Tetrahydropyridines and Furans from the Reaction of 4-*t*-Butylpyridine 1-Oxide with *t*-Butyl and 1-Adamantyl Mercaptan (1,2)

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The reaction of 4-*t*-butylpyridine 1-oxide (**1**) with *t*-butyl or 1-adamantyl mercaptan in acetic anhydride yielded the expected 2- and 3-alkylthio-4-*t*-butylpyridines and 1-acetyl-2,6-bis-(alkylthio)-3-acetoxy-4-*t*-butyl- and the *unexpected* 1-acetyl-2-acetoxy-3,6-bis(alkylthio-4-*t*-butyl-1,2,3,6-tetrahydropyridines. The addition of *t*-butyl mercaptan to a solution of **1** in acetic anhydride containing triethylamine produced the expected 1-acetyl-2-*t*-butylthio-3-acetoxy-4-*t*-butyl-6-hydroxy-1,2,3,4-tetrahydropyridine (**6a**) and the *unexpected* 1-acetyl-2,6-bis(hydroxy)-3-*t*-butylthio-4-*t*-butyl-1,2,3,6-tetrahydropyridine. Mild alkaline hydrolysis of **6a** yielded predominantly 2-[(acetamido) (*t*-butylthio)methyl]-3-*t*-butyl-5-hydroxy-2,5-dihydrofuran. The latter was converted by very mild acidic reagents to the corresponding furan and with 2,4-dinitrophenylhydrazine and sulfuric acid furnished 3-*t*-butylfurfural 2,4-dinitrophenylhydrazone.

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The reaction of 4-*t*-butylpyridine 1-oxide (**1**) with mercaptans in acetic anhydride was investigated to ascertain if a bulky substituents at C-4 would influence the course of the reactions and change the nature of the products which would be expected under several standard conditions (3-5).

The Reaction of **1** with *t*-Butyl Mercaptan in Acetic Anhydride.

In earlier experiments, there were isolated 2- and 3-*t*-butylthiopyridines (**2a** and **2b**) and two tetrahydropyridines (3). Reexamination of the tetrahydropyridine fraction from this reaction led to the isolation of the previously reported tris-sulfide (**3a**) and an acetoxy bis-sulfide whose published structure is corrected now (3). The structures of a related series of acetoxy bis-sulfides were revised (4), when it was shown that the acetoxy group resided on C-3 rather than at C-2 as had been deduced previously (3). Evidence for placing the oxy-function of **4a** at C-3 came from an analysis of the ^{1}H nmr spectra of this ester and those of the corresponding alcohol, **4b**. Signals for H-2, H-3, H-5 and H-6 in **4a** consisted of a series of complex multiplets between 5.3 and 6.2 ppm and to the presence of rotamers (3b, 6). The chemical shift for H-3 was around 5.7 ppm in the ester, **4a**, and 4.4 ppm for the alcohol, **4b** which is consistent for this change, C*H*OAc → C*H*(OH) (4).

From the same reaction there was isolated a small quantity of an alcohol, which proved to be isomeric with **4b**. The ^{1}H nmr spectrum was devoid of rotamers and relatively simple to interpret (Table I). Four upfield singlets in deuteriochloroform at 1.20, 1.45, 2.33 ppm represented the C- and *S*-*t*-butyl, and the methyl of the acetamido ($NCOCH_3$ = NAc) protons, respectively. In addition, an exchangeable, but not clearly coupled signal was found between 3 and 5 ppm for the hydroxyl proton (concentration dependent). The chemical shifts of three of the ring protons were between 5.5 and 6.2 ppm and that of the fourth ring proton at 3.65 ppm. Acetylation of this new alcohol produced an ester isomeric to **4a** which still showed a signal for one of the ring protons at 3.60 ppm. Since their uv spectra indicated an 1,2,3,6-

tetrahydropyridine system, structures **5b** and **5a** represent this new alcohol and ester. Assignment of H-3 to the 3.6 ppm signal was supported by a similar chemical shift for H-3 in **3a** (3.74 in deuteriochloroform, 3.84 in perdeuteriopyridine). Furthermore the 3.6 ppm signal was coupled to a proton signal which experienced the greatest chemical shift difference upon acetylation (5.62 → 6.50, *CH*OH → *CH*OAc, Table I). Therefore the hydroxyl group was attached to C-2.

The Reaction of 1-Adamantyl Mercaptan in Acetic Anhydride.

The reaction of **1** with 1-adamantyl mercaptan (1-AdmSH) produced the aromatic sulfides, **2c** and **2d** in the ratio of 45:1. Their structures were established by the ^{1}H nmr spectra which readily distinguished between the 2- and 3-sulfide (3). Apparently introduction of an 1-adamantylthio group β to the ring nitrogen was not inhibited since besides **2d** there was also isolated a substantial quantity of **5d** (see below).

The tetrahydropyridine fraction contained no tris-sulfide, **3b** and no obvious explanation for its absence is advanced at present.

There was isolated about an equal quantity of the isomeric esters, **4c** and **5c**. These were identified by means of their characteristic ^{1}H nmr spectra (Table I). The one for **4c** was, as usual, quite complex due to the existence of rotamers (6), while that for **5c** did not show rotamers and was easily analyzed. Mild alkaline hydrolysis of **4c** afforded the alcohol, **4d**, which could be reacetylated to form **4c**. However, extensive hydrolysis of **4c** (48 hours) yielded **2c**, which corroborated the structure assignment of this tetrahydropyridine. Hydrolysis of **5c** furnished **5d** whose ^{1}H nmr spectrum was similar to that **5b** (Table I) and in addition, in **5d**, visible coupling between the OH and ring proton ($J_{2,OH}$) corroborated the structural assignment.

To summarize this part of the work, isomeric oxy bis-sulfides types **4** and **5** have been isolated when **1** was used in this reaction with two mercaptans. Only type **4** had been encountered before (4). The mechanisms which have been proposed to explain the formation of various tetrahydropyridines all utilized an episulfonium ion intermediate which can also explain the formation of the new type, **5** (5).

The Reaction of **1** with *t*-Butyl Mercaptan in Acetic Anhydride and Triethylamine.

When the thiol was added last to a mixture of the *N*-oxide in acetic anhydride and triethylamine, there were formed **2c** and **2d** (8) and tetrahydropyridines (32% based on **1**). None of **3a**, or types **4** or **5** were isolated and the major product consisted of **6a** (22%). The structure of **6a** was established to be analogous to the *4-des-t*-butyl compound isolated from a cognate reaction using pyridine *N*-oxide (5). Presumably in acetic anhydride, the bis-acetate **6c** was formed which was partially hydrolyzed to **6a** during the work-up (5). Acetylation of **6a** in acetic anhydride could be followed *in situ* and H-6 moved downfield (5.58 → 6.75 in acetic anhydride) as **6a** was converted to the bis-acetate. Although **6a** could be hydrolyzed under carefully defined conditions to the diol, **6b**, the major products of the hydrolysis were usually the furans which are described below. This was a departure from the reaction of the 4-*des-t*-butyl analog which could be hydrolyzed to the corresponding diol. The ^{1}H nmr spectrum of **6b** contributed to the elucidation of **6a**, insofar, that the chemical shift of H-3 moved upfield in this transformation by 1.1 ppm (**6a** → **6b**; 5.45 → 4.37, Table I). Since the uv spectra placed **6a** into the 1,2,3,6-tetrahydropyridine series, and since the chemical shifts of H-2 in **6a**, **6b** and **6c** in deuteriochloroform remained relatively constant, the sulfide function was on C-2 and the oxy functions were on C-3 and C-6.

From the silica gel column, which already had yielded **6a**, there was isolated in the more polar fraction a dihydroxy monosulfide which was isomeric to **6b**. Unfortunately, its ^{1}H nmr spectra were complicated due to the presence of rotamers (6) and the closeness of the signals made an analysis in deuteriochloroform very difficult. In dry perdeuteriodimethyl sulfoxide, there was observed *CH*(*O*H) coupling, but after addition of deuterium oxide, the ^{1}H nmr parameters for both rotamers were established (Table I). The presence of rotamers was indicated when at 80°, the signals due to H-3 and H-5, sharpened as they coalesced, while those of H-2 and H-6 broadened. At higher temperatures, decomposition set in. Although there occurred profound changes in the ^{1}H nmr spectrum when **7** was heated in acetic anhydride, no analysis was possible with such complex multiplets and rotamers. Attempts to isolate pure acetates also failed. But prolonged heating in acetic anhydride (95°/24 hours) converted **7** into **2b** as the only identifiable product. This experiment established the presence of a sulfide group at C-3 in **7** and the fact that the chemical shift of H-3 in **7** was similar to that of H-3 of **3a**, **5c** and **5d** supported the structure of **7**. Besides **7**, the original silica gel column yielded another solid, whose tlc and elemental analysis indicated it to be an isomer of **7**. Its ^{1}H nmr spectrum contained, besides those signals attributable to **7**, additional small multiplets between 3.5 and 6.5 ppm and small singlets in the upfield region. It was concluded that it was a mixture of **7** and an epimer, such as **8**. As a matter of fact, when **7** was permitted to stand with methanolic sodium hydroxide, it equilibrated to a mixture of **7** and **8**. Acetic anhydride, as before, converted this

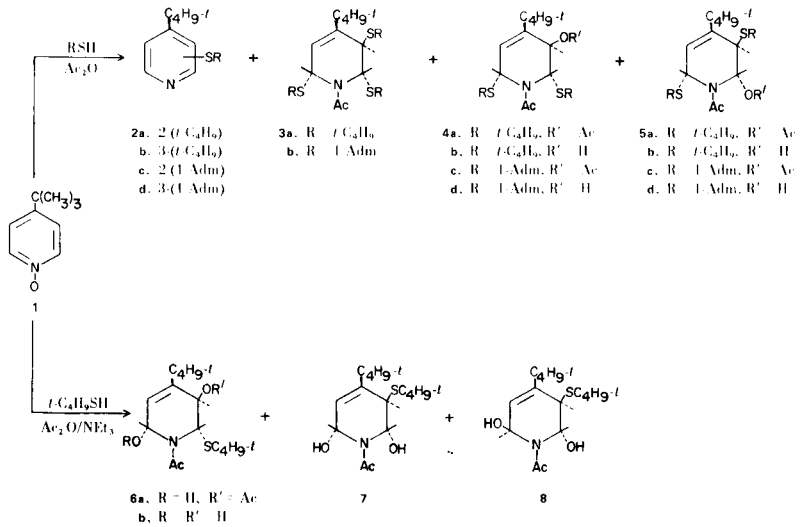
mixture to **2c**. Furthermore, **7**, or a mixture of **7** and **8**, reacted to form the same bis-2,4-dinitrophenylhydrazone, **9**. In view of the carbinolamide structure involving C-2 and C-6, it was expected that **7** (or **8**) would be converted by 2,4-dinitrophenylhydrazine into **9**.

The stereochemistry of these 1,2,3,6-tetrahydropyridines, **3-7** was judged to resemble those reported previously (3-5). This was based on the similar magnitude of the coupling constants in this series, $J_{2,3}$ and $J_{5,6}$ (Table I) and it is concluded that the substituents at C-2 and C-3 are trans-di*pseudo*axial and the one at C-6 to be *pseudo*axial (5).

2,5-Dihydrofurans and Furans.

Alkaline hydrolysis of the hydroxy acetate, **6a**, invariably furnished a mixture of products. Very mild conditions, such as 0.01 equivalent of sodium hydroxide in methanol at 25° for 1.5 hour, produced the diol **6b**, along with a solid, $C_{15}H_{25}NO_2S$, identified below as **13**. Potassium bicarbonate in boiling methanol quantitatively converted **6a** to another solid, $C_{15}H_{27}NO_3S$ which proved to be isomeric with **6b**. At first, it was thought that the last compound was the open aldehyde since the 4-*des*-*t*-butyl analog of **6a** was opened to an aldehyde (5) but this theory was discarded when the ^1H nmr spectrum did not show the typical aldehyde proton signal around 9.5 ppm. Spectral data and chemical transformations are consistent with the dihydrofuran structures, **11** and **12** for the isomers of **6b**. Although **11** and **12** are quite stable, they are extremely sensitive to mild acidic reagents. Even solutions in deuteriochloroform changed over a period of time and the complex spectrum of **11** and **12** was replaced by the very simple one, characteristic of **13** and consisting of the following downfield signals: two sharp doublets at 7.27 and 6.30 ppm (J = 4.0 Hz) and an AB quartet between these two doublets (6.40, 6.70 ppm, J = 9.6 Hz). Addition of deuterium oxide commenced a slow exchange (complete after 24 hours) when the 6.40 ppm signal vanished and the 6.70 ppm signal became a (broad) singlet. Since alcohols exchanged almost instantaneously with deuterium oxide, it was surmised that the slow exchange involved an amide NH and the presence of the NHCO group was confirmed by typical ir bands near 3440 and 1680 cm^{-1} for **11**, **12** and **13**.

To account for the formation of **11** and **12**, it is suggested that **6b** opens to the aldehyde **10** which cyclizes to form the furan hemiacetal **11** or **12** which possess an anomeric center at C-5. It was possible to epimerize the mixture with methanolic sodium hydroxide to provide pure **11** whose structure was elucidated through its ^1H nmr spectrum in perdeuteriodimethyl sulfoxide and deuteriochloroform. Subsequently, from an analysis of the ^1H nmr spectrum (with extensive decoupling experiments) of a mixture of **11** and **12** in deuteriochloroform it was possible to extract the nmr parameters for **12** since it was never isolated pure. ^1H Nmr parameters for both isomers had to be available to decide the stereochemistry at C-5 based on some literature findings which correlated the stereochemistry at C-2 and C-5 with vital coupling constant, $J_{2,5}$. In their detailed study on the interproton spin-spin coupling in 2,5-dihydrofurans, Barfield, Spear and Sternhell (9a) pointed out that in 2,5-dihydrofurans where one substituent at C-2 or C-5 is an oxygen-bearing substituent, both long-range coupling constants ($J_{2,5}$) decreased in magnitude and the *cis*-coupling constant becomes very small. In pure **11**, $J_{2,5}$ was 4.0 Hz and in the mixture of **11** and **12**, $J_{2,5}$ for **12** was determined to be about 1 Hz. Therefore **11** is the *trans*, and **12** the



cis-isomer. It is of interest to note that in perdeuteriopyridine or perdeuteriodimethyl sulfoxide a mixture of **11** and **12** equilibrated quickly to show the spectrum of **11** only while in chloroform the spectrum of both isomers was visible. However, in all solvents, a trace of trifluoroacetic acid or acetic anhydride showed fast transformation of **11** and **12** to **13**. The acid-catalyzed loss of water from the 2,5-dihydrofuran to the more stable furan is understandable.

It was further possible to characterize **11**, **12** or **13** with 2,4-dinitrophenylhydrazine sulfate to form 3-*t*-butylfurfural 2,4-dinitrophenylhydrazone. Again, as explained for the conversion of **7** or **8** to **9**, the α-acetamido sulfide function in **11**, **12** or **13** represents a potential aldehyde group.

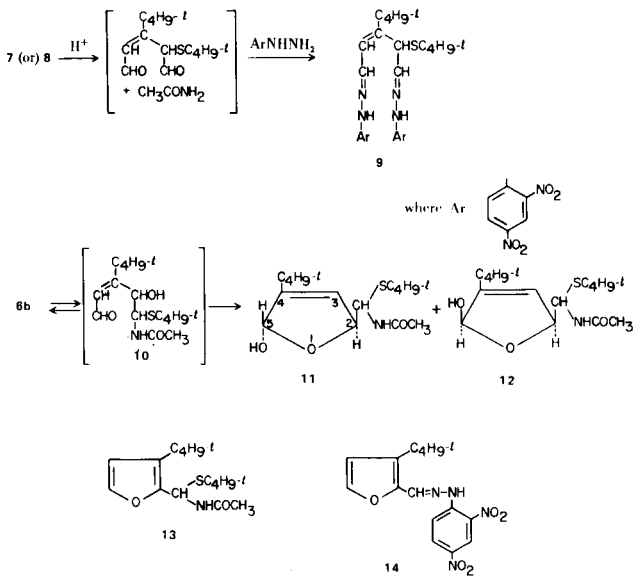
The isolation of these furan derivatives is new for this series and was not at all observed for the 4-des-*t*-butyl analogs. In blocking the 4-position of **6a** (**6b**), and equilibration with **10**, apparently blocks subsequent reactions involving C-4. Apparently, the 4-*t*-butyl group helps the formation of the thermodynamically stable furan hemiacetals, **11** or **12**, rather than 10 revert to **6b**. Thus, the presence of the 4-*t*-butyl group in **6a** (**6b**) changes the course of the reaction of this type to 3,6-dioxy substituted tetrahydropyridine (5).

Table I

^{1}H Nmr Parameters of **3-7** in Deuteriochloroform (a,b)

	Chemical Shift, δ, ppm downfield from TMS					Coupling constants, J, in Hz		
Structure	H-2	H-3	H-5	H-6	OH	$J_{2,3}$	$J_{5,6}$	Other
3a, Major Rotamer	6.27	3.74	5.33	5.73		2.4	3.2	
4b, Major Rotamer	5.17	4.28	5.71	6.00	~4.30	2.3	3.1	
4b, Minor Rotamer	6.07	4.41	5.81	5.37	~4.30	2.3	3.1	
4d, Major Rotamer	5.20	4.20	5.67	6.03	3.40	2.5	3.5	
4d, Minor Rotamer	6.10	4.30	5.67	5.43	3.40	2.5	3.5	
5a	6.50	3.60	5.68	5.95		2.6	3.6	
5b	5.62	3.65	5.78	6.12	~3.00	2.4	3.6	
5c	6.47	3.68	5.67	6.00		2.3	3.6	
5d	5.50	3.70	5.68	6.09	3.31	2.5	3.5	$J_{2,OH}$ = 8.0
6a	6.07	5.45	5.97	5.53	3.70	2.6	3.2	
6a (c)	6.47	5.70	5.90	5.17	3.51	3.5	4.5	
6a (d)	6.08	5.38	5.95	5.58		2.6	3.2	
6b	5.93	4.37	5.73	5.50	3.30 (3-OH) 3.63 (6-OH)	2.6	3.2	$J_{6,OH}$ = 12.0
6c (e)	6.03	5.34	5.70	6.75		2.6	3.2	
7, Major Rotamer (f)	6.05	3.52	5.52	5.32	5.15 (2-OH) 5.48 (6-OH)	2.8	2.2	$J_{2,OH}$ = 12.0 $J_{6,OH}$ = 8.0
7, Minor Rotamer (f)	5.37	3.57	5.50	5.58		2.8	2.2	
7, Major Rotamer	6.30	3.71	5.75	5.47	4.40 (broad)	2.5	2.0	
7, Minor Rotamer	g	3.67	5.85	5.47	4.40 (broad)	2.5	2.0	

(a) Unless another solvent is specified. (b) Signals were found [in ppm downfield from TMS] for *O*- and *N*-acetyl protons (~2.0 ppm), S-t-butyl (~1.3-1.4 ppm), *C*-*t*-butyl (~1.2 ppm) and adamantane protons (1.6-2.2 ppm). (c) In perdeuteriobenzene. (d) Dissolved in acetic anhydride at room temperature. (e) After heating **6a** in acetic anhydride at 95° for 3 hours and cooling at room temperature. (f) In perdeuteriodimethyl sulfoxide. When the solution was heated to 80°, the signals at 3.57 (H-3, H-3′) coalesced to a doublet, so did the signal at 5.55 (H-5, H-5′). The other signals broadeded. At 120°, decomposition set in. (g) The H-6 signal in the minor rotamer was under one of the signals centered around 5.8 or 5.5 ppm.



EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Uv spectra were obtained in methanol or ethanol on a Perkin Elmer 202 spectrophotometer. ^{1}H Nmr spectra were recorded on Varian T60A and HA-100 spectrometers and ^{13}C nmr spectra (at 25.2 MHz) on a Varian Fourier Tansform XL-100 Spectrometer. Chemical shifts are reported downfield from internal tetramethylsilane. Proton chemical shifts were checked by decoupling experiments, carbon-13 chemical shifts, by single frequency decoupling experiments. Mass spectra were obtained at 70 eV by Mr. Richard 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 were carried out 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) mixed with a fluorescent indicator (No. 6060). Developing solvents were petroleum ether-ether, 7:3 (solvent A) and ether (solvent B). The products were identified either by uv light and/or iodine vapor stains. For column chromatography (5), silica gel was Mallinckrodt's neutral SilicAR CC-7, 200-325 mesh and alumina was Alcoa's F-20.

The Reaction of **1** with *t*-Butyl Mercaptan (**10,11**).

A solution of **1** (15.1 g., 0.1 mole) and *t*-butyl mercaptan (32 ml., 0.3 mole) in acetic anhydride (100 ml.) was heated at 95° for 2 hours. Vacuum evaporation of solvents and the majority of the aromatic sulfides at 0.1 Torr (bath temperature no greater than 110°) provided a residue (28 g.) which was chromatographed on alumina (400 g.). Petroleum ether-benzene (7:3) eluted **3a** (7.0 g., 15%) which was recrystallized from petroleum ether m.p. 156-157°; tlc, Rf = 0.68, 0.88 (solvents A, B) and otherwise identical to the literature sample (3a). The ^{1}H nmr spectrum in perdeuteriopyridine has been analyzed (3a) and the one for the major rotamer observed in deuteriochloroform is listed in Table I.

The mother liquor from the crystallization of **3a** contained predominantly **2b** (3a).

Continued elution with benzene, and then ether, and recrystallization provided **4a** (6.4 g., 15%) m.p. 98-100°, identical to the literature sample (3); tlc Rfs = 0.36, 0.80 (solvents A, B). Its ^{1}H nmr spectrum at 60 MHz in deuteriochloroform showed multiplets between δ 6.2-5.3 for the ring protons, 4 singlets (δ 2.38, 2.15, 2.05, 1.98) about equal intensity, for *O* and N-COC*H*$_3$, the *S*-C$_4$H$_9$-*t* singlets around 1.4) and the *C*-C$_4$H$_9$-*t* singlet at 1.07 ppm. The spectrum indicated rotamers (6) of about equal concentration but no detailed analysis was attempted, since this has been achieved in perdeuteriopyridine (**3b**).

Hydrolysis of **4a** (1.25 g.) was achieved with potassium bicarbonate (0.15 g.) in refluxing methanol (25 ml.) for 18 hours. The solvents were evaporated *in vacuo* and the residue extracted with benzene. Benzene was removed and the product recrystallized from petroleum ether to give **4b** (0.58 g., 52%), m.p. 188-189°; tlc, Rf = 0.38 (solvent B); uv: nm (log ϵ), 207 (4.05); ^{1}H nmr, Table I. Reacetylation provided **4a**.

Anal. Calcd. for $C_{19}H_{35}NO_2S_2$: C, 61.08; H, 9.44; N, 3.75. Found: C, 60.79; H, 9.66; N, 3.61.

Elution of the original column with chloroform, and finally methanol provided **5b** (0.88 g.) m.p. 128-130°; tlc, Rfs = 0.21, 0.73 (solvents A, B); uv max (log ϵ) in ethanol, 212 nm (4.26); ^{1}H nmr, Table I.

Anal. Calcd. for $C_{19}H_{35}NO_2S_2$: C, 61.08; H, 9.44; N, 3.75. Found: C, 61.11; H, 9.71; N, 3.67.

Acetylation of **5b** (0.2 g.) with acetic anhydride (5 ml.) in pyridine (5 ml.) was carried out at 25° for 18 hours. The mixture was poured into water (50 ml.) and the solid collected, dried and recrystallized from petroleum ether to give **5a** (0.12 g.), m.p. 120-122°; tlc, Rf = 0.53, 0.87 (solvents A, B); ^{1}H nmr, Table I; high resolution mass spectrum (A.E.I. MS-9): m/e 415.2199 (i, Calcd. for $C_{21}H_{37}NO_3S_2$, 415.2215), other prominent ions were, m/e 326 (100, M-SC$_4$H$_9$), 266 (18, M-SC$_4$H$_9$-CH$_3$CO$_2$H), 224 (25), 210 (50), 168 (98), 152 (10), 136 (50), 125 (12), 121 (12), 120 (25), 57 (60).

The mass spectra of the isomeric esters, **4a** and **5a**, were examined to ascertain if they could distinguish between the two structures. The one for **4a** had been published, and interpreted, albeit on the basis of the wrong structure (3b), but interestingly enough was composed of identical fragment ions to the one for **5a** (70 eV) within 10% of their relative intensities. No further interpretation of these electron-bombardment induced fragmentation of **4a** or **5a** are offered until selected deuterium labelled compounds become available whose mass spectra might shed some light on this problem.

The mass spectra of the two isomeric alcohols, **4b** and **5b**, did not readily distinguish between their structures. These were determined on the same day under identical instrumental conditions. Features common to both are discussed first.

No molecular ion was observed for **4b**, while that for **5b** was less than 0.1% (m/e 373). Both showed the [M-(S-*t*-C$_4$H$_9$)]$^+$ ion, m/e 284, as the base peak. Lower molecular weight fragments for both ions were relatively few. The ones common to both were m/e 266 [loss of water from the M-(S-*t*-C$_4$H$_9$)ion] was 3 and 2% for **4b** and **5b**, respectively. For **4b**, the most intense subsequent fragment ions were m/e 228 (25) (loss of 56 or isobutylene from m/e 284 ion*), 210 (45), 168 (67), 152 (15), 136 (25), 125 (16), 90 (10) and 57 (75). On the other hand, **5b** showed more ions, but all of low intensity. The most significant ones, besides m/e 284, were m/e 356 (10, M-OH), 254 (12), 228 (15), 210 (10), 194 (10), 186 (11), 168 (15), 152 (25), 138 (20), 136 (23), 96 (40), 57 (30).

The Reaction of **1** with 1-Adamantyl Mercaptan.

A mixture of **1** (15 g., 0.1 mole) with 1-adamantyl mercaptan (17.3 g., 0.105 mole) was heated in acetic anhydride (100 ml.) on

a steam bath. When the internal temperature reached 60°, a spontaneous reaction ensued and the temperature rose to 90°. The flask was temporarily removed from the steam bath until the temperature dropped when heating was resumed for another 3 hours. The work up differed from the one described for *t*-butyl mercaptan, above, since the aromatic sulfides could not be distilled *in vacuo*. The higher boiling point of the pyridyl adamantyl sulfides would demand higher pot temperature and this in turn would jeopardize the stability of the required tetrahydropyridines since these are prone to pyrolysis (4). Therefore, solvents were removed at 20 Torr at bath temperatures up to 90° (rotary flash evaporator). The residue was dissolved in benzene (100 ml.) and stirred with 50% aqueous potassium carbonate solution for 1 hour to ensure the hydrolysis and subsequent neutralization of an acetic anhydride. The oil was taken up in benzene, dried (potassium carbonate) and solvents removed. The residue (31 g.) was subjected to a number of chromatographic separations which followed the usual methodology (5) and the isolation of pure components is described briefly.

The first column of alumina (400 g.) was prepared in petroleum ether and the crude product (31 g.) in benzene was placed on it. Four major fractions were collected and three of these were collected and three of these were rechromatographed. The products were characterized below. Pertoleum ether eluted first 1-adamantyl mercaptan. Then, a mixture of petroleum ether-benzene (1:1) produced a gum which was titurated with petroleum ether to afford pure **5c** (1.1 g.). Rechromatography of the mother liquors of **5c** (10 g.) on alumina (300 g.) furnished 2-(1-adamantanethio)-4-*t*-butylpyridine (4.4 g., 15%) when eluted with a mixture petroleum ether-benzene (4:1 to 3:2), m.p. 54-55°; tlc, Rf = 0.70 (solvent A); ^{1}H nmr (deuteriochloroform): showed the characteristic pattern for a 2,4-disubstituted pyridine (3a), with one doublet downfield for H-6, *viz.*, δ 8.47 (H-6), 7.60 (H-3), 7.13 (H-5), $J_{5,6}$ = 5.2, $J_{3,5}$ = 1.9 and $J_{3,6}$ = 0.7 Hz; δ 1.7 and 2.2 (two broad signals for the adamantane protons), 1.30 (*t*-C_4H_9).

Anal. Calcd. for $C_{19}H_{27}NS$: C, 75.69; H, 9.03; N, 4.65. Found: C, 75.46; H, 9.18; N, 4.47.

Further elution of the *original* column with benzene produced a gum, which, when covered with petroleum ether yielded **5c** (1.7 g.). Concentration of the petroleum ether filtrate produced some pure **4c** (0.35 g.). The mother liquors from thse two solids (5 g.) were rechromatographed on alumina (150 g.). Elution with a variety of mixtures of petroleum ether-benzene (7:3 to 1:1) furnished pure 3-(1-adamantanethio)-4-*t*-butylpyridine (0.1 g., 0.3%), m.p. 89-90°; tlc, Rf = 0.37 (solvent A); ^{1}H nmr (deuteriochloroform) was characteristic of a 3,4-disubstituted pyridine (3a), showing a broad singlet and doublet downfield, δ 8.68 (H-2), 8.43 (H-6), 7.32 (H-5), $J_{5,6}$ = 5.4 Hz; δ 1.6 and 2.1 (two broad signals for the adamantane protons), 1.47 (*t*-C_4H_9).

Anal. Calcd. for $C_{19}H_{27}NS$: N, 4.65; Found: N, 4.49.

Continued elution of this column with petroleum ether-benzene (1:1) yielded more **4c** (2.45 g.).

When the original column was eluted with methanol, a polar fraction (6.0 g.) was obtained which was rechromatographed on new alumina (150 g.) to provide pure **5d** (0.5 g., 0.9%) when the eluting solvent was benzene-chloroform, (3:2 to 2:3) which was identical to the product obtained below by independent mild hydrolysis of **5c**.

Characterization of Tetrahydropyridines.

The ester **4c** (overall yield, 2.8 g., 5%) possessed m.p. 186-187°; tlc, Rfs = 0.33, 0.88 (solvents A, B); ^{1}H nmr (deuteriochloroform), the ring signals were between δ 5.2 and 6.3 and the distribution of rotamers (6) were similar for those discussed for **4a**. The mass spectrum (70 eV) lacked a molecular ion at m/e 529.7 and the base peak was m/e 135 (1-adamantyl cation). The few prominent ions, m/e 301 (18), 286 (4), 359 (13) were not interpreted.

Anal. Calcd. for $C_{33}H_{49}NO_3S_2$: C, 69.31; H, 8.64; N, 2.45. Found: C, 69.37; H, 8.86; N, 2.28.

Mild hydrolysis of **4c** provided **4d**, (92%) m.p. 197-199°, after crystallization from petroleum ether; tlc, Rf = 0.44 (solvent B); ^{1}H nmr spectrum, Table I. The fragmentation pattern of the mass spectrum (70 eV) showed no molecular ion and was overshadowed by the intense m/e 135 ion and was not analyzed further.

Anal. Calcd. for $C_{31}H_{37}NO_2S_2$: C, 70.29; H, 8.94; N, 2.60. Found: C, 70.37; H, 9.14; N, 2.60.

This alcohol could be reacetylated in 60% to form **4c**, identical to the material isolated from the column. A more drastic hydrolysis of **4d** (0.19 g., 0.0003 mole) was carried out in refluxing methanol (10 ml.) containing sodium hydroxide (0.4 g., 0.01 mole) for 48 hours. The methanol was removed *in vacuo* the residue partitioned between water and chloroform, the chloroform dried (potassium carbonate), evaporated, and the oil (0.17 g.) analyzed by ^{1}H nmr and found to contain equimolar quantities of 1-adamantanethiol; tlc, Rf = 0.80 (solvent A) and 2-(1-adamantanethio)-4-*t*-butylpyridine, tlc, Rf = 0.70 (solvent A), which could be separated by further chromatography.

The isomeric ester, **5c**, was isolated from the column, as described, m.p. 210-211°; tlc, Rfs = 0.48, 0.93 (solvents A, B). Its ^{1}H nmr spectrum is in Table I and its mass spectrum was quite similar to that of **4c**.

Anal. Calcd. for $C_{33}H_{47}NO_3S_2$: N, 2.45. Found: N, 2.30. High resolution mass spectrum (A.E.I.-MS-9) m*e*/ 512.3012 (M-$C_2H_3O_2$, $C_{31}H_{46}NOS_{21}$, 512.3021).

Hydrolysis of **5c** provided **5d**, m.p. 165-167°; tlc, Rfs = 0.16, 0.76 (solvents A, B); ^{1}H nmr spectrum is in Table I; ^{13}C nmr spectrum at 25.2 MHz in deuteriochloroform was examined since this would provide data for the chemical shift of an α-carbon (to the amide) which was part of a carbinolamide. Prior ^{13}C nmr data (5) related to carbinol carbons at C-3 and C-4. Such carbons in these systems possessed chemical shifts around 67 to 70 ppm [from internal TMS] while in **5d**, this resonance is at 82.6 ppm. Similarly, this sample provides an opportunity to obtain the ^{13}C resonance with a sulfide at C-3, 40.6 ppm. The full spectrum is δ 168.5 (C=O), 139.0 (C-4), 123.5 (C-5), 82.6 (C-2), 47.6 (C-6), 49.0, 43.8, 36.2, 29.9 (α,β,γ and δ carbons of adamantane) 44.4 30.2 [C-$(CH_3)_3$], 22.7 ($COCH_3$).

Anal. Calcd. for $C_{31}H_{47}NO_2S_2$: N, 2.64. Found: N, 2.57. High resolution mass spectrum (A.E.I.-MS9) m/e 512.3002 (M-OH), $C_{31}H_{46}NOS_2$, 512.3021).

Reaction of **1** with *t*-Butyl Mercaptan in the Presence of Triethylamine.

To a preheated (95°, steambath) solution of **1** (52.8 g., 0.35 mole) in acetic anhydride (300 ml.) containing triethylamine (100 ml.) was added *t*-butyl mercaptan (40 ml., 0.35 mole) slowly through the condenser. The internal temperature rose spontaneously to 115°. After 5 minutes, when the temperature commenced to drop, the mixture was heated on the steam bath for 1.5 hours longer. Solvents and aromatic sulfides were distilled *in vacuo* (water bath ≤ 60° and 0.1 Torr). This distillate was not reexamined (8).

The residue (82 g.) was placed on a column of silica gel (600 g.) prepared in benzene. Elution was carried out, using

benzene, only. The first fraction consisted of 2-*t*-butylthio-4-*t*-butylpyridine (18.6 g.) (8). Subsequent elution brought forth a mixture of the last aromatic sulfide, together with a mixture of **6a**, **7** and **8** (18.5 g., Fraction A). Further benzene fractions contained pure **6a** (11.26 g.). These were followed by more **6a**, admixed with acetic acid. Such mixtures were dissolved in chloroform and neutralized by sodium bicarbonate solution to produce pure **6a** (4.53 g.). Finally, more of **7** and **8** were eluted. After concentrating the solvent and triturating the residue with ether **7** and **8** (1.0 g.) were obtained.

Fraction A (18.5 g.) was rechromatographed on silica gel (600 g.). Elution with benzene produced 2-*t*-butylthio-4-*t*-butylpyridine (1.5 g.), tlc, Rf = 0.78 (solvent A). Benzene-ether (1:1) then brough forth more **6a** (10.09 g.) followed by some **7** (0.47 g.).

Characterization of Products.

The major product was **6a** (25.88 g., 22.3%) which remained an oil: tlc, Rf = 0.25 (solvent B); ir (chloroform): 3500, 1740, 1660 cm^{-1} (ν OH, ν C=O); uv (methanol): λ max 212 nm (log ϵ, 3.75); ^1H nmr, Table I; mass spectrum (70 eV): m/e (relative intensity) 343 (1, M^+), 326 (1, M-OH), 283 (2, M-CH_3CO_2H), 254 (10, M-SC_4H_9), 236 (16, M-SC_4H_9-H_2O; m* for 254 → 236, 219.2), 212 (3), 194 (66, m* for 236 → 194, 159.4), 152 (66, m* for 194 → 152, 119), 136 (18), 43 (100).

Anal. Calcd. for $C_{17}H_{29}NO_4S$: C, 59.46; H, 8.51; N, 4.08. Found: C, 59.43; H, 8.67; N, 3.72.

One of the isomers, **7** or **8**, was isolated pure (0.84 g., 10%) m.p. 124-125°; tlc, Rf = 0.28 (solvent B); uv (methanol): λ max 209 nm (log ϵ, 3.86); ^1H nmr, Table I; the high resolution mass spectrum (A.E.I. MS-9 instrument), m/e 301.1706 (2.2, calcd. for $C_{15}H_{27}NO_3S$, 301.1866, other significant fragment ions were 284 (45, M-OH), 227 (18), 226 (13), 214 (16), 210 (16), 194 (13), 184 (18), 178 (19), 168 (27), 167 (34), 152 (40), 143 (18), 140 (25), 136 (21), 125 (42), 57 (100).

The remainder of **7** and **8** was an inseparable mixture (1.0 g., 1.0%), m.p. 131-132, tlc, Rf = 0.28 (Solvent B).

Anal. Calcd. for $C_{15}H_{27}NO_3S$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.85; H, 9.13; N, 4.64.

Acetylation of **7** and **8**.

A solution of the mixture of **7** and **8** in acetic anhydride was heated at 95° in a pmr tube for one hour. The ^1H nmr spectrum shows that the chemical shifts of H-2 and H-6 in **7** and **8** move downfield by about 1 ppm from δ 5.2-6.4 to 6.5-7.3. The proton at H-3 moved from δ 3.7 to 3.8. Thus the hydroxy groups must have been originally at position 2 and 6. When heating was continued for 24 hours, the ^1H nmr shows complete conversion to 3-*t*-butylthio-4-*t*-butylpyridine, ^1H nmr (acetic anhydride): δ 8.80 (H-2), 8.50 (H-6), 7.50 (H-5) ($J_{5,6}$ = 6.0 Hz).

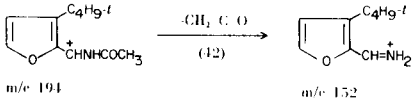
The Reaction of **7** and **8** with 2,4-Dinitrophenylhydrazine.

A solution of 2,4-dinitrophenylhydrazine (0.5 g.) in ethanol (5 ml.) containing 5 drops of concentrated sulfuric acid was prepared. When 0.1 g. of **7** and **8** was added to such a solution and the mixture warmed on the steam bath for a few minutes, orange crystals precipitated. The product (0.08 g.) was filtered and was washed with ethanol, m.p. 153-155°; tlc, Rf = 0.26, 0.83 (solvents A and B); ^1H nmr (deuteriochloroform): δ 1.30, 1.43 (C- and S-*t*-C_4H_9), 4.72 (d, H-2), 6.40 (d, H-4), 7.80 (d, 7.80), 8.42 (d, H-5), $J_{1,2}$ = 8.0, $J_{4,5}$ = 9.6 Hz, δ 11.13, 11.20 (two NH's). The aromatic signals for two different 2,4-disubstituted benzenes were not analyzed totally. The furthest signal downfield was for the proton between the nitro groups (δ 9.07) and the rest of the signals were between δ 7.70 and 8.50; the mass spectrum (70 eV) did not show a molecular ion (602), the first ion was m/e 404 (M-2,4-dinitrophenylhydrazine), 384 (100).

Anal. Calcd. for $C_{25}H_{30}N_8O_8S$: C, 49.83; H, 5.01; N, 18.59. Found: C, 49.99; H, 5.24; N, 18.42.

Hydrolyses of **6a**.

A solution of **6a** (1.7 g., 0.005 mole) sodium hydroxide (0.01 g., 0.00025 mole) in methanol (5 ml.) was permitted to stand at 25° until tlc indicated the disappearance of **6a** (2 hours). The mixture was diluted with water (10 ml.) and **13** (0.85 g., 61%) was filtered off, m.p. 162-163°, recrystallized from benzene or water); tlc, Rf = 0.03, 0.27 (solvents A, B); the ir spectrum (chloroform) showed a strong carbonyl stretching band at 1680 cm^{-1} and a medium band at 3445 cm^{-1} (NH) and several weak bands at 3580, 3620 and 3690 cm^{-1}. It was found that the product analyzed as the hydrate and this could explain the high frequency band (OH); ^1H nmr spectrum (deuteriochloroform): δ 1.33, 1.40 (C- and S-C_4H_9-*t*) 1.97 ($COCH_3$) 6.30 (H-4); 6.40 (NH), 6.70 (CH-NH), 7.27 (H-7), $J_{4,5}$ = 4.0, $J_{NH,CH}$ = 9.6 Hz. The NH signal exchanges slowly with deuterium oxide; the mass spectrum (70 eV) m/e (relative intensity) 283 (<0.01, M^+), 194 (95), 152 (100), 137 (20), 136 (25), 134 (18), 104 (30), 57 (25), 43 (25), The most intense ion represents an [M-S-C_4H_9-*t*] ion, which then looses ketene (m* 119.0).



Anal. Calcd. for $C_{15}H_{25}NO_2S \cdot H_2O$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.72; H, 8.96; N, 4.65. After drying at 80° *in vacuo*, to constant weight; Calcd. for $C_{15}H_{25}NO_2S$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.49; H, 9.03; N, 4.70.

The aqueous filtrate from **13** was saturated with sodium chloride was then extracted with chloroform to give an oil which was purified by dissolving it in hot water, filtering, and re-extracting the filtered aqueous cold solution with chloroform to give **6b** (0.64 g.) as a glass m.p. 70-80°, tlc, Rf = 0.40 (solvent B); ir (chloroform) showed OH and C=O bands; ^1H nmr spectrum is in Table I; the mass spectrum: (70 eV) showed a small molecular ion m/e 301 (1%) and m/e 83 as base peak.

Anal. Calcd. for $C_{15}H_{27}NO_3S$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.99; H, 9.04; N, 4.61.

When **6a** (1.7 g., 0.005 mole) was alternatively hydrolyzed by refluxing with potassium bicarbonate (0.25 g., 0.0025 mole) in methanol (20 ml.) for 1.5 hours, tlc revealed its complete disappearance. Methanol was removed *in vauco* and the residue partitioned between chloroform and water. The chloroform solution was dried (potassium carbonate) and evaporated to give a mixture of **11** and **12** (1.5 g., 100%), which was recrystallized from petroleum ether, m.p. 157-160°; tlc, Rf = 0.31 (solvent B); ir. (chloroform) ν OH 3700, 3640, ν NH 3450, ν C=O 1680, ν C=C 1540, 1520, 1500 cm^{-1}.

Anal. Calcd. for $C_{15}H_{27}NO_3S$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.41; H, 9.15; N, 4.56.

The mixture of **11** and **12** (0.16 g.) and sodium hydroxide (0.01 g.) was dissolved in methanol (5 ml.) and water (10 ml.). The solution was stirred at 25° for 18 hours. The resulting precipitate proved to be pure **11** (0.08 g., 50%), m.p. 152-154°.

Anal. Calcd. for $C_{15}H_{27}NO_3S$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.60; H, 9.19; N, 4.52.

Only ^{1}H nmr spectra distinguished between **11** and **12**. Tlc data were identical for **11** and **12**, Rf = 0.04 and 0.31 (solvents A and B); ir spectra did not help; the mass spectra of **11** or **12** appeared quite similar to those of **13** probably due to thermal elimination of water, showing strong ions, m/e 194, 152. Several spectra did show small molecular ions, m/e 301 (~ 1% of base peak, m/e 152); ^{1}H nmr spectrum of the pure *trans* isomer, **11**, in perdeuteriodimethyl sulfoxide, δ 4.87 (H-2), 5.53 (H-4), 5.82 (H-5), 5.53 (CH), 3.30 (OH), 6.15 (NH), 1.87 ($COCH_3$), 1.17, 1.26 (C_4H_9-*t*), $J_{2,5}$ = 4.5, $J_{2,4}$ = 2.0, $J_{H\text{-}2,CH}$ = 2.0, $J_{4,5} < 1$, $J_{5,OH}$ = 9.5 Hz; in deuteriochloroform (*trans* isomer) **11**, δ 5.15 (H-2), ~ 5.6 (H-4, C*H*-NH), 6.03 (H-5), 3.47 (OH), 6.57 (NH), 2.00 ($COCH_3$), 1.23, 1.33 (C_4H_9-*t*), $J_{2,5}$ = 4.5, $J_{2,4}$ = 2.0, $J_{H\text{-}2,CH}$ = 2.0, $J_{4,5}$ = 1.0 Hz; the *cis* isomer, **12**, in deuteriochloroform showed these important different ring proton characteristics, δ 4.88 (H-2), ~ 5.6 (H-4, CH) 5.77 (H-5), $J_{2,5}$ = 1.5, $J_{2,4}$ = 2.0, $J_{H\text{-}2,CH}$ = 2.0 and $J_{4,5}$ = 1.0 Hz.

Interconversion of **11** (or **12**) and **13**.

To a solution of **11** (0.05 g., 0.0017 mole) in chloroform (2 ml.) was added 2 drops of trifluoroacetic acid. After 5 minutes anhydrous potassium carbonate was added. The mixture was filtered, and solvents were removed to furnish **13** (0.04 g., 85%) m.p. 162-163°, identical in all respects to the above compound. An identical reaction was carried out with the mixture of **11** and **12** in deuteriochloroform: ^{1}H nmr analysis immediately after adding a drop of trifluoroacetic acid again showed total conversion to **13**. An identical conversion took place in deuteriochloroform alone after the solution stood for one week.

An attempt to acetylate **11** (0.5 g.) with pyridine (0.5 ml.) and acetic anhydride (0.5 ml.) for 18 hours at 25° followed by dilution with ice water and filtering again gave **13**, identical in all respects with the above compound.

Conversion of **13** to **11**.

A solution of **13** (0.14 g., 0.0005 mole) in methanol (5 ml.) was stirred with aqueous sodium hydroxide (0.01 g., 0.00025 mole) in 10 ml. for 24 hours at 25° and yielded **11** (0.15 g., 100%).

Preparation of **14**.

Reaction of **13** (0.1 g.) with ethanolic 2,4-dinitrophenylhydrazine sulfate solution at 25° (evolution of mercaptan) for 24 hours then provided **14** which was filtered and washed with ethanol (0.02 g.); m.p. 220-221° dec.; tlc, Rf's = 0.45, 0.83 (solvents A, B); ^{1}H nmr spectrum (deuteriochloroform): δ 1.43 (C_4H_9-*t*), 6.60 (H-4), 7.73 (H-5), C*H*=N), 12.93 (NH), 9.20 (aromatic proton between two nitro groups and 8.06-8.56 (complex multiplet for the aromatic protons) $J_{4,5}$ = 2.0 Hz; mass spectrum showed the m/e 332 as molecular ion and base peak, the other prominent ion was m/e 135 (50).

Anal. Calcd. for $C_{15}H_{16}N_4O_5$: C, 54.22; H, 4.85; N, 16.86. Found: C, 54.01; H, 4.79; N, 16.82.

Reaction of the mixture of **11** and **12** (0.1 g.) with 2,4-dinitrophenylhydrazine sulfate solution at 25° for 24 hours, gave **14** (0.02 g.) m.p. 220-221°, and identical in all respects to the above compound.

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(1) Part XV. The deoxydative substitution of pyridine *N*-oxides. For Part XIV, see *J. Heterocyclic Chem.*, **13**, 321 (1976).

(2) Support for this work by a Research Grant CA-13964 from the National Cancer Institute, NIH, US Public Health Service is most gratefully acknowledged.

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(5) J. M. Kokosa, L. Bauer and R. S. Egan, *J. Heterocyclic Chem.*, **13**, 321 (1976).

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A *B*

In addition, two *N*-acetyl methyl singlets were visible around 2.4 ppm. On heating, sets of signals from magnetically similar protons started to coalesce.

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(10) We thank the Reilly Tar and Chemical Company, Indianapolis, Indiana for their generous gift of 4-*t*-butylpyridine which was oxidized to the *N*-oxide (Reference 3a).

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