IR (neat) 1595 (s, C=N); NMR δ 1.23 (s, 9, t-C_4H_9), 3.93 (s, 3, CH_3).

Anal. Calcd for $C_6H_{12}NOCl$: C, 48.17; H, 8.08; N, 9.36; Cl, 23.70. Found: C, 48.07; H, 8.06; N, 9.37; Cl, 23.61.

Ethyl (*E*)-Acetohydroximate (9). Ethyl (*E*)-acetohydroximate (**9**) was prepared according to the procedure of Houben and Schmidt,[19] bp 69–71 °C (13 torr); NMR δ 1.29 (t, 3, *J* = 7 Hz, $COCH_2CH_3$), 1.99 (s, 3, CH_3C), 4.01 (q, 2, *J* = 7 Hz, $COCH_2CH_3$); lit. bp 59.0–59.5 °C (14 torr[8]); lit. NMR[7] δ 2.00 (CH_3CN), 3.99 ($COCH_3$).

Ethyl (*E*)-*O*-Benzylacetohydroximate (7a). A solution of sodium ethoxide was prepared by adding sodium (4.75 g, 0.207 mol) to anhydrous ethanol (100 mL) in a 250-mL round-bottomed flask fitted with a condensor and a drying tube. The reaction flask was immersed in an ice bath, and ethyl (*E*)-acetohydroximate (**9**, 150 g, 0.122 mol) was added followed by the slow addition of benzyl bromide (20.6 g, 0.122 mol). The reaction solution was heated with an oil bath at 50–60 °C for 62 h after which time the ethanol was removed by using a rotary evaporator. The residue was carefully acidified with cold, dilute hydrochloric acid, inorganic salts were removed by filtration, and the filter pad was washed with ether (645 mL). The ether layer was separated from the filtrate and the aqueous layer was extracted with ether (2 × 20 mL). The combined ether extracts were washed with 10% sodium bicarbonate solution (2 × 20 mL) and water (2 × 20 mL). The ether extract was dried over magnesium sulfate, the ether was evaporated, and the residue was distilled to give **7a** as a colorless oil (15.6 g, 60%); bp 65–68 °C (0.08 torr). Redistillation gave the analytical sample of **7a**: bp 91–92.5 °C/0.95 torr; IR (neat) 1640 (s, C=N); NMR δ 1.23 (t, *J* = 7 Hz, 3, OCH_2CH_3), 1.92 (s, 3, CH_3), 4.01 (q, *J* = 7 Hz, 2, OCH_2CH_3), 4.93 (s, $CH_2C_6H_5$), 7.33 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.51; H, 7.82; N, 7.23.

Reaction of (*Z*)-*O*-Benzylacetohydroximoyl Chloride (5a) with Sodium Ethoxide. (*Z*)-*O*-Benzylacetohydroximoyl chloride (**5a**, 4.00 g, 0.0218 mol) was added to a solution of sodium ethoxide (from 1.84 g of sodium) in ethanol (50 mL) and the solution was heated at 66–70 °C. The progress of the reaction was followed by removing 150-μL aliquots of the reaction solution and analyzing them by using the Beilstein test and GLC. After heating the reaction solution for 72 min, a negative Beilstein test was obtained and the hydroximoyl chloride **5a** was no longer detectable by GLC analysis. The GLC analysis indicated that the reaction product was almost entirely ethyl (*Z*)-*O*-benzylacetohydroximate (**7a**). The reaction mixture was filtered to remove precipitated sodium chloride, and the ethanol was evaporated from the filtrate at reduced pressure. The oily residue was filtered to remove inorganic salts and the filtered salts were washed with ethanol. The filtrate was poured into a beaker containing a mixed bed resin consisting of approximately 50% cation-exchange resin (Dowex 50-W-X2, 5.2 mequiv/dry gram) and 50% anion-exchange resin (Dowex 1-X2, 3.5 mequiv/dry gram). The resin was removed by filtration and the ethanol was evaporated in vacuo to give a clear, brownish oil (2.53 g, 52.3%). The oil was purified by preparative GLC and the major component was identified as the hydroximate **7a** by comparison of its ^1H NMR spectrum to the spectrum of an authentic sample of **7a** which had been prepared by the reaction of ethyl (*E*)-acetohydroximate with benzyl bromide. A minor product collected by preparative GLC was determined to be benzyl alcohol.

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Registry No. **2b**, 41071-36-7; **3b**, 29740-67-8; **4b**, 64214-63-7; **5a**, 95017-93-9; **5b**, 95017-94-0; **6a**, 95017-95-1; **7**, 95017-96-2; **7a**, 86208-93-7; **9**, 20703-41-7; benzyl acetohydroxamate, 4797-81-3; trimethylacetyl chloride, 3282-30-2.

Supplementary Material Available: Listings of final atomic positional parameters, anisotropic temperature factors, and intramolecular distances and angles (Tables IV–VI) (3 pages). Ordering information is given on any current masthead page.

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Tetrahydropyridines from 3-Picoline 1-Oxide and *tert*-Butyl and 1-Adamantyl Mercaptans in Acetic Anhydride. Structural Elucidation by Long-Range 2D *J*(C-H) Resolved NMR Spectroscopy[1]

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The reaction of 3-picoline 1-oxide with either *tert*-butyl or 1-adamantyl mercaptan in acetic anhydride yielded a mixture of 2-(alkylthio)-3-picolines, 2- and 3-(alkylthio)-5-picolines, and *trans,trans*-1-acetyl-2-(alkylthio)-3,4-diacetoxy-1,2,3,4-tetrahydropyridines **5**. When triethylamine was included in such reactions, the same picolyl sulfides (albeit in different yields) were obtained together with 1-acetyl-2-(alkylthio)-3-hydroxy-3-methyl-4-acetoxy-1,2,3,4-tetrahydropyridines **6**. The structure of **6d** was determined from an analysis of the long-range proton–carbon-13 spin coupling constants obtained from heteronuclear 2D *J* resolved experiments. The sulfide and alcohol of **6d** were found to be trans and the alcohol and acetoxy group cis.

The reaction of 3-picoline 1-oxide (**1**) with *tert*-butyl mercaptan in acetic anhydride produced the three isomeric sulfides **2–4** (R = t-C_4H_9)[2] together with the tetrahydropyridine **5a**.[3] However, it was found that the inclusion of triethylamine in such a reaction produced, besides the picolyl sulfides, the new tetrahydropyridine **6a**. When 1-adamantyl mercaptan (1-AdmSH) was used instead of *tert*-butyl mercaptan, the corresponding 1-adamantyl sulfides were isolated.

Pyridyl Sulfides, 2–4. When *tert*-butyl mercaptan was used, it was possible to separate the aromatic sulfides from tetrahydropyridines initially by high vacuum distillation, keeping the pot temperature between 100–120 °C. The

(1) Part 18. The Deoxydative Substitution of Pyridine 1-Oxides.
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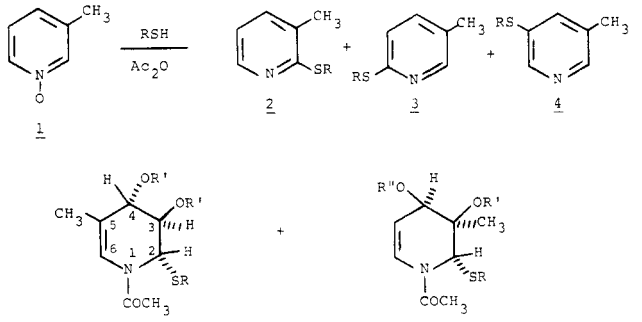
0022-3263/85/1950-0997$01.50/0

Table I. Distribution of Isomeric Sulfides

R	(alkylthio)picolines 2	3	4	yield, %
t-C_4H_9	45	19	36	66[2]
1-Adm[a]	48	18	34	70[b]
t-$C_4H_9(NEt_3)$	61	34	5	20[3]
1-Adm[a](NEt_3)	78	21	1	45[b]

[a] The yields are based on recrystallized pure solid sulfides. Crude yields were slightly higher. [b] Yields are not corrected for the isolation of either the starting N-oxide or thiol.

three isomeric sulfides, **2–4** (R = t-C_4H_9), were further separated by preparative gas chromatography and identified by ^1H nuclear magnetic resonance (NMR) spectroscopy.[2,3] However, such a separation scheme had to be modified drastically when 1-AdmSH was the thiol used. The corresponding sulfides **2–4** (R = 1-Adm) could not be distilled readily from the crude reaction mixture without risking the destruction of some, or all, of any tetrahydropyridines present. It had been shown that these tetrahydropyridines pyrolyzed readily to give pyridyl sulfides.[3] Therefore, the complex reaction mixtures obtained from the reaction of **1** with 1-AdmSH were separated entirely by repeated column chromatography on silica gel.



5a, R = t-C_4H_9; R' = R" = $COCH_3$
b, R = t-C_4H_9; R' = R" = H
c, R = 1-Adm; R' = R" = $COCH_3$
d, R = 1-Adm; R' = R" = H

6a, R = t-C_4H_9; R' = H; R" = $COCH_3$
b, R = t-C_4H_9; R' = R" = $COCH_3$
c, R = t-C_4H_9; R' = R" = H
d, R = 1-Adm; R' = H; R" = $COCH_3$
e, R = 1-Adm; R' = R" = $COCH_3$
f, R = 1-Adm; R' = R" = H

The deoxydative substitution of 3-picoline 1-oxide by mercaptans followed the pattern which had been established previously.[2-4] What was rather interesting that the percent substitution of 3-picoline 1-oxide by *tert*-butyl and 1-adamantyl mercaptans at C-2, C-5, and C-6 were remarkably similar (Table I). The effect of triethylamine in promoting almost exclusive α-substitution has also been discussed previously.[3-5] It was perhaps surprising that the bulky 1-AdmSH attacked C-2 of **1** preferentially, in spite of the methyl group at C-3. This observation is in accord with prior reports that the methyl group in 3-picoline seemingly directs incoming nucleophiles to C-2 rather than to the less hindered C-6 position.[6]

Tetrahydropyridines. From the reaction of **1** and *tert*-butyl mercaptan in acetic anhydride, there was isolated the tetrahydropyridyl sulfide diacetate **5a** whose structure was proved by UV, IR, NMR, and MS spectral data.[3-5,7] The stereodisposition of neighboring substituents was determined from the Karplus relationship between the magnitude of the spin–spin coupling constant of vicinal protons and the dihedral angle between them in the twist chair form of **5a**. The $J_{2,3}$ coupling constant of 1–2 Hz suggests that H-2 and H-3 are trans quasi-equatorial and hence the sulfide at C-2 and the acetoxy substituent at C-3 are trans quasi-axial. Similarly, the magnitude of $J_{3,4}$ (1–2 Hz) relates to the larger of the two dihedral angles between H-3 and H-4 and this suggests that these two protons are trans. Consequently, **5a** produced the diol **5b** whose stereochemistry remained unchanged.

When **1** was reacted with 1-AdmSH, there was isolated the tetrahydropyridyl sulfide diacetate **5c**. Since the UV and ^1H and ^{13}C NMR spectra of **5c** so closely resemble those of **5a**, it was concluded that the structure and stereochemistry of **5c** were the same as those of **5a**. Again, hydrolysis of **5c** gave the diol **5d**.

It was rather surprising to discover that the inclusion of triethylamine into otherwise identical reactions of **1** with either *tert*-butyl mercaptans or 1-AdmSH in acetic anhydride at 95 °C produced the new tetrahydropyridines **6a** and **6d**, respectively. From UV spectral data both appeared to be 1,2,3,4-tetrahydropyridine. Other spectral data (IR, MS, NMR) confirmed the presence of a hydroxy, an acetoxy, and a sulfide group. With their ^1H NMR spectra clearly showing two alkenyl proton resonance signals (H-5, H-6, $J \sim 8$ Hz), the other three substituents had to be on the remaining three aliphatic ring carbons. Comparison of the NMR data of **6** with that of related tetrahydropyridines[7] suggested that the sulfide group in **6** is at C-2 and the hydroxy and the acetoxy groups were at C-3 and C-4, respectively.

The location of these substituents were confirmed from an analysis of long-range proton–carbon-13 spin coupling constants which were obtained from heteronuclear 2D J resolved experiments using a selective proton π pulse as described by Bax and Freeman.[8] From these experiments long-range ^1H–^{13}C couplings were observed in the F1 dimension between the carbons and the irradiated proton. Thus, only one splitting was observed for each carbon which greatly facilitated the interpretations. A scalar coupling of 3.4 Hz was observed between the 1-Adm carbon and H-2. This can only be explained if *S*-Adm is attached to C-2 since attachment at a different site would require four or more intervening bonds which would be expected to exhibit little or no coupling. Analogously, the acetoxy group must be attached to C-4 since a coupling of 3.5 Hz was observed between the carbonyl carbon of the acetoxy group and H-4. The other ^1H–^{13}C couplings observed are also consistent with this structure.

Unlike previous investigations,[7] the stereochemistry of these molecules could not be discerned from vicinal ^1H–^1H coupling constants due to the absence of H-3 in **6**. However, three-bond carbon–proton couplings also have a dihedral angle dependence in a Karplus-like relationship,[9] and these heternuclear couplings were used to determine the stereochemistry at the different chiral centers of **6d**. The magnitude of the coupling observed between H-2 and C-4 (^3J = 6.4 Hz) supports a trans relationship between these two atoms which necessitates that H-2 be in an equatorial orientation. The CH_3 group attached to C-3,

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(5) Kokosa, J. M.; Bauer, L.; Egan, R. S. *J. Heterocycl. Chem.* **1976**, *13*, 321 and references quoted therein.
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(7) Kokosa, J. M.; Chu, I.; Bauer, L.; Egan, R. S. *J. Heterocycl. Chem.* **1978**, *15*, 785.
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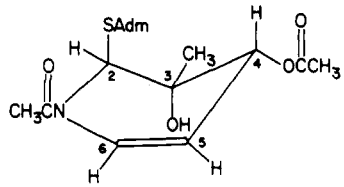
if either axial or equatorial, must therefore be gauche to H-2 and is supported by the magnitude of the relevant heteronuclear coupling constant (^3J = 2.3 Hz). Based on the couplings observed between H-4 and C-2 (^3J = 1.9 Hz) and CH_3 (^3J = 2.3 Hz), both C-2 and CH_3 must be in a gauche orientation to H-4. These results can only be explained by an axial orientation of H-4 (if equatorial, a large coupling would be observed with C-2) and an equatorial CH_3. Therefore, the NMR results indicate that the sulfide at C-2 and the alcohol at C-3 are oriented trans, and the two oxy functions at C-3 and C-4 are located cis to each other. Furthermore, the data support a twist chair conformation for **6d**.

It is not surprising that in the twist chair form of the piperideine ring, the bulky sulfide and hydroxy substituents at C-3 prefer the quasi-axial conformation to avoid repulsive nonbonding interactions. This is verified from the NMR data of **6d**. On the other hand, the cis or trans arrangement of the oxygenated functions at C-3 and C-4 in a quasi-axial–quasi-equatorial conformation shows less crowding in such twist chair forms (see structure **6d'**).

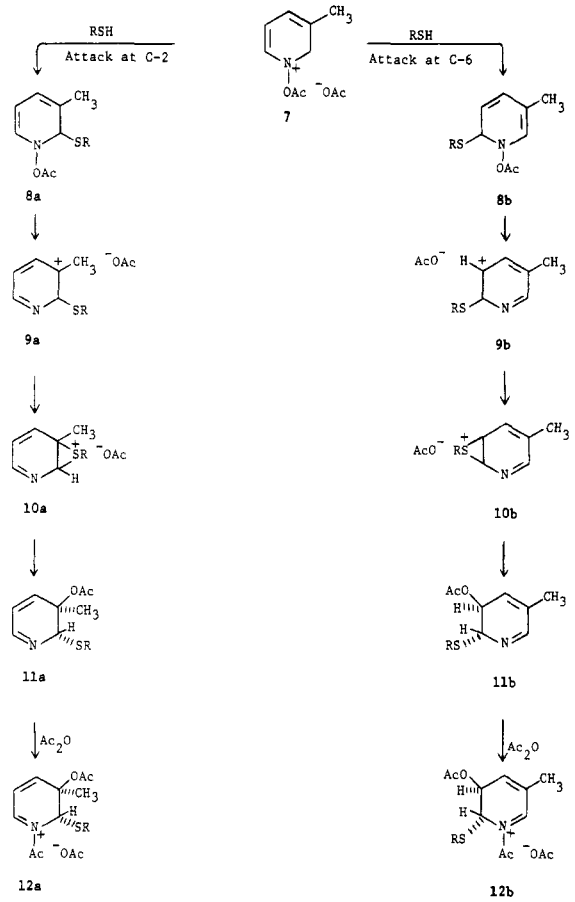


6d'

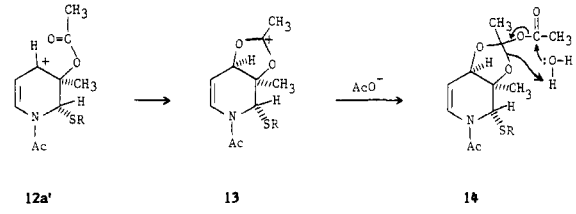
The formation of **5** and **6** can be explained by the mechanistic pathways proposed previously.[5] Nucleophilic attack of the thiol of **7** would give rise to the expected 1,2-dihydropyridines, **8a,b**. Separation of the *N*-acetoxy group leads to the cationic intermediates **9** which are potential precursors to episulfonium ion intermediates **10**.[5] Ring opening of **10** by acetate ion would create the trans-disubstituted dihydropyridines **11**. The reaction is completed when **11** quaternizes in acetic anhydride to form salts **12** which undergo nucleophilic attack by acetate ion at C-4 to form compounds of type **5** or **6**.

No reasonable explanation is advanced to solve the vexing problem on how triethylamine changes the course of tetrahydropyridine formation. Compound **5** must arise from **11b**, while **6** stems from **11a**. The role of triethylamine might be understood better if experimental results become available upon changing the size and nature of the group at C-3 in **1** and the inclusion of other organic amines in such reaction mixtures.

It is somewhat strange that the *cis*-hydroxy acetates **6a** and **6d** were isolated from these reactions in acetic anhydride. It was found that the corresponding diacetates **6b** and **6e** did not hydrolyze when deliberately chromatographed on columns similar to those used during the initial isolation procedures. One could argue that perhaps labile precursors are formed in the initial reaction mixture. There had been isolated a *cis*-hydroxy acetate in the 3-desmethyl series, along with a *trans*-diacetate.[5] It is suggested that the presence of the acetoxy group at C-3 in **11a** next to the electrophilic center at C-4 in **12a** (**12a'**) invites neighboring group participation of the acetoxy group via the 1,3-dioxolan-2-ylium intermediate **13**. Attack by acetate ion on **13** could take place in several different ways. One of these would lead to the orthoester **14**. Such a labile ester would hydrolyze readily during the aqueous workup or during column chromatography to generate the hydroxy acetates (**6a,d**). Alternatively, acetate ion could attack C-4 of **13** to yield a *trans*-diacetate (groupings found



in **5a** and **5c**) but compounds of this type were not isolated in the current experiments.



12a' **13** **14**

Experimental Section

Melting points were determined on a Unimelt Thomas Hoover capillary melting point apparatus and are uncorrected. UV spectra were obtained on a Varian Cary 118 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 710 spectrophotometer. Microanalyses were carried out by Micro-Tech Labs, Skokie, IL. Mass spectra (MS) were obtained at 70 eV by Richard Dvorak with a Hitachi-Perkin Elmer RMU-6D single focusing spectrometer. Usually, only the more intense ions (20% or more) are reported and relative intensities are shown in parentheses. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a T60A Varian (for proton) or a Bruker CXP-180 at 25.2 MHz and a Nicolet NT-360 at 90.8 MHz (for carbon) spectrometer, respectively. All chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane; signals are denoted as singlets (s), doublets (d), tripets (t), multiplets (m). For the long-range heteronuclear 2D J resolved NMR experiments, a $(\pi/2(C) - t/2 - \pi(H), \pi(C) - t/2 - \text{acquire})_n$ pulse sequence was employed with broad-band ^1H decoupling applied during acquisition. The selective proton π pulse was 20 ms in duration (γH_2 = 25 Hz) and was calibrated by using dichloroacetic acid as previously described.[10] A delay of 5 s was employed after data acquisition and before the initial $\pi/2(C)$ pulse. The $t/2$ values were incremented in 64 equal steps and 8K spectra were collected. Two-dimensional data processing was accomplished with exponential multiplication (line broadening = 2 Hz) in the F2 dimension and a shifted

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sine-bell window function followed by zero filling (2X) in the F1 dimension. Column chromatography was carried out on silica gel (Baker Chemical Co., 60–200 mesh). TLC chromatograms were run on 8 × 4 cm (0.25 mm thick) strips of silica gel mixed with a UV indicator, Brinkmann Instruments, Inc., Sil G/UV_{254}. Developing solvent A was petroleum ether/ether (7:3) and B was ether. Spots were detected by either UV light and/or iodine stains.

Removal of solvents in vacuo implies their distillation by means of a rotary flash evaporator. Petroleum ether refers to that fraction with bp 30–60 °C.

Materials. We are grateful to the following companies for gifts of research chemicals: 3-picoline 1-oxide (used as supplied by Reilly Tar and Chemical Co., Indianapolis, IN); *tert*-butyl mercaptan from Penn-Salt Chemical Co., and Phillips Petroleum Co. Extreme care must be exercised in the use of this thiol to prevent having its presence mistaken for "gas leaks". It is best to connect any apparatus containing this thiol, by means of glass tubing into a solution of aqueous $KMnO_4$ to effect oxidation to odorless products. 1-Adamantanethiol was prepared as described before.[11]

A. Reaction of 3-Picoline 1-Oxide with 1-Adamantyl Mercaptan in Acetic Anhydride and Triethylamine. 3-Picoline 1-oxide (21.8 g, 0.2 mol) was dissolved in freshly distilled acetic anhydride (150 mL) containing triethylamine (100 mL, 0.7 mol) by warming to 70 °C, (~15 min). A solution of 1-adamantyl mercaptan (33.6 g, 0.2 mol) in acetic anhydride (50 mL) was added dropwise to this warm solution (20 min), keeping the reaction temperature to about 95 °C. The mixture was then heated on the steam bath for 3 h. Volatile materials were distilled in vacuo (rotary flash evaporator, ~5–10 torr) by raising the bath temperature to no greater than 95 °C. The residue was cooled and stirred (15 min) with ice-cold 10% Na_2CO_3 (200 mL) to neutralize acidic materials. The mixture was extracted with toluene (4 × 100 mL) and the extract dried (Na_2SO_4). The residue (41.5 g, after evaporation of toluene in vacuo) was placed onto a column of silica gel (600 g) prepared in toluene. Elution with toluene (1.5 L) gave first 1-adamantyl thiolacetate (6.2 g, 14.8%): mp 60–61 °C (lit.[12] mp 60–62 °C). The next toluene fraction (0.5 L) yielded pure 2-(1-adamantylthio)-3-picoline (11.95 g), mp 118–119 °C, which was recrystallized from petroleum ether: mp 124–125 °C (90% recovery); TLC R_f 0.89 or 0.91 (solvents A or B); ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, H-6), 7.33 (dd, H-4), 6.93 (dd, H-5) ($J_{4,5}$ = 7.2, $J_{4,6}$ = 1.2, $J_{5,6}$ = 4.8 Hz), 2.29 (CH_3), 2.21, 1.71 (complex m, Adm); MS, 259 (M^+, 43), 258 (57), 226 (12), 135 (100), 125 (22), 93 (33), 91 (22), 79 (40). Anal. Calcd for $C_{16}H_{21}NS$: C, 74.08; H, 8.16; N, 5.40. Found: C, 74.09; H, 8.04; N, 5.24.

The next major toluene fraction (1 L) produced a mixture of **2** and **3** (R = 1-Adm, 10.5 g) whose separation is described below. Further elution with toluene (3.75 L) furnished 2-(1-adamantylthio)-5-picoline (4.2 g), mp 89–90 °C. Recrystallization from petroleum ether afforded 3.1 g of pure sulfide: mp 102–103 °C; TLC R_f 0.74 or 0.88 (solvents A or B); ^{1}H NMR ($CDCl_3$) δ 8.38 (br s, H-6), 7.32 (narrow m, H-3, H-4), 2.29 (CH_3), 2.00, 1.67 (complex m, Adm); MS, 259 (94), 258 (100), 226 (35), 135 (100), 125 (28), 93 (45), 79 (47). Anal. Calcd for $C_{16}H_{21}NS$: C, 74.08; H, 8.16; N, 5.40. Found: C, 74.33; H, 8.21; N, 5.31.

Toluene (0.9 L) eluted next 3-(1-adamantylthio)-5-picoline (0.9 g), mp 67–72 °C, which was recrystallized from petroleum ether: mp 87–88 °C (0.25 g); TLC R_f 0.35 or 0.76 (solvents A or B); ^{1}H NMR ($CDCl_3$) δ 8.46, 8.40 (d, H-2, d, H-6), 7.61 (t, H-4), $J_{2,4}$ = $J_{4,6}$ = 1.2 Hz), 2.35 (CH_3), 2.04, 1.62 (complex m, Adm); MS, 259 (32), 135 (100). Anal. Calcd for $C_{16}H_{21}NS$: C, 74.08; H, 8.16; N, 5.40. Found: C, 74.45; H, 8.08; N, 5.36.

The 10.5-g mixture of sulfides isolated above were rechromatographed on silica gel (300 g). Elution with 1.0 L of toluene furnished **2** (R = 1-Adm, 8.1 g) and then **3** (R = 1-Adm, 1.75 g) with an additional 3.1 L of toluene. The percent yield and distribution of the isomeric sulfides is listed in Table I.

Further elution of the *original* column with chloroform (8 L) yielded a dark oil (24.8 g) which was rechromatographed on silica gel (400 g) prepared in ether–chloroform (1:1). Elution with the same solvent mixture (1.4 L) gave an oily mixture (~1 g) which consisted of the picoline sulfides, and then **6d** (9.15 g from 1.8 L) as an oil which solidified upon standing under ether/petroleum ether (2:1) (5.42 g, 7.2%): mp 144–145 °C (unchanged upon crystallization from the same solvent mixture); TLC R_f 0.12 (solvent B); UV (95% EtOH) λ_{max} (log ϵ) 238 nm (4.04); IR (Nujol) 3380 (OH), 1720 (ester C=O) 1630 (amide C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.58 (dd, H-6), 5.73 (d, H-2), 5.45 (t, H-4), 4.94 (dd, H-5), ($J_{4,5}$ = 1.8, $J_{2,4}$ = $J_{4,6}$ = 1.2, $J_{5,6}$ = 8.4 Hz), 2.19 (s, $NCOCH_3$), 2.14 (s, OCOCH), 1.95 1.69 (m, Adm), 1.45 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.2, 167.7 (CO), 126.4 (C-6), 106.9 (C-5), 70.8 (C-4), 70.3 (C-3), 59.5 (C-2), 47.0, 43.8, 36.0, 29.9 (Adm), 23.6 (ring CH_3), 21.6, 20.8 (acyl CH_3); MS, 379 (9), 194 (60), 152 (100), 135 (95), 110 (95), 93 (33), 79 (29), 43 (66). Anal. Calcd for $C_{20}H_{29}NO_4S$: C, 63.29; H, 7.70; N, 3.69. Found: C, 63.21; H, 7.90; N, 3.65.

Acetylation of 6d (0.2 g, 0.5 mmol) was carried out with boiling acetic anhydride (5 mL, 5 h) until the TLC showed the disappearance of starting material. The solution was cooled and poured into ice–water (20 mL). The mixture was neutralized with 10% sodium carbonate and extracted with chloroform (3 × 30 mL). The extract was washed with water (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue (0.3 g) was placed onto a column of silica gel (20 g) prepared in petroleum ether. Elution with ether (100 mL) provided **6e** which was recrystallized from ether (0.12 g, 54%): mp 199–200 °C; TLC R_f 0.06 or 0.80 (solvent A or B); IR (Nujol) 1735, 1680 (ester C=O), 1638 (amide C=O), cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.65 (ddd, H-2), 6.56 (dd, H-6), 5.54 (dd, H-4), 4.91 (dd, H-5) ($J_{2,4}$ = $J_{2,5}$ = $J_{2,6}$ = $J_{4,6}$ = 1.0, $J_{4,5}$ = 2.0, $J_{5,6}$ = 8.0 Hz), 2.15 (s, $NCOCH_3$), 2.09, 1.97 (s, $OCOCH_3$), 2.0, 1.97 (m, Adm), 1.74 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.6, 166.6 (CO), 126.2 (C-6), 106.6 (C-5), 79.3 (C-3), 71.2 (C-4), 56.0 (C-2) 47.8, 44.1, 36.1, 30.1 (Adm), 21.5 (ring CH_3), 20.8, 19.6 (acyl CH_3); MS, 421 (3), 302 (50), 194 (23), 152 (28), 135 (100), 125 (50), 110 (63), 43 (63). Anal. Calcd for $C_{22}H_{31}NO_5S$: C, 62.68; H, 7.41; N, 3.32. Found: C, 62.63; H, 7.61; N, 3.22.

Hydrolysis of 6d was accomplished by stirring 0.3 g (0.8 mmol) with sodium hydroxide (0.016 g, 0.4 mmol) in methanol (5 mL) at 25 °C for 4 h. The solution was neutralized with hydrochloric acid and extracted with chloroform (3 × 40 mL). The extract was washed with water (2 × 20 mL), dried (Na_2SO_4), and evaporated in vacuo. The produced **6f** weighted 0.26 g (100%) and was recrystallized from methanol (~80% recovery): mp 198–199 °C; TLC R_f 0.16 (solvent B); IR (Nujol) 3165 (OH), 1618 (amide C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.45 (dd, H-6), 5.73 (ddd, H-2), 5.03 (dd, H-5), 4.16 (ddd, H-4) ($J_{2,4}$ = 1.7, $J_{2,5}$ = $J_{2,6}$ = $J_{4,6}$ = 1.1, $J_{4,5}$ = 2.2, $J_{5,6}$ = 8.1, $J_{H,OH}$ = 9.0 Hz), 2.58, 2.79 (d, OH), 2.18 (s, $NCOCH_3$), 1.94, 1.68 (m, Adm), 152 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.8 (CO), 124.8 (C-6), 112.1 (C-5), 71.0 (C-3), 68.1 (C-4), 59.5 (C-2), 47.0, 43.8, 36.0, 30.0 (Adm), 23.3 (ring CH_3), 21.6 (acyl CH_3); MS, 337 (6), 170 (44), 169 (33), 152 (100), 135 (84), 128 (42), 110 (82), 93 (25), 79 (28), 43 (45). Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15. Found: C, 64.33; H, 8.25; N, 4.07.

B. Reaction of 1 with 1-AdmSH in Acetic Anhydride. This reaction was carried out essentially as described in A. Modifications are indicated. 1-AdmSH (33.6 g, 0.2 mol) in acetic anhydride (50 mL) was added dropwise into a warm solution of 1 (21.8 g, 0.2 mol) in acetic anhydride (150 mL). After 3 h at 95 °C, the solution was cooled and pure **2** (R = 1-Adm, 11.3 g) was filtered off. The mother liquor was evaporated to dryness and worked up as described in A. The crude oil (37.0 g) was chromatographed on silica gel (600 g) in toluene. Elution with toluene (2 L) gave 1-$AdmSCOCH_3$ (2.3 g, 5.5%). The mixture of **2** and **3** (10.7 g from 1.5 L) was fractioned by recrystallization from petroleum ether to give **2** (5.55 g) and **3** (4.25 g). Further elution with toluene (7 L) produced a mixture of sulfides (13.26 g) which was recrystallized (petroleum ether) to furnish pure **4** (R = Adm, 11.25 g). The mother liquors from all of the sulfide recrystallizations were combined and concentrated to produce a mixture (7.0 g) which was rechromatographed on silica gel (300 g); petroleum ether/ether (7:3, 0.5 L) eluted pure **2** (0.7 g), then **3** (2.3 g from 3.5 L), followed by **4** (0.95 g) from 1 L of petroleum ether/ether (1:1).

Elution with chloroform (8.5 L) from the *original* column yielded an oil (18.0 g) which was rechromatographed on a column of silica gel (300 g in chloroform). Initial elution of chloroform (0.5 L) produced an oil (not identified) and with the next 1 L an oil (10.8 g) which was recrystallized from the mixture of petroleum ether/ether (1:1) to furnish **5c** (4.8 g), mp 126–127 °C. Recrys-

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tallization from ether gave pure **5c** (3.84 g, 4.6%): mp 142–143 °C; TLC R_f 0.08 or 0.55 (solvent A or B); UV (95% EtOH) λ_{max} (log ϵ) 240 nm (4.01); IR (Nujol) 1740, 1720 (ester C=O), 1660 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.53 (dd, H-6), 5.95 (ddd, H-2), 5.18 (dd, H-3), 4.95 (ddd, H-4) ($J_{2,6} = J_{4,6} = 1.0$, $J_{2,3} = J_{3,4} = 2.1$ Hz), 2.19 (s, $NCOCH_3$), 2.14, 2.01 (s, $OCOCH_3$), 1.96, 1.68 (m, Adm), 1.77 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.1, 169.1, 167.5 (CO), 123.7 (C-6), 113.6 (C-5), 72.8 (C-3), 68.2 (C-4), 48.5 (C-2), 47.1, 43.5, 29.9, 36.4 (Adm), 21.6 (ring CH_3), 20.7, 17.4 (acyl CH_3); MS, 421 (1), 135 (100), 93 (31), 79 (32), 43 (57). Anal. Calcd for $C_{22}H_{31}NO_5S$: C, 62.68; H, 7.41; N, 3.32. Found: C, 62.61; H, 7.48; N, 3.24.

Hydrolysis of 5c was carried out as described for **6d**. The mixture of **5c** (0.3 g, 0.7 mmol) and sodium hydroxide (0.014 g, 0.35 mmole) in methanol (15 mL) was stirred (2 h) at 25 °C and worked up as previously to give the product (0.33 g, 100%) as an oil. Recrystallization from petroleum ether/ether (1:3) furnished pure **5d** (0.15 g, 61.3%): mp 156–157 °C; TLC R_f 0.17 (B); IR (Nujol) 3345 (OH), 1630 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) signal were relatively broad (the addition of D_2O produced a sharp spectrum) δ 6.35 (dd, H-6), 5.83 (ddd, H-2), 4.31 (dd, H-3), 3.62 (ddd, H-4) ($J_{2,3} = 2.4$, $J_{2,4} = J_{3,4} = 1.8$, $J_{2,6} = J_{4,6} = 1.2$ Hz), 2.19 (s, $NCOCH_3$), 1.97, 1.70 (m, Adm), 1.90 (s, CH_3); MS, 337 (1), 152 (58), 135 (34), 110 (100), 82 (50), 79 (28). Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15. Found: C, 64.10; H, 8.12; N, 4.00.

C. Reaction of 1 with *tert*-Butyl Mercaptan in Acetic Anhydride in the Presence of Triethylamine. In the prior experiment,[3] triethylamine was added to the reaction mixture last. In the experiment described below, the thiol was added last. In this experiment, triethylamine was always present in large excess. *tert*-Butyl mercaptan (48 mL, 0.45 mol) was added dropwise (20 min) to a warm solution (70 °C) of **1** (32.7 g, 0.3 mol) in acetic anhydride (300 mL) containing triethylamine (100 mL, 0.7 mol). The reaction temperature rose up to 110 °C but dropped after 10 min. The mixture was heated at 95 °C for 3 h. Volatile materials were removed in vacuo (5–10 torr) by controlling the bath temperature ~95 °C. The residue (56 g) was dissolved in toluene (10 mL) and placed onto the column of silica gel (600 g) in toluene. The initial elution of toluene (2 L) gave pyridyl sulfides which were not examined further. Ether (1.3 L) elution gave a mixture (3.5 g) as an oil whose separation is described below. Ether/chloroform (1:1, 1 L) eluted an oil (5.3 g) which was triturated with petroleum ether to give **6a** (3.1 g, 3.4%), mp 130–131 °C, after recrystallization from ether (–30 °C): mp 131–132 °C; TLC R_f 0.02 or 0.23 (solvent A or B); UV (95% EtOH) λ_{max} (log ϵ) 238 nm (4.08); IR (Nujol) 3440 (OH), 1710 (ester C=O), 1650 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.58 (dd, H-6), 5.72 (d, H-2), 5.42 (ddd, H-4), 4.94 (dd, H-5) ($J_{2,4} = J_{4,6} = 1.2$ $J_{4,5} = 2.4$, $J_{5,6} = 8.4$ Hz), 2.20 (s, $NCOCH_3$), 2.14 (s, $OCOCH_3$), 1.45 (s, CH_3), 1.39 (s, t-C_4H_9); ^{13}C NMR ($CDCl_3$) δ 170.1, 168.0 (CO), 126.4 (C-6), 107.0 (C-5), 70.8 (C-4) 70.2 (C-3), 61.9 (C-2), 44.7, 31.4 (t-C_4H_9), 23.6 (ring CH_3), 21.5, 20.8 (acyl CH_3); MS, 301 (6), 195 (23), 152 (73), 110 (100), 43 (50). Anal. Calcd for $C_{14}H_{23}NO_4S$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.69; H, 7.63; N, 4.51.

Elution of the *original* column with chloroform (2.8 L) produced a dark yellow solid (3.5 g), mp 116–117 °C, which was crystallized from ether (–30 °C) to furnish pure **6a** (2.0 g, 2.2%), mp 131–132 °C.

The mixture (3.5 g) isolated above was rechromatographed on silica gel (200 g) prepared in toluene/ether (1:1). Elution with the same solvent (0.5 L) gave a mixture (not identified) and then (1 L) gave **6a** (2.1 g) which was further purified by recrystallization from ether (1.2 g, 1.3%).

Acetylation of 6a (0.2 g, 0.5 mmol) was accomplished with boiling acetic anhydride (5 mL) for 5 h. Solvents were removed in vacuo to furnish pure **6b** (0.18 g, 80%) as an oil: TLC R_f 0.05 or 0.57 (solvent A or B); ^1H NMR ($CDCl_3$) δ 6.65 (dd, H-2), 6.58 (ddd, H-6), 5.54 (ddd, H-4), 4.91 (dd, H-5) ($J_{2,4} = J_{2,6} = J_{4,6} = 1.0$, $J_{4,5} = 2.0$, $J_{5,6} = 8.0$ Hz), 2.15 (s, $NCOCH_3$), 2.05, 1.97 (s, $OCOCH_3$), 1.75 (s, CH_3), 1.41 (s, t-C_4H_9); MS, 343 (3), 194 (31), 152 (41), 110 (100), 82 (28), 43 (94). Anal. Calcd for $C_{16}H_{25}NO_5S$: C, 55.97; H, 7.34; N, 4.08. Found: C, 56.06; H, 7.30; N, 4.16.

Hydrolysis of 6a (0.3 g, 0.99 mmol) was carried out with sodium hydroxide (0.02 g, 0.5 mmol) in methanol (5 mL). The mixture was stirred at 25 °C for 4 h and methanol was removed in vacuo. The residue was neutralized with dilute hydrochloric acid and worked up as for **6d** to afford the product (0.25 g): mp 150–152 °C; TLC R_f 0.09 (solvent B). Recrystallization from ether yielded **6c** (0.17 g, 65.9%): mp 160–161 °C; IR (Nujol) 3420, 3320 (OH), 1630 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.47 (ddd, H-6), 5.72 (ddd, H-2), 5.02 (ddd, H-5), 4.14 (ddd, H-4) ($J_{2,4} = J_{4,6} = J_{2,5} = 1.2$, $J_{4,5} = 1.6$, $J_{5,6} = 8.0$ Hz), 2.38 (br, OH), 2.19 (s, $NCOCH_3$), 1.52 (s, CH_3), 1.39 (s, t-C_4H_9); MS, 259 (6), 170 (31), 152 (83), 128 (40), 110 (100), 57 (27), 43 (58). Anal. Calcd for $C_{12}H_{21}NO_3S$: C, 55.57; H, 8.16; N, 5.40. Found: C, 55.31; H, 7.97; N, 5.28.

D. Reaction of 1 with *tert*-Butyl Mercaptan in Acetic Anhydride. The reaction condition was similar to C. *tert*-Butyl mercaptan (48 mL, 0.45 mol) was added dropwise to a warm solution of **1** (32.7 g, 0.3 mol) in acetic anhydride (300 mL). The reaction mixture was heated (3 h) at 95 °C. The crude oil (68 g, after distillation at 95 °C (5 torr)) was placed onto a column of silica gel (600 g) prepared in toluene. After elution of some pyridyl sulfides (3 L), toluene (4 L) and then 1.5 L of toluene/ether (4:1) brought forth an oil (13.0 g) which was rechromatographed on silica gel (300 g) in petroleum ether. Initial elution with the same solvent (1 L) and then 2 L of petroleum ether/ether (2:1) gave a mixture which was not identified. Further elution with 1.5 L of the solvent mixture (1:1) furnished an oil (11.5 g) which was recrystallized from ether to provide **5a** (4.3 g, 4.2%): mp 125–126 °C [lit.[3] mp 123–124 °C]; TLC R_f 0.11 or 0.70 (solvent A or B); UV (95% EtOH) λ_{max} (log ϵ) 238 nm (4.06) reported[3] in hexane λ_{max} 239 (4.25) 200 (3.96); IR (Nujol) 1750, 1740 (ester C=O), 1660 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.55 (dd, H-6), 5.97 (ddd, H-2), 5.20 (dd, H-3), 4.99 (ddd, H-4) ($J_{2,3} = J_{3,4} = 2.0$, $J_{2,4} = J_{2,6} = J_{4,6} = 1.0$ Hz), 2.20 (s, $NCOCH_3$), 2.14, 2.01 (s, $OCOCH_3$), 1.78 (s, CH_3), 1.39 (s, t-C_4H_9). Although there were chemical shift differences to the ^1H NMR spectra reported in C_5D_5N[3] the coupling constants in either solvent were of similar magnitude.

The last elution with 4 L of chloroform from the *original* column gave a solid (2.0 g) which proved to be 3-methyl-2-pyridone. Recrystallization from ether gave 0.9 g (2.7%): mp 136–137 °C [lit.[13] mp 142–142 °C]; TLC R_f 0.25 (solvent B). This byproduct would be one of the products expected when **1** is reacted alone with acetic anhydride.[13]

Hydrolysis of 5a (0.3 g, 0.87 mmol) with Sodium Hydroxide (0.018 g, 0.4 mmol) in Methanol (15 mL). The reaction was stirred (1 h) at 25 °C and worked up as described in A to yield (0.23 g, 100%) product. Recrystallization from ether gave pure **5b** (0.18 g, 80%): mp 133–134 °C; TLC R_f 0.14 (solvent B); IR (Nujol) 3460, 3415 (OH), 1635 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) signals were relatively broad (the addition of D_2O produced a sharp spectrum) δ 6.35 (ddd, *H*-6), 5.80 (ddd, H-2), 4.32 (ddd, H-3), 3.66 (ddd, H-4) ($J_{2,3} = 2.4$, $J_{2,4} = J_{3,4} = 1.8$, $J_{2,6} = J_{3,6} = J_{4,6} = 1.2$ Hz), 2.20 (s, $NCOCH_3$), 1.88 (s, CH_3), 1.41 (s, t-C_4H_9); MS, 259 (2), 152 (33), 110 (100), 82 (61), 57 (36). Anal. Calcd for $C_{12}H_{21}NO_3S$: C, 55.57; H, 8.16; N, 5.40. Found: C, 55.57; H, 8.12; N, 5.33.

Registry No. **1**, 1003-73-2; **2** (R = 1-Adm), 94957-79-6; **2** (R = t-C_4H_9), 18833-87-9; **3** (R = 1-Adm), 94957-80-9; **3** (R = t-C_4H_9), 18794-46-2; **4** (R = 1-Adm), 94957-81-0; **4** (R = t-C_4H_9), 18794-47-3; **5a**, 31571-05-8; **5b**, 94957-90-1; **5c**, 94957-85-4; **5d**, 94957-86-5; **6a**, 94957-87-6; **6b**, 94957-88-7; **6c**, 94957-89-8; **6d**, 94957-82-1; **6e**, 94957-83-2; **6f**, 94957-84-3; 1-adamantyl mercaptan, 34301-54-7; *tert*-butyl mercaptan, 75-66-1.

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