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From the crude mixtures of isomeric 4-nitrophenylthieno[2,3-*b*]pyridines (**3**) previously reported [1] were isolated three analytically pure samples, *viz.* the 2-isomer (yellow needles, mp 258°, **3a**), the 6-isomer (red prisms, mp 182°, **3e**), and a ternary mixture of the 2-, 3-, and 4-isomers (orange needles, mp 213°, **3a:3b:3c** = 1.3:1.0:0.5). The 258° compound was identified as either **3a** or **3b** by its <sup>1</sup>H nmr spectrum and definitively as the former by its x-ray crystallographic analysis. The isomeric identities of the 182° and 213° samples were established from their <sup>1</sup>H nmr spectra only. No 5-isomer (**3d**) was identified. Semi-quantitatively, relative isomeric yields fit the pattern 2- (64%) >> 6- (14%) ≥ 3- (12%) > 4- (6%) ≥ 5- (≤4%). Crystallographic data for **3a** are presented.

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In a preceding paper [1] we reported an experimental procedure for the free-radical 4-nitrophenylation of thieno[2,3-*b*]pyridine (**1**) by means of the hypothetical intermediate 4-nitrophenyldiazoacetate (**2**) under buffered conditions to yield a mixture of monosubstituted 4-nitrophenyl derivatives **3**. Processing of this mixture led to two separable solid, crude products, *Y* (acetone-insoluble, chloroform-soluble, rust-colored) and *Z* (acetone-soluble, yellow-red sublimate) in yields of 12% and 20%, respectively. The present paper reports the isolation and identification of two chemically pure isomers and one analytically pure isomeric mixture from those products, as well as a semi-quantitative relationship amongst the yields of the five possible 4-nitrophenylthieno[2,3-*b*]pyridine isomers **3a-3e**.

Three variations on column chromatography with silica gel/chloroform were used to effect preliminary fractionations of the components of *Y* and *Z*. These fractions were analyzed qualitatively by thin-layer chromatography, with rejection of spots that were visible in ultraviolet light but were colorless in daylight as being non-nitrophenyl-bearing byproducts. Fractions were then subdivided further by thick-layer chromatography on silica gel into single-spot components (or ones which were only slightly contaminated by an impurity) for isolation and weighing. From *Y* (see Experiment II) was isolated the fast-moving (*R<sub>f</sub>* 0.76 with a solvent of chloroform-ethyl acetate, 1:1) 6-(4-nitrophenyl)thieno[2,3-*b*]pyridine isomer (**3e**) as red prisms, mp 181-182°, readily identified isomerically by means of its <sup>1</sup>H nmr spectrum (*vide infra*). Use of a column of activated silica gel for chromatography of part of *Z* (Experiment I) effected separation of the slower-moving (*R<sub>f</sub>* 0.63) 2-(4-nitrophenyl)thieno[2,3-*b*]pyridine isomer (**3a**), obtained as yellow needles, mp 257-258°, easily identifiable from <sup>1</sup>H nmr as bearing its nitrophenyl substituent in the thiophene ring of **1** (singlet for one proton at δ 7.64). Single-crystal x-ray crystallography then established the location of this substituent at position 2 on the parent molecule (*vide infra*).

Another portion of *Z* was chromatographed on a column of non-activated silica gel (Experiment III) and led to the successive isolations of **3e** (*R<sub>f</sub>* 0.76, mp 181.5-183°), a ternary mixture of **3a**, **3b**, and **3c** (*R<sub>f</sub>* 0.63 as above, or 0.57 with non-activated silica gel/chloroform), and **3a** alone (*R<sub>f</sub>* values identical to those of the ternary mixture, mp 259.5-261.5). The ternary mixture yielded analytically pure orange needles, mp 211-213°. Its isomeric composition (**3a:3b:3c** = 1.3:1.0:0.5) was established from its <sup>1</sup>H nmr spectrum which showed the signals for pure **3a**; a singlet at δ 7.68 for H-2 of **3b**; plus two extra singlets for H-2 and H-3, but without a signal near 8.15 for H-4, of **3c**. Integrations of appropriate signals led to the numerical ratios of the isomers in the mixture. No extended effort was made to find an alternative chromatographic system or other methodology which would serve to separate the ternary mixture into its components. No evidence for the formation of the 5-isomer (**3d**) was found, though a small quantity of a crude, crystalline unidentified product was separated from *Z*.

Distinguishing data for the preceding isolated products are presented in Table 1. As expected, the 6-isomer (**3e**) has the largest *R<sub>f</sub>* value on silica gel of all of the isomers. Thus, if one assumes that the main anchoring site of each isomer to the silica surface is the non-bonding electron-pair on the heteroatomic nitrogen, then the bulky, electron-withdrawing 4-nitrophenyl substituent should decrease adsorbability of the **3e** isomer over all of the others [2]. It

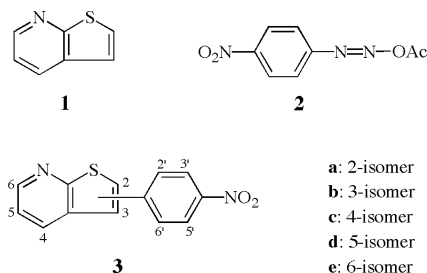


Table 1  
Melting Points, TLC Data, and Yields of the Isomers of **3** from Experiments I-III

Isomeric Component (s)	Mp °C	R <sub>f</sub> for TLC Conditions [a]			Expt. I	Yield in g [b]	
		A	B	C		Expt. II	Expt. III
<b>3a</b>	258	0.63	0.18	0.57	3.66	none	—
<b>3a, 3b, 3c</b>	213	0.63	0.18	0.57	—	1.29 [c]	1.17 [c]
<b>3e</b>	182	0.76	—	0.76	—	0.75	0.34
Unidentified [d]	—	0.58	—	0.62	—	—	0.34

[a] Conditions A, activated silica gel/chloroform-ethyl acetate (1:1); B, activated silica gel/chloroform; C, non-activated silica gel/chloroform. [b] Experiments I and III used separate portions of mixture Z, while Experiment II used only mixture Y. Thus, isomer yields are given only for Experiment I or III, whichever gave the more reliable data. All yields are calculated for the total quantity of the mixture available, *i.e.* 3.42 g of Y and 5.81 g of Z. The combined yield of these components is 7.55 g, or 82% recovery. [c] Total yield of **3a** = 3.66 + 0.46 (1.29 + 1.17) = 4.79 g. Yield of **3b** = 36% of 2.46 = 0.89 g; of **3c** = 18% of 2.46 = 0.44 g. [d] Largest crystalline unidentified component. No attempt was made to ascertain if this is, indeed, an isomer of **3**.

Table 2  
Crystallographic Data and Structural Refinement for **3a**

Empirical formula	C <sub>13</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub> S
Formula weight	256.28
Crystal appearance	pale yellow prism [a]
Crystal dimensions	0.065 × 0.16 × 0.54 mm
Crystal system	triclinic
Space group	P(-1)
dimensions (Å)	a = 7.080 (1) b = 7.106 (1) c = 12.050 (2)
Unit cell angles (°)	α = 100.73 (1) β = 93.33 (1) γ = 109.54 (1)
Unit cell volume	556.5 (2) Å <sup>3</sup>
Z	2
Density (calculated)	1.529 g/cm <sup>3</sup>
Linear absorption coefficient (μ)	2.84 cm <sup>-1</sup>
F (000)	264
Index ranges h, k, l	0→8, -8→7, -14→14
Scan mode	ω - 2θ
Scan speed (on ω)	4.1° min <sup>-1</sup>
Independent reflections scanned	1956
R <sub>int</sub> [on F <sup>2</sup> for ±(0kl)]	0.007
Reflections in refinement (N)	1651 [I ≥ σ(I)]
Absorption correction	none
Secondary extinction parameter (g)	Refined negative, set at 0
Number of parameters (V)	195
R(F), wR(F) [I ≥ σ(I)] [b]	0.039, 0.044
S [I ≥ σ(I)], S (all data) [b]	1.83
Maximum Δ/σ, last cycle	0.01
Maximum, minimum in final diffraction map	0.26 [near S(1)], -0.20 e/Å <sup>3</sup>

[a] The crystal used in this study was obtained by slow evaporation of a solution of **3a** in dimethyl sulfoxide over several months from a loosely stoppered beaker in the freezing compartment of a refrigerator. [b] For algebraic relationships see reference 8.

is surprising that the 2-, 3-, and 4-isomers (**3a-3c**) have identical R<sub>f</sub> values. Apparently, the three isomers elute together until all of the 3- and 4-isomers are gone. Then the excess 2-isomer elutes by itself.

Table 3  
Bond Angles for **3a** [a]

Bond Angle [b]	Degrees (°) [c]	Bond Angle [b]	Degrees (°) [c]
C2-S1-C7a	91.6 (1)	C3-C2-C1'	128.7 (2) [d]
S1-C2-C3	112.0 (2)	C2-C1'-C2'	120.1 (2) [d]
C2-C3-C3a	113.3 (2)	C1'-C2'-C3'	121.0 (2)
C3-C3a-C7a	111.7 (2)	C2'-C3'-C4'	119.1 (2)
C3a-C7a-S1	111.4 (2)	C3'-C4'-C5'	121.8 (2)
C4-C3a-C7a	116.9 (2)	C4'-C5'-C6'	118.7 (2)
C3a-C7a-N7	126.3 (2)	C5'-C6'-C1'	121.1 (2)
C7a-N7-C6	114.4 (2)	C6'-C1'-C2'	118.2 (2)
N7-C6-C5	124.3 (2)	C3'-C4'-N'	118.7 (2) [d]
C6-C5-C4	120.2 (2)	C4'-N'-O1	118.3 (2)
C5-C4-C3a	117.9 (2)	O1-N'-O2	123.4 (2)

[a] See Figure 1. [b] The middle atom in the triad forms the apex of the angle. [c] Standard deviations, shown in parentheses, refer to the least significant digits. [d] External angle to a ring.

The main purpose of this study is to obtain data on the relative susceptibilities of the five possible positions 2-6 in **1** to free-radical substitution, in particular to the electron-attracting 4-nitrophenyl group. Assuming that the unidentified product in Table 1 is the 5-isomer or is an upper limit to the quantity of 5-isomer formed, one calculates the isomeric distribution as: **3a**(64%) >> **3e**(14%) > **3b**(12%) > **3c**(6%) > **3d**(≤4%), where a difference of two percentage points is well within the accuracy of the experimental data. A discussion of these results and a comparison of them with predicted values will be presented in Part 3 [3].

Two advantages of having a 4-nitrophenyl substituent in an isomer of **3** are (a) the compound is colored and (b) the proton AB spin system of the *para*-disubstituted benzene ring is easily observed and identified in the <sup>1</sup>H nmr spectrum. Thus, for the 2-, 3- and 4-isomers (**3a-3c**), as well as for the 3- and 4-isomers of 4-nitrophenylpyridine [4], one observes two prominent, well-separated doublets for two protons each at *ca.* 8.35 and 7.8 ppm in deuteriochloroform. In contrast, however, for 6-isomer **3e** and

Table 4  
Selected Torsional Angles for **3a** [a]

Torsional Angle [b]	Degrees (°)	Torsional Angle [c]	Degrees (°)
<i>w</i> - <i>x</i> - <i>y</i> - <i>z</i>	[d]	<i>w</i> - <i>x</i> - <i>y</i> - <i>z</i>	[d]
S1-C2-C1'-C2'	-178.6 (2)	O1-N'-C4'-C3'	2.4 (3) [e]
S1-C2-C1'-C6'	0.8 (3)	O1-N'-C4'-C5'	-178.3 (2)
C2'-C1'-C2-C3	2.0 (3)	O2-N'-C4'-C3'	-177.9 (2)
C3-C2-C1'-C6'	-178.6 (2)	O2-N'-C4'-C5'	1.4 (3)

[a] See Figure 1. [b] These angles indicate twisting from coplanarity along bond C2-C1'. [c] These angles indicate twisting from coplanarity along bond C4'-N'. [d] The sign of the angle is positive if a clockwise motion of atom *w* would superimpose it on atom *z* when the direction of view is from atom *x* to atom *y*. See footnote *c* in Table 3. [e] Largest deviation from coplanarity in the total array of torsional angles in **3a**.

Table 5  
Bond Lengths for **3a** [a]

Bond	Distance (Å) [b]	Bond	Distance (Å) [b]
S1-C2	1.739 (2)	C2-C1'	1.468 (3)
C2-C3	1.359 (3)	C1'-C2'	1.393 (3)
C3-C3a	1.430 (3)	C2'-C3'	1.372 (3)
C3a-C4	1.394 (3)	C3'-C4'	1.373 (3)
C4-C5	1.372 (4)	C4'-C5'	1.376 (3)
C5-C6	1.385 (4)	C5'-C6'	1.372 (3)
C6-N7	1.334 (3)	C6'-C1'	1.399 (3)
N7-C7a	1.338 (3)	C4'-N'	1.466 (3)
C7a-S1	1.730 (2)	N'-O1	1.218 (3)
C7a-C3a	1.402 (3)	N'-O2	1.218 (3)

[a] See Figure 1. [b] See footnote *c* in Table 3.

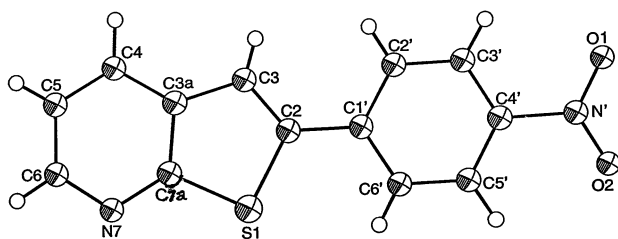


Figure 1. ORTEP drawing of compound **3a**.

2-(4-nitrophenyl)pyridine these doublets lie so close to one another as to give a strong interaction [5], with signals centered at 8.31 and 8.26 [4] ppm, respectively, for four protons. Additionally **3e** is identified by the absence of a downfield signal at 8.60-8.67 for a proton at C-6.

X-ray crystallographic data for **3a** are presented in Tables 2-5 and Figure 1. Bond lengths and angles lie within normal ranges. Remarkably, however, is the fact that the entire molecule is essentially coplanar in the crystal, with a maximal distortion of only 2.4° in out-of-plane rotation by the nitro group on the 4-nitrophenyl substituent.

## EXPERIMENTAL

Infrared spectra were determined on potassium bromide wafers by means of a Nicolet 5-DXB FTIR instrument and <sup>1</sup>H nmr spectra on deuteriochloroform solutions by means of a Varian INOVA 300 instrument. Electron-impact mass spectra were obtained at 70 eV by Dr. Brian Arbogast of Oregon State University, Corvallis, OR. Elemental analyses were conducted by Desert Analytics, Tucson, AZ.

Chromatographic Experiment I: Isolation of 2-(4-Nitrophenyl)thieno[2,3-*b*]pyridine (**3a**).

As indicated in the previous paper [1], the tar obtained from the free-radical 4-nitrophenylation of thieno[2,3-*b*]pyridine (**1**) was dissolved in acetone. The solution was evaporatively distilled to collect a yellow-red sublimate (Z, 5.81 g) at 100-205° (0.3 mm). The sample was powdered and mixed well. It was separated by column chromatography of 1.52 g of Z on 197 g of silica gel (preactivated by heating at 250° for 24 hours) with chloroform into three crystalline yellow-orange solids (95% recovery) plus tar as follows: #1, 0.83 g; #2, 0.13 g; #3, 0.49 g. Each fraction was analyzed qualitatively by thin-layer chromatography with activated silica gel F<sub>254</sub>/chloroform plus also quantitatively by thick-layer plates with the same adsorbent/solvent system. Components that showed dark spots (or bands) in ultraviolet light, but which were colorless in daylight were rejected as non-nitrophenyl byproducts. Fraction #1 showed seven spots, R<sub>f</sub> 0.73 and 0.54 (both colorless, not investigated further), 0.52 (light orange, 23.3 mg), 0.37 (faintly yellow, 10.4 mg), 0.27 (light yellow, 63.2 mg), 0.18 (bright yellow, 384.4 mg), 0.07 (colorless); #2, 0.27 (or 0.53 with silica gel/chloroform-ethyl acetate, 1:1) (17.5 mg) and 0.18 (84.2 mg); #3, 0.18 (bright yellow, 488 mg) and 0.07 (colorless, negligible weight).

Recrystallization of fraction #3 from chloroform gave yellow needles of **3a**, mp 257-258°, R<sub>f</sub> 0.18 as above or 0.63 with a solvent of chloroform-ethyl acetate (1:1), calculated total yield 1.87 g (as based on fraction #3 only) or 3.66 g (as based on all components with R<sub>f</sub> 0.18 from the chromatogram) ir: 1510 and 1339 (nitro group); 1104, 841 cm<sup>-1</sup>; ms: m/e 257 (16), 256 (M<sup>+</sup>, 100), 226 (M<sup>+</sup> - NO, 16), 210 (M<sup>+</sup> -NO<sub>2</sub>, 27) 209 (19); <sup>1</sup>H nmr: δ 8.60 (d, J<sub>5,6</sub> = 4.8 Hz, 1 H, H-6), 8.31 (d, J<sub>2,3'</sub> = J<sub>5,6'</sub> = 9.0 Hz, 2 H, H-3' and H-5'), 8.10 (d, J<sub>4,5</sub> = 8.4 Hz, 1H, H-4), 7.88 (d, 2 H, H-2' and H-6'), 7.64 (s, 1H, H-3), 7.36 (dd, 1H, H-5); X-ray crystallography, see Tables 2-5 and Figure 1.

Anal. Calcd. For C<sub>13</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>S: C, 60.93; H, 3.14; N, 10.93. Found: C, 60.79; H, 2.86; N, 10.69.

Chromatographic Experiment II: Isolation of 6-(4-Nitrophenyl)thieno[2,3-*b*]pyridine (**3e**).

Also, as noted in the previous paper [1], a rust-colored solid residue (Y, 3.42 g) was obtained from the free-radical 4-nitrophenylation of thieno[2,3-*b*]pyridine (**1**) after evaporation of the ether extract of the crude product mixture and subsequent removal of unreacted **1**. The entire sample was chromatographed on two columns of 170 g each of dried (*vide supra*) silica gel with chloroform to give three crystalline fractions, (89% recovery) plus tar, analyzed only by thin-layer chromatography using silica gel F<sub>254</sub>/chloroform-ethyl acetate (1:1). Fractions obtained were: #1 0.75 g of orange-red solid, mp 166-177°, one spot, R<sub>f</sub> 0.76

(lightly colored; #2, 1.54 g of orange solid, two spots, 0.76 (yellow) and 0.63 (nearly colorless); #3, 0.75 g of yellow-orange solid, mp 202-209°, one spot, 0.63, probably a mixture of **3a-3c** (*vide infra*). Thick-layer chromatography of fraction #2 with chloroform-ethyl acetate (1:1) showed it contained 84% by weight of the  $R_f$  0.63 component and no crystalline  $R_f$  0.76 component.

Slow evaporation of a chloroform solution of fraction #1 gave long, red prisms of **3e**, mp 177-178°, raised to 181-182° on recrystallization from absolute ethanol; ir: 1520 and 1354 (nitro group), 1109, 857  $\text{cm}^{-1}$ ; ms: m/e 257 (15), 256 ( $M^+$ , 100), 226 ( $M^+ - \text{NO}$ , 8), 210 ( $M^+ - \text{NO}_2$ , 42), 209 (19);  $^1\text{H}$  nmr:  $\delta$  8.31 (AB system,  $J_{2,3'} = J_{5',6'} = 9.0$  Hz,  $\Delta\delta = 18.0$  Hz, 4H, H2', H-3', H-5', H-6'), 8.20 (d,  $J_{4,5} = 8.4$  Hz, 1H, H-4), 7.84 (d, 1H, H-5), 7.62 (d,  $J_{2,3} = 5.9$  Hz, 1H, H-2), 7.33 (d, 1H, H-3).

Anal. Calcd. For  $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_2\text{S}$ : C, 60.93; H, 3.14; N, 10.93. Found: C, 60.72; H, 2.88; N, 11.00.

Chromatographic Experiment III: Isolation of a Ternary Mixture of 2-, 3-, and 4-(4-Nitrophenyl)thieno[2,3-*b*]pyridines (**3a**, **3b**, and **3c**).

A separate column chromatograph of 1.51 g of *Z* (*vide supra*) on non-activated silica gel with chloroform gave five crystalline fractions (analyzed by thin-layer chromatography using silica gel  $F_{254}$  of low activity/chloroform). Fractions obtained were the following: #1, 0.07 g of orange prisms after recrystallization from ethyl acetate, mp 181.5-183°, one spot,  $R_f$  0.76 (assigned structure of **3e**); #2, 0.25 g of yellow-orange solid, two spots,  $R_f$  0.76 and 0.62; #3, 0.14 g of yellow-orange solid, one spot, 0.57; #4, 0.65 g of orange solid, two spots, 0.57 (intense) and 0.49 (very small); #5, 0.23 g of yellow-orange needles after recrystallization from ethyl acetate, mp 259.5-261.5°, one spot, 0.57 (assigned structure of **3a**)-89% recovery of crystalline products.

A 100-mg sample of fraction #2 was separated into three components by means of a chromatotron [6] (silica gel/hexanes-ethyl acetate, 7:3);  $R_f$ 's (silica gel/chloroform-ethyl acetate, 1:1) 0.76 (7 mg, **3e**); 0.63 (60 mg, **3a-3c**); and 0.58 (35 mg, unidentified).

Recrystallization of fraction #3 from ethyl acetate gave orange needles, mp 211-213°;  $R_f$  0.63 with silica gel/chloroform-ethyl acetate (1:1); ir: 1514 and 1347 (nitro group), 1374, 1106, 838  $\text{cm}^{-1}$ ; ms: m/e 257 (16), 256 ( $M^+$ , 100), 226 ( $M^+ - \text{NO}$ , 14), 210 ( $M^+ - \text{NO}_2$ , 32), 209 (23);  $^1\text{H}$  nmr indicates a mixture of 2-isomer (**3a**) (*vide supra*), 3-isomer (**3b**), and 4-isomer (**3c**) in a ratio of 1.3:1.0:0.5 as based on integrations of signals for protons at positions 2, 3, 6, 2', and 6'. For the 3-isomer one has  $\delta$  8.67 (dd,  $J_{5,6} = 4.5$  Hz,  $J_{4,6} = 1.0$  Hz, 1H, H-6), 8.38 (d,  $J_{2,3'} = J_{5',6'} = 8.5$  Hz, 2H, H-3' and H-5'), 8.18 (dd,  $J_{4,5} = 8.1$  Hz, 1H, H-4), 7.75 (d, 2H, H-2' and H-6'), 7.68 (s, 1H, H-2), 7.32-7.43 (H-5 obscured). For the 4-isomer one has  $\delta$  8.67 (H-6 obscured), 8.40 (d,  $J_{2,3'} = J_{5',6'} = 8.2$  Hz, 2H, H-3' and H-5'), 7.78 (d, 2H, H-2' and H-6'), 7.64 and 7.63 (2s, 1H each, H-2 and H-3), 7.32-7.43 (H-5 obscured).

Anal. Calcd. For  $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_2\text{S}$ : C, 60.93; H, 3.14; N, 10.93. Found: C, 60.85; H, 3.11; N, 10.82.

X-ray Crystallography of **3a**.

The diffractometer, radiation wavelength, and monochromator used, as well as the algebraic relationships for  $R(F)$ ,  $wR(F)$ , and  $S$  were reported previously [7]. Experimental data are presented in Tables 2-5 and Figure 1.

#### REFERENCES AND NOTES

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