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Studies on the Syntheses of N-Heterocyclic Compounds. XXV.[1] Syntheses of Pyrido[3,4-*d*]pyridazine Derivatives. (2)[2]

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Investigations on the preparative methods and some chemical modifications of the previously reported potent diuretic, 1,4-dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (**1**: DS-511) were undertaken, producing a variety of derivatives shown in Table I. Comparison of the reactivity between the two chloro groups in 1,4-dichloropyrido[3,4-*d*]pyridazine showed that the 4-chloro group is more reactive toward nucleophilic substitution than the 1-chloro group. Some reaction of **1**, *e.g.* acid hydrolysis, reduction and Grignard addition reaction were also carried out. Significance of the ring nitrogen at the 6-position in **1** for diuretic activity is discussed.

In the previous paper,[2] we reported the syntheses of pyridopyridazine derivatives. Recent studies have revealed that several of them, especially 1,4-dimorpholino-7-phenylpyrido-[3,4-*d*]pyridazine (**1**: DS-511), possess significant diuretic activity. The result prompted us to the further chemical modifications of **1**. The present paper deals with the syntheses of homologues of **1** and some chemical reactions of the compounds.

According to the previously reported synthetic method,[2] 6-arylpyridine-2,3,4-tricarboxylic acid (**3**), prepared by hydrolysis and the subsequent permanganate oxidation of ethyl 6-aryl-2-methylpyridine-3,4-dicarboxylate (**2**, $R_2=CH_3$), was heated in acetic acid to afford 6-aryl-pyridine-3,4-dicarboxylic acid (**4**), in which only the α-carboxyl group underwent selective decarboxylation.

Although, in the previous report,[2] **4** was led to diethyl ester (**2**, $R_2=H$) (reaction a) and reacted with hydrazine to give 7-phenyl-1,2,3,4-tetrahydropyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (**6**, $R_1=C_6H_5$, $R_2=H$) which was a key intermediate to **1**, it was found that treatment of **4** with acetic anhydride readily afforded an anhydride (**5**) (reaction b), which could be led to **6** by the reaction with hydrazine. Furthermore, **5** could be obtained directly from **3** in excellent yields by heating in a mixture of acetic acid and acetic anhydride (reaction c). This method appears to provide the most preferable route to **6** because of the simplified procedure.

The chlorination of **6** to give 1,4-dichloro derivative (**7**) was formerly carried out with phosphorus oxychloride or a mixture of phosphorus oxychloride and phosphorus pentachloride, but the yield was rather unsatisfactory. This process, however, proved to be remarkably improved by employing tertiary amines such as N,N-dimethylaniline, triethylamine, pyridine and picolines with phosphorus oxychloride. A variety of desired homologues of **1** (**8a—g**), in which 7-phenyl or 1,4-dimorpholino group was modified, could be obtained by the reaction of **7** with various cyclic amines. Reactions of **7** with sodium hydrosulfide and sodium mercaptides gave 1,4-dimercapto (**9a**) and 1,4-bis(substituted thio) derivatives (**9b—d**) respectively. Derivatives bearing a methyl group at 5-position (**8h—t**) were prepared by the direct reaction

1) Part XXIV: A. Miyake, K. Itoh, N. Tada, Y. Oka, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **23**, 1505 (1975).
2) Part (1): S. Yurugi, T. Fushimi, H. Sugihara, and M. Hieda, *Yakugaku Zasshi*, **92**, 1333 (1972).
3) Location: *Juso, Yodogawa-ku, Osaka, 532, Japan.*

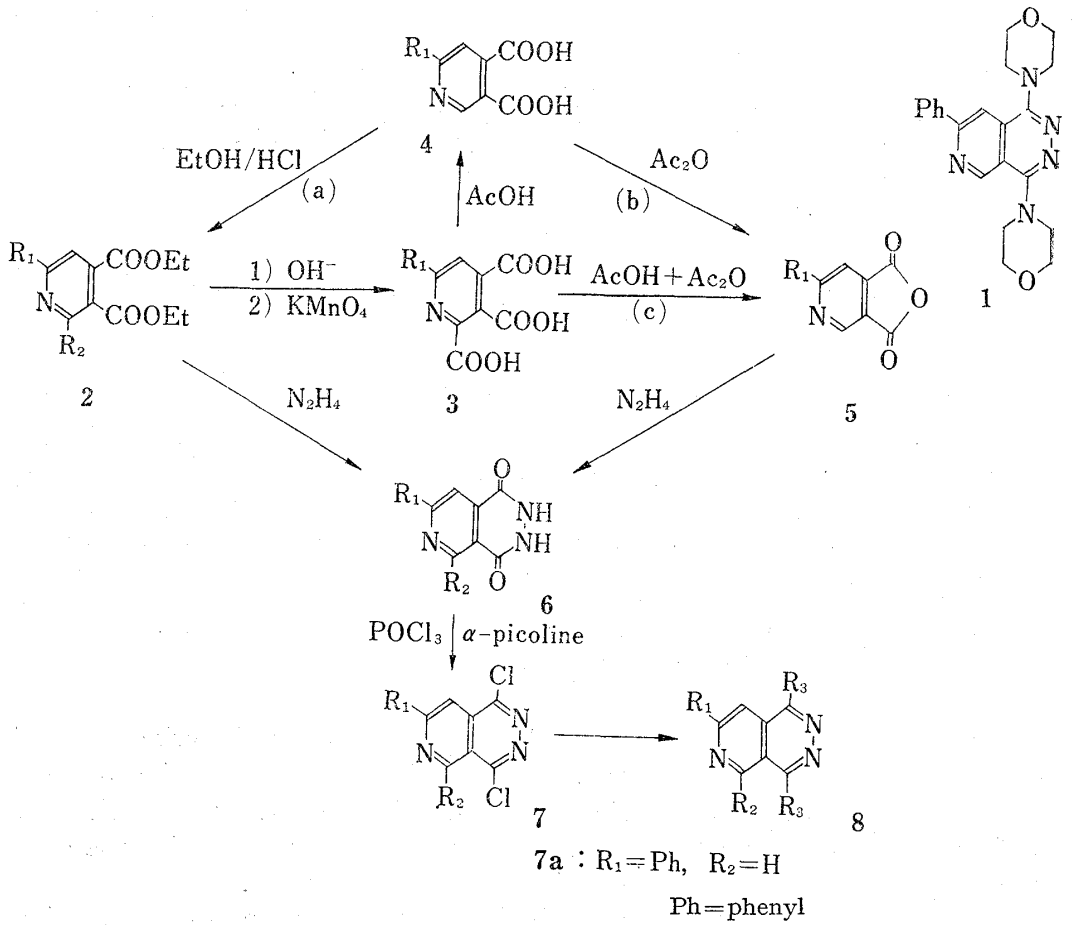


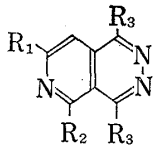
Chart 1

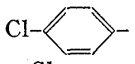
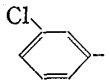
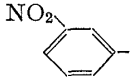
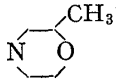
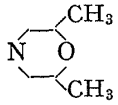
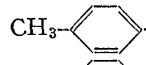
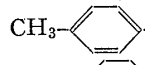
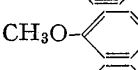
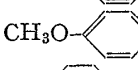
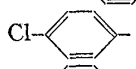
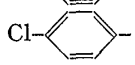
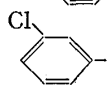
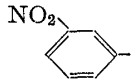
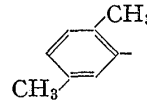
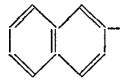
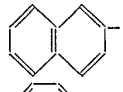
of **2** (R_2=CH_3) with hydrazine to give **6**, followed by the similar procedures as described above. 5-Benzyl derivatives (**8u**—**w**) were similarly synthesized from **2** (R_2=$C_6H_5CH_2$), prepared by the reaction of ethyl acylpyruvate with ethyl 3-amino-4-phenylcrotonate. The obtained derivatives (**8** and **9**) are listed in Table I.

The reaction of ethyl 2-methyl-6-(*p*-tolyl)pyridine-3,4-dicarboxylate (**2a**) with hydrazine in ethanol under reflux gave yellow needles (**10**), $C_{15}H_{17}O_2N_5$, which proved to be hydrazinium salt of **6a** from the ultraviolet (UV) spectrum (272 nm) and the formation of **6a** on acidification with acetic acid. On the other hand, the same reaction under room temperature afforded dihydrazide (**11**) having the same empirical formula with **10**. Since refluxing an ethanol solution of **11** with hydrazine afforded **10**, **11** is presumably an intermediate in the reaction of **2a** to **10**. Acidification of **11** with acetic acid gave rise to an isomer of **6a**, which proved to be a five membered dicarboximide (**12**) from the infrared (IR) spectrum (1720, 1780 cm^{-1}) and the formation of hydrazones (**13** and **14**) on treatment with acetone and benzaldehyde. Reaction of **11** with acetyl chloride also effected cyclization to give N-acetate (**15**) and the reaction with acetic anhydride gave N,N-diacetate (**16**), both of which were identical with the sample prepared by the acetylation of **12** with acetyl chloride and acetic anhydride respectively, whereas **10** and **6a** afforded O-acetate (**17**) on heating with acetic anhydride. Moreover, reaction of **12** with hydrazine at 80° effected irreversible conversion into **10**, suggesting that six membered pyridazine-dione (**6**) is more stable than five membered N-aminodicarboximide (**12**). Kondratéva, *et al.*[4] described that reaction of 2,5,6-trimethylpyridine-3,4-dicarboxylic acid with hydrazine yielded five membered N-aminoimide. It is assumed that, in this case

4) G. Ya. Kondratéva and C. H. Huang, *Dokl. Akad. Nauk SSSR*, **131**, 94 (1960).

TABLE I. 1,4,7-Tri- and 1,4,5,7-Tetra-substituted Pyrido[3,4-*d*]pyridazines



No.	R_1	R_2	R_3	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
8a		H		217—222	33	$C_{21}H_{22}O_2N_5Cl$	61.23	5.38	17.01	61.15	5.41	16.81
8b		H		179—182	30	$C_{21}H_{22}O_2N_5Cl$	61.23	5.38	17.01	61.25	5.40	17.10
8c		H		197—199	22	$C_{21}H_{22}O_3N_6$	59.43	5.29	19.62	59.21	5.07	19.52
8d		H		149—150	58	$C_{23}H_{27}N_5$	73.96	7.29	18.75	74.43	7.39	18.41
8e		H		75—81	83	$C_{23}H_{27}O_2N_5$	68.12	6.71	17.27	68.26	6.95	16.55
8f		H		248—250	77	$C_{25}H_{31}O_2N_5$	69.25	7.21	16.16	69.25	7.12	16.19
8g		H		130—131	62	$C_{21}H_{23}N_5$	73.01	6.71	20.28	72.90	6.62	19.96
8h		CH_3		222—224	53	$C_{23}H_{27}O_2N_5$	68.12	6.71	17.27	67.83	6.75	17.49
8i		CH_3		166—171	41	$C_{25}H_{31}N_5$	74.77	7.78	17.44	74.99	7.68	17.24
8j		CH_3		206—209	53	$C_{23}H_{27}O_3N_5$	65.54	6.46	16.62	65.54	6.51	16.43
8k		CH_3		174—176	54	$C_{25}H_{31}ON_5$	71.91	7.48	16.77	71.84	7.54	16.62
8l		CH_3		246—247	68	$C_{22}H_{24}O_2N_5Cl$	62.04	5.68	16.44	62.14	5.68	16.24
8m		CH_3		158—159	44	$C_{24}H_{28}N_5Cl$	68.31	6.69	16.60	68.14	6.57	16.58
8n		CH_3		184—186	63	$C_{22}H_{24}O_2N_5Cl$	62.04	6.58	16.44	62.10	5.66	16.43
8o		CH_3		218	41	$C_{22}H_{24}O_4N_6$	60.54	5.54	19.26	60.12	5.39	18.70
8p		CH_3		168—170	54	$C_{24}H_{29}O_2N_5$	68.71	6.97	16.70	68.68	7.01	16.53
8q		CH_3		163—165	60	$C_{20}H_{23}O_3N_5$	62.98	6.08	18.36	63.52	6.00	18.03
8r		CH_3		221—224	25	$C_{21}H_{24}O_2N_6$	64.27	6.16	21.24	64.15	6.00	21.33
8s		CH_3		240—242	21	$C_{26}H_{27}O_2N_5$	70.72	6.16	15.86	70.66	6.30	15.89
8t		CH_3		169—171	28	$C_{28}H_{31}N_5$	76.85	7.14	16.01	76.91	7.26	16.08
8u				165—168	27	$C_{23}H_{29}O_2N_5$	71.92	6.25	14.98	71.63	6.40	14.99

No.	R_1	R_2	R_3	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
8v	CH_3-	-CH_2	N O	181—183	26	$C_{29}H_{31}O_2N_5$	72.32	6.49	14.54	71.92	6.18	14.36
8w	CH_3O-	-CH_2	N O	178—180	41	$C_{29}H_{31}O_3N_5$	70.00	6.28	14.08	70.03	6.26	14.02
8x	CH_3-	H	N O	228—230	25	$C_{22}H_{25}O_2N_5$	67.50	6.44	17.89	67.55	6.55	17.61
8y	CH_3O-	H	N O	222—223	51	$C_{22}H_{25}O_3N_5$	64.85	6.13	17.19	65.05	6.44	16.73
9a	-	H	SH	212—215 (decomp.)	73	$C_{13}H_9N_3S_2$	57.53	3.35	15.50	57.24	3.55	15.46
9b	-	H	SCH_3	155	72	$C_{15}H_{13}N_3S_2$	60.17	4.38	14.04	60.02	4.29	14.33
9c	-	H	SCH_2-	167—168	97	$C_{27}H_{21}N_3S_2$	71.81	4.69	9.31	71.23	4.51	9.18
9d	-	H	S-	191—193	72	$C_{25}H_{17}N_3S_2$	70.89	4.05	9.92	71.01	4.03	9.85

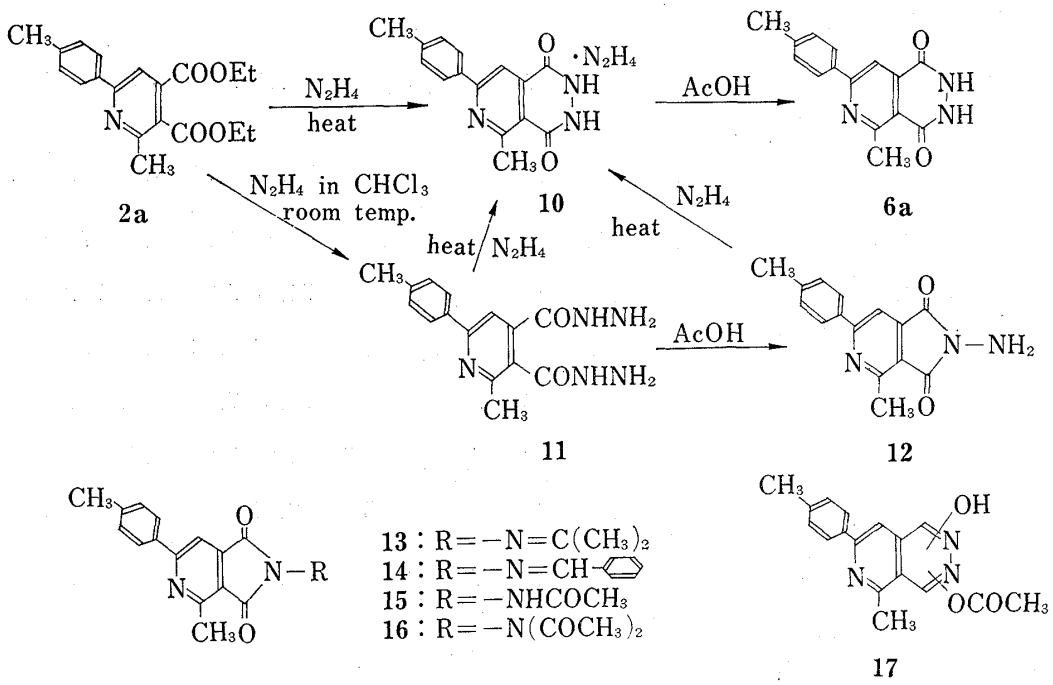


Chart 2

as well as in the reaction of **2a** to **12**, steric effect by the α-methyl group prevented the formation of hydrazide with six membered ring under a mild condition.

Tisler[5] suggested, from the calculation of frontier π-electron density, that in 1,4-dichloropyrido[3,4-*d*]pyridazine (**18**) the 4-chloro group would be more reactive toward nucleophilic substitution than the 1-chloro group, although the experimental support was not sufficient. A similar comparison was undertaken with respect to the reactivities of chloro groups at 1 and 4 positions of **7a**, the 7-phenyl derivative of **18**. Thus, when **7a** was allowed to react with morpholine under a milder condition, *i.e.* in a chloroform solution at room temperature,

5) M. Tisler and B. Stanovik, "Heterocyclic Compounds," Vol. 27, ed. by R.N. Castle, Academic Press, New York, 1973, p. 979.

only mono-substitution occurred to afford a chloro-morpholino compound. In order to define the substituted position, the following experiments were carried out.

Hydrolysis of **1** with 10% hydrochloric acid afforded a mixture of products, **19** and **20** (*ca.* 1:1), in which one of the two morpholino groups was displaced by a hydroxy group. The chlorination of **19** and **20** with phosphorous oxychloride in the presence of N,N-dimethylaniline gave chloro-morpholino derivatives, **21** and **22** respectively. The structural assignment of the both compounds was made by comparison of the nuclear overhauser effect (NOE) observed between the aromatic proton at the 5 position and the methylene protons at the 3 position of morpholino group. The value of 13.8% for **21** led to assign the structure 1-chloro-4-morpholino-7-phenylpyrido[3,4-*d*]pyridazine to **21** and hence the 4-chloro-1-morpholino isomer to **22**. The structure of **22** was also supported by a NOE of 10.1% between the aromatic proton at the 8 position and the methylene protons at the 3 position in the adjacent 1-morpholino group. The above compound obtained by the mono-substitution of **7a** showed complete identity with **21** in melting point, IR and nuclear magnetic resonance (NMR) spectra. The result that the 4-chloro group was more reactive than the 1-chloro group was in agreement with the Tisler's prediction in spite of the presence of 7-phenyl group. On the other hand, in our earlier report we described that in 5,8-dichloro-7-phenylpyrimido[4,5-*d*]pyridazine (**23**) the 8-chloro was more reactive toward substitution by morpholine than the 5-chloro group.[6] It is noteworthy that the relative reactivity between the two chloro groups has been reversed by introduction of a nitrogen into the adjacent ring.

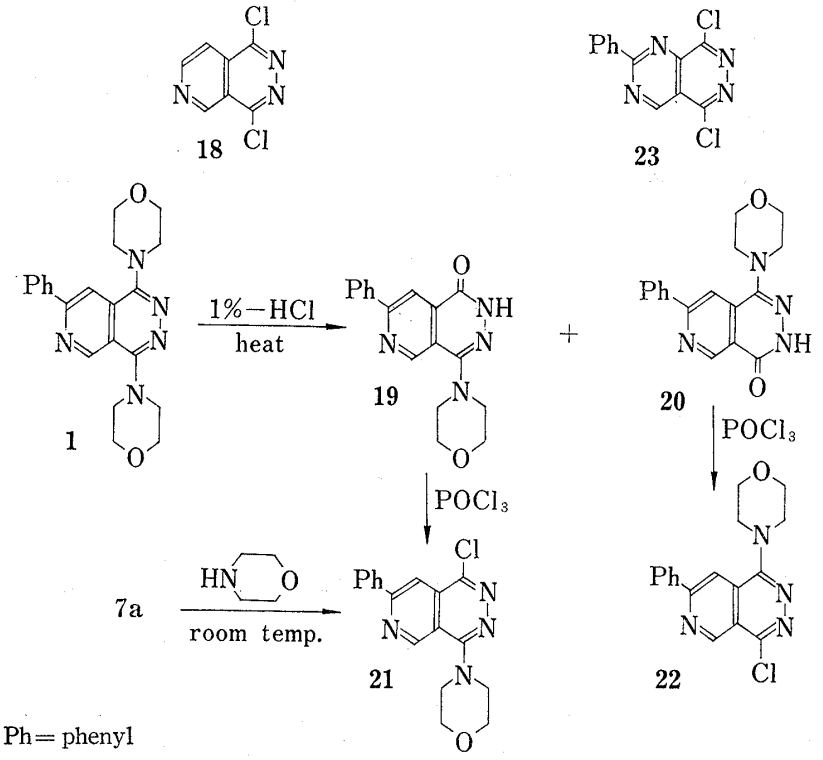
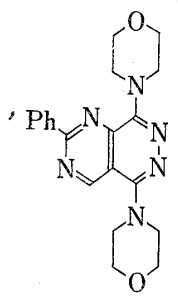


Chart 3

In the series of previously reported pyrimido[4,5-*d*]pyridazine derivatives, potent diuretic activities were exhibited not only by 5,8-dimorpholino-2-phenylpyrimido[4,5-*d*]pyridazine (**24**)[7] but also by its 3,4-dihydro derivative (**25**)[8] and 4-benzyl-3,4-dihydro derivative (**26**).[9]

6) S. Yurugi and M. Hieda, *Chem. Pharm. Bull.* (Tokyo), **20**, 1522 (1972).
7) S. Yurugi, M. Hieda, T. Fushimi, Y. Kawamatsu, H. Sugihara, and M. Tomimoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 1528 (1972).
8) S. Yurugi, T. Fushimi, and M. Hieda, *Yakugaku Zasshi*, **92**, 1316 (1972).
9) S. Yurugi, K. Itoh, A. Miyake, and K. Omura, *Yakugaku Zasshi*, **93**, 1043 (1973).



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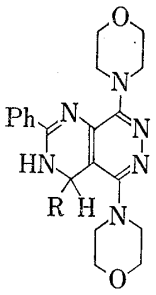
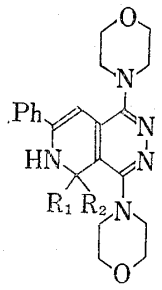
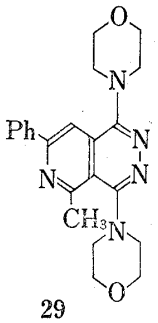


25 : R=H
26 : R=PhCH$_2$



27 : R$_1$=R$_2$=H
28a : R$_1$=H, R$_2$=PhCH$_2$
30 : R$_1$=CH$_3$, R$_2$=PhCH$_2$



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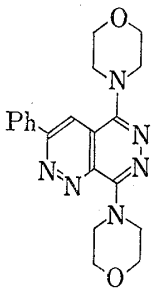
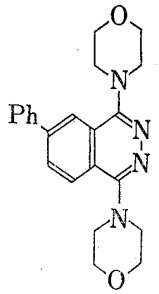


31

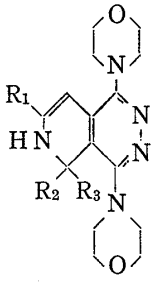


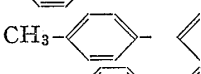
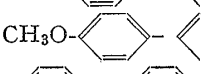
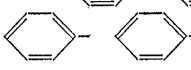
32

Ph=phenyl

Chart 4

TABLE II. 1,4-Dimorpholino-5,6-dihydropyrido[3,4-*d*]pyridazine Derivatives



No.	R$_1$	R$_2$	R$_3$	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
27		H	H	170—180	55[a]	$C_{21}H_{25}O_2N_5 \cdot HCl \cdot H_2O$	58.13	6.46	16.15	58.47	6.50	16.20
28a			H	168—170	33[a], 43[b], 60[c]	$C_{28}H_{30}O_2N_5$	71.61	6.65	14.92	71.41	6.74	14.63
28b			H	166—167	73[c]	$C_{27}H_{28}O_2N_5$	71.18	6.42	15.38	70.82	6.64	15.16
28c		$(CH_3)_3C$	H	168—172	46[b]	$C_{25}H_{32}O_2N_5$	68.94	7.64	16.08	68.87	7.80	15.69
28d			H	[d]	46[a]	$C_{29}H_{33}O_2N_5$	—	—	—	—	—	—
28e			H	[d]	59[a]	$C_{29}H_{33}O_3N_5$	—	—	—	—	—	—
30			CH_3	211—213	42[b]	$C_{29}H_{33}O_2N_5$	71.33	7.05	14.85	71.74	7.23	14.58

a) catalytic reduction *b*) Grignard reaction *c*) reaction with organolithium compound *d*) very unstable

In an attempt to prepare the similar derivatives in the present pyrido[3,4-*d*]pyridazine series, **1** was reduced with sodium borohydride to obtain expected 1,4-dimorpholino-7-phenyl-5,6-dihydropyrido[3,4-*d*]pyridazine (**27**), the structure of which was confirmed by the appearance of a singlet at 5.45 τ (2H) in place of an aromatic proton in **1** at 0.46 τ (1H) in the NMR spectrum. 5-Benzyl-5,6-dihydro derivative (**28a**) could be obtained by the catalytic reduction of **8u**, by the Grignard addition reaction of **1** with benzylmagnesium chloride, or by the reaction of **1** with benzyl lithium.[10] The Grignard addition occurred at the 5 position even with the 5-methyl derivative (**29**),[2] affording 5-benzyl-5-methyl-5,6-dihydro derivative (**30**). 5,6-Dihydro derivatives obtained by those methods are listed in Table II.

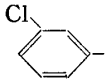
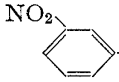
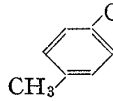
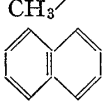
It was reported in the preceding paper[1] that **26** readily underwent oxidative elimination with potassium ferricyanide. The similar reaction was also observed in the ferricyanide oxidation of **28a**, affording **1** with the liberation of 5-benzyl group. This reaction provided a useful synthetic route to **8** (R_2=H), especially when R_1 involved functional groups labile to permanganate oxidation during the conversion of **2** to **3**. Thus, **8x** and **8y** could be synthesized by catalytic reduction of the corresponding 5-benzyl derivatives, **8v** and **8w**, followed by oxidative elimination of the benzyl group.

A series of our investigations on fused pyridazine derivatives has so far revealed that compound **1** and its azalogues, **24** and **31**, are all potent diuretics.[2,7,11] This fact prompted us further to the preparation of the corresponding phthalazine derivative (**32**), in which nitrogen in the pyridine ring of **1**, a component common with **24** and **31**, was removed. However, compound **32** prepared by the reaction of 1,4-dichloro-6-phenylphthalazine[12] with morpholine proved to posses virtually no diuretic activity. It became clear from the result that in those fused pyridazine derivatives, the presence of the above nitrogen atom in the ring adjacent to pyridazine is a requisite for the diuretic activity.

Experimental[13]

Ethyl Acylpyruvate (Table III)——General Procedure: To a solution of EtONa freshly prepared from Na (23 g) and EtOH (400 ml) was added R_1COCH_3 (1 mole) under cooling. After stirring for 30 min, to

Table III. Ethyl Acylpyruvates
R_1COCH_2COOEt

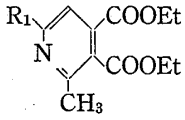
R_1	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
	51—52	45	$C_{12}H_{11}O_4Cl$	56.59	4.35		56.46	4.31	
	78—79	53	$C_{12}H_{11}O_6N$	54.34	4.18	5.28	54.32	3.98	5.28
	36—37	61	$C_{14}H_{15}O_4$	67.73	6.50		67.60	6.40	
	56—57	67	$C_{16}H_{14}O_4$	71.10	5.22		70.88	5.23	

10) A. Miyake, K. Itoh, N. Tada, Y. Oka, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **23**, 1488 (1975).
11) M. Hieda, K. Omura, and S. Yurugi, *Yakugaku Zasshi*, **92**, 1327 (1972).
12) C.M. Atkinson and C.J. Sharpe, *J. Chem. Soc.*, **1959**, 2858.
13) All melting points were measured on Kofler-type apparatus (Yanagimoto Co.) and are uncorrected. NMR spectra were measured on Varian T-60 high resolution spectrometer.

the reaction mixture was added ethyl oxalate (146 g). After standing overnight at room temperature, the reaction mixture was acidified with 10% H_2SO_4 (500 ml). Separated oil was extracted with C_6H_6, dried over Na_2SO_4 and evaporated to give ethyl acylpyruvate. Ethyl *p*-chlorobenzoyl,[14] *p*-methoxybenzoyl,[14,15] 2-furoyl[16] and nicotinoyl pyruvate[16] were prepared according to the methods in literatures.

Ethyl 2,6-Disubstituted Pyridine-3,4-dicarboxylate (**2**)——General Procedure: A mixture of ethyl acylpyruvate (10 g) and equimolar ethyl 3-aminocrotonate in EtOH (15 ml) was allowed to stand overnight under room temperature. Evaporation of the solvent yielded **2** ($R_2=CH_3$) (Table IV). Compounds in which R_1 are 2,5-dimethylphenyl, 2-furyl and 3-pyridyl were used for the subsequent reaction without purification. Similar procedure using ethyl 3-amino-4-phenylcrotonate gave **2** ($R_2=C_6H_5CH_2$), which was submitted to the subsequent reaction without purification.

Table IV. Ethyl 2-Methyl-6-substituted Pyridine-3,4-dicarboxylates (**2**)



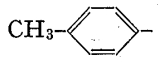
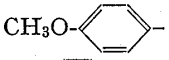
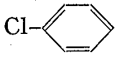
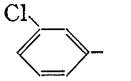
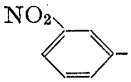
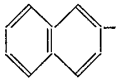
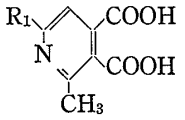
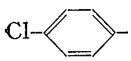
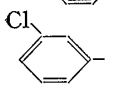
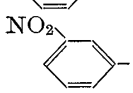
No.	R_1	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
2a		48—49	33	$C_{19}H_{21}O_4N$	69.70	6.47	4.28	69.63	6.51	4.30
2b		68—69	53	$C_{19}H_{21}O_5N$	66.46	6.16	4.08	66.40	6.23	4.01
2c		71—72	34	$C_{18}H_{18}O_4NCl$	62.16	5.22	4.03	62.09	5.08	4.08
2d		65—67	25	$C_{18}H_{18}O_4NCl$	62.16	5.22	4.03	61.84	5.06	4.08
2e		78—79	74	$C_{18}H_{18}O_6N_2$	60.33	5.06	7.82	60.31	4.89	7.89
2f		56—57	43	$C_{22}H_{21}O_4N$	72.71	5.82	3.85	72.71	5.81	3.56

Table V. 2-Methyl-6-substituted Pyridine-3,4-dicarboxylic Acids



R_1	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
	213—219 (decomp.)	91	$C_{14}H_{10}O_4NCl$	57.65	3.46	4.80	12.15	57.86	3.48	4.39	12.30
	187 (decomp.)	95	$C_{14}H_{10}O_4NCl$	57.65	3.46	4.80	12.15	57.17	3.33	4.73	12.13
	205—207	91	$C_{14}H_{10}O_6N_2$	55.63	3.34	9.27		55.50	3.14	9.29	

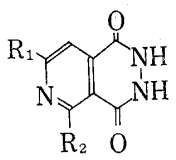
14) J.B. Wright, U.S. Patent, 3223703, Dec. 14 (1965).
15) R. Robinson and G. Schwarzenbach, *J. Chem. Soc.*, **1930**, 822.
16) F. Kipnis, I. Levy, and J. Ornfelt, *J. Am. Chem. Soc.*, **70**, 4265 (1948).

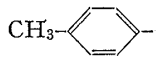
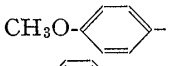
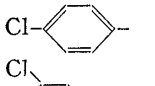
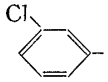
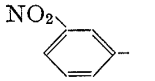
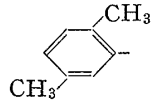
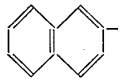
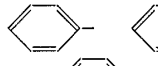
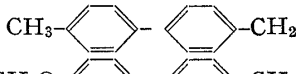
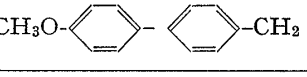
Hydrolysis of Ethyl 6-Aryl-2-methylpyridine-3,4-dicarboxylate (2, R_2=CH_3)——General Procedure: A mixture of **2** (5 g), KOH (2 equiv.), H_2O (10 ml) and EtOH (0.5 ml) was heated at 80° for 2 hr. After cooling the reaction mixture was acidified with conc. HCl, the resulting crystals were filtered to give 6-aryl-2-methylpyridine-3,4-dicarboxylic acid. (Table V).

Ethyl 6-(*m*-Nitrophenyl)pyridine-3,4-dicarboxylate (2, R_1=*m*-NO_2Ph, R_2=H) (Reaction a)——To a mixture of 2-methyl-6-(*m*-nitrophenyl)pyridine-3,4-dicarboxylic acid (15 g), H_2O (10 ml) and Na_2CO_3 (1.4 g) was added $KMnO_4$ (15 g) portionwise with vigorous stirring, keeping the temperature at 90—100°. After 10 hr the resulting MnO_2 was filtered off from the hot reaction mixture. The filtrate was refluxed with conc. HCl (6 ml) for 2 hr. Evaporation of the solvent *in vacuo* gave 6-(*m*-nitrophenyl)pyridine-2,3,4-tricarboxylic acid (3, R_1=*m*-NO_2Ph), which was refluxed with AcOH (100 ml) for 8 hr, The crude 6-(*m*-nitrophenyl)-pyridine-3,4-dicarboxylic acid (4, R_1=*m*-NO_2Ph), obtained by evaporation of AcOH, was refluxed with EtOH–HCl (100 ml) for 5 hr. After removal of the solvent, the residue was neutralized with aq. $NaHCO_3$ and extracted with AcOEt. The extract was dried over Na_2SO_4 and evaporated to give **2** (R_1=*m*-NO_2Ph, R_2=H), (2.2 g) as an oily material. IR ν_{max}^{Nujol} cm^{-1}: 1725 (C=O).

6-(*p* or *m*-Chlorophenyl)pyridine-3,4-dicarboxylic Anhydride (5, R_1=*p*-ClPh or *m*-ClPh) (Reaction b)——To a mixture of 6-(*p* or *m*-chlorophenyl)-2-methylpyridine-3,4-dicarboxylic acid (1 g), H_2O (4 ml) and Na_2CO_3 (1.4 g) was added $KMnO_4$ (1 g) portionwise with vigorous stirring, keeping the temperature at 90—100°. After 10 hr the resulting MnO_2 was filtered off from the hot reaction mixture. The filtrate was refluxed with

Table VI. 5,7-Disubstituted Pyrido[3,4-*d*]pyridazine-1,4 (2H, 3H)-diones (**6**)



No.	R_1	R_2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
6a		CH_3	>300	84	$C_{15}H_{13}O_2N_3$	67.40	4.90	15.72	67.28	4.84	15.37
6b		CH_3	>300	90	$C_{15}H_{13}O_3N_3$	63.59	4.63	14.83	63.44	4.41	15.31
6c		CH_3	>300	94	$C_{14}H_{10}O_2N_3Cl$	58.44	3.50	14.61	57.98	3.51	15.32
6d		CH_3	245 (decomp.)	91	$C_{14}H_{10}O_2N_3Cl$	58.44	3.50	14.61	57.93	3.23	14.66
6e		CH_3	>300	90	$C_{14}H_{10}O_4N_4$	56.38	3.38	18.79	56.19	3.43	18.92
6f		CH_3	295	65	$C_{16}H_{15}O_2N_3$	68.31	5.38	14.94	68.20	5.36	15.11
6g		CH_3	>300	87	$C_{12}H_9O_2N_3$	59.26	3.73	17.28	58.86	3.76	17.65
6h		CH_3	>300	62[a]	$C_{13}H_{10}O_2N_4$	—	—	—	—	—	—
6i		CH_3	>300	80	$C_{18}H_{13}O_2N_3$	71.27	4.32	13.86	71.42	4.04	13.87
6j			>300	61	$C_{20}H_{15}O_2N_3$	72.93	4.59	12.76	72.69	4.38	12.79
6k			>300	65[a]	$C_{21}H_{17}O_2N_3$	—	—	—	—	—	—
6l			>300	32[a]	$C_{21}H_{17}O_3N_3$	—	—	—	—	—	—

a) Crude; used for the subsequent process without further purification.

conc. HCl (3 ml) for 1 hr. After cooling the resulting precipitate was collected by filtration and refluxed with AcOH (5 ml) for 10 hr. Reflux was further continued for 1.5 hr after the addition of Ac_2O (5 ml) to the mixture. After cooling the resulting precipitate was collected by filtration to give **5**.

6-Phenylpyridine-3,4-dicarboxylic Anhydride (5, $R_1=C_6H_5$) (Reaction c)——A mixture of 6-phenylpyridine-2,3,4-tricarboxylic acid (**3**, $R_1=C_6H_5$) (5.3 g), AcOH (53 ml) and Ac_2O (11 ml) was refluxed for 6 hr. After being condensed to 10 ml, the resulting precipitate was collected to give **5** ($R_1=C_6H_5$) (3.7 g) as colorless needles. mp 200—201°. *Anal.* Calcd. for $C_{13}H_7O_3N$: C, 69.33; H, 3.13; N, 6.22. Found: C, 69.30; H, 3.02; N, 6.24. IR ν_{max}^{Nujol} cm^{-1}: 1790, 1850 (C=O).

7-Substituted or 5,7-Disubstituted Pyrido[3,4-*d*]pyridazine-1,4(2H, 3H)-dione (6) (Table VI)——General Procedure: a) To a solution of **2** (10 g) in EtOH (250 ml) was added 80% $N_2H_4\cdot H_2O$ (40 ml) and the mixture was refluxed for 3 hr. The resulting precipitate was filtered to give the hydrazinium salt of **6**, which was suspended in H_2O (150 ml) and acidified with AcOH with stirring. The resulting solid was filtered and washed with H_2O to give **6** as colorless powder.

b) To a suspension of **5** (1 g) in AcOH (10 ml) was added 80% $N_2H_4\cdot H_2O$ (1 ml), and the mixture was refluxed for 1 hr. After cooling, the resulting crystals were filtered to give **6**.

5-Methyl-7-(*p*-tolyl)pyrido[3,4-*d*]pyridazine-1,4(2H, 3H)-dione (6a) and the Hydrazinium Salt (10)—— To a solution of **2** ($R_1=p$-CH_3Ph, $R_2=CH_3$) (5 g) in EtOH (40 ml) was added 80% $N_2H_4\cdot H_2O$ (20 ml) and the mixture was refluxed for 3 hr. The resulting precipitate was filtered to give **10** (4.1 g). mp>300°. *Anal.* Calcd. for $C_{15}H_{17}O_2N_5$: C, 60.19: H, 5.72; N, 23.40. Found: C, 60.22; H, 5.67; N, 23.33. IR ν_{max}^{Nujol} cm^{-1}: 1630 (CONH). UV λ_{max}^{EtOH} nm (ε): 272 (21000). **10** (8.2 g) was suspended in H_2O (150 ml) and acidified with AcOH with stirring. The resulting solid was filtered, washed with H_2O to give **6a** (3.4 g) as colorless powder. IR ν_{max}^{Nujol} cm^{-1}: 1670 (CONH). UV λ_{max}^{EtOH} nm (ε): 274 (21000).

7-Aryl-1,4-bis(substituted amino)pyrido[3,4-*d*]pyridazine (8) (Table I)——General Procedure: A mixture of **6** (1 g), $POCl_3$ (15 ml) and N,N-dimethylaniline (1.5 ml) was heated at 100—110° for 3—4 hr. The excess $POCl_3$ was evaporated *in vacuo* and the residue was poured into ice water. The resulting crystals were filtered to give crude 7-aryl-1,4-dichloropyrido[3,4-*d*]pyridazine (**7**), which was refluxed with a cyclic amine (6 ml) for 1—3 hr. After removal of the excess amine, H_2O was added to the residue. The filtration and recrystallization of the resulting crystals gave **8**.

7-Phenylpyrido[3,4-*d*]pyridazine-1,4-dithiol (9a)——A mixture of 1,4-dichloro-7-phenylpyrido[3,4-*d*]-pyridazine (**7a**) (4.2 g) and 10% KSH–MeOH (150 ml) was stirred at room temperature for 3 hr. After removal of MeOH *in vacuo*, the residue was dissolved in H_2O (50 ml), and the resulting solution was acidified with AcOH. Filtration of the resulting yellow crystals gave **9a** (Table I).

1,4-Bis(methylthio or benzylthio)-7-phenylpyrido[3,4-*d*]pyridazine (9b or 9c)——To a solution of **9a** (3.5 g) in 10% NaOH (220 ml) was added CH_3I (3.7 g) or $C_6H_5CH_2Br$ (4.4 g) and the mixture was stirred at room temperature for 3 hr. Filtration and recrystallization of the resulting precipitate gave **9b** as colorless needles, or **9c** as pale yellow needles (Table I).

7-Phenyl-1,4-bis(phenylthio)pyrido[3,4-*d*]pyridazine (9d)——To a solution of MeONa freshly prepared from Na (0.46 g) and MeOH (20 ml) was added thiophenol (2.85 g), and the mixture was stirred at room temperature for 30 min. To the resulting solution was added **7a** (5 g) in MeOH (300 ml) and the mixture was further stirred at room temperature for 3 hr. After removal of the solvent *in vacuo*, H_2O was added to the residue. Filtration and recrystallization of the resulting crystals from AcOEt gave **9d** as pale yellow needles (Table I).

2-Methyl-6-(*p*-tolyl)pyridine-3,4-dicarbohydrazide (11)——To a solution of **2a** (3 g) in EtOH (100 ml) was added 80% $N_2H_4\cdot H_2O$ (1.5 ml) at room temperature. After standing overnight, the resulting precipitate was collected by filtration to give **11** (1.8 g, 66%). mp 213—216° (decomp.). *Anal.* Calcd. for $C_{15}H_{17}O_2N_5$: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.23; H, 5.51; N, 23.40. IR ν_{max}^{Nujol} cm^{-1}: 1640, 1670 (CONH). UV λ_{max}^{EtOH} nm (ε): 260 (16000).

N-Amino-2-methyl-6-(*p*-tolyl)pyridine-3,4-dicarboximide (12)——A suspension of **11** in H_2O (50 ml) was acidified with AcOH and the resulting precipitate was recrystallized from EtOH to give **12** as light yellow needles (1.3 g, 78%). mp 211—213°. *Anal.* Calcd. for $C_{15}H_{13}O_2N_3$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.44; H, 4.77; N, 15.69. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1730, 1780 (CO–N–CO). UV λ_{max}^{EtOH} nm (ε): 260 (14500), 340 (10000).

N-Isopropyrideneamino-2-methyl-6-(*p*-tolyl)pyridine-3,4-di-carboximide (13)——A mixture of **11** or **12** (1 g) and acetone (60 ml) was refluxed for 4 hr. Evaporation of excess acetone and recrystallization from EtOH gave **13** as yellow needles (0.8 g, 78%). mp 170—171°. *Anal.* Calcd. for $C_{18}H_{17}O_2N_3$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.42; H, 5.42; N, 13.73. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1770 (CO–N–CO). UV λ_{max}^{EtOH} nm (ε): 281 (18700), 330 (8840), 350 (8960). NMR (in $CDCl_3$) τ: 7.70 (3H, s, CH_3), 7.56 (3H, s, CH_3), 8.03 (3H, s, CH_3).

N-Benzylideneamino-2-methyl-6-(*p*-tolyl)pyridine-3,4-dicarboximide (14)——A mixture of **11** or **12** (1 g), benzaldehyde (4 ml) and EtOH (300 ml) was refluxed for 5 hr. After cooling the resulting precipitate was collected to give **13** as light yellow needles (0.77 g, 65%). mp 209—211°. *Anal.* Calcd. for $C_{22}H_{17}O_2N_3$: C, 74.35; H, 4.82; N, 11.84. Found: C, 74.33; N, 4.68; N, 11.84. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1780, 1800 (CO–N–CO).

N-Acetamido-2-methyl-6-(*p*-tolyl)pyridine-3,4-dicarboximide (15)——To a mixture of **11** or **12** (1 g) and pyridine (30 ml) was added dropwise acetyl chloride (1 g) stirring at room temperature. After standing overnight, pyridine was evaporated *in vacuo*. To the residue was added H_2O, and the resulting solid was filtered. Purification by silica gel column chromatography gave light yellow needles (0.4 g, 39%). mp 255—259°. *Anal.* Calcd. for $C_{17}H_{15}O_3N_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 66.88; H, 4.76; N, 13.59. IR ν_{max}^{Nujol} cm^{-1}: 1670 (CONH), 1750, 1800 (CO–N–CO). NMR (in d_6-DMSO) τ: 7.16 (3H, s, CH_3), 7.60 (3H, s, CH_3), 7.92 (3H, s, CH_3).

N,N-Diacetylamino-2-methyl-6-(*p*-tolyl)pyridine-3,4-dicarboximide (16)——A mixture of **11**, **12** or **15** (1 g) and Ac_2O (80 ml) was refluxed for 2 hr. Ac_2O was removed by evaporation, and to the residue was added petroleum ether. The resulting crystals were filtered to give **15** as light yellow needles (1.0 g, 76%). mp 203—204°. *Anal.* Calcd. for $C_{19}H_{17}O_4N_3$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.85; H, 4.67; N, 11.93. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1750, 1795 (C=O). UV λ_{max}^{EtOH} nm (ε): 263 (14600), 350 (11900). NMR (in $CDCl_3$) τ: 7.20 (3H, s, CH_3), 7.53 (9H, s, $3CH_3$).

Acetylation of 6a and 10——**10** or **6a** (0.5 g) was refluxed with Ac_2O (25 ml) for 3 hr, and the resulting precipitate was collected to give O-monoacetate of **6a** (**17**) as colorless needles (0.42 g, 81%). mp 275—279° (decomp.). *Anal.* Calcd. for $C_{17}H_{15}O_3N_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 66.00; H, 4.68; N, 13.52. IR ν_{max}^{Nujol} cm^{-1}: 1670 (CONH), 1770 (O–CO).

Hydrolysis of 1,4-Dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (1)——A mixture of **1** (1 g) and 1% HCl (100 ml) was refluxed for 4 hr. After cooling, the resulting precipitate was collected to give a mixture of **19** and **20** (0.77 g, 99%). Separation of these isomers (**19**, **20**) was carried out using silica gel column chromatography. Elution with C_6H_6–acetone (10: 1) afforded **19**, and further elution with C_6H_6–acetone (2: 1) afforded **20**. **19**: 0.29 g (37%) of light yellow crystals, mp 269—271°. *Anal.* Calcd. for $C_{17}H_{16}O_2N_4$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.46; H, 5.23; N, 17.92. IR ν_{max}^{Nujol} cm^{-1}: 1660 (CONH). NMR (in CF_3COOD) τ: 0.32 (1H, s, proton at 5-position), 0.88 (1H, s, proton at 8-position). **20**: 0.33 g (42%) of colorless crystals, mp 297—299°. *Anal.* Calcd. for $C_{17}H_{16}O_2N_4$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.33; H, 5.14; N, 17.96. IR ν_{max}^{Nujol} cm^{-1}: 1670 (CONH). NMR (in CF_3COOD) τ: 0.11 (1H, s, proton at 5-position), 1.38 (1H, s, proton at 8-position).

1-Chloro-4-morpholino-7-phenylpyrido[3,4-*d*]pyridazine (21)——a) A mixture of **19** (0.2 g), $POCl_3$ (3 ml) and N,N-dimethylaniline (0.3 ml) was heated at 100° for 2 hr. After removal of excess $POCl_3$ by evaporation *in vacuo*, the residue was poured into ice water, neutralized with aq. $NaHCO_3$, and extracted with AcOEt. The extract was dried over Na_2SO_4 and evaporated to dryness. Recrystallization of the residue from EtOH gave **21** as yellow needles (0.14 g, 68%). mp 162—164°. *Anal.* Calcd. for $C_{17}H_{15}ON_4Cl$: C, 62.48; H, 4.63; N, 17.15; Cl, 10.85. Found: C, 62.25; H, 4.58; N, 17.23; Cl, 10.90. NMR (in $CDCl_3$) τ: 0.53 (1H, s, proton at 5-position), 1.77 (1H, s, proton at 8-position).

b) To a solution of **7a** (5 g) in $CHCl_3$ (250 ml) was added morpholine (3.6 g) at room temperature. After standing overnight in an ice box, the solvent was removed *in vacuo* at room temperature. The residue was recrystallized from EtOH to give **21**.

4-Chloro-1-morpholino-7-phenylpyrido[3,4-*d*]pyridazine (22)——0.14 g (68%) of **22**, light yellow prisms, mp 158—159°, was obtained from 0.2 g of **20** by employing essentially the same procedure with the preparation of **21**. *Anal.* Calcd. for $C_{17}H_{15}ON_4Cl$: C, 62.48; H, 4.63; N, 17.15; Cl, 10.85. Found: C, 62.07; H, 4.61; N, 16.95; Cl, 10.75. NMR (in $CDCl_3$) τ: 0.42 (1H, s, proton at 5-position), 2.00 (1H, s, proton at 8-position).

1,4-Dimorpholino-7-phenyl-5,6-dihydropyrido[3,4-*d*]pyridazine Hydrochloride (27)——To a solution of **1** (3 g) in CH_2Cl_2 (30 ml) and MeOH (300 ml) was added $NaBH_4$ (20 g), and the mixture was warmed at 60° for 1 hr. After removal of the solvent, the residue was extracted with AcOEt, dried over Na_2SO_4, and evaporated to dryness. The residue was added 10% HCl (30 ml) and the resulting insoluble substance was filtered off. To the filtrate was added acetone (20 ml), and the solution was allowed to stand in an ice box to precipitate 1.8 g (55%) of **27** as reddish orange prisms, mp 170—180°. *Anal.* Calcd. for $C_{21}H_{25}O_2N_5 \cdot HCl \cdot H_2O$: C, 58.13; H, 6.46; N, 16.15; Cl, 8.19. Found: C, 58.47; H, 6.50; N, 16.20; Cl, 8.22. NMR (in D_2O) τ: 5.45 (2H, s, CH_2).

1,4-Dimorpholino-5,6-dihydropyrido[3,4-*d*]pyridazine Derivatives (Table II)——a) A solution of 5-benzyl-1,4-dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (**8u**) (3 g) in AcOH (30 ml) was hydrogenated over 5% Pd-C at room temperature under atmospheric pressure. The catalyst was filtered and washed with hot EtOH. The combined filtrate was condensed to dryness, and to the residue was added ether and cooled to give **28a**. **28d** and **28e** were prepared from **8v** and **8w** respectively by the similar procedure, but the purification was difficult owing to the liability to oxidation.

b) To a solution of **1** or **29** (0.95 g) in THF (20 ml) was added dropwise a Grignard reagent prepared from Mg (20—60 eq.) and an alkyl halide ($C_6H_5CH_2Cl$ or *t*-BuBr) (20—60 eq.) in tetrahydrofuran (THF) (30 ml) at room temperature. After 30 min the reaction mixture was added to an aqueous solution of NH_4Cl, extracted with AcOEt, and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from ether to give **28a**, **28c**, or **30**.

c) To a solution of **1** (0.95 g) in THF (20 ml) was added dropwise a solution of benzyl lithium or phenyl lithium (40 eq.) in THF (30 ml) at room temperature with stirring. The reaction was continued for 30 min

and the reaction mixture was poured into H_2O, extracted with AcOEt, dried over Na_2SO_4 and evaporated. Recrystallization of the residue from ether gave **28a** or **28b.**

Oxidation of 7-Aryl-5-benzyl-1,4-dimorpholino-5,6-dihydropyrido[3,4-*d*]pyridazine with $K_3Fe(CN)_6$——To a solution of **28a, 28d,** or **28e** (0.47 g) in C_6H_6 (20 ml) was added a solution of KOH (1.5 g) in H_2O (3.5 ml), and then followed addition of a solution of $K_3Fe(CN)_6$ (3 g) in H_2O (20 ml) with vigorous stirring. After 1 hr, C_6H_6 layer was separated, washed with 10% NaOH and H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. Recrystallization of the residue from ether or EtOH gave **1, 8x,** and **8y,** respectively.

1,4-Dimorpholino-6-phenylphthalazine (**32**)——A mixture of 1,4-dichloro-6-phenylphthalazine[12] (0.5 g) and morpholine (5 ml) was heated at 120° for 2 hr. After removal of the excess morpholine *in vacuo*, H_2O was added to the residue. The filtration and recrystallization from EtOH of the resulting crystals gave **32** as pale yellow tablets (0.42 g, 60%). mp 193—195°. *Anal.* Calcd for. $C_{22}H_{24}O_2N_4$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.29; H, 6.39; N, 14.88.

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