X-RAY CRYSTALLOGRAPHIC STUDIES OF FOUR MONOSUBSTITUTED THIENOPYRIDINES. COMPARISON OF EXPERIMENTAL DATA WITH CALCULATED OR MEASURED VALUES FOR THE PARENT COMPOUNDS

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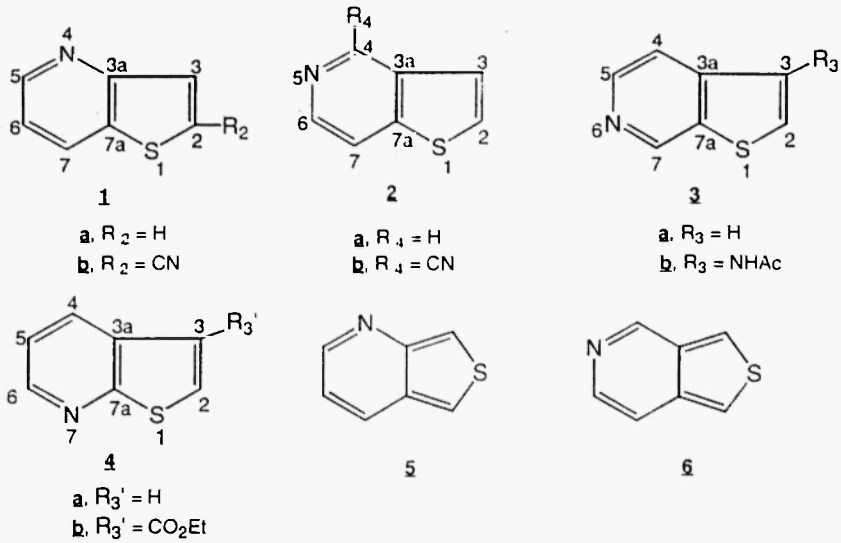
Abstract: X-ray crystallographic data are reported for thieno[3,2-*b*]pyridine-2-carbonitrile (**1b**), thieno[3,2-*c*]pyridine-4-carbonitrile (**2b**), 3-acetylaminothieno[2,3-*c*]pyridine (**3b**), and ethyl thieno[2,3-*b*]pyridine-3-carboxylate (**4b**). All of the thienopyridine ring systems are planar with internal bond angles of 90.7 ± 0.6° for C-S-C and 115.9 ± 1.9° for C-N-C. C-S and C-N bond lengths in the rings are 1.73 ± 0.02 Å and 1.34 ± 0.02 Å, respectively. Comparison is made of our measured data with bond angles and lengths calculated from molecular orbital theory for the parent unsubstituted compounds **1a**, **2a**, and **4a** and for reported experimental data for parent **3a**. In general, numerical values are remarkably close in the corresponding **a** and **b** systems. ^{13}C Nmr spectral data are also reported for **2b**-**4b**.

Introduction

Practical syntheses of the six possible parent thienopyridines over the past thirty years have made samples of four of them, **1a**-**4a**, readily available in our laboratory and elsewhere (1,2). While isomers **5** and **6** have also been prepared (3) they are unstable under regular laboratory conditions and have not been studied further. Meanwhile, in 1972, Helland and Skancke, using PPP and CNDO/2 methods, calculated bond lengths in all six of these parent molecules (4). More recently, in 1995, Webber and Woolley used *ab initio* Hartree-Fock theory to calculate both bond lengths and bond angles in the same molecules (5). It would be desirable to compare these theoretical values with experimental measurements, e.g. by X-ray crystallography. However, compounds **1a** and **4a** are regularly liquids (6), while **2a** and **3a** are low-melting solids (46° and 55°, respectively) (7). Despite the difficulty involved, an X-ray study of crystalline **3a** has recently been reported (8). Meanwhile, the availability of a large number of derivatives of **1a**-**4a** on our sample shelves from previous research led us to select one suitable, simple monosubstituted thienopyridine (**1b**-**4b**) from each of the parent systems for a broader comparison of experimental and theoretical results, as presented here. Additionally, we report ^{13}C nmr spectral data (9) for three of the samples used (10).

Experimental and Procedure

X-ray crystallographic studies of **1b**-**4b** were conducted at 22-23° C. with an Enraf-Nonius CAD-4 diffractometer and a graphite monochromator with Mo kα radiation of 0.71073 Å wavelength, with $2\theta_{max}$ of 50°, a scan mode of ω-2θ, a scan speed (on ω) of 1.0-4.1° min^{-1} and a scan width of [(0.95 ± 0.05) + 0.35tanθ]°. A SIR E-map (11), supplemented by a cycle of DIRDIF (12) as needed, served to locate all non-hydrogen atoms. The teXsan program suite (13), incorporating complex atomic scattering factors (14), was used in all calculations. Comparative crystallographic and structural parameters are presented in Table 1. Samples for study were selected from our research library shelves.



Thieno[3,2-*b*]pyridine-2-carbonitrile (**1b**), mp 110-111°C. (15-17), is shown as ORTEP figure 1.

Thieno[3,2-*c*]pyridine-4-carbonitrile (**2b**), mp 90-91.5°C. (18), is shown as ORTEP figure 2; ^{13}C NMR ($CDCl_3$) (19): δ 148.1 (s, C-7a), 143.2 (dd, J = 185.3, 2.0 Hz, C-6), 138.5 (s, C-4), 131.6 (dd, J = 187.4, 7.1 Hz, C-2), 129.0 (d, J = 5.5 Hz, C-3a), 121.4 (dd, J = 175.3, 4.1 Hz, C-7), 120.9 (dd, J = 167.7, 8.3 Hz, C-3), 116.4 (s, CN) (20).

3-Acetylaminothieno[2,3-*c*]pyridine (**3b**), mp 183-184°C. (24), is shown as ORTEP figure 3; ^{13}C NMR (DMSO-d_6): δ 168.5 (C=O), 145.0 and 142.4 (C-5 and C-7), 137.9, 133.5, and 129.7 (C-3, C-3a, and C-7a), 116.2 and 115.2 (C-2 and C-4), 23.2 (CH_3) (20).

Ethyl thieno[2,3-*b*]pyridine-3-carboxylate (**4b**), mp 72.5-73.5°C. (25), is shown as ORTEP figure 4; ^{13}C NMR ($CDCl_3$): δ 162.5 (C=O), 161.7 (C-7a), 147.5 (C-6), 136.6 C-2), 132.9 (C-4), 130.6 (C-3a), 125.4 (C-3) (26), 120.6 (C-5), 61.1 (CH_2), 14.6 (CH_3) (15).

Measured bond lengths for **1b**-**4b** are shown in Table 2 and measured bond angles for these compounds are given in Table 3.

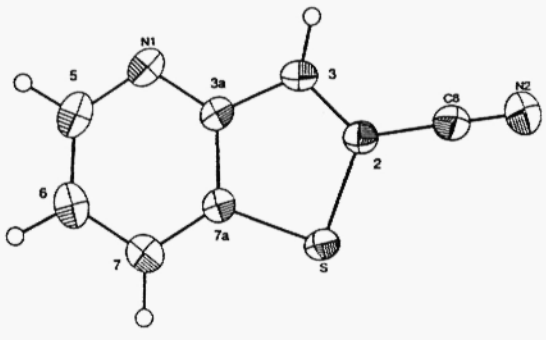


Figure 1: ORTEP of **1b**

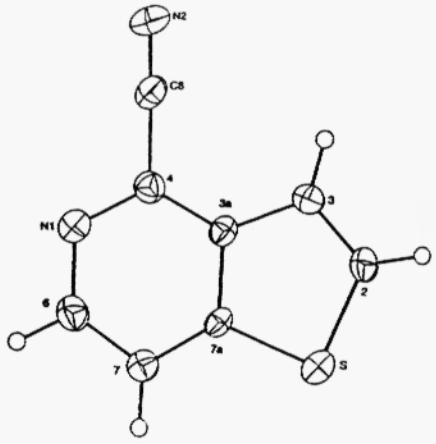


Figure 2: ORTEP of **2b**

Table 1: Crystallographic and Structural Parameters for Compounds **1b**-**4b**.

Parameter Found or Used[a]	Compound			
	1b	**2b**	**3b**	**4b**
Crystal appearance	colorless block	colorless rod	yellow prism	colorless prism
Crystal dimensions (mm)	0.18 x 0.25 x 0.43	0.045 x 0.080 x 0.53	0.23 x 0.25 x 0.57	0.23 x 0.24 x 0.47
Empirical formula	$C_8H_4N_2S$	$C_8H_4N_2S$	$C_9H_8N_2OS$	$C_{10}H_9NO_2S$
Formula weight	160.19	160.19	192.24	207.25
Crystal system	monoclinic	monoclinic	monoclinic	tetragonal
Space group	$P2_1/n$	Cc	$P2_1/c$	$P4_12_12$
Unit cell dimensions (Å): a	3.876 (1)	12.8224 (26)	7.2677 (10)	12.0203 (14)
b	15.105 (2)	8.5928 (13)	12.8678 (19)	———
c	12.840 (2)	7.3853 (22)	9.6636 (10)	13.5700 (26)
Unit cell angles: α,β,γ degrees	90, 98.56 (1), 90	90, 117.33 (2), 90	90, 103.323 (11), 90	———
Unit cell volume, Å^3	743.4 (3)	722.9 (6)	879.4 (2)	1960.7 (5)
Z	4	4	4	8
Calculated density (g/cm^3)	1.431	1.472	1.452	1.404
Linear absorption coeff. μ (cm^{-1})	3.58	3.52	3.23	3.01
F (000)	328	328	400	864
Index range: h, k, ℓ	0→4, 0→17, -15→15	0→14, 0→10, -8→7	0→8, 0→15, -11→11	0→14, 0→10, -16→16
Independent reflections scanned[b]	1376	680	1630	1069
R_{int}[c]	0.012	0.015	0.0094	0.0094
Absorption correction	none	none	none	azimuthal (ψ) scans
Sec. extinction parameter (g)	1.7 (5) x 10^{-6}	set at zero[d]	set at zero[d]	set at zero[d]
Reflections in refinement (N)	1085, $I \geq 1.5\sigma(I)$	633 (all); 546, $I \geq \sigma(I)$	1343, $I \geq 1.5\sigma(I)$	1050 (all); 731, $I \geq \sigma(I)$

Table 1: Continued

Parameter Found or Used[a]	Compound			
	1b	**2b**	**3b**	**4b**
Number of parameters (V)	117	98	151	127
Function minimized	$\Sigma w(\|F_o\|-\|F_c\|)^2$	$\Sigma w(\|F_o\|-\|F_c\|)^2$	$\Sigma w(\|F_o\|-\|F_c\|)^2$	$\Sigma w(\|F_o\|^2-\|F_c\|^2)^2$
R(F) [e]	0.032	0.049	0.036	0.044
wR(F) [f,g]	0.036	0.049 [$I \geq \sigma(I)$]	0.048	0.035 [$I \geq \sigma(I)$]
$R(F^2)$, $wR(F^2)$ all data [g,h]	———	0.091, 0.098	———	0.047, 0.070
S [i]	1.72	1.57 [$I \geq \sigma(I)$], 1.60 (all data)	2.61	1.93 [$I \geq \sigma(I)$], 1.71 (all data)
Max. Δ/σ, last cycle	0.02	0.01	0.01	0.06
Max., min. in final diffraction map (e Å^{-3})	0.20, -0.15	0.31, -0.37	0.20, -0.17	0.29, -0.31

a) Parameters which are identical for all four compounds are presented in the Experimental and Procedure section. b) Includes systematic absences. c) Obtained on F^2 for 0, k, $\pm \ell$. d) Predicted at 10^{-10} to 10^{12}. e) $R(F) = \Sigma||F_o|-|F_c||/\Sigma|F_o|$. f) $wR(F) = [\Sigma w(|F_o|-|F_c|)^2 / \Sigma w|F_o|^2]^{1/2}$.
g) Weighting factor $w = 1/\sigma^2(F)$. h) $wR(F^2) = [\Sigma w(|F_o|^2-|F_c|^2)^2 / \Sigma w|F_o|^4]^{1/2}$. i) $S = [\Sigma w(|F_o|-|F_c|)^2 / (N - V)]^{1/2}$.

Discussion of Results

Observation of Table 1 shows that compounds **1b**-**3b** form monoclinic crystals with Z = 4 (molecules per unit cell), while **4b** forms tetragonal crystals with Z = 8. However, parent molecule **3a** adopts an orthorhombic crystal system with Z = 8 (8). Figures 1-4 show ORTEP drawings for compounds **1b**-**4b**. As in **3a**, the thienopyridine ring structures for the **b** derivatives are planar within experimental error. For the carbonitriles **1b** and **2b** the whole molecules are planar and these planes stack in simple layers in the crystals. Intermolecular geometric relationships in **3b** and **4b**, which bear non-planar substituents, are more complicated in their crystal lattices.

Table 2 compares the lengths of analogous bonds in the thienopyridine rings of **1b**-**4b** with those calculated by molecular orbital theory for parent molecules **1a**, **2a**, and **4a** and those measured for **3a** (8). In general, numerical values in the **a** and **b** series are remarkably close to one another, i.e. they are either within the limits of the error of measurement or they differ by no more than 0.012 Å. There are, however, two cases (out of a total of twenty) where differences exceed that value, viz. bond S-C2 for **4** (Δ = 0.017 Å) and C3-C3a for **1** (Δ = 0.023 Å). Here electron-withdrawing groups 3-CO_2Et and 2-CN, respectively, are located on the thiophene ring in the **b** series and serve to shorten the ring bond which is β to the substituent. In particular, all measured C-S and C-N bond lengths in the various rings lie in the ranges of 1.73 ± 0.02 Å and 1.34 ± 0.02 Å, respectively.

Table 2: Comparison of Measured Bond Lengths in **1b** - **4b** with Calculated Bond Lengths for Parent Molecules **1a**, **2a**, and **4a** and Measured Ones for Parent Molecule **3a**.

Bond	Comp. Series	Bond Length in Å		Bond	Bond Length in Å	
		Found in **b**[a]	Value for **a**[b]		Found in **b**[a]	Value for **a**[b]
S(1)-2	1	1.740 (2)	(1.747)	2-3	1.350 (3)	1.355
	2	1.727 (7)	1.725		1.335 (9)	(1.341)
	3	1.726 (2)	[1.728]		1.360 (3)	[1.351]
	4	1.707 (4)	1.724		1.357 (5)	1.356
3-3a	1	1.420 (3)	(1.443)	3a-4	1.352 (3)	1.351 (N1)[c]
	2	1.439 (9)	(1.446)		1.393 (9)	(1.397)
	3	1.435 (3)	[1.433]		1.397 (3)	[1.402]
	4	1.440 (5)	(1.445)		1.383 (4)	(1.395)
4-5	1	1.324 (3)	(1.325)	5-6	1.387 (4)	(1.398)
	2	1.324 (9)	(1.320) (N1)[c]		1.350 (8)	(1.345)
	3	1.373 (3)	[1.373]		1.352 (3)	[1.354] (N1)[c]
	4	1.377 (5)	(1.381)		1.387 (5)	(1.397)
6-7	1	1.370 (3)	(1.381)	7-7a	1.390 (3)	(1.391)
	2	1.377 (9)	(1.378)		1.399 (8)	1.404
	3	1.332 (4)	[1.332]		1.388 (3)	[1.397]
	4	1.323 (5)	(1.326) (N)[c]		1.335 (5)	(1.329)
S(1)-7a	1	1.729 (2)	1.727	3a-7a[d]	1.403 (3)	1.405
	2	1.734 (6)	1.727		1.406 (8)	1.403
	3	1.728 (2)	[1.731]		1.402 (3)	[1.414]
	4	1.733 (4)	1.727		1.397 (5)	(1.401)

Other Measured Bond Lengths in **1b-4b**[e]

1b: 2-C8, 1.426 (3); C8-N2, 1.137 (3). **2b**: 4-C8, 1.466 (9); C8-N2, 1.113 (9).

3b: 3-N2, 1.400 (3); N2-C8, 1.345 (3); C8-O, 1.227 (2); C8-C9, 1.485 (3).

4b: 3-C8, 1.470 (5); C8-O2, 1.198 (4); C8-O1, 1.351 (4); O1-C9, 1.445 (4); C9-C10, 1.495 (6).

a) Measured in the present study. Standard deviations in parentheses refer to the least significant digits. b) Bond lengths in brackets were measured on **3a** by Nerenz et al. (ref. 8); those in parentheses were calculated by Webber and Wooley (ref. 5); the others were calculated by Helland and Skancke (ref.4). The calculated value shown is the one from references 4 and 5 which lies closer to the measured value found in our study. c) The N heteroatom forms one end of this bond, i.e. the larger positional number. d) Ring juncture of the pyridine and thiophene rings. e) For identification of these bonds see the ORTEP diagrams for **1b-4b.**

Table 3: Comparison of Measured Bond Angles in **1b**-**4b** with Calculated Bond Angles for Parent Molecules **1a**, **2a**, and **4a** and Measured Ones for Parent Molecule **3a**

Bond Angle	Comp. Series	Angle in Degrees Found in **b**[a]	Value for **a**[b]	Bond Angle	Angle in Degrees Found in **b**[a]	Value for **a**[b]
7a-S-2	**1**	90.1 (1)	90.6	S-2-3	114.2 (2)	113.7
	2	90.3 (4)	90.8		115.2 (5)	113.4
	3	91.2 (1)	[90.8]		113.2 (2)	[114.0]
	4	91.1 (2)	90.3		113.8 (3)	113.8
2-3-3a	**1**	111.5 (2)	113.3	3-3a-7a	112.6 (2)	112.3
	2	111.1 (6)	112.4		112.3 (6)	112.1
	3	112.2 (2)	[112.1]		111.7 (2)	[111.6]
	4	112.1 (4)	112.4		111.2 (4)	111.6
3a-7a-S	**1**	111.6 (2)	111.1	3a-4-5	115.3 (2)	118.2 (N)[c]
	2	111.2 (4)	111.2		124.4 (6)	121.9
	3	111.7 (2)	[111.5]		118.4 (2)	[118.3]
	4	111.8 (3)	111.8		118.2 (4)	118.4
4-5-6	**1**	124.8 (2)	123.0	5-6-7	120.5 (2)	119.5
	2	117.1 (6)	119.7 (N)[c]		125.1 (6)	119.9
	3	124.2 (3)	[124.8]		117.8 (2)	[117.6] (N)[c]
	4	119.3 (4)	119.5		125.1 (4)	122.7
6-7-7a	**1**	116.2 (2)	117.6	7-7a-3a	120.0 (2)	119.9
	2	116.0 (6)	117.3		121.0 (5)	123.1
	3	121.9 (2)	[122.1]		120.3 (2)	[120.0]
	4	114.0 (4)	117.7 (N)[c]		126.6 (4)	124.2
7a-3a-4	**1**	123.2 (2)	122.4			
	2	116.4 (5)	118.0			
	3	117.4 (2)	[117.3]			
	4	116.9 (4)	117.5			

Other Measured Bond Angles in **1b**-**4b**[d]

1b: S-2-C8, 118.8 (2); 3-2-C8, 127.0 (2); 2-C8-N2, 178.4 (3). **2b**: 3a-4-C8, 118.9 (6); 5-4-C8, 116.7 (6); 4-C8-N2, 177.9 (8). **3b**: 3a-3-N2, 121.2 (2); 2-3-N2, 126.6 (2); N2-C8-O, 121.6 (2); N2-C8-C9, 116.7 (2); O-C8-C9, 121.7 (2). **4b**: S-7a-7(N), 121.6 (3); 3-3a-4, 132.0 (4); 3a-3-C8, 123.2 (4); 2-3-C8, 124.7 (4); 3-C8-O2, 125.3 (4); 3-C8-O1, 111.3 (4); O1-C8-O2, 123.4 (4); C8-O1-C9, 115.2 (3); O1-C9-C10, 107.0 (4).

a) See footnote a, Table 2. b) Bond angles in brackets were measured on **3a** by Nerenz et al. (ref. 8); the others were calculated by Webber and Wooley (ref. 5). c) The N heteroatom forms the apex of this angle. d) For identification of angles see the ORTEP diagrams for **1b**-**4b**.

Table 3 compares the sizes of analogous ring internal angles in the **1**-**4** series in the aforementioned compounds. In only two cases, viz. angle N-C6-C7 in **2b** (Δ = 5.2°) and angle C6-N-C7a in **4b** (Δ = -3.7°), were measured values more than 3° different from calculated values. For all of the ring systems, internal C-S-C and C-N-C bond angles fall in the ranges of 90.7 ± 0.6° and 115.9 ± 1.9°, respectively. Also, Nerenz et al (8) noted the closeness of their data on **3a** to the calculated values.

Conclusions

X-ray crystallographic measurements were obtained on one monosubstituted thienopyridine in each of four different parent systems. The thienopyridine ring system is planar. Literature values (either calculated or measured) for bond lengths and bond angles in the parent molecules are remarkably close to our measured ones.

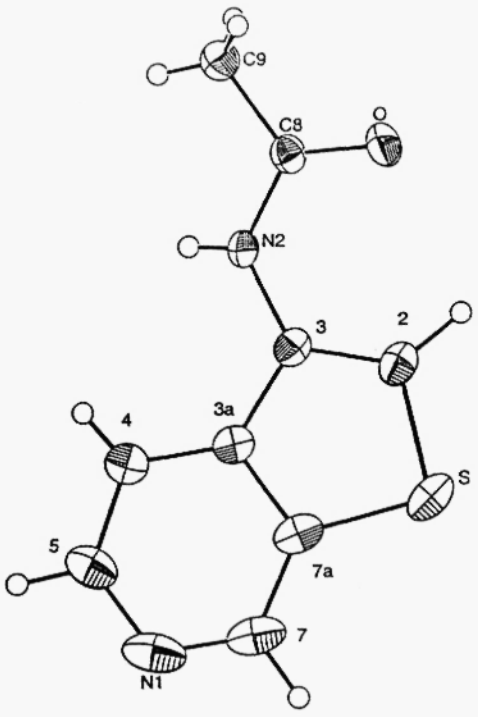


Figure 3: ORTEP of **3b**

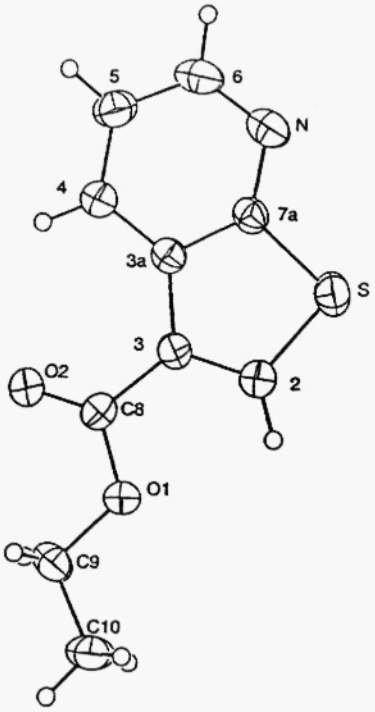


Figure 4: ORTEP of **4b**

References and Notes

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