Reaction of 2,5-Diisopropyl- and 2,5-Di-*sec*-butylpyrazine 1-Oxide. Derivatives with Phosphoryl Chloride and Acetic Anhydride

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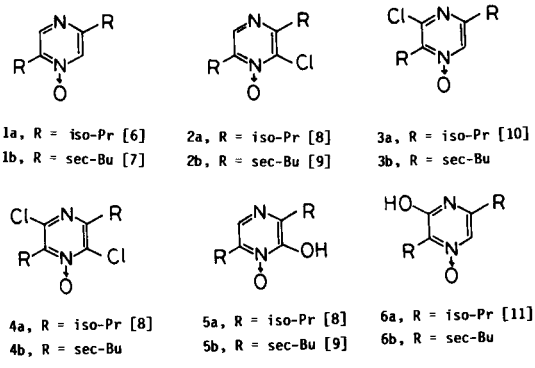
Received February 2, 1985

In order to examine the α-substitution of side chains, various derivatives of 2,5-diisopropyl- and 2,5-di-*sec*-butylpyrazine 1-oxides were subjected to the reaction with phosphoryl chloride and acetic anhydride. Chlorination and acetoxylation were recognized to take place on the pyrazine ring in almost all cases.

J. Heterocyclic Chem., **22**, 1291 (1985).

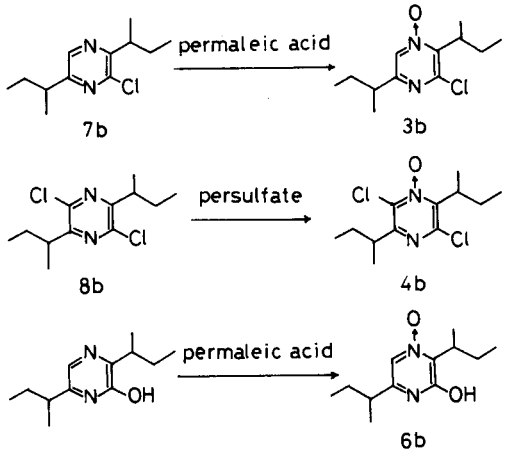
It is well known that aromatic amine oxides react to phosphoryl chloride and acetic anhydride to give the corresponding chloro- and acetoxyl- compounds [1]. Pyrazine *N*-oxides are no exception to these reactions [2]. The present authors performed already the syntheses of some naturally occurring pyrazines, utilizing these reactions [3,4]. However, during the course of the investigation on the syntheses of mutaaspergillic and *dl*-hydroxyaspergillic acids [5], it was observed that the α-carbons of isopropyl and *sec*-butyl groups in the pyrazine *N*-oxides are hardly affected by such chlorination and acetoxylation reactions. The reactions of several types of 2,5-diisopropyl- and 2,5-di-*sec*-butylpyrazine 1-oxide derivatives **1a,b-6a,b** with phosphoryl chloride and acetic anhydride were examined, and the results will be collectively described in the present paper.

Scheme I
Pyrazine N-Oxides Submitted to the Reaction with Phosphoryl Chloride and Acetic Anhydride



All compounds of two series **1a,b-6a,b** examined were prepared from the corresponding mono- and dichloropyrazines, which were respectively derived from DL-valine and DL-isoleucine anhydrides by the reported manners [6-11]. Among the new di-*sec*-butylpyrazine *N*-oxide derivatives, 2-chloro-3,6-di-*sec*-butylpyrazine 4-oxide (**3b**) and 3,6-di-*sec*-butyl-2-hydroxypyrazine 4-oxide (**6b**) were prepared by the permaleic acid oxidation of 2-chloro-3,6-di-*sec*-butylpyrazine (**7b**) [12] and 3,6-di-*sec*-butyl-2-hydroxypyrazine [12], respectively, while 2,5-dichloro-3,6-di-*sec*- butylpyrazine 1-oxide (**4b**) was obtained by the oxidation of 2,5-dichloro-3,6-di-*sec*-butylpyrazine (**8b**) [12] with potassium persulfate in sulfuric acid [13]. The preparation of 2,5-di-*sec*-butylpyrazine 1-oxide (**1b**) [7] was achieved by the palladium-catalyzed dechlorination [6] of **3b**.

Scheme II
Preparation of 2,5-Diisopropyl- and 2,5-Di-sec-butylpyrazine N-Oxides



Twelve compounds **1a,b-6a,b** thus prepared were heated with phosphoryl chloride under reflux or at 140-200° in a sealed tube. In the case of compounds **1a,b, 2a,b, 3a,b, 5a,b** and **6a,b** bearing an unsubstituted position on the pyrazine ring, the chlorination occurred on this position. Moreover, the hydroxy groups in compounds **5a,b** were replaced by chlorine atoms. Namely, the reaction of 2,5-diisopropylpyrazine 1-oxide (**1a**) [6] and **1b** [7] gave 2-chloro-3,6-diisopropylpyrazine (**7a**) [8] and **7b** [12], respectively. From compounds **2a,b, 3a,b** and **5a,b**, 2,5-di-

chloro-3,6-diisopropylpyrazine (**8a**) [8] and **8b** [12] were obtained in the same way. In the case of compounds **6a,b**, the chlorination took place on the pyrazine ring, giving 5-chloro-3,6-diisopropyl-2-hydroxypyrazine (**9a**) [11] and 5-chloro-3,6-di-*sec*-butyl-2-hydroxypyrazine (**9b**) [12], respectively, as shown in Table I. Compounds **4a,b** carrying no unsubstituted position on the pyrazine ring were completely recovered, even under heating at 200° in a sealed tube.

Table I

Reaction of Pyrazine *N*-Oxides **1a,b-6a,b** with Phosphoryl Chloride

Substrate	Reaction Temperature	Reaction Time (hours)	Product	Yield (%)
1a [6]	reflux	2	**7a** [8]	90
1b [7]	reflux	2	**7b** [12]	99
2a [8]	140-150°	4	**8a** [8]	92
2b [9]	180°	2	**8b** [12]	87
3a [10]	140°	2	**8a** [8]	93
3b	140°	2	**8b** [12]	87
4a [8]	200°	2	recovered	
4b	200°	2	recovered	
5a [8]	140-150°	2	**8a** [8]	88
5b [9]	140-150°	2	**8b** [12]	88
6a [11]	reflux	2	**9a** [11]	86
6b	140-150°	4	**9b** [12]	96

Next, the reaction of twelve pyrazines **1a,b-6a,b** with acetic anhydride will be described. The reaction of compounds **1a,b**, **3a,b** and **6a,b** was carried out under reflux and the ones of the others at a higher temperature in a sealed tube. Namely, the compounds carrying an unsubstituted position adjacent to the *N*-oxide group were submitted to the acetoxylation under milder conditions. The acetoxylation occurred at the unsubstituted position of the pyrazine ring and, moreover, the chlorine atoms of compounds **2a,b** and **3a,b** were replaced by the acetoxyl groups. As shown in Table II, main products were 2-acetoxy-3,6-diisopropyl- (**10a**) [11], 2-acetoxy-3,6-di-*sec*-butyl- (**10b**), 2,5-diacetoxy-3,6-diisopropyl- (**11a**) and 2,5-diacetoxy-3,6-di-*sec*-butylpyrazines (**11b**). Interestingly, 2-chloro-3,6-diisopropylpyrazine 1-oxide (**2a**) [8] carrying a chlorine atom adjacent to the *N*-oxide group gave four products, **11a**, 2-acetoxy-5-chloro-3,6-diisopropylpyrazine (**12**) [11], 2-acetoxy-6-isopropenyl-3-isopropylpyrazine (**13**) and 2-acetoxy-3-isopropenyl-6-isopropylpyrazine (**14**).

These results indicated that the acetoxylation may occur on the isopropyl side chain of the restricted 2,5-diisopropylpyrazine 1-oxides. The structure determination of **13** and **14** was made as follows. By the catalytic reduction with Raney-nickel, 2-hydroxy-6-(α-hydroxy)isopropyl-3-isopropylpyrazine 1-oxide (**17**) [9] was transformed to 2-hydroxy-6-(α-hydroxy)isopropyl-3-isopropylpyrazine (**18**), which was dehydrated under heating in the presence of potassium bisulfate. The product was completely consistent with the compound **15** derived from **13** by an alkaline hydrolysis. The structure of **14** was thus deductively determined. Compound **16**, an isomer of 2-hydroxy-6-isopropenyl-3-isopropylpyrazine (**15**), was also obtained by an alkaline hydrolysis of **14**.

Table II

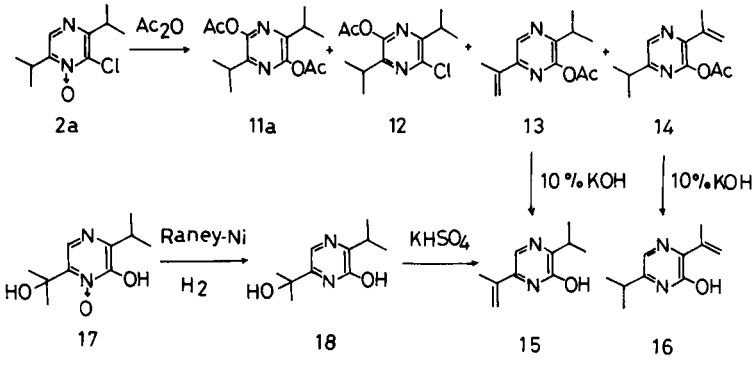
Reaction of Pyrazine *N*-Oxides **1a,b-6a,b** with Acetic Anhydride

Substrate	Reaction Temperature	Reaction Time (hours)	Product	Yield (%)
1a [6]	reflux	2	**10a** [11]	99
1b [7]	reflux	2	**10b**	96
2a [8]	210°	2	**11a**	52
			12 [11]	3
			13	24
			14	11
2b [9]	210°	2	**11b**	88
3a [10]	reflux	4	**11a**	88
			12 [11]	3
3b	reflux	4	**11b**	83
4a [8]	210°	2	**8a** [8]	3
			19	12
			20	24
4b	210°	2	recovered	
5a [8]	190°	2	**11a**	93
5b [9]	190°	2	**11b**	99
6a [11]	reflux	2	**11a**	78
6b	reflux	2	**11b**	77

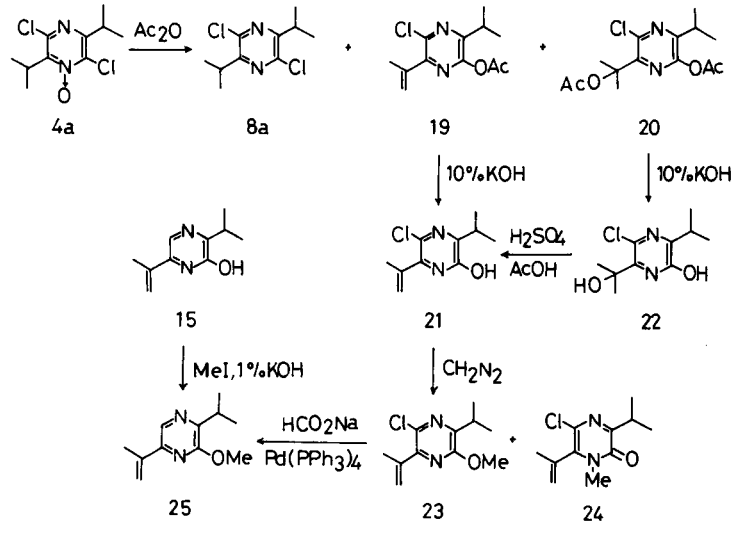
The reaction of 2,5-dichloro-3,6-diisopropylpyrazine 1-oxide (**4a**) afforded three products, **8a** [8], 2-acetoxy-5-chloro-6-isopropenyl-3-isopropylpyrazine (**19**) and 2-acetoxy-6-(α-acetoxy)isopropyl-5-chloro-3-isopropylpyrazine (**20**). Among the products, **8a** was perhaps formed by thermolysis, and the others by rearrangement of an acetoxyl group. The structure of **19** and **20** was determined on the basis of some reaction data, as shown in Scheme IV. By an alkaline hydrolysis of **19**, 5-chloro-2-hydroxy-6-isopropenyl-3-isopropylpyrazine (**21**) was obtained. This substance was also derived from **20** by hydrolysis and the following dehydration. By the treatment of **21** with diazomethane, two products, an *O*-methyl compound **23** and *N*-methyl one **24**, were obtained. The former was submitted to dechlorination [6], and the product was identified with the compound **25**, which was derived from **15** by methylation with methyl iodide. It is presumable that the chlorine atom adjacent to the *N*-oxide group was replaced by an acetoxyl group and that the acetoxylation occurred on the side chain near to the *N*-oxide group.

As mentioned above, some 2,5-diisopropyl- and 2,5-di-*sec*-butylpyrazine 1-oxides were subjected to the reaction with phosphoryl chloride and acetic anhydride in expecta-

Scheme III
Reaction of 2-Chloro-3,6-diisopropylpyrazine 1-Oxide (2a) with Acetic Anhydride



Scheme IV
Reaction of 2,5-Dichloro-3,6-diisopropyl-pyrazine 1-Oxide (4a) with Acetic Anhydride



tion of occurrence of chlorination and acetoxylation on the side chains near to the *N*-oxide group. In conclusion, the α-carbons of these alkyl groups were hardly affected by these reactions. Namely, chlorination and acetoxylation occurred mainly on the unsubstituted position in the pyrazine ring. Although the acetoxylation was observed to take place on the side chain in the case of some 2,5-diisopropylpyrazine 1-oxides carrying a chlorine atom adjacent to the *N*-oxide group, the reaction is thought to be of no utility value for organic syntheses, because of low yields.

EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro-melting point apparatus and are uncorrected. Boiling points are also uncorrected. The uv spectra were recorded in 95% ethanol using a Hitachi 557 spectrophotometer, ir spectra on Shimadzu IR-400 spectrometer and pmr spectra in deuteriochloroform using JEOL JNM-PS-100 and Varian EM-360 instruments with tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi M-80 spectrometer. For silica gel column chromatography, Wakogel C-200 (Wako Pure Chemical Industries, Ltd., Tokyo) was used. The hplc was carried out with a UVILOG ALPC-100 (Oyo-Bunko Kiki Co., Ltd., Tokyo) as a pump, a UVILOG 5 IIIA as a detector and Kieselgel 60 (Merck AG, Darmstadt) as a packing material.

2-Chloro-3,6-di-*sec*-butylpyrazine 4-Oxide (**3b**).

A solution of **7b** (11.325 g, 0.05 mole), 90% hydrogen peroxide (2.280 g, 0.06 mole) and maleic anhydride (6.680 g, 0.07 mole) in chloroform (100 ml) was allowed to stand overnight at room temperature and then refluxed for 2 hours. The reaction mixture was washed with water, 10% potassium bicarbonate and water, successively. After the organic layer was dried with sodium sulfate, the solvent was distilled *in vacuo* to leave a pale yellow oil (*ca.* 11 g), which was chromatographed on silica gel (50 g)

eluting with hexane and methylene chloride, successively. From the hexane fractions the starting material (3.871 g, 34%) was recovered. Methylene chloride eluted **3b** as a colorless oil (6.370 g, 53%), which was distilled to furnish a colorless oil, bp 112°/3 torr; uv: λ max 210 (log ε = 4.21), 230.5 (4.28), 274-276 (4.03), 302.5-303.5 (3.58, shoulder) nm; pmr: δ 0.85 (6H, t, J = 6 Hz, 2 × $CH(CH_3)CH_2CH_3$), 1.25 (3H, d, J = 6 Hz, $CH(CH_3)CH_2CH_3$), 1.39 (3H, d, J = 6 Hz, $CH(CH_3)CH_2CH_3$), 1.53-2.25 (4H, m, 2 × $CH(CH_3)CH_2CH_3$), 2.50-2.83 (1H, m, $CH(CH_3)CH_2CH_3$), 3.52-3.91 (1H, m, $CH(CH_3)CH_2CH_3$), 7.93 (1H, s, pyrazine H) ppm; ms: m/e 243 (M^+ + 1), 225 (M^+ - OH).

Anal. Calcd. for $C_{12}H_{19}ClN_2O$: C, 59.37; H, 7.89; N, 11.54. Found: C, 59.58; H, 7.87; N, 11.60.

3,6-Di-*sec*-butyl-2-hydroxypyrazine 4-Oxide (**6b**).

A solution of 3,6-di-*sec*-butyl-2-hydroxypyrazine (2.080 g, 10 mmoles), 90% hydrogen peroxide (570 mg, 15 mmoles) and maleic anhydride (1.740 g, 18 mmoles) in chloroform (100 ml) was allowed to stand overnight and then refluxed for 2 hours. The same work up as before gave a pale yellow solid (2.040 g), which was recrystallized from cyclohexane to furnish colorless prisms (1.898 g, 85%), mp 232° dec; uv: λ max 228-232 (log ε = 4.21), 277 (3.78), 328-334 (3.84) nm; ir (potassium bromide): 1620 cm^{-1} (C=O); pmr: δ 0.98 (6H, t, J = 8 Hz, 2 × $CH(CH_3)CH_2CH_3$), 1.34 (3H, d, J = 8 Hz, $CH(CH_3)CH_2CH_3$), 1.42 (3H, d, J = 8 Hz, $CH(CH_3)CH_2CH_3$), 1.60-2.22 (4H, m, 2 × $CH(CH_3)CH_2CH_3$), 2.42-2.65 (1H, m, $CH(CH_3)CH_2CH_3$), 3.64-3.87 (1H, m, $CH(CH_3)CH_2CH_3$), 7.12 (1H, s, pyrazine H), 13.00 (1H, broad s, OH) ppm; ms: m/e 224 (M^+), 207 (M^+ -OH).

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 63.97; H, 8.99; N, 12.25.

2,5-Dichloro-3,6-di-*sec*-butylpyrazine 1-Oxide (**4b**).

A solution of **8b** (5.220 g, 0.02 mole) and potassium persulfate (8.109 g, 0.03 mole) in concentrated sulfuric acid (30 ml) was stirred overnight at room temperature and then diluted with ice-water (100 ml). The solution was extracted with chloroform and the organic layer was washed with 5% sodium bicarbonate. After being dried with sodium sulfate, the solvent was removed by distillation to leave a pale yellow semi-solid (*ca.* 5.5 g), which was purified by column chromatography on silica gel (100 g), eluting with hexane containing an increasing amount of ether. Hexane eluted the starting material (2.088 g, 40%) and the hexane-ether (4:1) fractions gave **4b** (3.287 g, 59%) as a colorless solid, which was recrystallized from methanol to furnish colorless needles, mp 104-105°; uv: λ max 218.5 (log ε = 4.18), 241.5 (4.25), 276-279 (3.88), 311-322 (3.47) nm; pmr: δ 0.87 (6H, t, J = 7 Hz, 2 × $CH(CH_3)CH_2CH_3$), 1.27 (3H, d, J = 7 Hz, $CH(CH_3)CH_2CH_3$), 1.41 (3H, d, J = 7 Hz, $CH(CH_3)CH_2CH_3$), 1.57-2.40 (4H, m, 2 × $CH(CH_3)CH_2CH_3$), 3.03-3.75 (2H, m, 2 × $CH(CH_3)CH_2CH_3$), ppm; ms: m/e 277 (M^+ + 1), 259 (M^+ - OH).

Anal. Calcd. for $C_{12}H_{18}Cl_2N_2O$: C, 51.99; H, 6.55; N, 10.11. Found: C, 52.22; H, 6.57; N, 10.10.

2,5-Di-*sec*-butylpyrazine 1-Oxide (**1b**).

A mixture of **3b** (484 mg, 2 mmoles), sodium formate (272 mg, 4 mmoles), tetrakis(triphenylphosphine)palladium (117 mg, 0.1 mmole) and dimethylformamide (10 ml) was heated at 100° for 2 hours. The solvent was removed by distillation *in vacuo* and the residue was extracted with ether to give a brown oil, which was chromatographed on silica gel (10 g) eluted with hexane containing an increasing amount of ether. The hexane-ether (9:1) fractions gave a small amount of the starting material and a 4:1 mixture eluted **1b** (386 mg, 93%) as a pale yellow oil, which was purified by distillation to furnish a colorless oil, bp 116°/3 torr (bath temperature); uv: λ max 225 (log ε = 4.24), 268 (4.01) nm; pmr: δ 0.87 (3H, t, J = 7 Hz, $CH(CH_3)CH_2CH_3$), 0.91 (3H, t, J = 7 Hz, $CH(CH_3)CH_2CH_3$), 1.27 (3H, d, J = 7 Hz, $CH(CH_3)CH_2CH_3$), 1.30 (3H, d, J = 7 Hz, $CH(CH_3)CH_2CH_3$), 1.47-2.15 (4H, m, 2 × $CH(CH_3)CH_2CH_3$), 2.44-3.03 (1H, m, $CH(CH_3)CH_2CH_3$), 3.20-3.80 (1H, m, $CH(CH_3)CH_2CH_3$), 8.20 (1H, s, pyrazine H), 8.53 (1H, s, pyrazine H) ppm; ms: m/e 208 (M^+), 193 (M^+ -CH_3), 191(M^+ -OH).

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.20; H, 9.67; N, 13.57.

General Procedure for Reaction of Pyrazine *N*-Oxides **1a,b-6a,b** with Phosphoryl Chloride.

A pyrazine *N*-oxide (2 mmoles) was heated with phosphoryl chloride (5 ml) under the conditions as shown in Table I, and then poured into ice-water. The reaction mixture was made alkaline with powdered potassium carbonate and extracted with ether to give a solid or oil, which was purified by column chromatography on silica gel (10 g), eluting with hexane containing an increasing amount of ether. All the products were identified by comparing the ir spectra with the ones of the authentic specimens.

General Procedure for Reaction of Pyrazine *N*-Oxides **1a,b, 2b, 3b, 4b, 5a,b**, and **6a,b** with Acetic Anhydride.

A solution of pyrazine *N*-oxide (2 mmoles) in acetic anhydride (5 ml) was heated under the conditions as illustrated in Table II, and then treated with ice-water. The reaction mixture was made alkaline with powdered potassium carbonate and extracted with ether to give a pale yellow solid or oil, which was purified by column chromatography on silica gel (10 g), eluting with hexane containing an increasing amount of methylene chloride.

2-Acetoxy-3,6-di-*sec*-butylpyrazine (**10b**).

This compound had the following physical properties: colorless oil, bp 85-87°/0.5 torr; uv: λ max 276 (log ε = 4.25), 290-299 (3.84, shoulder) nm; ir (liquid film): 1785 cm^{-1} (C=O); pmr: δ 0.82 (3H, t, J = 7.5 Hz, $CH(CH_3)CH_2CH_3$), 0.86 (3H, t, J = 7.5 Hz, $CH(CH_3)CH_2CH_3$), 1.23 (3H, d, J = 6.5 Hz, $CH(CH_3)CH_2CH_3$), 1.30 (3H, d, J = 6.5 Hz, $CH(CH_3)CH_2CH_3$), 1.45-2.00 (4H, m, J = 7.5 Hz, 2 × $CH(CH_3)CH_2CH_3$), 2.37 (3H, s, $COCH_3$), 2.62-3.07 (2H, m, J = 6.5 Hz, 2 × $CH(CH_3)CH_2CH_3$), 8.38 (1H, s, pyrazine H) ppm; ms: m/e 250 (M^+).

Anal. Calcd. for $C_{14}H_{22}N_2O_2$: C, 67.12; H, 8.86; N, 11.19. Found: C, 66.80; H, 8.97; N, 11.16.

2,5-Diacetoxy-3,6-diisopropylpyrazine (**11a**).

This compound had the following physical properties: colorless needles (from hexane), mp 157-159°; uv: λ max 272 (log ε = 3.88), 285 (3.90) nm; ir (potassium bromide): 1770 cm^{-1} (C=O); pmr: δ 1.20 (12H, d, J = 7 Hz, 2 × $CH(CH_3)_2$), 2.36 (6H, s, 2 × $COCH_3$), 3.04 (2H, m, J = 7 Hz, 2 × $CH(CH_3)_2$) ppm; ms: m/e 280 (M^+), 238 (M^+ -CH_2CO), 196 (M^+ - 2 × CH_2CO).

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 59.98; H, 7.36; N, 10.21.

2,5-Diacetoxy-3,6-di-*sec*-butylpyrazine (**11b**).

This compound had the following physical properties: colorless needles (from hexane), mp 103-104°; uv: λ max 274 (log ε = 3.91), 286 (3.92) nm; ir (potassium bromide): 1770 cm^{-1} (C=O); pmr: δ 0.80 (6H, t, J = 7 Hz, 2 × $CH(CH_3)CH_2CH_3$), 1.18 (6H, d, J = 7 Hz, 2 × $CH(CH_3)CH_2CH_3$), 1.66 (4H, m, 2 × $CH(CH_3)CH_2CH_3$), 2.33 (6H, s, 2 × $COCH_3$), 2.78 (2H, m, 2 × $CH(CH_3)CH_2CH_3$) ppm; ms: m/e 308 (M^+), 226 (M^+ -CH_2CO), 224 (M^+ - 2 × CH_2CO).

Anal. Calcd. for $C_{16}H_{24}N_2O_4$: C, 62.31; H, 7.85; N, 9.09. Found: C, 62.55; H, 7.91; N, 9.02.

Reaction of 2-Chloro-3,6-diisopropylpyrazine 1-Oxide (**2a**) with Acetic Anhydride.

A mixture of **2a** (4.290 g, 20 mmoles) and acetic anhydride (40 ml) was heated at 210° for 2 hours in a sealed tube and then concentrated to dryness *in vacuo*. The resulting semi-solid was chromatographed on silica gel (32 g) and eluted with a mixture of hexane and methylene chloride. The fractions eluted with a 50:1 mixture gave **12** (256 mg, 3%) as a colorless oil. A 1:1 mixture eluted a mixture of **13** and **14** (*ca.* 1.6 g) as a colorless oil, and the methylene chloride fractions gave **11a** (2.900 g, 52%) as a colorless solid. Separation of **13** and **14** was achieved by preparative

hplc. The mixture of **13** and **14** was directly injected to the top of the silica gel column, 50 cm × 25 mm, and the flow rate of a hexane-tetrahydrofuran (10:1 v/v) mixture was 32 ml/minute under a pressure of 3 kg/cm². The peaks of **13** and **14** were monitored with a uv detector at 282 nm. The yields of **13** and **14** were 1.06 g (24%) and 498 mg (11%), respectively.

2-Acetoxy-6-isopropenyl-3-isopropylpyrazine (**13**).

This compound had the following physical properties: colorless oil, bp 90°/1 torr; uv: λ max 235 (log ε = 4.00), 287 (3.87) nm; ir (liquid film): 1785 cm^{-1} (C=O); pmr: δ 1.25 (6H, d, J = 8 Hz, $CH(CH_3)_2$), 2.16 (3H, m, J = 1 Hz, $C(CH_3)=CH_2$), 2.35 (3H, s, $COCH_3$), 3.10 (1H, m, J = 8 Hz, $CH(CH_3)_2$), 5.34 (1H, q, J = 1 Hz, $C(CH_3)=CH_2$), 5.90 (1H, s, $C(CH_3)=CH_2$), 8.62 (1H, s, pyrazine H) ppm; ms: m/e 220 (M^+), 178 ($M^+ -CH_2CO$).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.19; H, 7.39; N, 12.69.

2-Acetoxy-3-isopropenyl-6-isopropylpyrazine (**14**).

This compound had the following physical properties: colorless oil, bp 121-124°/2 torr (bath temperature); uv: λ max 228 (log ε = 3.98), 282 (3.97) 299 (3.88, shoulder) nm; ir (liquid film): 1780 cm^{-1} (C=O); pmr: δ 1.32 (6H, d, J = 7 Hz, $CH(CH_3)_2$), 2.17 (3H, dd, J = 2 and 1 Hz, $C(CH_3)=CH_2$), 2.30 (3H, s, $COCH_3$), 3.10 (1H, m, J = 7 Hz, $CH(CH_3)_2$), 5.43 (1H, q, J = 2 Hz, $C(CH_3)=CH_2$), 5.53 (1H, q, J = 1 Hz, $C(CH_3)=CH_2$), 8.40 (1H, s, pyrazine H) ppm; ms: m/e 220 (M^+), 178 ($M^+ -CH_2CO$), 163 ($M^+ -CH_2CO-CH_3$).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.13; H, 7.34; N, 12.67.

Hydrolysis of 2-Acetoxy-6-isopropenyl-3-isopropylpyrazine (**13**).

A solution of **13** (534 mg, 2.4 mmoles) in a mixture of 10% potassium hydroxide (8 ml) and methanol (8 ml) was stirred at room temperature for 4 hours, and then concentrated to dryness *in vacuo*. The residue was triturated with water (5 ml) and extracted with ether. The water layer was acidified with 10% hydrochloric acid, again made alkaline with 10% potassium bicarbonate, and then extracted with methylene chloride. After being dried with sodium sulfate, the solvent was removed by distillation to give **15** (741 mg, 94%) as a slightly yellow solid, which was recrystallized from methanol to furnish pale yellow prisms, mp 113-114°; uv: λ max 239 (log ε = 4.03), 335 (4.04); nm; ir (potassium bromide): 1650 cm^{-1} (C=O); pmr: δ 1.30 (6H, d, J = 8 Hz, $CH(CH_3)_2$), 2.23 (3H, d, J = 1 Hz, $C(CH_3)=CH_2$), 3.43 (1H, m, J = 8 Hz, $CH(CH_3)_2$), 5.37 (1H, q, J = 1 Hz, $C(CH_3)=CH_2$), 5.93 (1H, s, $C(CH_3)=CH_2$), 7.45 (1H, s, pyrazine H) ppm; ms: m/e 178 (M^+), 163 ($M^+ -CH_3$).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.39; H, 7.95; N, 15.66.

Hydrolysis of 2-Acetoxy-3-isopropenyl-6-isopropylpyrazine (**14**).

A solution of **14** (375 mg, 1.7 mmoles) in a mixture of 10% potassium hydroxide (8 ml) and methanol (8 ml) was stirred at room temperature for 2 hours, and then concentrated to dryness *in vacuo*. The working up of the residue was the same as described above and afforded **16** (276 mg, 91%) as a yellow solid, which was recrystallized from methanol to furnish pale yellow prisms, mp 143-144°; uv: λ max 243 (log ε = 3.62), 341 (3.84); nm; ir (potassium bromide): 1640 cm^{-1} (C=O); pmr: δ 1.33 (6H, d, J = 7 Hz, $CH(CH_3)_2$), 2.15 (3H, dd, J = 2 and 1 Hz, $C(CH_3)=CH_2$), 2.90 (1H, m, J = 7 Hz, $CH(CH_3)_2$), 5.63 (1H, m, J = 1 Hz, $C(CH_3)=CH_2$), 6.77 (1H, m, J = 2 Hz, $C(CH_3)=CH_2$), 7.38 (1H, pyrazine H) ppm; ms: m/e 178 (M^+), 163 ($M^+ -CH_3$).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.15; H, 7.97; N, 15.63.

Reduction of 2-Hydroxy-6-(α-hydroxy)isopropyl-3-isopropylpyrazine 1-Oxide (**17**).

A suspension of **17** (177 mg, 1 mmole) and Raney-nickel, prepared from nickel-aluminum alloy (1 g), in ethanol (20 ml) was shaken under hydrogen at 3 kg/cm² at room temperature for 8 hours. After removal of the catalyst by filtration, the solution was concentrated *in vacuo* to leave a slightly green solid, which was recrystallized from ethyl acetate to furnish **18** (145 mg, 89%) as colorless prisms, mp 168-169°; uv: λ max 225 (log ε = 3.86), 315 (3.87) nm; ir (potassium bromide): 1640 cm^{-1} (C=O); pmr: δ 1.20 (6H, d, J = 7 Hz, $CH(CH_3)_2$), 1.62 (6H, s, $C(OH)(CH_3)_2$), 3.38 (1H, m, J = 7 Hz, $CH(CH_3)_2$), 4.68 (1H, broad s, $C(OH)(CH_3)_2$), 7.37 (1H, s, pyrazine H) ppm; ms: m/e 196 (M^+), 181 ($M^+ -CH_3$).

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.11; H, 8.27; N, 14.12.

Dehydration of 2-Hydroxy-6-(α-hydroxy)isopropyl-3-isopropylpyrazine (**18**).

A mixture of **18** (30 mg, 0.15 mmole) and potassium bisulfate (48 mg, 0.35 mmole) was heated at 170° for 2 hours, triturated with water (1 ml) and then extracted with ethyl acetate. Removal of the solvent by distillation *in vacuo* left a brownish yellow solid (30 mg), which was chromatographed on silica gel (6 g). Elution with a mixture of chloroform and ethyl acetate (2:1) gave **15** (18 mg, 66%) as a pale yellow solid, which was recrystallized from methanol to furnish pale yellow prisms, mp 112-113°.

Reaction of 2-Chloro-3,6-diisopropylpyrazine 4-Oxide (**3a**) with Acetic Anhydride.

A solution of **3a** (1.073 g, 5 mmoles) in acetic anhydride (10 ml) was refluxed for 4 hours, and then concentrated to dryness under reduced pressure. The resulting solid was chromatographed on silica gel (33 g), eluting with hexane containing an increasing amount of methylene chloride. The fractions eluted with hexane gave **12** (36 mg, 3%) as a colorless oil, and the fractions eluted with a mixture of hexane and methylene chloride (1:1) yielded **11a** (1.232 g, 88%) as a colorless solid. The starting material (**3a**) (65 mg, 6%) was recovered from the methylene chloride fractions.

Reaction of 2,5-Dichloro-3,6-diisopropylpyrazine 1-Oxide (**4a**) with Acetic Anhydride.

A solution of **4a** (4.980 g, 23 mmoles) in acetic anhydride (50 ml) was heated in a sealed tube at 210° for 2 hours on an oil bath. After cooling, the reaction mixture was poured into crushed ice, made alkaline with powdered potassium carbonate, and extracted with ether. The ether layer was worked up as usual to give a dark brown oil, which was chromatographed on silica gel (100 g) and eluted with hexane containing an increasing amount of ether. Hexane eluted **8a** (136 mg, 3%), a mixture of hexane and ether (20:1) recovered the starting material (**4a**) (2.140 g, 43%), the 15:1 fractions gave **19** (709 mg, 12%), and the 10:1 fractions gave **20** (1.760 g, 24%).

2-Acetoxy-5-chloro-6-isopropenyl-3-isopropylpyrazine (**19**).

This compound had the following physical properties: colorless oil, bp 107°/2 torr (bath temperature); uv: λ max 217 (log ε = 3.94), 297 (3.97) nm; ir (liquid film): 1780 cm^{-1} (C=O); pmr: δ 1.22 (6H, d, J = 7 Hz, $CH(CH_3)_2$), 2.12 (3H, broad s, $C(CH_3)=CH_2$), 2.33 (3H, s, $COCH_3$), 3.07 (1H, m, J = 7 Hz, $CH(CH_3)_2$), 5.53 (2H, broad s, $C(CH_3)=CH_2$) ppm; ms: m/e 254 (M^+), 212 ($M^+ -CH_2CO$), 197 ($M^+ -CH_2CO-CH_3$).

Anal. Calcd. for $C_{12}H_{15}ClN_2O_2$: C, 56.58; H, 5.94; N, 11.00. Found: C, 56.66; H, 6.03; N, 10.97.

2-Acetoxy-6-(α-acetoxy)isopropyl-5-chloro-3-isopropylpyrazine (**20**).

This compound had the following physical properties: colorless needles (from hexane), mp 87-88°; uv: λ max 216.5 (log ε = 3.79), 276 (3.64), 290 (3.68) nm; ir (potassium bromide): 1740, 1780 cm^{-1} (C=O); pmr: δ 1.23 (6H, d, J = 7 Hz, $CH(CH_3)_2$), 1.77 (6H, s, $C(CH_3)_2COCH_3$), 2.07 (3H, s, $COCH_3$), 2.33 (3H, s, $COCH_3$), 3.03 (1H, m, J = 7 Hz, $CH(CH_3)_2$) ppm; ms: m/e 314 (M^+), 195 (M^+ -Cl-2 × CH_2CO).

Anal. Calcd. for $C_{14}H_{19}ClN_2O_4$: C, 53.42; H, 6.08; N, 8.90. Found: C, 53.67; H, 6.12; N, 8.89.

Hydrolysis of 2-Acetoxy-5-chloro-6-isopropenyl-3-isopropylpyrazine (**19**).

A solution of **19** (508 mg, 2 mmoles) in a mixture of 10% potassium hydroxide (5 ml) and methanol (5 ml) was stirred for 4 hours at room tempe-

rature and then concentrated to dryness *in vacuo*. The residual solid was triturated with water (5 ml), acidified with 10% hydrochloric acid, again made alkaline with powdered potassium bicarbonate, and then extracted with methylene chloride to give **21** (425 mg, 100%) as a yellow solid, which was recrystallized from methanol to furnish slightly yellow prisms, mp 189-190°; uv: λ max 238 (log ε = 3.71), 317 (3.70), 344 (3.61, shoulder) nm; ir (potassium bromide): 1620 cm^{-1} (C=O); pmr: δ 1.23 (6H, d, J = 7 Hz, $CH(CH_3)_2$), 2.15 (3H, d, J = 1 Hz, $C(CH_3)=CH_2$), 3.33 (1H, m, J = 7 Hz, $CH(CH_3)_2$), 5.40 (1H, broad s, $C(CH_3)=CH_2$), 5.50 (1H, q, J = 1 Hz, $C(CH_3)=CH_2$), ppm; ms: m/e 212 (M^+), 197 ($M^+ - CH_3$).

Anal. Calcd. for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.18; H, 6.11; N, 13.07.

Hydrolysis of 2-Acetoxy-6-(α-acetoxy)isopropyl-5-chloro-3-isopropylpyrazine (**20**).

A solution of **20** (499 mg, 1.6 mmoles) in a mixture of 10% potassium hydroxide (5 ml) and methanol (5 ml) was stirred for 3 hours at room temperature and then worked up as before to give **22** (360 mg, 98%) as a yellow solid, which was recrystallized from hexane to furnish slightly yellow prisms, mp 131-132°; uv: λ max 237 (log ε = 3.68), 328 (3.59) nm; ir (potassium bromide): 1630 cm^{-1} (C=O), 3300 (OH); pmr: δ 1.22 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.73 (6H, s, $C(OH)(CH_3)_2$), 3.33 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 4.68 (1H, broad s, $C(OH)(CH_3)_2$) ppm; ms: m/e 230 (M^+), 215 ($M^+ - CH_3$).

Anal. Calcd. for $C_{10}H_{15}ClN_2O_2$: C, 52.06; H, 6.55; N, 12.14. Found: C, 51.99; H, 6.56; N, 12.19.

Dehydration of 5-Chloro-2-hydroxy-6-(α-hydroxy)isopropyl-3-iospropylpyrazine (**22**).

After a solution of **22** (236 mg, 1 mmole) in a mixture of concentrated sulfuric acid (0.2 ml) and acetic acid (0.8 ml) was heated at 70° for 2 hours on a water bath, the reaction mixture was made alkaline with 10% potassium bicarbonate and extracted with methylene chloride to give **21** (180 mg, 83%) as a yellow solid, which was recrystallized from methanol to furnish pale yellow prisms, mp 187-189°.

Methylation of 5-Chloro-2-hydroxy-6-isopropenyl-3-isopropylpyrazine (**21**) with Diazomethane.

An ether solution (50 ml) of diazomethane, prepared from *N*-nitroso-*N*-methylurea (1.03 g, 10 mmoles), was added to a solution of **21** (1.063 g, 5 mmoles) in ether (30 ml), and the reaction mixture was allowed to stand for 2 hours at room temperature. Removal of the ether by distillation resulted in giving a slightly yellow oil (1.101 g), which was chromatographed on silica gel (10 g) and eluted with hexane containing an increasing amount of ether. The fractions eluted with a mixture of hexane and ether (9:1) afforded **23** (548 mg, 48%) as a colorless oil, and the ether fractions gave **24** (463 mg, 41%) as a colorless solid.

5-Chloro-6-isopropenyl-3-isopropyl-2-methoxypyrazine (**23**).

This compound had the following physical properties: colorless oil, bp 75°/1.5 torr (bath temperature); uv: λ max 227 (log ε = 3.92) nm; pmr: δ 1.25 (6H, d, J = 8 Hz, $CH(CH_3)_2$), 2.20 (3H, d, J = 1 Hz, $C(CH_3)=CH_2$), 3.31 (1H, m, J = 8 Hz, $CH(CH_3)_2$), 3.97 (3H, s, OCH_3), 5.53 (1H, q, J = 1 Hz, $C(CH_3)=CH_2$), 5.62 (1H, s, $C(CH_3)=CH_2$) ppm; ms: m/e 226 (M^+), 211 ($M^+ - CH_3$).

Anal. Calcd. for $C_{11}H_{15}ClN_2O$: C, 58.28; H, 6.67; N, 12.36. Found: C, 58.04; H, 6.92; N, 12.19.

5-Chloro-1,2-dihydro-6-isopropenyl-3-isopropyl-1-methyl-2-pyrazinone (**24**).

This compound had the following physical properties: colorless prisms, mp 60-61° (from hexane); uv: λ max 236.5 (log ε = 3.86), 336 (3.88) nm; ir (potassium bromide): 1640 cm^{-1} (C=O); pmr: δ 1.26 (6H, d, J = 8 Hz, $CH(CH_3)_2$), 2.08 (3H, m, J = 1 Hz, $C(CH_3)=CH_2$), 3.50 (3H, s, NCH_3), 3.51 (1H, m, J = 7 Hz, $CH(CH_3)_2$), 5.26 (1H, broad s, $C(CH_3)=CH_2$), 5.62 (1H, q, J = 1 Hz, $C(CH_3)=CH_2$) ppm; ms: m/e 226 (M^+), 211 ($M^+ - CH_3$).

Anal. Calcd. for $C_{11}H_{15}ClN_2O$: C, 58.28; H, 6.67; N, 12.36. Found: C, 58.02; H, 6.65; N, 12.64.

Dechlorination of 5-Chloro-6-isopropenyl-3-isopropyl-2-methoxypyrazine (**23**).

A suspension of **23** (226 mg, 1 mmole), sodium formate (84 mg, 1.2 mmoles), and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmole) in *N,N*-dimethylformamide (5 ml) was heated at 75° for one hour under stirring. The reaction mixture was exhaustively extracted with hexane to give an oil (*ca.* 200 mg), which was chromatographed on silica gel (3 g), eluting with a mixture of hexane and benzene. A 19:1 mixture recovered the starting material (**23**) (159 mg, 70%) and the 9:1 fractions gave **25** (29 mg, 15%) as a colorless oil, bp 77-79°/1 torr (bath temperature); uv: λ max 238 (log ε = 4.17), 309 (4.17) nm; pmr: δ 1.23 (6H, d, J = 8 Hz, $CH(CH_3)_2$), 2.13 (3H, d, J = 1 Hz, $C(CH_3)=CH_2$), 3.33 (1H, m, J = 8 Hz, $CH(CH_3)_2$), 3.93 (3H, s, OCH_3), 5.20 (1H, q, J = 1 Hz, $C(CH_3)=CH_2$), 5.93 (1H, broad s, $C(CH_3)=CH_2$), 8.20 (1H, s, pyrazine H) ppm; ms: m/e 178 (M^+), 163 ($M^+ - CH_3$).

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.71; H, 8.46; N, 14.37.

Methylation of 2-Hydroxy-6-isopropenyl-3-isopropylpyrazine (**15**) with Methyl Iodide.

To a solution of **15** (90 mg, 0.5 mmole) and tetrabutylammonium hydrogensulfate (10 mg) in 1% sodium hydroxide (5 ml), a solution of methyl iodide (0.5 ml) in ether (10 ml) was added, and the mixture was stirred at room temperature for 2 hours. The ether layer was separated and dried over sodium sulfate. Removal of the solvent by distillation resulted in giving **25** (75 mg, 77%) as a colorless oil, which was purified by distillation at 80°/1 torr.

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