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Received for review August 24, 1987. Accepted January 15, 1988. The investigation reported in this paper was supported by the U.S. Department of Agriculture—Agricultural Research Service under Cooperative Agreement No. 58-43YK-7-0027 and is published with the approval of the Director of the Kentucky Agricultural Experiment Station (Paper 87-3-2-188). Presented in part at the Agricultural and Food Division of the 193rd National Meeting of the American Chemical Society, Denver, CO, April 1987.

Olfactive Properties of Alkylpyrazines and 3-Substituted 2-Alkylpyrazines

Hideki Masuda and Satoru Mihara*

Odor profiles were determined for the series of alkylpyrazines and 3-substituted 2-alkylpyrazines. The odor threshold decreases with an increasing number of carbon atoms in the side chain. It is at a minimum in pentylpyrazines and increases again irrespective of the substituents at the 3-position. In general, the odor thresholds of 3-substituted 2-alkylpyrazines increase in the following order: $OCH_3 < OC_2H_5 \leq SCH_3 < SC_2H_5 < OC_6H_5 \leq SC_6H_5$. The alkyl substituents play an important role in the tonalities of the pyrazines.

It has been well recognized that the alkylpyrazines significantly contribute to the flavor of heat-treated food (Fors and Olofsson, 1986). 2-Isobutyl-3-methoxypyrazine was isolated from bell peppers and was shown to possess an extremely low odor threshold (Buttery et al., 1969a,b). The odor thresholds of some alkylpyrazines and 3-substituted 2-alkylpyrazines in water were reported in the literature (Fors and Olofsson, 1985; Calabretta, 1978; Takken et al., 1975; Teranishi et al., 1974; Seifert et al., 1970). In general, the odor thresholds decrease with increasing chain length within each isomer. One should be careful in drawing conclusions from a comparison of threshold values determined by the different groups. In order to derive the relationship between chemical structures and their odor thresholds, we have studied the effects of varying the alkyl chain length of the alkylpyrazine and 3-substituted 2-alkylpyrazines on their olfactive properties.

EXPERIMENTAL SECTION

Instrumentation. IR, NMR, and mass spectral data were obtained on a Jasco IR-S, a JNM-PMX 60, and a Hitachi Model M-80A, respectively.

Materials. All starting chemicals were obtained from reliable commercial sources and used without further purification. Pyrazine and methyl-, ethyl-, and methoxy-, 2-methoxy-3-methyl-, 2-ethyl-3-methoxy-, 2-ethoxy-3-ethyl-, and 2-ethyl-3-(methylthio)pyrazine were commercially available (Pyrazine Specialties).

Synthesis of Alkylpyrazines 1–7. Alkylpyrazines were prepared from the parent pyrazine by alkylation with the appropriate aldehyde in sodium dimethoxyethane solution (Bramwell et al., 1971).

Ogawa & Company, Ltd., 6-32-9 Akabanenishi, Kita-ku, Tokyo 115, Japan.

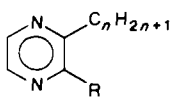
Synthesis of Ethoxy-, Phenoxy-, (Methylthio)-, (Ethylthio)-, and (Phenylthio)pyrazine (15, 20, 24, 29, 36). Chloropyrazine was reacted with sodium ethoxide, sodium phenoxide, sodium thiomethoxide, sodium thioethoxide, or sodium thiophenoxide to obtain **15**, **20**, **24**, **29**, and **36**, respectively (Masuda et al., 1981).

Synthesis of 3-Substituted 2-Alkylpyrazines. A series of alkylpyrazines has been chlorinated specifically in the 3-position with sulfuryl chloride in the presence of *N,N*-dimethylformamide (Bramwell et al., 1972). These chloro derivatives were subsequently allowed to react with the corresponding sodium alkoxide, sodium phenoxide, sodium thioalkoxide, or sodium thiophenoxide to obtain the desired alkoxy-, phenoxy-, (alkylthio)-, and (phenylthio)alkylpyrazines, respectively (Masuda et al., 1981).

Sensory Evaluation. The threshold values and the odor characteristics of the pyrazines were determined as described previously (Masuda and Mihara, 1986).

RESULTS AND DISCUSSION

The yields and mass spectral data of the pyrazines I are shown in Table I. The IR and ^1H NMR spectral data of the new pyrazines were recorded and analyzed. (See paragraph at the end of paper regarding supplementary material.)



I, n = 0–10

Figure 1 shows the relation between log $1/T$, where T is the odor threshold, and the carbon number of the alkyl side chain, n, for various alkylpyrazines and 3-substituted 2-alkylpyrazines. The log $1/T$ increases with increasing carbon number and has a maximum value at 5. It then

0021-8561/88/1436-0584$01.50/0

Table I. Yields and Mass Spectral Data of Pyrazines I

no.	C_nH_{2n+1}	R	yield, %	MS, m/z (%)	ref
1	C_3H_7	H	28[a]	123 (7), 122 (53, M^+), 121 (19), 107 (60), 95 (14), 94 (100), 80 (7), 67 (13), 53 (7)	c, d
2	C_4H_9	H	42[a]	136 (4, M^+), 135 (2), 121 (5), 108 (4), 107 (15), 95 (7), 94 (100), 80 (1), 67 (2), 53 (1), 41 (1)	c
3	C_5H_{11}	H	38[a]	151 (9), 150 (20, M^+), 135 (10), 121 (34), 108 (17), 107 (78), 95 (33), 94 (100), 93 (14), 80 (6), 67 (8), 53 (4), 41 (8)	c
4	C_6H_{13}	H	51[a]	164 (5, M^+), 135 (10), 121 (6), 107 (16), 95 (7), 94 (100)	c
5	C_7H_{15}	H	58[a]	178 (4, M^+), 149 (2), 135 (4), 121 (4), 107 (14), 95 (7), 94 (100)	
6	C_8H_{17}	H	61[a]	192 (5, M^+), 149 (2), 135 (3), 127 (2), 121 (3), 107 (12), 95 (7), 94 (100), 57 (4)	
7	$C_{10}H_{21}$	H	69[a]	220 (5, M^+), 135 (2), 121 (2), 107 (10), 95 (7), 94 (100)	
8	C_3H_7	OCH_3	30[a]	152 (4, M^+), 137 (22), 125 (7), 124 (100), 109 (2), 95 (11), 94 (19), 93 (7), 81 (11), 68 (2), 54 (2), 42 (3)	
9	C_4H_9	OCH_3	32[a]	166 (1, M^+), 151 (2), 138 (3), 137 (11), 125 (7), 124 (100), 123 (3), 95 (7), 94 (14), 81 (7)	
10	C_5H_{11}	OCH_3	39[a]	180 (1, M^+), 151 (5), 137 (16), 125 (7), 124 (100), 95 (5), 94 (11), 81 (5)	
11	C_6H_{13}	OCH_3	36[a]	195 (6), 194 (10, M^+), 179 (4), 166 (6), 165 (6), 151 (26), 138 (17), 137 (92), 125 (40), 124 (100), 123 (17), 111 (11), 95 (25), 94 (50), 93 (9), 81 (23)	e
12	C_7H_{15}	OCH_3	43[a]	208 (2, M^+), 179 (2), 151 (3), 138 (3), 137 (17), 125 (7), 124 (100), 111 (2), 95 (3), 94 (7), 81 (3)	
13	C_8H_{17}	OCH_3	41[a]	222 (4, M^+), 194 (2), 193 (2), 179 (4), 151 (6), 138 (6), 137 (35), 125 (17), 124 (100), 123 (4), 111 (5), 95 (5), 94 (11), 81 (5)	
14	$C_{10}H_{21}$	OCH_3	45[a]	250 (6, M^+), 222 (3), 207 (3), 193 (3), 179 (4), 151 (7), 138 (8), 137 (45), 125 (24), 124 (100), 111 (6), 95 (5), 94 (10), 81 (5)	
15	H	OC_2H_5	94[b]	124 (44, M^+), 116 (21), 114 (65), 109 (40), 96 (62), 81 (14), 80 (34), 79 (35), 68 (100), 52 (14), 41 (16)	f
16	CH_3	OC_2H_5	92[b]	139 (12), 138 (81, M^+), 123 (67), 122 (14), 121 (16), 110 (96), 109 (15), 95 (17), 94 (40), 93 (18), 82 (100), 81 (60), 68 (10), 55 (10), 54 (11), 42 (15)	g
17	C_5H_{11}	OC_2H_5	36[a]	194 (6, M^+), 179 (1), 165 (20), 151 (59), 139 (34), 138 (100), 137 (20), 123 (51), 110 (99), 109 (20), 95 (68), 94 (78), 82 (26), 81 (63), 54 (33), 53 (23), 41 (48)	
18	C_8H_{17}	OC_2H_5	45[a]	236 (8, M^+), 221 (2), 208 (5), 207 (5), 193 (7), 179 (2), 165 (12), 151 (68), 139 (38), 138 (100), 123 (33), 110 (87), 95 (48), 94 (53), 81 (41), 68 (8), 55 (19), 54 (19), 43 (26), 41 (51)	
19	$C_{10}H_{21}$	OC_2H_5	43[a]	264 (3, M^+), 165 (2), 152 (2), 151 (15), 139 (11), 138 (100), 125 (2), 123 (4), 110 (9), 95 (5), 94 (5)	
20	H	OC_6H_5	59[b]	173 (15), 172 (100, M^+), 171 (23), 144 (63), 118 (11), 117 (62), 94 (13), 90 (21), 79 (10), 77 (15), 65 (6), 52 (8)	h
21	CH_3	OC_6H_5	63[b]	187 (13), 186 (100, M^+), 185 (13), 158 (40), 157 (19), 131 (19), 130 (12), 117 (12), 93 (8), 90 (6), 77 (5), 66 (7), 42 (13)	i
22	C_5H_{11}	OC_6H_5	38[a]	242 (2, M^+), 213 (3), 199 (9), 187 (12), 186 (100), 185 (26), 171 (2), 169 (2), 157 (6), 149 (5)	
23	$C_{10}H_{21}$	OC_6H_5	35[a]	312 (4, M^+), 220 (18), 219 (100), 133 (2), 107 (3), 94 (12)	
24	H	SCH_3	94[b]	128 (8), 127 (16), 126 (100, M^+), 125 (51), 111 (9), 93 (23), 84 (30), 82 (10), 81 (22), 80 (28), 73 (20), 72 (9), 57 (10), 53 (16), 52 (13)	j
25	CH_3	SCH_3	95[b]	142 (5), 141 (10), 140 (100, M^+), 125 (23), 107 (39), 106 (22), 94 (11), 93 (15), 84 (15), 81 (7), 73 (7), 66 (6), 42 (17)	k
26	C_5H_{11}	SCH_3	28[a]	196 (8, M^+), 181 (9), 153 (8), 149 (7), 141 (7), 140 (100), 139 (6), 107 (8), 94 (5)	
27	C_8H_{17}	SCH_3	37[a]	238 (5, M^+), 223 (6), 191 (6), 153 (10), 141 (8), 140 (100), 107 (5), 94 (4)	
28	$C_{10}H_{21}$	SCH_3	39[a]	266 (6, M^+), 251 (6), 219 (8), 153 (10), 141 (9), 140 (100), 139 (6), 107 (5), 94 (5), 43 (7), 41 (10)	
29	H	SC_2H_5	91[b]	142 (5), 141 (10), 140 (100, M^+), 125 (26), 112 (39), 107 (68), 84 (15), 81 (9), 80 (12), 79 (7), 68 (31)	f
30	CH_3	SC_2H_5	89[b]	156 (5), 155 (11), 154 (100, M^+), 139 (23), 126 (52), 125 (24), 121 (84), 119 (15), 94 (15), 93 (25), 84 (20), 82 (31), 42 (12)	
31	C_2H_5	SC_2H_5	38[a]	170 (6), 169 (10), 168 (100, M^+), 153 (11), 140 (36), 139 (77), 135 (88), 134 (16), 133 (21), 119 (19), 107 (33), 105 (14), 95 (9), 84 (33), 80 (13), 79 (13), 57 (15), 52 (17), 45 (11)	
32	C_4H_9	SC_2H_5	40[a]	198 (1), 197 (4), 196 (19, M^+), 167 (59), 163 (29), 154 (100), 139 (16), 126 (25), 121 (26), 94 (27), 84 (18), 41 (16)	
33	C_5H_{11}	SC_2H_5	35[a]	211 (1), 210 (13, M^+), 181 (30), 177 (15), 167 (11), 155 (9), 154 (100), 149 (3), 139 (10), 126 (12), 121 (14), 94 (9)	
34	C_8H_{17}	SC_2H_5	43[a]	253 (1), 252 (7, M^+), 223 (17), 219 (8), 191 (9), 167 (13), 155 (8), 154 (100), 139 (9), 126 (10), 121 (11), 94 (10), 84 (5), 43 (8), 41 (13)	
35	$C_{10}H_{21}$	SC_2H_5	38[a]	281 (1), 280 (6, M^+), 251 (15), 247 (7), 219 (9), 167 (11), 155 (10), 154 (100), 139 (7), 126 (9), 121 (9), 94 (8), 55 (6)	
36	H	SC_6H_5	78[b]	190 (2), 189 (50), 188 (50, M^+), 187 (100), 160 (2), 135 (3), 117 (2), 109 (3), 84 (2), 79 (2), 77 (2), 52 (2)	
37	CH_3	SC_6H_5	65[b]	204 (2), 203 (10), 202 (48, M^+), 201 (100), 187 (2), 125 (2), 93 (7), 66 (3), 42 (5)	
38	C_3H_7	SC_6H_5	35[a]	232 (5), 231 (18), 230 (100, M^+), 215 (16), 202 (38), 201 (53), 153 (43), 119 (10), 109 (11), 93 (9), 84 (10), 77 (21), 65 (17), 51 (19), 43 (11), 41 (25)	
39	C_5H_{11}	SC_6H_5	41[a]	259 (4), 258 (21, M^+), 257 (6), 229 (5), 215 (11), 203 (17), 202 (100), 201 (64), 181 (10), 169 (9), 149 (18), 109 (7), 77 (11), 65 (10), 51 (9), 41 (17)	
40	C_8H_{17}	SC_6H_5	39[a]	301 (2), 300 (12, M^+), 255 (4), 229 (2), 223 (3), 215 (7), 204 (5), 203 (15), 202 (100), 201 (26), 191 (14), 169 (2), 135 (4)	
41	$C_{10}H_{21}$	SC_6H_5	44[a]	329 (2), 328 (11, M^+), 252 (2), 229 (2), 220 (2), 218 (14), 215 (5), 204 (4), 203 (14), 202 (100), 201 (19), 200 (4), 169 (2), 107 (4)	

[a] Relative to the quantity of pyrazine or the corresponding alkylpyrazine. [b] Relative to the quantity of chloropyrazine or the corresponding alkylchloropyrazine. [c] Behun and Levine (1961). [d] Goldman et al. (1967). [e] Seifert et al. (1970). [f] Konakahara and Takagi (1977). [g] Hirschberg and Spoerri (1961). [h] Kushner et al. (1952). [i] Behun et al. (1961). [j] Cheeseman (1960). [k] Kolor and Rizzo (1971).

decreases with numbers over 5. That is to say, the odor thresholds are at a minimum when the number of carbons is 5 irrespective of the substituents at the 3-position. The odor thresholds of pyrazines, having an odd-numbered chain, in most cases, are slightly lower than those of pyrazines having the next higher even-numbered chain. In general, the 3-substituted 2-alkylpyrazines are stronger in odor potency than the corresponding alkylpyrazines except for 2-pentyl-3-phenoxypyrazine and 2-pentyl-3-(phenylthio)pyrazine. Generally speaking, the odor thresholds of 3-substituted 2-alkylpyrazines increase in the following order: $OCH_3 < OC_2H_5 \leq SCH_3 < SC_2H_5 < OC_6H_5 \leq SC_6H_5$. The 2-alkyl-3-methoxypyrazines have a ca. 1000 times lower threshold than the corresponding alkyl-

Table II. Odor Descriptions and Odor Thresholds[a] of Substituted Pyrazines I

	R						
C_nH_{2n+1}	H	SCH_3	OCH_3	SC_2H_5	OC_2H_5	SC_6H_5	OC_6H_5
H	sweet nutty green 3.0×10^2	sweet nutty 2.0×10^{-1}	roasted nutty sweet 4.0×10^{-1}	nutty roasted sweet 9.0×10^{-1}	sweet fruity roasted 8.0×10^{-2}	sulfurous chemical dusty 4.0×10^{-1}	phenol-like cresol-like medicine-like 3.0×10^{-2}
CH_3	nutty green 3.0 × 10	nutty sweet weakly green 4.0×10^{-3}	nutty roasted sweet 7.0×10^{-3}	nutty sweet brown earthy 7.0×10^{-2}	nutty roasted weakly green earthy 8.0×10^{-4}	sweet nutty roasted chemical medicine-like gummy 3.0×10^{-1}	phenol-like sweet medicine-like 2.0×10^{-1}
C_2H_5	nutty green sweet 4.0	nutty green roasted vegetable 4.0×10^{-2}	sweet brown nutty roasted 1.0×10^{-2}	nutty sweet decayed tropical fruit-like 6.0×10^{-2}	dusty nutty roasted weakly woody 2.0×10^{-2}		
C_3H_7	nutty green vegetable 3.0×10^{-1}		green earthy ginseng-like vegetable 1.2×10^{-4}			earthy burdock-like nutty chemical 9.0×10^{-2}	
C_4H_9	green earthy burdock-like 4.0×10^{-1}		green earthy ginseng-like burdock-like 5.0×10^{-5}	earthy green burdock-like vegetable 4.0×10^{-3}			
C_5H_{11}	green fatty earthy vegetable 5.0×10^{-3}	burdock-like earthy weakly green 1.2×10^{-4}	green earthy ginseng-like burdock-like 2.0×10^{-5}	green vegetable burdock-like ginseng-like 1.0×10^{-3}	burdock-like earthy green vegetable 8.0×10^{-5}	earthy burdock-like vegetable 1.0×10^{-2}	earthy green vegetable 5.0×10^{-2}
C_6H_{13}	green nutty fatty 2.0×10^{-1}		green earthy burdock-like vegetable 7.0×10^{-5}				
C_7H_{15}	waxy green earthy 1.0×10^{-1}		green earthy burdock-like vegetable 2.6×10^{-5}				
C_8H_{17}	waxy green earthy fatty 4.0×10^{-1}	ginseng-like green sharp earthy burdock-like 7.0×10^{-4}	green earthy burdock-like 6.0×10^{-5}	vegetable green earthy burdock-like 2.0×10^{-3}	burdock-like vegetable 2.0×10^{-3}	nutty weakly waxy dusty earthy burdock-like 8.0×10^{-2}	
$C_{10}H_{21}$	fatty waxy 1.1	ginseng-like earthy slightly sweet heavy green 2.0×10^{-2}	green earthy burdock-like waxy 4.0×10^{-2}	earthy green waxy 1.2×10^{-1}	fatty sweet burdock-like earthy 6.0×10^{-2}	dusty nutty waxy earthy metallic 3.0×10^{-1}	medicine-like phenol-like 7.0×10^{-2}

[a] Threshold in ppm of water.

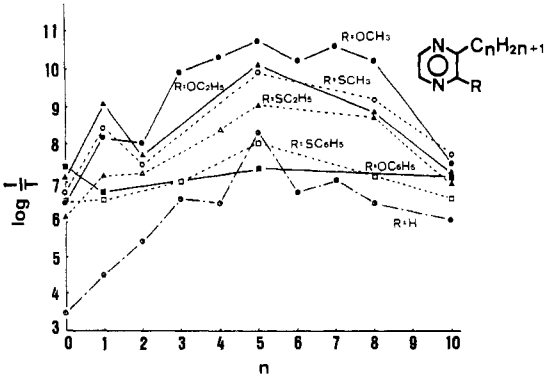


Figure 1. Relation between log $1/T$, where T is the odor threshold, and the number of carbons in the alkyl side chain, n, for alkylpyrazines and 3-substituted 2-alkylpyrazines.

pyrazines. The substitution of an alkyl group at the ortho position on the phenoxypyrazine scarcely affects its odor threshold. The pentyl group is the most prominent group for lowering the odor thresholds of the pyrazines. The odor threshold of pentylpyrazine is 10^{-5} times that of pyrazine.

The odor descriptions and odor thresholds of substituted pyrazines I are listed in Table II. Monosubstituted pyrazines and substituted methylpyrazines have nutty and/or roasted notes. All alkylpyrazines, except decylpyrazine, have a green odor. The higher alkyl substituted pyrazines possess fatty and/or waxy odors. Substitution of the methylthio, methoxy, ethylthio, ethoxy, phenylthio, or phenoxy group at the 3-position of the 2-alkylpyrazines did not decrease the fatty and/or waxy odors. The pentylpyrazines, which have the lowest odor threshold, have green, earthy, burdock-like, and/or ginseng-like odors ir-

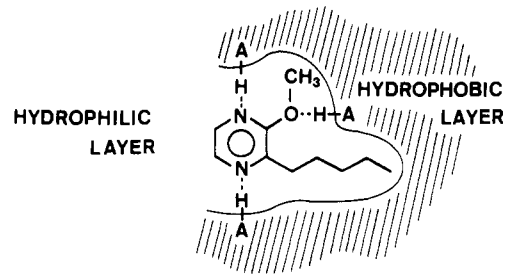


Figure 2. Specific receptor interaction of 2-methoxy-3-pentylpyrazine.

respective of the substituent at the 3-position. The decylpyrazines have fatty and/or waxy odors. It appears that the alkyl substituents play an important role in the tonalities of the pyrazines. Several researchers have reported that 2-isobutyl-3-methoxypyrazine, the characteristic highly potent aroma component of bell peppers, binds specifically and saturably to bovine and rat nasal epithelium (Pelosi et al., 1981; Pevsner et al., 1985). The above results show that a structure/odor relationship is emerging, and from this the structural features essential for odor can be proposed as shown in Figure 2. The fact that the odor thresholds are at a minimum in pentylpyrazines irrespective of the substituents at the 3-position indicates the pentyl group's ideal occupation of the hydrophobic pocket in the cavity of the active sites. The pyrazine ring probably exists in the hydrophilic layer, because pyrazine is soluble in water. Rebek et al. (1987) has demonstrated pyrazine as a suitable substrate because its binding involves hydrogen-bonding interaction with receptors in which two carboxylic acids converge to define a molecular cleft. The methoxy group participates via an intermolecular hydrogen bond (Calabretta, 1978).

ACKNOWLEDGMENT

We thank Kazuhiro Takada for assistance with sensory evaluation.

Registry No. 1, 18138-03-9; 2, 29460-91-1; 3, 6303-75-9; 4, 28217-91-6; 5, 84005-70-9; 6, 110823-72-8; 7, 113685-78-2; 8, 25680-57-3; 9, 32737-11-4; 10, 32737-12-5; 11, 25680-56-2; 12, 113685-79-3; 13, 113685-80-6; 14, 113685-81-7; 15, 38028-67-0; 16, 32737-14-7; 17, 113685-82-8; 18, 113685-83-9; 19, 113685-84-0; 20, 107697-82-5; 21, 91137-78-9; 22, 113685-86-2; 23, 113685-86-2; 24, 21948-70-9; 25, 2882-20-4; 26, 113685-87-3; 27, 113685-88-4; 28, 113685-89-5; 29, 65032-06-6; 30, 32740-98-0; 31, 113685-90-8; 32, 113685-91-9; 33, 113685-92-0; 34, 113685-93-1; 35, 113685-94-2; 36, 107697-83-6; 37, 91091-02-0; 38, 113685-95-3; 39, 113685-96-4; 40, 113685-97-5; 41, 113685-98-6; I (n = 0, R = H), 290-37-9; I (n = 0, R = OCH_3), 3149-28-8; I (n = 1, R = H), 109-08-0; I (n = 1, R = OCH_3), 2847-30-5; I (n = 2, R = H), 13925-00-3; I (n = 2, R = SCH_3), 21948-70-9; I (n = 2, R = OCH_3), 25680-58-4; I (n = 2, R = OC_2H_5), 35243-43-7.

Supplementary Material Available: IR and ^1H NMR spectral data for new pyrazines I (15 pages). Ordering information is given on any current masthead page.

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Received for review August 31, 1987. Accepted December 29, 1987.