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Syntheses and Reactions of Some 2,5-Disubstituted Pyrazine Monoxides

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The reactions of 2,5-dimethylpyrazine 1-oxide (XI), 2,5-diethylpyrazine 1-oxide (XIII), 2-methyl-5-phenylpyrazine 1-oxide (XV), and 2-methyl-5-phenylpyrazine 4-oxide (XVI) with phosphoryl chloride or acetic anhydride were studied. 2,5-Dichloro-3,6-dimethylpyrazine (III) and 2,5-dichloro-3,6-diethylpyrazine (VII) were converted to the diketopiperazines, alanine anhydride (I) and α-aminobutyric anhydride (V), respectively, which were shown to exist in a *cis* configuration by examination of their PMR spectra.

Keywords——2,5-dimethylpyrazine 1-oxide; 2,5-diethylpyrazine 1-oxide; 2-methyl-5-phenylpyrazine 1-oxide; 2-methyl-5-phenylpyrazine 4-oxide; alanine anhydride; α-aminobutyric anhydride

Many 3,6-dialkyl-2-hydroxypyrazines have been isolated from fungi, especially from Aspergillaceae,[2,3] and it is known that these hydroxypyrazines are biosynthesized from the corresponding amino acids *via* diketopiperazines.[2] Some alkylpyrazines have also been found as alarm pheromones in ants.[4,5] Although the reactivity of pyrazines has been studied for a long time[6,7] and some of the naturally occurring pyrazines have been synthesized,[8] the reactivity of pyrazines is not completely understood. This paper describes some reactions of 2,5-dimethyl- (IV), 2,5-diethyl- (VIII), and 2-methyl-5-phenyl-pyrazines (IX). In order to establish a procedure to synthesize α-amino acids, the conversions of IV and VIII to the corresponding diketopiperazines were also investigated.

The synthesis of IV was reported about 40 years ago[9] and we prepared VIII in a similar manner *via* oximinomethyl ethyl ketone.[10] In addition to this method, the catalytic hydrogenation of chloropyrazines, derived from alanine (I') and α-aminobutyric anhydrides (V')[11] by modification of Baxter's procedure,[12] was adopted for the syntheses of IV and VIII. On the other hand, the preparation of IX was carried out by the condensation of phenylglyoxal with propylenediamine, followed by dehydrogenation by heating in the presence of sodium hydroxide. In this reaction, 2-methyl-6-phenylpyrazine[13] (X) was formed simultaneously and the two compounds, IX and X, were separated by column chromatography.

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1) Location: *1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan.*
2) P.G. Sommes, *Fortschr. Chem. Org. Naturst.*, **32**, 51 (1975).
3) W.B. Turner, "Fungal Metabolites," Academic Press, New York, 1971, p. 320.
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7) G.W.H. Cheeseman and E.S.G. Werstink, *Adv. Heterocycl. Chem.*, **14**, 99 (1972).
8) A. Ohta, Y. Akita, K. Takizawa, M. Kurihara, S. Masano, and T. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **26**, 2046 (1978).
9) L. Vanino, "Handbuch der Präparative Chemie," Ferdinand Enke, Stuttgart, 1937, Vol. II, p. 794.
10) W. Sharp and F.S. Spring, *J. Chem. Soc.*, **1948**, 1862.
11) C. Sannie, *Bull. Soc. Chim. Fr.*, **9**, 487 (1942).
12) R.A. Baxter and F.S. Spring, *J. Chem. Soc.*, **1947**, 1179.
13) X was also prepared from 2-hydroxy-3-methyl-6-phenylpyrazine 1-oxide (G. Dunn, J.A. Elvidge, G.Y. Newbold, D.W.C. Ramsay, F.S. Spring, and W. Sweeny, *J. Chem. Soc.*, **1949**, 2707) through several steps. Experimental details will be reported elsewhere.

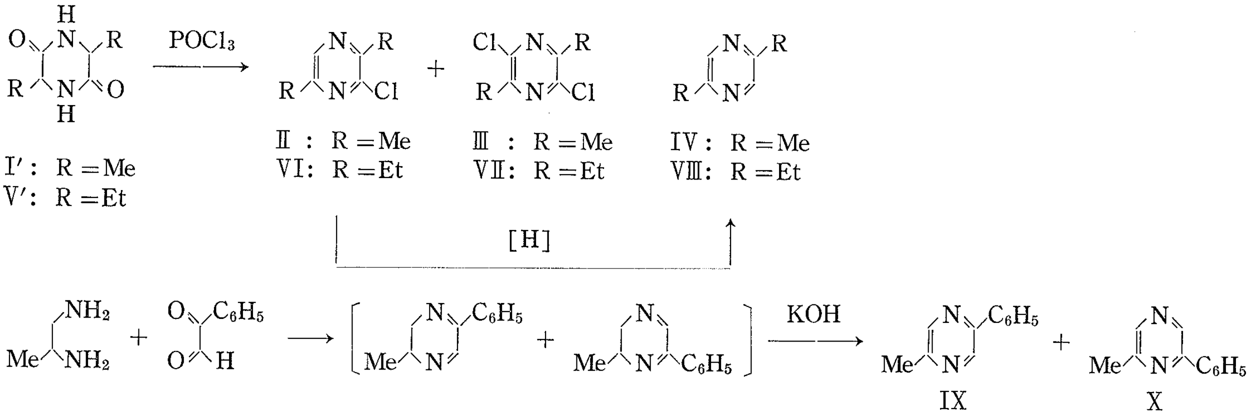

Chart 1

N-Oxidation of IV with peracetic acid was achieved by Newbold and Spring,[14] and by Koelsch and Gumprecht.[15] Under the same conditions, VIII was oxidized with peracetic acid to give 2,5-diethylpyrazine 1-oxide (XIII) and 2,5-diethylpyrazine 1,4-dioxide (XIV). On the other hand, oxidation of IX was undertaken using permaleic acid. Namely IX was heated with permaleic acid in chloroform to afford 2-methyl-5-phenylpyrazine 1-oxide (XV), 2-methyl-5-phenylpyrazine 1,4-dioxide (XVII), and a small amount of 2-methyl-5-phenylpyrazine 4-oxide (XVI), which were separated by column chromatography. XVI was also prepared from 2-chloro-6-methyl-3-phenylpyrazine 4-oxide (XX), as will be described later. Which peracid should be used for oxidation depends on the water solubility of the products.

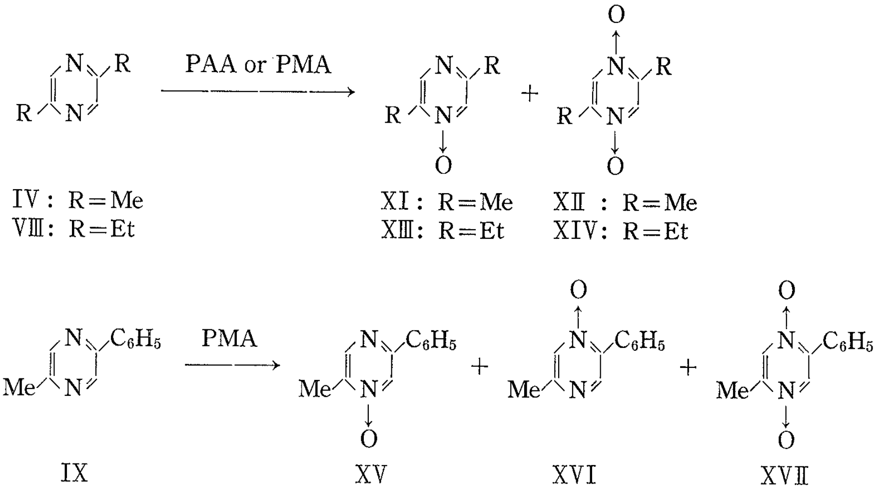

Chart 2

The structures of XV and XVI were elucidated on the basis of mass and proton magnetic resonance (PMR) spectral data, as described below. It is known that an M^{+}-17 ion peak appears in the mass spectra of aromatic N-oxides carrying an alkyl group α to the N–O group.[16] An M^{+}-17 peak was observed in the mass spectrum of XV, while an M^{+}-16 peak appeared in the spectrum of XVI. It is also known that the signal of the methyl protons of 2-methylpyrazine 1-oxide appears at higher field than that of the parent amine.[17] The signal of the methyl protons of XV shifted to higher field than that of IX, while the signal

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14) G.T. Newbold and F.S. Spring, *J. Chem. Soc.*, **1947**, 1183.
15) C.F. Koelsch and W.H. Gumprecht, *J. Org. Chem.*, 23, 1603 (1958).
16) F. Uchimaru, S. Okada, A. Kosasayama, and T. Konno, *J. Heterocycl. Chem.*, **8**, 99 (1971).
17) T.J. Batterhan, "NMR Spectra of Simple Heterocycles," John Wiley & Sons, Inc., New York, 1973, p. 8 and 118.

of the methyl protons of XVI was observed in the same position as that of IX. These spectral data are in good agreement with the proposed structures.

Baxter and Spring[12] prepared 2-chloro-3,6-dimethylpyrazine (II) by heating XI with phosphoryl chloride. Under the same reaction conditions, XIII afforded 2-chloro-3,6-diethylpyrazine (VI) in good yield. XV was also treated with phosphoryl chloride to give 2-chloro-6-methyl-3-phenylpyrazine (XVIII) and 2-chloro-3-methyl-6-phenylpyrazine (XIX), in a ratio of 16:1. XVI was also reacted with phosphoryl chloride to afford only XIX. In the reaction of 2-picoline 1-oxide with phosphoryl chloride, chlorination occurred mainly on the pyridine ring.[18] XI, XIII, and XV, which have the same partial structure as 2-picoline 1-oxide, also gave ring-substitution products.

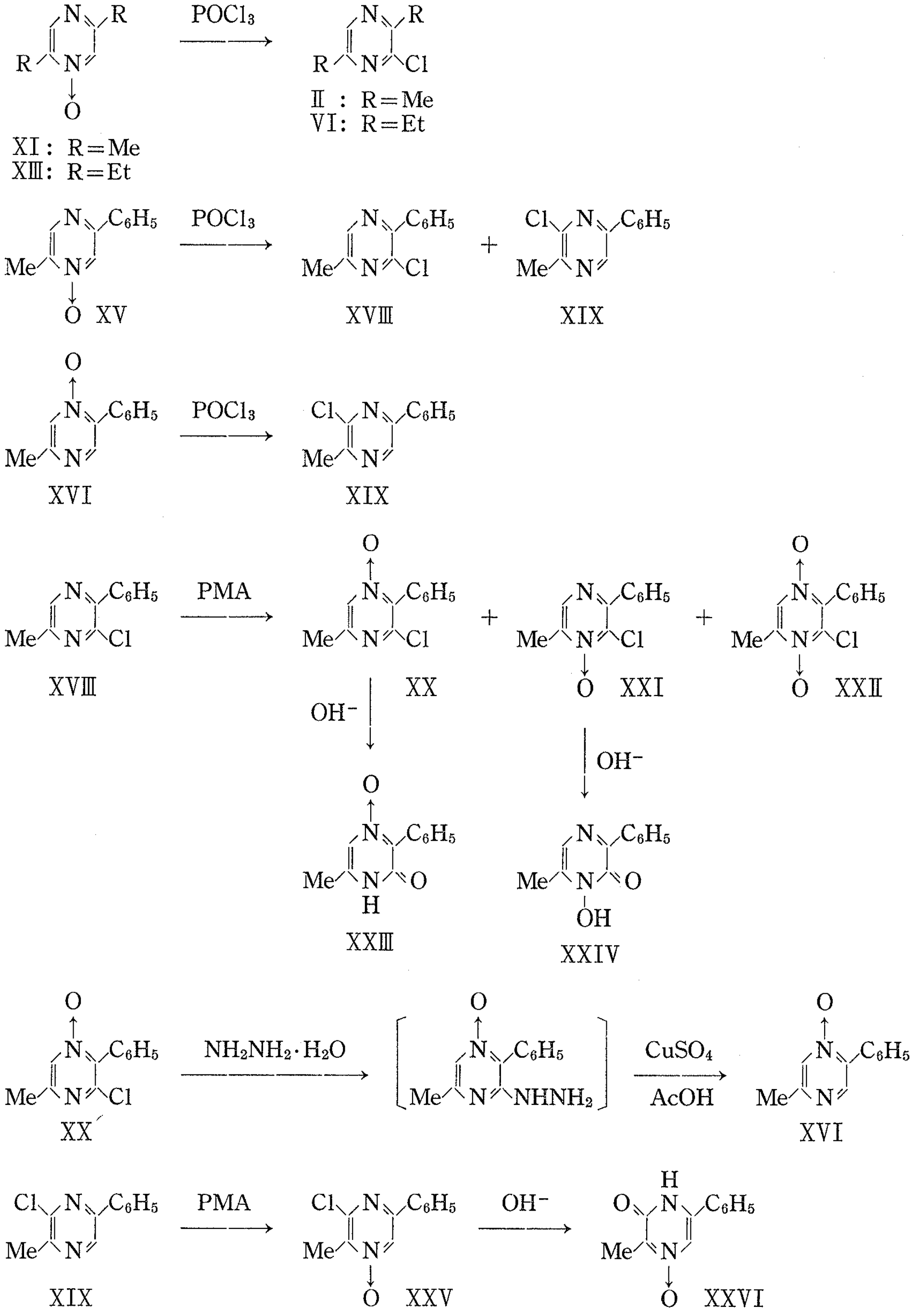

Chart 3

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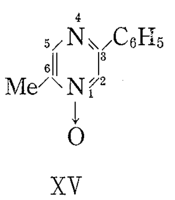
[18] T. Kato, *Yakugaku Zasshi*, 75, 1239 (1955).

In the course of elucidation of the structures of XVIII and XIX, various N-oxides and hydroxamic acids were prepared. Oxidation of XVIII with permaleic acid gave a crystalline mixture, which was separated by column chromatography into XX, 2-chloro-6-methyl-3-phenylpyrazine 1-oxide (XXI), and 2-chloro-6-methyl-3-phenylpyrazine 1,4-dioxide (XXII). A peak at *m/e* M^+-16 was observed in the mass spectrum of XX, while an M^+-17 peak was detected in the spectrum of XXI. These data clarified the relation between the methyl and N-oxide groups. Other reactions, described below, also supported the proposed structures, XX and XXI.

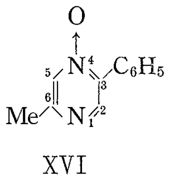
XX was hydrolyzed by heating in methanolic potassium hydroxide solution to yield 2-hydroxy-6-methyl-3-phenylpyrazine 4-oxide (XXIII), which did not give a color reaction with ferric chloride in methanol. XX was dechlorinated via a hydrazino compound to give XVI, as shown in Chart 3. Hydrolysis of XXI in an alkaline medium produced a cyclic hydroxamic acid, 2-hydroxy-6-methyl-3-phenylpyrazine 1-oxide (XXIV), which gave a red coloration with ferric chloride in methanol. XIX was also treated with permaleic acid to give only one monoxide, 2-chloro-3-methyl-6-phenylpyrazine 4-oxide (XXV), whose mass spectrum showed a peak at *m/e* M^+-17. XXV was hydrolyzed in potassium hydroxide solution to afford 2-hydroxy-3-methyl-6-phenylpyrazine 4-oxide (XXVI), which did not give the color reaction of a hydroxamic acid.

It is interesting that a nucleophilic reaction of XV with phosphoryl chloride took place at the β-position of the N-oxide group, as described above. Substitution at the β-position of an N–O group in mono-substituted pyrazine N-oxides has already been described in a few reports.[19a–c] Although the reaction mechanism of the conversion of XV to XIX was not studied in detail, it was ascertained that the displacement of a chlorine atom took place at the position of lowest π-electron density in the pyrazine ring. The π-electron density of each carbon in the molecules of XV and XVI was calculated by the simple Hückel method[20] and is shown in Fig. 1. In both cases, substitution occurred mainly at the position of lowest π-electron density.



XV

1.	1.68720
2.	0.80332
3.	1.00535
4.	1.13209
5.	1.01010
6.	0.70248



XVI

1.	0.95196
2.	1.18588
3.	0.87869
4.	1.67192
5.	0.86892
6.	0.87540

Fig. 1

Spring *et al.*[21] obtained 2-chloro-3,6-dimethylpyrazine 4-oxide (XXVII) by the oxidation of II with peracetic acid. The conversions of XXVII to III using phosphoryl chloride[21] and to XXXI by alkaline hydrolysis have been reported.[22] In the present work, II and VI were oxidized with permaleic acid to yield the corresponding 4-oxides (XXVII and XXIX) and 1,4-dioxides (XXVIII and XXX). Three monochloropyrazine monoxides (XX, XXV and XXIX) obtained in this work were treated with phosphoryl chloride under the same conditions used for XXVII, to give dichloropyrazines (VII and XXXIII), as shown in Chart 4.

Some reactions of XXVIII and XXX were also examined. The two dioxides were converted in high yields to the corresponding dichloropyrazine monoxides (XXXIV and

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19) *a*) L. Bernadi, G. Palamidessi, A. Leone, and G. Larini, *Gazz. Chim. Ital.*, **91**, 1431 (1961); *b*) G. Palamidessi and L. Bernadi, *Gazz. Chim. Ital.*, **93**, 339 (1963); *c*) S. Okada, A. Kosasayama, T. Konno, and F. Uchimaru, *Chem. Pharm. Bull.* (Tokyo), **19**, 1344 (1971).

20) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, 1961.

21) R.A. Baxter, G.T. Newbold, and F.S. Spring, *J. Chem. Soc.*, **1948**, 1859.

22) B. Klein, E. O'Donnell, and J.M. Gordon, *J. Org. Chem.*, **29**, 2623 (1964).

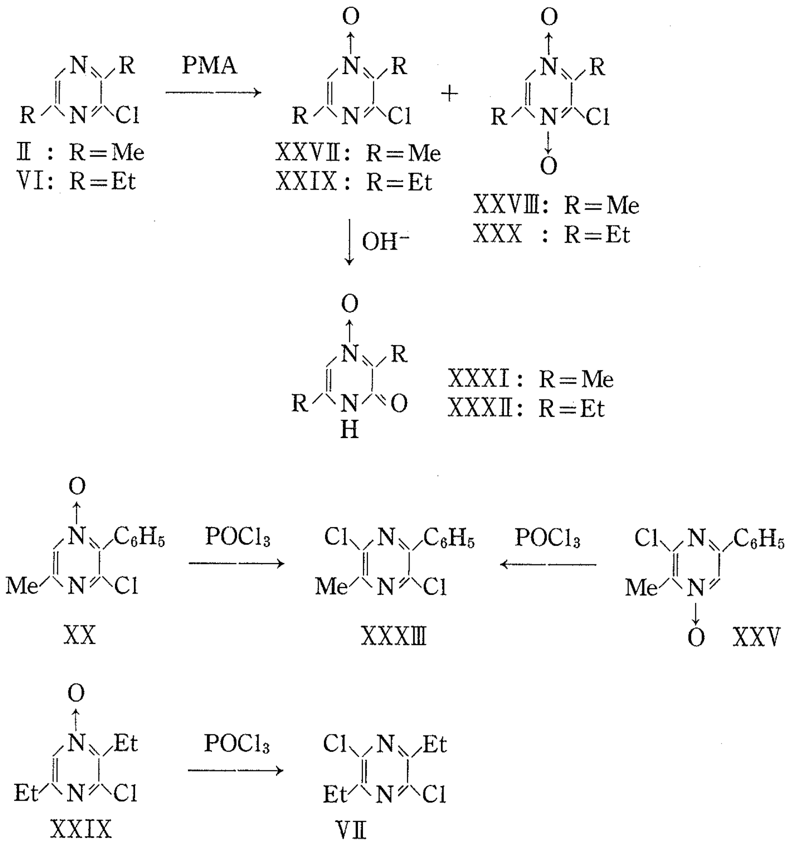

Chart 4

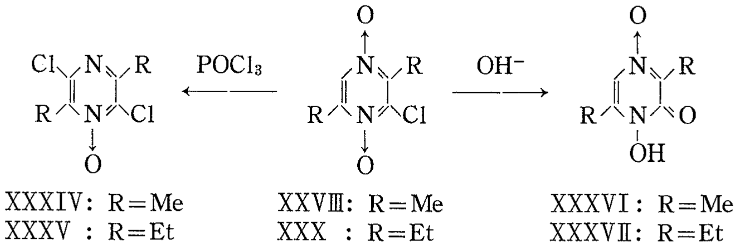

Chart 5

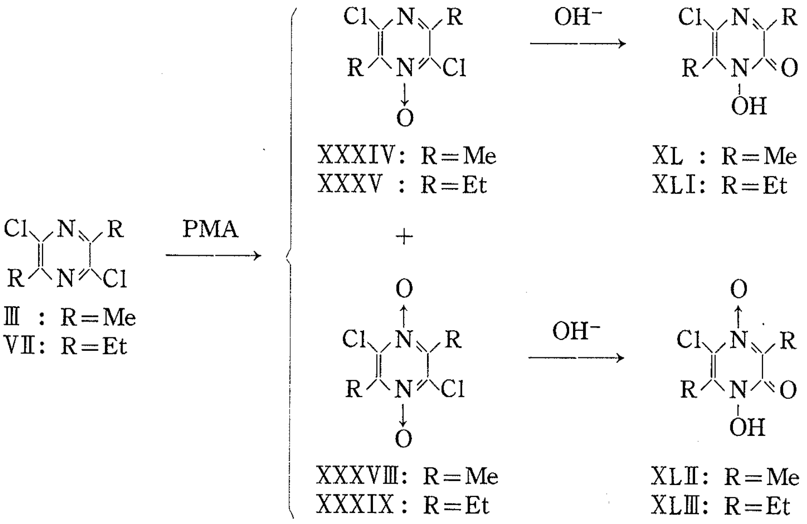

Chart 6

XXXV) by heating with phosphoryl chloride, and to hydroxamic acids (XXXVI and XXXVII) by alkaline hydrolysis.

N-Oxidation of 2,5-dichloropyrazines, III and VII, with permaleic acid was achieved successfully. Oxidation of III with per trifluoroacetic acid has already been reported to afford 2,5-dichloro-3,6-dimethylpyrazine 1,4-dioxide[23] (XXXVIII), and the oxidation of III and VII with permaleic acid also proceeded smoothly to give the corresponding monoxides and dioxides (XXXIV and XXXVIII, XXXV and XXXIX), which were easily separated by column chromatography. All the monoxides and dioxides thus obtained were converted to hydroxamic acids (XL, XLI, and XLIII) by hydrolysis in an alkaline medium, under conditions similar to those used for the preparation of XLII.[23] In all cases, dihydroxyl compounds could not be obtained. The inert character of the second chlorine atom is probably due to the formation of an anion of the hydroxamic acid which inhibits further attack by hydroxyl anion.[24]

The conversion of XI to 2-acetoxymethyl-5-methylpyrazine (XLIV) by treatment with acetic anhydride was reported by Koelsch and Gumprecht,[15] and was reexamined in the present work. In a manner similar to that reported, acetoxylation of four pyrazine monoxides (XI, XIII, XV, and XVI) was carried out as shown in Chart 7. XI gave only XLIV, while XIII afforded two acetoxyl compounds (XLVI and XLVII), which were purified by column chromatography and characterized on the basis of their PMR spectra. Interestingly, the formation ratio of XLVI and XLVII was 2: 5 under reflux, but 5: 7 at 140° in a sealed tube.

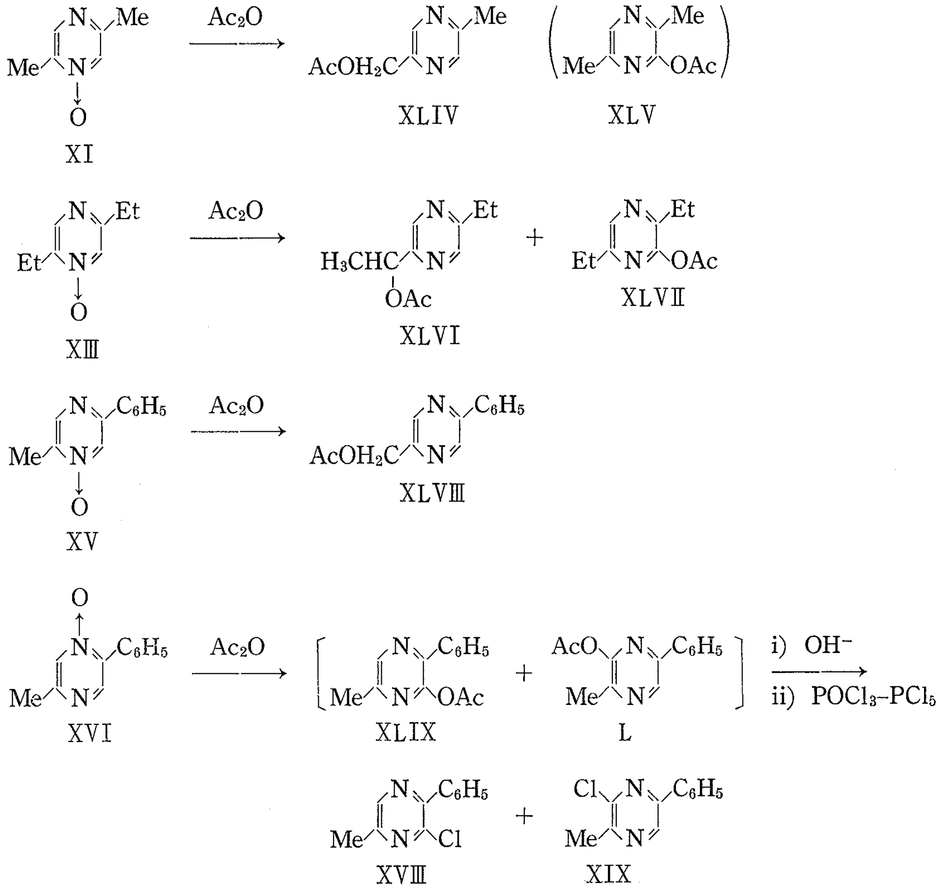

Chart 7

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23) K.W. Blake and P.G. Smmes, *J. Chem. Soc.* (*C*), **1970**, 1070.
24) G.W.H. Cheeseman and E.S.G. Törzs, *J. Chem. Soc.*, **1965**, 6681.

Kobayashi and Furukawa,[25a)] and Okuda[25b)] reported that refluxing of 2-picoline 1-oxide with acetic anhydride afforded 2-acetoxymethylpyridine, with small amounts of 3- and 5-acetoxy-2-picolines as by-products. The reaction of XI with acetic anhydride gave XLIV, but not XLV. Thus, the results of the reaction of XI were analogous to those in the case of 2-picoline 1-oxide. On the other hand, the substitution occurred preferentially on the pyrazine ring in the case of XIII. However, the reasons for these results are not clear.

Phenylpyrazines, XV and XVI, behaved differently. 2-Acetoxymethyl-5-phenylpyrazine (XLVIII) was derived from XV as a sole product on refluxing in acetic anhydride. On the other hand, XVI gave a mixture of two acetoxyl compounds which could not be separated from each other even by repeated column chromatography. In the PMR spectrum of this mixture, no signal due to methylene protons on an acetoxymethyl group was observed. This suggests that the acetoxylation occurred at the carbon atoms of the pyrazine ring and not on the side chain. The mixture was hydrolyzed in an alkaline medium without further purification and the product was treated with a mixture of phosphoryl chloride and phosphorus pentachloride to yield a mixture of chloropyrazines, which was shown by gas chromatography to be composed of XVIII and XIX in a 1: 10 ratio. On the basis of these data, it seemed reasonable to assume that the mixture derived from XVI by acetoxylation might be composed of 2-acetoxy-6-methyl-3-phenylpyrazine (XLIX) and 2-acetoxy-3-methyl-6-phenylpyrazine (L) in a 1: 10 ratio. Thus, an acetoxyl group was preferentially introduced at the position of lowest π-electron density.

3,6-Dimethyl-2-hydroxy- (LI), 3,6-diethyl-2-hydroxy-(LII), and 2-hydroxy-6-methyl-3-phenylpyrazines (LIII) were prepared from the monochloro derivatives (II, VI, and XVIII, respectively). Although Baxter and Spring[12)] obtained LI from II by alkaline hydrolysis, this hydrolysis proceeded more smoothly under acidic conditions. The products (LI and LII) gave the corresponding monoxides (XXXI and XXXII) on oxidation with peracetic acid, though in poor yield. As already shown in Chart 4, XXXI and XXXII were also produced from the chloropyrazine monoxides by alkaline hydrolysis. XXXI was converted to 2-chloro-3,6-dimethyl-5-hydroxypyrazine (LIV) by reaction with sulfonyl chlorides and further converted to III. The PMR spectrum of the crude product obtained from the reaction of XXXI with tosyl chloride contained no signal due to methylene protons. Thus, substitution occurred only on the pyrazine ring, as in the reaction of XI with phosphoryl chloride. This result differed from that in the reaction of 2-picoline 1-oxide with tosyl chloride,[26)] but the reason for this is not clear.

In order to modify the methyl groups of dimethylpyrazines, some reactions of III were also investigated. First, III was oxidized with potassium permanganate to afford 3,6-dichloro-5-methylpyrazine-2-carboxylic acid (LV) in 56% yield, and this was in turn converted to the methyl ester (LVI) by treatment with diazomethane. However, attempts to prepare the dicarboxylic acid under stronger conditions failed. Secondly, acetoxylation of the methyl group of III was carried out by refluxing XXXIV in acetic anhydride to yield a monoacetoxyl compound (LVII); its structure was elucidated from its PMR spectrum and analytical data. Thirdly, the dioxide (XXXVIII) was also treated with acetic anhydride to give an acetoxyl compound (LVIII), which gave a PMR spectrum consistent with the proposed structure. Namely, a singlet due to the methylene protons of the acetoxymethyl group appeared at lower field than in LVII; this behavior is similar to that of XXXV.

LIX and LX were converted to diketopiperazines, I and V, respectively, in good yield by catalytic hydrogenolysis in the presence of palladium-charcoal. Both products were optically inactive. The IR spectra and behavior on thin-layer chromatography (TLC)[27)] of I and

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25) *a*) G. Kobayashi and S. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **1**, 347 (1953); *b*) S. Okuda, *Chem. Pharm. Bull.* (Tokyo), **3**, 316 (1955).

26) E. Matsumura, *Nippon Kagaku Zasshi*, **74**, 363 (1953).

27) J.W. Westley, V.A. Close, D.N. Nitecki, and B. Halpern, *Anal. Chem.*, **40**, 1888 (1968).

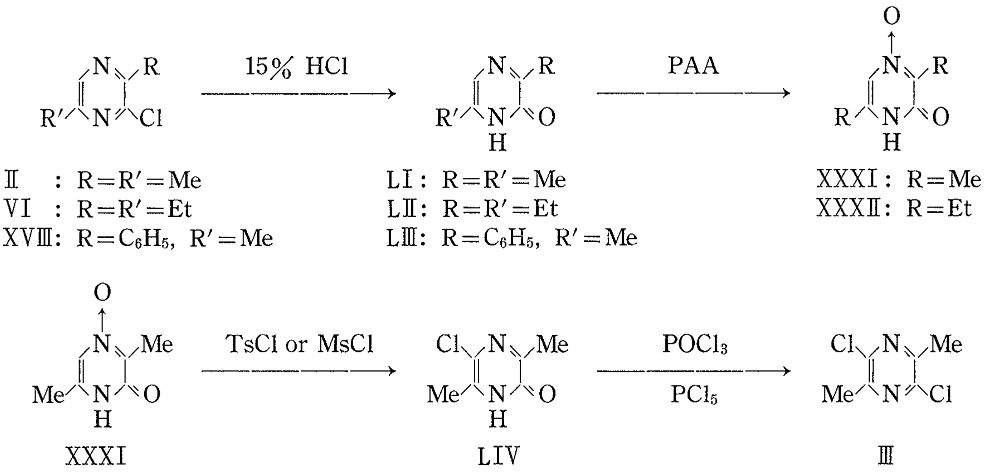

Chart 8

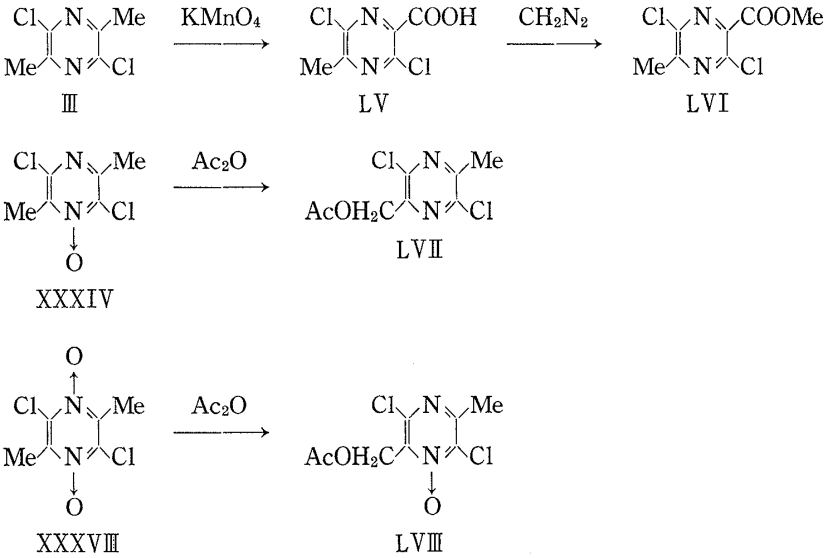

Chart 9

alanine anhydride (I'), prepared directly from DL-alanine by heating in ethylene glycol,[11] were the same. However, the PMR spectra of the two substances were different. The spectrum of I exhibited one doublet at 1.72 ppm (in CF_3COOD) due to the methyl protons, and this suggests that this product is a mixture of equal amounts of DD- and LL-alanine anhydride.[27] On the other hand, I' showed two doublets at 1.66 and 1.72 ppm. Namely, I' is a mixture of DD-, LL-, and DL-alanine anhydrides.

α-Aminobutyric anhydride (V'), which was prepared from DL-α-aminobutyric acid by the reported method,[11] gave two spots on a TLC plate.[27] On the other hand, V, derived from LX by reduction, gave only one spot, which was coincident with the lower spot of V'. V might therefore exist in a *cis* configuration. The PMR spectrum of V also supports this

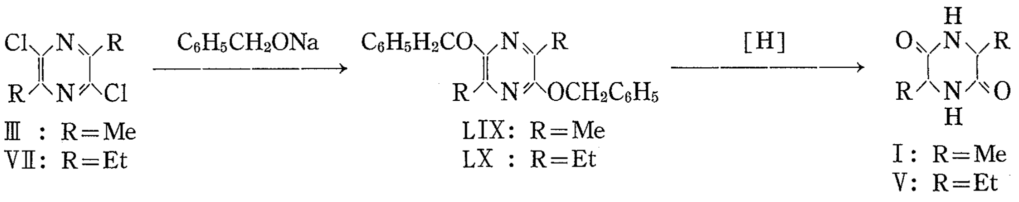

Chart 10

view. Namely, the signal of two methine protons on the diketopiperazine ring appears at 4.39 ppm (in CF_3COOD) as a triplet, indicating that these protons possess the same orientation. Consequently, the *cis* configuration is the more probable for V. On the other hand, V′, which was prepared directly from DL-α-aminobutyric acid, shows two triplets due to the methine protons in its PMR spectrum. This suggests that the methylenes on the diketopiperazine ring are not equivalent. This substance may be a mixture of DD-, LL-, and DL-α-aminobutyric anhydrides.

Experimental

Melting points were recorded on a Yanagimoto micro-melting point apparatus and are uncorrected. Boiling points are also uncorrected. Gas chromatograms were recorded on a Shimadzu GC-4B unit, UV spectra on a Hitachi 323 spectrometer, IR spectra on a Shimadzu IR-400 spectrometer, and PMR spectra on a JEOL JNM-PS-100 instrument with tetramethylsilane as an internal standard. Mass spectra were obtained with a Hitachi RMU-7L spectrometer.

(1) **Reaction of Alanine Anhydride (I′) with $POCl_3$**——A mixture of 21.32 g (150 mmol) of I′ and 100 ml of $POCl_3$ was heated under reflux for 30 min. The mixture was poured into ice-water, made alkaline with solid K_2CO_3, and extracted with ether. The ether layer was dried over Na_2SO_4 and evaporated down to give a brown oil, which was dissolved in hexane. The hexane layer was extracted with conc. HCl, dried over Na_2SO_4, and evaporated down to afford 6.59 g (25%) of III as colorless prisms, which were purified by sublimation, mp 70—72° (lit.[12] mp 73°). The HCl layer was made alkaline with solid K_2CO_3 and extracted with ether. The ether layer was dried over Na_2SO_4 and evaporated down to yield a brown oil of II, which was purified by distillation to give a colorless oil (7.72 g, 36%), bp 84—88°/35 Torr (lit.[12] bp 76°/15 Torr).

(2) **Reaction of α-Aminobutyric Anhydride (V′) with a Mixture of $POCl_3$ and PCl_5**——A mixture of 10 g (58.5 mmol) of V′, 30 ml of $POCl_3$, and 5 g of PCl_5 was heated in a sealed tube at 140° for 1 hr and the mixture was worked up as described in (1). VI: colorless oil, bp 80—85°/7 Torr (yield 3.82 g, 38%) (lit.[28] bp 81°/5 Torr—91°/6 Torr).

VII: colorless oil, bp 123—126°/25 Torr (yield 2.30 g, 19%). *Anal.* Calcd. for $C_8H_{10}Cl_2N_2$: C, 46.85; H, 4.92; N, 13.65. Found: C, 46.53; H, 5.07; N, 13.95. MS *m/e*: 204 (M^+), 189 (M^+-CH_3). PMR ($CDCl_3$) δ ppm: 1.28 (6H, t, $J=8$ Hz), 2.90 (4H, q, $J=8$ Hz). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 220.5 (3.95), 280 (3.69, shoulder,) 296.5 (3.82).

(3) **2,5-Dimethylpyrazine (IV)**——A solution of II (25 g, 0.175 mol) and AcONa (17.26 g, 0.21 mol) dissolved in a mixture of MeOH (80 ml) and H_2O (30 ml) was shaken in an H_2 stream in the presence of 3 g of 20% Pd-C. After filtration of the reaction mixture and removal of the solvent by evaporation, the residue was made alkaline by adding K_2CO_3 and ertracted with ether. The ether layer was extracted with 10% HCl. After the usual work-up of the extract, IV was obtained as a colorless oil, bp 150—155° (lit.[9] bp 155°), in almost quantitative yield. The ether layer gave a small amount of the starting material.

(4) **2,5-Diethylpyrazine (VIII)**——A solution of 17.05 g (0.1 mol) of VI and 9.02 g (0.11 mol) of AcONa dissolved in a mixture of 50 ml of H_2O and 50 ml of MeOH was treated as in (3) in the presence of 3 g of 20% Pd-C. The product was a colorless oil, bp 98—101°/36 Torr (lit.[29] 188—189°/760 Torr); yield, 11.93 g (88%).

(5) **2-Methyl-5-phenylpyrazine (IX)**——Phenylglyoxal (11.2 g, 0.083 mol) was added to a solution of propylenediamine (7.4 g, 0.1 mol) dissolved in EtOH (400 ml) under ice cooling with stirring. The reaction mixture was stirred for 1.5 hr at room temperature and then heated on a water bath for 9 hr, after adding KOH (5 g, 0.089 mol). After removal of the solvent *in vacuo*, the residue was extracted with ether. The usual work-up of the ether extract gave a brownish oil, which was chromatographed on silica gel (Wakogel C-200, 270 g) with hexane containing increasing amounts of ether. The fractions eluted with a mixture of hexane and ether (7: 3) were purified by distillation to give 2.7 g (18%) of X as a colorless oil, bp 158—160°/21 Torr.[13] The fractions eluted with a mixture of hexane and ether (3: 7) gave 3.0 g (20%) of IX as colorless prisms, which were recrystallized from hexane, mp 93—94°. *Anal.* Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.77; H, 6.00; N, 16.47. MS *m/e*: 170 (M^+). PMR ($CDCl_3$) δ ppm: 2.60 (3H, s), 7.52 (3H, m), 8.04 (2H, m), 8.56 (1H, s) and 8.96 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 249 (4.13), 290 (3.96).

(6) **Oxidation of 2,5-Diethylpyrazine (VIII)**——a) A solution of 16.5 g (0.12 mol) of VIII and 13.2 ml of 30% H_2O_2 in 300 ml of AcOH was heated at 70—75° for 9 hr. AcOH was then removed by distillation under reduced pressure, H_2O was added, and distillation was repeated. The residue was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The semi-solid residue obtained from the $CHCl_3$ extract by the usual work-up was triturated with hexane, and the insoluble solid, collected by suction, was recrystallized from EtOH to give 3.64 g (18%) of XIV as pale yellow plates, mp 208—209°. The filtrate was evaporated to dryness and the residue was purified by distillation to yield 9.51 g (52%) of XIII as a colorless oil, bp 135—140°/10 Torr.

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28) H. Gainer, M. Kokorudz, and W.K. Langdon, *J. Org. Chem.*, **26**, 2360 (1961).

29) W.K. Langdon, U.S. Patent 3067199 (1962) [*C.A.*, **58**, 10216*g* (1963)].

b) A solution of 16.5 g (0.12 mol) of VIII, 5.5 g (0.146 mol) of 90% H_2O_2, and 14.9 g (0.152 mol) of maleic anhydride dissolved in 300 ml of $CHCl_3$ was allowed to stand overnight at room temperature. The reaction mixture was washed successively with H_2O, 10% $KHCO_3$, and H_2O. The $CHCl_3$ extract was worked up as usual to give a semisolid, which was triturated with hexane. The insoluble crystals were collected by suction and recrystallized from EtOH to afford 1.89 g (9%) of XIV. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel, using a mixture of benzene, $CHCl_3$, and AcOEt as an eluant. The fractions eluted with a mixture of benzene and $CHCl_3$ (1: 1) gave 0.54 g of the starting material. The fractions eluted with $CHCl_3$ and a mixture of $CHCl_3$ and AcOEt (1: 1) yielded 11.57 g (63%) of XIII. XIII: *Anal.* Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.02; H, 7.74; N, 18.81. MS *m/e*: 152 (M^+), 135 (M^+-OH). PMR ($CDCl_3$) δ ppm: 1.32 (6H, t, $J=8$ Hz), 2.76 (2H, q, $J=8$ Hz), 2.88 (2H, q, $J=8$ Hz), 8.02 (1H, s), 8.32 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 225.5 (4.19), 268.5 (4.04), 295 (3.61, shoulder), 3.04 (3.51, shoulder). XIV: *Anal.* Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.09; H, 7.01; N, 16.50. MS *m/e*: 168 (M^+), 151 (M^+-OH). PMR ($CDCl_3$) δ ppm: 1.30 (6H, t, $J=8$ Hz), 2.86 (4H, q, $J=8$ Hz), 8.04 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 236 (4.27), 308 (4.20).

(7) **Oxidation of 2-Methyl-5-phenylpyrazine (IX)**——A solution of 11.9 g (0.07 mol) of IX, 5.29 g (0.14 mol) of 90% H_2O_2, and 15.05 g (0.154 mol) of maleic anhydride dissolved in 300 ml of $CHCl_3$ was allowed to stand overnight at room temperature, and then refluxed for 3 hr. The reaction mixture was worked up as described in (6-b) to give a crystalline product, which was chromatographed on silica gel (Wakogel C-200, 120 g), eluting successively with benzene, ether, and AcOEt. The fractions eluted with a mixture of benzene and ether (20: 1) gave 4.0 g (31%) of XV, which was recrystallized from a mixture of benzene and cyclohexane (1: 1) to furnish colorless needles, mp 161—162°. The fractions eluted with a mixture of benzene and ether (10: 1) yielded 0.053 g (0.4%) of XVI, which was recrystallized from benzene to give pale yellow needles, mp 128—129°. The AcOEt fractions afforded 2.8 g (20%) of XVII as colorless needles, which were recrystallized from MeOH to yield colorless prisms, mp 260—262° (dec.). XV: *Anal.* Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.97; H, 5.40; N, 15.34. MS *m/e*: 186 (M^+), 169 (M^+-OH). PMR ($CDCl_3$) δ ppm: 2.48 (3H, s), 7.46 (3H, m), 7.88 (2H, m), 8.46 (1H, s), 8.56 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 261.5 (4.42), 319 (3.61).

XVI: *Anal.* Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.58; H, 5.41; N, 15.17. MS *m/e*: 186 (M^+), 170 (M^+-O). PMR ($CDCl_3$) δ ppm: 2.54 (3H, s), 7.40 (3H, m), 7.66 (2H, m), 8.02 (1H, s), 8.42 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 252.5 (4.47), 280 (4.00), 320 (3.60).

XVII: *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.14; H, 5.00; N, 13.84. MS *m/e*: 202 (M^+), 186 (M^+-O). PMR (CF_3COOD) δ ppm: 2.72 (3H, s), 7.50—7.80 (5H, m), 8.84 (1H, s), 8.88 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 259.5 (4.26), 278.5 (4.11), 317 (4.25).

(8) **Reaction of 2,5-Diethylpyrazine 1-Oxide (XIII) with $POCl_3$**——A mixture of XIII (1.98 g, 13 mmol) and 10 ml of $POCl_3$ was refluxed for 20 min. The mixture was poured into ice-water, made alkaline with solid K_2CO_3, and extracted with ether. After working up as usual, the product was purified by distillation to give 1.92 g (87%) of VI as a colorless oil, bp 80—85°/7 Torr.

(9) **Reaction of 2-Methyl-5-phenylpyrazine 1-Oxide (XV) with $POCl_3$**——A mixture of 6.12 g (33 mmol) of XV and 66 ml of $POCl_3$ was refluxed for 1 hr. Excess reagent was distilled off under reduced pressure. The residue was treated with ice-water, made alkaline with solid K_2CO_3, and extracted with ether. A crystalline mass (8.42 g), obtained by the usual work-up of the ether layer, was chromatographed on silica gel (Wakogel C-200, 140 g), eluting with a mixture of hexane and ether. The fractions eluted with a mixture of hexane and ether (10: 1) gave 0.27 g (4%) of XIX, which was recrystallized from hexane to furnish colorless prisms, mp 67°. Further elution with a mixture of hexane and ether (8: 1) gave XVIII as a colorless oil, which was distilled *in vacuo*, bp 150—155°/5 Torr (4.4 g, 65%).

XVIII: *Anal.* Calcd. for $C_{11}H_9ClN_2$: C, 64.56; H, 4.40; N, 13.68. Found: C, 64.79; H, 4.35; N, 13.62. MS *m/e*: 204 (M^+). PMR ($CDCl_3$) δ ppm: 2.54 (3H, s), 7.36 (3H, m), 7.64 (2H, m), 8.32 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 241—247 (4.01), 290 (3.89), 303 (3.89).

XIX: *Anal.* Calcd. for $C_{11}H_9ClN_2$: C, 64.56; H, 4.40; N, 13.68. Found: C, 64.55; H, 4.34; N, 13.61. MS *m/e*: 204 (M^+). PMR ($CDCl_3$) δ ppm: 2.68 (3H, s), 7.40 (3H, m), 7.90 (2H, m), 8.72 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 253.5 (4.30), 219.5—293 (4.10), 314 (4.23).

(10) **Reaction of 2-Methyl-5-phenylpyrazine 4-Oxide (XVI) with $POCl_3$**——A mixture of XVI (93 mg, 0.5 mmol) and $POCl_3$ (1 ml) was refluxed for 1 hr and worked up as in the case of (9) to yield 40.4 mg (40%) of XIX.

(11) **Oxidation of 2-Chloro-6-methyl-3-phenylpyrazine (XVIII)**——A solution of XVIII (4.28 g, 21 mmol), maleic anhydride (8.23 g, 84 mmol), and 90% H_2O_2 (1.59 g, 42 mmol) dissolved in $CHCl_3$ (300 ml) was worked up as described in (7) to give colorless crystals, which were chromatographed on silica gel (Wakogel C-200, 180 g), eluting successively with benzene, ether, AcOEt, and MeOH. Elution with a mixture of benzene and ether (20: 1) gave XXI (0.45 g, 10%), which was recrystallized from MeOH to furnish colorless prisms, mp 113—114°. The fractions eluted with a mixture of benzene and ether (10: 1) gave XX (1.58 g, 34%), which was recrystallized from hexane to yield colorless prisms, mp 119—121°. XXII (0.94 g, 19%) was obtained from the fractions eluted with a mixture of AcOEt and MeOH (50: 1), and recrystallized from MeOH to furnish colorless prisms, mp 219—220°.

XX: *Anal.* Calcd. for $C_{11}H_9ClN_2O$: C, 59.68; H, 4.42; N, 12.65. Found: C, 59.99; H, 4.07; N, 12.99. MS *m/e*: 220 (M^+), 204 (M^+-O). PMR ($CDCl_3$) δ ppm: 2.48 (3H, s), 7.40 (5H, m), 7.96 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 235 (4.21), 249.5 (4.17), 312.5 (3.53).

XXI: *Anal.*Calcd. for $C_{11}H_9ClN_2O$: C, 59.68; H, 4.42; N, 12.65. Found: C, 59.70; H, 4.10; N, 12.62. MS *m/e*: 220 (M^+), 203 (M^+-OH). PMR ($CDCl_3$) δ ppm: 2.60 (3H, s), 7.40 (3H, m), 7.80 (2H, m), 8.42 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 265.5 (4.31), 328 (3.55).

XXII: *Anal.* Calcd. for $C_{11}H_9ClN_2O_2$: C, 55.83; H, 3.83; N, 11.83. Found: C, 55.93; H, 3.80; N, 11.96. MS *m/e*: 236 (M^+). PMR ($CDCl_3$) δ ppm: 2.52 (3H, s), 7.30—7.60 (5H, m), 8.13 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 259 (4.31), 278 (4.14), 315.5 (4.31).

(12) **2-Hydroxy-6-methyl-3-phenylpyrazine 4-Oxide (XXIII)**——A solution of 110 mg (0.5 mmol) of XX in a mixture of 1 ml of MeOH and 2 ml of 10% KOH was refluxed for 1 hr, then MeOH was evaporated off under reduced pressure. The residue was acidified with 20% HCl and extracted with CH_2Cl_2. After the usual work-up of the CH_2Cl_2 layer, 54 mg (58%) of XXIII was obtained as pale yellow crystals and recrystallized from EtOH to give pale yellow needles, mp 257° (dec.). *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.26; H, 4.99; N, 14.02. MS *m/e*: 202 (M^+), 186 (M^+-O). PMR (CF_3COOD) δ ppm: 2.50 (3H, s), 7.56 (5H, s), 7.68 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 240.5 (4.21), 292 (3.62), 353 (3.93). IR $_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1620 (C=O).

(13) **2-Methyl-5-phenylpyrazine 4-Oxide (XVI)**——A mixture of 884 mg (4 mmol) of XX, 10 ml of $NH_2NH_2 \cdot H_2O$, and 20 ml of EtOH was heated at 140° for 2.5 hr in a sealed tube. The solvent was removed by distillation *in vacuo*, then the residue was dissolved in $CHCl_3$ and washed with H_2O. A yellow oil, obtained by the usual work-up of the $CHCl_3$ layer, was dissolved in a mixture of 40 ml of AcOH and 40 ml of H_2O, and heated on a water bath. $CuSO_4 \cdot 5H_2O$ (2.4 g) dissolved in 16 ml of H_2O was added during a period of 10 min. The reaction mixture was further heated for 1 hr on a water bath, made alkaline with solid K_2CO_3, and extracted with ether. The ether layer was worked up as usual to give a brown oil, which was purified by silica gel (Wakogel C-200, 15 g) column chromatography. Elution with a mixture of benzene and ether (10: 1) afforded 313 mg (42%) of XVI as pale yellow crystals, which were recrystallized from benzene to give colorless prisms, mp 128—129°.

(14) **2-Hydroxy-6-methyl-3-phenylpyrazine 1-Oxide (XXIV)**——XXI (110 mg, 0.5 mmol) was heated in a mixture of 2 ml of MeOH and 2 ml of 10% KOH on a water bath for 1 hr, and worked up as described in (12) to yield 31 mg (31%) of XXIV as pale brown plates, which were recrystallized from iso-PrOH to furnish pale yellow prisms, mp 235° (dec.). XXIV gave a positive $FeCl_3$ test in MeOH. *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.08; H, 4.90; N, 13.71. MS *m/e*: 202 (M^+), 185 (M^+-OH). PMR (CF_3COOD) δ ppm: 2.62 (3H, s), 7.62 (5H, m), 7.92 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 250 (4.29), 341 (3.98). IR $_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1630 (C=O).

(15) **2-Chloro-3-methyl-6-phenylpyrazine 4-Oxide (XXV)**——A solution of XIX (102 mg, 0.5 mmol), maleic anhydride (98 mg, 1 mmol), and 90% H_2O_2 (30.1 mg, 0.8 mmol) dissolved in $CHCl_3$ (15 ml) was worked up as described in (7) to give 100 mg of a colorless solid. Chromatography on silica gel (Wakogel C-200, 7 g) using benzene as an eluant and subsequent recrystallization from MeOH afforded 61 mg (56%) of XXV as colorless prisms, mp 151—152°. *Anal.* Calcd. for $C_{11}H_9ClN_2O$: C, 59.68; H, 4.42; N, 12.65. Found: C, 59.84; H, 4.09; N, 12.51. MS *m/e*: 220 (M^+), 203 (M^+-OH). PMR ($CDCl_3$) δ ppm: 2.62 (3H, s), 7.40 (3H, m), 7.80 (2H, m), 8.44 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 265.5 (4.43), 328.5 (3.69).

(16) **2-Hydroxy-3-methyl-6-phenylpyrazine 4-Oxide (XXVI)**——A suspension of 55 mg (0.25 mmol) of XXV in a mixture of 1 ml of MeOH and 1 ml of 10% KOH was worked up as described in (12) to give 21 mg (38%) of XXVI, which was recrystallized from iso-PrOH to furnish colorless prisms, mp 247° (dec.). *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.04; H, 5.00; N, 13.71. MS *m/e*: 202 (M^+), 185 (M^+-OH). PMR (CF_3COOD) δ ppm: 2.72 (3H, s), 7.66 (5H, m), 8.04 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 250 (4.41), 341.5 (4.04). IR $_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1630 (C=O).

(17) **Oxidation of 2-Chloro-3,6-dimethylpyrazine (II)**——A solution of 0.425 g (2.5 mmol) of II, 1.13 g (30 mmol) of 90% H_2O_2, and 3.36 g (35 mmol) of maleic anhydride dissolved in 40 ml of $CHCl_3$ was allowed to stand overnight at room temperature and then refluxed for 3 hr. The reaction mixture was worked up as described in (7) to afford a crystalline mass, which was chromatographed on silica gel (Wakogel C-200, 8 g), eluting successively with hexane, AcOEt, and MeOH. The fraction eluted with a mixture of hexane and AcOEt (1: 1) gave 0.243 g (52%) of XXVII as colorless needles, which were recrystallized from a mixture of hexane and benzene (1: 1), mp 110—112° (lit.[21] mp 113—115°). The fractions eluted with a mixture of AcOEt and MeOH (4: 1) afforded 0.036 g (5%) of XXVIII, which was recrystallized from EtOH to furnish colorless prisms, mp 193—193.5°. *Anal.* Calcd. for $C_6H_7ClN_2O_2$: C, 41.26; H, 4.06; N, 16.04. Found: C, 41.60; H, 3.82; N, 15.78. MS *m/e*: 174 (M^+), 157 (M^+-OH). PMR ($CDCl_3$) δ ppm: 2.44 (3H, s), 2.60 (3H, s), 8.06 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 242 (4.40), 308 (4.33).

(18) **Oxidation of 2-Chloro-3,6-diethylpyrazine (VI)**——A solution of 17 g (0.1 mol) of VI, 11.33 g (0.3 mol) of 90% H_2O_2, and 33.6 g (0.35 mol) of maleic anhydride dissolved in 400 ml of $CHCl_3$ was allowed to stand overnight at room temperature, and then refluxed for 2 hr. The reaction mixture was worked up as in the case of (7) to give a semi-solid (*ca.* 20 g), which was chromatographed on silica gel (Wakogel C-200, 180 g), eluting with $CHCl_3$ containing increasing amounts of AcOEt. The fractions eluted with $CHCl_3$

and a mixture of $CHCl_3$ and AcOEt (1: 1), gave 12.53 g (67%) of XXIX, which was recrystallized from MeOH–H_2O to afford colorless crystals, mp 38—39°. The fractions eluted with a mixture of $CHCl_3$ and AcOEt (1: 1) and with AcOEt yielded 4.66 g (23%) of XXX, which was recrystallized from MeOH to give pale yellow plates, mp 127—129°.

XXIX: *Anal.* Calcd. for $C_8H_{11}ClN_2O$: C, 51.49; H, 5.94; N, 15.00. Found: C, 51.52; H, 5.99; N, 15.23. MS *m/e*: 186 (M^+), 169 (M^+-OH). PMR ($CDCl_3$) δ ppm: 1.24 (3H, t, $J=8$ Hz), 1.30 (3H, t, $J=8$ Hz), 2.72 (2H, q, $J=8$ Hz), 3.08 (2H, q, $J=8$ Hz), 7.94 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 233 (4.27), 273 (4.08), 301.5 (3.62), 312 (3.58).

XXX: *Anal.* Calcd. for $C_8H_{11}ClN_2O_2$: C, 47.41; H, 5.47; N, 13.80. Found: C, 47.53; H, 5.36; N, 13.49. MS *m/e*: 202 (M^+), 185 (M^+-OH). PMR ($CDCl_3$) δ ppm: 1.26 (6H, m), 2.90 (2H, q, $J=8$ Hz), 3.10 (2H, q, $J=8$ Hz), 8.00 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 243—244 (4.40), 311 (4.31).

(19) **3,6-Dimethyl-2-hydroxypyrazine 4-Oxide (XXXI)**——A solution of 158.5 mg (1 mmol) of XXVII in a mixture of 5 ml of 10% KOH and 5 ml of MeOH was refluxed for 3 hr and worked up as described in (12) to give 98 mg (70%) of XXXI, which was recrystallized from EtOH to furnish colorless prisms, mp 261—264° (dec.) (lit. mp 250°,[21] mp 270—272°[22]).

(20) **3,6-Diethyl-2-hydroxypyrazine 4-Oxide (XXXII)**——After refluxing 186 mg (1 mmol) of XXIX dissolved in a mixture of 10 ml of 10% KOH and 12 ml of MeOH for 1 hr, the reaction mixture was worked up as described in (12) to give 100 mg (60%) of XXXII, which was recrystallized from EtOH to furnish colorless prisms, mp 257—259°. *Anal.* Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.12; H, 7.23; N, 16.62. MS *m/e*: 168 (M^+), 151 (M^+-OH). PMR (CF_3COOD) δ ppm: 1.32 (3H, t, $J=8$ Hz), 1.40 (3H, t, $J=8$ Hz), 2.80 (2H, q, $J=8$ Hz), 3.16 (2H, q, $J=8$ Hz), 7.60 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 226 (4.21), 231 (4.22), 274 (3.83), 330 (3.84). IR $_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1635 (C=O).

(21) **2,5-Dichloro-3-methyl-6-phenylpyrazine (XXXIII)**——(a) A mixture of 110 mg (0.5 mmol) of XX and 2 ml of $POCl_3$ was refluxed for 1 hr and worked up as described in (8) to afford 100 mg (84%) of XXXIII, which was recrystallized from MeOH to give colorless prisms, mp 76—79°. *Anal.* Calcd. for $C_{11}H_8Cl_2N_2$: C, 55.26; H, 3.37; N, 11.71. Found: C, 55.25; H, 3.27; N, 11.89. MS *m/e*: 238 (M^+). PMR ($CDCl_3$) δ ppm: 2.60 (3H, s), 7.38 (3H, m), 7.72 (2H, m). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 250 (4.04, shoulder), 255 (4.05), 309.5 (4.08).

(b) A mixture of 220 mg (1 mmol) of XXV and 5 ml of $POCl_3$ was heated under reflux for 1 hr and worked up as before to yield 208 mg (87%) of XXXIII, which was recrystallized from MeOH to give colorless prisms, mp 76—79°.

(22) **2,5-Dichloro-3,6-diethylpyrazine (VII)**——A mixture of 3.73 g (20 mmol) of XXIX and 20 ml of $POCl_3$ was heated for 1 hr under reflux and worked up as described in (8) to give 3.46 g (85%) of VII as a colorless oil, bp 123—126°/25 Torr.

(23) **2,5-Dichloro-3,6-dimethylpyrazine 1-Oxide (XXXIV)**——A solution of 174.5 mg (1 mmol) of XXVIII dissolved in 5 ml of $POCl_3$ was refluxed for 20 min and worked up as described in (8) to yield a brown solid, which was purified by sublimation at 115—120°/3 Torr and subsequent recrystallization from EtOH to furnish 58 mg (30%) of XXXIV as colorless prisms, mp 116.5—117.5°. *Anal.* Calcd. for $C_6H_6Cl_2N_2O$: C, 37.33; H, 3.13; N, 14.51. Found: C, 37.68; H, 3.24; N, 14.35. MS *m/e*: 192 (M^+), 175 (M^+-OH). PMR ($CDCl_3$) δ ppm: 2.60 (6H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 215 (4.23), 236 (4.30), 271—272 (3.96), 309 (3.45), 314 (3.46), 319—320 (3.46).

(24) **2,5-Dichloro-3,6-diethylpyrazine 1-Oxide (XXXV)**——A mixture of 202 mg (1 mmol) of XXX and 5 ml of $POCl_3$ was heated for 20 min under reflux and worked up as before to give a brown oil, which was purified by silica gel (Wakogel C-200, 8 g) column chromatography. Elution with a mixture of hexane and AcOEt (100: 3) gave 170 mg (77%) of XXXV, which was recrystallized from MeOH–H_2O to afford colorless prisms, mp 39—41°. *Anal.* Calcd. for $C_8H_{10}Cl_2N_2O$: C, 43.46; H, 4.56; N, 12.67. Found: C, 43.20; H, 4.51; N, 12.79. MS *m/e*: 220 (M^+), 203 (M^+-OH). PMR ($CDCl_3$) δ ppm: 1.24 (3H, t, $J=8$ Hz), 1.30 (3H, t, $J=8$ Hz), 2.92 (2H, q, $J=8$ Hz), 3.10 (2H, q, $J=8$ Hz). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 216.5 (4.23), 239 (4.30), 273.5 (3.96), 310.5 (3.50), 316—321 (3.52).

(25) **3,6-Dimethyl-2-hydroxypyrazine 1,4-Dioxide (XXXVI)**——A suspension of 87.2 mg (0.5 mmol) of XXVIII in 3 ml of 2 N NaOH was heated under reflux for 1 hr. The mixture was acidified with dil. HCl and evaporated to dryness *in vacuo*. The residue was sublimed at 185°/5 Torr and then recrystallized from EtOH to afford 65 mg (83%) of XXXVI as colorless prisms, mp 223—224°, which gave a red coloration with $FeCl_3$ in MeOH. *Anal.* Calcd. for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.36; H, 5.17; N, 17.79. MS *m/e*: 156 (M^+). PMR (CD_3OD) δ ppm: 2.36 (6H, s), 7.76 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 230 (4.36), 279 (3.93), 335 (3.79). IR $_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1640 (C=O).

(26) **3,6-Diethyl-2-hydroxypyrazine 1,4-Dioxide (XXXVII)**——A mixture of 2.02 g (10 mmol) of XXX, 20 ml of 10% KOH and 20 ml of EtOH was refluxed for 2 hr and worked up as before to yield 1.78 g (98%) of XXXVII, which was recrystallized from acetone to furnish pale yellow plates, mp 243—245° (dec.). These crystals gave a positive $FeCl_3$ test. *Anal.* Calcd. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.38; H, 6.51; N, 15.23. MS *m/e*: 184 (M^+), 167 (M^+-OH). PMR (CF_3COOD) δ ppm: 1.34 (3H, t, $J=8$ Hz), 1.42 (3H, t, $J=8$ Hz), 3.04 (2H, q, $J=8$ Hz), 3.24 (2H, q, $J=8$ Hz), 7.76 (1H, s). UV $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ nm (log ε): 230 (4.35), 282 (3.93), 336 (3.84). IR $_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1630 (C=O).

(27) **Oxidation of 2,5-Dichloro-3,6-dimethylpyrazine (III)**——III (1.77 g, 10 mmol) was oxidized with permaleic acid, prepared from 90% H_2O_2 (2.03 g, 60 mmol) and maleic anhydride (7.38 g, 75 mmol), in 50 ml of $CHCl_3$ under reflux for 8 hr and worked up as described in (6-b) to yield a crystalline mass, which was chromatographed on silica gel (Wakogel C-200, 60 g) and eluted with benzene containing increasing amounts of $CHCl_3$. The fractions eluted with benzene and a mixture of benzene and $CHCl_3$ (1: 1) gave 1.33 g (69%) of XXXIV, which was recrystallized from EtOH to furnish colorless prisms, mp 116.5—117.5°. The $CHCl_3$ fractions gave 0.49 g (24%) of XXXVIII, which was recrystallized from MeOH to furnish colorless prisms, mp 224—225° (dec.) (lit.$^{23)}$ mp 231° (dec.)).

(28) **Oxidation of 2,5-Dichloro-3,6-diethylpyrazine (VII)**——A solution of 16.4 g (0.08 mol) of VII, 12.09 g (0.32 mol) of 90% H_2O_2, and 35.28 g (0.36 mol) of maleic anhydride dissolved in 400 ml of $CHCl_3$ was allowed to stand overnight at room temperature and then refluxed for 8 hr. The reaction mixture was worked up as before (7) to give an oily product, which was chromatographed on silica gel (Wakogel C-200, 60 g), eluting successively with benzene, $CHCl_3$, and AcOEt. The starting material was recovered from the benzene fractions (4.69 g). The fractions, eluted with a mixture of benzene and $CHCl_3$ (3: 1) and with $CHCl_3$ gave 10.04 g (57%) of XXXV, which was recrystallized from MeOH–H_2O to furnish colorless prisms, mp 39—41°. The fractions eluted with a mixture of $CHCl_3$ and AcOEt (3: 1) afforded 1.49 g (8%) of XXXIX, which was recrystallized from iso-PrOH to furnish colorless prisms, mp 206—207°.

XXXIX: *Anal.* Calcd. for $C_8H_{10}Cl_2N_2O_2$: C, 40.53; H, 4.24; N, 11.81. Found: C, 40.56; H, 4.32; N, 11.96. MS *m/e*: 236 (M^+). PMR ($CDCl_3$) δ ppm: 1.30 (6H, t, $J=8$ Hz), 3.18 (4H, q, $J=8$ Hz). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 215 (4.24), 254 (4.47), 314 (4.28).

(29) **5-Chloro-3,6-dimethyl-2-hydroxypyrazine 1-Oxide (XL)**——A suspension of 96.5 mg (0.5 mmol) of XXXIV in 5 ml of 2 N NaOH was heated on a water bath (80—90°) for 2 hr. After cooling, the reaction mixture was acidified with dil. HCl and extracted with $CHCl_3$ to afford a brownish product (76 mg), which was sublimed at 170–180°/5 Torr and then recrystallized from EtOH to furnish 61 mg (70%) of XL as colorless needles, mp 165—166.5°. XL gave a red coloration with $FeCl_3$ in MeOH. *Anal.* Calcd. for $C_6H_7ClN_2O_2$: C, 41.28; H, 4.04; N, 16.04. Found: C, 41.58; H, 4.39; N, 15.96. MS *m/e*: 174 (M^+). PMR ($CDCl_3$) δ ppm: 2.52 (3H, s), 2.58 (3H, s), 7.00 (1H, broad s). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 235—236 (4.30), 335 (3.89). IR $_{\max}^{\text{KBr}}$ cm^{-1}: 1620 (C=O).

(30) **5-Chloro-3,6-diethyl-2-hydroxypyrazine 1-Oxide (XLI)**——A solution of 1.1 g (5 mmol) of XXXV in a mixture of 15 ml of 5% KOH and 15 ml of dioxane was heated under reflux for 2 hr. The solvent was removed by distillation *in vacuo*. The residue was triturated with a small amount of H_2O and extracted with ether to give 65 mg of the starting material. The H_2O layer was acidified with dil. HCl. Extraction of the mixture with CH_2Cl_2 and the usual work-up gave a brownish solid (1.0 g), which was recrystallized from hexane to furnish 0.82 g (81%) of XLI as colorless prisms, mp 108—109°. *Anal.* Calcd. for $C_8H_{11}ClN_2O_2$: C, 47.42; H, 5.47; N, 13.82. Found: C, 47.43; H, 5.49; N, 14.06. MS *m/e*: 202 (M^+). PMR (CF_3COOD) δ ppm: 1.44 (6H, m), 3.16 (4H, m). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 242 (4.27), 352 (3.88). IR $_{\max}^{\text{KBr}}$ cm^{-1}: 1630 (C=O).

(31) **5-Chloro-3,6-diethyl-2-hydroxypyrazine 1,4-Dioxide (XLIII)**——A solution of 237 mg (1 mmol) of XXXIX in a mixture of 5 ml of 5% KOH and 10 ml of THF was heated at 50° for 1 hr. The reaction mixture was worked up as described in (12) to give a brownish solid, which was recrystallized from iso-PrOH to furnish 65 mg (30%) of XLIII as pale brown plates, mp 181—182°. *Anal.* Calcd. for $C_8H_{11}ClN_2O_3$: C, 43.95; H, 5.07; N, 12.81. Found: C, 44.05; H, 5.13; N, 13.00. MS *m/e*: 218 (M^+), 201 (M^+-OH). PMR ($CDCl_3$) δ ppm: 1.20 (3H, t, $J=8$ Hz), 1.34 (3H, t, $J=8$ Hz), 3.00 (2H, q, $J=8$ Hz), 3.08 (2H, q, $J=8$ Hz), 7.34 (1H, broad s). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 233.5 (4.17), 245 (4.16), 263.5 (4.15), 298.5 (3.79), 375 (3.91). IR $_{\max}^{\text{KBr}}$ cm^{-1}: 1625 (C=O).

(32) **Reaction of 2,5-Diethylpyrazine 1-Oxide (XIII) with Ac_2O**——a) A solution of 152 mg (1 mmol) of XIII in 2 ml of Ac_2O was refluxed for 6 hr, poured into ice water, made alkaline with solid K_2CO_3 and extracted with ether. The usual work-up of the extract gave a red-brown oil (171 mg), which was chromatographed on silica gel (Wakogel C-200, 5 g), eluting with hexane containing increasing amounts of AcOEt. The fractions eluted with a mixture of hexane and AcOEt (20: 1) gave 45 mg (23%) of XLVI as a colorless oil, bp 94—100°/3 Torr (bath temp.). Elution with a mixture of hexane and AcOEt (10: 1) afforded 113 mg (58%) of XLVII as a colorless oil, bp 78—85°/3 Torr (bath temp.).

b) A solution of 760 mg (5 mmol) of XIII in 8 ml of Ac_2O was heated at 140° for 3 hr in a sealed tube. The reaction mixture was worked up as described in a) to give a red-brown oil, which was chromatographed on silica gel (Wakogel C-200, 20 g) and eluted as in a) to yield 331 mg (34%) of XLVI and 460 mg (47%) of XLVII.

XLVI: *Anal.* Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.53; H, 6.98; N, 14.56. MS *m/e*: 194 (M^+), 151 (M^+-COCH_3). PMR ($CDCl_3$) δ ppm: 1.32 (3H, t, $J=8$ Hz), 1.60 (3H, d, $J=8$ Hz), 2.10 (3H, s), 2.84 (2H, q, $J=8$ Hz), 5.94 (1H, q, $J=8$ Hz), 8.40 (1H, s), 8.50 (1H, s). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 275 (3.90), 297 (3.80, shoulder). IR $_{\max}^{\text{film}}$ cm^{-1}: 1780 (C=O).

XLVII: *Anal.* Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; 7.27; N, 14.42. Found: C, 61.61; H, 7.33; N, 14.51. MS *m/e*: 194 (M^+), 152 (M^+-CH_2CO). PMR ($CDCl_3$) δ ppm: 1.28 (6H, m), 2.32 (3H, s), 2.70 (2H, q, $J=8$ Hz), 2.78 (2H, q, $J=8$ Hz), 8.28 (1H, s). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 270 (3.91), 275 (3.89), 298—309 (3.04). IR $_{\max}^{\text{film}}$ cm^{-1}: 1740 (C=O).

(33) **2-Acetoxymethyl-5-phenylpyrazine (XLVIII)**——A mixture of 186 mg (1 mmol) of XV and 2 ml of Ac_2O was heated under reflux for 1 hr and worked up as described in (32) to give a crystalline mass, which was recrystallized from hexane to yield 87 mg (38%) of XLVIII as pale yellow prisms, mp 85—87°. *Anal.* Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.43; H, 5.27; N, 12.39. MS *m/e*: 228 (M^+), 186 (M^+-CH_2CO). PMR ($CDCl_3$) δ ppm: 2.16 (3H, s), 5.24 (2H, s), 7.40 (3H, m), 7.90 (2H, m), 8.60 (1H, s), 8.90 (1H, s). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 250.5 (4.14), 290.5 (4.08). IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O).

(34) **Reaction of 2-Methyl-5-phenylpyrazine 4-Oxide (XVI) with Ac_2O**——After refluxing 93 mg (0.5 mmol) of XVI with 1 ml of Ac_2O for 1 hr, the mixture was worked up as described in (32). The product was hydrolyzed by heating in an alkaline medium (1 ml, 10% each of KOH and MeOH) to give a crystalline mass, which was heated under reflux in 1 ml of $POCl_3$ and a small amount of PCl_5 for 1 hr. The usual work-up gave a colorless oil, which gave peaks of XVIII and XIX (intensity 1: 10) on GLC (1.5% SE-30 on Shimalite, 1.5 m × 3 mm, column temp. 130°, N_2 flow rate: 40 ml/min).

(35) **3,6-Dimethyl-2-hydroxypyrazine (LI)**——After refluxing II (720 mg, 5.1 mmol) in 15 ml of 15% HCl for 1 hr, the mixture was made alkaline with solid K_2CO_3 and evaporated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was worked up as usual to afford colorless crystals, which were recrystallized from benzene to furnish 615 mg (98%) of LI as colorless needles, mp 206—207° (lit.[12] mp 208—210°).

(36) **3,6-Diethyl-2-hydroxypyrazine (LII)**——After refluxing a solution of 1.93 g (11 mmol) of VI in 20 ml of 15% HCl for 4 hr, the reaction mixture was made basic with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was worked up as usual to give 1.36 g (79%) of LII, which was recrystallized from acetone to furnish colorless prisms, mp 136—137° (lit.[30] mp 135°).

(37) **2-Hydroxy-6-methyl-3-phenylpyrazine (LIII)**——A solution of 666 mg (3 mmol) of XVIII in 15 ml of 15% HCl was refluxed for 4 hr. The reaction mixture was worked up as described in (36) to give 461 mg (83%) of LIII, which was recrystallized from iso-PrOH to furnish colorless needles, mp 214—214.5°. *Anal.* Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.97; H, 5.38; N, 15.11. MS *m/e*: 186 (M^+), 158 (M^+-CO). PMR ($CDCl_3$) δ ppm: 2.36 (3H, s), 7.38—7.60 (3H, m), 8.24—8.44 (2H, m), 13.50 (1H, broad s). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 228—231 (3.78), 253 (3.87), 352.5 (4.07). IRν_{max}^{KBr} cm^{-1}: 1650 (C=O).

(38) **3,6-Dimethyl-2-hydroxypyrazine 4-Oxide (XXXI)**——A mixture of 685 mg (5.5 mmol) of LI, 1.1 ml of 30% H_2O_2 and 20 ml of AcOH was heated at 65° for 5 hr. The mixture was distilled to dryness under reduced pressure and the residue was recrystallized from EtOH to give 720 mg (95%) of XXXI as colorless prisms, mp 261—264° (dec.) (lit. mp 250°,[21] mp 270—272°[22]).

(39) **3,6-Diethyl-2-hydroxypyrazine 4-Oxide (XXXII)**——A mixture of 760 mg (5 mmol) of LII, 1.1 ml of 30% H_2O_2 and 20 ml of AcOH was heated at 65—70° for 6 hr and worked up as described in (38) to give a pale yellow solid, which was recrystallized from EtOH to furnish 280 mg (37%) of XXXII as colorless needles, mp 257—259° (dec.).

(40) **2-Chloro-3,6-dimethyl-5-hydroxypyrazine (LIV)**——a) A solution of 175 mg (1.25 mmol) of XXXI and 358 mg (1.8 mmol) of TsCl dissolved in 15 ml of CH_3CN was refluxed for 3 hr. The mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from a mixture of hexane and benzene (1:1) to afford 143 mg (72%) of LIV as colorless needles, mp 220° (lit.[21] mp 222—224°).

b) A solution of 350 mg (2.5 mmol) of XXXI and 430 mg (3.75 mmol) of MsCl dissolved in 20 ml of CH_3CN was refluxed for 1.5 hr. After removing the solvent by distillation, the residue was dissolved in ether and extracted with 2 N NaOH. The ether layer was discarded. The H_2O layer was acidified with dil. HCl and extracted with $CHCl_3$. The usual work-up of the extract gave 203 mg (51%) of LIV.

(41) **2,5-Dichloro-3,6-dimethylpyrazine (III)**——A mixture of 158.5 mg (1 mmol) of LIV, 2 ml of $POCl_3$, and a small amount of PCl_5 was heated in a sealed tube at 150° for 5 hr. The usual work-up gave 170 mg (97%) of III as colorless prisms, mp 71—73° (lit.[12] mp 73°).

(42) **3,6-Dichloro-5-methylpyrazine-2-carboxylic Acid (LV)**——A solution of 88.5 mg (0.5 mmol) of III and 40 mg (0.25 mmol) of $KMnO_4$ in a mixture of pyridine (3 ml) and H_2O (1 ml) was warmed on a water bath (70°) for 2 hr. After removing MnO_2 by suction, the filtrate was acidified with 2 N HCl and evaporated to dryness. Extraction of the residue with acetone gave 57 mg of crystals, which were recrystallized from H_2O to give 28.5 mg (28%) of LV as colorless needles, mp 122—123°. *Anal.* Calcd. for $C_6H_4Cl_2N_2O_2$: C, 34.81; H, 1.95; N, 13.53. Found: C, 34.87; H, 2.08; N, 13.34. MS *m/e*: 206 (M^+), 162 (M^+-CO_2). PMR (CD_3OD) δ ppm: 2.65 (3H, s). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 224—226 (3.98), 291 (3.83). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O).

(43) **3,6-Dichloro-5-methylpyrazine-2-carboxylic Acid Methylester (LVI)**——An ether solution of CH_2N_2 was added to a solution of 206 mg (1 mmol) of LV dissolved in 10 ml of ether, and the mixture was allowed to stand for 0.5 hr at room temperature. The solvent was evaporated off, then the residue was recrystallized from MeOH–H_2O to give 185 mg (84%) of LVI as colorless needles, mp 56—57°. *Anal.* Calcd. for $C_7H_6Cl_2N_2O_2$: C, 38.03; H, 2.74; N, 12.67. Found: C, 38.06; H, 2.65; N, 12.31. MS *m/e*: 220 (M^+), 189 (M^+-OCH_3). PMR ($CDCl_3$) δ ppm: 2.70 (3H, s), 3.98 (3H, s). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 227 (4.05), 295 (3.90). IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O).

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(44) **2-Acetoxymethyl-3,6-dichloro-5-methylpyrazine (LVII)**——A mixture of 384 mg (2 mmol) of XXXIV and 5 ml of Ac_2O was heated in a sealed tube at 190° for 2 hr and worked up as described in (32) to give a brown oil, which was chromatographed on Florisil (10 g). Elution with a mixture of hexane and AcOEt (20: 1) afforded 85 mg (18%) of LVII, which was recrystallized from hexane to furnish colorless prisms, mp 88—89°. *Anal.* Calcd. for $C_8H_8Cl_2N_2O_2$: C, 40.88; H, 3.43; N, 11.91. Found: C, 41.08; H, 3.47; N, 12.11. MS *m/e*: 234 (M^+), 192 (M^+-CH_2CO). PMR ($CDCl_3$) δ ppm: 2.40 (3H, s), 2.48 (3H, s), 4.72 (2H, s). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 219.5 (4.04), 279.5 (3.87, shoulder), 291.5 (3.97). IR $_{\max}^{\text{KBr}}$ cm^{-1}: 1780 (C=O).

(45) **2-Acetoxymethyl-3,6-dichloro-5-methylpyrazine 1-Oxide (LVIII)**——A solution of 338 mg (1.6 mmol) of XXXVIII in 20 ml of Ac_2O was refluxed for 0.5 hr. The solvent was distilled off under reduced pressure, then the residue was treated with H_2O and extracted with CH_2Cl_2. The usual work-up of the extract gave a brown oil, which was chromatographed on Florisil (6 g) and eluted with benzene to yield 63.2 mg (16%) of LVIII as colorless crystals. These crystals were recrystallized from EtOH to furnish colorless plates, mp 119—120.5°. *Anal.* Calcd. for $C_8H_8Cl_2N_2O_3$: C, 38.27; H, 3.21; N, 11.16. Found: C, 38.65; H, 3.26; N, 10.91. MS *m/e*: 250 (M^+), 233 (M^+-OH). PMR ($CDCl_3$) δ ppm: 2.16 (3H, s), 2.63 (3H, s), 5.22 (2H, s). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 217 (4.22), 239 (4.29), 273.5 (3.97), 310 (3.36), 321 (3.33). IR $_{\max}^{\text{KBr}}$ cm^{-1}: 1738 (C=O).

(46) **2,5-Dibenzyloxy-3,6-dimethylpyrazine (LIX)**——A mixture of III (3.54 g, 20 mmol) and sodium benzyloxide, prepared from 1.38 g (60 mg atom) of Na and 70 ml of benzylalcohol, was heated at 160—165° for 7 hr in a sealed tube. The solvent was distilled off *in vacuo*, then the yellow residue was triturated with H_2O and extracted with ether. The ether layer was dried over Na_2SO_4 and evaporated down to give yellowwish crystals (*ca.* 5 g), which were chromatographed on alumina (150 g). Elution with a mixture of hexane and ether (9: 1) afforded 3.29 g (51%) of LIX, which was recrystallized from MeOH to give colorless needles, mp 94.5—95.5°. *Anal.* Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.72. Found: C, 74.95; H, 5.91; N, 8.75. MS *m/e*: 320 (M^+). PMR ($CDCl_3$) δ ppm: 2.36 (6H, s), 5.30 (4H, s), 7.24—7.50 (10H, m). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 275 (3.24), 317 (3.99).

(47) **2,5-Dibenzyloxy-3,6-diethylpyrazine (LX)**——A mixture of VII (214 mg, 1 mmol) and sodium benzyloxide, prepared from Na (115 mg, 5 mg atom) and benzylalcohol (6 ml), was heated in a sealed tube at 160—165° for 6 hr and worked up as described for the synthesis of LIX to yield 97 mg (28%) of LX, which was recrystallized from hexane to give colorless needles, mp 78°. *Anal.* Calcd. for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.68; H, 6.99; N, 8.03. MS *m/e*: 348 (M^+). PMR (CCl_4) δ ppm: 1.24 (6H, t, $J=8$ Hz), 2.76 (4H, q, $J=8$ Hz), 5.32 (4H, s), 7.10—7.50 (10H, m). UV $\lambda_{\max}^{95\%\ \text{EtOH}}$ nm (log ε): 273 (3.14), 317 (3.99).

(48) **Alanine Anhydride (I)**——LIX (320 mg, 1 mmol) was catalytically reduced in the presence of 100 mg of 10% Pd-C in 10 ml of EtOH. The catalyst was removed by suction and the solvent was evaporated off *in vacuo* to give colorless crystals, which were recrystallized from H_2O to furnish 135 mg (95%) of I as colorless prisms, mp 276—277° (lit.mp 279°,[31] mp 272°[32]). PMR (CF_3COOD) δ ppm: 1.72 (6H, d, $J=8$ Hz), 4.49 (2H, q, $J=8$ Hz).

(49) **Alanine Anhydride[11] (I′) derived from DL-Alanine**——PMR (CF_3COOD) δ ppm: 1.66 (d, $J=8$ Hz), 1.72 (d, $J=8$ Hz), 4.48 (q, $J=8$ Hz).

(50) **α-Aminobutyric Anhydride (V)**——LX (35 mg, 0.1 mmol) was catalytically reduced in the presence of 10 mg of 5% Pd-C in 5 ml of MeOH. After work-up as before, the product was purified by recrystallization from ethylene glycol monomethyl ether to give 16 mg (94%) of V as colorless needles, mp 246—248° (lit. mp 265—266°,[33] mp 254—255°[34]). PMR (CF_3COOD) δ ppm: 1.14 (6H, t, $J=9$ Hz), 2.08 (2H, m), 4.39 (2H, t, $J=5$ Hz).

(51) **α-Aminobutyric Anhydride (V′) derived from DL-α-Aminobutyric Acid**——PMR (CF_3COOD) δ ppm: 1.12 (t, $J=8$ Hz), 1.16 (t, $J=8$ Hz), 2.14 (m), 4.40 (t, $J=6$ Hz), 4.48 (t, $J=6$ Hz).

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