STRUCTURE AND OXIDATION OF 2-HYDROXY-3,6-DIISOBUTYLPYRAZINES

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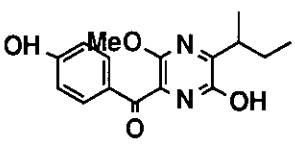
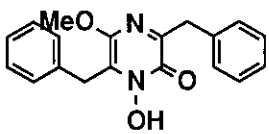
Abstract —— Tautomeric structures of 2-hydroxy-3,6-diisobutylpyrazine (1), 5-chloro-2-hydroxy-3,6-diisobutylpyrazine (2) and 2-hydroxy-3,6-diisobutyl-5-methoxypyrazine (3) are discussed. The oxidation of 1, 2, and 3 with permaleic acid gave the corresponding monoxides 2-hydroxy-3,6-diisobutylpyrazine (12), 5-chloro-2-hydroxy-3,6-diisobutylpyrazine 1-oxide (13), and 2-hydroxy-3,6-diisobutyl-5-methoxypyrazine 1-oxide (14), respectively.

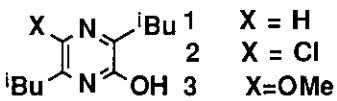
Recently, certain hydroxypyrazines, such as septorine[1] and emeheterone[2] carrying a methoxyl group on their pyrazine ring, have been found in nature.



Septorine[1]



Emeheterone[2]



1-3

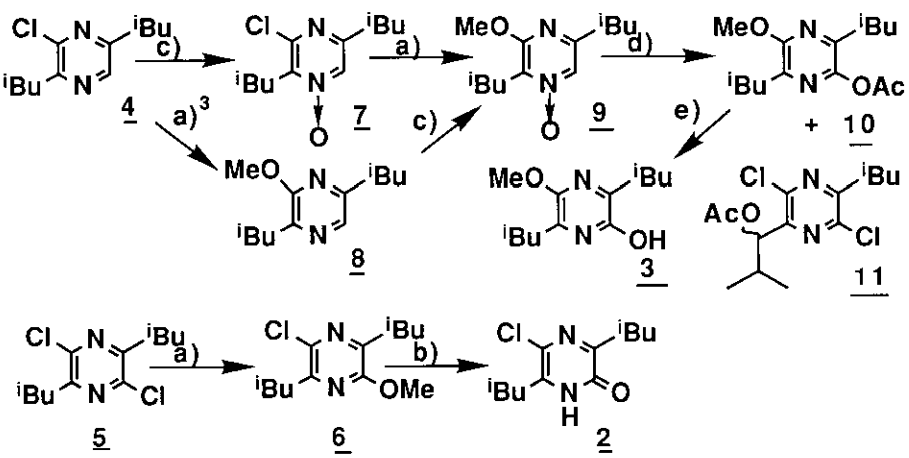
While conducting a study on pyrazine chemistry, our attention was directed to the synthesis of the hydroxy-methoxypyrazines. For this purpose, 2-hydroxy-3,6-diisobutyl-5-methoxypyrazine (3) was initially prepared and its chemical properties were compared with those of 2-hydroxy-3,6-diisobutylpyrazine (1)[3] and

5-chloro-2-hydroxy-3,6-diisobutylpyrazine (2).[4]

Although the synthesis of the chloro-hydroxypyrazine (2) has already been reported in our previous paper,[4] an alternate synthesis is shown in this paper. The reaction of 2,5-dichloro-3,6-diisobutylpyrazine (5)[5] with sodium methoxide gave 5-chloro-3,6-diisobutyl-2-methoxypyrazine (6), whose treatment with trimethylsilyl iodide afforded compound 2 (Scheme 1).

The hydroxy-methoxypyrazine (3) was prepared via several steps from 2-chloro-3,6-diisobutylpyrazine (4).[5] 2-Chloro-3,6-diisobutylpyrazine (4) was oxidized with permaleic acid to afford the 4-oxide (7), which was further converted to 3,6-diisobutyl-2-methoxypyrazine 4-oxide (9) by treatment with sodium methoxide in methanol. Compound 9 was also obtained from 4 via 3,6-diisobutyl-2-methoxypyrazine (8) in better yield than the above. Treatment of 9 with acetic anhydride furnished a mixture of acetoxyl compounds (10 and 11), which could be separated by column chromatography. Alkaline hydrolysis of the acetoxy-methoxypyrazine (10) gave the desired hydroxy-methoxypyrazine (3).

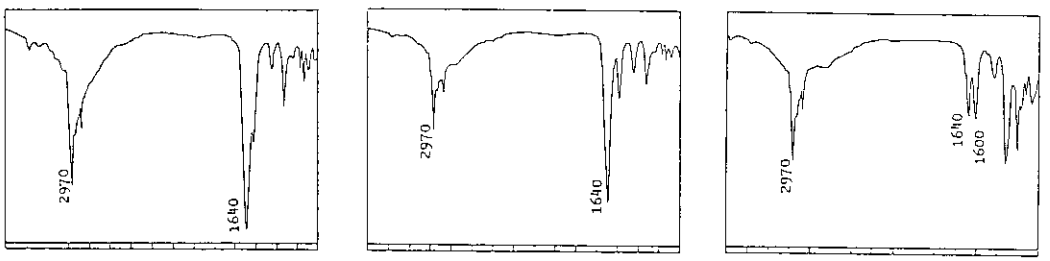
(Scheme 1)



Scheme 1. **Synthesis of 2-Hydroxypyrazines (1-3)**

2-Hydroxypyrazines have two possible tautomers such as the amido (pyrazinone type) and iminol (pyrazinol type) forms, as in the case of 2-hydroxypyridine.[6] As already reported,[3,7] the ir spectra of 1 and 5-chloro-2-hydroxy-3,6-diisopropylpyrazine indicate a strong band near 1650 cm^{-1} due to the amido carbonyl group. Based on

this information, it would be reasonable to consider that 3,6-dialkyl-2-hydroxypyrazines and 3,6-dialkyl-5-chloro-2-hydroxypyrazines predominated as the pyrazinone form. The ir spectrum of 3 indicated no strong band in the region of 1600-1650 cm^{-1} and hence this compound might exist primarily in the pyrazinol form (Figure 1).



1 2 3

Figure 1. Ir-Spectra of 2-Hydroxypyrazines (1-3) in $CHCl_3$.

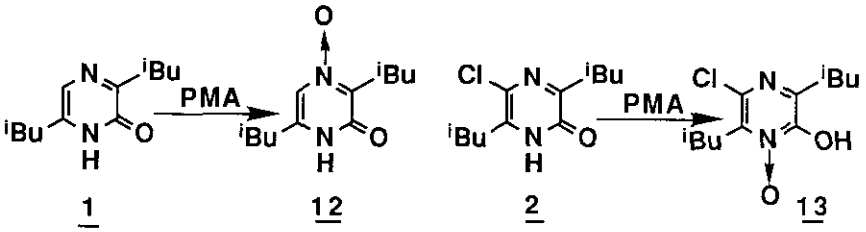
The heat of formation for the amido and iminol forms of 1, 2, and 3 was calculated by the AM1 method.[8] The values in Table 1 indicate that the pyrazinone form is more stable than the pyrazinol form in compounds 1 and 2 and that the pyrazinol form is more stable in compound 3.

Compound	Heat of formation(kcal/mol)		Stable form	Difference
	amide	iminol		(kcal/mol)
1	-46.23	-44.316	amide	1.923
2	-49.671	-47.981	amide	1.690
3	-79.156	-79.319	iminol	0.163

Table 1. Heat of Formation for Compounds 1-3

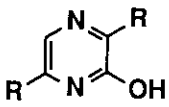
The oxidation of 2-hydroxypyrazines was subsequently carried out. The peracetic acid oxidation of 1 occurs at N-4.[4] In this study, the hydroxypyrazine (1) was oxidized with permaleic acid to obtain the corresponding 4-oxide (12).[4] Since compound 2 preferentially takes on the pyrazinone form, its oxidation was

expected to occur at N-4. However, only the corresponding 1-oxide (13)[9] was obtained. (Scheme 2) Because of the electron-withdrawing effect of chlorine atom, the electron density at N-4 atom may be higher than that of N-4 atom and the oxidation probably occurred at N-1.



Scheme 2. Oxidation of 2-Hydroxypyrazines (1-2).

The oxidation of the hydroxy-methoxypyrazine (3) with permaleic acid gave 2-hydroxy-3,6-diisobutyl-5-methoxypyrazine 1-oxide (14), which showed the ferric chloride color reaction, thus indicating the oxidation to occur at N-1.
The melting points of 3,6-dialkyl-2-hydroxypyrazine 1-oxides are generally lower than those of the parent hydroxypyrazines. 3,6-Dialkyl-2-hydroxypyrazine 4-oxides tend to melt at temperatures higher than those of the mother hydroxypyrazines (Table 2). The melting point of 14 is lower than that of compound 3. Judging from melting point, 14 must surely be 1-oxide.
^{13}C-Nmr data for 14 confirmed also oxidation to occur at N-1. In a previous study,[14] the C-2 carbon signal of pyrazine 1-oxides appeared in a higher region than that of the parent pyrazines. The signal due to the C-2 of 14 appeared in a field higher than that of the parent pyrazine 3, thus certifying the oxidation of 3 to occur at N-1 in contrast to the case of 1 (Figure 2, Scheme 3).
Next, for the synthesis of 2-hydroxy-3,6-diisobutyl-5-methoxypyrazine 4-oxide (18), the hydroxyl group of 3 was protected with various groups such as diphenyl-t-butylsilyl, benzyloxycarbonyl and p-nitrobenzoyl groups. The protected compounds were obtained in satisfactory yields, but attempts to conduct their oxidation were unsuccessful.



R	(℃)	1-Oxide (℃)	4-Oxide (℃)
Me	206-207[10]	194-195[11]	260-264[10]
Et	136-137[10]	135-137(d)[11]	257-259[10]
Pr	140-142[3]	113.5-116.5[9]	-
Pr	141-142[3]	74-76[9]	260-262[3]
Bu	150-151[4]	125-126[12]	237-238[4]
Ph	206-207[13]	-	256-260[13]
Bz	201-202[13]	-	255.5-257[13]

Table 2.
Melting Points of Some Hydroxypyrazines.

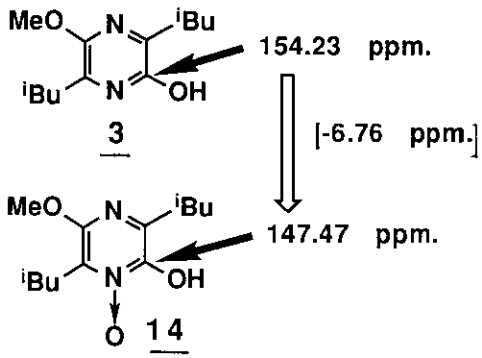
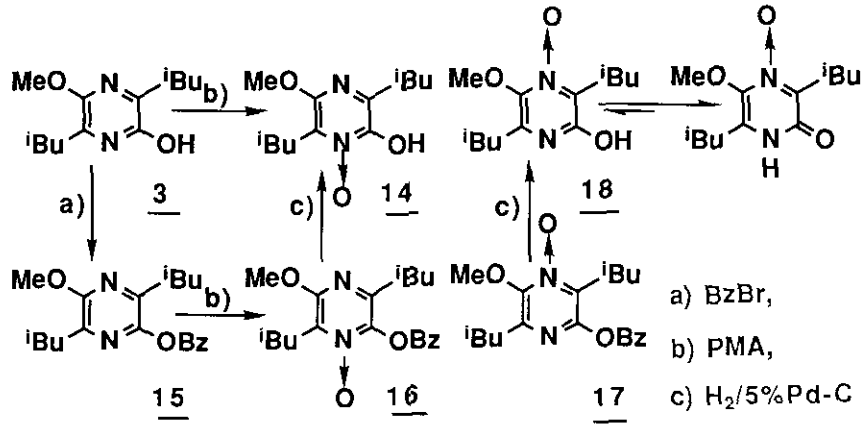


Figure 2. ^{13}C-Nmr Spectral Data for 2-Hydroxy-3,6-diisobutyl-5-methoxypyrazine (3) and Its 1-Oxide (14)

Consequently, the benzyl group was used as a protecting group and the oxidation of 2-benzyloxy-3,6-diisobutyl-5-methoxypyrazine (15) with permaleic acid gave a mixture of 2-benzyloxy-3,6-diisobutyl-5-methoxypyrazine 1-oxide (16) and 2-benzyloxy-3,6-diisobutyl-5-methoxypyrazine 4-oxide (17), which were separated by silica gel column chromatography. The structures of 16 and 17 were assigned on the basis of their ^{13}C-nmr data. The signals due to C-2 of 16 and C-5 of 17 were observed in a field higher than those due to C-2 and C-5 of 15, respectively, thus supporting the structures of 16 and 17.

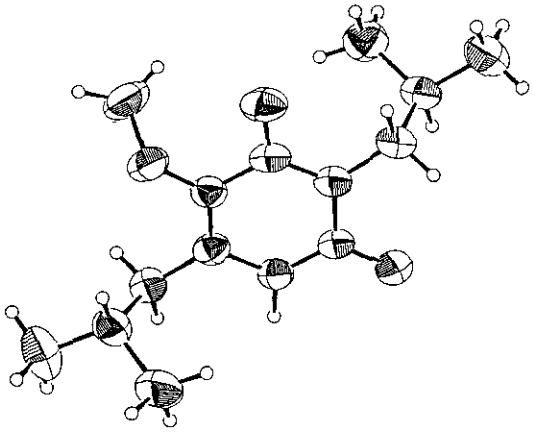
After the hydrogenolysis of 16 and 17 using 5% palladium on carbon, the product from 16, positive to ferric chloride coloration, was found to be identical with 14 derived from 3 by direct oxidation. The other one showed no ferric chloride coloration and its melting point exceeded that of the starting material 3. These findings clearly demonstrate the successful synthesis of compound 18. The ^{13}C-nmr spectrum was consistent with the proposed structure (18). (Scheme 3) To determine the structure of 18, X-Ray analysis was carried out. As shown in Figure 3, an oxygen atom exists at the N-4.

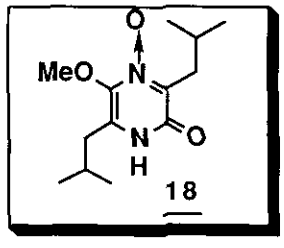
The structures of certain 2-hydroxy-3,6-diisobutylpyrazines have been conclusively demonstrated by the results of this study and the oxidation of these compounds was successively conducted with permaleic acid.



3 14 18 15 16 17

Scheme 3. Synthesis of 2-Hydroxy-3,6-diisobutyl-5-methoxypyrazine 1- and 4-Oxides (14,18).





a = 12.072(2) Å, α = 94.44(1) °
b = 13.158(2) Å, β = 93.69(1) °
c = 4.7925(6) Å, γ = 111.16(1) °
V = 704.3(2) Å^3, R = 0.051

Figure 3. X-Ray Diffraction of 2-Hydroxy-3,6-diisobutyl-5-methoxypyrazine 4-oxide (18).

EXPERIMENTAL

No correction was made for the melting or boiling points. ^{1}H-Nmr spectral data were obtained by a Varian EM-390 or Brucker AM-400 in $CDCl_3$ using TMS as the internal standard. ^{13}C-Nmr spectra were taken in $CDCl_3$ with a Brucker AM-400, using TMS as the internal standard. For the silica gel column chromatography, Wakogel C-200 (WAKO Pure Chemical Ind. Ltd., Tokyo) was used as the packing material. Medium-pressure column chromatography was conducted by using a UVILOG ALPC-100 as the pump, UVILOG 5IIIa as the UV detector (Oyo-Bunko Kiki Co., Ltd., Tokyo) and Kieselgel 60 (Merck AG, Darmstadt) as the packing material. The following instruments were used to obtain other spectral data: Ir spectra, Japan Spectroscopic Co. A-100; Ms, Hitachi M-80B spectrometer. X-Ray diffraction data

were obtained by Rigaku AFC5R diffractometer with graphite monochromated Cu Kα radiation and a 12 KW rotating anode generator.

General Procedure for Chlorine Atom Replacement on the Pyrazine Ring with a Methoxyl Group

A chloropyrazine (20 mmol) was added to a MeOH solution of NaOMe, prepared from Na (100 mg atom) and MeOH (50 ml), and the reaction mixture was refluxed for 3 h. Following removal of the solvent in vacuo, the residue was triturated with H_2O and extracted with Et_2O. The Et_2O layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was then evaporated in vacuo and the product was purified by distillation or recrystallization.

5-Chloro-3,6-diisobutyl-2-methoxypyrazine (6): colorless oil; bp 83-85°C/1 torr; yield: 98%; ms: m/z 256 (M^+); ^{1}H-nmr (90 MHz): δ 0.84 (d, J = 6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.89 (d, J = 6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.90-2.27 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.53 (d, J = 6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.60 (d, J = 6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.86 (s, 3H, OCH_3) ppm; Anal. Calcd for $C_{13}H_{21}ClN_2O$: C, 60.81; H, 8.24; N, 10.91. Found: C, 60.71; H, 8.28; N, 10.89.

3,6-Diisobutyl-2-methoxypyrazine (8): colorless oil; bp 98-105°C/6 torr (lit.,[15] bp 102-104°C/3 torr); yield: 95%.

3,6-Diisobutyl-2-methoxypyrazine 4-Oxide (9): colorless needles (hexane); mp 46-47°C; yield: 95%; ms: m/z 238 (M^+), 221 (M^+-OH); ^{1}H-nmr (90 MHz): δ 0.87 (d, J = 6 Hz, 12 H, 2 x $CH_2CH(C\underline{H}_3)_2$), 2.00-2.33 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.36 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.67 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.89 (s, 3H, OCH_3), 7.61 (s, 1H, C_5-H) ppm; Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.78; H, 9.35; N, 11.73.

General Procedure for the Oxidation of 2-Chloro-3,6-diisobutylpyrazine (4) and 3,6-Diisobutyl-2-methoxypyrazine (8) with Permaleic Acid

A mixture of 4 or 8 (50 mmol), 60% H_2O_2 (14.2 g, 250 mmol) and maleic anhydride (24.5 g, 250 mmol) in $CHCl_3$ (500 ml) was allowed to stand for 12 h at room temperature, and then washed with H_2O, 5% $KHCO_3$ and saturated NaCl, successively. The organic layer was worked up as usual to give the corresponding N-oxide, which was purified by recrystallization.

2-Chloro-3,6-diisobutylpyrazine 4-Oxide (7): colorless needles (hexane); mp 59-60°C (lit.,[5] mp 56.5-57°C); yield: 68%.

3,6-Diisobutyl-2-methoxypyrazine 4-Oxide (9): yield: 90%.

Synthesis of 5-Chloro-2-hydroxy-3,6-diisobutylpyrazine (2): Me_3SiI (2.1 ml, 15 mmol) was added to a solution of 6 (2.40 g, 10 mmol) in dry $CHCl_3$ (50 ml) over a 10 min period under ice-cooling and stirring. The reaction mixture, after stirring for 24 h, was treated with MeOH (30 ml). The precipitates were collected by suction and washed with a small amount of MeOH. The filtrate was evaporated to dryness in vacuo to give a brown solid, which was subsequently dissolved in Et_2O. The Et_2O solution was washed with 5% $NaHSO_3$ and saturated NaCl, successively, and worked up as usual to give a colorless solid, whose recrystallization from hexane provided colorless needles; mp 139-140°C (lit.,[4] mp 141-142°C); yield: 95%.

Reaction of 3,6-Diisobutyl-2-methoxypyrazine 4-Oxide (9) with Ac_2O

A solution of 9 (7.14 g, 30 mmol) in Ac_2O (100 ml) was refluxed for 1.5 h. The reaction mixture was concentrated to dryness in vacuo to give an oily residue, which was poured into ice-water. The mixture was made alkaline with K_2CO_3 and extracted with Et_2O. After the usual work-up of the Et_2O extract, the products (10 and 11) were separated and purified by column chromatography, eluting with a mixture of hexane-Et_2O (100:1). 2-Acetoxy-3,6-diisobutyl-5-methoxypyrazine (10) was used to synthesize 3 without further purification. 3-(α-Acethoxyisobutyl)-6-isobutyl-2-methoxypyrazine (11) was not purified any further.

2-Acetoxy-3,6-diisobutyl-5-methoxypyrazine (10): colorless oil; yield: 73%; ms: m/z 280 (M^+), 238 (M^+-$COCH_2$); ir (neat): 1780 (νCO) cm^{-1}; ^{1}H-nmr (90 MHz): δ 0.87 (d, J = 6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.89 (d, J = 6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.93-2.40 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.26 (s, 3H, $COCH_3$), 2.42 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.56 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.84 (s, 3H, OCH_3) ppm. High-resolution ms Calcd for $C_{13}H_{22}N_2O_2$: 238.1679. Found: 238.1673.

3-(α-Acetoxyisobutyl)-6-isobutyl-2-methoxypyrazine (11): colorless oil; yield: 12%; ms: m/z 280 (M^+); ir (neat): 1740 (νCO) cm^{-1}; ^{1}H-nmr (90 MHz): δ 0.77-0.97 (m, 12H, $CH(OAc)CH(C\underline{H}_3)_2$, $CH_2CH(C\underline{H}_3)_2$), 2.03 (s, 3H, $COCH_3$), 2.10-2.37 (m, 1H, $CH(OAc)C\underline{H}(CH_3)_2$), 2.45 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.90 (s, 3H, OCH_3), 5.71 (d, J = 8 Hz, 1H, $C\underline{H}(OAc)CH(CH_3)_2$), 7.84 (s, 1H, C_5-H) ppm. High-resolution ms Calcd for $C_{15}H_{24}N_2O_3$: 280.1785. Found: 280.1759.

2-Hydroxy-3,6-diisobutyl-5-methoxypyrazine (3)

A solution of 10 (5.60 g, 20 mmol) in 10% K_2CO_3 (50 ml) and MeOH (100 ml) was refluxed gently for 0.5 h and then MeOH was removed by distillation in vacuo. The resulting solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated NaCl and worked up as usual to give a solid, which was purified by recrystallization. Pale yellow needles (MeOH); mp 101-102°C; yield: 99%; ms: m/z 238 (M^+), 223 (M^+-CH_3); ^{1}H-nmr (400 MHz): δ 0.92 (d, J = 6.7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.97 (d, J = 6.7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 2.01-2.08 (m, J = 6.8 Hz, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.19-2.26 (m, J = 6.8 Hz, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.54 (d, J = 7.3 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.62 (d, J = 7.1 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.88 (s, 3H, OCH_3), 12.49 (br s, 1H, NH or OH) ppm; ^{13}C-nmr; δ 22.38 (q, $CH_2CH(\underline{C}H_3)_2$), 22.63 (q, $CH_2CH(\underline{C}H_3)_2$), 27.42 (d, $CH_2\underline{C}H(CH_3)_2$), 28.46 (d, $CH_2\underline{C}H(CH_3)_2$), 38.24 (t, $\underline{C}H_2CH(CH_3)_2$), 40.59 (t, $\underline{C}H_2CH(CH_3)_2$), 54.03 (q, OCH_3), 133.01 (s, C-3 or C-6), 142.77 (s, C-3 or C-6), 150.49 (s, C-5), 154.23 (s, C-2) ppm; Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.57; H, 9.31; N, 11.62.

2-Benzyloxy-3,6-diisobutyl-5-methoxypyrazine (15)

A solution of 3 (0.238 g, 1 mmol), BzBr (257 mg, 1.5 mmol), 10% KOH (10 ml) and a catalytic amount of Me_4NBr in $CHCl_3$ (10 ml) was subjected to ultrasonic treatment at 30°C. After 1.5 days, the $CHCl_3$ layer was separated, washed with saturated NaCl and worked up as usual. The product was purified by column chromatography, eluting with a mixture of hexane-Et_2O (9:1) to give 15 as a colorless oil; yield: 80%; bp 160°C/1 torr; ms: m/z 328 (M^+); ^{1}H-nmr (400 MHz): δ 0.95 (d, J = 6.7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.97 (d, J = 6.7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.95-2.35 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.60 (d, J = 7.2 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.66 (d, J = 7.1 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.92 (s, 3H, OCH_3), 5.38 (s, 2H, OCH_2Ph), 7.31-7.48 (m, 5H, benzene H) ppm; ^{13}C-nmr; δ 22.62 (q, $CH_2CH(\underline{C}H_3)_2$), 22.64 (q, $CH_2CH(\underline{C}H_3)_2$), 27.45 (d, $CH_2\underline{C}H(CH_3)_2$), 27.68 (d, $CH_2\underline{C}H(CH_3)_2$), 40.07 (t, $\underline{C}H_2CH(CH_3)_2$), 40.11 (t, $\underline{C}H_2CH(CH_3)_2$), 53.53 (q, OCH_3), 67.66 (OCH_2Ph), 127.47 (d), 127.67 (d,), 128.29 (d,), 137.92 (s), 138.03 (s), 138.18 (s), 152.22 (s, C-2), 153.07 (s, C-5) ppm; Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.13; H, 8.59; N, 8.53. Found: C, 72.98; H, 8.72; N, 8.48.

General Procedure for the Permaleic Acid Oxidation of Hydroxypyrazines (1, 2 and 3) and 2-Benzyloxy-3,6-diisobutyl-5-methoxypyrazine (15)

A solution of 90% H_2O_2 (113 mg, 3 mmol), maleic anhydride (294 mg, 3 mmol) in

$CHCl_3$ (15 ml) was refluxed for 5 min. After cooling, a starting pyrazine (1 mmol) was added and the reaction mixture was stirred for 1-2 days at room temperature, washed with H_2O and worked up as usual. The products were purified by column chromatography (hexane:Et_2O = 9:1) followed by recrystallization or distillation.

2-Hydroxy-3,6-diisobutylpyrazine 4-Oxide (12): colorless needles (MeOH); mp 244°C (decomp.) (lit.,[4] mp 238-239°C); yield: 90%.

5-Chloro-2-hydroxy-3,6-diisobutylpyrazine 1-Oxide (13): colorless needles (hexane); mp 124-125°C (lit.,[9] mp 125°C); yield: 63% (25% recovery).

2-Hydroxy-3,6-diisobutyl-5-methoxypyrazine 1-Oxide (14): colorless needles (MeOH); mp 97-98°C; yield: 82%; ms: m/z 254 (M^+), 237 (M^+-OH); ^{1}H-nmr (400 MHz): δ 0.94 (d, J = 6.3 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.96 (d, J = 6.5 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 2.15-2.22 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.64 (d, J = 7.2 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.78 (d, J = 7.4 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.88 (s, 3H, OCH_3), 8.81 (br s, 1H, NOH or OH) ppm; ^{13}C-nmr: δ 22.45 (q, $CH_2CH(\underline{C}H_3)_2$), 22.51 (q, $CH_2CH(\underline{C}H_3)_2$), 26.66 (d, $CH_2\underline{C}H(CH_3)_2$), 27.42 (d, $CH_2\underline{C}H(CH_3)_2$), 33.04 (t, $\underline{C}H_2CH(CH_3)_2$), 40.56 (t, $\underline{C}H_2CH(CH_3)_2$), 54.04 (q, OCH_3), 128.06 (s, C-6), 137.45 (s, C-3), 147.47 (s, C-2), 150.52 (s, C-5) ppm; Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.42; H, 8.74; N, 10.93.

2-Benzyloxy-3,6-diisobutyl-5-methoxypyrazine 1-Oxide (16): colorless oil; bp 170°C/1 torr; yield: 30%; ms: m/z 344 (M^+), 327 (M^+-OH); ^{1}H-nmr (400 MHz): δ 0.86 (d, J = 6.7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.94 (d, J = 6.7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 2.05-2.12 (m, J = 6.8 Hz, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.25-2.32 (m, J = 6.9 Hz, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.41 (d, J = 7.2 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.60 (d, J = 7.3 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.89 (s, 3H, OCH_3), 5.30 (s, 2H, OCH_2Ph), 7.30-7.45 (m, 5H, benzene H) ppm; ^{13}C-nmr: δ 22.39 (q, $CH_2CH(\underline{C}H_3)_2$), 22.59 (q, $CH_2CH(\underline{C}H_3)_2$), 25.83 (d, $CH_2\underline{C}H(CH_3)_2$), 27.41 (d, $CH_2\underline{C}H(CH_3)_2$), 32.73 (t, $\underline{C}H_2CH(CH_3)_2$), 40.27 (t, $\underline{C}H_2CH(CH_3)_2$), 53.87 (q, OCH_3), 73.55 (t, OCH_2Ph), 128.41 (d), 128.50 (d), 128.93 (d), 133.86 (s), 136.00 (s), 143.61 (s), 148.01 (s, C-2), 156.09 (s, C-5) ppm; Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.52; H, 8.28; N, 7.94.

2-Benzyloxy-3,6-diisobutyl-5-methoxypyrazine 4-Oxide (17): colorless oil; bp 175°C/1 torr; yield: 40%; ms: m/z 344 (M^+), 327 (M^+-OH); ^{1}H-nmr (400 MHz): δ 0.94 (d, J = 6.7 Hz, 12H, 2 x $CH_2CH(C\underline{H}_3)_2$), 2.12-2.19 (m, J = 6.8 Hz, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.19-2.28 (m, J = 6.8 Hz, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.58 (d, J = 7.1 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$),

2.82 (d, J = 7.0 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 4.00 (s, 3H, OCH_3), 5.36 (s, 2H, OCH_2Ph), 7.31-7.43 (m, 5H, benzene H) ppm; ^{13}C-nmr: δ 22.46 (q, $CH_2CH(\underline{C}H_3)_2$), 22.71 (q, $CH_2CH(\underline{C}H_3)_2$), 26.00 (d, $CH_2\underline{C}H(CH_3)_2$), 27.67 (d, $CH_2\underline{C}H(CH_3)_2$), 32.80 (t, $\underline{C}H_2CH(CH_3)_2$), 40.31 (t, $\underline{C}H_2CH(CH_3)_2$), 59.77 (q, OCH_3), 69.21 (t, OCH_2Ph), 127.79 (d), 127.85 (d), 128.39 (d), 134.16 (s), 136.88 (s), 142.89 (s), 149.74 (s, C-5), 155.47 (s, C-2) ppm; High mass Calcd for $C_{20}H_{28}N_2O_3$: 344.2098. Found: 344.2087.

Hydrogenolysis of 2-Benzyloxy-3,6-diisobutyl-5-methoxypyrazine 1-Oxide (16) and 2-Benzyloxy-3,6-diisobutyl-5-methoxypyrazine 4-Oxide (17)

A solution of 16 or 17 (1 mmol) in EtOH (5 ml) was shaken in the presence of 5% Pd-C (344 mg) in a stream of H_2. The absorption speed of H_2 was reduced (30 min), the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by recrystallization.

2-Hydroxy-3,6-diisobutyl-5-methoxypyrazine 1-Oxide (14): yield: 70%.

2-Hydroxy-3,6-diisobutyl-5-methoxypyrazine 4-Oxide (18): colorless needles (benzene); mp 172-173°C, yield: 90%; ms: m/z 254 (M^+), 237 (M^+-OH); ir (KBr): 1640 (νCO) cm^{-1}; ^{1}H-nmr (400 MHz): δ 0.96 (d, J = 6.8 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 0.99 (d, J = 6.7 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 2.09-2.16 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.22-2.28 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.49 (d, J = 7.4 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.78 (d, J = 7.2 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.93 (s, 3H, OCH_3), 13.28 (br s, 1H, OH or NH) ppm; ^{13}C-nmr: δ 22.28 (q, $CH_2CH(\underline{C}H_3)_2$), 22.92 (q, $CH_2CH(\underline{C}H_3)_2$), 26.03 (d, $CH_2\underline{C}H(CH_3)_2$), 27.91 (d, $CH_2\underline{C}H(CH_3)_2$), 33.42 (t, $\underline{C}H_2CH(CH_3)_2$), 36.40 (t, $\underline{C}H_2CH(CH_3)_2$), 61.53 (q, OCH_3), 129.59 (s, C-6), 141.43 (s, C-3), 144.37 (s, C-5), 158.88 (s, C-2) ppm; Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02. found: C, 61.37; H, 8.64; N, 10.85.

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REFERENCES

1. M. Devys, M. Barbier, A. Kollmann, and J.-F. Bousquet, Tetrahedron Lett., 1982, 23, 5409.

2. N. Kawahara, K. Nozawa, S. Nakajima, and K. Kawai, Phytochemistry, 1988, **27**, 3022.
3. A. Ohta, M. Shimazaki, H. Tamamura, Y. Mamiya, and T. Watanabe, J. Heterocycl. Chem., 1983, **20**, 951.
4. A. Ohta, Chem. Pharm. Bull., 1964, **12**, 125.
5. A. Ohta, Chem. Pharm. Bull., 1968, **16**, 1160.
6. A. J. Boulton and A. R. McKillop, "Comprehensive Heterocyclic Chemistry", Vol. 2, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, p.1.
7. T. Yokotsuka, M. Sasaki, T. Kikuchi, Y. Asao, and A. Nobuhara, Nippon Nogeikagaku Kaishi, 1967, **41**, 32.
8. Dewar Research Group and J. J. Stewart; Quantum Chemistry Program Exchange Bulletin, Vol. **8**, Department of Chemistry, Indiana University, 1988, program nr. 549.
9. A. Ohta, S. Masano, M. Tsutsui, F. Yamamoto, S. Suzuki, H. Makita, H. Tamamura, and Y. Akita, J. Heterocycl. Chem., 1981, **18**, 555.
10. A. Ohta, Y. Akita, and M. Hara, Chem. Pharm. Bull., 1979, **27**, 2027.
11. D. W. C. Ramsay and F. S. Spring, J. Chem. Soc., 1950, 3409.
12. R. G. Micetich and J. C. MacDonald, J. Chem. Soc., 1964, 1507.
13. A. Ohta, Y. Akita, and K. Nakane, Chem. Pharm. Bull., 1979, **27**, 2980.
14. M. Matsuo, S. Matsumoto, T. Kurihara, Y. Akita, T. Watanabe, and A. Ohta, Org. Magn. Reson., 1980, **13**, 172.
15. A. Ohta, S. Masano, E. Maeda, T. Ohwada, Y. Akita, and T. Watanabe, Chem. Pharm. Bull., 1977, **25**, 817.

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