

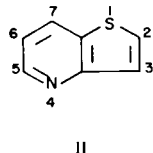
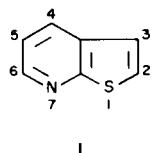
Chemistry of Thienopyridines. IX. Direct Nitration of Thieno[2,3-*b*]pyridine and Thieno[3,2-*b*]pyridine (1)

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Thieno[2,3-*b*]pyridine (I) and thieno[3,2-*b*]pyridine (II) were nitrated at C-3 in *ca.* 50% yield by means of nitric-sulfuric acids. Reduction of 3-nitro-I (Ia) with tin and hydrochloric acid gave 3-amino-I (Ib) (39%), which was converted to 3-acetylamino-I (Ic) and to dipyrido[2,3-*b*:2',3'-*d*]thiophene (V). Reduction of 3-nitro-II (IIa) with iron and acetic acid at 100° gave 3-acetylamino-II (IIb) (25%), while use of tin and hydrochloric acid at room temperature gave 2-chloro-3-amino-II (IIc). Assignments of position of nitration are based on nmr spectral data (which indicate that substitution occurs in the thiophene ring) and on non-identities of Ic, IIb, and V with authentic samples of 2-acetylamino-I, 2-acetylamino-II, and dipyrido[2,3-*b*:3',2'-*d*]thiophene (VI), respectively. Results are consistent with reactivity indices for I and II as calculated from simple Hückel Molecular Orbital theory and with observations on nitration and reduction in the isoteric quinoline system.

In a preceding paper (6) in this series predictions were made on preferred positions of substitution into thieno[2,3-*b*]pyridine (I). In particular, it was noted that electrophilic substitution into I should occur predominantly in the



thiophene ring, and with considerable preference for attack at C-3 over C-2. Limited investigation on I (6) showed that, indeed, deuteriodeprotonation occurs at both C-2 and C-3 (but faster at C-3) in the presence of deuteriosulfuric acid. Moreover, treatment of I with aqueous bromine gave the 2,3-dibromo derivative. On the other hand, nitration of thieno[2,3-*b*]pyridine 7-oxide with nitric-sulfuric acids gave the 4-nitro derivative (in analogy with the isosteric quinoline 1-oxide system), while nitration with nitric-acetic acids gave the 5-nitro derivative (for which close analogy in the quinoline 1-oxide system has not been observed) (7). No studies on direct substitution into II have been reported. The availability of quantities of I and II from practical syntheses developed in our laboratory (6,8) led us to investigate the direct nitrations of these two parent compounds by means of mixed nitric-sulfuric acids, conditions conducive to electrophilic attack by nitronium ions (9). Structural investigations on the products formed are presented in this paper.

Compounds I and II gave mononitro derivatives (Ia and IIa, respectively) in *ca.* 50% yield at a reaction temperature of 65-110°. From the nmr spectrum of each nitro compound it was apparent that the thiophene ring AB pattern for the parent compound (6) had been replaced by a downfield-shifted singlet. Thus, substitution had occurred in the thiophene ring, but specific assignment of the nitro group to C-2 or C-3 could not be made from this information alone. Chemical studies presented herewith lend strong support to the location of the nitro group at C-3 in each derivative (10).

In the thieno[2,3-*b*]pyridine (I) series, reduction of Ia with tin and hydrochloric acid gave the 3-amino compound Ib (39%), while reduction with iron and glacial acetic acid at 100° gave only the condensation product bis-(3-thieno[2,3-*b*]pyridyl)amine (IV) (14%). Compound Ib was converted to the 3-acetylamino derivative Ic (90%) by means of acetic anhydride and to dipyrido[2,3-*b*:2',3'-*d*]thiophene (V) (18%) by means of malondialdehyde tetraethyl acetal. Direct comparisons showed that Ic and V were different from authentic samples of 2-acetylamino-

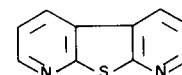
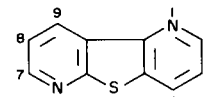
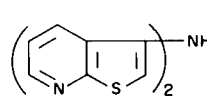


TABLE I
Nuclear Magnetic Resonance Data for Thieno[2,3-*b*] - and Thieno[3,2-*b*] pyridines
Substituted in the 2- and/or 3-positions

Compound No.	Solvent (a)	Substituent(s)	Chemical Shift, in δ (b)			Other Signals
			H-2 or H-3	H- α	H- β	
Ia	A	3-NO ₂	8.78	8.69	7.55	8.85
Ib	A	3-NH ₂	6.44	8.67	7.32	7.96
Ic	B	3-NHAc	8.17	8.78	7.58	8.65
Id (g)	C	2-C(=NOH)CH ₃	7.59 (c)	8.72	7.35 (d)	8.14
Ie	B	2-NHAc	7.01	8.54	7.47	8.18
Ie	AB	2-NHAc	6.90	8.40	7.30	8.01
IV (e)	AB	3-NH(3'-TP)	7.15	8.65	7.49	8.54
IIa	D	3-NO ₂	9.95	9.38	8.42	9.62
IIb	A	3-NHAc	8.19	8.49	7.17	8.02
IIc	A	2-Cl-3-NH ₂	—	8.57	7.20	7.90
IIId (f)	AB	2-Cl-3-NHAc	—	8.72	7.44	8.41
IIe	A	2-Cl-3-NAc ₂	—	8.66	7.27	8.03
IIIf (g)	C	2-C(=NOH)CH ₃	(c)	8.89	7.27 (d)	8.25
IIg	AB	2-NHAc	7.14	8.54	7.16	8.21

(a) Solvents used: A, deuteriochloroform; B, DMSO-*d*₆; C, pyridine-*d*₅; AB, mixture of A and B; D, deuterium chloride in deuterium oxide with sodium γ -trimethylsilylpropanesulfonate as internal standard. (b) α , β , and γ refer to positions on the pyridine ring with respect to the hetero nitrogen atom. In system I: H- α \equiv H-6, H- β \equiv H-5, H- γ \equiv H-4. In system II: H- α \equiv H-5, H- β \equiv H-6, H- γ \equiv H-7. In every case $J_{\alpha\gamma} = 1.5$ Hz and $J_{\beta\gamma} = 8.8$ - 3 Hz. With the exception of IIa in solvent D (where $J = 6$ Hz), $J_{\alpha\beta} = 4.5$ - 4.8 Hz in every case. (c) Uncertain assignment. (d) Center of irregular multiplet. (e) 3'-TP = 3-thieno[2,3-*b*]pyridyl. (f) Monohydrate. (g) Prepared by pyridine-absolute ethanol method. (h) Also 2.90 (d, $J = 5$ Hz, NHCH₃), assigned to ca. 16% impurity of TP-2-C(=O)NHCH₃, 11h. H- α and H- γ signals also showed some broadening. (i) NH-signal was not observed.

TABLE II

Quantum Chemical Reactivity Indices for
Thieno[3,2-*b*]pyridine (II) (a)

Position r	q_r	$S_r^{\text{elec.}}$	$S_r^{\text{nucl.}}$
1 (S)	1.31	3.16	0.55
2	1.09	1.22	0.80
3	1.22	2.17	0.49
3a	1.05	1.14	0.73
4 (N)	1.32	1.60	0.95
5	0.92	0.91	1.15
6	1.06	1.14	0.72
7	0.94	0.95	1.18
7a	1.08	1.05	0.63

(a) S_r is given in units of β_C^{-1} . For parameters used and assumptions made see similar calculations for I in reference 6.

thieno[2,3-*b*]pyridine (Ie) and of dipyrido[2,3-*b*: 3',2'-*d*]thiophene (VI), respectively. Hence, substituents in Ia, Ib, and Ic are assigned to position C-3.

Compound Ie was obtained from the known 2-acetylthieno[2,3-*b*]pyridine (6) by the two-step process of oxime formation (80%) and Beckmann rearrangement (77%). The nmr spectrum of Ie showed that it was, indeed, the acetyl amino derivative (methyl proton singlet at δ 2.23), rather than the alternative thieno[2,3-*b*]pyridine-2-(*N*-methyl)carboxamide (expected methyl proton doublet at *ca.* δ 2.8) (11) (see Table I). In turn, this result implies that the oxime intermediate Id was the geometric isomer with the OH and thienopyridyl moieties in an *anti* arrangement (13).

Compound VI was available from the heterogeneously catalyzed sulfur-bridging reaction which occurs on 3,3'-bipyridyl in the presence of hydrogen sulfide at 630° (14). Its characteristic nmr spectrum — three well-separated sets of doublets of doublets, with equal areas — is much simpler than the spectrum of the unsymmetrical V.

Further support for the positional assignment of the nitro group in Ia is found on comparison of chemical shifts for the aromatic protons in Ia and amine Ib (Table I). The gross difference in electronic natures of the nitro and amino groups should result in a large decrease in δ -value for the remaining thiophene-ring proton on going from either the 2- or 3-nitro compound to the corresponding amine. On the other hand, the effect of this chemical transformation on δ_4 should be significantly large, only if the substituent is located at C-3 rather than at C-2. Observed $\Delta\delta_4$ is -0.89, as compared to much smaller changes in δ_5 (-0.23) and δ_6 (-0.02) [and a large change (-2.3) in δ_2]. Thus, assignment of the substituent in Ia to C-3 is again indicated.

Attempts to repeat the preceding methodology for elucidation of the structure of nitro compound IIa were beset with chemical variations. Thus, the corresponding free amino compound was not isolated. Instead, reduction of IIa with tin and hydrochloric acid gave 2-chloro-3-aminothieno[3,2-*b*]pyridine (IIc) (*vide infra*), while reduction with iron and glacial acetic acid at 100° led to the 3-acetyl amino derivative IIb (25%) directly. Compound IIc was converted to 2-chloro-3-acetyl amino[3,2-*b*]pyridine (IIId) by means of refluxing benzene-acetic anhydride and to 2-chloro-3-(*N,N*-bis-acetyl)aminothieno[3,2-*b*]pyridine (IIe) by means of refluxing acetic anhydride alone. The absence of thiophene ring protons in IIc, IIId, and IIe was readily apparent in the nmr spectra. A low field signal at *ca.* δ 8.7 for the amide NH group in IIId was absent in IIe.

For comparison with IIb, a sample of 2-acetyl aminothieno[3,2-*b*]pyridine (IIg) was prepared from the known 2-acetylthieno[3,2-*b*]pyridine (6) by conversion to the oxime IIh (96%) and Beckmann rearrangement thereof (53%). Though the Beckmann product melted sharply and gave typical infrared bands for a secondary amide, it appeared, by nmr, to consist of IIg contaminated with isomeric thieno[3,2-*b*]pyridine-2-(*N*-methyl)carboxamide (IIh) (15). The presence of IIh was indicated primarily by the appearance of a doublet ($J = 5$ Hz) of small intensity at δ 2.90 (ascribed to methyl protons on the NHCH₃ group) (11). Since the nmr spectrum of the major component (IIg) of this mixture is considerably different from that of IIb (Table I) it is apparent that IIb should be the 3-isomer. The assignment of the chloro substituent in IIc to the 2-position then follows.

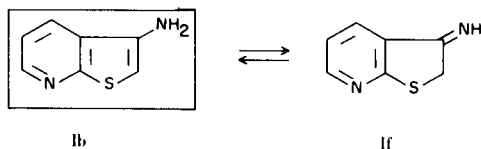
In Table II are presented quantum chemical reactivity indices q_r (π -electron density) and S_r (exact superdelocalizabilities for electrophilic and nucleophilic attack) for direct substitution into II. Observation of this table indicates that electrophilic substitution into II should occur predominantly in the thiophene ring with a strong preference for position C-3 over that of C-2 (analogous to observations for benzo[*b*]thiophene) (16a). Nucleophilic substitution, on the other hand, should occur predominantly in the pyridine ring with preference shown for C-5 and C-7 (α and γ positions, respectively, with regard to *N*-analogous to observations for quinoline and to predictions for I) (6, 16b).

Nitration of quinoline in nitric-sulfuric acids at 0° gives about equal amounts of 5- and 8-nitro derivatives (17), in accordance with $S_r^{\text{elec.}}$ calculations (18). Protonated quinoline is involved in this process (19). Presumably protonated thienopyridines are also involved in the present nitrations. It is interesting that Ia (*i.e.* 3-nitro-I) is an isostere (20) of 5-nitroquinoline, while IIa (*i.e.* 3-nitro-II) is an isostere of 8-nitroquinoline. Thus, the nitrations of I and II are analogous to the nitration of quinoline.

The isosteric analogies are even more remarkable in regard to reduction of Ia and IIa with tin and hydrochloric acid at room temperature. Thus, it has been reported that heating 8-nitroquinoline with stannous chloride-hydrochloric acid gives 5- and 7-chloro-8-aminoquinolines, while 5-chloro-8-nitroquinoline gives a little 5,7-dichloro-8-aminoquinoline (21, 22). The transformations, 8-nitroquinoline \rightarrow 7-chloro-8-aminoquinoline and 3-nitrothieno[3,2-*b*]pyridine (IIa) \rightarrow 2-chloro-3-aminothieno[3,2-*b*]pyridine (IIc), represent completely analogous results in isosteric systems, though (to be sure) reaction conditions were somewhat different in the two cases. Dikshoorn noted (23), however, that tin plus hydrochloric acid and stannous chloride plus hydrochloric acid give similar results with regard to ring chlorination during the reduction of a nitroaromatic compound. In contrast to the 8-isomer, Dikshoorn (23) found that reduction of 5-nitroquinoline with stannous chloride-hydrochloric acid gave chlorine-free 5-aminoquinoline. Similarly, 3-chloro-5-nitroquinoline was converted to 3-chloro-5-aminoquinoline without attendant ring chlorination (21). Again the conversion, 3-nitrothieno[2,3-*b*]pyridine (Ia) \rightarrow 3-aminothieno[2,3-*b*]pyridine (Ib), is analogous. Blanksma (24) proposed that ring chlorination which accompanies reduction of a nitro group occurs *via* the sequential steps $-\text{NO}_2 \rightarrow -\text{NHOH} \rightarrow -\text{NHCl} \rightarrow o$ - and/or *p*-chloroamine. In IIa, only an *ortho* position (at C-2) is available for chlorine substitution into the same ring. However, the possible intermediacy of hydroxylamines in the ring chlorinations considered here has not been investigated (25).

Dikshoorn (23, 25) proposed that one should use iron and acetic acid for reduction of nitroaromatic compounds in order to avoid ring chlorination. Indeed, when IIa was treated with iron and glacial acetic acid at 100° the desired 3-acetylamino derivative IIb was obtained, albeit only in 25% yield. Although similar treatment of Ia (but for a shorter reaction period) gave reduction of the nitro group, neither the amine Ib nor its acetyl derivative Ic was isolated. Instead, a small yield of the condensation product IV was obtained (*vide supra*).

Formation of IV may be ascribed to condensation (with loss of ammonia) of amino form Ib with its tautomer If. However, infrared and nmr spectra indicated the presence of only Ib in chloroform solution at room temperature (26). The former spectrum showed N-H stretching



bands at 3470 (asym.) and 3390 cm^{-1} (sym.) for a primary amino group wherein the two hydrogens are equivalent

(27). The nmr spectrum (Table I), moreover, showed the presence of only aromatic protons (four well-separated signals) and an amino group (broad signal at δ 3.86). In particular, there was no evidence for proton resonance at *ca.* δ 9.7, as would be expected for an imino group (28). Exactly analogous arguments apply to the assignment of an amino structure to IIc, where there are only three aromatic protons indicated in the nmr spectrum and the signal for the amino group is shifted somewhat downfield.

EXPERIMENTAL (29)

Thieno[2,3-*b*]pyridine (I) System

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

To 55 ml. of 96% sulfuric acid (stirred, and cooled in a water bath) was added 30 g. (0.22 mole) of thieno[2,3-*b*]pyridine (I) (6) at such rate as to maintain a temperature of less than 50°. Then 22.6 ml. (0.36 mole) of 70% nitric acid was added dropwise (without cooling) at such rate as to maintain the reaction temperature at $110 \pm 5^\circ$. The cooled mixture was poured onto ice, neutralized with sodium bicarbonate, and extracted with chloroform. Evaporation of the organic extract and recrystallization of the residue from benzene-ligroin (60-90°) gave 22.1 g. (55%) of Ia, m.p. 87-90°. An analytical sample (faintly yellow needles, m.p. 98-99°) was obtained by successive steps of crystallization from ethanol-cyclohexane, chromatography with benzene-chloroform and Brinkmann neutral alumina, and finally sublimation at 90° (20 mm.); *ir* (chloroform) 1565, 1335 cm^{-1} (nitro group); *uv* max (ethanol) 220 nm (ϵ 26,400), 245 (6,300), 308 (8,720).

Anal. Calcd. for $\text{C}_7\text{H}_4\text{N}_2\text{O}_2\text{S}$: C, 46.66; H, 2.24; N, 15.55; S, 17.79. Found: C, 46.78; H, 2.34; N, 15.26; S, 17.55.

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

To a stirred solution of 3.6 g. (0.02 mole) of nitro compound Ia in 60 ml. of concentrated hydrochloric acid was added 7 g. (0.06 g.-atom) of granular tin over a period of 30 minutes. The mixture was stirred 15 hours longer, poured into ice-water, basified with potassium hydroxide, and extracted with chloroform. The organic extract was percolated through 50 g. of Alcoa F-20 alumina. The residue from evaporation of the chloroform crystallized from cyclohexane as a pale brown solid, yield 1.16 g. (39%), m.p. 100-103°, converted to faintly cream-colored prisms (m.p. 101-102°) on repetitive evaporation distillation at 105° (0.4 mm.); *ir* (chloroform) 3470, 3390, 1620 cm^{-1} (NH).

Anal. Calcd. for $\text{C}_7\text{H}_6\text{N}_2\text{S}$: C, 55.97; H, 4.03; N, 18.65; S, 21.35. Found: C, 55.90; H, 4.12; N, 18.64; S, 21.13.

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

A mixture of 0.5 g. (3.3 mmoles) of amine Ib, 0.36 g. (3.5 mmoles) of acetic anhydride, and 20 ml. of benzene was refluxed for one hour. Slow cooling of the solution gave 0.57 g. (90%) of Ic, m.p. 158-160°, purified further by evaporative distillations at 170° (0.1 mm.) and recrystallization from ether-ethanol (white prisms, m.p. 159.5-160.5°); *ir* (nujol) 3310 (NH), 1670, 1540 cm^{-1} (amide).

Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2\text{S}$: C, 56.23; H, 4.20; N, 14.58; S, 16.68. Found: C, 56.05; H, 4.27; N, 14.58; S, 16.53.

Dipyrido[2,3-*b*:2',3'-*d'*]thiophene (V) (30).

To a stirred mixture of 3.5 g. (0.019 mole) of nitro compound Ia, 25 ml. of ethanol, and 65 ml. of concentrated hydrochloric acid in a nitrogen atmosphere was added 7 g. (0.06 g.-atom) of powdered tin over a period of one hour. Stirring was continued for 40 hours, whereupon 2 g. of crushed, fused zinc chloride was added and heating was started. Then 6 g. (0.027 mole) of malondialdehyde tetraethyl acetal (Aldrich) was added dropwise over a period of 15 minutes and the mixture was refluxed for 24 hours (nitrogen atmosphere). The cooled reaction mixture was washed with chloroform (discarded), basified with potassium hydroxide, and extracted with chloroform. The organic extract was washed with water, dried, and chromatographed with 20 g. of Alcoa F-20 alumina plus chloroform. Sublimation at 110° (0.15 mm.) of the residue obtained on evaporation of the effluent gave 0.62 g. (18%) of product, m.p. 118-120°. An analytical sample (m.p. 116-117°) was obtained as white prisms from cyclohexane-petrol; nmr (deuteriochloroform) δ 8.7-9.0 (m, 3H, H-2, H-7, H-9), 8.29 (d of doublets, 1H, J_{2,4} = 1.4 Hz, J_{3,4} = 9 Hz, H-4), 7.56 and 7.48 ppm (2 overlapping sets of d of doublets, 2H total, J_{2,3} = J_{7,8} = 4.5-5 Hz, J_{8,9} = 9 Hz, H-3 and H-8).

Anal. Calcd. for C₁₀H₆N₂S: C, 64.49; H, 3.25; N, 15.04; S, 17.22. Found: C, 64.79; H, 3.41; N, 15.04; S, 17.39.

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

A mixture of 0.38 g. of 2-acetylthieno[2,3-*b*]pyridine (6,31), 0.57 g. of hydroxylammonium chloride, 4.5 ml. of absolute ethanol, and 4.5 ml. of anhydrous pyridine was refluxed for 3 hours. Evaporation of the solvent, trituration of the residue with water, and crystallization of the solid from 50% ethanol gave 0.33 g. (80%) of oxime, m.p. 265-266°; converted to white prisms on recrystallization, m.p. 269-270° dec.

Anal. Calcd. for C₉H₈N₂OS: C, 56.23; H, 4.20; N, 14.58; S, 16.68. Found: C, 56.26; H, 4.20; N, 14.81; S, 16.40.

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

To a cold (10°) solution of 0.66 g. of oxime Id in benzene was added 0.82 g. of phosphorus pentachloride. The mixture was refluxed for 15 minutes, poured onto ice, and neutralized with sodium hydroxide. The precipitate was collected by filtration and combined with the residue from evaporation of ethyl acetate extracts of the filtrate, yield 0.5 g. (77%), m.p. 229-234°; raised to 235-236° dec. by repeated sublimations at ca. 150° (0.1 mm.) and then recrystallization from ethanol to give faintly cream-colored prisms; ir (Nujol) 3440 (NH), 1685, 1550 cm⁻¹ (amide).

Anal. Calcd. for C₉H₈N₂OS: C, 56.23; H, 4.20; N, 14.58; S, 16.68. Found: C, 56.07; H, 4.32; N, 14.62; S, 16.74.

Bis(3-thieno[2,3-*b*]pyridyl)amine (IV).

A mixture of 1.8 g. (0.01 mole) of nitro compound Ia, 2.23 g. (0.04 g.-atom) of iron powder, and 40 ml. of glacial acetic acid was stirred at 100° for 2 hours and then processed as in the preparation of Ib (but without alumina percolation). Concentration of the chloroform extract gave 0.2 g. (14%) of yellow solid, m.p. 213-215°. Crystallization from ethanol-dimethylformamide gave shiny, amber-colored plates, m.p. 221.5-222.5°; ir (Nujol-hexachlorobutadiene) 3290, 3115 cm⁻¹ (NH); positive test (32) for a secondary amine.

Anal. Calcd. for C₁₄H₉N₃S₂: C, 59.34; H, 3.20; N, 14.83; S, 22.63; Found: C, 59.37; H, 3.37; N, 14.74; S, 22.43.

Thieno[3,2-*b*]pyridine (II) System3-Nitrothieno[3,2-*b*]pyridine (IIa).

To 24.5 ml. of 96% sulfuric acid was added (with stirring and

cooling) 8.5 g. (0.063 mole) of thieno[3,2-*b*]pyridine (6,8). The solution was warmed to 65°, treated dropwise with 6 ml. (0.095 mole) of 70% nitric acid over a period of 10 minutes, stirred 15 minutes longer, cooled, and poured into a mixture of ice and water. The aqueous mixture was filtered and neutralized with sodium hydroxide. The precipitate which formed was washed with water and then ether, dried, and crystallized from acetonitrile (charcoal) to give 5.4 g. (48%) of cream-colored leaves, m.p. 216.5-217.5°. Alternatively, crystallization from ethanol followed by sublimation at 130° (0.5 mm.) gave a yellow powder of the same melting point; ir (chloroform) 1560, 1340 cm⁻¹ (nitro group).

Anal. Calcd. for C₇H₄N₂O₂S: C, 46.66; H, 2.24; N, 15.55; S, 17.79. Found: C, 46.72; H, 2.38; N, 15.68; S, 17.58.

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

A mixture of 3.95 g. (0.022 mole) of preceding nitro compound IIa, 4.5 g. (0.08 g.-atom) of iron powder, and 75 ml. of glacial acetic acid was stirred at 100° for 6 hours and then at room temperature overnight. The mixture was poured into water, basified with potassium hydroxide, and extracted with ether. Evaporation of the dried extract gave a liquid which solidified on cooling, yield 1.07 g. (25%). Crystallization from benzene-hexane (charcoal) gave yellow needles, m.p. 108-109°; ir (chloroform) 3420 (NH), 1695, 1540 cm⁻¹ (amide).

Anal. Calcd. for C₉H₈N₂OS: C, 56.24; H, 4.20; N, 14.57; S, 16.68. Found: C, 55.96; H, 4.34; N, 14.42; S, 16.61.

2-Chloro-3-aminothieno[3,2-*b*]pyridine (IIc).

To a cooled solution of 3.6 g. (0.02 mole) of nitro compound IIa, in 75 ml. of concentrated hydrochloric acid was added in small portions over a period of one hour (at such rate as to maintain a temperature below 30°) 7 g. (0.06 g.-atom) of powdered tin. The mixture was stirred at room temperature for 20 hours, poured into water, basified with sodium hydroxide, and extracted with ether and chloroform. Evaporation of the organic extracts gave a liquid which solidified on standing. Crystallization from acetonitrile (charcoal) gave crude product (2.5 g., melting range 85-125°). Three sublimations at 110° (0.3 mm.) and recrystallization from acetonitrile gave faintly cream-colored prisms, m.p. 138-139°; ir (chloroform) 3520, 3420, 1620 cm⁻¹ (NH).

Anal. Calcd. for C₇H₅ClN₂S: C, 45.53; H, 2.73; Cl, 19.20; N, 15.17; S, 17.36. Found: C, 45.71; H, 2.77; Cl, 19.11; N, 15.44; S, 17.28.

2-Chloro-3-acetylaminothieno[3,2-*b*]pyridine (II_d).

A solution of 0.87 g. (47 mmoles) of IIc in 20 ml. of benzene and 0.67 ml. (71 mmoles) of acetic anhydride was refluxed for 2 hours, filtered hot, evaporated partially, and cooled. The crystals which formed were washed with ether, dried, and recrystallized from acetonitrile (not anhydrous) to give 0.68 g. (59%) of II_d monohydrate, m.p. 162-163°, obtained as faintly cream-colored needles; ir (Nujol-hexachlorobutadiene) 3100-3500 (OH and NH), 1670, 1550 cm⁻¹ (amide).

Anal. Calcd. for C₉H₉ClN₂O₂S: C, 44.18; H, 3.71; Cl, 14.49; N, 11.45; S, 13.10. Found: C, 43.69; H, 3.59; Cl, 14.28; N, 11.35; S, 12.91.

2-Chloro-3-(*N,N*-bisacetyl)aminothieno[3,2-*b*]pyridine (IIe).

A. From Chloroamine (IIc).

A mixture of 0.61 g. of IIc and 10 ml. of acetic anhydride was refluxed for 2 hours, cooled, and poured into a stirred mixture of ice and water. The hydrolysate was neutralized with sodium bicarbonate and extracted with chloroform. Evaporation of the extract left a residue which was triturated with ether and crystal-

lized from aqueous isopropanol to form white needles, yield 0.6 g. (67%), m.p. 95-108°, raised to 108-109° on recrystallizations from the same solvent and then from hexane; ν (chloroform) 1730 cm^{-1} (carbonyl).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{ClN}_2\text{O}_2\text{S}$: C, 49.17; H, 3.38; Cl, 13.20; N, 10.42; S, 11.93. Found: C, 48.81; H, 3.32; Cl, 13.10; N, 10.11; S, 11.73.

B. From Chloroamide (II_d).

Treatment of II_d monohydrate with acetic anhydride and processing as in A gave a crude product, obtained as plates on crystallization from hexane; yield 73%, m.p. 108-109°.

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

A. Using Pyridine-Ethanol as Solvent.

With exactly the same procedure as used for preparation of oxime I_d, 2-acetylthieno[3,2-*b*]pyridine (6,31) was converted to its oxime II_f, obtained as white powder from aqueous ethanol, yield 92%, m.p. 265-267° dec., raised to 269.5-270.5° on recrystallization, depressed more than 25° on admixture with oxime I_d.

Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{OS}$: C, 56.23; H, 4.20; N, 14.58; S, 16.68. Found: C, 56.53; H, 4.41; N, 14.46; S, 16.43;

B. Using Aqueous Ethanolic Sodium Acetate.

A mixture of 1.38 g. of 2-acetylthieno[3,2-*b*]pyridine, 0.81 g. of hydroxylammonium chloride, 2.1 g. of sodium acetate trihydrate, 40 ml. of ethanol, and 10 ml. of water was refluxed for one hour. The cooled solution was diluted with water, neutralized with sodium bicarbonate, and extracted with chloroform. Evaporation of the extract left 1.44 g. (96%) of crude oxime II_f, m.p. 255-258°, used without further purification in the next step (33).

Beckmann Rearrangement of Oxime II_f (15).

A cold (0°), stirred mixture of 1.12 g. of crude, preceding oxime II_f (from procedure B.) and 50 ml. of dry tetrahydrofuran was treated with 1.8 g. of phosphorus pentachloride. The yellow suspension which formed was stirred at 0° for 3 hours longer, poured into ice-water, neutralized with sodium bicarbonate, and extracted with chloroform. Evaporation of the extract and crystallization of the residue from acetonitrile gave 0.59 g. (53%) of mixed amides, obtained as amber-colored needles, m.p. 231.5-232.5°, depressed on admixture with I_e; ν (Nujol-hexachlorobutadiene) 3210 (NH), 1680 cm^{-1} (amide carbonyl).

Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{OS}$: C, 56.23; H, 4.20; N, 14.58; S, 16.68. Found: C, 56.56; H, 4.24; N, 14.67; S, 16.42.

The nmr spectrum of this product indicates that it consists of about 84% 2-acetylaminothieno[3,2-*b*]pyridine (II_g) (cf. Table I) and 16% thieno[3,2-*b*]pyridine-2-(*N*-methyl)carboxamide (II_h) (cf. footnote i, Table I).

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- (4) NSF Undergraduate Research Participant, summer 1967.
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(30) Procedure developed with the assistance of Dr. S. B. Mathur.

(31) An improved procedure for separation and purification of the components of mixtures of 2-acetylthieno[2,3-*b*]pyridine (**1i**) and 2-acetylthieno[3,2-*b*]pyridine (**2c**) (**6**) is as follows. The mixture is stirred directly with 0.2 *N* hydrochloric acid at room temperature for 2 hours. The suspension is extracted with carbon

tetrachloride, the organic layer is evaporated, and the residue is crystallized from benzene-hexane to yield pure **1i**. Extraction of the basified aqueous extract with carbon tetrachloride, evaporation of the organic solvent, and crystallization of the residue from benzene-hexane gives pure **2c**.

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