Reactions of the Monoxides of 2,6-Disubstituted Pyrazines with Phosphoryl Chloride and Acetic Anhydride

Akihiro Ohta*, Akiko Imazeki, Yohko Itoigawa, Hiroko Yamada, Chieko Suga, Chiseko Takagai, Hiroko Sano and Tokuhiro Watanabe

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Received July 14, 1982

The monoxides of 2,6-dimethyl- (**1**), 2,6-diphenyl- (**2**), and 2-methyl-6-phenylpyrazines (**3**) were subjected to the reactions with phosphoryl chloride and acetic anhydride. Some reactions of the chloropyrazines and hydroxypyrazines obtained thus were also investigated.

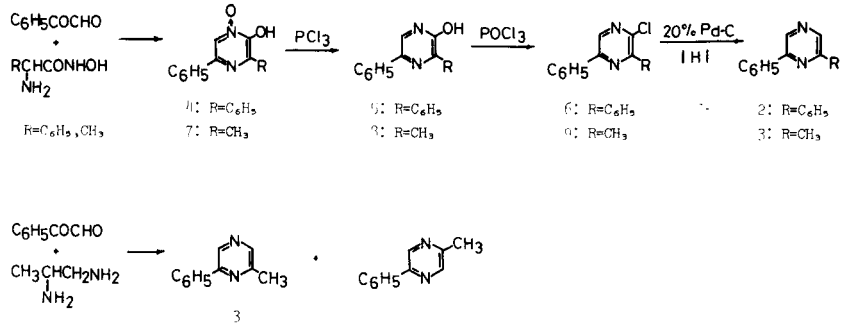
J. Heterocyclic Chem., **20**, 311 (1983).

The nucleophilic substitutions take place on the aromatic *N*-heterocycles when their *N*-oxides are treated with phosphoryl chloride and acetic anhydide (1). In the course of the investigations on pyrazines, we have reported such reactions on mono- (2), 2,3-di- (3), and 2,5-disubstituted pyrazine monoxides (4). In continuation of this work, this paper reports the reactions of the monoxides of 2,6-dimethylpyrazine (**1**) (5), 2,6-diphenylpyrazine (**2**), and 2-methyl-6-phenylpyrazine (**3**) with phosphoryl chloride and acetic anhydride.

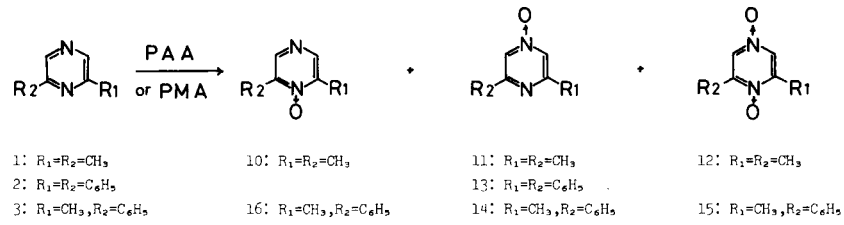
Compound **2** was supplied with preparation by the method reported (6). 2,5-Diphenylpyrazine, formed simultaneously, was separated by column chromatography. Compound **2** was prepared also by the dechlorination of 3-chloro-2,6-diphenylpyrazine (**6**) (7), derived from 2,6-diphenyl-3-hydroxypyrazine (**5**) (8). Compound **3** was obtained by the condensation of propylenediamine and phenylglyoxal as reported (4), and derived also from 3-hydroxy-2-methyl-6-phenylpyrazine (**8**) (8) by chlorination and successive reduction.

Compounds **1**, **2**, and **3** were converted to their *N*-oxides by heating with peracids. Although Klein *et al.* reported the separation of the monoxides of **1** by a fractional recrystallization (9), 2,6-dimethylpyrazine 1-oxide (**10**) and 2,6-dimethylpyrazine 4-oxide (**11**), formed by the reaction with peracetic acid, were successfully separated by column chromatography on silica gel in the present work. Compound **2** was oxidized with permaleic acid to give a monoxide **13**, and in spite of the treatment under these drastic conditions, a dioxide was not detected. By the oxidation of **3** with permaleic acid, 2-methyl-6-phenylpyrazine 4-oxide (**14**), as a sole monoxide, and 2-methyl-6-phenylpyrazine 1,4-dioxide (**15**) were obtained. The other 1-oxide **16** could be barely prepared by a different route as will be explained later.

The determination of the structures of the monoxides was made on the basis of pmr spectral data (10). The signals (7.85 and 8.53 ppm) due to the ring protons in the pmr spectra of **11** and **13** appeared at a higher field than those (8.35 and 9.07 ppm) of the corresponding parent pyr-



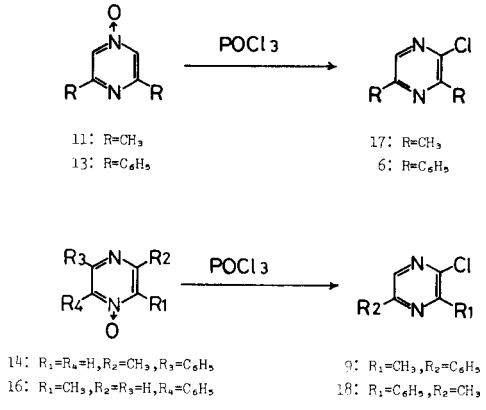
Scheme 1



Scheme 2

azines **1** and **2**, while the ring proton signals (8.34 ppm) of **10** showed the same chemical shifts as those of **1**. On the other hand, the discrimination of **14** and **16** was made on the observation of chemical shifts of the methyl proton signals. The methyl signal of **14** indicated the same chemical shift as the one due to **3**, while the methyl signal of **16** appeared in a higher field than the one of **3**.

The reaction of the monoxides with phosphoryl chloride was performed as reported previously (2-4) and afforded the monochloropyrazines carrying a chlorine atom on the pyrazine ring in satisfactory yields, except in the case of **10**. While **11** gave 3-chloro-2,6-dimethylpyrazine (**17**) as already reported (11), the reaction of **10** gave resinous products. The product, 3-chloro-2-methyl-6-phenylpyrazine (**9**) and 5-chloro-2-methyl-6-phenylpyrazine (**18**), derived from **16**, were recovered only in poor yields. In these two cases, the chlorination would take place mainly on the methyl group and probably the products could not be acquired, because of instability.



Scheme 3

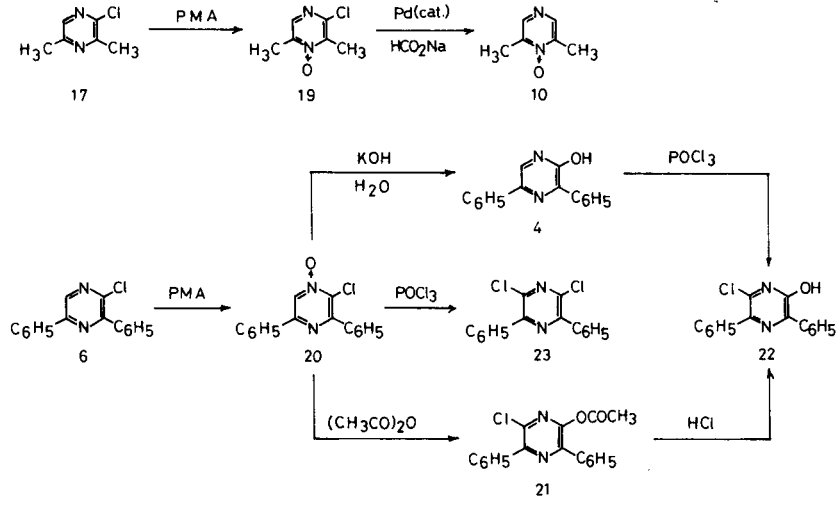
The separation of the products, **9** and **18**, derived from **14** and **16**, was achieved by column chromatography. The product **9** was shown to be identical with the compound derived from **8** and, therefore, the structure of **18** was deductively determined.

The monochloropyrazines **6, 9, 17**, and **18** were oxidized with permaleic acid. The oxidation of **17** (11) occurred only at N-1 to give 3-chloro-2,6-dimethylpyrazine 1-oxide (**19**), whose structure was determined on the basis of the results of reduction, thus by treatment of **19** with sodium formate and tetrakis(triphenylphosphine)palladium (12), **10** was obtained.

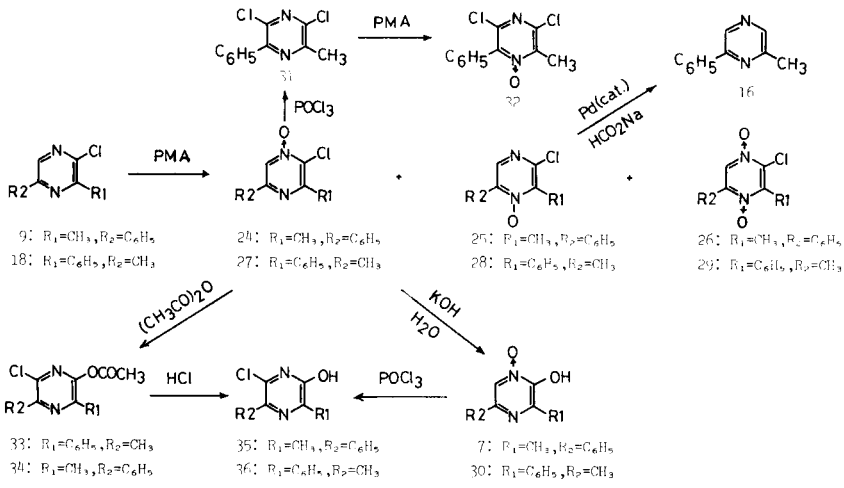
Compound **6** gave a monoxide **20** as a sole product, which was transformed in alkaline medium to a hydroxamic acid **4** (8). Namely, the N-4 of **6** was oxidized, in contrast to the case of **17**. By treatment with acetic anhydride and successive acidic hydrolysis, **20** was transformed into 3-chloro-2,6-diphenyl-5-hydroxypyrazine (**22**), which was derived also from **4** as previously reported (13). Compound **20** was converted to 3,5-dichloro-2,6-diphenylpyrazine (**23**) by treatment with phosphoryl chloride.

The oxidation of **9** and **18** afforded two monoxides and a dioxide, respectively. The structures of the two monoxides, **24** and **27**, were elucidated on the basis of the results of hydrolysis, by which **24** and **27** gave hydroxamic acids, **7** (8) and **30** (13), respectively. The structures of the monoxides **25** and **28** were thus deductively determined.

As shown in Scheme 5, some reactions of the monochloropyrazine monoxides were examined. The reactions of **24** and **27** with phosphoryl chloride led to the same product **31**, whose oxidation with permaleic acid yielded solely a monoxide **32**. On the other hand, by a treatment of **24** and **27** with acetic anhydride, monoacetoxymonochloro-



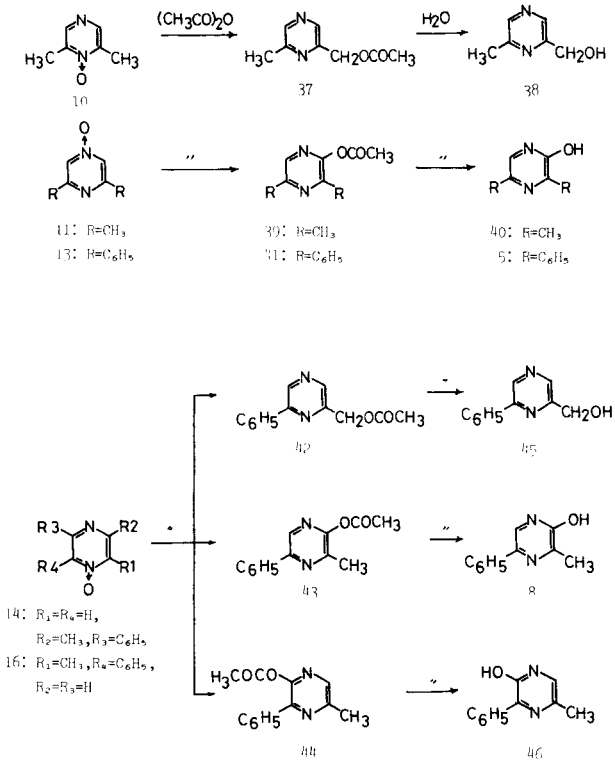
Scheme 4



Scheme 5

pyrazines, **33** and **34**, were obtained. By hydrolysis under acidic conditions, **33** and **34** were further converted to the corresponding hydroxypyrazines, **36** (13) and **35** (13), which were also prepared from **30** and **7** respectively by a reported method (13). Monoxides **25** and **28** were transformed into **16** as a common product by dechlorination under the reported conditions (12). Thus, two isomers of the monoxides of **3** could be successfully prepared.

In order to prepare the hydroxypyrazines, the reaction



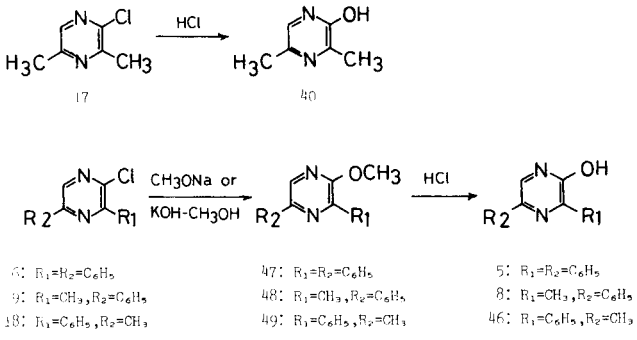
Scheme 6

of the monoxides with acetic anhydride was performed under the same conditions as reported (2-4). The acetoxylation of **10** occurred on the side chain to give 2-acetoxymethyl-6-methylpyrazine (**37**), which was hydrolysed to 2-hydroxymethyl-6-methylpyrazine (**38**) in an alkaline medium. On the other hand, the substitution to **11** took place on the ring and gave an acetoxypyrazine **39**, which was converted to 2,6-dimethyl-3-hydroxypyrazine (**40**) (8,14,15) by alkaline hydrolysis. Compound **40** was obtained also by an acidic hydrolysis of **17**. Compound **13** afforded similarly a ring substitution product **41** as crystals, which was hydrolysed to **5**.

The acetoxylation of **14** and **16** gave complicated mixtures. In both cases, product **42**, bearing an acetoxyl group on the side chain, and two acetoxyl pyrazines, **43** and **44**, were isolated from the reaction mixtures by column chromatography on silica gel. Interestingly, the main products derived from **14** were the ring-acetoxylated pyrazines. On the other hand, the acetoxylation of **16** occurred mainly on the side chain. Discrimination of the structures of **43** and **44** was achieved on the basis of the results of their hydrolysis, by which hydroxypyrazines were obtained. Among the hydroxypyrazines, the one derived from **43** was identical with **8**. Therefore, the structure of **43** could be determined, and the ones of **44** and **46** were clarified deductively. Compound **42** gave also the corresponding hydroxypyrazine **45** by alkaline hydrolysis.

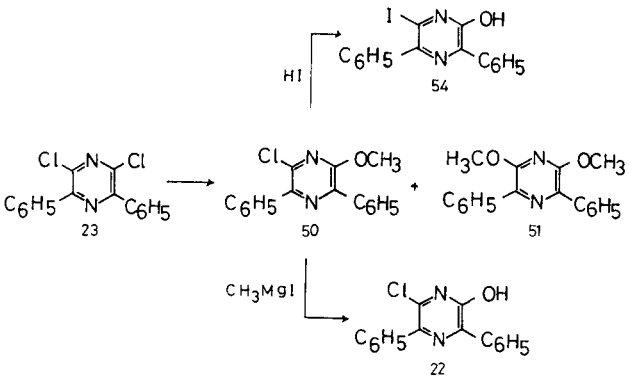
The derivation of the monochloropyrazines to the hydroxypyrazines was also attempted. As described before, **17** was readily hydrolysed by heating in hydrochloric acid to give **40**. However, the other monochloropyrazines **6**, **9**, and **18** could not be hydrolysed under such conditions. The preparation of the hydroxypyrazines **5**, **8**, and **46** was achieved barely *via* the corresponding methoxypyrazines

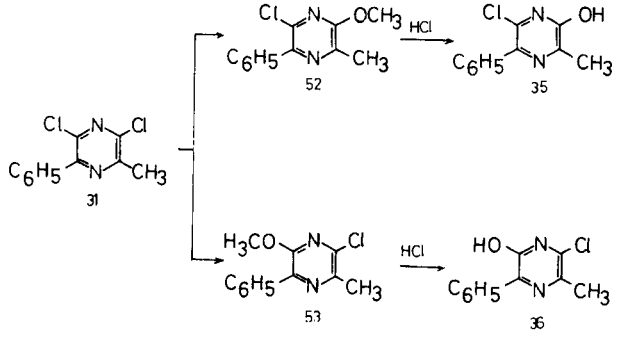
47, **48**, and **49**, which were obtained from the chloropyrazines by heating with sodium methoxide or potassium hydroxide in methanol. Compounds **47** and **48** were readily prepared by both reactions in satisfactory yields. However, the transformation of **18** to **49** succeeded only by heating with sodium methoxide.



Scheme 7

Attempts to hydrolyse the dichloropyrazines **23** and **31** to the corresponding dihydroxypyrazines were unsuccessful. Next, reactions of the dichloropyrazines with the methoxyl anion were examined. Both compounds were treated with sodium methoxide or with potassium hydroxide in methanol, respectively. Compound **23** gave 3-chloro-2,6-diphenyl-5-methoxypyrazine (**50**) (13) as the sole product by reaction in a mixture of potassium hydroxide and methanol. On the other hand, the dimethoxyl compound **51** (13) was obtained by the reaction with sodium methoxide. From **31**, two monomethoxyl compounds, **52** (13) and **53** (13) were prepared under both conditions, while a dimethoxyl compound was not obtained. The structures of **52** and **53** were elucidated on the basis of their hydrolysis, by which **52** and **53** led to give 5-chloro-3-hydroxy-3-methyl-6-phenylpyrazine (**35**) and 3-chloro-5-hydroxy-2-methyl-6-phenylpyrazine (**36**), respectively.





Scheme 8

In order to hydrolyse the methoxy pyrazines, some reactions were investigated. Although **50** could not be hydrolysed in 20% hydrochloric acid, treatment with methylmagnesium iodide afforded **22** successfully. The reaction of **50** with hydriodic acid resulted in preparation of an iodo compound **54**.

EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro-melting point apparatus and are uncorrected. Boiling points are also uncorrected. All uv spectra were taken in 95% ethanol using Hitachi Model 323 and 557 spectrometers, ir spectra on a Shimadzu IR-400 spectrometer, and pmr spectra in deuteriochloroform using JEOL PS-100 and Varian EM-360 instruments with tetramethylsilane as an internal standard. Mass spectra were obtained with Hitachi RMU-7L and M-80 spectrometers. For silica gel column chromatography, Wakogel C-200 (Wako Pure Chemical Industries, Ltd., Tokyo) was used.

1) 2,6-Diphenylpyrazine (**2**).

a) A mixture of 2,5-diphenylpyrazine and **2**, which was prepared by the reaction of phenacyl bromide (19.90 g, 0.1 mole) with 28% ammonium hydroxide (70 ml) in ethanol (100 ml) as reported (6), was triturated with ether and the less soluble 2,5-diphenylpyrazine (14.20 g) was collected by suction as a pale yellow powder. The filtrate was concentrated to dryness and the resulting solid (*ca.* 8 g) was chromatographed on silica gel (100 g), using hexane, ether, and ethyl acetate as developers. The fractions eluted with a mixture of hexane and ether (30:1) gave **2** (6.64 g, 28%), mp 85-86° [lit (16) mp 80-81°], as colorless prisms. The fractions eluted with a mixture of ether and ethyl acetate (1:1) afforded 2,5-diphenylpyrazine (0.96 g, total yield 65%) as pale yellow prisms.

b) A solution of **6** (26.65 g, 0.1 mole) and sodium acetate trihydrate (20.63 g, 0.15 mole) in ethanol (250 ml) was shaken under a hydrogen stream in the presence of 20% palladium carbon (5 g). After removal of the catalyst by filtration, the solvent was evaporated *in vacuo* to give **2** as a pale yellow solid, which was recrystallized from ethanol to furnish pale yellow needles (14.10 g, 79%), mp 87-88°.

2) 3-Chloro-2-methyl-6-phenylpyrazine (**9**).

After a solution of **7** (10.10 g, 50 mmoles) and phosphorus trichloride (7.50 ml, 84 mmoles) in dry ethyl acetate (600 ml) was heated under reflux for 1.5 hours, the solution was poured into ice water (200 ml) and made alkaline with potassium carbonate. The organic layer was separated and dried over sodium sulfate. Removal of the solvent by distillation afforded a dark brown oil (10.81 g), which was heated with a mixture of phosphoryl chloride (30 ml) and phosphorus pentachloride (*ca.* 5 g) at 140° for 1 hour in a sealed tube. The mixture was poured into ice water (200 ml), made alkaline with potassium carbonate, and extracted with methylene chloride. Removal of the solvent by distillation gave **9** as a brown semi-solid (*ca.* 7 g), which was purified by column chromatography on silica gel (50 g), eluting with benzene, to afford colorless crystals (5.26 g, 51%). The product was recrystallized from methanol to furnish colorless needles, mp 74-75°.

Compound **9**.

This compound had the following physical constants: uv: λ max 253 (log ε = 4.12), 290 (3.94), 311 (4.04) nm; pmr: δ 2.70 (3H, s, CH_3), 7.45 (3H, m, benzene H), 7.95 (2H, m, benzene H), 8.58 (1H, s, pyrazine H) ppm; ms: m/e 204 (M^+).

Anal. Calcd. for $C_{11}H_9ClN_2$: C, 64.55; H, 4.33; N, 13.68. Found: C, 64.37; H, 4.27; N, 13.97.

3) 2-Methyl-6-phenylpyrazine (**3**).

a) Phenylglyoxal (11.20 g, 0.083 mole) was added to a solution of propylenediamine (7.40 g, 0.1 mole) dissolved in ethanol (400 ml), under ice cooling with stirring during 30 minutes. The reaction mixture was stirred for an additional 1.5 hours at room temperature and then refluxed for 9 hours, after adding potassium hydroxide (5 g, 0.089 mole). After removal of the solvent *in vacuo*, the oily residue was extracted with ether. The usual work-up of the ether extract gave a brownish oil (6.10 g), which was chromatographed on silica gel (270 g) eluting with hexane, containing an increasing amount of ether. The fractions eluted with a mixture of hexane and ether (7:3) were distilled to give **3** (2.70 g, 19%) as a colorless oil, bp 158-160°/21 torr. The fractions eluted with a (3:7) mixture afforded 2-methyl-5-phenylpyrazine (3.0 g, 21%) as a colorless solid, which was recrystallized from hexane to furnish colorles needles, mp 93-94° [lit (6) mp 93-94°].

b) A solution of **9** (3.30 g, 16 mmoles) and sodium acetate (1.50 g, 18 mmoles) in ethanol (50 ml) was shaken under a hydrogen stream in the presence of 20% palladium carbon (2.00 g). After removal of the catalyst by suction, the solvent was evaporated *in vacuo* to give **3** as an oil, which was purified by distillation to furnish a colorless oil (2.02 g, 74%), bp 130°/7 torr.

Compound **3**.

This compound had the following physical constants: uv: λ max 247 (log ε = 4.03), 290 (4.03) nm; pmr: δ 2.65 (3H, s, CH_3), 7.53 (3H, m, benzene H), 8.07 (2H, m, benzene H), 8.47 (1H, s, pyrazine H), 8.90 (1H, s, pyrazine H) ppm; ms: m/e 170 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.45. Found: C, 77.48; H, 5.65; N, 16.72.

4) Oxidation of 2,6-Dimethylpyrazine (**1**).

A mixture of the two monoxides **10** and **11** and the dioxide **12**, prepared from **1** (5.50 g, 0.05 mole) by the reported procedure (9), was chromatographed on silica gel (150 g), eluting with methylene chloride, ethyl acetate, and methanol, successively. The fractions eluted with methylene chloride gave **10** (1.20 g, 19%) as colorless prisms (from hexane), mp 105-106° [lit (9) mp 108-110°] and the ones eluted with ethyl acetate afforded **11** (2.63 g, 42%) as colorless prisms (from hexane), mp 57-58° [lit (9) mp 55°]. Further elution with a mixture of ethyl acetate and methanol (1:1) yielded **12** (0.50 g, 8%) as colorless prisms (from hexane), mp 224-225° [lit (9) mp 227°].

5) Oxidation of 2,6-Diphenylpyrazine (**2**).

A solution of **2** (23.20 g, 0.1 mole), 90% hydrogen peroxide (18.90 g, 0.5 mole), and maleic anhydride (58.80 g, 0.6 mole) in chloroform (300 ml) was allowed to stand over night at room temperature, and then refluxed for 4 hours. The reaction mixture was washed with water, 10% potassium bicarbonate, and water, successively, and dried over sodium sulfate. The solvent was distilled off to give a pale yellow solid (*ca.* 21 g), which was chromatographed on silica gel (10:1) to afford **13** (20.24 g, 82%) as pale yellow crystals. The product was recrystallized from methanol to furnish colorless needles, mp 208-209°.

Compound **13**.

This compound had the following physical constants: uv: λ max 270 (log ε = 4.63), 340 (3.80) nm; pmr: δ 7.53 (6H, m, benzene H), 8.13 (4H, m, benzene H), 8.53 (2H, s, pyrazine H) ppm; ms: m/e 248 (M^+), 232 ($M^+ - O$).

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.76; H, 4.87; N, 11.41.

6) Oxidation of 2-Methyl-6-phenylpyrazine (**3**).

A solution of **3** (3.40 g, 20 mmoles), 90% hydrogen peroxide (3.78 g, 0.1 mole), and maleic anhydride (8.58 g, 0.11 mole) in chloroform (100 ml) was allowed to stand over night, and then refluxed for 4 hours. The solution was worked up as before to afford a colorless solid (3.53 g), which was chromatographed on silica gel (30 g) and eluted with benzene, chloroform, ethyl acetate, and methanol, successively. The fractions eluted with a mixture of benzene and chloroform (1:1) afforded **14** (2.94 g, 79%) as a colorless solid, which was recrystallized from cyclohexane to furnish colorless prisms, mp 130-131°. Further elution with a mixture of ethyl acetate and methanol (8:2) gave **15** (0.48 g, 12%) as colorless crystals, which was recrystallized from isopropyl alcohol to furnish colorless prisms, mp 187-188°.

Compound **14**.

This compound had the following physical constants: uv: λ max 229 (log ε = 4.04, shoulder), 262 (4.46), 321 (3.78) nm; pmr: δ 2.65 (3H, s, CH_3), 7.50 (3H, m, benzene H), 7.70 (2H, m, benzene H), 8.25 (1H, s, pyrazine H), 8.27 (1H, s, pyrazine H) ppm; ms: m/e 186 (M^+), 170 ($M^+ - O$).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.16; H, 5.36; N, 15.33.

Compound **15**.

This compound had the following physical constants: uv: λ max 260 (log ε = 4.35), 276.5 (4.14, shoulder), 315.5 (4.15) nm; pmr: δ 2.48 (3H, s, CH_3), 7.58 (3H, m, benzene H), 7.83 (2H, m, benzene H), 8.20 (1H, s, pyrazine H), 8.30 (1H, s, pyrazine H) ppm; ms: m/e 202 (M^+), 186 ($M^+ - O$).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.85. Found: C, 65.51; H, 4.89; N, 14.01.

7) 3-Chloro-2,6-diphenylpyrazine (**6**).

A mixture of **13** (12.4 g, 0.05 mole) and phosphoryl chloride (50 ml) was refluxed for 30 minutes, and worked up as before to give **6** (11.8 g, 89%) as pale yellow crystals, which was recrystallized from methanol to give pale yellow needles, mp 109-110° [lit (7) mp 108-109°].

8) Reaction of 2-Methyl-6-phenylpyrazine 4-Oxide (**14**) with Phosphoryl Chloride.

A mixture of **14** (5.00 g, 26.9 mmoles) and phosphoryl chloride (50 ml) was refluxed for 30 minutes, poured into ice water, made alkaline with potassium carbonate, and extracted with methylene chloride. Removal of methylene chloride gave a brownish semi-solid (5.17 g), which was chromatographed on silica gel (80 g) using benzene as a developer. The firstly eluted fractions yielded **9** (3.50 g, 64%) as pale yellow needles. The secondly eluted fractions afforded **18** (1.22 g, 22%) as a colorless oil, which was distilled under reduced pressure and then recrystallized from hexane to furnish colorless prisms, bp 130°/2 torr, mp 69-70°.

Compound **18**.

This compound had the following physical constants: uv: λ max 235 (log ε = 3.80), 252 (3.73, shoulder), 290 (3.79), 304 (3.70) nm; pmr: δ 2.58 (3H, s, CH_3), 7.45 (3H, m, benzene H), 7.73 (2H, m, benzene H), 8.17 (1H, s, pyrazine H) ppm; ms: m/e 204 (M^+).

Anal. Calcd. for $C_{11}H_9ClN_2$: C, 64.55; H, 4.43; N, 13.68. Found: C, 64.82; H, 4.30; N, 13.93.

9) Reaction of 2-Methyl-6-phenylpyrazine 1-Oxide (**16**) with Phosphoryl Chloride.

A mixture of **16** (186 mg, 1 mmole) and phosphoryl chloride (5 ml) was refluxed for 1 hour. The reaction mixture was worked up as before to give a brown oil (135 mg), which was chromatographed on silica gel (6 g), eluting with hexane and benzene, successively. The fractions eluted with hexane gave **9** (63 mg, 31%) as a colorless solid, which was recrystallized from methanol to furnish slightly yellow needles, mp 74–75°. The fractions eluted with a mixture of hexane and benzene (8:2) afforded **18** (60 mg, 29%) as a colorless solid, which was recrystallized from hexane to furnish colorless prisms, mp 69–70°.

10) 3-Chloro-2,6-dimethylpyrazine 1-Oxide (**19**).

After a mixture of **17** (115 mg, 0.8 mmole), 90% hydrogen peroxide (40 mg, 1.06 mmoles), maleic anhydride (108 mg, 1.1 mmoles), and methylene chloride (5 ml) was allowed to stand over night at room temperature and then refluxed for 4 hours, the mixture was worked up as described in 5) to give a colorless oil, which was distilled under a reduced pressure to give **19** (121 mg, 95%) as colorless solid, mp 34–36°, bp 80–86°/5 torr.

Compound **19**.

This compound had the following physical constants: uv: λ max 229 (log ε = 3.83), 269 (3.90), 298 (3.89), 304 (2.64), 310 (2.63) nm; pmr: δ 2.43 (3H, s, CH_3), 2.62 (3H, s, CH_3), 8.18 (1H, s, pyrazine H) ppm; ms: m/e 158 (M^+), 141 ($M^+ - OH$).

Anal. Calcd. for $C_6H_7ClN_2O$: C, 45.44; H, 4.44; N, 17.66. Found: C, 45.72; H, 4.56; N, 17.43.

11) Dechlorination of 3-Chloro-2,6-dimethylpyrazine 1-Oxide (**19**).

A mixture of **19** (72 mg, 0.45 mmole), tetrakis(triphenylphosphine)-palladium (26 mg, 0.0225 mmole), sodium formate (49 mg, 0.68 mmole), and *N,N*-dimethylformamide (5 ml) was heated at 100° for 2 hours and then extracted with hexane. The usual work-up of the hexane layer gave **10** (52 mg, 94%) as colorless needles, mp 106–107° [lit (9) mp 108–110°].

12) 3-Chloro-2,6-diphenylpyrazine 4-Oxide (**20**).

A mixture of **6** (5.33 g, 0.02 mole), 90% hydrogen peroxide (3.02 g, 0.08 mole), and maleic anhydride (8.00 g, 0.082 mole) in chloroform (200 ml) was allowed to stand over night at room temperature, refluxed for 5 hours, and then worked up as described in 5) to give **20** (5.43 g, 96%) as colorless crystals, which was recrystallized from methylene chloride to furnish colorless needles, mp 187–188°.

Compound **20**.

This compound had the following physical constants: uv: λ max 268.5 (log ε = 4.16), 340 (3.24) nm; pmr: δ 7.50 (6H, m, benzene H), 7.90 (4H, m, benzene H), 8.65 (1H, s, pyrazine H) ppm; ms: m/e 282 (M^+), 266 ($M^+ - O$).

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.95; H, 3.74; N, 10.01.

13) 2,6-Diphenyl-3-hydroxypyrazine 4-Oxide (**4**).

After a solution of **20** (283 mg, 1 mmole) and potassium hydroxide (560 mg, 10 mmoles) in methanol (10 ml) and water (10 ml) was refluxed for 1 hour, methanol was evaporated off *in vacuo*. The resulting oil was diluted with water (10 ml) and extracted with methylene chloride. The water layer was acidified with 20% hydrochloric acid and extracted with methylene choride to give **4** (232 mg, 88%) as a pale yellow solid, which was recrystallized from ethyl acetate to furnish pale yellow leaflets, mp 162–163° [lit (8) mp 165–166°].

14) 3-Chloro-2,6-diphenyl-5-hydroxypyrazine (**22**).

A mixture of **21** (148 mg, 0.5 mmole) and 20% hydrochloric acid (10 ml) was stirred at room temperature for 2 hours. The precipitates were collected by suction, washed with water, and recrystallized from methanol to give **22** (134 mg, 95%) as colorless needles, mp 246–247° [lit (13) mp 244–246°].

15) 3-Acetoxy-5-chloro-2,6-diphenylpyrazine (**21**).

A mixture of **20** (283 mg, 1 mmole) and acetic anhydride (5 ml) was heated at 120–130° on an oil bath for 1 hour and poured into ice water. The solution was made alkaline with sodium carbonate and extracted with methylene chloride. The usual work-up of the extract yielded **21** (263 mg, 81%) as a colorless solid, which was recrystallized from hexane to furnish yellow needles, mp 102–103°.

Compound **21**.

This compound had the following physical constants: uv: λ max 234 (log ε = 3.94, shoulder), 251 (4.00), 340 (3.88) nm; ir (liquid film): 1782 cm^{-1} (C=O); pmr: δ 2.28 (3H, s, CH_3), 7.50 (6H, m, benzene H), 7.87 (4H, m, benzene H) ppm; ms: m/e 324 (M^+), 289 ($M^+ - Cl$), 282 ($M^+ - CH_2CO$).

Anal. Calcd. for $C_{18}H_{13}ClN_2O_2$: C, 66.57;, H, 4.03; N, 8.62. Found: C, 66.85; H, 4.21; N, 8.56.

16) 3,5-Dichloro-2,6-diphenylpyrazine (**23**).

A solution of **20** (283 mg, 1 mmole) in phosphoryl chloride (5 ml) was refluxed for 30 minutes, and poured into ice water. The yellowish crystalline precipitates were collected by filtration and recrystallized from methanol to furnish pale yellow needles (257 mg, 85%), mp 100–101°.

Compound **23**.

This compound had the following physical constants: uv: λ max 235 (log ε = 3.58, shoulder), 257 (3.75), 322 (3.62) nm; pmr: δ 7.48 (6H, m, benzene H), 7.85 (4H, m, benzene H) ppm; ms: m/e 300 (M^+).

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2$: C, 63.80; H, 3.34; N, 9.30. Found: C, 63.59; H, 3.21; N, 9.53.

17) Oxidation of 3-chloro-2-methyl-6-phenylpyrazine (**9**).

A solution of **9** (8.20 g, 40 mmoles), 90% hydrogen peroxide (2.92 g, 80 mmoles), and maleic anhydride (7.84 g, 80 mmoles) in chloroform (300 ml) was allowed to stand over night at room temperature and then refluxed for 3 hours. The reaction mixture was worked up usually to give a colorless solid (8.38 g), which was chromatographed on silica gel (60 g) eluting with benzene, chloroform, and ethyl acetate, successively. The fractions eluted with a mixture of benzene and chloroform (8:2) gave **25** (1.62 g, 18%) as pale yellow needles. The fractions eluted with a mixture of benzene and chloroform (1:1) afforded **24** (1.98 g, 22%) as colorless needles. Further elution with a mixture of chloroform and ethyl acetate (1:1) yielded **26** (0.30 g, 3%) as colorless needles.

Compound **24**.

This compound had the following physical constants: mp 153–154° (from methanol); uv: λ max 231 (log ε = 3.99, shoulder), 264 (4.45), 327 (3.71) nm; pmr: δ 2.70 (3H, s, CH_3), 7.52 (3H, m, benzene H), 7.70 (2H, m, benzene H), 8.27 (1H, s, pyrazine H) ppm; ms: m/e 220 (M^+), 204 ($M^+ - O$).

Anal. Calcd. for $C_{11}H_9ClN_2O$: C, 59.87; H, 4.11; N, 12.69. Found: C, 59.55; H, 3.95; N, 12.53.

Compound **25**.

This compound had the following physical constants: mp 141–142° (from methanol); uv: λ max 253 (log ε = 4.29), 290 (3.78, shoulder), 348 (3.45, shoulder) nm; pmr: δ 2.73 (3H, s, CH_3), 7.47 (3H, m, benzene H), 7.90 (2H, m, benzene H), 8.53 (1H, s, pyrazine H) ppm; ms: m/e 220 (M^+), 203 ($M^+ - OH$).

Anal. Calcd. for $C_{11}H_9ClN_2O$: C, 59.87; H, 4.11; N, 12.69. Found: C, 59.98; H, 3.94; N, 12.70.

Compound **26**.

This compound had the following physical constants: mp 177–178° (from methanol); uv: λ max 210 (log ε = 4.19), 266 (4.45), 316 (4.29) nm; pmr: δ 2.75 (3H, s, CH_3), 7.57 (5H, m, benzene H), 8.33 (1H, s, pyrazine H) ppm; ms: m/e 236 (M^+), 220 ($M^+ - O$), 219 ($M^+ - OH$).

Anal. Calcd. for $C_{11}H_9ClN_2O_2$: C, 55.82; H, 3.83; N, 11.83. Found: C, 55.88; H, 3.71; N, 12.05.

18) Oxidation of 5-Chloro-2-methyl-6-phenylpyrazine (**18**).

A solution of **18** (3.16 g, 15.5 mmoles), 90% hydrogen peroxide (1.167 g, 30.9 mmoles) and maleic anhydride (3.14 g, 32 mmoles) in chloroform (50 ml) was worked up as described in 17) to give a pale yellow solid (3.03 g), which was chromatographed on silica gel (40 g) eluting with benzene containing an increasing amount of acetone. The fractions eluted with a 60:1 mixture gave **28** (1.613 g, 48%) as colorless needles. The fractions eluted with a 45:1 mixture afforded **27** (588 mg, 17%) as colorless needles. Further elution with acetone yielded **29** (768 mg, 21%) as colorless prisms.

Compound **27**.

This compound had the following physical constants: mp 123 – 124° (from methanol); uv: λ max 232 (log ε = 4.22), 254 (4.22), 316 (3.59) nm; pmr: δ 2.10 (3H, s, CH_3), 7.57 (5H, m, benzene H), 8.17 (1H, s, pyrazine H) ppm; ms: m/e 220 (M^+), 204 ($M^+ - O$).

Anal. Calcd. for $C_{11}H_9ClN_2O$: C, 59.87; H, 4.11; N, 12.69. Found: C, 60.02; H, 4.15; N, 12.81.

Compound **28**.

This compound had the following physical constants: mp 134 – 135° (from hexane); uv: λ max 232 (log ε = 4.33), 248 (4.24, shoulder), 280 (3.95, shoulder), 313 (3.59) nm; pmr: δ 2.45 (3H, s, CH_3), 7.53 (5H, broad s, benzene H), 8.33 (1H, s, pyrazine H) ppm; ms: m/e 220 (M^+), 203 ($M^+ - OH$).

Anal. Calcd. for $C_{11}H_9ClN_2O$: C, 59.87; H, 4.11; N, 12.69. Found: C, 59.61; H, 4.03; N, 12.81.

Compound **29**.

This compound had the following physical constants: mp 204 – 205° (from methanol); uv: λ max 242 (log ε = 4.22), 259 (4.05), 311 (4.26) nm; pmr: δ 2.45 (3H, s, CH_3), 7.60 (5H, broad s, benzene H), 8.33 (1H, s, pyrazine H) ppm; ms: m/e 236 (M^+), 220 ($M^+ - O$), 219 ($M^+ - OH$), 203 ($M^+ - O - OH$).

Anal. Calcd for $C_{11}H_9ClN_2O_2$: C, 55.83; H, 3.83; N, 11.84. Found: C, 56.02; H, 3.98; N, 11.67.

19) 3-Hydroxy-2-methyl-6-phenylpyrazine 4-Oxide (**7**).

A solution of **24** (220 mg, 1 mmole) in a mixture of 20% potassium hydroxide (10 ml) and methanol (10 ml) was refluxed for 2 hours and methanol was distilled off *in vacuo*. The concentrated solution was neutralized with 10% hydrochloric acid and the precipitates were collected by suction (183 mg, 91%). The products were recrystallized from methanol to furnish slightly yellow needles, mp 187 – 188° [lit (8) mp 185°].

20) 5-Hydroxy-2-methyl-6-phenylpyrazine 4-Oxide (**30**).

A mixture of **27** (189 mg, 0.86 mmole), 20% potassium hydroxide (5 ml) and methanol (5 ml) was refluxed for 2 hours and then methanol was removed by distillation under a reduced pressure. The resulting solution was shaken with ether and the water layer was acidified with 10% hydrochloric acid. The crystalline precipitates (58 mg, 33%) were collected by suction and recrystallized from benzene to furnish colorless needles, mp 147 – 148° [lit (13) mp 149 – 150°]. The starting material (16 mg, 8%) was recovered from the ether layer.

21) 3,5-Dichloro-2-methyl-6-phenylpyrazine (**31**).

a) A mixture of **24** (221 mg, 1 mmole) and phosphoryl chloride (5 ml) was refluxed for 1 hour, and then poured into ice water. The resulting solution was made alkaline with potassium carbonate and extracted with ether to give **31** (241 mg) as a slightly brown oil, which was purified by distillation to furnish a colorless solid (220 mg, 92%). The product was recrystallized from methanol to furnish colorless needles, bp 135 – 140°/3 torr, mp 58 – 59°.

b) A mixture of **27** (55 mg, 0.25 mmole) and phosphoryl chloride (3 ml) was worked up as described before to give **31** (54 mg, 90%) as colorless needles.

Compound **31**.

This compound had the following physical constants: uv: λ max 243 (log ε = 3.70), 255 (3.81), 309 (3.75), nm; pmr: δ 2.68 (3H, s, CH_3), 7.28 (3H, m, benzene H), 7.78 (2H, m, benzene H) ppm; ms: m/e 238 (M^+).

Anal. Calcd. for $C_{11}H_8Cl_2N_2$: C, 55.25; H, 3.37; N, 11.71. Found: C, 55.45; H, 3.63; N, 11.98.

22) 3,5-Dichloro-2-methyl-6-phenylpyrazine 1-Oxide (**32**).

A mixture of **31** (1.912 g, 8 mmoles), 90% hydrogen peroxide (816 mg, 22 mmole), and maleic anhydride (2.744 g, 28 mmoles) in chloroform (50 ml) was allowed to stand over night at room temperature, then refluxed for 4 hours, and worked up usually to give a colorless solid (2.096 g), which was chromatographed on silica gel (30 g) and eluted with hexane, benzene, and chloroform, succesively. The starting material (614 mg, 32%) was recovered from the fractions eluted with a mixture of hexane and benzene (8:2). A mixture of benzene and chloroform (1:1) eluted **32** (1.04 g, 51%) as a colorless solid, which was recrystallized from hexane to furnish colorless needles, mp 109 – 110.5°.

Compound **32**.

This compound had the following physical constants: uv: λ max 214 (log ε = 4.22), 242 (4.29), 262 (4.13, shoulder), 282 (3.91, shoulder), 318 (3.59) nm; pmr: δ 2.75 (3H, s, CH_3), 7.27 (3H, m, benzene H), 7.80 (2H, m, benzene H) ppm; ms: m/e 254 (M^+), 219 ($M^+ - Cl$).

Anal. Calcd. for $C_{11}H_8Cl_2N_2O$: C, 51.79; H, 3.16; N, 10.98. Found: C, 51.71; H, 3.04; N, 11.36.

23) 5-Acetoxy-3-chloro-2-methyl-6-phenylpyrazine (**33**).

A solution of **24** (220 mg, 1 mmole) in acetic anhydride (5 ml) was refluxed for 2 hours and then concentrated to dryness *in vacuo* to afford a colorless solid (262 mg), which was recrystallized from hexane to furnish colorless needles (226 mg, 86%), mp 88 – 89°.

Compound **33**.

This compound had the following physical constants: uv: λ max 251 (log ε = 4.03), 307 (3.95) nm; ir (potassium bromide): 1775 cm^{-1} (C=O); pmr: δ 2.27 (3H, s, CH_3), 2.73 (3H, s, CH_3), 7.53 (3H, m, benzene H), 7.87 (2H, m, benzene H) ppm; ms: m/e 262 (M^+), 220 ($M^+ - CH_2CO$).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.67. Found: C, 59.56; H, 4.21; N, 10.87.

24) 3-Acetoxy-5-chloro-2-methyl-6-phenylpyrazine (**34**).

A mixture of **27** (220 mg, 1 mmole) and acetic anhydride (5 ml) was heated at 120 – 130° on an oil bath for 1 hour and then worked up as described before to afford **34** (217 mg, 83%) as a colorless solid, which was recrystallized from hexane to furnish colorless needles, mp 92 – 93°.

Compound **34**.

This compound had the following physical constants: uv: λ max 241 (log ε = 4.01), 250 (4.01), 303 (3.99) nm; ir (potassium bromide): 1775 cm^{-1} (C=O); pmr: δ 2.38 (3H, s, CH_3), 2.52 (3H, s, CH_3), 7.53 (3H, m, benzene H), 7.83 (2H, m, benzene H) ppm; ms: m/e 262 (M^+), 220 ($M^+ - CH_2CO$).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.43; H, 4.22; N, 10.66. Found: C, 59.72; H, 4.02; N, 10.43.

25) 5-Chloro-3-hydroxy-2-methyl-6-phenylpyrazine (**35**).

A mixture of **34** (131 mg, 0.5 mmole) and 20% hydrochloric acid (5 ml) was stirred at room temperature for 2 hours and then made alkaline with potassium carbonate. The colorless precipitates were collected by suction (102 mg, 93%) and recrystallized from ethanol to furnish colorless prisms, mp 180 – 181° [lit (13) mp 181 – 182°].

26) 3-Chloro-5-hydroxy-2-methyl-6-phenylpyrazine (**36**).

A mixture of **33** (132 mg, 0.5 mmole) and 20% hydrochloric acid (10 ml) was stirred at room temperature for 5 hours, made alkaline with potassium carbonate, and extracted with methylene chloride. The usual work-up of the extract afforded **36** (103 mg, 93%) as a colorless solid, which was recrystallized from ethanol to furnish colorless prisms, mp 189 – 190° [lit (13) mp 185 – 186°].

27) 2-Methyl-6-phenylpyrazine 1-Oxide (**16**).

a) A mixture of **25** (440 mg, 2 mmoles), tetrakis(triphenylphosphine)-palladium (116 mg, 0.1 mmole), sodium formate (204 mg, 3 mmoles), and *N,N*-dimethylformamide (20 ml) was heated at 100° for 2 hours and then extracted with hexane to afford **16** (352 mg, 95%) as a colorless solid, which was recrystallized from hexane to furnish colorless prisms, mp 85 – 86°.

b) A mixture of **28** (220 mg, 1 mmole), tetrakis(triphenylphosphine)-palladium (58 mg, 0.05 mmole), sodium formate (102 mg, 1.5 mmoles), and *N,N*-dimethylformamide (10 ml) was worked up as before to give **16** (172 mg, 92%).

Compound **16**.

This compound had the following physical constants: uv: λ max 249 (log ε = 4.35), 282 (3.94) nm; pmr: δ 2.53 (3H, s, CH_3), 7.38 (3H, m, benzene H), 7.83 (2H, m, benzene H), 8.48 (1H, s, pyrazine H), 8.57 (1H, s, pyrazine H) ppm; ms: m/e 186 (M^+), 169 ($M^+ - OH$).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.81; H, 5.40; N, 14.92.

28) Reaction of 2,6-Dimethylpyrazine 1-Oxide (**10**) with Acetic Anhydride.

A mixture of **10** (1.20 g, 9.7 mmoles) in acetic anhydride (15 ml) was heated at 120–130° on an oil bath for 1 hour and then treated with water. The solution was made alkaline with potassium carbonate and extracted with ether to give an oil (1.04 g), which was chromatographed on silica gel (20 g) and eluted with hexane and methylene chloride, succesively. The hexane and methylene chloride (1:1) mixture gave **37** (648 mg, 40%) as a colorless oil, bp 55–58°/60 torr. The fractions eluted with methylene chloride afforded **38** (148 mg, 12%) as a colorless oil, bp 50–60°/60 torr (bath temperature).

Compound **37**.

This compound had the following physical constants: uv: λ max 269 (log ε = 3.88), 274 (3.88), 223 (2.68, shoulder), 295 (2.66, shoulder) nm; ir (liquid film): 1745 cm^{-1} (C=O); pmr: δ 2.18 (3H, s, CH_3), 2.60 (3H, s, CH_3), 5.20 (2H, s, CH_2O), 8.40 (1H, s, pyrazine H), 8.45 (1H, s, pyrazine H) ppm; ms: m/e 166 (M^+), 124 ($M^+ - CH_2CO$), 123 ($M^+ - CH_3CO$).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.06; N, 16.85. Found: C, 57.70; H, 6.18; N, 17.01.

Compound **38**.

This compound had the following physical constants: uv: λ max 271 (log ε = 3.89), 275 (3.90), 310 (2.66, shoulder) nm; ir (liquid film): 3390 cm^{-1} (OH); pmr: δ 2.53 (3H, s, CH_3), 4.77 (2H, s, CH_2O), 8.43 (1H, s, pyrazine H), 8.53 (1H, s, pyrazine H) ppm; ms: m/e 124 (M^+), 106 ($M^+ - H_2O$).

High resolution ms: Calcd. for $C_6H_8N_2O$: 124.06364. Found: 124.06372.

29) 2-Hydroxymethyl-6-methylpyrazine (**38**).

A mixture of **37** (304 mg, 1.8 mmoles) and 20% hydrochloric acid (10 ml) was stirred at room temperature for 5 hours, then diluted with water (15 ml), made alkaline with potassium carbonate, and extracted with ether to give **38** (203 mg, 91%) as a colorless oil, which was purified by distillation to give a colorless oil, bp 50–60°/60 torr (bath temperature).

30) 3-Acetoxy-2,6-dimethylpyrazine (**39**).

A mixture of **11** (1.24 g, 10 mmoles) and acetic anhydride (5 ml) was refluxed for 2 hours, and acetic anhydride was removed by distillation *in vacuo*. The resulting oil (1.36 g) was chromatographed on alumina (Wakoalumina, 10 g) and eluted with hexane to give **39** (1.44 g, 87%) and as a colorless oil, bp 85–89°/70 torr.

Compound **39**.

This compound had the following physical constants: uv: λ max 273 (log ε = 3.42), 294 (3.13, shoulder) nm; ir (liquid film): 1745 cm^{-1} (C=O); pmr: δ 2.35 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.52 (3H, s, CH_3), 8.08 (1H, s, pyrazine H) ppm, ms: m/e 166 (M^+), 124 ($M^+ - CH_2CO$).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.06; N, 16.85. Found: C, 58.01; H, 6.29; N, 16.56.

31) 2,6-Dimethyl-3-hydroxypyrazine (**40**).

a) A solution of **39** (332 mg, 2 mmoles) in 10% potassium carbonate (5 ml) was stirred at room temperature for 30 minutes and then concentrated to dryness *in vacuo*. The residue was extracted with ether to give **40** (232 mg, 94%) as a slightly yellow solid, which was sublimed at 140° under 20 torr and then recrystallized from cyclohexane to furnish colorless needles, mp 149–151° [lit (8 and 15) mp 146–147°; lit (14) mp 145–146°].

b) A solution of **17** (50 mg, 0.35 mmole) in 15% hydrochloric acid (1 ml) was refluxed for 4 hours. The *p*H value of the solution was adjusted to 5, and then the solution was extracted with chloroform exhaustly, to afford **40** (6 mg, 14%).

32) 3-Acetoxy-2,6-diphenylpyrazine (**41**).

A solution of **13** (124 mg, 0.5 mmole) in acetic anhydride (2 ml) was refluxed for 2 hours, and concentrated to dryness *in vacuo*. The resulting oil was triturated with water and extracted with ether. The ether extract was washed with 10% potassium bicarbonate and water successively, and worked up as usual to give a brown solid (ca. 130 mg), which was chromatograghed on silica gel (10 g) and eluted with benzene to give **41** (101 mg, 70%) as colorless crystals. Recrystallization from methanol furnished colorless needles, mp 121–122°.

Compound **41**.

This compound had the following physical constants: uv: λ max 244 (log ε = 3.81), 255 (3.81), 283 (3.56, shoulder), 322 (3.56) nm; ir (potassium bromide): 1762 cm^{-1} (C=O); pmr: δ 2.30 (3H, s, CH_3), 7.53 (6H, m, benzene H), 8.17 (4H, m, benzene H), 8.83 (1H, s, pyrazine H) ppm; ms: m/e 290 (M^+), 248 ($M^+ - CH_2CO$).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.75; H, 4.86; N, 9.77.

33) 2,6-Diphenyl-3-hydroxypyrazine (**5**).

A mixture of **41** (145 mg, 0.5 mmole), 10% potassium carbonate (5 ml), and methanol (5 ml) was refluxed for 1 hour. After removal of methanol by distillation *in vacuo*, the colorless precipitates (120 mg, 96%) were collected and recrystallized from acetic acid to furnish colorless needles, mp 290–291° [lit (7) mp 272–274°; lit (8) mp 270–272°; lit (13) mp 273–274°].

34) Reaction of 2-Methyl-6-phenylpyrazine 4-Oxide (**14**) with Acetic Anhydride.

A solution of **14** (3.72 g 20 mmoles) in acetic anhydride (50 ml) was refluxed for 2 hours. After removal of acetic anhydride by distillation *in vacuo*, the resulting brown oil was triturated with water (5 ml), made alkaline with potassium carbonate, and extracted with ether to give a viscous oil (4.23 g), which was chromatographed on silica gel (80 g), eluting with methylene chloride and a mixture of chloroform and methanol (10:1). Methylene chloride eluted **44** (2.328 g, 40%) as a colorless oil, bp 134–138°/1 torr, **43** (1.164 g, 20%) as colorless crystals (from hexane), mp 70–71°, and **42** (0.157 g, 3%) as a colorless oil, bp 145–149°/4 torr, successively. Further elution with the mixture afforded **46** (0.261 g, 5%) as colorless needles (from hexane), mp 149–150°.

Compound **42**.

This compound had the following physical constants: uv: λ max 251 (log ε = 3.90), 281 (3.91), 360 (3.25) nm; ir (liquid film): 1750 cm^{-1} (C=O); pmr: δ 2.17 (3H, s, CH_3), 5.35 (2H, s, CH_2O), 7.50 (3H, m, benzene H), 8.08 (2H, m, benzene H), 8.47 (1H, s, pyrazine H), 9.00 (1H, s, pyrazine H) ppm; ms: m/e 228 (M^+), 169 ($M^+ - CH_3CO_2$).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.29; N, 12.27. Found: C, 68.46; H, 5.37; N, 12.28.

Compound **43**.

This compound had the following physical constants: uv: λ max 232 (log ε = 3.71), 246 (3.70), 288 (3.82), 302 (3.80) nm; ir (potassium bromide): 1770 cm^{-1} (C=O); pmr: δ 2.45 (3H, s, CH_3), 2.62 (3H, s, CH_3), 7.45 (3H, m, benzene H), 7.97 (2H, m, benzene H), 8.57 (1H, s, pyrazine H) ppm; ms: m/e 228 (M^+), 186 ($M^+ - CH_2CO$).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.29; N, 12.27. Found: C, 68.51; H, 5.46; N, 12.37.

Compound **44**.

This compound had the following physical constants: uv: λ max 210 (log ε = 3.92), 248 (4.00), 285 (3.90), 305 (3.94) nm; ir (liquid film): 1765 cm^{-1} (C=O); pmr: δ 2.30 (3H, s, CH_3), 2.70 (3H, s, CH_3O), 7.50 (3H, m, benzene H), 7.80 (2H, m, benzene H), 8.18 (1H, s, pyrazine H) ppm; ms: m/e 228 (M^+), 186 ($M^+ - CH_2CO$).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.29; N, 12.27. Found: C, 67.75; H, 5.45; N, 12.65.

Compound **46**.

This compound had the following physical constants: uv: λ max 227 (log ε = 3.62), 252 (3.65), 355 (3.76), nm; ir (potassium bromide): 1650 cm^{-1} (C=O); pmr: δ 2.35 (3H, s, CH_3), 7.08 (1H, s, pyrazine H), 7.50 (3H, m, benzene H), 8.40 (2H, m, benzene H) ppm; ms: m/e 186 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.25; H, 5.22; N, 14.78.

35) Reaction of 2-Methyl-6-phenylpyrazine 1-Oxide (**16**) with Acetic Anhydride.

A mixture of **16** (116 mg, 0.6 mmole) and acetic anhydride (5 ml) was refluxed for 1 hour and then worked up as before. The methylene chloride extract gave a dark brown oil (105 mg), which was chromatographed on silica gel (10 g), eluting with benzene and chloroform. The benzene fractions afforded a mixture of **43** and **44** (8:7, 16 mg, 12%) as a colorless oil. A mixture of benzene and chloroform (9:1) eluted **42** (62 mg, 45%) as a slightly yellow oil. Further elution with a mixture of benzene and chlorofrom (1:1) yielded the starting material (34 mg, 22%).

36) 2-Hydroxymethyl-6-phenylpyrazine (**45**).

A mixture of **42** (58 mg, 0.25 mmole), 10% potassium bicarbonate (2 ml), and methanol (3 ml) was refluxed for 1 hour and concentrated to dryness *in vacuo*. The oily residue was diluted with water and extracted with methylene chloride to give **45** (33 mg, 71%) as a brown oil, which was purified by distillation (bp 143–160°/4 torr, bath temperature) and the following recrystallization from hexane to furnish colorless prisms, mp 71–72°.

Compound **45**.

This compound had the following physical constants: uv: λ max 251 (log ε = 3.88), 283 (3.83), 362 (3.20) nm; pmr: δ 4.87 (2H, s, CH_2O), 7.50 (3H, m, benzene H), 8.00 (2H, m, benzene H), 8.67 (1H, s, pyrazine H), 8.98 (1H, s, pyrazine H) ppm; ms: m/e 186 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.71; H, 5.44; N, 15.05.

37) 3-Hydroxy-2-methyl-6-phenylpyrazine (**8**).

A solution of **43** (228 mg, 1 mmole) and potassium hydroxide (220 mg, 4 mmoles) in a mixture of methanol (5 ml) and water (2 ml) was stirred at room temperature for 2 hours and then concentrated to dryness *in vacuo*. The resulting oil was triturated with water and extracted with methylene chloride. The water layer was acidified (pH 5) with 20% hydrochloric acid. The yellowish precipitates (171 mg, 92%) were collected by suction and recrystallized from methanol to furnish colorless needles, mp 227–228° [lit (8) mp 222–223°; lit (14) mp 212–213°].

38) 5-Hydroxy-2-methyl-6-phenylpyrazine (**46**).

A mixture of **44** (228 mg, 1 mmole), potassium hydroxide (220 mg, 4 mmoles), methanol (5 ml), and water (2 ml) was stirred at room temperature for 2 hours and then worked up as before to afford **46** (176 mg, 95%) as a pale yellow crystalline mass, which was recrystallized from hexane to furnish pale yellow needles, mp 149–150°.

39) 3-Methoxy-2,6-diphenylpyrazine (**47**).

a) A mixture of **6** (680 mg, 2.6 mmoles) and sodium methoxide, prepared from sodium (138 mg, 6 mg atoms) and absolute methanol (10 ml), was refluxed for 3 hours and then concentrated to dryness *in vacuo*. The residue was treated with water (2 ml) and extracted with methylene chloride to yield **47** (657 mg, 97%) as a pale yellow solid, which was recrystallized from cyclohexane to furnish slightly yellow needles, mp 67–68°.

b) A mixture of **6** (267 mg, 1 mmole), potassium hydroxide (560 mg, 10 mmoles), water (0.5 ml), and methanol (15 ml) was refluxed for 3 hours and concentrated to dryness *in vacuo*. The oily residue was treated with water (3 ml) and extracted with methylene chloride to give **47** (237 mg, 90%) as pale yellow needles.

Compound **47**.

This compound had the following physical constants: uv: λ max 234 (log ε = 4.06), 264 (3.98), 335 (3.87) nm; pmr: δ 3.90 (3H, s, CH_3), 7.30 (6H, m, benzene H), 7.83 (4H, m, benzene H), 8.32 (1H, s, pyrazine H), ppm; ms: m/e 262 (M^+).

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.77; H, 5.33; N, 10.61.

40) 3-Methoxy-2-methyl-6-phenylpyrazine (**48**).

a) After a mixture of **9** (102 mg, 0.5 mmole) and sodium methoxide, prepared from sodium (230 mg, 10 mg atoms) and absolute methanol (10 ml), was heated at 120° for 1 hour in a sealed tube, the solvent was distilled off under a reduced pressure. The oily residue was triturated with water and extracted with ether to give **48** (88 mg, 88%) as colorless crystals, which was recrystallized from methanol to furnish colorless needles, mp 59–60°.

b) A mixture of **9** (102 mg, 0.5 mmole), potassium hydroxide (560 mg, 10 mmoles), methanol (5 ml), and water (0.5 ml) was refluxed for 2 hours and then concentrated to dryness *in vacuo*. The oily residue was treated with water (1 ml) and extracted with ether to afford **48** (76 mg, 76%) as colorless needles.

Compound **48**.

This compound had the following physical constants: uv: λ max 212 (log ε = 3.96), 255 (4.06), 313 (3.97) nm; pmr: δ 2.46 (3H, s, CH_3), 3.96 (3H, s, OCH_3), 7.40 (3H, m, benzene H), 7.90 (2H, m, benzene H), 8.33 (1H, s, pyrazine H) ppm; ms: m/e 200 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04; N, 13.98. Found: C, 72.21; H, 6.30; N, 14.11.

41) 5-Methoxy-2-methyl-6-phenylpyrazine (**49**).

A mixture of **18** (102 mg, 0.5 mmole) and sodium methoxide, prepared from sodium (115 mg, 5 mg atoms) and absolute methanol (10 ml), was heated at 140° for 10 hours in a sealed tube, and then concentrated to dryness *in vacuo*. The oily residue was triturated with water (1 ml) and extracted with methylene chloride to give **49** (96 mg, 96%) as a pale yellow oil, bp, 115–116°/2 torr.

Compound **49**.

This compound had the following physical constants: uv: λ max 221 (log ε = 3.90), 245 (4.01), 318 (4.12), nm; pmr: δ 2.47 (3H, s, CH_3), 3.97 (3H, s, OCH_3), 7.37 (3H, m, benzene H), 7.87 (1H, s, pyrazine H), 8.00 (2H, m, benzene H) ppm; ms: m/e 200 (M^+).

High resolution ms: Calcd. for $C_{12}H_{12}N_2O$: 200.09493. Found: 200.09501.

42) Hydrolysis of 2,6-Diphenyl-3-methoxypyrazine (**47**).

A mixture of **47** (103 mg, 0.4 mmole) and 20% hydrochloric acid (10 ml) was refluxed for 3 hours. After cooling, the crystalline precipitates of **5** (89 mg, 90%) were collected by suction and recrystallized from acetic acid or ethanol to furnish colorless prisms, mp 290–292° [lit (7) mp 272–274°; lit (8) mp 270–272°; lit (13) mp 273–274°].

43) Hydrolysis of 3-Methoxy-2-methyl-6-phenylpyrazine (**48**).

A mixture of **48** (100 mg, 0.5 mmole) and 20% hydrochloric acid (10 ml) was refluxed for 3 hours, made alkaline with potassium carbonate, and extracted with methylene chloride to give **8** (91 mg, 97%) as colorless crystals, which was recrystallized from benzene to furnish colorless

prisms, mp 225 – 226° [lit (8) mp 222 – 223°; lit (14) mp 212 – 213°].

44) Hydrolysis of 5-Methoxy-2-methyl-6-phenylpyrazine (**49**).

A mixture of **49** (100 mg, 0.5 mmole) and 20% hydrochloric acid (5 ml) was refluxed for 3 hours, made alkaline with potassium carbonate, and extracted with methylene chloride to give **46** (84 mg, 90%) as a colorless solid, which was recrystallized from hexane to furnish colorless needles, mp 148 – 149°.

45) Reaction of 3,5-Dichloro-2,6-diphenylpyrazine (**23**) with Sodium Methoxide.

A mixture of **23** (602 mg, 2 mmoles) and sodium methoxide, prepared from sodium (138 mg, 6 mg atoms) and absolute methanol (20 ml), was heated at 100 – 110° for 3 hours in a sealed tube. After cooling, the precipitates of **50** (381 mg) were collected by suction and washed with water. The filtrate was concentrated to dryness *in vacuo* and the oily residue was extracted with methylene chloride to give a pale yellow solid (236 mg), which was chromatographed on silica gel (23 g), eluting with hexane containing an increasing amount of methylene chloride. The fractions eluted with the mixtures of hexane and methylene chloride (100 :1 and 50:1) gave **50** (118 mg, total yield; 74%) as a crystalline solid, which was recrystallized from hexane to furnish colorless needles, mp 98 – 99° [lit (13) mp 95 – 96°]. The 25:1 fractions afforded **51** (108 mg, 19%) as a colorless mass, which was recrystallized from hexane to furnish colorless needles, mp 91 – 92° [lit (13) mp 98 – 99°].

46) Reaction of 3,5-Dichloro-2,6-diphenylpyrazine (**23**) with Potassium Hydroxide in Methanol.

A mixture of **23** (301 mg, 1 mmole), potassium hydroxide (560 mg, 10 mmoles), water (0.5 ml) and methanol (30 ml) was refluxed for 5 hours and then concentrated to dryness *in vacuo*. The oily residue was extracted with methylene chloride to afford **50** (293 mg, 98%) as a colorless solid, which was recrystallized from methanol to furnish colorless needles, mp 94 – 95° [lit (13) mp 98 – 99°].

47) Reaction of 3,5-Dichloro-2-methyl-6-phenylpyrazine (**31**) with Sodium Methoxide.

A mixture of **31** (236 mg, 1 mmole) and sodium methoxide, prepared from sodium (75 mg, 3.26 mg atoms) and absolute methanol (7 ml), was refluxed for 1.5 hours and concentrated to dryness *in vacuo*. The oily residue was triturated with water (1 ml) and extracted with ether to give a brown oil (219 mg), which was chromatographed on silica gel (8 g) eluting with hexane containing an increasing amount of benzene. The 6:1 fractions gave **53** (30 mg, 13%) as a crystalline mass, which was recrystallized from benzene to furnish colorless prisms, mp 58 – 59° [lit (13) mp 55 – 56°]. The 4:1 fractions afforded **52** (198 mg, 84%) as colorless crystals, which was recrystallized from benzene to yield colorless needles, mp 81 – 82° [lit (13) mp 80 – 81°].

48) Reaction of 3,5-Dichloro-2-methyl-6-phenylpyrazine (**31**) with Potassium Hydroxide in Methanol.

A mixture of **31** (240 mg, 1 mmole), potassium hydroxide (280 mg, 5 mmoles), water (0.5 ml), and methanol (3 ml) was refluxed for 8 hours and then concentrated to dryness. The oily residue was triturated with water and extracted with ether to give a colorless solid (206 mg), which was chromatographed on silica gel (30 g) as described in 47) to give **52** (54 mg, 23%), **53** (5 mg, 2%), and **31** (137 mg, 57%).

49) Reaction of 3-Chloro-2,6-diphenyl-5-methoxypyrazine (**50**) with Methylmagnesium Iodide.

A mixture of **50** (148 mg, 0.5 mmole) and methylmagnesium iodide, prepared from magnesium (40 mg, 1.5 mg atoms) and methyl iodide (0.5 ml) in dry ether (5 ml), was concentrated to dryness and the residue was heated at 150° for 30 minutes on an oil bath. After cooling, the resulting dark brown mass was crushed, triturated with water, and extracted with methylene chloride to give a brown oil (136 mg), which was chromatographed on silica gel (10 g), using methylene chloride as eluant. The starting material (19 mg, 13%) was recovered firstly and the secondly eluted fractions gave **22** (28 mg, 20%) as a colorless solid, which was recrystallized from ethanol to furnish colorless needles, mp 247 – 248° [lit (13) 244 – 246°].

50) 2,6-Diphenyl-5-hydroxy-3-iodopyrazine (**54**).

A mixture of **50** (106 mg, 0.36 mmole) and 57% hydroiodic acid (1 ml) in methanol (5 ml) was refluxed for 3 hours and concentrated to dryness *in vacuo*. The yellow residue was recrystallized from methanol to give **54** as pale yellow prisms (63 mg, 47%), mp 258 – 259.5°.

Compound **54**.

This compound had the following physical constants: uv: λ max 231 (log ε = 3.88), 263 (3.83), 332 (3.83) nm; pmr: δ 7.49 (6H, m, benzene H), 7.86 (4H, m, benzene H) ppm; ms: m/e 374 (M^+), 247 ($M^+ - I$).

Anal. Calcd. for $C_{16}H_{11}IN_2O$: C, 51.35; H, 2.96; N, 7.48. Found: C, 51.50; H, 3.15; N, 7.28.

51) Hydrolysis of 5-Chloro-3-methoxy-2-methyl-6-phenylpyrazine (**52**).

A mixture of **52** (117 mg, 0.5 mmole) and concentrated hydrochloric acid (10 ml) was refluxed for 5 hours, neutralized with potassium carbonate, and then extracted with methylene chloride to afford a yellow solid (102 mg), which was chromatographed on silica gel (5 g), eluting with methylene chloride to give **35** (93 mg, 85%) as a crystalline solid. The product was recrystallized from methanol to furnish colorless needles, mp 179 – 181° dec [lit (13) mp 181 – 182° dec].

52) Hydrolysis of 3-Chloro-5-methoxy-2-methyl-6-phenylpyrazine (**53**).

A mixture of **53** (59 mg, 0.25 mmole) and concentrated hydrochloric acid (5 ml) was refluxed for 5 hours. The mixture was worked up as before to give **36** (44 mg, 80%) as a yellow solid, which was recrystallized from ethanol to furnish colorless needles, mp 186 – 187° [lit (13) mp 185 – 186°].

Acknowledgement.

The authors are grateful to the members of the analytical center of the college for elemental analyses and spectral measurements.

REFERENCES AND NOTES

(1) E. Ochiai, "Aromatic Amine Oxides", Elsevier Publishing Company, Amsterdam, 1967; A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides", Academic Press, London, 1971.

(2) A. Ohta, T. Watanabe, Y. Akita, M. Yoshida, S. Toda, T. Akamatsu, H. Ohno and A. Suzuki, *J. Heterocyclic Chem.*, **19**, 1061 (1982).

(3) A. Ohta, S. Masano, S. Iwakura, A. Tamura, H. Watahiki, M. Tsutsui, Y. Akita and T. Watanabe, *ibid.*, **19**, 465 (1982).

(4) A. Ohta, Y. Akita and M. Hara, *Chem. Pharm. Bull.*, **27**, 2027 (1979).

(5) This compound was purchased from Aldrich Chemical Company, Incorporation, Milwaukee, Wisconsin, U. S. A.

(6) F. Tutin, *J. Chem. Soc.*, **97**, 2495 (1910).

(7) P. J. Lont and H. C. van der Plas, *Rec. Trav. Chim.*, **92**, 449 (1972).

(8) G. Dunn, J. A. Elvidge, G. T. Newbold, D. W. C. Ramsay, F. S. Spring and W. Sweeny, *J. Chem. Soc.*, 2707 (1949).

(9) B. Klein and J. Berkowitz, *J. Am. Chem. Soc.*, **81**, 5160 (1959).

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

(11) B. Klein, N. E. Hetman and M. E. O'Donnell, *J. Org, Chem.*, **28**, 1682 (1963).

(12) Y. Akita and A. Ohta, *Heterocycles*, **16**, 1325 (1981).

(13) G. W. Cheeseman and R. A. Godwin, *J. Chem. Soc.*, (C), 2977 (1971).

(14) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 78 (1949).

(15) G. Karmas and P. E. Spoerri, *ibid.*, **74**, 1580 (1952).

(16) S.-J. Chen and F. W. Fowler, *J. Org. Chem.*, **35**, 3987 (1970).