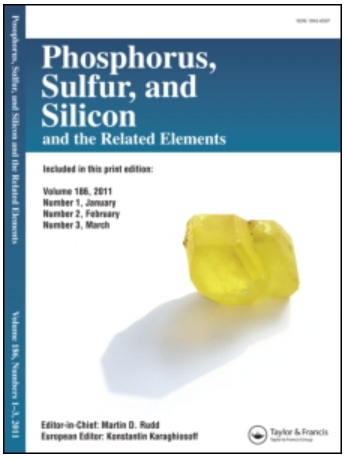

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THE MASS SPECTRAL FRAGMENTATION BEHAVIOR OF PYRIDINE CARBOXYLIC AND THIOCARBOXYLIC ACID ESTERS

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THE MASS SPECTRAL FRAGMENTATION BEHAVIOR OF PYRIDINE CARBOXYLIC AND THIOCARBOXYLIC ACID ESTERS[1]

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The mass spectral fragmentation behavior of pyridine carboxylic acid and thioacid methyl esters shows several peculiarities not observed with other aromatic esters, viz., i.a., (a) $COOCH_3$ groups in α-position are involved in rearrangement processes under participation of N; (b) neighboring $COOCH_3$ groups fragment by *ortho*-effects; (c) $COSCH_3$, $CSOCH_3$ and $CSSCH_3$ groups suffer complex rearrangements leading to, e.g. loss of CO, CH_2CO or S_2 from M^+, especially when located in α-position.

INTRODUCTION

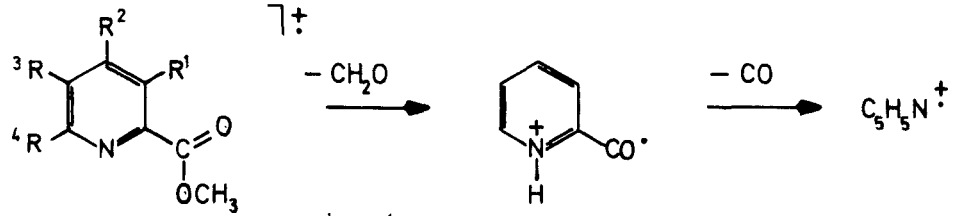
During our investigations on bacterial constituents[2] pyridine carboxylic acids and their thioanalogs have been encountered, whose methyl esters partially show an unexpected fragmentation behavior. To facilitate the mass spectroscopic identification of these compounds and of related quinoline and phenazine derivatives which often only occur in quantities sufficient for a GC/MS analysis, we have examined a number of representatives.

RESULTS AND DISCUSSION

Carboxylic Acids

Pyridine monocarboxylic acid methyl esters

The fragmentation behavior of the three isomers has been described in literature.[3] While the spectra of the 3- and 4- ester do not show any particularities ($M^{\cdot+} \rightarrow [M - {}^{\cdot}OCH_3]^+$, *m/z* 106, $\rightarrow [m/z\ 106 - CO]^+$, *m/z* 78, $\rightarrow [m/z\ 78 - HCN]^+$, *m/z* 51), this sequence decreases in importance with the 2-isomer (**1**) as compared with the loss of CH_2O from M^+ (accompanied by transfer of an H-atom to N, *m/z* 107) and subsequent elimination of CO (*m/z* 79). The same "atypical" behavior (formation of $[M - COOCH_2]^+$) is observed with the methyl esters of the phenazine 1-carboxylic acid,[4] quinoline 2- as well as 8-carboxylic acid[5] and harmane 3-carboxylic acid.[6] This electron impact induced process must not be confused with the sometimes observed thermal loss of CH_2CO_2 before the ionization.[7]

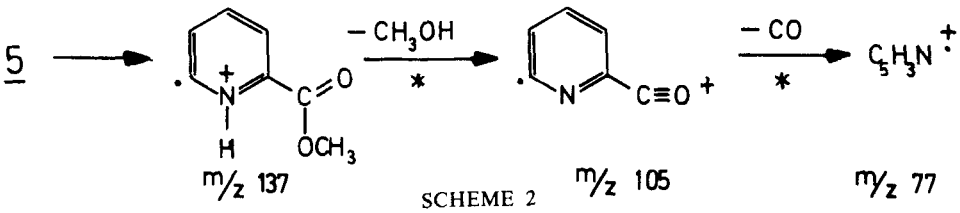


1: $R^1 - R^4 = H$
2: $R^2 - R^4 = H$, $R^1 = COOCH_3$
3: $R^1 = R^3 = R^4 = H$, $R^2 = COOCH_3$
4: $R^1 = R^2 = R^4 = H$, $R^3 = COOCH_3$
5: $R^1 - R^3 = H$, $R^4 = COOCH_3$

SCHEME 1

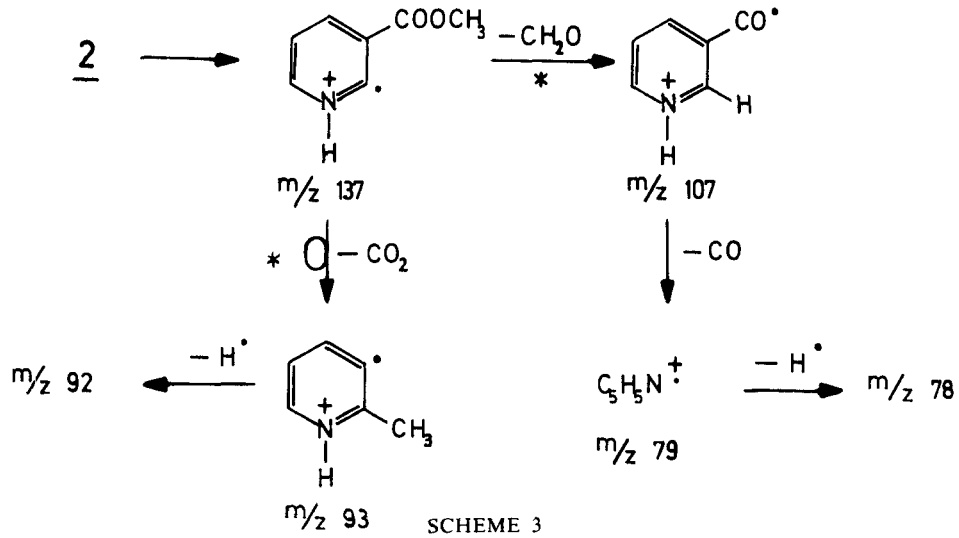
Pyridine dicarboxylic acid dimethyl esters (Figure 1)

As **2–5** all possess a $COOCH_3$ group in α-position to N, elimination of $\cdot OCH_3$ (*m/z* 164) and $\cdot COOCH_3$ (*m/z* 136) as well as of $COOCH_2$ (*m/z* 137) is observed. While in the case of **3** and **4** the second $COOCH_3$ group is degraded only to a minor extent (*m/z* 77), **5** shows loss of CH_3OH from *m/z* 137 (*ortho* effect; the 2,5-di-trideutero methyl ester loses CD_2O followed by CD_3OD).



SCHEME 2

An irregular fragmentation behavior is observed[8] also with **2**: CH_2O (*m/z* 107) and subsequently CO (*m/z* 79) are lost from *m/z* 137 possibly accompanied a transfer of H to the radical site at C-2. Analogous CH_3 migration leads to the elimination of CO_2 (*m/z* 93).



SCHEME 3

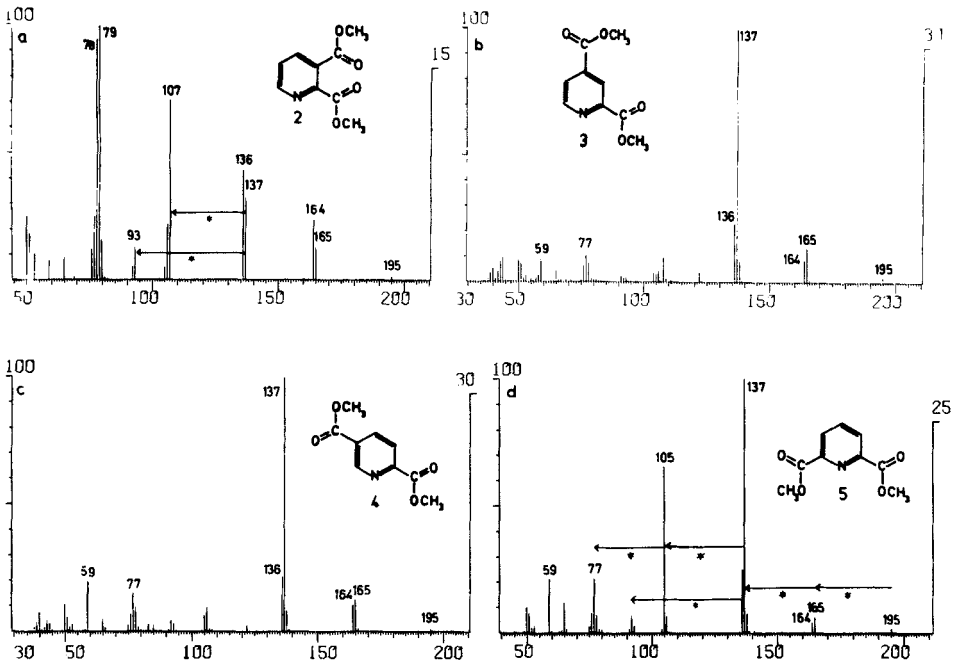


FIGURE 1 Mass spectra of pyridine dicarboxylic acid methyl esters: (a) 2.3, (b) 2.4, (c) 2.5, (d) 2.6.

Thiocarboxylic Acids

General remarks

Aliphatic and aromatic S-alkyl thioesters fragment in general like the corresponding carboxylic acid esters.[9-11] In the case of O-alkyl thioesters loss of ·SR in addition to ·OR is observed which is explained by a rapid isomerization —CSOR → —COSR (the reverse process seems to occur only to a low extent for O-alkyl esters, but is of importance for O-phenyl esters[12]). H migration from R to the thiocarbonyl-S leads to $[M - \cdot SH]^+$ and R′—CSH^+ ions. For the loss of ·CHO (followed by CS) from M^+ of thiobenzoic acid[13] as well as from $C_6H_5COSH^+$ formed by *McLafferty* loss[14] of C_2H_4 from both thiobenzoic acid O- and S-ethyl esters, migration of S to a position *ortho* to the original COSH-group has been shown to occur by labeling studies.[14] In the spectrum[10] of $C_6H_5CSOCH_3$ (and to a lesser extent in that of $C_6H_5COSCH_3$) ions $[M - \cdot C_2H_3O]^+$ and $[M - \cdot C_2H_3O - CS]^+$ have been found, the formation of which also necessitates an S-migration. The more facile cleavage of a C—S as compared with a C—O bond can be observed in the positive ($RCOS^+$) and especially in the negative mode (abundant $[M - \cdot CH_3]^-$ ions from $C_6H_5COSCH_3$ and from $C_6H_5CSSCH_3$).[15] The spectrum of the dithiobenzoic acid methyl ester[16] shows no particularities.

Pyridine carbothioic acid S-methyl esters (Figure 2)

The 3- and 4-isomers **7** and **8** show no particularities: loss of $\cdot SCH_3$ (in the case of **6** in the *m** region also as a 2-step process $M^+ \rightarrow [M - \cdot CH_3]^+ \rightarrow [M - \cdot SCH_3]^+$) is

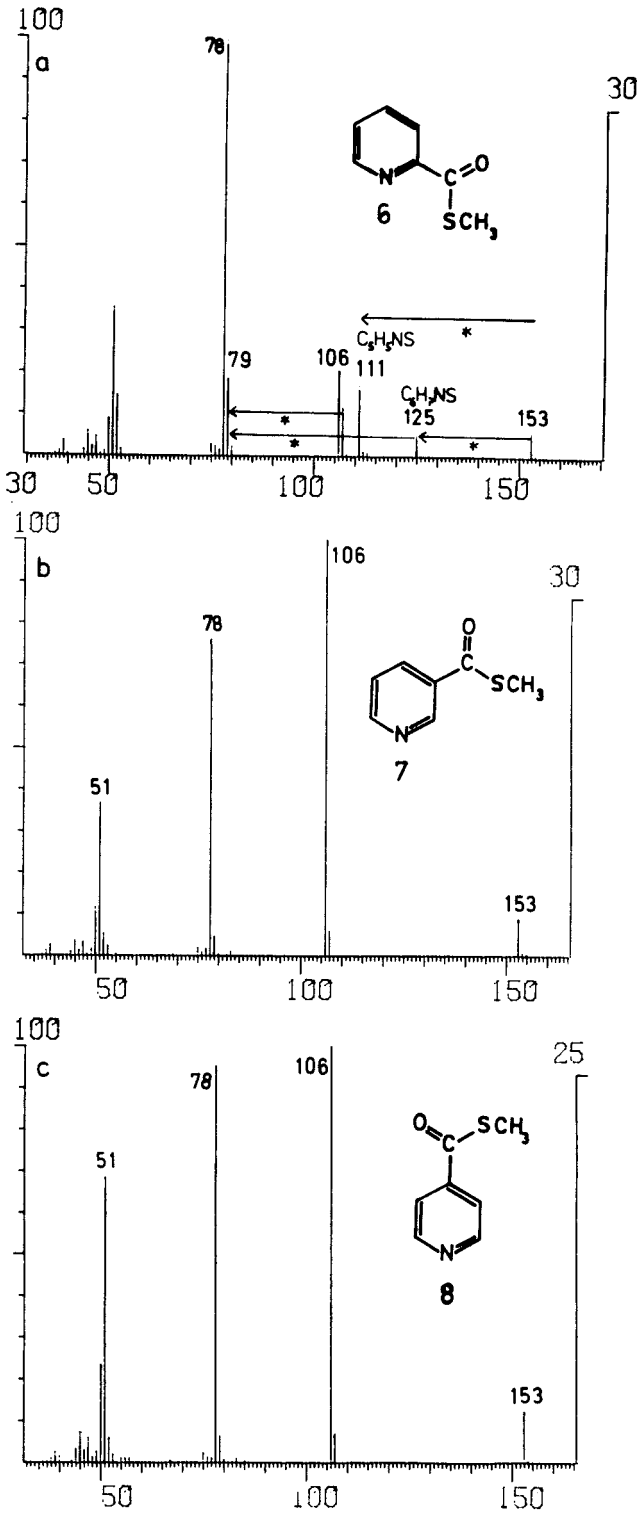
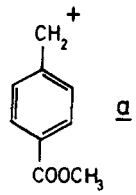


FIGURE 2 Mass spectra of pyridine carbothioic acid S-methyl esters: (a) 2, (b) 3, (c) 4.

followed by that of CO and HCN. The sequence $M^+ \rightarrow [M - CH_2S]^+$ (*m/z* 107) $\rightarrow$ $[M - CH_2SCO]^+$ (*m/z* 79) (cf. Scheme 1) is not very pronounced for **6**. The lower bond energy of the C—S— (289 kJ/mole) as compared with the C—O—bond (345 kJ/mole), which encourages α-cleavage, and the lower stability of CH_2S can be taken for an explanation (note that 2-methyl thiobenzoic acid S-methyl ester does scarcely lose CH_3SH by an *ortho*-effect[17]).

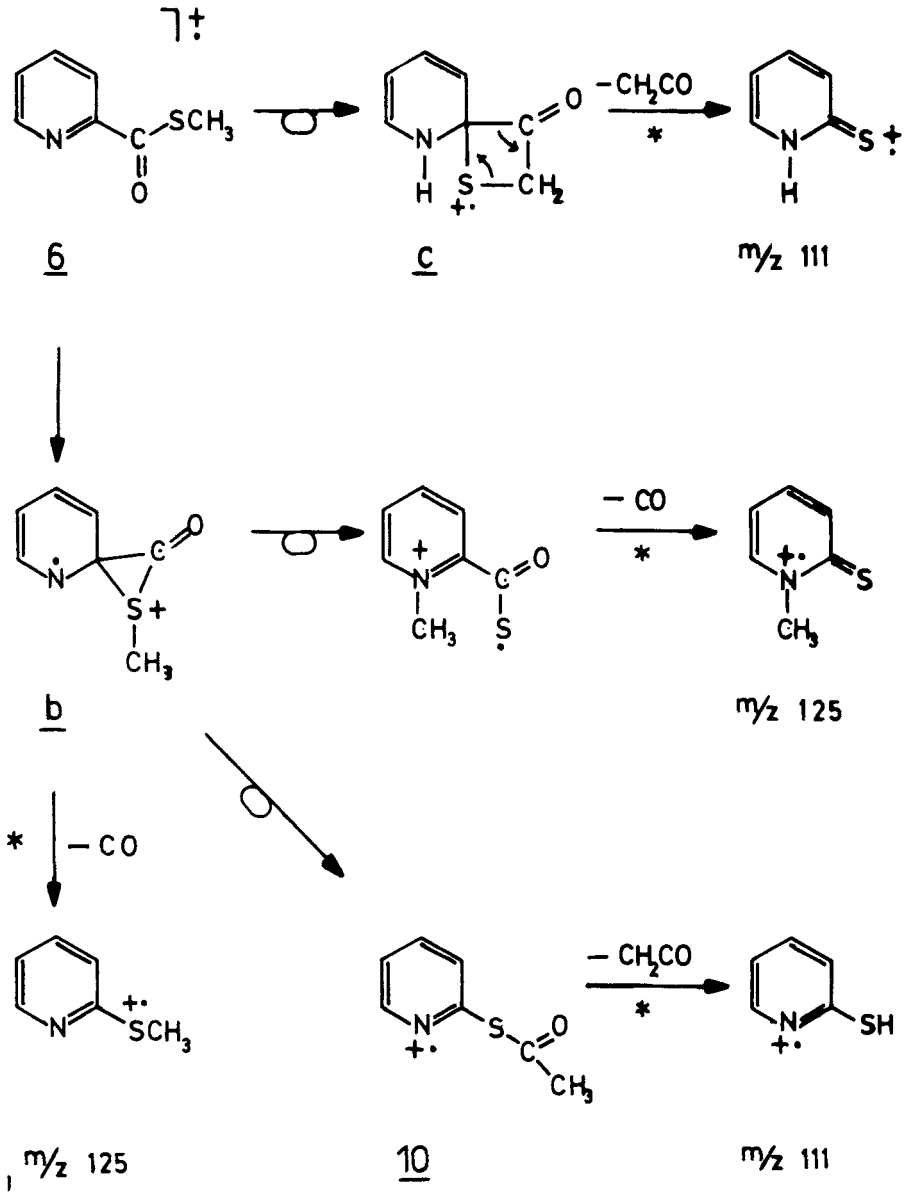
Mechanistically more interesting are the ions *m/z* 111 ($[M - CH_2CO]^+$) and 125 ($[M - CO]^+$), for which no parallels have been found in the spectrum of **1**. Loss of CO from $COOCH_3$ has been observed[18] before with benzyl cations (**a**), where it could be shown that the methoxyl remains at the place of the original $COOCH_3$ group. If one assumes **b** as a transition state one can formulate the formation of ionized methylthio pyridine (**9**) as well as a rearrangement to the ionized acetate of the 2-mercapto pyridine (**10**), from which loss of ketene would be expected. The ion *m/z* 125 loses (as to be expected for **9**) CH_2S (*m/z* 79). But as only **6** shows those decomposition processes, mechanisms under participation of N (e.g. via **c**) are not to be excluded *a priori*).†



a

A comparison of the CA-spectra of *m/z* 125 from **6** and of genuine **9** does not give a conclusive answer. If one disregards those ions which also occur in the *m** spectra[19] the fragmentation patterns coincide with one exception: **9** shows an ion of medium abundance at *m/z* 110 (loss of CH_3) which is almost lacking for **6**. The CA-spectrum of the isomeric 4-methylthio pyridine (which had been measured to check the reliability of the comparison of CA-spectra) shows clear-cut differences. N-methyl-α-thiopyridone has not been available for comparison. The CA-spectra of *m/z* 111 from **6** and of 2-mercapto pyridine again show differences which, however, could be due to the formation of α-thiopyridone via **c** (keto-enol tautomerisation is known to be a slow process for ions in the mass spectrometer).

† It should be mentioned in this context that 2-acetyl and 2-benzoyl pyridine in contrast to their 3- and 4-isomers lose CO from M^+ (A. Feretti and V. P. Flanagan, *J. Agr. Food Chem.*, **19**, 245 (1971), M. D. Migahed, A. I. Helal and S. B. El-Kholy, *Org. Mass Spectrom.*, **7**, 1423 (1973); H.-F. Grützmacher, H. Kuschel und P. Adamietz, *Adv. Mass Spectr.*, **5**, 654 (1971), H.-F. Grützmacher und R. Schubert, *Org. Mass Spectrom.*, **14**, 567 (1979)). Migration of CH_3 to N has been suggested for the acetyl compound, while intermediacy of the tricyclic ion (attack of the N at the phenyl ring in a position *ortho* to the carbonyl group) is considered for the 2-benzoyl compound (R. Schubert and H.-F. Grützmacher, *Org. Mass Spectrom.*, **15**, 122 (1980)). In the case of di-2-pyridyl ketone which also shows $[M - CO]^+$ of high abundance formation of 2,2'-bipyridyl is assumed to occur (N. G. Keats and L. A. Summers, *J. Heterocyclic Chem.*, **13**, 1289 (1976)). Substantiating evidence has not been offered for either suggestion.



SCHEME 4

Pyridinedi (carbothioic acid) di-S-methyl esters (Figure 3)

The mass spectra of **11–13** differ only in the rel. intensities of some ions. The α-position of one of the two ester groups is evidenced by the processes described for **6**. Loss of CO also occurs starting from $[M - {}^{\cdot}COSCH_3]^+$ giving *m/z* 124, which further loses ${}^{\cdot}CH_3$ (*m/z* 109) or HCN (*m/z* 97). Surprisingly (cf. **2–5**) *m/z* 105 is formed in all three spectra with about equal intensity. Apparently not the sequence depicted in Scheme 1 (cf. the discussion of **6**) prevails here, but rather the loss of ${}^{\cdot}SCH_3$ from $[M - {}^{\cdot}COSCH_3]^+$.

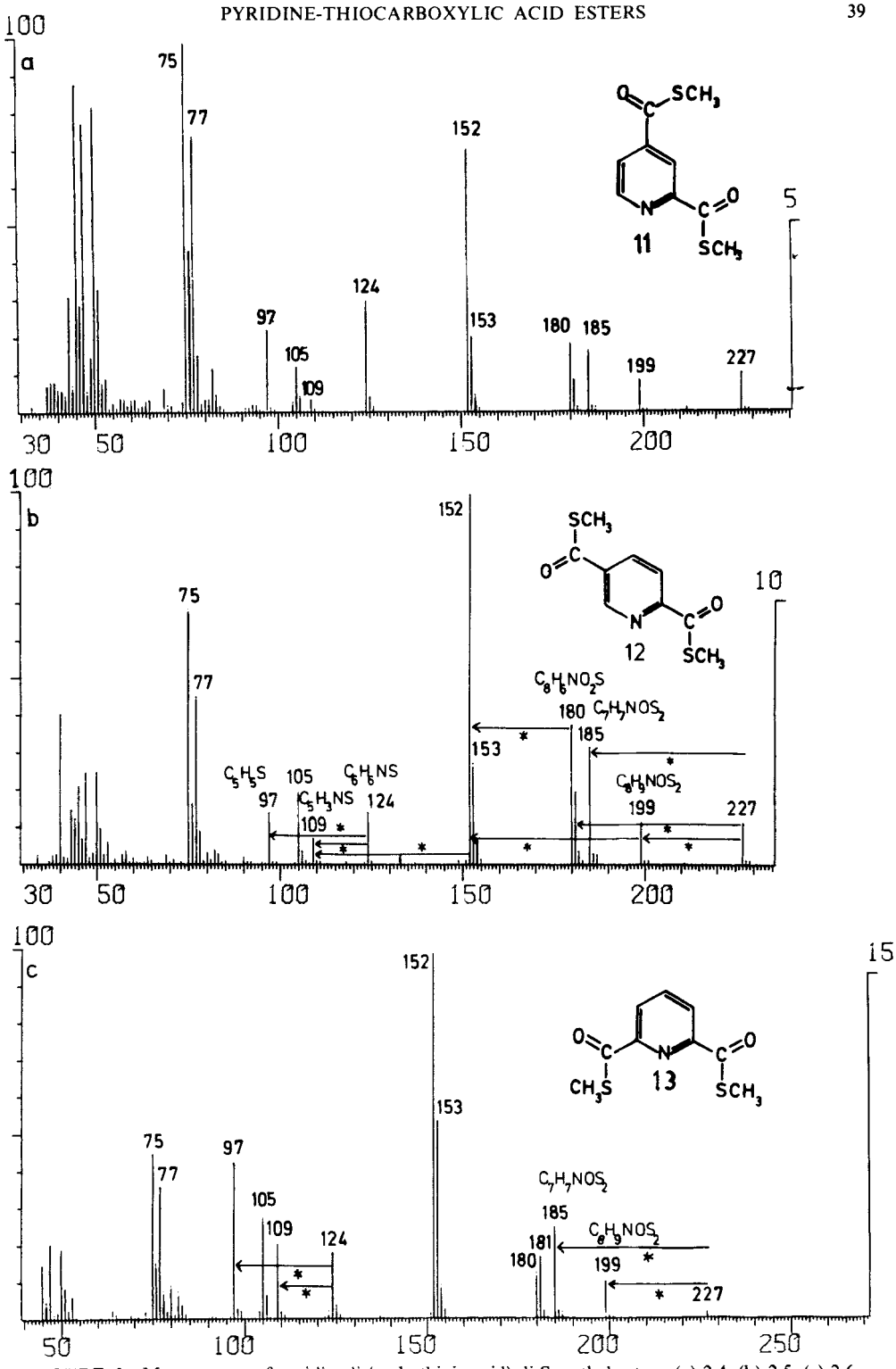


FIGURE 3 Mass spectra of pyridinedi (carbothioic acid) di-S-methyl esters: (a) 2.4, (b) 2.5, (c) 2.6.

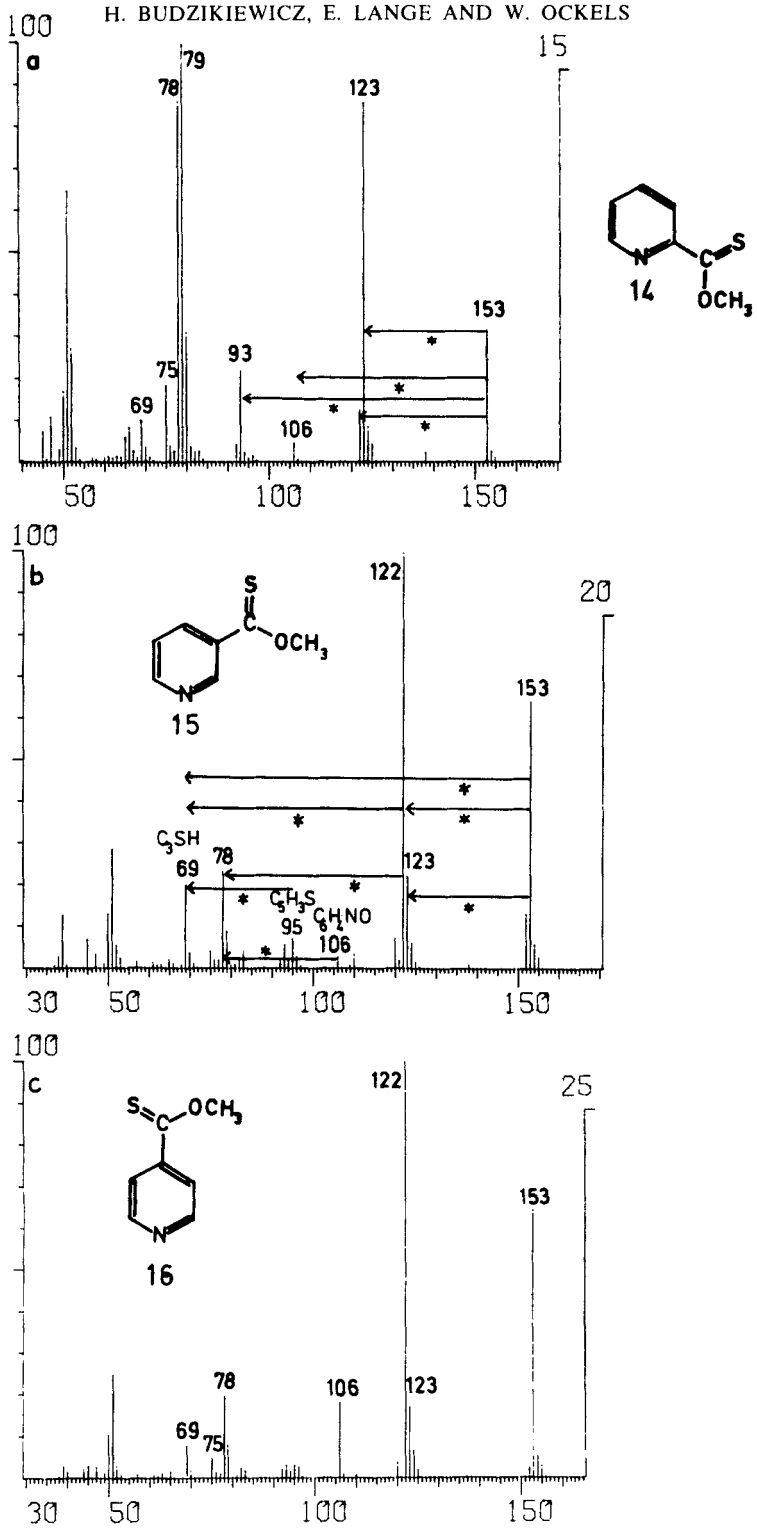
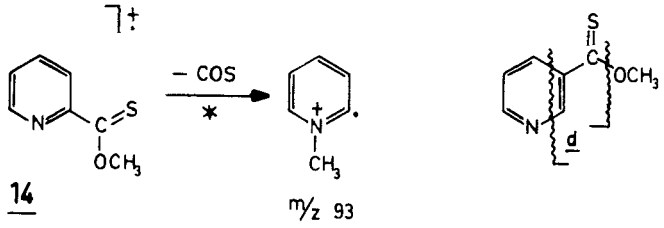


FIGURE 4 Mass spectra of pyridine carbothioic acid O-methyl esters: (a) 2, (b) 3, (c) 4.

Pyridine carbothioic acid O-methyl esters (Figure 4)

The most important feature in the spectra of **15** and **16** is the loss of $\cdot OCH_3$ (*m/z* 122) (further degradation by loss of CS, *m/z* 78, or HCN—*m**—, *m/z* 95) either in a one or a two step (loss of CH_2O followed by H) process (*m**). Loss of $\cdot SCH_3$ (mass measurement)—most distinctively with **16**—is also observed (cf. General Remarks). One should, however, note that in the spectrum of **14** the fragments *m/z* 107, 111, 125 characteristic for **6**—the expected rearrangement product for the loss of $\cdot SCH_3$—are missing. If one does not want to attribute this to different internal energy of the **6** $^{+\cdot}$-ions formed from **14** and **6**, one could invoke alternatively a step-by-step loss of $\cdot CH_3$ and S in lieu of the rearrangement. For $[M - \cdot CH_3]^+ \rightarrow [M - \cdot SCH_3]^+$ an *m** is observed (the appearance of an *m** for the total step $M^{+\cdot} \rightarrow [M - \cdot SCH_3]^+$ does not exclude a two-step process). Characteristic for **14–16** is *m/z* 69 (C_3HS^+, probably H—C≡C—C≡S$^+$, **d**) which—as various *m** show—can be formed in different ways (directly from $M^{+\cdot}$ by combined loss of $\cdot OCH_3$ and C_3H_3N, from $[M - \cdot OCH_3]^+$ by loss of C_3H_3N or in two steps by loss of HCN (*m/z* 95) and C_2H_2).

The spectrum of **14** again shows particularities: as with **1** the loss of CH_2O from M^+ (*m/z* 123) dominates, which accordingly is followed by elimination of CS (*m/z* 79). An ion of the composition $C_6H_5N^+$ (*m/z* 93) with a comparably high intensity is noticed for the formation of which methyl migration to the N can be assumed to occur:



SCHEME 5

Pyridine carbodithioic acid methyl esters (Figure 5)

The spectra of **18** and **19** do not show any particularities: $[M - \cdot SCH_3]^+$ (*m/z* 122) loses CS (*m/z* 78) or HCN (*m/z* 95). Regarding *m/z* 69 see above. The fragmentation behavior of **17**, however, is more complex (for the loss of CH_2S from M^+ see **6**). The ion *m/z* 105 has the composition $C_7H_7N^+$ and it is formed directly from M^+ (linked scan measurements) by the loss of S_2! One can only speculate about the mechanisms of decomposition; however, as *m/z* 105 only appears in the spectrum of **17** the participation of N can be assumed. The CA-spectrum of *m/z* 105 disregarding intensity differences due to *m**-transitions[19] corresponds with that of 2-vinyl pyridine which in turn cannot be distinguished from that of 4-vinyl pyridine. One could assume an isomerization of all three ions to a common structure but one should also keep in mind that CA-spectra might be a tool not sensitive enough to differentiate between isomeric aromatic species.

Pyridine-2-carboxylic acid methyl ester 6-carbothioic acid S-methyl ester (**20**) *(Figure 6)*

The fragmentation behavior is dominated by the decomposition of the thioester group (see above). $[M - \cdot OCH_3]^+$ and $[M - \cdot COOCH_3]^+$ are scarcely perceptible; $[M - COSCH_2]^{+\cdot}$ decomposes by loss of CH_3OH and subsequently of CO (cf. **5**).

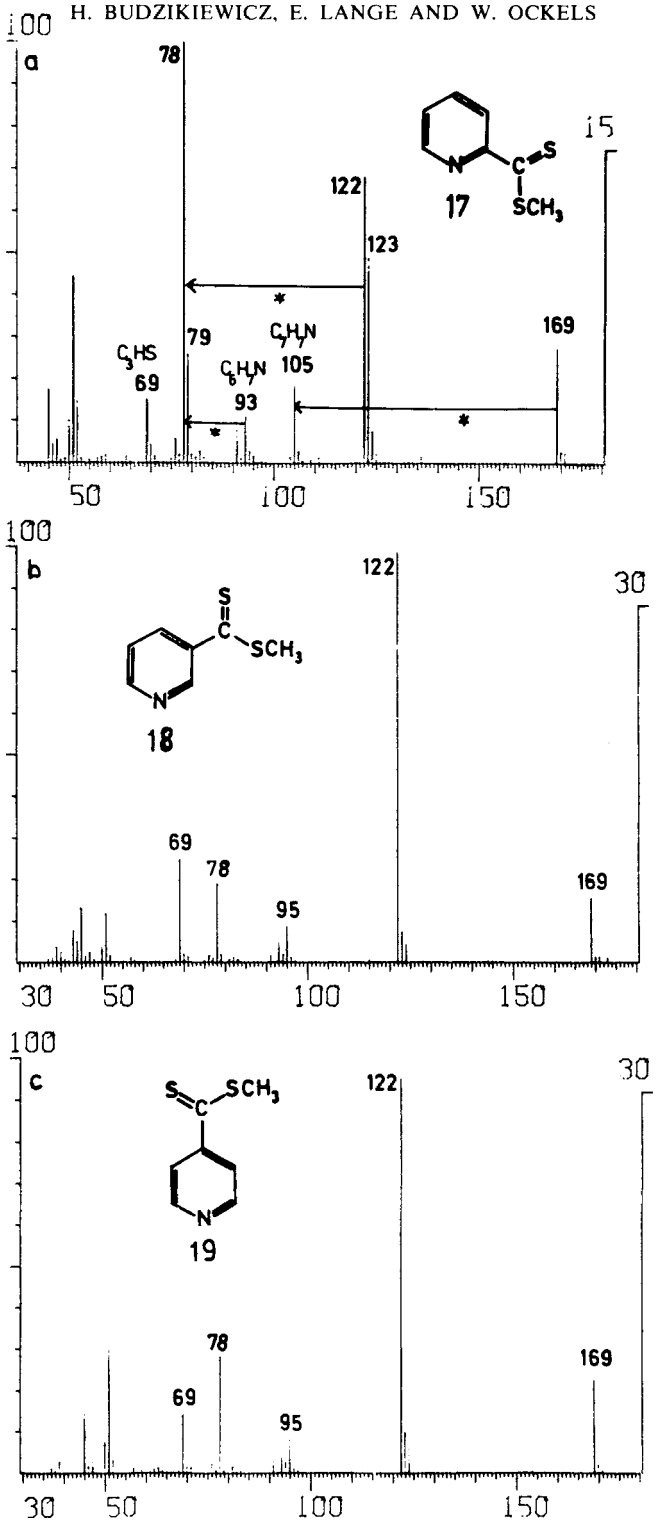
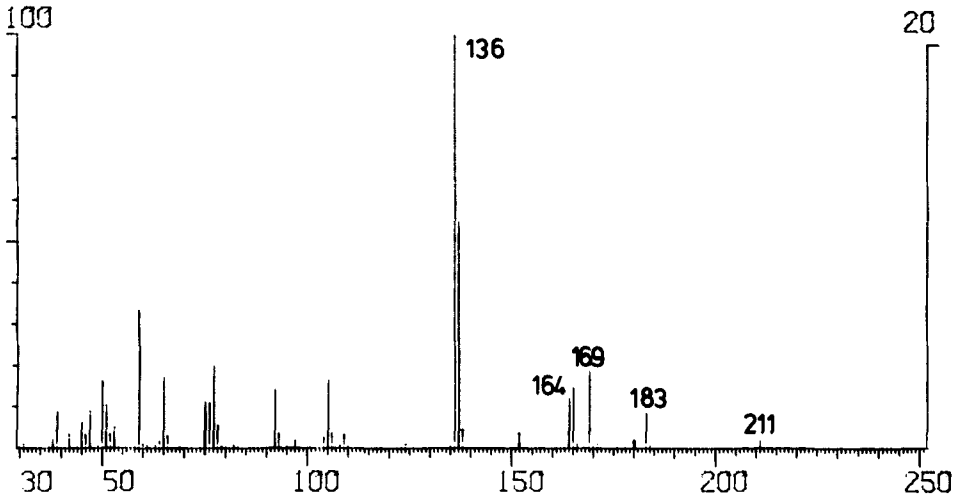
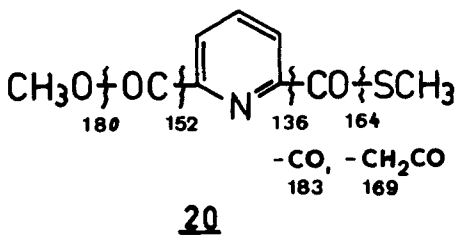


FIGURE 5 Mass spectra of pyridine carbodithioic acid methyl esters: (a) 2, (b) 3, (c) 4.





20

FIGURE 6 Mass spectrum of pyridine-2-carboxylic acid methyl ester 6-carbothioic acid S-methyl ester.

EXPERIMENTAL PART

Instruments

Mass Spectra. EI: Finnigan 3200 with gas chromatograph 9500. 70 eV, source 150°C. Exact mass measurements: Varian MAT 731 (indicated by elemental compositions in the Figures).
Metastables: Varian MAT 731 (defocussing technique) or Varian MAT 212 (linked scan). CA: Varian MAT 212, collision chamber in the first field-free region, collision gas air.
NMR. Varian EM 309 (90 MHz)
UV. Beckman 25 (CH_3OH)
IR. *Perkin-Elmer 720 (liquids film, solids KBr).*

From the thioesters discussed in this paper only **7** and **8** had been described in literature.[20-21] All compounds were purified by chromatography on silicagel and characterized by their spectral data (v. infra; Table I and Figures 2–6). The following general procedures were used for the syntheses.

Pyridine carbothioic acid S-methylesters (**6–8, 11–12**)

Pyridincarboxylic acid was refluxed with a large excess of thionyl chloride until all acid was dissolved. The excess of thionyl chloride was removed by distillation and the remaining acid chloride-hydrochlo-

TABLE I

NMR-Data: (δ-values in ppm: **11–13** in $CDCl_3$, otherwise in CCl_4; TMS)

Substance	$-CH_3$	H^2	H^3	H^4	H^5	H^6
6	2,38 (s)	—	7,98 (br. d)	7,83 (dt)	7,47 (ddd)	8,70 (ddd)
J:			8,1	8,1; 8,1; 1,8	8,1; 4,8; 2,1	4,8; 1,8; 1,2
7	2,49 (s)	9,14 (br. s)	—	8,20 (dt)	7,36 (ddd)	8,78 (dd)
J:				7,9; 1,8; 1,8	7,9; 5,0; 0,9	5,0; 1,8
8	2,46 (s)	8,80 (br. d)	7,73 (br. d)	—	$H^5 = H^3$	$H^6 = H^2$
J:		5,1	5,1			
11	2,49 (s)	—	8,49 (dd)	—	8,04 (dd)	8,96 (dd)
	2,55 (s)					
J:			2,1; 0,8		5,1; 2,1	5,1; 0,6
12	2,45 (s)	—	8,1 (dd)	8,43 (dd)	—	9,30 (dd)
	2,54 (s)					
J:			8,3; 0,9	8,3; 0,1		3,1; 0,9
13	2,47 (s)	—	8,20 (m)	8,15 (m)	$H^5 = H^3$	—
	(6 prot)		AB_2-systeme; J_{AB}	= 4,1 Hz		
14	4,34 (s)	—	8,29 (dt)	7,74 (dt)	7,38 (ddd)	8,64 (ddd)
J:			7,5; 1,2; 1,2	7,5; 7,5; 1,8	7,5; 4,5; 1,2	4,5; 1,8; 1,2
15	4,30 (s)	9,30 (br. d)		8,41 (dt)	7,28 (dd)	8,71 (br dd)
J:		1,8				
16	4,31 (s)	8,72 (dd)	7,91 (dd)	—	$H^5 = H^3$	$H^6 = H^2$
J:		5,1; 1,0	5,1; 1,7; 1,0			
17	2,68 (s)	—	8,37 (br. d)	7,78 (ddd)	7,44 (br. dd)	8,65 (br. d)
J:			7,8	7,8; 7,2; 1,8	7,2; 4,3	4,3
18	2,82 (s)	9,24 (br. s)	—	8,29 (br. d)	7,36 (dd)	8,79 (br. d)
J:				8,0	8,0; 4,5	4,5
19	2,78 (s)	8,68 (dd)	7,72	—	$H^5 = H^3$	$H^6 = H^2$
J:		5,1; 1,0	5,1; 1,7; 1,0			

ride (purified by sublimation i.v.) was stirred for 4 hours with an excess of CH_3SH under cooling with ice/NaCl. The excess CH_3SH was distilled off and the residue was stirred with toluene pyridine-hydrochloride remaining undissolved. Work-up of the toluene solution as usual.

Substance	Yield	mp °C	ν (C=O) cm^{-1}	UV λ nm, (ϵ)
6	2%	57–58	1665	276; 227 (5300; 6600)
7[20]	43%	19	1660	269; 226 (4700; 5800)
8[21]	25%	50–51	1665	273; 221 (5200; 5900)
11	41%	89	1655; 1675	281; 229 (8550; 11300)
12	10%	129	1660	290; 138 (11700; 13700)

Pyridine carbothioic acid O-methyl esters (**14–16**)

Cyanopyridine dissolved in toluene and methanol was treated with gaseous HCl for 6 hrs. (cooling with ice/NaCl). The white precipitate of pyridine carboxylic acid iminoester hydrochloride was filtered off and stirred with pyridine saturated with H_2S. Under cooling (ice/NaCl) this mixture was treated for 6 hrs. with H_2S. The pyridine was distilled off, the residue extracted with ether, the ether phase worked up as usual.

Pyridine carbodithioic acid methyl esters (**17–19**)

As described for **14–16** by using CH_3SH instead of CH_3OH.

Substance	Yield	mp °C	UV λ nm (ε)
14	45%	(liqu.)	420; 289; 233 (110; 7800; 5800)
15	31%	24–25	417; 285; 236 (110; 9650; 7150)
16	15%	34	424; 280; 228 (100; 9400; 8700)
17	2%	51	513; 343; 297 (100; 6500; 11400)
18	1%	(liqu.)	501; 326; 281 (100; 7100; 10400)
19	1%	(liqu.)	505; 325; 256 (110; 8700; 13200)

2-Methylthiopyridine (**9**) was obtained from 2-mercapto pyridine by selective S-alkylation with CH_3I by phase-transfer catalysis.[22]

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