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Mass Spectrometry of 1,2,4,5-Tetrazines

CHARLES LARSEN and ERNST BINDERUP

Chemical Laboratory II (General and Organic Chemistry), University of Copenhagen, The H.C. Ørsted Institute, Copenhagen, Denmark

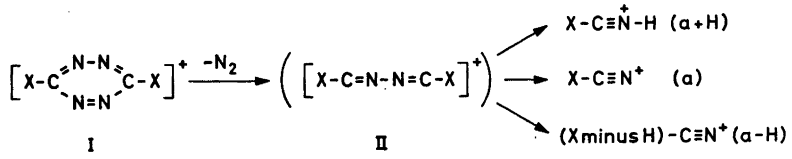
JØRGEN MØLLER

Physical Laboratory II, University of Copenhagen, The H.C. Ørsted Institute, Copenhagen, Denmark

The mass spectra of 1,2,4,5-tetrazine and some 3,6-dialkyl- and 3,6-bis-dialkylamino-1,2,4,5-tetrazines (I) have been recorded.

A characteristic feature for all substituted tetrazines is the unusually wide mass range, where no peaks appear at all. The fragment ion with the highest mass is usually found at $m/e = (M/2)-13$.

The major fragmentation mode, common to both types of substituted tetrazines, is initiated by loss of N_2 from the molecular ions, followed by a simple cleavage, with formation of ions with a nitrilo structure, (a), and, by simultaneous rearrangement of one hydrogen atom, (a + H) ions, and in some cases (a—H) ions:



I II

X=H, CH_3, C_2H_5, C_3H_7, *i*-C_3H_7, *tert*-C_4H_9

X=$N(CH_3)_2$, $N(C_2H_5)_2$, $N(C_3H_7)_2$, $N(i\text{-}C_3H_7)_2$

In the mass spectrum of 1,2,4,5-tetrazine itself, we find the M—28 peak (*m/e* 54) to have an intensity of 2.4 % of $\sum_{12}$ (*cf.* Weininger and Thornton[1]), but among the substituted tetrazines only the most simple one, 3,6-dimethyl-

Table 1. Abundances of M, (a + H), (a), (a−H), and the base peaks given in percent of Σ_{12}.

Compound	M		(a + H)		(a)		(a−H)		Base	
	m/e	%	*m/e*	%	*m/e*	%	*m/e*	%	*m/e*	%
1,2,4,5-Tetrazine	82	15.3	28	35.3	27	26.6	26	3.3	28	35.3
3,6-Dimethyl-1,2,4,5-tetrazine	110	5.9	42	29.6	41	18.5	40	11.3	42	29.6
3,6-Diethyl-1,2,4,5-tetrazine	138	2.1	56	16.6	55	5.2	54	11.4	28	29.4
3,6-Dipropyl-1,2,4,5-tetrazine	166	0.73	70	17.3	69	1.0	68	0.28	41	19.6
3,6-Diisopropyl-1,2,4,5-tetrazine	166	0.35	70	7.9	69	3.2	68	6.1	43	18.7
3,6-Di-*tert*-butyl-1,2,4,5-tetrazine	194	0.23	84	5.8	83	1.3	82	0.8	42	23.0
3,6-Bis-(dimethylamino)-1,2,4,5-tetrazine	168	10.8	71	14.2	70	19.1	69	23.1	69	23.1
3,6-Bis-(diethylamino)-1,2,4,5-tetrazine	224	5.8	99	9.2	98	5.3	97	0.6	83	23.4
3,6-Bis (dipropylamino)-1,2,4,5-tetrazine	280	3.1	127	6.2	126	1.7	125	0.26	43	16.5
3,6-Bis-(diisopropylamino)-1,2,4,5-tetrazine	280	1.2	127	2.9	126	1.3	125	0.44	69	24.9

1,2,4,5-tetrazine, has an M—28 peak (0.85 % of $\sum_{12}$). The resonance stabilization of the open-chain intermediates (II) is too weak to cause a peak, and thus the M—28 ions decompose completely. The ratio between the abundances of (a) and (a + H) varies considerably (Table 1), but, apart from 3,6-dimethylamino-1,2,4,5-tetrazine, (a + H) is always more abundant than (a). The (a—H) ion is significant only in those molecules for which the chain length of the radicals attached to the ring does not exceed 2 atoms (including N).

In the spectrum of dimethyltetrazine a peak at *m/e* 54 (0.34 % of $\sum_{12}$) is present. By exact mass measurement the composition of this ion was found by Weininger and Thornton [1] to be $C_4H_6^+$. It seems plausible that this is a dimethylacetylene ion arising from decomposition of the dimethyldiazacyclobutadiene cation, as stated in Ref. 1.

There is no evidence that any of the other substituted tetrazines form fragment ions according to this fragmentation mode. Apart from small peaks at *m/e* 81 and 82 — probably ions with tetrazine structure — found in highest abundances in the spectrum of diisopropyltetrazine (1.4 % and 1.2 %, respectively), the fragmentation scheme depicted above is in accord with all other peaks in the spectra.

EXPERIMENTAL

Microanalyses were carried out in the microanalysis department of this laboratory. The nitrogen values were consistently 1—2 % too low, but this is not unusual for hydrazine derivatives.

The mass spectra were obtained on an Atlas CH4 mass spectrometer. The inlet system was maintained at a temperature of 150°C and the temperature of the ion source was 250°C. An electron current of 35 A and an ionizing potential of 70 eV were applied.

1,2,4,5-Tetrazine was prepared according to Curtius *et al.*[2] *via* 1,2,4,5-tetrazine-3,6-dicarboxylic acid;[3] *cf.* also Spencer *et al.*[4] The compound was purified by resublimation *in vacuo*.

3,6-Dimethyl-1,2,4,5-tetrazine. This compound was prepared from acetonitrile and anhydrous hydrazine, following essentially the directions given by Curtius *et al.*[5] To purify the crude product it was sublimed at 20°C/0.05 mm Hg until the red crystals had a m.p. of 73—74°C and gave a correct analysis. Total yield 0.5 %. (Found: C 43.40; H 5.71. Calc. for $C_4H_6N_4$: C 43.63; H 5.49).

3,6-Diethyl-1,2,4,5-tetrazine. Müller and Herrdegen [6] observed that this compound was formed as a red oil in addition to 2,5-diethyl-1-aminotriazole when propionitrile and anhydrous hydrazine were refluxed in abs. ethanol for 4½ days. The yield obtained was not reported and the compound was only partly characterized by hydrolysis to propionic acid, determined as the silver(I) salt. Curtius *et al.*[5] have shown that solvents should be avoided when the maximum yield of tetrazine, relative to aminotriazole, is wanted. Preliminary experiments showed addition of abs. ethanol to be unnecessary, since propionitrile and anhydrous hydrazine form a homogeneous mixture at the boiling point. Taking this into account, the following directions for the preparation afforded the purest compound.

Propionitrile (33 g) and anhydrous hydrazine (19.2 g) were boiled under reflux for 3½ days. The unreacted reagents were removed *in vacuo* leaving the dihydrotetrazine as a colourless crystalline compound. Since this material is extremely sensitive to oxidation to the highly volatile tetrazine, the apparatus was flushed with nitrogen. To remove adherent starting materials the crude product was dried over *conc.* sulfuric acid in high vacuum. It was then dissolved in water (50 ml) and oxygen was bubbled through the solution until the orange-red colour did not intensify further. A condenser was necessary to avoid loss of tetrazine. The aqueous solution was extracted with five 10-ml portions of ether, and the vividly violet-coloured extract dried over magnesium sulfate. The ether was carefully removed with nitrogen at 40°C, leaving the tetrazine as a violet oil.

The residue (170 mg) was distilled bulb-to-bulb at 20°C/0.5 mm Hg to give 100 mg of pure tetrazine, which resisted all attempts to induce crystallization. (Found: C 52.39; H 7.30. Calc. for $C_6H_{10}N_4$: C 52.15; H 7.30).

3,6-Dipropyl-1,2,4,5-tetrazine was prepared in the same way from butyronitrile (55.5 g). The tetrazine was purified by distillation at 80°C/0.5 mm Hg. Müller and Herrdegen [6] reported this compound to be formed in amounts insufficient to isolate, but by omitting absolute ethanol from the reaction mixture a similar yield (50 mg) as in the case of the lower homologues was obtained. The pure tetrazine is a violet oil. (Found: C 57.80; H 8.59. Calc. for $C_8H_{14}N_4$: C 57.80; H 8.49). In the same way isobutyronitrile (55.5 g) gave 300 mg of *3,6-diisopropyl-1,2,4,5-tetrazine* as a violet oil after distillation at 60°C/0.5 mm Hg. (Found: C 57.85; H 8.46). Like the aforementioned dialkyltetrazines this compound is moderately soluble in water, but dissolved readily in CS_2, CCl_4, ethanol, benzene *etc.*

3,6-Di-tert-*butyl-1,2,4,5-tetrazine*. Attempted preparation of this compound analogously to the above method from pivalonitrile showed that only very minute amounts of the tetrazine were formed. In the search for a better method we finally succeeded with a modification of the tetrazine synthesis developed by Jensen and Pedersen,[7] consisting in base-catalyzed condensation of two molecules of *S*-alkylthiohydrazidium iodides to dihydrotetrazines, followed by oxidation. A solution of *S*-methylthiopivaloylpiperidinium iodide [8] (8.0 g) and anhydrous hydrazine (2.5 g) in water (100 ml) was refluxed for 5 h while a steady stream of oxygen was led through. The supernatant red oil was extracted with ether and separated by column chromatography into the violet tetrazine (negligible yield) and N,N'-*bis-(1-piperidino-2,2-dimethylpropylidene)-hydrazine* (400 mg), colourless crystals, m.p. 105—106°C. (Found: C 72.02; H 11.50; N 16.30. Calc. for $C_{20}H_{38}N_4$: C 72.00; H 11.40; N 16.70). To minimize the formation of this product the following method was finally adopted: *S*-methylthiopivaloylpiperidinium iodide (11.7 g) and anhydrous hydrazine (15 g) in absolute ethanol (200 ml) were refluxed for 10 h with oxygenation as above. A violet compound precipitated on addition of water, which was purified by recrystallization from ethanol/water to give 155 mg of violet crystals of the tetrazine, m.p. 94—95°C. The compound sublimes readily *in vacuo*. (Found: C 61.75; H 9.28. Calc. for $C_{10}H_{18}N_4$: C 61.86; H 9.28).

3,6-Bis-(dimethylamino)-1,2,4,5-tetrazine. This compound has been claimed in a patent.[9] A modified method is described in the accompanying paper.[10] Before recording the mass spectra, the compound was purified twice by column chromatography.

3,6-Bis(diethylamino)-1,2,4,5-tetrazine. This compound was prepared in an analogous way to the methyl homologue,[10] using 4,4-diethylthiosemicarbazide [11] (10 g). The reaction mixture was taken to dryness, and the tetrazine extracted with benzene. Column chromatography afforded 300 mg of a red crystalline compound, m.p. 40—42°C. (Found: C 53.40; H 9.22. Calc. for $C_{10}H_{20}N_6$: C 53.54; H 8.99). In an identical manner we prepared *3,6-bis-(dipropylamino)-1,2,4,5-tetrazine* in 5 % yield as a red oil. (Found: C 59.65; H 9.89. Calc. for $C_{14}H_{28}N_6$: C 59.96; H 10.07). Furthermore, *3,6-bis-(diisopropylamino)-1,2,4,5-tetrazine* was obtained as ruby-red, rhomboid crystals in 4.5 % yield, m.p. 133—135°C. (Found: C 60.35; H 10.07).

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