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Short communication

Identification of 2,3-butanedione monoxime hydrogenation products by gas chromatography–mass spectrometry in an ion trap mass spectrometer

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Abstract

The reduced products of 2,3-butanedinone monoxime by reaction with hydrogen in the presence of homogeneous catalysts were identified by gas chromatography coupled to an ion trap mass spectrometer operating either in the electron impact or chemical ionization mode. The major hydrogenation products were found to be several heterocyclic nitrogen-containing compounds: tetramethylpyrazine, 2,4-dimethyl-3-ethylpyrrole, 3,4,5-trimethylpyrazole, 2,5-dimethyl-1-propylpyrrole, 3-acetyl-2,4-dimethylpyrrole, 3,5-dimethyl-4-allypyrazole and tetramethylpyrazine *N*-monoxide.

Keywords: Butanedione monoxime; Pyrroles; Pyrazoles; Pyrazines

1. Introduction

The reduction of α-hydroxyimine carbonyl compounds is one of the most important methods for the synthesis of 2,3,5,6-tetrasubstituted and 2,5-disubstituted pyrazines [1]. We recently studied the preparation of 2,3,5,6-tetramethylpyrazine (TMP), which has been widely used in the treatment of patients with cerebral ischemic diseases in China [2], via reduction of 2,3-butanedione monoxime (BDM) with hydrogen in the presence of homogeneous catalyst [3].

Besides TMP, other products with a nitrogen-containing heterocyclic ring appear to be present in the reaction. Although the reaction has been researched, relatively few studies of the identification of the reaction products apart from TMP have been reported, due to their smaller amounts and difficulty of isolation. The identification of these products and intermediate products is required for TMP used as a medicine material, a study on the mechanism of the reaction is also important. The combination of quadrupole ion trap mass spectrometry interfaced with gas chromatography (GC–MS) is now becoming widely available with its high sensitivity, high specificity and the relatively low cost of instrument [4]. Thus the GC–MS method can be widely used in the studies on more reaction products and the mechanisms of their formation. The basic objective

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of the present work was to identify the principal BDM hydrogenation products.

2. Experimental

2.1. Sample

The catalytic hydrogenation of BDM in ethanol solution of 0.2 *M* initial concentration was carried out in a 24-ml glass-lined stainless steel autoclave at 80 to 150°C under H_2 pressure of 0.6~2.4 MPa for 1–6 h. A mixture of homogeneous transition metal catalyst [3] and BDM (0.1 mmol) in ethanol (5 ml) was added to the autoclave. The reactor was purged five times with hydrogen, before setting the required H_2 pressure. Hydrogen up to the required H_2 pressure was introduced and the reaction vessel was placed in a preheated thermostatic oven, which could be agitated by shaking (12 times min^{-1}). The reaction mixture was constantly agitated and kept at 150°C for 6 h. After being cooled to room temperature, the reaction solution was immediately analyzed by GC–MS. In the meantime, the TMP product was isolated and purified by preparative thin-layer chromatography (TLC) on silica gel (cyclopentane–ethyl acetate, 2:1) and further identified by ^{1}H-nuclear magnetic resonance (NMR), IR and melting point determining.

2.2. Apparatus

All the GC–MS experiments were performed on a Finnigan Mat Magnum GC–MS ion trap system. This instrument could be operated in electron impact (EI) and chemical ionization (CI) mode. The computer was equipped with the NIST mass spectral library which enabled ready comparison of experimental and reference spectra. GC was performed using a DB-5 capillary column (30 m×0.25 mm I.D., 0.25 μm film thickness) from J&W, (Folsom, CA, USA), which was inserted directly into the ion trap through a transfer line heated to 220–240°C.

2.2.1. Gas chromatography

Introduction of the samples was performed via spitless injection of 1 μl of sample solution at 220~240°C. In order to get the information of the intermediates; we analyzed the reaction mixture by GC–MS after removing the catalysts simply through a silica gel filter column, which has been employed in the front of the capillary column of gas chromatography. The GC column temperature program was initial temperature 70°C for 1 min followed by a 10°C min^{-1} ramp to 130°C, a hold at 130°C for 1 min and then a 10°C min^{-1} ramp to 250°C and a hold for 2 min. Helium gas was used as the mobile phase at a linear velocity of 32 cm s^{-1}, corresponding to a flow ~1 ml min^{-1} into the ion trap.

2.2.2. Mass spectrometry

The ion trap temperature was maintained at 220°C, The multiplier voltage was optimized to give a gain of 10^5. Mass range was 32 to 336 u. Scan rate was 1 scan s^{-1}. The filament current was held at 10 μA, A/M amplitude 3.5 V. Ionization time was 62 500 μs. In CI mode, methane was used as the reagent gas.

2.3. Synthesis of tetramethylpyrazine N-monoxide (TMPO)

In order to identify the BDA hydrogenation products, TMPO which was one of the suspected compounds has to be synthesized.

TMPO was prepared by placing a mixture of 0.1 g TMP and 1 ml acetic acid into a glass beaker, stirring at 70°C, adding 0.1 ml of H_2O_2 (30%) to the solution, and then held at 70°C for 4 h. The ensuing reaction is shown in Fig. 1.

The reaction solution was neutralized by sodium carbonate, extracting it with ethyl ether, then removing ethyl ether. The approximate yield 80% of TMPO was obtained.

3. Results and discussion

Fig. 2 shows a typical total ion chromatogram of a 0.2 *M* BDM solution after hydrogenation. Apart from the BDM peak (peak 1), various other peaks representing hydrogenation and condensation products are evident.

Peaks 2–7 and peak 9 were found to be tetramethylpyrazine (TMP), 2,4-dimethyl-3-ethylpyrrole (DEPR), 3,4,5-trimethylpyrazole (TPZ), 2,5-di-

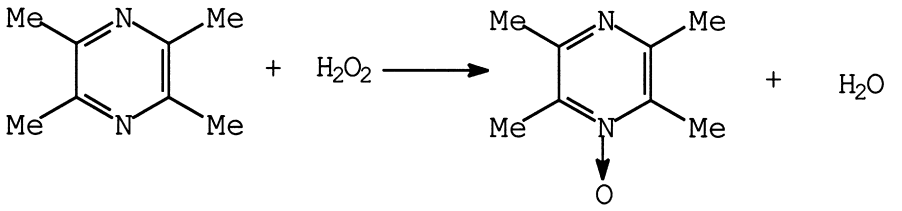


Fig. 1. Reaction for the synthesis of tetramethylpyrazine *N*-monoxide.

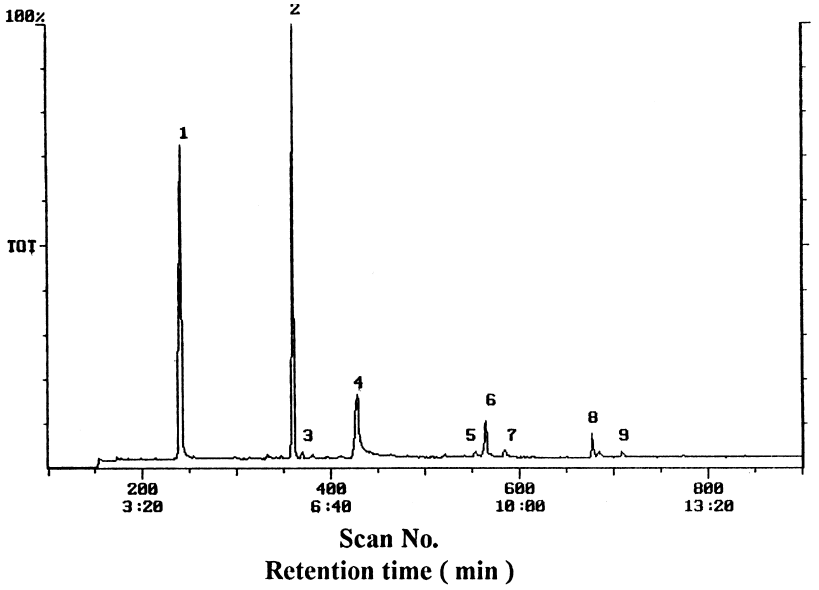


Fig. 2. Total ion chromatogram of BDM solution of 0.2 *M* initial concentration, reduced at 150°C under a hydrogen partial pressure of 2.4 MPa for 6 h.

methyl-1-propylpyrrole (DPPR), 3-acetyl-2,4-dimethypyrrole (ADPR), 3,5-dimethyl-4-allylpyazole (DAPZ), and 2,2′-bipyridine (BPY), respectively, by matching their EI mass spectra with NIST library spectra stored in the GC–MS instrument. TMP (peak 2) isolated with TLC also was confirmed by ^{1}H-

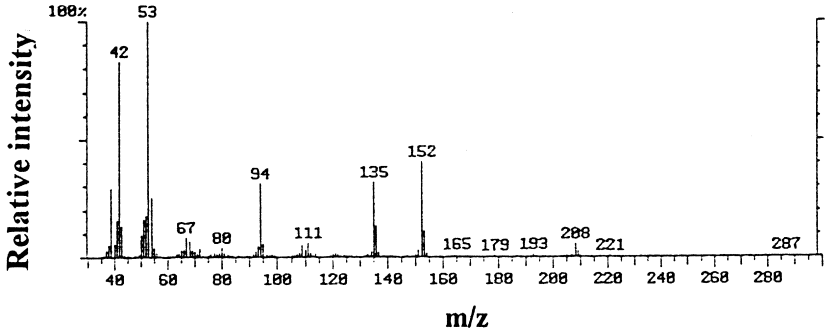


Fig. 3. EI mass spectrum of peak of peak 8.

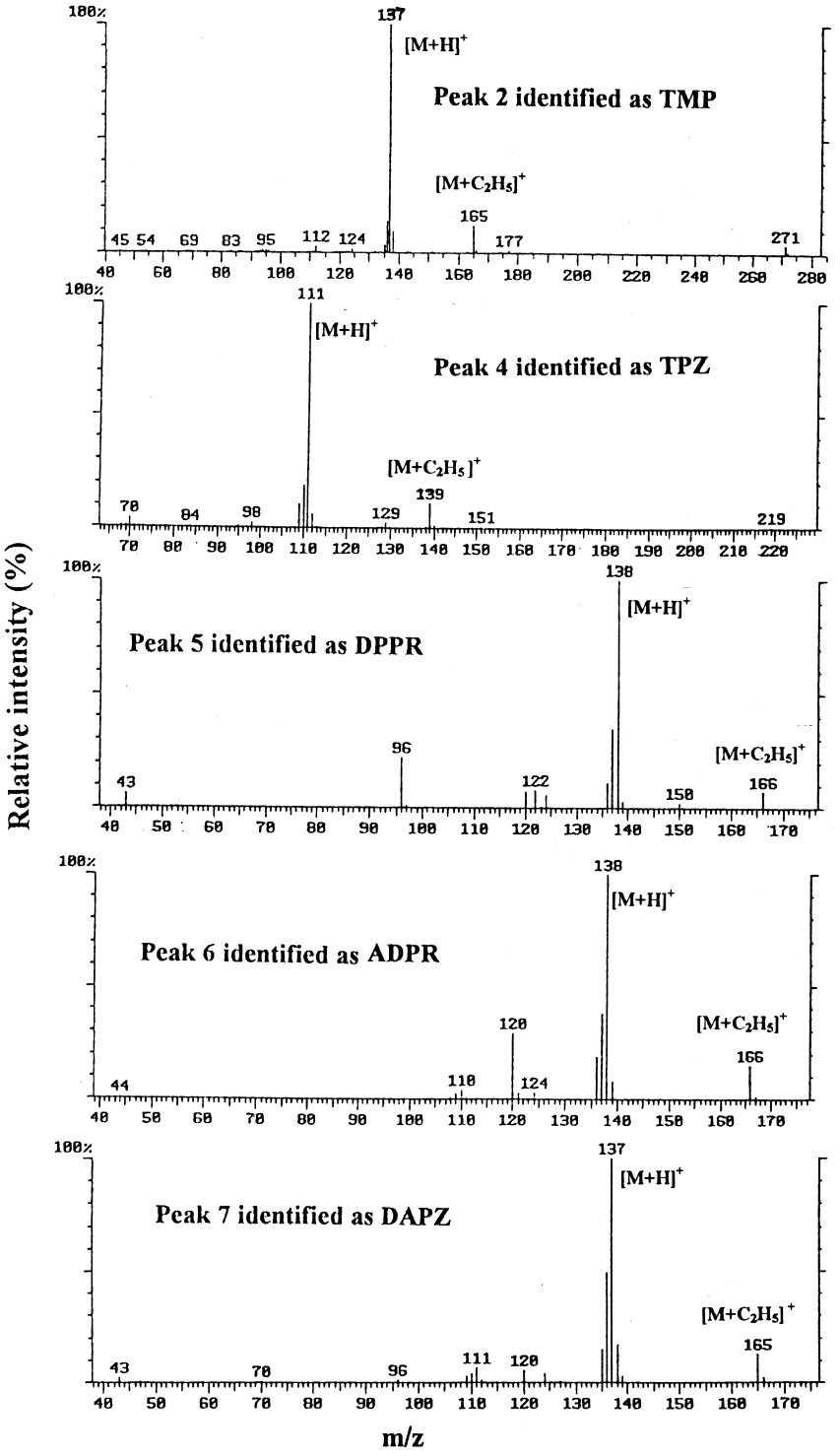


Fig. 4. CI mass spectra of peaks 2, 4, 5, 6 and 7.

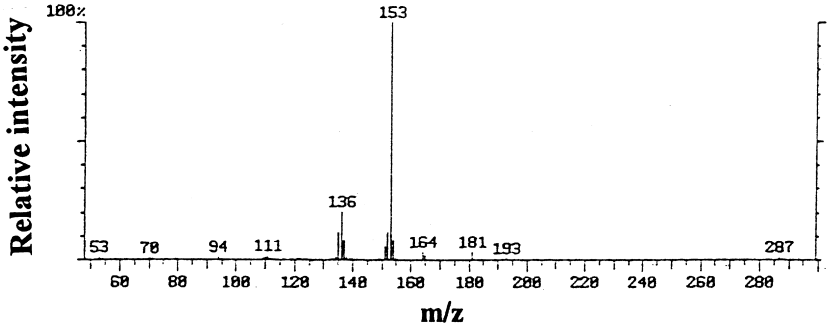


Fig. 5. Methane CI mass spectrum of peak 8.

NMR, IR, and melting point determining. 2,2′-Bipyridine was one of the ligands of homogeneous catalysts added previously [3]. It was clear that peaks 2, 3, 4, 5, 6 and 7 were the products of BDM hydrogenation and condensation. Their EI mass spectra match with those of NIST library spectra very well.

Peak 8, whose EI mass spectrum is given in Fig.

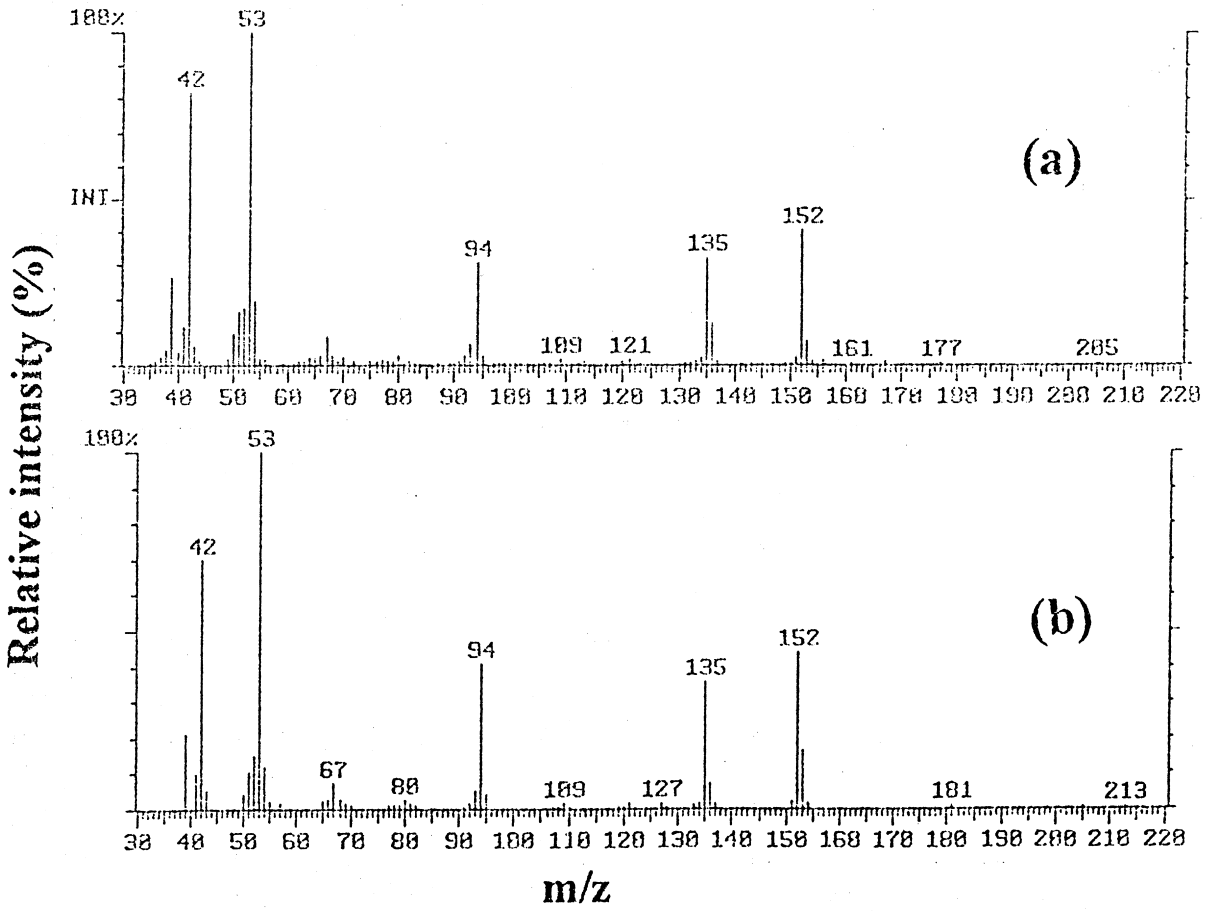


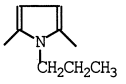
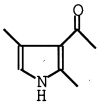
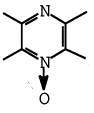
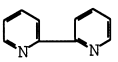
Fig. 6. EI mass spectrum of peak 8 with ionization time 100 μs (a) and TMPO synthesized in the laboratory (b).

3, was an unknown product. Although the fragment pattern suggested the compound to be some type of pyrazine, no satisfactory match with a library mass spectrum was found. Based on Fig. 3, the molecular peak was thought to contain 208 u. However, no plausible compound with a molecular mass of 208 could be formulated.

The molecular masses of the compounds were determined by CI-MS. CI mass spectra of peaks 2, 4, 5, 6 and 7 are shown in Fig. 4. It was evident that the peaks of protonated molecule $[M+H]^+$ and molecular cluster $[M+C_2H_5]^+$ are very distinctive in the methane CI spectra compared with the molecular ion peaks in EI spectra. The methane CI mass spectrum of peak 8 is shown in Fig. 5. Although the molecular ion peak appears to be 208 u. in the EI spectrum, the methane CI spectrum corresponding to peak 8 shows a protonated molecule peak of 153 u, thus indicating a molecular mass of 152 u. The 208 u may be due to the molecular cluster of $[M+C_4H_8]^+$. The similar molecular clusters often occur in an ion trap mass spectrometer [4]. The 208 u ion peak disappeared when the ionization time in ion trap (see Fig. 6a) was cut down to 100 μs. This clearly indicates proper ionization time selection is very important for the identification of the molecular ion and fragment ions in an ion trap mass spectrometer.

Careful inspection of the EI spectrum of peak 8

Table 1
Compounds identified from BDM hydrogenation products[a]

Peak No	Retention time / min	Proposed chemical structure	Proposed compound name	Molecular mass	Distribution (GC area %)
1	4:00		2,3-butanedinone monoxime (BDM)	101	——
2	6:00		Tetramethylpyrazine (TMP)	136	60.29
3	6:10		2,4-dimethyl-3-ethyl pyrrole (DEPR)	123	0.90
4	7:09		3,4,5-Trimethylpyrazole (TPZ)	110	21.54
5	9:15		2,5-dimethyl-propyl pyrrole (DPPR)	137	1.08
6	9:25		3-acetyl-2.4-dimethyl pyrrole (ADPR)	137	7.27
7	9:44		3,5-dimethyl-4-allyl pyrazole (DAPZ)	136	1.15
8	11:18		tetramethylpyrazine N-monoxide (TMPO)	152	3.38
9	11:48		2,2'-bypyridine (BPY)	156	——
10		———	others	—	4.40

[a] Determining conditions as in Experimental.

and comparison with that of the TMP also suggested the compound containing an alkylpyrazine ring similar to TMP. The difference between their molecular mass is 16 u. Based on this information, we thought peak 8 to be tetramethylpyrazine monoxide. As a further check, tetramethylpyrazine monoxide was synthesized as described before. Its retention time in the GC column and its mass spectrum were compared with those of peak 8. A good match was found and tetramethylpyrazine *N*-monoxide was thus confirmed as being responsible for peak 8. The mass spectrum of synthesized tetramethylpyrazine *N*-monoxide is shown in Fig. 6b.

The compounds identified from the reaction mixtures and their distributions (GC area, %) are shown in Table 1. It is seen that TMP is the principal product. Apart from TMP, 2,4-dimethyl-3-ethylpyrrole, 3,4,5-trimethylpyrazole, 2,5-dimethyl-1-propylpyrrole, 3-acetyl-2,4-dimethypyrrole, 3,5-dimethyl-4-allylpyazole and tetramethylpyrazine *N*-monoxide were found to be formed during the hydrogenation of 2,3-butanedinone monoxime with hydrogen in the presence of homogeneous catalysts. This means that the hydrogenation and condensation of BDM can proceed via several paths. The information will be helpful not only to the understanding of the hydrogenation and condensation of α-hydroxyimine carbonyl compounds in the presence of catalysts, but also providing a path of synthesis of some useful pyrazoles and pyrroles.

In conclusion, the major BDM hydrogenation products have been identified by GC coupled with EI- and CI-MS.

Besides the eight products mentioned above, a few of very unstable intermediates have been detected occasionally. Further investigation of the intermediates and the reaction mechanism is under way.

Acknowledgements

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