

The Reissert-Henze Reaction as a Route to Simple *C*-Substituents *alpha* to the Heteronitrogen Atom (1)

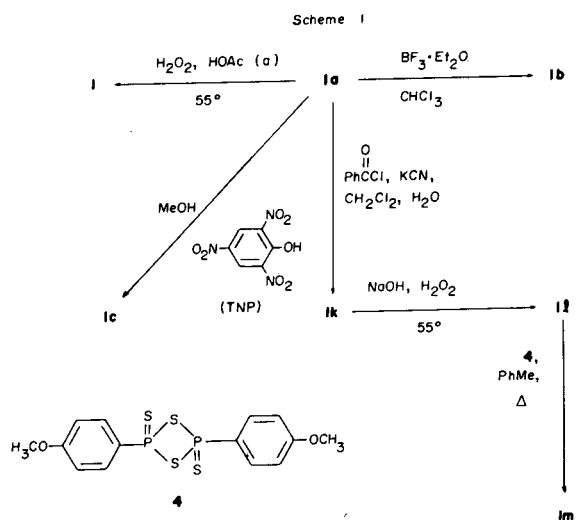
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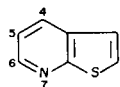
Treatment of a thienopyridine *N*-oxide with benzoyl chloride and cyanide ion (Reissert-Henze reaction) was shown to produce the corresponding cyanothienopyridine (43-84% yield in three parent systems), where in the cyano substituent occurs *alpha* to the heteronitrogen atom. In further transformations (in two systems) the cyano group was converted successively to carbamoyl (66-89%) and thiocarbamoyl (35-43%) functions. For 4-substituted thieno[2,3-*b*]pyridine 7-oxides, methyl and chloro substituents were retained on Reissert-Henze reaction, but the nitro group was replaced by Cl or H. Some new *N*-oxides and *N*-oxide complexes are reported.

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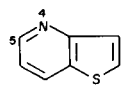
The Reissert-Henze reaction serves to introduce a cyano group into an *alpha* (or occasionally *gamma*) position to the heteronitrogen atom of an azine ring. To accomplish this nucleophilic substitution one commonly treats the azine *N*-oxide with benzoyl chloride and cyanide ion. The reaction has been applied in the quinoline, isoquinoline, quinazoline, and allied systems (3-7). We now report the successful extension of this reaction to the syntheses of aromatic nitriles in the thienopyridine series **1-3** and the transformations of some initial products into carbamoyl and thiocarbamoyl derivatives. As part of this study we also prepared the new *N*-oxides **1e** and **3a** and characterized the *N*-oxide **1a** as its crystalline boron trifluoride (**1b**) and picric acid (**1c**) complexes. The chemical conversions



(a) See reference 8.



1

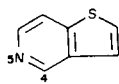


2

- a**, 7-oxide
b, 7-oxide·BF₃
c, 7-oxide·TNP
d, 4-Me
e, 4-Me-7-oxide
f, 4-Cl-7-oxide
g, 4-NO₂-7-oxide

- h**, 4-Me-6-CN
i, 4-Cl-6-CN
j, 5-NO₂-7-oxide
k, 6-CN
l, 6-C(=O)NH₂
m, 6-C(=S)NH₂

- a**, 4-oxide
b, 5-CN
c, 5-C(=O)NH₂
d, 5-C(=S)NH₂



3

- a**, 5-oxide·1/2 H₂O
b, 4-CN

effected in the **1** series are summarized in Scheme 1.

The *N*-oxidations **1** → **1a**, **2** → **2a**, and 4-chloro-**1** → **1f** were reported previously (8-10). They have now been extended to the cases **1d** → **1e** and **3** → **3a**. As with its isosteric quinoline 1-oxide (4,11), **1a** forms crystalline addition compounds (**1b** and **1c**) with boron trifluoride and

picric acid. The former is readily purified by evaporative distillation. Structures of **1e** and **3a** were corroborated by infrared (*N*-oxide absorption at *ca.* 1250 cm⁻¹) and mass spectrometry (facile loss of oxygen; for **1e** also ejection of formyl radical) (9,12). In contrast, complexes **1b** and **1c** lacked absorption in the region of 1250 cm⁻¹, consistent with coordination of the Lewis acid (boron trifluoride and the proton, respectively) with the oxide oxygen (13). As expected, the mass spectrum of **1b** shows its most abundant peak at *m/e* 135 (*i.e.* for 1⁺) from the loss of both oxygen and boron trifluoride. Next in abundance (40%) is a fragment at 151 for **1a**⁺ (confirmed by high resolution). However, the overall fragmentation patterns of **1a** and **1b** at *m/e* < 135 differ considerably, and the latter also shows an appreciable peak at 196. No peaks for boron trifluoride *per se* (14a) are apparent. Contrariwise, the mass spectrum of **1c** is essentially a composite of those of **1a** and picric acid (14b).

The Reissert-Henze reaction was developed as a varia-

Table I

Comparative Ultraviolet Absorption Maxima in 95% Ethanol

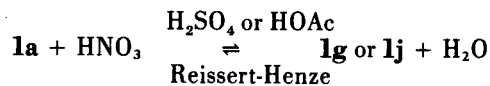
Compound No.	λ max (nm)	log ϵ	Compound No.	λ max (nm)	log ϵ
1a	235	4.55	1e	236	4.54
	281	3.97		285	3.89
	310	3.69		312	3.70
	320	3.69		322	3.72
1b	237	4.55	1c	236	4.81
	285	3.78			
	312	3.61		326 sh	4.26
	320	3.61		358	4.39
1k	243	4.46	1h	245	4.55
	286	3.81		287	4.00
1i	248	4.58	1l	241	4.38
	289	3.98		286	4.14
	321	3.74			
1m	244	4.26	2b	244	4.68
	300 sh	4.12			
	322	4.20			
2c	241	4.72	2d	251	4.59
				322	4.09
3a	253	4.46	3b	236	4.51
	281	4.03			

(a) The designation sh means a shoulder, not a true maximum.

tion (replacement of an azine, as the substrate, by its *N*-oxide) of the better known Reissert reaction (3-7,15). Probably for this historical reason various investigators have used identical or closely similar experimental procedures in both reactions. In following this trend, we selected the methodology of Dyke and Ellis (for Reissert reaction on 6,7-methylenedioxyisoquinoline) (16) to use in our studies. Thus, the seven *N*-oxides **1a**, **1e-1g**, **1j**, **2a**, and **3a** were stirred at room temperature with a large excess of potassium cyanide-benzoyl chloride in a two-phase mixture of water-methylene chloride for 16 hours. Under these conditions five of the seven substrates, *i.e.* all but the nitro compounds **1g** and **1j**, reacted "normally" to effect *N*-deoxygenation plus α cyanation (17). These transformations were easily verified by means of infrared spectra (loss of *N*-oxide band at *ca.* 1250 cm^{-1} , appearance of nitrile absorption at *ca.* 2220 cm^{-1}), while the location of the cyano substituent (including the conversion of the isoquinoline analog **3a** into the 4-cyano product, **3b**) followed from the disappearance of the most-downfield signal in the pmr spectrum of each starting heterocycle. Yields varied from *ca.* 45% for the parent thieno[*b*]pyridine systems **1** and **2** to 60-70% for the 4-methyl and 4-chloro derivatives of **1** and 84% for the parent thieno[*c*]pyridine system **3**.

The nitro *N*-oxides underwent Reissert-Henze reaction with loss of the nitro group. However, there was a marked difference in the reactivities and product yields of the two

isomers. Thus, the 5-nitro derivative **1j** reacted under the aforementioned conditions; but it produced a tarry mixture, which showed infrared absorption for the presence of the cyano group but not for the nitro group. Isolated was a small yield (7%) of 6-cyanothieno[2,3-*b*]pyridine (**1k**). In contrast, the 4-nitro isomer was recovered unchanged under the previous reaction conditions. It did react, nonetheless, in a refluxing water-chloroform mixture to give a nearly quantitative yield of two products, **1k** (51%) and 4-chloro-6-cyanothieno[2,3-*b*]pyridine (**1i**) (46%). Replacement of the 4-nitro substituent by chlorine has precedent in the reaction of **1g** with refluxing acetyl chloride to form **1f** (8) and in the observation that the isosteric 4-nitroquinoline 1-oxide produces 4-chloro-2-cyanoquinoline in the Reissert-Henze reaction (18). It was suggested that a chloride ion displaces the nitro group as a nitrite ion in this reaction (7). In contrast, replacement of the nitro group by hydrogen in either **1g** or **1j** can be considered a reversal (hydrolysis) of the electrophilic nitration of **1a** (8). Loss of



the 5-nitro group from **1j** contrasts with the results of Kaneko (19) who obtained a 20% yield of 2-cyano-3-nitroquinoline from the isosteric 3-nitroquinoline 1-oxide.

According to the correlation concept of Klemm (20) the Reissert-Henze reaction should yield isosteric products in the quinoline, thieno[2,3-*b*] (**1**), and thieno[3,2-*b*]pyridine (**2**) series. This correlation holds very well for **1a**, **1e-1g** (7,18), and **2a**. It can even be invoked in the systems **3a** and isoquinoline 2-oxide (3). At this point, however, the aforementioned contrast in isolated products from Reissert-Henze reactions of **1j** and its isostere may be an exception to the rule and warrants further investigation.

Mass spectra of the nitriles **1k**, **2b**, and **3b** showed loss of hydrogen cyanide from the molecular ion (corroborated by a metastable peak) and formation of the thioformyl ion (*m/e* 45). The first two compounds also ejected carbon monosulfide. Methyl derivative **1h** lost both a hydrogen atom and hydrogen cyanide, while chloro compound **1i** lost a chlorine atom and produced thioformyl ion. These fragmentation patterns are consistent with published data for thienopyridines and nitriles (10,12,20,21).

Surprisingly, experimental procedures for the Reissert or the Reissert-Henze reaction (6,16) fail to mention the formation of a considerable quantity of byproduct benzoic anhydride (usually contaminated with a small amount of benzoic acid from hydrolysis). This byproduct is separated from the cyanoheterocycle either by recrystallization of the crude product mixture or by direct, preparative tlc on silica gel.

In two cases (**1k** and **2b**) the cyanoheterocycle was hydrated to the corresponding carboxamide (**1l** and **2c**) in

yields of ca. 68% by means of warm alkaline hydrogen peroxide (23). An effort to convert **1k** to its sulfone by means of hydrochloric acid and sodium hypochlorite in aqueous solution, as effected on **1** (24), was unsuccessful. However, continuing the reaction for 5 days at room temperature also produced **1l** (89%). The correlation of the reactions **1k** → **1l** and 6-cyanobenzo[*b*]thiophene → 6-carbamoylbenzo[*b*]thiophene has been noted (20). The carboxamides were characterized by three amide NH and NH₂ bands in the region 3180-3450 cm⁻¹ and carbonyl absorptions in the region 1650-1705 cm⁻¹ (25), as well as the presence of an appreciable signal at *m/e* 135 for loss of HNCO (100% for **2c**) and/or 134 (65% for **1l**, 54% for **2c**) (26) in the mass spectra.

Compounds **1l** and **2c** were converted to their yellow thiocarboxamides (**1m** and **2d**) in yields of ca. 40% by heating with Lawesson's reagent (**4**) in toluene (27). These were characterized by the presence of three sharp bands for NH and NH₂ in the region 3155-3360 cm⁻¹ and a sharp combination (NH deformation plus C-N stretching) band at 1605 cm⁻¹ (28,29), as well as significant mass spectral peaks at *m/e* 160 for loss of hydrogen sulfide (79% for **1m**, 100% for **2d**), 134 for loss of H₂NCS (38% and 21%), and 45 for formation of the thioformyl ion (100% and 15%) (14c,22).

Ultraviolet absorption spectral data for **1a** and the thirteen new compounds reported in this paper are presented in Table I. As expected, the spectra for the pairs (**1a,1e**) and (**1k,1h**) are closely similar but with corresponding maxima shifted bathochromically by 1.5 nm due to the 4-methyl group. Complexation of **1a** with boron trifluoride (see **1b**) gives an effect similar to that of the 4-methyl group.

The contrast in the spectra of the amides and thioamides is rationalized in terms of the greater polarizability of sulfur than of oxygen.

EXPERIMENTAL (30)

Thieno[3,2-*c*]pyridine 5-Oxide Hemihydrate (**3a**).

A solution of 1.37 g of thieno[3,2-*c*]pyridine (**3**) (31) in 3 ml of glacial acetic acid and 3.4 ml of 30% hydrogen peroxide was maintained at 55° for 24 hours. It was poured into water, basified with solid sodium bicarbonate, treated with aqueous sodium bisulfite until a starch-iodide test was negative, and extracted repeatedly with chloroform. Evaporation of the extract left 1.08 g (67%) of **3a**, mp 65-77°, converted to a cream powder (mp 82-84°) by sublimation at 40-45° (0.005 mm) and recrystallization from acetone-cyclohexane; ir: 3300 (broad H₂O), 1250 cm⁻¹ (N → O); pmr: δ 8.77 (d, J_{4,6} = 1.8 Hz, H-4), 8.17 (d of d, J_{6,7} = 7 Hz, H-6), 7.75 (d, H-7) which overlaps 7.68 (d, J_{2,3} = 5.5 Hz, H-2), 7.30 (d, H-3), 2.92 (s, 1H, 0.5 H₂O); ms (110°): 152 (10), 151 (M⁺, 100), 136 (11), 135 (M-O), 94, 134 (15), 124 (11), 96 (27), 70 (13), 69 (11), 63 (10), 45 (CHS⁺, 12).

Anal. Calcd. for C₇H₇NOS·½H₂O: C, 52.5; H, 3.8; N, 8.8. Found: C, 52.3; H, 3.5; N, 8.6. Calcd. for C₇H₇NOS: exact mass, 151.009. Found: exact mass: 151.009.

4-Methylthieno[2,3-*b*]pyridine 7-Oxide (**1e**) (32).

In the preceding manner 4 g of 4-methylthieno[2,3-*b*]pyridine (**1d**) (33) was converted into **1e**, yield 0.7 g (16%) of pale yellow needles, mp 184-186° dec, unchanged on sublimation at 100° (0.005 mm); ir: 1240 cm⁻¹ (N-oxide); pmr: δ 8.25 (d, J_{5,6} = 7 Hz, H-6), 7.59 (d, J_{2,3} = 6 Hz, H-2), 7.39 (d, H-3), 7.13 (d, H-5), 2.65 (s, Me); ms (110°): 165 (M⁺, 100), 149 (M-O), 55, 136 (M-CHO), 65, 109 (23), 69 (22), 65 (23), 63 (33), 51 (31), 50 (22), 45 (CHS⁺, 40).

Anal. Calcd. for C₈H₇NOS: C, 58.2; H, 4.3; N, 8.5; exact mass, 165.025. Found: C, 57.9; H, 4.6; N, 8.4; exact mass, 165.024.

Thieno[2,3-*b*]pyridine 7-Oxide (**1a**).

Thieno[2,3-*b*]pyridine (**1**) was synthesized and converted to **1a** as previously indicated (8,33); uv (see Table I); ms (100°): 153 (5), 152 (9), 151 (M⁺, 100), 135 (M-O), 34, 134 (6), 123 (M-CHO), 5, 122 (19), 96 (26), 70 (6), 69 (7), 63 (5), 45 (CHS⁺, 6).

Anal. Calcd. for C₇H₅NOS: exact mass, 151.009. Found: exact mass, 151.009.

Thieno[2,3-*b*]pyridine 7-Oxide-Trifluoroborane (**1b**) (11).

To a solution of 1.02 g (6.75 mmoles) of anhydrous thieno[2,3-*b*]pyridine 7-oxide (**1a**) in chloroform was added a slight excess (1 g, 7.05 mmoles) of boron trifluoride-etherate (Aldrich) in ether solution. Heat was evolved. The cooled reaction mixture was evaporated to yield white, hygroscopic adduct, purified by slow evaporative distillation at 130-140° (0.05 mm) to yield 0.96 g (65%) of **1b** as a white powder, mp 126-129°; ir: 3140 cm⁻¹ (aromatic CH); pmr (hexadeuterioacetone): δ 9.00 (d, J_{5,6} = 6.4 Hz, H-6), 8.87 (d, J_{4,5} = 8.1 Hz, H-4), 8.18 (d, J_{2,3} = 5.8 Hz, H-2), 7.9-8.14 (complex m, H-5), 7.80 (d, H-3); ms (130°): 196 (13), 151 (1a⁺, 40; HR), 135 (1⁺, 100), 134 (17), 132 (23), 104 (13), 102 (36), 74 (15), 53 (13).

Anal. Calcd. for C₇H₃BF₃NOS: C, 38.4; H, 2.3; N, 6.4. Found: C, 38.3; H, 2.1; N, 6.3.

7-Hydroxythieno[2,3-*b*]pyridinium Picrate (**1c**).

Solutions of 1 g of thieno[2,3-*b*]pyridine 7-oxide (**1a**) and 1.52 g (an equimolar amount) of picric acid in methanol were stirred together for several hours and then evaporated to dryness. The residue was recrystallized from methanol to give 2.41 g (96%) of yellow powder, mp 142.5-144°; ir: 3090 (aromatic CH), 1570 and 1340 cm⁻¹ (NO₂); pmr (hexadeuterioacetone): δ 9.02 (s, 2H, TNP aromatic CH), 8.66 (d, J_{5,6} = 6.0 Hz, H-6), 8.28 (d, J_{4,5} = 7.8 Hz, H-4), 8.00 (d, J_{2,3} = 5.7 Hz, H-2), 7.85-7.55 (m, 2H, H-3 and H-5); pmr (hexadeuteriodimethylsulfoxide): δ 8.64 (s, 2H, TNP aromatic CH), 8.55 (d, J_{5,6} = 6.2 Hz, H-6), 8.10 (d, J_{4,5} = 8.1 Hz, H-4), 7.98 (d, J_{2,3} = 5.7 Hz, H-2), 7.75-7.5 (m, 2H, H-3 and H-5); ms (180°): 229 (TNP⁺, 60), 199 (TNP-NO), 79, 151 (1a⁺, 100; HR), 135 (1⁺, 40), 122 (20), 96 (31), 91 (16), 69 (12), 63 (13), 62 (16), 51 (10), 45 (CHS⁺, 12).

Anal. Calcd. for C₁₃H₈N₄O₈S: C, 41.1; H, 2.1; N, 14.7. Found: C, 41.2; H, 2.2; N, 14.9.

6-Cyanothieno[2,3-*b*]pyridine (**1k**).

A well-stirred mixture of 1 g (6.6 mmoles) of thieno[2,3-*b*]pyridine 7-oxide (**1a**), 1.7 g (26 mmoles) of potassium cyanide, 14 ml of methylene chloride, and 4 ml of water at 25° was treated dropwise (over a period of 10 minutes) with 2.8 g (20 mmoles) of benzoyl chloride. After 16 hours of additional stirring the organic layer was separated, washed successively with water, 10% hydrochloric acid, water, 2 N sodium hydroxide, and water, dried (sodium sulfate), and evaporated. The residue was recrystallized from methylene chloride and then from ethanol to give 0.49 g (46%) of shiny leaflets, mp 113-114.5°, raised to 116-117.5° on sublimation at 40° (0.02 mm); ir: 2220 cm⁻¹ (CN); pmr: δ 8.17 (d, J_{4,5} = 8.2 Hz, H-4), 7.81 (d, J_{2,3} = 6 Hz, H-2), 7.64 (d, H-5), 7.35 (d, H-3); ms (60°): 160 (M⁺, 100), 134 (18), 133 (M-HCN), 32, 116 (M-CS), 43, 105 (16), 82 (17), 80 (M⁺, 41), 69 (21), 63 (21), 50 (15), 45 (CHS⁺, 43); 110.5* (160 → 133).

Anal. Calcd. for C₈H₄N₂S: C, 60.0; H, 2.5; N, 17.5; S, 20.0; exact mass, 160.010. Found: C, 60.0; H, 2.6; N, 17.6; S, 19.7; exact mass, 160.009.

Evaporative distillation at 100° (0.015 mm) of the residues from recrystallization mother liquors gave a white solid (mp 37-38°), identified as benzoic anhydride by direct comparison (mixture mp, ir, and pmr spectra) with an authentic sample.

5-Cyanothieno[3,2-*b*]pyridine (**2b**).

In the preceding manner, 5.6 g of thieno[3,2-*b*]pyridine 4-oxide (**2a**) (9) was converted into **2b**, yield 2.54 g (43%) of shiny needles (ethanol), mp 169-173°, raised to 173-174° on sublimation at 60° (0.005 mm); ir: 2220 cm⁻¹ (CN); pmr: δ 8.46 (d of d, J_{6,7} = 8.6 Hz, J_{3,7} = 1 Hz, H-7), 7.97 (d, J_{2,3} = 5.7 Hz, H-2), 7.65 (d, H-3), which overlaps 7.64 (d, H-6); ms (90°): 162 (5), 161 (11), 160 (M⁺, 100), 133 ([M-HCN], 5), 116 ([M-CS], 4), 45 (CHS⁺, 4); 110-111* (160 - 133).

Anal. Calcd. for C₆H₄N₂S: C, 60.0; H, 2.5; N, 17.5; S, 20.0; exact mass 160.010. Found: C, 60.2; H, 2.3; N, 17.7; S, 19.8; exact mass, 160.011.

The mother liquor from recrystallization of **2b** yielded 0.96 g of white solid, shown to be a mixture of benzoic acid and benzoic anhydride by means of ir, pmr, and tlc analyses involving authentic reference compounds.

4-Cyanothieno[3,2-*c*]pyridine (**3b**).

Analogously, *N*-oxide **3a** (0.45 g) yielded **3b**. In this case the residue (1.09 g) from evaporation of the methylene chloride solution was directly fractionated into **3b** [0.38 g (84%), mp 88-90°; raised to 90-91.5° by sublimation; R_f 0.34] and benzoic acid-benzoic anhydride [0.27 g, semisolid, R_f 0.63; pmr: δ 11.49 (s, small peak), 8.3-8.0 and 7.8-7.3 (complex patterns - area ratio 1:1.55)] by preparative tlc with chloroform and four 20 × 20-cm plates bearing 30 g of silica gel each. Product **3b** showed these spectral properties; ir: 2220 cm⁻¹ (CN); pmr: δ 8.56 (d, J_{6,7} = 5.5 Hz, H-6), 8.05 (d of d, J_{3,7} = 1 Hz, H-7), 7.80 (d, J_{2,3} = 5.5 Hz, H-2), 7.64 (d of d, H-3); ms (100°): 162 (5), 161 (11), 160 (M⁺, 100), 133 ([M-HCN], 14), 69 (5), 63 (5), 45 (CHS⁺, 7); 110-111* (160 - 133).

Anal. Calcd. for C₆H₄N₂S: C, 60.0; H, 2.5; N, 17.5; S, 20.0; exact mass, 106.010. Found: C, 60.2; H, 2.4; N, 17.5; S, 19.9; exact mass, 160.010.

4-Methyl-6-cyanothieno[2,3-*b*]pyridine (**1h**).

As in the preparation of **3b**, 0.3 g of 4-methyl-thieno[2,3-*b*]pyridine 7-oxide (**1e**) was converted into **1h** and separated by preparative tlc. Recrystallization from ethanol gave 0.19 g (60%), mp 123-126° (shiny needles, mp 124-126°, after sublimation); ir: 2220 cm⁻¹ (CN); pmr: δ 7.82 (d, J_{2,3} = 6 Hz, H-2), 7.4-7.6 (complex, H-3 and H-5), 2.71 (s, Me); ms (100°): 176 (5), 175 (13), 174 (M⁺, 100), 173 (21), 147 ([M-(H + HCN)], 7), 146 (7); 172-173* (174 - 173); 124-125* (174 - 147, 173 - 147).

Anal. Calcd. for C₆H₆N₂S: C, 62.0; H, 3.5; N, 16.1; exact mass, 174.025. Found: C, 61.9; H, 3.7; N, 16.3; exact mass, 174.025.

4-Chloro-6-cyanothieno[2,3-*b*]pyridine (**1i**).

By the procedure used for **1k** there was obtained from 0.6 g of 4-chlorothieno[2,3-*b*]pyridine 7-oxide (**1f**) (8) 0.44 g (70%) of **1i**, elongated prisms, mp 128-130° (95% ethanol, unchanged on sublimation), positive tests for Cl and S by sodium fusion (34); ir: 2230 cm⁻¹ (CN); pmr: δ 7.92 (d, J_{2,3} = 5.8 Hz, H-2), 7.69 (s, H-5), 7.53 (d, H-3); ms (80°): 196 (M⁺, 38), 195 (11), 194 (M⁺, 100), 159 ([M-Cl], 15), 63 (8), 45 (CHS⁺, 7).

Anal. Calcd. for C₆H₄ClN₂S: C, 49.4; H, 1.6; N, 14.4; exact mass, 193.971. Found: C, 49.5; H, 1.5; N, 14.4; exact mass, 193.971.

Reissert-Henze Reaction of 5-Nitrothieno[2,3-*b*]pyridine 7-Oxide (**1j**).

A mixture of 1.3 g (6.6 mmoles) of **1j** (8), 1.7 g (26 mmoles) of potassium cyanide, 14 ml of methylene chloride, and 4 ml of water was treated with 1.15 ml (9.9 mmoles) of benzoyl chloride by the procedure used for reaction of **1a**. In contrast to the reaction of **1a**, however, the original mixture turned red-brown as soon as stirring was started and before benzoyl chloride was added. The crude dark product showed ir absorption (chloroform) at 2240 cm⁻¹ (CN), but no bands for the nitro group. Tlc (silica gel-chloroform) gave a spot which corresponded to that of **1k**. Kügelrohr purification of the crude mixture at 40-50° (0.005 mm) yielded 73 mg (7%) of white solid, mp 112.5-114°, identified as **1k** by direct comparison therewith. The dark, tarry residue was not investigated fur-

ther.

Reissert-Henze Reaction of 4-Nitrothieno[2,3-*b*]pyridine 7-Oxide (**1g**).

A mixture of 0.6 g (3.06 mmoles) of **1g** (8), 0.8 g (12.3 mmoles) of potassium cyanide, 1.1 ml (9.5 mmoles) of benzoyl chloride, 30 ml of chloroform, and 3 ml of water was stirred and refluxed for 16 hours. The organic layer was washed in the same manner as used in methylene chloride runs and evaporated. On standing the brown residue crystallized partially. Tlc of this residue with silica gel-chloroform showed three spots corresponding to **1k** (smallest R_f), **1i**, and benzoic anhydride (largest R_f). Removal of the benzoic anhydride was effected by trituration with carbon tetrachloride to leave a solid mixture of nitriles. Further crops of solids were obtained by dissolving the trituration residues in 95% ethanol, adding water to incipient precipitation, and refrigeration. The solids were then recrystallized from ethanol to give 4-chloro-6-cyanothieno[2,3-*b*]pyridine (**1i**, 271 mg, 46%, mp 128-130°; separating first) and 6-cyanothieno[2,3-*b*]pyridine (**1k**, 248 mg, 51%, mp 112.5-114°).

An attempt to carry out the Reissert-Henze reaction on **1g** by the method used on **1a** and **1f** gave only recovered starting material.

6-Carbamoylthieno[2,3-*b*]pyridine (**1l**).

(a) Use of Alkaline Hydrogen Peroxide.

To a well-stirred mixture of 0.15 g (0.94 mmole) of nitrile **1k**, 1.5 ml of 95% ethanol, and 1.5 ml of 1 *N* sodium hydroxide was added dropwise 1.5 ml (5.3 mmoles) of 12% hydrogen peroxide (with occasional cooling to moderate foaming). The solution was then maintained at 50-60° for one hour, diluted with water, and refrigerated to yield shiny needles of **1l**, recrystallized from aqueous ethanol, yield 0.11 g (66%), mp 176-178°, raised to 177-179° on sublimation at 70-80° (0.005 mm); ir 3450 (free amide NH₂), 3280 and 3220 (H-bonded amide NH), 1680 and 1650 cm⁻¹ (C=O); pmr: δ 8.25 (broad s, 2H, H-4 and H-5), 7.71 (d, J_{2,3} = 6.2 Hz, H-2), 7.36 (d, H-3); ms (100°): 180 (6), 179 (11), 178 (M⁺, 100), 162 ([M-NH₂], 7), 135 (8), 134 ([M-H₂NCO], 65) (133) (44).

Anal. Calcd. for C₆H₆N₂OS: C, 53.9; H, 3.4; N, 15.7; exact mass, 178.020. Found: C, 53.9; H, 3.4; N, 15.6; exact mass, 178.020.

(b) Use of Sodium Hypochlorite.

To a vigorously stirred mixture of 0.2 g (1.25 mmoles) of nitrile **1k** and 5 ml (2.5 mmoles) of 0.5 *M* hydrochloric acid at room temperature was added dropwise over a period of one hour 7.6 ml (2.5 millimoles) of 0.33 *M* aqueous sodium hypochlorite. The mixture was stirred for 5 days, whereupon it showed a negative starch-iodide test and a pH > 7. A chloroform extract of the mixture was dried (magnesium sulfate) and evaporated to yield 0.198 g (89%) of **1l**, mp 169-172°, raised to 176-178° on recrystallizations from chloroform, identical with product from part (a) as based on mixture mp and spectral comparisons.

6-Thiocarbamoylthieno[2,3-*b*]pyridine (**1m**) (27).

A mixture of 356 mg (2 mmoles) of preceding carboxamide **1l**, 492 mg (1.2 mmoles) of Lawesson's reagent (**4**) (35) (Aldrich), and 2.5 ml of toluene was refluxed in an atmosphere of nitrogen for 5 hours. The solvent was evaporated and the residue was sublimed slowly at 110-120° (0.05 mm) to give 168 mg (43%) of **1m** as yellow discs, mp 174-176°; ir: 3360, 3250, and 3160 (sharp, NH and NH₂), 1605 cm⁻¹ (sharp, combination band); pmr: δ 8.76 and 8.17 (d of d, J_{4,5} = 8.4 Hz, H-4 and H-5), 7.72 and 7.35 (d of d, J_{2,3} = 5.8 Hz, H-2 and H-3); ms (190°): 194 (M⁺, 24), 161 (36), 160 ([M-H₂S], 79), 134 ([M-H₂NCS], 38), 82 (27), 81 (24), 69 (40), 64 (32), 63 (46), 62 (30), 60 (H₂NCS⁺, 47), 58 (34), 51 (29), 50 (33), 45 (HCS⁺, 100).

Anal. Calcd. for C₆H₆N₂S₂: C, 49.5; H, 3.1; N, 14.4; exact mass, 193.997. Found: C, 49.4; H, 3.0; N, 14.3; exact mass, 193.997.

5-Carbamoylthieno[3,2-*b*]pyridine (**2c**).

As in foregoing method (a) for the formation of **1l**, a mixture of 323 mg of 5-cyanothieno[3,2-*b*]pyridine (**2b**), 3 ml of 95% ethanol, and 3 ml of 1 *N* sodium hydroxide was treated with 3 ml of 12% hydrogen peroxide to produce 250 mg (70%) of **2c**, mp 146-148°, raised to 151-153° after re-

crystallization (needles from ethanol) and sublimation at 50° (0.005 mm); ir: 3440, 3260, and 3180 (NH and NH₂ bands), 1705-1675 (broad, C=O); pmr: δ 8.32 (d, J_{6,7} = 8.4 Hz, H-7), 8.17 (d, H-6), 7.82 (d, J_{2,3} = 5.5 Hz, H-2), 7.54 (d, H-3); ms (110°): 179 (10), 178 (M⁺, 93), 136 (12), 135 ([M-HNCO], 100), 134 ([M-H₂NCO], 54), 90 (10), 63 (12), 45 (8), 44 (8); 102-103* (178 - 135).

Anal. Calcd. for C₈H₆N₂OS: C, 53.9; H, 3.4; N, 15.7; exact mass, 178.020. Found: C, 53.8; H, 3.2; N, 15.7; exact mass 178.021.

5-Thiocarbamoylthieno[3,2-b]pyridine (2d).

Following the exact procedure for the conversion of **1f** into **1m** gave 137 mg (35%) of thiocarboxamide **2d**, yellow granules, mp 189-191°, from preceding **2c**. Spectral data found for **2d** are ir: 3330, 3240, and 3155 (sharp, NH and NH₂), 1605 cm⁻¹ (sharp, combination band); pmr (hexadeuterioacetone): δ 8.71 and 8.55 (d of d, J_{6,7} = 8.6 Hz, H-6 and H-7), 8.17 (d, J_{2,3} = 5.5 Hz, H-2), 7.58 (d, H-3); ms (170°): 194 (M⁺, 38), 161 ([M-HS], 38), 160 ([M-H₂S], 100), 135 (27), 134 ([M-H₂NCS], 21), 69 (14), 63 (15), 45 (HCS⁺, 15).

Anal. Calcd. for C₈H₆N₂S₂: C, 49.5; H, 3.1; N, 14.4; exact mass, 193.997. Found: C, 49.3; H, 3.0; N, 14.2; exact mass, 193.997.

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