Synthesis and Odor Properties of Some Additional Compounds Related to 2-Isobutyl-3-methoxypyrazine

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The compounds 2-isobutyl-3-methoxy-5-methylpyrazine, 2-isobutyl-3-methoxy-6-methylpyrazine, 2-isobutyl-3-methoxy-5,6-dimethylpyrazine, 2-methoxy-3-isobutylpyridine, and 2-ethoxy-3-ethylpyrazine have been systhesized and their odor properties compared to those of the potent bell pepper component 2-isobutyl-3-methoxypyrazine. Adding methyl groups to the pyrazine ring decreased the bell pepper character and odor potency considerably. Replacing the pyrazine ring by a pyridine ring resulted in an even greater decrease in potency and change of character. Replacing the methoxy group in 2-ethyl-3-methoxypyrazine with an ethoxy group resulted in a moderate decrease in potency but with very little change in character.

The major characteristic aroma component of bell peppers (2-isobutyl-3-methoxypyrazine) has an extremely potent aroma and useful flavoring properties (Buttery *et al.*, 1969). This compound is already finding commercial use as a flavoring material (French Co., 1970). Because of the value and potency of this compound the authors synthesized several related compounds (Seifert *et al.*, 1970), some of which were later independently found to be naturally occurring in other vegetables (Murray *et al.*, 1970). The present work continues this exploration of compounds with structures related to 2-isobutyl-3-methoxypyrazine in the hope of finding new potent compounds that could be useful as flavoring materials for nutritious high protein foods which may have flavor problems.

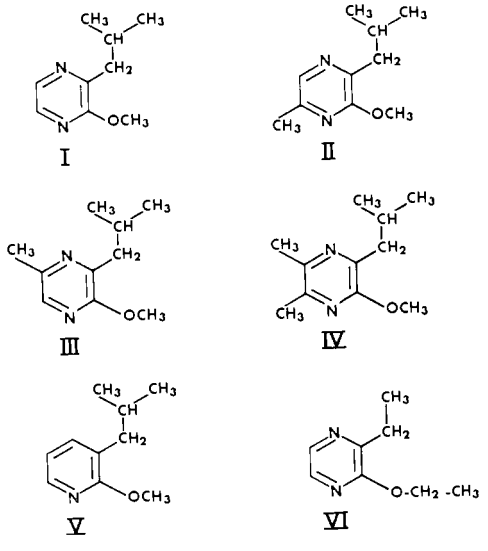
EXPERIMENTAL

Synthesis of Compounds. 2-ISOBUTYL-3-METHOXY-5-METHYLPYRAZINE (II) and 2-ISOBUTYL-3-METHOXY-6-METHYLPYRAZINE (III). The procedure used for the synthesis of these compounds was essentially the same as that described previously by the authors and other workers (Seifert *et al.*, 1970; Jones, 1949; Karmus and Spoerri, 1952) for 2-isobutyl-3-methoxypyrazine (I) and related compounds except using the appropriate starting materials. Leucine amide was condensed with pyruvic aldehyde and the resultant mixture of hydroxypyrazines was methylated with diazomethane. The -5- and -6-methyl components (*ca.* 10% overall yield) were then separated from each other and the coformed pyrazinones by gas chromatography.

Approximately twice as much -6- compound was obtained as the -5- compound. Mass and infrared spectra of both compounds were consistent with that expected of isobutylmethoxymethylpyrazine. The assignment of the methyl group position was based on the greater bathochromic shift of the -6- compound (III) in its ultraviolet absorption spectrum relative to the -5- compound (II).

2-ISOBUTYL-3-METHOXY-5,6-DIMETHYLPYRAZINE (IV). This was also synthesized by the methods already described for related compounds (Seifert *et al.*, 1970) except that leucine amide was condensed with buta-2,3-dione to give the hydroxypyrazine which was methylated with diazomethane. The resultant methoxypyrazine was purified from the coformed pyrazinone by gas chromatography. The overall yield was again about 10%.

2-METHOXY-3-ISOBUTYLPYRIDINE (V). 3-Isobutylpyridine



was synthesized in 45% yield by reacting isopropyl bromide with 3-methylpyridine and sodium amide in liquid ammonia (Vogel, 1962). The 3-isobutylpyridine was converted to its *N*-oxide by oxidation with peracetic acid (Rabjohn, 1963).

The crude dry *N*-oxide was added dropwise to a 5 *M* excess of $POCl_3$, warmed on a 50° C bath 1 hr, and refluxed an additional hr. The conditions and work-up are essentially the same as that used by Klein and Berkowitz (1959). This gave the three (2-, 4-, and 6-) monochloro-3-isobutylpyridines in approximately equal amounts in 44% yield (based on the 3-isobutylpyridine). The mixture of monochloroisobutylpyridines was then refluxed with sodium methoxide in methanol for 18 hr to give 2-, 4-, and 6-methoxy-3-isobutylpyridines in 13, 40, and 4% yields, respectively. 2-Methoxy-3-isobutylpyridine (V) was separated in its pure state from the 4 and 6 isomers by gas chromatography and its structure was confirmed by comparison of the pmr spectra of all three isomers.

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2-ETHOXY-3-ETHYLPYRAZINE (VI). 2-Hydroxy-3-ethylpyrazine, prepared as outlined previously (Seifert *et al.*, 1970), was treated with $POCl_3$ according to the general method described by Karmus and Spoerri (1952) to give a 67% yield of 2-chloro-3-ethylpyrazine. This compound was then refluxed with ethanolic KOH (Karmus and Spoerri, 1952) to give 2-ethoxy-3-ethylpyrazine (VI) (46% yield) which was purified by gas chromatography.

Gas–Liquid Chromatography (glc). All samples were purified by gas chromatography as described previously (Seifert *et al.*, 1970).

Mass Spectrometry. Low-resolution mass spectra were measured on a Consolidated 21-620 cycloidal type instrument. High-resolution data were obtained on a Consolidated 21-110B double focusing instrument.

Infrared (ir) Spectra. These were recorded of the pure materials as films using a Perkin-Elmer 237 double-beam grating instrument.

Ultraviolet (uv) Absorption Spectra. These were run in methanol using a Cary 15 uv spectrophotometer.

Proton Magnetic Resonance (pmr) Spectra. These were measured in CCl_4 at 100 MHz using a Varian HA-100.

Odor Thresholds. Thresholds of the glc purified compounds were determined as described previously (Guadagni *et al.*, 1963) except that Teflon, instead of polyethylene, bottles and tubing were used as containers for the odor solutions.

RESULTS AND DISCUSSION

There are several ways of modifying the 2-isobutyl-3-methoxypyrazine (I) molecule. The approach used by the authors in their previous paper (Seifert *et al.*, 1970) was to vary the alkyl side chain to produce several 2-alkyl-3-methoxypyrazines with the side chain varying in length from 0 to 6 carbons. Other ways of slightly modifying the molecule include: (1) putting alkyl groups into the 5 and/or 6 positions of the pyrazine ring; (2) substituting a pyridine ring for the pyrazine; and (3) replacing the methyl of the methoxy group with other alkyl groups. Following variation (1), methyl glyoxal was condensed with leucine amide and the resulting hydroxypyrazines were methylated with diazomethane to give 2-isobutyl-3-methoxy-5-methylpyrazine (II) and 2-isobutyl-3-methoxy-6-methylpyrazine (III). The methyl group position in each molecule was assigned according to a comparison of the uv spectra. The suspected -6-methyl isomer with the methyl group para to the methoxyl showed a bathochromic shift (absorption at 303 mμ) compared to the suspected -5-methyl isomer (absorption at 298 mμ) which has the methyl meta to the methoxyl.

In a similar approach biacetyl was condensed with leucine amide and the resultant hydroxypyrazine was methylated with diazomethane to give 2-isobutyl-3-methoxy-5,6-dimethylpyrazine (IV). Yields of hydroxypyrazine from the condensations using methyl glyoxal and biacetyl were poorer than had been obtained using glyoxal (Seifert *et al.*, 1970) probably because of the greater amount of self condensation of these alkyl glyoxals under the alkaline conditions used for the condensation.

Following variation (2), 2-methoxy-3-isobutylpyridine (V) was prepared by treating a mixture of the three monochloro-3-isobutylpyridines with sodium methoxide. Pmr spectra were used to distinguish between the three isomers.

Using variation (3), 2-chloro-3-ethylpyrazine (obtained by treating 2-hydroxy-3-ethylpyrazine with phosphorus oxychloride) was treated with sodium ethoxide to give 2-ethoxy-3-ethylpyrazine (VI). This compound included a further variation with an ethyl side chain instead of the isobutyl but can be compared to the corresponding 2-ethyl-3-methoxypyrazine already reported (Seifert *et al.*, 1970).

Table I. Odor Thresholds in Water Solution Compared to that of 2-Isobutyl-3-methoxypyrazine

Compd	Odor threshold in parts of compound per 10^{12} parts of water
2-Isobutyl-3-methoxypyrazine (I)	2
2-Isobutyl-3-methoxy-5-methylpyrazine (II)	260
2-Isobutyl-3-methoxy-6-methylpyrazine (III)	2600
2-Isobutyl-3-methoxy-5,6-dimethylpyrazine (IV)	315,000
2-Methoxy-3-isobutylpyridine (V)	11,000
2-Ethoxy-3-ethylpyrazine (VI)	11,000

Molecular weights found for these compounds using a high-resolution consolidated 21-110B double-focusing mass spectrometer were as follows. 2-Isobutyl-3-methoxy-5-methylpyrazine, found 180.12625 ($C_{10}H_{16}N_2O$ requires 180.12625). 2-Isobutyl-3-methoxy-6-methylpyrazine, found 180.12672 ($C_{10}H_{16}N_2O$ requires 180.12625). 2-Isobutyl-3-methoxy-5,6-dimethylpyrazine, found 194.13903 ($C_{11}H_{18}N_2O$ requires 194.14190). 3-Isobutyl-2-methoxypyridine, found 165.1162 ($C_{10}H_{15}NO$ requires 165.1153).

The mass spectra found for these compounds using a Consolidated 21-620 cycloidal instrument are listed below (above *m/e* 40, intensities in parentheses with the largest peak taken as 100): 2-isobutyl-3-methoxy-5-methylpyrazine: mol ion 180(5.1), major ions 138(100), 108(21), 41(21), 109(19), 107(15), 165(15), 56(14), 54(14), 53(12), 95(7).

2-Isobutyl-3-methoxy-6-methylpyrazine: mol ion 180(4), major ions 138(100), 41(24), 108(20), 42(19), 165(15), 54(15), 109(13), 139(12), 107(11), 43(10).

2-Isobutyl-3-methoxy-5,6-dimethylpyrazine; mol ion 194(6), major ions 42(23), 41(25), 122(18), 53(17), 151(15), 179(13), 153(13), 123(13), 121(10), 54(10).

2-Methoxy-3-isobutylpyridine: mol ion 165(28), major ions 122(100), 92(72), 150(31), 165(28), 93(21), 41(15), 65(14), 94(12), 53(11), 43(11).

2-Ethoxy-3-ethylpyrazine: mol ion 152(60), major ions 124(100), 123(94), 95(71), 41(60), 81(42), 57(32), 68(30), 107-(27), 108(25), 56(25).

Infrared absorption spectra found for thin films of the pure materials were as follows (in the region 5–15 μ, absorption maxima in μ, S means strong, M medium, W weak).

2-Isobutyl-3-methoxy-5-methylpyrazine, S (6.9, 7.3, 8.5, 9.6), M (6.3, 6.5, 7.7, 9.2, 9.9), W (7.9, 9.01, 10.3, 11.3).

2-Isobutyl-3-methoxy-6-methylpyrazine, S (6.8, 7.2, 7.7, 8.5, 9.8) M (6.5, 7.4, 7.0, 9.2, 10.2), W (6.3, 7.9, 8.1, 11.1, 12.0, 13.0, 13.9).

2-Isobutyl-3-methoxy-5,6-dimethylpyrazine, S (6.9, 7.2, 7.6, 8.3, 8.5, 9.8), M (6.4, 7.8, 8.0, 8.8, 10.1), W (5.7, 6.4, 9.2, 14.4).

2-Methoxy-3-isobutylpyridine, S (6.3, 6.8, 7.1, 9.8, 12.8), M (7.7, 7.9, 8.0, 8.4, 8.9), W (7.2, 7.3, 7.5, 7.8, 9.28, 9.35, 11.3, 11.6, 12.2).

2-Ethoxy-3-ethylpyrazine, S (6.5, 6.8, 7.0, 7.3, 7.4, 7.5, 7.6, 8.5, 8.6, 8.7, 9.6, 9.7), M (7.9, 11.9), W (6.3, 9.1, 10.3, 10.8).

Odor Properties. Table I lists the odor thresholds of these compounds in water solution. It can be seen that they are all weaker odorants than 2-isobutyl-3-methoxypyrazine, but still reasonably potent odorants, and in the authors' opinion useful

flavoring materials. It appears that one side of the pyrazine ring must be unsubstituted for the extreme high odor potency found in the hexyl, isobutyl, and isopropyl 2-alkyl-3-methoxypyrazines (Seifert *et al.*, 1970). To confirm this it would, however, be necessary to study 2,5- and 2,6-alkylmethoxypyrazines.

From the relatively high threshold found for 2-methoxy-3-isobutylpyridine compared to that of 2-isobutyl-3-methoxypyrazine it can be seen that replacing the pyrazine ring by a pyridine ring decreases the odor potency by a very large factor, indicating the importance of the pyrazine structure. Here again it would be useful to examine 2-isobutyl-3-methoxypyridine where the position of the isobutyl and methoxy groups is reversed in respect to the single pyridine nitrogen.

The importance of the methoxy group rather than any alkoxy group is emphasized by comparison of the threshold of the 2-ethoxy-3-ethylpyrazine (11 ppb) with that of 2-ethyl-3-methoxypyrazine (0.4 ppb; Seifert *et al.*, 1970) showing a decrease in potency by a factor of about 27 times.

Odor quality of the compounds reported in this paper was evaluated informally by the authors. In our opinion 2-isobutyl-3-methoxy-5-methylpyrazine has an odor similar to that of bell peppers but with some minty notes. The odor of 2-isobutyl-3-methoxy-6-methylpyrazine was primarily minty–camphoraceous in character with slight bell pepper undertones. Of the three methyl derivatives 2-isobutyl-3-methoxy-5,6-dimethylpyrazine had the most pronounced minty–camphoraceous odor and the least bell pepper-like aroma.

The 2-methoxy-3-isobutylpyridine had an odor which was not very characteristic but perhaps somewhat camphoraceous.

The odor character of 2-ethoxy-3-ethylpyrazine was very like that of 2-ethyl-3-methoxypyrazine, which has an odor similar to that of raw potatoes (Seifert *et al.*, 1970).

With these compounds it is apparent that molecular shape alone is not very important to the character of the odor, as the shape of the molecules of 2-methoxy-3-isobutylpyridine and 2-isobutyl-3-methoxypyrazine should be almost identical. It is also apparent that the protons on the unsubstituted side of the pyrazine ring are important to the odor character as well as potency. The addition of extra carbons to the methoxy or isobutyl group does not seem to influence the potency or character nearly as much. The C_3–C_6 2-alkyl-3-methoxypyrazines all possessed odors with very similar potency and character (Seifert *et al.*, 1970), and in the present work replacement of the methoxy group in 2-ethyl-3-methoxypyrazine with an ethoxy group gave only a relatively small change in character and only a moderate change in potency.

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