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Studies on the Syntheses of N-Heterocyclic Compounds. V.[1] 2-Aryl-5,8-dichloropyrimido[4,5-*d*]pyridazine

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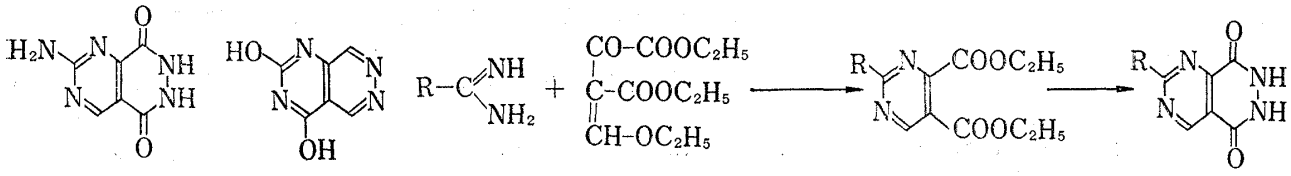
2-Substituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-diones (**6**) having a variety of substituents at 2-position were synthesized. Chlorination reaction of **6** were carried out, and it was found that only the compound which have aryl substituent at 2-position could be converted to 2-aryl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**14**), while other derivatives gave no corresponding dichlorides (**14**). 2,4-Diphenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (**9**) was not obtained because of its structural unstability caused by steric interference of phenyl group at 4-position.

Among tetraazanaphthalene derivatives a number of pharmacologically active compounds have been known. As for the pteridine derivatives many folic acid antagonists were synthesized since the discovery of folic acid and 2-phenyl-3,5,7-triaminopteridine (triamterene) is employed as a diuretic agent. 2,7-Bis(2-hydroxyethyl)amino-4,8-dipiperidinopyrimido-[5,4-*d*]pyrimidine (dipyridamol) is also employed as a useful cardio-vasodilator. We have been interested in the syntheses of the pyridazine-containing tri- and tetraazanaphthalene derivatives to test their pharmacological activities because 1-hydrazinophthalazine (hydralazine) is well known as hypotensive agent. We wish to report some findings on the chlorination and nucleophilic substitution in this system. As for the pyrimido[4,5-*d*]pyridazine ring system only two papers have previously been presented; syntheses of 2-amino-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (**1**) by Jones[3] and 2,4-dihydroxypyrimido[4,5-*d*]-pyridazine (**2**) and its derivatives by Castle, *et al.*[4,5] Since 2-substituted-5,8-dichloropyrimido[4,5-*d*]pyridazine (**14**) was expected to be obtained by chlorination of 2-substituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (**6**), synthesis of **6** were carried out according to the procedure in the preparation of **1**,[3] employing a variety of substituted amidines (**3**) (Chart 1 and 2).



1 2 3 4

Chart 1

5 6

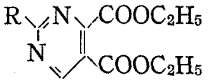
Chart 2

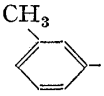
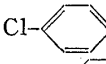
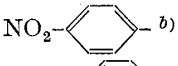
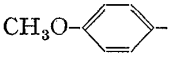
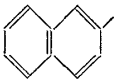
Thus substituted amidines (**3**) were condensed with ethyl ethoxymethyleneoxalacetate (**4**) to afford 2-substituted-4,5-diethoxycarbonylpyrimidines (**5**). **4** was considered to be a

1) S. Yurugi, A. Miyake, and M. Tomimoto, Part IV was presented at the 21th Annual Kinki district meeting of the Pharmaceutical Society of Japan, Osaka, November, 1971.
2) Location: *Jūso, Higashiyodogawa-ku, Osaka.*
3) R.G. Jones, *J. Am. Chem. Soc.*, **78**, 159 (1956).
4) L. DiStefano and R.N. Castle, *J. Heterocyclic Chem.*, **5**, 53 (1968).
5) T. Kinoshita and R.N. Castle, *J. Heterocyclic Chem.*, **5**, 846 (1968).

mixture of *cis* and *trans* isomers because in the nuclear magnetic resonance (NMR) spectrum (in $CDCl_3$) of **4**, which was prepared according to the literature,[6] methine signal appeared as doublet at 2.07 and 2.10 τ in a ratio of 4: 1. In view of the high yields of some diesters (**5**) in Table I, however, it is clear that both isomers were acceptable for the reaction with the amidine (**3**) to give **5**. Physical data and yields of the diesters (**5**) in this reaction are listed in Table I.

Table I. 2-Substituted-4,5-diethoxycarbonylpyrimidine (**5**)



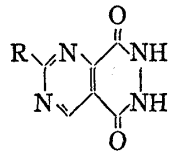
No.	R	mp or bp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	H	oil[a]	37.4	$C_{10}H_{12}O_4N_2$	—	—	—	—	—	—
b	CH_3 [7]	—	—	—	—	—	—	—	—	—
c	C_2H_5	128—129/0.2	39.6	$C_{12}H_{16}O_4N_2$	57.13	6.39	11.11	56.84	6.31	11.32
d	NH_2[4]	—	—	—	—	—	—	—	—	—
e	$HOCH_2$	153—160/0.1	29.5	$C_{11}H_{14}O_5N_2$	51.96	5.55	11.01	51.69	5.75	8.94
f	C_5H_{11}	oil[a]	51.5	$C_{15}H_{22}O_5N_2$	—	—	—	—	—	—
g		175—179/0.3 (80)	85.0	$C_{16}H_{16}O_4N_2$	63.98	5.37	9.33	64.29	5.50	9.30
h		150—180/0.6	76.5	$C_{17}H_{18}O_4N_2$	64.79	5.73	8.92	64.95	5.95	8.51
i		95—96	93.4	$C_{16}H_{15}O_4N_2Cl$	57.41	4.52	8.37	57.26	4.40	8.33
j	 [b]	124—125	83.6	$C_{16}H_{15}O_6N_3$	55.65	4.38	12.17	39.70	3.22	8.37
k		95	53.0	$C_{17}H_{18}O_5N_2$	61.81	5.49	8.48	62.00	5.39	8.50
l		94—95.8	53.1	$C_{20}H_{18}O_4N_2$	68.56	5.18	8.00	68.75	5.15	7.79
m		145 (decomp.)	87.1	$C_{15}H_{16}O_4N_3Cl$	53.34	4.77	12.47	53.19	4.75	12.67
n		65	89.3	$C_{14}H_{14}O_5N_2$	57.93	4.86	9.65	57.67	4.81	9.74
o		74	89.6	$C_{14}H_{14}O_4N_2S$	54.90	4.61	9.15	55.20	4.55	9.26

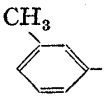
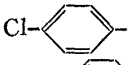
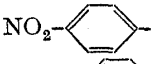
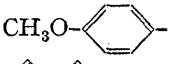
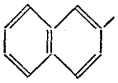
a) The structures of **6a** and **6f** was recoginized by NMR in crude products.
b) A further purification wa difficult. The structure was assigned by IR and NMR.

The reaction of the diesters (**5**) with hydrazine hydrate gave the hydrazonium salts of 2-substituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-diones (**6**), the treatment of which with hydrochloric acid in water afforded **6**. In the infrared (IR) spectrum of **6** in solid state a strong absorption band due to lactam carbonyl was observed at 1630—1650 cm^{-1} instead of the band due to two hydroxy groups on pyridazine ring. This fact suggests that **6** is represented by lactam structure. Physical data and yields of the diones (**6**) are summarized in Table II.

6) R.G. Jones, *J. Am. Chem. Soc.*, **73**, 3684 (1951).
7) T.J. Schwan and H. Tieckelmann, *J. Heterocyclic. Chem.*, **2**, 202 (1965).

TABLE II. 2-Substituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (6)



No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	H	>300	61.6	$C_6H_4O_2N_4$	43.91	2.46	34.14	36.96	3.15	32.98
b	CH_3[a]	>300	67.0	$C_7H_6O_2N_4 \cdot N_2H_4$	40.00	4.80	39.98	39.40	4.63	39.98
c	C_2H_5[a]	>300	100	$C_8H_8O_2N_4 \cdot N_2H_4$	42.85	5.39	37.48	42.35	5.39	37.48
d	NH_2[3]	—	—	—	—	—	—	—	—	—
e	$HOCH_2$[a]	>300	87.0	$C_7H_6O_3N_4 \cdot N_2H_4$	37.17	4.46	37.16	37.13	4.46	37.12
f	C_5H_{11}	>300	46.8	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.91	53.97	7.18	24.89
g		>300	95.0	$C_{12}H_8O_2N_4$	60.00	3.33	23.33	59.91	3.45	22.20
h		>300	59.5	$C_{13}H_{11}O_2N_4$	61.41	3.94	22.04	60.86	3.93	21.58
i		>300	95.7	$C_{12}H_8O_2N_4Cl$	52.47	2.57	20.40	51.98	2.59	20.66
j		>300	66.5	$C_{12}H_8O_4N_5$	50.53	2.47	24.56	47.30	2.82	22.99
k		>300	100	$C_{13}H_{11}O_3N_4$	57.77	3.73	20.73	54.70	4.02	19.97
l		>300	90.0	$C_{16}H_{10}O_2N_4$	66.21	3.48	19.29	65.64	3.48	20.12
m		>300	83.0	$C_{11}H_7O_2N_5$	54.77	2.93	29.04	54.52	2.99	29.01
n		>300	98.5	$C_{10}H_6O_3N_4$	52.18	2.63	24.34	51.88	2.72	24.29
o		>300	98.3	$C_{10}H_6N_4S \cdot H_2O$	45.46	3.05	21.21	45.43	2.99	21.26

a) The corresponding hydrazonium salt was analyzed.

In the case of the synthesis of 2,4-diphenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (**9**), however, treatment of the hydrazonium salt (**8**), which was prepared from diester (**7**),[8] with hydrochloric acid gave 2-amino-4,6-diphenyl-1,3-dihydropyrrolo[3,4-*d*]pyridazine-1,3-dione (**10**), in which the pyridazine ring of the expected compound (**9**) underwent a ring contraction. The structure of **10** was determined by the fact that the reaction of **10** with acetone gave 2-isopropylideneamino-4,6-diphenyl-1,3-dihydropyrrolo[3,4-*d*]pyridazine-1,3-dione (**11**). Compound (**8**) was acetylated by acetylchloride to give the monoacetylated compound (**12**) which has an acetyloxy group either at 5- or 8-position in **12**. Although the structure of **12** could not be determined directly, acetylation of **8** is considered to occur preferentially at 8-position because of the steric hindrance by phenyl group at 4-position. Therefore the structure of **12** is presumed to be 2,4-diphenyl-8-acetyloxy-5,6-dihydropyrimido[4,5-*d*]pyridazin-5-one (Chart 3).

8) V.M. Cherkasov, N.A. Kapran, and V.N. Zavatskii, *Kim. Geterosikl. Soedin*, 2, 350 (1969).

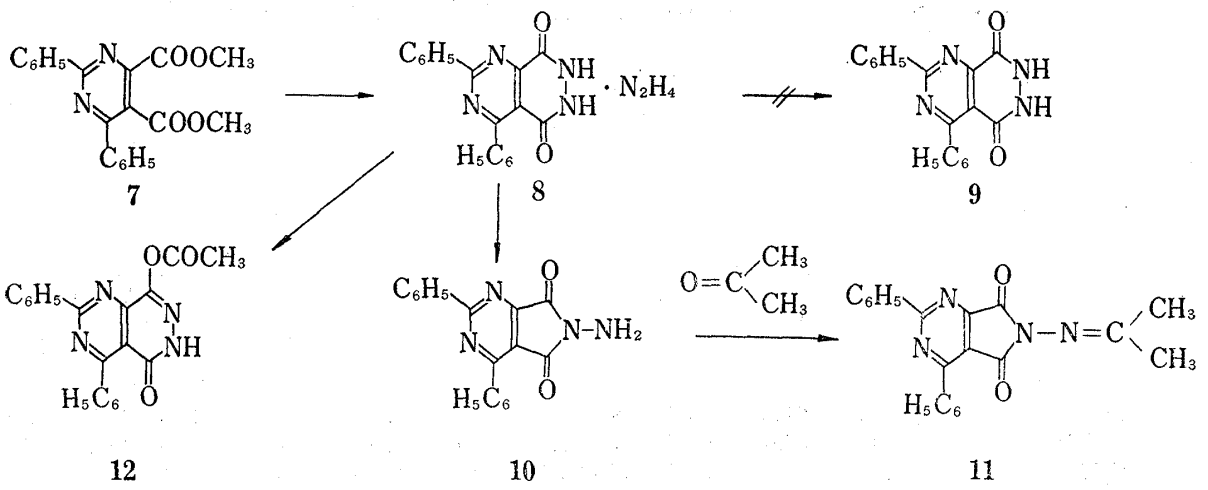


Chart 3

The fact that **10** was obtained instead of **9** might also be attributed to the interference between phenyl group at 4-position and carbonyl group at 5-position. The ring contraction is supposed to proceed as shown in Chart 4.

During the course of chlorination reaction of the diones (**6**), it was found that the reaction is much affected by the substituent at 2-position. In chlorination of **6a—f** which have nonaromatic group at 2-position, none of the corresponding dicloride (**14**) was obtained even under a variety of chlorinating conditions. On the other hand, compound (**6g—o**) which have an aryl group at 2-position were readily chlorinated by heating in a mixture of phosphorous oxychloride and phosphorous pentachloride to give 2-aryl-5,8-dichloropyrimido-[4,5-*d*]pyridazine (**14g—o**) in high yields. Physical data and yields of the dichlorides (**14g—o**) is shown in Table III.

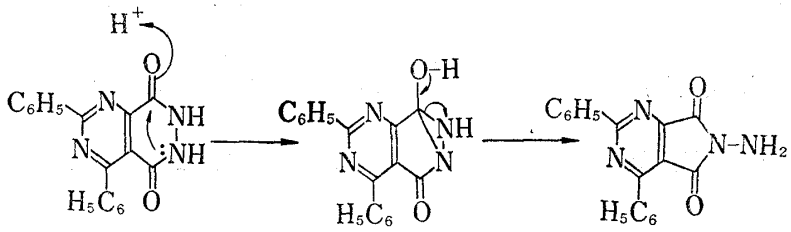


Chart 4

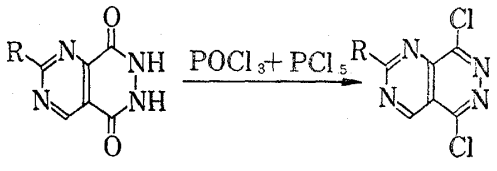
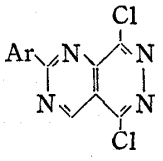


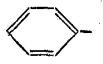
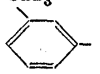
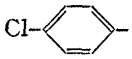
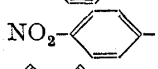
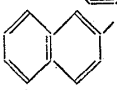
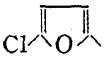
Chart 5

Chlorination of 2-(4-methoxyphenyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (**6k**), however, led to recovery of starting material accompanied by partial decomposition owing to its insolubility to solvents. In order to examine effects of substituents on the benzene ring toward chlorination, the preparation of 2-(2-substituted-phenyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-diones was undertaken, but none of them could be obtained owing to the difficulty in the preparation of the starting material, 2-substituted-phenylamidines. In the chlorination of **6n**, 5-position of furyl group was chlorinated to give 2-[2-(5-chloro)furyl]-5,8-dichloropyrimido[4,5-*d*]pyridazine (**14n**).

Although it does not seem to be easy to explain theoretically the fact that the reactivity in the chlorination of **6** was affected by the substituent at 2-position of **6**, a brief survey of literatures on the chlorination of condensed pyridazine-diones (**15**) was made expecting to clarify the reaction. Phthalazine-1,4-dione (**16**) has been converted to 1,4-dichlorophthala-

TABLE III. 2-Aryl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**14**)



No.	Ar	mp (°C)	Yield (%)	Formula	Method[a]	Analysis (%) Calcd. C	H	N	Found C	H	N
g		212—214	90.0	$C_{12}H_6Cl_2N_4$	A, B	51.99	2.18	20.22	51.82	2.04	19.98
h		175—177	73.0	$C_{13}H_8Cl_2N_4$	A, B	53.61	2.75	19.24	53.34	2.69	19.43
i		245—246	85.0	$C_{12}H_5Cl_3N_4$	A	46.26	1.62	17.98	40.48	2.02	14.59
j		240—242	87.0	$C_{12}H_5Cl_2N_5O_2$	A	44.74	1.56	21.74	44.66	1.23	21.80
l		>300	99.1	$C_{16}H_8Cl_2N_4$	A	58.69	2.47	17.21	62.56	3.40	16.95
m		180—185	87.0	$C_{11}H_5Cl_2N_5$	C	47.50	1.80	25.19	47.90	1.75	24.85
n		159	43.0	$C_{10}H_3ON_4Cl_3$	A	39.83	1.00	18.58	39.56	1.21	18.26
o		180	93.0	$C_{10}H_4N_4Cl_2S$	A	42.42	1.42	19.78	42.79	1.39	20.12

a) Three preparative procedures were described in experimenatal section.

zine (**17**) by the reaction with phosphorous pentachloride,[9] or with phosphorous oxychloride and phosphorous pentachloride.[10]

As for triazanaphthalene-dione system, two examples have hitherto been reported; chlorination of 5,6,7,8-tetrahydropyrido[2,3-*d*]pyridazine-5,8-dione (**18**) with phosphorous oxychloride and dimethylaniline to give the corresponding dichloride in 78% yield,[11] and chlorination of 5,6,7,8-tetrahydropyrido[3,4-*d*]pyridazine-5,8-dione (**19**) with phosphorous oxychloride and pyridine to give the corresponding dichloride in 65% yield.[12] Thus, in the case of triazanaphthalenes the chlorination proceeded only in the presence of bases as catalysts. On the other hand, chlorination of tetraazanaphthalene-diones which have two more ring-nitrogens than **16** has been extremely difficult. The only successful example in this series has been reported in the case of 5,6,7,8-tetrahydropyrazino[2,3-*d*]pyridazine-5,8-dione (**20**),[13] although yields of the corresponding dichloride was markedly low. Chlorination of 5,6,7,8-tetrahydropyridazino[4,5-*c*]pyridazine-5,8-dione (**21**)[14] and 5,6,7,8-tetrahydropyridazino[4,5-*d*]pyridazine-5,8-dione (**22**)[15] have been reported to have failed, and our attempt to chlorinate 5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (**6a**) was also unsuccessful.

9) H.D.K. Drew and H.H. Hatt, *J. Chem. Soc.*, **1937**, 16.
10) T. Satoda, F. Kusuda, and K. Mori, *Yakugaku Zasshi*, **82**, 233 (1962).
11) Y. Nitta, I. Matsuura, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **13**, 586 (1965).
12) I. Matsuura and K. Okui, *Chem. Pharm. Bull.* (Tokyo), **17**, 2266 (1969).
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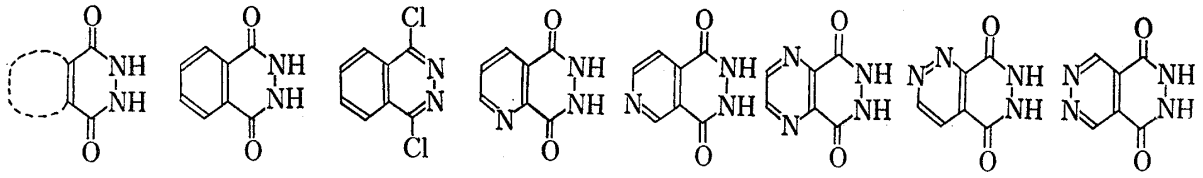
15) L.C. Dorman, *J. Heterocyclic Chem.*, **4**, 491 (1967).

From the above facts it seems to be clear that chlorination of diones (**15**) becomes more and more difficult as the number of ringnitrogen introduced into the benzene ring in **16** increases.

Although nothing has been reported with respect to the mechanism of chlorination of these diones (**15**), these results led us to the following discussion on the chlorination process of the condensed pyridazine-diones (**15**). 1,2,3,4-Tetrahydrophthalazine-1,4-dione (**16**) exists in dilactam form in solid state, but an equilibrium exists among dilactam form (**16**), lactam-hydroxy form (**23**) and dihydroxy form (**24**) in a solution.



15 16 17 18 19 20 21 22

Chart 6

It is well known[16–18] that the first step of chlorination of lactam is acylation of hydroxy form lactam by chlorinating agents such as phosphorous oxychloride, phosphorous pentachloride and so on, and the second step is the nucleophilic substitution of acyloxy group by chloride ion to afford chloride. In the case of 16 both the monohydroxy form (**23**) and the dihydroxy form (**24**) can undergo acylation by chlorinating agent finally to effect the diacylated compound (**27**).

Although the compound (**27**) was not isolated in the course of the chlorination, formation of 1,4-diacetyloxyphthalazine (**28**) in our study suggests the presence of **27** as an intermediate.

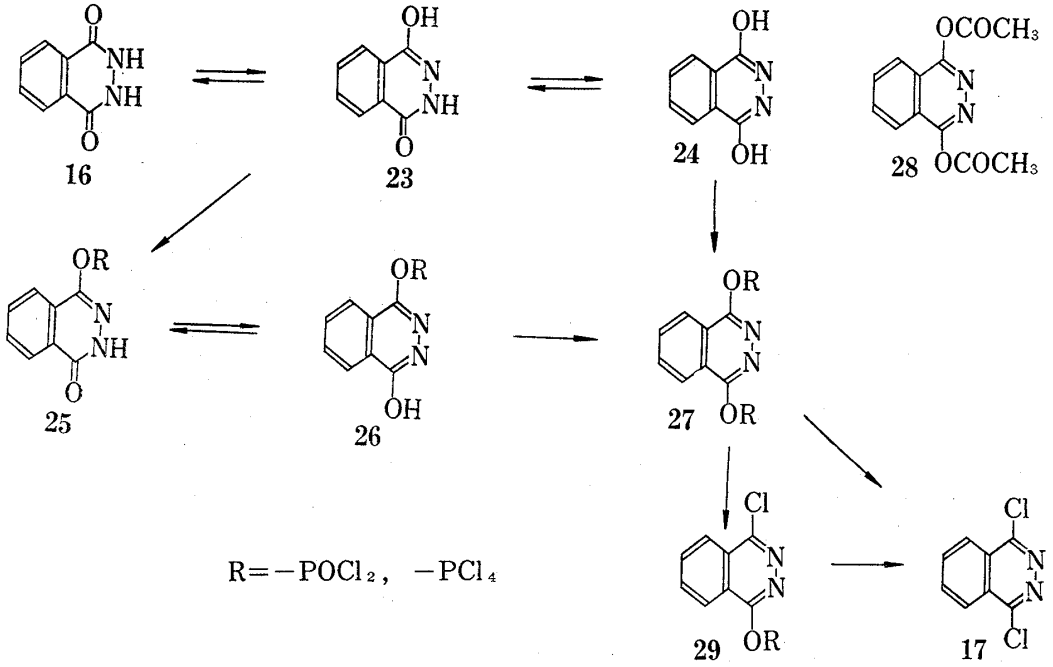


Chart 7

16) A. Albert, *J. Chem. Soc.*, **1960**, 1790.
17) H. Rapoport and A.D. Batcho, *J. Org. Chem.*, **28**, 1753 (1963).
18) J.G. Murray and C.R. Hauser, *J. Org. Chem.*, **19**, 2008 (1954).

It was found that 1-chloro-3,4-dihydrophthalazin-4-one (**30**) which was obtained by partial hydrolysis of **17** did not undergo chlorination. This is probably because the equilibrium between lactam form (**30**) and enol form (**31**) is on the side of **30** owing to the inductive effect of chlorine atom at 4-position (Chart 8). Therefore the possibility of intervention of compound (**30**) in the chlorination process to give **17** is excluded.

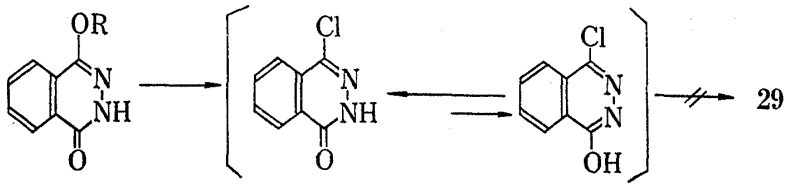


Chart 8

These facts suggest that the enolization of lactam carbonyl group is essential to the chlorination of the lactam. This principle can also be applied to chlorination of triaza- or tetraazanaphthalene-diones. Electron density of the ring carbon atom in a fusedpyridazine ring will be decreased when nitrogen atoms are introduced into the adjacent ring owing to "Resonance effect",[19] so that enolization of lactam carbonyl group in the pyridazine ring would become more difficult as the number of introduced nitrogen increases. As described earlier, chlorination of 2-substitutedpyrimido[4,5-*d*]pyridazine-5,8-dione (**6**) to afford dichloride proceeds only when substituent at 2-position is aryl group. This shows that the aryl group at 2-position made some contribution to the chlorination of **6**. Although the higher solubility of aryl-substituted **6** appeared to be one of reasons, this possibility is unlikely because $\mathbf{6_f}$ which has a lipophilic amyl group could not be converted to the dichloride (**14**).

Aryl group at 2-position in **6** has very little steric effect to the substituent at 5- or 8-position because they have enough distance not to interfere each other. Hence it is suggested that the aryl group assists the enolization of lactam carbonyl group by some electronic effect. The fact that treatment of $\mathbf{6_g}$ with acetic anhydride led to 2-phenyl-5,8-diacetyloxy-

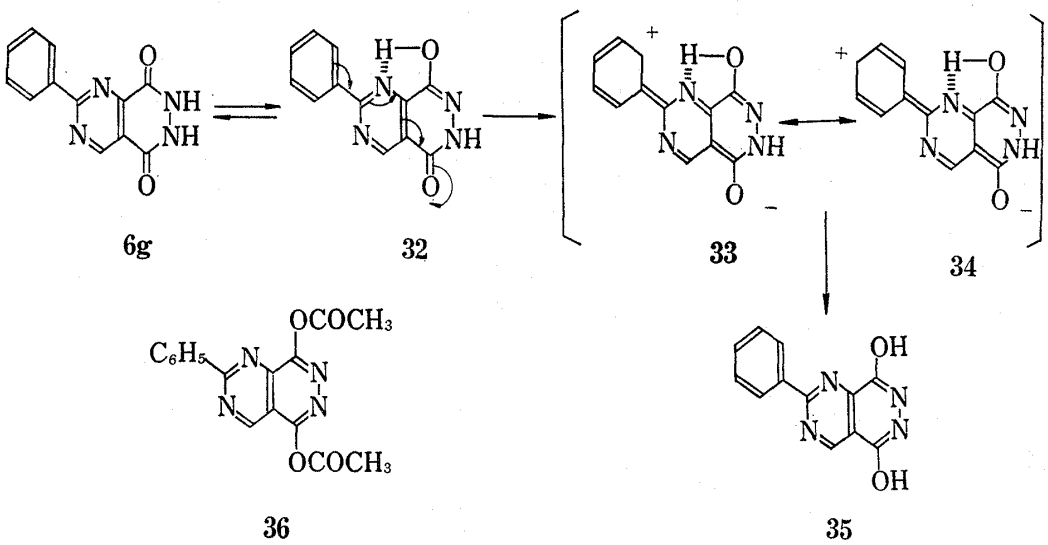


Chart 9

19) A. R. Katritzky, A. J. Boulton and J. M. Lagowski (eds.), "Advances in Heterocyclic Chemistry," Vol. 3, Academy Press, New York and London, 1964.

pyrimido[4,5-*d*]pyridazine (**36**) but acetylation of **6a** and **6f** were unsuccessful would be considered to support the above suggestion. This electronic effect might be interpreted as follows, which is illustrated taking the case of 2-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]-pyridazine-5,8-dione (**6g**) as an example (Chart 9): The carbonyl group at 8-position can be readily enolized due to the "Peri effect"[20] by the ring nitrogen at 1-position and exist as the structure **32**, while enolization of the carbonyl group at 5-position, on the other hand, is considered to be promoted by the resonance effect of the phenyl group which is located at the favorable 2-position.

Experimental

Substituted Amidines (3)——All the amidines used in this paper were prepared according to the method in the literature.[21] The general procedure is as follows: Into a solution of nitrile (1.11 mole) and EtOH (1.11 mole) in C_6H_6 (200 ml) was passed HCl gas under cooling for about 5 hr. After the reaction mixture was allowed to stand in ice box overnight, ether (500 ml) was added to it and the resulting crystals were filtered to give the hydrochloride of the substituted imido-ether. To a cooled mixture of 50% NaOH (215 ml) and $CHCl_3$ (1610 ml) was added the hydrochloride of imido-ether with stirring. $CHCl_3$ layer was separated, washed with H_2O twice and dried. The solvent was evaporated *in vacuo* to give free substituted imido-ether as colorless oil, which was dissolved in 75% EtOH (1130 ml) and an equimolecular weight of NH_4Cl was added. After the resulting solution was heated at 75° for 4 hr, the solvent was evaporated *in vacuo* to give the hydrochloride of the substituted amidine (3) as crystals.

2-Substituted-4,5-diethoxycarbonylpyrimidine (5) (**Table I**)——The general procedure is as follows: To a solution of the hydrochloride of 3 (0.723 mole) in EtOH (700 ml) was added dropwise a solution of EtONa prepared from Na (18 g) and EtOH (350 ml) under cooling. To the solution was added 188 g (0.77 mole) of ethyl ethoxymethyleneoxalacetate (4) in about 2 hr and the mixture was stirred for 3 hr. The reaction mixture was allowed to stand at room temperature overnight and the solvent was removed. The residue was extracted with $CHCl_3$, washed with dil-HCl, dried over Na_2SO_4 and the solvent was evaporated to give crystalline residue. After a small protion of MeOH was added to it, it was allowed to stand in an ice box overnight to give **5** as colorless crystals of free base. 2-(2-Pyridyl)-4,5-diethoxycarbonylpyrimidine (**5m**) was crystallized as the hydrochloride salt.

2-Substituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (6) (**Table II**)——To a solution of **5** (0.0397 mole) in MeOH (250 ml) was added 80% $N_2H_4 \cdot H_2O$ (12.0 g) and the mixture was refluxed for 3—4 hr. The resulting yellow crystals were filtered to give the hydrazonium salts of **6**. It was suspended in H_2O (200 ml) and acidified with 10%-HCl with stirring [AcOH was employed in the case of 2-(2′-pyridyl)-derivative (**6n**)]. After color of the crystals changed from yellow to colorless, the resulting solid was filtered, washed with H_2O and MeOH to give 6 as colorless powder.

Hydrazonium salt (8) **of 2,4-diphenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione**——To a solution of 2,4-diphenyl-5,6-dimethoxycarbonylpyrimidine (7) (1.8 g) in MeOH (50 ml) was added $N_2H_4 \cdot H_2O$ (2.0 g). After it was refluxed for 1 hr, the resulting crystals were filtered, washed with a small portion of MeOH and dried to give **8** as slight yellow needles (1.3 g, 72.2%), mp 236—238° (decomp.). *Anal.* Calcd. for $C_{18}H_{16}O_2N_4$: C, 62.06; H, 4.63; N, 24.13. Found: C, 62.10; H, 4.63; N, 24.65. IR (in Nujol) cm^{-1}: 3250 (NH), 1675 (CONH).

2-Amino-4,6-diphenyl-1,3-dihydropyrrolo[3,4-*d*]pyrimidine-1,3-dione (10)——Hydrazonium salt (8) (3.0 g) was suspended in H_2O (60 ml) and it was acidified with 10% HCl (20 ml) with stirring at room temperature. After stirring was continued for 6 hr, the resulting crystals were filtered, washed with H_2O, dried *in vacuo* to give **10** as colorless powder (2.8 g, 86.8%), mp 261—264°. *Anal.* Calcd. for $C_{18}H_{12}O_2N_4$: C, 68.35; H, 3.82; N, 17.71. Found: C, 67.95; H, 3.81; N, 17.74. IR (in Nujol) cm^{-1}: 3150 (NH), 1795, 1710 (C=O).

2-N-Isopropyridenamino-4,6-diphenylpyrrolo[3,4-*d*]pyrimidine-1,3-dione (11)——To a solution of 10 (0.5 g) in Me_2CO (5 ml) was added 5 drops of AcOH and the mixture was refluxed for 1 hr. After the solvent was evaporated *in vacuo*, H_2O was added to the oily residue and the resulting crystals were filtered to give 11 as slight yellow fine needles (0.4 g, 71%), mp 163—164°. *Anal.* Calcd. for $C_{21}H_{16}O_2N_4$: C, 70.97; H, 4.53; N, 15.72. Found: C, 71.08; H, 4.48; N, 15.80. IR (in Nujol) cm^{-1}: 1780, 1706 (C=O). NMR (in $CDCl_3$) τ: 7.67 (3H, s, CH_3), 8.00 (3H, s, CH_3).

2,4-Diphenyl-8-acetyloxy-5,6-dihydropyrimido[4,5-*d*]pyridazin-5-one (12)——To a solution of 8 (1.0 g) in pyridine (5 ml) was added CH_3COCl (1.0 g) and the mixture was allowed to stand at room temperature

20) A.R. Katritzky (ed.), "Advances in Heterocyclic Chemistry," Vol. 1, Academy Press, New York and London, 1963.

21) A.W. Dox, "Organic Syntheses," Coll. Vol. I, ed. by H. Gilman, John Wiley and Sons, Inc., New York, 1941, p. 6.

overnight. After the solvent was evaporated *in vacuo*, ice water was added. The resulting crystals were filtered and recrystallized from MeOH to give **12** as colorless needles (1.0 g, 97.5%), mp 225—226°. *Anal.* Calcd. for $C_{20}H_{14}O_3N_4$: C, 67.03; H, 3.94; N, 15.64. Found: C, 67.23; H, 3.97; N, 15.55. IR (in Nujol) cm^{-1}: 1740 ($CH_3 \cdot CO \cdot O$), 1690 (CONH). NMR (in d_6-DMSO) τ: −0.80 (1H, s, NH), 7.90 (3H, s, CH_3CO).

2-Aryl-5,8-dichloropyrimido[4,5-*d*]pyridazine (14) (Table III)——General procedure is as follows: A) The dione (**6**) (5.0 g) was heated with a mixture of $POCl_3$ (100 ml) and PCl_5 (20 g) at 100—120° for 2—10 hr. After cooling, $POCl_3$ was removed *in vacuo* and the residue was poured into ice water. The resulting crystals were filtered and recrystallized from hexane to give **15** as colorless needles.

B) After **8** was treated in similar manner to A), the reaction mixture was allowed to stand at room temperature overnight. The dichloride (**14**) was crystallized from the reaction mixture as a colorless needles and the crystals were filtered, washed with a small portion of ether to give **14**.

C) **6m** (1.0 g) was refluxed with a mixture of $POCl_3$ (50 ml) and PCl_5 (1.0 g) for 20 hr. After cooling, $POCl_3$ was removed *in vacuo* and the residue was poured into ice water. The resulting solution was neutralized with $NaHCO_3$ to give **14m.**

1,4-Diacetyloxyphthalazine (29)——A mixture of **16** (1.0 g) and Ac_2O was refluxed for 4 hr. After evaporation of Ac_2O, the residue was treated with H_2O to give crystals which were filtered and recrystallized from AcOEt to give 27 as colorless needles (1.2 g, 80%), mp 132—134°. *Anal.* Calcd. for $C_{12}H_{10}O_4N_2$: C, 58.54; H, 4.00; N, 11.38. Found: C, 59.32; H, 3.82; N, 11.42.

1-Chloro-3,4-dihydrophthalazin-4-one (30)——1,4-Dichlorophthalazine (1) (2.0 g) was refluxed in 10% NaOH (50 ml) for 1 hr. Insoluble substance was filtered and the filtrate was adjusted to pH 2—3 with conc-HCl. The resulting crystals were filtered and recrystallized from EtOH to give **30** as colorless granules (1.6 g, 88.9%), mp 250—260° (sublimation). *Anal.* Calcd. for $C_8H_5ON_2Cl$: C, 53.74; H, 2.77; N, 15.46. Found: C, 53.12; H, 2.61; N, 15.64. IR (in Nujol) cm^{-1}: 1665 (CONH).

2-Phenyl-5,8-diacetyloxypyrimido[4,5-*d*]pyridazine (36)——A mixture of **7** g (3.0 g) and Ac_2O (60 ml) was refluxed for 8 hr and allowed to stand at room temperature overnight. The resulting crystals from the reaction mixture were filtered and washed with ether to give **36** as colorless needles (1.8 g, 42%), mp 205—207°. *Anal.* Calcd. for $C_{16}H_{12}O_4N_4$: C, 59.26; H, 3.70; N, 17.28. Found: C, 59.17; H, 3.50; N, 17.27. IR (in Nujol) cm^{-1}: 1772 ($CH_3 \cdot CO \cdot O$).

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