Chemistry of Thienopyridines. XXXII. Direct Introduction of *C*-Substituents *gamma* to the Heteronitrogen Atom in the Thieno[2,3-*b*]pyridine System

L. H. Klemm*, Daniel R. Muchiri [1], and John N. Louris [2]

Department of Chemistry, University of Oregon,
Eugene, Oregon 97403

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Treatment of the *N*-oxide **1a** of thieno[2,3-*b*]pyridine (**1**) with either (a) acetic anhydride and ethyl cyanoacetate or (b) benzoyl chloride and an enamine of cyclohexanone (Hamana reactions) serves to introduce a *C*-substituent at the 4-position of **1**. In case (a) one obtains a yellow, isolable vinylogous *N*-ylide **5** (23% yield), which undergoes facile transformation into ethyl 2-(4-thieno[2,3-*b*]pyridyl)cyanoacetate (**1e**) (88-93%). Acetic anhydride reconverts **1e** to **5** (95%). Case (b) produces 2-(4-thieno[2,3-*b*]pyridyl)cyclohexanone (39%), hydrolyzable to 6-(4-thieno[2,3-*b*]pyridyl)hexanoic acid (45%). The hydrochloride of **1a** is also reported. Structural formulations are based on spectral studies (including ^{13}C nmr data for **1** and **1e**) and chemical transformations. Major contrasts (plus some similarities) between the systems **1** and quinoline in the Hamana reactions are discussed.

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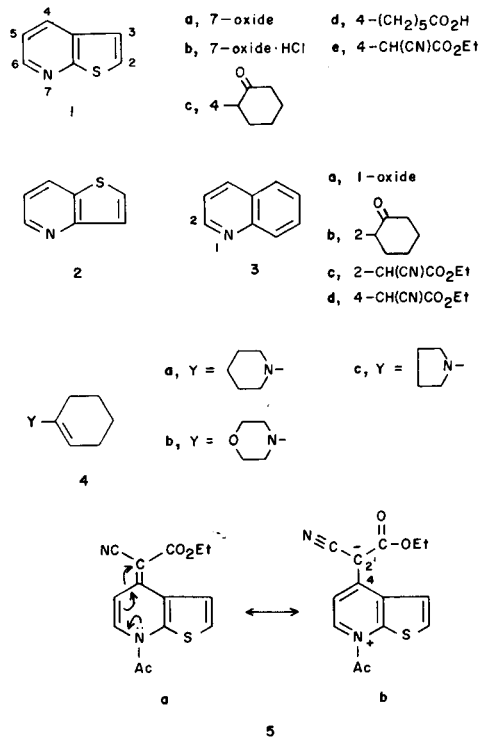
In a preceding paper [3] we reported the use of the Reissert-Henze reaction on thieno[2,3-*b*]pyridine 7-oxide (**1a**) to introduce a cyano group directly into the 6-position of thieno[2,3-*b*]pyridine (**1**) *i.e. alpha* to the heteronitrogen atom. The cyano group was then elaborated into a variety of other *C*-substituents at the 6-position [3,4]. Analogously, the Reissert-Henze reaction occurs in the isosteric systems quinoline and thieno[3,2-*b*]pyridine (**2**) to yield α-cyano derivatives [5]. Hamana and coworkers reported that quinoline 1-oxide (**3a**) also reacts with compounds containing reactive hydrogens in the presence of acetic anhydride [6] and with enamines of cyclohexanone in the presence of benzoyl chloride [7] to produce α-substituted quinolines [8]. In contrast, however, we now report that the Hamana reactions of **1a** effect the introduction of substituents *gamma to the heteronitrogen atom, i.e.* into the 4-position, instead. This paper discusses the syntheses, structures, and transformations of these Hamana products in the thieno[2,3-*b*]pyridine system.

As a control and exploratory investigation we stirred *N*-oxide **1a** with benzoyl chloride in benzene for several hours at room temperature to give a high yield of the hydrochloride **1b** (plus benzoic anhyride). More directly, **1b** was obtained from **1a** plus anhydrous hydrogen chloride. This addition compound can be sublimed *in vacuo* without decomposition, *i.e.* presumably by dissociation-reassociation. The presence of free hydrogen chloride in the gaseous phase is apparent from a series of peaks at m/e 35-38 in the mass spectrum of **1b**. Moreover, the spectrum at m/e > 38 is very similar to that of **1a** [3], albeit with significant variations in relative intensities of the various fragment ions. Formulation of **1b** as 7-hydroxythieno[2,3-*b*]pyridinium chloride is based on the presence of broad bands at 2390 and 2080 cm^{-1} [9] and the absence of an *N*-oxide band at 1250 cm^{-1} [3] in the infrared spectrum.



Refluxing **1a** with benzoyl chloride and enamine **4a** in chloroform, followed by acid hydrolysis, produced the substituted cyclohexanone **1c** (39%). Other enamines **4b** and **4c** likewise gave **1c** in essentially the same yield. The position of substitution onto the thienopyridine ring is established as C-4 on the basis of pmr spectrometry. Thus, the presence of a pair of doublets (J = 6.2 Hz) at δ 7.49 and 7.14 shows that substitution did not occur in the thiophene ring. On the other hand, an undistorted doublet (J = 4.7 Hz) at δ 8.52 is consistent only with the presence of aromatic protons at C-5 and C-6 [10]. Refluxing **1c** with aqueous

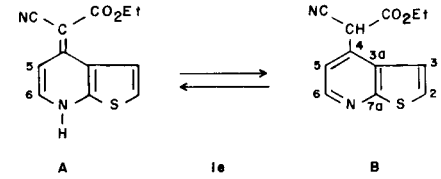
ethanolic potassium hydroxide [7] caused hydrolysis to the ω-thienopyridylhexanoic acid **1d** (45%). The pmr spectrum of **1d** in the aromatic region is closely similar to that of **1c** and, thus, confirms the position of substitution as C-4.

Our results contrast with the observations of Hamana and Noda for reaction of quinoline 1-oxide (**3a**) with benzoyl chloride and an enamine **4a-4c** in chloroform at room temperature [7]. Their reaction effected substitution *alpha* to the heteronitrogen atom to form **3b** (49-73%) [11]. There was no evidence for *gamma* substitution, and the yield of **3b** varied with the enamine used. Moreover, our original attempt to conduct the reaction of **1a** at room temperature gave only recovered starting material. Thus, it seems clear that Hamana cyclohexanonylation requires more strenuous conditions in the thieno[2,3-*b*]pyridine system than it does in the quinoline system.

Stirring *N*-oxide **1a** with slightly more than equimolar quantities of acetic anhydride and ethyl cyanoacetate at room temperature for 12 hours produced a small yield (6%) of a bright yellow precipitate, to which we ascribe structure **5**. Adding additional increments of acetic anhydride alone or of both acetic anhydride and ethyl cyanoacetate to the filtered mixture in a recycling process gave an ultimate yield of 23% of **5**. Unfortunately, various attempts to improve the yield and methodology for this reaction were unsuccessful [12]. Surprisingly, elemental analysis, as well as infrared, mass, and pmr spectra, established the fact that **5** contains an acetyl group, in addition to the expected ethyl cyanoacetate moiety. This acetyl group (evident as a singlet for three protons at δ 2.78 in hexadeuteriodimethyl sulfoxide) is labile, as indicated by the fact that it is completely hydrolyzed to acetic acid in undried dimethyl sulfoxide at room temperature in *ca.* 45 hours. Alternatively, it is removed by standing in 95% ethanol for 10 days or by treatment with hydrogen chloride gas in chloroform solution for only 7 minutes. Completion of the reaction in the third case is readily apparent by loss of the yellow color of **5**. Although the fate of the acetyl group was not established in the second and third reactions, the main product in each of the three cases was found to be the same, *i.e.* ethyl 2-(4-thieno[2,3-*b*]pyridyl)cyanoacetate (**1e**) (88-93%).

Of major importance for formulation of the structure of **5** is the observation that **1e** is readily reconverted into **5** (96%) on treatment with acetic anhydride in chloroform at room temperature for one hour. Thus, it seems almost certain that the cyanoacetate moiety remains affixed to one particular carbon atom throughout the interconversions between **1e** and **5**. As noted later, this carbon atom is established as C-4 in **1e** by a combination of pmr and cmr studies.

Various spectral investigations indicate that **1e** occurs in two tautomeric forms (**A** and **B**), as shown. Form **A** is



A 1e B

favored in DMSO or its hexadeuterio derivative (yellow solution, no signal for the labile proton, and $J_{5,6}$ = 7.2 Hz for a *cis* carbon-carbon double bond [13]); while form **B** is favored in chloroform or deuteriochloroform solution where one observes little or no color, a singlet at δ 5.11 for the methinyl proton (exchangeable with deuterium on shaking with deuterium oxide), and a coupling constant $J_{5,6}$ = 4.7 Hz [10]. Both forms may be present in the solid state (faintly yellow needles; infrared absorptions in a potassium bromide pellet at 3440 cm^{-1} for NH, at 2190 cm^{-1} for a conjugated enaminonitrile [14], and at both 1735 (weak) and 1695 cm^{-1} (strong) for ester carbonyl groups), in 95% ethanol (light yellow color), and in absolute methanol (ultraviolet absorption tailing into the visible region of the electronic spectrum). Analogous forms, **A′** and **B′**, were reported for the quinoline isostere **3d** [15]; where however, only form **A′** is observed in the solid state (infrared ab-

Table I

^{13}C NMR Spectral Data for Thieno[2,3-*b*]pyridine (**1**)

^{13}C Atom	δ, ppm [a]	$^1J(^{13}C\text{-}^1H)$, Hz	Long Range Coupling signal	Hz	coupler(s) [b]
C-2	126.9	184	d	8	H-3
C-3	121.4	170	pseudo t	3-4	H-2, H-4
C-3a	132.4		m		
C-4	130.9	163	d	7	H-6
C-5	119.3	164	d	9	H-6 [c]
C-6	146.4	180	dd	7, 4	H-4, H-5
C-7a	161.8		m		

[a] Chemical shift from tetramethylsilane signal. [b] Assignments made with the assistance of R. E. Merrill and, especially, H. J. Jakobsen and M. Hansen. See ref [16]. [c] Based on a value of $^2J(^{13}C_3\text{-}^1H_2)$ = 8.47 Hz in pyridine. See ref [18].

Table II

^{13}C NMR Spectral Data for Compound **1e**

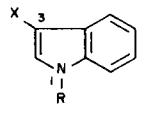
^{13}C Atom	δ, ppm [a]	$^{1}J(^{13}C\text{-}^{1}H)$, Hz	Long Range Coupling signal	Hz	coupler(s)
C-2	129.1	187	d	5	H-3
C-3	118.7	173	d	2	H-2
C-3a	130.3		m		
C-4	132.8		pseudo t	8	H-6, NCC*H* [b]
C-5	118.9	164	dd	9, 5	H-6, NCC*H* [b]
C-6	147.0	183	d	3	H-5
C-7a	163.0		m		
*C*N	114.3		d	11	NCC*H* [b]
NC*C*HCO$_2$Et	42.2	137	d	5	[c]
C=O	163.4		dt	9, 3	C*H*CO$_2$C*H*$_2$ [b,d]
*C*H$_2$CH$_3$	64.0	149	q	4	CH$_2$C*H*$_3$
CH$_2$*C*H$_3$	13.9	128	t	3	C*H*$_2$CH$_3$

[a] Chemical shift from tetramethylsilane signal. [b] Determined by a low-power selective decoupling experiment. [c] Not investigated. [d] Although C-7a and *C*=O signals are very close in chemical shift, one can distinguish between them unambiguously by low-power selective decoupling. The J = 9 Hz is associated with C*H*CO$_2$ and the J = 3 Hz, with CO$_2$C*H*$_2$.

sorptions at 2170 and 1670 cm^{-1}) and a mixture of forms (carbonyl bands at 1750 and 1675 cm^{-1}) is extant in chloroform solution. The absorption spectrum of **3d** in methanol shows a maximum in the visible region (λ 420 nm, log ε 4.50), consistent with the presence of form **A′**.

Corroboration of the structure of tautomer **B** for **1e** in deuteriochloroform was provided by cmr studies. Careful investigation of parent molecule **1** shows the following one-bond C-H coupling constants: C-2 (184 Hz), C-3 (170), C-4 (163), C-5 (164), C-6 (180) [16]. Corresponding coupling constants found in **1e** are 187, 173, 164, and 183 Hz. Thus, it is clear that the cyanoacetate substituent in **1e** is located either at C-4 or C-5, and certainly not at C-6 or in the thiophene ring. Long-range coupling (LRC) for C-3 in **1** gives a pseudotriplet (J = 3-4 Hz), which has been analyzed by Jakobsen [17] in an iterative computer program as resulting from $^{2}J(^{13}C_3\text{-}^{1}H_2)$ = 3.39 Hz and $^{3}J(^{13}C_3\text{-}^{1}H_4)$ = 3.14 Hz, where the subscripts refer to the ring positions. In **1e**, LRC for C-3 gives only a doublet (J = 2 Hz) and implies that either H-2 or H-4 (certainly the latter) is absent due to substitution at that position. Confirmatory evidence is also available from the LRC of C-6 in **1**, which shows a doublet of doublets for coupling both to H-4 and to H-5. In **1e** this signal occurs as a simple doublet. A series of studies with low-power selective decoupling established that the substituent at C-4 in **1e** must bear a methinyl group, as shown in the **B** tautomer. Other characteristics of the cmr spectra of **1** and **1e** are presented in Tables I and II.

It is instructive to compare the chemistry of the **A** tautomer of **1e** with that of indole **6a** as a well-studied model compound. Refluxing indole with acetic anhydride yields 1,3-diacetylindole (**6b**) [19], from which the 1-acetyl group



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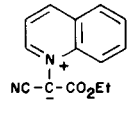
a, R = X = H
b, R = X = Ac
c, R = H, X = Ac
d, R = Ac, X = H

is readily hydrolyzed to give **6c** by heating with water alone [20] or with added alkali [19]. Likewise, **6d** is easily hydrolyzed in aqueous alkali or acid [21,22]. The acetyl group of **6d** shows carbonyl absorption at 1720 cm^{-1} (neat?) [22] and a methyl group resonance at δ 2.36 in deuteriochloroform [23]. Corresponding data for **5** are 1695 cm^{-1} (potassium bromide pellet) and δ 2.78 in hexadeuteriodimethyl sulfoxide.

Compound **5** is shown in the *Z*-stereoisomeric form in formula **5a**. However, a resonance contributor to structure **5** is the dipolar form **5b**, a vinylog of a simple nitrogen ylide. Intervention of form **5b** may allow rotation around the C-2′, C-4 bond to produce the *E*-isomer (not shown). We have not attempted to identify the stereoisomeric nature of our compound **5**.

In contrast to the reaction of **1a**, quinoline 1-oxide (**3a**) reacts with acetic anhydride and ethyl cyanoacetate (without added solvent) at 30-40° to yield yellow crystals of the 2-substituted quinoline **3c** (88%) [6]. In reactions at room temperature or below, however, Hamana *et al.* [8,24] found that not only **3c**, but also the 4-substituted quinoline **3d**, and the ylide **7** could be obtained if one adds a suitable solvent (DMF, DMSO, or pyridine). The highest yields of



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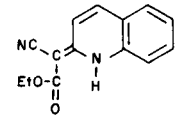

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3d (4%) and **7** (54%) were obtained with DMF. Use of water, methanol, acetone, or ethyl acetate as solvent gave only **3c**. Following this lead (as well as others) we were unable to improve the yield of **5** by adding a solvent (yield decreased), adding anyhydrous sodium acetate (no effect), or raising the reaction temperature (yield decreased) [12].

Hamana *et al.* did not consider the possibility that **3c** and **3d** might occur in tautomeric forms. However, Borror and Haeberer [25] reported structure **8** (the tautomer of **3c**) as the product from reaction of 2-chloroquinoline with sodium ethylcyanoacetate in dimethylformamide. Both groups obtained yellow crystals of melting point 165 ± 2°, and absorption of light at wavelengths > 400 nm [6,24]. Other spectral evidence by Borror and Haeberer is consistent only with structure **8** and makes the presence of an appreciable amount of tautomer **3c** highly doubtful. Similarly, Podmore [15] reacted 4-chloroquinoline with sodium ethylcyanoacetate to give **A′** and **B′** tautomers (*vide supra*) of **3d**, mp 190-192° from aqueous acetic acid. Although Podmore did not report the color of this product, its intense absorption at 420 nm suggests it should be orange or red. In fact, Hamana and coworkers [24] report red neeedles, mp 174-176° from methanol, for **3d**, consistent with the presence of the **A′** tautomer. It seems likely that both groups obtained the same product despite the discrepancy in melting points.

At this point we have no satisfactory rationalization of the differences between systems **1a** and **3a** in the Hamana reactions, especially since both compounds undergo cyanation at the *alpha* position in the Reissert-Henze reaction. While low solubility of **5** in the reaction mixture could account for its isolation, this situation does not prevail in the preparation of ketone **1c**.

EXPERIMENTAL [26]

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

(a) Use of Hydrogen Chloride.

The white precipitate which resulted from bubbling excess hydrogen chloride gas into a stirred solution of 0.75 g of thieno[2,3-*b*]pyridine 7-oxide (**1a**) in benzene was collected by filtration, yield 0.88 g (94%), mp 164-167°, obtained as a powder (mp 166-168°, sintering at 163-164°) from sublimation at 60-65° (0.005 mm); positive Beilstein test; ir: 2390 and 2080 (broad, N^+ - OH) [9], 1430, 1400, 1340, 1300, 800, 685 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 8.74 (d, $J_{5,6}$ = 6 Hz, H-6), 8.29 (d, $J_{4,5}$ = 8 Hz, H-4), 8.08 (d, $J_{2,3}$ = 5.5 Hz, H-2), 7.6-7.9 (overlapping doublets, 2 H, H-3 and H-5); ms (120°): m/e 151 (M^+, 42), 122 (M^+ - CHO, 22), 96 (52), 70 (32), 69 (60), 63 (48), 62 (26), 58 (27), 51 (46), 50 (49), 45 (CHS^+, 100), 39 (49); m/e 39 (20), 38 (46), 37 (25), 36 (100), 35 (51) [27]; uv: λ max 233 nm (log ε 4.66), 252 shoulder (3.73), 284 (3.83), 314 (3.77).

Anal. Calcd. for C_7H_6ClNOS: C, 44.80; H, 3.22; N, 7.47; neut equiv, 187.6. Found: C, 44.30; H, 3.62; N, 7.23; neut equiv, 186.9.

(b) Use of Benzoyl Chloride.

A mixture of 0.76 g (5 mmoles) of **1a** and 0.75 ml (6.5 mmoles) of benzoyl chloride in 45 ml of benzene was stirred in an open flask for 12 hours at room temperature and then evaporated to dryness. The residue was triturated with petroleum ether (30-60°) and filtered to yield 0.8 g (85%) of **1b**, mp 160-164°, changed to 166-168° on sublimation *in vacuo*, identical with product from part (a). Evaporation of the filtrate gave a viscous liquid, shown to contain benzoic anhydride by spectral means [3].

2-(4-Thieno[2,3-*b*]pyridyl)cyclohexanone (**1c**).

A stirred, ice-cold solution of 761 mg (5.04 mmoles) of **1a** and 1.67 g (10 mmoles) of *N*-(1-cyclohexen-1-yl)piperidine (**4a**) [28] in 5 ml of chloroform was treated dropwise with 848 mg (6 mmoles) of benzoyl chloride. The reddish mixture was refluxed for 12 hours, cooled, treated with 10 ml of 20% hydrochloric acid, and evaporated to dryness. A solution of the residue in 10 ml of 20% hydrochloric acid was washed twice with benzene-ether (1:1 by vol) basified with solid sodium carbonate, and extracted with three 60-ml portions of benzene. The brown liquid residue from evaporation of the dried (sodium sulfate) benzene extracts was evaporatively distilled at 90-110° (0.005 mm) to produce 451 mg (39%) of **1c** as a colorless liquid which crystallized on standing. Recrystallizations from aqueous ethanol gave 270 mg of shiny needles, mp 93-96°; ir (neat liquid): 2940 and 2865 (sharp), 1710 (carbonyl), 1570, 1350, 1125, 785, 760 cm^{-1}; pmr: δ 8.52 (d, $J_{5,6}$ = 4.7 Hz, H-6), 7.49 (d, $J_{2,3}$ = 6.2 Hz, H-2 or H-3), 7.14 (d, H-3 or H-2) which overlaps 7.12 (d, 2 H total, H-5), 4.2-3.9 (m, 1 H, ArC*H*), 2.7-1.5 (m, methylene protons); ms (150°): m/e 231 (M^+, 100), 187 (42), 174 (30), 162 (23), 149 (20); uv: λ max 231 nm (log ε 4.42), 273 (3.80), 282 shoulder (3.78), 293 shoulder (3.68).

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06; exact mass, 231.072. Found: C, 67.76; H, 5.68; N, 6.11; exact mass, 231.072.

Repetition of the foregoing procedure, but with *N*-(1-cyclohexen-1-yl)-morpholine (**4b**) or *N*-(1-cyclohexen-1-yl)pyrrolidine (**4c**) instead of **4a** gave nearly identical yields of **1c**.

6-(4-Thieno[2,3-*b*]pyridyl)hexanoic Acid (**1d**).

A mixture of 309 mg of **1c**, 6.3 ml of 75% aqueous ethanol, and 0.4 g (total) potassium hydroxide (added in two portions) was refluxed for 57 hours, whereupon tlc (alumina F_{254}/chloroform) indicated that all **1c** had reacted. The residue from evaporation of the dark reaction mixture was treated with 40 ml of water and extracted with chloroform (discarded). The aqueous layer was acidified with 1 *M* hydrochloric acid and extracted twice with chloroform and twice with ethyl acetate. Evaporation of the combined, dried (sodium sulfate) extracts gave 336 mg of solid, mp 120-126°. Recrystallization from aqueous ethanol gave 150 mg (45%) of light yellow powder, mp 134-136°; ir: 3420 (broad) and 2510 (broad, carboxylic acid OH), 1710 cm^{-1} (carbonyl); pmr: δ 8.47 (d, $J_{5,6}$ = 4.8 Hz, H-6), 7.52 and 7.34 (dd, $J_{2,3}$ = 6.1 Hz, H-2 and H-3), 7.12 (d, H-5), 2.96 (t, J = 7 Hz, 2 H, ArCH_2), 2.38 (t, J = 7 Hz, 2 H, CH_2CO_2H), 2.0-1.2 (broad m, 6 H, 3 CH_2 groups); ms (200°): m/e 249 (M^+, 35), 162 (M^+ - $(CH_2)_3CO_2H$, 100), 149 (54), 148 (M^+ - $(CH_2)_4CO_2H$, 40), 91 (22).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.58; H, 6.02; N, 5.40.

4-(1-Cyano-1-carboethoxy)methylene-7-acetyl-4,7-dihydrothieno[2,3-*b*]-pyridine (**5**).

(a) From *N*-Oxide **1a**.

A mixture of 2.3 g (15.2 mmoles) of **1a**, 1.95 g (19 mmoles) of acetic anhydride, and 1.95 g (20 mmoles) of ethyl cyanoacetate was stirred at room temperature for 12 hours. The yellow precipitate (**5**) which formed (6% yield) was collected by filtration. The filtrate was recycled six more times until no further precipitation occurred. In three of these recyclizations both fresh acetic anhydride (1.95 g) and ethyl cyanoacetate (1.95 g) were added; while only additional acetic anhydride (1.95 g) was used in each of the others. The mixtures were stirred and filtered each time. The combined precipitate was washed with carbon tetrachloride to yield 986 mg (23%) of shiny, yellow powder, mp 216-218°. Recrystallization from 95% ethanol produced short yellow needles, mp 218-220°; ir: 2185 (conjugated aminonitrile) [14], 1735 and 1695 (carbonyls), 1620, 1520, 1235 (vs), 1205, 1025, 995 cm^{-1}; pmr (see part b); ms (260°): m/e 288 (M^+, 10), 246 (M^+ - CH_2=C=O, HR, 10), 201 (21), 175 (13), 174 (M^+ - CH_2=C=O

$-CO_2C_2H_4$, 100), 173 (42), 146 (17), 68 (11), 44 (10), 42 (CH_2=C=O$^+$, 35), 41 (13); 122-123* (174 → 146, 246 → 174); 210-211* (288 → 246); uv (absolute methanol): λ max 229 nm (log ε 4.63), *ca.* 263 shoulder (3.98), 354 (4.46), tailing beyond 400.

Anal. Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72; exact mass, 288.057. Found: C, 58.28; H, 3.99; N, 9.47; exact mass, 288.057.

(b) From Cyanoacetate **1e**.

A quantity of 66.5 mg (0.65 mmole) of acetic anhydride was added to a solution of 80 mg (0.33 mmole) of **1e** (*vide infra*) in 100 ml of chloroform and the mixture was stirred for one hour at room temperature. The intensely yellow solution was evaporated to dryness. The residue was triturated with carbon tetrachloride and filtered to leave 90 mg (96%) of **5**, mp 216-218°, identical with product from part (a) as based on mixture mp and spectra; pmr (hexadeuteriodimethyl sulfoxide, < 4% hydrolysis, *vide infra*): δ 8.43 (d, $J_{2,3}$ = 6 Hz, H-2 or H-3) which overlaps 8.2-8.6 (m, H-3, H-5, H-6), 7.72 (d, H-3 or H-2), 4.21 (q, J_{Et} = 7 Hz, CH_2CH_3), 2.78 (s, Ac), 1.28 (t, CH_2CH_3).

Ethyl 2-(4-Thieno[2,3-*b*]pyridyl)cyanoacetate (**1e**).

(a) Use of Aqueous Ethanol.

A solution of 106 mg of yellow compound **5** in 200 ml of 95% ethanol was stirred at room temperature for 10 days and then evaporated to give 100 mg of light yellow solid, mp 156-159°. Recrystallization from aqueous ethanol gave faintly yellow needles of **1e**, yield 84 mg (93%), mp 161-162°, unchanged on sublimation at 80-90° (0.005 mm); ir: 3440 (broad NH), 2840-3210 (broad, NH and CH), 2190 (conjugated CN) [14], 1750 (w), 1605, 1550, 1460, 1315, 1245, 1175 cm^{-1}; pmr: δ 8.64 (d, $J_{5,6}$ = 4.7 Hz, H-6), 7.69 (d, $J_{2,3}$ = 6.0 Hz, H-2 or H-3), 7.48 (d, H-3 or H-2) which overlaps 7.46 (d, 2 H total, H-5), 5.11 (s, 1 H, decreases to 0.1 H on shaking with one drop of deuterium oxide, ArCH), 4.25 (q, J_{Et} = 7 Hz, 2 H, CH_2CH_3), 1.25 (t, 3 H, CH_2CH_3); pmr (hexadeuteriodimethyl sulfoxide): δ 8.5-8.3 (2 overlapping d, 2 H, H-2 or H-3, and H-6), 7.99 (d, $J_{5,6}$ = 7.2 Hz, H-5), 7.62 (d, $J_{2,3}$ = 6.0 Hz, H-3 or H-2), 4.12 (q, J_{Et} = 7 Hz, 2 H, CH_2CH_3), 1.23 (t, 3 H, CH_2CH_3); ms (200°): m/e 246 (M$^+$, 40), 175 (15), 174 (M$^+$ - $CO_2C_2H_4$, 100), 173 (47), 146 (16), 45 (CHS^+, 10); 122-124* (246 → 174, 174 → 146); uv: λ max 228 nm (log ε 4.42), 362 (4.23), 381 shoulder (4.18), tails slightly beyond 400 nm; cmr: see Table II in the Experimental section.

Anal. Calcd. for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; exact mass, 246.048. Found: C, 58.82; H, 4.29; N, 11.05; exact mass, 246.046.

(b) Use of Hydrogen Chloride.

Hydrogen chloride gas was bubbled (one bubble per second) into the stirred, intensely yellow solution of 138 mg of **5** in 140 ml of chloroform (open to the atmosphere) until the color disappeared (7 minutes). Evaporation of the solvent left 120 mg of solid, mp 156-158°. Recrystallization from aqueous ethanol gave 107 mg (91%) of **1e**, mp 161-162°, identical with product from part (a), as based on mixture mp and spectra.

(c) Use of Dimethylsulfoxide.

A solution of 110 mg of **5** in 3.5 ml of dimethylsulfoxide (undried) was stirred for 3 days at room temperature, while the acidity of the solution increased spontaneously (from *p*H 5.9 to 3.8, as measured by indicator paper). The solution was diluted with 100 ml of ethyl acetate. The resultant mixture was washed five times with 80-ml portions of saturated aqueous sodium chloride, dried (sodium sulfate), and evaporated to give 109 mg of residue. Preparative tlc [one 20 × 20-cm plate, 30 g of silica gel F_{254}/chloroform-ether (3:2)] showed three zones at R_f's 0.08 (5 mg, discarded), 0.23 (91 mg, mp 156-158°), and 0.36 (19 mg, discarded). Recrystallization from aqueous ethanol of product from the middle one gave 83 mg (88%) of **1e**, mp 161-162°, identical with compound from part (a).

Rate Study of the Conversion of **5** → **1e**.

A sample of compound **5**, dissolved in hexadeuteriodimethyl sulfoxide in an nmr tube, was maintained at room temperature for nearly 10 days while the pmr spectrum was determined periodically. The percent of reaction (*i.e.* of hydrolysis by means of the water contained in the solvent) was ascertained by the formula,

$$\% \text{ reaction} = 100\ I_{1.90}/(I_{1.90} + I_{2.78}),$$

where $I_{1.90}$ is the integration of the singlet for CH_3CO_2H at δ 1.90 and $I_{2.78}$ is the integration of the singlet for the acetyl protons of **5** at δ 2.78. Reaction was complete after 45 hours. Addition of a drop of glacial acetic acid to a separate solution of a reacting sample caused an immediate enhancement of the singlet at δ 1.90. The earliest spectrum observed (< 4% reaction, *ca.* 4 minutes reaction time) is given as that of **5**, while 100% reaction corresponds to **1e** plus an equimolar amount of acetic acid. Spectra at intermediate times are composites of these two, observed as follows. The methyl triplet, methylene quartet, and acetyl singlet shift to higher fields (Δδ = −0.05, −0.09, and −0.88, respectively). In the aromatic region a doublet (J = 6 Hz) shifts from δ 7.72 to 7.62, a doublet (J = 7.2 Hz) appears at 7.99, and a multiplet at 8.2-8.6 changes shape and area (3 H → 2 H).

^{13}C NMR Spectra of Thienopyridines.

The cmr spectra of **1** and **1e** were determined as part of a general survey of available parent and derivatized compounds in the thieno[2,3-*b*]- and thieno[3,2-*b*]pyridine systems [29]. These spectra were obtained on a Nicolet NTC-360 FT NMR instrument with 12-mm tubes containing 0.2-6% (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. Either broad band proton-decoupled spectra or proton-coupled spectra were used to determined ^{13}C chemical shifts. Frequencies for specific proton decoupling were ascertained by observing the proton spectrum through the coils of the ^{13}C probe. This permits correlation of specific ^{13}C signals with specific ^{1}H signals in previously recorded pmr spectra from our laboratoy. Typical conditions of measurement used are the following: frequency 91 MHz, tip angle 30°, pulse delay 4 sec, spectral width 19,000 Hz, and 16,384 data points. Complete spectral data for **1** and **1e** are present in Tables I and II, respectively.

For **1**, certain structural assignments of the signals in the spectra are based on the following considerations. First, the values of the one-bond coupling constants are consistent with data from a number of monosubstituted thieno[2,3-*b*]pyridines of established structures [29]. The large couplings for C-2 and C-6 are likewise observed at positions alpha to the heteroatom in thiophene, benzo[*b*]thiophene, pyridine, and quinoline systems [18, 30-33]. Signals for carbons 3a and 7a at the ring juncture are identified by their low intensities and lack of large splitting from a bonded proton. The large difference in chemical shift of 29.9 ppm between the signals for C-3a and C-7a permits one to assign the more downfield signal to C-7a, the carbon alpha to the nitrogen atom, as in quinoline [33]. For **1e**, this methodology is supplemented by comparison of long-range coupling signals found in **1**. Low-power selective decoupling also allows determination of the specific proton(s) which couple(s) to specific carbon atoms.

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[12] Once one has established the structure of **5** it is apparent that an alternative synthetic route from **1a** to **5**, *i.e.* **1a** → 4-chloro-**1** → **1e** → **5**, is plausible. The first step (54%) was investigated by L. H. Klemm and R. Hartling [*J. Heterocycylc Chem.*, **13**, 1197 (1976)]. The second reaction occurs in the isosteric quinoline system, *cf.* ref [15]. Step 3 is reported herewith.

[13] Compare coupling constants in the following systems, $J_{5,6}$ = 7.5 Hz in thieno[3,2-*b*]pyridin-7(4*H*)-one [J. M. Barker, P. R. Huddleston and A. W. Jones, *J. Chem. Research (M)*, 4701 (1978)], $J_{2,3}$ = 6.8 Hz in 4-quinolone and $J_{2,3}$ = 7.6 Hz in 4-pyridone [P. Bellingham, C. D. Johnson and A. R. Katritzky, *J. Chem. Soc. (B)*, 1226 (1967)].

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[27] For the region m/e 39-151 compare the ms spectrum with that of **1a**, run at 100°. The region 35-39 is also shown independently here to emphasize that HCl^+ and Cl^+ are present from the reaction **1b** → **1a** + HCl. However, relative abundances in this latter region do not conform to simple chlorine isotopic ratios.

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