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# Structural Identification of the Methoxymethylpyrazine Isomers

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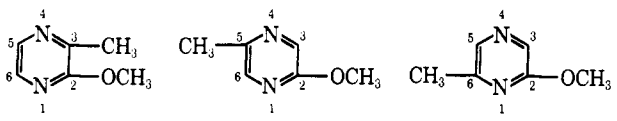
The methoxymethylpyrazine isomers were synthesized and isolated. They were characterized by gas chromatography, infrared, Raman, and nuclear magnetic resonance techniques. The 2-methoxy-3-methyl- and the 2-methoxy-6-methylpyrazine were obtained according to published procedures. A new route for the synthesis of 2-substituted 5-methoxypyrazines was used in the preparation of 2-methoxy-5-methylpyrazine. The authors believe this is the first time that this compound has been isolated and characterized.

The methoxymethylpyrazines are of considerable interest to workers in the area of flavor because of their organoleptic properties. This is borne out in a Firmenich patent (Firmenich *et al.*, 1967) which deals with the three isomers as well as with related compounds. The methoxymethylpyrazines exhibit strong and characteristic "baked"



2-methoxy-3-methylpyrazine | 2-methoxy-5-methylpyrazine | 2-methoxy-6-methylpyrazine

flavor notes and have potential application as additives to a variety of baked or toasted goods. The higher alkyl homologs of the methoxymethylpyrazines are very different in flavor and odor intensity from their parent compounds; this has been demonstrated with 2-methoxy-3-methylpyrazine and its homologs (Murray *et al.*, 1970; Seifert *et al.*, 1970). We can assume that subtle but important flavor differences exist also among the pure methoxymethylpyrazine isomers themselves. These differences may, at least in part, be deciding factors in achieving natural or true flavor characteristics in specific flavor compositions. Therefore, it was of interest to us to prepare the three methoxymethylpyrazines in pure form and to assign to each isomer the correct structure.

## APPARATUS

Isolation and purification of compounds was accomplished using an F&M research chromatograph (No. 5750) employing the thermal conductivity detector. A $^1/_4$-in., 10-ft long stainless steel column packed with 10% Carbowax 20M on Chromosorb W, temperature programmed from 100 to 200°C at 8°C/min, was used to isolate the three methoxymethylpyrazine isomers from the various reaction mixtures. The methylpyrazine *N*-oxide isomers, used as starting materials in the preparation of the methoxymethylpyrazines, were isolated using a $^1/_4$-in, 10-ft long stainless steel column packed with 10% SF96 on Chromosorb W; the column temperature was maintained at 140°C.

Infrared spectra were recorded with a Perkin-Elmer model 621 grating infrared spectrometer. Samples were run as neat liquids between cesium bromide plates. Nuclear magnetic resonance spectra were recorded with a Varian HA-100 spectrometer using the capillary microtechnique as described by Haynes and Sazavsky (1970). A Cary 81 Raman spectrometer equipped with an argon ion laser source was used for recording Raman spectra on neat samples contained in sealed capillary tubes.

## REAGENTS

**2,3-, 2,5-, and 2,6-Dimethylpyrazines.** These compounds were commercially obtained and were purified by gas chromatography.

**2-Methylpyrazine 1-Oxide and 2-Methylpyrazine 4-Oxide.** A mixture of the two methylpyrazine oxides was prepared as described by Koelsch and Gumprecht (1958). Several milligrams of each isomer were isolated by gas chromatography using the column conditions specified above. The melting points of the isolates were 90°C (2-methylpyrazine 1-oxide) and 64°C (2-methylpyrazine 4-oxide). Structural assignments of these isomers are based on the discussions of Gumprecht *et al.* (1964).

## PROCEDURES

**2-Methoxy-3-methyl- and 2-Methoxy-6-methylpyrazine.** Firmenich *et al.* (1967) report the preparation of the three methoxymethylpyrazine isomers by two methods. In the first method the methoxymethylpyrazines were obtained by

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**Table I. Spectroscopy Data for Disubstituted Pyrazines**

**nmr (Δ units)**

| Compound | Methyl | Methoxy | Ring protons | Coupling constant between ring protons |
|---|---|---|---|---|
| 2-$OCH_3$, 3-$CH_3$ | 2.42 ± 0.05 ppm | 3.91 ± 0.05 ppm | 7.87 ± 0.05 ppm d[a]<br>7.95 d | 3.0 ± 0.2 Hz |
| 2-$OCH_3$, 5-$CH_3$ | 2.40 | 3.86 | 7.86 d<br>8.04 d | 1.4 |
| 2-$OCH_3$, 6-$CH_3$ | 2.37 | 3.86 | 7.88 p<br>7.94 p | <0.5 |

**Raman and infrared ($cm^{-1}$)**

| | Ring vibrations (Raman) | | C–H out-of-plane deformation, ir | Aromatic C–H stretch, ir |
|---|---|---|---|---|
| 2-$CH_3$, 3-$CH_3$ | 1079 s ± 2 | 721 s ± 2 | 840 s ± 5 | 3050 ± 2 |
| 2-$OCH_3$, 3-$CH_3$ | 1082 s | 757 s | 835 s | 3058 |
| 2-$CH_3$, 5-$CH_3$ | 862 s | 651 m | 880 s | 3085 |
| 2-$OCH_3$, 5-$CH_3$ | 865 s | 645 m | 885 s | 3080 |
| 2-$CH_3$, 6-$CH_3$ | 1020 s | 709 s | 865 s | 3042 |
| 2-$OCH_3$, 6-$CH_3$ | 1019 s | 708 s | 865 s | 3052 |

[a] d = doublet, p = singlet, s = strong intensity, m = medium intensity. [b] Tentative assignment based on discussions by Varsanyi (1969).

treating a mixture of the two methylpyrazine oxides with phosphorus oxychloride and then with sodium methoxide. In the second method direct ring-chlorination of methylpyrazine to a mixture of the monochloromethylpyrazine isomers (Hirschberg and Spoerri, 1961), followed by sodium methoxide treatment, led to the three methoxymethylpyrazine isomers. Using these methods Firmenich and coworkers report the isolation of 2-methoxy-3-methylpyrazine and a mixture of the 2,5- and 2,6- derivatives. Following these procedures as described we obtained only the 2-methoxy-3-methylpyrazine and the 2-methoxy-6-methylpyrazine. When we used the pure methylpyrazine oxides instead of a mixture of these isomers as described in the Firmenich patent and carried out the specified reaction sequence we obtained 2-methoxy-3-methyl- and 2-methoxy-6-methylpyrazine, starting with 2-methylpyrazine-1-oxide, and only 2-methoxy-3-methylpyrazine, starting with 2-methylpyrazine-4-oxide.

**2-Methoxy-5-methylpyrazine.** 2-Methoxy-5-methylpyrazine was prepared by a modification of a method described by Grabowski *et al.* (1968) for the synthesis of 2-methoxy-5-substituted pyrazines. A fast stream of chlorine gas (approx. 1 mol) was introduced into a solution of 94 g (1 mol) of methylpyrazine in 200 ml of glacial acetic acid, maintained at 100–110°C, and irradiated by two General Electric 275-W sunlamps. Under these conditions the methyl group is preferentially chlorinated and the respective mono-, di-, and trichlorides are formed. The reaction was stopped when an optimum amount of the monochloride had formed, as monitored by gas chromatography. The acetic acid was evaporated, 100 ml of water was added, and the solution was extracted three times with 25 ml of ethyl ether. The ether extract was dried over anhydrous magnesium sulfate. About 2 ml of a mixture of mono-, di-, and trichloro compounds was obtained by distillation at 55–60° and 0.4 mm pressure. The distillate was added to 25 ml of an excess of sodium methoxide in methanol and heated for 1 hr at 80°C in a sealed tube. After filtration, the solvent was stripped off and the residue was dissolved in ethyl ether and dried over anhydrous magnesium sulfate. Five pyrazine compounds were isolated and purified by gas chromatography under conditions described earlier. These are listed according to their relative retention times: methylpyrazine, 2-methoxy-3-methylpyrazine, 2-methoxy-5-methylpyrazine, (methoxymethyl)pyrazine, and 2-(methoxymethyl)-5-methoxypyrazine. The (methoxymethyl)-

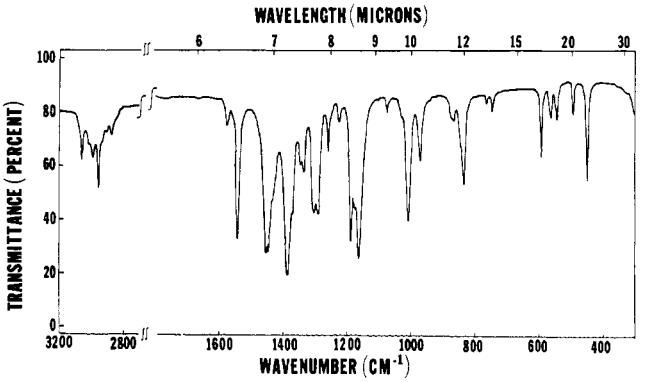


**Figure 1. Infrared spectrum of 2-methoxy-3-methylpyrazine**

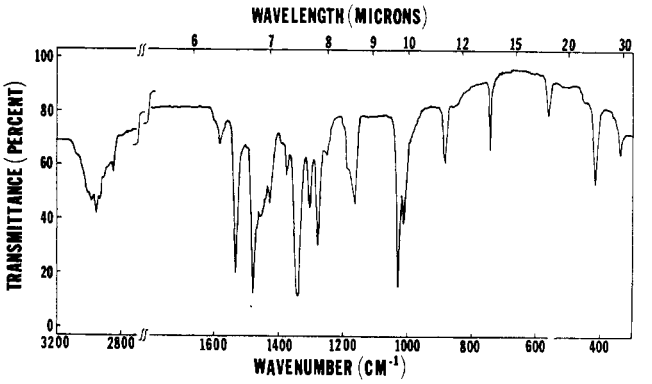


**Figure 2. Infrared spectrum of 2-methoxy-5-methylpyrazine**

pyrazine and 2-(methoxymethyl)-5-methoxypyrazine were tentatively identified by nmr.

## RESULTS AND DISCUSSION

Structural assignments of the three isolated methoxymethylpyrazine isomers were based on the nuclear magnetic resonance, infrared, and Raman data given in Table I. The nmr spectrum of each isomer contained a sharp singlet of intensity 3 for each of the methyl and methoxy groups and two closely spaced peaks of intensity 1 for the two aromatic ring protons. Tentative assignment of the structures to the iso-

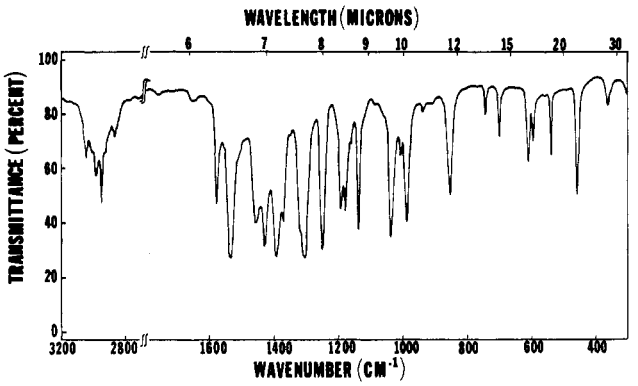


**Figure 3. Infrared spectrum of 2-methoxy-6-methylpyrazine**

lated isomers was made by comparing the values of the coupling constants between the two aromatic ring protons with literature data. Cox and Bothner-By (1968a,b) report coupling constants between the aromatic ring protons in the range of 2.5 to 5.0 Hz for a series of 2,3-disubstituted pyrazines. In a series of monosubstituted pyrazines they report coupling constants between the aromatic ring protons of $J_{56} \cong 2.5$ to 4.0 Hz, $J_{36} \cong 1.3$ to 1.6 Hz, and $J_{35} \cong 0$ to 0.5 Hz. Grabowski *et al.* (1968) report a coupling constant of 1.5 Hz between the aromatic protons of 2-dimethoxymethyl-5-methoxypyrazine.

For further structural proof the Raman and infrared spectra of 2,3-, 2,5-, and 2,6-dimethylpyrazine were compared to the spectra of the three methoxymethylpyrazine isolates. Structural assignments were made by comparing the band positions of the ring vibrations which are strong in the Raman spectra and also the C–H out-of-plane deformations which are strong in the infrared (Table I). These assignments were consistent with the assignments based on the nmr coupling constant data. The Raman spectra appear to be particularly useful for determining the substitution pattern of these disubstituted pyrazine analogs.

The infrared spectra of the three methoxymethylpyrazine isomers are given in Figures 1, 2, and 3. The infrared spectrum of 2-methoxy-3-methylpyrazine is consistent with the infrared data published by Firmenich *et al.* (1967). The infrared data which they report for the mixture of the 2,5 and 2,6 isomers are consistent with the spectrum we obtained for the 2,6 isomer; however, no bands were reported in the region of five of the seven major bands in our spectrum of 2-methoxy-5-methylpyrazine, indicating that their mixture was mostly 2-methoxy-6-methylpyrazine.

Following structural assignment, the aromas of the three methoxymethyl isomers were evaluated by a ten-member panel and described as being characteristic of "baked" or "toasted." 2-Methoxy-3-methylpyrazine was judged to have the most "baked" note, while the aroma of 2-methoxy-6-methylpyrazine was preferred because of a "sweet" by-note.

From the above we conclude that we are the first to prepare and characterize the 2-methoxy-5-methylpyrazine, which was made possible by the chlorination and rearrangement reaction of Grabowski *et al.* (1968), whereas our efforts to prepare the three methoxymethylpyrazines *via* the other literature methods led only to the 2,3 and 2,6 isomers.

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