CARBON-13 NMR CHEMICAL SHIFTS OF ALKYL 3-HYDROXYTHIOPHENE-2-CARBOXYLATES AND 3-ALKYLAMINO-1-(3-THIENYLOXY)-2-PROPANOLOLS

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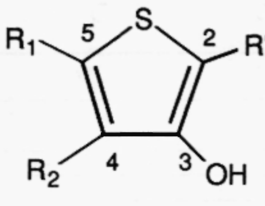
ABSTRACT:

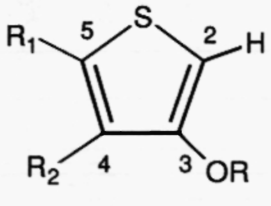
A compilation of ^{13}C NMR chemical shifts for 35 thiophene derivatives of types **Ia** and **Ib** is reported. The data have been analyzed assuming an additive model $\delta_n = a_0 + \Sigma a_i x_i$, where n is the thiophene carbon considered (n = 2-5) and a_i the contribution of each substituent (x_i = 1 if the substituent is present and x_i = 0 if absent).

INTRODUCTION

Alkyl 3-hydroxythiophene-2-carboxylates, of structural formula **Ia** (1,2) are valuable intermediates for the preparation of 3-thienyloxopropanolamines **Ib**, which can be regarded as thiophene isosteres of β-adrenergic blocking (3-5) and platelet antiaggregant agents (6). We have described the synthesis and biological activities of these compounds elsewhere (7,8) and we now wish to report the ^{13}C NMR data of both these series.



Ia



Ib

EXPERIMENTAL

^{13}C NMR spectra were measured at room temperature on a Varian XL300 spectrometer working at 7.05 T, 10% solutions in $CDCl_3$ was used for **Ia** and 10% solutions in [$^2H_6$]DMSO for **Ib** (maleate salts). Chemical shifts are in ppm (δ).

Table 1. ^{13}C Chemical shifts of thiphene derivatives **Ia** and **Ib**

		Ia		**Ib**			**Ia**					**Ib**	
Comp.	R_1	R_2	R'	R	C-2	C-3	C-4	C-5	Comp.	C-2	C-3	C-4	C-5
1	H	H	$CO_2C_2H_5$	a	103.6	164.4	119.9	131.3	**22**	98.5	157.0	119.3	125.4
2	CH_3	H	CO_2CH_3	--	101.5	164.5	117.7	147.0					
3	C_6H_5	H	CO_2CH_3	--	103.6	164.5	114.6	149.1					
4	CH_3	CH_3	CO_2CH_3	--	99.5	163.3	124.6	140.7					
5	C_6H_5	CH_3	CO_2CH_3	--	101.7	163.3	124.4	144.0					
6	H	C_6H_5	CO_2CH_3	a	104.5	162.0	132.5	133.2	**23**	99.4	153.9	122.5	127.0
7	H	CH_3	CO_2CH_3	a	103.2	163.1	127.0	128.5	**24**	97.6	155.0	120.4	128.2
8	$-CH(CH_3)(CH_2)_3-$		CO_2CH_3	a	99.8	162.4	126.5	149.9	**25**	94.0	153.7	126.5	141.0
9	$-(CH_2)_2CH(CH_3)CH_2-$		CO_2CH_3	a	100.1	162.6	127.0	143.4	**26**	94.0	153.6	126.9	135.9
10	$-(CH_2)_5-$		$CO_2C_2H_5$	a	99.4	162.7	131.4	148.0	**27**	92.3	154.0	131.0	138.4
11	$-(CH_2)_6-$		$CO_2C_2H_5$	a	100.2	162.7	129.5	146.4	**28**	96.8	154.0	128.9	136.8
12	$-CH_2-S-CH_2-$		CO_2CH_3	--	106.9	158.1	134.3	145.9					
13	$-(CH_2)_2-S-$		CO_2CH_3	a	106.2	157.7	129.5	140.7	**29**	101.2	149.6	128.9	132.5
14	$-(CH_2)_2-S-CH_2-$		CO_2CH_3	a	98.1	160.4	121.8	142.0	**30**	93.1	153.1	122.8	134.6
15	$-(CH_2)_3-S-$		CO_2CH_3	a	100.1	160.1	117.7	134.6	**31**	95.0	151.8	117.0	127.0
16	$-CH_2-S-CH_2-S-$		CO_2CH_3	--	100.0	160.3	118.5	129.6					
17	$-CH=CH-S-$		CO_2CH_3	a	103.4	157.4	140.9	141.7	**32**	99.7	149.4	135.6	137.7
18	Cl	H	CO_2CH_3	--	105.5	162.6	119.1	136.8					
19	Cl	Cl	CO_2CH_3	a	100.8	158.2	116.3	132.1	**33**	97.5	149.8	114.5	122.6
20	H	Cl	CO_2CH_3	a	109.7	159.6	123.0	125.4	**34**	99.7	151.2	115.5	120.6
21	Cl	CH_3	CO_2CH_3	a	100.4	161.8	126.6	133.1	**35**	95.6	153.1	122.8	126.3

a R' = $CH_2CHOHCH_2NH\textit{t}Bu$

RESULTS AND DISCUSSION

The ^{13}C NMR shifts of carbons C-2, C-3, C-4 and C-5 of the thiophene ring are gathered in Table 1. Instead to discuss these data in a conventional way, we have preferred to use a Free-Wilson matrix which we have succesfully employed to rationalize ^{13}C NMR chemical shifts (9-11). Thus, the data have been analyzed assuming an additive model $\delta_n = a_0 + \Sigma a_i x_i$, where n is the thiophene carbon considered (n = 2-5) and a_i the contribution of each substituent ($x_i = 1$ if the substituent is present and $x_i = 0$ if absent). For 35 compounds, the squared correlation coefficients are always larger than 0.9, showing that the interaction between substituents is not important. For instance, Table 2 contains the a_i values for substituents CH_3, C_6H_5 and Cl at positions 4 and 5.

Table 2. Coefficients of the contribution of substituents to the ^{13}C chemical shifts

Position-4	C-2	C-3	C-4	C-5
CH_3	-1.78	-1.34	6.71	-3.10
C_6H_5	-0.41	-2.53	8.85	0.40
Cl	0.86	-4.93	-0.57	-6.30
Position-5				
CH_3	-3.75	-0.02	-2.17	12.26
C_6H_5	-2.10	-0.02	-3.82	14.96
Cl	-2.59	-1.69	-1.51	3.55

For CH_3 and Cl these coefficients are in good agreement with those calculated by Gronowicz (12) for monsubstituted thiophenes. The coefficients for the phenyl group are new; they are strongly dependent on the position of the phenyl ring (compare the *ipso* effects 4-Ph on C-4 = 8.8 and 5-Ph on C-5 = 15.0 ppm) and on the considered carbon (compare the *ortho* effects 4-Ph on C-3 = -2.5, 4-Ph on C-5 = 0.4 and 5-Ph on C-4 = -3.8 ppm).

Compounds **25**, **27**, **28** and **35** show antiplatelet activity at DI_{50} (mg/mL) < 50. Essays of correlation between antiplatelet activity (**Ib** series) and Table 1 chemical shifts proved unsuccessful.

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