Electron-Impact Induced Fragmentation of Alkylthiopyridines. The Extent of Ring Nitrogen Involvement.

Kenneth F. King (1), Fred M. Hershenson (1,2), Ludwig Bauer and Charles L. Bell

Department of Chemistry, College of Pharmacy, University of Illinois at the Medical Center

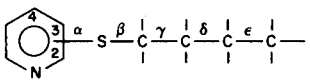
The fragmentation patterns obtained upon electron impact of 2-, 3-, and 4-alkylthiopyridines were examined to determine the extent that the ring nitrogen is involved. The effect of the size of the alkyl group, as well as the ring position of the sulfide on the fragmentation of the methyl-, ethyl-, *n*-propyl-, *n*-butyl- and *t*-butylthiopyridines, is discussed. The mass spectrum of 2-*n*-octylthiopyridine is also recorded.

The molecular ions decomposed with rupture of the bonds α, β, γ, and δ from the heteroaromatic ring. The molecular ions also exhibited the loss of alkenes *via* a number of mechanisms, notably the loss of $C_{n-1}H_{2n}$ from the alkyl group of 2-alkylthiopyridines by a transition involving the rupture of a C-C bond γ to the ring and the transfer of a proton on a carbon ϵ to the ring. The role of the pyridine sp^2 nitrogen in this and other fragmentations is discussed. An elimination of HS radical is also observed in a number of these alkylthiopyridines.

INTRODUCTION

Current interest in the electron-impact induced fragmentation of sulfides (3,4), and aromatic sulfides in particular (5-9), prompts us to record our observations for a number of alkyl pyridyl sulfides (10). The mass spectra were examined to determine the influence of the ring heteroatom on the electron-impact induced fragmentation of a series of homologous 2-, 3- and 4-alkylthiopyridines.

This study affords us the opportunity to compare the fragmentation of alkylthiopyridines, represented in broad terms by **1**, with analogous members in the benzene series (5). Even more interesting is the parallel behavior of some of the fragmentations of a series of 2-alkylthiothiazolo[5,4-*d*]pyrimidines, represented by structure **2**, with those of 2-alkylthiopyridines, in particular. In systems **1** and **2** one might expect the sp^2 pyridine nitrogen atom to exert similar effects on the decomposition of the molecular ion.



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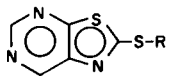


2

The nomenclature used here to indicate bond cleavage is that practiced for alkylpyridines (12), *i.e.*, the first bond between the aromatic ring and the first side chain atom (in this instance, S) is designated by α, etc., as shown in **1**.

RESULTS AND DISCUSSION

The 70-eV spectra of 2-, 3-, and 4-(methyl, ethyl, *n*-propyl, *n*-butyl and *t*-butyl) thiopyridines are presented in Figures 1 to 5, respectively, that for 2-*n*-octylthiopyridine, in Figure 6. The sulfides were prepared by literature methods (11) and their spectra obtained by means of a Hitachi-Perkin Elmer RMU-6D single focusing mass spectrometer equipped with a Honeywell 1508 Visicorder and using the liquid sample inlet system with a source temperature of 200° and minimum sample heating. In order to facilitate comparisons between the various spectra, they are plotted in terms of percent total ion current (% Σ_{29}). Only the fragments or fragmentation pathways that are unique, or offer an interesting comparison with similar systems in the literature will be discussed. Metastable ions for pertinent transitions are indicated in the text by m*.

Molecular Ion Abundance.

The effect of the proximity of the alkylthio group to the ring nitrogen atom is evident in the abundances of the molecular ions. It is clear from Figures 1 to 5 that the 3- and 4-thiopyridines gave an abundant molecular ion while the 2-substituted sulfides gave a less abundant molecular ion.

Analogous phenomena are observed in the spectra of alkylpyridines (13), alkylquinolines (14), and alkyl aryl sulfides (5,8) where it is seen that an increase in size in the *S*-alkyl group usually brings about a decrease in the abundance of the corresponding molecular ion. In the present study, the molecular ion is the base peak in 2-, 3-, and 4-methylthiopyridines, in 3- and 4-(ethyl and *n*-propyl)-thiopyridines, but decreases in 3- and 4-(*n*-butyl and *t*-butyl)thiopyridines. The decrease in the molecular ion abundance with an increase in the size of the alkyl group appears more pronounced for the 2-pyridyl sulfides. For example, the molecular ion abundance decreases from 23.2 to 8.6% Σ_{29} as the *S*-alkyl group increases from methyl to *n*-propyl in 2-alkylthiopyridines compared to a much smaller decrease of 37.9 to 23.9% Σ_{29} for the corresponding 3-isomers.

The uniqueness of the 2-substituted compound will be ascribed to the proximity of the ring nitrogen allowing its participation in the fragmentation processes.

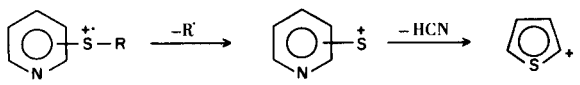
α-Cleavage.

Rupture of the α-bond (as defined in **1**) between the ring and the sulfur atom would lead to an ion, m/e 78. This ion has been shown from the existence of appropriate metastable ions to be the product of different fragmentation pathways (see below). No conclusion can be presented to what extent this ion is produced directly from **1**. It does appear in modest abundance in all spectra except those of 3- and 4-*t*-butylthiopyridines and with greatest abundance in 2-alkylthiopyridines.

β-Cleavage.

β-Cleavage (as defined above) would involve rupture of the S-C_{sp^3} bond with the loss of the *S*-alkyl group as a radical and is pronounced only in the spectrum of 3-methylthiopyridine (m/e 110, 8.1% Σ_{29}). This is in concert with the general observation that β-bond cleavage in the side chain is favored most in 3-substituted pyridines (15). It is relatively minor, but constant, in all other spectra, with the three isomer always showing the greater abundance. In alkylthiobenzenes, this type of β-cleavage takes place to the greatest extent in thioanisole, $C_6H_5SCH_3$, and tapers off rapidly in the higher homologs (5). It is found that similar β-cleavage in the fragmentation of **2** (8) appears to be minor, but constant, as R in **2** changes from methyl to *n*-decyl.

Paralleling the abundance of the m/e 110 fragment produced by β-cleavage is the m/e 83 fragment which undoubtedly is produced from the former by the loss of HCN, as depicted by the general process.



m/e 110 m/e 83

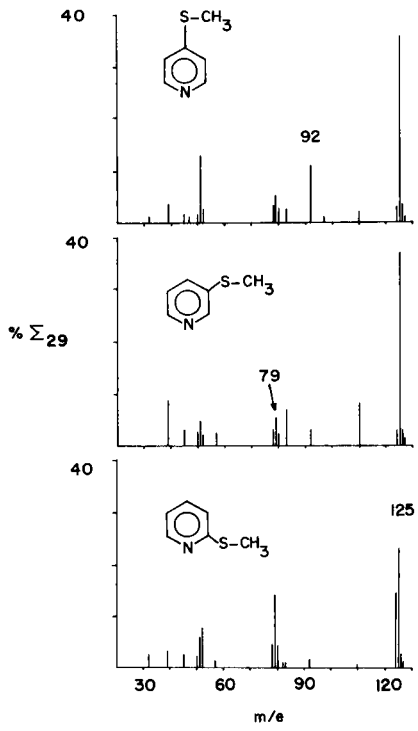


FIGURE 1

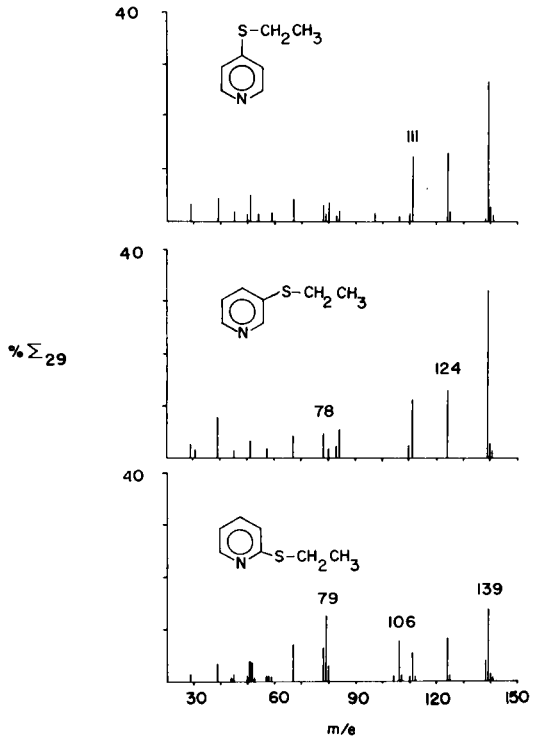


FIGURE 2

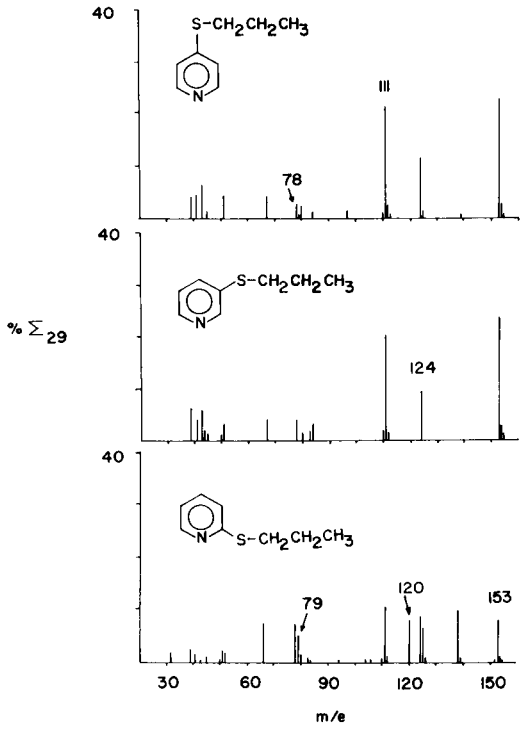


FIGURE 3

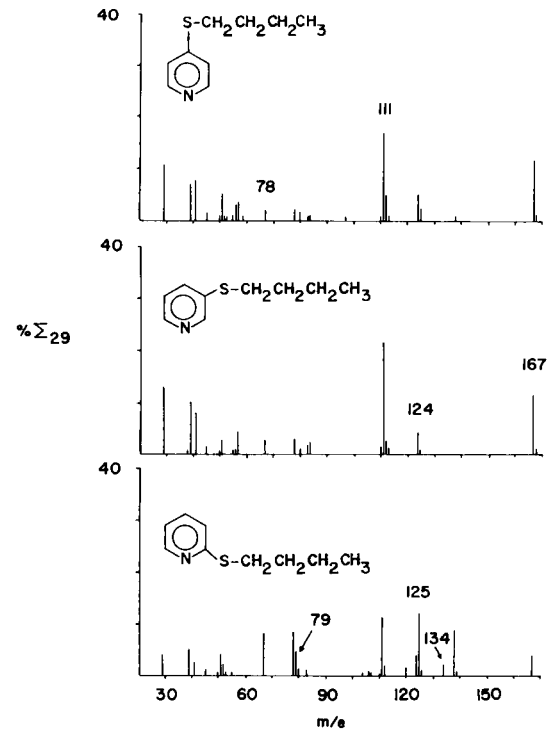


FIGURE 4

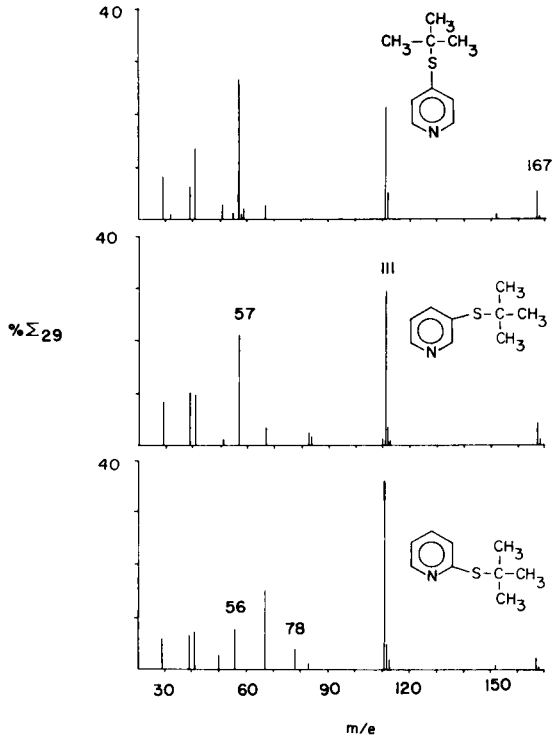


FIGURE 5

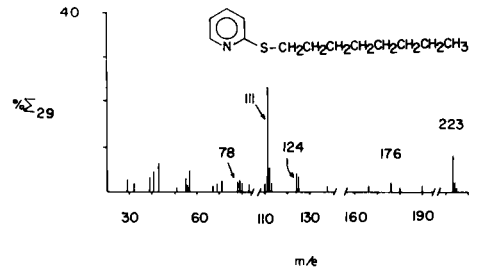
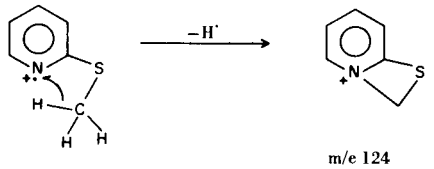


FIGURE 6

Two other β-cleavage deserve comment. An elimination unique in the spectrum of 2-*t*-butylthiopyridine is that which consists of the loss of 2-pyridthione to produce the molecular ion of isobutylene, m/e 56 (7.7% Σ_{29}). Contrary to the 2-isomer, 3- and 4-*t*-butylthiopyridine fragment with the rupture of the S-Csp^3 bond to form 3- and 4-pyridinethiyl radical and $C_4H_9^+$, presumably the *t*-butyl cation, m/e 57, (21 and 26.4% Σ_{29}, respectively). The above transitions are not observed for *n*-butylthiopyridines.

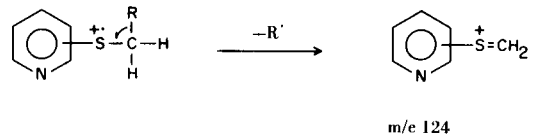
γ-Cleavage.

This type of fragmentation could involve the rupture of either a C-H or C-C bond. In 2-methylthiopyridine, the loss of a hydrogen radical to produce m/e 124 ion is pronounced (14.6% Σ_{29}) while the corresponding transition in the 3- and 4-isomers is less than 3.5% Σ_{29}. The preferential loss of H· from the molecular ion of 2-methylthiopyridine can be explained if ring nitrogen involvement is as illustrated. An ion of similar structure



was proposed by Lawrence and Waight (10) to explain why the (M-1) ion (m/e 124) in the spectrum of 1-methyl-2-pyridthione was more intense than an (M-1) ion in the spectrum of 2-pyridthione itself. As the chain of the *S*-alkyl group in **1** increases, the intensity of the (M-1) ion diminishes rapidly, but in any one series, the 2-isomer always shows this ion in greatest abundance.

An even-electron ion, m/e 124, is also produced from the higher homologs of **1** by γ-bond cleavage involving the loss of an alkyl radical as shown. Although the



same mass/charge ion as above is produced, m/e 124, a complete reversal of the abundances occurs in 3- and 4-ethylthiopyridines with 13% Σ_{29} compared to 8.4% Σ_{29} for the 2-isomer. The apparent increase in abundance of this ion in 3- and 4-ethylthiopyridine compared to the methyl analogs is marked and simply cannot reflect the differences in the precursor molecular ion abundance. The low abundance of m/e 124 in 3- and 4-methylthiopyridines can be accounted for if it is recognized that the molecular ions of these sulfides undergo competing alternate fragmentations. 3-Methylthiopyridine loses CH_3· most easily, while 4-methylthiopyridine readily loses HS· in greatest abundance (m*).

Also significant is the decrease in the abundance of the m/e 124 ion in 2-ethyl- compared to 2-methylthiopyridine. This is misleading since it will be shown that apparently alternative and more favorable fragmentations prevail involving particularly the 2-*S*-ethyl, and to a lesser extent 2-*S*-*n*-propyl and *S*-*n*-butyl groups.

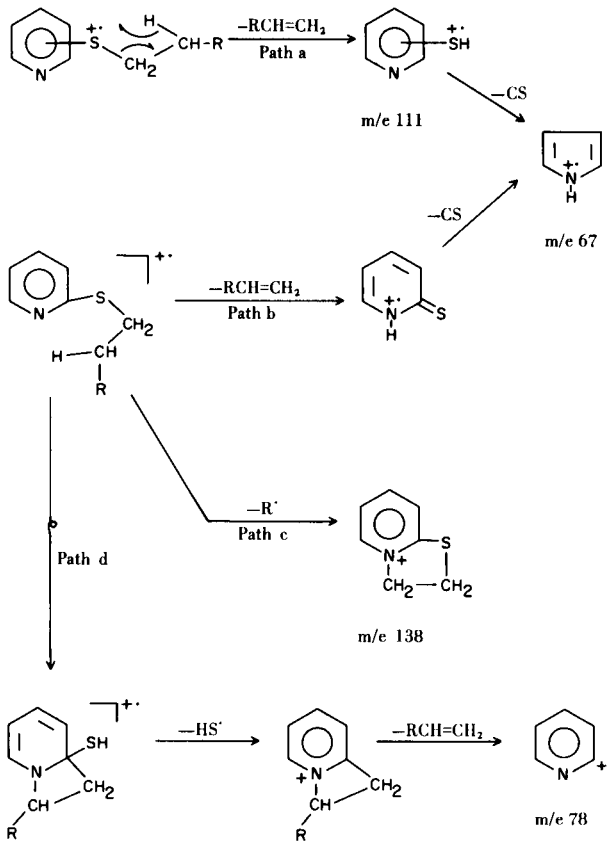
The m/e 124 ion produced by appropriate alkyl radical losses from *n*-propyl and *n*-butyl pyridyl sulfides becomes progressively less abundant and appears relatively independent of ring positions of the sulfide group. The corresponding loss in the *t*-butylthiopyridines would produce m/e 152 which is not observed apparently due to more facile competing fragmentations.

By way of comparison, the corresponding fragmentation in alkylthiobenzenes (5) and in **2** (8) was relatively minor.

δ-Cleavage.

The discovery of a large (M-CH_3) peak (10% Σ_{29}), at m/e 138, in the spectrum of 2-*n*-propylthiopyridine was surprising since it is absent from the spectra of the 3- or 4-isomers or in those of the analogous alkylthiobenzenes (5). Even more revealing is the presence of such an ion of fairly high intensity (8.5% Σ_{29}) in the spectrum of 2-*n*-butylmercaptopyridine. The latter corresponds to a loss of C_2H_5· from the molecular ion of 2-*n*-butylthiopyridine, which significantly enough does not lose CH_3·. Since only 2-*n*-propyl- and *n*-butylthiopyridines give rise to the ion, m/e 138, ring nitrogen involvement appears obvious and such a transformation is pictured by Path c in Chart I.

CHART I

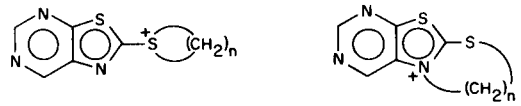


The (M-1) fragment ion, m/e 138, from 2-ethylthiopyridine could, of course, possess the same structure.

Facile γ and δ-cleavage have been reported in alkyl chains at C-4 and C-8 positions of quinoline (14), however, cyclization of the resulting radicals to the *peri* position accounted for their formation.

Tatematsu *et al.* (8) report fragment ions from the molecular ions of *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-octyl and *n*-decyl sulfides derived from **2** involving the loss of alkyl groups of varying lengths. Although fragment ions arising

from similar transitions are weak in their series (*e.g.* the loss of $C_2H_5^{\cdot}$ from their *n*-butyl sulfide is less than 7% *relative* abundance), they postulate that losses of alkyl radicals give rise to cyclic sulfonium ions. It is quite possible that such sulfonium ions are formed, but there is an equal probability that some or all of these fragments have a thiazolium ion structure, as shown.



We have eliminated the formation of cognate sulfonium ions from the decomposition involving δ-cleavage of alkylthiopyridines since only the 2-isomers exhibit relatively high intense ions for such a process (92.2 and 72.6% relative abundance for 2-*n*-propyl- and 2-*n*-butylthiopyridine, respectively). Involvement of the ring nitrogen appears essential in explaining this behavior.

Loss of an Alkene.

An important process in the fragmentation of **1** involves the loss of an alkene and is represented in general terms by Path a in Chart I. No site specificity for the hydrogen transferred is intended since deuterium studies in aliphatic thioethers (16) and in aryl alkyl ethers and sulfides (6) have shown that α, β, γ, and δ hydrogens are transferred in the formation of the alkene and similar behavior is anticipated for alkyl 3- and 4-pyridyl sulfides. The extent of the elimination of an alkene appears to depend on both the structure of the *S*-alkyl group and the ring position to which it is attached. The ring nitrogen would be expected to exert a strong influence in promoting a McLafferty rearrangement for the molecular ion of 2-alkylthiopyridines to expel an alkene, C_nH_{2n}, from the C_nH_{2n+1} alkyl group resulting in a high abundance for the m/e 111 fragment. This conclusion is particularly relevant if the alkyl group is *t*-butyl as shown in Table I. However, several additional observations can be made from Table I.

1) Loss of an alkene containing the same number of carbons as the *S*-alkyl group is substantial irrespective where the sulfide is attached and this would suggest a more direct mechanism (Path a). It is felt that for 2-pyridyl sulfides the McLafferty rearrangement plays a substantial role and is probably preferred since the ring nitrogen can serve as the hydrogen acceptor (Path b). Moreover, the resulting 2-pyridthione radical ion readily loses CS (17) to produce the odd-electron pyrrole ion, m/e 67. This ion is present and in greatest abundance in the spectra of 2-alkylthiopyridines.

2) Contrary to expectations, for the ethyl, *n*-propyl and *n*-butyl pyridyl sulfides, the loss of ethene, propene and butene, respectively, is observed, at least in the spectra of the 2-pyridyl isomers. Their relatively low abundance can be rationalized by recalling that these compounds exhibit a number of unique fragmentation routes involving the *S*-alkyl moiety.

TABLE I

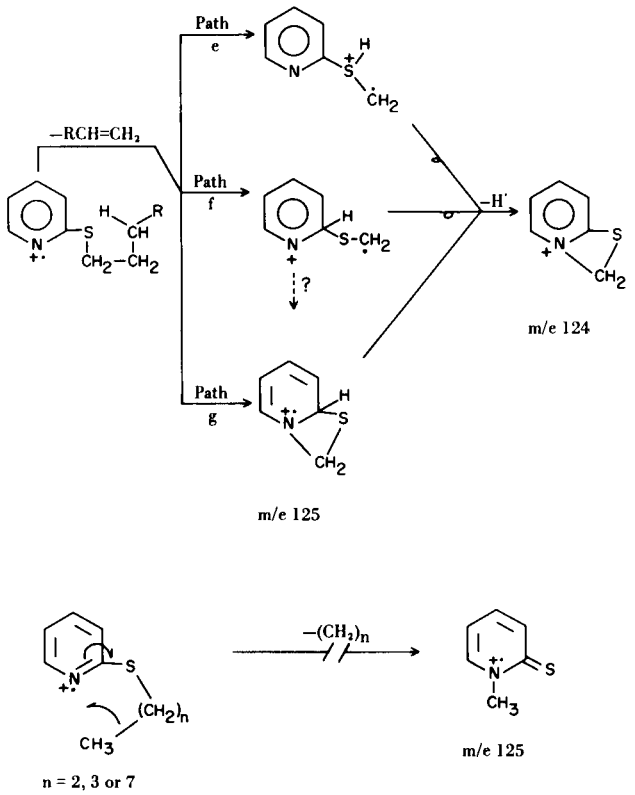
% Σ_{29} Fragment Ion Radicals Produced by the Loss of an Alkene

Alkyl Group in **1**	Process	Ring Position of Sulfide in **1** 2	3	4
C_2H_5	M-C_2H_4	5.4	11.1	12.5
n-C_3H_7	M-C_3H_6	11.0	20.3	21.2
	M-C_2H_4	6.9	0	1.6
n-C_4H_9	M-C_4H_8	11.5	21.6	16.7
	M-C_3H_6	12.1	0.9	2.5
	M-C_2H_4	0.9	0	0
t-C_4H_9	M-C_4H_8	36.5	29.2	21.1
n-C_8H_{17}	M-C_8H_{16}	23.4	–	–
	M-C_7H_{14}	3.3	–	–

3) Besides the loss of an alkene involving all of the carbon atoms of the *S*-alkyl group, S-C_nH_{2n+1}, three of the sulfides eliminate alkenes of type $C_{n-1}H_{2n}$. Thus, 2-*n*-propylthiopyridine gives rise to ions m/e 111 and m/e 125, due to losses of propene and ethene, respectively (Table I). Even more significantly, the molecular ion from 2-*n*-butylthiopyridine loses both butene and propene to produce ions, m/e 111 and 125, the latter being the most intense peak in the spectrum. Unlike the propyl sulfide, the butyl analog does not lose ethene. And perhaps even more striking, the molecular ion from 2-*n*-octylthiopyridine does not exhibit reasonable losses of alkenes from ethene to hexene, but very definitely eliminates both heptene and octene to create ions, m/e 125 and 111, respectively (Figure 6). This would constitute, under the terms of our nomenclature, "γ-cleavage + 1" process. The proton most likely involved is one γ to the sulfur atom (*i.e.* ε-cleavage as shown in **1**), and such a H-transfer has been reported previously from deuterium studies of neopentylthiobenzene (15). Even more *apropos* is the demonstration of the phenomenon in the spectra of the sulfides related to **2** in which the data (without comments) from deuterium labelling of 2-*n*-butylthio-5-aminothiazolo[5,4-*d*]pyridine clearly indicates that H-transfer is from the carbon γ to the sulfur atom (8).

In the present study this cleavage is pronounced in only 2-alkylthiopyridines and it is, therefore, reasonable to assume that stabilization of the resulting ion by the ring nitrogen is a strong contributing factor. A number of plausible schemes may be written (Chart II) to form a

CHART II



m/e 125 ion radical. However, it should be noted that no new fragment ions appear in the spectra along with the m/e 125 ion, and the exact pathway cannot be proven. The analogous behavior to neopentylthiobenzene, *via* Path e (Chart II) would involve H-transfer to an electrophilic sulfur atom to yield an ion-radical as shown. Alternatively, H-transfer to an electrophilic α-ring position with concomitant attack of the carbon α to the sulfur atom onto the ring nitrogen yields an ion m/e 125 and an alkene (Path f). Another alternative exists if the last ion cyclizes to an ion which could be found *via* Path g. Subsequent loss of H· could produce the previously proposed fragment ion, m/e 124. This would introduce no new fragment ions with the appearance of the m/e 125 ion.

The transfer of a methyl group to the ring nitrogen to produce the 1-methyl-2-pyridthione ion (Chart II) is unlikely since one would expect to observe subsequent loss of CS from the 1-methyl-2-pyridthione ion radical to produce m/e 81, as had been reported in the spectrum of the pure thione (10).

The Loss of HS Radical.

A characteristic fragmentation of alkyl aryl sulfides (5,7,10) is the presence of an (M-HS) fragment which is generally absent in the aliphatic thioethers (16). This (M-HS) peak has also been found previously in 2-pyridthiones (17), 2-ethylthiopyridine (10), and in derivatives of **2** (8). For this loss to occur, a skeletal rearrangement is required with the formation of a new carbon-carbon bond.

In alkylthiopyridines this fragment ion is important in 2-, 3-, and 4-methylthiopyridines as well as 2-(ethyl, *n*-propyl, and *n*-butyl)thiopyridines. Lawrence and Waight have proposed a fragmentation pathway for the loss of the HS· for 2-ethylthiopyridine (10). However, in alkylthiopyridines the loss of the HS· is found to be a function of the ring position and not of chain length. Evidence from the present study supports this proposition for alkyl groups of ethyl or larger.

It is apparent, however, that several rearrangement pathways are involved. The molecular ion from 2-methylthiopyridines yields only a small (M-HS) ion, m/e 92 (1.6% Σ_{29}, m*) while the 4-isomer produces (M-HS) to a larger extent (11.1% Σ_{29}, m*). In the spectrum for the ethyl-, *n*-propyl-, and *n*-butylthiopyridines the only significant abundance of any m–HS fragment is visible in the spectra of the 2-isomers (12.8%, 8.4% and 2.3% Σ_{29} for the ethyl, *n*-propyl and *n*-butyl, respectively). This latter observation suggests that the adjacent ring nitrogen participates in the process for the alkylthiopyridines when the *S*-alkyl group is ethyl or longer. An adaptation of the pathway proposed by Lawrence and Waight (10) satisfies this requirement and is represented by Path d in Chart I. Subsequent loss of alkene from the (M-HS) fragment would produce the m/e 78 ion, as shown, which is found in all of the spectra showing an initial loss of HS·.

Selective deuteration studies for the analogous rearrangement in 2-*n*-butylthio-5-aminothiazolo[5,4-*d*]pyrimidines, **2**, shows that the process is not very site-specific in that nearly equal amounts of hydrogen in the departing HS· are derived from the α, β, and δ carbons from the *S*-atom.

The (M-CH_3) fragmentation reported by the Japanese workers (8) is significant in their system but is found only in the 2-*n*-butylthiopyridine spectrum and in minor abundance, 1.8% Σ_{29}. While the above mechanism *via* Path d is very probable, a number of questions arise on inspection of the spectra. First, the 2-*t*-butylthiopyridine does not exhibit an (M-HS) fragment although Path d does not exclude it. The most facile fragmentation for the *t*-butylthiopyridines is the expulsion of isobutylene and the resulting m/e 111 fragment in the 2-*t*-butylthiopyridine spectrum accounts for 36.5% Σ_{29}. This extremely facile fragmentation could account for the lack of significant amount of rearrangement ion to produce an ion (M-HS).

Another question arises concerning the fate of the (M-HS) ion. Path d suggests that subsequent loss of an alkene would produce an ion, m/e 78. Such a process seems

quite feasible and the ion at m/e 78 is seen in many spectra in modest abundances whether an (M-HS) fragment is produced or not. It is quite possible that the m/e 78 ion is produced by a number of different processes. However, the fragment ion at m/e 79 exactly parallels the abundance of the (M-HS) fragment and is absent if an (M-HS) ion is absent. This suggests that the m/e 79 ion rather than the m/e 78 ion is the decomposition product of the (M-HS) ion.

α-Cleavage with Hydrogen Transfer.

If the odd-electron ion, m/e 79, only coincidently appears with the (M-HS) ion and instead is produced directly from the molecular ion, such a process would represent an "α-cleavage + 1" process. Such a fragmentation is known for 2-substituted pyridines possessing a 2-carbon atom side chain. For example, 2-ethylpyridine is reported to eliminate ethene to give an ion, m/e 79. For such an ion to be created directly from the alkylthiopyridines, the molecular ion would have to lose a $C_nH_{2n}S$ molecule which could represent a thioaldehyde or a cyclic sulfide.

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