Tetrahydropyridinediols and Related Aldehydes from the Reactions of Pyridine *N*-Oxide with Mercaptans (1,2)

*John M. Kokosa and Ludwig Bauer**

Department of Medicinal Chemistry, College of Pharmacy, University of Illinois (Medical Center), P. O. Box 6998, Chicago, Illinois 60680

Richard S. Egan

Abbott Laboratories, North Chicago, Illinois 60064

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A new series of tetrahydropyridines was isolated when 1-adamantyl or *t*-butyl mercaptan was added *last* to a solution of pyridine *N*-oxide and triethylamine in acetic anhydride. Under these conditions, the predominant tetrahydropyridines proved to be 1-acetyl-2-alkylthio-3-acetoxy-6-hydroxy-1,2,3,6-tetrahydropyridines. These carbinolamides were isomerized in part during silica gel column chromatography to *trans*-4-acetoxy-5-alkylthio-5-acetamido-2-pentenals.

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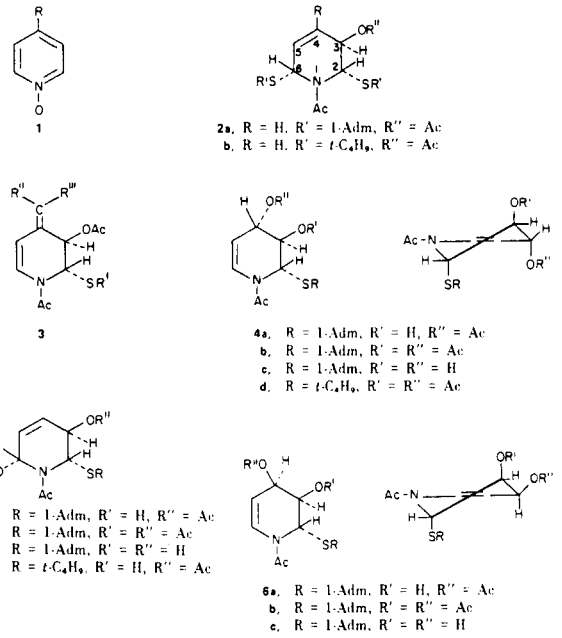
The reaction of pyridine *N*-oxides with mercaptans in acetic anhydride has yielded primarily pyridyl sulfides together with a variety of highly substituted tetrahydropyridines. The major type of tetrahydropyridine which can be expected from these reactions can now be predicted with some degree of centainty and its formation appears to be governed by the structure of the starting *N*-oxide, **1**, and the conditions of the reaction (3-6). It was shown that the reaction of **1**(R = H, CH_3, C_2H_5, *n*- and *iso*-C_3H_7, *t*-C_4H_9 and C_6H_5) with a mercaptan, [RSH being either *n*- or *t*-C_4H_9SH, or 1-AdmSH (1-adamantanethiol)] in acetic anhydride at 80° produced *predominantly* **2**, which could be isolated either as esters or alcohols, [R″ = Ac ($COCH_3$) or H] (3,5). When triethylamine was included in similar reactions of **1**, two different series of tetrahydropyridines have been identified. In the presence of an active methylene group at C-4 in **1**, as for example in 4-picoline, 4-ethyl-, 4-*n*- or isopropylpyridine 1-oxides, **3** was formed exclusively (R″ and R‴ being H or alkyl) (4,5). But, with pyridine 1-oxide (**1**, R = H), which lacked an active methylene group, it had been reported that **4** was the major product (4,6). In those experiments, triethylamine was added last to a solution of pyridine 1-oxide and mercaptan in acetic anhydride. In the present work it was found that, when the mercaptan was added *last* to a solution of pyridine 1-oxide in acetic anhydride already containing triethylamine, the major product was **5**. It would appear that **5** is the kinetically-controlled product since prolonged heating of **5** in acetic anhydride converted it to **4**.



Besides the major products, there were always minor byproducts, the most interesting of which were the aldehydes, **15**, which represent the first open chain compounds obtained from these reactions.

Structure of **5**.

Besides the aromatic pyridines, which were not investigated, compounds **5** were the major tetrahydropyridines

isolated from the reactions of pyridine *N*-oxide with 1-adamantanethiol or *t*-butyl mercaptan under the conditions described now. It was surprising to isolate the hydroxy acetoxy sulfides, **5a** and **5d**, instead of the expected *bis*-acetoxy derivatives of **5** (R′ = R″ = Ac). Apparently the latter were formed initially in the acetic anhydride medium but were preferentially hydrolyzed during the workup which involved extensive column chromatography on silica gel. Attempts to acetylate **5a** and **5d** wtih acetic anhydride produced the *bis*-acetoxy derivative, as was evident from their ^{1}H nmr spectra (in acetic anhydride) and tlc (thin-layer chromatography) data, but an aqueous workup, always afforded the impure *bis*-ester. The facile hydrolysis of the 6-acetoxy group in **5** is not unexpected since it is part of a carbinolamide function. This behavior of **5a** and **5d** was not the only difference in reactivity of these *bis*-oxy functionalized tetrahydropyridines when compared to the isomers in the known **6** series (5). Unlike the acetoxy derivatives in series **2** and **6**, attempts to hydrolyze **5a** and **5d** under mild conditions (5) did not produce the diols, **5** (R′ = R″ = H). Nor, did a hydrolysis with more concentrated alkaline reagents yield any aromatic derivatives, such as a pyridyl sulfide or pyridinol. It was this last type of reaction which proved to be most important in proving the structure of some of the earlier tetrahydropyridines, *viz.*, **2** and **3** (5).

The hydroxy acetates underwent two different reactions, in good yield, which supported the assigned structure. In boiling benzene, **5a** and **5d** were converted by 1-adamantyl and *t*-butyl mercaptans to **2a** and **2b**, respectively. The facile displacement of a hydroxy by a sulfide group to furnish the known **2a** and **2b** pointed to the skeletal background of **5a** and **5d**. It would seem logical that a carbinolamide hydroxyl group at C-6 in **5** could be displaced by a thiol to give **2**. It was perhaps surprising to find that prolonged heating of **5a** or **5d** in acetic anhydride produced the stable and known **4a** and **4d**, respectively. One could speculate, that, since the acetylation of the hydroxyl group at C-6 proceeds rapidly (see above), the acetoxy group at C-6 in **5** undergoes an S_N2' type displacement by acetate ion attacking C-4. Alternatively, perhaps, solvolysis of the 6-acetoxy group at C-6, forming an allylic carbonium ion, would take up the acetate ion to form the thermodynamically most stable product.

Besides these chemical transformations, their spectra were analyzed in detail. Their uv spectra indicated that the alkene was not conjugated with the ring nitrogen atom (max at 213 nm, log ϵ 3.6-3.8). Their mass spectra provided a molecular ion but otherwise could not be utilized for further clear-cut structure elucidation (7). Fortunately, the ^{1}H nmr spectra were devoid of rotamers and conformers, and provided good evidence for **5a** and **5d**. The discussion shall center primarily around **5a** and the data can be extrapolated for **5d**. In deuteriochloroform and perdeuteriobenzene, a large coupling constant due to CH(OH) coupling was observed, but no such coupling was seen in perdeuteriopyridine. The spectra in perdeuteriobenzene and perdeuteriopyridine spaced the signals sufficiently apart to permit an analysis. It was anticipated that a hydroxyl group or sulfide group at C-3 of the tetrahydropyridine system would give rise to a signal for H-3 around 3.5-4.5 ppm (5). However, the signals in **5a** and **5d** appeared with shifts below 5.0 ppm (Table I). Furthermore, the hydroxyl proton signal around 3.9 ppm was coupled with the signal at 5.49 and 5.19 ppm, in deuteriochloroform and perdeuteriobenzene, respectively. After extensive decoupling experiments, it was possible to establish which of the ring protons of **5a** and **5d** were vicinal to each other. Since the alkene was between C-4 and C-5, and using ^{1}H nmr data from **2** (5), the assignments in Table I were possible. The chemical shift of the methine proton, which carries the hydroxyl group, indicated that this proton was too deshielded to be H-3 and therefore had to be either H-2 or H-6. Since this methine proton coupled to one of the alkene protons, *viz.*, H-5 (J ~ 3 Hz), it had to be H-6. The absence of a non-exchangeable ^{1}H nmr signal around 4 ppm meant that the sulfide group could not be on C-3, but had to reside at C-2. By this process of elimination, the remaining acetoxy group had to be placed on C-3. The magnitude of the various coupling constants compared to those observed in the analogous systems, **2**, (3b) suggested similar steric relationships for the substituents in **5**, *i.e.*, the substituents at C-2 and C-3 are *trans*-dipseudoaxial (using cyclohexene nomenclature) and that at C-6 was pseudoaxial (3b). Further support for **5** arose from an experiment were **5a** or **5d** were converted on alumina to the isomeric aldehydes, **15**.

The carbon-13 nmr spectra of **5a** and **5d** also supported their structures (Table II). The crucial assignments were those of the chemical shifts of the three sp^3-hybridized ring carbons. The vinyl carbon chemical shifts were in the expected regions but the problem was to establish which of the signals around 50, 67 and 75 ppm arose from C-2, C-3 and C-6, respectively. Prior carbon-13 chemical shift data from similar ring carbons in series **2** (5) revealed that the upfield signal around 50 ppm belonged to C-2, *i.e.* the carbon carrying the sulfide group. To settle the chemical shifts of the carbons bearing the hydroxy and acetoxyl groups, respectively, single frequency decoupling experiments were performed using the frequency for the H-6 resonance (5.47 ppm). The intensity of the signal at 75.2 ppm was enhanced and therefore this line was

assigned to the chemical shift of C-6 in **5a**. Thus, the 67.4 ppm signal can be attributed to C-3 and all the chemical shifts of the ring carbons were then accounted for.

Mechanisms for the Formation of **4**, **5** and **6**.

The proposed mechanisms explain not only the formation of the aromatic sulfides, but also the various tetrahydropyridines *via* comon intermediates and are summarized in Chart I. As suggested some time ago (3a), the reaction logically begins with the quaternization of **1** (R = H) to form **7** which is prone to nucleophilic attack at C-2. The best candidate in the medium at the beginning is the mercaptan and this step would produce the neutral 1,2-dihydropyridine, **8**. Although "straight" elimination of acetic acid from **8** could explain the formation of one of the major products, the 2-alkylthiopyridines, it is imagined that more complex processes are involved to produce the 3-alkythiopyridines and the tetrahydropyridines.

It was postulated (3a) that the decomposition of **8** commences with the initial separation of the N-O bond into an nitrenium-acetate ion-pair, in a solvent cage, **9**. With the creation of the incipient nitrenium ion, C-3 and C-5 become electrophilic and highly susceptible to nucleophilic attack at those points. It is logical for the neighboring sulfide group at C-2 to attack C-3 and form the episulfonium ion, **10**. The intermediacy of **10** could readily explain the subsequent formation of all of the tetrahydropyridines isolated so far, as well as that of the aromatic sulfides, particularly those with the sulfide group β to the ring nitrogen.

Since episulfonium ions are extremely reactive (8), species like **10** would be expected to ring open even with a poor nucleophile, like acetate ion, to furnish either **11** or **12**. Furthermore, the stereochemistry of the formation of **11** or **12** should be *trans*. Most of the tetrahydropyridines isolated bear *vicinal* acetoxy and sulfide functions at C-2 and C-3. On the Basis of ^{1}H nmr data, these tetrahydropyridines were in one conformation with the C-2, C-3 substituents *trans*-dipseudoaxial. This assignment was based on the observed coupling constant ($J_{2,3}$, 2-3 Hz) which suggests (from the Karplus relationships) that the dihedral angle between H-2 and H-3 is about 60° and which correlates best if H-2 and H-3 are *trans*-di pseudoequatorial in **2-6**. Thus, **10** and **11** are considered to be vital intermediates for the production of **2** through **6** (9). It has not been possible to detect (nmr), isolate or trap such an intermediate, **11**, up to this point.

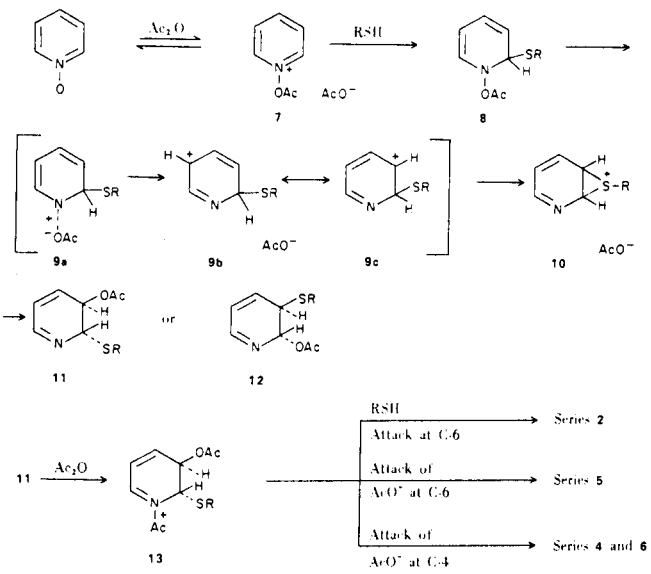
To complete the conversion of **11** to the final products, it is suggested that acetic anhydride quaternizes **11** to form **13**. With excess mercaptan in the medium, nucleophilic attack at C-6 affords product of type **2**. So far, no tetrahydropyridine has been isolated resulting from the attack of RSH at C-4 of **11**. However, attack of acetate ion on the ring of **11** has provided three different kinds of products so far: at C-6 there is formed **5**, while attack at C-4 forms either **4** or **6**. One might surmise that the presence of triethylamine in this reaction helps to create a large concentration of acetate ion and at the same time the base catalyzes the reaction of RSH with acetic anhydride to form the thiol ester, RSAc, thus facilitating the removal of any mercaptan for further reaction. This could explain the preponderance of products **4** and **6** over **2** in those reactions in which triethylamine is included in the reaction, even when three equivalents of mercaptan were used.

Apparently, triethylamine altered the sequence of events but all the products can be explained in terms of intermediates like **8**, **11**, or possibly, **12**.

Structure of **6**.

From the presently described reaction of pyridine 1-oxide and 1-adamantanethiol, a small quantity of a new hydroxy acetate, **6a** (0.04%) was isolated, besides some of the known bis-acetate, **4b** (1.1%). The new compound, **6a**, was converted to the bis-ester, **6b**, and diol **6c**. Uv spectra supported the enamide structure of **6**. The nmr spectra of members of series **6** were quite similar to those of **4** (5), (Table I) and subtle differences were attributed to the difference in the stereochemistry of the oxy-substituent at C-4 in **6**. On examining the difference in the magnitude of the coupling constants between H-3 and H-4, H-4 and H-5 and using models and the Karplus relationship, it is suggested that in series **6**, the substituents at C-4 are *cis* to those at C-3, *i.e.*, H-4 and H-3 are pseudoaxial and pseudoequatorial, respectively.

Chart I

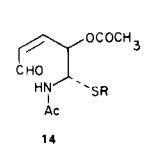


The formation of **6** can be explained by the mechanisms outlined in Chart I. Apparently members of type **4** are formed in preference to those of **6**. Type 4 was isolated previously (6) and in the present experiments is found in greater abundance to those of **6**. Apparently, once formed, it is not converted to other products in acetic anhydride. It was shown that **6a** was only acetylated to give **6b** after treatment with acetic anhydride and triethylamine at 95° for 3 hours and was not isomerized to **4b** or transformed to other products.

Structure of **15**.

One of the products isolated from the present reactions was an aldehyde (downfield doublet around 9.6 ppm), (ν CH = 2850, 2740 cm^{-1}, ν C=O = 1700 cm^{-1}). It was reasonable to expect that the carbinolamide, **5**, was in equilibrium with the *cis* aldehydoamide, **14**. However, the isolated aldehyde possessed the *trans* configuration, **15**, which was evident from the large coupling constant between H-2 and H-3. The pmr spectra readily revealed an exchangeable NH proton (ν NH = 3320 cm^{-1}) and together with the cmr data fits structure **15**. The ^1H nmr assignments were checked by double irradiation experiments and all crucial ^{13}C chemical shifts were verified by single frequency decoupling experiments. It would be expected that the stereochemistry about C-4 and C-5 in **15** would be maintained (relative to **5**) although free rotation about the C-C bonds would be expected.

The transformation of **5** to **15** can be explained *via* the α, β-unsaturated aldehyde **14**. Nucleophilic attack by Nu could create the intermediate anion **16** which could eliminate the attacking nucleophile to produce the thermodynamically more stable *trans*-isomer, **15**. Attempts to hydrolyze **15a** under mild alkaline conditions in methanol produced a new alcohol whose structure is under investigation. It was quite clear that the new product was devoid of an aldehyde group, but appeared to possess methoxy groups (singlets around 3.5 ppm).



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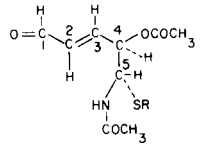
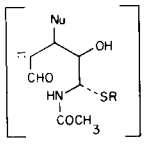


15a, R = 1-Adm
b, R = t-C_4H_9



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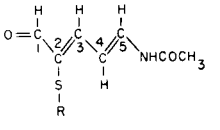

17a, R = 1-Adm
b, R = t-C_4H_9

Structure of **17**.

In the tlc of the crude reaction product from pyridine *N*-oxide and 1-AdmSH there appeared a highly fluorescent spot. This product subsequently appeared in a number of

Table I

^1H Nmr Parameters **4-6** in Deuteriochloroform (a,b)

Structure	Chemical Shifts, δ, in ppm, downfield from Internal Tetramethylsilane						Coupling Constants, J in Hz (c,d)						
	H-2	H-3	H-4	H-5	H-6	OH	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{3,5}$	$J_{4,6}$	$J_{H,OH}$
5a	(e)	5.25	(e)	(e)	5.49	3.84	2.0	5.5	--	2.5	--	--	11.5
5a (f)	6.57	5.45	5.94	5.83	5.19	3.93	2.0	5.5	--	3.0	--	--	11.5
5a (g)	6.59	5.54	6.28	6.43	5.89	--	2.0	5.5	9.8	3.0	--	1.5	--
5d	(h)	5.27	(h)	(h)	5.49	3.96	2.0	5.5	--	2.5	--	--	--
6a	5.78	4.84	5.78	4.84	6.60	2.72	2.0	4.0	2.0	8.5	2.0	--	4.0
6b (j)	5.78	5.34	5.97	4.86	6.61	--	3.5	4.5	2.0	8.5	2.0	2.0	--
6c	5.80	3.99	4.72	4.91	6.50	2.70	3.0	4.0	2.0	8.0	2.5	--	--
4a	5.93	4.29	4.94	5.17	6.77	2.62	2.5	1.5	4.5	8.0	1.5	--	--
4b	6.01	5.25	4.98	5.18	6.79	--	3.0	<1	4.5	8.0	--	1.5	--
4c	5.95	4.36	3.90	5.35	6.70	3.30 3.00	1.0	<1	4.5	8.0	1.8	--	--

(a) Unless another solvent is specified; (b) Usually, *O*- and *N*-acetyl methyl singlets were found around 2.0 ppm, *t*-butyl methyl signals as a singlet at 1.33 ppm and adamantane protons as two broad singlets between 1.6 and 2.2 ppm; (c) Although small long-range spin-spin coupling constants (*ca.* 0.5 to 1.5 Hz) were frequently observed, these were not all recorded at this time; (d) In a previous Table (Reference 6) the data for columns for $J_{3,5}$ and $J_{4,6}$ should be reversed; (e) Part of a complex multiplet between 5.85 and 6.40 ppm; (f) In perdeuteriobenzene; (g) In perdeuteriopyridine; (h) Part of complex multiplet between 6.0 and 6.5 ppm; (j) The computer-simulated ^1H nmr spectrum (100 MHz) for the 5-spin system of **6b** fitted very well when the following parameters were used: 578 (H-2), 534 (H-3), 597 (H-4), 486 (H-5), 661 (H-6) Hz, $J_{2,3}$ = 3.5, $J_{2,4}$ = 0.5, $J_{2,5}$ = 0.5, $J_{2,6}$ = 0.5, $J_{3,4}$ = 4.5, $J_{3,5}$ = 2.0, $J_{3,6}$ = 2.0, $J_{4,5}$ = 2.0, $J_{4,6}$ = -2.0, $J_{5,6}$ = 8.5 Hz.

Table II

^{13}C Nmr Parameters of **4-6** in Deuteriochloroform

Structure	Chemical Shifts, δ, in ppm downfield from Internal Tetramethylsilane							Adamantane Carbons				*t*-Butyl	
	C-2	C-3	C-4	C-5	C-6	Acyl C=O	Acyl CH_3	S-α-C	β-CH_2's	γ-CH's	δ-CH_2's	S-C	CH_3
5a	48.8	67.6	124.3	133.8	75.2	170.2	21.9 20.9	48.4	43.5	29.9	36.0		
5d	51.2	67.4	124.3	133.8	75.1	170.6 170.2	21.9 20.8					46.1	31.3
6a	53.5	67.9	67.4	104.0	126.6	170.6 168.0	21.7 21.1	47.2	43.8	29.9	36.1		
6c	53.6	69.8	63.5	109.1	125.0	170.0	21.9	47.2	43.9	30.0	36.1		
4a	51.6	67.4	71.7	105.2	127.8	170.6 168.9	21.9 21.2	46.7	43.7	29.9	36.9		
4b	48.7	72.9	65.2	105.3	128.3	169.9 169.0 167.5	21.1 20.8	47.2	43.6	30.0	36.1		
4c	51.0	73.6	67.0	110.2	125.2	168.4	21.6	47.6	43.9	29.9	36.1		

fractions during column chromatography but was finally separated pure from these columns. Its structure was postulated to be the glutaconic aldehyde derivative **17a**. The ^1H spectrum of **17a** displayed an aldehyde proton signal as a singlet at 9.46 ppm indicating that there was a substituent on the α-carbon. The other chemical shifts and coupling constants corroborate the assignment of structure **17a** to this byproduct. A cognate reaction using *t*-butyl mercaptan produced the analog **17b** in minute amounts which was also characterized by the ir, ^1H nmr and mass spectra. It would be too speculative at this point to propose a mechanism for the formation of **17**.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^1H nmr spectra were recorded on a Varian HA-100 and ^{13}C nmr spectra (at 25.2 MHz) on a Varian Fourier transform XL-100 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Proton chemical shifts were checked whenever possible by a series of decoupling experiments. Whenever certain carbon-13 chemical shifts could not be assigned with any degree of certainty, these were checked by single frequency decoupling experiments. Unless otherwise noted, infrared spectra were obtained in potassium bromide on a Perkin Elmer 337 spectrometer. Ultraviolet spectra were determined in methanol with a Perkin Elmer 202 spectrometer. Mass spectra were obtained by Mr. Richar Dvorak using a Hitachi-Perkin Elmer RMU-6D single focusing spectrometer. Only the more intense ions are reported, unless essential to a structure proof. Microanalyses for nitrogen were carried out in this Department with a Coleman D29 analyzer, those for carbon, hydrogen by Micro-Tech Laboratories, Skokie, Illinois. Thin layer chromatograms (tlc) were obtained on 8 x 4 cm. strips of Eastman chromagram silica gel sheets (No. 13181) with fluorescent indicator (No. 6060). Developing solvents were petroleum ether-ether, 7:3 (solvent A) and ether (solvent B). The products were identified whenever possible by uv light and/or iodine vapor stains. All silica gel for column chromatography consisted of neutral Mallinckrodt SilicAr CC-7, 200-325 mesh. For chromatography, pure dry solvents were used. Petroleum ether was that fraction, b.p. 30-60°;

The Reaction of Pyridine 1-Oxide with 1-Adamantanethiol.

In general, this procedure differs somewhat from the one previously published (6) in two respects: The thiol was added last to the solution of *N*-oxide in acetic anhydride and triethylamine. It would be expected that under these conditions there would be a relatively larger concentration of acetate ion compared to that of the mercaptan. This could explain why derivatives of **4** **5** and **6** are abundantly formed in preference to those of **2**. It was further found, that a larger quantity of type **5** than **4** and **6** is formed if the reaction is conducted at a more elevated temperature. It would appear that **5b** is the kinetically controlled product, since it is converted to **4b** very slowly at 95° in acetic anhydride. Under the conditions described below, the maximum yield of **5** was realized.

To a stirred solution of pyridine 1-oxide (11) (33.25 g., 0.35 mole) in acetic anhydride (200 ml.) and triethylamine (100 ml.) at 90° (measured internally) was added at once, 1-adamantanethiol (61.2 g., 0.36 mole in 100 ml. acetic anhydride). The temperature rose to 115° and fell after 5 minutes. The mixture was then heated on the steam bath for another 90 minutes. Solvents were then removed *in vacuo* and the residue stirred with a 50% aqueous potassium carbonate solution (300 ml.) at 25° for 1 hour to remove acetic anhydride, acetic acid and starting *N*-oxide. The organic phase was extracted with benzene (3 x 200 ml.). The benzene layer was dried (potassium carbonate) and solvents removed *invacuo* to provide 103 g. of crude product whose ^1H nmr spectrum and tlc revealed the presence of 1-adamantyl 2- and 3-pyridyl sulfides (6), and predominantly, **5b**, some **4b**, and the highly fluorescent (uv, tlc), **17a**. It would appear that the hydroxy acetates, **4a**, **5a** and **6a** which were subsequently isolated by means of extensive column chromatography, arose from partial hydrolyses of the *bis*-acetates, **4b**, **5b** and **6b**. Also, the open

Table III

Chromatography of Crude Reaction Mixture (103 g.) on Silica Gel (600 g.)

Eluating Solvent	Fraction	Crude Products	Weight (g.)	Crystallizing Solvent	Pure Product (weight)
Benzene	A	2- and 3- pyridyl sulfides and 1-AdSH (not examined further)			
Benzene	B	**4b**, **5b**	3.9	Petroleum ether	**4b** (1.0 g.)
Ether	C	**4b**, **5a**, **5b**, **15a**, **17a**	11.8		
Ether	D	**5a**, **5b**, **15a**, **17a**	4.9	ether	**17a** (0.35 g.)
Ether	E	**6a**, **15a**, **17a**	4.8		
		Rechromatography of Mother Liquors of Fractions B, C, and D (17.9 g.) on Silica Gel (600 g.)			
Ether	F	**4b**	0.63		
Ether	G	**5a**	3.99	ether (a)	**5a** (0.30 g.)
Ether	H	**5a**, **17a**	4.30	Petroleum ether (a)	**17a** (0.02 g.)
Ether	I	**5a**, **17a**	1.7	ether (a)	**17a** (0.10 g.)
Ether	J	**5a**, **15a**	1.2	ether (a)	**15a** (0.65 g.)

(a) The mother liquors from these fractions were combined and recrystallized from petroleum ether to give an additional 5.5 g. of **5a**.

		Rechromatography of the Mother Liquors of E and K (4.0 g.) on Silica Gel (300 g.)			
Ether	L	**17a**	0.34		
Ether	M	**15a**	0.23		
Ether	N	**15a**, **6a**	2.58	ether	**6a** (0.50 g.)

aldehyde, **15a**, appeared after extensive contact on the silica gel column.

Alumina had previously been used (6) for the isolation of the pyridyl sulfides and **4a** and **4b**, but it was found that the more polar hydroxy acetates were separated best on neutral silica gel.

Rather than describe the intimate details of the chromatographic separation, only vital steps are indicated. Basically, elution was followed by tlc and fractions containing similar components were combined and the solvent removed under reduced pressure, (rotary evaporator, *ca.* 30 Torr, water bath) taking care not to overheat the residues since some of these tetrahydropyridines were quite sensitive to pyrolysis. Residues were first respotted for tlc (to ascertain their survival during removal of solvents) and then triturated with a cold solvent (see Table III). Frequently, one pure compound crystallized out from a mixture and sometimes this was the only way to obtain pure samples.

Characterization of Products.

The nmr data were assembled in Tables I and II; the yields are based on starting *N*-oxide. The major product was **5a** (8.75 g., 6.8%); m.p. 106-107°; tlc, Rf's in solvents A and B were 0.18 and 0.50; ir: ν OH 3470 cm^{-1}, ν C=O 1740 (ester), 1670 cm^{-1} (amide); uv: (log ϵ) 213 nm (3.62); mass spectrum: 70 eV (relative intensity) 365 (< 1, molecular ion), 305 (6, M^+-60), 198 (30, M^+-SAdm), 180 (13, M-SAdm-18, m* = 164, indicative of the loss of water for the last transition) 138 (100, representing the loss of ketene from the ion, m/e 180) 135 (78, Adm^+) and 96 (45, which represents the loss of ketene from m/e 138 ion).

Anal. Calcd. for $C_{19}H_{27}NO_4S$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.52; H, 7.44; N, 3.80.

Reactions of **5a** with Acetic Anhydride.

After being exposed to acetic anhydride for 24 hours at 25°, **5a** appeared unchanged (tlc, ^1H nmr). After 24 hours, **5a** was converted by acetic anhydride and pyridine (1:1) into a mixture consisting of **5a**, **5b** (tlc for **5b**, Rf = 0.57 and 0.28, in solvents A and B, respectively. The spot due to **5b** *does not* fluoresce in the uv but does stain with iodine. Attempts to isolate **5b** by crystallization or chromatography resulted in mixtures, admixed with starting **5a**. Apparently, the allylic carbinolamide acetate is hydrolyzed relatively fast compared to the acetates in series **2** and **4** (5).

After 1 hour at 95°, **5a** was converted in part to **15a** (tlc, ^1H nmr) together with some **4b**. After 24 hours at 95°, **5a** (0.1 g.) was converted to **4b** (0.1 g.), m.p. 147-148°, identical with the lit. (6) sample (m.p., ir, ^1H nmr). For the last experiment, there appeared to be no **15a** in the final product (tlc) and the product was obtained on evaporating the acetic anhydride (*in vacuo*) and crystallizing from petroleum ether.

Reaction of **5a** with 1-Adamantanethiol.

A solution of **5a** (0.36 g., 0.001 mole) and 1-AdmSH (0.17 g., 0.001 mole) in benzene (10 ml.) was refluxed for 3 hours. During this time droplets of water were collected on the condenser (water solubility). After removal of benzene, the solid was triturated with petroleum ether to give **2a** (0.45 g., 86%), m.p. 195-197°, identical to the lit. (5) sample (m.p., ir, ^1H nmr).

Characterization of **15a** and **17a**.

The mixture obtained after the reaction was devoid of **15a** (tlc, ^1H nmr) but this aldehyde was isolated from the column

(0.88 g., 0.7%), m.p. 164-166°, Rf = 0.07 and 0.38 in solvents A and B, respectively; ir: ν NH 3320, ν C=O ester 1760, aldehyde 1700, amide 1650 cm^{-1}; uv: (log ϵ) 222 nm (4.07); ^1H nmr (deuteriochloroform): δ 9.59 (H-1), 6.80 (H-3), 6.31 (H-2), 5.97 (NH, slowly exchanged with deuterium oxide, 24 hours), 5.68 (H-5), 5.43 (H-4), 2.13 ($OCOCH_3$), 1.98 ($NCOCH_3$), 2.20-1.60 (Adm) ($J_{1,2}$ = 7.5, $J_{2,3}$ = 16.0, $J_{2,4}$ = 1.5, $J_{3,4}$ = 4.5, $J_{4,5}$ = 4.5, $J_{NH,5}$ = 9.0 Hz); ^{13}C nmr (deuteriochloroform): δ 192.6 (C-1), 169.7, 168.7 (CO), 149.2 (C-3), 134.0 (C-2), 74.9 (C-4), 51.2 (C-5), 47.3 (S-α-C) 43.6 (β-CH_2), 36.0 (δ-CH_2), 29.8 (γ-CH), 23.3, 20.8 ($COCH_3$); mass spectrum (relative intensity) was quite similar to that of **5a**, but differed in the relative intensities of the major ions; the most pronounced difference was the appearance of the ion, m/e 135, as the base peak: other relevant ions were m/e 365 (<0.01, M^+), 305 (6), 238 (17), 198 (9), 156 (4), 138 (48), 136 (13), 135 (100), 114 (11), 107 (5), 96 (11).

Anal. Calcd. for $C_{19}H_{27}NO_4S$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.36; H, 7.29; N, 3.78.

When pure **5a** was placed on a new silica gel column, it was in part eluted as the isomer **15a**.

Another aldehyde, **17a**, (0.61 g., 0.5%) was eluted from the original columns and was characterized on the tlc plate by its intense yellow fluorescence under long wave uv; m.p. 162-163°; Rf = 0.06 and 0.36 (solvents A and B); ir: ν NH 3450, ν C=O 1680 (aldehyde) 1605 (amide) cm^{-1}; uv: (log ϵ), 336 nm (4.43); ^1H nmr (DMSO-d_6): δ 10.81 (NH), 9.46 (H-1), 7.97 (H-3), 7.67 (H-5), 6.73 (H-4), 2.03 ($NCOCH_3$), 2.10-1.50 (Adm) ($J_{3,4}$ = 11.0, $J_{4,5}$ = 14.0 $J_{NH,5}$ = 11.0 Hz); ^{13}C nmr (DMSO-d_6): δ 191.6 (C-1), 168.2 (CO), 160.5 (C-3), 138.8 (C-5), 126.0 (C-2), 108.9 (C-4), 49.8 (S-α-C), 43.8 (β-CH_2), 35.6 (δ-CH2), 29.3 (γ-CH), 22.8 ($COCH_3$); mass spectrum: (relative intensity) 305 (1, M^+), 245 (14), 136 (12), 135 (100), 107 (9), 93 (19), 91 (7), 81 (6), 79 (23), 77 (9).

Anal. Calcd. for $C_{17}H_{23}NO_2S$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.27; H, 7.67; N, 4.34.

Characterization of **4b** and **6a**.

From earlier eluates of the columns (Table III), there was isolated **4b** (1.63 g., 1.1%), identical in m.p. (150-151°), tlc, ir and ^1H nmr spectra to lit. (6) sample. Later fractions yielded **6a** (0.5 g., 0.4%), m.p. 167-168°, Rf = 0.04 and 0.25 (solvents A and B); uv: (log ϵ) 236 nm (4.11). The mass spectrum differed considerable from the isomer, **4a** (6), *viz.*, **4a** showed a base peak, m/e 96 and a molecular ion of m/e 365. Most fragment ions of **6a** were less than 10% of the base peak of m/e 136. Prominent ions were m/e 305 (1, M^+-60), 288 (2), 245 (9), 210 (1), 198 (1), 197 (1), 180 (6), 168 (4), 156 (2), 138 (10), 136 (12), 135 (100), 96 (10).

Anal. Calcd. for $C_{19}H_{27}NO_4S$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.24; H, 7.62; N, 3.67.

Acetylation of **6a** (0.18 g., 0.0005 mole) with acetic anhydride (1 ml.) in pyridine (1 ml.) at 25° for 18 hours gave, after dilution with water, 0.2 g. (100%) of **6b** which was recrystallized from petroleum ether, m.p. 134-135°; tlc, Rf = 0.28 and 0.60 (solvents A and B). The major differences in the mass spectrum of **6b** compared to the isomer **4b** (6) were an extremely weak molecular ion for **6b**, m/e 407, and its base peak at 180, instead of m/e 138 for **4b**.

Anal. Calcd. for $C_{21}H_{29}NO_5S$: C, 61.90; H, 7.17; N, 3.44. Found: C, 62.11; H, 7.29; N, 3.58.

When **6b** (0.02 g.) was heated with acetic anhydride (2 ml.) at 95° for 24 hours, it was recovered unchanged.

After mixing **6a** (0.15 g.) with methanolic sodium hydroxide (0.01 g. in 5 ml.) at 25° for 5 minutes and dilution with water, **6c** was obtained, m.p. 100-102° (from benzene-petroleum ether) Rf = 0.01 and 0.13 (solvents A and B).

The mass spectrum of **6c** was quite different from **4c** (5), insofar that **6c** again showed a relatively weak molecular ion, m/e 323, the base peak was m/e 43, with the most intense ions as m/e 138 (30), 135 (30), 96 (95). Using an A. E. I. MS-9 mass spectrometer, and the peak matching technique, the molecular weight for $C_{17}H_{25}NO_3S$ was calcd. for 323.1555 and obs., 323.1547.

Reaction of Pyridine 1-Oxide with *t*-Butyl Mercaptan.

An analogous reaction of pyridine 1-oxide (33.25 g., 0.35 mole) in acetic anhydride (300 ml.) and triethylamine (100 ml.) with *t*-butyl mercaptan (32 ml., 0.1 mole) (12) gave, after removal of the solvents and most of the pyridyl sulfides ($\leq$ 40°, 0.015 Torr), a residue (42 g.) which was chromatographed on 600 g. of silica gel prepared in benzene. The work up procedure is described in Table IV.

Characterization of Products.

Nmr data were assembled in Tables I and II. The yields were based on the starting *N*-oxide. The major product was **5d** (6.92 g., 6.9%); an oil which slowly crystallized, m.p. 58-63°; Rf = 0.22 and 0.57 (solvents A and B); ir: ν OH 3400, ν C=O 1740 (ester), 1650 (amide) cm^{-1}; uv: (log ϵ) 212 nm (3.78), the mass spectrum was quite similar to that of **5a**, except that the one for **5d** was not influenced by the adamantyl moiety, m/e (relative intensity) 287 (<1), 227 (3), 198 (26), 180 (10), 138 (100), 96 (89).

Anal. Calcd. for $C_{13}H_{21}NO_4S$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.18; H, 7.46; N, 4.85.

Conversion of **5d** to **4d**.

After **5d** (1.0 g., 0.0035 mole) was heated with acetic anhydride (10 ml.) and triethylamine (5 ml.) for 24 hours, solvents were removed *in vacuo*. The residue was dissolved in ether, extracted with water and removal of the solvents afforded **4d** (1.15 g., 100%) m.p. 91-92°, identical to the lit. sample (4) in all respects. The same *bis*-acetate, **4d** was also isolated (0.60 g., 0.5%) form the original column (Table IV).

Conversion of **5d** to **2b**.

When **5d** (0.32 g., 0.001 mole) was refluxed with *t*-butyl mercaptan (5 ml.) for 3 hours, the solvents were removed, *in vacuo* to yield **2b** (0.21 g., 66%) m.p. 115-116°, identical to lit. sample (3a).

Characterization of **15b** and **17b**.

The new aldehyde, **15b**, (2.0 g., 2.0%) was isolated (Table IV), m.p. 96-98°, Rf = 0.06 and 0.37 (solvents A and B); ir: ν NH 3250, ν C=O 1745 (ester), 1700 (aldehyde) 1650 (amide) cm^{-1}; uv: (log ϵ) 220 nm (3.86) 332 (2.88); ^1H nmr (deuteriochloroform): δ 9.57 (H-1), 6.80 (H-3), 6.37 (NH), 6.31 (H-2), 5.67 (H-4), 5.42 (H-5), 2.12 ($OCOCH_3$), 1.36 (t-C_4H_9) ($J_{1,2}$ = 7.5, $J_{2,3}$ = 16.0, $J_{2,4}$ = 1.5, $J_{3,4}$ = 4.5, $J_{4,5}$ = 4.5, $J_{NH,5}$ = 9.0 Hz); ^{13}C nmr (deuteriochloroform): δ 192.7 (C-1), 169.8, 169.2 (CO), 149.1 (C-3), 134.0 (C-2), 74.7 (C-4), 53.5 (C-5), 45.0 (S-CCH_3), 31.2 (S-CCH_3), 23.2, 20.8 ($COCH_3$); mass spectrum: (relative intensity) m/e 287 (<1, M^+), 245 (1), 227 (3), 198 (22), 189 (12), 188 (7), 180 (4), 171 (16), 160 (20), 139 (10), 138 (100), 114 (44), 104 (62), 96 (46).

Table IV

Chromatography of Crude Reaction Mixture (42 g.) on Silica Gel (600 g.)

Eluating Solvent	Fraction	Crude Products	Weight (g.)	Crystallizing Solvent	Pure Product (weight)
Benzene	A	2-pyridyl sulfide (not examined further)			
Benzene	B	3-pyridyl sulfide, **4d**		petroleum ether	**4d** (0.25 g.)
Benzene	C	**4d, 5d**		petroleum ether	**4d** (0.20 g.)
					5d (0.30 g.) mother liquor)
Ether	D	**4d, 5d, 15b**	12.1		
Ether	E	**5d, 15b, 17b**	2.3		
		Rechromatography of D (12.1 g.) on Silica Gel (600 g.)			
Ether	F	**4d**		petroleum ether	**4d** (0.15 g.)
Ether	G	**4d, 5d**	1.08		
Ether	H	**5d**	6.60		
Ether	I	**5d, 15b**	1.06		
Ether	J	**15b**	1.60		
		Rechromatography of E (2.3 g.) on Silica Gel (100 g.)			
Ether	K	**17b**		ether	**17b** (several mg)
Ether	L	**5d**	0.02		
Ether	M	**15b**	0.40		

Anal. Calcd. for $C_{13}H_{21}NO_4S$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.38; H, 7.46; N, 4.81.

The column also yielded a few milligrams of **17b**, m.p. 193-194°, Rf = 0.07 and 0.04 (solvent A and B); ir: ν C=O 1680 (aldehyde) 1610 (amide cm^{-1}; ^1H nmr: identical to that of **17a** (except for the *t*-butyl protons); mass spectrum: (relative intensity), m/e mass spectrum, 227 (24, M^+), 171 (91), 167 (6), 149 (9), 129 (31), 128 (25), 113 (23), 112 (91), 111 (44), 101 (8), 100 (15), 99 (11), 96 (15), 68 (10), 67 (21), 60 (100).

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(1) Part XIV. The deoxydative substitution of pyridine *N*-oxides. For Part XIII, see, *J. Heterocyclic Chem.*, **12**, 797 (1975).

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(7) Great care was exercised not to utilize mass spectral analytical data to prove the structure in this series since such interpretations led to erroneous results on the structure of the 4,5-doubly bonded series, **2** (Reference 5).

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(9) It is quite possible that **11** is formed directly from the attack of acetate ion on **8** and thereby "pushing" the acetoxy group off the ring nitrogen. The attractiveness of the episulfonium intermediate is that it explains (a) the *trans*-stereochemistry of the substituents at C-2 and C-3, and (b) explains the formation of products bearing sulfide groups on carbons β (C-3 or C-5) to the ring nitrogen.

(10) Differences in chemical shifts for conformers and diastereomers in related systems have been reported recently; some leading references are C. A. Kingsbury and C. R. Cowles, *J. Org. Chem.*, **40**, 1302 (1975); Y. Takeuchi, P. J. Chivers and T. A. Crabb, *J. Chem. Soc., Perkins Trans., II*, 51 (1975); P. A. J. Gorin and M. Mazurek, *Can. J. Chem.*, **53**, 1212 (1975); K. Bock and C. Pedersen, *Acta Chem. Scand.*, **B, 29**, 258 (1975).

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(12) We are indeed indebted to Penn-Salt Chemical Co., and Phillips Petroleum Co. for research samples of this mercaptan.