Chemistry of Thienopyridines. XXXI. A New Synthesis of Thieno[3,2-*b*]pyridine and Studies on Direct Substitution into Its Thiophene Ring [1]

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Thieno[3,2-*b*]pyridine (**1**) is synthesized in 65% overall yield for two steps which consist of addition of toluene-α-thiol to 2-ethynylpyridine plus vacuum pyrolysis of the addend (**7**). *Cis* and *trans* forms of **7** are described. Compound **1** undergoes (a) electrophilic substitution at C-3 to give chloro, bromo, and iodo derivatives (44-57% yields) and (b) lithiation at C-2 (to give **1a**). Intermediate **1a** is converted into derivatives of **1** with halo (19-48%), formyl (54%), acetyl, and hydroxymethyl (40%) substituents at C-2. Also described are 2-cyano and 2,3-dibromo derivatives of **1**. Structural assignments are based on chemical transformations plus ^1H and ^{13}C nmr spectral data. The substitution pattern of **1** is compared with predictions made on the bases of analogous ring systems and molecular orbital calculations.

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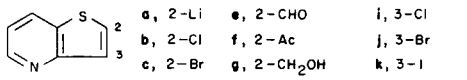
Several synthetic routes to the parent molecule thieno[3,2-*b*]pyridine (**1**) from (a) a 2-substituted pyridine, (b) a 3-substituted thiophene, or (c) a 2-substituted thiophene as starting material have been reported. The most direct route involves a heterogeneously catalyzed reaction between 2-vinylpyridine (**2**) and hydrogen sulfide but produces **1** in very low isolable yield [3]. More promising is the pyrolysis of benzyl 2-(2-pyridyl)ethyl sulfide (**3**), the addend from **2** and toluene-α-thiol, but again the isolation of pure **1** from the reaction mixture proves difficult [4,5]. Most of the physical and chemical properties reported for **1** to date [3,6-16] were obtained on samples which result from a four-step synthesis wherein the initial step consists of nitration of thiophene to a mixture of 2-and 3-nitrothiophenes and the final step involves the separation of **1** (in 1.5% overall yield) from the major product, thieno[2,3-*b*]pyridine (**4**) [6,17]. This procedure as a route to **1** becomes very attractive if one has a source of 3-nitrothiophene of high isomeric purity, but production of this intermediate in our laboratory has proved to be arduous and capricious. However, use of 3-acetylthiophene [18,19] in a modification of this synthesis produces **1** in 62% yield for two steps. 3-Bromothiophene [18] also has been converted to **1** by means of a modified Friedländer synthesis in 12% yield for five steps [20]. Most recently Hickson and McNab reported the three-step synthesis of **1** from 2-formylthiophene [18] in 15% overall yield [21]. Their final step involves vacuum pyrolysis of the oxime *O*-methyl ether **5** in 33% yield on a preparative scale of less than two grams. Meanwhile, we have now developed an alternative vacuum pyrolysis procedure which gives purified **1** reproducibly in 20-gram quantities and 65% yield for two steps.



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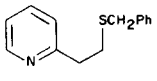

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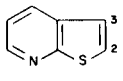

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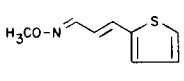

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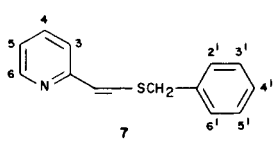

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Our preparative synthesis starts with 2-ethynylpyridine (**6**), either available commercially [22] or obtainable in 60% yield from the readily available **2** by the procedure of Brandsma [23]. Addition of toluene-α-thiol to **6** occurs in the presence of base to give a mixture (94% yield) of *cis* (89%) and *trans* (11%) isomers of benzyl 2-(2-pyridyl)vinyl sulfide (**7**), used directly in the vacuum pyrolysis step at 600 ± 25° (0.01 mm). The synthesis of **7** was reported previously in a comunication to the editor [24], but experimental details were not provided. We were able to separate *cis* (mp 45°) and *trans* (mp 57°) isomers by crystallizations at low temperature and to characterize them by pmr spectral properties (J_{cis} = 10.6 Hz, J_{trans} = 15.3 Hz). This difficult separation was omitted in the synthetic route to **1**, since limited investigation showed that either isomer formed **1** under pyrolysis conditions.

The availability of appreciable quantities of **1** allowed us to proceed with a systematic study of direct substitution into the thieno[3,2-*b*]pyridine nucleus and to compare orientation effects in **1** with those previously observed in the isomer **4**, as well as in the analogs quinoline and benzo[*b*]-thiophene [15]. The present study is concerned with substitution into the thiophene ring of **1**. Only one example of direct substitution into that ring, specifically of nitration

at C-3 by means of nitric and sulfuric acids [7], has been recorded. We now report that direct halogenation (with chlorine, bromine, or iodine) in other S_E reactions also occurs at C-3 to give **1i-1k** and that lithiation (plus subsequent reaction with various reagents) gives substitutuion at C-2 to produce **1b-1g**. Direct halogenation of **1** was effected by means of elemental chlorine (50% yield of **1i**) or iodine (44% yield of **1k**) plus silver sulfate in sulfuric acid or by means of elemental bromine (57% yield of **1j**) plus a mixture of buffer salts in chloroform. These monohalo derivatives are different from those which result from initial treatment of **1** with *n*-butyllithium in tetrahydrofuran at 0° plus subsequent reaction of presumed intermediate **1a** with *N*-chlorosuccinimide (19% yield of **1b**), elemental iodine (48% yield of **1d**), or elemental bromine (38% yield of **1c**, plus 5% of **1***l*), respectively. That each halogen atom in **1b-1d** and **1i-1k** occupies a position in the thiophene ring is apparent from its pmr spectrum which shows a singlet in place of the pair of doublets for H-2 and H-3 present in **1** [6]. Limited evidence that lithiation of **1** plus subsequent reaction with a nucleophile results in 2-substitution was provided by treatment of **1a** with *N,N*-dimethylacetamide to yield 2-acetylthieno[3,2-*b*]pyridine (**1f**) (15%), identical with the substance previously synthesized in a structurally unequivocal manner from 4-nitro-2-acetylthiophene by successive steps of reduction and cyclization [6]. In similar fashion **1a** reacts with *N,N*-dimethylformamide to give the 2-aldehyde **1e** (54%) and with paraformaldehyde to give the 2-hydroxymethyl compound **1g** (40%). In each case reaction of **1a** is accompanied by considerable tar formation. In a separate reaction iodo compound **1d** was converted into nitrile **1h** (65%) with cuprous cyanide in dimethylformamide.

Final positional assignments to the substituents in **1b-1k** were made by ^{13}C nmr spectral studies, wherein attention was directed to the magnitude of the one-bond ^{13}C-^{1}H coupling constant for the unsubstituted 2- or 3-position remaining in the thiophene ring [25]. In this regard $^{1}J(^{13}C\text{-}^{1}H)$ = 192 Hz for the 2-position in 3-nitrothieno-[3,2-*b*]pyridine, of established structure [7], and falls in the range of 190-193 Hz for the same position in compounds **1i-1k**. In contrast compounds **1b-1h** (including the known 2-acetylthieno[3,2-*b*]pyridine, *vide supra*) exhibit $^{1}J(^{13}C\text{-}^{1}H)$ in the range of 170-178 Hz for the 3-position. These data are consistent with the general observation that $^{1}J(^{13}C_{\alpha}\text{-}^{1}H_{\alpha})$ is greater than $^{1}J(^{13}C_{\beta}\text{-}^{1}H_{\beta})$, where α and β refer to ring positions relative to the heterosulfur atom, in the thiophene [26,27], benzo[*b*]thiophene [28], thienothiophene [29], and parent thienopyridine **1** and **4** [25] systems.

According to the correlational concept proposed by Klemm [15] and data from molecular orbital calculations [7,30], the pattern of substitution into the thiophene ring in a series of reactions should be closely similar in **1**, its isomer **4** and benzo[*b*]thiophene. Moreover, one should find similarities to substitution into the benzene ring of quinoline (where C-3 of **1** corresponds to C-8 of quinoline). In fact the 3-halo derivatives of **1** were prepared by the same methodologies which yielded 3-halo derivatives of **4** [31]. Also, the chlorination and iodination procedures used here were reported to effect substitution at C-8 and/or C-5 (analogous position not available in **1**) in quinoline [32]. Moreover, benzo[*b*]thiophene yields predominantly the 3-chloro and 3-bromo derivatives, albeit under reaction conditions different from those used with **1**. Lithiations of **1**, **4**, and benzo[*b*]thiophene all occur at C-2 and lead to formyl derivatives in comparable yields (60 ± 6%). No effort was made to find conditions which would effect alkylation of **1** alpha to the heteronitrogen atom, a process which occurs on treatment of **4** and quinoline with an alkyllithium [32].

EXPERIMENTAL [33]

Benzyl 2-(2-Pyridyl)vinyl Sulfide (**7**).

To a mechanically stirred solution of sodium ethoxide in ethanol (prepared from 3 g of sodium and 475 ml of absolute ethanol) at 0° and in a nitrogen atmosphere was added all at once, 126.7 g (1.23 moles) of 2-ethynylpyridine (**6**) [pmr: δ 8.59 (d of m, H-6), 7.1-7.8 (complex m, 3H), 3.21 (s, C≡CH)] [23] and then, dropwise, 152.6 g (an equimolar amount) of toluene-α-thiol over a period of 50 minutes. The mixture was stirred 4 hours longer to give a thick suspension which was treated with 10 ml of water and then 48 ml of 10% hydrochloric acid (to adjust the *p*H to 7).

After removal of most of the ethanol by rotary evaporation, the mixture was treated with 250 ml of water and extracted three times with chloroform (1.3 ℓ total). Volatile components of the dried (sodium sulfate) extract were removed by rotoevaporation and then evaporative distillation (Kugelrohr) at 20-40° (0.1 mm) to leave a residue of 263.7 g (94%) of **7**, a light orange liquid which solidified on standing at -30°. Pmr analysis (*vide infra*) showed that the product contained 89% *cis* isomer and 11% *trans* isomer (as based on integrations of signals for the methylene groups at δ 3.95 and 4.07, respectively). It was used directly in the thermolysis step.

In a smaller run using 5 g of **6**, the liquid product was crystallized from ether-pentane at -78° to give 8.71 g (79%) of crude *cis*-**7**, pale yellow plates, mp 41-45°. One g of this material was chromatoraphed on 100 g of Baker 40-140 mesh silica gel with ether as eluent. Evaporation of the first 100 ml of effluent gave liquid which crystallized from 5 ml of ether (-30° to -45°, with seeding) to yield 0.91 g of pure *cis*-**7**, white plates, mp 43-45°; pmr: δ 8.64 (d of broad singlets, 1 H, H-6), 7.56 (pseudotriplet of doublets, $J_{3,4}$ = 7.8 Hz, $J_{4,5}$ = 7.6 Hz, $J_{4,6}$ = 1.9 Hz, 1 H, H-4), 7.37 (d, 2 H, H-2' and H-6'), 7.31 (pseudotriplet, $J_{2',3'}$ = 7.2 Hz, 2 H, H-3' and H-5'), 7.24 (pseudotriplet, $J_{3',4'}$ = 7.2 Hz, 1 H, H-4'), 7.17 (d, 1 H, H-3), 7.01 (dd, $J_{5,6}$ = 4.6 Hz, 1 H, H-5), 6.59 (d, J_{cis} = 10.6 Hz, 1 H, C*H*=CH), 6.43 (d, 1 H, CH=C*H*), 3.95 (s, 2 H, methylene); ms: m/e 227(M^+, 4), 137 (12), 136 (M^+ -$PhCH_2$, 100), 91 ($C_7H_7^+$, 22), 78 (10), 65 (10).

Anal. Calcd. for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16. Found: C, 73.98; H, 5.68; N, 6.08.

The ether-pentane mother liquor from the crystallization of the *cis* isomer (*vide supra*) was evaporated to dryness and the residue was crystallized first from ether-pentane at -78° and then from ether at -30° to give 0.79 g (7%) of crude *trans*-**7**, yellow needles, mp 42-52°. Recrystallization from ether plus chromatography (50 g of adsorbent) as before gave white needles, mp 56-57°; pmr: δ8.47 (d of broad singlets, 1 H, H-6),

7.54 (pseudotriplet of doublets, $J_{3,4}$ = 7.8 Hz, $J_{4,5}$ = 7.7 Hz, $J_{4,6}$ = 1.8 Hz, 1 H, H-4), 7.44 (d, J_{trans} = 15.3 Hz, 1 H, C*H*=CH), 7.38 (d, 2 H, H-2′ and H-6′), 7.32 (pseudotriplet, $J_{2',3'}$ = 7.3 Hz, 2 H, H-3′ and H-5′), 7.25 (pseudotriplet, $J_{3',4'}$ = 7.3 Hz, 1 H, H-4′), 7.05 (d, 1 H, H-3), 7.03 (dd, $J_{5,6}$ = 3.9 Hz, 1 H, H-5), 6.50 (d, 1 H, CH=C*H*), 4.07 (s, 2 H, methylene); ms: m/e 227 (M^+, 11), 137 (11), 136 (M^+ - $PhCH_2$, 100), 91 ($C_7H_7^+$, 37), 78 (14), 65 (14).

Anal. Calcd. for $C_{14}H_{13}NS$: *vide supra.* Found: C, 74.09; H, 5.71; N, 6.04.

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

An all-glass apparatus with ground joints for vacuum pyrolysis of preceding **7** was assembled. It consisted of three main parts, *viz.* (a) an oil-jacketed distillation flask, (b) a thermolysis tube, and (c) a condenser-receiver (plus an attached vacuum system). Part (a) was prepared from a 250-ml round-bottomed flask bearing an extended neck which was bent at a right angle so as to protrude through the side of the surrounding, electrically heated oil bath and join to part (b). Thermolysis occurred in a horizontal vycor tube, 3 cm o.d., heated by a surrounding, electrical furnace 30 cm in length. Pyrolysate impinged on a cold finger kept at -45° by circulating refrigerated ethanol and collected in a vertical trap cooled by liquid nitrogen. In a typical reaction 50 g of molten sulfide **7** (agitated vigorously by a magnetic stirring bar) was vaporized at 170-180° (0.1 mm) in part (a) and passed through part (b) at a constant furnace temperature in the range of 550-650°. Reaction time was 45-90 minutes.

After reaction the pyrolysate was allowed to warm to room temperature and was evaporatively distilled at 25-85° (0.05 mm). A chloroform solution of the distillate was extracted three times with 250-ml portions of 10% hydrochloric acid. Combined acid extracts were basified with 50% sodium hydroxide and extracted with chloroform. The residue from removal of solvent from the latter dried (sodium sulfate) extract was evaporatively distilled at 25-50° (0.05 mm) to give thieno[3,2-*b*]pyridine (**1**) as a light yellow liquid, identified by pmr spectrometry [6]. Yields as a function of furnace temperature were 41% (550°); 63% (575°); 68% (600°); 20.6 g, 69% (625°); 59% (650°).

3-Chlorothieno[3,2-*b*]pyridine (**1i**).

A stirred, hot (100°) solution of 4.62 g (14.8 mmoles) of silver sulfate in 30 ml of concentrated sulfuric acid was treated first with 2 g (equimolar amount) of thieno[3,2-*b*]pyridine (added all at once) and then with chlorine gas (introduced in a rapid stream over a period of 1.5 hours). The mixture was poured onto ice, basified with 20% aqueous sodium hydroxide solution, and steam-distilled until one ℓ of distillate resulted. A chloroform extract of the distillate was dried (magnesium sulfate) and evaporated. Crystallization of the residue from hexane gave 1.26 g (50%) of **1i** as needles, mp 98-99°, raised to 100-101° on recrystallization; ir: 1550, 1500, 1390, 1345, 1145, 975, 845, 830, 780, 700 cm^{-1}; pmr: δ 8.82 (dd, $J_{5,6}$ = 4.6 Hz, $J_{5,7}$ = 1.3 Hz, H-5), 8.19 (dd, $J_{6,7}$ = 8.2 Hz, H-7), 7.66 (s, H-2), 7.35 (dd, H-6); ms: m/e 171 (M^+, 38), 169 (M^+, 100), 134 (M^+ -Cl, 15), 45 (CHS^+, 25), 39 (24).

Anal. Calcd. for C_7H_4ClNS: C, 49.56; H, 2.38; N, 8.26. Found: C, 49.29; H, 2.24; N, 8.29.

3-Bromothieno[3,2-*b*]pyridine (**1j**).

In the manner of Klemm *et al.* [31] a mixture of 2.51 g (18.6 mmoles) of thieno[3,2-*b*]pyridine (**1**), 1.56 g (equimolar amount) of sodium bicarbonate, 4.84 g (27.8 mmoles) of anhydrous dipotassium monohydrogen orthophosphate, 3 g of anhydrous magnesium sulfate, and 50 ml of chloroform was stirred vigorously and refluxed in a nitrogen atmosphere while 3.7 g (23.2 millimoles) of bromine was added dropwise and for 72 hours longer.

The cooled mixture was shaken with water and the chloroform layer, plus chloroform extracts of the aqueous layer, was dried (magnesium sulfate) and evaporated. The residue was chromatographed (50 g of neutral alumina/chloroform) and a fraction (2.56 g, mp 95-105°) was recrystallized from cyclohexane to yield 2.25 g (57%) of needles, mp 108.5-110°, raised to 109-110° on further recrystallizations plus sublimation at 82°/0.05 mm [34]; ir: 1545, 1385, 1140, 945, 845, 820, 780, 690 cm^{-1}; pmr: δ 8.83 (dd, $J_{5,6}$ = 4.6 Hz, $J_{5,7}$ = 1.4 Hz, H-5), 8.20 (dd, $J_{6,7}$ = 8.2 Hz, H-7), 7.79 (s, H-2), 7.35 (dd, H-6); ms: m/e 215 (M^+, 100), 213 (M^+, 99), 134 (M^+ -Br, 24), 39 (18).

Anal. Calcd. for C_7H_4BrNS: C, 39.27; H, 1.88; N, 6.54. Found: C, 39.10; H, 1.67; N, 6.52.

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

To a stirred solution of 4.62 g (14.8 mmoles) of silver sulfate in 30 ml of concentrated sulfuric acid at 110° and in a nitrogen atmosphere was added 2.01 g (equimolar amount) of thieno[3,2-*b*]pyridine all at once and then, in small portions over a period of 50 min, 4.69 g (18.5 mmoles) of iodine. The mixture was poured onto ice, basified (*p*H 10) with 20% aqueous sodium hydroxide, and steam-distilled (13 ℓ of distillate collected) [35]. A methylene chloride extract of the distillate was evaporated and the residue was evaporatively distilled at 20-75° (0.005 mm) and then chromatographed on 100 g of neutral alumina (methylene chloride-carbon tetrachloride 3:7 as initial eluent, then chloroform) to yield 1.71 g (44%) of needles, mp 75-79° (on crystallization from cyclohexane). Recrystallizations from petroleum ether (50-110°), cyclohexane, and ether as well as sublimation at 60° (0.05 mm) gave a powder, mp 81-82°; ir: 1385, 1145, 1065, 780, 685 cm^{-1}; pmr: δ 8.82 (dd, $J_{5,6}$ = 4.6 Hz, $J_{5,7}$ = 1.3 Hz, H-5), 8.19 (dd, $J_{6,7}$ = 8.1 Hz, H-7), 7.94 (s, H-2), 7.32 (dd, H-6); ms: m/e 262 (11), 261 (M^+, 100), 134 (M^+ - I, 24), 39 (17).

Anal. Calcd. for C_7H_4INS: C, 32.20; H, 1.54; N, 5.37. Found: C, 32.02; H, 1.59; N, 5.50.

General Procedure for Lithiation Reactions.

Lithiation of thieno[3,2-*b*]pyridine (**1**) was accomplished in an oven-dried 250-ml three-necked round-bottomed flask containing a magnetic stirring bar and an atmosphere of nitrogen. The flask was fitted with a rubber septum, a gas outlet tube, and (in the middle neck) a filtration funnel [36] bearing a gas inlet tube. A dried (powdered potassium hydroxide) solution of **1** (*ca.* 2.02 g, 14.8 mmoles) in 75 ml. of tetrahydrofuran was filtered into the reaction flask. This solution was stirred and maintained at 0° while a solution of *n*-butyllithium in hexane (*ca.* 10.2 ml, 1.65 *M*) was added dropwise by syringe (over a period of 15 minutes) and for 30-90 minutes longer. The dark solution of 2-lithiothieno[3,2-*b*]pyridine (**1a**) was treated with various reagents, added all at once in slight excess. The mixture was stirred for one hour at 0° and then for varying amounts of time (as noted in each case) after removal of the cooling bath. The mixture was treated with 50 ml of water and (usually) 20 g of sodium chloride. The phases were separated and the aqueous layer was extracted several times with chloroform or chloroform and ether. Combined organic layers (extract no. 1) were evaporated and the residue (no. 1) was dissolved in chloroform alone (extract no. 2). The latter extract was dried (usually with sodium sulfate) and evaporated. The residue (no. 2) was evaporatively distilled in the range of 20-130° (0.05 mm) and chromatographed. Variations on this procedure are noted in subsequent paragraphs.

2-Chlorothieno[3,2-*b*]pyridine (**1b**).

Solution **1a** was treated with 2.1 g (15.6 mmoles) of purified, powdered *N*-chlorosuccinimide and stirred for 12 hours at room temperature. Extract no. 2 was, in turn, extracted with excess 10% hydrochloric acid. This acidic solution was basified to *p*H 10 and re-extracted into chloroform. This solution was now treated as regular extract no. 2 in the general procedure. Chromatography (250 g of 60-200 mesh silica gel/chloroform-ether, 9:1) gave two products: 0.45 g (23%) of recovered **1** (Rf 0.17) and 0.5 g (19%) of liquid **1b** (Rf 0.27), which solidified on cooling. Recrystallizations from pentane at -20° and sublimation at 30° (0.005 mm) gave **1b** as a powder, mp 35-36°; ir: 1550, 1510, 1395, 1140, 980, 825, 785 cm^{-1}; pmr: δ 8.64 (dd, $J_{5,6}$ = 4.7 Hz, $J_{5,7}$ = 1.3 Hz, H-5), 8.02 (dd, $J_{6,7}$ = 8.2 Hz, H-7), 7.42 (s, H-3), 7.24 (dd, H-6); ms: m/e 171 (M^+, 34), 170 (10), 169 (M^+, 100), 134 (M^+ - Cl, 17), 133 (7), 39 (10).

Anal. Calcd. for C_7H_4ClNS: C, 49.56; H, 2.38; N, 8.26. Found: C, 49.39; H, 2.28; N, 8.15.

2-Bromothieno[3,2-*b*]pyridine (**1c**) and 2,3-Dibromothieno[3,2-*b*]pyridine (**1l**).

Solution **1a** was treated with 0.8 ml (15.6 mmoles) of bromine and stirred for 6 hours at room temperature. Chromatography (200 g of silica gel/chloroform-ether, 4:1) gave three fractions: 0.34 g (17%) of recovered **1** (Rf 0.21), 1.21 g (38%) of **1c**, mp 46-48° (Rf 0.30); and crude **1ℓ** (Rf 0.48). Compound **1c** was purified further by chromatography on alumina (Alcoa F-20/chloroform), recrystallization (needles) from pentane at -20°, and sublimation at 30° (0.05 mm) to give a powder, mp 47-48°; ir: 1545, 1500, 1390, 1140, 940, 825, 785 cm^{-1}; pmr: δ 8.63 (dd, $J_{5,6}$ = 4.7 Hz, $J_{5,7}$ = 1.4 Hz, H-5), 8.04 (dd, $J_{6,7}$ = 8.0 Hz, H-7), 7.58 (s, H-3), 7.23 (dd, H-6).

Anal. Calcd. for C_7H_4BrNS: C, 39.27; H, 1.88; N, 6.54. Found: C, 39.27; H, 1.62; N, 6.39.

Preceding crude **1ℓ** was chromatographed repeatedly on thick layer plates of silica gel (Merck GF-254) with chloroform to give 0.22 g (5%) of yellow **1ℓ**, mp 125-131°. Recrystallizations from ether plus sublimation at 74° (0.05 mm) gave a white powder, mp 138-139°; ir: 1550, 1495, 1390, 1325, 1150, 1000, 795, 715 cm^{-1}; pmr: δ 8.76 (dd, $J_{5,6}$ = 4.6 Hz, $J_{5,7}$ = 1.3 Hz, H-5), 8.07 (dd, $J_{6,7}$ = 8.2 Hz, H-7), 7.32 (dd, H-6); ms: m/e 295 (M^+, 54), 293 (M^+, 100), 291 (M^+, 54), 214 (M^+ - Br, 17), 212 (M^+ - Br, 18), 133 (M^+ - 2Br, 43), 106 (M^+ - 2Br - HCN, 18).

Anal. Calcd. for $C_7H_3Br_2NS$: C, 28.69; H, 1.03; N, 4.78. Found: C, 28.54; H, 1.00; N, 4.71.

2-Iodothieno[3,2-*b*]pyridine (**1d**).

Solution **1a** was treated with 4.06 g (16 mmoles) of powdered iodine and stirred for one hour at room temperature. Extract no. 1 was washed with 10% aqueous sodium bisulfite. Chromatography (100 g of alumina/-chloroform) gave 1.89 g (48%) of crude **1d**, mp 110-120°. Recrystallizations from ether plus sublimation at 65° (0.05 mm) gave a white powder mp 127-128°; ir: 1550, 1390, 1275, 1140, 1070, 825, 780 cm^{-1}; pmr: δ 8.60 (broad d, H-5), 8.07 (d, $J_{6,7}$ = 8.2 Hz, H-7), 7.79 (s, H-3), 7.20 (dd, $J_{5,6}$ = 4.6 Hz, H-6); ms: m/e 261 (M^+, 100), 134 (M^+ - I, 44), 127 (I^+, 43), 107 (M^+ -I - HCN, 15), 90 (M^+ - I - CS, 19), 69 (17), 63 (33).

Anal. Calcd. for C_7H_4INS: C, 32.20; H,1.54; N, 5.37. Found: C, 32.10; H, 1.27; N, 5.26.

2-Formylthieno[3,2-*b*]pyridine (**1e**).

Solution **1a** was treated with 1.5 g (21 mmoles) of *N,N*-dimethylformamide and stirred for one hour at room temperature. Evaporative distillation (without chromatography) gave 1.33 g (54%) of **1e**, mp 116-122°; purified further by crystallization (needles) from ether-pentane and sublimation at 60-80° (0.05 mm) to give a powder, mp 134-135°; ir: 2835 and 2820 (w, aldehyde CH), 1680 (vs, carbonyl), 1550, 1520, 1240, 1155, 1145, 870, 785, 660 cm^{-1}; pmr: δ 10.22 (s, CHO), 8.82 (dd, $J_{5,6}$ = 4.5 Hz, $J_{5,7}$ = 1.4 Hz, H-5), 8.27 (dd, $J_{6,7}$ = 8.3 Hz, H-7), 8.25 (s, H-3), 7.42 (dd, H-6); ms: m/e 163 (M^+, 75), 162 (M^+ - H, 100), 135 (M^+ - CO, 18), 134 (I^+, 34), 90 (M^+ - CS - CHO, 17), 82 (21), 69 (15), 63 (24).

Anal. Calcd. for C_8H_5NOS: C, 58.88; H, 3.09; N, 8.58. Found: C, 58.80; H, 3.32; N, 8.22.

2-Acetylthieno[3,2-*b*]pyridine (**1f**).

Solution **1a** was treated with 3 ml (32 mmoles) of dry *N,N*-dimethylacetamide [37] and stirred for 18 hours at room temperature. Chromatography (100 g of alumina/chloroform) (without evaporative distillation) and crystallization from ether at -20° gave 0.41 g (15%) of **1f**, mp 154-156°; lit. [6] 156-157°; identified by mixture melting point and spectral comparisons with authentic **1f** [6]; ir: 1655 (carbonyl), 1550, 1515, 1260, 1195, 885, 800 cm^{-1}. Crystallization mother liquors yielded 0.77 g (38%) of recovered **1**.

2-Hydroxymethylthieno[3,2-*b*]pyridine (**1g**).

Solution **1a** was treated with 1.21 g (40 mmoles) of dry (from heating *in vacuo* at 100° for one hour) paraformaldehyde and stirred for 17 hours at room temperature. Chromatography (300 g of alumina/chloroform-methanol, 9:1) gave 1.0 g (40%) of crude **1g** (mp 103-106°), purified further by recrystallizations (prisms) from ether at -18° and sublimation at 80° (0.005 mm) to give a white powder, mp 107-108°; ir (chloroform, calcium fluoride cell): 3180 cm^{-1} (broad, OH); ir: 1400, 1360, 1120, 1055, 825, 795 cm^{-1}; pmr: δ 8.59 (dd, $J_{5,6}$ = 4.7 Hz, $J_{5,7}$ = 1.4 Hz, H-5), 8.11 (dd, $J_{6,7}$ = 8.1 Hz, H-7), 7.36 (s, H-3), 7.20 (dd, H-6), 4.97 (s, CH_2), 3.55 (broad s, OH); ms: m/e 165 (M^+, 95), 164 (M^+ - H, 26), 148 (M^+ - OH, 19), 136 (M^+ -CHO, 100), 39 (38) [38].

Anal. Calcd. for C_8H_7NOS: C, 58.16; H, 4.27; N, 8.48. Found: C, 58.11; H, 4.29; N, 8.46.

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

A solution of 1.01 g (3.9 mmoles) of 2-iodothieno[3,2-*b*]pyridine (**1d**) in 6 g of dimethylformamide was stirred and refluxed with 0.42 g (4.6 mmoles) of cuprous cyanide in a nitrogen atmosphere for 4 hours. The cooled mixture was poured into 30 ml of 25% aqueous sodium cyanide and extracted with chloroform. Solvent was removed by evaporative distillation at 22° (finally at 0.05 mm). Chromatography (290 g of alumina/chloroform) of the residue gave 0.4 g (65%) of **1h**, mp 110-111°, unchanged on crystallization (needles) from ether or sublimation at 85° (0.05 mm); ir: 2225 (nitrile), 1545, 1395, 1150, 880, 780, 615 cm^{-1}; pmr: δ 8.85 (dd, $J_{5,6}$ = 4.5 Hz, $J_{5,7}$ = 1.3 Hz, H-5), 8.23 (dd, $J_{6,7}$ = 8.3 Hz, H-7), 8.12 (s, H-3), 7.45 (dd, H-6); ms: m/e 160 (M^+, 100), 133 (M^+ - HCN, 42), 82 (49), 69 (40), 63 (40), 51 (36), 45 (CHS^+, 53), 44 (76), 39 (76).

Anal. Calcd. for $C_8H_4N_2S$: C, 59.98; H, 2.52; N, 17.49. Found: C, 59.92; H, 2.86; N, 17.10.

^{13}C Nuclear Magnetic Resonance Studies.

These spectra were recorded on a Nicolet NTC-360 FT NMR instrument with 12-mm tubes containing 0.2-10% (wt/wt) solutions of compounds in deuteriochloroform, plus tetramethylsilane as an internal standard. Proton-coupled spectra were obtained with or without gated decoupling for nuclear Overhauser enhancement.

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[34] C. E. Klopfenstein [Ph.D. thesis, University of Oregon, August, 1966, pp 96-97] reported the synthesis of a monobromothieno[3,2-*b*]pyridine, postulated to be **1j**, from treatment of an aqueous mixture of **1** with excess bromine for one hour at room temperature. The sublimed product (believed to contain both mono- and dibromo derivatives on the basis of its pmr spectrum) was recrystallized from cyclohexane to yield white needles, mp 102-103°, correct elemental analysis for C_7H_4BrNS.

[35] It seems likely that this lengthy steam distillation could be omitted and extraction with solvent used directly.

[36] The apparatus is similar to that shown in Fig. 7.9 of D. F. Shriver, "The Manipulation of Air-Sensitive Compounds", McGraw-Hill, New York, 1969.

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[38] The mass spectrum of **1g** exhibits many of the characteristics associated with that of benzyl alcohol. H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, 1967, pp 119-120, 122.