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Anticoccidials. VII.[1] Synthesis of 4,5-Dihydro-5-oxo-2-pyrazinecarboxylic Acid 1-Oxides

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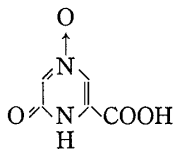
Hydrolysis of 1,6-dihydro-6-oxo-2,3-pyrazinedicarbonitrile (**4**) gave sodium hydrogen 1,6-dihydro-6-oxo-2,3-pyrazinedicarboxylate (**6**), which was converted to methyl 1,6-dihydro-6-oxo-2-pyrazinecarboxylate (**10**) and methyl 4,5-dihydro-5-oxo-2-pyrazinecarboxylate (**12**) *via* a sequence of reactions including decarboxylation and esterification. Although the synthesis of 4,5-dihydro-5-oxo-2-pyrazinecarboxylic acid 1-oxide (**2**) from **12** was unsuccessful, its 6-methyl derivative **3** was synthesized from the 5-methyl analog of **4**.

Keywords——sodium hydrogen 1,6-dihydro-6-oxo-2,3-pyrazinedicarboxylate; decarboxylation; methyl 1,6-dihydro-6-oxo-2-pyrazinecarboxylate; methyl 4,5-dihydro-5-oxo-2-pyrazinecarboxylate; 4,5-dihydro-6-methyl-5-oxo-2-pyrazinecarboxylic acid 1-oxide; anticoccidial activity

In the preceding paper of this series we reported that 1,6-dihydro-6-oxo-2-pyrazinecarboxylic acid 4-oxide (**1**) has potent anticoccidial activity.[1] In connection with our synthetic studies of pharmacologically active 2(1*H*)-pyrazinone 4-oxides,[3] we became particularly interested in the synthesis of 4,5-dihydro-5-oxo-2-pyrazinecarboxylic acid 1-oxide (**2**) and its 6-methyl derivative **3** for biological evaluation. In fact we did not succeed in the synthesis of **2**, but found a convenient route to **3**.



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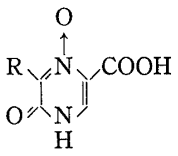

2: R=H
3: R=CH_3

Our initial work in this project was concentrated on the preferential decarboxylation of 1,6-dihydro-6-oxo-2,3-pyrazinedicarboxylic acid and its derivatives. Hydrolysis of the readily accessible 1,6-dihydro-6-oxo-2,3-pyrazinedicarbonitrile (**4**)[4] under various conditions (see Chart 1) gave the mono sodium salt **6**. Refluxing **6** in thionyl chloride for 3 hr and subsequent treatment of the resulting anhydride **8** with methanol gave the half ester **9** in 55% yield. Heating **9** in nitrobenzene at 180—190° gave methyl 1,6-dihydro-6-oxo-2-pyrazinecarboxylate (**10**)[5] in 56% yield. On the other hand, refluxing **6** in acetic acid caused decarboxylation to give the sodium salt **11** in 33% yield; this was esterified by treatment with thionyl chloride and methanol to afford the isomeric methyl ester **12**.[5] This ester was also

1) Part VI: K. Imai, M. Mano, T. Seo, and T. Matsuno, *Chem. Pharm. Bull.*, "accepted".
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
3) *a*) M. Mano, T. Seo, and K. Imai, *Chem. Pharm. Bull.*, **28**, 2720 (1980); *b*) M. Mano, T. Seo, T. Hattori, T. Kaneko, and K. Imai, *ibid.*, **28**, 2734 (1980).
4) Kuraray Co., Ltd. and Kyowa Gas Chemical Industry Co., Ltd., Japan Patent Kokai 75-59379 (1975) [*Chem. Abstr.*, **83**, 193380*u* (1975)].
5) *a*) H. Foks and J. Sawlewicz, *Acta Pol. Pharm.*, **23**, 437 (1966) [*Chem. Abstr.*, **66**, 94996*s* (1967)]; *b*) S. Okada, A. Kosasayama, T. Konno, and F. Uchimaru, *Chem. Pharm. Bull.*, **19**, 1344 (1971); *c*) F. Uchimaru, S. Okada, A. Kosasayama, and T. Konno, *ibid.*, **20**, 2204 (1972).

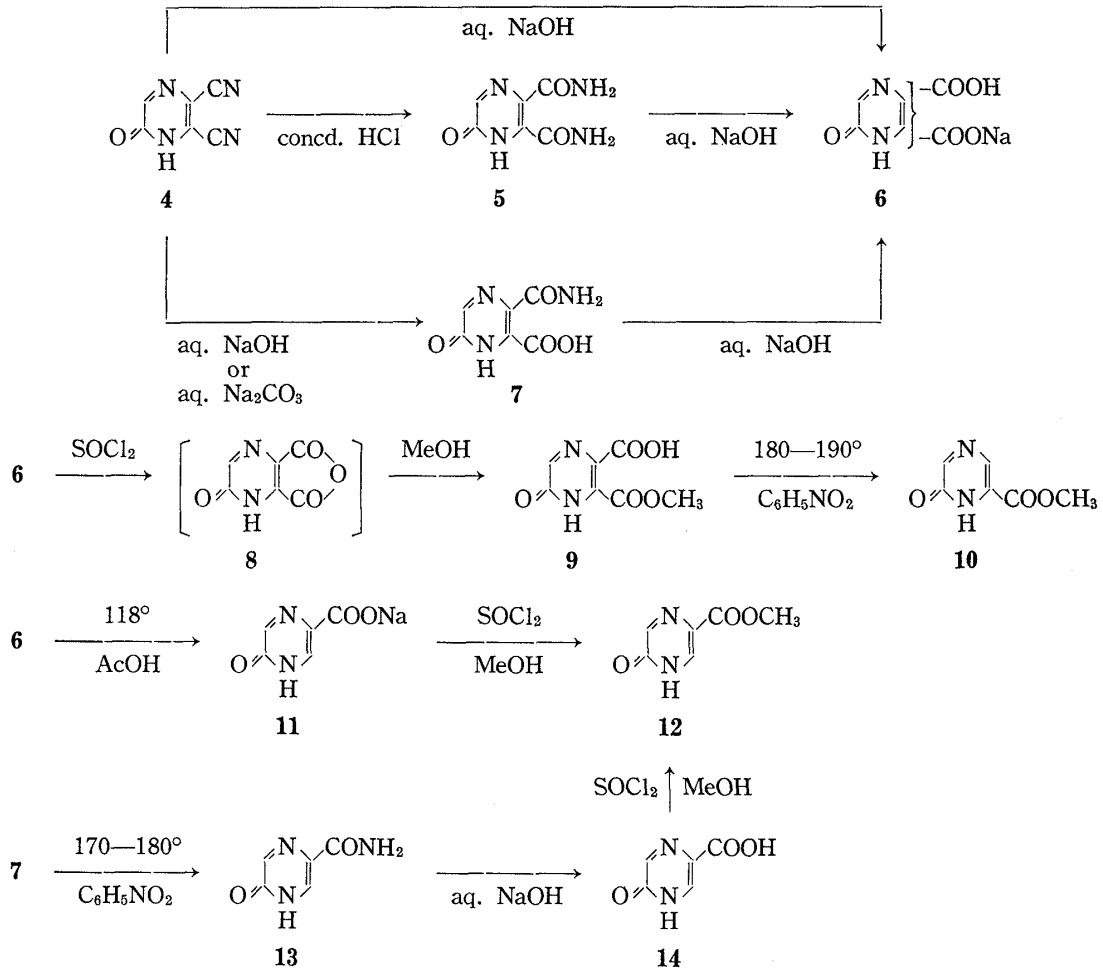

Chart 1

obtained by decarboxylation of 3-carbamoyl-1,6-dihydro-6-oxo-2-pyrazinecarboxylic acid (**7**) in nitrobenzene at 170—180°, followed by hydrolysis and esterification.

The resulting **12** was converted into 5-chloropyrazine **15** by treatment with phosphoryl chloride and N,N-dimethylformamide (DMF). Oxidation of **15** with *m*-chloroperbenzoic acid (MCPBA) gave the N-oxide **16**. The structure of **16** was assigned on the basis of proton magnetic resonance (PMR) spectral evidence. It is known that in the 2-chloro-5-phenylpyrazine system, N-oxidation at the 1-position does not affect the chemical shifts of 3-H and 6-H, whereas N-oxidation at the 4-position causes a high-field shift (*ca.* 0.4 ppm) of these proton signals.[6] In fact, the chemical shifts of 3-H and 6-H of **16** are shifted 0.55 ppm to higher field compared to the corresponding proton signals of **15**. Mild hydrolysis of **16** with aqueous potassium carbonate gave the carboxylic acid **17**, which was further treated with aqueous sodium hydroxide to afford two products. Direct treatment of **16** with aqueous sodium hydroxide also gave two products. The major product was assigned as 5,6-dihydroxy-2-pyrazinecarboxylic acid (**19**)[7] on the basis of elemental analysis and spsectral evidence (see

6) N. Sato, *J. Org. Chem.*, **43**, 3367 (1978).

7) Reaction of **10** with MCPBA gave the methyl ester of **19**, mp >300°. *Anal.* Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.40; H, 3.45; N, 16.47. PMR (DMSO-d_6, EM-390): 3.74 (3H, s, OCH_3), 7.07 (1H, s, 3-H), 10.97—11.80 (2H, br, 2×OH). IR ν_{max}^{KBr} cm^{-1}: 1720, 1695, 1650. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 272 (10900), 292 shoulder (10800), 302.5 (11000), 318 shoulder (8500), 337 shoulder (3500); $\lambda_{max}^{H_2O}$ nm (ε): 272 (11100), 292 shoulder (10900), 302.5 (11100), 318 shoulder (8400), 337 shoulder (3600); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 285 shoulder (8700), 325 (15300), 346 shoulder (8800). MS *m/e*: 170 (M^+), 142, 110.

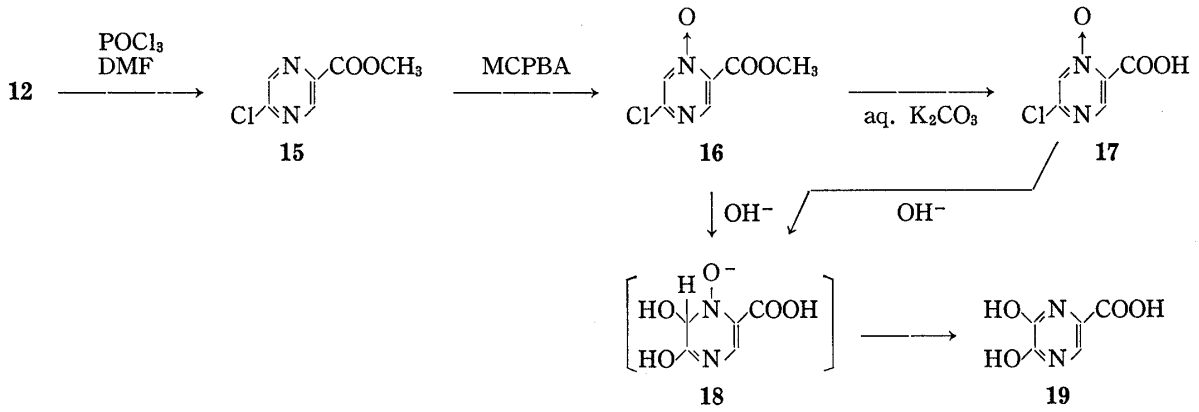

Chart 2

"Experimental"). The formation of **19** can be rationalized in terms of the intermediate **18** (Chart 2). An analogous reaction has been reported with a quinazoline 1-oxide derivative.[8] The minor product was not further examined.

Although the synthesis of **2** was unsuccessful, the reaction sequence described above could be applied to the preparation of **3**. This is outlined in Chart 3. The structure of **3** was deduced from its elemental analysis data, infrared (IR), ultraviolet (UV) and PMR spectra, and from its negative ferric chloride test.[9]

None of the compounds prepared showed significant anticoccidial activity against *Eimeria tenella* in chickens.

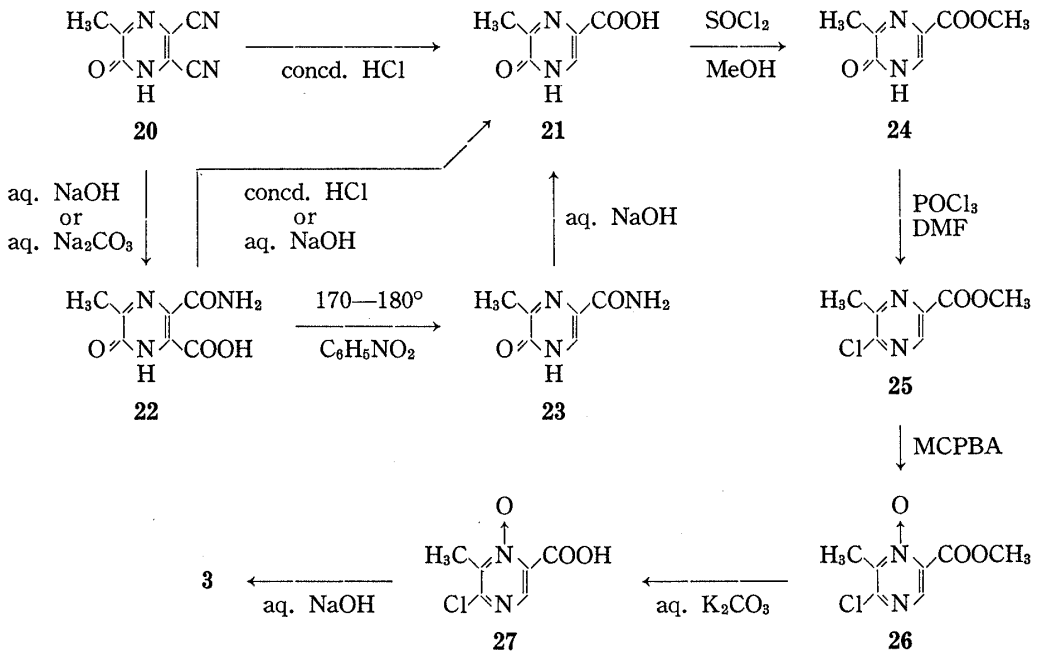

Chart 3

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer and UV spectra were measured with a Perkin-Elmer 450 spectrophotometer. Mass spectra (MS) were measured with a Hitachi RMU-6D mass

8) E. Hayashi and T. Higashino, *Chem. Pharm. Bull.*, **12**, 43 (1964).
9) J.D. Dutcher, *J. Biol. Chem.*, **171**, 321 (1947).

spectrometer. PMR spectra were taken with a Varian T-60 or EM-390 spectrometer and chemical shifts are expressed in ppm, using tetramethylsilane as an internal standard. When 4% NaOD in D_2O was used as a solvent, sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used as an internal standard. The following abbreviations are used: s, singlet; d, doublet; br, broad. Paper electrophoresis (PE) was carried out in 0.1 M acetate buffer (pH 4.0) (buffer 1) or 0.05 M phosphate buffer (pH 7.5) (buffer 2) at 500 V/40 cm. Solutions were concentrated under reduced pressure with a rotary evaporator.

1,6-Dihydro-6-oxo-2,3-pyrazinedicarboxamide (**5**)——A mixture of **4** (500 mg, 3.4 mmol) and concentrated HCl (2.5 ml) was stirred at room temperature for 3 hr and allowed to stand overnight. The precipitate was collected by filtration, washed with acetone, and recrystallized from EtOH to give needles (186 mg, 30%), mp 257—259° (dec.). *Anal.* Calcd for $C_6H_6N_4O_3$: C, 39.57; H, 3.32; N, 30.76. Found: C, 39.41; H, 3.19; N, 30.94. PMR (DMSO[10]-d_6, T-60): 7.35 (1H, br s, $CONH_2$), 7.64 (2H, br s, $CONH_2$), 7.95 (1H, br s, $CONH_2$), 7.97 (1H, s, 5-H), 12.2—13.5 (1H, br, NH).

3-Carbamoyl-1,6-dihydro-6-oxo-2-pyrazinecarboxylic Acid (**7**)——i) A mixture of **4** (1 g, 6.9 mmol) and 10% NaOH (20 ml) was refluxed for 10 min with stirring and the ice-cooled solution was adjusted with 20% HCl to pH 1. The precipitate was collected by filtration, washed with H_2O, and recrystallized from EtOH to give needles (723 mg, 58%), mp 229—230° (dec.). *Anal.* Calcd for $C_6H_5N_3O_4$: C, 39.35; H, 2.75; N, 22.95. Found: C, 39.26; H, 2.70; N, 23.19. PMR (DMSO-d_6, T-60): 7.77 (1H, br s, $CONH_2$), 8.04 (1H, br s, $CONH_2$), 8.12 (1H, s, 5-H). UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 263 (11900), 307.5 (5800); $\lambda_{max}^{H_2O}$ nm (ε): 256 (12300), 315 (6900); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 268 (15200), 310 (8600).

ii) A mixture of **4** (500 mg, 3.4 mmol) and 10% Na_2CO_3 (10 ml) was refluxed for 8 hr with stirring and the ice-cooled solution was adjusted with concentrated HCl to pH 1. The precipitate was collected by filtration, washed with H_2O, and recrystallized from MeOH to give a crystalline powder (165 mg, 26%), mp 228—231° (dec.).

Sodium Hydrogen 1,6-Dihydro-6-oxo-2,3-pyrazinedicarboxylate (**6**)——i) A mixture of **4** (200 mg, 1.4 mmol) and 10% NaOH (4 ml) was refluxed for 8 hr with stirring. After cooling, the solution was adjusted with concentrated HCl to pH 1. The precipitate was collected by filtration, washed with a small volume of cold H_2O and acetone, and recrystallized from 70% EtOH to give needles (145 mg, 51%), mp 275—280° (dec.). *Anal.* Calcd for $C_6H_3N_2NaO_5 \cdot 1/4H_2O$: C, 34.22; H, 1.68; N, 13.30. Found: C, 34.16; H, 1.49; N, 13.26. PMR (DMSO-d_6, T-60): 8.14 (1H, s, 5-H). IR ν_{max}^{KBr} cm^{-1}: 1665.

ii) A mixture of diaminomaleonitrile (27 g, 250 mmol), glyoxylic acid monohydrate (23 g, 250 mmol) and 2 N HCl (250 ml) was stirred at room temperature for 3 hr and concentrated. The concentrate was dissolved in 10% NaOH (600 ml) and the solution was refluxed for 8 hr with stirring. The ice-cooled solution was adjusted with concentrated HCl to pH 1. The deposited crystals were collected by filtration and washed with H_2O and acetone to give needles (50.5 g), mp 275—280° (dec.).

iii) A mixture of **5** (300 mg, 1.7 mmol) and 10% NaOH (6 ml) was refluxed for 5 hr with stirring. After cooling, the solution was adjusted with 20% HCl to pH 1. The precipitate was collected by filtration, washed with H_2O, and recrystallized from H_2O–EtOH to give a crystalline powder (215 mg, 63%), mp 265—270° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1665.

iv) A mixture of **7** (100 mg, 0.6 mmol) and 10% NaOH (2 ml) was refluxed for 3 hr with stirring and worked up according to the procedure described in iii) to give needles (50 mg, 44%), mp 274—278° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1665.

1*H*-Furo[3,4-*b*]pyrazine-2,5,7-trione (**8**)——A mixture of **6** (206 mg, 1 mmol) and $SOCl_2$ (5 ml) was refluxed for 3 hr with stirring and $SOCl_2$ was removed. The residue was triturated with toluene (10 ml) and the solvent was evaporated off. The residue was extracted with hot toluene (150 ml). The extract was treated with activated charcoal, concentrated to *ca.* 50 ml, and cooled to give crystals (20 mg), mp 175—180° (dec.). *Anal.* Calcd for $C_6H_2N_2O_4$: C, 43.39; H, 1.21; N, 16.87. Found: C, 43.07; H, 1.30; N, 16.51. IR ν_{max}^{KBr} cm^{-1}: 1865, 1785, 1680, 1665.

Methyl 3-Carboxy-1,6-dihydro-6-oxo-2-pyrazinecarboxylate (**9**)——A mixture of **6** (40 g, 194 mmol) and $SOCl_2$ (400 ml) was refluxed for 3 hr with stirring. After removal of $SOCl_2$, the residue was triturated with toluene (500 ml) and the solvent was evaporated off. The residue was dissolved in MeOH (600 ml) and the solution was refluxed for 5 hr with stirring. After treatment with activated charcoal, the filtrate was evaporated to dryness. The residue was heated with ether (500 ml) and cooled to give crystals (containing NaCl) (36.8 g). For analysis, a sample (5 g) was recrystallized from H_2O to give needles (3.02 g), mp 198—200° (dec.), yield 55%. *Anal.* Calcd for $C_7H_6N_2O_5 \cdot 1/2H_2O$: C, 40.59; H, 3.41; N, 13.52. Found: C, 40.65; H, 3.31; N, 13.18. PMR (DMSO-d_6, T-60): 3.82 (3H, s, OCH_3), 8.16 (1H, s, 5-H).

Methyl 1,6-Dihydro-6-oxo-2-pyrazinecarboxylate (**10**)——A mixture of **9** (991 mg, 5 mmol) and nitrobenzene (50 ml) was stirred at 180—190° for 7 hr and undissolved materials were filtered off. The filtrate was evaporated to dryness and the residue was dissolved in hot MeOH. After treatment with activated charcoal, the filtrate was evaporated to dryness and the residue was recrystallized from MeOH to give needles (432 mg, 56%), mp 195—197° (dec.) [lit.[5b] mp 196—197° (dec.)]. *Anal.* Calcd for $C_6H_6N_2O_3$: C, 46.76; H,

10) Dimethyl sulfoxide.

3.92; N, 18.18. Found: C, 46.69; H, 3.88; N, 18.15. PMR (DMSO-d_6, T-60): 3.87 (3H, s, OCH_3), 8.27 (1H, s, 3-H or 5-H), 8.43 (1H, s, 5-H or 3-H). IR ν_{max}^{KBr} cm^{-1}: 1720. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 237 (5300), 315 (6500); $\lambda_{max}^{H_2O}$nm (ε): 237.5 (5300), 315.5 (6400); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 238.5 (7500), 325 (6500).

Sodium 4,5-Dihydro-5-oxo-2-pyrazinecarboxylate (11)——A mixture of **6** (500 mg, 2.4 mmol) and AcOH (50 ml) was refluxed for 20 hr with stirring. After cooling, undissolved materials were filtered off and the filtrate was evaporated to dryness. The residue was triturated with ether. The precipitate was collected by filtration, washed with ether, and recrystallized from H_2O–EtOH to give colorless needles (143 mg, 33%), mp>300°. *Anal.* Calcd for $C_5H_3N_2NaO_3 \cdot H_2O$: C, 33.34; H, 2.80; N, 15.55. Found: C, 33.16; H, 2.71; N, 15.46. IR ν_{max}^{KBr} cm^{-1}: 1725, 1655, 1635, 1620.

Methyl 4,5-Dihydro-5-oxo-2-pyrazinecarboxylate (12)——i) $SOCl_2$ (15.2 ml) was added dropwise to MeOH (500 ml) at −20 to −10°, followed by stirring at the same temperature for 30 min. After addition of **11** (9.4 g, 58 mmol) to this solution at −10°, the mixture was refluxed for 2 hr with stirring, then concentrated. The residue was recrystallized from MeOH to give needles (7.05 g, 79%), mp 178—179° (lit.[5a] mp 183—185°).

ii) Compound **12** (690 mg, 64%) was obtained from **14** (980 mg, 7 mmol), $SOCl_2$ (1.95 ml) and MeOH (70 ml) in the manner described in i), mp 180—181°. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 256 (15900), 305 (5500); $\lambda_{max}^{H_2O}$ nm (ε): 256 (15400), 305 (5600); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 263 (14400), 310.5 (7800).

4,5-Dihydro-5-oxo-2-pyrazinecarboxamide (13)——A mixture of **7** (4.12 g, 22.5 mmol) and nitrobenzene (250 ml) was stirred at 170—180° for 3 hr. After cooling, the precipitate was collected by filtration, washed with ether, and recrystallized from EtOH to give needles (1.9 g, 61%), mp 290—295° (dec.) [lit.[11] mp 295° (dec.)]. *Anal.* Calcd for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 42.92; H, 3.49; N, 30.11. PMR (DMSO-d_6, EM-390): 7.35 (1H, br s, $CONH_2$), 7.55 (1H, br s, $CONH_2$), 7.92 (2H, s, 3-H and 6-H), 11.5—13.2 (1H, br, NH).

4,5-Dihydro-5-oxo-2-pyrazinecarboxylic Acid (14)——A mixture of **13** (1.9 g, 13.7 mmol) and 10% NaOH (10 ml) was refluxed for 3 hr with stirring. The ice-cooled solution was adjusted with concentrated HCl to pH 1. The precipitate was collected by filtration, washed with H_2O, and recrystallized from EtOH to give needles (1.472 g, 77%), mp 292—295° (dec.) (lit.[12] mp>300°). *Anal.* Calcd for $C_5H_4N_2O_3$: C, 42.87; H, 2.88; N, 20.00. Found: C, 42.75; H, 2.73; N, 19.76. PMR (DMSO-d_6, T-60): 8.00 (1H, d, J=1.5 Hz, 3-H or 6-H), 8.05 (1H, d, J=1.5 Hz, 6-H or 3-H), 11.4—13.4 (1H, br, NH or COOH).

Methyl 5-Chloro-2-pyrazinecarboxylate (15)——A mixture of **12** (500 mg, 3.3 mmol), $POCl_3$ (2.5 ml) and DMF (2 drops) was refluxed for 2 hr with stirring. The cooled reaction mixture was poured into ice-H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was recrystallized from petroleum ether to give colorless needles (384 mg, 68%), mp 89—90° (lit.[5b] mp 90.5—91.5°). PMR ($CDCl_3$, T-60): 4.04 (3H, s, OCH_3), 8.72 (1H, d, J=1 Hz, 3-H or 6-H), 9.10 (1H, d, J=1 Hz, 6-H or 3-H). IR ν_{max}^{KBr} cm^{-1}: 1715. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 223.5 (11300), 279 (9900); $\lambda_{max}^{H_2O}$ nm (ε): 223.5 (11300), 279 (9900); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 279 (8500).

Methyl 5-Chloro-2-pyrazinecarboxylate 1-Oxide (16)——A mixture of **15** (5 g, 28.9 mmol), MCPBA (5.8 g, 33.3 mmol) and 1,2-dichloroethane (50 ml) was stirred at 65° for 19 hr. Additional MCPBA (3 g, 17.4 mmol) was added and the mixture was stirred for 20 hr. After cooling, the crystals formed were filtered off and washed with 1,2-dichloroethane. The filtrate and the washings were combined, washed successively with 5% $NaHCO_3$ (50 ml), 5% $Na_2S_2O_4$ (50 ml) and 5% $NaHCO_3$ (25 ml), and then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (Merck) (50 g) with dichloromethane as the eluent. The first fraction was evaporated to dryness to recover **15** (2.65 g). The second fraction was evaporated to dryness and the residue was extracted with hot hexane (3×100 ml). The extract was concentrated and the residue was recrystallized from ether–petroleum ether to give **16** as colorless needles (345 mg, 6%), mp 52—53°. *Anal.* Calcd for $C_6H_5ClN_2O_3$: C, 38.22; H, 2.67; N, 14.86. Found: C, 37.98; H, 2.56; N, 15.01. PMR ($CDCl_3$, T-60): 3.97 (3H, s, OCH_3), 8.17 (1H, s, 3-H or 6-H), 8.65 (1H, s, 6-H or 3-H).

5-Chloro-2-pyrazinecarboxylic Acid 1-Oxide (17)——A mixture of **16** (636 mg, 3.4 mmol) and aqueous K_2CO_3 (K_2CO_3 1.38 g, H_2O 7 ml) was stirred at room temperature for 2 hr and undissolved materials were filtered off. The filtrate was adjusted with 20% HCl to pH 1. The precipitate was collected by filtration and washed with cold H_2O to give colorless needles (531 mg, 91%), mp 163—164°. *Anal.* Calcd for $C_5H_3ClN_2O_3$: C, 34.41; H, 1.73; N, 16.05. Found: C, 34.32; H, 1.67; N, 16.25. PMR ($CDCl_3$, EM-390): 8.29 (1H, s, 3-H or 6-H), 9.27 (1H, s, 6-H or 3-H), 14.1—14.7 (1H, br, COOH). IR ν_{max}^{KBr} cm^{-1}: 1715. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 233.5 (19100), 268 (9300), 302.5 (3100); $\lambda_{max}^{H_2O}$nm (ε): 233 (13600), 270 (9600), 302.5 (3300); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 269 (10000), 302.5 (3400).

5,6-Dihydroxy-2-pyrazinecarboxylic Acid (19)——i) A mixture of **16** (1.377 g) and aqueous NaOH (NaOH 876 mg, H_2O 15 ml) was stirred at 70—80° for 5 hr, and the ice-cooled solution was adjusted with 20% HCl to pH 1—2. The precipitate was collected by filtration and recrystallized from H_2O to give crystals (655 mg). The crystals (360 mg) were recrystallized twice from H_2O with activated charcoal to give colorless needles (62 mg), mp>300°, yield 10%. *Anal.* Calcd for $C_5H_4N_2O_4 \cdot H_2O$: C, 34.50; H, 3.47; N, 16.09. Found:

11) G. Palamidessi, A. Vigevani, and F. Zarini, *J. Heterocycl. Chem.*, **11**, 607 (1974).
12) E. Felder, D. Pitré, and E.B. Grabitz, *Helv. Chim. Acta*, **47**, 873 (1964).

C, 34.46; H, 3.58; N, 15.95. PMR (4% NaOD in D_2O, EM-390): 7.54 (1H, s, 3-H). IR ν_{max}^{KBr} cm^{-1}: 1710, 1670, 1610. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 267 (10400), 302 (10300), 318 shoulder (8100), 337.5 shoulder (3200); $\lambda_{max}^{H_2O}$ nm (ε): 258 (8800), 305 (9500), 323 shoulder (7700), 341 shoulder (3500); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 276 (9900), 312.5 (13200), 327 shoulder (12300), 342 shoulder (6300). MS *m/e*: 156 (M^+), 110. PE: M_1[13] 0.87 (buffer 1); M_1 0.66 (buffer 2).

ii) A mixture of **17** (500 mg, 2.9 mmol) and 1 N NaOH (8.6 ml) was refluxed for 2 hr with stirring and the ice-cooled solution was adjusted with 20% HCl to pH 1. The precipitate was collected by filtration and recrystallized from H_2O to give crystals (213 mg). PE: M_1 0.66 (major), 1.1 (minor) (buffer 2).

3-Carbamoyl-1,6-dihydro-5-methyl-6-oxo-2-pyrazinecarboxylic Acid (22)——i) Compound **22** (563 mg, 57%) was prepared from 1,6-dihydro-5-methyl-6-oxo-2,3-pyrazinedicarbonitrile (**20**)[4,14] (800 mg, 5 mmol) and aqueous NaOH (NaOH 2 g, H_2O 25 ml) in the manner described for **7**, mp 236—239° (dec.) (DMF). *Anal.* Calcd for $C_7H_7N_3O_4$: C, 42.64; H, 3.58; N, 21.31. Found: C, 42.77; H, 3.71; N, 21.43. PMR (DMSO-d_6, EM-390): 2.36 (3H, s, CH_3), 8.22 (2H, br s, $CONH_2$). IR ν_{max}^{KBr} cm^{-1}: 1675, 1600. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 271 (7000), 305 (4500); $\lambda_{max}^{H_2O}$ nm (ε): 260 (8700), 307.5 (6500); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 273 (11700), 307.5 (9000).

ii) Compound **22** (1.01 g, 83%) was prepared from **20** (1 g, 6.2 mmol) and 10% Na_2CO_3 (20 ml) in the manner described for **7**, mp 235—237° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1675, 1600.

4,5-Dihydro-6-methyl-5-oxo-2-pyrazinecarboxamide (23)——Compound **23** (595 mg, 77%) was prepared from **22** (1 g, 5.1 mmol) in the manner described for **13**, mp 277—278°. *Anal.* Calcd for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 46.86; H, 4.54; N, 26.93. PMR (DMSO-d_6, T-60): 2.30 (3H, s, CH_3), 7.37 (1H, br s, $CONH_2$), 7.50 (1H, br s, $CONH_2$), 7.77 (1H, s, 3-H), 12.5 (1H, br s, NH). IR ν_{max}^{KBr} cm^{-1}: 1655.

4,5-Dihydro-6-methyl-5-oxo-2-pyrazinecarboxylic Acid (21)——i) A mixture of **22** (500 mg, 2.5 mmol) and concentrated HCl (5 ml) was refluxed for 10 hr with stirring. After cooling, the precipitate was collected by filtration, washed with H_2O, and recrystallized from DMF to give needles (205 mg, 53%), mp>300°. *Anal.* Calcd for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.34; H, 3.96; N, 17.89. PMR (DMSO-d_6, EM-390): 2.28 (3H, s, CH_3), 7.89 (1H, s, 3-H), 10.5—13.2 (1H, br, NH or COOH). IR ν_{max}^{KBr} cm^{-1}: 1720, 1660.

ii) A mixture of **22** (1 g, 5.1 mmol) and 10% NaOH (20 ml) was refluxed for 3 hr with stirring and the ice-cooled solution was adjusted with concentrated HCl to pH 1. The precipitate was collected by filtration, washed with H_2O, and recrystallized from DMF to give needles (150 mg, 19%), mp>300°. IR ν_{max}^{KBr} cm^{-1}: 1720, 1660.

iii) Compound **21** (50 mg, 33%) was prepared from **23** (153 mg, 1 mmol) and 10% NaOH (1 ml) in the manner described for **14**, mp>300°. IR ν_{max}^{KBr} cm^{-1}: 1720, 1660.

iv) A mixture of **20** (1 g, 6.3 mmol) and concentrated HCl (10 ml) was refluxed for 4 hr with stirring. After cooling, the precipitate was collected by filtration, washed with H_2O, and recrystallized from DMF to give needles (750 mg, 78%), mp >300°. IR ν_{max}^{KBr} cm^{-1}: 1720, 1660.

Methyl 4,5-Dihydro-6-methyl-5-oxo-2-pyrazinecarboxylate (24)——Compound **24** (6.536 g, 75%) was prepared from **21** (8.05 g, 52.2 mmol), $SOCl_2$ (14.7 ml), and MeOH (500 ml) in the manner described for **12**, mp 270—271°. *Anal.* Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.77; H, 4.82; N, 16.75. PMR (DMSO-d_6, T-60): 2.28 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 7.95 (1H, s, 3-H), 12.6 (1H, br s, NH). IR ν_{max}^{KBr} cm^{-1}: 1720, 1690—1655. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 259 (15000), 300 (7100); $\lambda_{max}^{H_2O}$ nm (ε): 259 (15000), 300 (7400); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 271 (13300), 302.5 (11200).

Methyl 5-Chloro-6-methyl-2-pyrazinecarboxylate (25)——Compound **24** (1 g, 6 mmol) was treated with $POCl_3$ (5 ml) and DMF (3 drops) in the manner described for **15**. After removal of $CHCl_3$, the residue was chromatographed on silica gel (50 g) with $CHCl_3$ as the eluent. The eluate was concentrated to give colorless crystals (850 mg, 77%), mp 40—43°. *Anal.* Calcd for $C_7H_7ClN_2O_2$: C, 45.06; H, 3.78; N, 15.01. Found: C, 44.74; H, 3.65; N, 14.96. PMR ($CDCl_3$, T-60): 2.78 (3H, s, CH_3), 4.05 (3H, s, OCH_3), 8.97 (1H, s, 3-H). IR ν_{max}^{KBr} cm^{-1}: 1705. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 225.5 (9400), 283 (10200); $\lambda_{max}^{H_2O}$ nm (ε): 225.5 (9400), 283 (10200); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 220 (19800), 283 (9200).

Methyl 5-Chloro-6-methyl-2-pyrazinecarboxylate 1-Oxide (26)——Compound **25** (5.05 g, 27.1 mmol) was treated with MCPBA (5.45 g, 2.8 g) and 1,2-dichloroethane (60 ml) in the manner described for **16**. After separation by column chromatography on silica gel, the first fraction was concentrated to recover **25** (1.875 g). The second fraction was concentrated to give **26** as an oil (475 mg, 9%). PMR (CCl_4, T-60): 2.52 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 8.39 (1H, s, 3-H). MS *m/e*: 202 (M^+), 185, 170, 156, 139, 127.

5-Chloro-6-methyl-2-pyrazinecarboxylic Acid 1-Oxide (27)——Compound **27** (935 mg, 67%) was prepared from **26** (1.49 g, 7.4 mmol) and aqueous K_2CO_3 (K_2CO_3 3.05 g, H_2O 20 ml) in the manner described for **17**, mp 118—119° (AcOEt–petroleum ether). *Anal.* Calcd for $C_6H_5ClN_2O_3$: C, 38.22; H, 2.67; N, 14.86. Found: C, 38.26; H, 2.54; N, 15.02. PMR ($CDCl_3$, EM-390): 2.73 (3H, s, CH_3), 9.14 (1H, s, 3-H), 14.8—15.8 (1H, br,

13) Relative mobility compared to **1**.

14) Sagami Chemical Research Center, Japan Patent Kokai 76-34175 (1976) [*Chem. Abstr.*, **85**, 78165*g* (1976)].

COOH). IR ν_{max}^{KBr} cm^{-1}: 1720. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 229.5 (19700), 266 (7100), 307.5 (4100); $\lambda_{max}^{H_2O}$ nm (ε): 230 (14900), 269 (8200), 305 (4100); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 270 (8300), 305 (4100).

4,5-Dihydro-6-methyl-5-oxo-2-pyrazinecarboxylic Acid 1-Oxide (3)——A mixture of **27** (810 mg, 4.3 mmol) and 1 N NaOH (12.9 ml) was refluxed for 2 hr with stirring and the ice-cooled solution was adjusted with 20% HCl to pH 1. The precipitate was collected by filtration, washed with H_2O, and recrystallized twice from EtOH to give needles (220 mg, 30%), mp 229—230° (dec.). *Anal.* Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.29; H, 3.48; N, 16.43. PMR (DMSO-d_6, EM-390): 2.28 (3H, s, CH_3), 8.26 (1H, s, 3-H), 11.5—16.8 (2H, br, NH and COOH). IR ν_{max}^{KBr} cm^{-1}: 1720, 1655, 1620. UV $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 238 (24800), 315 (5900); $\lambda_{max}^{H_2O}$ nm (ε): 233 (19100), 270 (4800), 322.5 (6000); $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 239.5 (23700), 330 (7500).

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