Chemistry of Thienopyridines. XXV. Comparative Mass Spectra of Some Amino and Acylamino Derivatives (1)

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Electron-impact mass spectral fragmentation patterns are reported for various aminothienopyridines ($TPNH_2$) and acylaminothienopyridines. The molecular ion $TPNH_2^{+\cdot}$ shows loss of atomic hydrogen, hydrogen cyanide and both thioformyl radical and cation. $TPNH_2^{+\cdot}$ is the most abundant ion in the spectrum of each acylamino compound investigated. A semiquantitative mass spectrum of the amine $TPNH_2$ can be obtained by deletion of selected peaks (for the acetylium and molecular ions) from the observed mass spectrum of the *N*-acetyl derivative.

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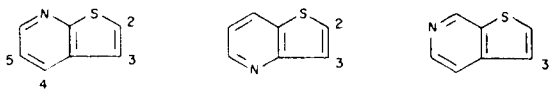
Except for the presence of peaks at m/e 43 (Ac^+) and 135 (molecular ion) the ion-impact mass spectral pattern of acetanilide is qualitatively very similar to that of aniline (4). It has been proposed that this similarity can be ascribed to the facile transformation acetanilide$^{+\cdot}$ → aniline$^{+\cdot}$ + ketene, which occurs in the ionization chamber of the mass spectrometer (5). Thus, most of the peaks found for acetanilide result from the effective presence of aniline in the chamber, though only the molecular ion of aniline (and not aniline, *per se*) is involved.

The limited stabilities of aminothiophenes under laboratory conditions pose problems in the handling and investigation of them. However, *N*-acylation serves to markedly enhance their stabilities. Recently, we reported (6) a convenient procedure for direct reductive acetylation of nitro-substituted thiophenes into acetylamino derivatives. In the present paper we consider the possibility that one might ascertain an approximate mass spectrum of an amino-substituted thiophene system from the spectrum of its *N*-acetyl or other *N*-acyl derivative. To look for spectral correlations we have chosen examples of thienopyridine systems **1**, **2**, and **3**, wherein the free amino compound retains analytical purity after relatively short exposure to laboratory conditions (7).

Syntheses and structural investigations on compounds **1a-1g** and **2a-2d** were reported previously (6,8-10). 3-Nitrothieno[2,3-*c*]pyridine (**3a**) was obtained by nitration of the parent compound (**3**) under conditions similar to those used by others (11). Reduction of **3a** with iron and acetic acid (12) produced both **3b** and **3c**. Assignment of position 3 to the nitro substituent in **3a** was made by Gronowitz and Sandberg (13) on the basis of the pmr



1

a, 2-NHAc
b, 3-NH_2
c, 3-NHAc
d, 4-NH_2
e, 4-NHC(=O)-NH-C(=O)-NH-C(=O)-O
f, 5-NH_2
g, 5-NHC(=O)$CH_2CH_2CO_2Me$
h, 2-NH_2

2

a, 2-Cl, 3-NH_2
b, 2-Cl, 3-NHAc
c, 2-Cl, 3-NAc_2
d, 3-NHAc
e, 3-NH_2

3

a, 3-NO_2
b, 3-NH_2
c, 3-NHAc

spectrum. This assignment is corroborated by noting the marked upfield shifts ($\Delta\delta$ = -0.8 and -2.47 ppm) observed in the signals for H-4 and H-2 on conversion of **3a** into **3b** (14).

Figures 1 and 2 (which contain all peaks of relative abundance ≥ 3%) show the closely similar patterns which one finds in the mass spectra of the pairs 3-amino- and 3-acetylaminothieno[2,3-*b*]pyridines (**1b** and **1c**) and 3-amino- and 3-acetylaminothieno[2,3-*c*]pyridines (**3b** and **3c**), respectively. It is readily apparent that if one deletes the peaks for the acetylaminothienopyridine molecular ion (m/e 192) and the acetylium ion (Ac^+, m/e 43) from the spectrum of the acetylamino compound the remaining peaks in the difference spectrum (designated M′) have nearly a one-to-one correspondence with those in the mass spectrum of the corresponding amine $TPNH_2$. Peak-for-peak comparison of the relative abundances in the M′ and $TPNH_2$ spectra show differences of only 0-4% (in absolute value) in all cases except two. The larger differences occur at m/e = 45 (CHS^+ formation) in system **3** only (where

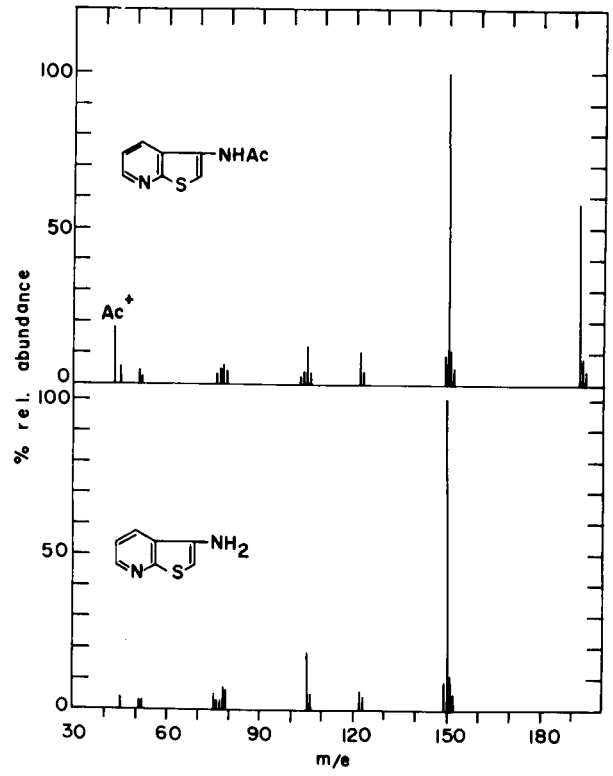


Figure 1. Comparative mass spectra of 3-acetylaminothieno[2,3-*b*]-pyridine (**1c**) and 3-aminothieno[2,3-*b*]pyridine (**1b**).

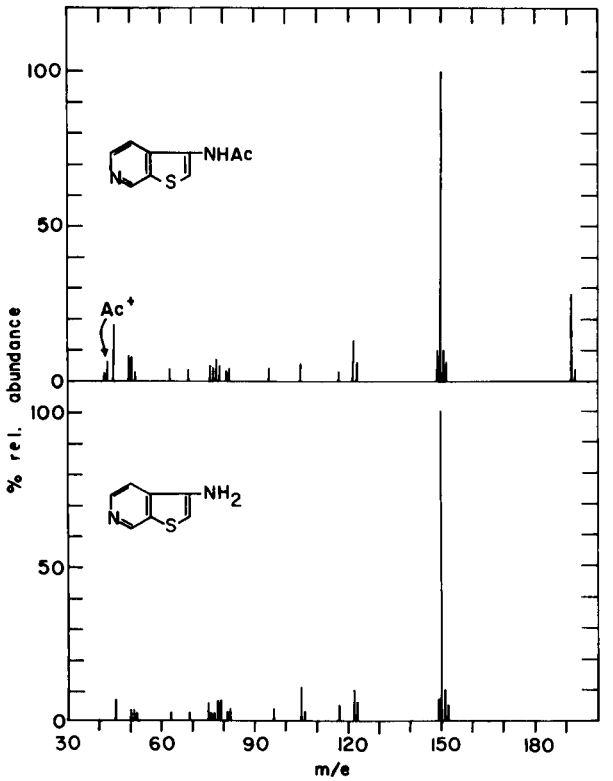


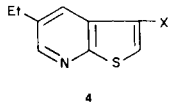
Figure 2. Comparative mass spectra of 3-acetylaminothieno[2,3-*c*]-pyridine (**3c**) and 3-aminothieno[2,3-*c*]pyridine (**3b**).

the M′ peak is 11% greater than the $TPNH_2$ one) and at m/e = 105 (ejection of ĊHS from $TPNH_2^{+\cdot}$) in both systems (where the $TPNH_2$ peak is 6% greater than the M′ one). However, the sum of the intensities of the peaks at 45 and 105 in all of these four spectra is 20 ± 3%. Hence, it is apparent that the quantitative discrepancies noted can be ascribed to differences in the extent of partitioning of the unpaired electron between the two fragments which result from decomposition of the $TPNH_2$ ion radical (see pathways *a* and *b* in equation 1). It is especially noteworthy that the most abundant ion in the spectrum of the acetylamino compound occurs at m/e = 150, *i.e.*, at the value for $TPNH_2^{+\cdot}$.

$$\dot{C}HS + C_6H_5N_2^+ \xleftarrow{a} C_7H_6N_2S^{+\cdot} \xrightarrow{b} {}^+CHS + C_6H_5N_2\cdot \qquad (1)$$

105 150 45

Scheme 1 depicts in a general way the significant mass spectral fragmentation ions formed from the acetylaminothienopyridines **1a**, **1c**, **2d**, and **3c** and the aminothienopyridines **1b** and **3b**. It seems likely that this scheme will also apply to the unknown free amines **1h** and **2e**. Analogous fragmentation of amide **4a** to produce acetylium ion and **4b**$^{+\cdot}$ (100%) was noted earlier (15).

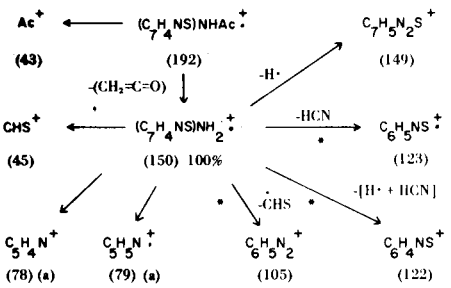


a, X = NHAc
b, X = NH_2

4

Scheme 1

General Mass Spectral Fragmentation Patterns of Aminothienopyridines and Their *N*-Acetyl Derivatives



• This transformation is corroborated by the presence of a metastable peak in at least one case. (a) This peak has an intensity ≤ 3% when the amino group is attached to the pyridine ring.

Figure 3 gives a comparison amongst the mass spectra (for all peaks ≥ 3%) of 2-chloro-3-aminothieno[3,2-*b*]-pyridine (**2a**) and its *N*-acetyl (**2b**) and *N*,*N*-diacetyl (**2c**) derivatives. The spectrum of **2c** shows an intense acetylium ion and the successive ejections of two molecules of ketene (**2c**$^{+\cdot}$ → **2b**$^{+\cdot}$ → **2a**$^{+\cdot}$) from the molecular ion. A small peak at m/e 211 is ascribed to the loss of both ketene and

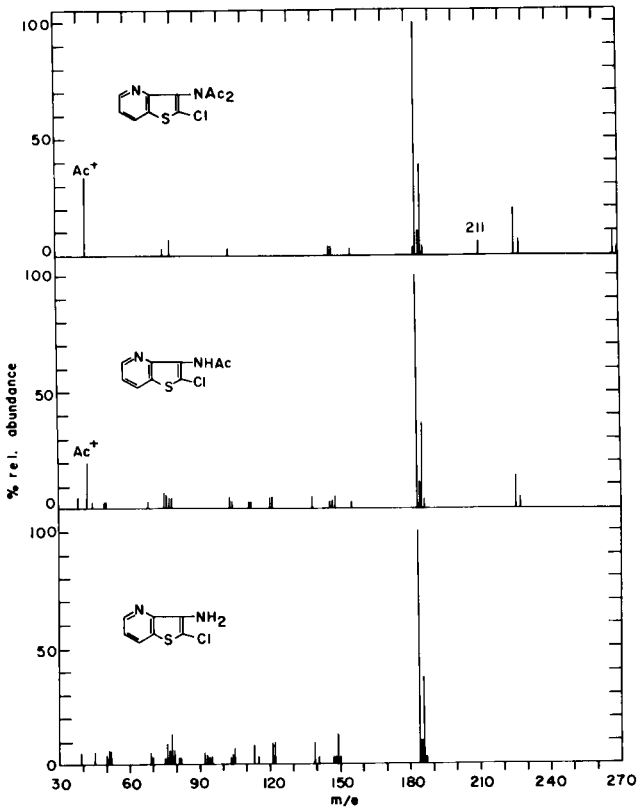


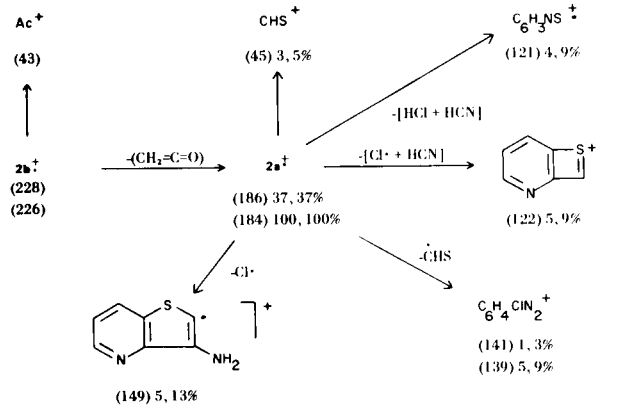
Figure 3. Comparative mass spectra of 2-chloro-3-(*N*,*N*-bisacetyl)-aminothieno[3,2-*b*]pyridine (**2c**), 2-chloro-3-acetylaminothieno-[3,2-*b*]pyridine (**2b**), and 2-chloro-3-aminothieno[3,2-*b*]pyridine (**2a**).

methyl free radical from $2c^{+\cdot}$. Although the two most abundant peaks in all three spectra correspond to the isotopic doublet for the molecular ion $2a^{+\cdot}$ it is clear that one cannot derive a suitable difference spectrum for amine **2a** from the spectrum of **2c**. However, a satisfactory difference spectrum M′ is obtainable from **2b**. Thus, M′ contains all of the structurally pertinent peaks produced by **2a** and (except for the peak at m/e 149) shows quantitative consistency within 5% (absolute value) on a peak-for-peak basis with the spectrum of **2a**. Correlation of the significant fragmentation patterns for **2a** and **2b** is presented in Scheme 2. This scheme resembles very closely that proposed for fragmentation of 2-acetylamino-3-bromo-[2,3-*b*]pyridine (6).

Scheme 3 presents the mass spectral decomposition pathways for oxamide **1e**. The most abundant peak again appears to be the molecular ion of the corresponding

Scheme 2

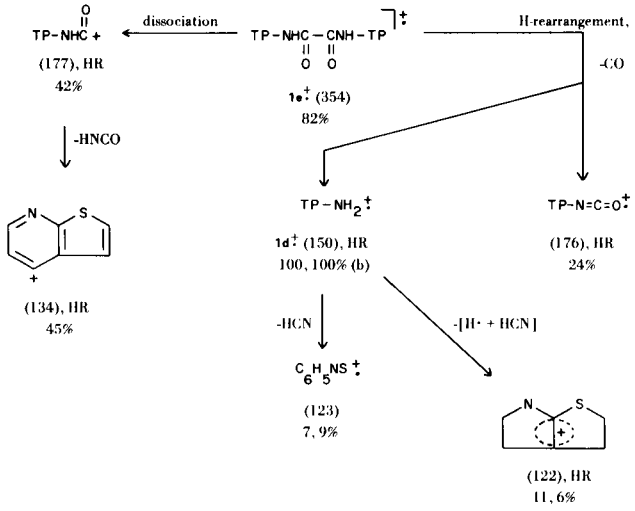
Correlation of Pertinent Mass Spectral Fragmentation Patterns for **2a** and **2b** (a)



(a) For other peaks of relative abundance ≥ 5% see the Experimental section. Where two numbers are listed for % relative abundances the first number refers to the **2b** series; the second, to the **2a** series.

Scheme 3

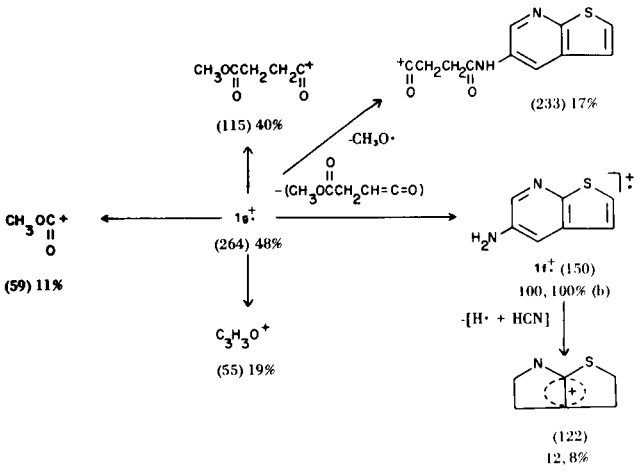
Mass Spectral Fragmentation Pathways for Oxamide **1e** (a)



(a) TP = 4-thieno[2,3-*b*]pyridyl in this Scheme. HR indicates that the ion formula was established by high resolution mass spectrometry. For other peaks of relative abundance ≥ 5% see the Experimental section. (b) Where two numbers are listed for % relative abundances the first number refers to the **1e** series; the second, to the amine **1d** series.

Scheme 4

Mass Spectral Fragmentation Pathways for Ester-Amide **1g** (a)



(a) The scheme includes all peaks for **1g** of relative abundance > 8%, except for one at m/e 151. (b) Where two numbers are listed for % relative abundances they refer to the **1g** and **1f** series, respectively.

amine **1d**. However, the spectrum is so complicated by the presence of prominent peaks from competing fragmentation pathways of **1e**$^{+\cdot}$ that one cannot extract a satisfactory difference spectrum for **1d** from it. Scheme 4 shows the spectral decomposition pathways for compound **1g**. The situation is analogous to that described for Scheme 3.

As in Scheme 1 the free amines **1d** and **1f** show peaks at m/e 150 (100%), 149, 123, 122, 105, and 45; plus various others in the range of 50-110.

EXPERIMENTAL (16)

3-Nitrothieno[2,3-*c*]pyridine (**3a**).

Nitration of thieno[2,3-*c*]pyridine (17) was conducted in a manner similar to that reported by Gronowitz and Sandberg (11) except that the nitric acid used was 70% (rather than fuming) and the reaction temperature was 25-85° (no ice cooling). The product **3a** was obtained as yellow needles (m.p. 160-161°; lit. 158-159°) from acetonitrile; ir (chloroform): 1525 and 1340 cm^{-1}; pmr (deuteriochloroform): δ 9.30 (d, 1, $J_{4,7} < 1$ Hz, H-7), 8.98 (s, 1, H-2), 8.82 (d, 1, $J_{4,5}$ = 6 Hz, H-5), 8.50 ppm (d of d, 1, H-4); mass spectrum closely similar to that previously reported (11).

Reduction of **3a** with Iron-Acetic Acid. A. For Reaction Time of 8 Hours.

Essentially in the same manner as used with 3-nitrothieno-[3,2-*b*]pyridine (10) compound **3a** was treated with iron powder and glacial acetic acid at 100° for 8 hours. From ether-chloroform extracts was obtained a solid which formed amber-colored prisms of 3-acetylaminothieno[2,3-*c*]pyridine (**3c**) from acetonitrile, m.p. 183-184°, yield 49%; ir (nujol-hexachlorobutadiene): 3325 (NH), 1660 cm^{-1} (amide carbonyl); pmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide, 2:1): δ 10.30 (broad s, 1, NH), 9.17 (broad s, 1, H-7), 8.51 (d, 1, $J_{4,5}$ = 5.5 Hz, H-5), 8.25 (s, 1, H-2), 8.10 (d of d, 1, $J_{4,7} \simeq 1$ Hz, H-4), 2.22 ppm (s, 3, methyl group).

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.24; H, 4.20; N, 14.57; S, 16.68. Found: C, 56.06; H, 4.16; N, 14.31; S, 16.80.

B. For Reaction Time of 1.5 Hours.

Procedure A was repeated but for a reaction time of only 1.5 hours. The extract (in ether only) was evaporated to leave a residue which was chromatographed on Alcoa F-20 alumina with benzene-ether (1:1). Two cream-colored bands were eluted separately to give faintly yellow solutions. Evaporation of each eluate gave pale green crystals, recrystallized from acetonitrile. The later eluate yielded 0.29 g. (14%) of tan prisms, m.p. 182-183°, identified as amide **3c**.

The earlier eluate gave 0.24 g. (16%) of 3-aminothieno[2,3-*c*]-pyridine (**3b**), obtained as shiny, green needles, m.p. 148-150°, changed to 148.5-149.5° on recrystallization from benzene; ir (chloroform): 3450, 3360, 1615 cm^{-1} (NH bands); pmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide, 2:1): δ 8.98 (d, 1, $J_{4,7}$ = 1 Hz, H-7), 8.42 (d, 1, $J_{4,5}$ = 6 Hz, H-5), 7.70 (d of d, 1, H-4), 6.51 (s, 1, H-2), 3.98 ppm (s, amino group).

Anal. Calcd. for $C_7H_6N_2S$: C, 55.97; H, 4.03; N, 18.65; S, 21.35. Found: C, 56.30; H, 4.01; N, 18.31; S, 20.96.

Mass Spectra.

Mass spectra were determined by means of a CEC model 21-110 double-focusing mass spectrometer, operated at 70 eV. Data for all peaks of relative intensities ≥ 5% above mass number 38 are given herewith, as temperature (°C.) of ion source, m/e (relative abundance). Selected peaks of relative abundance < 5% are also included. Metastable peaks observed are designated by an asterisk.

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

This compound had the following data: (200°), 192 (36), 151 (10), 150 (100), 149 (6), 123 (10), 122 (11), 105 (2), 79 (6), 78 (3), 63 (5), 45 (3), 43 (19), 100-101* (150 → 123).

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

This compound had the following data: (85°), 152 (5), 151 (10), 150 (100), 149 (9), 123 (4), 122 (6), 105 (18), 79 (6), 78 (7), 45 (4).

3-Acetylaminothieno[2,3-*b*]pyridine (**1c**) (Figure 1).

This compound had the following data: (170°), 193 (8), 192 (58), 152 (5), 151 (10), 150 (100), 149 (8), 123 (4), 122 (9), 105 (12), 79 (4), 78 (6), 45 (5), 43 (18), 99-102* (150 → 123, 150 → 122), 73-74* (150 → 105).

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

This compound had the following data: (100°), 152 (5), 151 (10), 150 (100), 149 (3), 123 (9), 122 (6), 105 (3), 75 (5), 45 (3), 100-101.5* (150 → 123).

N,N'-Bis(4-thieno[2,3-*b*]pyridine)oxamide (**1e**) (Scheme 3).

This compound had the following data: (250°), 356 (9), 355 (16), 354 (82), 178 (7), 177 (42), 176 (24), 152 (5), 151 (10), 150 (100), 149 (6), 135 (6), 134 (45), 123 (7), 122 (11), 90 (7), 63 (11), 45 (6).

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

This compound had the following data: (100°), 152 (5), 151 (10), 150 (100), 149 (3), 123 (7), 122 (8), 105 (2), 96 (5), 45 (2), 99-102* (150 → 123, 150 → 122).

Methyl *N*-(5-Thieno[2,3-*b*]pyridine)succinamate (**1g**) (Scheme 4).

This compound had the following data: (165°), 265 (7), 264 (48), 233 (17), 232 (6), 152 (5), 151 (11), 150 (100), 149 (6), 134 (5), 122 (12), 115 (40), 95 (6), 59 (11), 55 (19), 45 (3).

2-Chloro-3-aminothieno[3,2-*b*]pyridine (**2a**) (Figure 3, Scheme 2).

This compound had the following data: (110°), 186 (37), 185 (10), 184 (100), 149 (13), 141 (3), 139 (9), 122 (9), 121 (9), 113 (8), 105 (7), 92 (5), 79 (6), 78 (13), 77 (6), 76 (9), 69 (5), 52 (6), 51 (6), 45 (5), 39 (5), 119-120* (186 → 149).

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

This compound had the following data: (130°), 228 (5), 226 (14), 186 (37), 185 (12), 184 (100), 149 (5), 139 (5), 122 (5), 121 (4), 104 (5), 79 (5), 78 (5), 77 (6), 76 (7), 45 (3), 43 (20), 39 (5).

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

This compound had the following data: (110°), 270 (4), 268 (9), 228 (7), 226 (20), 211 (6), 186 (39), 185 (11), 184 (100), 79 (7), 43 (34).

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

This compound had the following data: (130°), 192 (30), 177 (8), 152 (6), 151 (11), 150 (100), 149 (7), 123 (5), 122 (10), 105

(5), 79 (10), 78 (6), 45 (6), 117-118* (192 → 150), 100-101* (150 → 123).

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

This compound had the following data: (110°), 152 (5), 151 (10), 150 (100), 149 (7), 123 (6), 122 (10), 117 (5), 105 (11), 79 (7), 78 (7), 75 (6), 45 (7), 100-102* (150 → 123).

3-Acetylaminothieno[2,3-*c*]pyridine (**3c**) (Figure 2).

This compound had the following data: (180°), 192 (28), 152 (6), 151 (10), 150 (100), 149 (10), 123 (6), 122 (13), 105 (5), 79 (5), 78 (7), 76 (5), 51 (8), 50 (8), 45 (18), 43 (6).

REFERENCES AND NOTES

(1) For Paper XXIV see L. H. Klemm and R. Hartling, *J. Heterocyclic Chem.*, **13**, 1197 (1976). This publication also constitutes Paper IV in the series on Reductive Acetylation of Nitro Compounds; for the preceding paper, see reference 6.

(2) Research Associate, 1967-1968.

(3) Research Associate, 1967.

(4) H. Budzikiewicz, C. Djerassi and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p. 350; R. H. Shapiro and K. B. Tomer, *Org. Mass Spectrom.*, **2**, 579 (1969).

(5) J. L. Cotter, *J. Chem. Soc.*, 5477 (1964); A. A. Gamble, J. R. Gilbert and J. G. Tillett, *Org. Mass Spectrom.*, **3**, 1223 (1970); N. Uccella, I. Howe and D. H. Williams, *ibid.*, **6**, 229 (1972).

(6) L. H. Klemm and W. Hsin, *J. Heterocyclic Chem.*, **12**, 1183 (1975).

(7) These amines can be stored for hours to days without apparent deterioration, as based on physical and spectral criteria. Longer storage results in observable change.

(8) L. H. Klemm and R. Zell, *J. Heterocyclic Chem.*, **5**, 773 (1968).

(9) L. H. Klemm, I. T. Barnish and R. Zell, *ibid.*, **7**, 81 (1970).

(10) L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopfenstein and D. R. McCoy, *ibid.*, **7**, 373 (1970).

(11) S. Gronowitz and E. Sandberg, *Arkiv Kemi*, **32**, 249 (1970).

(12) The more recently developed procedure of reference 6 was not tried on **3a**.

(13) S. Gronowitz and E. Sandberg, *Arkiv Kemi*, **32**, 269 (1970).

(14) See reference 10 for the analogous relationship which occurs on conversion of 3-nitro-**1** into **1b**.

(15) L. H. Klemm and H. Lund, *J. Heterocyclic Chem.*, **10**, 871 (1973). Decomposition of the **4b** molecular ion is dominated by ejection of a methyl free radical.

(16) Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Infrared spectra were determined by means of a Beckman IR-5A or IR-7 spectrometer; pmr spectra, by means of a Varian A-60 spectrometer with tetramethylsilane as internal standard.

(17) L. H. Klemm, D. R. McCoy, J. Shabtai and W. K. T. Kiang, *J. Heterocyclic Chem.*, **6**, 813 (1969).