Thermal Reactions of 6-Methyl-5-[(substituted hydrazono)methyl]-2,4(1*H*,3*H*)-pyrimidinediones with Electron-Deficient Olefins and Acetylene[1)]

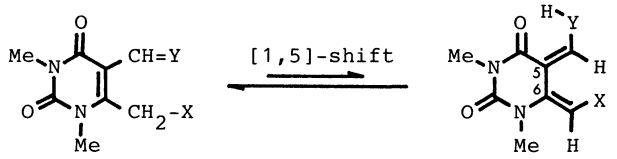
Michihiko NOGUCHI,* Yasutoshi KIRIKI, Takashi TSURUOKA, Takahiro MIZUI, and Shoji KAJIGAESHI
Department of Industrial Chemistry, Faculty of Engineering, Yamaguchi University, Tokiwadai, Ube 755
(Received July 20, 1990)

The thermal reactions of some 6-methyl-5-[(substituted hydrazino)methyl]-2,4(1*H*,3*H*)-pyrimidinediones (**1**) were investigated. The 1,5-hydrogen shift in **1** gave 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione intermediates, while the 1,2-hydrogen shift in **1** gave azomethine imine intermediates. These reaction profiles depend on the substituents of hydrazone moieties.

Much attention has been paid for the heterocyclic compounds containing pyrimidine nuclei, since the ring systems are widely found in biologically active compounds.[2)]

Some 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinediones (**B**) have been reported as being useful intermediates for the synthesis of fused pyrimidine derivatives.[3)] Intermediates **B** could be formed by a 1,5-hydrogen shift of the corresponding precursors **A**. Recently, intermediate **2a** from 1,3,6-trimethyl-5-[(dimethylhydrazono)methyl]-2,4(1*H*,3*H*)-pyrimidinedione (**1a**; R^1=R^2=Me) was confirmed by a [4+2]cycloaddition reaction with *N*-methylmaleimide (**3**), giving a pyrrolo[3,4-*g*]quinazoline derivative **4a**.[3d)]

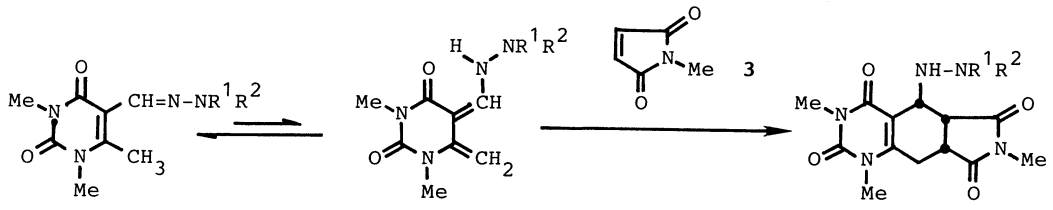
In order to obtain a better understanding of the reaction profiles, the thermal reactions of some 6-methyl-5-[(substituted hydrazono)methyl]-2,4(1*H*,3*H*)-pyrimidinediones and their pyrimidine analogs were investigated.



A **B**

Results and Discussion

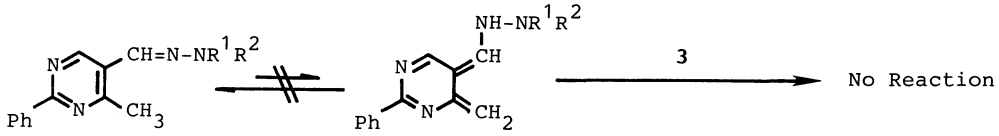
Heating of 5-(disubstituted hydrazono)methyl derivatives **1b** (R^1,R^2=-$(CH_2)_5$-) and **1c** (R^1,R^2=-$(CH_2)_2$-O-$(CH_2)_2$-) and **3** in dioxane under reflux gave the



1a: R^1 = R^2 = Me **2a-c** **4a-c**

1b: R^1, R^2 = -$(CH_2)_5$-

1c: R^1, R^2 = -$(CH_2)_2$-O-$(CH_2)_2$-



5a: R^1 = R^2 = Me **6a-c**

5b: R^1, R^2 = -$(CH_2)_5$-

5c: R^1, R^2 = -$(CH_2)_2$-O-$(CH_2)_2$-

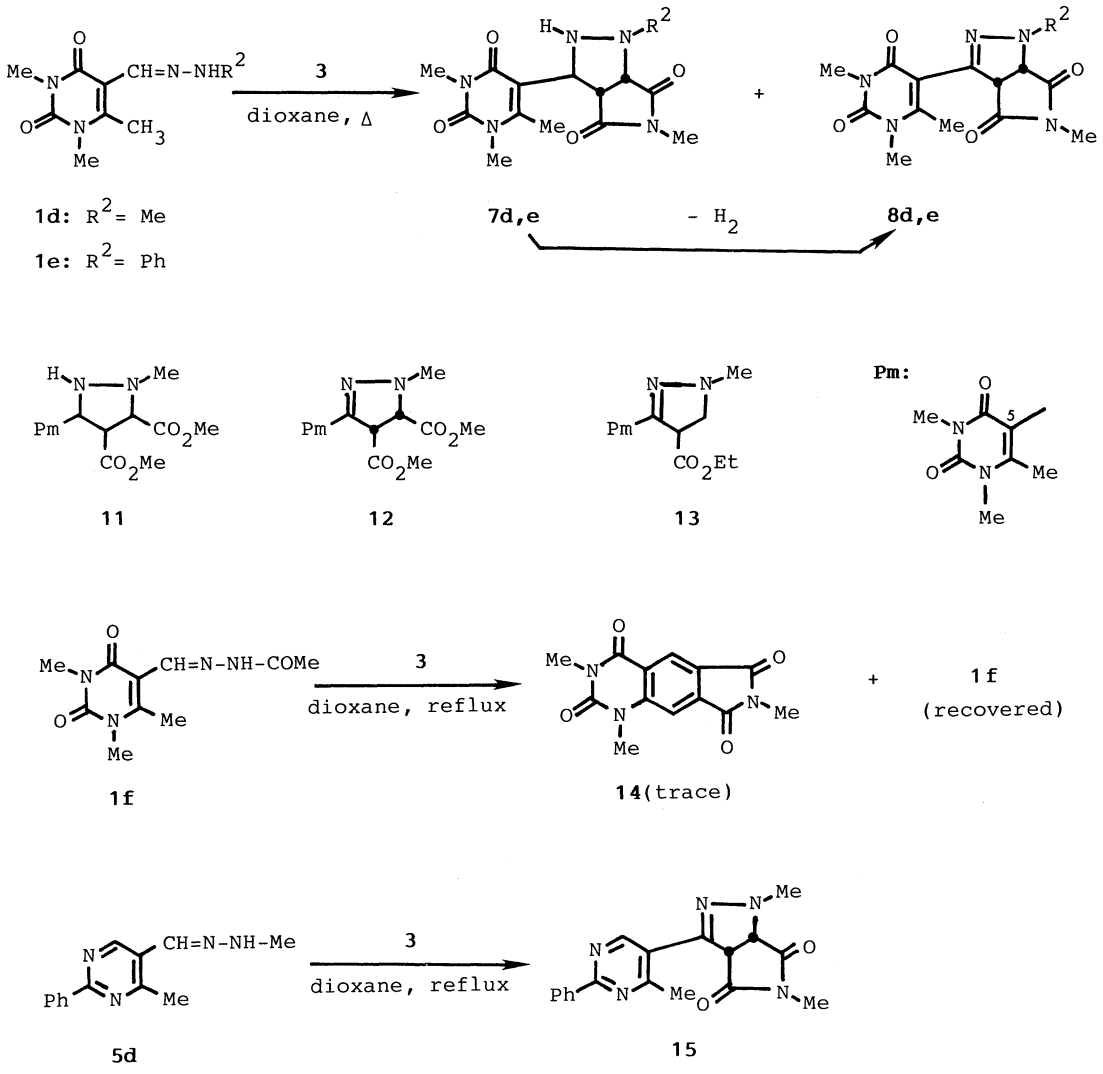
Scheme 1.

expected 5-(2,2-disubstituted hydrazino)pyrrolo[3,4-*g*]-quinazolines **4b**, **c** in good yields (Scheme 1). The synthetic usefulness of the 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione intermediate **2a** leading to quinazoline derivatives was briefly described in a preliminary paper.[3d]

However, a similar reaction of 4-methyl-2-phenyl-5-[(disubstituted hydrazono)methyl]pyrimidines **5a** (R^1=R^2=Me), **5b** (R^1,R^2=$-(CH_2)_5-$), and **5c** (R^1,R^2=$-(CH_2)_2-O-(CH_2)_2-$) with **3** did not give any adducts. This means that a 1,5-hydrogen shift in **5a**—**c** leading to diene-intermediates **6** would be unfavorable because of a loss of the aromaticity of the pyrimidine ring (Scheme 1).

The effect of the N-substituent of the hydrazone moiety on the reaction profiles was also investigated. Heating of 1,3,6-trimethyl-5-[(methylhydrazono)-methyl]-2,4(1*H*,3*H*)-pyrimidinedione (**1d**) and **3** in dioxane under reflux gave two products, **7d** and **8d**, in 86% total yield. Their molecular formula indicate that **7d** is a 1:1 adduct of **1d** and **3**, while **8d** is a dehydrogenated product from **7d**. The pyrrolo[3,4-*c*]-pyrazole structures of **7d** and **8d** were determined by their spectral data; their ^{1}H NMR spectra showed the existence of a 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl moiety. The five signals in the ^{13}C NMR spectrum of **7d**, δ=51.2(3a-C), 60.7(6a-C), 69.7(3-C), 174.7, 175.6(4- and 6-C), were assignable to carbons of the pyrrolo[3,4-*c*]pyrazole moiety. On the other hand, the ^{13}C NMR spectrum of **8d** showed two sp^3-carbon signals, δ=55.0(3a-C) and 65.0(6a-C), and three sp^2 signals, δ=152.5(3-C), 172.3, 173.4(4- and 6-C), for the pyrrolo[3,4-*c*]pyrazole moiety. The ratio of products **7d** and **8d** depended on both the reaction conditions and the procedures, while the combined yield of **7d** and **8d** was almost constant. The initially formed product **7d** was easily converted to **8d** during the work-up.

In order to elucidate the reaction profiles, **1d** was allowed to react with methyl fumarate (**9**) and ethyl acrylate (**10**). The pyrazolidine **11** and 2-pyrazoline derivatives **12** and **13** were obtained, respectively. The



Scheme 2.

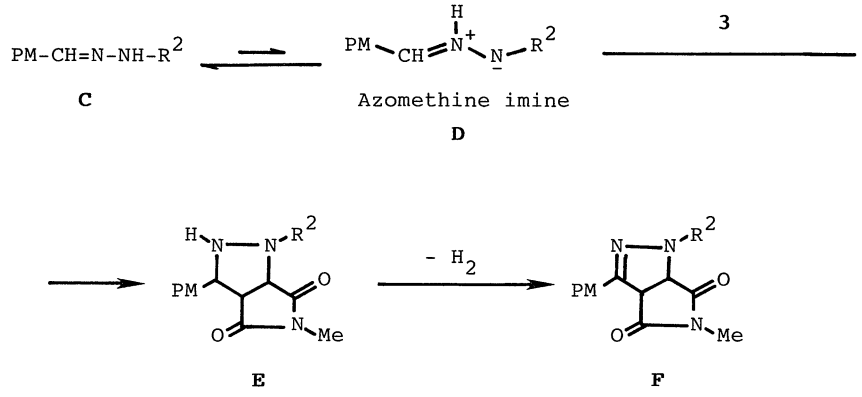
reaction of 5-(phenylhydrazono)methyl derivative **1e** with **3** gave pyrrolopyrazoles **7e** and **8e** in good total yield. On the other hand, the reaction of 5-(acetylhydrazono)methyl derivative **1f** with **3** gave a trace of pyrrolo[3,4-*g*]quinazoline **14**[3d] (in 3% yield) with a recovery of the starting materials. A similar reaction of 4-methyl-5-[(methylhydrazono)methyl]-2-phenylpyrimidine (**5d**) with **3** in refluxing dioxane gave a pyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione **15** in 75% yield (Scheme 2).

These pyrrolopyrazole preparations are explainable by the intermediacy of azomethine imine 1,3-dipole (**D**), which could be formed via a 1,2-hydrogen shift in hydrazone **C**, as demonstrated by Grigg et al.[4] The 1,3-dipolar cycloaddition of **D** with **3** gave tetrahydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione **E**, which was dehydrogenated to 3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione **F** (Scheme 3).

The differences on the reaction profiles between 5-(monosubstituted hydrazono)methyl derivatives and 5-(disubstituted hydrazono)methyl ones were found in the reaction with dimethyl acetylenedicarboxylate (**16**). Heating of **1a** and **16** in dioxane under reflux gave 5-cyano-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**17**) in 58% yield. The same type of product **18** was obtained by the reaction of **5a** with **16**.

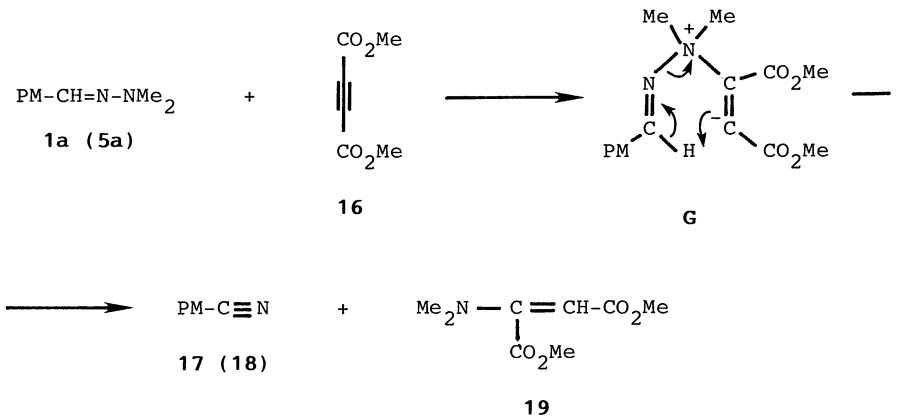
A nucleophilic attack of hydrazone nitrogen to acetylenic carbon would initially take place to give a betaine **G**, which is converted to the cyano compounds, **17** and **18**, with the elimination of 2-(dimethylamino), maleate **19** (Scheme 4). Recently, a similar reaction pathway was proposed for the formation of 2-cyanothiophene by the reaction of 2-[(dimethylhydrazono)methyl]thiophene with **16**.[5]

Heating of **1d** and **16** in dioxane under reflux gave 2-pyrazoline **12**, the same product from the reaction of



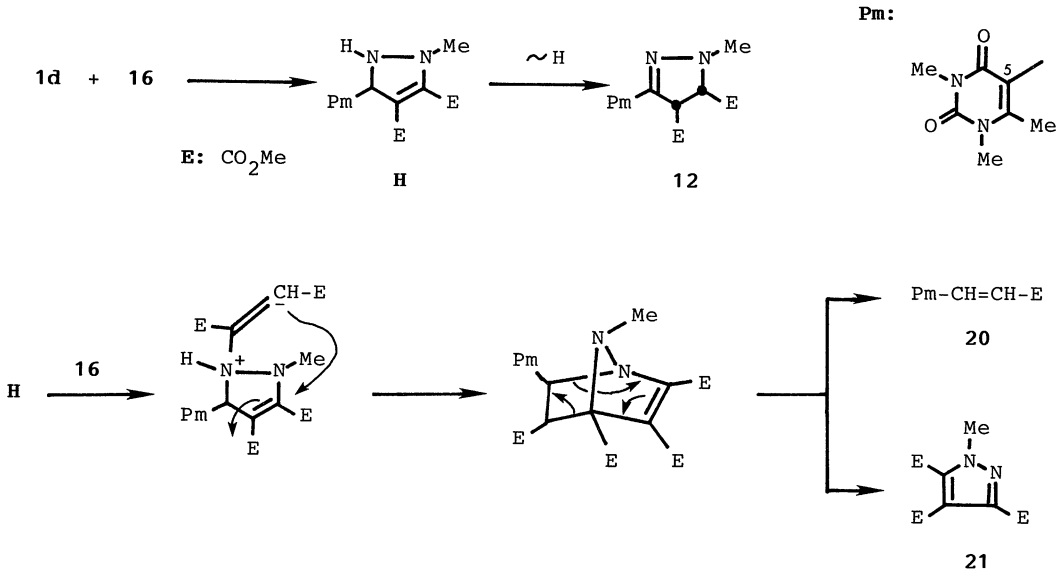
PM: 1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl; 4-Methyl-2-phenyl-5-pyrimidinyl

Scheme 3.



PM: 1,2,3,4-Tetrahydro-1,3,6-trimetyl-2,4-dioxo-5-pyrimydinyl; 4-Methyl-2-phenyl-5-pyrimidinyl

Scheme 4.



Scheme 5.

1d with dimethyl fumarate (**9**), methyl 2-(1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl)-acrylate (**20**), and 3,4,5-tris(methoxycarbonyl)-1-methyl-1*H*-pyrazole (**21**). In this reaction a thermal 1,2-hydrogen shift in **1d** gave the 1,3-dipole, which underwent a cycloaddition reaction with **16** to give a 3-pyrazoline derivative **H**. Its isomerization gave 2-pyrazoline derivative **12** with 4,5-cis configuration. A plausible pathway for the formation of **20** and **21** via **H** is demostrated in Scheme 5, which is based on the result of the reaction of benzaldehyde phenylhydrazone with **16**.[6]

In conclusion, the reaction profiles of 6-methyl-5-[(substituted hydrazono)methyl]-2,4(1*H*,3*H*)-pyrimidinediones **1** and their pyrimidine analogs **5** depended not only upon the nature of the pyrimidine rings, but also upon the substituents of the hydrazone moieties. The thermal reaction of 6-methyl-5-[(disubstituted hydrazono)methyl]-2,4(1*H*,3*H*)-pyrimidinediones **1a—c** gave 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione intermediates (**B**) via the 1,5-hydrogen shift, while that of 6-methyl-5-[(monosubstituted hydrazono)methyl]-2,4(1*H*,3*H*)-pyrimidinediones **1d, e** and their pyrimidine analog **5d** gave azomethine imine intermediates (**D**) via the 1,2-hydrogen shift. The cycloaddition reaction using these intermediates, **B** and **D**, gave a useful synthetic tool for the heterocycles containing pyrimidine nuclei.

Experimental

General. All melting points are uncorrected. The IR spectra were measured on a JASCO IR-Report-100 spectrophotometer. The ^{1}H NMR spectra were obtained on JEOL GSX-400, 270, and/or JMN-MH-100 spectrometers. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal; and ov, overlapping with each other. The ^{13}C NMR spectra were obtained on a JEOL GSX-400 or 270 spectrometer. The mass spectra were determined with a JEOL JMS-012G-2 or JMS-D spectrometer at an ionization energy of 75 eV. Elemental analyses were performed on a Hitachi 026 CHN analyzer. All nonaqueous reactions were run under a positive pressure of argon. All solvents were dried by standard methods before use. The progress of most reactions was monitored by thin-layer chromatography (Silica Gel 60F-254, Merck). Visualization was made ultraviolet light (254 and 365 nm). Chromatographic purification was performed with Wakogel C-200 (100—200 mesh, Wako Pure Chemical Industries) and/or Silica Gel 60 (230—400 mesh, Merck).

Unknown hydrazones **1b—d,f** and **5a—d** were prepared by usual methods.

1,3,6-Trimethyl-5-[(1-piperidinyl)iminomethyl]-2,4-(1*H*, 3*H*)-pyrimidinedione (1b): Colorless prisms (ethanol); mp 138—140 °C. Calcd for $C_{13}H_{20}N_4O_2$: C, 59.07; H, 7.63; N, 21.20%. Found: C, 59.21; H, 7.64; N, 21.35%.

1,3,6-Trimethyl-5-[(morpholinoimino)methyl]-2,4(1*H*,3*H*)-pyrimidinedione (1c): Colorless prisms (ethanol); mp 180—181 °C. Calcd for $C_{12}H_{18}N_4O_3$: C, 54.12; H, 6.81; N, 21.04%. Found: C, 53.93; H, 6.92; N, 21.17%.

1,3,6-Trimethyl-5-[(methylhydrazono)methyl]-2,4(1*H*,3*H*)-pyrimidinedione (1d): Colorless prisms (ethanol); mp 108—110 °C. Calcd for $C_9H_{14}N_4O_2$: C, 51.42; H, 6.71; N, 26.65%. Found: C, 51.76; H, 6.80; N, 26.74%.

5-[(Acetylhydrazono)methyl]-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (1f): Colorless prisms (ethanol); mp 268—271 °C. Calcd for $C_{10}H_{14}N_4O_3$: C, 50.42; H, 5.92; N, 23.52%. Found: C, 50.44; H, 6.00; N, 23.40%.

6-Methyl-5-[(dimethylhydrazono)methyl]-2-phenylpyrimidine (5a): Yellow prisms (hexane); mp 98—99 °C. Calcd

for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.31%. Found: C, 70.02; H, 6.73; N, 23.22%.

6-Methyl-5-[(1-piperidinyl)iminomethyl]-2-phenylpyrimidine (5b): Pale yellow prisms (ethanol); mp 98—100 °C. Calcd for $C_{17}H_{20}N_4$: C, 72.82; H, 7.19; N, 19.99%. Found: C, 72.75; H, 7.38; N, 19.90%.

6-Methyl-5-[(morpholinomethyl)methyl]-2-phenylpyrimidine (5c): Pale yellow plates (ethanol); mp 134—136 °C. Calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.85%. Found: C, 68.25; H, 6.46; N, 19.80%.

6-Methyl-5-[(methylhydrazono)methyl]-2-phenylpyrimidine (5d): Pale yellow needles (ethanol); mp 108—112 °C. Calcd for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76%. Found: C, 68.93; H, 6.00; N, 24.45%.

Reaction of 6-Methyl-5-[(disubstituted hydrazono)methyl]-2,4(1*H*,3*H*)-pyrimidinediones with *N*-Methylmaleimide (3). General Procedure: A solution of **1b** (264 mg, 1.0 mmol) and **3** (122 mg, 1.1 mmol) in dioxane (5 ml) was heated under reflux for 2 days. The reaction mixture was evaporated under reduced pressure to give a residue, which was subjected to column chromatography on silica gel to afford **4b** (339 mg, 90%) as an eluate of hexane/ethyl acetate (1/5).

5a,8a-Dihydro-1,3,7-trimethyl-5-[(1-piperidinyl)amino]-1*H*-pyrrolo[3,4-*g*]quinazoline-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetrone (4b): Colorless prisms (ethanol); mp 208—209 °C; IR(KBr) 3200 (NH), 1770, 1700, 1650(CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.72 (1H, br s, NH), 1.27, 1.50, 2.08, 2.55—2.75 (total 10H, 4m, piperidinyl methylene), 2.82 (1H, dd, 5a-H, J_{5-5a}=3.9 and J_{5a-8a}=8.8 Hz), 3.05 (3H, s, $-CH_3$), 3.1—3.2 (total 2H, ov, 8a- and 9-H), 3.31(1H, dd, 9-H, J_{8a-9}=5.9 and J_{gem}=15.6 Hz), 3.36, 3.49 (each 3H, 2s, $-CH_3$), 5.02 (1H, d, 5-H, J_{5-5a}=3.9 Hz); ^{13}C NMR ($CDCl_3$) δ=23.0 (9-C), 25.0, 28.4, 31.7 ($-CH_3$), 38.0 (8a-C), 44.8 (5a-C), 48.0 (5-C), 24.0, 25.8, 56.8 (piperidinyl methylene-C), 108.1 (4a-C), 151.6 (9a-C), 151.9 (2-C), 160.8 (4-C), 176.3, 179.2 (6- and 8-C); MS *m/z* 376 (M^+). Calcd for $C_{18}H_{25}N_5O_4$: C, 57.58; H, 6.71; N, 18.66%. Found: C, 57.85; H, 6.69; N, 18.38%.

5a,8a-Dihydro-1,3,7-trimethyl-5-morpholinomethyl-1*H*-pyrrolo[3,4-*g*]quinazoline-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetrone (4c): Yield 92%; colorless prisms (hexane–dichloromethane); mp 251—252 °C; IR(KBr) 3200 (NH), 1770, 1700, 1650 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ=2.15, 2.35, 2.66 (total 4H, 3m, morpholino methylene), 2.82 (1H, dd, 5a-H, J_{5-5a}=3.9 and J_{5a-8a}=8.3 Hz), 2.96 (3H, s, $-CH_3$), 3.17 (1H, br s, NH), 3.2—3.4 (total 3H, ov, 8a- and 9-H), 3.28, 3.47 (each 3H, 2s, $-CH_3$), 3.6 (4H, m, morpholino methylene), 4.87 (1H, d, 5-H, J_{5-5a}=3.9 Hz); ^{13}C NMR (DMSO-d_6) δ=21.3 (9-C), 23.2, 26.7, 30.0 ($-CH_3$), 30.1 (8a-C), 43.3 (5a-C), 46.1 (5-C), 54.1, 65.0 (morpholino methylene-C), 105.9 (4a-C), 150.2 (9a-C), 150.7 (2-C), 159.2 (4-C), 175.0, 177.8 (6- and 8-C); MS *m/z* 377 (M^+). Calcd for $C_{17}H_{23}N_5O_5$: C, 54.10; H, 6.14; N, 18.56%. Found: C, 54.25; H, 6.11; N, 18.40%.

Reaction of 6-Methyl-5-[(monosubstituted hydrazono)-methyl]-2,4(1*H*,3*H*)-pyrimidinediones with 3. General Procedure: A solution of **1d** (1.0 mmol) and **3** (1.1 mmol) in dioxane (5 ml) was heated under reflux for 20 h. The reaction mixture was evaporated under reduced pressure to give a residue, which was subjected to column chromatography on silica gel to afford **7d** (137 mg, 43%) (hexane/ethyl acetate=1/3) and **8d** (138 mg, 43%) (ethyl acetate). The ratio of **7d** and **8d** varied according to the reaction conditions; prolonged heating (for 36 h) gave **7d** (19%) and **8d** (60%). A treatment of the reaction mixture (under reflux for 20 h) with flash chromatography on silica gel (hexane/ethyl acetate=1/2—1/4) gave **7d** (55%) and **8d** (29%).

Tetrahydro-3-(1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl)-1,5-dimethylpyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (7d): Colorless crystals; mp 110—113 °C; IR(KBr) 3300(NH), 1770, 1710, 1630(CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.40 (3H, s, 6'-CH_3), 2.76, 2.95, 3.22, 3.50 (each 3H, 4s, N-CH_3), 3.4 (1H, ov, 3a-H), 4.10 (1H, dd, 3-H, J_{2-3}=7.7 and J_{3-4a}=9.0 Hz), 4.65 (1H, d, 6a-H, J_{3a-6a}=7.1 Hz), 5.8 (1H, br d, NH, J_{2-3}=7.7 Hz); ^{13}C NMR ($CDCl_3$) δ=16.8 (6'-CH_3), 25.1, 28.0, 32.4, 41.7 (N-CH_3), 51.2 (3a-C), 60.7 (6a-C), 69.7 (3-C), 104.8 (5'-C), 151.0, 153.0 (2'- and 6'-C), 160.8 (4'-C), 172.3, 173.4 (4- and 6-C). Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.80%. Found: C, 52.70; H, 5.77; N, 22.12%.

1,3a-Dihydro-3-(1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl)-1,5-dimethylpyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (8d): Colorless prisms (benzene); mp 144—146 °C; IR(KBr) 1780, 1700, 1630(CO)cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.31 (3H, s, 6'-CH_3), 2.99, 3.12, 3.38, 3.47 (each 3H, 4s, N-CH_3), 4.27 (1H, d, 3a-H, J_{3a-6a}=10.7 Hz), 5.16 (1H, d, 6a-H, J_{3a-6a}=10.7 Hz); ^{13}C NMR ($CDCl_3$) δ=17.9 (6'-CH_3), 25.1, 28.3, 32.5, 42.6 (N-CH_3), 55.7 (3a-C), 69.8 (6a-C), 104.2 (5'-C), 140.8 (3-C), 151.5, 152.4 (2'- and 6'-C), 161.4 (4'-C), 173.2, 174.3 (4- and 6-C); MS *m/z* 320 (M^+). Calcd for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93%. Found: C, 52.90; H, 5.37; N, 22.00%.

A similar reaction of **1e** with **3** gave **7e** and **8e** in a total yield of 98%.

Tetrahydro-3-(1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl)-5-methyl-1-phenylpyrrolo[3,4-*c*]pyrazole-4,6-(1*H*,5*H*)-dione (7e): Colorless prisms (ethyl acetate); mp 190—193 °C; IR(KBr) 3290 (NH), 1790, 1700, 1630 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.31 (3H, s, 6'-CH_3), 3.00, 3.27, 3.48 (each 3H, 3s, N-CH_3), 3.40(1H, dd, 3a-H, J_{3-3a}=9.0 and J_{3a-6a}=7.7 Hz), 4.30 (1H, dd, 3-H, J_{2-3}=12.3 and J_{3-3a}=9.0 Hz), 4.82 (1H, d, 6a-H, J_{3a-6a}=7.7 Hz), 6.15 (1H, d, NH, J_{2-3}=12.3 Hz), 6.8—7.0, 7.2—7.4 (total 5H, 2m, phenyl); ^{13}C NMR ($CDCl_3$) δ=16.6 (6'-CH_3), 25.2, 28.0, 32.6 (N-CH_3), 51.2 (3a-C), 60.7 (6a-C), 69.7 (3-C), 102.7 (5'-C), 114.4, 120.8, 129.3, 150.4 (phenyl-C), 150.8, 151.4 (2'- and 6'-C), 163.0 (4'-C), 174.7, 175.6 (4- and 6-C); MS *m/z* 383 (M^+). Calcd for $C_{19}H_{21}N_5O_4$: C, 59.52; H, 5.52; N, 18.27%. Found: C, 59.22; H, 5.71; N, 18.62%.

3a,6a-Dihydro-3-(1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl)-5-methyl-1-phenylpyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (8e): Colorless prisms (benzene), mp 313—316 °C; IR(KBr) 1790, 1710, 1640(CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.38 (3H, s, 6'-CH_3), 3.02, 3.40, 3.50 (each 3H, 3s, N-CH_3), 5.08 (1H, d, 3a-H, J_{3a-6a}=11.0 Hz), 5.46 (1H, d, 6a-H, J_{3a-6a}=11.0 Hz), 6.9—7.0, 7.2—7.5 (total 5H, 2m, phenyl); ^{13}C NMR ($CDCl_3$) δ=18.0 (6'-CH_3), 25.4, 28.3, 32.6 (N-CH_3), 55.0 (3a-C), 65.0 (6a-C), 103.9 (5'-C), 114.4, 121.6, 129.2, 140.3 (phenyl-C), 144.6 (6'-C), 151.5, 152.5 (3- and 2'-C), 161.3 (4'-C), 172.3, 173.4 (4- and 6-C); MS *m/z* 381 (M^+). Calcd for $C_{19}H_{19}N_5O_4$: C, 59.83; H, 5.02; N, 18.36%. Found: C, 59.98; H, 5.16; N, 18.40%.

1,3,7-Trimethyl-1*H*-pyrrolo[3,4-*g*]quinazoline-2,4,6,8(3*H*,7*H*)-tetrone (14): Yellow prisms (benzene–ethanol); mp 253—238 °C; IR(KBr) 1700, 1650(CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.69 (1H, dd, 9-H, J_{gem}=17.6 and J_{8a-9}=17.1 Hz), 3.10, 3.39, 3.57 (each 3H, 3s, N-CH_3), 3.43 (1H, dd, 9-H, J_{gem}=17.6 and

J_{8a-9}=8.3 Hz), 3.62 (1H, ddd, 8a-H, J_{5-8a}=2.9 and J_{8a-9}=17.1 and 8.3 Hz), 7.56 (1H, d, J_{5-8a}=2.9 Hz); ^{13}C NMR ($CDCl_3$) δ=24.8 (9-C), 25.6, 28.5, 32.3 (N-CH_3), 37.9 (8a-C), 107.6 (4a-C), 120.2, 124.9 (5- and 5a-C), 151.3, 151.5 (2- and 9a-C), 160.0 (4-C), 166.8, 174.1 (6- adn 8-C); MS *m/z* 275 (M^+). Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27%. Found: C, 56.85; H, 4.75; N, 15.04%.

The reaction of **1d** with dimethyl fumarate (**9**) gave **11** and **12** in a total yield of 59%. It is too difficult to isolate each other from the mixture as pure forms. The mixture of **11** and **12** in dioxane was heated under reflux in the presence of palladium/charcoal for 5 h to give only product **12**.

3-(1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl)-4,5-bis(methoxycarbonyl)-1-methylpyrazolidine (11): ^{1}H NMR ($CDCl_3$) δ=2.44 (3H, s, 6'-CH_3), 3.37, 3.53 (each 3H, 2s, N-CH_3), 3.80, 3.91 (each 3H, 2s, O-CH_3), 3.4—3.5, 3.5—3.6 (each 1H, ov, 5- and 6-H).

3-(1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl)-4,5-bis(methoxycarbonyl)-1-methyl-2-pyrazoline (12): Colorless needles (benzene); mp 124—126 °C; IR(KBr) 1750, 1730, 1700, 1650(CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.36 (3H, s, 6'-CH_3), 3.04, 3.33, 3.47 (each 3H, 3s, N-CH_3), 3.68, 3.82 (each 3H, 2s, O-CH_3), 4.18 (1H, d, 4-H, J_{4-5}=12.5 Hz), 4.57 (1H, d, 5-H, J_{4-5}=12.5 Hz); ^{13}C NMR ($CDCl_3$) δ=17.9 (6'-CH_3), 28.1, 32.5, 42.7 (N-CH_3), 52.7, 52.8 (O-CH_3), 57.7 (4-C), 71.9 (5-C), 104.9 (5'-C), 142.6 (3-C), 151.7, 151.9 (2'- and 6'-C), 161.3 (4'-C), 169.4, 169.8 (COO); MS *m/z* 353 (M^+). Calcd for $C_{15}H_{20}N_4O_6$: C, 51.13; H, 5.72; N, 15.90%. Found: C, 51.14; H, 5.72; N, 15.55%.

The cis configuration between 4- and 5-position of **12** was confirmed by a NOE measurement; the 7.0% enhancement of signal area of 5-H was observed on irradiation at 4-H. Compound **12** was also obtained in the reaction of **1d** and dimethyl acetylenedicarboxylate (**16**). This implies that **12** with the 4,5-cis configuration is more stable than the 4,5-trans isomer. A similar reaction of **1d** with dimethyl maleate gave only an unseparable mixture of products. We therefore proposed the formation of **12** as follows: the 1,3-dipolar cycloaddition of the azomethine imine to fumarate **9** would proceed stereoselectively to give a trans-adduct (*trans*-**11**), as known from many examples.[7] Isomerization to the 4,5-cis configuration should occur during the dehydrogenation process of **11** to **12**, but the mechanism has not been clear.

4-Ethoxycarbonyl-3-(1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl)-1-methyl-2-pyrazoline (13): Yield 20%; pale yellow oil; ^{1}H NMR ($CDCl_3$) δ=1.20 (3H, t, -CH_3, J=6.5 Hz), 2.46 (3H, s, 6'-CH_3), 2.90, 3.36, 3.50 (each 3H, 3s, N-CH_3), 3.3—3.5 (1H, ov, 5-H), 3.63 (1H, dd, 5-H, J_{gem}=9.8 and J_{4-5}=5.9 Hz) 4.12 (2H, q, -CH_2-, J=6.5 Hz), 4.57 (1H, dd, 4-H, J_{4-5}=5.9 and J_{4-5}=10.8 Hz); ^{13}C NMR ($CDCl_3$) δ=14.2 (-CH_2-CH_3), 18.0 (6'-CH_3), 28.1, 32.5 (1'- and 3'-CH_3), 43.0 (1-CH_3), 53.2 (4-C), 59.4 (5-C), 61.4 (O-CH_4-), 105.9 (5'-C), 145.4 (3-C), 151.7, 151.9 (2'- and 6'-C), 161.6 (4'-C), 170.8 (COO); MS *m/z* 309 (M^+). This compound could not be isolated as a pure form and did not give satisfactory analytical data.

3a,6a-Dihydro-1,5-dimethyl-3-(4-methyl-2-phenyl-5-pyrimidinyl)pyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (15): Colorless prisms (ethanol); mp 199—200 °C; IR(KBr) 1780, 1690(CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.82 (3H, s, 4'-CH_3), 3.02, 3.24 (each 3H, 2s, N-CH_3), 4.33 (1H, d, 3a-H, J_{3a-6a}=10.7 Hz), 4.78 (1H, d, 6a-H, J_{3a-6a}=10.7 Hz), 7.4—7.5, 8.4—8.5 (total 5H, 2m, phenyl), 9.14 (1H, s, 6'-H); ^{13}C NMR ($CDCl_3$) δ=25.4 (4'-CH_3), 26.7, 41.9 (N-CH_3), 54.6 (3a-C), 68.9 (6a-C), 121.5 (5'-C), 128.4, 128.6, 130.8, 137.3 (phenyl-C), 138.8 (3-C), 156.3 (6'-C), 162.1 (4'-C), 165.9 (2'-C), 172.4, 173.2 (4- and 6-C); MS *m/z* 336 (M^+). Calcd for $C_{18}H_{17}N_5O_2$: C, 64.46; H, 5.11; N, 20.89%. Found: C, 64.68; H, 5.10; N, 21.22%.

Reaction of 1a with Dimethyl Acetylenedicarboxylate (16). General Procedure: A solution of **1a** (100 mg, 0.45 mmol) and **16** (71 mg, 0.50 mmol) in dioxane (2 ml) was heated under reflux for 2 d. The reaction mixture was evaporated to dryness, and then subjected to column chromatography on silica gel to give **17** (47 mg, 58%), and dimethyl 2-(dimethylamino)maleate (**19**; 37%) was obtained as eluate of hexane/ethyl acetate (5/1).

5-Cyano-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (17): Colorless needles (hexane); mp 149—151 °C; IR(KBr) 2220 (CN), 1650(CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.58 (3H, s, 6-CH_3), 3.32, 3.51 (each 3H, 2s, N-CH_3); MS *m/z* 179 (M^+). Calcd for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45%. Found: C, 53.75; H, 4.98; N, 23.59%.

Dimethyl 2-(Dimethylamino)maleate (19): ^{1}H NMR ($CDCl_3$) δ=2.86 (6H, s, N-CH_3), 3.60, 3.90 (each 3H, 2s., O-CH_3), 4.56 (1H, s, -CH_3); MS *m/z* 187 (M^+).

5-Cyano-4-methyl-2-phenylpyrimidine (18): Yield 66%; pale yellow needles (ethanol); mp 171—173 °C; IR(KBr) 2210(CN) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.92 (3H, s, -CH_3), 7.7—7.9, 8.7—8.9 (total 5H, 2m, phenyl), 9.22 (1H, s, 6-H); MS *m/z* 195 (M^+). Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53%. Found: C, 73.43; H, 4.55; N, 21.20%.

Reaction of 1d with 16. A solution of **1d** (210 mg, 1.0 mmol) and **16** (0.18 ml, 1.4 mmol) in dioxane (5 ml) was heated under reflux for 8 h. The reaction mixture was evaporated to dryness and subjected to column chromatography on silicagel to afford **21** (100 mg, 39%) (hexane/ethyl acetate=3/1), **20** (86 mg, 36%) (2/1), and **12** (79 mg, 23%) (1/1).

Methyl 3-(1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinyl)acrylate (20): This was obtained as *E/Z* (= 10/9) mixture.

(*E*)-20: Colorless needles (ethanol); mp 181—183 °C; IR(KBr) 1720, 1700, 1640(CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.48 (3H, s, 6'-CH_3), 3.39, 3.54 (each 3H, 2s, N-CH_3), 3.78 (3H, s, O-CH_3), 7.12 (1H, d, 2-H, J=15.6 Hz), 7.58 (1H, d, 3-H, J=15.6 Hz); ^{13}C NMR ($CDCl_3$) δ=17.0 (6'-CH_3), 28.4, 32.8 (N-CH_3), 51.6 (O-CH_3), 107.1 (5'-C), 120.8 (2-C), 135.7 (2-C), 149.7 (6'-C), 151.8 (4'-C), 161.1 (2'-C), 165.8 (1-C); MS *m/z* 239 (M^+). Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H., 5.92; N, 11.76%. Found: C, 55.38; H, 6.03; N, 12.02%.

(*Z*)-20: Colorless plates (ethanol); mp 116—117 °C; IR (KBr) 1720, 1700, 1640(CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.24 (3H, s, 6'-CH_3), 3.36, 3.48 (each 3H, 2s, N-CH_3), 3.69 (3H, s, O-CH_3), 6.15 (1H, d, 2-H, J_{1-2}=11.7 Hz), 6.79 (1H, d, 1-H, J_{1-2}=11.7 Hz); ^{13}C NMR ($CDCl_3$) δ=18.2 (6'-CH_3), 28.3, 32.3 (N-CH_3), 51.5 (O-CH_3), 108.1 (5'-C), 123.5 (2-C), 137.0 (3-C), 149.7 (6'-C), 151.8 (4'-C), 161.1 (2'-C), 165.8 (1-C); MS *m/z* 239 (M^+). Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76%. Found: C, 55.38; H, 6.03; N, 12.02%.

3,4,5-Tris(methoxycarbonyl)-1-methyl-1*H*-pyrazole (21): Colorless primsms (ethanol); mp 96—97 °C; IR(KBr) 1740, 1720(CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.00 (total 6H, s, O-CH_3), 4.30 (3H, s, N-CH_3); ^{13}C NMR ($CDCl_3$) δ(off

resonance)=40.7 (q, N-CH_3), 52.5, 52.8, 52.9 (each q, O-CH_3), 121.6 (s, 4-C), 131.6 (s, 5-C), 138.8 (s, 3-C), 158.4, 160.7, 163.6 (each s, COO); MS *m/z* 256(M^+). Calcd for $C_{10}H_{12}N_2O_6$: C, 46.88; H, 4.72; N, 10.93%. Found: C, 46.93; H, 4.72; N, 10.67%.

The authors wish to thank UBE Scientific Analysis Laboratory for the help of the structural analyses using NMR spectrometers at 270 and/or 400 MHz.

References

1) Studies on Fused Pyrimidine Derivatives. Part IX. Part IIIV in this series: M. Noguchi, Y. Kiriki, T. Ushijima, and S. Kajigaeshi, *Bull. Chem. Soc. Jpn.*, **63**, 2938 (1990).

2) D. J. Brown and S. F. Mason, "The Chemistry of Heterocyclic Compounds. The Pyrimidines," ed by A. Weissberger, Interscience, New York (1962); D. J. Brown, R. F. Evans, and T. J. Batterham, "The Chemistry of Heterocyclic Compounds. The Pyrimidines Supplement I," ed by A. Weissberger and E. C. Taylor, Wiley-Interscience, New York (1970); J. H. Lister, "Heterocyclic Compounds Fused Pyrimidines Part II; Purines," ed by A. Weissberger and E. C. Taylor, Wiley-Interscience, New York (1871). G. Maury, "Special Topics in Heterocyclic Chemistry," ed by A. Weissberger and E. C. Taylor, Wiley-Interscience, New York (1977), p. 179.

3) a) S. Senda, T. Asao, I. Sugiyama, and K. Hirota, *Tetrahedron Lett.*, **21**, 531 (1980); b) M. Noguchi, K. Sakamoto, S. Nagata, and S. Kajigaeshi, *J. Heterocycl. Chem.*, **25**, 205 (1988); c) M. Noguchi, Y. Kiriki, and S. Kajigaeshi, *Bull. Chem. Soc. Jpn.*, **62**, 3043 (1989); d) M. Noguchi, K. Doi, Y. Kiriki, and S. Kajigaeshi, *Chem. Lett.*, **1989**, 2115.

4) R. Grigg, J. Kemp, and N. Thompson, *Tetrahedron Lett.*, **1978**, 2827.

5) M. E. Gonzalez, P. Sancho, C. Soriano, R. Ballesteros, B. Abarca, and J. Sepulveda, *Heterocycles*, **27**, 1227 (1988).

6) H. Ogura, K. Kubo, Y. Watanabe, and T. Itoh, *Chem. Pharm. Bull.*, **21**, 2026 (1973).

7) R. Grashey, "1,3-Dipolar Cycloaddition Chemistry. Azomethine Imines", ed by A. Padwa, Wiley-Interscience, New York (1984), p. 733.