Polycyclic *N*-Hetero Compounds. XXII [1]. Reaction of Pyridine *N*-Oxides and Pyrazine Di-*N*-oxides with Formamide

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Reactions of pyridine *N*-oxides, pyrazine di-*N*-oxides, and their benzologues with formamide are described. Carbamoylation mainly occurred at aromatic ring with loss of the *N*-oxide oxygen atom, however, 2,4,6-trimethylpyridine 1-oxide gave 2- and 4-pyrimidinyl derivatives.

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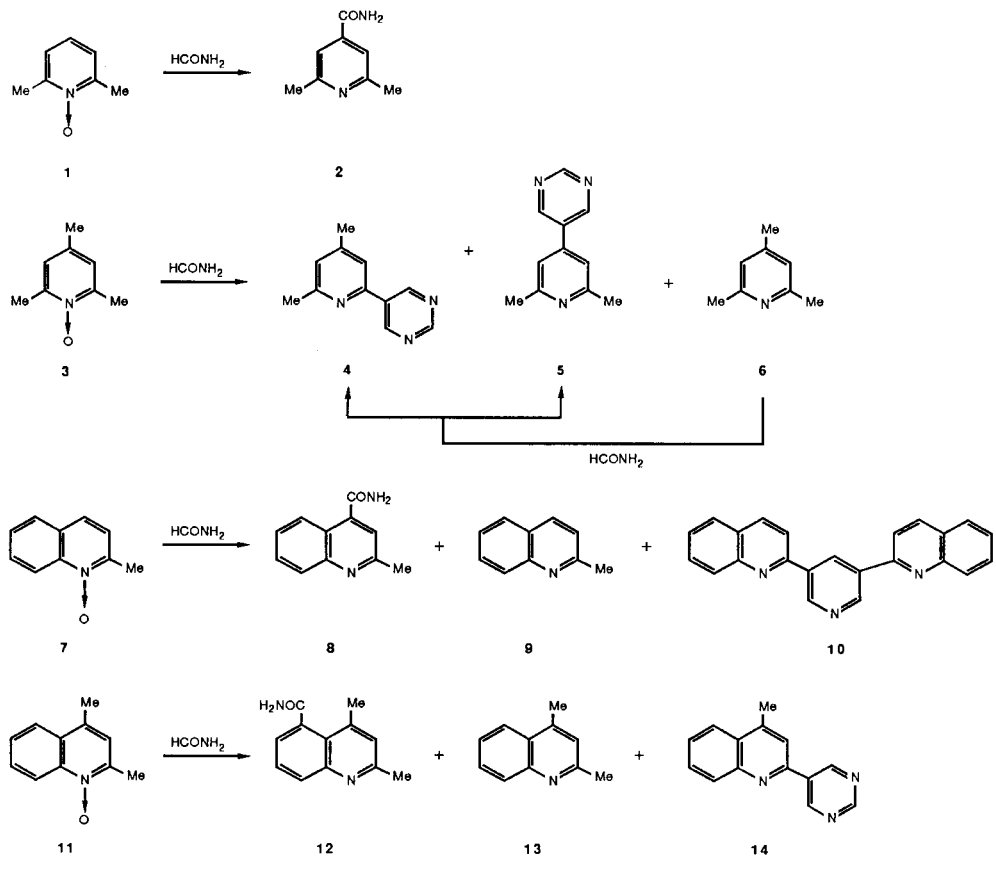
In a previous paper [2], we have reported a novel carbamoylation reaction by heating pyridine *N*-oxides with formamide. Carbamoylation occurred at the pyridine ring carbon (α-position) adjacent to the nitrogen atom with loss of the *N*-oxide oxygen atom in this reaction unless substituent occupied both α-positions in the starting materials. In order to investigate further scope and limitations of this carbamoylation reaction, the present paper deals with a similar reaction for pyridine and quinoline *N*-oxides with methyl groups at both the α- and/or the γ-positions. Furthermore, reactivity of pyrazine and quinoxaline di-*N*-oxides with formamide were also interested.

As shown in Chart 1, reaction of 2,6-dimethylpyridine 1-oxide (**1**) with hot formamide gave 2,6-dimethylpyridine-4-carboxamide (**2**), because the 4-position is also an anionic site as well as the 2-position of pyridine *N*-oxide. A similar reaction of 2,4,6-trimethylpyridine 1-oxide (**3**), all of whose anionic sites were blocked by methyl groups, did not afford a carbamoylated product, however, 2- and 4-pyrimidinyl derivatives **4** and **5** could be isolated in almost equal yields. These pyrimidines **4** and **5** were also produced in somewhat better yield in spite of the time-consuming reaction by treatment of 2,4,6-trimethylpyridine (**6**) with hot formamide. Similar observation was

Chart 1



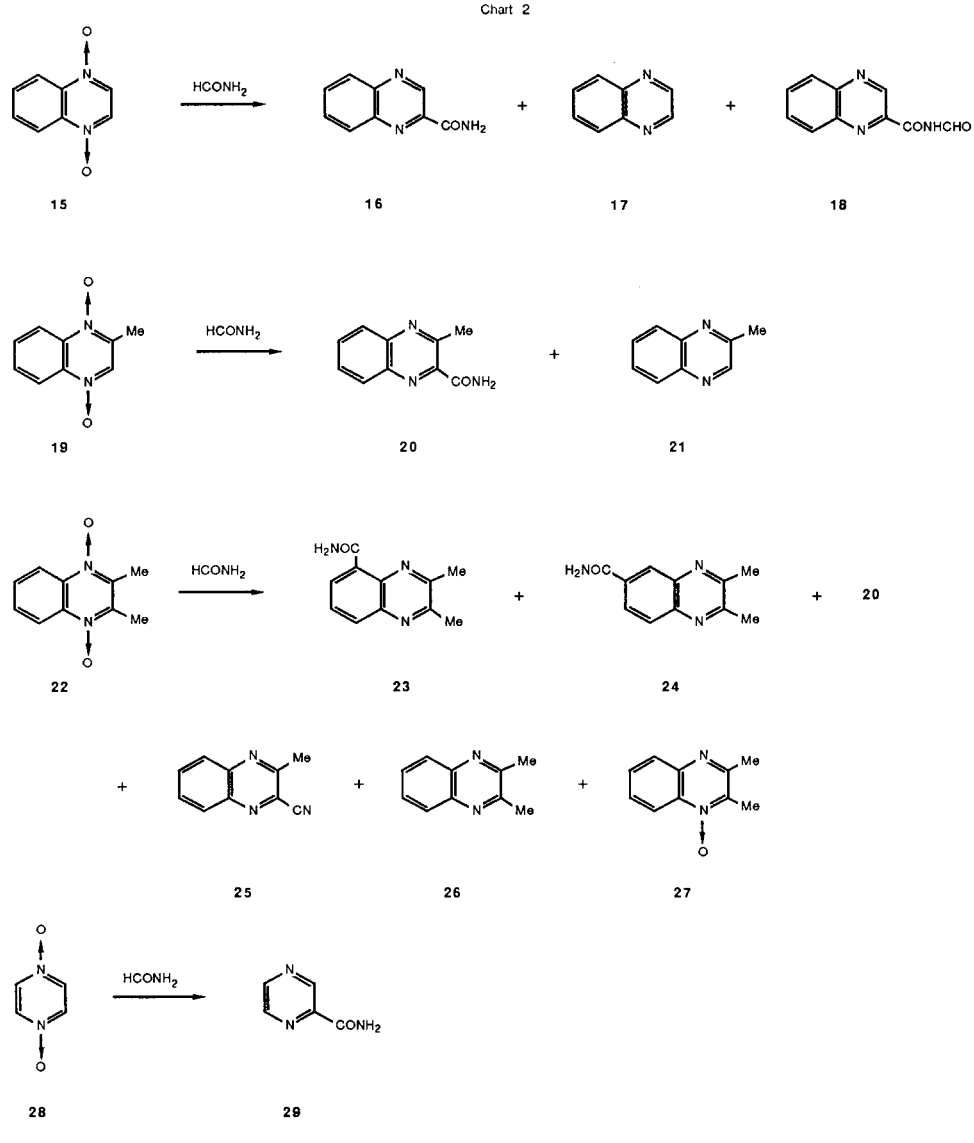
reported by us, that is, a heteroaromatic active methyl group could be converted to the pyrimidinyl ring with hot formamide [3].

Analogously, 2-methylquinoline 1-oxide (**7**) was allowed to react with formamide and 2-methylquinoline-4-carboxamide (**8**) [4] was expectedly obtained with a pyridine derivative **10** as a by-product. This type of pyridine cyclization was observed in a similar reaction for 2-methylquinoline (**9**) [3c] and 2-methylbenzothiazole [3b] with hot formamide. 2,4-Dimethylquinoline 1-oxide (**11**) was an interesting compound for this reaction whether carbamoylation or pyrimidinyl cyclization of the methyl group should occur, and 2,4-dimethylquinoline-5-carboxamide (**12**) resulted. The 5-position of quinoline *N*-oxide is also an anionic site as well as the 2- and 4-positions. However, reaction of **11** with formamide at a higher temperature gave the 2-pyrimidinyl derivative **14** without producing **12**. Deoxygenated products **6**, **9**, and **13** of all of the starting *N*-oxides were isolated in all reactions except for that of *N*-oxide **1** [5]. For formation of pyrimidinyl cyclization products **4**, **5**, and **14**, there is little doubt that the cyclization of each methyl group should take place after loss of the *N*-oxide oxygen atom. Deoxygenation rather than carbamoylation preferentially proceeds in the case of pyridine and quinoline *N*-oxides bearing substituents at both α-positions.

Next we carried out a reaction of 1,4-diazine di-*N*-oxides with formamide to examine the reactivity of this carbamoylation reaction. Double carbamoylation was expected in the reaction because these compounds contain two *N*-oxide moieties.

As shown in Chart 2, reaction of quinoxaline 1,4-dioxide (**15**) with formamide gave quinoxaline-2-carboxamide (**16**) [6] and loss of both *N*-oxide oxygen atoms was determined

Chart 2



by the spectral data and elemental analysis. 2-*N*-Formylcarbamoylquinoxaline (**18**) was isolated as a by-product. This functional group was determined by instrumental data (see Experimental). A possible formation route to **18** could be considered *via* formylation of **16** with hot formamide during the reaction, however, upon heating **16** with formamide, we could not detect **18** on thin-layer chromatography (tlc). Another possibility for the formation of **18** seemed to be a result of the reaction of **15** with formylimide, which was anticipated as one of thermal-decomposition and -reformation products of formamide [7].

Similar reaction of the 2-methyl derivative **19** afforded 3-methylquinoxaline-2-carboxamide (**20**) [8], as expected. For our carbamoylation reaction, the 2,3-dimethyl derivative **22** was an interesting compound as well as 2,4-dimethylquinoline 1-oxide (**11**). 2,3-Dimethylquinoxaline-5-carboxamide (**23**) and the 6-carboxamide (**24**) [9] were obtained as carbamoylation products at the benzene ring. Both 5- and 6-positions of quinoxaline di-*N*-oxide are also anionic sites. Surprisingly, 3-methylquinoxaline-2-carboxamide (**20**) and the 2-carbonitrile (**25**) were produced in low yield. Spectral data for **20** was completely in agreement with the product of the reaction of **19** with formamide. The structure of (**25**) was determined by direct comparison with the product obtained by treatment of **20** with phosphoryl chloride. However, the formation pathway of products **20** and **25** is not clear. The carbamoylation products, **23**, **24**, and **20**, were obtained in the ratio of 10:5:1.

Finally, reaction of pyrazine 1,4-dioxide (**28**) with formamide afforded pyrazine-2-carboxamide (**29**) [10], a well-known tuberculostatic agent. The reaction of 1,4-diazine di-*N*-oxides with formamide, contrary to our expectation, did not afford a product due to double carbamoylation, however, a single carbamoylation mainly took place simultaneously resulting in carbamoylation and deoxygenation corresponding to the two *N*-oxide bonds.

Double deoxygenated products **17**, **21**, and **26** of the starting materials were obtained in all reactions except for that of *N*-oxide **28**. Mono-*N*-oxide (**27**) was only obtained in the reaction of **22**. Deoxygenation of heteroaromatic *N*-oxides with formamide has not been reported except for our previous paper [2]. We considered that this mechanism should be either thermal-decomposition [11] of aromatic *N*-oxides with formamide or reaction with thermal decomposition products (formic acid, ammonia, and carbon monoxide) of formamide [12].

The mechanism of the carbamoylation reaction at the α-position was suggested in the previous paper [2], however, a new mechanism should be considered in this reaction at another anionic site based on our mechanism of carbamoylation of the α-position. It included a two-molecule intermediate through intermolecular proton transfer as shown in Chart 3. This mechanism consistently interprets the carbamoylation at all anionic sites of heteroaromatic *N*-oxides, although the details remain to be elucidated.

Similar carbamoylation reactions with formamide were reported for pyridines, quinolines, and 1,4-diazines by Minisci *et al.* [13], for quinoline *N*-oxides by Dziembowska and Szafran [14], for pyrimidines by Sakamoto *et al.* [15], and for pyridines by Langhals *et al.* [16] including the homolytic substitution reaction of protonated π-electron deficient *N*-heteroarenes with formamide. It is especially noteworthy that the homolytic reaction of quinoline *N*-oxide with formamide [14] did not involve a loss of the *N*-oxide oxygen atom in contrast with our carbamoylation reaction.

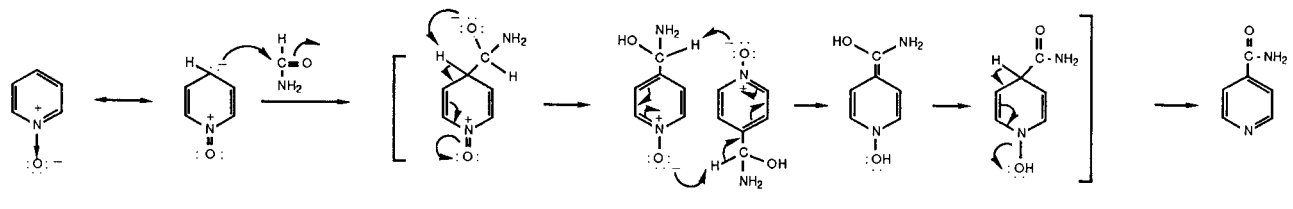
EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Boiling points are also uncorrected. Analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. Infrared spectra (ir) were recorded using a Nihon Bunko DS-301 spectrometer as potassium bromide disks (unless otherwise indicated). Proton magnetic resonance spectra (pmr) were measured with a Hitachi R-22 spectrometer (90 MHz) with tetramethylsilane as an internal standard (δ value). Mass spectra (ms) were taken with a Shimadzu LKB-9000 instrument by electron impact with an ionising voltage of 70 eV. Column chromatography was carried out on silica gel (Wakogel C-200; Wako Pure Chemicals Industries, Ltd. Osaka).

Reaction of 2,6-Dimethylpyridine 1-Oxide (1) with Formamide.

A mixture of **1** (3.69 g, 0.03 mole) and formamide (13.5 g, 0.3 mole) was stirred at 180-190° for 22 hours. After cooling, *ca.* 30 ml of saturated brine was added to the reaction mixture, and then the mixture was continuously extracted with boiling benzene. The benzene layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was recrystallized from cyclohexane to give 0.14 g (3%) of 2,6-dimethylpyridine-4-carboxamide (**2**) as colorless needles, mp 236-238.5°; ir: 3255, 3050, 1690 cm^{-1}; pmr (deuteriochloroform): 2.52 (6H, s, CH_3 x 2), 7.27

Chart 3



(2H, s, H-3 and 5), 5.9 and 7.5 (each 1H, br, $CONH_2$, disappeared with deuterium oxide); ms: m/e 150 (M^+).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.79; H, 6.80; N, 18.45.

Reaction of 2,4,6-Trimethylpyridine 1-Oxide (**3**) [17] with Formamide.

A mixture of **3** (4.11 g, 0.03 mole) and formamide (13.5 g, 0.3 mole) was stirred at 195-205° for 7 hours. After cooling, the mixture was diluted with chloroform. The whole was washed with brine, dried over sodium sulfate, and evaporated. The oily residue was chromatographed on silica gel with a gradient of chloroform and acetone. Distillation of the first chloroform eluate gave 1.03 g (28%) of 2,4,6-trimethylpyridine (**6**) as a colorless oil, bp 60-65°/22 mm Hg. The second chloroform eluate was recrystallized from hexane to give 0.18 g (3%) of 4,6-dimethyl-2-(5-pyrimidinyl)pyridine (**4**) as colorless needles, mp 76.5-77.5°; pmr (deuteriochloroform): 2.42 (3H, s, 4-CH_3), 2.60 (3H, s, 6-CH_3), 7.04 (1H, br s, H-5), 7.36 (1H, br s, H-3), 9.23 (1H, s, H-2 of pyrimidine ring), 9.30 (2H, s, H-4 and 6 of pyrimidine ring); ms: m/e 185 (M^+).

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.21; H, 6.02; N, 22.61.

The further chloroform/acetone (19:1) eluate was recrystallized from hexane to give 0.16 g (3%) of 2,6-dimethyl-4-(5-pyrimidinyl)pyridine (**5**) as colorless needles, mp 95.5-97°; pmr (deuteriochloroform): 2.63 (6H, s, CH_3 x 2), 7.19 (2H, s, H-3 and 5), 8.97 (2H, s, H-4 and 6 of pyrimidine ring), 9.27 (1H, s, H-2 of pyrimidine ring); ms: m/e 185 (M^+).

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.17; H, 6.13; N, 22.58.

Reaction of 2,4,6-Trimethylpyridine (**6**) with Formamide.

A mixture of **6** (3.63 g, 0.03 mole) and formamide (13.5 g, 0.3 mole) was stirred at 195-205° for 48 hours, however, the starting material **6** remained in the reaction mixture on tlc. Using the procedure described for the reaction of **3**, the pyrimidinyl compounds **4** and **5** were obtained in each 4% yield, based on consumed starting material, respectively. In addition, the starting compound **6** was recovered in 35% yield.

Reaction of 2-Methylquinoline 1-Oxide (**7**) [18] with Formamide.

A mixture of **7** (4.77 g, 0.03 mole) and formamide (13.5 g, 0.3 mole) was stirred at 190-205° for 3 hours. After cooling, *ca.* 30 ml of brine was added to the reaction mixture, and then the mixture was continuously extracted with boiling benzene. The benzene layer was washed with brine, dried over sodium sulfate, and evaporated. The oily residue was chromatographed on silica gel with a gradient of benzene and chloroform. Distillation of the benzene eluate gave 1.26 g (29%) of 2-methylquinoline (**9**) as a colorless oil, bp 130-135°/26 mm Hg. The benzene/chloroform (1:2) eluate was recrystallized from benzene to give 0.03 g (1%) of 3,5-bis(2-quinolyl)pyridine (**10**) as colorless scales, mp 149.5-150.5°, identical with the previously obtained sample [3c]. The further chloroform eluate was recrystallized from benzene/methanol (7:3) to give 0.12 g (2%) of 2-methylquinoline-4-carboxamide (**8**) as colorless prisms, mp 236-238° (lit [4] mp 238°); ir: 3330, 3060, 1697 cm^{-1}; pmr (DMSO-d_6): 2.68 (3H, s, CH_3), 7.50-8.34 (4H, m, H-5, 6, 7, and 8), 7.54 (1H, s, H-3), 5.1 and 7.6 (each 1H, br, $CONH_2$, disappeared with deuterium oxide); ms: m/e 186 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.85; H, 5.38; N, 14.94.

Reaction of 2,4-Dimethylquinoline 1-Oxide (**11**) [19] with Formamide.

(**A**) A mixture of **11** (5.19 g, 0.03 mole) and formamide (13.5 g, 0.3 mole) was stirred at 195-205° for 3.5 hours. After cooling, *ca.* 30 ml of brine was added to the reaction mixture, and then the mixture was continuously extracted with boiling benzene. The benzene layer was washed with brine, dried over sodium sulfate, and evaporated. Distillation of the oily residue gave 1.65 g (35%) of 2,4-dimethylquinoline (**13**) as a colorless oil, bp 140-147°/15 mm Hg. The distillation residue was chromatographed on silica gel with a gradient of benzene and chloroform. The benzene/chloroform (1:1) eluate was recrystallized from benzene to give 0.22 g (4%) of 2,4-dimethylquinoline-5-carboxamide (**12**) as colorless prisms, mp 249-251°; ir: 3421, 3273, 1658 cm^{-1}; pmr (deuteriochloroform): 2.65 (6H, s, CH_3 x 2), 7.06 (1H, s, H-3), 7.47 (1H, t, J = 8 Hz, H-7), 8.01 (1H, dd, J = 8 Hz, 2 Hz, H-8), 8.69 (1H, dd, J = 8 Hz, 2 Hz, H-6), 6.1 and 11.1 (each 1H, br, $CONH_2$, disappeared with deuterium oxide); ms: m/e 200 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.85; H, 5.98; N, 13.84.

(*B*) A mixture of **11** (3.35 g, 0.02 mole) and formamide (9 g, 0.2 mole) was stirred at 215-225° for 2 hours. Using the procedure described for the reaction **A** of **11**, the resulting oily residue was chromatographed on silica gel with a gradient of benzene and chloroform. The benzene eluate containing 5-25% chloroform gave 0.51 g (17%) of 2,4-dimethylquinoline (**13**) as a colorless oil; picrate, mp 194-195° (lit [20] mp 196°). The chloroform eluate was recrystallized from benzene to give 0.11 g (3%) of 4-methyl-2-(5-pyrimidinyl)quinoline (**14**) as colorless needles, mp 156-159°, identical with an authentic sample (lit [3c] mp 158-159.5°).

General Procedure for Reaction of Quinoxaline Di-*N*-oxides with Formamide.

A mixture of quinoxaline di-*N*-oxides (0.02 mole) and formamide (0.4 mole) was stirred at 185-205° until disappearance of the starting *N*-oxide on tlc. After cooling, *ca.* 20 ml of brine was added to the reaction mixture, and then the mixture was extracted with benzene. The benzene layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The crystalline residue was recrystallized from the appropriate solvent to give a main product, quinoxalinecarboxamides **16**, **20**, and **23**. Other products by each reaction were obtained by column chromatography on silica gel with mixtures of benzene/chloroform and chloroform/acetone. All deoxygenated products **17**, **21**, **26**, and **27** were identical with each authentic sample.

Reaction of Quinoxaline 1,4-Dioxide (**15**) [21] with Formamide.

A mixture was stirred at 200-205° for 1 hour. The benzene extract was recrystallized from benzene to give 1.25 g (36%) of quinoxaline-2-carboxamide (**16**) as colorless needles, mp 197-199° (gradually began to sublime at 145°) (lit [6] mp 200°); ir: 3417, 3172, 1700 cm^{-1}; pmr (deuteriochloroform): 7.82 (2H, m, H-6 and 7), 5.8 and 7.9 (each 1H, br, $CONH_2$, disappeared with deuterium oxide), 8.10 (2H, m, H-5 and 8), 9.66 (1H, s, H-3); ms: m/e 173 (M^+).

Anal. Calcd. for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.28; H, 4.11; N, 24.36.

The mother liquor of **16** was evaporated and the residue was chromatographed. The first benzene eluate gave 0.07 g (3%) of quinoxaline (**17**) as a colorless oil, whose tlc showed a single spot. The second benzene eluate was recrystallized from petroleum ether to give 0.09 g (2%) of 2-(*N*-formylcarbamoyl)quinoxaline (**18**) as colorless prisms, mp 164.5-165.5°; ir: 3240, 1734, 1685 cm^{-1}; pmr (deuteriochloroform): 7.25 (1H, br, CONH, disappeared with deuterium oxide), 7.88 (2H, m, H-6 and 7), 8.10 (2H, m, H-5 and 8), 9.36 (1H, d, J = 12 Hz, NH-C*H*O, changed to a singlet with deuterium oxide), 9.62 (1H, s, H-3); ms: m/e 201 (M^+).

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.87; H, 3.57; N, 20.77.

Reaction of 2-Methylquinoxaline 1,4-Dioxide (**19**) [22] with Formamide.

A mixture was stirred at 185-190° for 20 minutes. The benzene extract was recrystallized from benzene to give 0.37 g (10%) of 3-methylquinoxaline-2-carboxamide (**20**) as colorless fine needles, mp 193-194° (gradually began to sublime at 160°) (lit [8] mp 192-193°); ir: 3398, 3174, 1700 cm^{-1}; pmr (deuteriochloroform): 3.08 (3H, s, 3-CH_3), 7.70 (2H, m, H-6 and 7), 7.92 (2H, m, H-5 and 8), 5.7 and 8.8 (each 1H, br, $CONH_2$, disappeared with deuterium oxide); ms: m/e 187 (M^+).

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.07; H, 4.83; N, 22.51.

The mother liquor of **20** was evaporated and the residue was chromatographed. The benzene eluate gave 0.03 g (1%) of 2-methylquinoxaline (**21**) as a colorless oil; picrate: mp 134-135° (lit [23] mp 137°).

Reaction of 2,3-Dimethylquinoxaline 1,4-Dioxide (**22**) [23] with Formamide.

A mixture was stirred at 190-195° for 1 hour. The benzene extract was recrystallized from methanol to give 0.28 g (7%) of 2,3-dimethylquinoxaline-5-carboxamide (**23**) as brownish prisms, mp 259-262° (gradually began to sublime at 200°); ir: 3291, 3132, 1684 cm^{-1}; pmr (DMSO-d_6): 2.76 and 2.80 (each 3H, s, CH_3 x 2), 7.78 (1H, t, J = 8 Hz, H-7), 8.13 (1H, dd, J = 8 Hz, 2 Hz, H-8), 8.58 (1H, dd, J = 8 Hz, 2 Hz, H-6), 6.3 and 10.5 (each 1H, br, $CONH_2$, disappeared with deuterium oxide); ms: m/e 201 (M^+).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.61; H, 5.57; N, 20.85.

The aqueous solution extracted with benzene was re-extracted with chloroform. The chloroform layer was washed with brine, dried over sodium sulfate, and evaporated. The chloroform extract was recrystallized from methanol to give 0.16 g (4%) of 2,3-dimethylquinoxaline-6-carboxamide (**24**) as colorless prisms, mp 247-250° (gradually began to sublime at 210°), (lit [9] mp 259° dec); ir: 3365, 3175, 1675 cm^{-1}; pmr (deuteriochloroform): 2.78 (6H, s, CH_3 x 2), 6.1 and 8.0 (each 1H, br, $CONH_2$, disappeared with deuterium oxide), 8.11 (1H, dd, J = 8 Hz, 2 Hz, H-7), 8.13 (1H, d, J = 8 Hz, H-8), 8.41 (1H, d, J = 2 Hz, H-5); ms: m/e 201 (M^+).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.54; H, 5.49; N, 20.96.

The combined mother liquors of **23** and **24** were evaporated and the residue was chromatographed. The first benzene eluate was recrystallized from methanol to give 0.06 g (2%) of 3-methylquinoxaline-2-carbonitrile (**25**) as colorless prisms, mp 149.5-150.5° (lit [8] mp 151-152°), identical with an authentic sample, which was almost quantitatively prepared by treatment of **20** with phosphoryl chloride in boiling benzene; ir: 2240, 1605 cm^{-1}; pmr (deuteriochloroform): 2.96 (3H, s, CH_3), 7.82 (2H, m, H-6 and 7), 8.02 (2H, m, H-5 and 8); ms: m/e 169 (M^+).

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.95; H, 4.23; N, 24.90.

The second benzene eluate was recrystallized from hexane to give 1.26 g (40%) of 2,3-dimethylquinoxaline (**26**) as colorless needles, mp 105-106°. The further benzene/chloroform (3:2) eluate was recrystallized from petroleum benzin to give 0.13 g (4%) of 2,3-dimethylquinoxaline 1-oxide (**27**) as colorless needles, mp 85-87.5° (lit [24] mp 92-93°). The benzene/chloroform (1:1) eluate was recrystallized from benzene to give 0.05 g (1%) of 3-methylquinoxaline-2-carboxamide (**20**) as colorless fine needles, mp 181-184° (gradually began to sublime at 160°), identical with the product obtained from reaction of **19** with formamide. The chloroform eluate gave 0.12 g (2%, total 10%) of **23** as brownish prisms, mp 259.5-262.5° (gradually began to sublime at 200°), identical with the product obtained from the benzene extract. The eluate of chloroform/-acetone (1:1) gave 0.05 g (1%, total 5%) of **24** as colorless prisms, mp 247.5-249.5 (gradually began to sublime at 210°), identical with the product obtained from the chloroform extract.

Reaction of Pyrazine 1,4-Dioxide (**28**) [25] with Formamide.

A mixture of **28** (2.24 g, 0.02 mole) and formamide (18.0 g, 0.4 mole) was stirred at 200-210° for 1 hour. After cooling, the reaction mixture was diluted with chloroform. The whole was washed with brine, dried over sodium sulfate, and evaporated. The chloroform extract was recrystallized from methanol to afford 0.72 g (29%) of pyrazine-2-carboxamide (**29**) as pale yellow fine needles, mp 187-189° (gradually began to sublime at 60°) (lit [10] mp 189-191°), identical with an authentic sample.

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