Some Reactions of Mono Substituted Pyrazine Monoxides

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The reactions of the monoxides of propylpyrazine and phenylpyrazine with phosphoryl chloride or acetic anhydride were investigated. Except in the case of the reaction of 2-propylpyrazine 1-oxide with acetic anhydride, chlorination or acetoxylation occurred on the pyrazine ring in all cases; moreover, these reactions occurred preferentially at the position poorest in π-electron density. The *N*-oxidation and the successive chlorination of monochloro-phenylpyrazines were also investigated, and the structures of the products were confirmed.

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As well known, by the treatment of 2-methylpyrazine monoxides with acetic anhydride, acetoxylation takes place on the pyrazine ring or the side chain (1). In the course of work on the reaction of pyrazines, the present report describes some reactions of 2-substituted pyrazine monoxides, above all 2-propylpyrazine and 2-phenylpyrazine monoxides, with phosphoryl chloride or acetic anhydride.

The preparative methods of alkylpyrazines have been reviewed in detail by Cheeseman and Werstiuk (2). Moreover, a procedure using alkyl 2-pyrazinyl sulfones was reported recently by Konakahara and co-workers (3). In the present work, the catalytic hydrogenolysis of a chloropyrazine was adopted for the synthesis of the starting material. Namely, 2-chloro-3-propylpyrazine (**2**), prepared from 2-hydroxy-3-propylpyrazine (**1**) (4), was hydrogenolysed over palladium on carbon to afford 2-propylpyrazine (**3**) in satisfactory yields. On the other hand, 2-phenylpyrazine (**4**) (5) was prepared by the condensation of phenylglyoxal with ethylenediamine and subsequent dehydrogenation by heating in the presence of sodium hydroxide.

The permaleic acid oxidation of **3** gave 2-propylpyrazine 1-oxide (**5**) and 2-propylpyrazine 4-oxide (**6**), which were carefully separated by silica gel chromatography from each other. 2-Propylpyrazine 1,4-dioxide (**7**) was prepared by the oxidation of the parent amine (**3**) with an excess of permaleic acid or by the additional oxidation of the monoxides (**5** and **6**) with permaleic acid. Under the same conditions **4** gave 2-phenylpyrazine 4-oxide (**8**) (5) as a sole product in good yields. On the other hand, 2-phenylpyrazine 1-oxide (**9**) (5) was prepared from 2-chloro-3-phenylpyrazine 4-oxide (**25**) by dechlorination *via* a hydrazino compound.

The structures of **5** and **6** were elucidated by their mass spectral data. An $M^+ - 17$ ion peak was observed in the mass spectra of **5**, while an $M^+ - 16$ peak appeared in that of **6** (6). The structural disparity between **8** and **9** was clarified by comparison of the chemical shifts of the ring protons. In the nmr spectrum of the former, the signals due to two ring protons were observed in a higher field than in the spectrum of the parent amine (**4**) (7). In the case of the latter, the signal due to one proton shifted to a higher field.

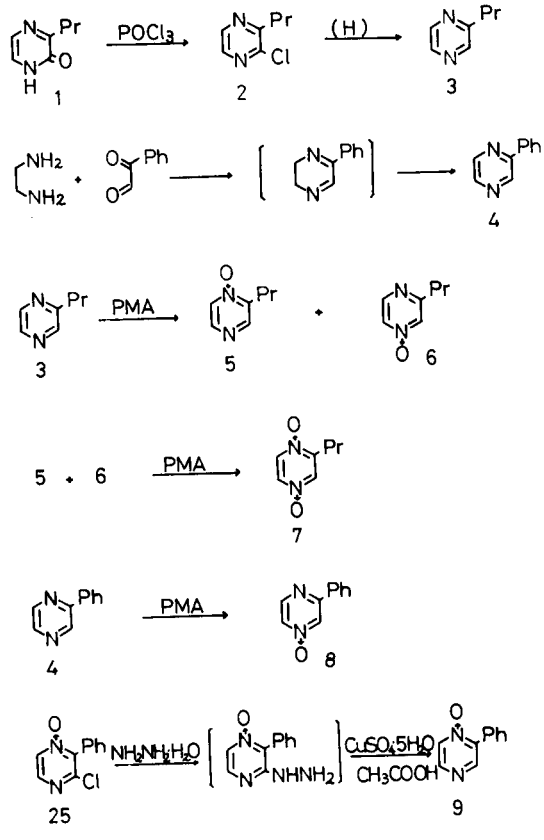


Chart 1

Compound **5** was treated with phosphoryl chloride under reflux to give an oily mixture of the chloro compounds, which could not be separated by column chromatography. On the basis of the nmr spectral investigation, it was confirmed that the mixture was composed of chloropyrazines, **2**, 5-chloro-2-propylpyrazine (**10**), and 6-chloro-

2-propylpyrazine (**11**), carrying chloro atoms on the pyrazine ring and, moreover, in a 2:2:3 ratio. By the same treatment **6** gave a mixture of **2**, **10**, and **11** in a 4:1:1 ratio. The authentic sample of **11** was prepared from DL-glycylnorvalyl anhydride (**12**) by treatment with a mixture of phosphoryl chloride and phosphorus pentachloride. Namely, a dichloropyrazine and a monochloropyrazine were obtained and the former ought to be 2,5-dichloro-6-propylpyrazine (**13**) on the basis of the reaction process. On the other hand, the structure of the monochloropyrazine was confirmed as 2-chloro-6-propylpyrazine (**11**) by comparing the nmr spectrum with that of **2**. Since **10** did not come to our hand, the spectrum of the chloropyrazines derived from **5** could not be directly compared with that of **10**. However, the triplet at 2.84 ppm ought to be due to the α-methylene protons of **10** on the basis of elimination.

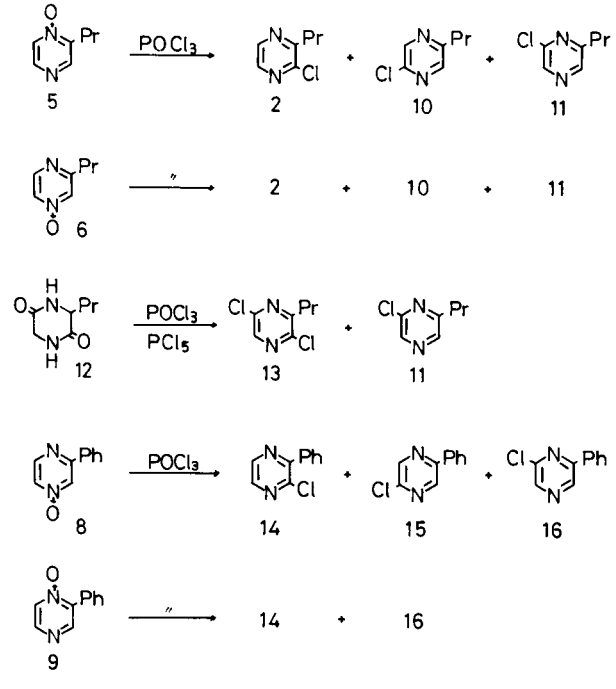
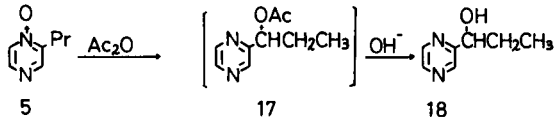
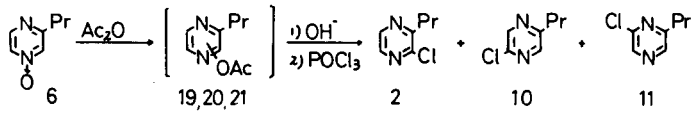


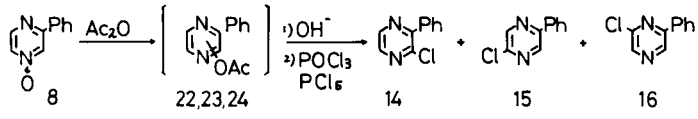
Chart 2

Whereas the reaction of **8** with phosphoryl chloride yielded 3-chloro-2-phenylpyrazine (**14**), 5-chloro-2-phenylpyrazine (**15**), and 6-chloro-2-phenylpyrazine (**16**) in a 9:2:9 ratio, **14** and **16** were obtained in 1:8 by the reaction of **9**. The chlorophenylpyrazines **14**, **15**, and **16** could be separated by column chromatography and their structures were determined by comparison of their physical constants with the reported ones (8,9,10).

As described above, the reaction of mono-substituted pyrazine monoxides with phosphoryl chloride took place also at the β-position of the *N*-oxide group. Although a substitution mechanism at the β-position of mono-substituted pyrazine monoxides has been suggested by Bernardi, *et al.*, and Okada, *et al.* (11,12), it can also be explained that the introduction of a chlorine atom took place mainly at the position where the π-electron density is the least in the pyrazine ring. As the parameter on the propyl group was not known and there might be a similarity in π-electron density of the pyrazine ring between 2-methylpyrazine and 2-propylpyrazine monoxides, the π-electron density of each carbon atom of 2-methylpyrazine 1- and 4-oxides was calculated by the simple Hückel method (13) and is shown in Figure 1. The π-electron density of **8** and **9** was also given in Figure 1.







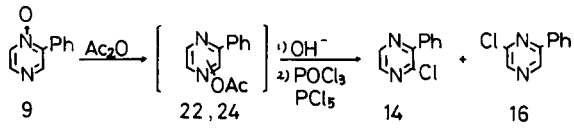
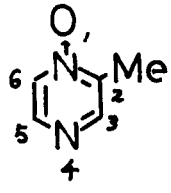


Chart 3

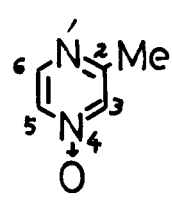
Under similar conditions as described by Asai (1), acetoxylation of the pyrazine monoxides **5**, **6**, **8**, and **9** was achieved and the results are shown in Chart 3. Compound **5** gave solely 2-(α-acetoxy)propylpyrazine (**17**), which was hydrolysed in a methanolic potassium hydroxide solution to yield 2-(α-hydroxy)propylpyrazine (**18**). On the other hand, **6** gave a mixture of the acetoxyl compounds which could not be separated by column chromatography. In the nmr spectrum of the mixture, no signal of the methine proton on the acetoxylated side chain was observed. Without further purification, the mixture was hydrolysed in an alkaline medium and the products were heated with phosphoryl chloride to give a mixture of monochloropropylpyrazines. This mixture was composed of **2**, **10**, and **11** in a 3:2:1 ratio. This result may suggest that the acetoxylation of **6** took place at C-3, C-5, and C-6 on the pyrazine ring in a 3:2:1 ratio and, moreover, mainly at the position poorest in π-electron density.

Figure I

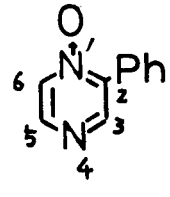
Calculated π-Electron Density of Some Pyrazine Monoxides



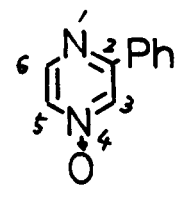
1	1.68838
2	0.69721
3	1.01365
4	1.11449
5	1.00541
6	0.81496



1	1.18465
2	0.86750
3	0.86252
4	1.65529
5	0.85202
6	0.96542



1	1.67422
2	0.84368
3	0.95374
4	1.13073
5	0.97824
6	0.81409



1	1.14758
2	0.96973
3	0.79646
4	1.65606
5	0.82262
6	0.96364

The treatment of **8** in a similar manner to that of **6** afforded a mixture of the chloropheneylpyrazines **14, 15,** and **16**. The formation ratio of this mixture was 4:1:2. Compound **9** gave **14** and **16** in a 1:3 ratio. On the basis of these data, it seemed reasonable to assume that the mixture of the acetoxylated compounds derived from **8** might be composed of 2-acetoxy-3-phenyl- (**22**), 2-acetoxy-5-phenyl- (**23**), and 2-acetoxy-6-phenypyrazines (**24**) in a 4:1:2 ratio; the corresponding mixture produced from **9** might be composed of **22** and **24** in a ratio of 1:3. Namely, the acetoxylation of **8** and **9** occurred preferentially at the position poorest in π-electron density, as in the case of chlorination.

Next, oxidation of the chlorophenylpyrazines **14, 15,** and **16** with permaleic acid was carried out. While a sole product was prepared from **16**, the two former starting materials gave two or three *N*-oxides. In the course of determining the position of the N-O group in these *N*-oxides, some hydroxy compounds were prepared. 2-Chloro-3-phenylpyrazine 4-oxide (**25**) was hydrolysed by heating in a methanolic potassium hydroxide solution to afford 2-hydroxy-3-phenylpyrazine 4-oxides (**31**), which indicated no hydroxamic acid coloration. 2-Chloro-5-phenylpyrazine 1-oxide (**27**) was also treated similarly to give 2-hydroxy-5-phenylpyrazine 1-oxide (**32**), which showed red coloration with ferric chloride. 2-Hydroxy-5-phenylpyrazine 4-oxide (**33**) and 2-hydroxy-6-phenylpyrazine 4-oxide

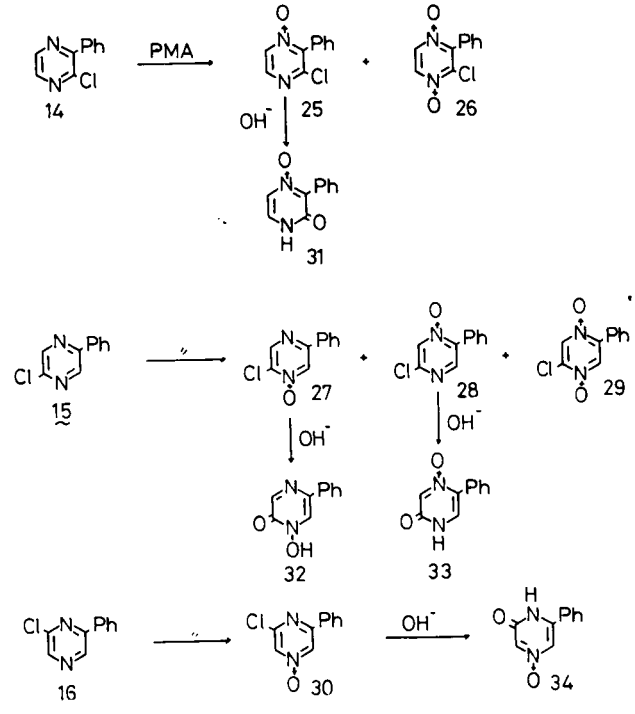


Chart 4

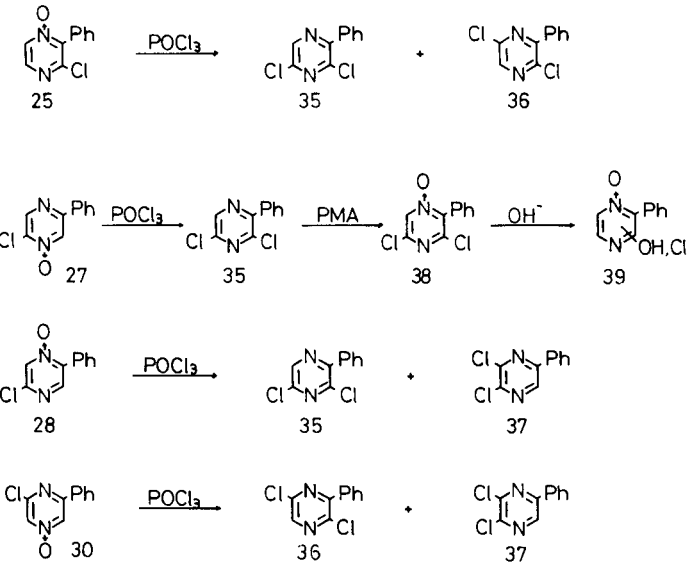


Chart 5

(**34**) derived, respectively, from 2-chloro-5-phenylpyrazine 4-oxide (**28**) and 2-chloro-6-phenylpyrazine 4-oxide (**30**), did not color with ferric chloride.

As shown in Table 1, the chlorophenylpyrazine monoxides were converted to the dichloro compounds on treatment with phosphoryl chloride. While **27** provided a sole product, 2,6-dichloro-3-phenylpyrazine (**35**), all other compounds gave two products. Determination of the position of the newly incorporated chlorine atom in the pyrazine ring of **35** was achieved by *N*-oxidation with permaleic acid and the following hydrolysis with potassium hydroxide solution. Namely, 2,6-dichloro-3-phenylpyrazine 4-oxide (**38**) derived from **35** yielded a mixture of the hydroxyl compounds, which could not be separated by silica gel column chromatography. This mixture did not indicate a coloration according to the hydroxamic acid structure, and this fact suggested that no chlorine atom was present at the α-position of the N-O group in the molecule of **38** and the structure of **35** was therefore correct.

The chlorination of **25** and **28** gave respectively oily products, which were composed of two dichlorophenylpyrazines. These products could not be separated even by repeated column chromatography. The structures of 2,5-dichloro-3-phenylpyrazine (**36**) and 2,3-dichloro-5-phenylpyrazine (**37**) were determined on the basis of their nmr spectral data. On the other hand, **30** gave a crystalline mixture, which was composed of **36** and **37**; only **37** was isolated by fractional recrystallization from hexane.

Table I

Reaction of Monochloro-phenylpyrazine Monoxides with Phosphoryl Chloride

Starting Material	Product	Ratio (a)	Yield (%)
25	2,6-Dichloro-3-phenylpyrazine (**35**)	1 : 1	83 (b)
	2,5-Dichloro-3-phenylpyrazine (**36**)(13)		
27	2,6-Dichloro-3-phenylpyrazine (**35**)		68
28	2,6-Dichloro-3-phenylpyrazine (**35**)	5 : 1	94 (b)
	2,3-Dichloro-5-phenylpyrazine (**37**)		
30	2,3-Dichloro-5-phenylpyrazine (**37**)	1 : 1	98 (b)
	2,5-Dichloro-3-phenylpyrazine (**36**)(13)		

(a) The ratio of the products was determined by the measurements of the nmr spectra. (b) Total yield.

EXPERIMENTAL

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

a) 2-Chloro-3-propylpyrazine (**2**).

A mixture of **1** (690 mg, 5 mmoles) and phosphoryl chloride (5 ml) was refluxed for 1 hour. The mixture was poured into ice water, made alkaline with potassium carbonate, and extracted with ether. The ether layer was dried over sodium sulfate and the solvent was removed by distillation to give **2** as a brown oil, which was purified by distillation to furnish a colorless oil (320 mg, 41%), bp 85-95°/30 torr; uv (95% ethanol): λ max 270 nm (log ϵ = 3.64, shoulder), 276 (3.82), 300 (3.27, shoulder); nmr (deuteriochloroform): δ 1.00 (3H, t, $-CH_3$, J = 7 Hz), 1.75 (2H, m, $-CH_2-$, J = 7 Hz), 2.90 (2H, t, $-CH_2-$, J = 7 Hz), 8.08 (1H, d, pyrazine H, J = 2 Hz), 8.30 (1H, d, pyrazine H, J = 2 Hz) ppm; ms: m/e 156 (M^+).

Anal. Calcd. for $C_7H_9ClN_2$: C, 53.68; H, 5.79; N, 17.89. Found: C, 53.94; H, 5.66; N, 17.63.

b) 2-Propylpyrazine (**3**).

A solution of **2** (25.3 g, 0.161 mole) and sodium acetate trihydrate (20.63 g, 0.15 mole) dissolved in methanol (250 ml) was shaken under a stream of hydrogen gas in the presence of 16.0 g of 5% palladium on carbon. After filtration of the reaction mixture, the solvent was evaporated to give an oil, which was purified by distillation to yield 4.75 g (24%) of **3** as a colorless oil bp 89-93° [lit (14) bp 90-92°].

c) 2-Phenylpyrazine (**4**).

Into a solution of ethylenediamine (7.2 g, 0.12 mole) in ethanol (200 ml), phenylglyoxal monohydrate (15.2 g, 0.1 mole) was added in 10 minutes under ice cooling. After potassium hydroxide (6 g) was added, the reaction mixture was refluxed on a water bath for 5 hours and then evaporated to dryness *in vacuo*. The chloroform extract of the residue was purified by sublimation at 70-80°/2-3 torr (oil bath temperature) to afford **4** (5.32 g, 34%) as pale yellow needles (pale yellow needles from

methanol-water), mp 68-69° [lit (5) mp 72-73°].

d) Oxidation of 2-Propylpyrazine (**3**).

A solution of **3** (4.75 g, 38.9 mmoles), 90% hydrogen peroxide (1.59 g, 46.7 mmoles) and maleic anhydride (5.72 g, 58.4 mmoles) in dichloromethane (230 ml) was allowed to stand overnight at room temperature and then was refluxed for 2 hours. The mixture was washed successively with water, 10% potassium bicarbonate and water. The dichloromethane layer was dried over sodium sulfate and the solvent was removed by distillation to give an oily residue (4.1 g), which was chromatographed on silica gel (Wakogel C-200, 200 g) eluting with a mixture of benzene and ethyl acetate (10:1), to afford **5** and **6**.

Compound **5**.

This compound (1.02 g, 20%) was obtained as a colorless oil, bp 150-160°/37 torr (oil bath temperature); uv (95% ethanol): λ max 222 nm (log ε = 4.23), 268-269 (4.02); nmr (deuteriochloroform): δ 1.04 (3H, t, $-CH_3$, J = 7 Hz), 1.74 (2H, m, $-CH_2-$, J = 7 Hz), 2.85 (2H, t, $-CH_2-$, J = 7 Hz), 8.08 (1H, d, pyrazine H, J = 4 Hz), 8.28 (1H, d, pyrazine H, J = 4 Hz), 8.28 (1H, s, pyrazine H) ppm; ms: m/e 138 (M^+), 121 ($M^+ - OH$); high resolution ms: Calcd. for $C_7H_{10}N_2O$: 138.0793. Found: 138.0816.

Compound **6**.

This compound (1.53 g, 28%) was obtained as a colorless oil, bp 160-165°/36 torr (oil bath temperature): uv (95% ethanol): λ max 227.5 nm (log ε = 4.10), 269 (4.05); nmr (deuteriochloroform): δ 1.00 (3H, t, $-CH_3$, J = 7 Hz), 1.82 (2H, m, $-CH_2-$, J = 7 Hz), 2.72 (2H, t, $-CH_2-$, J = 7 Hz), 7.94 (1H, d, pyrazine H, J = 4 Hz), 7.95 (1H, s, pyrazine H), 8.34 (1H, d, pyrazine H, J = 4 Hz) ppm; ms: m/e 138 (M^+), 122 ($M^+ - O$); high resolution ms: Calcd. for $C_7H_{10}N_2O$: 138.0793. Found: 138.0816.

e) Oxidation of a Mixture of 2-Propylpyrazine 1-Oxide (**5**) and 2-Propylpyrazine 4-Oxide (**6**).

A solution of a mixture of **5** and **6** (860 mg, 16 mmoles), 90% hydrogen peroxide (681 mg, 18 mmoles), and maleic anhydride (2.35 g, 24.5 mmoles) in chloroform (50 ml) was refluxed for 2 hours. The reaction mixture was worked up as described in d) to give a crystalline mass of **7**, which was recrystallized from benzene to furnish colorless prisms (132 mg, 14%), mp 195.5-196.5°; uv (95% ethanol): λ max 230.5 nm (log ε = 4.31), 313 (4.34); nmr (deuteriochloroform): δ 1.04 (3H, t, $-CH_3$, J = 7 Hz), 1.76 (2H, m, $-CH_2-$, J = 7 Hz), 2.76 (2H, t, $-CH_2-$, J = 7 Hz), 7.80-8.00 (3H, m, pyrazine H) ppm; ms: m/e 154 (M^+).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.36; H, 6.50; N, 18.51.

f) Oxidation of 2-Phenylpyrazine (**4**).

A solution of **4** (9.44 g, 60.5 mmoles), 90% hydrogen peroxide (2.75 g, 72 mmoles), and maleic anhydride (8.0 g, 82 mmoles) in dichloromethane (300 ml) was allowed to stand overnight at room temperature and then was refluxed for 2 hours. The reaction mixture was worked up as described in d) to give a pale yellow solid (9.7 g), which was purified by silica gel (Wakogel C-200, 200 g) column chromatography. Elution with a mixture of chloroform and methanol (9:1) gave **8**, which was recrystallized from aqueous methanol to furnish pale yellow prisms (7.9 g, 76%), mp 138-139° [lit (5) mp 141-142°].

g) 2-Phenylpyrazine 1-Oxide (**9**).

A mixture of **25** (412 mg, 2 mmoles), hydrazine hydrate (5 ml), and ethanol (15 ml) was heated in a sealed tube at 140° for 2 hours. After the solvent was removed by distillation *in vacuo*, the residual oil was dissolved in chloroform and the solution was washed with water. A yellow oil, obtained by the usual work-up of the chloroform solution, was dissolved in a mixture of acetic acid (20 ml) and water (20 ml), and heated on a water bath. Cupric sulfate pentahydrate (1.2 g, 4.8 mmoles) dissolved in water (8 ml) was added in 10 minutes. The reaction mixture was heated further for 1 hour on a water bath, made alkaline with solid potassium carbonate, 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, 25 g) column chromatography. Elution with a mixture of benzene and ether (20:1 and 10:1) afforded 110 mg (23%) of **9**, which was recrystallized from cyclohexane to give colorless prisms, mp 127-128° [lit (5) mp 132-133°].

h) Reaction of 2-Propylpyrazine 1-Oxide (**5**) with Phosphoryl Chloride.

A mixture of **5** (138 mg, 1 mmole) and phosphoryl chloride (2 ml) was refluxed for 1 hour. The reaction mixture was worked up as described in a) to give a brown oil (130 mg), which was purified by distillation under reduced pressure to afford a colorless oil (57 mg). The nmr spectrum of this product showed three triplets at 2.95, 2.84, and 2.77 ppm for α-methylene protons of the propyl group of **2**, **10**, and **11** in a 2:2:3 ratio.

i) Reaction of 2-Propylpyrazine 4-Oxide (**6**) with Phosphoryl Chloride.

A mixture of **6** (138 mg, 1 mmole) and phosphoryl chloride (2 ml) was refluxed for 1 hour. The reaction mixture was worked up as described in a) to give a colorless oil (93 mg), the nmr of which showed three triplets at 2.96, 2.84, and 2.78 ppm for the α-methylene protons of the propyl group of **2**, **10**, and **11** in a ratio of 4:1:1.

j) DL-Glycylnorvalyl Anhydride (**12**).

A mixture of DL-glycylnorvaline (106 g, 0.62 mole) and β-naphthol (318 g, 2.75 moles) was heated at 140-150° on an oil bath for 3 hours. After cooling, the reaction mixture was triturated with ether. The insoluble solids were collected by suction (71 g, 73%) and recrystallized from water to furnish pale yellow prisms, mp 238-239°; ir (potassium bromide): 1680 cm^{-1} (C=O); nmr (deuteriotrifluoroacetic acid): δ 1.04 (3H, t, $-CH_3$, J = 6 Hz), 1.58 (2H, m, $-CH_2-$), 2.02 (2H, m, $-CH_2-$), 2.40 (3H, s, -CO-CH=, $-CO-CH_2-NH-$) ppm; ms: m/e 156 (M^+).

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 53.83; H, 7.76; N, 17.98.

k) Reaction of DL-Glycylnorvalyl Anhydride (**12**) with a Mixture of Phosphoryl Chloride and Phosphorus Pentachloride.

A mixture of **12** (22.5 g, 0.144 mole), phosphoryl chloride (110 ml) and phosphorus pentachloride (5.7 g) was heated in a sealed tube at 130° for 1 hour. The reaction mixture was worked up as described in a) to give a brown oil (7.3 g), which was chromatographed on silica gel (Wakogel C-200, 220 g), using hexane including an increasing amount of ether. The fractions eluted with a mixture of hexane-ether (100:1) gave **13** (2.03 g, 7.4%) as a colorless oil, bp 140-145°/160 torr. The fractions eluted with a mixture of hexane-ether (90:1) gave **11** (0.823 g, 4%) as a colorless oil, bp 95-105°/40 torr (oil bath temperature).

Compound **11**.

This compound had uv (95% ethanol): λ max 208.5 nm (log ε = 3.97), 270 (3.69, shoulder), 276.5 (3.77), 297.5 (3.30, shoulder); nmr (deuteriochloroform): δ 0.98 (3H, t, $-CH_3$, J = 6 Hz), 1.76 (2H, m, $-CH_2-$, J = 6 Hz), 2.76 (2H, t, $-CH_2-$, J = 6 Hz), 8.27 (1H, s, pyrazine H), 8.34 (3H, s, pyrazine H) ppm; ms: m/e 156 (M^+).

Anal. Calcd. for $C_7H_9ClN_2$: C, 53.68; H, 5.79; N, 17.89. Found: C, 53.69; H, 5.90; N, 18.14.

Compound **13**.

This compound had uv (95% ethanol): λ max 218-219 nm (log ε = 3.99), 281.5 (3.72, shoulder), 293-295 (3.77); nmr (deuteriochloroform): δ 1.00 (3H, t, $-CH_3$, J = 7 Hz), 1.78 (2H, m, $-CH_2-$, J = 7 Hz), 2.88 (2H, t, $-CH_2-$, J = 7 Hz), 8.16 (1H, s, pyrazine H) ppm; ms: m/e 190 (M^+).

Anal. Calcd. for $C_7H_9Cl_2N_2$: C, 44.00; H, 4.22; N, 14.66. Found: C, 43.61; H, 4.29; N, 14.63.

l) Reaction of 2-Phenylpyrazine 4-Oxide (**8**) with Phosphoryl Chloride.

A mixture of **8** (6 g, 35 mmoles) and phosphoryl chloride (60 ml) was refluxed for 1 hour. The reaction mixture was worked up as described in a) to give a brown oil (6.4 g), which was chromatographed on silica gel (Wakogel C-200, 150 g), using a mixture of hexane and ether. The frac-

tions eluted with a mixture of hexane-ether (50:1) gave **15** (0.603 g, 8%) as colorless needles, which was recrystallized from hexane, mp 97-98° [lit (9) mp 97-99°]. The fractions eluted with a mixture of hexane and ether (20:1) gave **16** (2.770 g, 38%) as a colorless oil, bp 100-105°/1 torr [lit (10) bp 111-112°/1 torr]. Further elution with a mixture of hexane and ether (10:1) gave **14** (2.850 g, 39%) as a crystalline mass, which was recrystallized from hexane to furnish colorless prisms, mp 60-62° [lit (8) mp 60-62°].

m) Reaction of 2-Phenylpyrazine 1-Oxide (**9**) with Phosphoryl Chloride.

A mixture of **9** (86 mg, 0.5 mmole) and phosphoryl chloride (3 ml) was refluxed for 1 hour. The work-up as described in a) gave a brown oil (80 mg), which was chromatographed on silica gel (Wakogel C-200, 3 g) and eluted with a mixture of hexane and ether. Elution with a 50:1 mixture gave **16** (58.3 mg, 61%) and with a 20:1 mixture gave 14 (7.2 mg, 7%).

n) Reaction of 2-Propylpyrazine 1-Oxide (**5**) with Acetic Anhydride.

A mixture of **5** (138 mg, 1 mmole) and acetic anhydride (2 ml) was refluxed for 1 hour. The reaction mixture was poured into ice water, made alkaline with potassium carbonate, and extracted with ether. The usual work-up of the ether layer gave a brown oil (112 mg), which was hydrolysed by heating in an alkaline medium (1 ml of 10% potassium hydroxide and 2 ml of methanol) for 1 hour. The solvent was removed by distillation and the residue was extracted with ether. The ether layer was worked up usually to afford a red brown oil, which was purified by distillation to furnish a colorless oil (**18**) (28 mg, 20%), bp 100-110°/1 torr (oil bath temperature); uv (95% ethanol): λ max 222 nm (log ε = 3.71), 272 (3.65, shoulder), 300-305 (2.66); ir (film): 3550 cm^{-1} (OH); nmr (deuteriochloroform): δ 0.97 (3H, t, $-CH_3$, J = 8 Hz), 1.85 (2H, m, $-CH_2-$), 3.44 (1H, broad s, -OH), 4.80 (1H, t, $-CH_2-$, J = 8 Hz), 8.50 (2H, s, pyrazine H), 8.65 (1H, s, pyrazine H) ppm; ms: m/e 109 ($M^+ - C_2H_5$).

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.55; H, 7.53; N, 20.02.

o) Reaction of 2-Propylpyrazine 4-Oxide (**6**) with Acetic Anhydride.

A mixture of **6** (276 mg, 2 mmoles) and acetic anhydride (3 ml) was heated under reflux for 1 hour and worked up as described in n). The product was hydrolysed by heating in an alkaline medium (3 ml of 10% potassium hydroxide and 5 ml of methanol) to give a brown oil, which was heated under reflux in phosphoryl chloride (3 ml). The nmr spectrum of the colorless oily product showed three triplets due to the α-methylene protons of the propyl group of **2**, **10**, and **11** in a ratio of 3:2:1.

p) Reaction of 2-Phenylpyrazine 4-Oxide (**8**) with Acetic Anhydride.

A solution of **8** (516 mg, 3 mmoles) in acetic anhydride (6 ml) was refluxed for 1 hour. The mixture was worked up as described in n) and the product was hydrolysed by heating with an alkaline medium (6 ml of 10% potassium hydroxide and 20 ml of methanol) for 1 hour to afford an oil, which was heated with phosphoryl chloride (6 ml) and a small amount of phosphorus pentachloride in a sealed tube at 160° for 1 hour. The usual work-up of the reaction mixture gave a brown oil, which was chromatographed on silica gel (Wakogel C-200, 15 g) eluting with hexane containing an increasing amount of ether to yield **14** (81.9 mg, 13%), **15** (22.8 mg, 4%), and **16** (49.6 mg, 8%).

q) Reaction of 2-Phenylpyrazine 1-Oxide (**9**) with Acetic Anhydride.

After **9** (86 mg, 0.5 mmole) was refluxed in acetic anhydride (2 ml) for 1 hour, the reaction mixture was worked up as described in n). The product was hydrolysed by heating in an alkaline medium (2 ml of 10% potassium hydroxide and 6 ml of methanol) for 1 hour to give an oil, which was heated with phosphoryl chloride (2 ml) and small amount of phosphorus pentachloride in a sealed tube at 160° for 1 hour. A brown oil obtained was chromatographed on silica gel (Wakogel C-200, 5 g) and eluted with hexane containing an increasing amount of ether to yield **14** (4.2 mg, 4%) and **16** (13.4 mg, 13%).

r) General Procedure for Oxidation of the Chloro-Phenylpyrazines (**14**, **15**, and **16**).

A mixture of a chloro-phenylpyrazine (2.85 g, 15 mmoles), 90% hydrogen peroxide (1.62 g, 45 mmoles), and maleic anhydride (5.88 g, 60 mmoles) in chloroform (150 ml) was allowed to stand overnight at room temperature and then refluxed for 3 hours. The work-up gave a crystalline mass, which was purified by column chromatography on silica gel (Wakogel C-200) and then recrystallized.

2-Chloro-3-phenylpyrazine 4-Oxide (**25**).

This compound (1.63 g, 49%) was obtained as colorless prisms from methanol, mp 150-151° [lit (5) mp 151-152°].

2-Chloro-3-phenylpyrazine 1,4-Dioxide (**26**).

This compound (500 mg, 15%) was obtained as colorless needles from methanol, mp 238.5-239.5° dec; uv (95% ethanol): λ max 226 nm (log ε = 4.06, shoulder), 238.5 (4.15), 254-257 (3.97), 277-281 (3.88), 317 (4.28); nmr (deuteriotrifluoroacetic acid): δ 7.40-7.70 (5H, m, benzene H), 8.76 (2H, s, pyrazine H) ppm; ms: m/e 222 (M^+).

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found: C, 53.78; H, 2.99; N, 12.69.

2-Chloro-5-phenylpyrazine 1-Oxide (**27**).

This compound (846 mg, 27%) was obtained as pale yellow needles from methanol, mp 148-150° [lit (14), mp 151°].

2-Chloro-5-phenylpyrazine 4-Oxide (**28**).

This compound (790 mg, 25%) was obtained as pale yellow needles from methanol, mp 139-141° [lit (5) mp 146°].

2-Chloro-5-phenylpyrazine 1,4-Dioxide (**29**).

This compound (78 mg, 2%) was obtained as pale yellow prisms from methanol, mp 248-250.5° dec; uv (95% ethanol): λ max 218.5-220 nm (log ε = 4.07), 263-265 (4.26), 285 (4.05, shoulder), 318.5 (4.19); nmr (deuteriotrifluoroacetic acid): δ 7.50-7.90 (5H, m, benzene H), 8.92 (1H, s, pyrazine H), 9.02 (1H, s, pyrazine H) ppm; ms: m/e 222 (M^+).

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found: C, 54.09; H, 3.15; N, 12.67.

2-Chloro-6-phenylpyrazine 4-Oxide (**30**).

This compound (2.30 g, 74%) was obtained as pale yellow prisms from methanol, mp 115-116° [lit (5) mp 121-122°].

s) General Procedure for the Preparation of Hydroxy-phenylpyrazine *N*-Oxides.

A mixture of a chloro-phenylpyrazine (1 mmole), 10% potassium hydroxide (5 ml), and ethanol (5 ml) was refluxed for 1 hour. The solvent was evaporated off *in vacuo* and the residue was diluted with water. The aqueous solution was washed with ether and acidifed with 2*N* hydrochloric acid. The precipitates were extracted with chloroform and recrystallized.

2-Hydroxy-3-phenylpyrazine 4-Oxide (**31**).

This compound (56 mg, 30%) was obtained as pale yellow prisms from methanol, mp 268.5-269.5° dec; uv (95% ethanol): λ max 238-240 nm (log ε = 4.24), 297 (3.68), 348-354 (3.90); ir (potassium bromide): 1630 cm^{-1} (C=O); nmr (deuteriotrifluoroacetic acid): δ 7.60 (5H, s, benzene H), 7.83 (2H, s, pyrazine H) ppm; ms: m/e 188 (M^+).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.57; H, 4.12; N, 14.88.

2-Hydroxy-5-phenylpyrazine 1-Oxide (**32**).

This compound (103 mg, 55%) was obtained as pale yellow needles from methanol, mp 182-185°; uv (95% ethanol): λ max 267.5 nm (log ε = 4.31), 281 (4.28, shoulder), 358 (3.76); ir (potassium bromide): 1675 cm^{-1} (C=O); nmr (deuteriotrifluoroacetic acid): δ 7.68 (5H, s, benzene H), 8.75 (1H, s, pyrazine H), 8.92 (1H, broad s, pyrazine H) ppm; ms: m/e 188 (M^+).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.87; H, 4.43; N, 14.90.

2-Hydroxy-5-phenylpyrazine 4-Oxide (**33**).

This compound (133 mg, 71%) was obtained as pale brown plates from methanol, mp 265-266° dec; uv (95% ethanol): λ max 255 nm (log ε = 3.88), 282 (3.41, shoulder), 358 (3.18); ir (potassium bromide): 1680 cm^{-1} (C=O); nmr (deuteriotrifluoroacetic acid): δ 7.54 (5H, s, benzene H), 7.94 (1H, s, pyrazine H), 8.42 (1H, broad s, pyrazine H) ppm; ms: m/e 188 (M^+).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.76; H, 4.10; N, 14.83.

2-Hydroxy-6-phenylpyrazine 4-Oxide (**34**).

This compound (161 mg, 86%) was obtained as colorless needles from methanol, mp 280-281° dec; uv (95% ethanol): λ max 252 nm (log ε = 4.45), 340-344 (3.97); ir (potassium bromide): 1620 cm^{-1} (C=O); nmr (deuteriotrifluoroacetic acid): δ 7.60-7.80 (5H, m, benzene H), 8.06 (1H, s, pyrazine H), 8.24 (1H, s, pyrazine H) ppm; ms: m/e 188 (M^+).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.57; H, 4.01; N, 14.94.

t) General Procedure for the Preparation of Dichlorophenylpyrazines.

A mixture of a monochlorophenylpyrazine monoxide (2 mmoles) and phosphoryl chloride (5 ml) was refluxed for 0.5 hour and worked up as usual to give a dichlorophenylpyrazine, which was purified by recrystallization or distillation.

2,6-Dichloro-3-phenylpyrazine (**35**).

This compound (304 mg, 68%) was obtained as a colorless oil, bp 150-156°/2 torr (oil bath temperature); uv (95% ethanol): λ max 240 nm (log ε = 4.06, shoulder), 257.5 (4.09), 309-311 (4.01); nmr (deuteriochloroform): δ 7.40-7.60 (3H, m, benzene H), 7.60-7.85 (2H, m, benzene H), 8.53 (1H, s, pyrazine H) ppm; ms: m/e 224 (M^+).

Anal. Calcd. for $C_{10}H_6Cl_2N_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.60; H, 2.64; N, 12.47.

2,3-Dichloro-5-phenylpyrazine (**37**).

This compound (188 mg, 42%) was obtained as colorless needles from hexane, mp 107-108°; uv (95% ethanol): λ max 260.5 nm (log ε = 4.21), 321 (4.16); nmr (deuteriochloroform): δ 7.40-7.60 (3H, m, benzene H), 7.90-8.05 (2H, m, benzene H), 8.18 (1H, s, pyrazine H) ppm; ms: m/e 244 (M^+).

Anal. Calcd. for $C_{10}H_6Cl_2N_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.61; H, 2.58; N, 12.62.

u) Oxidation of 2,6-Dichloro-5-phenylpyrazine (**35**).

A mixture of **35** (400 mg, 1.8 mmoles), 90% hydrogen peroxide (684 mg, 18 mmoles) and maleic anhydride (2.59 g, 27 mmoles) in chloroform (60 ml) was allowed to stand overnight at room temperature and then was refluxed for 4 hours. A colorless oil obtained by the usual work-up was chromatographed on silica gel (Wakogel C-200, 10 g) and eluted with hexane containing an increasing amount of ethyl acetate. The fractions eluted with a mixture of hexane-ethyl acetate (20:1) gave the starting material (140 mg), and the 10:1 and 4:1 fractions afforded **38** (280 mg, 65%), which was recrystallized from aqueous methanol to furnish colorless prisms, mp 82-83°; uv (95% ethanol): λ max 245.5 nm (log ε = 4.25), 267 (4.13, shoulder), 285 (3.91, shoulder), 318-321 (3.45); nmr (deuteriochloroform): δ 7.30-7.60 (5H, m, benzene H), 8.20 (1H, s, pyrazine H) ppm; ms: m/e 240 (M^+), 224 ($M^+ - 0$).

Anal. Calcd. for $C_{10}H_6Cl_2N_2O$: C, 49.82; H, 2.51; N, 11.62. Found: C, 49.68; H, 2.58; N, 11.78.

v) Hydrolysis of 3,5-Dichloro-2-phenylpyrazine 1-Oxide (**38**).

A mixture of **38** (80 mg, 0.33 mmole), 10% potassium hydroxide (5 ml), and ethanol (5 ml) was refluxed for 5 hours. The alkaline soluble fraction gave red brown crystals (**39**, 44 mg), which did not indicate a red coloration with ferric chloride in methanol.

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