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MASS SPECTRA OF DIMETHYLPYRIMIDINES

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Abstract—The mass spectra of the four dimethylpyrimidines are compared with those of the isomeric dimethylpyrazines. It was necessary to synthesise three of the dimethylpyrimidines, and methods are described.

Pyrazines, and particularly alkylpyrazines, are frequently detected amongst the volatile flavour components of heat-treated foods (e.g. meat, coffee) and generally they bestow important roast or burnt notes to the overall aroma profile. Such compounds are also to be located in other types of environmental samples when thermal processes have been involved, e.g. wood smoke, gaseous industrial effluents. In all these circumstances the pyrazines are present in minute quantities in complex admixture with numerous other volatile components. Invariably the method of analysis which has to be adopted for these types of samples is GC–MS and thus the pyrazines have been identified almost exclusively based on mass spectral evidence alone (although gas chromatography retention data also play a part).

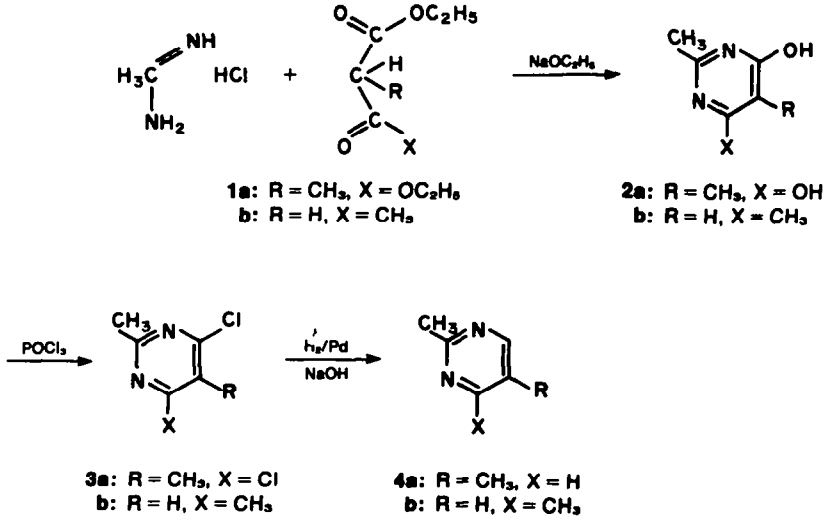
Pyrimidines are isomeric with pyrazines and it might be expected that in some instances mass spectra of such analogues might be similar. Since the mass spectra of some simple pyrimidines, such as the dimethylpyrimidines, have not been reported in the literature, there does appear some slight risk of confusion and possible wrong assignments (the dimethylpyrazines are widely reported components of samples such as those previously mentioned). For this reason the project described here was undertaken. Of the four possible dimethylpyrimidines one was available commercially so only three had to be synthesised. All their mass spectra were recorded very carefully and compared with those of the dimethylpyrazines recorded under identical conditions. Perhaps due to their new importance all the required pyrazines are commercially available.

2,5-Dimethylpyrimidine **4a** was prepared as shown in Scheme 1. The first two steps of the synthesis are based on those employed by Gershon *et al.* to prepare 2-methyl-4,5,6-trichloropyrimidine from diethyl chloromalonate.[1] The third and final step employed the general method of Smith and Christensen for the catalytic dehalogenation of chloropyrimidines.[2]

Previously reported methods of preparation of 2,4-dimethylpyrimidine **4b** were not very successful, so a procedure based on that used to prepare the 2,5-analogue was devised as shown in Scheme 1 for the b series of compounds. Some slight modifications in experimental methods were however necessary.

4,5-Dimethylpyrimidine was prepared in a one-step reaction from N,N′,N″-methylidynetrisformamide and butanone in a modification of the method reported by Bredereck *et al.*[3] 4,6-Dimethylpyrimidine was available commercially.

Purity and identity of all four dimethylpyrimidines and the three purchased dimethylpyrazines were assessed and confirmed by gas chromatography and spectroscopic methods other than mass spectrometry (i.e. IR and ^{1}H NMR). Mass spectra of the seven compounds were



1a: R = CH_3, X = OC_2H_5
b: R = H, X = CH_3

2a: R = CH_3, X = OH
b: R = H, X = CH_3

3a: R = CH_3, X = Cl
b: R = H, X = CH_3

4a: R = CH_3, X = H
b: R = H, X = CH_3

Scheme 1. Preparation of dimethylpyrimidines.

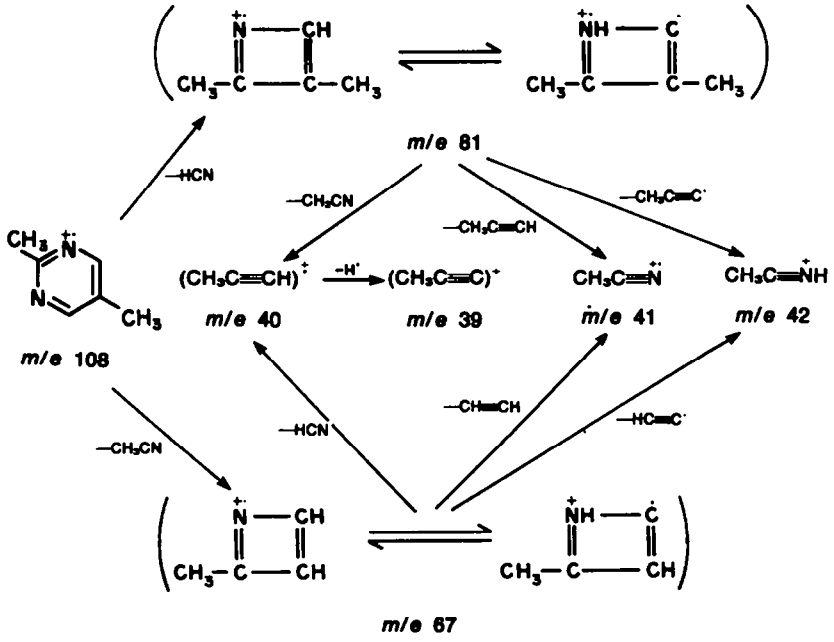
Table 1. Mass spectral data for dimethylpyrimidines and dimethylpyrazines

	Percentage relative abundance						
	dimethylpyrimidines				dimethylpyrizines		
m/e	2,5	2,4	4,5	4,6	2,3	2,5	2,6
109	0.5	9	8	8	2	7	8
108	43	100	100	100	44	100	100
107	0.5	15	25	17	2	2	3
93	1	25	10	8	3	1	2
81	8	11	8	27	2	12	5
67	1	57	10	8	100	2	6
66	0.5	18	10	19	5	2	3
52	3	27	16	5	15	10	8
51	1	25	14	6	19	6	8
42	100	46	23	44	49	81	78
41	12	70	12	14	27	2	5
40	10	84	28	36	52	21	27
39	25	74	40	52	40	35	40

then recorded in one session under as identical conditions as possible, and the results are listed in some detail in Table 1. The spectra recorded for the pyrazines agree well with those previously published, e.g.[4].

Scheme 2 suggests the likely origins of the main fragment ions of dimethylpyrimidines using the 2,5-isomer as the example.

It can be seen from Table 1 that all the dimethylpyrimidines give the same fragment ions, the only differences being in the relative abundances of these ions. In explanation, it can be readily appreciated from Scheme 2 that all dimethylpyrimidines would be capable of this same fragmentation scheme, wherever the methyl substituents. Similarly the same scheme indeed applies to



Scheme 2. Proposed fragmentations of dimethylpyrimidines.

all the dimethylpyrazines, and exactly the same structure of fragment ions and mechanisms would be expected for these isomers. The fact that this is the case is seen in Table 1 for the spectra of the pyrazines. Thus the only differences between the mass spectra of the dimethylpyrimidines and the dimethylpyrazines are in the relative abundances of a common set of fragment ions. The question with regard to the validity of any interpretations based on these data alone is whether these differences are of sufficient significance.

It can be seen from Table 1 that 2,3-dimethylpyrazine, with the base peak of its spectrum at *m/e* 67, can be readily distinguished from the other pyrazines which have the molecular ion at *m/e* 108 as their base peak. This same feature enables discrimination between 2,3-dimethylpyrazine and all the dimethylpyrimidines, none of which has *m/e* 67 as base peak—so this pyrazine can be clearly recognised. Similarly, the spectrum of 2,5-dimethylpyrimidine is distinctive due to the unique base peak at *m/e* 42. However, the spectra of the remaining three dimethylpyrimidines could be confused both between themselves and in comparison with the other two dimethylpyrazines. Thus all five show the molecular ion as the base peak and although there are slight differences in the relative intensities of some fragment ions between the two groups of compounds these are not very significant. Most noticeable, however, are the greater intensities of the ions at *m/e* 107 and 93, and to a lesser extent at *m/e* 41 and 40, for the pyrimidines compared with the pyrazines, and also the somewhat lower abundance of the fragment ion at mass 42 in the pyrimidines. Furthermore, within either group the spectra are very similar and particularly so for the remaining two pyrazines, and it has been asserted that these two compounds cannot be differentiated by mass spectrometry.[5] The situation is not quite so severe for the remaining dimethylpyrimidines and quite a few distinguishing features can be observed in their mass spectra as shown in Table 1.

However, in conclusion it would appear that there is serious risk of confusion of identities based on mass spectral evidence alone between three of the dimethylpyrimidines and two of the dimethylpyrazines. Such differences as there are in the spectra are slight and due to instrumental variations, etc. these might well not be apparent unless reference standards were always assessed at the same time as unknown samples. It would be wise therefore not to characterise 2,5- and 2,6-dimethylpyrazines in environmental and similar samples on mass spectral evidence alone.

EXPERIMENTAL

Mass spectra were recorded using a Kratos/AEI MS30 double focussing instrument equipped with a Kratos AEI DS50 data processing system. Samples were introduced via a conventional solid probe and relevant instrument operating conditions were: source temp., 175°; ionising voltage, 70 eV; accelerating voltage, 4 kV; ionising current, 300 μA; resolving power, 1500.

4,6-Dihydroxy-2,5-dimethylpyrimidine **2a**. To abs EtOH (250 ml) containing Na (5.75 g, 0.25 mol) was added diethylmethylmalonate **1a** (43.5 g, 0.25 mol). The mixture was shaken for 5 min and acetamidine hydrochloride (23.6 g, 0.25 mol) was added. The mixture was shaken for 1 hr and then left stirring for 24 hr. Water (100 ml) was then added and the soln acidified to Congo Red using conc HCl. After cooling for 3 days in the refrigerator the product was obtained in 32.4% yield (11.4 g) as a white crystalline solid, m.p. > 300° (lit. [6]m.p. > 300°).

4,6-Dichloro-2,5-dimethylpyrimidine **3a**. **2a** (3.5 g, 0.025 mol) was refluxed with freshly distilled $POCl_3$ (40 ml, 0.43 mol) for 16 hr with stirring. Then 25 ml of $POCl_3$ were distilled off and the residue poured onto ice. The solid so produced was taken up in di-isopropyl ether and upon removal of the ether by distillation a pale yellow solid resulted. This was purified by sublimation to produce **3a** in 55.4% yield (2.45 g) as fine white crystals, m.p. 39–40° (lit. [7]m.p. 39°).

2,5-Dimethylpyrimidine **4a**. A slight excess of 20% carbonate-free NaOH aq (5 ml), sufficient to neutralise the HCl produced during reaction, was placed in a low pressure hydrogenation bottle followed by 5% Pd on C catalyst (0.2 g) and **3a** (1.77 g, 0.01 mol) dissolved in diethyl ether (20 ml). The mixture was shaken with hydrogen at an initial pressure of *ca.* 4 atm and room temp. (22°) until H_2 uptake ceased. The mixture was filtered, the residue washed with 2 × 5 ml portions of hot water, and the combined filtrates made strongly alkaline by the addition of NaOH (1 g) with external cooling such that the temp. remained below 5°. The soln was then continuously extracted with diethyl ether for 12 hr. The dried ($MgSO_4$) extract was evaporated to dryness, and distilled *in vacuo* (b.p. 45–6°/5 mm) to give **4a** in 47% yield (0.51 g) as pure white crystals, m.p. 19–20° (lit. [8]m.p. 19°).

2,4-Dimethyl-6-hydroxypyrimidine **2b**. Acetamidine hydrochloride (18 g, 0.19 mol) ethyl acetoacetate **1b** (25.5 g, 0.19 mol) and NaOH (7.8 g, 0.19 mol) in 100 ml water were allowed to react for 7 days at room temp. The mixture was then neutralised with conc. HCl and evaporated to dryness under vacuum. The residue was extracted with abs EtOH and concd. Sublimation of the residue gave **2b** in 39% yield (9.24 g) as a white crystalline solid, m.p. 192–3° (lit.[9] m.p. 192°).

6-Chloro-2,4-dimethylpyrimidine **3b**. **2b** (1.12 g, 0.01 mol) was refluxed with freshly distilled $POCl_3$ (16.5 ml, 0.18 mol) for 24 hr with stirring and in the absence of moisture. Then 10 ml of $POCl_3$ were distilled off and the residue poured onto ice. The mixture was taken up in diethyl ether and upon removal of the ether by distillation a yellow solid resulted. This was purified by sublimation to produce **3b** in 52.2% yield (0.744 g) as a white crystalline solid, m.p. 39–40° (lit.[10] m.p. 39–40°).

2,4-Dimethylpyrimidine **4b**. This was prepared by catalytic dehalogenation of **3b** in exactly the same way as for the preparation of **4a**. It was purified by distillation (b.p. 44–6°/15 mm) and was thus obtained in 43% yield as a colourless liquid, b.p. 151–2° (lit.[11] b.p. 150–1°).

4,5-Dimethylpyrimidine. Formamide (6 ml, 0.15 mol), butanone (3.5 ml, 0.04 mol),N,N',N"-methylidynetrisformamide (11.6 g, 0.08 mol) and toluene-*p*-sulphonic acid (0.3 g, 1.7×10^{-3} mol) were heated in a 16 cm^3 stainless steel autoclave at a temp. of 155° for 8 hr with stirring. The mixture was then rendered alkaline with NaOH aq and continuously extracted with $CHCl_3$ for 10 hr. The dried ($MgSO_4$) chloroform extract was evaporated to dryness *in vacuo* to give crude 4,5-dimethylpyrimidine. Distillation (b.p. 50°/10 mm) provided 2.1 g (49%) of the required product as a colourless liquid, b.p. 169–72°, m.p. 3–4° (lit.[3] b.p. 169–71°/750 mm, m.p. 2°).

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