Deoxydative Substitution of Pyridine 1-Oxides by Thiols. Part XX. Reactions of (2, 3, and 4-Phenyl)-, 3-Acetamido-, 3-Bromo-, 3-Acetoxy-, 3-Ethoxypyridine 1-Oxides with 1-Adamantanethiol in Acetic Anhydride [1]

Supaluk Prachayasittikul, George Doss and Ludwig Bauer*

Department of Medicinal Chemistry and Pharmacognosy, M/C 781,
College of Pharmacy, University of Illinois at Chicago,
Chicago, Illinois 60680-6998 USA

Received April 14, 1991

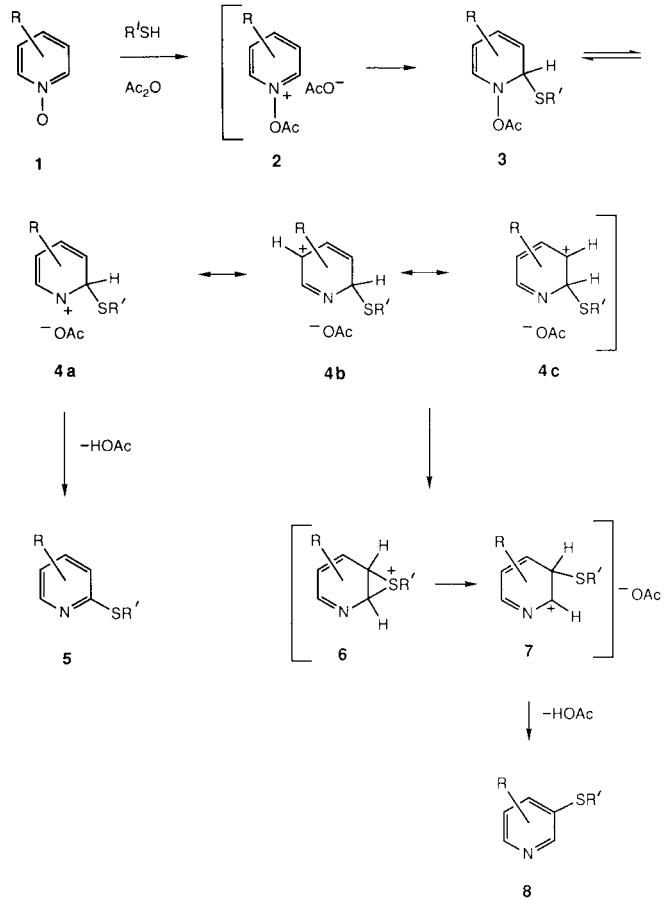
Substitutions of 2, 3, and 4-substituted pyridine 1-oxides by 1-adamantanethiol in acetic anhydride takes place at available α-, to a lesser degree at β-, and rarely at γ-ring carbons. It was found that 2-phenylpyridine 1-oxide produces a mixture of 5- and 6-(1-adamantylthio)-2-phenylpyridines, and 4-phenylpyridine 1-oxide a mixture of 2- and 3-isomeric sulfides. Substitutions of the 1-oxides of 3-phenyl-, 3-acetamido-, 3-acetoxy-, 3-bromo-, and 3-ethoxypyridine by 1-adamantanethiol in acetic anhydride led to mixtures consisting predominantly of 2- and 6-sulfide, and to a lesser extent, the 5-sulfide. When triethylamine is present in otherwise identical reaction mixtures, the ratio of α to β-sulfides increases. From the reactions of 3- and 4-phenylpyridine 1-oxides, there were isolated some *N*-acetyl hydroxy (or acetoxy) 1-adamantylthio substituted 1,2,3,4-and 1,2,3,6-tetrahydropyridines, whose structures are discussed.

J. Heterocyclic Chem., **28**, 1051 (1991).

Pyridine 1-oxides **1** are substituted by thiols (R'SH) in acetic anhydride (Ac_2O) [2] to furnish primarily α- and β- (seldom γ-) pyridyl sulfides [2]. This study investigated the effect of the phenyl group on substitutions of 2-, 3-, and 4-phenylpyridine 1-oxides by 1-adamantanethiol (AdmSH) in acetic anhydride. It was of further interest to compare the substitution pattern of 3-phenylpyridine 1-oxide with AdmSH in acetic anhydride with that of the 1-oxides of 3-picoline [3], nicotinamide [4], (3-acetamido-, 3-acetoxy-, 3-ethoxy-, and 3-bromo)pyridine. Also, the effect of added triethylamine on the course of these substitutions was established.

While introduction of a sulfide group at an α-position of **1** is quite plausible within the tenets of pyridine *N*-oxide chemistry, the attachment of a sulfide at a β-ring carbon demands a somewhat different pathway. A plausible hypothesis has been advanced to account for both α- and β-substitution through common intermediates [2]. Initial quaternization of **1** in acetic anhydride leads to an 1-acetoxypyridinium ion **2**, in which one of the highly electrophilic α-ring carbons is attacked by the nucleophilic R'SH to generate 1,2-dihydropyridine **3**. In order for **3** to aromatize, acetic acid has to be eliminated. Since the aliphatic α-proton of **3** is not particularly acidic, it is suggested that the acetate ion separates from the ring nitrogen to create initially the ion pair **4a**. It is easy to visualize the aromatization to the α-substituted sulfide **5** by the departure of H-2.

However, as the burgeoning nitrenium cation **4** develops, C-3 and C-5 assume carbocationic character, symbolized by resonance-hybrid structures, **4b** and **4c**. The electrophilic center at C-3 in **4c** now invites nucleophilic attack by the neighboring sulfide to form episulfonium ion **6**. Although **6** could revert to **4c**, it is more likely to open to the more favored resonance-stabilized carbocation **7**, which then aromatizes to **8**.



Intermediacy of episulfonium ion **6** can explain not only the formation of β-pyridyl sulfides **8**, but also the presence

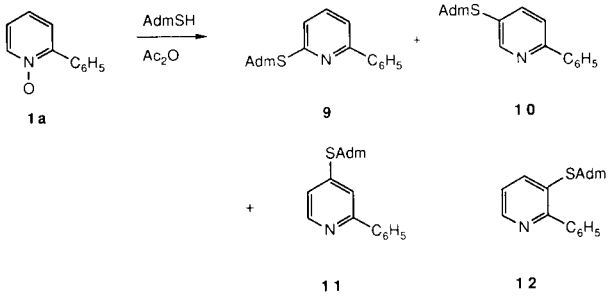
of *trans* 2,3-oxy (or acetoxy) sulfides in tetrahydropyridines isolated from some of these reactions, and this aspect is elaborated on below. Such a pair of *trans* vicinal functional groups is the logical outcome of *trans* ring opening of **6** by acetate ion.

When triethylamine is included into otherwise identical reaction mixtures, several important differences in the products are noted. In reactions utilizing equimolar amounts of *N*-oxide and thiol, the overall yield of sulfides drops with a marked increase in α-pyridyl sulfides **5** (Table 1) [2,5]. It seems reasonable that triethylamine in the reaction mixture greatly facilitates the abstraction of H-2 in **4a** to form **5**. Another factor operating in this system is that of removal of R'SH by acylation before it can be used to substitute. Indeed, it was shown that triethylamine catalyzes the acetylation of AdmSH by acetic anhydride to form AdmSAc [4], thereby removing some of R'SH before it has a chance to attack **2**. As a matter of fact, in a number of experiments which included triethylamine a considerable quantity of AdmSAc was isolated. It was also established that AdmSAc (instead of AdmSH) is totally ineffective in bringing about any substitution of **1** [4].

The inclusion of triethylamine has some other ramifications. With acetic acid in the reaction medium, there is then also present a relatively high concentration of acetate ion. With depletion of R'SH and a marked increase of acetate anion, it is not surprising that some of the tetrahydropyridines isolated possessed more oxygenated (rather than sulfide) substituents [2,5].

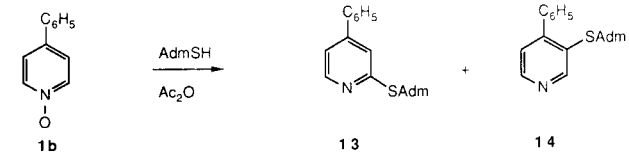
Substitution of Phenylpyridine 1-Oxides.

Deoxydative substitution of 2-phenylpyridine 1-oxide (**1a**) by AdmSH in acetic anhydride is discussed first. The predominant products are **9** and **10**, in the ratio of 3:1 (Table 1). In a similar reaction of **1a**, but containing triethylamine, there is isolated virtually only **9**, along with 2% of the γ-substituted sulfide **11**. Close scrutiny of all chromatographic fractions failed to detect the presence of the remaining isomer **12**.



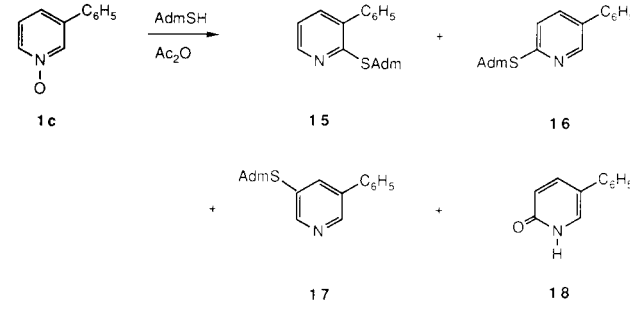
In prior experiments of 2-substituted pyridine 1-oxides and R'SH in acetic anhydride, C-5 sulfides were isolated, but the C-3 isomers could never be found [2]. This observation supports the pathways expressed above to account for α- and β-substitution. With, or without triethylamine, so far, reactions of 2-substituted pyridine 1-oxides with R'SH in acetic anhydride have not yielded any tetrahydropyridines. Whether these types of compounds from 2-substituted pyridine 1-oxides are just not formed, or too unstable to be isolated remains a mute point.

As anticipated, 4-phenylpyridine 1-oxide (**1b**) reacted with AdmSH in acetic anhydride to form **13** and **14**, (2:1, Table 1). Remarkably, the ratio of **13** to **14** is quite similar to that obtained from the substitution of pyridine 1-oxide (**1**, R = H) by AdmSH (Table 1) [2].



Apparently, there is relatively little steric hindrance towards the introduction of a bulky sulfide, like an 1-adamantyl of *t*-butyl sulfide at C-3. For example, the reaction of **1b** was with *t*-butylmercaptan in acetic anhydride afforded 2- and 3-*t*-butylthio-4-phenylpyridines, albeit in poor overall yield (18%), but in the ratio of 44:56 [6].

Substitution of 3-phenylpyridine 1-oxide (**1c**) by AdmSH in (with or without triethylamine) furnishes three of the four possible 1-adamantyl pyridyl sulfides, **15-17**.

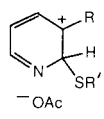


The data (Table 1) indicates that R'SH attacks **1c** at C-2 and C-6, about equally **1c**, forming the dihydropyridine intermediates **3a** and **3b** (R = C_6H_5).

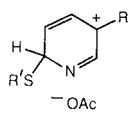
There is quite a difference in the distribution of α- and β-sulfides from **1c** and from 3-picoline 1-oxide (**1d**). Without triethylamine, **1c** gave about 5%, and **1d**, 35% β (C-5) substitution. While **3a** can simply aromatize to **15**, **3b** to **16**, **3b** must rearrange before it can aromatize to **17**.

Since so little of **17** was obtained from **1c**, one can surmise that aromatization of **3a** to **15** and that of **3b** to **16** takes place faster than the conversion of **3b** to **17**.

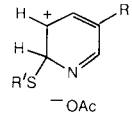
This difference in β-substitution is attributed to the phenyl and methyl groups at C-3. Introspection of **3a**, **3b**, as well as nitrenium-carbonium ion intermediates, **4d-4f** provide some clues. It is suggested that the phenyl (vs the methyl) group inductively renders H-2 in **3a** and, to a lesser degree H-6, in **3b** more acidic (when R = C_6H_5), thereby facilitating faster aromatization to **15** and **16**, compared to the CH_3 analogs.



4d



4e



4f

The most favored resonance hybrid structures of the nitrenium-carbonium ions from **3a** and **3b**, when R = C_6H_5, are **4d** and **4e**, being the most conjugated allylic-benzylic carbocations. Aromatization of **4d** and **4e** would be expected to be faster than sulfide migration for the phenyl analog and this could account for the little C-5 sulfide formation from **1c** (compared to the larger amount from **1d** (R = CH_3)). In the presence of triethylamine, both **1c** and **1d** produce only 1-5% of β-(C-5) sulfides.

The only other simple by-product from these reactions of **1c** was 5-phenyl-2-pyridone. The compound is the result of the well-established substitution of pyridine 1-oxides by acetic anhydride to produce first, 2-pyridyl acetates, which readily hydrolyze to 2-pyridones [2].

Substitution of Other 3-Substituted Pyridine 1-Oxides.

It was of interest to see if structures **3** and **4** might explain the substitution pattern of some of the other 3-substituted pyridine 1-oxides by AdmSH in acetic anhydride. If the premise that a combination of inductive and resonance effects explains preferred C-2 substitution, then other groups R which could stabilize the carbocationic charge (see **4d**) should greatly encourage C-2 substitution. Indeed, without triethylamine, 3-ethoxypyridine 1-oxide (**1e**), 3-acetamidopyridine 1-oxide (**1f**) and 3-bromopyridine 1-oxide (**1g**) were substituted almost exclusively at the seemingly more hindered C-2 carbon of **1**. In acetic anhydride, 3-pyridinol 1-oxide is acetylated first and then its 3-acetate **1h** was substituted primarily at C-2, to some extent at C-6, but not at all at C-5. The facile decomposition of **3a** produces the kinetically favored product, namely the 2,3-disubstituted pyridine. A small deviation from expected products was the isolation of 2-(1-adamantylthio)-3-acetoxypyridine (3.5%) from the reaction of 3-bromopyridine 1-oxide (**1g**) with AdmSH in acetic anhydride. No explanation on its mode of formation is rendered at present.

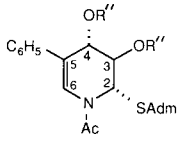
However, nicotinanide and nicotinonitrile 1-oxides are also preferentially substituted at C-3 [4]. Although the amide and nitrile groups would not be expected to stabilize the carbocationic charge (as in **4d**), the inductive effective of these electron-attracting groups at C-3 might be responsible for fast elimination of acetic acid from **3a** (R = $CONH_2$, or CN) thereby encouraging C-2 substitution. In summary, it appears that nucleophilic attack by thiols is preferred at the more hindered α-positions (C-2). Attack at the more hindered position is quite common and experienced many other related pyridine substitutions, for example, the cyanation of 3-substituted pyridine 1-oxides [6,7], and the reaction of pyridine 1-oxides with isocyanates [8].

The Structures of the Tetrahydropyridines.

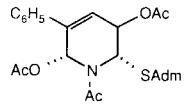
A byproduct from some of these substitutions were a number of interesting tetrahydropyridines. Most of these compounds were analogs whose structures had been fully established previously [2]. The nature of the substituents and their stereochemistry was established primarily through infrared (ir), ultraviolet (uv), ^1H and ^{13}C nuclear magnetic resonance (nmr) and mass (ms) spectra. The uv spectra quickly distinguished between ene-amides, as in **19** and **22**, and the 1,2,3,6-tetrahydropyridine structure **20**, **21** and **23**.

The ir spectra confirmed the presence of OH, NH, and ester and amide type of groups. Chemical shift data clearly indicated that each ring alkene carried a hydrogen and a phenyl group. Each of the alkyl ring carbons was of the methine type bearing either a sulfide, acetoxy or hydroxy group. From the size of vicinal ^1H-^1H coupling constants and the Karplus relationship, it was possible to assign relative stereochemistry to the sundry substituents. The data support twist chair forms for each of the tetrahydropyridines isolated in this study.

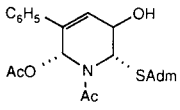
From the reaction of 3-phenylpyridine 1-oxide (**1c**) there were isolated two tetrahydropyridyl ester sulfides, **19a** and **20**. The uv spectra distinguished between these two isomers. For these isomers, the ^{13}C-signal, around 50 ppm placed the sulfide substituent at C-2 (since if at C-3, that ^{13}C shift would be around 45 ppm). From the Karplus relationship, the small vicinal coupling constants in **19a** ($J_{2,3}$ of 1.8, $J_{3,4}$ of 1.2 Hz), suggest dihedral angles compatible with *trans* quasi equatorial disposition of vicinal protons in twist chair conformation of the ring. Hence, the C-2 sulfide and 3-acetoxy groups, as well as the 3,4-acetoxy groups are each *trans* quasi axial to each other. Mild alkaline hydrolysis of **19a** yielded the bis-alcohol, **19b**, of unchanged stereochemistry.



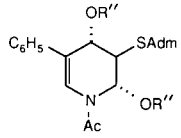
19a, R ″ = Ac
b, R ″ = H



20



21



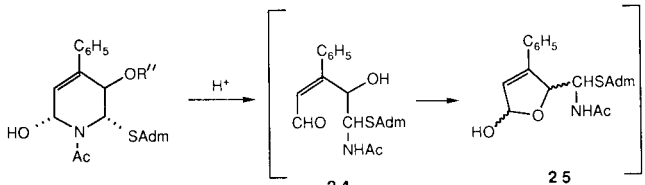
22a, R ″ = Ac
b, R ″ = H

The uv data of the isomer **20** indicates that the alkene is isolated. Coupling constants, ($J_{2,3}$ = 0.7 and $J_{3,4}$ = 4.8 Hz) correlate with substituents at C-2, C-3 being *trans* quasi axial in a twist chair form of the ring. Long range allylic coupling, $J_{4,6}$ >1 Hz, suggests angular relationships which places H-4 and H-6 quasi equatorial and hence the acetoxy group at C-6, quasi axial [10].

In the presence of triethylamine, the reaction of **1c** gave slightly different substituted tetrahydropyridines, **21** and **22b**. The major difference between **21** and **20** is that the C-3 acetate is hydrolyzed to the C-3 alcohol, with unchanged stereochemistry. Since the work up of the reaction mixtures seem identical, it is plausible that during additional columns, or other unknown factors, the 3-acetoxy group was hydrolyzed. Attempts to acetylate **21** to form **20** proved unsuccessful. Using data from previous analogs [2] and related compounds in this series, helped to establish the structure of **21**.

Along those lines, it was the bis-alcohol **22b**, and not the expected bis-(or mono-)acetate of which was isolated. The uv spectra support the ene-amide structure of **22b** and vicinal coupling constants ($J_{2,3}$ = $J_{3,4}$ = 1.8 Hz) confirm a *trans, trans* relationship for C-2, 3 and 4 substituents. The structure of **22** is radically different from those of **19**, **20** and **21** in the sense that the sulfide (at C-3) and the acetoxy group (at C-2) are reversed. This represents no problem within the framework of an episulfonium intermediate **6**. The major clue for the assignment was the upfield shift of H-3 (δ = 3.59), typical of a methine in this series, which bears a sulfide group [2]. Otherwise, the stereochemistry of **21** was arrived at through an analysis of the coupling constants.

The reaction of 4-phenylpyridine 1-oxide (**1b**) with AdmSH in acetic anhydride containing triethylamine yielded the hydroxy-acetoxytetrahydropyridyl thioether **23a**. Its uv spectrum placed it into the 1,2,3,6-tetrahydropyridine family. The large CH-OH coupling (12 Hz) was traced to the 6-OH (δ H-6 = 5.66, compared to δ H-6 of C*H*OAc of **20** and **21**, of 6.71 and 7.03, respectively). Mild basic hydrolysis of the C-3 acetoxy group of **23a** by dilute sodium hydroxide yields **23b**. This hydroxy hemiacetal **23b** is most sensitive to acids, being transformed by traces of trifluoroacetic acid to the furan **26**. It is reasonable to assume that hemi-aminal ring of **23b** opens to the aldehyde amide **24** which now cyclizes through the 3-OH to produce the five-membered hemiacetal **25**. Loss of water from **25** furnishes the furan **26**. There is precedence for such a sequence of reactions [11].



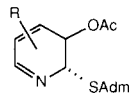
23a, R ″ = Ac
b, R ″ = H

24

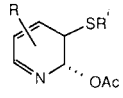
25

26

Threads of similarity run throughout the mechanisms for the formation of these tetrahydropyridines. It is the episulfonium ion **6** which can be opened by acetate ion in two way to form C-2, C-3 *trans* acetoxy sulfides, **27** or **28**, which are indeed a part of the structure of each of these tetrahydropyridines.



27



28

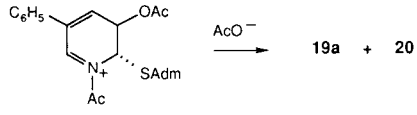
To illustrate, for example how **19a** or **20** are formed, **27** is quaternized by acetic anhydride to produce the cation **29**. Attack of acetate ion at either the electrophilic γ (C-4) or α (C-6) carbons leads to **19a** or **20**. The same rationale can be applied for the formation of **23a** from 4-phenylpyridine 1-oxide. However, the more labile C-6 acetoxy group (being part of a hemiaminal ester) is hydrolyzed during the work up to provide **23a** [2]. In the same way,

Table 1
Yields and Distribution of Pyridyl Sulfides

	R	R'	Method [a]	Yield % [b]	Substitutions α-C's C-2	α-C's C-6	β-C's C-3	β-C's C-5	γ-C C-4
1	H [c]	1-Adm	A	44	68	-	32	-	-
1	H [c]	1-Adm	B	35	80	-	20	-	-
1a	2-C_6H_5	1-Adm	A	81	-	76	-	24	-
1a	2-C_6H_5	1-Adm	B	79	-	98	-	0	2
1b	3-C_6H_5	1-Adm	A	51	52	43	-	5	-
1b	3-C_6H_5	1-Adm	B	41	45	52	-	3	-
1c	4-C_6H_5	1-Adm	A	56	66	-	34	-	-
1c	4-C_6H_5	1-Adm	B	49	92	-	8	-	-
1c	4-C_6H_5 [d]	*t*-C_4H_9	A	18	44	-	56	-	-
1d	3-CH_3[e]	1-Adm	A	70	48	18	-	34	-
1d	3-CH_3[e]	1-Adm	B	45	78	21	-	1	-
1d	3-CH_3[e]	*t*-C_4H_9	A	66	45	19	-	36	-
1d	3-CH_3[e]	*t*-C_4H_9	B	20	61	34	-	5	-
1e	3-OC_2H_5	1-Adm	A	74	99	1	-	-	-
1e	3-OC_2H_5	1-Adm	B	33	92	8	-	-	-
1f	3-NHAc	1-Adm	A	65	93	4	-	-	3
1g	3-Br	1-Adm	A	33	82	-	-	18	-
1h	3-OAc	1-Adm	A	59	83	16	-	-	1
1h	3-OAc	1-Adm	B	25	73	27	-	-	-
1i	3-$CONH_2$ [f]	1-Adm	A	68	91	8.5	-	0.5	-

[a] Method A: reactions were conducted in acetic anhydride at 95-130° for 3 hours; Method B: reactions contained triethylamine. [b] Yields are based on recovered *N*-oxide and are based on pure isolated sulfides. [c] Ref 2. [d] Ref 6. [e] Ref 3. [f] Represents α- and β-substitution, although the amide function might have been changed [Ref 4].

one can write a mechanism which transforms **28** (R = 3-C_6H_5, R' = Adm) to **22a**.



29

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The uv spectra were obtained in 95% ethanol using a Varian Cary 118 spectrophotometer. The ir spectra were recorded on a FT-IR spectrometer, Model MX-1, Nicolet Instrument Corporation. Electron-impact mass spectra were generated at 70 eV by Mr. Richard Dvorak by means of a Hitachi-Perkin-Elmer RMU-6D single focusing mass spectrometer or Finnigan mass spectrometer Model MAT 112 S. Usually, ions with 20% or more of the base peak are recorded. Elemental analyses were performed by Micro-Tech Labs, Skokie Illinois.

All nmr spectra were recorded in deuteriochloroform, unless specified otherwise. The ^1H nmr spectra were recorded on a Varian XL-300 and ^{13}C nmr spectra were determined at 75.4 MHz on a Varian XL-300 spectrometer, or at 90.8 MHz on a Nicolet NMC360 spectrometer. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are described as s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet and br is used to describe broad signals. In a number of instances, the multiplets arising from phenyl protons are not reported.

We are grateful for complimentary samples of 4-phenylpyridine 1-oxide, 3-bromopyridine and 3-aminopyridine from Reilly Chemical Co, Indianapolis, Indiana. All other research chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI unless specified otherwise, and were used as supplied. Pyridine, *N,N*-dimethylacetamide, *N,N*-dimethylformamide and dimethyl sulfoxide were stored over 4Å molecular sieves once the container had been opened. 1-Adamantanethiol was prepared by literature methods [12]. Chloroform, toluene and benzene were ACS grade and were purchased from Scientific Supply Co. Petroleum ether refers to that fraction boiling between 30-60°.

Evaporation or removal of solvents, *in vacuo*, implies that solvents were removed by means of a rotary flash evaporator at the water pump (20-30 Torr) at temperatures of 40°, or below, unless specified otherwise. All analytical samples were dried at room temperature in a vacuum desiccator. Thin layer chromatography was performed on Aldrich or Brinckman Instruments silica gel coated polyester plates with 254 nm fluorescent indicator. Developing solvent A consisted of petroleum ether-ether 7:3, solvent B, ether, solvent C, acetone-petroleum ether, 7:3, and solvent D was methanol-petroleum ether, 7:3. Spots were detected by either uv light or iodine staining. Column chromatography was performed on silica gel, Aldrich grade 60 (230-400 mesh), or that from Baker Chemical Co, (60-200 mesh), unless noted otherwise.

Method A. Reaction of 2-Phenylpyridine 1-Oxide (**1a**) with 1-Adamantanethiol in Acetic Anhydride.

This general method was used for these reactions and variations are noted for specific experiments. Whenever solids appeared they were filtered and purified either by recrystallization or column chromatography. Mixtures were always chromatographed, frequently a number of times until pure fractions were obtained. The progress of purification was closely followed by tlc and ^{1}H nmr spectra. Major departures from these general instructions are described in detail.

A cold solution of AdmSH (16.8 g, 0.1 mole) in acetic anhydride (25 ml) was added dropwise to a warm solution (70°) of **1a** (17.1 g, 0.1 mole) in acetic anhydride (75 ml) over 0.5 hour. The mixture was heated at 95° for an additional 3.5 hours. Upon cooling to 0-5°, 2-phenyl-6-(1-adamantylthio)pyridine (**9**, 18.2 g, 57%) was filtered off, mp 104-105° (unchanged after crystallization from ether); R_f 0.72 (solvent A), 0.95 (solvent B); ^{1}H nmr: δ 8.00 (dd, H-3), 7.58-7.39 (m, H-4, C_6H_5), 7.18 (dd, H-5), ($J_{3,4}$ = 6.8, $J_{3,5}$ = 1.8 Hz), 2.20-1.72 (m, Adm); ms: m/z (relative intensity) 321 (M^+, 27), 288 (24), 135 (100), 93 (39), 79 (57), 77 (28), 67 (30).

Anal. Calcd. for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.76; H, 7.15; N, 4.36.

Upon cooling the mother liquor in a refrigerator, 2-phenyl-5-(1-adamantylthio)pyridine (**10**, 4.95 g, 15%) was collected, mp 127-128° (recrystallized from ether, mp 129-130°); R_f 0.68 (solvent A), 0.95 (solvent B); ^{1}H nmr: δ 8.75 (dd, H-6), 8.03 (dd, H-3), 7.85 (dd, H-4), ($J_{3,4}$ = 8.1, $J_{4,6}$ = 2.1, $J_{3,6}$ = 0.6 Hz), 7.73-7.38 (m, C_6H_5), 2.05-1.58 (m, Adm); ms: m/z (relative intensity) 321 (M^+, 9), 135 (100), 93 (28), 79 (39), 67 (21).

Anal. Calcd. for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.68; H, 7.34; N, 4.32.

Additional quantities of sulfides were obtained when all of the mother liquors were pooled and worked up for further product. As a general method, the following guidelines can be followed. All mother liquors were combined and if no precipitate appeared, the solution was evaporated to dryness, *in vacuo*, neutralized with saturated cold aqueous sodium bicarbonate and extracted by toluene (3 x 50 ml). After washing the extract with water, drying (sodium sulfate), the solvent was removed, *in vacuo*. Some times, a part of the residue could be induced to crystallize by trituration with solvents, but in most instances whole residue was chromatographed on silica gel. For, this experiment, elution with petroleum ether afforded first **9** (1.5 g, 5%) and then, **10** (1.2 g, 4%).

Method B. Reaction of 2-Phenylpyridine 1-Oxide (**1a**) with 1-adamantanethiol in Acetic Anhydride Containing Triethylamine.

To a hot solution (70°) of **1a** (17.1 g, 0.1 mole) in acetic anhydride (75 ml) and triethylamine (50 ml, 0.35 mole) was added, dropwise (0.5 hour) a cold solution of AdmSH (16.8 g, 0.1 mole) in acetic anhydride (25 ml). The mixture was then heated at 95° for 3 hours. Upon cooling to 0-5°, **1a** (5.4 g, 32%) was filtered off. After 24 hours in a refrigerator, some of **9** (0.5 g, 2%) precipitated and was filtered. The filtrate was concentrated, *in vacuo*, the residue neutralized with ice-cold 50% sodium carbonate solution and extracted with toluene (3 x 100 ml). The extract was washed with water (50 ml), dried (sodium sulfate) and solvents evaporated, *in vacuo*. The solid (23.7 g) was chromatographed on silica gel (300 g). Elution with petroleum ether (7 *l*) furnished pure **9** (16.5 g, 75%). Continued elution with petroleum ether-ether (5:1, 0.5 *l*) furnished 2-phenyl-4-(1-adamantylthio)pyridine (**11**, 0.6 g, mp 87-89°), which was recrystallized from petroleum ether to produce 0.35 g (2%), mp 97-98°; R_f 0.3 (solvent A), 0.7 (solvent B); ^{1}H nmr: δ 8.61 (d, H-6), 7.99 (dd, H-5), 7.33 (d, H-3), ($J_{3,5}$ = 1.4, $J_{5,6}$ = 5.0 Hz), 7.51-7.42 (m, C_6H_5), 2.00-1.60 (m, Adm); ms: m/z (relative intensity) 321 (M^+, 24), 135 (100).

Anal. Calcd. for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.62; H, 7.19; N, 4.26.

Substitution of 4-Phenylpyridine 1-Oxide (**1b**), Method A.

The reaction of **1b** (17.1 g) was carried out as described in Method A. Upon cooling, starting material (**1b**, 4.95 g, 29%) was recovered. The mother liquor was processed according to Method A. Chromatography on silica gel (500 g) of the residue (34.5 g) from the toluene extract yielded upon elution, first with petroleum ether-toluene (1:3, 0.5 *l*) AdmSAc (1.5 g, 7%), then 2-(1-adamantylthio)-4-phenylpyridine (**13**, 7.2 g, 32%). Continued elution with toluene afforded a mixture which was chromatographed on a new column of silica gel. Elution with petroleum ether-toluene (1:1) furnished more **13** (1.2 g, 5%), mp 118-119°; R_f 0.71 (solvent A), 0.92 (solvent B); ^{1}H nmr: δ 8.55 (d, H-6, $J_{5,6}$ = 4.8 Hz), 7.58-7.28 (m, H-3, H-5, and C_6H_5), 2.11-1.69 (m, Adm); ms: m/z (relative intensity) 321 (M^+, 87), 320 (94), 135 (100), 93 (26), 79 (27).

Anal. Calcd. for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.56; H, 7.21; N, 4.29.

Continued elution with toluene produced 3-(1-adamantylthio)-4-phenylpyridine (**14**, 17%), mp 74-76°; R_f 0.45 (solvent A), 0.82 (solvent B); ^{1}H nmr: δ 8.81 (s, H-2), 8.57 (d, H-6, $J_{5,6}$ = 4.8 Hz), 7.42 (br s, C_6H_5), 7.30 (d, H-5), 1.84-1.51 (m, Adm); ms: m/z (relative intensity) 321 (M^+, 72), 320 (68), 135 (100), 93 (28), 79 (30).

Anal. Calcd. for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.77; H, 7.26; N, 4.29.

Substitution of 4-Phenylpyridine 1-Oxide (**1b**), Method B.

The reaction of **1b** (34.2 g) with AdmSH (33.6 g) in acetic anhydride (200 ml), containing triethylamine (100 ml) was heated 3 hours and then cooled extensively (-20°). A brown solid (29 g) was isolated and was crystallized from ether to yield **13** (18 g, 28%). The original mother liquor, upon further refrigeration yielded another 7.1 g of **13** (11%). All mother liquors were pooled, processed as described in Method B, and chromatographed on silica gel: petroleum ether-toluene (1:1) gave AdmSAc (17.5 g, 42%), while toluene eluted some more **13** (3 g, 5%). Elution with chloroform provided an oil which was tritured with ether to yield crystalline **23a**, mp 138-140°, which was recrystallized from ether, mp 141-142° (1.2 g, 1.4%); R_f 0.49 (solvent B); ir (Nujol): 3353 (OH), 1739, 1630 (C=O) cm^{-1}; uv (95% ethanol): λ max 247 nm (log ϵ 4.37), 204 nm (log ϵ 3.62); ^{1}H nmr: δ 6.42 (d, H-5), 6.26 (d, H-2), 5.81 (d, H-3), 5.66 (dd, H-6), ($J_{2,3}$ = 2.4, $J_{5,6}$ = 3.8, $J_{6,OH}$ = 12 Hz); ^{13}C nmr: δ 170.2, 170.0 (acyl C=O), 75.9 (C-6), 125.8 (C-5), 135.6 (C-4), 67.3 (C-3), 49.2 (C-2), 21.7, 20.7 (CH_3); ms: m/z (relative intensity) 441 (M^+, 0.1), 381 (M^+ - HOAc, 6), 256 (32), 214 (63), 172 (68), 155 (21), 135 (100), 93 (20), 79 (21), 43 (29).

Anal. Calcd. for $C_{25}H_{31}NO_4S$: C, 67.99; H, 7.07; N, 3.17. Found: C, 68.08; H, 7.02; N, 3.10.

When all mother liquors were combined and rechromatographed on silica gel, some more **13** was eluted with petroleum ether-ether (7:3, 0.7 g, 0.6%), followed then by **14** (2.5 g, 4%), and then more **23a** (2.15 g, 2.4%).

Hydrolysis of **23a**.

A solution of **23a** (0.30 g, 0.68 mmole) was stirred at room temperature with methanolic sodium hydroxide (13.6 mg, 0.34 mmole in 2 ml) for 1 hour and then diluted with water (10 ml). The colorless precipitate (0.247 g) was washed with water and recrystallized from methanol to provide **23b** (0.29 g, 74%), mp 158-159°; R_f 0.12 (solvent B); uv (95% ethanol): λ max 246 (log ε 3.40), 203 (log ε 3.46) nm; ms: m/z (relative intensity) 238 (30), 172 (25), 135 (100), 43 (24).

Anal. Calcd. for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.50. Found: C, 68.91; H, 7.56; N, 3.40.

A similar hydrolysis can also be carried out, on the same scale, with sodium bicarbonate (28 mg, 0.34 mmole) in boiling methanol (5 ml) for 1 hour to produce **23b** in excellent yield.

Conversion of **23b** to **26**.

A solution of **23b** (0.13 g) in chloroform (15 ml) containing half a drop of trifluoroacetic acid was stirred for 18 hours. Solvents were removed at room temperature, *in vacuo*, and the residue chromatographed on silica gel (50 g). Elution with petroleum ether-ether (7:3, then 1:1) provided **26** (0.08 g), mp 106-108°, recrystallized from ether, mp 115-116° (0.03 g, 23%); R_f 0.61 (solvent B); ir (Nujol): 3242 (NH), 1653 cm^{-1} (C=O); ^1H nmr: δ 7.55-7.31 (m, C_6H_5), 7.39 (d, H-5), 6.60 (d, CH), 6.48 (d, H-4), 6.30 (d, NH), ($J_{4,5}$ = 1.9, $J_{CH,NH}$ = 9.4 Hz), 1.96-1.57 (m, Adm); ms: m/z (relative intensity) 214 (M^+ - AdmS), 172 (94), 43 (41).

Anal. Calcd. for $C_{23}H_{27}NO_2S$: C, 72.40; H, 7.13; N, 3.67. Found: C, 72.32; H, 7.25; N, 3.63.

Substitution of 3-Phenylpyridine 1-Oxide (**1c**), Method A.

After 3 hours, the reaction of **1c** (17.1 g) with AdmSH (16.8 g), as described in Method A, was cooled in ice-water. A solid was filtered, washed with petroleum ether and proved to be 2-(1-adamantylthio)-3-phenylpyridine (**15**, 8.4 g, 26%), mp 150-151° which was recrystallized from ether (80% recovery) to yield pure **15**, mp 152-153°; R_f 0.80 (solvent A), 0.85 (solvent B); ^1H nmr: δ 8.47 (dd, H-6, $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.8 Hz), 7.45-6.90 (complex m, H-4, H-5, including 7.37 as a br s, C_6H_5), 2.17-1.69 (m, Adm); ms: m/z (relative intensity) 321 (M^+, 17), 320 (30), 135 (100), 93 (40), 79 (53), 77 (22), 67 (28), 55 (28).

Anal. Calcd. for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.90; H, 7.19; N, 4.22.

The mother liquor was processed as described in Method A. Chromatography of the evaporated toluene extract (26 g) on silica gel (400 g) separated the following: Elution first with petroleum ether-toluene (1:1. 2 ℓ) produced 2-(1-adamantylthio)-5-phenylpyridine (**16**, 5.4 g), then with toluene (1 ℓ) gave another 2.4 g of **16** (total 24%), which was recrystallized from ether, mp 79-81°; R_f 0.77 (solvent A), 0.85 (solvent B); ^1H nmr: δ 8.76 (d, H-6), 7.73 (dd, H-4), ($J_{3,4}$ = 8.4, $J_{4,6}$ = 2.4 Hz), 7.47-7.34 (m, H-3, C_6H_5), 2.11-1.70 (m, Adm); ms: m/z (relative intensity) 321 (M^+, 27), 320 (40), 135 (100), 93 (35), 79 (50), 77 (20), 67 (25), 55 (23).

Anal. Calcd. for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.87; H, 7.29; N, 4.24.

Continued elution with toluene-chloroform (1:1) brought forth 3-(1-adamantylthio)-5-phenylpyridine (**17**, 0.9 g, 3%), mp 108-109° (from ether); R_f 0.35 (solvent A), 0.78 (solvent B); ^1H nmr: δ 8.80, 8.65 (br s, H-6), 8.65 (d, H-2), 8.00 (t, H-4), ($J_{2,4}$ = $J_{4,6}$ = 1.2 Hz), 2.01-1.64 (m, Adm); ms: m/z (relative intensity) 321 (M^+, 12), 135 (100), 93 (27), 79 (37).

Anal. Calcd. for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.91; H, 7.37; N, 4.26.

Continued elution with chloroform (1.5 ℓ) produced an oil (1.1 g) which crystallized from ether (**19a**, 0.7 g), mp 203-204°; R_f = 0.12 (solvent A), 0.76 (solvent B); ir (Nujol): 1742, 1727, 1648 cm^{-1} (C=O); uv (95% ethanol): λ max 276 nm (log ε 390); ^1H nmr: δ 7.32 (m, C_6H_5), 7.06 (br s, H-6), 6.04 (d, H-2), 5.71 (d, H-4), 5.33 (dd, H-3), ($J_{2,3}$ = 1.8, $J_{3,4}$ = 1.2 Hz), 2.29 , 2.04 (two s, CH_3), 2.00-1.69 (m, Adm); ^{13}C nmr: δ 170.2, 169.1. 168.0 (acyl C=O), 127.4 (C-6), 117.1 (C-5), 65.4 (C-4), 72.5 (C-3), 48.5 (C-2), 21.7, 20.7 (CH_3); ms: m/z (relative intensity) 483 (M^+, 6), 256 (41), 214 (100), 172 (79), 135 (46), 93 (23), 79 (35).

Anal. Calcd. for $C_{27}H_{33}NO_5S$: C, 67.06; H, 6.88; N, 2.89. Found: C, 67.32; H, 6.92; N, 2.76.

Further elution with chloroform (2 ℓ) afforded an oil (9.2 g) which solidified under ether to release another 3.8 g of **19a**. The mother liquor from that solid was rechromatographed on another column of silica gel. Elution with chloroform gave a mixture which was fractionally crystallized from ether. The first fraction consisted of **20**, mp 169-170° (0.34 g); R_f 0.07 (solvent A), 0.83 (solvent B); ir (Nujol): 1751, 1733, 1669 cm^{-1} (C=O); uv (95% ethanol): λ max 232 nm (log ε 3.68); ^1H nmr: δ 7.35 (m, C_6H_5), 6.71 (d, H-6), 6.67 (d, H-4), 5.66 (d, H-2), 5.45 (dd, H-3), ($J_{2,3}$ = 0.7, $J_{3,4}$ = 4.8, $J_{4,6}$ = 1.0 Hz), 2.42, 2.18, 2.15 (s, CH_3), 1.90-1.59 (m, Adm); ^{13}C nmr: 74.3 (C-6), 142.1 (C-5), 120.2 (C-4), 67.0 (C-3), 50.3 (C-2); ms: m/z (relative intensity) 483 (M^+, 3), 214 (45), 172 (100), 135 (26), 79 (22), 55 (20).

Anal. Calcd. for $C_{27}H_{33}NO_5S$: C, 67.06; H, 6.88; N, 2.89. Found: C, 67.07; H, 6.81; N, 2.79.

The second fraction yielded an additional 0.06 g (overall 9.4%) of **19a**, mp 201-202°.

Hydrolysis of **19a**.

A mixture of **19a** (0.30 g, 0.6 mmole) and sodium hydroxide (0.125 g) in methanol (20 ml) was stirred at room temperature (1.5 hours). Solvents were removed, *in vacuo*, and the residue partitioned between water (20 ml) and chloroform (2 x 30 ml). The organic extract was dried (sodium sulfate) and the solvent removed, *in vacuo*. The gum was crystallized from petroleum ether-ether (1:1) to yield **19b** (0.215 g, 87%), mp 158-159°; R_f = 0.32 (solvent B); ir (Nujol): 3462 (OH), 1640 cm^{-1} (C=O); uv (95% ethanol): λ max 278 nm (log ε 4.17); ^1H nmr: δ 7.32 (m, C_6H_5), 6.91 (s, H-6), 5.92 (d, H-2), 4.60 (dd, H-3), 4.43 (d, H-4), ($J_{2,3}$ = 1.4, $J_{3,4}$ = 1.1, $J_{3,OH}$ = 11.2 Hz), 3.72 (d, 3-OH), 3.36 (s, 4-OH), 2.28 (s, CH_3), 2.13-1.65 (m, Adm); ^{13}C nmr: δ 168.6 (C=O), 126.0 (C-6), 121.5 (C-5), 73.1 (C-3), 68.1 (C-4), 50.8 (C-2), 21.8 (CH_3); ms: m/z (relative intensity) 399 (M^+, 13), 214 (86), 172 (100), 144 (66), 135 (5146), 93 (26), 79 (40), 77 (20), 67 (21), 55 (23).

Anal. Calcd. for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.50. Found: C, 69.31; H, 7.29; N, 3.43.

Substitution of 3-Phenylpyridine 1-Oxide (**1c**), Method B.

The reaction of **1c** (34.2 g) with AdmSH (33.6 g), in acetic anhydride (200 ml), containing triethylamine (100 ml) was conducted as in Method B. After 3 hours the solution was cooled in a refrigerator when 2-(1-adamantylthio)-3-phenylpyridine (**15**, 3.0 g, 5%) crystallized out. The acetic anhydride solution was then processed, as before. The residue (70.0 g) was chromatographed on silica gel (600 g): Elution with petroleum ether-toluene (1:3, 1.5 ℓ) produced first AdmSAc (15.1 g, 36%); the next 0.5 ℓ of toluene gave more **15** (9.0 g, 14%), while the next 2.5 ℓ eluted 2-(1-adamentylthio)-5-phenylpyridine (13.65 g, 21%).

Chloroform (7.7 l) eluted an oil (8.0 g) which was rechromatographed on silica gel (250 g). Petroleum ether (1.2 l) eluted first another 0.7 g (1%) of 2-(1-adamantylthio)-3-phenylpyridine, then (with another 1 l) an oil, which solidified when covered by ether to yield pure **19a** (0.43 g, 0.4 %). Continued elution with petroleum ether-ether (1:1) led to another oil, which upon repeated recrystallization from ether furnished pure **21** (0.39 g, 0.4%), mp 185-186°; R_f 0.03 (solvent A), 0.57 (solvent B); ir (Nujol): 3331 (OH), 1742, 1610 cm^{-1} (C=O); uv (95% ethanol): λ max 238 nm (log ε 3.16); ^1H nmr: δ 7.03 (d, H-6), 6.00 (d, H-4), 5.58 (d, H-2), 4.90 (dd, H-3), ($J_{2,3}$ = 1.2, $J_{3,4}$ = 4.2, $J_{4,6}$ = 1.0 Hz); ms: m/z (relative intensity) 441 (M^+, 3), 274 (44), 232 (34), 214 (43), 172 (100), 135 (40).

Anal. Calcd. for $C_{25}H_{31}NO_4S$: C, 67.99; H, 7.07; N, 3.17. Found: C, 67.93; H, 7.27; N, 3.30.

Continued elution with petroleum ether-ether (1:1, 1.9 l) yielded first an oily **22b** which also crystallized from ether (0.39 g, 0.5%), mp 159-160°; R_f = 0.02 (solvent A), 0.34 (solvent B); ir (Nujol): 3355, 3245 (OH), 1648 cm^{-1} (C=O); uv (95% ethanol): λ max 278 (log ε 3.86), 214 (log ε 3.06) nm; ^1H nmr: δ 6.87 (s, H-6), 6.02 (d, H-2), 4.54 (d, H-4), 3.54 (dd, H-3), ($J_{2,3}$ = $J_{3,4}$ = 1.8 Hz); ms: m/z (relative intensity) 399 (M^+, 2), 381 (M^+-18, 2), 321 (25), 135 (100), 43 (28).

Anal. Calcd. for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.50. Found: C, 68.78; H, 7.56; N, 3.39.

Final elution from this column with chloroform (7 l) produced a dark solid which crystallized from ether and proved to be 5-phenyl-2-pyridone, (**18**, 3.2 g, 9%), mp 116-117°; R_f = 0.03 (solvent B); ^1H nmr: δ 8.45 (d, H-6), 8.20 (dd, H-4), ($J_{3,4}$ = 7.2, $J_{4,6}$ = 1.2 Hz), 7.49-7.18 (m, H-3, C_6H_5), 2.16 (NH); ms: m/z (relative intensity) 171 (M^+, 100), 144 (20), 116 (23), 115 (83).

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.02; H, 5.44; N, 8.17.

Substitution of other 3-Substituted Pyridine 1-Oxides by 1-AdmSH.

3-Ethoxypyridine 1-Oxide (**1e**), Method A.

A solution of AdmSH (13.4 g, 0.08 mole) in (30 ml) was added to a solution of **1e** (10.0 g, 0.072 mole) in acetic anhydride (50 ml). After heating at 95° for 2 hours, then at 125° for 2 hours, the mixture was cooled. 2-(1-adamantylthio)-3-ethoxypyridine (13.5 g, 65%) was filtered, washed with petroleum ether and recrystallized from acetone, mp 169-170°; R_f 0.57 (solvent A); ms: m/z (relative intensity) 289 (M^+, 10), 135 (100), 93 (26), 79 (40), 67 (24), 41 (36), 39 (51). 29 (27), 27 (26).

Anal. Calcd. for $C_{17}H_{23}NOS$: C, 70.57; H, 8.01; N, 4.83. Found: C, 70.47; H, 7.98; N, 4.78.

The ^1H nmr spectrum consisted of what seemed to be a "doublet" (δ 6.97, 2H) and a "triplet" (δ 8.06, 1H), separation of 3.1 Hz, characteristic of an AX_2 system, except that two of the three protons have identical chemical shifts. A computer simulated spectrum (using a modified LAOCOON program (LAME), with chemical shifts for H-6, 8.06 and for H-4, H-5, 6.97, and $J_{4,6}$ = 1.4, and $J_{5,6}$ = 4.8 Hz, but omitting $J_{4,5}$ of 7.8 Hz, proved to be identical to the experimental spectrum; other signals were δ 4.06 (q, CH_2), 2.25-1.73 (m, Adm), 1.45 (t, CH_3).

The mother liquor from the original precipitate was processed according to Method A. Elution of 10 g of residual oil (from silica gel) with petroleum ether yielded AdmSAc (1.5 g, 9%). With 9:1 petroleum ether-ether there was eluted 2-(1-adamantylthio)-3-ethoxypyridine (1.7 g, 8%), followed by 2-(1-adamantylthio)-5-ethoxypyridine (0.2 g, 1%), mp 116-117° (from acetone); R_f 0.46 (solvent A); ^1H nmr: δ 8.29 (d, H-6), 7.38 (d, H-3), 7.08 (dd, H-4), ($J_{3,4}$ = 7.2, $J_{4,6}$ = 3.0 Hz), 4.17 (q, CH_2), 1.95-1.61 (m, Adm), 1.43 (t, CH_3); ms: m/z (relative intensity) 289 (M^+, 24), 288 (24), 135 (100), 93 (21), 79 (27).

Anal. Calcd. for $C_{17}H_{23}NOS$: C, 70.57; H, 8.01; N, 4.83. Found: C, 70.34; H, 8.20; N, 4.77.

3-Ethoxypyridine 1-Oxide (**1e**), Method B.

In a similar reaction, AdmSH (2.68 g, 16.0 mmoles) in acetic anhydride (10 ml) was added to a solution of **1e** (2.0 g, 14.4 mmoles) in warm acetic anhydride (10 ml, 80°). After heating at 120-125° for 3 hours, then cooling, there was isolated 2-(1-adamantylthio)-3-ethoxypyridine (1.55 g, 27%). Work up according to Method B, gave after chromatography, AdmSAc (1.9 g, 57%), then 2-(1-adamantylthio)-3-ethoxypyridine (0.2 g, 4%), and 2-(1-adamantylthio)-5-ethoxypyridine (0.14 g, 2.5%).

3-Acetamidopyridine 1-Oxide (**1f**), Method A.

A solution of AdmSH (11.05 g, 66.0 mmoles) in acetic anhydride (25 ml) was added (20 minutes) to a solution of **1f** (10.0 g, 66.0 mmoles) in acetic anhydride (125 ml). After heating at 130° for 3 hours, the mixture was cooled and since no precipitate, the mixture was worked up as described in Method A. Chromatography on silica gel provided as the first fraction (petroleum ether-ether, 5:1) AdmSAc (2.5 g, 18%), followed by a crude solid (petroleum ether-ether, 7:3, then 1:1). Recrystallization (ether) of this solid gave 2-(1-adamantylthio)-3-diacetamidopyridine (8.0 g, 35%), mp 119-120°; R_f 0.56 (solvent B); ir (Nujol) 1724, 1706 cm^{-1} (C=O); ^1H nmr: δ 8.47 (dd, H-6), 7.32 (dd, H-4), 7.10 (dd, H-5), ($J_{4,5}$ = 7.8, $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.7 Hz), 2.29, 2.26 (two s, CH_3), 2.01-1.64 (m, Adm); ms: m/z (relative intensity) 344 (M^+, 27), 301 (32), 285 (31). 244 (21), 135 (100), 93 (25), 79 (27), 43 (69).

Anal. Calcd. for $C_{19}H_{24}N_2O_2S$: C, 66.26; H, 7.02; N, 8.14. Found: C, 66.18; H, 6.97; N, 9.07.

Repeated purifications and re-analyses did not improve the analytical data.

The next fraction, eluted by 20-70% chloroform in petroleum ether, was 2-(1-adamantylthio)-3-acetamidopyridine (4.95 g, 25%), mp 127-128°; R_f 0.49 (solvent B); ir (Nujol): 3401, 3286 (NH), 1698 cm^{-1} (C=O); ^1H nmr: δ 8.72 (dd, H-4), 8.31 (dd, H-6), 7.22 (dd, H-5), ($J_{4,5}$ = 8.4, $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.8 Hz), 2.24 (CH_3), 2.00-1.67 (m, Adm); ms: m/z (relative intensity) 302 (M^+, 7), 135 (100), 93 (23), 79 (27).

Anal. Calcd. for $C_{17}H_{22}N_2OS$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.47; H, 7.29; N, 9.26.

3-Acetamido-4-(1-adamantylthio)pyridine (0.4 g, 2%) was eluted by chloroform and chloroform containing 1% methanol, mp 139-140°; R_f 0.28 (solvent B); ir (Nujol): 3227 (NH) 1694 cm^{-1} (C=O); ^1H nmr: δ 9.71 (dd, H-6), 8.57 (br s, NH), 8.29 (dd, H-2), 7.35 (d, H-5, $J_{5,6}$ = 4.2 Hz), 2.24 (s, CH_3), 2.01-1.64 (m, Adm); ms: m/z (relative intensity) 302 (M^+, 34), 135 (100), 93 (26), 79 (26), 43 (30).

Anal. Calcd. for $C_{17}H_{22}N_2OS$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.44; H, 7.42; N, 9.17.

The final fraction (1-3% methanol in chloroform) consisted of 2-(1-adamantylthio)pyridine-5-acetamidopyridine (0.5 g, 2.5%), mp 181-182°; R_f 0.23 (solvent B); ir (Nujol): 3231 (NH) 1697 cm^{-1}

(C=O); ^{1}H nmr: δ 8.52 (dd, H-6), 8.05 (dd, H-3), 7.40 (d, H-4), ($J_{3,4}$ = 8.4, $J_{4,6}$ = 2.4 Hz), 2.20 (s, CH_3), 1.98-1.65 (m, Adm); ms: m/z (relative intensity) 302 (M^+, 50), 301 (67), 135 (100), 93 (29), 79 (31), 43 (48).

Anal. Calcd. for $C_{17}H_{22}N_2OS$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.48; H, 7.37; N, 9.37.

3-Pyridinol 1-Oxide, *via* 3-acetoxypyridine 1-Oxide (**1h**), Method A.

To a solution of 3-pyridinol 1-oxide (22.22 g, 0.2 mole) in acetic anhydride (at 90°) was added a solution of AdmSH (33.6 g, 0.22 mole) in acetic anhydride (50 ml) over 20 minutes. After 3 hours at 95°, the mixture was cooled and 2-(1-adamantylthio)-3-acetoxypyridine (32.16 g, mp 177-178°) was filtered off. After recrystallization from ether, the mp was 184-185°: R_f 0.46 (solvent A); ir (Nujol): 1751 cm^{-1} (C=O); ^{1}H nmr: δ 8.37 (dd, H-6), 7.31 (dd, H-4), 7.07 (dd, H-5), ($J_{4,5}$ = 7.8, $J_{5,6}$ = 4.2, $J_{4,6}$ = 1.8 Hz), 2.34 (s. CH_3), 2.16-1.71 (m, Adm); ms: m/z (relative intensity) 303 (M^+, 8), 135 (100), 93 (24), 79 (28).

Anal. Calcd. for $C_{17}H_{21}NO_2S$: C, 67.31; H, 6.98; N, 4.53. Found: C, 67.50; H, 7.07; N, 4.53.

Work up of the acetic anhydride filtrate, as in Method A produced an oil (20 g) which was chromatographed to yield first, 2-(1-adamantylthio)-3-acetoxypyridine (from petroleum ether-ether 1:1, 0.5 g, bringing up the total of *pure* product to 29.8 g, (49%), then 2-(1-adamantylthio)-5-acetoxypyridine (3.08 g, 5%), mp 162-163°; R_f 0.39 (solvent A); ir (Nujol): 1759 cm^{-1} (C=O); ^{1}H nmr: δ 8.35 (dd, H-6), 7.36 (m, H-3, H-4), ($J_{3,6}$ = 0.9, $J_{4,6}$ = 1.5 Hz), 2.31 (s, CH_3), 2.16-1.69 (m, Adm); ms: m/z (relative intensity) 303 (M^+, 7), 135 (100), 93 (25), 79 (30).

Anal. Calcd. for $C_{17}H_{21}NO_2S$: C, 67.31; H, 6.98; N, 4.53. Found: C, 67.59; H, 7.04; N, 4.51.

Elution with ether yielded 2-(1-adamantylthio)-5-pyridinol (1.21 g), mp 207-208°; R_f 0.05 (solvent A), 0.58 (solvent B); ir (Nujol): 3100-2400 (br, OH) cm^{-1}; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 8.11 (d, H-6), 7.30 (d, H-3), 7.06 (dd, H-4), ($J_{3,4}$ = 8.4, $J_{4,6}$ = 2.4 Hz), 1.86-1.60 (m, Adm); ms: m/z (relative intensity) 261 (M^+, 11), 135 (100), 93 (32), 79 (40).

Anal. Calcd. for $C_{15}H_{19}NOS$: C, 68.92; H, 7.33; N, 5.36. Found: C, 68.96; H, 7.21; N, 5.42.

Continued elution with ether gave a solid (2.0 g) which was rechromatographed on silica gel (100 g). After a short forerun with petroleum ether-ether (7:3), there was obtained an additional quantity of 2-(1-adamantylthio)-5-pyridinol (1.1 g, with an overall yield of 4%). The pure fraction turned out to be 4-(1-adamantylthio)-3-pyridinol (0.3 g, 0.6%), mp 185-186° (from ether); R_f 0.43 (solvent B); ir (Nujol): 3000-2400 (OH) cm^{-1}; ^{1}H nmr: δ 8.41 (d, H-2), 8.12 (d, H-6), 7.29 (d, H-5), 7.06 (d, H-4), ($J_{5,6}$ = 5.4 Hz), 1.89-1.64 (m, Adm); ms: m/z (relative intensity) 261 (M^+, 15), 135 (100).

Anal. Calcd. for $C_{15}H_{19}NOS$: C, 68.92; H, 7.33; N, 5.36. Found: C, 69.02; H, 7.34; N, 5.36.

Hydrolysis of 2-(1-Adamantylthio)-3-acetoxypyridine to 2-(1-adamantylthio)-3-pyridinol.

A solution of the ester (7.0, 0.023 mole) was stirred in methanolic sodium hydroxide (0.8 g, 0.02 mole in 80 ml) for 3 hours at room temperature. After removing solvents, *in vacuo*, the residue was neutralized with concentrated hydrochloric acid and extracted with chloroform (3 x 80 ml). The extract was washed with water, (2 x 20 ml), dried (sodium sulfate) and evaporated to furnish 2-(1-adamantylthio)-3-pyridinol (5.16 g, 98%), mp 185-186°. Recrystallization from acetone provided the pure product, mp 185-189°; R_f 0.24 (solvent A), 0.63 (solvent B); ir (Nujol): 3200-2300 (OH) cm^{-1}; ^{1}H nmr: δ 8.20 (dd, H-6), 7.23 (m, H-4, H-5), ($J_{5,6}$ = 3.84, $J_{4,6}$ = 2.4 Hz), 1.97-1.64 (m, Adm); ms: m/z (relative intensity) 261 (M^+, 18), 135 (100).

Anal. Calcd. for $C_{15}H_{19}NOS$: C, 68.92; H, 7.33; N, 5.36. Found: C, 69.16; H, 7.44; N, 5.25.

A similar hydrolysis converted 2-(1-adamantylthio)-5-acetoxypyridine to 2-(1-adamantylthio)-5-pyridinol (quantitatively), identical to the compound isolated from the column.

3-Acetoxypyridine 1-Oxide (**1h**), Method B.

When the reaction of **1h** (11.11 g, 0.1 mole in 75 ml acetic anhydride) were carried with AdmSH (16.8 g, 0.1 mole in 25 ml acetic anhydride) in the presence of triethylamine (50 ml) at 90°, as described in Method B, there was isolated by crystallizations, and chromatography, AdmSAc (8.7 g, 49%), 2-(1-adamantylthio)-3-acetoxypyridine (5.5 g, 18%), 2-(1-adamantylthio)-5-acetoxypyridine (1.7 g, 6%) and 2-(1-adamantylthio)-5-pyridinol (0.3 g, 1%).

3-Bromopyridine 1-Oxide (**1g**), Method A.

A solution of AdmSH (10.65 g, 63.0 mmoles) in acetic anhydride (30 ml) was added (20 minutes) to a solution of **1g** (10.0 g, 57.0 mmoles) in acetic anhydride (80 ml). After heating at 95° for 3 hours, the mixture was cooled to yield a solid (5.4 g). Recrystallization from acetone furnished first 2-(1-adamantylthio)-3-acetoxypyridine (0.32 g), identical to the sample prepared, above from **1h**.

From the ether mother liquor, there crystallized 2-(1-adamantylthio)-3-bromopyridine (4.3 g, 23%), mp 146-147°; R_f 0.72 (solvent D); ^{1}H nmr: δ 8.35 (dd, H-6), 7.69 (dd, H-4), 6.83 (dd, H-5), ($J_{4,5}$ = 8.4, $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.2 Hz), 2.29-1.75 (m, Adm); ms: m/z (relative intensity) 324, 322 (M^+, 24, 20), 135 (100).

Anal. Calcd. for $C_{15}H_{18}BrNS$: C, 55.56; H, 5.59; N, 4.32. Found: C, 55.67; H, 5.67; N, 4.48.

The original acetic anhydride mother liquor was concentrated, *in vacuo*, and the dark gummy residue chromatographed on silica gel (250 g). Petroleum ether-chloroform (7:3) eluted AdmSAc (5.7 g, 43%), and then petroleum ether-methanol (7:3 to 1:1) yielded an oil (3 g) which was triturated with acetone to produce some more 2-(1-adamantylthio)-3-acetoxypyridine (0.22 g, 1%). The acetone mother liquor was rechromatographed on new silica gel. Petroleum ether-chloroform (7:3) eluted 3-(1-adamantylthio)-5-bromopyridine (1.1 g, 6%), mp 73-74° (from ether); R_f 0.77 (solvent D); ^{1}H nmr: δ 8.64, 8.58 (d's, H-2, H-6), 7.69 (three lines, separation 1.8 Hz), 2.03-1.64 (m, Adm); ms: m/z (relative intensity) 324 (M^+, 3), 135 (100), 93 (22), 19 (25).

Anal. Calcd. for $C_{15}H_{18}BrNS$: C, 55.56; H, 5.59; N, 4.32. Found: C, 55.56; H, 5.60; N, 4.34.

Further elution of this column gave some additional 2-(1-adamantylthio)-3-acetoxypyridine (0.07 g, bringing the total yield to 3.5%).

REFERENCES AND NOTES

[1a] Taken in part from the PhD Dissertation (SP), University of Illinois at Chicago, Health Science Center, June 1985; [b] Presented at

the 189th National Meeting, American Chemical Society, Miami Beach Florida, April 28, 1985, ORGN ABSTR, p 266.

[2] For a review of these substitutions, consult L. Bauer and S. Prachayasittikul, *Heterocycles*, **24**, 161 (1986).

[3] S. Prachayasittikul, J. M. Kokosa, L. Bauer and S. W. Fesik, *J. Org. Chem.*, **50**, 997 (1985).

[4] S. Prachayasittikul and L. Bauer, *J. Heterocyclic Chem.*, **22**, 771 (1985).

[5] L. Bauer, T. E. Dickerhofe and K.-Y. Tserng, *J. Heterocyclic Chem.*, **12**, 797 (1975).

[6] F. M. Hershenson and L. Bauer, *J. Org. Chem.*, **34**, 665 (1969).

[7] H. Vorbrüggen and K. Krolikiewicz, *Synthesis*, 316 (1983).

[8] T. Sakamoto, S. Kaneda, S. Nishimura and H. Yamanake, *Chem. Pharm. Bull.*, **33**, 565 (1985).

[9] K. Harano, R. Kondo, M. Murase, T. Matsuoka and T. Hisano, *Chem. Pharm. Bull.*, **34**, 966 (1986).

[10] R. S. Egan, F. M. Hershenson and L. Bauer, *J. Org. Chem.*, **34**, 665 (1969).

[11] J. M. Kokosa, I. Chu, L. Bauer and R. S. Egan, *J. Heterocyclic Chem.*, **13**, 861 (1976).

[12] K. K. Khullar and L. Bauer, *J. Org. Chem.*, **36**, 3038 (1971).