13	9.73				
VII	$C_9H_7NO_4S$	225.2	47.96	3.11	14.22	6.22	0.63	17	90—91
			48.09	3.08	14.26	5.86			
VIII	$C_8H_7NO_6S$	245.2	39.15	2.85	13.05	5.71	1.22	40	119—120
			39.18	2.75	13.01	5.67			

Table 2

IR and ^{1}H-NMR spectral data of dimethyl 4-X-2,3-thiophenedicarboxylates

Compound	$\nu(C=O)_I$ cm^{-1}	$\nu(C=O)_{II}$ cm^{-1}	$\Delta\bar{\nu}$ cm^{-1}	δ_{5-H} (p.p.m.)
I	1734	1714	20	6.29
II	1737	1704	33	8.13
III	1739	1734	5	7.46
IV	1750	1734	16	7.35
V	1750	1733	17	7.45
VI	1748	1733	15	7.61
VII	1743	1736	8	8.05
VIII	1757	1742	15	8.45

IR: CCl_4, 25°C.
^{1}H-NMR: $CDCl_3$, 25°C, 80 MHz, tetramethylsilane.

Results and discussion

Diazotization of the starting dimethyl 4-amino-2,3-thiophenedicarboxylate followed by replacement of the diazonium group for chlorine, bromine, iodine, and a cyano group (Scheme 1) afforded the respective products in up to 30% yields;

	X		R
I	NH$_2$	IX	OH
II	NHCOCH$_3$	X	NH$_2$
III	H		
IV	Cl		
V	Br		
VI	I		
VII	CN		
VIII	NO$_2$		
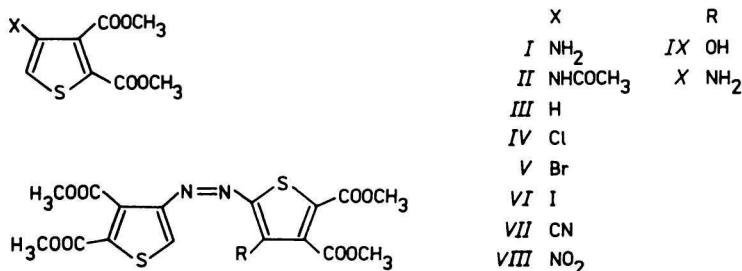
Scheme 1

these were lower than those obtained when replacing the diazonium group in benzene. Substitution of the diazonium group by a nitro group proceeded in relatively good yields from the proper diazonium tetrafluoroborate, whilst substitution of the same group by a methoxy grouping according to [11] failed.

As found, all diazonium salts of *I* furnished with the unreacted *I* the azo compound *IX*, or with dimethyl 4-hydroxy-2,3-thiophenedicarboxylate, originating from the diazonium salt, the azo compound *X* by an S_E reaction under conditions described in Experimental. Formation of the above-mentioned azo compounds in yields up to 15% is certainly associated with an enhanced ability of thiophene to undergo electrophilic substitutions in position 2.

Infrared spectra of dimethyl 4-X-2,3-thiophenedicarboxylates were characteristic of two $\nu(C=O)$ absorption bands, compound *VIII* with three bands being the exception. Bands at 1757 and 1742 cm^{-1} of compound *VIII* were ascribed to stretching (C=O) vibrations on the basis of intensity comparisons. From data obtained from compounds *I—VIII* (Table 2) the stretching (C=O) vibrations can be classified into two series: the first one with higher wavenumbers (1757—1734 cm^{-1}) denoted as $\nu(C=O)_I$ and the second one with lower wavenumbers (1742—1714 cm^{-1}), $\nu(C=O)_{II}$.

The wavenumber associated with the stretching (C=O) vibration of methyl 3-thiophenecarboxylate is higher (1714 cm^{-1}) than that of methyl 2-thiophenecarboxylate (1710 cm^{-1}) and therefore, $\nu(C=O)_I$ can be assigned, with a great deal of probability, the methoxycarbonyl group in position 3 and $\nu(C=O)_{II}$ the methoxycarbonyl group at C-2 of the thiophene ring.

The wavenumber significantly altered with the change of the substituent X. This fact stimulated us to correlate the constants of substituents in position 4 with wavenumbers $v(C=O)_I$ and $v(C=O)_{II}$, respectively. The measured wavenumber values were correlated with σ_p, σ_m, σ_p^+, and σ_m^+ constants. The statistically most significant correlations were found between $v(C=O)_I$ and σ_m^+ constants of substituents ($r = 0.989$), and between $v(C=O)_{II}$ and σ_p^+ constants of substituents ($r = 0.969$) (Table 3). The measured pK_a values of 4-X-3-thiophenecarboxylic acids best correlate [9] with σ_m constants; this finding is in a good agreement with assignment of the $v(C=O)_I$ to the methoxycarbonyl group in position 3. The best accord of σ_m^+ constants in transmission of the substituent effects from position 4 to position 3 (the hypo-*ortho* position) is due to the structure of the thiophene skeleton, where the character of the bond between C-3 and C-4 approached a single bond and the σ_m constant preponderantly involved the induction effect; of course, the conjugation effect could also not be neglected ($\sigma_m = \sigma_I + 0.33\ \sigma_R$). The high value for $\varrho_I = 27.5$ indicated a relatively high transmission of the substituent effect, although, as already noticed, a transmission through a hypo-*ortho* position was involved. Considering the $v(C=O)_{II}$ correlation, concerning the transmission of the substituent effect from position 4 to position 2, the statistically best correlations were achieved with σ_p^+ and σ_p constants (Table 3). Here, a considerable role is also played by the conjugation effect, which is in agreement with the π electron distribution patterns through thiophene ring (the enhanced localization of the π bond between carbons 2 and 3). Transmissions of substituent effects proceed better into position *ortho* than *meta*, as evidenced by the measured values $\varrho_I = 27.5$ and $\varrho_{II} = 12.4$. Their ratio $\varrho_I/\varrho_{II} = 2.21$ is in a good accordance with that (2.05) reported in [10] for the substitution rate of replacement of bromine from

Table 3

Statistical evaluation of correlations of $v(C=O)$ with substituent constants[a]

$v(C=O)$	Substituent constants	r[b]	ϱ[c]	v_0[d]	s[e]	s_ϱ[f]	s_q[g]
I	σ_p	0.893	17.77	1743.3	3.52	0.58	3.18
I	σ_m	0.962	26.80	1738.9	0.88	0.86	1.27
I	σ_p^+	0.892	10.84	1746.5	4.22	−0.13	2.74
I	σ_m^+	0.989	27.52	1738.6	0.42	0.43	0.63
II	σ_p	0.959	19.15	1729.2	2.94	0.87	2.83
II	σ_m	0.802	26.60	1721.4	7.66	9.32	9.43
II	σ_p^+	0.969	12.42	1731.4	2.32	0.28	1.39
II	σ_m^+	0.819	23.00	1725.2	4.68	5.32	6.07

a) $n = 7$; b) correlation coefficient; c) line slope; d) wavenumber intercept; e) residual scattering; f) standard deviation ϱ_0; g) standard deviation q.

2-nitro-3-bromo-4-X-thiophene and 2-nitro-3-bromo-5-X-thiophene by sodium benzenethiolate.

Position of the chemical shift value of the proton in position 5 of the thiophene ring altered due to the substituent X of dimethyl 4-X-2,3-thiophenedicarboxylate (Table 2) and therefore, we correlated the chemical shift value (δ, p.p.m.) with substituent constants, which proved to be helpful for investigation of transmission of the substituent effect through position 2—3 (hyper-*ortho* position). The measured 5-H proton signal value δ was correlated with σ_p, σ_p^+, σ_m, and σ_m^+ substituent constants. Statistical evaluation of linear correlations showed that the best correlability was with σ_p constants of substituents (Table 4). In this case, transmission from position 4 into position 5 (hyper-*ortho* position) was involved, where also conjugation effect was taken into account, as already mentioned. Therefore, and in accord with the structure of thiophene and other investigations [6, 10] σ_p constants best fit for positions 2—3.

Although the study [12] claimed that $\delta_{\alpha-H} > \delta_{\beta-H}$ for thiophene, statistically better results were obtained when ascribing reverse values. A statistically unsatisfying value for NHCOCH$_3$ could be rationalized by an anisotropic effect of this group [12] evidently arising mostly with *ortho*-proton signals. The downfield shift of the 5-H proton signal of dimethyl 4-halo-2,3-thiophenedicarboxylates is proportional to the increasing molecular mass of the halogen; this was also observed with halogen derivatives of benzene [12].

As known, the transmission of the substituent effect of a thiophene system is by 1.1—1.3 times more effective than that of benzene [3, 9]. Aimed to compare this value (obtained for position 2—5) with our series of compounds (position 2—3), theoretical values of chemical shifts of 5-H protons were calculated from an analogous relationship as derived for the *ortho* position of benzene [12]: $\delta_{ortho} = 7.46 + \sigma_{os}$, where σ_{os} is the substitution increment calculated for *ortho* position from ^{1}H-n.m.r. spectral data of benzene derivatives. A series of chemical shift

Table 4

Statistical evaluation of correlations of chemical shifts of 5-H protons (p.p.m.) with substituent constants, $n = 7$

	Substituent constants	r	ϱ	ν_0	s	s_ϱ	s_q
	σ_p	0.972	1.38	7.24	0.17	0.07	0.14
δ_{5-H}	σ_m	0.892	1.98	6.89	0.33	0.37	0.44
4-X	σ_p^+	0.940	0.91	7.41	0.25	0.04	0.14
	σ_m^+	0.879	1.98	6.89	0.35	0.41	0.48

values obtained in this way would fully satisfy providing the transmission through the thiophene ring be equally effective as through the benzene ring. Quantitative expression of the difference in effectiveness of transmission of the substituent effect

Table 5

Comparison of the effectiveness of transmission of the substituent effect at the thiophene and benzene systems

X	σ_{os}	σ_{ortho}	δ_{5-H}	$\delta_{5-H} = f(\delta_{ortho})$
NH₂	-0.75	6.71	6.29	$r = 0.987$
H	0.00	7.46	7.46	$\varrho = 1.225$
Cl	0.03	7.49	7.35	$v_0 = -1.87$
Br	0.18	7.64	7.45	$n = 7$
I	0.39	7.85	7.61	$s = 0.125$
CN	0.36	7.82	8.05	$s_\varrho = 1.872$
NO₂	0.95	8.41	8.45	$s_q = 0.101$

in both systems is the line slope of the function $\delta_{5-H} = f(\delta_{ortho})$, where δ_{ortho} is the calculated chemical shift value for *ortho* position, and δ_{5-H} the actual value. The found value $\varrho = 1.23$ (Table 5) indicates that transmission from position 3 to position 2 (hyper-*ortho* position) is greater than transmission into *ortho* position in benzene.

Results from the i.r. and ^{1}H-n.m.r. spectral data are in a good agreement particularly with those reported in [9].

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