Chemistry of Thienopyridines. XXXIII. Synthetic Routes to 5- and 7-Substituted Thieno[3,2-*b*]pyridines from the *N*-Oxide [1]

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Thieno[3,2-*b*]pyridine (**1**) is oxidized to *N*-oxide **1a** by means of *m*-chloroperoxybenzoic acid (83%). Compound **1a** forms adducts with hydrogen chloride and picric acid and gives ring substitution *alpha* or *gamma* to the heteronitrogen atom. Thus, **1a** plus nitric and sulfuric acids produces the 7-nitro-*N*-oxide **1m** (63%), or plus phosphorus oxychloride gives a mixture of 5-chloro and 7-chloro (**1j**) derivatives of **1**. Compound **1m** is convertible into a variety of other derivatives of **1**, *viz.* 7-chloro-*N*-oxide, **1j**, 7-bromo-*N*-oxide, 7-nitro and 7-amino. 5-Cyano-**1**, formed from **1a**, is, in turn, transformed into a methyl imidate (93%), cyclic amidines, and a 5-tetrazolyl-**1** (91%). These results confirm the prediction that **1a**, thieno[2,3-*b*]pyridine-4-oxide and quinoline 1-oxide should exhibit closely similar (*i.e.* analogous) chemical reactions.

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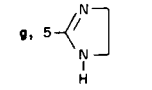
In previous studies we reported that halogenation and nitration of thieno[3,2-*b*]pyridine (**1**) and thieno[2,3-*b*]pyridine (**2**) occur at C-3, while lithiation of these two compounds occurs at C-2 [5-7]. Analogously, it is predicted that reactions of *N*-oxides in the **1**, **2**, and quinoline systems should exhibit closely similar substitution patterns in the pyridine ring [8]. The present study is an attempt to probe the accuracy of this prediction by conducting some of the same reactions in system **1** as have already been pursued in the other ones.

As a starting material for these studies we employed thieno[3,2-*b*]pyridine-4-oxide monohydrate (**1a**), obtained in markedly improved yield (83%) from parent compound **1** by *N*-oxidation with *m*-chloroperoxybenzoic acid instead of hydrogen peroxide/acetic acid, as used previously [9]. Compound **1a** adds hydrogen chloride or picric acid to give crystalline derivatives **1b** and **1c**, as with **2a** [10,11] and quinoline 1-oxide [12,13a]. Nitration of **1a** by means of nitric acid/sulfuric acid occurs at C-7 (*gamma* to the heteronitrogen atom) to give nitro *N*-oxide **1m** (63%), converted (a) to the 7-chloro *N*-oxide **1n** (73%) in refluxing acetyl chloride (b) to a mixture of 7-bromo *N*-oxide **1o** (39%) and 7-nitro-**1** (**1k**) (36%) by means of acetyl bromide, and (c) to 7-amino-**1** hydrate (**1l**) (56%) on reduction with iron/acetic acid. The nitration plus subsequent steps (a) and (c) are analogous to reactions which have been reported for systems **2a** [14] and quinoline 1-oxide [13b,13d,15].

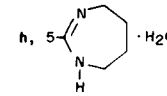
Refluxing **1a** with phosphorus oxychloride produced an isomeric mixture of 7-chloro (**1j**) and 5-chloro (**1d**) derivatives of **1** in a ratio of 1.4:1, as based on pmr analysis of the crude product. These isomers are easily separated by thick-layer chromatography on silica gel, whereon the γ-isomer (*i.e.* **1j**) is more tenaciously retained [16], and are readily distinguished and structurally identified by means

1

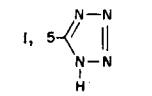
a, 4-oxide · H_2O
b, 4-oxide · HCl
c, 4-oxide · TNP
d, 5-Cl
e, 5-CN
f, 5-C(=NH)OCH_3



g, 5-

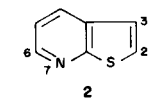


h, 5- · H_2O



i, 5-

j, 7-Cl
k, 7-NO_2
l, 7-NH_2·1/3 H_2O
m, 7-NO_2-4-oxide
n, 7-Cl-4-oxide
o, 7-Br-4-oxide



2

a, 7-oxide
b, 6-CN

of the chemical shift (δ 8.08 for **1d**, 8.57 for **1j**) of the lowest field doublet in the pmr spectrum. Additionally, the structure of **1j** was corroborated by direct comparison with the chlorothienopyridine which results from *N*-deoxygenation of the aforementioned **1n**. Moreover, both **1d** and **1j** have been reported before from independent syntheses [19-21]. It was noted previously that action of phosphorus oxychloride on quinoline 1-oxide or thieno[2,3-*b*]pyridine 7-oxide (**2a**) yields a preponderance (1.7:1) of γ-chloro over α-chloro substitution [17]. Apparently, a similar predominance of γ- to α-substitution occurs with **1a**, but our total yield (24%) of isolated chloro isomers is too small to establish this relationship with assurance.

An earlier paper described the conversion of *N*-oxide **1a** into nitrile **1e** (43%) by means of the Reissert-Henze reaction [10], conducted in a two-phased system (methylene chloride/water) with magnetic stirring. Repetition of this reaction but with more efficient mixing (motor-driven stirrer and a creased flask [22]) increased the yield to 99%. As with the isomeric **2b** [23], **1e** was transformed first into a methyl imidate (**1f**, 93%) by treatment with methanolic sodium methoxide and then into the cyclic amidines **1g** (48%) and **1h** (39%) by reaction with ethylene diamine and 1,4-diaminobutane, respectively. Additionally, nitrile **1e** reacted with ammonium azide in dimethylformamide to produce tetrazole **1i** (91%). Compound **1i** is thermally unstable, as evidenced by the evolution of gas at its melting point (238°) and the loss of four nitrogen atoms from its molecular ion to give the most abundant fragment at m/e 147 in its mass spectrum (inlet temperature 200°).

In summary, it is now clear that the *N*-oxides of quinoline, thieno[2,3-*b*]pyridine, and thieno[3,2-*b*]pyridine exhibit analogous reactions to yield isosteric products in (a) adduction with proton acids [10-12,13a], (b) electrophilic nitration *gamma* to the heteronitrogen atom by means of nitric acid/sulfuric acid at elevated temperature [13b,14,15], (c) nucleophilic α-cyanation plus *N*-deoxygenation in the Reissert-Henze reaction [10,13c], and (d) either α- or γ-chlorination plus *N*-deoxygenation on treatment with phosphorus oxychloride [17]. Moreover, primary products from (b) and (c) undergo the analogous secondary transformations (e) γ-nitro *N*-oxide → γ-chloro *N*-oxide by means of acetyl chloride [14,24], (f) γ-nitro *N*-oxide → γ-amino compound on reduction by means of iron/acetic acid [13d,14], and (g) α-cyano derivative → α-carbamoyl derivative on hydration with alkaline hydrogen peroxide [10,25] in all three series, plus (h) α-cyano derivative → methyl imidate → amidines in both thienopyridine series (*vide supra*) [26].

EXPERIMENTAL [27]

Thieno[3,2-*b*]pyridine 4-Oxide Monohydrate (**1a**).

To a stirred solution of 75 g (0.555 mole) of thieno[3,2-*b*]pyridine (**1**) [7] in 2.5 ℓ of chloroform was added, in small portions over a period of 2 hours, 120 g (0.6 ± 0.04 mole) of *m*-chloroperoxybenzoic acid (Aldrich, 80-90%). Stirring at room temperature was continued for 4 days. The solution was extracted twice with 1.2-ℓ portions of 10% aqueous sodium hydroxide. The organic layer, combined with chloroform extracts of the alkaline layer, was dried (sodium sulfate) and evaporated. Evaporative distillation of the brown residue gave 77.7 g (83%) of **1a** as a yellow solid, mp 78-82°; lit 79-80° [9]; pmr: δ 8.31 (d, $J_{5,6}$ = 6.3 Hz, H-5), 7.87 (d, $J_{2,3}$ = 5.7 Hz, H-3), 7.77 (d, $J_{6,7}$ = 8.2 Hz, H-7), 7.72 (d, H-2), 7.24 (dd, H-6) [28]; ms (50°): m/e 151 (**1**-*N*-oxide$^+$, 60), 135 (**1**$^+$, 100), 134 (11), 96 (21), 45 (CHS^+, 12).

4-Hydroxythieno[3,2-*b*]pyridinium Chloride (**1b**).

A stirred solution of 0.75 g of *N*-oxide hydrate **1a** in benzene was treated with anhydrous hydrogen chloride gas for 10 minutes. The white precipitate of **1b** was dried in a desiccator and sublimed at 60° (0.25 mm) to yield 0.57 g (69%) of crystals, mp 185-190°, raised to 187.5-190° on repeated sublimation; ir: 2140 cm^{-1}, (broad, O-H-Cl) [12]; pmr (hexadeuteriodimethyl sulfoxide): δ 8.96 (d, $J_{5,6}$ = 6 Hz, H-5), 8.82 (d, $J_{6,7}$ = 8 Hz, H-7), 8.55 (d, $J_{2,3}$ = 5.5 Hz, H-2), 8.0-7.7 (m, 2H, H-3 and H-6), 6.82 (s, 4H, sequestered H_2O?); ms (110°): m/e 152 (32), 151 (**1**-*N*-oxide$^+$, 100).

Anal. Calcd. for C_7H_6ClNOS: C, 44.80; H, 3.22; N, 7.47. Found: C, 44.53; H, 3.09; N, 7.33.

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

Separate solutions of *N*-oxide hydrate **1a** (0.5 g) and picric acid (0.76 g, 1.12 molar amount) in absolute methanol (50 ml total) were mixed, heated to dissolve the precipitate, and allowed to cool. The solid which formed was recrystallized from the same solvent to yield yellow needles, 0.91 g (81%), mp 130-131.5°; ir: 3080 (aromatic CH), 1560 and 1320 cm^{-1} (nitro); pmr (hexadeuteriodimethyl sulfoxide): δ 8.73 (d, $J_{5,6}$ = 6 Hz, H-5), 8.62 (s, 2H, TNP aromatic CH), 8.46 (d, $J_{6,7}$ = 9 Hz, H-7) which overlaps 8.39 (d, $J_{2,3}$ = 6 Hz, H-2 or H-3), 7.82 (d, H-3 or H-2), 7.65 (dd, J = 6 and J = 9 Hz, H-6); ms (170°): m/e 229 (TNP$^+$, 5), 153 (5), 152 (11), 151 (**1**-*N*-oxide$^+$, 100), 135 (**1**$^+$, 42), 134 (9), 122 (11).

Anal. Calcd. for $C_{13}H_8N_4O_8S$: C, 41.06; H, 2.12. Found: C, 40.87; H, 2.15.

7-Nitrothieno[3,2-*b*]pyridine 4-Oxide (**1m**).

To a stirred mixture of 23 ml of concentrated sulfuric acid (96%) and 26 ml of nitric acid (71%) at 0° was added 25 g of *N*-oxide hydrate **1a** over a period of 20 minutes. The reaction mixture was warmed to 120-130° over a period of 1.5 hours and maintained at this temperature for one hour longer. The cooled mixture was poured onto ice. The yellow precipitate was collected by filtration and washed successively with water, 5% aqueous sodium carbonate, and water. The dried solid (18.2 g, 63%, mp 186-190°) was recrystallized from acetone to form yellow needles, mp 196-198°; ir: 1560, 1510, 1350, 1335 (nitro), 1260 (N→O), 1200, 995, 735 cm^{-1}; pmr: δ 8.33 and 8.19 (2d, $J_{5,6}$ = 7.0 Hz, H-5 and H-6), 7.89 and 7.87 (2d, $J_{2,3}$ = 5.9 Hz, H-2 and H-3); ms (110°): m/e 196 (M^+, 67), 166 ([M - NO]$^+$, 26), 95 (25), 69 (56), 63 (53), 45 (CHS^+, 100).

Anal. Calcd. for $C_7H_4N_2O_3S$: C, 42.85; H, 2.05; N, 14.28. Found: C, 42.84; H, 2.13; N, 14.18.

7-Chlorothieno[3,2-*b*]pyridine 4-Oxide (**1n**).

A suspension of 10 g of 7-nitro-4-oxide **1m** in 90 ml of acetyl chloride was refluxed in a nitrogen atmosphere for 4 hours. The solution was concentrated by rotoevaporation and poured onto ice. Sodium carbonate was added to *p*H 9 and the mixture was extracted five times with 250-ml portions of chloroform. Evaporation of the dried (sodium sulfate), combined organic layers and column chromatography (490 g of Alcoa F-20 alumina/chloroform) of the residue gave 6.95 g (73%) of **1n** as a light yellow solid, mp 126-128°. Recrystallization from acetone, acetone-pentane, and ether plus sublimation (at 65°/0.05 mm) produced a white powder, mp 129-130°; ir: 1440, 1385, 1275 (N→O), 755 cm^{-1}; pmr: δ 8.25 (d, $J_{5,6}$ = 6.6 Hz, H-5), 7.88 and 7.75 (2d, $J_{2,3}$ = 5.7 Hz, H-2 and H-3), 7.23 (d, H-6); ms (110°): m/e 187 (M^+, 34), 185 (M^+, 100), 171 ([M - O]$^+$, 11), 169 ([M - O]$^+$, 26), 134 ([M - O - Cl]$^+$, 43), 130 (39), 122 (71), 95 (47) [29].

Anal. Calcd. for C_7H_4ClNOS: C, 45.29; H, 2.17; N, 7.55. Found: C, 45.17; H, 2.16; N, 7.47.

5- and 7-Chlorothieno[3,2-*b*]pyridines **1d** and **1j**. A. directly from *N*-Oxide **1a**.

A total quantity of 6.2 ml of phosphorus oxychloride was added dropwise to 514 mg of ice-cooled *N*-oxide **1a**. The mixture was refluxed for 4 hours and excess reagent was removed *in vacuo*. The residue was neutralized with 5% aqueous sodium bicarbonate and extracted with chloroform. The dried (sodium sulfate) extract was evaporated to leave a reddish brown liquid, which was separated into two zones (R_f = 0.34, 5-chloro isomer **1d**, and R_f = 0.1, 7-chloro isomer **1j**) by thick-layer chromatography on two 20 × 20-cm plates, with 30g of silica gel F_{254} each and chloroform as eluent. The pmr spectrum of the crude liquid indicated a ratio of **1d**:**1j** = 0.72 (as based on integration of the signals at δ 8.08 and 8.57, respectively), while corresponding isolated yields were 88

mg (17%) and 36 mg (7%).

Product **1d** showed these data: mp 62-66°, raised to 72-73.5° on sublimation at 23° (0.005 mm), lit [19,20] mp 64°; ir: 1560, 1535, 1390, 1145, 1115, 810, 765 cm^{-1}; pmr: δ 8.08 (dd, $J_{6,7}$ = 8.3 Hz, $J_{3,7}$ = 0.9 Hz, H-7), 7.76 (d, $J_{2,3}$ = 5.5 Hz, H-2), 7.48 (dd, H-3), 7.25 (d, H-6) [30]; uv: λ max 235 nm (log ε 4.51), 278 (3.81), 291 (3.80), 302 (3.71), [31]; ms: (60°) m/e 171 (M^+, 30), 169 (M^+, 82), 134 ([M - Cl]$^+$, 100), 90 (12), 63 (16).

Anal. Calcd. for C_7H_4ClNS: C, 49.56; H, 2.38; N, 8.26; exact mass (for ^{35}Cl), 168.975. Found: C, 49.63; H, 2.11; N, 8.30; exact mass, 168.975.

Sample **1j** was identified by direct comparison with product from part B (*vide infra*).

B. 7-Chlorothieno[3,2-*b*]pyridine from 7-Chloro *N*-Oxide **1n**.

A mixture of 976 mg of chloro *N*-oxide **1n**, 43 ml of glacial acetic acid, and 1.2 g of iron powder was stirred vigorously and heated to 100°, where the temperature was maintained for 2 hours. The cooled mixture was poured onto ice and solid sodium hydroxide was added to *p*H 11. Chloroform extracts of the mixture were dried (sodium sulfate) and evaporated. Molecular distillation of the residue, followed by crystallization from pentane, produced 0.48 g (54%) of needles (**1j**), mp 34-35.5°, lit [21] 46°; ir: 1565, 1530, 1325, 815, 765 cm^{-1}; pmr spectral data consistent with reported values [21]; ms: (40°) m/e 171 (M^+, 39), 169 (M^+, 100), 134 ([M - Cl]$^+$, 55), 63 (15); exact mass calcd: 168.975; found: 168.975.

7-Bromothieno[3,2-*b*]pyridine 4-Oxide (**1o**).

To 2.03 g of nitro *N*-oxide **1m** at room temperature was added 20 g of acetyl bromide (Aldrich). When the vigorous reaction (evolution of red-brown fumes) had subsided (5 minutes) the mixture was heated at 60° in a reflux apparatus for 4 hours. The mixture was poured onto ice and sufficient sodium carbonate was added to give a *p*H of 8. The chloroform extract of this alkaline mixture was dried (sodium sulfate) and evaporated. Chromatography (270 g of Alcoa F-20 alumina/chloroform) of the residue gave two fractions (R_f 0.68 and 0.11). The latter fraction was rechromatographed (50 g of 60-200 mesh Baker silica gel/acetone) to give 0.93 g (39%) of **1o**, mp 139-141°. Recrystallizations from acetone plus sublimation at 80° (0.05 mm) produced a light yellow powder, mp 148-149° dec; ir: 1440, 1385, 1270 (N→O), 755 cm^{-1}; pmr: δ 8.18 (d, $J_{5,6}$ = 6.6 Hz, H-5), 7.94 and 7.76 (2d, $J_{2,3}$ = 5.7 Hz, H-2 and H-3), 7.37 (d, H-6); ms: (110°) m/e 231 (M^+, 100), 229 (M^+, 100), 215 ([M - O]$^+$, 38), 213 ([M - O]$^+$, 26), 150 (29), 134 (54), 122 (83), 95 (27), 45 (32) [29].

Anal. Calcd. for C_7H_4BrNOS: C, 36.54; H, 1.75; N, 6.09. Found: C, 36.36; H, 1.72; N, 5.97.

7-Nitrothieno[3,2-*b*]pyridine (**1k**).

The fraction of R_f 0.68 from the preceding reaction of nitro *N*-oxide (**1m**) with acetyl bromide was purified by preparative thin layer chromatography (14 plates, 30 g of silica gel per plate/chloroform) to give 0.68 g (36%) of **1k**, mp 110-118°, obtained as light yellow needles on recrystallization from ether, mp 124-125°; ir: 1515 and 1350 (NO_2), 1270, 730 cm^{-1}; pmr: δ 8.99 (d, $J_{5,6}$ = 5.1 Hz, H-5), 8.12 (d, H-6), 8.02 (d, $J_{2,3}$ = 5.7 Hz, H-2), 7.74 (d, H-3) [28]; ms: (110°) m/e 180 (M^+, 73), 134 ([M - NO_2]$^+$, 100), 90 (29), 63 (97), 45 (CHS^+, 30).

Anal. Calcd. for $C_7H_4N_2O_2S$: C, 46.66; H, 2.24; N, 15.55. Found: C, 46.57; H, 2.19; N, 15.52.

7-Aminothieno[3,2-*b*]pyridine Hydrate (**1ℓ**).

To a mixture of 2.03 g of 7-nitrothieno[3,2-*b*]pyridine 4-oxide (**1m**) and 50 ml of glacial acetic acid at 100° was added cautiously 2.8 g of iron powder. One hour later the mixture was allowed to cool. It was poured onto ice, basified with 70 ml of 50% sodium hydroxide solution, and extracted repeatedly with chloroform. The residue from evaporation of the extract was dissolved in hot benzene. Concentration and cooling of the filtered solution yielded 0.9 g (56%) of **1ℓ** as tan plates, mp 123-133°, converted to colorless needles, mp 134-136°, on sublimation at 90° (0.05 mm); ir (1.3% in chloroform; calcium fluoride cell): 3500 and 3410 (NH), 1625, 1560 cm^{-1}; ir: 3500-2700 (broad, water?) 3430, 3390, 3180, 1655, 1580 cm^{-1}; pmr: δ 8.38 (d, $J_{5,6}$ = 5.3 Hz, H-5), 7.62 (d, $J_{2,3}$ = 5.4 Hz, H-2), 7.49 (d, H-3), 6.52 (d, H-6), 4.46 (s, 2H, NH_2), 1.93 (s, 0.6 H, ⅓ H_2O); ms: (110°) m/e 150 (M^+, 100), 123 ([M - HCN]$^+$, 42), 122 (22), 96 ([M - 2 HCN]$^+$, 19).

Anal. Calcd. for $C_7H_6N_2S \cdot \frac{1}{3}\ H_2O$: C, 53.82; H, 4.30; N, 17.94. Found: C, 53.58; H, 4.43; N, 17.94.

Methyl Thieno[3,2-*b*]pyridine-5-imidate (**1f**).

To a solution of sodium methoxide (0.01 mole) in 100 ml of methanol was added 16.7 g (0.104 mole) of 5-cyanothieno[3,2-*b*]pyridine (**1e**) [32]. The mixture was stirred in an atmosphere of nitrogen for 51 hours. During this period suspended **1e** dissolved. The reaction mixture was neutralized (*p*H 7) by addition of a 5% solution of acetic acid in methanol. Rotoevaporation of the solvent plus sublimation of the residue at 70° (0.05 mm) gave 18.6 g (93%) of **1f**, mp 91-97°; changed to 93.5-96° on recrystallization (fine, matted needles) from hexane plus sublimation at 33° (0.005 mm); ir (chloroform): 3290 (NH), 1645 cm^{-1} (C=N) [33]; pmr: δ 9.26 (broad s, NH), 8.25 (d, $J_{6,7}$ = 8 Hz, H-7), 7.84 (d, H-3) which overlaps 7.84 (d, H-6), 7.59 (d, $J_{2,3}$ = 6 Hz, H-2), 4.07 (s, methyl group); ms: (70°) m/e 192 (M^+, 63), 162 (15), 161 ([M - OCH_3]$^+$, 67), 160 (34), 135 (1^+, 100), 134 (42).

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.58; exact mass, 192.035. Found: C, 56.35; H, 4.01; N, 14.59; exact mass, 192.036.

5-(4,5-Dihydroimidazol-2-yl)thieno[3,2-*b*]pyridine (**1g**).

A solution of 0.35 ml (5.2 mmoles) of ethylene diamine and 1 g (equimolar amount) of methyl imidate **1f** in 8.5 ml of absolute ethanol was refluxed for three days, whereupon a test by thin-layer chromatography with alumina/chloroform showed that all of the **1f** (R_f 0.85) had reacted. The residue from evaporation of the solvent was dissolved in ether. This solution was filtered and evaporated. Sublimation of the residue at 60-65° (0.05 mm) plus crystallization from 60% ethanol gave 511 mg (48%) of needles, mp 81-84°; ir: 3220 (NH), 1590 cm^{-1} (N-C=N stretch) [34]; pmr (hexadeuterioacetone): δ 8.45 (d, $J_{6,7}$ = 8 Hz, H-7), 8.13 (d, H-6) which overlaps 8.06 (d, $J_{2,3}$ = 5 Hz, H-2), 7.52 (d, H-3), 3.78 (s, 4H, CH_2CH_2); ms: (70°) m/e 203 (M^+, 100), 202 (33), 174 ([M - C_2H_3]$^+$, 52), 161 (TPC≡NH$^+$, 23), 138 (25), 135 (1^+, 29; HR), 134 (TP$^+$, 73) [35].

Anal. Calcd. for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67; exact mass, 203.052. Found: C, 58.84; H, 4.65; N, 20.57; exact mass, 203.052.

5-(4,5,6,7-Tetrahydro-1,3-diazepin-2-yl)thieno[3,2-*b*]pyridine monohydrate (**1h**).

A solution of 0.52 ml (5.2 mmoles) of 1,4-diaminobutane and 1 g (equimolar amount) of **1f** in 8.5 ml of absolute ethanol was refluxed for two days and then rotoevaporated to give a yellow liquid which solidified on standing. Sublimation of the solid at 120° (0.05 mm) gave an initial analytically pure fraction of 31 mg of long needles, mp 89-90°, and a second fraction of 480 mg of less pure crystals, mp 73-90° (39% total yield of **1h**). Spectral data for the needles; ir: 3480 (OH), 3375 (NH), 1655 cm^{-1} (N-C=N stretch) [34]; pmr (hexadeuterioacetone): δ 8.58 (d, $J_{6,7}$ = 8 Hz, H-7), 8.14 (d, $J_{2,3}$ = 5 Hz, H-2) which overlaps 8.12 (d, H-6), 7.56 (d, H-3), 3.6-3.1 (m, 4H, 2 NCH_2), 2.76 (broad s, H_2O), 1.8-1.5 (m, 4H, CH_2CH_2); pmr (hexadeuterioacetone plus a little 20% deuterium chloride in deuterium oxide): δ 9.51 (d, $J_{6,7}$ = 8 Hz, H-7), 8.89 (d, $J_{2,3}$ = 6 Hz, H-2), 8.76 (d, H-6), 8.21 (d, H-3), 4.0-3.6 (m, 2 NCH_2), 2.1-1.8 (m, CH_2CH_2); ms: (160°) m/e 249 ($M \cdot H_2O^+$, 2), 232 ([M + 1]$^+$, 100), 180 (82), 163 (35), 162 (84), 149 (50), 136 (40), 135 (1^+, > 100; HR), 134 (TP$^+$, > 100) [36].

Anal. Calcd. for $C_{12}H_{13}N_3S \cdot H_2O$: C, 57.81; H, 6.06; N, 16.85. Found: C, 57.52; H, 6.11; N, 16.73.

5-(5-Tetrazolyl)thieno[3,2-*b*]pyridine (**1i**).

A mixture of 1.5 g (9.4 millimoles) of 5-cyanothieno[3,2-*b*]pyridine (**1e**) [32], 0.65 g (12 millimoles) of ammonium chloride, 0.79 g (12 millimoles) of sodium azide, and 5.3 ml of dimethylformamide was heated (under an atmosphere of nitrogen) in an oil bath at 125° for 10 hours. At first most of the solids dissolved, but shortly thereafter the mixture gelled. The cooled gel was poured into water and 10% hydrochloric acid was added to *p*H 4. The precipitate was collected by filtration, washed with water, and dried *in vacuo*, yield 1.74 g (91%) of **1i**, mp 237-238° dec, unchanged

on recrystallization (fine needles) from 95% ethanol or methanol, but sublimable (mp 240-242°) at 160° (0.05 mm); ir (hexachlorobutadiene mull): 3120 (NH), 1535, 1410, 1365, 1295, 1055, 750 cm^{-1} [37,38]; pmr (hexadeuteriodimethyl sulfoxide): δ 8.78 (d, $J_{6,7}$ = 8 Hz, H-7), 8.35 (d, $J_{2,3}$ = 6 Hz, H-2), 8.20 (d, H-6), 7.72 (d, H-3), 3.6 (very broad signal, NH); ms: (200°) m/e 204 (11), 203 (M^+, 84), 175 ($[M - N_2]^+$, 12, HR), 161 (58), 160 (**1e**$^+$, 28 HR), 148 (18), 147 ($[M - 2N_2]^+$, 100, HR), 146 (21), 135 (**1**$^+$, 15), 134 (81), 120 (14).

Anal. Calcd. for $C_8H_5N_3S$: C, 47.28; H, 2.48; N, 34.46; exact mass, 203.027. Found: C, 47.13; H, 2.52; N, 34.06; exact mass, 203.026.

REFERENCES AND NOTES

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[16] The relationship γ-isomer > γ-isomer in R_f value on silica gel also occurs in the chlorothieno[2,3-*b*]pyridines [17]. It is consistent with the concept that an α-chloro group will decrease (as compared to a γ-chloro group) the tendency to form hydrogen bonds between the heteronitrogen atom and the silica gel as a result of both steric and inductive effects by the substituent [18].

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[26] Identical methodology has not been reported in the quinoline series.

[27] Unless otherwise indicated, infrared spectra were determined on potassium bromide wafers by means of a Pye Unicam SP3-200 instrument; and pmr spectra, on deuteriochloroform solutions by means of a Varian XL-100 or a Nicolet 360 MHz instrument. Dr. Richard Wielesek of this laboratory obtained mass spectra with a CEC model 21-110 double-focusing apparatus. Unless otherwise designated, the mass spectral data for each compound include all peaks of m/e and relative intensity > the minimum values shown. The symbol HR is used to designate a mass spectral ionic fragment which has been identified by high resolution technique. Elemental analyses were obtained by MicAnal Laboratories, Tucson, Arizona.

[28] Assignments of the respective signals to H-2 and H-3 are based on cmr decoupling experiments, to be described later.

[29] Compare with the mass spectrum of 4-chlorothieno[2,3-*b*]pyridine 7-oxide reported previously (L. H. Klemm, S. Rottschaefer and R. E. Merrill, *J. Heterocyclic Chem.*, **12**, 1265 (1975)].

[30] Minor variations in the pmr spectrum are reported in references 19 and 20.

[31] Spectrum determined on a 95% ethanol solution by means of a Cary model 15 instrument.

[32] Obtained by a modification of the procedure reported previously [10]. See the discussion section.

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[35] Compare with the mass spectrum of the isostere in the thieno-[2,3-*b*]pyridine series [23].

[36] In order to observe the small peak at m/e 249 attenuation of signals was decreased until the peak at 232 just fell on scale, while those at 135 and 134 fell off scale. Except for m/e 249, peaks of relative abundance < 20% are not reported.

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