DEOXYDATIVE SUBSTITUTIONS OF PYRIDINE 1-OXIDES BY THIOLS

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Abstract - Deoxydative substitutions of pyridine 1-oxides by thiols in the presence of a variety of acid chlorides and anhydrides provide a mixture of 2- and 3-pyridyl sulfides. In addition to these sulfides, there were also isolated some interesting tetrahydropyridyl sulfides from some of the reactions conducted in acetic anhydride. Modes of formation of the various products are discussed.

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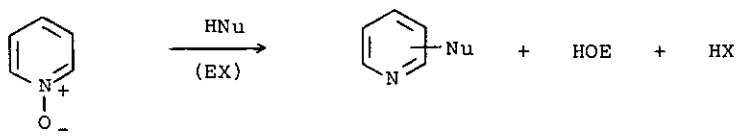
I. OVERVIEW OF DEOXYDATIVE SUBSTITUTIONS OF PYRIDINE 1-OXIDES

Substitution of pyridine 1-oxide (**1**) by a variety of reagents with the simultaneous loss of the N-oxide function is well-established. There are formed variously substituted pyridines (**2**) and the overall reaction is summarized by this equation:



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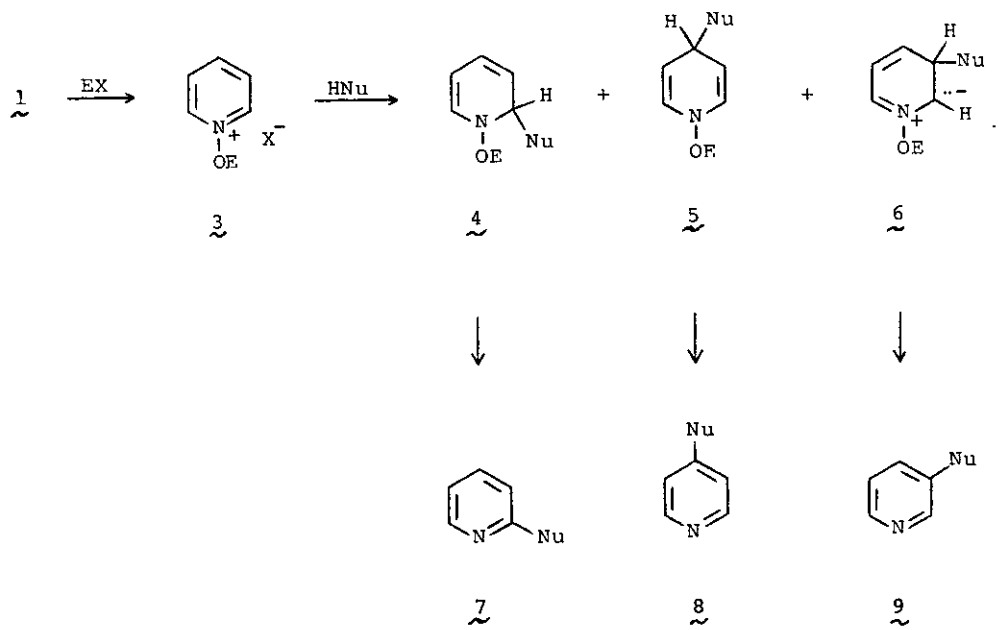
Such a substitution takes place satisfactorily only if an auxiliary reagent, such as an alkylating or acylating agent is included in the reaction mixture. This auxiliary reagent is represented here by EX, where E is an electrophilic atom and X becomes a nucleofuge. The process begins after **1** is quaternized by EX to form the salt **3**. Although such salts can sometimes be isolated readily, they are most frequently generated, in situ. Attack by a nucleophile, Nu:, at an α-(C-2 or C-6) or γ- (C-4) ring position of **3** leads to the neutral dihydropyridines, **4** or **5**, respectively, while β-attack (at C-3 or C-5) would generate the dipolar ion, **6**. Elimination of HOE from **4**, **5** and **6** produces the pyridines, **7**, **8**, or **9**, respectively. From these considerations, α- and γ-attack should predominate. This holds for many reactions, but frequently a considerable quantity of a β-substituted pyridine is isolated also. Since the initial steps in these reactions involves nucleophilic attack which is followed by the loss of the N-oxy function, these reactions are classified as **deoxydative nucleophilic substitutions.**



Many differently substituted pyridines are formed during this type of substitution of pyridine 1-oxides.[1] Attacking nucleophiles can be a halide ion or a group spearheaded by a nucleophilic oxygen, sulfur, carbon, nitrogen or phosphorus atom. Some representative reactions are provided to demonstrate the breadth of these substitutions. One of the best ways to introduce an oxygenated function into the pyridine ring is through the reaction of pyridine 1-oxides with acetic anhydride to form pyridyl acetates, which are readily hydrolyzed to either pyridones or pyridinols.[2] Antimony pentachloride has been shown recently to effect the same reaction.[3] Another useful conversion is brought about by reactions with phosphorus halides to form 2-and 4-halopyridines.[4] Several standard cyanation procedures of pyridine 1-oxides have been developed for the synthesis of 2- and 4-pyridinecarbonitriles.[5] Some of the other reagents containing inherent carbon nucleophiles which react with these N-oxides are active methylene compounds,[6] organometallic reagents,[7] certain trialkylsilanes,[8] indoles,[9] and enamines.[10] Amino functions are introduced when N-oxides are treated with isocyanates.[11] The dialkyl phosphonate anion (the attacking nucleophile) was used in the synthesis of pyridinephosphonates.[12] The mechanism and scope of these conversions is not discussed in detail since this review deals almost exclusively with the deoxydative substitution of pyridine 1-oxides by thiols.[13-32]

II. DEOXYDATIVE SUBSTITUTIONS BY THIOLS

A. Introduction

In the wake of the reports by Feely and Tani and their coworkers that 1-alkoxypyridinium salts are readily substituted by cyanide ion to form 2- and 4-pyridinecarbonitriles,[5c,5d] it was felt that mercaptide and thiophenoxide ions should react analogously and furnish 2- and 4-pyridyl sulfides, **7** and **8** (Nu = SR). However, when 1-alkoxypyridinium salts were treated with mercaptide salts, a mixture of pyridyl sulfides was isolated which always included a substantial quantity of the 3-isomer, **9** (Nu = SR). The substitution of 1-alkoxypyridinium salts by mercaptide ions was abandoned in favor of the more efficient and reproducible reactions of 1-acyloxy- and 1-sulfonyloxypyridinium salts with thiols.

B. Scope of the Reaction Using Acid Chlorides

Substitution of pyridine 1-oxides by thiols takes place quickly and conveniently in the presence of an acid halide or anhydride. Since 1-acyloxypyridinium salts (**3**, OE is OCOR) are somewhat difficult to isolate in a pure state (primarily due to their facile hydrolysis),[33] they are generated, in situ, in one-pot reactions. It was difficult to find a universal solvent which would keep all reagents in solution. Aqueous and alcoholic solvents, as well as dimethyl sulfoxide and N,N-dimethylformamide, had to be avoided since these could react with the acid halide. Benzene was chosen as the vehicle to conduct a number of related reactions which are summarized in Table 1.[17]

TABLE 1: DEOXYDATIVE SUBSTITUTION OF 1 BY RSH AND ACID CHLORIDES IN BENZENE TO FORM 7a AND 9a

R in RSH	Acid Chloride	Method[a]	Yields of **7a** and **9a**, %	Ratio of **7a:9a**
n-C_4H_9	$(C_2H_5)_2NCOCl$	A	68	98:2
n-C_4H_9	$(C_2H_5)_2NCOCl$	B	67	100:0
t-C_4H_9	$(C_2H_5)_2NCOCl$	A	61	92:8
t-C_4H_9	$(C_2H_5)_2NCOCl$	B	74	90:10
n-C_4H_9	$(CH_3)_2NCOCl$	A	37	98:2
t-C_4H_9	$(CH_3)_2NCOCl$	A	21	93:7
n-C_4H_9	$COCl_2$	A	10	81:19
n-C_4H_9	$COCl_2$	B	67	89:11
n-C_4H_9	$ClCO_2C_2H_5$	A	8	92:8
n-C_4H_9	$ClCO_2C_2H_5$	B	19	97:3
n-C_4H_9	n-C_4H_9SCOCl	B	20	80:20
n-C_4H_9	C_6H_5COCl	A	16	85:15
n-C_4H_9	C_6H_5COCl	B	26	92:8
n-C_4H_9	$C_6H_5SO_2Cl$	B	34	68:32
t-C_4H_9	$C_6H_5SO_2Cl$	A	18	35:65
t-C_4H_9	$C_6H_5SO_2Cl$	B	35	45:55
C_6H_5	$C_6H_5SO_2Cl$	A	30	41:59
4-(t-C_4H_9)C_6H_4	$C_6H_5SO_2Cl$	A	33	32:68
n-C_4H_9	$(CH_3)_2NSO_2Cl$	B	57	62:38
t-C_4H_9	$(CH_3)_2NSO_2Cl$	A	31	48:52
t-C_4H_9	$(CH_3)_2NSO_2Cl$	B	37	38:62

[a]In Method A, no triethylamine is present; in Method B, triethylamine was added.

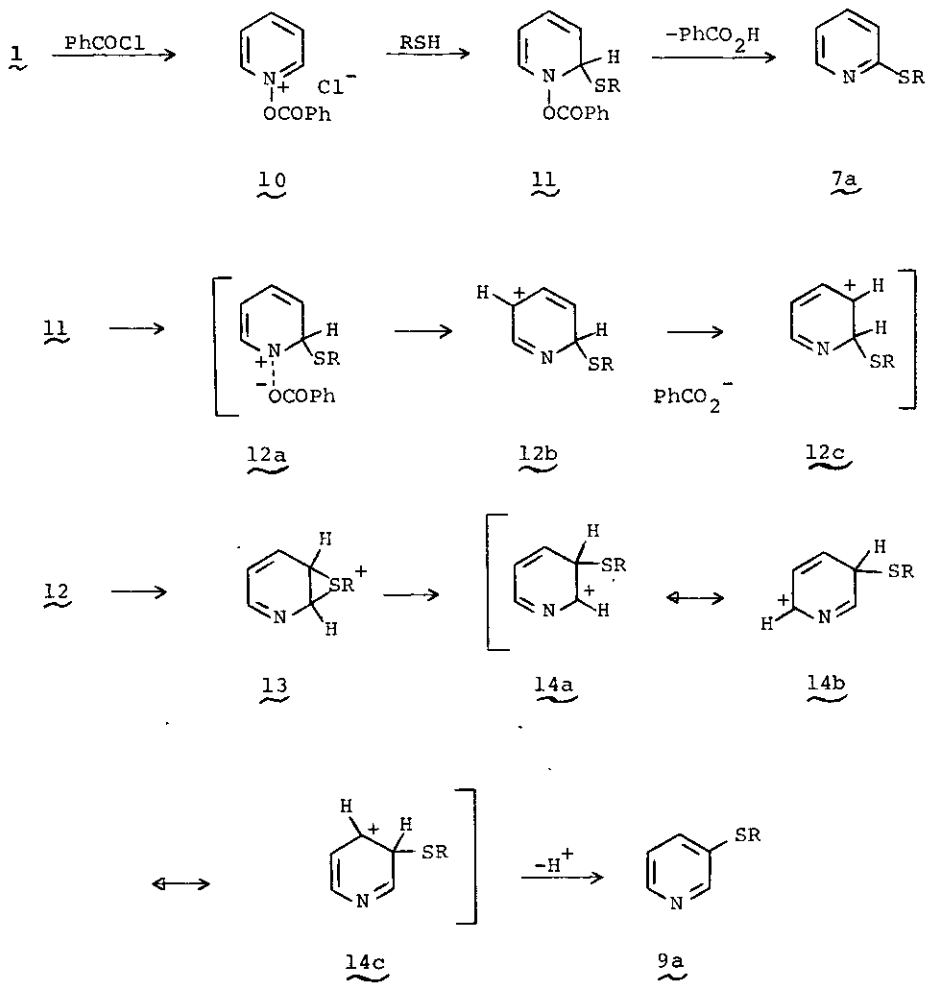
The acid chlorides were acetyl chloride, benzoyl chloride, N,N-dialkylcarbamyl chlorides, phosgene, benzenesulfonyl chloride and dimethylsulfamyl chloride. Invariably, there was isolated a mixture of 2- and 3-substituted sulfides. When triethylamine was added to these reactions to scavenge hydrogen chloride which otherwise might tie up some of the starting N-oxide (as its hydrochloride), unexpected changes in the yields and isomer distributions of pyridyl sulfides were noted (Tables 1 and 2). The role of triethylamine in effecting the course of these substitutions is discussed in Section IIE.

C. Mechanism of the Formation of 2- and 3-Pyridyl Sulfides

As a representative example of these substitutions, the reaction of pyridine 1-oxide (**1**) with mercaptans (RSH) in the presence of benzoyl chloride is discussed in detail. There was isolated a mixture of 2- and 3-pyridyl sulfides. One can explain the formation of the 2-, but not the 3-pyridyl sulfide, in terms of the well established Reissert type of reaction. One can speculate that the two isomers are formed either from independent attack of RSH at C-2 or C-3 of **1** (realistically from the salt, **10**), or from a common intermediate. A mechanism is advanced that supports the formation of both sulfides from a common intermediate.

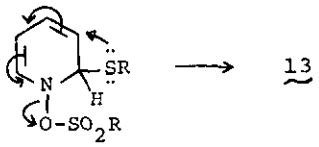
The sequence of events really begins with 1-benzoyloxypyridinium chloride (**10**). Attack by the highly nucleophilic mercaptan at one of the very electrophilic α-ring carbons (C-2 or C-6) of **10** generates the 1,2-dihydropyridine **11**. Elimination of the elements of benzoic acid from **11** is a logical driving force to form **7a**. The simple elimination of the carboxylic acid does not account for the formation of a substantial quantity of the 3-substituted sulfide (**9a**) (Tables 1 and 2). It is unlikely that the 3-sulfide arises from independent attack of the mercaptan on **10** due to the intermediacy of such an unfavorable dipolar intermediate, **6** (Nu = SR). There are other facts which are presented later to support the thesis that **7a** and **9a** are formed from **11**.

It is suggested that the elimination of the carboxylic acid begins with the separation of the carboxylate ion from the nitrogen ring of **11** to create an ion-pair in a solvent cage, **12a**. In this burgeoning nitrenium-ion the positive charge is delocalized at C-3 and C-5 as pictured by the resonance hybrids, **12b** and **12c**. As these carbocationic centers develop, the sulfide at C-2 is attracted to the electrophilic center at C-3 to form the episulfonium ion, **13**. Although **13** could reopen to **12**, it is more likely to open to the carbonium ion **14**, which is devoid of nitrenium ion character since all the positive charges are delocalized on ring carbons. The loss of a proton from **14** leads to **9a**. It is this sulfide migration which holds the key for the explanation of not only the formation of the 3-substituted sulfide, but also to some of the other products which are isolated from reactions in acetic anhydride (Section III). Neighboring group migration of sulfides <u>via</u> episulfonium ions is a recognized phenomenon in a number of aliphatic reactions.[34] There are other pieces of evidence which support the intermediacy of nitrenium-carbonium and episulfonium ions in these substitutions and these are discussed in Section III.



D. Substitutions in the Presence of Sulfonyl and Sulfamyl Halides

Although carbonyl halides serve as excellent auxiliary reagents, EX, reactions using either a sulfonyl or sulfamyl halide proceed extremely quickly to form mixtures of sulfides, particularly the β-substituted sulfide. The results are interpreted within the framework of the hypothesis which has just been advanced. Since sulfonate ion is a better leaving group than carboxylate ion, one can almost picture that the departure of the sulfonate ion is accompanied by concerted vinylogous sulfide participation, as pictured in **15**. The resultant episulfonium ion (**13**) can then form the 3-substituted sulfide (**9a**).



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Substitution of **1** by thiophenols failed when acid chlorides or anhydrides were employed, but took place readily in the presence of sulfonyl chlorides to produce a mixture of 2- and 3-pyridyl aryl sulfides in respectable yields.[25] Usually, the 3-substituted sulfide was the major product. These facile substitutions can be linked to several factors. The electron-attracting nature of an N-sulfonyloxy group in **3** (OE is RSO_3), encourages ArSH at the highly electrophilic C-2 to form a dihydropyridine, like **15**. The facile departure of the sulfonate (or of a sulfamate) ion from the ring nitrogen in **15** then causes quick aromatization of **15** to give rise to 2- and 3-pyridyl aryl sulfide.

One of the unavoidable by-products from the reactions of **1** with RSH and sulfonyl halides is the disulfide, RS-SR. Thiols are known to react with sulfonyl halides in the presence of a weak base, even pyridine, to form disulfides.[35]

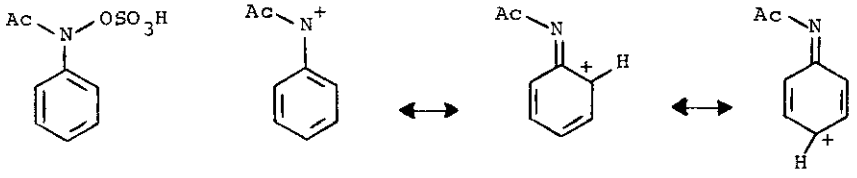
An interesting set of substitutions of **1** by thiophenol in the presence of N-phenylarylimidoyl chlorides has been reported. In 1,2-dichloroethane, there was isolated 2-anilinopyridine (49%), 3-phenylthiopyridine (35%) and 3-chloropyridine (1%).[36] The formation of these products is explicable within the framework of the mechanisms elaborated upon above.

E. The Role of Triethylamine

When triethylamine is included in these deoxydative substitutions, the proportion of the 2-pyridyl sulfides increases to that of the 3-isomer in almost all instances (see, Tables 1 and 2). In terms of the mechanisms discussed above, it is proposed that this (relatively) strong base aids in the abstraction of H-2 in 1,2-dihydropyridines of type **11**, or **15**, thereby increasing the yield of **7a**. One exception to this rule seems to be for the reactions using N,N-dialkylcarbamoyl chlorides. These acid halides really have a "built-in" amine in the sense that the departing ion, $R_2NCO_2^-$ (from **11**) decomposes to R_2NH thereby providing an amine, in situ, which can exert the same action as added NEt_3. The addition of triethylamine to substitutions carried out in acid anhydrides also caused an increase of the 2- over the 3-pyridyl sulfides.

F. Related Reactions Involving N-O Cleavage *via* Nitrenium-Carbonium Ion Intermediates

The whole question of N-O cleavage *via* resonance-stabilized aromatic nitrenium-carbonium ion intermediates is receiving considerable attention in another system. The metabolism of many N-arylacetamides, ($ArNHCOCH_3$) is believed to proceed *via* hydroxamic acids of type $ArN(OH)COCH_3$. The latter are then further metabolized to O-sulfates, type **16** (Ac = $COCH_3$) which then undergo further transformations. Hydrolytic and related studies on the model compound, **16**, provide new compounds whose formation can be explained in terms of nitrenium-carbonium ion intermediates, **17**. It is suggested that **17** reacts with nucleophilic reagents at various electrophilic aromatic sites.[37] It is carbonium ions, like **17**, which have been labelled as the "ultimate hepatocarcinogen".[38]



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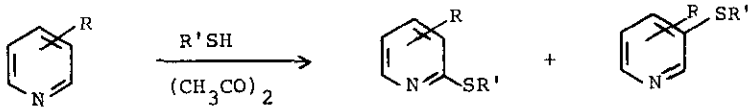
III. DEOXYDATIVE SUBSTITUTIONS OF MERCAPTANS IN THE PRESENCE OF ACID ANHYDRIDES

A. General Considerations and a Discussion of Competing Reactions

Although acid halides are excellent auxiliary reagents (EX), acid anhydrides are very effective in promoting these substitutions to form a mixture of 2- and 3-pyridyl sulfides (Table 2). Acetic anhydride (Ac_2O), is a convenient vehicle, acting both as solvent and reagent. One of the advantages of using acid anhydrides instead of acid chlorides is that the by-product are carboxylic acids instead of HCl. A carboxylic acid is less likely to tie up the weakly basic starting N-oxide, unlike HCl which forms stable salts with N-oxides. Furthermore, the presence of HCl can prove to be quite deleterious with regards to the isolation of some of the acid-sensitive tetrahydropyridyl sulfides (Section IIIB).

The well-established reaction of N-oxides with acetic anhydride to form pyridyl acetates,[2] is usually carried out at relatively high temperatures (e.g., in the boiling solvent, about 140 °C). Most of the substitutions of N-oxides by t-butyl and 1-adamantyl mercaptan (AdmSH) in acetic anhydride took place readily at lower temperatures. Furthermore, it was concluded that attack by a mercaptan on the 1-acetoxypyridinium cation is considerably faster than one by acetate ion in forming a 1,2-dihydropyridine. The reactions of pyridine N-oxides with mercaptans in acetic anhydride yielded primarily sulfides and seldom pyridyl esters, particularly if a large excess of thiol is employed.

TABLE 2: SUBSTITUTIONS OF PYRIDINE 1-OXIDES BY MERCAPTANS IN ACETIC ANHYDRIDE



R	R'	Method[a]	Yield of Sulfides, %	Distribution of Sulfide group α-Carbons C-2	α-Carbons C-6	β-Carbons C-3	β-Carbons C-5	Ref.
H	CH_3	A	38	52	-	48	-	18
H	n-C_3H_7	A	46	76	-	24	-	18
H	n-C_4H_9	A	67	61	-	39	-	14
H	t-C_4H_9	A	62	70	-	30	-	18
H	t-C_4H_9	B	41	90	-	10	-	19
H	1-Adm	A	44	68	-	32	-	20
H	1-Adm	B	35	80	-	20	-	20
2-CH_3	t-C_4H_9	A	32[b]	-	84	-	16	18
2-C_6H_5	1-Adm	A	81	-	76	-	24	22
2-C_6H_5	1-Adm	B	79	-	98	-	2	22
3-CH_3	t-C_4H_9	A	66	45	19	-	36	18
3-CH_3	t-C_4H_9	B	20	61	34	-	5	19
3-CH_3	1-Adm	A	70	48	18	-	34	32
3-CH_3	1-Adm	B	45	78	21	-	1	32
3-C_6H_5	1-Adm	A	51	52	43	-	5	22
3-C_6H_5	1-Adm	B	41	45	52	-	3	22
3-$CONH_2$	1-Adm	A	67	90	9	-	1	22
3-$CONH_2$	1-Adm	B	3	100	-	-	-	23
3-CO_2H	1-Adm	A	23	100	-	-	-	23

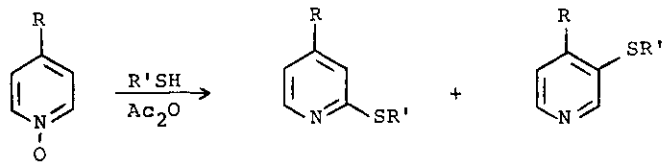
TABLE 2 (continued):

R	R'	Method[a]	Yield of Sulfides, %	Distribution of Sulfide group α-Carbons C-2	α-Carbons C-6	β-Carbons C-3	β-Carbons C-5	Ref.
4-CH_3	n-C_3H_7	A	31	50	-	50	-	16
4-CH_3	t-C_4H_9	A	41[c]	71	-	29	-	18
4-CH_3	t-C_4H_9	B	33	82	-	18	-	19
4-C_2H_5	t-C_4H_9	A	49	67	-	33	-	19
4-C_2H_5	t-C_4H_9	B	32	87	-	13	-	19
4-n-C_3H_7	t-C_4H_9	A	54	63	-	37	-	19
4-n-C_3H_7	t-C_4H_9	B	45	70	-	30	-	19
4-i-C_3H_7	t-C_4H_9	A	61	62	-	38	-	19
4-i-C_3H_7	t-C_4H_9	B	39	80	-	20	-	19
4-t-C_4H_9	t-C_4H_9	A	48	83	-	17	-	18
4-t-C_4H_9	t-C_4H_9	B	48	96	-	4	-	19
4-t-C_4H_9	1-Adm	A	15	98	-	2	-	29
4-C_6H_5	t-C_4H_9	A	18	44	-	56	-	18
4-C_6H_5	1-Adm	A	56	66	-	34	-	22
4-C_6H_5	1-Adm	B	49	92	-	8	-	22
2,6-di-CH_3	t-C_4H_9	A	0[d]	-	-	-	-	18
3,4-di-CH_3	t-C_4H_9	A	35[e]	48	23	29		18
3,5-di-CH_3	t-C_4H_9	A	66[f]	100	-	-	-	18
3,5-di-CH_3	1-Adm	A	50	100	-	-	-	30

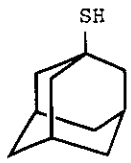
[a]In Method A, no triethylamine was added; Method B contained triethylamine. [b]The product also contained 10% of 2-(t-butylthio)methylpyridine, due to active methylene substitution. [c]3% of 4-(t-butylthio)methylpyridine was also isolated. [d]1% of 2-(t-butylthio)methyl-6-picoline was also isolated. [e]1% of 4-(t-butylthio)methyl-3-picoline was also isolated. [f]There was also obtained 3-(t-butylthio)methyl-5-picoline in 6% yield.

There is one reaction which competes with deoxydative substitutions, namely, the acylation of the mercaptan to form the thiol ester, (RSH → RSAc). The acetylation of 1-adamantyl mercaptan in acetic anhydride was examined in some detail. It was found that acylation took place relatively slowly, compared to the substitutions by thiols, but the acylation is strongly catalyzed by triethylamine. This observation reflects on the relatively poor yields of pyridyl sulfides when triethylamine is included into otherwise identical reaction mixtures (see, Table 2). Since the base-catalyzed acylation removes the thiol, one would have to use a relatively large excess of thiol. This is only practical when dealing with readily available commercial thiols, e.g., methyl or t-butyl mercaptans. But with less accessible thiols, like 1-adamantanethiol, only equivalent quantities were used. From the latter experiments, there was isolated relatively large quantities of S-1-adamantyl thiolacetate, together with considerable quantities of starting N-oxides. Unfortunately, S-1-adamantyl thiolacetate is totally ineffective as a source of 1-AdmSH needed in the substitution, since only starting materials were recovered after boiling pyridine 1-oxide and 1-AdmSAc in acetic anhydride. Apparently, the thiol ester did not equilibrate with the N-oxide to form any of the 1-acyloxypyridinium cation (like **10**) and release (even small quantities) of the thiol, which in turn could attack **10** to start the substitution. Therefore, once the thiol is acylated it is no longer available for substitution.

The reaction of a series of 4-substituted pyridine 1-oxides (**18**) with t-butyl and 1-adamantyl mercaptans in acetic anhydride yielded a mixture of 2- and 3-pyridyl sulfides, **19** and **20** (Table 2).

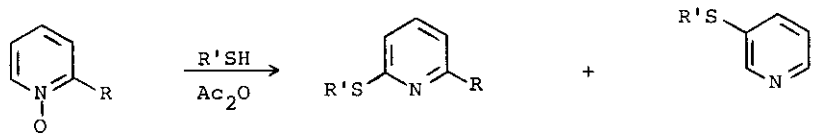


18 **19** **20**

where R'SH = (a) $(CH_3)_3CSH$; (b) 

As the size of the 4-substituent in **18** was increased from methyl to t-butyl, the percentage of 3-substituted sulfide decreased from 29 to 17% in the mixture of **19** and **20**. From 4-phenylpyridine 1-oxide, the sulfide mixture contained 56% of the 3-substituted product, i.e. **20** (R = C_6H_5, R' = t-C_4H_9). From the same N-oxide and using the bulky 1-AdmSH there then was isolated 34% of the 3-sulfide. Independent attack of such bulky thiols at C-3 in the face of a relatively large substituent as t-butyl at C-4 to form **20** is less likely to occur than through the migration of the sulfide group, via an episulfonium ion, as postulated above.

The substitution of 2-picoline and 2-phenylpyridine 1-oxides (**21**, R = CH_3 or C_6H_5, respectively) by mercaptans yielded **22** and **23** as the only pyridyl sulfides. It would appear that the sulfide group entered the pyridine ring at C-5 and C-6, but not at C-3. This observation again supports the assertion that the β-sulfide (**23**) arises from the initial dihydropyridine, **24**. One would surmise that the other dihydropyridine (**25**) is not involved. As a matter of fact, t-butyl mercaptan in acetic anhydride failed to substitute the ring of 2,6-lutidine 1-oxide, but gave some 2-(alkylthio)methyl-6-picoline due to active methylene substitution.

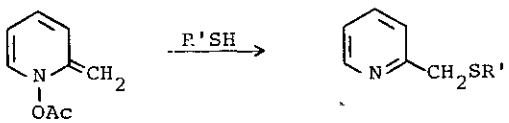


21 a, R=CH_3
b, R=C_6H_5

22 **23**

24 **25**

Active methylene substitutions during deoxydative substitutions are well-documented. In acetic anhydride, 2-and 4-picoline 1-oxides are substituted by acetate ion to form the corresponding (acetoxymethyl)-pyridines.[2] The methyl group of 2-picoline 1-oxide is substituted by a thioether during the reaction with a thiol in acetic anhydride. The active methylene substitution by a thiol is expected to proceed <u>via</u> an anhydrobase (like **26**, from **21a**) to form **27**.



26 **27**

B. **Formation of Tetrahydropyridyl Sulfides**

Although pyridyl sulfides are the major products from the reactions of pyridine 1-oxides and mercaptans in acetic anhydride, quite often some interesting higher molecular weight compounds are isolated as by-products (1-10%). Since these new compounds tend to decompose upon heating, care had to be exercised during the work-up so as not to overheat the pot during distillations of solvents or the lower molecular weight pyridyl sulfides. The by-products are obtained only after extensive column chromatography.

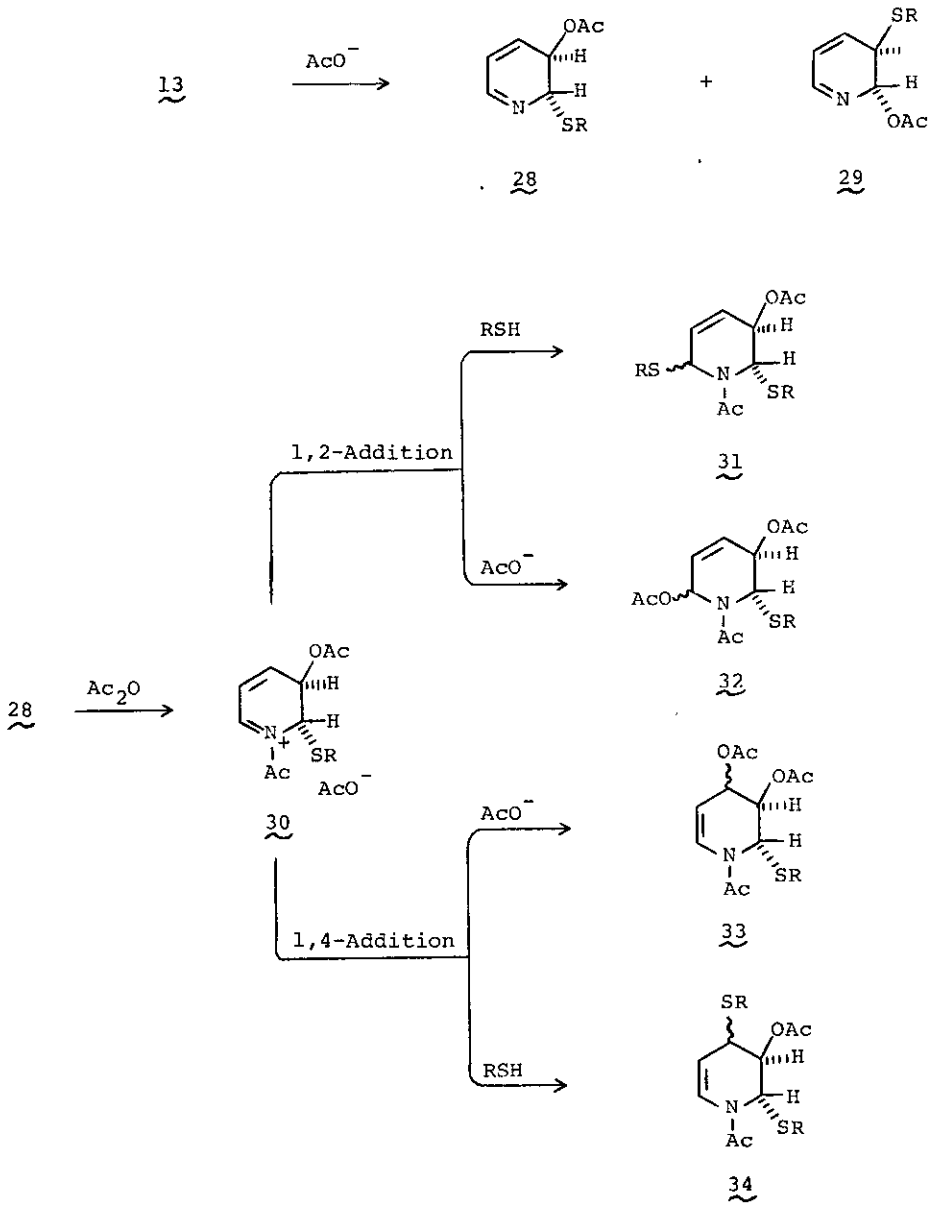
These higher molecular weight compounds turned out to be tetrahydropyridines, represented by some typical examples, **31-37**.[27-32] The structures of these compounds were established primarily by spectral methods. UV spectra distinguished readily between the tetrahydropyridines with an isolated double bond (e.g., **31** and **32**) from those in which the alkene is part of an enamide system (e.g., **33** and **34**). IR spectra confirmed the presence of esters and amides. Electron-impact mass spectra provided fairly good molecular ions, or molecular ions which have lost a discreet, but recognizable fragment from these systems.

There are relatively few reactions which can aid their structure determinations. Mild base-catalyzed hydrolysis of the acetoxy groups to alcohols, and the acetylation of alcoholic groups to form new esters are among the most useful reactions. These compounds were highly sensitive to strong acids since, after all they are α-amino sulfides which are susceptible to mild hydrolysis to glutaconic aldehyde derivatives with the release of acetamide and a mercaptan. Pyrolysis of these high molecular weight sulfides to apparently corresponding pyridyl sulfides appeared at first very useful until it was discovered that sulfide migration takes place during the pyrolysis of some of these compounds which led to some wrong structural assignments.[27]

Proton and carbon NMR spectra were instrumental in elucidation the structure and stereochemistry of these compounds.[27-32] It became apparent that substituents associated with these tetrahydropyridines were attached to different ring carbons. Chemical shift data and coupling constants provided the essential information to assign structures. There emerged a series of N-acetyltetrahydropyridines bearing at least one sulfide and one or two oxy functions. Tetrahydropyridines from mono-substituted pyridine 1-oxides usually possessed three methine protons. Unfortunately, the chemical shifts of these methine and alkene protons were downfield and relatively close to each other making NMR analyses frequently tedious. Carbon NMR spectra, particularly those involving the newer techniques, aided structure proofs immensely.[32]

Differently substituted tetrahydropyridines were isolated when triethylamine was included into otherwise identical reaction mixtures. Those tetrahydropyridines tended to possess only one sulfide group and two oxy functions. This might be attributed to the presence of a larger concentration of acetate ion, compared to that of the thiol, and at certain stages of their formation, acetate attacks in preference to the expected, but by now depleted, mercaptan.

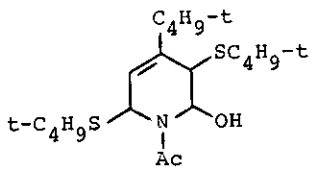
There is one aspect of the structure of these tetrahydropyridines which remained constant and is important in terms of the overall picture. In most of these compounds, a sulfide group resides at C-2 and is


13
AcO⁻
OAc
H
H
N
SR
28
+
SR
H
N
OAc
29
28
Ac2O
OAc
H
H
N+
SR
Ac
AcO⁻
30
1,2-Addition
RSH
RS
N
SR
Ac
31
AcO⁻
AcO
N
SR
Ac
32
1,4-Addition
AcO⁻
OAc
OAc
H
H
N
SR
Ac
33
RSH
SR
OAc
H
H
N
SR
Ac
34

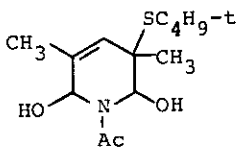
trans to an oxy function at C-3 (see, **31-34**). In some tetrahydropyridines, the sulfide is at C-3, but is still trans to an oxy function at C-2. This point is important since it bears on a part of their formation.

It is suggested that these tetrahydropyridines are formed via an episulfonium ion intermediate (**13**) which had been implicated in the formation of the aromatic sulfides. trans-Opening of **13** by acetate ion would then generate either dihydropyridine **28** or **29**. These dihydropyridines can become a source for many tetrahydropyridines. These further reactions are discussed briefly. Not all of the possible tetrahydropyridines have been isolated, although quite a few of different types have been characterized.

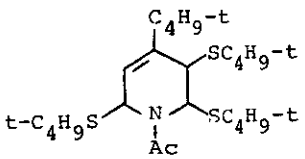
It is suggested that the reaction sequence is completed in the following way. Quaternization of **28** would generate the conjugated imminium salt, **30** which is highly susceptible to nucleophilic attack by either the thiol or acetate ion in an 1,2- or 1,4-addition to provide any one of the structures, **31-34**. No preferred stereochemistry of **31-34** is predicted. A similar sequence of events can take place starting from **29**. There have indeed been isolated some tetrahydropyridines in which the sulfide is at C-3 and the oxy function at C-2, e.g. **35** and **36**. Although seldom found, a tris-sulfide (**37**), has been isolated from 4-t-butylpyridine 1-oxide, t-butyl mercaptan in acetic anhydride.[26] Vicinal sulfides (which are trans) can also be formed if the mercaptan attacks **13**. The trans-bis-sulfide can then undergo any one of the routes outlined above from **28** → **31**. It is remarkable that in all of these piperideines, the stereochemistry at C-2 and C-3 is trans. At the other chiral centers in the molecule either configuration can prevail. Thus, in effect one could consider these (and other related tetrahydropyridines) as evidence for an episulfonium ion intermediate, or one can regard these compounds as a trap for such an intermediate.



35

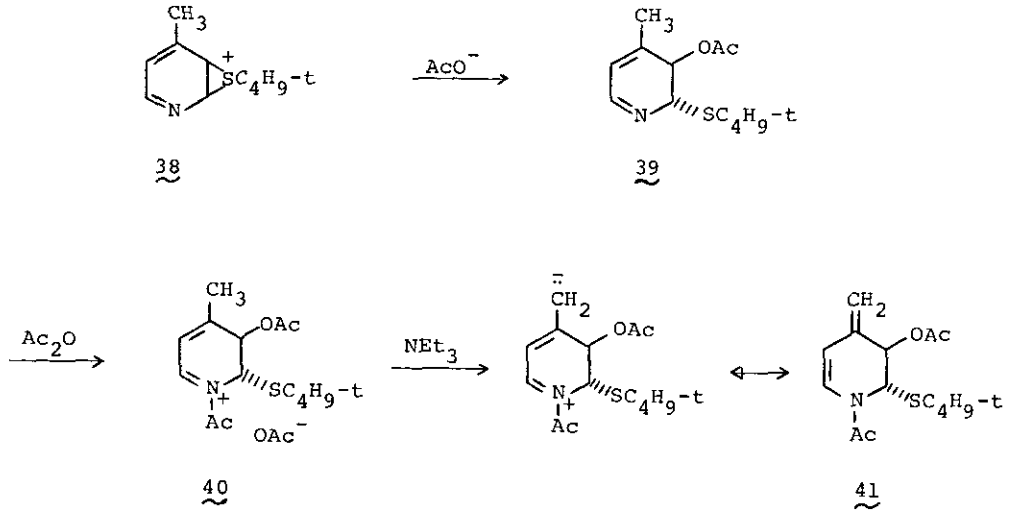


36



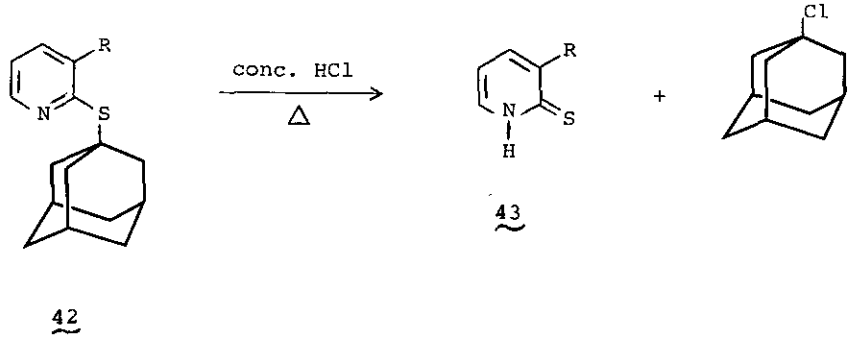
37

One of the simplest tetrahydropyridines which has been isolated is the one from 4-picoline 1-oxide, t-butyl mercaptan and acetic anhydride in the presence of triethylamine.[19] Its structure (**41**) can be arrived by involving ring opening of the requisite episulfonium ion (**38**) by acetate ion to form **39**. Quaternization of **39** by acetic anhydride then forms **40**. The protons of the active methylene group in **40** are sufficiently acidic to be neutralized by triethylamine to generate the product, **41**. In the absence of triethylamine, the same reaction yielded a tetrahydropyridine which is the 4-methyl analog of **31**.



IV. FORMATION OF PYRIDTHIONES (PYRIDINETHIOLS)

Although most of this review concentrates on the introduction of sulfides, there is a corollary to this work regards introducing sulfur-bearing groups into the pyridine ring. It was found that 1-adamantyl 2-pyridyl sulfides (**42**) are readily cleaved quantitatively by boiling concentrated hydrochloric acid to form 1-chloroadamantane and 2-pyridinethiones (**43**, R = H, CN, $CONH_2$).[20,23]



V. CONCLUSIONS

The deoxydative substitution of pyridine 1-oxides by mercaptans in the presence of acid halides or anhydrides represents a viable route for the synthesis of 2- and 3-substituted pyridyl sulfides. To increase the yield of 2-substituted isomers, the addition of triethylamine is recommended. To produce more of the 3-substituted isomers it is suggested that the auxiliary reagent be a sulfonyl or sulfamyl chloride. Pyridine 1-oxides are substituted by thiophenols only if a sulfonyl chloride is used as acylating agent. Besides the pyridyl

sulfides, uniquely substituted tetrahydropyridyl sulfides are formed when pyridine 1-oxides are reacted with mercaptans in acetic anhydride.

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