Chemistry of Thienopyridines. XXXV. Synthesis, Tautomerism, and Reactions of Quinoline and Thienopyridine Systems Which Bear a 1-Carboethoxy-1-cyanomethyl Substituent in the Pyridine Ring, Part 2 [1,2]

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A comparison is made amongst the isosteric systems quinoline, thieno[2,3,-*b*]pyridine, and thieno[3,2-*b*]-pyridine which bear the 1-carboethoxy-1-cyanomethyl substituent (R) *alpha* or *gamma* to the heterocyclic nitrogen atom. Treatment of thieno[3,2-*b*]pyridine 4-oxide with ethyl cyanoacetate and acetic anhydride at room temperature (Hamana reaction) gives the *alpha* R-derivative **6** (27%), formulated as an intramolecular H-bonded structure. Neither **6** nor its quinoline *alpha* analog reacts with refluxing acetic anhydride, while the quinoline *gamma* isomer **8**, existing as NH and CH tautomers, yields an *N*-acetyl derivative **10** (70%) under similar conditions. For each of **6** and **8** one can isolate two crystalline forms which differ considerably in color. Compound **10** and its *gamma* analog in the thieno[2,3-*b*]pyridine series (previously obtained directly from a Hamana reaction) serve as acetylating agents for aniline, 1-aminobutane, morpholine, and cholesterol. Correlations and contrasts in the three systems are presented.

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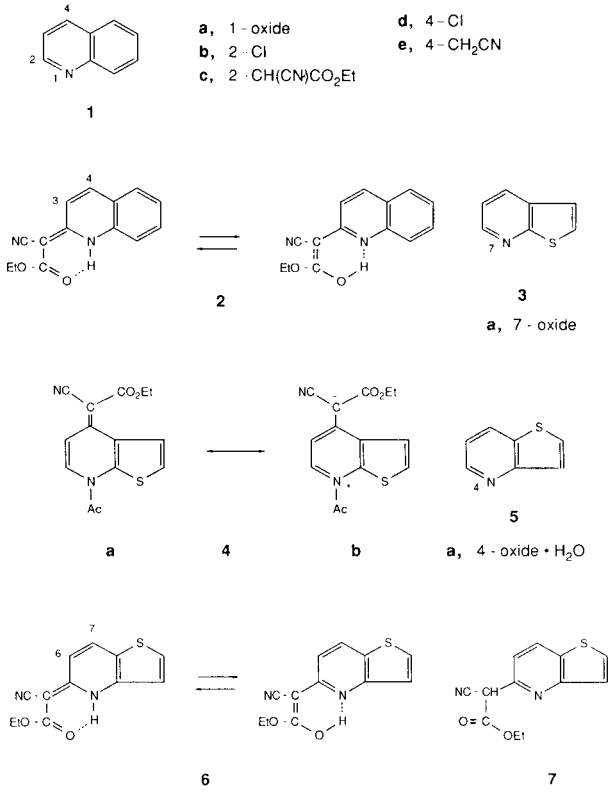
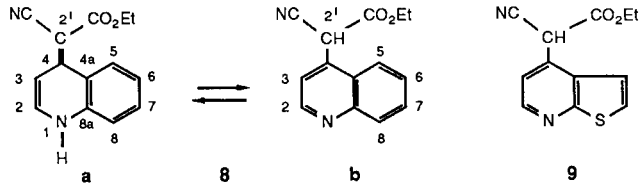
In part **1** of this series of papers [1] it was noted that reaction of quinoline 1-oxide (**1a**) with acetic anhydride and ethyl cyanoacetate (Hamana reaction) gives substitution of a 1-carboethoxy-1-cyanomethyl group into the pyridine ring in the *alpha* position to the heteronitrogen atom [6]. The product was formulated as the simple quinoline derivative **1c** by Hamana and Yamazaki [6]. However, Borror and Haeberer ostensibly obtained the same compound by reaction of 2-chloroquinoline (**1b**) with sodio ethyl cyanoacetate in dimethylformamide, but they proposed cyclic structure **2** for it, as based largely on its ultraviolet and infrared spectra [7]. We have now repeated the Borror and Haeberer synthesis and find that the pmr spectrum of the product also corroborates structure **2** since there is a broad singlet at 13.5 ppm (in deuteriochloroform), ascribed to an O··H··N chelate, plus a coupling constant of 9.3 Hz for a carbon-carbon double bond between C-3 and C-4. Interestingly, the electron-impact mass spectrum of this product shows the most abundant fragment at m/e 194, which corresponds to the loss of a molecule of ethanol from the molecular ion.

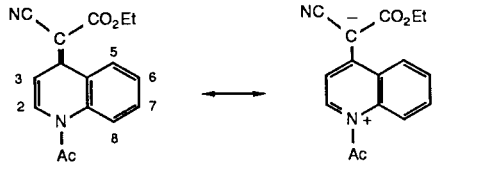
As noted before, the Hamana reaction of thieno[2,3-*b*]-pyridine 7-oxide (**3a**) gives *gamma* substitution of a 1-carboethoxy-1-cyanomethyl group into the pyridine ring plus *N*-acetylation of the NH tautomeric form to produce **4** [1]. We have now extended the Hamana reaction to the thieno[3,2-*b*]pyridine system by stirring *N*-oxide **5a** with excess acetic anhydride and ethyl cyanoacetate at room temperature to give a 27% combined yield of two crystalline products, both formulated as cyclic structure **6** (analogous to the Borror and Haeberer product **2**) from substitution *alpha* to the heteronitrogen atom. An analytically pure sample of **6** bearing one-fourth mole of solvent (mp 201°) was obtained after recrystallization from absolute ethanol, plus sublimation at 100° *in vacuo*. On the basis of this analytical result, we suggest that tenacious solvation of **6** may account for our finding that three closely related products were obtained from the Hamana reaction, as summarized here. First, a greenish yellow precipitate (mp 173°) was collected directly from the anhydrous



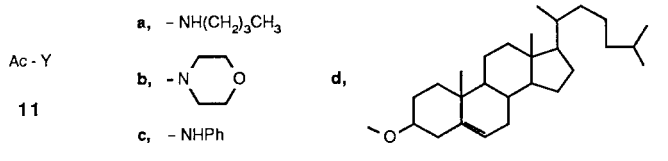
mixture. A pmr spectrum of this precipitate in pentadeuteriopyridine indicated that two structurally similar products were actually present in this sample, but only the major component (mp 200°) was isolable as a tractable substance on chromatography with chloroform-pyridine. Second, treatment with water of the filtrate from the 173° precipitate gave a dark green precipitate, mp 196° (perhaps bearing water of solvation), shown to be identical with the 200° product by tlc, mixture mp, and spectra under identical conditions, but different in color and in solubility in organic solvents. The 200° product, in particular, is represented by the tautomeric mixture **6** (rather than by the simple structure **7**) primarily on the basis of its infrared spectra in chloroform solution and as a mull in hexachlorobutadiene where one finds bands at 3100, 2200, and 1615-1620 cm^{-1}, ascribed to O··H··N chelate, conjugated aminonitrile, and C=C-O functions, respectively [7-10]. There is no significant absorption in the range of



a **8** **b** **9**



a **10** **b**



1745-1770 cm^{-1} for a simple ester function, as one should have for **7** [11]. Although the pmr spectrum of the 200° compound in deuteriochloroform did not show a downfield singlet (as found in **2**), a coupling constant of 9 Hz for the protons at C-6 and C-7 is consistent with the presence of a double bond at this location. As with **2**, the most abundant mass spectral fragment corresponds to the loss of ethanol from the molecular ion. In fact, the entire mass spectral fragmentation patterns of **2** and **6** are very similar. However, neither we nor Borror and Haeberer [7] noted marked variations in physical properties of various fractions in the preparation of **2**.

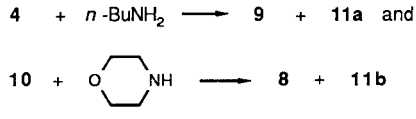
Podmore reported the synthesis of **8**, a positional isomer of **2** from 4-chloroquinoline (**1d**) by the method of Borror and Haeberer [12]. In our first attempt to reproduce this work it was found that no precipitate formed when the reaction mixture was poured into the equivalent amount of water used for **2**. After 12 hours this alkaline solution was concentrated and deposited crystalline 4-cyanomethylquinoline (**1e**) (31%) directly, as well as some red **8** (mp 187°) after acidification with acetic acid. Formation of **1e**, presumed to occur by alkaline hydrolysis plus decarboxylation of **8**, was subsequently avoided by using less water in the processing step and then immediately precipitating **8** (55%) by addition of excess 2% aqueous hydrochloric acid. Surprisingly, when the maroon alkaline solution was divided into two portions before addition of acid, one portion gave a bright yellow precipitate and the other gave a dark red (maroon) precipitate. Each solid (mp 187°) was recrystallized from dioxane *without* change in color and was found to be identical with the other one by mixture melting point, as well as by infrared, pmr, and cmr spectra (obtained in the same solvent in each case). In particular, the nmr spectrum in hexadeuteriodimethyl sulfoxide (orange solution) shows a broad singlet at 13.07 ppm for an imino proton, a singlet at 69.91 ppm for C-2′, and a constant of 9 Hz for coupling between H-2 and H-3, as would occur in tautomer **8a**. However, the pmr spectrum in deuteriochloroform (also an orange solution) indicates the presence of an equimolar mixture of tautomers **8a** (broad singlet for an imino proton at 9.59) and **8b** (sharp singlet for H-2′ at 5.40). In addition this spectrum shows a doubling of the signals for H-2, for the methylene group, and for the methyl group. Thus, it is apparent that the tautomeric ratio **8a/8b** is dependent on the solvent used, but the color of the solution is not simply dependent on the solvent. In contrast to the case for isomer **2**, the molecular ion from **8** shows loss of a carboethoxy group instead of a molecule of ethanol for its most prevalent fragmentation pathway. This same fragmentation was noted in the mass spectrum of the analogous molecule **9** [1].

In addition to formation of the *N*-acetyl cyanoester **4** from the Hamana reaction of **3a**, one can also obtain **4** by stirring simple cyanoester **9** with acetic anhydride in chloroform at room temperature [1]. However, neither **2** nor **6** reacts with acetic anhydride at room temperature (with or without the presence of chloroform) or at reflux temperature. It seems likely that this resistance to *N*-acetylation is a consequence of the cyclic structures shown for **2** and **6**. Contrariwise, the *gamma* derivative of quinoline **8** undergoes *N*-acetylation in refluxing acetic anhydride. However, the reaction attains equilibrium as shown. By use of slow distillation of the acetic acid formed

8 + Ac_2O ⇌ **10** + HOAc

and gradual replacement of it with more acetic anhydride it was possible to obtain a 70% yield of **10**. From these results it is apparent that the thienopyridine compound **4** is more stable chemically than **10** [13].

In order to show that **4** and **10** can be used as acetylating agents we treated these compounds with 1-aminobutane, morpholine, aniline, and cholesterol [14] under various conditions such that the acetylated compounds could be isolated and identified. These results are summarized in Table I, where it is apparent that **4** and **10** give comparable results under similar reaction conditions. For reaction of 1-aminobutane and morpholine the acetylating agent was converted into **9** (from **4**) or **8** (from **10**), respectively, as established by isolation experiments. Thus, stoichiometric equations such as



may be written. As reported previously, **4** also reacts with 95% ethanol over a period of 10 days or with anhydrous hydrogen chloride in chloroform at room temperature in only 7 minutes to give high yields (88-93%) of cyanoester **9**, though the fate of the acetyl group was not determined in these cases [1]. With either **4** or **10** the reactivities of the amines follow the order of their basicities, 1-aminobutane (pK_b 3.3) > morpholine (5.6) > aniline (9.4) [16].

At this point it seems appropriate to compare and contrast the results of the Hamana reactions on the *N*-oxides **1a, 3a** and **5a**. Compounds **1a** and **5a** give *alpha* substitution of a 1-carboethoxy-1-cyanomethyl (R) group and resist *N*-acetylation because of the formation of a stabilized chelate structure (as shown in **2** and **6**). *N*-Acetylation becomes feasible when the R group enters the ring *gamma* to the heteronitrogen atom. For the thieno[2,3-*b*]pyridine system **3** both *gamma* substitution and *N*-acetylation occur in the Hamana reaction proper. For the quinoline system **1**, however, one must first introduce a *gamma* R group by an alternative route (*e.g.* displacement of a *gamma* chloro function) and then *N*-acetylation can proceed. To complete this comparative series there remain the goals of introducing the R group into the *alpha* position of the thieno[2,3-*b*]pyridine system **3** and into the *gamma* position of the thieno[3,2-*b*]pyridine system **5** [17].

Table II compares the reported orientation effects in the three isosteric *N*-oxide systems **1a, 3a**, and **5a** which result from various nucleophilic substitution reactions that occur with attendant de-*N*-oxygenation. From this table it is apparent that no major differences in substitution patterns for these systems occur in reactions 1 and 2, where nucleophilic attack by a relatively hard anion (cyanide or chloride), Nu^-, on an *N*-oxide ester (Figure 1) is probably involved [24,25]. Interaction between the anion and the pyridine ring results primarily from Coulombic attraction, and partitioning between *alpha* and *gamma* substitution may be ascribed to differences in nucleophilicities of the anions (cyanide > chloride). The effect of the fused ring **A** on the orientation of Nu^- is minimal. In contrast, it has been proposed that reaction 3 involves attack by the 1-carboethoxy-1-cyanomethyl carbanion (R^-) and reaction 4, by the uncharged enamine **12** [26] (Figure 2). Interaction of either soft base **12** or R^- with the pyridine ring should depend primarily on the extent of overlap of the frontal molecular orbital (HOMO) of the soft base with the *alpha*, or alternatively the *gamma*, frontal molecular orbital (LUMO) of the ester of **1a, 3a**, and **5a**, in turn [25]. Thus, the orientation of the soft nucleophile should be markedly influenced by the composition of ring **A**, *i.e.* by the electronic effects of the sulfur atom in the thienopyridine cases. Taking into consideration the observation that a sulfur atom donates electronic charge by resonance effect and withdraws electronic charge by inductive effect [27,28], one can predict the order **3** >> **1** > **5** in hardness of the *alpha* position as an electrophile

Table I

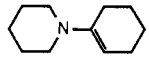
Comparative Acetylation Reactions of Compounds **4** and **10**

Substrate	Acetylating agent	Solvent used	Reaction temp [a]	Reaction time	Product formed	Yield, % [b]
1-aminobutane	**4**	$CHCl_3$	25°	13 minutes	**11a**	84
1-aminobutane	**10**	$CHCl_3$	25°	10 minutes	**11a**	96
morpholine	**4**	$CHCl_3$	25°, △	10 minutes, 14 minutes	**11b**	98
morpholine	**10**	$CHCl_3$	25°	18 minutes	**11b**	99
aniline	**4**	DMSO	100°	5 hours	**11c**	76
aniline	**10**	DMSO	100°	2.5 hours	**11c**	66
cholesterol	**4**	Py [c], DMF	△	14 hours	**11d**	51
cholesterol	**10**	Py [c], DMF	△	10 hours	**11d**	35

[a] △ denotes reflux temperature. [b] Based on quantity of acetylating agent used. [c] Pyridine serves as a catalyst [15].

Table II

Comparative Orientations in Substitution Reactions of Quinoline *N*-Oxide and Its Isosteric Thienopyridine *N*-Oxides

Reaction No.	Reagent(s) used	Substituent introduced	Position of substitution in **1a**	in **3a**	in **5a**
1	PhC(=O)Cl, CN^-	-CN	α [18]	α [19]	α [19]
2	$POCl_3$	-Cl	γ:α = 1.7:1.0 [20]	γ:α = 1.7:1.0 [21]	γ:α = 1.4:1.0 [22]
3	$NCCH_2CO_2Et$, Ac_2O	-CH(CN)CO_2Et	α [6]	γ [1]	α
4	PhC(=O)Cl, 		α [23]	γ [1]	[a]
	 (12)				

[a] Not yet reported.

in these parent systems, and probably also in their corresponding OZ esters. Additionally one should have the order *alpha* > *gamma* in hardness in systems **1** and **3** alone and, possibly, *gamma* ≥ *alpha* in system **5**. Based on these relationships one can rationalize the fact that **3a** gives *gamma* substitution with the soft bases R^- and **12**, but gives a similar substitution pattern to **1a** and **5a** with harder bases.

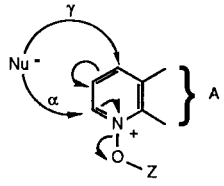


Figure 1. Orientation of hard anionic nucleophile in substitution reaction of 1a, 3a, or 5a. For $Nu^- = CN^-$ and Z = PhC(=O)– only *alpha* attack occurs. For $Nu^- = Cl^-$ and Z = $POCl_2$ both *alpha* and *gamma* attacks occur (see Table II).

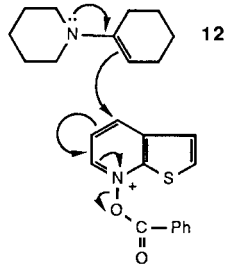


Figure 2. Orientation of soft nucleophile in γ-substitution reaction of **3a** (see reaction 4, Table II)

EXPERIMENTAL [29]

Thieno[2,3-*b*]pyridine 7-oxide (**3a**).

A stirred solution of 3 g (22.2 mmoles) of thieno[2,3-*b*]pyridine (**3**) [30] in 100 ml of chloroform at room temperature was treated, in portions over a period of 2 hours, with 4.8 g (27.8 mmoles) of *m*-chloroperoxybenzoic acid. Stirring was continued for 45 hours. The solution was washed with 10% aqueous sodium hydroxide, dried (sodium sulfate), and evaporated to give a brown liquid, which was evaporatively distilled at 100° (0.05 mm) to form white crystals coated with a yellow solid deposit. Washing the crystals with chloroform removed the yellow deposit to leave 2.22 g (66%) of **3a**, mp 85.5-86.5°; lit yield 53%, mp 87-89° [31].

7-Acetyl-4-(1-carboethoxy-1-cyano)methylene-4,7-dihydrothieno[2,3-*b*]-pyridine (**4**).

This compound was prepared from *N*-oxide **3a**, as previously described [1].

4-(1-Carboethoxy-1-cyano)methylene-1,4-dihydroquinoline (**8**).

A quantity of 2.64 g (0.066 mole) of sodium hydride (60% dispersion in mineral oil) was washed three times with anhydrous petroleum ether, suspended in 10 ml of anhydrous dimethylformamide (nitrogen atmosphere), and treated dropwise with 6.84 g (0.06 mole) of ethyl cyanoacetate. The stirred mixture was warmed to 50°, treated dropwise with a solution of 5 g (0.031 mole) of 4-chloroquinoline (**1d**) (Aldrich) in 15 ml of dimethylformamide, and heated at 120° for 2.7 days, whereupon tlc (silica gel/ether) indicated reaction was complete (intensely yellow spot at R_f 0.06, absence of spot for **1d** at R_f 0.4). The mixture was cooled, rotoevaporated, and added to 100 ml of water to give a maroon solution. A portion of this solution was immediately acidified with excess 2% hydrochloric acid to give a *bright yellow* precipitate, collected by filtration and rinsed with a little water. Immediately thereafter the remainder of the solution was treated in the same manner, but it gave a *dark red* precipitate, instead. The precipitates were recrystallized from 1,4-dioxane separately, without change in color (maroon shiny flakes produced from the latter). Both melted at 186-187°, lit 190-192° [12], 174-176° [32], unchanged on admixture, combined yield 3.98 g (53%); ir (chloroform, calcium fluoride windows): 3400 (NH), 2160 (CN), 1740 (w) and 1670 (s, C=O) cm^{-1}. Each sample was readily soluble in hexadeuteriodimethylsulfoxide to give the same orange solution of **8a**; pmr: δ 13.07 (broad s, NH), 9.01 (d, $J_{2,3}$ = 9 Hz, H-2), 8.30 (d, $J_{7,8}$ = 7 Hz, H-8), 8.04 (d, $J_{5,6}$ = 7 Hz, H-5), 7.78 (t, $J_{6,7}$ = 7 Hz, H-7), 7.69 (d, H-3), 7.50 (t, H-6), 4.14 (q, 2H, methylene group), 1.23 (t, 3H, methyl group); cmr: δ 14.50 (q, J = 127 Hz, methyl group), 59.01 (split t, J = 148, 4 Hz, methylene group), 69.91 (s, C-2'), 108.36 (d, J = 172 Hz, C-3), 119.26 (dd, J = 165, 7 Hz, C-5 or C-8), 120.53 and 123.37 (2 s, CN and C-4), 124.13 and 126.18 (2 dd, J = 154, 8 Hz, J = 149, 5 Hz, C-6 and C-7), 132.11 (dd, J = 165, 8 Hz, C-8 or C-5), 136.32 (d, J = 184 Hz, C-2), 137.93 (pseudo q, J = 8 Hz,

C-4a), 154.07 (d, J = 4 Hz, C-8a), 166.56 (s, C=O). Each sample was less soluble in deuteriochloroform to give the same orange solution bearing equimolar quantities of tautomers **8a** and **8b**; pmr: δ 9.59 (broad s, NH of **8a**, disappears on shaking with deuterium oxide), 9.20 (d, $J_{2,3}$ = 9 Hz, H-2 of **8a**), 9.00 (d, $J_{2,3}$ = 5 Hz, H-2 of **8b**), 8.40, 8.25, and 8.08 (3d, 1H each), 7.9-7.3 (m), 5.40 (sharp s, H-2' of **8b**, reduced in intensity slightly on shaking with deuterium oxide), 4.30 (2 overlapping q, 4H, methylene groups of **8a** and **8b**), 1.35 and 1.25 (2 t, methyl groups of **8a** and **8b**). The mass spectrum (maroon crystals) at 170° was m/e 240 (M^+, 42), 168 (**1e**$^+$, 100), 167 (23), 140 (18).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: Exact mass, 240.090. Found: Exact mass, 240.089.

1-Acetyl-4-(1-carboethoxy-1-cyano)methylene-1,4-dihydroquinoline (**10**).

A magnetically stirred mixture of 997 mg (4.15 mmoles) of **8** (both yellow and maroon products) and 60 ml of acetic anhydride was heated at 90-95° while slow distillation of acetic acid and acetic anhydride occurred. Fresh acetic anhydride was added to the distillation flask as needed in order to keep the volume of solvent constant, while progress of the reaction therein was followed by tlc (silica/ethyl acetate; R_f 0.5 for **8**, R_f 0.6 for **10**) until maximum conversion was apparent (9 hours). Solvent was then removed immediately *in vacuo* to give a brownish yellow solid. Recrystallization from absolute ethanol produced 820 mg (70%) of **10** as orange needles, mp 136-137°; ir (chloroform, calcium fluoride windows) 2180 (CN), 1700 (m) and 1615 (s, C=O), 1525 cm^{-1}; pmr (deuteriochloroform): δ 8.75 (dd, $J_{7,8}$ = 7 Hz, $J_{5,8}$ = 2 Hz, H-8), 8.31 (d, $J_{5,6}$ = 7 Hz, H-5), 8.14 (d, $J_{2,3}$ = 9 Hz, H-2), 7.67 (d, H-3), 7.64 (t, $J_{6,7}$ = 7 Hz, H-7), 7.48 (t, H-6), 4.32 (q, methylene group), 2.66 (s, Ac), 1.38 (t, methyl group); pmr (hexadeuteriodimethylsulfoxide): δ 8.63 (d, $J_{7,8}$ = 7 Hz, H-8), 8.41 (d, $J_{5,6}$ = 7 Hz, H-5), 8.25 (d, $J_{2,3}$ = 9 Hz, H-2), 8.02 (d, H-3), 7.76 (t, $J_{6,7}$ = 7 Hz, H-7), 7.56 (t, H-6), 4.24 (q, methylene group), 2.69 (s, Ac), 1.27 (t, methyl group); ms: (180°) m/e 282 (M^+, 8), 240 (M^+ - CH_2=C=O, 46), 195 (M^+ -[EtO + CH_2=C=O], 20), 169 (12), 168 (**1e**$^+$, 100), 167 (22), 140 (22), 43 (Ac^+, 46), 42 (CH_2=C=O^+, 11).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92, exact mass, 282.100. Found: C, 68.22; H, 4.89; N, 9.95, exact mass, 282.099.

5-(1-Carboethoxy-1-cyano)methylene-4,5-dihydrothieno[3,2-*b*]pyridine (**6**).

A solution of 2.3 g (13.6 moles) of thieno[3,2-*b*]pyridine-4-oxide monohydrate (**5a**) [22] in a mixture of 1.95 g of acetic anhydride and 1.95 g of ethyl cyanoacetate was stirred at room temperature for one hour, whereupon appreciable greenish yellow precipitate had formed. The precipitate was collected by filtration. The filtrate was diluted with 1.95 g more of each liquid reagent and stirring was renewed. This recycling was conducted a total of five times, until no additional precipitate formed. The final filtrate was treated further as indicated in a following paragraph. Combined precipitates were washed with carbon tetrachloride and dried, yield 1.31 g, mp 172-173.5°. Tlc of this sample (silica/chloroform-pyridine) showed two yellow spots (one of high R_f, one of low R_f) in white light [33] and the pmr spectrum (pentadeuteriopyridine) indicated that two components with closely similar structural features were present in a ratio of about 7:3. Thick-layer chromatography (sample applied to the plate in chloroform-pyridine, 1:1) showed 6 distinct zones. Only the major zone (broad, second from the top) yielded a tractable product, consisting of greenish yellow, fluorescent needles, mp 199.5-201°, readily soluble in acetone but not in chloroform (yield, 60% of sample weight) [34]; ir (hexachlorobutadiene mull): 3100 (O··H··N chelate) [8], 2200 (conjugated aminonitrile) [10], 1615 (C=C-O) [9], 1570, 1180, 980, 850, 790, 655 cm^{-1}; pmr (hexadeuteriodimethylsulfoxide): δ 8.41 (d, $J_{6,7}$ = 9 Hz, H-7), 8.18 and 7.73 (dd, $J_{2,3}$ = 5 Hz, H-2 and H-3), 7.20 (d, H-6), 4.23 (q, J_{Et} = 7 Hz, methylene group), 1.27 (t, methyl group); ms: (170°) m/e 246 (M^+, 100), 201 (24), 200 (M^+ - EtOH, 88), 174 (M^+ - $CH_2CH_2CO_2$, 82), 173 (38), 172 (41), 146 (M^+ - [EtOC=O + HCN], 34).

Recrystallization of the preceding sample from absolute ethanol plus sublimation at 95-100° (0.005 mm) gave fine, bright yellow needles, mp 200.5-201°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2S \cdot \frac{1}{4}C_2H_5OH$: C, 58.25; H, 4.49; N, 10.86. Found: C, 58.08; H, 4.32; N, 10.58 [35]. Calcd. for $C_{12}H_{10}N_2O_2S$: Exact mass, 246.046. Found: Exact mass, 246.047.

The aforementioned final filtrate from recycling **5a** with acetic anhydride and ethyl cyanoacetate was treated with water and rotoevaporated to give 0.13 g of dark green needles, mp 195-196.5°, soluble in chloroform but not in acetone; ir (chloroform): 3100, 2200, 1620, 1320, 1290, 1180, 1040 cm^{-1}; pmr (deuteriochloroform): δ 7.95 (d, $J_{6,7}$ = 9 Hz, H-7), 7.77 (d, $J_{2,3}$ = 5 Hz, H-2 or H-3), 7.29 (H-6), 7.21 (H-3 or H-2), 4.31 (d, J_{Et} = 7 Hz, methylene group), 1.61 (s, disappears on shaking solution with deuterium oxide, ?), 1.36 (t, methyl group). This sample did not depress the mp (199.5-201°) of the preceding greenish yellow, fluorescent product. Moreover, these two products were found to be indistinguishable as based on criteria of tlc, pmr spectra in hexadeuteriodimethylsulfoxide, ir spectra in hexachlorobutadiene mull, mass spectra, and exact masses. The combined yield of greenish yellow and dark green needles was 0.92 g (27%) of **6**.

2-(1-Carboethoxy-1-cyano)methylene-1,2-dihydroquinoline (**2**).

This compound was prepared from 2-chloroquinoline (**1b**) (Aldrich) by the procedure of Borror and Haeberer [7], except that the reaction time was 19 hours. Recrystallization of the crude product from chloroform-ether (1:1) gave yellow crystals, mp 163-165°, lit 163-164° [7], 166-167° [6]; ir (methylene chloride): 3100 (O··H··N chelate) [8], 2200 (conjugated aminonitrile) [10], 1630 (C=C-O) [9], 1590, 1250-1280, 1175, 1045, 680-780 cm^{-1}; pmr (deuteriochloroform): δ 13.5 (broad s, O··*H*··N chelate), 7.84 (d, J = 9.3 Hz, 1H, H-4), 7.60 (2 overlapping d, 2H), 7.45-7.33 (m, 3H), 4.29 (q, J_{Et} = 7.1 Hz, 2H, methylene group), 1.36 (t, 3H, methyl group); ms: (160°) m/e 240 (M^+, 100), 195 (35), 194 (M^+ - EtOH, 85), 168 (M^+ - $CH_2CH_2CO_2$, 43), 166 (39), 140 (M^+ - [EtOC=O + HCN], 38).

4-Cyanomethylquinoline (**1e**).

In a modification of the preceding procedure used for the synthesis of **8**, the crude reaction mixture (from 2 g of 4-chloroquinoline) was cooled to room temperature, rotoevaporated, and poured into 300 ml of water. The resulting solution was allowed to stand overnight and then concentrated by rotoevaporation at elevated temperature to give a precipitate. Recrystallization of the precipitate from methanol gave 0.63 g (31%) of crude **1e**, mp 130-135° (raised to 141-142°, lit 144-145°) [36]; ir (chloroform, calcium fluoride cell): 2260 (sharp, CN), 910, 730, 640 cm^{-1}; pmr (deuteriochloroform): 8.92 (d, J = 5 Hz, 1H, H-2), 8.18 (dd, J = 8, 2 Hz, 1H, H-8), 7.5-8.0 (m, 4H, H-3, H-5, H-6, H-7), 4.12 (s, 2H, methylene group); ms: (120°) m/e 169 (13), 168 (M^+, 100), 167 (14), 140 (M^+ - H_2CN, 12), 117-118* (167→140).

Acidification with acetic acid of the aqueous filtrate from collection of **1e** gave a red precipitate of **8**, mp 186-187° after recrystallization from methanol.

Reactions of **4** and **10** with 1-Aminobutane.

A suspension of 75 mg (0.26 mmole) of **4** in 1.5 ml of chloroform was treated with 0.05 ml (0.5 mmole) of dried (potassium hydroxide pellets) 1-aminobutane. The mixture was swirled for 13 minutes until a clear yellow solution resulted. The residue from rotoevaporation of the solution was extracted with 0.5 ml of chloroform to leave 16 mg (25% yield) of ethyl 2-(4-thieno[2,3-*b*]pyridyl)-2-cyanoacetate (**9**), identified by melting point (162-163°, lit 161-162° [1]) and pmr spectrum. The extract was chromatographed with chloroform and neutral alumina to give (from the first eluted band) 25 mg (84%) of liquid *N*-*n*-butylacetamide (**11a**); pmr: δ 0.92 (t, J = 7 Hz, 3H, -CH_2CH_3), 1.36 (m, 2H, -CH_2CH_3), 1.48 (m, 2H, -$CH_2CH_2CH_3$), 1.98 (s, 3H, Ac), 3.22 (2 overlapping t, 2H, $NHCH_2$), 5.8 (broad s, NH). Admixture of an authentic sample of **11a**, bp 208° [37], with the preceding isolated liquid did not change the appearance of the pmr spectrum. Isolated compounds **9** (yellow, R_f 0) and **11a** (colorless, but visible in an iodine chamber, R_f 0.6) were also identical with reference compounds as based on tlc (alumina/chloroform).

Compound **10** (105 mg) was swirled with a solution of excess 1-amino-

butane for 10 minutes and the products were processed further in the aforementioned manner. Isolated were yellow **8**, mp 182-184°, and *N*-*n*-butylacetamide (41 mg, 96%), identified by comparison with authentic samples.

Reactions of **4** and **10** with Morpholine.

A mixture of 56 mg (0.19 mmole) of **4**, 1 ml of chloroform, and 0.03 ml (0.34 mmole) of freshly distilled morpholine was swirled for 10 minutes and then refluxed for 14 minutes until a clear, yellow solution resulted. The residue from evaporation of the solvent was extracted with 0.5 ml of chloroform to leave 23 mg (49%) of yellow **9**, mp 162-164°. The first eluted band from column chromatography of the extract with neutral alumina/ethyl acetate gave 24 mg (98%) of liquid *N*-acetylmorpholine (**11b**), R_f 0.2 (detection by iodine), pmr: δ 2.1 (s, 3H, Ac), 3.4-3.8 (m, 8H), unchanged on admixture with an authentic, reference sample (Aldrich, mp 14°). Isolated and reference samples were also identical as based on tlc.

Similarly, 106 mg of **10** and excess morpholine reacted, but with only swirling for 18 minutes, to give **8** and **11b** (48 mg, 99%). Identification was established in the same manner.

Reactions of **4** and **10** with Aniline.

A solution of 103 mg (0.36 mmole) of **4** and 0.056 ml (0.61 mmole) of reagent grade aniline in 4 ml of anhydrous dimethylsulfoxide was heated at 100° for 5 hours. The cooled solution was then chromatographed directly (neutral alumina/chloroform). From the second eluting band (R_f 0.26) was isolated 37 mg (76%) of acetanilide, **11c**, mp 112-114°, pmr: δ 2.15 (s, 3H, Ac), 7.09 (t, J = 7.2 Hz, H-4), 7.29 (t, H-3 and H-5), 7.50 (d, J = 8.4 Hz, H-2 and H-6), 7.17 (broad s, NH), unchanged on addition of authentic **11c** (Aldrich, mp 114°). A mixture melting point of the two samples showed no depression.

Similarly, a solution of 110 mg of **10** and excess aniline in 5 ml of anhydrous dimethylsulfoxide was heated at 100° for 2.5 hours. The cooled solution was diluted with chloroform and washed ten times with saturated aqueous sodium chloride to remove most of the dimethylsulfoxide. Chromatography of the dried (sodium sulfate), concentrated residual solution yielded 35 mg (66%) of acetanilide, identified as before.

Reactions of **4** and **10** with Cholesterol.

A solution of 71 mg (0.25 mmole) of **4**, 102 mg (0.26 mmole) of cholesterol (Aldrich, recrystallized from methanol, mp 147-148°), 0.05 ml of pyridine (dried over potassium hydroxide), and 10 ml of anhydrous dimethylformamide was refluxed overnight. The cooled mixture was diluted with 15 ml of ether and extracted five times with 10-ml portions of saturated aqueous sodium chloride to remove dimethylformamide. The dried (sodium sulfate) ether layer was concentrated and chromatographed (silica gel/ether). From the first eluted band was obtained 55 mg (51%) of slightly yellowish cholesteryl acetate (**11d**), R_f 0.83, pmr: δ 0.6-2.03 (m plus s, 41H), 2.03 (s, Ac), 2.30 (m, 2H), 4.6 (m, 1H), 5.4 (m, 1H), unchanged on admixture with an authentic sample of **11d** (Aldrich), R_f also 0.83.

Likewise, refluxing a mixture of 81 mg of **10**, excess cholesterol, pyridine, and dimethylformamide for 10 hours, followed by processing as before gave 43 mg (35%) of **11d**, identified in the previous manner.

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[34] Another zone yielded a tan-orange powder, 21% by weight, mp 170-330° dec, not investigated further.

[35] It should be noted that recrystallizations, without accompanying sublimation, of samples of the greenish yellow or the dark green needles (*vide infra*) of **5** consistently provided low values for C, H, and N, as if the samples contained non-combustible components (complexed silica?).

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