Chemistry of Thienopyridines. IV. Syntheses of 5-Substituted Thieno[2,3-*b*]pyridines (1)

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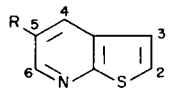
Chemical transformations on 5-acetylthieno[2,3-*b*]pyridine produced 5-NH_2, 5-CO_2H, and 5-CH_2CO_2H substituents. The 5-amino compound underwent facile diazotization (plus Sandmeyer reaction), Schiff's base formation, and acylation. Treatment of the derived 5-bromo compound with potassium amide in liquid ammonia gave a mixture of 4-amino (major) and 5-amino isomers. Nmr spectral data are reported for the 5-substituted thieno[2,3-*b*]pyridine system.

Recently we reported (3) successful syntheses on a preparative scale of thieno[2,3-*b*]pyridine (**1**) and its 5-acetyl derivative (**7**) by direct pyridine ring-closure. These syntheses make feasible investigations of the chemical and pharmacological properties associated with the system **1**. Parent compound **1** was found (3) to undergo electrophilic substitution preferentially at C-3 and



1: R=H
7: R=Ac

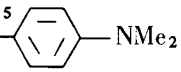
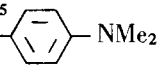
less readily at C-2 (analogous to the case for benzo[*b*]-thiophene). It also underwent addition to the C=N group (as in quinoline) in competition with metalation at C-2 (as occurs in benzo[*b*]thiophene) on treatment with an alkyllithium. In the present paper we report a number of chemical transformations which use **7** as a primary starting material and yield a variety of other 5-substituted thieno[2,3-*b*]pyridines.

Oxidation of **7** with hypochlorite solution gave the 5-carboxylic acid (58%), which was converted readily with methanolic hydrogen chloride to the methyl ester (**8**) (89%, as the hydrochloride). Reduction of **7** by the Huang-Minlon method to the 5-ethyl derivative (**10**) (65%, as the picrate) was reported previously (3). Kindler reaction (with morpholine and sulfur) transformed **7** into the thiomorpholide (**12**) (49%), which was hydrolyzed by aqueous hydroxide to the corresponding α-substituted acetic acid (72%), and in turn esterified to the methyl ester (**11**) (88%, as the hydrochloride). Treatment of **7** with hydroxylammonium chloride in refluxing pyridine-absolute ethanol gave the oxime (**22**) (91%). Presumably **22** was the geometrically pure isomer with the OH and the thienopyridyl moieties in an *anti* arrangement (4). Thus, in the Beckmann reaction only one amide (**13**) (isomerically pure, as adjudged by nmr) was obtained in 95% yield. Also, hydrolysis of **13** with refluxing concentrated hydrochloric acid gave the 5-aminothienopyridine (**5**) (74%), but gave no evidence for the presence of the 5-carboxylic acid. An alternative two-step route to **5** from bis(2-thienylammonium)hexachlorostannate (IV) was sought in the initial reaction of the latter compound with sodium nitromalondialdehyde to give the 5-nitrothienopyridine (**6**) (10%), but this pathway was abandoned due to the low yield of **6** and experimental difficulties (5). From the foregoing reactions it is apparent that system (**1**) is, indeed, chemically stable in a practical sense that it resists destruction by treatment (a) with strong aqueous and alcoholic mineral acids and bases, (b) with selected oxidizing and reducing agents, and (c) with electrophiles (6) and nucleophiles.

The amine (**5**) gave two kinds of reactions which are typical of primary aryl amines. Thus, it was readily converted to the diazonium salt (which underwent subsequent replacement of the diazonium group) and it formed Schiff's bases with aromatic aldehydes. Formed by Sandmeyer reactions were 5-bromo (**2**, 48%), 5-chloro (**3**, 40%), and 5-cyano (**9**, 13%) derivatives. Hydrolysis of the diazotized amine also produced the 5-hydroxy compound (**4**, 65%). Compound **9** was obtained in higher purity by treatment of **2** with cuprous cyanide in refluxing dimethylformamide (14% overall yield from **5**). Diazotization, Sandmeyer reaction, and cyanodebromina-

TABLE I

Nuclear Magnetic Resonance Data for 5-Substituted Thieno[2,3-*b*]pyridines (a)

Cmpd. No.	Substituent R	Chemical Shift, in δ H-2	H-3	H-4	H-6	$J_{4,6}$ (b) in Hz	Other Signals
2	Br	7.54	7.15	8.15	8.59	2	
3	Cl	7.58	7.18	8.02	8.58	2	
4	OH (c)	8.17	7.68	7.98	8.61	2.6	10.27(s,OH)
5	NH_2 (c)	7.68	7.21	7.45	8.14	2.5	3.92(s, NH_2)
6	NO_2	7.80	7.45	8.89	9.40	2.4	
7	Ac (d)	7.60	7.35	8.58	9.10	1.9	2.69(s,Ac)
8	CO_2Me	7.57	7.28	8.64	9.16	2	3.96(s,CH_3)
9	CN	7.71	7.34	8.34	8.75	1.8	
10	C_2H_5 (d)	7.41	7.10	7.79	8.38	1.8	2.68(q,2H,CH_2), 1.22(t,3H,CH_3) (e)
11	CH_2CO_2Me 	7.46	7.13	7.95	8.47	2.2	3.66(s,5H, superimposed CH_2 and CH_3)
12	$CH_2C(=S)N$ 	7.53	7.21	8.15	8.48	2	4.2-4.5(m,4H,-CH_2OCH_2-) (f)
13	NHAc (c)	7.88	7.46	8.62	8.75	2	4.12(s,NH), 2.20(s,CH_3)
14	$NHC(=O)CH_2CH_2CO_2H$ (g)	7.86	7.44	(8.7)	(8.7)	- (h)	2.67(s,CH_2CH_2)
15	$NHC(=O)CH_2CH_2CO_2Me$ (c)	7.68	7.33	8.76	8.76	- (i)	3.72(s,3H,CH_3), 2.75(s,4H,CH_2CH_2)
16	$N=CHC_6H_5$	(7.49) (j)	7.18	(7.78) (j)	(8.50) (k)	> 2	8.48(s,-N=CH-), 7.3-8.1(m,5H,C_6H_5)
17	N=CH  NMe_2	7.47	7.17	7.76	8.48	2.4	8.34(s,-N=CH-), 2.98(s,6H,2CH_3) (l)
18	N=CH 	7.52	7.22	7.86	8.54	2.3	8.37(s,-N=CH-) (m)
19	$NHCH_2C_6H_5$	(7.25) (n)	6.90	7.03	8.03	2.5	4.35(broad s,1H,NH), 4.22(s,2H,CH_2) (n)
20	$NHCH_2$  NMe_2	7.39	7.04	7.20	8.07	2.5	4.23(s,2H,CH_2), *ca.* 4.0 (broad,1H,NH) (o)
21	$NHCH_2$  (c)	7.68	7.22	7.42	8.22	2.5	*ca.* 4.2-4.5(m,NH and CH_2) (p)

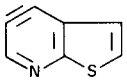
(a) Unless otherwise indicated, solvent is $CDCl_3$. (b) $J_{2,3}$ = 6Hz for every case. (c) In DMSO-d_6 as solvent. (d) See ref. 3. (e) J_{Et} = 7.5 Hz. (f) Also 3.3-3.9 [m,6H,-$CH_2C(=S)N(CH_2$-$)_2$]. (g) In $CDCl_3$-DMSO-d_6 as solvent. A signal for CO_2H was not observed. (h) Signals for H-4 and H-6 are only partially resolved into a multiplet at 8.68-8.85. (i) Signals for H-4 and H-6 appear as a singlet for 2 protons. (j) Partial overlap with signals for the phenyl protons. (k) Partial overlap with signal for -N=CH- group. (l) Also 7.76 (d, 2H, $J_{2',3'}$ = 9 Hz, H-2′ and H-6′), 6.68 (d, 2H, H-3′ and H-5′). (m) Also 6.55 (d of doublets $J_{3',4'}$ = 3.4 Hz, $J_{4',5'}$ = 1.8 Hz, H-4′), 7.01 (d, H-3′), 7.62 (d, H-5′). (n) Partial overlap of the signals for H-2 and for the phenyl protons (sharp singlet at 7.26) occurs. (o) Also 2.91 (s, 2CH_3), 6.72 (d, $J_{2',3'}$ = 8.5 Hz, 2H, H-3′ and H-5′), 7.24 (d, 2H, H-2′ and H-6′). (p) Also 6.39 (broad s, 2H, H-3′ and H-4′); partial overlap of signal for H-5′ (at *ca.* 7.57) with that of H-2.

tion are characteristic of the isosteric 3-substituted quinoline system, but not of the 2- or 4-substituted quinoline systems (7) [*cf.* pyridine systems (8)].

Condensation of **5** with benzaldehyde, *p*-dimethylaminobenzaldehyde, and furaldehyde was effected in refluxing benzene with trapping of evolved water to give the corresponding Schiff's bases, **16** (71%), **17** (89%), and **18** (78%). The aldimino groups (C=N) in **16** and **18** were easily reduced by means of sodium borohydride in refluxing methanol to produce the secondary amines, **19** (83%) and **21** (89%), respectively. Reduction of **17** required more strenuous conditions (refluxing in ethanol for a longer time and with a larger quantity of borohydride) and gave a poorer yield of product (**20**, 26%). This difference in facility of reduction is consistent with resonance donation of electronic charge to the aldimino moiety by the *p*-dimethylamino group and nucleophilic attack of borohydride at the C=N bond.

In other experiments the amine (**5**) reacted with succinic anhydride to give the succinamic acid (**14**, 71%), convertible to the methyl ester (**15**) in quantitative yield) and with succinoyl chloride to give the *N,N'*-disubstituted succinamide (**23**, 62%).

Treatment of the bromo compound (**2**) with potassium amide in liquid ammonia at -35° to -70° gave *ca.* 40% yield of 4-aminothieno[2,3-*b*]pyridine (**24**) plus 0-13% of the isomer **5** (9). It is presumed that the reaction proceeds *via* the intermediate thienopyridyne (**25**), though efforts to establish this presumption were not made.



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Compound **25** is analogous to 3,4-pyridyne, 3,4-quinolyne, and 3,4-dehydro-1,5-naphthyridine (10), proposed intermediates in the conversions of the corresponding 3- and 4-bromoazarenes to mixed 3- and 4-aminoazarenes under similar reaction conditions (-33°). However, selectivity for formation of the γ-amino isomer over the alternative β-amino isomer (with respect to the pyridine ring) is considerably greater in the thienopyridine system than in other ones.

In Table I are presented chemical shifts and coupling constants for many of the 5-substituted thieno[2,3-*b*]-pyridines which are reported in this paper. In general, it will be noted that the four thienopyridine protons produce a series of four nmr doublets ($J_{2,3}$ = 6 Hz, $J_{4,6}$ = 1.8-2.6) which occur in the order δ_3, (δ_2 or δ_4), δ_6. In most cases $\delta_4 > \delta_2$, but in the hydroxy derivative **4** and the amino derivatives **5** and **19-21**, $\delta_2 > \delta_4$. The change to the latter order is ascribable to an appreciable degree of electron-donation by hydroxy and amino groups (as compared to hydrogen) at C-5 to C-4 [*cf.* benzene system (11) and the order $\delta_4 > \delta_2$ in **1** (3)].

EXPERIMENTAL (12)

Methyl Thieno[2,3-*b*]pyridine-5-carboxylate (**8**).

A mixture of 1.77 g. (0.01 mole) of **7** (3), 5 ml. of dioxane, and 19 ml. of aqueous potassium hypochlorite solution (*ca.* 0.046 *M*, prepared from 5 g. of calcium hypochlorite) was stirred at room temperature for 2 hours and then at 60° for 5 minutes. The solution was acidified to *p*H 6, cooled, and filtered to give 1.03 g. (58%) of thieno[2,3-*b*]pyridine-5-carboxylic acid, obtained as a white powder, m.p. 284-286°.

Into a suspension of 0.54 g. of preceding acid in 5 ml. of anhydrous methanol was passed hydrogen chloride gas until a clear solution resulted. Evaporation of the solution gave 0.61 g. (89%) of crude **8** hydrochloride. The hydrochloride was lost on recrystallization from methanol-ether to give free **8** as white needles, m.p. 132-133°; infrared band (chloroform) at 1720 cm^{-1} (ester carbonyl).

Anal. Calcd. for $C_9H_7NO_2S$: C, 55.95; H, 3.65; N, 7.25; S, 16.59. Found: C, 56.22; H, 3.87; N, 6.98; S, 16.81.

α-(5-Thieno[2,3-*b*]pyridine)acetothiomorpholide (**12**).

A mixture of 1.06 g. of **7** (3), 0.29 g. of sulfur, and 0.8 g. of morpholine was heated at 140° for 17 hours. A chloroform solution of the cold reaction mixture was percolated through 20 g. of alumina and then evaporated. A methanol extract of the residue was filtered, diluted with water to the point of persistent cloudiness, and allowed to cool slowly. The powder (0.82 g., 49%, m.p. 103-104°) which formed was recrystallized from aqueous methanol to give yellow prisms, m.p. 107-108°; infrared bands (chloroform) at 1110 (C=S) and 1490 cm^{-1} (C-N stretching in S=C-N) (13).

Anal. Calcd. for $C_{13}H_{14}N_2OS_2$: C, 56.08; H, 5.07; N, 10.06; S, 23.04. Found: C, 56.09; H, 5.22; N, 9.61; S, 22.81.

Methyl α-(5-Thieno[2,3-*b*]pyridine)acetate (**11**).

A mixture of 348 mg. of **12** and 20 ml. of 20% aqueous potassium hydroxide solution was heated at 100° for 10 hours and then refluxed for 3 hours. The cooled mixture was acidified to *p*H 3 and filtered to give 174 mg. (72%) of α-(5-thieno[2,3-*b*]pyridine)-acetic acid, obtained as a white powder, m.p. 181-182°.

Into a refluxing suspension of 1.19 g. of the acetic acid in 50 ml. of anhydrous methanol was passed dry hydrogen chloride gas until a clear solution resulted. The solution was concentrated and treated with ether to precipitate 1.32 g. (88%) of **11** hydrochloride. A sample for analysis was obtained by repeated recrystallization from methanol-ether containing anhydrous hydrogen chloride yielding grayish white prisms, m.p. 173-174° with sintering at 165°.

Anal. Calcd. for $C_{10}H_{10}ClNO_2S$: C, 49.28; H, 4.14; Cl, 14.55; N, 5.75; S, 13.16. Found: C, 49.05; H, 4.13; Cl, 14.37; N, 5.87; S, 12.88.

Free **11** was obtained by neutralization of the hydrochloride with 10% aqueous potassium hydroxide solution at 0°, m.p. 51-52°; infrared band (chloroform) at 1730 cm^{-1} (ester carbonyl).

5-Acetylthieno[2,3-*b*]pyridine Oxime (**22**).

A solution of 5 g. of **7** (3) and 6.3 g. hydroxylamine hydrochloride in 50 ml. of anhydrous pyridine and 50 ml. of absolute ethanol was refluxed for 3 hours and then evaporated. The

residue was triturated with water and crystallized from aqueous ethanol or ethanol-ether to yield 4.9 g. (91%) of cream-colored prisms, m.p. 187-188°.

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.20; N, 14.58; S, 16.68. Found: C, 55.96; H, 4.16; N, 14.36; S, 16.55.

5-Acetylaminothieno[2,3-*b*]pyridine (**13**).

To a cold (5-10°) suspension of 29.5 g. (0.153 mole) of oxime **22** in benzene was added 36.9 g. (0.177 mole) of phosphorus pentachloride. The mixture was stirred and carefully heated to refluxing, where it was maintained for 15 minutes. The hot mixture was poured into ice-water and carefully neutralized with 40% aqueous potassium hydroxide. The precipitate was separated by filtration and combined with the residue obtained on evaporation of an ethyl acetate extract (total volume 3 l.) of the filtrate, yield 28 g. (95%) of crude, yellow crystals. This was used without purification in the next step (hydrolysis).

An analytical sample was obtained by two sublimations at 180-200° (0.05 mm.) and one recrystallization from ethanol to give white needles, m.p. 192-193° (dec.); infrared bands (Nujol) at 1690, 1535, and 1300 cm^{-1} (amide).

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.20; N, 14.58; S, 16.68. Found: C, 56.33; H, 4.32; N, 14.03; S, 16.68.

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

A mixture of 28 g. of crude preceding amide, (**13**), 400 ml. of ethanol, and 200 ml. of concentrated hydrochloric acid was refluxed in a nitrogen atmosphere for 20 hours and then evaporated to a small volume. The solution was basified with 40% aqueous sodium hydroxide solution and extracted with 800 ml. of chloroform. Evaporation of the dried extract gave brown crystals which were sublimed at 140° (1 mm.) to yield a white solid (16.1 g., 74%), m.p. 110-112°. An analytical sample was prepared by recrystallization from water to form white needles, m.p. 114-115°, infrared bands (chloroform) at 3400 (NH stretching) and 1630 cm^{-1} (NH bending).

Anal. Calcd. for $C_7H_6N_2S$: C, 55.97; H, 4.03; N, 18.65; S, 21.35. Found: C, 56.18; H, 4.22; N, 18.71; S, 21.26.

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

To a mixture of 6 g. (0.04 mole) of amine **5** and 12 ml. of 48% hydrogen bromide at 0-5° was added dropwise a solution of 2.8 g. (0.04 mole) of sodium nitrite in 5 ml. of water. This mixture was then added slowly to a refluxing solution of 3.2 g. cuprous bromide in 4 ml. of 48% hydrogen bromide. The solution was poured onto ice, basified with 40% aqueous potassium hydroxide solution, and extracted with chloroform. Evaporation of the extract gave a brown solid which was reextracted with petrol (30-60°). From the cold petrol solution was obtained 4.1 g. (48%) of white needles, m.p. 58-62°. An analytical sample was obtained as white, sticky prisms after recrystallization and repeated evaporative distillation at 80° (0.05 mm.), m.p. 68-69°.

Anal. Calcd. for C_7H_4BrNS: C, 39.27; H, 1.88; Br, 37.33; N, 6.54; S, 14.98. Found: C, 39.78; H, 1.98; Br, 37.58; N, 6.54; S, 15.21.

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

In the same manner as used for **2** except that concentrated hydrochloric acid and cuprous chloride were used in place of the bromides there was obtained a 40% yield of **3** after evaporative distillation of the crude product from chloroform extraction, m.p. 63-64°. Crystallization from petrol (30-60°) and further evaporative distillation gave faintly cream-colored needles, m.p. 64-65°.

Anal. Calcd. for C_7H_4ClNS: C, 49.56; H, 2.38; Cl, 20.90; N, 8.26; S, 18.90. Found: C, 49.78; H, 2.69; Cl, 20.98; N, 8.29; S, 18.82.

5-Hydroxythieno[2,3-*b*]pyridine (**4**).

To a mixture of 1.05 g. of amine **5** and 10 ml. of 6 *N* sulfuric acid at 0-5° was added dropwise a solution of 0.5 g. of sodium nitrite in 1 ml. of water. The solution was poured slowly into refluxing 5% aqueous sulfuric acid solution. The cooled, bright orange solution was neutralized carefully with 10% aqueous sodium hydroxide solution. The precipitate which formed was collected by filtration and crystallized from ethyl acetate to give 0.69 g. (65%) of red crystals, m.p. 167-169°. Repetitive sublimation at 135° (0.4 mm.) and recrystallization (charcoal) from ethanol gave white prisms, m.p. 168-169°; infrared band (potassium bromide) at *ca.* 3440 cm^{-1} (OH).

Anal. Calcd. for C_7H_5NOS: C, 55.61; H, 3.33; N, 9.27; S, 21.21. Found: C, 55.77; H, 3.48; N, 9.45; S, 21.05.

5-Cyanothieno[2,3-*b*]pyridine (**9**).

A. From Amine (**5**).

The diazonium chloride (4 mmoles) solution from **5**, prepared as previously, was carefully neutralized by addition of solid sodium carbonate and then poured slowly into a refluxing solution of 0.72 g. of cuprous cyanide, 0.72 g. of potassium cyanide, and 3 ml. of water. The cooled mixture was processed as for **3** to give 0.08 g. (13%) of sublimed product, m.p. 114-117°. Additional sublimations and one recrystallization from carbon tetrachloride produced faintly cream-colored platelets, m.p. 116-117°; infrared band (chloroform) at 2240 cm^{-1} (CN).

Anal. Calcd. for $C_8H_4N_2S$: C, 59.98; H, 2.52; N, 17.49; S, 20.02. Found: C, 60.27; H, 2.82; N, 17.22; S, 20.41.

B. From Bromo Compound (**2**).

A mixture of 0.43 g. of **2**, 0.43 g. of cuprous cyanide, and 2 ml. of *N,N*-dimethylformamide was refluxed for 5 hours and then poured into a solution of 4 g. of sodium cyanide in 12 ml. of water. Processing as in A. gave 92 mg. (29%) of once-sublimed crystals, m.p. 117-120°. Recrystallization from benzene-hexane raised the m.p. to 122-122.5°. A mixture m.p. with product from A was 116-117°. Nmr spectra of samples from A and B were identical.

N-(5-Thieno[2,3-*b*]pyridine)succinamic Acid (**14**).

A mixture of 0.45 g. of amine **5** and 0.3 g. (equimolar quantity) of succinic anhydride in 10 ml. of benzene was refluxed for 10 minutes. Cooling and filtration produced 0.57 g. (71%) of pale brown crystals of **14**, m.p. 184-186°. An analytical sample was obtained as white needles by recrystallizations from aqueous acetone-cyclohexane, m.p. 191-192°; infrared bands (Nujol) at 3310 (NH), 1730 (acid carbonyl), 1660 and 1530 cm^{-1} (amide).

Anal. Calcd. for $C_{11}H_{10}N_2O_3S \cdot H_2O$: C, 49.24; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.20; H, 4.53; N, 10.70; S, 11.78.

Methyl *N*-(5-Thieno[2,3-*b*]pyridine)succinamate (**15**).

Into a refluxing suspension of 2.96 g. of preceding acid amide **14** in 50 ml. of anhydrous methanol was passed hydrogen chloride gas for 30 minutes. The mixture was cooled and filtered to yield 3.4 g. of **15** hydrochloride as white needles, m.p. 189-191°, raised to 192.5-193.5° on recrystallizations from methanol.

Anal. Calcd. for $C_{12}H_{13}ClN_2O_3S$: C, 47.92; H, 4.36; Cl, 11.79; N, 9.32; S, 10.66. Found: C, 48.00; H, 4.41; Cl, 11.44; N, 9.58; S, 10.30.

The free base **15** was obtained as a solid on treatment of the

hydrochloride with a calculated amount of potassium hydroxide, m.p. 173-174°; infrared bands (Nujol) at 3220 (NH), 1730 (ester carbonyl), 1680 and 1530 cm^{-1} (amide).

N,N'-Bis(5-thieno[2,3-*b*]pyridine)succinamide (**23**).

To a stoppered flask containing a stirred solution of 1.5 g. (10 mmoles) of amine **5** in 40 ml. of anhydrous chloroform was added (by syringe) 1.08 ml. (1.51 g., 9.7 mmoles) of succinoyl chloride. Fifteen minutes later, 3 ml. of anhydrous diethyl amine was also added. After 15 hours of stirring, water was added, the cooled mixture was filtered and the solid was crystallized from *N,N*-dimethylformamide to yield 1.18 g. (62%) of white plates, m.p. 285-286°; infrared bands (Nujol) at 3280 (NH), 1640 and 1530 cm^{-1} (amide).

Anal. Calcd. for $C_{18}H_{14}N_4O_2S_2$: C, 56.52; H, 3.69; N, 14.65; S, 16.77. Found: C, 56.80; H, 3.81; N, 14.68; S, 16.58.

Schiff's Bases from Amine (**5**).

An equimolar mixture (10-50 mmoles each) of amine **5** and an aromatic aldehyde in 20-40 ml. of anhydrous benzene was refluxed for 2-3 hours in a flask equipped with a trap for continuous separation of water condensate. Concentration of the solution and cooling caused deposition of crystals, crude yields: 71% of 5-(benzylideneimino)thieno[2,3-*b*]pyridine (**16**) from benzaldehyde; 89% of 5-(*p*-dimethylaminobenzylideneimino)-thieno[2,3-*b*]pyridine (**17**) from *p*-dimethylaminobenzaldehyde; and 78% of 5-(2-furfurylideneimino)thieno[2,3-*b*]pyridine (**18**) from 2-furaldehyde.

Recrystallization of **16** from benzene gave cream-colored needles, m.p. 104-105°; infrared band (chloroform) at 1630 cm^{-1} (C=N stretching).

Anal. Calcd. for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.76; S, 13.46. Found: C, 70.83; H, 4.23; N, 11.76; S, 13.25.

Recrystallization of **17** from benzene-cyclohexane gave bright yellow needles, m.p. 163-164°; infrared band (chloroform) at 1605 cm^{-1} (C=N).

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93; S, 11.40. Found: C, 68.01; H, 5.39; N, 14.59; S, 11.23.

Recrystallization of **18** from benzene-petrol (60-90°) gave yellow-orange prisms, m.p. 98-99°; infrared band (chloroform) at 1620 cm^{-1} (C=N).

Anal. Calcd. for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.27; S, 14.05. Found: C, 63.45; H, 3.67; N, 12.05; S, 13.78.

5-(2-Furylmethylamino)thieno[2,3-*b*]pyridine (**21**).

A mixture of 1 g. (4.4 mmoles) of Schiff's base **18**, 0.08 g. (2.1 mmoles) of sodium borohydride, and 25 ml. of dry methanol was refluxed for 2 hours, treated cautiously with water, neutralized with dilute hydrochloric acid, and evaporated to dryness. The residue was crystallized from benzene to give 0.9 g. (89%) of yellow solid **21**, converted to cream-colored prisms on recrystallizations from benzene-petrol (60-90°), m.p. 103-104° (sintering at 92°); infrared bands (chloroform) at 3400 (NH stretching), 1590 cm^{-1} (NH bending).

Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.61; H, 4.66; N, 12.03; S, 13.56.

5-Benzylaminothieno[2,3-*b*]pyridine (**19**).

By a procedure similar to that used for **21** there was obtained from **16** pale brown needles of **19** (83%) on crystallization of the crude product from benzene-cyclohexane, m.p. 128-130°. Repeated crystallizations gave white nacreous plates, m.p. 128-129°; infrared bands (chloroform) at 3440 and 1590 cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 69.94; H, 4.95; N, 11.43; S, 12.95.

5-(*p*-Dimethlaminobenzylamino)thieno[2,3-*b*]pyridine (**20**).

A mixture of 1.72 g. (6.1 mmoles) of Schiff's base **17**, 0.25 g. (6.6 mmoles) of sodium borohydride, and 25 ml. of absolute ethanol was refluxed for 3 hours. Excess dilute hydrochloric acid was added cautiously and then excess potassium hydroxide was added. The product was extracted into chloroform and transferred to benzene solution, which was percolated through 30 g. of Alcoa F-20 alumina. The residue from evaporation of the filtrate was crystallized from benzene-cyclohexane to give 0.45 g. (26%) of **20**, m.p. 152-153°, raised to 155-156° on recrystallizations and obtained as cream-colored prisms; infrared bands (chloroform) at 3440 and 1610 cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.81; H, 6.05; N, 14.83; S, 11.31. Found: C, 68.11; H, 6.10; N, 14.70; S, 11.08.

Reaction of Bromo Compound **2** with Potassium Amide.

To 200 ml. of stirred liquid ammonia at *ca.* -70° were added, in succession, a small piece of potassium, 1.5 g. of crystalline iron (II) nitrate hexahydrate, and (portionwise) additional potassium (total wt. 7.5 g., 0.19 gram-atom). Twenty minutes later a solution of 6 g. (0.028 mole) of **2** in 75 ml. of anhydrous ether was added dropwise, over a period of 40 minutes. After 2 more hours, 11 g. (0.21 mole) of ammonium chloride was added. The stirred mixture was allowed to warm to room temperature to effect evaporation of the solvent. A chloroform extract of the residue was chromatographed by means of 25 g. of Alcoa F-20 alumina and chloroform as eluent to give 2.45 g. of yellow crystals. These crystals were stirred with a mixture of chloroform and 9 ml. of 1 *N* HCl for 1 hour. Basification of the acidic layer, extraction with chloroform, and evaporation of solvent gave 1.25 g. of 4-aminothieno[2,3-*b*]pyridine (**24**) as white crystals, m.p. 139-140°. Evaporation of the organic layer gave 1.1 g. of crystals, shown by nmr to contain equal amounts of **5** and **24** (14). Reprocessing of this mixture as before gave total yields of 0.55 g. (13%) of **5** and 1.8 g. (42%) of **24** (9).

An analytical sample of **24** was obtained as white prisms, m.p. 144.5-145°, after several sublimations at 165° (0.3 mm.); infrared bands (Nujol) at 3460, 3330 (NH stretching), 1640 cm^{-1} (NH bending); nmr signals (deuteriochloroform): doublets at δ = 8.16 (H-6, $J_{5,6}$ = 5.5 Hz), 7.26 (H-2, $J_{2,3}$ = 6 Hz), 7.10 (H-3), and 6.41 (H-5); broad signal at *ca.* 4.6 ppm (NH_2).

Anal. Calcd. for $C_7H_6N_2S$: C, 55.97; H, 4.03; N, 18.65; S, 21.35. Found: C, 56.16; H, 4.20; N, 18.53; S, 21.09.

Repetition of the foregoing procedure, but at a reaction temperature of -35° instead, gave **24** exclusively (37%).

5-Nitrothieno[2,3-*b*]pyridine (**6**).

To a stirred mixture of 42.2 g. (0.08 mole) of bis-(2-thienylammonium)hexachlorostannate (IV) (3, 15), 250 ml. of ethanol, and 50 ml. of concentrated hydrochloric acid in an atmosphere of nitrogen was added 25 g. (0.16 mole) of sodium nitromalondialdehyde hydrate (16). The thick, yellow precipitate (which formed immediately) dissolved when the mixture was refluxed for 2 hours. The mixture was poured onto ice, basified with 40% aqueous potassium hydroxide solution, and extracted with chloroform. The residue from evaporation of the extract was crystallized from ethanol to give 2.8 g. (10%) of gray solid, m.p. 158-161°. An analytical sample was obtained by repeated sublimation at 110° (0.1 mm.) and recrystallization from benzene to form cream-colored needles, m.p. 160-161°; infrared bands (chloroform) at

1570 (NO_2 asym. stretching) and 1340 cm^{-1} (NO_2 sym. stretching).

Anal. Calcd. for $C_7H_4N_2O_2S$: C, 46.66; H, 2.24; N, 15.55; S, 17.80. Found: C, 47.08; H, 1.90; N, 15.44; S, 17.69.

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