

Mass Spectrometry of 3-Hydroxypyridines

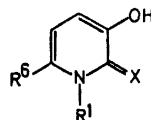
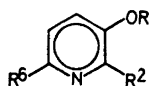
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The fragmentation of substituted 3-hydroxypyridines has been investigated. CO expulsion, and in simple derivatives HCN expulsion, are the major primary fragmentations. With 2-substituents which can exert an *ortho* effect or otherwise fragment, the CO expulsion may be fully or partly preceded by other primary fragmentations. γ -Cleavage occurs in substituents *ortho* to the annular nitrogen.

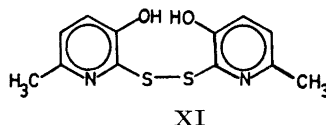
Alkyl pyridines on mass spectrometry have been widely studied.¹ A recent publication has appeared on pyrid-2-ones, pyrid-2-thiones, and 2-alkylthiopyridines.² Earlier reports have appeared on the three isomeric hydroxypyridines,³ on *N*-methylpyrid-2-one,⁴ on 6-methylpyrid-2-one,⁵ and on highly substituted pyrid-2-ones such as the alkaloid ricinine⁶ and related structures.⁷

Our interest in the pyrolytic behaviour in the mass spectrometer of *N*-quaternary compounds⁸ in the pyridine series required the establishment of the mass spectral behaviour of substituted 3-hydroxypyridines. For this purpose the following compounds were selected for study.



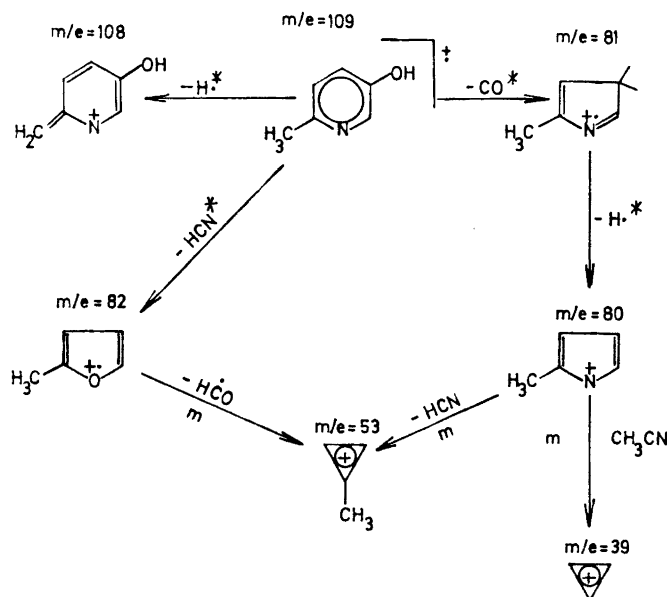
Comp.	R	R ²	R ⁶
I	H	H	CH ₃
Ia	H	D	CH ₃
II	H	CH ₃	H
IIa	H	CH ₃	D
III	H	SCH ₃	CH ₃
IIIa	H	SCD ₃	CH ₃
IV	H	SC ₂ H ₅	CH ₃
V	H	SCH ₂ CH ₂ OH	CH ₃
VI	C ₂ H ₅	SCH ₃	CH ₃
VIa	C ₂ H ₅	SCD ₃	CH ₃

Comp.	X	R ¹	R ⁶
VII	O	H	H
VIII	S	H	H
IX	S	H	CH ₃
X	S	C ₂ H ₅	CH ₃

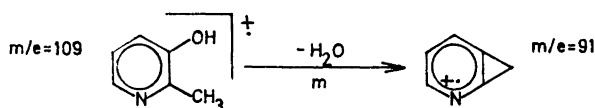


The compositions of the discussed fragments have been determined by high resolution. Metastable transitions, where not present in the ordinary spectrum, were deduced by the defocusing technique.⁹

The base peak in the mass spectra of simple 3-hydroxypyridines often corresponds to the molecular ion due to the great stability of the aromatic ring. Thus the molecular ion (m/e 109) is the base peak in the spectrum of 3-hydroxy-6-methylpyridine (Fig. 1). In 3-hydroxypyridine HCN is slightly more favourable than CO expulsion.³ In the 6-methyl homologue (I), however, CO expulsion is the more important pathway (Scheme 1). This is followed by hydrogen expulsion to the species m/e 80 which can lose HCN (m/e 53) or CH_3CN (m/e 39). The significant $[\text{M}-1]$ peak is due to proton loss from the methyl group since the intensity of the $[\text{M}-\text{H}]$ peak in the 2-deuterated analogue (Ia) is unchanged and 3-hydroxypyridine does not lose its phenolic proton to any extent.³ In agreement with the postulated fragmentation pattern the deuterated analogue has its major fragment at m/e 81. The absence of a peak at m/e 83 shows that it is the 2-hydrogen which is expelled in HCN in the formation of m/e 82 $[\text{M}-\text{HCN}]$.

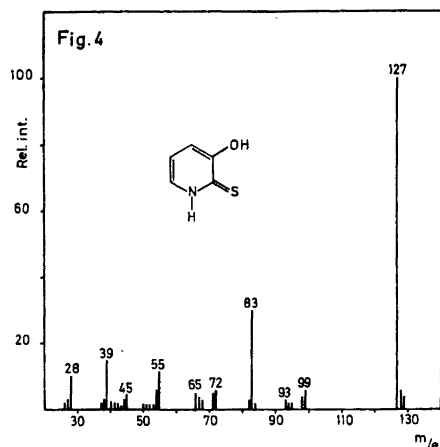
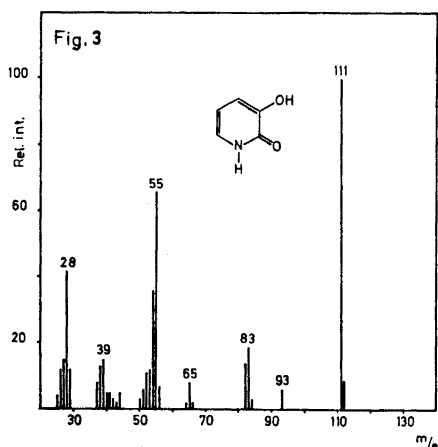
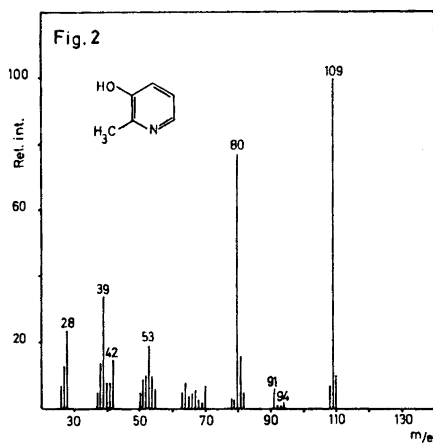
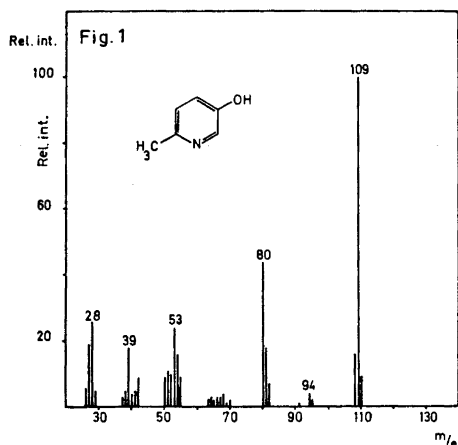


The isomeric 2-methyl-3-hydroxypyridine (II) shows a similar spectrum (Fig. 2) with some relative increase in the m/e 80 peak $[\text{M}-\text{CHO}]$. The *ortho* effect leads to water elimination (m/e 91). Another difference is reduced $[\text{M}-\text{H}]$ intensity. The weak signal from $[\text{M}-15]$, due to expulsion of the methyl group in I, is hardly affected in II.

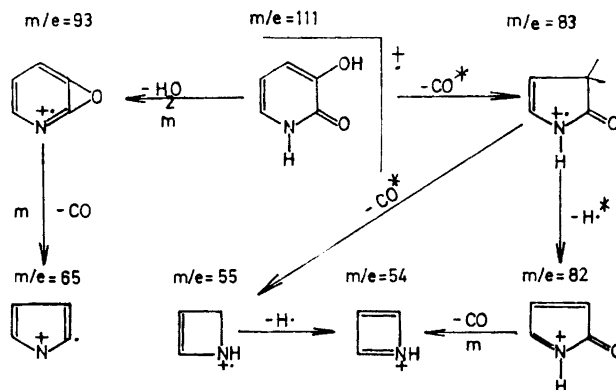


Scheme 2.

In both pyrid-2-one³ and in the 3-hydroxy analogue (VII) the most intense ion in the spectrum is the molecular ion. The only important fragment in the spectrum of the former is due to CO expulsion. This is also the major primary process in the 3-hydroxy derivative (m/e 83). An additional fragmentation mode arises, however, because of interaction between the *ortho* hydroxy groups with water expulsion (m/e 93, 6 %). The latter species can go on to expel CO (m/e 65). The m/e 83 species $[M - CO]$ fragments further either by

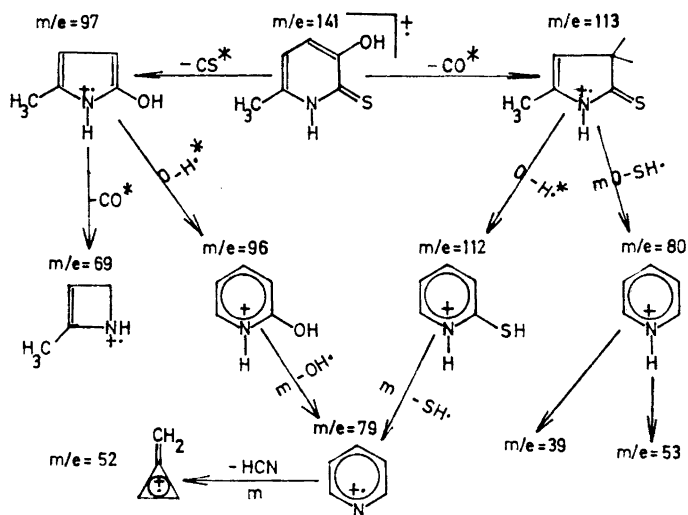


hydrogen expulsion (m/e 82) followed by CO loss (m/e 54) or by direct CO expulsion (m/e 55) from $[M-CO]$.

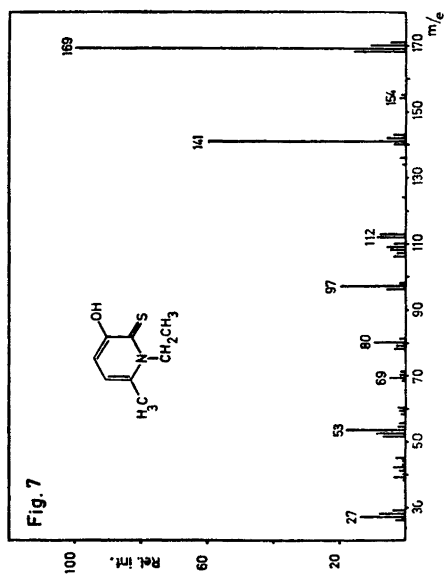
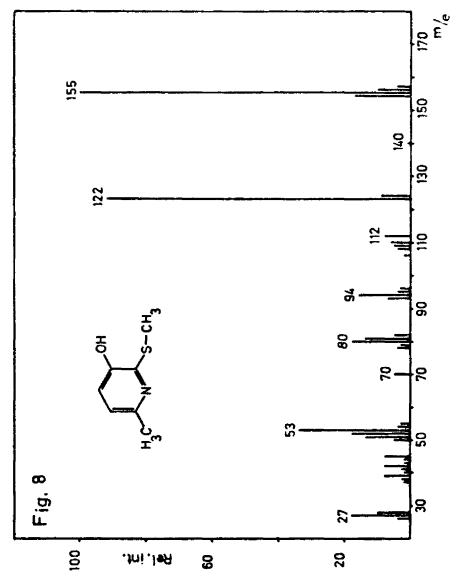
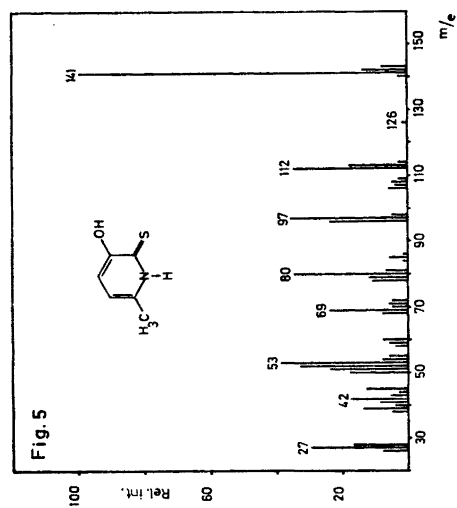
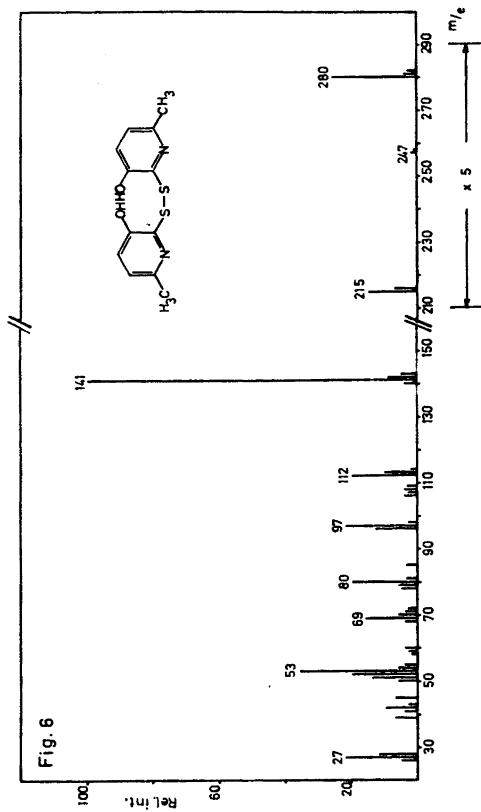


Scheme 3.

Pyrid-2-thione on electron impact gives rise to several strong peaks in the higher mass region.² Fig. 4 shows that the 3-hydroxy group (VIII) confers great stability on the molecule. The major peak, besides the molecular ion (m/e 127), is at m/e 83 due to CS expulsion. Other ions in the high mass range are of low intensities but correspond to analogue fragments in the 6-methyl homologue (IX) (Scheme 4, Fig. 5). Sulphur and SH radical losses in the 6-methyl homologue account for weak signals at m/e 109 and m/e 108, respectively. The major pathways are CS and CO expulsions. This is different from the corresponding pyrimidine analogue where the major fragments were $[M-SH]$ and $[M-CH_3CN]$.¹⁰



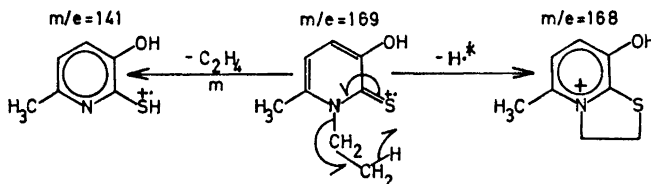
Scheme 4.



The $[M - CS]$ species at m/e 97 can lose CO (m/e 69) or a hydrogen (m/e 96) which through OH expulsion gives the m/e 79 species formulated as a pyridine and in an analogous fashion expels HCN to m/e 52. The $[M - CO]$ species at m/e 113 can either expel SH (m/e 80) or hydrogen (m/e 112) to species which through SH loss give the pyridyl species at m/e 79.

The spectrum (Fig. 6) of the corresponding disulphide (XI) has the base peak at m/e 141. The formation of the latter probably involves hydrogen transfer from one half of the molecule with expulsion of the latter as a thioquinonoid neutral structure. The tendency for the charge to remain on this part is very small. The molecular ion (m/e 280) has 25 % intensity. Very weak signals are present for S (m/e 248) and SH (m/e 247) expulsions. More important are S_2 (m/e 216) and especially S_2H (m/e 215) expulsions.

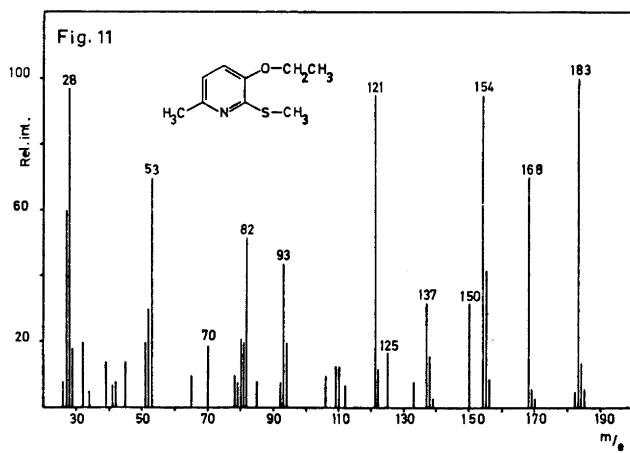
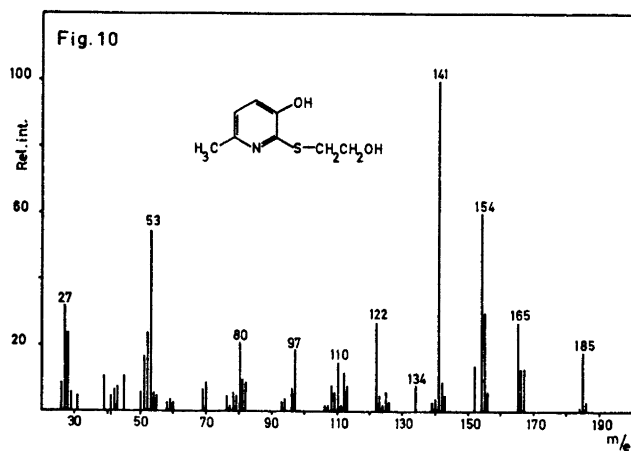
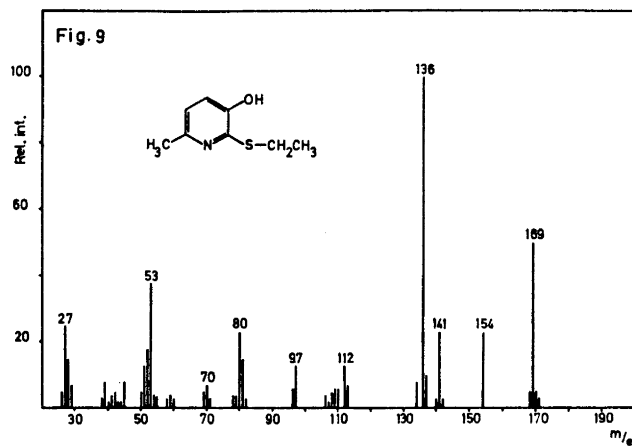
The important fragmentation of the *N*-ethylpyrid-2-thione (X) goes through a McLafferty type rearrangement with expulsion of the ethyl group as ethylene and generation of the parent thione (IX) at m/e 141. The base peak in the spectrum is due to the molecular ion (m/e 169). The CS and CO expulsions, important in the parent thione (IX), are hardly seen as the fragmentation is dominated by the McLafferty rearrangement. High resolution of the $[M - 28]$ peak at m/e 141 showed this to be due only to ethylene expulsion. The spectrum (Fig. 7) also shows a relatively intense (15 %) peak at m/e 168 from hydrogen loss. The $[M - H]$ species are practically absent in the spectrum of the parent thione (IX). The hydrogen is therefore expelled from the ethyl group, presumably from the β -carbon with formation of a thiazolinium structure.

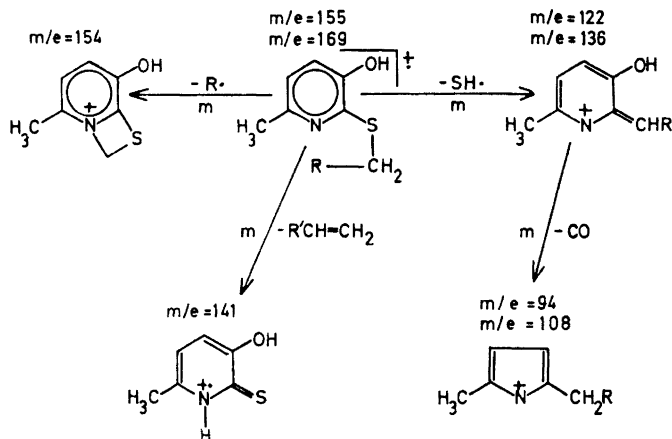


Scheme 5.

The fragmentation of the *S*-ethyl isomer (IV) shows a different pattern from X. Both the *S*-ethyl (IV) and the *S*-methyl (III) analogues fragment similarly and are treated together (Scheme 6). SH expulsion is the major pathway (Figs. 8 and 9). The base peak in the spectrum of the methyl derivative is the molecular ion (m/e 155) while the molecular ion for the ethyl derivative (IV) has about 50 % relative intensity of the base peak $[M - SH]$ at m/e 136. The fragmentation of the *S*-trideuteriomethyl derivative (IIIa) shows that only about 60 % of the hydrogen expelled in SH originate from the *S*-methyl group. In thioanisole it has been found that the corresponding figure is 69 %.¹¹

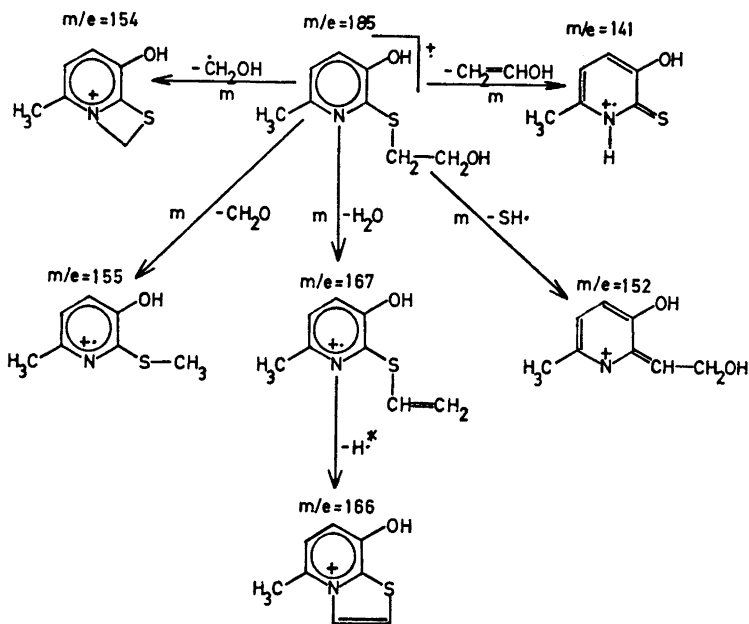
The $[M - SH]$ species appears relatively stable but will lose CO (Scheme 6). The loss of the 2-substituent does not appear to be important (m/e 108). γ -Cleavage in the *S*-sidechain gives the species at m/e 154. In the methyl derivative (III) this involves hydrogen expulsion, in the ethyl derivative the more stable methyl radical as reflected in higher intensity of the m/e 154 species in the spectrum of the latter. The ethyl derivative (IV) can also undergo





a McLafferty type rearrangement with expulsion of ethylene and generation of the parent thione (IX) at m/e 141.

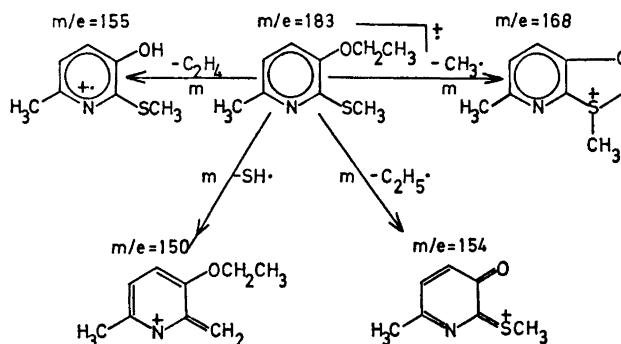
A β -hydroxy group in the *S*-ethyl sidechain (V) leads to drastic fragmentation changes (Fig. 10). The SH expulsion is greatly suppressed (m/e 152). The molecular ion has only about 20 % intensity. Instead McLafferty rearrangement is strongly favoured with expulsion of C_2H_4O and generation of the



corresponding thiolactam (m/e 141) which fragments further in the usual way. γ -Cleavage with CH_2OH expulsion is also important (m/e 154) while m/e 155 comes from formyl expulsion. Water is probably expelled thermally (m/e 167) and these species lose a hydrogen probably with formation of a thiazolo system (m/e 166). This fragmentation pattern corresponds closely to the earlier reported behaviour of a pyrimidine analogue.¹⁰

The *S*-methyl-*O*-ethyl derivative (VI) shows an intense fragmentation spectrum (Fig. 11). Methyl radical expulsion is important (m/e 168) from the molecular ion (m/e 183), the base peak. Ethyl radical expulsion also leads to a peak with high intensity (m/e 154). The mass spectrum of the trideuterio-methyl analogue (VIa) shows that these are not simple expulsions and involve prior rearrangements. Thus about 70 % of the $[\text{M}-\text{CH}_3]$ peak was due to CH_3 expulsion, the remainder was due to CHD_2 . Direct expulsion of CD_3 was not seen. The ethyl radical expelled also contained a high proportion of $\text{C}_2\text{H}_4\text{D}$. These observations are in complete agreement with our findings for the corresponding pyrimidine analogue¹⁰ and are subject for a separate study.

McLafferty ethylene expulsion gives the species m/e 155 corresponding to the hydroxy compound (III). The loss of SH is suppressed (m/e 150). Other fragments such as m/e 121 are arrived at through secondary fragmentations.



Scheme 8.

EXPERIMENTAL

The mass spectra were recorded on an AEI MS 902 mass spectrometer. Direct insertion at $160-170^\circ$ was used. The electron energy was 70 eV and the trap current $100 \mu\text{A}$.

Syntheses for most of the compounds used have been reported previously.¹² The other syntheses are described below.

2-Deuterio-3-hydroxy-6-methylpyridine (Ia). To 2-bromo-3-hydroxy-6-methylpyridine (0.50 g, 0.0025 mol) in deuterioacetic acid (10 ml) was added zinc powder (0.65 g), and the mixture was stirred in the cold overnight. TLC (CHCl_3/THF , 2:1) showed that the reaction had gone to completion. Evaporation and sublimation of the residue at $140-150^\circ/0.1 \text{ mmHg}$ furnished the white title compound; yield 0.20 g (72 %).

6-Deuterio-3-hydroxy-2-methylpyridine (IIa). The title compound was prepared as above from 2-bromo-5-hydroxy-6-methylpyridine, the latter obtained by bromination of 3-hydroxy-2-methylpyridine with bromine in pyridine. The chemical shifts in NMR of the aromatic protons in IIa and the coupling constants show that the deuterium atom

is in the 6-position. NMR in TFA: CH_3 7.22 τ , H^4 1.95 τ , H^5 2.23 τ and $J_{4,5}$ 9.0 cps.

3-Hydroxy-6-methyl-2-trideuteriomethiopyridine (IIIa). To the sodium salt of 3-hydroxy-6-methylpyrid-2-thione (0.11 g, 7.5×10^{-4} mol) in methanol (8 ml) was added trideuteriomethyl iodide (0.14 g, 10^{-3} mol) in methanol (2 ml). The solution was left in the cold overnight. TLC (CHCl_3/THF) showed the alkylation to be complete. The solution was evaporated, a little water added to the residue, the pH brought to 5–6, and the title compound extracted into chloroform. Evaporation left the desired crystalline material.¹²

3-Ethoxy-6-methyl-2-methiopyridine (VI). 3-Ethoxy-6-methylpyrid-2-thione¹³ (0.18 g, 0.001 mol) was dissolved in N NaOH (20 ml), and methyl iodide (0.16 g, 0.0011 mol) was added dropwise during 5 min in the cold. After stirring for 1 h the separated oily material was extracted into chloroform, and the solution was washed and dried before evaporation. The residue was a crystalline material which was recrystallized from dilute ethanol; yield 0.12 g (67 %), m.p. 58°. (Found: C 59.14; H 6.89; N 7.68. Calc. for $\text{C}_9\text{H}_{13}\text{NOS}$: C 58.98; H 7.18; N 7.65.) UV absorption in 0.1 N HCl/EtOH at 338 $m\mu$ ($\log \epsilon$ 4.15), 248 $m\mu$ (3.85), 224 $m\mu$ (3.65); in 0.1 N NaOH/EtOH at 303 $m\mu$ ($\log \epsilon$ 4.11), 248 $m\mu$ (4.11).

3-Ethoxy-6-methyl-2-trideuteriomethiopyridine (VIa) was prepared as above by S-alkylation with trideuteriomethyl iodide.

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