Revised Structures of Some Tetrahydropyridines Isolated from the Reaction of Pyridine *N*-Oxides with Mercaptans and Acid Anhydrides[1,2]

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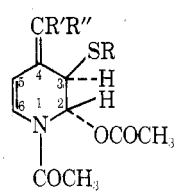
The structures of a number of previously reported tetrahydropyridines were revised. These were established to be 1-acetyl-2-alkylthio-3-hydroxy-4-alkylidene-1,2,3,4-tetrahydropyridines and 1-acetyl-2,6-bis(alkylthio)-3-hydroxy-1,2,3,6-tetrahydropyridines and their corresponding acetoxy derivatives. The change from the published structures involved reversal of the sulfide and oxy functions at C-2 and C-3 in these tetrahydropyridines.

The reaction of pyridine 1-oxides with mercaptans in acetic anhydride afforded a variety of tetrahydropyridyl sulfide esters.[3-5] Two of the most frequently isolated series of tetrahydropyridines were represented by structures **1** and **2**.[5]



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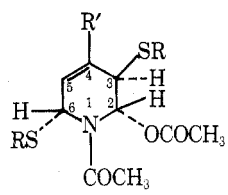

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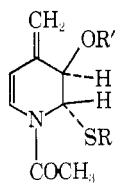
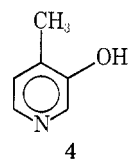
New evidence reported in this paper reverses the substituents at C-2 and C-3 in both series and these compounds will then be referred to as shown in **3** and **5**, respectively. Structures based on **3** are discussed first, because their proton magnetic resonance (^{1}H NMR) spectra are considerably less complicated than those of **5**.

The reaction of 4-picoline 1-oxide with *tert*-butyl mercaptan[5] *or* 1-adamantanethiol (1-AdmSH) in acetic anhydride containing triethylamine provided **3a** [previously formulated as **1**[5] (R = *t*-C_4H_9; R′ = R″ = H)] and **3b**, respectively. Mild alkaline hydrolysis of these esters produced **3c** and **3d**. An analysis of the ^{1}H NMR spectra of these four





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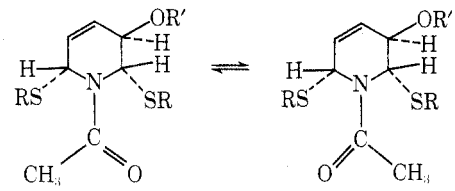
3a, R = *t*-C_4H_9; R′ = $COCH_3$
b, R = 1-Adm; R′ = $COCH_3$
c, R = *t*-C_4H_9; R′ = H
d, R = 1-Adm; R′ = H

compounds revealed remarkable similarities. The assignment of chemical shifts for the four ring protons utilized data reported previously.[5] With the assumption that the signal furthest downfield in **3** was due to H-6 and with the aid of a series of decoupling experiments, the chemical shifts of the ring protons were established. Since H-3 was the proton which experienced an upfield shift of about 1 ppm when the esters were converted to the alcohols (-CHOAc → -CHOH), the oxygenated functions in **3** must be attached to C-3. Attempts to obtain ^{1}H NMR spectra of the alcohols, **3c** and **3d**, which would show $J_{H\text{-}3,OH}$, proved unsuccessful.[6] Chemical transformations supported the structure of **3**. Hydrolysis with excess sodium hydroxide converted **3a** or **3c** to a mixture of 4-methyl-3-pyridinol and 2-*tert*-butylthio-4-picoline. Although these data support the structure of **3**, there remains the question of why **3a** pyrolyzed to provide 3-*tert*-butylthio-4-picoline.[5,7a] The mass spectra of the esters or alcohols, **3**, were consistent with their structure. The molecular ion lost the thiyl radical, RS·, followed by losses of ketene, and HO· to produce the molecular ion of 4-picoline, *m/e* 93.

The reaction of a number of pyridine *N*-oxides with *tert*-butyl mercaptan in acetic anhydride without triethylamine produced a series of tetrahydropyridines[3,4] whose structure is represented by **5**. Mild alkaline hydrolysis of these esters



A B

5a, R = *t*-C_4H_9; R′ = $COCH_3$
b, R = *n*-C_4H_9; R′ = $COCH_3$
c, R = 1-Adm; R′ = $COCH_3$
d, R = *t*-C_4H_9; R′ = H
e, R = *n*-C_4H_9; R′ = H
f, R = 1-Adm; R′ = H

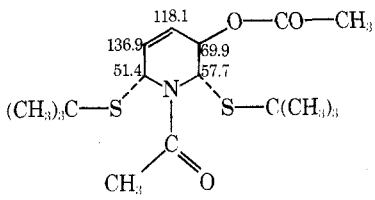
furnished the corresponding alcohols which were also easily reacetylated to the starting esters. The chemical shift of the ring protons of **5a-c** were between 6.6 and 5.8 ppm while in the ^{1}H NMR spectra of the alcohols one of the ring proton signals moved upfield to ~4.5 ppm. This spectral behavior resembled that observed in series **3**.

However, since the ^{1}H NMR spectra of **5** showed rotamers A and B (due to the $NCOCH_3$ group), analyses of these spectra was unduly complicated.[4] By means of an analysis of the 2,6-d_2 analog of **5d**, and a series of decoupling experiments on **5d** and **5f**, it was established that the signal in the 4.5-ppm region arose from H-3. Again, no coupling between H-3 and the OH proton could be observed. In addition, chemical evidence was obtained which supports **5**. Prolonged hydrolysis under alkaline conditions converted **5d** and **5f** to their respective 2-alkylthiopyridines in good yields.[7b]

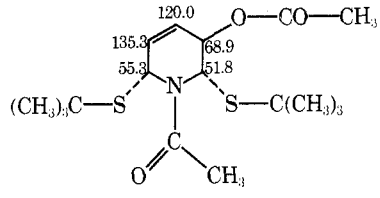
The carbon-13 magnetic resonance (^{13}C NMR) spectra were in accord with structure **5**. Signals due to the various carbons were recorded with the anticipated shifts[8a-f] and those pertinent to the structure proof are discussed only. A full discussion of the ^{13}C NMR spectra of **5a** and **5d** is pre-

Chart I
Carbon-13 Shifts [Parts per Million from $Si(CH_3)_4$] of the Two Rotamers of 5a and 5d

AcCO, 170.4, 167.9
$AcCH_3$, 20.9, 20.9
tert-butyl C, 45.4, 45.4
tert-butyl CH_3, 31.4, 31.4



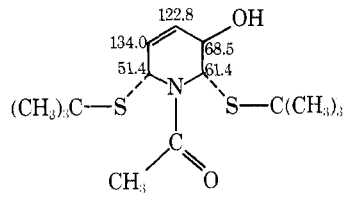
Major rotamer A of **5a**



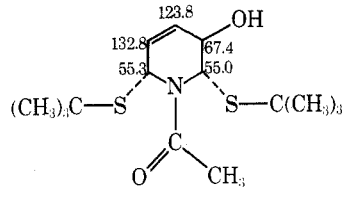
Minor rotamer B of **5a**

AcCO, 170.1, 169.4
$AcCH_3$, 22.4, 21.8
tert-butyl C, 45.3, 45.1
tert-butyl CH_3, 31.9, 31.7

AcCO, 169.3
$AcCH_3$, 22.1
tert-butyl C, 45.0, 45.0
tert-butyl CH_3, 31.4, 31.4



Major rotamer A of **5d**

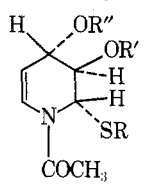


Minor rotamer B of **5d**

AcCO, 170.7
$AcCH_3$, 22.1
tert-butyl C, 45.0, 45.0
tert-butyl CH_3, 31.9, 31.7

sented. From the ^1H NMR spectra, it was determined that rotamer A predominated in $CDCl_3$. Thus, it was possible to sort the duplicate set of ^{13}C resonances to those belonging to A and B of **5a** and **5d**, respectively (Chart I). Chemical shift assignments for the sp^3 ring carbons, C-2 and C-6, was in terms of the anisotropic effect of the amide C=O in rotamer A or B and these are the signals between 51 and 61 ppm. Thus, the signals around 69 ppm arose from the carbinol carbon at C-3 in **5a** and **5d**. The alkene carbon assignments were based on the "β effect" reported for alcohols and their corresponding esters.[8c-f] Briefly, this refers to the relative shifts of the ^{13}C β to the carbinol carbon (which is considered as the α carbon). In system **5**, C-2 and C-4 are "β" carbons, C-5, a "γ" carbon. Thus, in converting the alcohol, **5d**, to the corresponding acetate, **5a**, the "β" carbons exhibited upfield shifts and the "γ" carbons a downfield shift. All other signals in these systems were remarkably constant and are assigned in Chart I.

It was found that[3] the use of *tert*-butyl mercaptan in this deoxidative substitution reaction of pyridine 1-oxide in acetic anhydride produced almost exclusively **5a**. If triethylamine was added to such a reaction mixture, **6a** was isolated as the predominant tetrahydropyridine.[5] However, a



6a, R = *t*-C_4H_9; R′ = R″ = $COCH_3$
b, R = *t*-C_4H_9; R′ = R″ = H
c, R = *n*-C_4H_9; R′ = R″ = $COCH_3$
d, R = *n*-C_4H_9; R′ = H; R″ = $COCH_3$
e, R = 1-Adm; R′ = R″ = $COCH_3$
f, R = 1-Adm; R′ = H; R″ = $COCH_3$
g, R = 1-Adm; R′ = R″ = H

study using two other mercaptans showed that the nature of the tetrahydropyridines could vary. When *n*-butyl mercaptan or 1-adamantanethiol were used in this reaction with pyridine 1-oxide and the temperature of the reaction kept below 80°, products in the **5** series were isolated almost exclusively. However, when the temperature was permitted to rise initially to 110°, these reactions yielded predominantly **6**. The products **6c** had been isolated previously when *n*-butyl mercaptan and triethylamine had been employed.[5] The tetrahydropyridine **6e** had been reported when 1-adamantanethiol had been utilized, with or without triethylamine.[10] In conclusion, it was found that tetrahydropyridines, **5**, were the major products when the temperature was controlled and not permitted to rise initially above 80°.

Experimental Section

Apparati and starting materials used here were described previously.[5] The generous gifts of pyridine and picoline *N*-oxides from Reilly Tar and Chemical Co. and *n*- and *tert*-butyl mercaptans from Phillips Petroleum and the Pennsalt Chemical Co. are gratefully acknowledged. Extreme caution had to be taken in handling *tert*-butyl mercaptan since its odor warns of gas leaks.[5]

1-Adamantanethiol. Considerable difficulty was experienced in recrystallizing and drying this waxy solid. The following modification of the published method[9] provided good yields of pure starting material.

A suspension of *S*-(1-adamantyl)isothiuronium bromide (110 g, 0.36 mol) was stirred for 18 hr at 25° with 5% sodium hydroxide (700 ml) and the mixture then acidified (pH 2) with concentrated hydrochloric acid. The white solid was extracted with benzene (3 × 200 ml) and dried (K_2CO_3), and the benzene removed in vacuo to yield pure thiol (61.5 g, quantitative).

Thin Layer Chromatography. The R_f values were determined on Eastman Chromagram 13181 silica gel sheets with a fluorescent indicator (no. 6060) using the following solvent systems (designated by letters): petroleum ether–ether, 7:3 (A); ether (B).

A. Reaction of 1-Adamantanethiol with Pyridine 1-Oxide. Previous experiments[10] described the isolation of **6e** and **6f**, irrespective of whether or not triethylamine was included in the reaction mixture. It is now reported that with or without triethylamine, that besides **6e** and **6f**, the tetrahydropyridines, **5c** and **5f**, were also isolated. Reexamination of the reaction conditions revealed that the relative proportion of members of the series **5** and **6** depended on the temperatures employed for the reaction. The present work describes the isolation of a number of tetrahydropyridinols. These arose from the hydrolysis of the corresponding acetates during slow chromatographic separations on alumina. The initial crude reaction mixtures contained no tetrahydropyridinols (TLC). The proportion of alcohols to acetates very much depended upon column contact time. Although one of the possible hydroxy acetates, **6f**, was isolated previously from a similar reaction,[10] the corresponding diol (**6g**), whose independent synthesis is described below, was never isolated from a column, even after a prolonged contact time (4 days).

1-Adamantanethiol (18.0 g, 0.1 mol) was added to a solution of distilled pyridine 1-oxide (9.5 g, 0.1 mol) in acetic anhydride (180 ml). The solution was immediately placed in a water bath at 75°, whereupon the temperature rose to 85° for 5 min and then fell to 75°. After an additional 3 hr at 75°, solvents were removed at 20 Torr (water bath 75°). The residue was cooled and stirred at 25° for 1 hr with 100 ml of 50% aqueous potassium carbonate solution to remove acidic by-products and the water-soluble pyridine *N*-oxide. The organic layer was extracted with benzene and dried (K_2CO_3) and the solvent was removed (20 Torr). The oil (25 g) was dissolved in benzene and chromatographed on alumina (Alcoa

F-20, 400 g). The first benzene fractions contained 2- and 3-pyridyl 1-adamantyl sulfides, 1-adamantanethiol, and its acetate.[10] These were not examined further. The later benzene fractions, after evaporation and addition of petroleum ether, yielded pure **5c** (3.0 g): TLC (A) R_f 0.21; mp 196–198°; ^{1}H NMR (C_5D_5N) for rotamer A of **5c**, δ 6.73 (H-2), 5.57 (H-3), ~6.06 (H-4), 6.30 (H-5), 5.57 (H-6) ($J_{2,3}$ = 2.0, $J_{2,4}$ = 1.0, $J_{3,4}$ = 6.0, $J_{4,5}$ = 10.0, $J_{4,6}$ = 2.0, $J_{5,6}$ = 3.5 Hz); for rotamer B of **5c** δ 5.61 (H-2), 5.45 (H-3), ~6.16 (H-4), 6.25 (H-5), 6.42 (H-6) ($J_{2,3}$ = 2.0, $J_{2,4}$ = 1.0, $J_{3,4}$ = 6.0, $J_{4,5}$ = 10.0, $J_{4,6}$ = 2.0, $J_{5,6}$ = 3.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 515 (1), 348 (9), 288 (9), 246 (10), 245 (7), 180 (0.5), 168 (2), 135 (100), 93 (16), 79 (23); it is not surprising that the *m/e* 135 ion (1-Adm$^+$) is the base peak in this adamantane derivative.[11] Again, the (M − SR) ion is visible and the loss of acetic acid (348 → 288) is accompanied by a large metastable ion (m*, 238.3). Another prominent m* was observed for the subsequent loss of ketene (288 → 246; m* 210.1). Anal. Calcd for $C_{29}H_{41}NO_3S_2$: C, 67.55; H, 8.01; N, 2.72. Found: C, 67.54; H, 7.99; N, 2.69.

Further elution of this column with chloroform (2 l.) provided a residue which was stirred with petroleum ether to separate **5f** (0.60 g): TLC (B), R_f 0.36; mp 200–201°; ^{1}H NMR (C_5D_5N) for rotamer A of **5f**, δ 6.62 (H-2), 4.69 (H-3), 6.29 (H-4), 6.17 (H-5), 5.64 (H-6) ($J_{2,3}$ = 1.5, $J_{2,4}$ = 1.0, $J_{3,4}$ = 5.2, $J_{4,5}$ = 10.0, $J_{4,6}$ = 1.0, $J_{5,6}$ = 2.5 Hz); rotamer B of **5f** δ 5.54 (H-2), 4.58 (H-3), 6.13 (H-4), 6.11 (H-5), 6.38 (H-6) ($J_{2,3}$ = 1.5, $J_{2,4}$ = 0.5, $J_{3,4}$ = 3.0, $J_{4,5}$ = 10.0, $J_{4,6}$ = 2.0, $J_{5,6}$ = 2.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 473 (2), 306 (22, M − 1-AdmS), 288 (3, M − 1-AdmS − H_2O), 264 (5), 230 (3), 168 (1), 154 (2), 138 (32, M − 1-AdmS − 1-AdmSH), 136 (10), 135 (100), 96 (32), 93 (22), 80 (18), 79 (25). Anal. Calcd for $C_{27}H_{39}NO_2S_2$: C, 68.47; H, 8.30; N, 2.96. Found: C, 68.63; H, 8.19; N, 2.91.

The petroleum ether filtrates from **5f** were evaporated to yield 3-(1-adamantanethio)pyridine (0.61 g), after recrystallization from petroleum ether, TLC (A), R_f 0.44, mp 90.5–91.5° (lit.[10] mp 87–90°). Subsequent chloroform eluates (1 l.) and methanol eluates (0.5 l.) from this original column gave, after crystallization from acetone, pure **6f**[10] (0.5 g), TLC (B), R_f 0.49, mp 191–192° (lit.[10] mp 194–195°).

In order to recover more of compounds of series **5**, the mother liquors of some of the original benzene fractions (those containing **5c**) were rechromatographed on alumina (800 g). Elution with petroleum ether–benzene (1:1, 6 l.) provided first 2-(1-adamantanethio)pyridine (7.4 g), TLC (A), R_f 0.73, mp 82° (lit.[10] mp 82°). Final elution with methanol (0.5 l.) yielded, after crystallization from acetone, pure **5f** (0.80 g).

Based on pyridine 1-oxide, the yield of **5c** was 5.7%, **5f** was 3.0%, and **6f** was 1.4%.

B. Reaction of Pyridine 1-Oxide with *n*-Butyl Mercaptan. The original experiment was conducted in boiling acetic anhydride and no attempt was made to isolate tetrahydropyridines.[12] The success of the present experiment depended on moderating the temperature of the reaction, since it was discovered that these particular tetrahydropyridines were more prone to thermal decomposition than either the *tert*-butyl or the 1-adamantyl analogs. Furthermore, chromatographic separations of the more polar fractions became essential since a large portion of the acetoxy derivatives were hydrolyzed on the alumina to the corresponding polar tetrahydropyridinols.

The thiol (33 ml, 0.33 mol) was added to a stirred solution of distilled pyridine 1-oxide (9.5 g, 0.1 mol) in acetic anhydride (100 ml) at 25°. The temperature rose spontaneously to 80° (5 min) and when the temperature commenced to drop (15 min) the mixture was heated on a steam bath for an additional 1 hr. The mixture was concentrated in vacuo (20 Torr) at a temperature below 75°, then distilled at 0.01 Torr (oil bath ≤60°) to remove pyridyl sulfides and acetates.[12] These distillates were not examined further. Higher oil bath temperatures were avoided to prevent potential pyrolyses of the desired tetrahydropyridines. The residue (25 g) was dissolved in petroleum ether, filtered to remove precipitates, and placed on a column of alumina (Alcoa F-20, 450 g), prepared in petroleum ether. Petroleum ether and benzene eluted primarily 2- and 3-pyridyl sulfides.[12] The first chloroform fraction (1 l.) produced 2.2 g of oil which consisted of a mixture of **5b** (major) [TLC (A), R_f 0.41] with some **5e** [TLC (B), R_f 0.53] with minor quantities of **6c**[5] [TLC (A), R_f 0.29] and the unreported hydroxy acetate, **6d.** This compound was isolated pure from the chloroform fractions of a previously described experiment:[5] TLC (B), R_f 0.59; mp 108–109°; ^{1}H NMR (C_5D_4N) δ 6.42 (H-2), 4.82 (H-3), 5.50 (H-4), 5.40 (H-5), 7.06 (H-6), 7.82 (OH) ($J_{2,3}$ = 2.5, $J_{2,4}$ = 1.2, $J_{2,6}$ ~ 1, $J_{3,4}$ = 1.4, $J_{3,5}$ = 1.8, $J_{4,5}$ = 4.6, $J_{4,6}$ = 1.2, $J_{5,6}$ = 8.2, $J_{3,OH}$ = 4.6 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 287 (6, M$^+$), 96 (100). Anal. Calcd for $C_{13}H_{21}NO_4S$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.38; H, 7.44; N, 4.97. Attempts to separate **6d** by crystallization provided impure fractions and this mixture was not rechromatographed further.

Additional chloroform fractions (3.5 l.) provided 3.6 g which consisted primarily of **5e** which contained a trace (TLC) of the hydroxy acetate, **6d.** Additional quantities of pure **5e** (4.1 g) were obtained from chloroform–methanol eluates (95:5, 4 l.).

An analytical sample was recrystallized from ether at −78°, mp 50–52°. The ^{1}H NMR spectrum was unduly complicated because of rotamers. The pattern between δ 6.20 and 5.10 ($CDCl_3$) for four of the five ring protons was identical with that for **5f** in $CDCl_3$ and that for H-3 of A and B was at δ 4.25 and the OH proton δ 4.45 (exchangeable with D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 318 (2), 317 (10, M$^+$), 228 (79, M − C_4H_9S), 210 (6), 186 (63), 138 (71, M − C_4H_9S − C_4H_9SH), 113 (11), 96 (100, M − C_4H_9S − C_4H_9SH − CH_2=C=O), 80 (58). Anal. Calcd for $C_{15}H_{27}NO_2S_2$: C, 56.77; H, 8.57; N, 4.41. Found: C, 56.62; H, 8.69; N, 4.38.

The total yield of crude **5b** was estimated to be 6.2% and that of **5e** was 24%, based on pyridine 1-oxide.

C. Reaction of 4-Picoline 1-Oxide with 1-Adamantanethiol in the Presence of Triethylamine. 1-Adamantanethiol (61.5 g, 0.35 mol) was added to a solution of 4-picoline 1-oxide (33.2 g, 0.35 mol) and triethylamine (84 ml, 0.60 mol) in acetic anhydride (400 ml). The reaction was worked up as in procedure A and the residue (114 g) chromatographed over 2 kg of F-20 alumina. The first benzene fractions contained 1-adamantanethiol and its acetate and were not examined further. Further benzene fractions (4 l.) yielded, after crystallization with petroleum ether, pure **3b** (2.5 g): TLC (A), R_f 0.36; mp 126–128°; ^{1}H NMR ($CDCl_3$) δ 6.00 (H-2), 5.40 (H-3), 5.60 (H-5), 6.50 (H-6), 5.22 (H-7, 7′) ($J_{2,3}$ = 2.9, $J_{2,6}$ ~ 1.0, $J_{3,5}$ = 1.5, $J_{5,6}$ = 8.0, $J_{5,7}$ = $J_{5,7'}$ ~ 1.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 361 (3), 302 (4), 301 (<1), 260 (6), 194 (57), 152 (100), 135 (33), 110 (80), 93 (32), 79 (13). Anal. Calcd for $C_{20}H_{27}NO_3S$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.61; H, 7.66; N, 3.71.

The last benzene fractions (8 l.) gave 3-(1-adamantanethio)-4-picoline (2.0 g), purified by vacuum sublimation (0.01 Torr, 50°): TLC (A), R_f 0.37; mp 70–72°; ^{1}H NMR ($CDCl_3$) δ 8.70 (H-2), 8.45 (H-6), 7.23 (H-5), 2.50 (CH_3), 2.30–1.50 (Adm-H) ($J_{5,6}$ = 5.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 259 (20), 135 (100), 107 (13), 93 (12), 79 (32). Anal. Calcd for $C_{16}H_{21}NS$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.93; H, 8.27; N, 5.25.

The residues from the chloroform eluates (20 l.) were triturated with petroleum ether and gave **3d** (4.0 g) which was recrystallized from ether (charcoal): TLC (B), R_f 0.44; mp 191–192°; ^{1}H NMR ($CDCl_3$) δ 6.00 (H-2), 4.40 (H-3), 5.65 (H-5), 6.50 (H-6), 5.22 (H-7, 7′), 3.40 (OH) ($J_{2,3}$ = 2.9, $J_{2,6}$ ~ 1.0, $J_{3,5}$ = 1.5, $J_{5,6}$ = 8.0, $J_{5,7}$ = $J_{5,7'}$ = 1.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 319 (22), 302 (25), 260 (6), 152 (100), 135 (34), 110 (75), 93 (40), 82 (55). Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.50; H, 8.02; N, 4.27.

The petroleum ether soluble portion of the residue from the last benzene fractions was rechromatographed over 400 g of F-20 alumina. Petroleum ether–benzene (1:1, 3.5 l.) gave pure 2-(1-adamantanethio)-4-picoline (8.3 g): TLC (A), R_f 0.21; mp 72–73°; ^{1}H NMR ($CDCl_3$) δ 8.35 (H-6), 7.20 (H-3), 6.90 (H-5), 2.25 (CH_3), 2.30–1.60 (Adm-H) ($J_{5,6}$ = 5.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 259 (44), 258 (60), 226 (21), 135 (100), 126 (16), 125 (19), 107 (16), 93 (26), 92 (18), 91 (18), 79 (43). Anal. Calcd for $C_{16}H_{21}NS$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.12; H, 8.22; N, 5.17.

The residues from the methanol fraction were recrystallized from petroleum ether to produce more **3d** (1.4 g), mp 189–190°. The yield of **3b** was 2.5 g (2.0%) and the total yield of **3d** was 5.4 g (4.8%), based on 4-picoline 1-oxide.

D. Hydrolysis of Acetates. The ester **5c** (0.30 g, 5.8 × 10^{-4} mol) was dissolved in warm methanol (50 ml), the solution cooled to 25°, and methanolic sodium hydroxide (0.75 ml, 0.012 g NaOH) added. The solution was concentrated to 20 ml at 25° (20 Torr) and poured onto 50 g of cracked ice. The precipitate was filtered and washed with water to give **5f** (250 mg, 93%), mp 198–200°, identical with the specimen described in procedure A.

A similar hydrolysis of **5a** (1.2 g) gave **5d** (1.01 g, 95%): mp 117–119°; ^{1}H NMR (C_5D_5N) for rotamer A of **5d** δ 6.54 (H-2), 4.61 (H-3), 6.20 (H-4), 6.20 (H-5), 5.56 (H-6) ($J_{2,3}$ = 2.0, $J_{3,4}$ = 3.5 Hz), for rotamer B of **5d** δ 5.46 (H-2), 4.56 (H-3), 6.08 (H-4), 6.08 (H-5), 6.36 (H-6); mass spectrum (70 eV) *m/e* (rel intensity) 317 (5), 260 (2), 228 (44), 210 (1), 186 (11), 172 (10), 138 (47), 130 (23), 113 (11),

112 (9), 96 (100), 80 (33). The major fragments from the molecular ion were successive losses of C_4H_9S, C_4H_9SH, and ketene. Anal. Calcd for $C_{15}H_{27}NO_2S_2$: N, 4.41. Found: N, 4.39.

When the crude reaction mixture from a reaction of pyridine 1-oxide (9.5 g, 0.10 mol), *tert*-butyl mercaptan, and acetic anhydride[3] (after removal of solvents at 20 Torr) was worked up as described under procedure A, it yielded **5a** as expected.[3] However, chromatography (contact time 4 days) over 450 g of F-20 alumina yielded only **5d** (2.2 g, 6.9% based on pyridine 1-oxide), mp 117–119°, as a result of complete hydrolysis of the ester on the column.

Hydrolysis of **5a**-2,6-d_2[4] (0.18 g) was carried out by refluxing with potassium bicarbonate (0.028 g) in methanol (5.0 ml) for 3 hr. Removal of the solvent (20 Torr) and crystallization of the residue with petroleum ether gave **5d**-2,6-d_2 (0.062 g, 39%): TLC (B), R_f 0.31; mp 117–118°; ^{1}H NMR (C_5D_5N) for rotamer A of **5d**-2,6-d_2, δ 4.64 (H-3), 6.20 (H-4), 6.20 (H-5); rotamer B of **5d**-2,6-d_2, δ 4.56 (H-3), 6.08 (H-4), 6.08 (H-5); mass spectrum (70 eV) *m/e* (rel intensity) 320 (1), 319 (6), 318 (1), 262 (3), 230 (51), 212 (3), 188 (21), 174 (11), 140 (52), 132 (30), 131 (12), 115 (10), 114 (10), 113 (8), 98 (100), 97 (16), 82 (33).

Hydrolysis of **3a** (1.70 g) gave **3c** (after extraction with chloroform, 1.35 g, 93%): mp 137–138°; ^{1}H NMR (C_5D_5N) δ 5.88 (H-2), 4.32 (H-3), 5.59 (H-5), 6.51 (H-6), 5.13, 5.17 (H-7, 7′), 3.40 (OH) ($J_{2,3}$ = 3.0, $J_{2,6}$ = 1.5, $J_{3,5}$ = 1.5, $J_{5,6}$ = 8.0, $J_{5,7}$ = $J_{5,7'}$ ~1.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 242 (6), 241 (30), 224 (9), 182 (4), 152 (100), 110 (90), 109 (15), 93 (21), 92 (15), 82 (70), 80 (27). Anal. Calcd for $C_{12}H_{19}NO_2S$: N, 5.80. Found: 5.77.

A similar hydrolysis of **3b** (0.36 g) gave **3d** (0.32 g, 100%), mp 188–189°, identical with the sample in procedure C.

Hydrolysis of bisacetate **6e** (0.80 g) with $KHCO_3$ (0.24 g) in refluxing methanol gave diol **6g** (0.55 g, 86%): mp 164–165°; TLC (B), R_f 0.25; ^{1}H NMR ($CDCl_3$) δ 5.95 (H-2), 4.36 (H-3), 3.90 (H-4), 5.35 (H-5), 6.70 (H-6), ~3.30 (OH) ($J_{2,3}$ ~ 1.0, $J_{3,5}$ = 1.8, $J_{4,5}$ = 4.5, $J_{5,6}$ = 8.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 323 (5), 156 (6), 138 (41), 135 (43), 114 (9), 96 (39), 79 (25), 78 (100). Anal. Calcd for $C_{17}H_{25}NO_3S$: N, 4.33. Found: N, 4.11.

Diol **6g** was similarly obtained by the hydrolysis of the hydroxy acetate **6f**.[10]

Hydrolysis of bisacetate **6a** (2.0 g, 6.1 × 10^{-3} mol) with $KHCO_3$ (0.61 g) in refluxing methanol gave diol **6b** (1.3 g, 86%): TLC (B), R_f 0.23; mp 109–110°; ^{1}H NMR ($CDCl_3$) δ 5.90 (H-2), 4.36 (H-3), 3.90 (H-4), 5.35 (H-5), 6.70 (H-6), ~3.30 (OH) ($J_{2,3}$ = 1.5, $J_{3,5}$ = 1.8, $J_{4,5}$ = 4., $J_{5,6}$ = 8.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 245 (10), 156 (14), 138 (45), 114 (24), 96 (100), 86 (8), 84 (7), 80 (3). Anal. Calcd for $C_{11}H_{19}NO_3S$: N, 5.71. Found: N, 5.58.

E. Acetylation of Alcohols. Alcohol **5f** (2.0 g, 4.2 × 10^{-3} mol) was dissolved in pyridine (10 ml) and acetic anhydride (10 ml) added. After 18 hr at 25°, the mixture was diluted with water (100 ml) and the solid filtered and washed with water to give **5c** (2.1 g, 96%), mp 201–202°.

Alcohol **5e** (1.0 g, 3.2 × 10^{-3} mol) was similarly acetylated. From the ether extract was obtained **5b** (1.1 g, 100%), pure by TLC and ^{1}H NMR. Attempts to distil the oil (0.01 Torr, 50°) resulted in partial decomposition and codistillation of 3-*n*-butylthiopyridine.[5] Crystallization from ether (−78°) gave a white solid: mp ~−20°; TLC (A), R_f 0.41; the ^{1}H NMR ($CDCl_3$) spectrum for the four ring protons is identical with that of **5a** in $CDCl_3$ absorbing as multiplets, δ 6.4–5.7 and 5.5–5.1; mass spectrum (70 eV) *m/e* (rel intensity) 359 (2), 270 (9), 210 (32), 180 (4), 168 (100), 112 (14), 96 (43), 80 (65). Anal. Calcd for $C_{17}H_{29}NO_3S_2$: N, 3.90. Found: N, 3.90.

Similar acetylations of **5d**, **3c**, and **3d** gave **5a** (88%), **3a** (65%), and **3b** (56%), respectively.

Extensive Hydrolysis. A solution of **3a** (1.44 g, 0.004 mol) in methanol (35 ml) containing sodium hydroxide (3.2 g, 0.08 mol) was refluxed for 1 hr. Methanol was removed, and the residue was diluted with water. Extraction with chloroform provided a mixture (0.094 g) which contained a small quantity of 2-*tert*-butylthio-4-picoline[14] (identified by TLC). The basic solution was neutralized with dilute hydrochloric acid and reextracted with chloroform. This extract yielded 4-methyl-3-pyridinol (0.187 g, 43%) which crystallized from benzene–petroleum ether: mp 120–121° (lit.[13] mp 120–121.2°); ^{1}H NMR ($CDCl_3$) δ 11.70 (OH, exchangeable), 8.20, 7.95 (H-2, H-6), 7.15 (H-5), 2.30 (CH_3); mass spectrum *m/e* (rel intensity) 109 (100), 91 (15), 80 (68), 64 (11), 53 (27).

The same products were observed when **3c** was subjected to a similar experiment.

A similar extended hydrolysis on **5d** (0.317 g, 0.001 mol) with 8 ml of 10% methanolic sodium hydroxide (18 hr) yielded, from the basic aqueous layer, 2-*tert*-butylthiopyridine (0.127 g, 76%), identified by TLC (B), R_f 0.77, and ^{1}H NMR spectrum.[14] No pyridinol could be isolated from the aqueous layer after the basic solution had been neutralized.

Extensive hydrolysis of **5f** (0.160 g, 0.005 mol) yielded, on similar work-up, a mixture (0.087 g) of 2-(1-adamantanethio)pyridine,[10] TLC (A), R_f 0.71, and 1-adamantanethiol, TLC (A), R_f 0.56, which was also substantiated by ^{1}H NMR.

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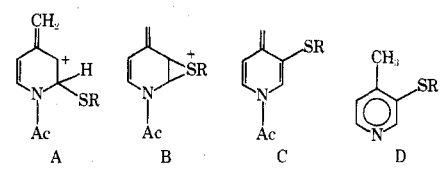
Registry No.—**3a**, 56363-48-5; **3b**, 56363-49-6; **3c**, 56363-50-9; **3d**, 56363-51-0; **5a**, 56363-52-1; **5a**-2,6-d_2, 56363-53-2; **5b**, 56391-05-0; **5c**, 56363-54-3; **5d**, 56363-55-4; **5d**-2,6-d_2, 56391-06-1; **5e**, 56363-56-5; **5f**, 56363-57-6; **6a**, 31579-91-6; **6b**, 56363-58-7; **6d**, 56363-59-8; **6e**, 56363-60-1; **6f**, 54851-58-0; **6g**, 56363-61-2; 1-adamantanethiol, 34301-54-7; *S*-(1-adamantyl)isothiuronium bromide, 30771-94-9; sodium hydroxide, 1310-73-2; pyridine 1-oxide, 694-59-7; 3-(1-adamantanethio)pyridine, 54476-12-9; 2-(1-adamantanethio)pyridine, 54476-11-8; *n*-butyl mercaptan, 109-79-5; 4-picoline 1-oxide, 1003-67-4; 3-(1-adamantanethio)-4-picoline, 56363-62-3; 2-(1-adamantanethio)-4-picoline, 56363-63-4; 4-methyl-3-pyridinol, 1121-19-3.

References and Notes

(1) Part XII. The Deoxydative Substitution of Pyridine *N*-Oxides.
(2) Support for this work by Research Grant CA-13964 from the National Cancer Institute, NIH, U.S. Public Health Service, is most gratefully acknowledged.
(3) F. M. Hershenson and L. Bauer, *J. Org. Chem.*, **34**, 660 (1969).
(4) R. S. Egan, F. M. Hershenson, and L. Bauer, *J. Org. Chem.*, **34**, 665 (1969).
(5) B. A. Mikrut, F. M. Hershenson, K. F. King, L. Bauer, and R. S. Egan, *J. Org. Chem.*, **36**, 3749 (1971).
(6) Molecular sieve was heated at 350° for 18 hr, then permitted to cool in a desiccator over P_2O_5. All subsequent operations were conducted in a drybox, over P_2O_5. Me_2SO-d_6 was allowed to stand over the dried molecular sieve for 18 hr and used to prepare the solution for the ^{1}H NMR experiment.
(7) (a) It is suggested that the pyrolysis of **3a** involved migration of the sulfide group. Initial formation of an allylic carbonium ion A, from **3a**, could facilitate migration of the thioether group via B and C to produce the thioether D eventually. (b) It should be noted that the results from this



wet method differed considered from prior pyrolyses of these compounds. Part of the reason for the original structure assignment, **1**, rested on the pyrolysis of the esters in this series, which afforded 3-alkylthiopyridines (ref 3). Similar pyrolyses of the corresponding alcohols also yielded the 3-pyridyl sulfides. No mechanisms are advanced at present for these transformations.
(8) (a) Carbon-13 spectra in $CDCl_3$ were recorded by means of a Varian Fourier transform XL-100 spectrometer operating at 25.2 MHz, using $(CH_3)_4Si$ as internal standard. (b) ^{13}C resonances exhibited chemical shifts in ranges expected for the diverse carbons in **5a** and **5d**: J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972. (c) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975). (d) H. J. Reich, M. Jautelat, M. T. Messe, J. F. Weigert and J. D. Roberts, *ibid.*, **91**, 7445 (1969). (e) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *ibid.*, **92**, 1338 (1970). (f) Y. Senda, S. Imaizumi, S. Ochiai, and K. Fujita, *Tetrahedron*, **30**, 539, 3813 (1974).
(9) K. K. Khullar and L. Bauer, *J. Org. Chem.*, **36**, 3038 (1971).
(10) B. A. Mikrut, K. K. Khullar, P. Y. P. Chan, J. M. Kokosa, L. Bauer, and R. S. Egan, *J. Heterocycl. Chem.*, **11**, 713 (1974).
(11) K. K. Khullar, C. L. Bell, and L. Bauer, *J. Org. Chem.*, **38**, 1042 (1973).
(12) L. Bauer and T. E. Dickerhofe, *J. Org. Chem.*, **29**, 2183 (1964).
(13) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **77**, 1281 (1955).
(14) F. M. Hershenson and L. Bauer, *J. Org. Chem.*, **34**, 655 (1969).