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Syntheses and Reactions of Chloro-2-isopropyl-5-isobutylpyrazines Syntheses of Deoxymutaaspergillic Acid and 2-Hydroxy-3-isobutyl-6-isopropylpyrazine 1-Oxide

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DL-Valyl-leucyl anhydride (III) was converted to mono- and di-chloro-isopropyl-isobutylpyrazines by treatment with phosphoryl chloride. These mono-chloropyrazines (VII and VIII) were oxidized and the products were converted to 2-isobutyl-5-isopropylpyrazine 1- and 4-oxides (XIV and XV) *via* hydrazino compounds. On the other hand, starting from 2-chloro-3-isobutyl-6-isopropylpyrazine (VII), two fungal metabolites, deoxymutaaspergillic acid (I) and 2-hydroxy-3-isobutyl-6-isopropylpyrazine 1-oxide (II), were prepared.

Keywords——deoxymutaaspergillic acid; 2-hydroxy-3-isobutyl-6-isopropylpyrazine 1-oxide; pyrazine; pyrazinol; hydroxamic acid; *Aspergillus sojae*

A considerable number of pyrazinol derivatives has been isolated as fungal metabolites from Aspergillaceae.[2,3] Some of the pyrazinol metabolites are characteristic of the powerful antibiotic action, and the hydroxamic group is essential for the antibiotic behavior.[4] We have already reported the synthesis of some naturally occurring pyrazinols[5–7] and, in relation to this work, we have investigated on the syntheses of mono- and di-chloro-2-isopropyl-5-isobutylpyrazines, starting from DL-valyl-leucyl anhydride (III).[8] We now wish to report the results and especially describe the syntheses of deoxymutaaspergillic acid (I) and 2-hydroxy-3-isobutyl-6-isopropylpyrazine 1-oxide (II), isolated from *Aspergillus sojae*,[9] starting from 2-chloro-3-isobutyl-6-isopropylpyrazine (VII).

The synthesis of aspergillic acid started with dehydration of DL-leucyl-isoleucyl anhydride (IV)[8] in chloroform, using phosphoryl chloride, and 2-hydroxy-3-sec-butyl-6-isobutylpyrazine (V) was obtained in about 34% yield.[7] In the present work, we tried to find the optimum condition for dehydration of III with phosphoryl chloride and preparation of either of two hydroxypyrazines, I and 2-hydroxy-3-isopropyl-6-isobutylpyrazine (XI), but we merely obtained a mixture of the two compounds, which could not be separated from each other. Therefore, III was heated with phosphoryl chloride under reflux and an oily product was carefully chromatographed over silica gel to give 2,5-dichloro-3-isobutyl-6-isopropylpyrazine (VI), VII, and 2-chloro-3-isopropyl-6-isobutylpyrazine (VIII), by successive elution with hexane and ether. The structure of VI was elucidated on the basis of analytical data, and from mass and UV spectral data. The PMR (proton magnetic resonance) spectrum of VI did not indicate any signal according to protons on the pyrazine ring. However, the structure of the two isomeric monochloro compounds could not be clarified at this stage. Therefore,

1) Location: *1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan.*
2) P.G. Sammes, "Fortschritte der Chemie Organischer Naturstoffe," Springer-Verlag, Wien, 1975, p. 51.
3) W.B. Turner, "Fungal Metabolites," Academic Press, New York, 1971, p. 320.
4) J.B. Neilands, *Science*, **156**, 1443 (1967).
5) A. Ohta, *Chem. Pharm. Bull.* (Tokyo), **12**, 125 (1964).
6) A. Ohta, *Chem. Pharm. Bull.* (Tokyo), **16**, 1160 (1968).
7) A. Ohta and S. Fujii, *Chem. Pharm. Bull.* (Tokyo), **17**, 851 (1969).
8) E. Fischer and H. Scheibler, *Ann.*, **363**, 136 (1908).
9) M. Sasaki, Y. Asao, and T. Yokotsuka, *Nippon Nogeikagaku Kaishi*, **42**, 351 (1968).

both compounds were converted to pyrazinols, I and XI, respectively, *via* methoxyl derivatives, 2-methoxy-3-isobutyl-6-isopropylpyrazine (IX) and 2-methoxy-3-isopropyl-6-isobutylpyrazine (X). Because the pyrazinol (I), derived from VII, was identified with an authentic sample of deoxymutaaspergillic acid,[8] the structure of VII and VIII was elucidated, retrospectively. In PMR spectrum, the methine proton of isopropyl group in VII resonated at a higher field than that of VIII, whereas the methylene protons of isobutyl group in VII appeared in a lower field than that of VIII. These phenomena may be caused by an electron-withdrawing effect of the chlorine atom.

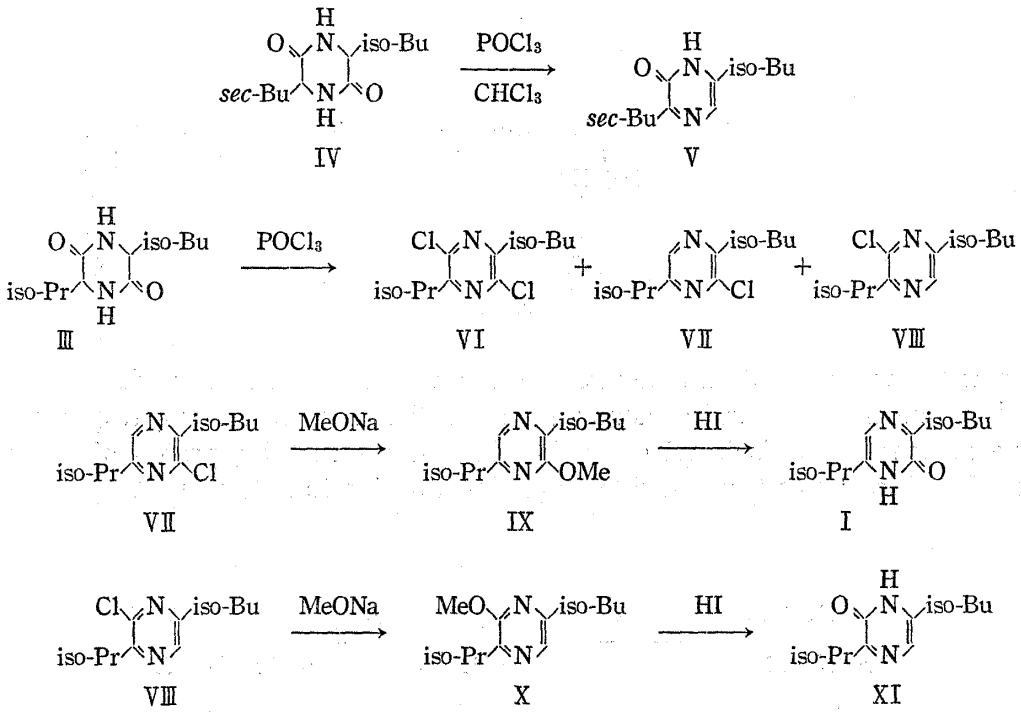
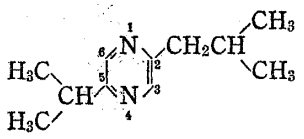


Chart 1

TABLE I. PMR Spectra of Chloro-isobutyl-isopropyrazines and Their Monoxides



	$CH_2CH(CH_3)_2$	$CH(CH_3)_2$	3-H	6-H
VII	2.80	3.04		8.30
XVI	2.92	2.94		7.92
VIII	2.58	3.44	8.16	
XVIII	2.50	3.92	7.84	

Compound (VI) was catalytically hydrogenolyzed in the presence of palladium-charcoal and sodium acetate to give 2-isopropyl-5-isobutylpyrazine (XII), which was then oxidized with permaleic acid. The products were carefully chromatographed over silica gel to afford a dioxide (XIII) and a mixture of two monoxides, 2-isobutyl-5-isopropylpyrazine 1-oxide (XIV) and 2-isobutyl-5-isopropylpyrazine 4-oxide (XV). In the PMR spectrum, the methylene protons of isobutyl group indicated that the mixture was composed of XIV and XV in 5: 1

ratio. However, two monoxides could not be separated, even by repeated column chromatography. Without further purification the mixture of XIV and XV was heated with phosphoryl chloride under reflux and afforded a mixture of VII and VIII. The formation ratio of VII and VIII was 1: 5, same as in the starting mixture of XIV and XV.

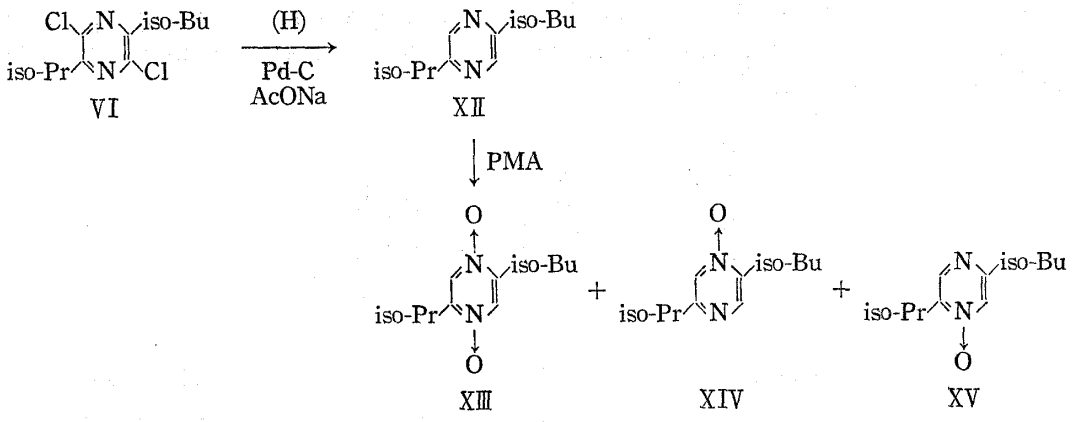


Chart 2

In order to prepare pure XIV and XV, VII and VIII were oxidized with permaleic acid in chloroform under reflux, and a monoxide and a dioxide were formed, respectively. The methylene protons of the isobutyl group in VII and the methine proton of the isopropyl group in VIII shifted to a lower field by mono-N-oxidation to XVI and XVIII, respectively.

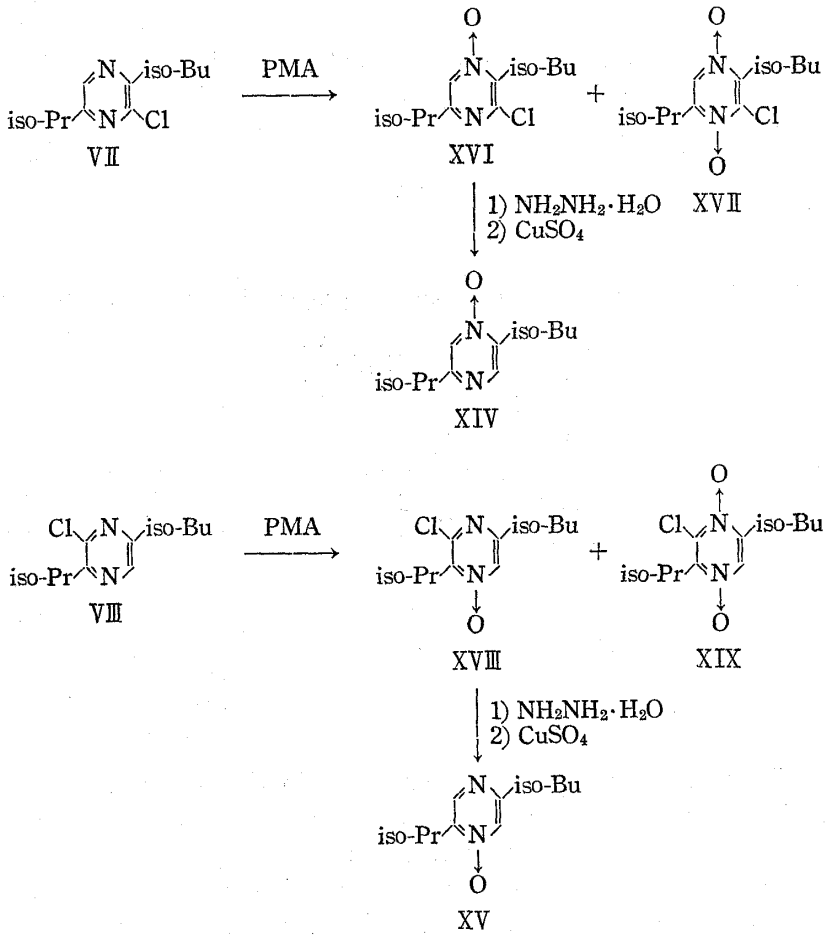
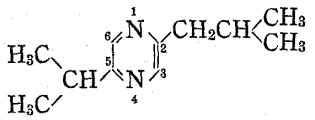


Chart 3

This observation was consistent with the case of 2,5-diisopropyl- and 2,5-diisobutyl-pyrazine 1-oxides.[10]

The monoxides, 2-chloro-3-isobutyl-6-isopropylpyrazine 4-oxide (XVI) and 2-chloro-3-isopropyl-6-isobutylpyrazine 4-oxide (XVIII), were dechlorinated *via* hydrazino compounds,

Table II. PMR Spectra of 2-Isobutyl-5-isopropylpyrazine (XII) and Its Monoxides (XIV and XV)



	$2CH_2$	5CH	3-H	6-H
XII	2.62	3.06	8.30	8.38
XIV	2.70	2.98	8.30	8.04
XV	2.56	3.60	7.98	8.36

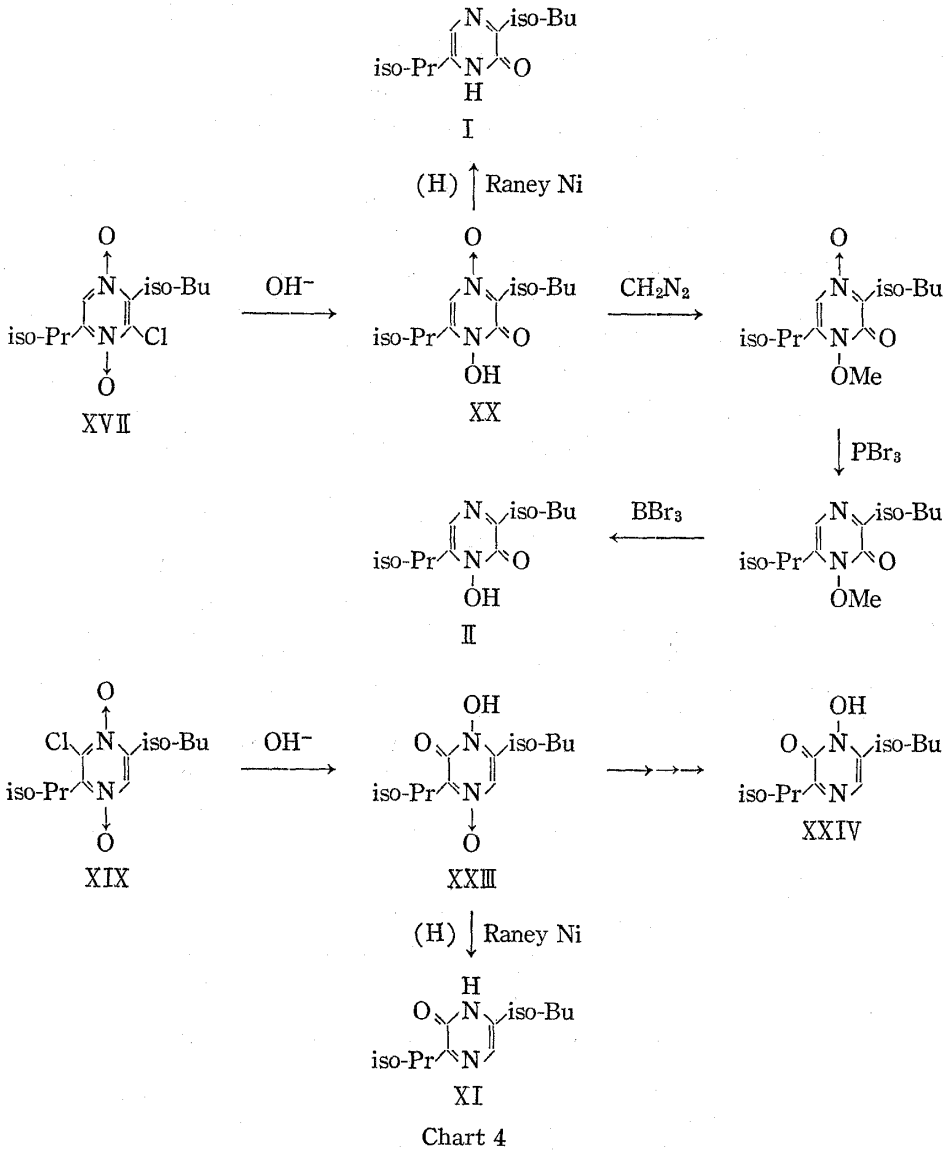


Chart 4

10) A. Ohta, Y. Akita, and C. Takagai, *Heterocycles*, **6**, 1881 (1977).

prepared by heating XVI and XVIII with hydrazine hydrate, to afford XIV and XV, respectively, in a moderate yield. The structure of XIV and XV was elucidated on the basis of analytical and spectral data, as described below. The methine proton of the 2-isopropyl group in 2,5-diisopropylpyrazine 1-oxide and the methylene protons of the 2-isobutyl group in 2,5-diisobutylpyrazine 1-oxide resonated in a lower field than those of the parent amines. As shown in Table II, the methylene protons of the isobutyl group of XIV and the methine proton of the isopropyl group in XV appeared in a lower field than those of the original amine (XII). These PMR data were consistent with the structure of XIV and XV.

The dioxides, 2-chloro-3-isobutyl-6-isopropylpyrazine 1,4-dioxide (XVII) and 2-chloro-3-isopropyl-6-isobutylpyrazine 1,4-dioxide (XIX), were hydrolysed by heating in a methanolic potassium hydroxide solution to yield cyclic hydroxamic acids, 2-hydroxy-3-isobutyl-6-isopropylpyrazine 1,4-dioxide (XX) and 2-hydroxy-3-isopropyl-6-isobutylpyrazine 1,4-dioxide (XXIII), respectively, which indicated red coloration with ferric chloride in methanol. Catalytic reduction of XX in the presence of Raney nickel gave a pyrazinol, which was characterized as deoxymutaaspergillic acid (I), mp 113.5—115°, undepressed with an authentic sample. In the same way, XXIII was converted to XI, whose structure was elucidated by comparing its UV spectrum with that of I.

Conversion of XX to II was achieved through successive methylation, deoxygenation, and demethylation. The oily product, prepared from XX by treatment with diazomethane, was stirred for 19 hr at room temperature with phosphorus tribromide in ethyl acetate and, without purification, the resulting oil was treated with boron tribromide in dry chloroform. The crystals, which were soluble in 10% potassium carbonate solution, was purified by sublimation under a reduced pressure and recrystallized from aqueous methanol to give a cyclic hydroxamic acid, whose IR spectrum was identical with that of 2-hydroxy-3-isobutyl-6-isopropylpyrazine 1-oxide (II), isolated from *Aspergillus sojae X*-1. XXIII was also treated in the same manner as XX to yield a cyclic hydroxamic acid (XXIV), whose structure was determined by comparing the UV spectrum with that of II.

Consequently DL-valyl-leucyl anhydride (III) was able to be converted to 2-isobutyl-5-isopropylpyrazine (XII), and its 1- and 4-oxides (XIV and XV). Two fungal metabolites, deoxymutaaspergillic acid (I) and 2-hydroxy-3-isobutyl-6-isopropylpyrazine 1-oxide (II), and their isomers were also prepared from III *via* several steps.

Experimental

Melting points were recorded on a Yanagimoto Micro Melting Point Apparatus and were uncorrected. Boiling points were also uncorrected. UV spectra were recorded on Hitachi Model 323, IR spectra on Shimadzu IR-400, and PMR spectra were recorded on JEOL Model JNM-PS-100 instrument with tetramethylsilane as an internal standard. Mass spectra were obtained on Hitachi RMU-7L spectrometer.

Reaction of DL-Valyl-leucyl Anhydride (III) with Phosphoryl Chloride——A mixture of 17 g (80 mmol) of III and 80 ml of $POCl_3$ was refluxed for 2 hr. After residual $POCl_3$ was distilled off under a reduced pressure, the residue was treated with ice-water, made alkaline with solid K_2CO_3 and extracted with Et_2O. The solvent was evaporated and the resulting brown oil was chromatographed on silica gel, using hexane as an eluant, to give VI, VII, and VIII. VI: 5.80 g (27.4%), colorless oil, bp 96—98°/2 Torr. *Anal.* Calcd. for $C_{11}H_{16}Cl_2N_2$: C, 53.46; H, 6.53; N, 11.33. Found: C, 53.17; H, 6.53; N, 11.26. NMR ($CDCl_3$) δ: 0.98 (6H, d, J=8 Hz), 1.28 (6H, d, J=8 Hz), 2.20 (1H, m, J=8 Hz), 2.75 (2H, d, J=8 Hz), 3.41 (1H, m, J=8 Hz). MS *m/e*: 246 (M^+), 231 (M^+-CH_3), 189 ($M^+-C_4H_9$). UV $\lambda_{max}^{95\%\,EtOH}$ nm (log ε): 285 (3.87), 299 (3.92). VII: 2.40 g (14.2%), colorless oil, bp 89—90°/2 Torr. *Anal.* Calcd. for $C_{11}H_{17}ClN_2$: C, 62.11; H, 8.06; N, 13.16. Found: C, 61.50; H, 8.03; N, 13.10. NMR ($CDCl_3$) δ: 0.99 (6H, d, J=8 Hz), 1.34 (6H, d, J=8 Hz), 2.21 (1H, m, J=8 Nz), 2.80 (2H, d, J=8 Hz), 3.04 (1H, m, J=8 Hz), 8.30 (1H, s). MS *m/e*: 212 (M^+), 197 (M^+-CH_3), 155 ($M^+-C_4H_9$). UV $\lambda_{max}^{95\%\,EtOH}$ nm (log ε): 282 (3.98), 301 (3.63, shoulder). VIII: 2.60 g (15.3%), colorless oil, bp 75—80°/2 Torr. *Anal.* Calcd. for $C_{11}H_{17}ClN_2$: C, 62.11; H, 8.06; N, 13.16. Found: C, 61.63; H, 8.03; N, 13.10. NMR ($CDCl_3$) δ: 0.93 (6H, d, J=8 Hz), 1.28 (6H, d, J=8 Hz), 2.08 (1H, m, J=8 Hz), 2.58 (2H, d, J=8 Hz), 3.44 (1H, m, J=8 Hz), 8.16 (1H, s). MS *m/e*: 212 (M^+), 197 (M^+-CH_3), 155 ($M^+-C_4H_9$). UV $\lambda_{max}^{95\%\,EtOH}$ nm (log ε): 282 (3.92), 302 (3.53, shoulder).

2-Methoxy-3-isobutyl-6-isopropylpyrazine (IX)——A mixture of 115 mg (0.5 mmol) of VII and NaOMe, prepared from 35 mg (1.5 mg atom) of Na and 10 ml of dehyd. MeOH, was heated in a sealed tube at 120°

for 3 hr. Usual work-up gave 80 mg (71%) of IX as a colorless oil, bp 65°/1.5 Torr. High-resolution mass spectrum calcd. for $C_{12}H_{20}N_2O$: 208.157540. Obs. 208.158964. NMR ($CDCl_3$) δ: 0.92 (6H, d, J=8 Hz), 1.28 (6H, d, J=8 Hz), 2.61 (1H, m, J=8 Hz), 2.66 (2H, d, J=8 Hz), 2.96 (1H, m, J=8 Hz), 3.92 (3H, s), 7.88 (1H, s). MS *m/e*: 208 (M^+), 193 (M^+-CH_3), 151 ($M^+-C_4H_9$). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 281.5 (3.85, shoulder), 298 (3.96).

2-Methoxy-3-isopropyl-6-isobutylpyrazine (X)——A mixture of 345 mg (1.5 mmol) of VIII and NaOMe, prepared from 345 mg (15 mg atom) of Na and 12 ml of dehyd. MeOH, was worked up as in the case of VII to give 300 mg (89%) of X as a colorless oil, bp 80°/7 Torr. *Anal.* Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 68.85; H, 9.72; N, 13.75. NMR ($CDCl_3$) δ: 0.94 (6H, d, J=8 Hz), 1.26 (6H, d, J=8 Hz), 2.10 (1H, m, J=8 Hz), 2.50 (2H, d, J=8 Hz), 3.28 (1H, m, J=8 Hz), 3.92 (3H, s), 7.78 (1H, s). MS *m/e*: 208 (M^+), 193 (M^+-CH_3). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 280 (3.71, shoulder), 297 (3.81).

2-Isobutyl-5-isopropylpyrazine (XII)——VI (1.46 g, 5.9 mmol) was catalytically hydrogenolysed in 15 ml of MeOH in the presence of 1.63 g (24.6 mmol) of AcONa and 0.25 g of 20% Pd-C. The product was purified by chromatography over silica gel ,using a mixture of hexane and Et_2O as an eluant, and by distillation to give 530 mg (50%) of XII as a colorless oil, bp 89—90°/4 Torr (oil bath temp.). *Anal.* Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 73.74; H, 10.36; N, 15.72. NMR ($CDCl_3$) δ: 0.92 (6H, d, J=8 Hz), 1.32 (6H, d, J=8 Hz), 2.08 (1H, m, J= 8Hz), 2.62 (2H, d, J=8 Hz), 3.06 (1H, m, J=8 Hz), 8.30 (1H, s), 8.38 (1H, s). MS *m/e*: 178 (M^+), 163 (M^+-CH_3), 121 ($M^+-C_4H_9$). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 273 (3.96), 277 (3.95).

Oxidation of 2-Isobutyl-5-isopropylpyrazine (XII)——A solution of 530 mg (3 mmol) of XII, 316 mg (3.6 mmol) of 90% H_2O_2, and 440 mg (4.5 mmol) of maleic anhydride in 35 ml of $CHCl_3$ was allowed to stand overnight at room temperature, and then washed successively with H_2O, 5% $KHCO_3$ solution, and H_2O. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated. The residual oil was chromatographed over silica gel and eluted with a mixture of benzene and Et_2O (20: 1) to give a mixture of monoxides (210 mg). In the PMR spectrum of the mixture, two doublets appeared at 2.56 and 2.70 ppm for the methylene protons of isobutyl group, in the integration ratio of 1: 5. This fact may indicate that this mixture was composed of XV and XIV in the ratio of 1: 5.

The fraction eluted with a mixture of benzene and Et_2O (8: 2) gave 260 mg (42%) of XIII, which was recrystallized from benzene to colorless prisms, mp 170—171°. *Anal.* Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.64; H, 8.67; N, 13.21. NMR ($CDCl_3$) δ: 1.02 (6H, d, J=8 Hz), 1.32 (6H, d, J=8 Hz), 2.20 (1H, m, J=8 Hz), 2.66 (2H, d, J=8 Hz), 3.56 (1H, m, J=8 Hz), 8.02 (2H, s). MS *m/e*: 210 (M^+), 193 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ 95% nm (log ε): 239 (3.54), 311 (3.34).

Reaction of a Mixture of Two Monoxides (XIV and XV) with Phosphoryl Chloride——After the mixture of the monoxides (19.4 mg, 0.1 mmol) and 1 ml of $POCl_3$ was refluxed for 0.5 hr, the reaction mixture was poured into ice-water, made alkaline with powdered K_2CO_3, and extracted with Et_2O. The Et_2O extract was dried over Na_2SO_4 and evaporated to leave a brown oil, which was decolorized by chromatography over silica gel, using a mixture of hexane and Et_2O (100: 1) as a developer. The PMR spectrum of a mixture of monochloropyrazines thus obtained showed two doublets at 2.82 and 2.62 ppm for the methylene protons of isobutyl groups in VII and VIII in the ratio of 1: 5.

Oxidation of 2-Chloro-3-isobutyl-6-isopropylpyrazine (VII)——A solution of 4.74 g (0.022 mol) of VII, 3.34 g (0.080 mol) of 90% H_2O_2, and 8.64 g (0.090 mol) of maleic anhydride in 60 ml of $CHCl_3$ was allowed to stand overnight at room temperature, washed successibely with H_2O, 10% $KHCO_3$, and H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel. The fraction eluted with a mixture of benzene and $CHCl_3$ (1: 1) was recrystallized from hexane to give 2.40 g (47%) of XVI as pale yellow needles, mp 76.5—77.5°. *Anal.* Calcd. for $C_{11}H_{17}ClN_2O$: C, 57.76; H, 7.49; N, 12.25. Found: C, 57.60; H, 7.43; N, 12.50. NMR ($CDCl_3$) δ: 0.98 (6H, d, J=8 Hz), 1.26 (6H, d, J=8 Hz), 2.28 (1H, m, J= 8 Hz), 2.92 (2H, d, J=8 Hz), 2.94 (1H, m, J=8 Hz), 7.92 (1H, s). MS *m/e*: 228 (M^+), 211 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 235.5 (4.25), 275 (3.99), 304.5 (3.55), 315 (3.51). The fraction eluted with $CHCl_3$ gave 2.33 g (41%) of XVII, which was recrystallized from aqueous MeOH to give colorless prisms, mp 94—95°. *Anal.* Calcd. for $C_{11}H_{17}ClN_2O_2$: C, 53.98; H, 7.00; N, 11.45. Found: C, 53.84; H, 6.75; N, 11.58. NMR ($CDCl_3$) δ: 1.00 (6H, d, J=8 Hz), 1.30 (6H, d, J=8 Hz), 2.32 (1H, m, J=8 Hz), 2.96 (2H, d, J=8 Hz), 3.59 (1H, m, J=8 Hz), 7.96 (1H, s). MS *m/e*: 244 (M^+), 227 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 247.5 (4.43), 314.5 (4.28).

Oxidation of 2-Chloro-3-isopropyl-6-isobutylpyrazine (VIII)——A solution of 7.20 g (0.034 mol) of VIII, 5.17 g (0.123 mol) of 90% H_2O_2, and 13.33 g (0.136 mol) of maleic anhydride in 100 ml of $CHCl_3$ was worked up in the same way as for VII. The products were purified by column chromatography over silica gel to give 4.55 g (59%) of XVIII, as a colorless oil, bp 120—123°/1 Torr, and 2.43 g (29%) of XIX ,as colorless prisms, mp 95—96°. XVIII: *Anal.* Calcd. for $C_{11}H_{17}ClN_2O$: C, 57.76; H, 7.49; N, 12.25. Found: C, 57.41; H, 7.60; N, 12.64. NMR ($CDCl_3$) δ: 0.94 (6H, d, J=8 Hz), 1.40 (6H, d, J=8 Hz), 2.10 (1H, m, J=8 Hz), 2.50 (2H, d, J=8 Hz), 3.92 (1H, m, J=8 Hz), 7.84 (1H, s). MS *m/e*: 228 (M^+), 211 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 236 (4.31), 276 (4.05), 305 (3.58), 315.5 (3.52). XIX: *Anal.* Calcd. for $C_{11}H_{17}ClN_2O_2$: C, 53.98; H, 7.00; N, 11.45. Found: C, 54.12; H, 7.11; N, 11.60. NMR ($CDCl_3$) δ: 1.00 (6H, d, J=8 Hz), 1.46 (6H, d, J=8 Hz), 2.22 (1H, m, J= 8Hz), 2.68 (2H, d, J=8 Hz), 3.96 (1H, m, J=8 Hz), 7.94 (1H, s). MS *m/e*: 244 (M^+), 227 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 248 (4.39), 315.5 (4.23).

2-Isobutyl-5-isopropylpyrazine 1-Oxide (XIV)——A mixture of 342 mg (1.5 mmol) of XVI, 2 ml of hydrazine, hydrate and 2 ml of EtOH was heated in a sealed tube at 120° for 2 hr. After the solvent was evaporated under a reduced pressure, a small amount of H_2O was added to the residue and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over Na_2SO_4 and evaporated. The resulting yellow oil was dissolved in 3 ml of AcOH and 3 ml of H_2O, to which a solution of $CuSO_4 \cdot 5H_2O$ (0.8 g) in 3 ml of H_2O was added. This mixture was heated on a water bath (80—90°) for 0.5 hr, made alkaline with solid K_2CO_3, and extracted with Et_2O. The extract was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by silica gel column chromatography with a mixture of hexane: Et_2O (9: 1) to give 203 mg (70%) of XIV as a colorless oil, bp 155°/7 Torr. *Anal.* Calcd. for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 67.75: H, 9.35; N, 14.26. NMR ($CDCl_3$) δ: 0.96 (6H, d, J=8 Hz), 1.30 (6H, d, J=8 Hz), 2.23 (1H, m, J=8 Hz), 2.70 (2H, d, J=8 Hz), 2.98 (1H, m, J=8 Hz), 8.03 (1H, s) 8.30 (1H, s). MS *m/e*: 194 (M^+), 177 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 227 (4.26), 270 (4.02), 298 (3.57, shoulder), 306.5 (3.49, shoulder).

2-Isobutyl-5-isopropylpyrazine 4-Oxide (XV)——XVIII (342 mg, 1.5 mmol) was worked up in the same way as XVI to give 135 mg of XV (46%) as a pale yellow oil, bp 134—136°/3 Torr. *Anal.* Calcd. for $C_{11}H_{18}N_2O$: C, 68.00 H, 9.34; N, 14.42. Found: 67.61; H, 9.39; N, 14.66. NMR ($CDCl_3$) δ: 0.94 (6H, d, J=8 Hz), 1.32 (6H, d, J=8 Hz), 2.10 (1H, m, J=8 Hz), 2.56 (2H, d, J=8 Hz), 3.60 (1H, m, J=8 Hz), 7.98 (1H, s), 8.36 (1H, s), MS *m/e*: 194 (M^+), 177 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 225.5 (4.35), 270 (4.11), 298.5 (3.65, shoulder), 307 (3.55, shoulder).

2-Hydroxy-3-isobutyl-6-isopropylpyrazine 1,4-Dioxide (XX)——After a solution of 249 mg (1.02 mmol) of XVII, 10 ml of 10% KOH solution, and 10 ml of EtOH was refluxed for 1 hr, the solvent was removed by distillation. A small amount of H_2O was added to the residue and the mixture was washed with Et_2O. The aqueous layer was acidified slightly with 2 N HCl and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to dryness. The resulting crystals were recrystallized from cyclohexane to give 113 mg (42%) of XX as colorless prisms, mp 156°, which indicated red coloration with $FeCl_3$ in MeOH. *Anal.* Calcd. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.29; H, 8.28; N, 12.17. NMR ($CDCl_3$) δ: 0.94 (6H, d, J=8 Hz), 1.34 (6H, d, J=8 Hz), 2.26 (1H, m, J=8 Hz), 2.82 (2H, d, J=8 Hz), 3.32 (1H, m, J=8 Hz), 5.00 (1H, broad s), 7.18 (1H, broad s). IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O). MS *m/e*: 226 (M^+), 209 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 228.5 (4.22), 239.5 (4.17, shoulder), 260 (4.21), 297.5 (3.89), 368 (4.04).

2-Hydroxy-3-isopropyl-6-isobutylpyrazine 1,4-Dioxide (XXIII)——XIX (183 mg, 0.75 mmol) was treated in a mixture of 5 ml of EtOH and 5 ml of 10% KOH solution and worked up as in the case of the reaction of XVII. The resulting crystals were purified by recrystallization from aqueous MeOH to give 80 mg (47%) of XXIII as colorless prrisms, mp 144.5—145°. *Anal.* Calcd. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.33; H, 8.26; N, 12.34. NMR ($CDCl_3$) δ: 1.00 (6H, d, J=8 Hz), 1.36 (6H, d, J=8 Hz), 2.18 (1H, m, J=8 Hz), 2.58 (2H, d, J=8 Hz), 3.88 (1H, m, J=8 Hz), 6.00 (1H, broad s). 7.12 (1H, broad s). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O). MS *m/e*: 226 (M^+), 209 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 231 (4.20), 239 (4.17, shoulder), 260.5 (4.08), 294 (3.83), 362 (3.89).

Deoxymutaaspergillic Acid (I)——1) A mixture of 104 mg (0.5 mmol) of IX, 1 ml of HI and 1 ml of EtOH was refluxed for 2 hr, the solvent was evaporated in vacuo, and the residue dissolved in CH_2Cl_2 was extracted with 2 N NaOH. From the organic layer, 66 mg of IX was recovered. After acidification of the NaOH solution with 2 N HCl, the aqueous layer was extracted with CH_2Cl_2, the extract was dried over Na_2SO_4, and evaporated to dryness. Recrystallization of the residue from iso-Pr_2O gave 30 mg (31%) of I as colorless prisms, mp 113—114°, which were identified as deoxymutaaspergillic acid. *Anal.* Calcd. for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.09; H, 9.03; N, 14.44. NMR ($CDCl_3$) δ: 0.98 (6H, d, J=8 Hz), 1.34 (6H, d, J=8 Hz), 2.14 (1H, m, J=8 Hz), 2.66 (2H, d, J=8 Hz), 2.88 (1H, m, J=8 Hz), 7.20 (1H, s), 13.90 (1H, broad s). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O). MS *m/e*: 194 (M^+), 179 (M^+-CH_3). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 227 (3.91), 324.5 (3.92).

2) XX (67 mg, 0.3 mmol) was reduced in the presence of Raney-Ni, prepared from 200 mg of the alloy, in 10 ml of MeOH in H_2 stream at room temperature. Usual work-up gave a colorless solid, which was recrystallized from iso-Pr_2O to yield 41 mg (70%) of I as colorless prisms, mp 113.5—115°.

2-Hydroxy-3-isopropyl-6-isobutylpyrazine (XI)——1) A mixture of 104 mg (0.5 mmol) of X, 2 ml of HI, and 2 ml of EtOH was heated in a sealed tube at 120° for 3 hr. Work-up in the same way as in the reaction of IX gave 53 mg (54%) of XI as colorless needles (from iso-Pr_2O), mp 141—142°. *Anal.* Calcd. for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.13; H, 9.53; N, 14.34. NMR ($CDCl_3$) δ: 1.00 (6H, d, J=8 Hz), 1.26 (6H, d, J=8 Hz), 2.08 (1H, m, J=8 Hz), 2.41 (2H, d, J=8 Hz), 3.41 (1H, m, J=8 Hz), 7.20 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O). MS *m/e*: 194 (M^+), 179 (M^+-CH_3). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 228 (3.88), 324 (3.89).

2) XXIII (80 mg, 0.35 mmol) was worked up as XX to give 74 mg (99%) of XI as colorless needles (from iso-Pr_2O), mp 141—142°.

2-Hydroxy-3-isobutyl-6-isopropylpyrazine 1-Oxide (II)—An Et_2O solution of CH_2N_2 was added to the solution of 113 mg (0.5 mmol) of XX in 2 ml of MeOH and the mixture was allowed to stand for 30 min. After the solvent was evaporated to dryness, the residue was dissolved in 15 ml of dry AcOEt, to which 0.5 ml of PBr_3 was added. The solution was stirred for 19 hr at room temperature, then poured into ice-water, and made alkaline with solid K_2CO_3. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined extract was dried over Na_2SO_4 and evaporated to dryness. The resulting

solid was dissolved in 20 ml of $CHCl_3$ and 0.5 ml of BBr_3 was added to this solution under ice-cooling. After stirring for 1.5 hr at room temperature, the reaction mixture was poured into ice-water, the $CHCl_3$ layer was separated, and extracted with 10% K_2CO_3 solution. The aqueous layer was acidified with 2 N HCl and extracted with CH_2Cl_2. The extract was evaporated to dryness, and the residue, after sublimation at 110—120°/3 Torr and recrystallization from aqueous MeOH, gave 24 mg (23%) of II as pale yellow needles, mp 92—94°, which indicated a positive $FeCl_3$ test. *Anal.* Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.93; H, 8.73; N, 13.26. NMR ($CDCl_3$) δ: 0.94 (6H, d, J=8 Hz), 1.16 (6H, d, J=8 Hz), 2.20 (1H, m, J=8 Hz), 2.71 (2H, d, J=8 Hz), 3.34 (1H, m, J=8 Hz), 7.33 (1H, s), 8.64 (1H, broad s). IR ν_{max}^{KBr} cm^{-1}: 1620 (C=O). MS m/e: 210 (M^+), 193 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 237.5 (4.15), 340.5 (3.90).

2-Hydroxy-3-isopropyl-6-isobutylpyrazine 1-Oxide (XXIV)——XXIII (210 mg, 1 mmol) was worked up in the same way as XX to give 48 mg (23%) of XXIV as colorless prisms (from aqueous MeOH), mp 86—87°. *Anal.* Calcd. for $C_{11}H_{18}N_2O_2$; C, 62.83; H, 8.63; N, 13.32. Found: C, 62.80; H, 8.67; N, 13.02. NMR ($CDCl_3$) δ: 0.98 (6H, d, J=8 Hz), 1.25 (6H, d, J=8 Hz), 2.16 (1H, m, J=8 Hz), 2.62 (2H, d, J=8 Hz), 3.43 (1H, m, J=8 Hz), 7.28 (1H, s), 7.90 (1H, broad s). IR ν_{max}^{KBr} cm^{-1}: 1630 (C=O). MS m/e: 210 (M^+), 193 (M^+-OH). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 238 (4.18), 341 (3.93).

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