^{13}C-NMR SPECTRAL DATA FOR SUBSTITUTED THIENO[2,3-*b*]- AND THIENO[3,2-*b*]PYRIDINES AND THE CORRELATION OF IPSO SUBSTITUENT CHEMICAL SHIFTS

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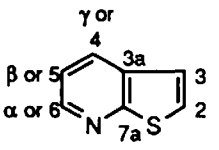
Abstract: The ^{13}C NMR chemical shifts in $CDCl_3$ for the parent thieno[2,3-*b*]- and thieno[3,2-*b*]pyridines and 44 of their monosubstituted derivatives are reported. Linear correlations of ipso substituent chemical shifts in these compounds and in the corresponding benzene derivatives are found and are compared with reported data for compounds with substituted pyridine or thiophene rings. In the two thienopyridine systems the slope of the correlation line characterizes the position of substitution with respect to the heteroatom in the substituted ring.

Introduction

Various research groups obtained ^{13}C NMR spectra of a number of simple monosubstituted thiophenes (1,2), pyridines (3), thienothiophenes (4), and isoquinolines (5). These workers directed special attention to the ipso substituent chemical shift (ISCS), i.e. the difference in chemical shifts between the substituted carbon atom in the derivative and that in its parent compound (with H attached to the carbon). Meanwhile, literature ISCS values for monosubstituted benzenes were accumulated in a table by Ewing (6), who noted that theoretical calculations were inadequate to account for these data (7). Nonetheless, as shown in references 1-5, if one keeps the solvent and the position of substitution on the heterocyclic ring constant one obtains a linear plot for ISCS for the heterocyclic system versus ISCS for the same array of substituents in the benzene system. In the present paper we report ^{13}C NMR data for chemical shifts in the parent system thieno[2,3-*b*]pyridine **1** and 25 of its derivatives **2**-**26**, as well as the parent system thieno[3,2-*b*]pyridine **27** and 19 of its derivatives **26**-**46** (see Tables 1 and 2). Data derived from ISCS plots are also presented (see Tables 3 and 4).



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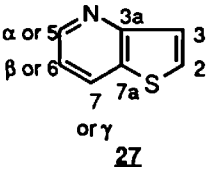

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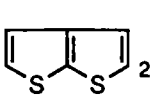

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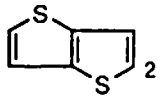

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Experimental and Procedure

Compounds **1**-**46** were available from previous studies (8-17) and were converted to analytical purity before use. ^{13}C NMR spectra were obtained on a Nicolet NTC-360 FT NMR instrument with 12-mm tubes containing 0.2-6% (wt/wt) solutions of these compounds in $CDCl_3$, plus tetramethylsilane as an internal standard. Both proton-coupled and proton-decoupled spectra were used, to aid in the positional assignments of frequencies and to correlate specific ^{13}C signals with specific ^{1}H signals previously reported. ^{13}C chemical shifts for system **1** are given in Table 1, while those for system **27** are shown in Table 2. Data are estimated to be accurate to ±0.1 ppm in most cases. One-bond CH coupling constants

were also measured for the protons in the thiophene rings of the parent systems **1** and **27** as well as their 2- and 3-mono-substituted derivatives **2**-**9** and **28** **38** to an accuracy of ±1 Hz. Thienopyridine ISCS values for those functional groups which also appear in the table of Ewing (6) are collected in Table 3. These thienopyridine values were plotted versus those for the benzene system by means of a Mathcad computer program (18) which determines the least-squares linear fit of the data and calculates the slope *k* and intercept *c* of the line as well as the correlation coefficient *r* for the data. The numerical results are presented in Table 4.

Table 1: ^{13}C NMR Chemical Shifts (δ) for Substituted Thieno[2,3-*b*]pyridines[a]

Comp.	Substituent	C-2	C-3	C-3a	C-4	C-5	C-6	C-7a	Other C[b]	
1	none	126.9	121.4	132.4	130.9	119.3	146.4	161.8		
2	2-C(=O)H	143.0	130.6	132.1	133.8	120.5	150.3	163.6	184.8	
3	2-C(=O)CH_3	143.6	127.0	132.8	133.5	120.3	149.7	163.5	192.1	26.6
4	3-NO_2	132.4	140.2	124.4	132.2	121.9	148.7	159.3		
5	3-NH_2	100.4	136.1	126.9	127.5	118.5	146.7	161.0		
6	3-NHC(=O)CH_3	114.0	126.7	126.4	127.4	118.9	147.0	159.6	168.5	23.9
7	3-Cl	121.4	118.8	129.8	129.4	119.8	147.6	159.6		
8	3-Br	124.2	105.2	131.3	130.7	120.0	147.5	159.9		
9	3-I	129.9	75.3	134.1	132.7	120.3	147.5	160.0		
10	4-CH_3	126.1	119.6	132.7	142.0	120.2	146.5	161.6	19.1	
11	4-Cl	127.8	119.7	131.5	138.5	119.6	146.9	162.6		
12	4-NH_2	123.4	116.9	120.4	148.1	104.0	147.7	163.0		
13	5-Cl	129.4	120.8	133.3	130.2	128.3	145.5	159.5		
14	5-NO_2	131.1	122.2	130.7	126.1	141.8	141.4	166.5		
15	5-NH_2	127.8	120.7	133.1	115.3	139.7	137.3	152.4		
16	5-CN	130.1	121.3	131.6	134.4	105.4	147.7	164.8	117.3	
17	5-C(=O)CH_3	128.7	122.2	132.0	130.8	128.7	146.6	165.5	196.6	26.9
18	5-C(=O)OCH_3	128.6	122.0	132.0	132.5	122.2	147.2	165.3	166.1	52.4
19	5-CH_2CH_3	127.1	121.2	132.6	129.8	135.2	147.3	159.4	26.0	15.8
20	6-Cl	127.4	121.1	131.3	133.1	120.1	147.9	161.1		
21	6-CN	132.1	121.5	134.7	131.6	123.4	129.4	162.2	117.6	
22	6-C(=O)CH_3	131.0	121.5	134.9	131.3	117.4	150.5	160.7	199.7	25.8
23	6-C(=O)NH_2	130.0	121.6	134.8	131.9	118.2	146.5	160.2	166.7	
24	6-C(=S)NH_2	130.6	121.6	134.7	131.4	121.1	147.4	159.3	195.6	
25	6-C(=NH)NH_2	129.0	121.5	133.6	131.6	116.7	147.8	160.3	160.8	
26	6-C(=NH)OCH_3	129.4	121.3	133.8	131.8	116.9	144.5	161.3	166.7	54.0

a) Chemical shifts are in ppm from tetramethylsilane in $CDCl_3$ as solvent. b) Listed in order of the carbon atoms in the substituent as shown in the second column.

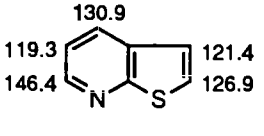
Table 2: ^{13}C NMR Chemical Shifts (δ) for Substituted Thieno[3,2-*b*]pyridines[a]

Comp.	Substituent	C-2	C-3	C-3a	C-5	C-6	C-7	C-7a	Other C[b]	
27	none	130.5	125.1	156.0	147.2	118.5	130.3	133.0		
28	2-Cl	137.2	124.1	154.9	147.7	119.0	129.5	133.1		
29	2-Br	120.9	127.9	155.7	147.6	118.9	129.3	135.1		
30	2-I	84.1	134.8	156.6	147.4	118.7	128.9	138.3		
31	2-C(=O)H	145.9	134.6	154.6	149.0	121.7	131.4	136.9	184.6	
32	2-CH_2OH	151.1	121.1	155.6	146.7	118.5	130.6	133.7	60.5	
33	2-C(=O)CH_3	146.9	130.2	155.1	148.6	121.2	131.0	136.9	192.1	26.8
34	2-CN	113.8	135.7	153.4	149.4	121.5	130.5	135.4	113.8	
35	3-Cl	124.8	122.8	150.5	147.9	119.6	131.0	132.2		
36	3-Br	127.4	110.0	151.8	148.1	119.5	130.9	132.1		
37	3-I	132.5	82.3	154.5	148.2	119.4	130.6	131.4		
38	3-NO_2	135.4	142.2	145.6	150.0	120.7	131.4	133.0		
39	5-Cl	132.2	124.5	155.8	149.1	119.3	132.6	131.6		
40	5-CN	133.7	125.0	156.7	130.9	122.1	131.4	136.2	117.7	
41	5-C(=O)NH_2	132.2	124.8	154.7	147.3	117.2	131.4	136.0	167.2	
42	5-C(=S)NH_2	132.5	124.9	153.7	148.4	120.0	131.0	136.0	196.2	
43	6-C(=O)CH_3	135.3	125.2	158.7	147.7	127.5	130.7	132.8	196.2	26.9
44	7-Cl	131.4	125.8	157.4	148.0	118.6	138.2	132.9		
45	7-NH_2	128.0	126.1	157.5	148.6	103.4	147.9	119.3		
46	7-NO_2	135.5	125.3	160.8	148.3	112.0	148.5	125.2		

a) See footnote *a*, Table 1. b) See footnote *b*, Table 1.

Discussion of Results

The following figures compare the ^{13}C NMR chemical shifts for positions in the heterocyclic rings of our parent thienopyridines with those of thiophene, benzo[*b*]thiophene, pyridine and quinoline—all compared to trimethylsilane as a reference (19,20).



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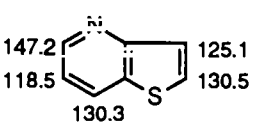

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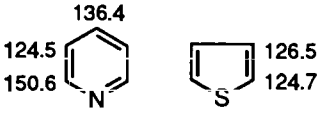

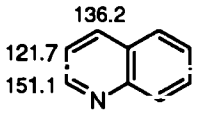

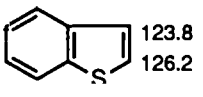

First one notes that the chemical shifts of the α, β and γ carbons, respectively, in the pyridine rings of 1 and 27 are closely similar, i.e. less than one ppm different. Thus, the orientation of the fused thiophene ring in the two systems has very little

difference in its interring effect. The order of the shifts is α > γ > β, the same as in pyridine and quinoline, though the fused thiophene ring causes all of the shifts to be smaller in **1** and 27. In contrast, signals for C-2 and C-3 in the thiophene ring of **27** fall 3.6-3.7 ppm downfield from those of **1**. The order of shifts 2- > 3- for the thienopyridines is the same as reported for benzo[*b*]thiophene (20), but the reverse of the order for thiophene (19). Therefore, to corroborate our positional assignments of the C-2 and C-3 signals in **1** and **27** we also measured the one-bond CH coupling constants ($^1J_{CH}$ = 184 and 170 Hz, respectively, in **1** and 186 and 172 Hz in **27**). These were then compared with the corresponding coupling constants found in the 3- and 2-monosubstituted derivatives (of known chemical structures) in the two systems ($^1J_{CH}$ = variously 181-192 for **4**-**9**, 171 for **2** and **3** in system 1; variously 190-193 for **35**-**38**, 170-178 for **28**-**34** in system **27**). For thiophene $^1J_{CH}$ values are 189 for position 2 and 168 for position 3, consistent with the thienopyridine results (21).

Table 3: Ipso ^{13}C NMR Substituent Chemical Shifts (ISCS) Calculated for the Thieno[2,3-*b*]pyridine **1** Thieno[3,2-*b*]pyridine **27** and Benzene **47** Systems[a]

Substituent	ISCS[b]			Substituent	ISCS[b]		
	For **1**	For **27**	For **47**[c]		For **1**[d]	For **27**[e]	For **47**[c]
2-Cl		6.7	6.3	α-Cl	1.5	1.9	6.3
2-Br		-9.6	-5.8	α-Ac	4.1		8.9
2-I		-46.4	-34.1	α-CN	-17.0	-16.3	-15.7
2-CHO	16.1	15.4	8.4	α-C(=O)NH_2	0.1	0.1	5.0
2-Ac	16.7	16.4	8.9	β-Cl	9.0		6.3
2-CH_2OH		20.6	12.4	β-NO_2	22.5		19.9
2-CN		-16.7	-15.7	β-NH_2	20.4		18.2
3-Cl	-2.6	-2.3	6.3	β-Ac	9.4	9.0	8.9
3-Br	-16.2	-15.1	-5.8	β-CN	-13.9		-15.7
3-I	-46.1	-42.8	-34.1	β-CO_2Me	2.9		2.0
3-NO_2	18.8	17.1	19.9	β-Et	15.9		15.6
3-NH_2	14.7		18.2	γ-Ci	7.6	7.9	6.3
3-NHAc	5.3		9.7	γ-NO_2		18.2	19.9
				γ-NH_2	17.2	17.6	18.2
				γ-Me	11.1		9.2

a) Positions of substituents refer only to compounds **1** and **27**. b) ISCS values are in ppm for $CDCl_3$ as a solvent.
c) See reference 6. d) For compound **1**: α = 6, β = 5, and γ = 4. e) For compound **27**: α = 5, β = 6, and γ = 7.

In Table 3 ISCS data are grouped according to (a) the chemical nature of the substituent and (b) the location of the substituent (in systems **1** and **27**) with respect to the heteroatom in its own ring. Thus, for substituents in the thiophene ring (where the S atom is designated as position 1) numbers 2 and 3 represent analogous locations in both systems. In contrast, for substituents in the pyridine ring the Greek letters α, β, and γ are used to show positions relative to the N heteroatom. This grouping shows closely similar numerical ISCS values (12% maximum variation from the average) for the twelve pairs of corresponding thienopyridine derivatives (e.g. the 2-Ac pair, the α-Cl pair, etc.) in Table 3. For the eight chlorothienopyridines listed, one notes a marked effect of ISCS on the position of substitution in the order β- (9.0) > γ- (7.7 ave.) > 2- (6.7) > α- (1.7 ave.) > 3- (-2.5 ave.). The more limited nitro and amino compounds fall in the same partial

order β- > γ- ≥ 3-, while the acetyl compounds give an altered order 2- > β- > α-. For chlorothiophenes the positional order is also 2- (4.1) > 3- (-1.6) (2); while for chloropyridines it is β- (8.2) > α- (1.4) (3,22) and for chloroquinolines one has γ- (6.7) > α- (0.2) (23).

Table 4: Linear Regression Data for Plots of ^{13}C NMR Ipso Substituent Chemical Shifts (ISCS) in Thiophene *T* and Pyridine *P* Rings versus ISCS in Benzene *B* Rings

Equation: $ISCS_{T \text{ or } P} = k(ISCS_B) + c$

Parent Comp.	Substituted Position	Solvent[a]	Slope *k*	Intercept *c*	No. of Points, *n*	Corr. Coeff., *r*	Reference
1 & **27**	2-*T*	C	1.427	2.25	9	0.992	—[b]
1 & **27**	3-*T*	C	1.143	-6.34	10	0.991	—[b]
1 & **27**	α-*P*	C	0.830	-3.21	7	0.987	—[b]
1 & **27**	β-*P*	C	1.014	1.14	8	0.995	—[b]
1 & **27**	γ-*P*	C	0.875	1.61	6	0.988	—[b]
T	2-*T*	A	1.37	-0.55	11	0.96	(2)[c]
T	3-*T*	A	1.17	-2.38	9	0.96	(2)[c]
T	2-*T*	N	1.514	0.58	6	0.991	(1)
T	3-*T*	N	1.343	-1.99	6	0.980	(1)
48	2-*T*	A	1.273	0.94	8	0.922	(4)
49	2-*T*	A	1.087	3.66	8	0.929	(4)
P	α-*P*	N[d]	0.604	2.16	10	0.927	(3)
P	β-*P*	N[e]	0.861	0.93	8	0.997	(3)
P	γ-*P*	N[f]	0.999	0.15	10	0.988	(3)
IsoQ[g]	1-*P*[h]	C	0.483	-4.76	7	0.951	(5)
IsoQ[g]	3-*P*[h]	C	0.755	-3.44	7	0.985	(5)
IsoQ[g]	4-*P*[i]	C	0.849	3.69	7	0.991	(5)

a) A = acetone-d_6; C = $CDCl_3$; N = neat or none. b) This study. c) Data taken directly from the reference. d) Exception: one solid was measured in CCl_4 as solvent. e) Exceptions: two solids were measured in CCl_4. f) Exceptions: one solid was measured in dioxane and another, in ethanol. g) Isoquinoline. For the isoquinoline substituents NC_5H_{10} and OEt, reported benzene values are used for NC_6H_{12} and OMe, instead. h) These positions are alpha to the heteronitrogen atom. i) Beta to the nitrogen atom. j) Exception: one compound was measured in $CDCl_3$-CD_3OD.

Table 4 gives data for the linear regression plots of ISCS for our monosubstituted thienopyridine systems versus ISCS for the same array of monosubstituted benzenes. In accordance with the data in Table 3 and the discussion in the previous paragraph five separate plots were made for the combined systems **1** and **27**, namely for substitutions at positions 2, 3, α, β, and γ. The large values (0.987-0.995) for the correlation coefficients *r* for these plots reflect the accuracy of measurements shown in Tables 1 and 2 and serve to justify the combination of data from the two thienopyridine systems.

We propose to designate the slope *k* as a ^{13}C NMR sensitivity factor, the value of which depends on the nature of the parent system, the position of substitution, and the solvent used. The standard of reference is benzene, for which *k* = 1 in whatever solvent is chosen. From the data in Table 4 one notes that the ^{13}C NMR chemical shift for either C-2 or C-3 in a thiophene ring is more responsive to changes in the nature of the substituent than is the ipso carbon in benzene and

that the effect on C-2 exceeds that on C-3. For the two thienopyridines, changing substituents in the α or γ positions elicit similar responses which are less than in benzene, while such changes in the β position give a response about the same as in benzene. Substitutions into pyridine or the heterocyclic ring of isoquinoline again show low sensitivity factors. We are not ready to offer a theoretical explanation of these results at this time.

Compounds **24**-**26** and **42** are not included in Table 3 because their substituents, viz. thiocarbamoyl, guanyl and methyl imidate are not listed in Ewing's table. From the regression equations one can estimate values of 5.1, 5.6, and 1.6, respectively, for these benzene ISCS values in $CDCl_3$.

Conclusions

From data on the ^{13}C NMR chemical shifts of thieno[2,3-*b*]pyridine and thieno[3,2-*b*]pyridine plus 44 monosubstituted derivatives of these parent compounds one obtains linear relationships between ipso substituent chemical shifts (ISCS) in the thienopyridine systems versus those in the benzene system. The slope *k* of the regression line is dependent on the specific position of substitution in the thiophene or pyridine ring. Values of *k* (termed sensitivity factors) are larger for substitution into the thiophene ring than for substitution into the pyridine ring.

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