[Chem. Pharm. Bull.
27(12)2980—2987(1979)]

UDC 547.861.2.04 : 547.586.2.04

Conversion of 2,5-Diphenyl- and 2,5-Dibenzyl-pyrazines to 2,5-Diketopiperazines

Akihiro Ohta, Yasuo Akita, and Yumiko Nakane

Tokyo College of Pharmacy[1]

(Received May 14, 1979)

The reactions of 2,5-diphenyl- (I) and 2,5-dibenzyl-pyrazine 1-oxides (II) with phosphoryl chloride and acetic anhydride were examined. 2,5-Dichloro-3,6-diphenyl- (XI) and 2,5-dichloro-3,6-dibenzyl-pyrazines (XIII) were converted to the corresponding 2,5-diketopiperazines, α-phenylglycine anhydride (XXV) and phenylalanine anhydride (XXVI), respectively. The stereochemistry of the products is discussed. However, attempts to convert 2,5-dichloro-3,6-dihydroxymethylpyrazine (XXXIV) to serine anhydride were unsuccessful.

Keywords——2,5-diphenylpyrazine; 2,5-dibenzylpyrazine; 2,5-diacetoxymethylpyrazine; α-phenylglycine anhydride synthesis; phenylalanine anhydride synthesis

Our previous report in this series has described the reactivity of 2,5-dimethyl-, 2,5-diethyl-, and 2-methyl-5-phenyl-pyrazines, and the conversion of the former two compounds to the corresponding 2,5-diketopiperazines.[2] This paper reports some of the reactions of 2,5-diphenyl- (I) and 2,5-dibenzyl-pyrazines (II), and conversion of I and II to α-phenylglycine anhydride (XXV) and phenylalanine anhydride (XXVI), respectively. However, an attempt to synthesize serine anhydride from 2,5-dimethylpyrazine 1,4-dioxide (XXVII) was unsuccessful.

Compound (I) was prepared by the reaction of phenacyl bromide with ammonia as described by Tutin.[3] Preparation of II was carried out by a method similar to that used for the synthesis of 2,5-dimethylpyrazine,[4] starting from oximinoacetophenone.[5]

Oxidation of I and II was achieved with permaleic acid to give the corresponding monoxides, 2,5-diphenylpyrazine 1-oxide (III) and 2,5-dibenzylpyrazine 1-oxide (IV), and the dioxides, 2,5-diphenylpyrazine 1,4-dioxide (V) and 2,5-dibenzylpyrazine 1,4-dioxide (VI), which were separated by column chromatography. The mass spectra of III and V gave an M^+–O peak, while the spectra of IV and VI exhibited an M^+–OH peak. The difference depends on the presence or absence of an α-proton of the side chain on the carbon attached to the N–O group.[6]

In order to introduce a chlorine atom into the pyrazine ring, III and IV were treated with phosphoryl chloride to give 2-chloro-3,6-diphenyl- (VII) and 2-chloro-3,6-dibenzyl-pyrazines (VIII), respectively, in good yields. For the preparation of 2,5-dichloro-3,6-diphenyl- (XI) and 2,5-dichloro-3,6-dibenzyl-pyrazines (XII), VII and VIII were oxidized with permaleic acid to yield 2-chloro-3,6-diphenylpyrazine 4-oxide (IX) and 2-chloro-3,6-dibenzylpyrazine 4-oxide (X), which were then treated with phosphoryl chloride. While IX gave XI as the sole product, X afforded a crystalline mixture, which was composed of XII and 2-chloro-3-(α-chloro)benzyl-6-benzylpyrazine (XIII).

---

1) Location: *1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan.*
2) A. Ohta, Y. Akita, and M. Hara, *Chem. Pharm. Bull.* (Tokyo), **27**, 2027 (1979).
3) F. Tutin, *J. Chem. Soc.*, **97**, 2495 (1910).
4) L. Vanino, "Handbuch der Präparative Chemie," Vol. II, Ferdinand Enke, Stuttgart, 1937, p. 793.
5) W. Sharp and F.S. Spring, *J. Chem. Soc.*, **1951**, 932.
6) F. Uchimaru, S. Okada, A. Kosasayama, and T. Konno, *J. Heterocycl. Chem.*, **8**, 99 (1971).

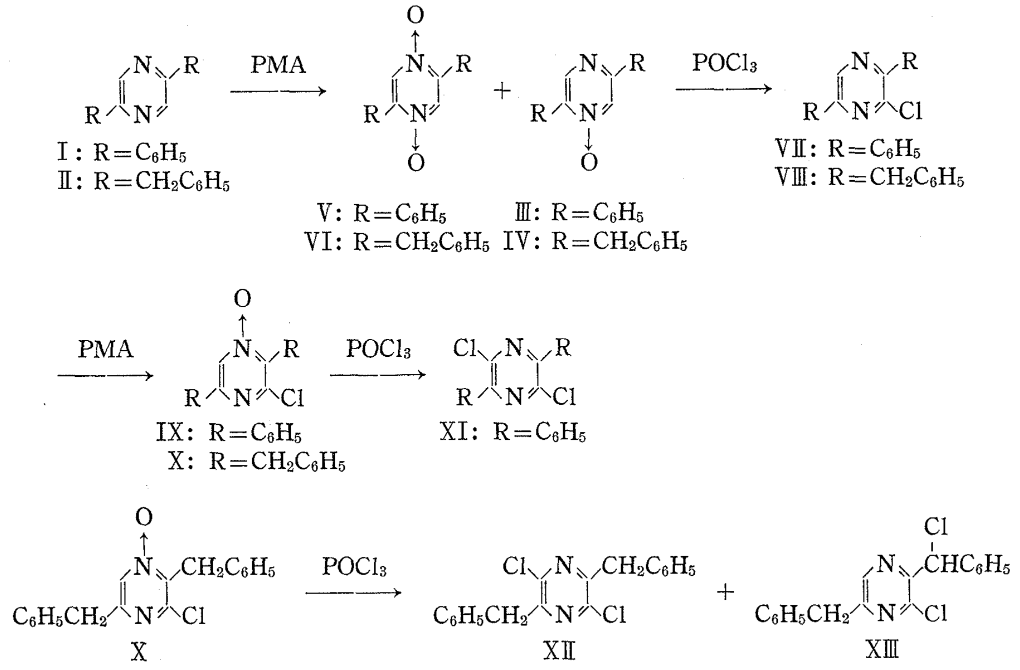

Chart 1

Although Baxter and Spring[7] described the preparation of 3,6-dimethyl-2-hydroxypyrazine by alkaline hydrolysis of 2-chloro-3,6-dimethylpyrazine, hydrolysis of VII and VIII under the same conditions was not successful. However, VIII was hydrolyzed with concentrated hydrochloric acid by heating in a sealed tube to yield 3,6-dibenzyl-2-hydroxypyrazine (XV) in 51% yield. On the other hand, hydrolysis of VII did not proceed under the same conditions. For the preparation of 3,6-diphenyl-2-hydroxypyrazine (XIV), 3,6-diphenyl-2-ethoxypyrazine (XVI), derived from VII by reaction with sodium ethoxide, was cleaved by refluxing in 15% hydrochloric acid. In a similar way, VIII was converted to XV *via* 3,6-dibenzyl-2-ethoxypyrazine (XVII) in good yield.

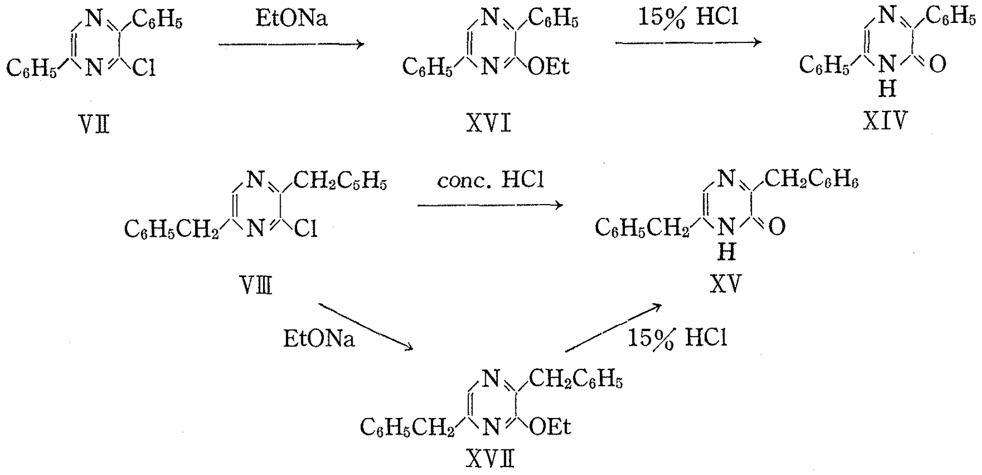

Chart 2

In order to obtain XIV and XV, the reactions of III and IV with acetic anhydride were also examined. III and IV were each heated with acetic anhydride under reflux to yield acetoxy compounds. In the former case, acetoxylation occurred on the pyrazine ring, giving

---

7) R.A. Baxter and F.S. Spring, *J. Chem. Soc.*, **1947**, 1179.

2-acetoxy-3,6-diphenylpyrazine (XVIII), which was readily hydrolyzed in 10% potassium carbonate to give XIV. On the other hand, acetoxylation took place only on the side chain in the latter case to afford 2-(α-acetoxy)benzyl-5-benzylpyrazine (XIX), whose proton magnetic resonance (PMR) spectrum exhibited a singlet at 6.74 ppm due to the methine proton on the acetoxylated benzyl group.

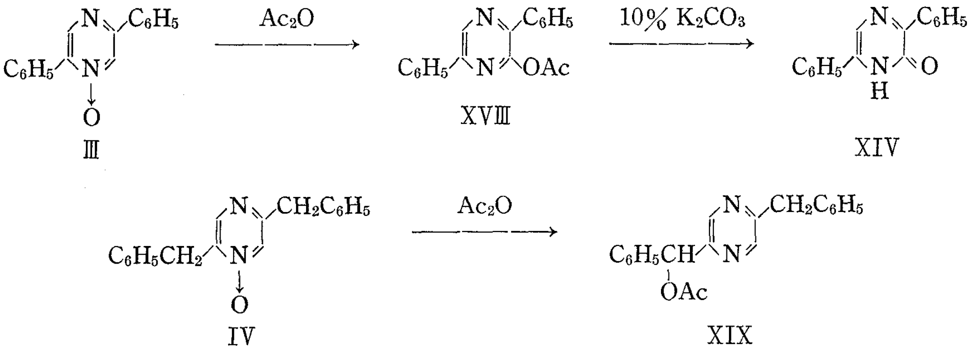

Chart 3

Although oxidation of the hydroxypyrazines, XIV and XV, was also carried out with permaleic acid, the necessary reaction conditions were different. While oxidation of XIV with permaleic acid was achieved to afford 3,6-diphenyl-2-hydroxypyrazine 4-oxide (XX) under reflux in chloroform, XV was oxidized to give 3,6-dibenzyl-2-hydroxypyrazine 4-oxide (XXI) only under milder conditions, and in poor yield. These two oxides were treated with phosphoryl chloride under heating. XX gave a crystalline product (XXII), which was then converted to XI by heating with a mixture of phosphoryl chloride and phosphorus pentachloride. On the other hand, a resinous compound was obtained from XXI under various reaction conditions.

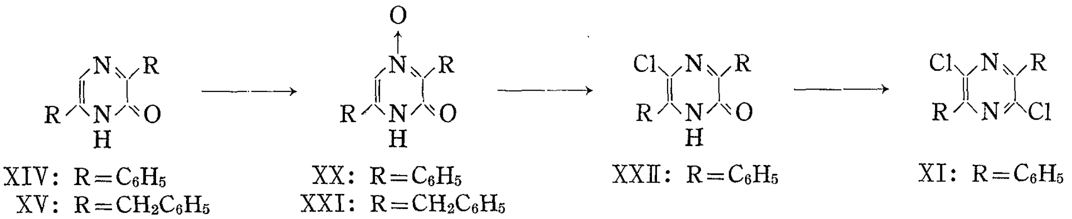

Chart 4

Conversion of the dichloropyrazines, XI and XIII, to the corresponding diketopiperazines was achieved through benzyloxylation and successive hydrogenolysis in the reported manner.[2] XI and XIII were each heated with sodium benzyloxide at above 160° to give 2,5-dibenzyloxy-3,6-diphenylpyrazine (XXIII) and 2,5-dibenzyloxy-3,6-dibenzylpyrazine (XXIV), respectively, which were then subjected to catalytic hydrogenolysis in the presence of palladium-charcoal to yield the diketopiperazines, XXV and XXVI.

XXV and α-phenylglycine anhydride (XXV′), derived from DL-α-phenylglycine,[8] had identical infrared (IR) spectra. While XXV′ gave two spots on a thin–layer chromatography (TLC) plate,[9] XXV exhibited only one spot, which corresponded to the lower spot of XXV′. As already known,[9] this suggests that XXV exists in the *cis*-configuration. Interestingly, the PMR spectra of both compounds, XXV and XXV′, were the same. However, the PMR spectrum of DL-phenylalanine anhydride (XXVI′a) is different from that of a mixture of the

---

[8] G. Ovakimian, M. Kuna, and P.A. Levene, *J. Biol. Chem.*, **135**, 91 (1940).
[9] J.W. Westley, V.A. Close, D.N. Nitecki, and B. Halpern, *Anal. Chem.*, **40**, 1888 (1968).

DD- and LL-isomers (XXVI′b), as will be described later, and similar phenomena were recognized in the case of alanine anhydride and α-aminobutyric anhydride.[2] These results may be due to a difference of the 2,5-diketopiperazine ring conformation between α-phenylglycine anhy- dride and other α-amino acid anhydrides. The stereochemistry of α-phenylglycine anhydride is now under investigation, and will be reported elsewhere.

A mixture of DL-, DD-, and LL-phenylalanine anhydrides (XXVI′) was prepared from DL-phenylalanine in the reported manner,[10] and subjected to column chromatography to separate DL-phenylalanine anhydride (XXVI′a) and a 1: 1 mixture of DD- and LL-phenylalanine anhydrides (XXVI′b). In the PMR spectra, XXVI′ exhibited a multiplet at 3.97 ppm due to the methine protons, and XXVI′b gave a double doublet at 4.62 ppm due to the methine protons. As XXVI gave two spots on a TLC plate,[9,11] and showed a multiplet and a double doublet at 3.92 and 4.60 ppm (intensity ratio, 1: 7), respectively, XXVI seems to be composed of DL-phenylalanine anhydride (XXVI′) and a mixture of DD- and LL-phenylalanine anhydride (XXVI′b) in a 1: 7 ratio.

Synthesis of serine anhydride starting from 2,5-dimethylpyrazine 1,4-dioxide[12] (XXVII) was also attempted by the route shown in Chart 6. 2,5-Diacetoxymethylpyrazine (XXVIII),

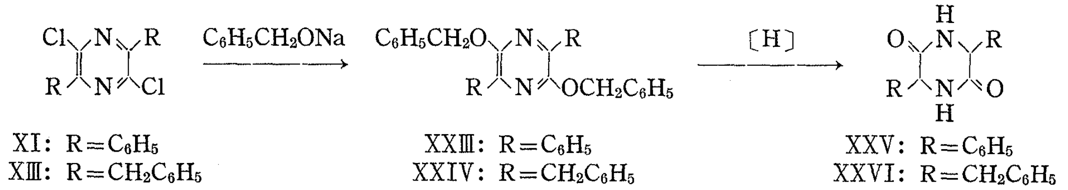

Chart 5

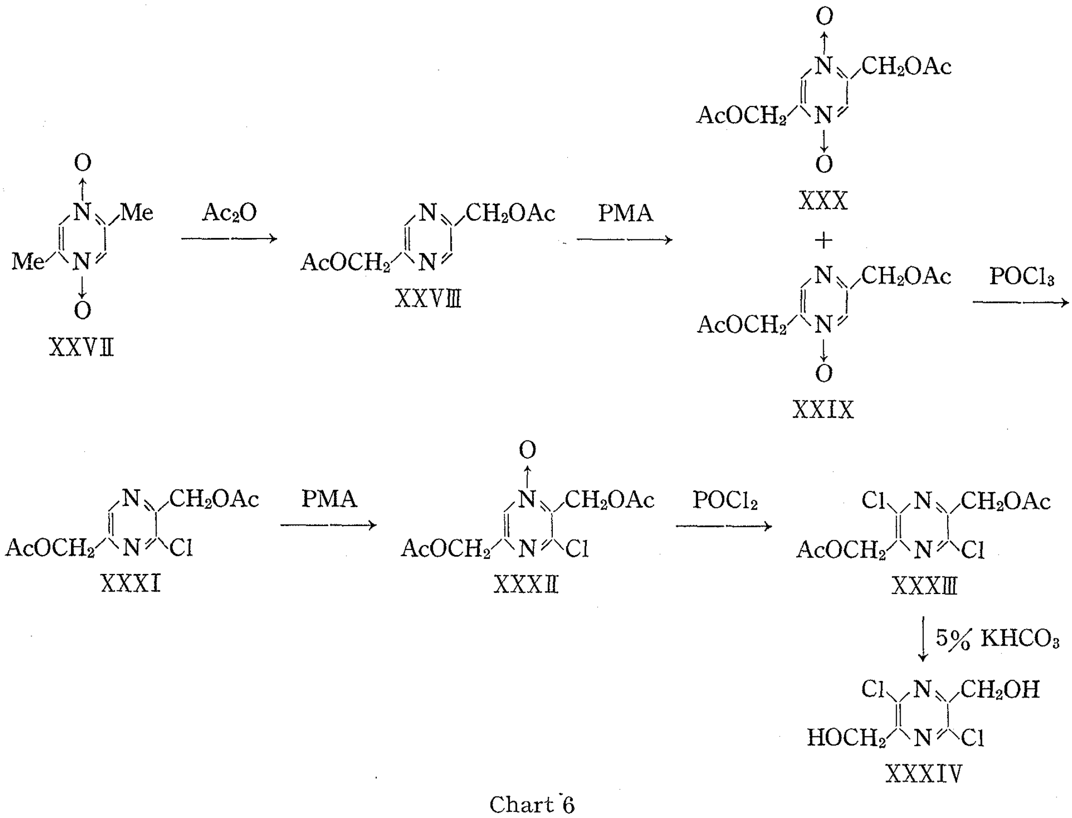

Chart 6

---

[10] C. Sannie, *Bull. Soc. Chim. Fr.*, 9, 487 (1942).

[11] D.N. Nitecki, B. Halpern, and J.W. Westley, *J. Org. Chem.*, 33, 8641 (1968).

[12] C.F. Koelsch and W.H. Gumprecht, *J. Org. Chem.*, 23, 1603 (1958).

obtained from XXVII by the reported method,[12] was oxidized with permaleic acid to afford a monoxide (XXIX) and a dioxide (XXX), in 68 and 7% yields, respectively. The former was converted to 2-chloro-3,6-diacetoxymethylpyrazine (XXXI) by treatment with phosphoryl chloride. Oxidation with permaleic acid and subsequent reaction with phosphoryl chloride, further converted XXXI to 2,5-diacetoxymethyl-3,6-dichloropyrazine (XXXIII), which was hydrolyzed under alkaline conditions to yield 2,5-dichloro-3,6-dihydroxymethylpyrazine (XXXIV). Although benzyloxylation of XXXIV was examined by heating with sodium benzyloxide under various conditions, no crystalline product was obtained.

Experimental

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

(1) **Oxidation of 2,5-Diphenylpyrazine (I)**——A solution of 2.32 g (10 mmol) of I, 0.456 g (12 mmol) of 90% H_2O_2, and 1.47 g (15 mmol) of maleic anhydride in 40 ml of $CHCl_3$ was refluxed for 8 hr. The reaction mixture was washed successively with H_2O, 10% $KHCO_3$, and H_2O. The $CHCl_3$ layer was dried over Na_2SO_4 and the solvent was evaporated off. The residue was chromatographed on silica gel (Wakogel C-200, 40 g) and eluted with a mixture of $CHCl_3$ and AcOEt (4: 1) to give III (1.53 g, 62%), which was recrystallized from benzene to furnish colorless needles, mp 204—205°. The fractions eluted with a mixture of AcOEt and EtOH (4: 1) gave V (0.31 g, 12%), which was recrystallized from AcOH to yield pale yellow needles, mp 308—310° (dec.). III: *Anal.* Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.32; H, 4.67; N, 11.04. MS *m/e*: 248 (M^+), 232 (M^+-O). PMR ($CDCl_3$) δ: 7.44—7.60 (6H, m), 7.80—8.00 (4H, m), 8.64 (1H, s), 8.69 (1H, s). UV $\lambda_{\max}^{95\%\mathrm{EtOH}}$ nm (log ε): 272.5 (4.34), 329 (3.76, shoulder). V: *Anal.* Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.80; H, 4.73; N, 10.58. MS *m/e*: 264 (M^+), 248 (M^+-O). PMR (CF_3COOD) δ: 7.60—7.96 (10H, m), 8.98 (2H, s). UV $\lambda_{\max}^{95\%\mathrm{EtOH}}$ nm (log ε): 283 (4.26), 326—327 (3.92).

(2) **Oxidation of 2,5-Dibenzylpyrazine (II)**——A solution of 3.96 g (15 mmol) of II, 0.647 g (17 mmol) of 90% H_2O_2, and 1.75 g (18 mmol) of maleic anhydride in 50 ml of CH_2Cl_2 was allowed to stand overnight at room temperature and then refluxed for 7.5 hr. The reaction mixture was worked up as described in (1) to give a colorless solid, which was chromatographed on silica gel (Wakogel C-200, 80 g). The fractions eluted with a mixture of benzene and $CHCl_3$ (1: 1) gave IV (3.03 g, 74%), which was recrystallized from EtOH to furnish colorless prisms, mp 102—104°. Elution with $CHCl_3$ afforded VI (0.65 g, 16%), which was recrystallized from AcOH to give colorless prisms, mp 221—225°. IV: *Anal.* Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.08; H, 5.63; N, 10.06. MS *m/e*: 276 (M^+), 259 (M^+-OH). PMR ($CDCl_3$) δ: 4.04 (2H, s), 4.12 (2H, s), 7.28 (10H, broad s), 7.94 (1H, s), 8.16 (1H, s). UV $\lambda_{\max}^{95\%\mathrm{EtOH}}$ nm (log ε): 227 (4.38), 268—269 (4.05). VI: *Anal.* Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.25; H, 5.32; N, 9.74. MS *m/e*: 292 (M^+), 275 (M^+-OH). PMR (CF_3COOD) δ: 4.28 (4H, s), 7.20—7.50 (10H, m), 8.32 (2H, s). UV $\lambda_{\max}^{95\%\mathrm{EtOH}}$ nm (log ε): 234 (4.36), 311 (4.27).

(3) **2-Chloro-3,6-diphenylpyrazine (VII)**——A solution of 3.72 g (15 mmol) of III in 30 ml of $POCl_3$ was refluxed for 0.5 hr, then the mixture was treated with ice-water, neutralized with solid $KHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over Na_2SO_4 and the solvent was evaporated off. The resulting solid was purified by column chromatography on silica gel (Wakogel C-200, 100 g) with benzene to yield VII (2.25 g, 59%), which was recrystallized from EtOH to furnish colorless prisms, mp 86—87°. *Anal.* Calcd. for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 71.96; H, 4.14; N, 10.57. MS *m/e*: 266 (M^+), 231 (M^+-Cl). PMR ($CDCl_3$) δ: 7.40—7.60 (6H, m), 7.78—7.92 (2H, m), 7.92—8.12 (2H, m), 8.98 (1H, s). UV $\lambda_{\max}^{95\%\mathrm{EtOH}}$ nm (log ε): 268 (4.24), 327.5 (4.32).

(4) **2-Chloro-3,6-dibenzylpyrazine (VIII)**——A solution of 3.0 g (10.9 mmol) of IV in 20 ml of $POCl_3$ was refluxed for 0.5 hr and worked up as described in (3) to give a colorless solid, which was recrystallized from hexane to furnish 3.04 g (95%) of VIII as colorless prisms, mp 35.5—37°. *Anal.* Calcd. for $C_{18}H_{15}ClN_2$: C, 73.33; H, 5.13; N, 9.50. Found: C, 73.49; H, 4.88; N, 9.46. MS *m/e*: 294 (M^+), 259 (M^+-Cl). PMR ($CDCl_3$) δ: 4.08 (2H, s), 4.24 (2H, s), 7.24 (10H, s), 8.24 (1H, s). UV $\lambda_{\max}^{95\%\mathrm{EtOH}}$ nm (log ε): 282—283 (4.11).

(5) **2-Chloro-3,6-diphenylpyrazine 4-Oxide (IX)**——A mixture of 1.00 g (3.75 mmol) of VII, 0.334 g (8.8 mmol) of 90% H_2O_2, and 1.213 g (12.4 mmol) of maleic anhydride in 50 ml of CH_2Cl_2 was refluxed for 8 hr and worked up as described in (1) to afford a pale yellow solid, which was recrystallized from EtOH to furnish 0.814 g (76%) of IX as pale yellow needles, mp 149—150°. *Anal.* Calcd. for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.85; N, 9.91. Found: C, 67.83; H, 3.83; N, 9.65. MS *m/e*: 282 (M^+), 266 (M^+-O). PMR ($CDCl_3$) δ: 7.44—7.60 (6H, m), 7.84—8.00 (4H, m), 8.60 (1H, s). UV $\lambda_{\max}^{95\%\mathrm{EtOH}}$ nm (log ε): 271.5 (4.46), 335 (3.89).

(6) **2-Chloro-3,6-dibenzylpyrazine 4-Oxide (X)**——A solution of 4.49 g (15 mmol) of VIII, 1.13 g (30 mmol) of 90% H_2O_2, and 3.43 g (35 mmol) of maleic anhydride in 50 ml of CH_2Cl_2 was refluxed for 3 hr. Work-up as described in (1) gave X (3.60 g, 73%), which was recrystallized from EtOH to afford colorless

needles, mp 100—103°. *Anal.* Calcd. for $C_{18}H_{15}ClN_2O$: C, 69.56; H, 4.87; N, 9.01. Found: C, 69.37; H, 4.66; N, 9.17. MS *m/e*: 310 (M^+), 293 (M^+-OH). PMR ($CDCl_3$) δ: 4.00 (2H, s), 4.36 (2H, s), 7.20—7.40 (10H, m), 7.80 (1H, s). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 235 (4.28), 274—275 (3.95), 301—307 (3.55), 315 (3.84, shoulder).

(7) **2,5-Dichloro-3,6-diphenylpyrazine (XI)**——a) A solution of 478 mg (1.7 mmol) of IX in 10 ml of $POCl_3$ was heated in a sealed tube at 140° for 1 hr, and worked up as described in (3) to give XI (422.5 mg, 82%), which was recrystallized from EtOH to furnish colorless prisms, mp 159—160°. *Anal.* Calcd. for $C_{16}H_{10}Cl_2N_2$: C, 63.80; H, 3.34; N, 9.30. Found: C, 63.88; H, 3.36; N, 9.14. MS *m/e*: 300 (M^+), 265 (M^+-Cl). PMR ($CDCl_3$) δ: 7.40—7.60 (6H, m), 7.80—8.00 (4H, m). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 270 (4.08), 327 (4.14).

b) A solution of 113 mg (0.4 mmol) of XXII and a small amount of PCl_5 in 3 ml of $POCl_3$ was heated in a sealed tube at 150° for 1 hr and worked up as before to give XI (59 mg, 47%), which was recrystallized from EtOH to furnish colorless prisms, mp 159—160°.

(8) **Reaction of 2-Chloro-3,6-dibenzylpyrazine 4-Oxide (X) with $POCl_3$**——A mixture of 1.55 g (5 mmol) of X and 20 ml of $POCl_3$ was heated in a sealed tube at 160—170° for 0.5 hr. Work-up as described in (3) gave a brown oil, which was chromatographed on silica gel (Wakogel C-200, 30 g) with hexane to afford 0.444 g (29%) of XII as colorless crystals. The product was recrystallized from iso-PrOH to furnish colorless prisms, mp 107—109°. Further elution with hexane gave XIII (0.764 g, 47%), which was recrystallized from EtOH to afford colorless needles, mp 82—83°. XII: *Anal.* Calcd. for $C_{18}H_{14}Cl_2N_2$: C, 65.67; H, 4.29; N, 8.51. Found: C, 65.52; H, 4.10; N, 8.48. MS *m/e*: 328 (M^+), 293 (M^+-Cl). PMR ($CDCl_3$) δ: 4.20 (4H, s), 7.20—7.36 (10H, m). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 222—224 (4.13), 287 (3.88, shoulder), 300.5 (4.00). XIII: *Anal.* Calcd. for $C_{18}H_{14}Cl_2N_2$: C, 65.67; H, 4.29; N, 8.51. Found: C, 65.92; H, 4.22; N, 8.63. MS *m/e*: 328 (M^+), 293 (M^+-Cl). PMR ($CDCl_3$) δ: 4.12 (2H, s), 6.50 (1H, s), 7.20—7.40 (8H, m), 7.46—7.60 (2H, m), 8.36 (1H, s). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 223 (4.16, shoulder), 285.5 (4.01), 310 (3.71, shoulder).

(9) **3,6-Diphenyl-2-ethoxypyrazine (XVI)**——A mixture of 666 mg (2.5 mmol) of VII and NaOEt, prepared from 86 mg (3.7 mg atom) of Na and 20 ml of EtOH, was refluxed for 4 hr. After removal of EtOH by distillation *in vacuo*, the residue was triturated with H_2O and extracted with ether. The usual work-up of the ether extract gave XVI (617 mg, 89%), which was recrystallized from EtOH to furnish colorless needles, mp 78.5—79.5°. *Anal.* Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 77.85; H, 5.67; N, 9.98. MS *m/e*: 276 (M^+), 261 (M^+-CH_3), 248 ($M^+-C_2H_4$). PMR ($CDCl_3$) δ: 1.52 (3H, t, $J=8$ Hz), 4.64 (2H, q, $J=8$ Hz), 7.40—7.60 (6H, m), 8.00—8.24 (4H, m), 8.70 (1H, s). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 265 (4.13), 340 (4.42).

(10) **3,6-Dibenzyl-2-ethoxypyrazine (XVII)**——A mixture of 1.47 g (5 mmol) of VIII and NaOEt, prepared from 0.575 g (25 mg atom) of Na and 40 ml of dehyd. EtOH, was worked up as described in (9) to afford 1.505 g (99%) of XVII as a pale yellow oil, bp 140—150° (bath temp.)/0.005 torr. *Anal.* Calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.97; H, 6.53; N, 9.18. MS *m/e*: 304 (M^+), 275 ($M^+-C_2H_5$), 259 ($M^+-OC_2H_5$). PMR ($CDCl_3$) δ: 1.36 (3H, t, $J=8$ Hz), 3.94 (2H, s), 4.08 (2H, s), 4.36 (2H, q, $J=8$ Hz), 7.10—7.40 (10H, m), 7.88 (1H, s). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 284 (3.87, shoulder), 300.5 (3.99).

(11) **3,6-Diphenyl-2-hydroxypyrazine (XIV)**——a) A suspension of 10 g (70.2 mmol) of XVI in 200 ml of 15% HCl was refluxed for 4 hr and neutralized with solid $KHCO_3$. A yellow solid formed (7.52 g) was collected by filtration and recrystallized from pyridine to furnish XIV as yellow prisms (7.29 g, 84%), mp 206—207°. *Anal.* Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.14; H, 4.65; N, 11.39. MS *m/e*: 248 (M^+). PMR (CF_3COOD) δ: 7.60—7.94 (8H, m), 8.00 (1H, s), 8.16 (1H, m), 8.24 (1H, m). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 263 (4.08), 362 (4.28). IR $_{max}^{KBr}$ cm^{-1}: 1630 (C=O).

b) A solution of 290 mg (1 mmol) of XVIII dissolved in a mixture of 10 ml of MeOH and 5 ml of 10% K_2CO_3 was refluxed for 1 hr. MeOH was evaporated off *in vacuo*, then the mixture was acidified with AcOH. The precipitate formed was collected by filtration and recrystallized from pyridine to give 200 mg (81%) of XIV as yellow prisms, mp 205—207°.

(12) **3,6-Dibenzyl-2-hydroxypyrazine (XV)**——a) A solution of 666 mg (2.5 mmol) of VIII in a mixture of 3 ml of conc. HCl and 3 ml of EtOH was heated in a sealed tube at 160° for 9 hr. The solvent was distilled off under reduced pressure and the residue was extracted with 2 N NaOH. The alkaline extract was acidified with 2 N HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was worked up as usual to give XV (320 mg, 51%), which was recrystallized from EtOH to furnish colorless prisms, mp 201—202°.

b) A suspension of 152 mg (0.5 mmol) of XVII in 10 ml of 15% HCl was refluxed for 1 hr, then the precipitate formed was collected by filtration and recrystallized from EtOH to give 116 mg (84%) of XV as colorless prisms, mp 200—201°. *Anal.* Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.34; H, 5.88; N, 10.28. MS *m/e*: 276 (M^+). PMR ($CDCl_3$) δ: 3.80 (2H, s), 4.08 (2H, s), 7.20—7.40 (11H, m), 12.90 (1H, broad s). IR $_{max}^{KBr}$ cm^{-1}: 1640 (C=O).

(13) **3,6-Diphenyl-2-hydroxypyrazine 4-Oxide (XX)**——A mixture of 992 mg (4 mmol) of XIV, 447 mg (12 mmol) of 90% H_2O_2, and 1.466 g (15 mmol) of maleic anhydride in 200 ml of $CHCl_3$ was refluxed for 8 hr and worked up as described in (1) to yield XX (540 mg, 51%), which was recrystallized from AcOH to furnish yellow needles, mp 256—260°. *Anal.* Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.85; H, 4.62; N, 10.70. MS *m/e*: 264 (M^+), 248 (M^+-O). PMR (CF_3COOD) δ: 7.50—7.90 (10H, m), 8.18 (1H, s). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 276.5 (4.18), 324—328 (3.77). IR $_{max}^{KBr}$ cm^{-1}: 1620 (C=O).

(14) **3,6-Dibenzyl-2-hydroxypyrazine 4-Oxide (XXI)**——A solution of 552 mg (2 mmol) of XV, 114 mg (3 mmol) of 90% H_2O_2, and 441 mg (4.5 mmol) of maleic anhydride in 30 ml of $CHCl_3$ was allowed to stand overnight at room temperature and worked up as in (1) to give XXI (153 mg, 25%), which was recrystallized from MeOH to furnish pale yellow needles, mp 255.5—257°. *Anal.* Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.81; H, 5.26; N, 9.64. MS *m/e*: 292 (M^+), 275 (M^+-OH). PMR (CF_3COOD) δ: 4.00 (2H, s), 4.38 (2H, s), 7.26 (11H m). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm (log ε): 233 (4.22), 280 (3.82), 331—332 (3.91). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1620 (C=O).

(15) **2-Chloro-3,6-diphenyl-5-hydroxypyrazine (XXII)**——A solution of 132 mg (0.5 mmol) of XX in 3 ml of $POCl_3$ was refluxed for 1 hr and worked up as described in (3) to yield XXII (123 mg, 87%), which was recrystallized from AcOEt to furnish yellow needles, mp 265—266°. *Anal.* Calcd. for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.90. Found: C, 67.87; H, 3.66; N, 9.85. MS *m/e*: 282 (M^+). PMR (CF_3COOD) δ: 7.66 (8H, m), 7.98 (2H, m). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm (log ε): 265 (4.04), 360 (4.11). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1640 (C=O).

(16) **2-Acetoxy-3,6-diphenylpyrazine (XVIII)**——A solution of 1.24 g (5 mmol) of III in 30 ml of Ac_2O was refluxed for 1 hr, then the reaction mixture was poured into ice-water, and made alkaline with K_2CO_3. Extraction of the solution with ether gave a colorless solid (1.22 g), which was recrystallized from MeOH to furnish 1.12 g (77%) of XVIII as colorless needles, mp 120—121°. *Anal.* Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.80; N, 9.65. Found: C, 74.36; H, 4.72; N, 9.61. MS *m/e*: 290 (M^+), 248 (M^+-CH_2CO). PMR ($CDCl_3$) δ: 2.28 (3H, s), 7.40—7.60 (6H, m), 7.80—7.94 (2H, m), 7.94—8.12 (2H, m), 9.04 (1H, s). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm (log ε): 265—267 (4.24), 325—327 (4.36). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1770 (C=O).

(17) **2-(α-Acetoxy)benzyl-5-benzylpyrazine (XIX)**——A solution of 276 mg (1 mmol) of IV in 5 ml of Ac_2O was refluxed for 1.5 hr and worked up as before to give a brown solid (322 mg), which was chromatographed on silica gel (Wakogel C-200, 10 g). Elution with $CHCl_3$ afforded XIX (207 mg, 65%), which was recrystallized from hexane to furnish colorless prisms, mp 88—89°. *Anal.* Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.47; H, 5.66; N, 8.81. Found: C, 75.11; H, 5.78; N, 8.78. MS *m/e*: 318 (M^+), 276 (M^+-CH_2CO). PMR (CCl_4) δ: 2.12 (3H, s), 4.06 (2H, s), 6.74 (1H, s), 7.10—7.50 (10H, m), 8.24 (1H, s), 8.50 (1H, s). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm (log ε): 278.5 (3.99), 307.5 (3.23, shoulder). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1745 (C=O).

(18) **2,5-Dibenzyloxy-3,6-diphenylpyrazine (XXIII)**——A mixture of XI (300 mg, 1 mmol) and $NaOCH_2$-C_6H_5, prepared from 57.5 mg (2.5 mg atom) of Na and 10 ml of benzyl alcohol, was heated in a sealed tube at 160—165° for 7 hr. After cooling, the reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with H_2O and worked up as usual to afford a yellow solid, which was purified by column chromatography on silica gel (Wakogel C-200, 10 g), eluting with hexane. The colorless solid obtained was recrystallized from EtOH to furnish 289 mg (65%) of XXIII as colorless needles, mp 160—161°. *Anal.* Calcd. for $C_{30}H_{24}N_2O_2$: C, 81.06; H, 5.44; N, 6.30. Found: C, 80.99; H, 5.36; N, 6.37. MS *m/e*: 444 (M^+). PMR ($CDCl_3$) δ: 5.58 (4H, s), 7.24—7.60 (16H, m), 8.20—8.34 (4H, m). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm (log ε): 235 (4.12), 267.5 (4.32), 367 (4.46).

(19) **2,5-Dibenzyloxy-3,6-dibenzylpyrazine (XXIV)**——A mixture of XIII (328 mg, 1 mmol) and Na-$OCH_2C_6H_5$, prepared from 70 mg (3 mg atom) of Na and 15 ml of benzyl alcohol, was heated in a sealed tube at 165—175° for 8 hr and worked up as before to afford XXIV (216 mg, 46%), which was recrystallized from MeOH to furnish colorless needles, mp 100—101°. *Anal.* Calcd. for $C_{32}H_{28}N_2O_2$: C, 81.33; H, 5.97; N, 5.93. Found: C, 81.41; H, 5.87; N, 5.94. MS *m/e*: 472 (M^+). PMR ($CDCl_3$) δ: 4.00 (4H, s), 5.30 (4H, s), 7.10—7.30 (20H, m). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm (log ε): 229.5 (4.57, shoulder), 280 (3.85), 323.5 (4.46).

(20) **α-Phenylglycine Anhydride (XXV)**——XXIII (50 mg, 0.11 mmol) was catalytically hydrogenolyzed in 10 ml of EtOH in the presence of 100 mg of 10% Pd-C. The catalyst was filtered off, and the reaction mixture was evaporated to dryness *in vacuo* to give colorless crystals, which were recrystallized from ethylene glycol monomethyl ether to furnish colorless needles (12.5 mg, 43%) of XXV, mp 297—298° (dec.). PMR (CF_3COOD) δ: 5.62 (2H, s), 7.44 (10H, s). TLC (Wakogel B-5F): *Rf*=0.20 (iso-Pr_2O: $CHCl_3$: AcOH=6: 3: 1).

(21) **α-Phenylglycine Anhydride (XXV′), derived from DL-α-Phenylglycine**[8]——Colorless needles (recrystallized from ethylene glycol monomethyl ether), mp 267—268° (dec.). PMR (CF_3COOD) δ: 5.61 (2H, s), 7.48 (10H, s). TLC (Wakogel B-5F): *Rf*=0.31 and 0.20 (iso-Pr_2O: $CHCl_3$: AcOH=6: 3: 1).

(22) **Phenylalanine Anhydride (XXVI)**——A mixture of XXIV (164 mg, 0.5 mmol) and 20% Pd-C (200 mg) in 30 ml of EtOH was shaken in a stream of H_2 and worked up as before to give colorless crystals, which were recrystallized from ethylene glycol monomethyl ether to furnish colorless prisms (112 mg, 64%) of XXVI, mp 279—282° (dec.). PMR (CF_3COOD) δ: 2.34 (dd, J=10 Hz, J=18 Hz), 3.09 (dd, J=4 Hz, J=18 Hz), 3.92 (m), 4.60 (dd, J=4 Hz, J=10 Hz), 7.00—7.20 (m), 7.20—7.50 (m).

(23) **Phenylalanine Anhydride (XXVI′), derived from DL-Phenylalanine**[10]——XXVI′ (400 mg), derived from DL-phenylalanine, was chromatographed on silica gel (Wakogel C-200, 60 g) and eluted with $CHCl_3$ containing an increasing amount of MeOH. The fractions eluted with a mixture of $CHCl_3$ and MeOH (150: 1 and 100: 1) gave XXVI′a (155 mg), which was recrystallized from MeOH to yield colorless fine needles, mp 277—280° (dec.) (lit.[11] mp 289—290°). The fractions eluted with a mixture of $CHCl_3$ and MeOH (50: 1) gave XXVI′b (172 mg); this was recrystallized from ethylene glycol monomethyl ether to furnish colorless fine needles, mp 290—292° (dec.) (lit.[11] LL-phenylalanine anhydride, mp 308—310°).

DL-Phenylalanine Anhydride (XXVI′a): PMR (CF_3COOD) δ: 3.22 (4H, m), 3.97 (2H, m), 7.18 (4H, m), 7.96 (6H, m).

Mixture of DD- and LL-phenylalanine anhydride (XXVI'b): PMR (CF_3COOD) δ: 2.34 (2H, dd, $J=10$ Hz, $J=20$ Hz), 3.10 (2H, dd, $J=6$ Hz, $J=20$ Hz), 4.62 (2H, dd, $J=6$ Hz, $J=10$ Hz), 7.18 (4H, m), 7.40 (6H, m).

(24) **Oxidation of 2,5-Diacetoxymethylpyrazine (XXVIII)**——A solution of 896 mg (4 mmol) of XXVIII, 204 mg (6 mmol) of 90% H_2O_2, and 738 mg (7.5 mmol) of maleic anhydride in 20 ml of CH_2Cl_2 was refluxed for 8 hr and worked up as described in (1). The crystalline product (946.5 mg) was chromatographed on Florisil (25 g), eluting successively with hexane, ether, CH_2Cl_2, and MeOH. The fractions eluted with a mixture of hexane and ether (7: 3) gave the starting material (72.4 mg, 8%). The fractions eluted with a mixture of hexane and ether (7: 3 and 6: 4) afforded XXIX (656.5 mg, 68%), which was recrystallized from EtOH to furnish colorless needles, mp 108.5—111°. The CH_2Cl_2/MeOH (8: 2) fractions gave XXX, (73.8 mg, 7%), which was recrystallized from $CHCl_3$ to furnish colorless prisms, mp 237—237.5°.

XXIX: *Anal.* Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 50.11; H,5.06; N, 11.58. MS *m/e*: 240 (M^+). PMR ($CDCl_3$) δ: 2.16 (6H, s), 5.17 (2H, s), 5.30 (2H, s), 8.17 (1H, s), 8.50 (1H, s). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm ($\log \varepsilon$): 226 (4.29), 269 (4.03). IR $^{\text{KBr}}_{\max}$ cm^{-1}: 1750 (C=O).

XXX: *Anal.* Calcd. for $C_{10}H_{12}N_2O_6$: C, 46.88; H, 4.72; N, 10.93. Found: C, 47.12; H, 4.67; N, 10.94. MS *m/e*: 256 (M^+). PMR (CF_3COOD) δ: 2.35 (6H, s), 5.56 (4H, s), 8.93 (2H, s). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm ($\log \varepsilon$): 232 (4.35), 311 (4.32). IR $^{\text{KBr}}_{\max}$ cm^{-1}: 1760 (C=O).

(25) **2-Chloro-3,6-diacetoxymethylpyrazine (XXXI)**——A mixture of XXIX (120 mg, 0.5 mmol) and $POCl_3$ (3 ml) was refluxed for 15 min, then the reaction mixture was poured into ice-water, made alkaline with solid K_2CO_3, and extracted with CH_2Cl_2. The usual work-up of the CH_2Cl_2 extract afforded a brown oil (118 mg), which was purified by column chromatography on Florisil (5 g) eluting with hexane containing an increasing amount of ether. The fractions eluted with 9: 1 and 7: 3 mixtures of hexane and Et_2O gave 87 mg (67%) of XXXI as a colorless oil, bp 128—138° (bath temp.)/1 torr. *Anal.* Calcd. for $C_{10}H_{11}ClN_2O_4$: C, 46.43; H, 4.29; N, 10.83. Found: C, 46.45; H, 4.26; N, 10.99. MS *m/e*: 216 (M^+-CH_2CO). PMR ($CDCl_3$) δ: 2.16 (6H, s), 5.20 (2H, s), 5.32 (2H, s), 8.50 (1H, s). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm ($\log \varepsilon$): 247 (4.15, shoulder), 256.5 (4.18), 309 (4.10). IR $^{\text{KBr}}_{\max}$ cm^{-1}: 1750 (C=O).

(26) **2-Chloro-3,6-diacetoxymethylpyrazine 4-Oxide (XXXII)**——A solution of 370 mg (1.3 mmol) of XXXI, 146 mg (3.8 mmol) of 90% H_2O_2, and 528 mg (3.4 mmol) of maleic anhydride in 30 ml of CH_2Cl_2 was refluxed for 8 hr and worked up as described in (1). The crystalline product (406 mg) was purified by column chromatography on Florisil (9 g), eluting with a mixture of hexane and ether (1: 1), and the eluted product was recrystallized from MeOH to furnish 343 mg (87%) of XXXII as colorless needles, mp 114—116°. *Anal.* Calcd. for $C_{10}H_{11}ClN_2O_5$: C, 43.73; H, 4.04; N, 10.20. Found: C, 44.01; H, 3.97; N, 10.30. MS *m/e*: 274 (M^+). PMR ($CDCl_3$) δ: 2.12 (3H, s), 2.20 (3H, s), 5.16 (2H, s), 5.42 (2H, s), 8.16 (1H, s). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm ($\log \varepsilon$): 238 (4.30), 275 (4.03). IR $^{\text{KBr}}_{\max}$ cm^{-1}: 1760 (C=O).

(27) **2,5-Dichloro-3,6-diacetoxymethylpyrazine (XXXIII)**——A mixture of 100 mg (0.36 mmol) of XXXII and 4 ml of $POCl_3$ was heated in a sealed tube at 130—140° for 1 hr and worked up as described in (3) to give brown needles (84.3 mg), which were subjected to column chromatography on Florisil (2 g). Elution with a mixture of hexane and ether (9: 1) afforded colorless crystals, which were recrystallized from hexane to furnish 60.2 mg (56%) of XXXIII as colorless needles, mp 109.5—110°. *Anal.* Calcd. for $C_{10}H_{10}Cl_2N_2O_4$: C, 40.98; H, 3.44; N, 9.56. Found: C, 41.11; H, 3.50; N, 10.07. MS *m/e*: 292 (M^+). PMR ($CDCl_3$) δ: 2.16 (6H, s), 5.25 (4H, s). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm ($\log \varepsilon$): 222 (4.13), 293 (3.93). IR $^{\text{KBr}}_{\max}$ cm^{-1}: 1745 (C=O).

(28) **2,5-Dichloro-3,6-dihydroxymethylpyrazine (XXXIV)**——A suspension of 150 mg (0.51 mmol) of XXXIII in a mixture of 5 ml of 5% $KHCO_3$ and 5 ml of MeOH was warmed at 45° for 3 hr. After cooling, the reaction mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was worked up as usual to give a crystalline product, which was recrystallized from EtOH to furnish 72.5 mg (67%) of XXXIV as colorless prisms, mp 173—175°. *Anal.* Calcd. for $C_6H_6Cl_2N_2O_2$: C, 34.47; H, 2.90; N, 13.40. Found: C, 34.42; H, 2.80; N, 13.92. MS *m/e*: 208 (M^+). PMR (CD_3OD) δ: 4.78 (4H, s). UV $\lambda_{\max}^{95\%\text{EtOH}}$ nm ($\log \varepsilon$): 222 (4.05), 293 (3.40). IR $^{\text{KBr}}_{\max}$ cm^{-1}: 3375 (OH).

Acknowledgement The authers are grateful to Mr. C. Watanabe for technical assistance, to Mr. S. Suzuki for elemental analyses, to Mr. Y. Shida for mass spectral measurements, and to Miss C. Takagai for PMR spectral measurements.