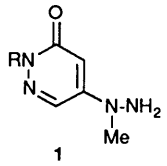
Novel Heterocyclization of Hydrazinopyridazinones with Dimethyl Acetylenedicarboxylate with Dehydrogenation and Rearrangement

Tetsuo Yamasaki, Eiji Kawaminami, Tomomi Yamada, Tadashi Okawara and Mitsuru Furukawa *
Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862, Japan

5-Hydrazinopyridazin-3(2*H*)-ones **1** reacted with dimethyl acetylenedicarboxylate **2** to give 4,6-dihydropyridazino[4,5-*c*]pyridazin-5-(1*H*)-ones **3** by cyclization with dehydrogenation. On the other hand, the reaction of 4-bromo-5-hydrazino-and 5-bromo-4-hydrazinopyridazin-3(2*H*)-ones **8** and **10** with diester **2** resulted in the novel cyclization with rearrangement to give compounds **3** and **9** together with the expected cyclization products.

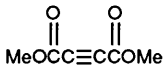
Fused pyridazinones have attracted widespread synthetic interest because of their potential biological and pharmacological activities.[1] As part of our studies on the new preparation of fused heterocyclic ring systems containing the pyridazinone moiety, we have recently reported in a preliminary communication[2] the condensations of hydrazinopyridazinones **1** and the bromo compounds **8** and the regioisomer **10**, whose structure includes the synthetically interesting enehydrazine moiety, with dimethyl acetylenedicarboxylate (DMAD, **2**). The reaction of compounds **1** with diester **2** unexpectedly gave 1,4-dihydropyridazino[4,5-*c*]pyridazinones by cyclization with dehydrogenation between the enehydrazine moiety and the carbon–carbon triple bond of DMAD. In the cyclization of bromides **8** and **10** with diester **2**, an entirely unexpected rearrangement took place along with the expected reaction products. This is the first example of this route to fused 1,4-dihydropyridazinones using DMAD by direct cyclization with dehydrogenation. We describe herein these novel heterocyclizations and the extension of hydrazinopyridazinones **1** with DMAD in detail.

When 5-(1-methylhydrazino)pyridazinones **1** were heated with DMAD in acetic acid at 80 °C, 4,6-dihydropyridazino[4,5-*c*]pyridazin-5(1*H*)-ones **3** were provided in good yield by the initial Michael addition followed by cyclization with dehydrogenation. The resulting products **3** were purified by silica-gel column chromatography (chloroform–hexane, 10:1). The results are shown in Table 1. The structure of compounds **3** was assigned on the basis of their spectral data and elemental analyses. The IR spectra showed two ester carbonyl absorptions at 1710–1750 cm^{-1} and the ^1H NMR spectra exhibited the methine signal of the 1,4-dihydropyridazine ring at δ 4.93–5.05. Moreover, the ^{13}C NMR spectrum of compound **3c** exhibited the sp^3-methine signal at δ_C 34.4. These data support the assigned structure **3** for the product.

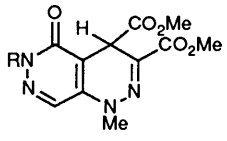


1

a; R = Ph
b; R = Me
c; R = H
d; R = $PhCH_2$
e; R = *p*-$ClC_6H_4CH_2$



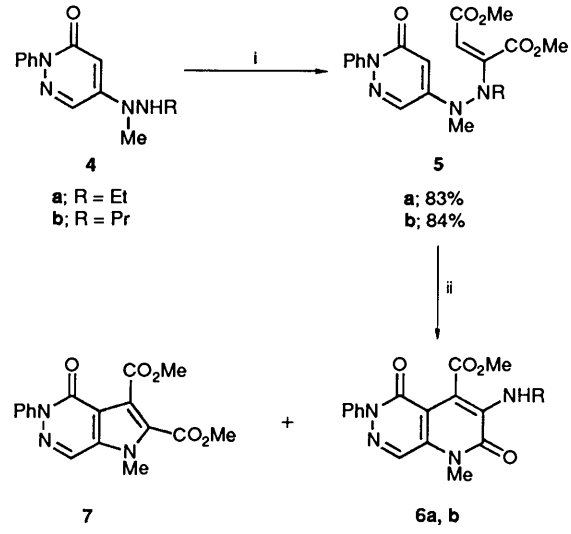
2



3

a; R = Ph
b; R = Me
c; R = H
d; R = $PhCH_2$
e; R = *p*-$ClC_6H_4CH_2$

As an extension of this reaction, we examined the cyclization of 5-(1,2-disubstituted hydrazino)pyridazinones **4** with DMAD under similar conditions and obtained the corresponding Michael adduct **5** as the sole product. Heating of the adduct **5** at 220 °C in 1,2,3,4-tetrahydronaphthalene (tetralin) underwent Diels–Reese reaction to afford pyrido[2,3-*d*]pyridazines **6** and the pyrrolo[2,3-*d*]pyridazine **7** (Scheme 1). To our knowledge, this cyclization of an enehydrazine, containing a heterocyclic ring in the structure, and DMAD is the first example, though there have been a few reports of the Diels–Reese reaction.[3] The structure of the products **6** and **7** was assigned as follows. The IR spectra of compounds **6a** and **6b** showed absorptions assignable to the NH group at 3325 and 3340 cm^{-1}, respectively, and that of compound **7** showed two ester carbonyl absorptions at 1730 and 1745 cm^{-1}. The mass spectral data of compounds **6** indicated the molecular ion peak corresponding to the elimination of methanol from enehydrazines **5**. On the other hand, in the mass spectrum of compound **7**, the ion peak equivalent to the elimination of an alkyl amine from compounds **5** was observed. The ^1H NMR spectra and elemental analyses also supported the structural assignment of the products as compounds **6** and **7**.



4

a; R = Et
b; R = Pr

5

a; 83%
b; 84%

7

6a, b

Scheme 1 *Reagents and conditions:* i, AcOH, reflux; tetralin, 220 °C

Treatment of the bromo compounds **8** with DMAD in DMF at room temperature produced compounds **3** and the entirely unexpected regioisomers **9** in 17–20 and 28–39% yield, respectively. The analytical data are shown in Table 2. The structure of the regioisomers **9**, which possess the same mass spectral data and elemental analysis values as compounds **3**, could not, therefore, be determined by these spectral and elemental data. To confirm the structure of compounds **9**, we measured the NOE difference spectra of isomers **3a** and **9a** by irradiation of the sp^2-methine proton of the pyridazinone ring. An NOE was observed on the methyl proton substituted at N-1

Table 1 6-Substituted-4,6-dihydropyridazino[4,5-*c*]pyridazin-5(1*H*)-ones **3**

	M.p. (°C)	Yield (%)	ν_{max}(KBr) (cm^{-1})	δ_H in [$^2H_6$]DMSO	*m/z* (M^+)	Formula	Found (%) (required) C	H	N
3a	189–190	80	1729 (C=O), 1710 (C=O), 1654 (C=O),	3.64 (3 H, s, Me) 3.72 (3 H, s, Me) 3.83 (3 H, s, Me), 5.10 (1 H, s, CH) 7.54 (5 H, s, Ph), 8.35 (1 H, s, =CH)	357[a] ($M + 1$)$^+$	$C_{17}H_{16}N_4O_5$	57.4 (57.30)	4.7 (4.53)	15.75 (15.72)
3b	147	80	1735 (C=O), 1716 (C=O), 1650 (C=O)	3.60 (3 H, s, Me), 3.64 (3 H, s, Me) 3.66 (3 H, s, Me), 3.81 (3 H, s, Me) 5.01 (1 H, s, CH), 8.10 (1 H, s, =CH)	294	$C_{12}H_{14}N_4O_5$	48.9 (48.98)	4.8 (4.80)	19.3 (19.04)
3c[b]	218–220	68	3150 (NH), 1738 (C=O), 1718 (C=O), 1645 (C=O)	3.62 (3 H, s, Me), 3.65 (3 H, s, Me) 3.81 (3 H, s, Me), 5.01 (1 H, s, CH) 8.12 (1 H, s, =CH) 12.99 (1 H, br, NH)	280	$C_{11}H_{12}N_4O_5$	47.3 (47.15)	4.3 (4.32)	19.8 (19.99)
3d	97–98	94	1740 (C=O), 1719 (C=O), 1650 (C=O)	3.59 (3 H, s, Me), 3.63 (3 H, s, Me) 3.80 (3 H, s, Me), 5.02 (1 H, s, CH) 5.26 (2 H, s, CH_2), 7.30 (5 H, s, Ph) 8.14 (1 H, s, =CH)	370	$C_{18}H_{18}N_4O_5$	58.5 (58.37)	4.9 (4.90)	14.9 (15.13)
3e	162–163	81	1745 (C=O), 1720 (C=O), 1650 (C=O)	3.60 (3 H, s, Me), 3.64 (3 H, s, Me) 3.81 (3 H, s, Me), 5.04 (1 H, s, CH) 5.28 (2 H, s, CH_2) 7.27–7.42 (5 H, m, Ph) 8.18 (1 H, s, =CH)	404	$C_{18}H_{17}ClN_4O_5$	53.7 (53.41)	4.2 (4.23)	14.0 (13.84)

[a] The parent ion was determined with CI-MS. [b] For compound **3c**: δ_C([$^2H_6$]DMSO; $SiMe_4$) 34.4 (CH), 39.0 (Me), 52.5 (Me), 52.7 (Me), 105.8 (C), 126.8 (C), 130.2 (C), 137.5 (C), 159.7 (C=O), 162.9 (C=O) 168.8 (C=O).

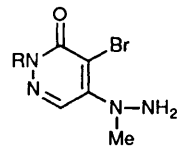
Table 2 7-Substituted-1,7-dihydropyridazino[4,5-*c*]pyridazin-8(4*H*)-ones **9**

	M.p. (°C)	ν_{max}(KBr) (cm^{-1})	δ_H($CDCl_3$)	*m/z* (M^+)	Formula	Found (%) (required) C	H	N
9a	131	1724(C=O), 1652 (C=O)	3.67 (3 H, s, Me), 3.93 (3 H, s, Me), 4.13 (3 H, s, Me), 4.91 (1 H, s, CH), 7.49 (5 H, s, Ph), 7.79 (1 H, s, =CH)	356	$C_{17}H_{16}N_4O_5$	57.0 (57.30)	4.3 (4.53)	15.6 (15.72)
9b	115	1732 (C=O), 1705 (C=O), 1655 (C=O)	3.65 (3 H, s, Me), 3.67 (3 H, s, Me), 3.84 (3 H, s, Me), 4.04 (3 H, s, Me), 4.77 (1 H, s, CH), 7.55 (1 H, s, =CH)	294	$C_{12}H_{14}N_4O_5$	49.2 (48.98)	4.85 (4.80)	19.2 (19.04)
9c	202–203	3150 (NH), 1745 (C=O), 1715 C=O), 1650 (C=O)	3.65 (3 H, s, Me), 3.83 (3 H, s, Me), 4.03 (3 H, s, Me), 4.81 (1 H, s, CH), 7.63 (1 H, s, =CH), 11.50 (br, NH, 1 H)	280	$C_{11}H_{12}N_4O_5$	47.1 (47.15)	4.4 (4.32)	19.7 (19.99)
9d	128	1742 (C=O), 1715 (C=O), 1655 (C=O)	3.68 (3 H, s, Me), 3.88 (3 H, s, Me), 4.07 (3 H, s, Me), 4.79 (1 H, s, CH), 5.24 (2 H, s, CH_2), 7.18–7.48 (5 H, m, Ph), 7.63 (1 H, s, =CH)	370	$C_{18}H_{18}N_4O_5$	58.6 (58.37)	4.9 (4.90)	15.1 (15.13)

in compound **3a** and on the methine proton at the C-4 in compound **9a**. Moreover, compounds **3b** and **9b** were provided in the reaction of compound **10**, a regioisomer of **8b**, with DMAD under the same conditions in 38 and 23% yield, respectively. These results supported the structural assignment of the product as **9**.

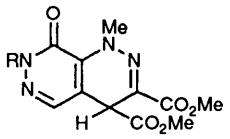
In order to elucidate the formation pathway of adducts **3** from substrates **1** and **2**, the reaction of compound **1a** with DMAD was carried out under milder conditions in dichloromethane at room temperature, and the intermediate Michael adduct **11** was successfully isolated. Heating of the intermediate **11** at 80 °C in acetic acid afforded compounds **3a** as expected. The cyclization seems to proceed *via* nucleophilic attack of the negatively polarized C-4 on the α-methylene carbon followed by dehydrogenation.

The formation pathway of bicycles **6** and **7** by the reaction of pyridazones **4** and DMAD is presumed to be as follows. Nucleophilic attack of the negatively polarized C-4 of the Michael adduct **5** on the olefinic carbon bearing an ester group produces intermediate **12** with cleavage of the N–N bond, and subsequently the methyl amino group at C-5 of the pyridazone ring attacks the ester carbonyl group or the double bond carbon atom to give compound **6** with elimination of methanol, or compound **7** with elimination of alkyl amine, respectively. As to



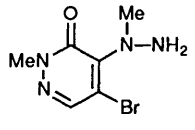
8

a; R = Ph
b; R = Me
c; R = H
d; R = $PhCH_2$

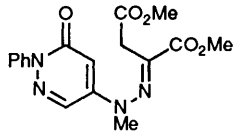


9

a; R = Ph
b; R = Me
c; R = H
d; R = $PhCH_2$



10



11

the reaction pathway of the bromide **8** with DMAD to form isomers **3** and **9**, an ionic-type reaction was supported by the observation that different reaction solvents resulted in different ratios of the products, **3** and **9** [in dimethyl sulphoxide (DMSO): **3a** 2%, **9a** 41%; in acetic acid: **3a** 49%, **9a** 1%; in dichloromethane: no cyclization]. From these results we presumed that the formation of isomers **3** and **9** from substrates **8** and **2** proceeds as follows. The negatively polarized C-4 of the initially formed Michael adducts **13** attacks the olefinic carbon to afford compounds **3** with elimination of hydrogen bromide. On the other hand, intramolecular rearrangement of the vinylhydrazino group by nucleophilic attack of the olefinic carbon on C-5 of adduct **13** followed by cyclization by attack of the methylamino group on C-4 of the pyridazinone ring gives regioisomer **9**. The reaction pathway of the reaction of bromide **10** with DMAD to give compound **3b** and **9b** is assumed to proceed *via* the initially formed azirine intermediate, followed by attacks on C-4 and C-5 to give compound **3b** and **9b**, respectively (Scheme 2). Further studies on the application and extension of these reactions are in progress.

Experimental

M.p.s were determined using a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO IRA-1 grating IR spectrometer. ^1H NMR spectra were determined on a Hitachi R-600 spectrometer, and ^{13}C NMR spectra were measured with a JEOL JNM-GX400 spectrometer with tetramethylsilane as internal standard. *J*-Values are given in Hz. Mass spectra were obtained with a JEOL JMS-DX303 mass spectrometer.

2-Substituted 5-(1-methylhydrazino)pyridazin-3(2H)-ones **1a–d**.—These compounds were prepared by the reported method.[4]

2-(p-Chlorobenzyl)-5-(1-methylhydrazino)pyridazin-3(2H)-one **1e**.—This compound was synthesized according to a procedure used by Kaji *et al.*[5] To a mixture of *p*-chlorobenzyl chloride (8.05 g, 50 mmol) and potassium carbonate (27.64 g, 200 mmol) in DMF (100 cm^3) was added 4,5-dibromopyridazin-3(2*H*)-one[6] (10.16 g, 40 mmol), and the mixture was stirred for 1 h, poured into water (300 cm^3), and kept at room temperature. Precipitated solid was collected and extracted with hot ethanol. The extract was evaporated and the residue was recrystallized from ethanol to give *4,5-dibromo-2-(p-chlorobenzyl)pyridazin-3(2H)-one* (12.01 g, 79%), m.p. 132–133 °C (Found: C, 35.0; H, 1.8; N, 7.5. $C_{11}H_7Br_2ClN_2O$ requires C, 34.91; H, 1.86; N, 7.40%); ν_{max}(KBr)/cm^{-1} 1642 (C=O); δ_H($CDCl_3$) 5.26 (2 H, s, CH_2), 7.16–7.50 (4 H, m, ArH) and 7.79 (1 H, s, =CH); *m/z* 377 and 379 (M^+).

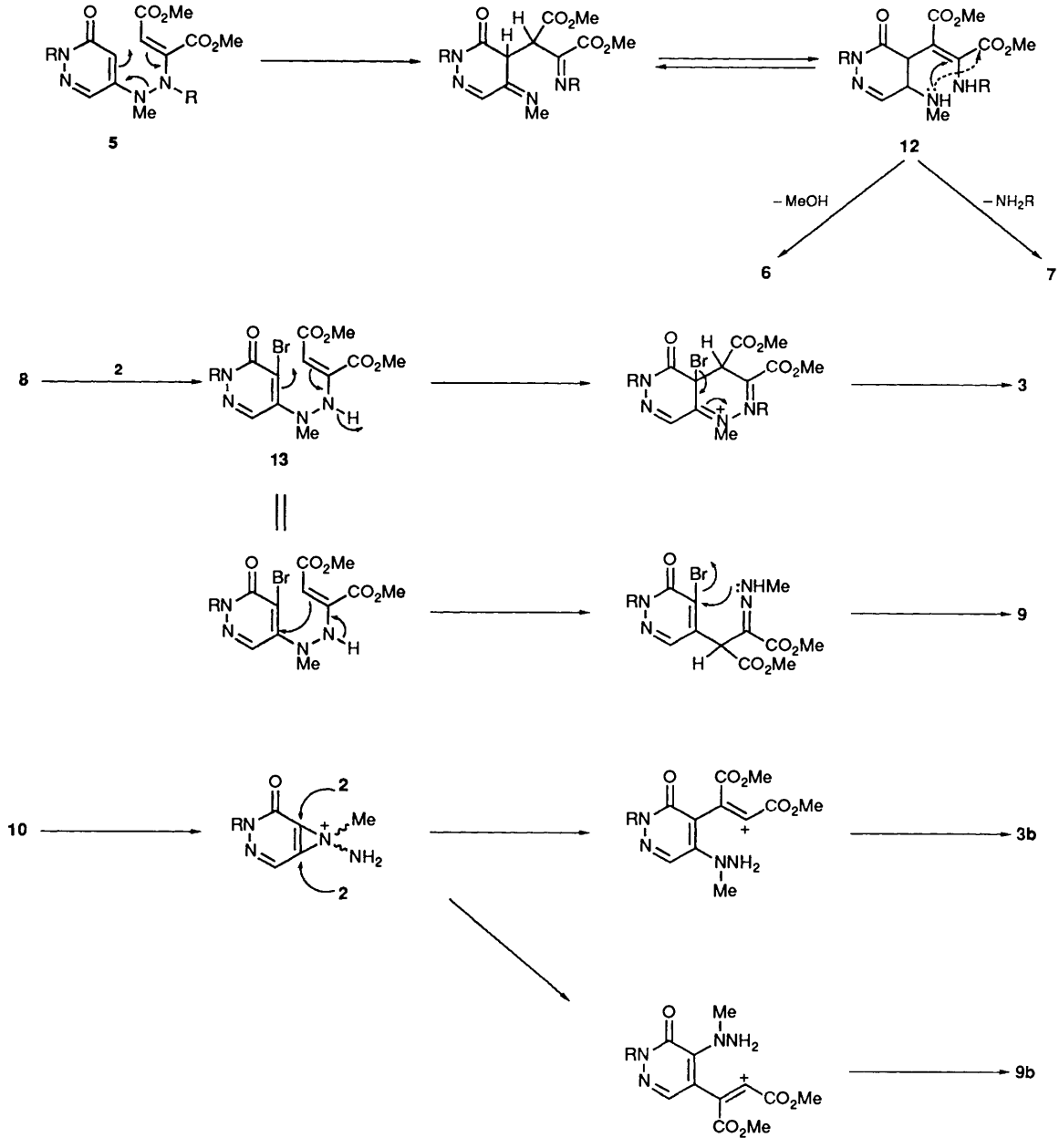
To a stirred solution of 4,5-dibromo-2-(*p*-chlorobenzyl)pyridazin-3(2*H*)-one (11.35 g, 30 mmol) in methanol (100 cm^3) was added dropwise methylhydrazine * 4.79 cm^3, (90 mmol) at room temperature and the mixture was stirred for 6 h, then cooled to 0 °C, and the resulting precipitate was collected. Recrystallization from ethanol gave *4-bromo-2-(p-chlorobenzyl)-5-(1-methylhydrazino)pyridazin-3(2H)-one* (6.10 g, 59%), m.p. 117–118 °C (Found: C, 42.3; H, 3.5; N, 16.2. $C_{12}H_{12}BrClN_4O$ requires C, 41.95; H, 3.52; N, 16.3%); ν_{max}(KBr)/cm^{-1} 3300 (NH) and 3200 (NH); δ_H([$^2H_6$]DMSO) 3.35 (3 H, s, Me), 4.96 (2 H, s, NH_2), 5.19 (2 H, s, CH_2), 7.21–7.52 (4 H, m, ArH) and 8.20 (1 H, s, =CH); *m/z* 342 and 344 (M^+).

A solution of **8e** (5.15 g, 15 mmol) and KOH (0.95 g, 17 mmol) in methanol (350 cm^3) was hydrogenated catalytically with 5% palladium on carbon (0.80 g) at atmospheric pressure. After the uptake of an equimolar amount of hydrogen, the catalyst was filtered off and the solvent was removed under reduced pressure. The residue was treated with water and extracted with chloroform. The crude product obtained upon removal of chloroform was recrystallized from ethyl acetate to give *compound* **1e** (2.82 g, 71%), m.p. 208–209 °C (Found: C, 54.7; H, 5.0; N, 21.4. $C_{12}H_{13}ClN_4O$ requires C, 54.45; H, 4.95; N, 21.17%); ν_{max}(KBr)/cm^{-1} 3400 (NH) and 3195 (NH); δ_H([$^2H_6$]DMSO) 3.06 (3 H, s, Me), 4.83 (2 H, s, NH_2), 5.11 (2 H, s, CH_2), 5.65 (1 H, d, *J* 2, =CH), 7.11–7.50 (4 H, m, ArH) and 8.09 (1 H, d, *J* 2, =CH); *m/z* 264 (M^+).

General Procedure for the Preparation of 4,6-Dihydropyridazino[4,5-c]pyridazin-5(1H)-ones **3a–e** *from 5-(1-Methylhydrazino)pyridazin-3(2H)-ones* **1a–e** *and DMAD*.—DMAD (1.84 cm^3, 15 mmol) was added dropwise to a stirred solution of a 5-(1-methylhydrazino)pyridazin-3(2H)-ones **1a–e** (10 mmol) in acetic acid (20 cm^3). The mixture was stirred for 12–24 h at room temperature until the material **1a–e** had disappeared (TLC) and then the mixture was heated at 80 °C for 24–48 h. After evaporation of acetic acid under reduced pressure, the residue was purified by column chromatography on silica gel with chloroform as eluent to give compounds **3a–e**. Analytical samples were purified by recrystallization from ethanol (see Table 1 for compounds 3).

5-(2-Ethyl-1-methylhydrazino)-2-phenylpyridazin-3(2H)-one **4a**.—To a stirred solution of compound **1a** (4.72 g, 22 mmol) in methanol (100 cm^3) was added acetaldehyde (6.10 cm^3, 110 mmol). After being stirred for 12 h, the reaction mixture was evaporated under reduced pressure to give the crude product (5.09 g, 95%), 5-(2-ethylidene-1-methylhydrazino)-2-phenylpyridazin-3(2*H*)-one. To a stirred solution of this crude product (5.08 g, 21 mmol) in methanol (100 cm^3) was added excess of sodium borohydride (7.94 g, 210 mmol). After being stirred for 24 h, the mixture was evaporated under reduced pressure. A solution of 20% aq. NaOH (100 cm^3) was poured into the residue, which was then extracted with dichloromethane (100 cm^3 × 3) and the extract was dried over anhydrous magnesium sulphate. The residue obtained by concentration of the extract was recrystallized from ethanol to give *compound* **4a** (4.51 g, 88%), m.p. 109.5–110 °C (Found: C, 63.95; H, 6.7; N, 22.9. $C_{13}H_{16}N_4O$ requires C, 63.91; H, 6.60; N, 22.93%); ν_{max}(KBr)/cm^{-1} 3240 (NH) and 1640 (C=O); δ_H($CDCl_3$) 1.09 (3 H, t, *J* 7, CH_2Me), 2.90 (2 H, q, *J* 7, CH_2Me), 3.08 (3 H, s, NMe), 3.52 (1 H, br, NH), 5.78 (1 H, d, *J* 2, =CH), 7.27–7.72 (5 H, m, Ph) and 8.30 (1 H, d, *J* 2, =CH); *m/z* 244 (M^+).

* **CAUTION**: Methylhydrazine is highly toxic and highly carcinogenic.



Scheme 2

5-(1-*Methyl*-2-*propylhydrazino*)-2-*phenylpyridazin*-3(2H)-*one* **4b**.—The pyridazinone **1a** (4.33 g, 20 mmol) was allowed to react with propionaldehyde (7.21 cm^3, 100 mmol) in methanol (100 cm^3); reduction with sodium borohydride (7.57 g, 200 mmol) in the same manner as described for compound **4a** then afforded *title compound* **4b** (3.60 g, 70%), m.p. 98 °C (Found: C, 65.3; H, 7.1; N, 21.5. $C_{14}H_{18}N_4O$ requires C, 65.09; H, 7.11; N, 21.69%); ν_{max}(KBr)/cm^{-1} 3235 (NH) and 1635 (C=O); δ_H-($CDCl_3$) 0.96 (3 H, t, *J* 7, CH_2CH_2Me), 1.42 (2 H, sextet, *J* 7, CH_2CH_2Me), 2.83 (2 H, t, *J* 7, CH_2CH_2Me), 3.04 (3 H, s, Me), 3.56 (1 H, br, NH), 5.73 (1 H, d, *J* 3, =CH), 7.24–7.73 (5 H, m, Ph) and 8.28 (1 H, d, *J* 3, =CH); *m*/*z* 258 (M^+).

Michael Adducts **5** *of Compounds* **4** *with DMAD*.—To a solution of a compound **4** (15 mmol) in acetic acid (30 cm^3) was added DMAD (2.77 cm^3, 22.5 mmol) and the solution was refluxed for 24 h. After removal of the solvent under reduced pressure, water (200 cm^3) was poured into the residue, which was then extracted with dichloromethane (60 cm^3 × 3). The extract was dried over anhydrous magnesium sulphate, evaporated, and chromatographed on silica gel with chloroform as eluent to afford the corresponding oily compound **5**. *Compound* **5a**: (4.70 g, 82%), ν_{max}(film)/cm^{-1} 1750 (C=O), 1710 (C=O) and 1655 (C=O); HR-CI (Found: M^+ + 1, 387.1694. $C_{19}H_{23}N_4O_5$ requires *M* + 1, 387.1669); δ_H($CDCl_3$) 1.17 (3 H, t, *J* 7, CH_2Me), 3.05 (3 H, s, Me), 3.34 (2 H, q, *J* 7, CH_2Me), 3.61 (3 H, s, OMe), 3.79 (3 H, s, OMe), 4.85 (1 H, s, =CH), 5.87 (1 H, d, *J* 2, =CH), 7.23–7.63 (5 H, m, Ph) and 7.76 (1 H, d, *J* 2, =CH).

Compound **5b**: (5.09 g, 84%), ν_{max}(film)/cm^{-1} 1755 (C=O), 1715 (C=O) and 1660 (C=O); HR-CI (Found: M^+ + 1, 401.1833. $C_{20}H_{25}N_4O_5$ requires *M* + 1, 401.1825); δ_H($CDCl_3$) 0.91 (3 H, t, *J* 7, CH_2CH_2Me), 1.72 (2 H, m, CH_2CH_2Me), 3.07 (3 H, s, NMe), 3.20 (2 H, t, *J* 7, CH_2CH_2Me), 3.66 (3 H, s, Me), 3.85 (3 H, s, OMe), 4.88 (1 H, s, =CH), 5.95 (1 H, d, *J* 3, =CH), 7.18–7.71 (5 H, m, Ph) and 7.78 (1 H, d, *J* 3 =CH).

Cyclization of Michael Adducts **5**.—A solution of a compound **5** (10 mmol) in tetralin (30 cm^3) was heated at 220 °C for 24 h. After removal of the solvent by evaporation, the residue was chromatographed on silica gel with benzene–diethyl ether (4:1)

as eluent to give compounds **6** and **7**. Analytical samples of compounds **6** and **7** were purified by recrystallization from ethanol.

Methyl-3-ethylamino-1-methyl-2,5-dioxo-6-phenyl-1,2,5,6-tetrahydropyrido[2,3-d]*pyridazine-4-carboxylate* **6a**. (1.45 g, 44%), m.p. 240–241 °C (Found: C, 60.7; H, 5.2; N, 15.8. $C_{18}H_{18}N_4O_4$ requires C, 61.01; H, 5.12; N, 15.18%); ν_{max}(KBr)/cm^{-1} 3325 (NH), 1730 (C=O), 1660 (C=O) and 1640 (C=O); δ_H($CDCl_3$) 1.28 (3 H, t, *J* 8, CH_2Me), 3.24 (2 H, q, *J* 8, CH_2Me), 3.74 (3 H, s, Me), 3.89 (3 H, s, OMe), 5.95 (1 H, br, NH), 7.14–7.73 (5 H, m, Ph) and 8.02 (1 H, s, =CH); *m/z* 354 (M^+).

Methyl 1-methyl-2,5-dioxo-6-phenyl-3-propylamino-1,2,5,6-tetrahydropyrido[2,3-d]*pyridazine-4-carboxylate* **6b**. (1.21 g, 33%), m.p. 285 °C (Found: C, 61.65; H, 5.5; N, 15.0. $C_{19}H_{20}N_4O_4$ requires C, 61.95; H, 5.47; N, 15.21%); ν_{max}(KBr)/cm^{-1} 3340 (NH), 1740 (C=O), 1665 (C=O) and 1645 (C=O); δ_H($CDCl_3$) 0.87 (3 H, t, *J* 7, CH_2CH_2Me), 1.59 (2 H, sextet, *J* 7, CH_2CH_2Me), 3.12 (2 H, t, *J* 7, CH_2CH_2Me), 3.76 (3 H, s, NMe), 3.79 (3 H, s, OMe), 6.57 (1 H, br, NH), 7.50 (5 H, s, Ph) and 8.45 (1 H, s, =CH); *m/z* 368 (M^+).

Dimethyl 1-methyl-4-oxo-5-phenyl-4,5-dihydro-1H-pyrrolo-[2,3-d]*pyridazine-2,3-dicarboxylate* **7**. (0.51 g, 12% from **5a**; 0.34 g, 10% from **5b**); m.p. 196.5–197.5 °C (Found: C, 59.7; H, 4.4; N, 12.1. $C_{17}H_{15}N_3O_5$ requires C, 59.82; H, 4.42; N, 12.31%); ν_{max}(KBr)/cm^{-1} 1745 (C=O), 1730 (C=O) and 1680 (C=O); δ_H($CDCl_3$) 3.89 (3 H, s, NMe), 3.95 (3 H, s, OMe), 4.07 (3 H, s, OMe), 7.26–7.71 (5 H, m, Ph) and 8.20 (1 H, s, =CH); *m/z* 341 (M^+).

2-Benzyl-4,5-dibromopyridazin-3(2H)-one.—4,5-Dibromopyridazin-3(2H)-one (25.39 g, 0.1 mol) was allowed to react with benzyl chloride (13.81 cm^3, 0.12 mol) in DMF (150 cm^3) in the same manner as described for 4,5-dibromo-2-(*p*-chlorobenzyl)pyridazin-3(2*H*)-one to give *2-benzyl-4,5-dibromopyridazin-3(2H)-one* (19.01 g, 53%), m.p. 102–103 °C (Found: C, 38.5; H, 2.4; N, 8.2. $C_{11}H_8Br_2N_2O$ requires C, 38.41; H, 2.34; N, 8.14%); ν_{max}(KBr)/cm^{-1} 1660 (C=O); δ_H($CDCl_3$) 5.33 (2 H, s, CH_2), 7.18–7.53 (5 H, m, Ph) and 7.82 (1 H, s, =CH); *m/z* 344 (M^+).

General Procedure for the Preparation of 2-Substituted-4-bromo-5-(1-methylhydrazino)pyridazin-3(2H)-ones **8**.—These compounds were synthesized according to a procedure used by Kaji *et al.*[4] To a solution of a 2-substituted-4,5-dibromopyridazin-3(2*H*)-one (40 mmol)[6,7] in methanol (50 cm^3) was added dropwise methylhydrazine (6.38 cm^3, 120 mmol). The mixture was stirred for 6 h and then the separated product was collected. Recrystallization from the appropriate solvent afforded the corresponding compound **8**.

Compound **8a**. (7.72 g, 65%), m.p. 107–108 °C (from EtOH–DMF) (Found: C, 44.6; H, 3.7; N, 19.0. $C_{11}H_{11}BrN_4O$ requires C, 44.77; H, 3.76; N, 18.98%); ν_{max}(KBr)/cm^{-1} 3315 (NH), 3225 (NH) and 1630 (C=O); δ_H([$^2H_6$]DMSO) 3.45 (3 H, s, Me), 5.04 (2 H, s, NH_2), 7.47 (5 H, s, Ph) and 8.35 (1 H, s, =CH); *m/z* 294 and 296 (M^+).

Compound **8b**. (5.09 g, 55%), m.p. 111–112 °C (from EtOH–Et_2O) (Found: C, 31.0; H, 3.9; N, 24.1. $C_6H_9BrN_4O$ requires C, 30.92; H, 3.89; N, 24.04%); ν_{max}(KBr)/cm^{-1} 3310 (NH), 3220 (NH) and 1610 (C=O); δ_H([$^2H_6$]DMSO) 3.33 (3 H, s, Me), 3.58 (3 H, s, NMe), 4.89 (2 H, s, NH_2) and 8.12 (1 H, s, =CH); *m/z* 232 and 234 (M^+).

Compound **8c**. (6.52 g, 74%), m.p. 141–142 °C (from EtOH–DMF) (Found: C, 27.6; H, 3,3; N, 25.6. $C_5H_7BrN_4O$ requires C, 27.42; H, 3.22; N, 25.58%); ν_{max}(KBr)/cm^{-1} 3325 (NH), 3225 (NH) and 1645 (C=O); δ_H([$^2H_6$]DMSO) 3.32 (3 H, s, NMe), 4.85 (2 H, s, NH_2), 8.10 (1 H, s, =CH) and 12.47 (1 H, br, CONH); *m/z* 218 and 220 (M^+).

Compound **8d**. (10.39 g, 84%), m.p. 103 °C (from EtOH–Et_2O) (Found: C, 46.5; H, 4.2; N, 18.1. $C_{12}H_{13}BrN_4O$ requires C, 46.62; H, 4.24; N, 18.12%); ν_{max}(KBr)/cm^{-1} 3310 (NH), 3215 (NH) and 1650 (C=O); δ_H($CDCl_3$) 3.36 (3 H, s, NMe), 3.94 (2 H, br, NH_2), 5.28 (2 H, s, CH_2), 7.11–7.62 (5 H, m, Ph) and 8.10 (1 H, s, =CH); *m/z* 308 and 310 (M^+).

General Procedure for the Cyclization of Compounds with DMAD.—DMAD (1.84 cm^3, 15 mmol) was added dropwise to a stirred solution of a compound **8** (10 mmol) in DMF (15 cm^3) at room temperature. After being stirred for 6 h, the reaction mixture was treated with water (200 cm^3), then extracted with dichloromethane (70 cm^3 × 3) and the extract was dried over anhydrous magnesium sulphate. The residue obtained by concentration of the extract was purified by column chromatography on silica gel with hexane–chloroform as eluent to give the regioisomers **3** and **9**. Analytical samples were purified by recrystallization from ethanol. Yields were as follows compound **3a**: 20%; compound **9a**: 32%; compound **3b**: 22%; compound **9b**: 28%; compound **3c**: 24%; compound **9c**: 34%; compound **3d**: 17%; compound **9d**: 39%. (See Table 2 for data on compound **9**.

5-Bromo-2-methyl-4-(1-methylhydrazino)pyridazin-3(2H)-one **10**.—To a stirred solution of 4,5-dibromo-2-methylpyridazin-3(2*H*)-one (26.79 g, 0.1 mol) in toluene (300 cm^3) was added dropwise methylhydrazine (15.96 cm^3, 0.3 mol) at room temperature. After being stirred for 24 h, the precipitates were filtered off and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with chloroform as eluent to give *compound* **10** (4.50 g, 19%). An analytical sample was purified by recrystallization from ethanol, m.p. 64–65 °C (Found: C, 30.8; H, 3.85; N, 23.9. $C_6H_9BrN_4O$ requires C, 30.92; H, 3.89; N, 24.04%); ν_{max}(KBr)/cm^{-1} 3310 (NH), 3205 (NH) and 1615 (C=O); δ_H($CDCl_3$) 3.07 (3 H, s, NMe), 3.58 (2 H, s, NH_2) 3.69 (3 H, s, NMe) and 7.75 (1 H, s, =CH); *m/z* 232 and 234 (M^+).

Cyclization of Compound **10** *with DMAD*.—Compound **10** (2.33 g, 10 mmol) was allowed to react with DMAD (1.8 cm^3, 15 mmol) in DMF (15 cm^3) in the same manner as described for the cyclization of compounds **8** with DMAD, to afford compounds **3b** and **9b**.

Isolation of Michael Adduct **11**.—DMAD (1.48 cm^3, 12 mmol) was added to a solution of compound **1a** (2.16 g, 10 mmol) in dichloromethane (20 cm^3) and the mixture was stirred for 7 days. After removal of the solvent under reduced pressure, the resulting oily residue was cooled to 0 °C to give a crude solid. Recrystallization from dichloromethane–hexane afforded the *Michael adduct* **11** (2.88 g, 81%), m.p. 85–87 °C (Found: C, 56.7; H, 5.0; N, 15.6. $C_{17}H_{18}N_4O_5$ requires C, 56.98; H, 5.06; N, 15.63%); ν_{max}(KBr)/cm^{-1} 1725 (C=O) and 1660 (C=O); δ_H($CDCl_3$) 3.43 (3 H, s, NMe), 3.74 (3 H, s, OMe), 3.82 (2 H, s, CH_2), 3.88 (3 H, s, OMe), 6.25 (1 H, d, *J* 2, =CH), 7.22–7.78 (5 H, m, Ph) and 8.34 (1 H, d, *J* 2 =CH); *m/z* 358 (M^+).

References

1 T. Miyamoto and J. Matsumoto, *Chem. Pharm. Bull.*, 1989, **37**, 93; K. Kaji, H. Nagashima, Y. Ohhata, T. Tabashi and H. Oda, *J. Heterocycl. Chem.*, 1985, **22**, 161; S. Chen and R. P. Panzica, *J. Org. Chem.*, 1981, **46**, 2467; P. Singh and S. P. Gupta, *Indian J. Med. Res.*, 1979, **69**, 804.

2 T. Yamasaki, E. Kawaminami, T. Yamada, T. Okawara and M. Furukawa, *J. Chem. Soc., Chem. Commun.*, 1990, 645.

3 O. Diels and J. Reese, *Justus Liebigs. Ann. Chem.*, 1934, **511**, 168;

1935, **519**, 147; E. H. Huntress, J. Bornstein and W. M. Hearon, *J. Am. Chem. Soc.*, 1956, **78**, 2225.
4 K. Kaji, H. Nagashima, Y. Hirose and H. Oda, *Chem. Pharm. Bull.*, 1985, **33**, 982.
5 K. Kaji, M. Kuzuya and R. N. Castle, *Chem. Pharm. Bull.*, 1970, **18**, 147.
6 P. Schmit and J. Druey, *Helv. Chim. Acta*, 1954, **37**, 134.
7 K. H. Pilgram and G. E. Pollard, *J. Heterocycl. Chem.*, 1977, **14**, 1039 and references cited therein.

Paper 0/05345G
Received 27*th November* 1990
Accepted 13*th December* 1990