The Synthesis of Pyrazolo[3,4-*d*]pyridazines. Photochemical Cyclization to Pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones with Subsequent Functionalization

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The synthesis of 1,3-disubstituted and 1,3,5-trisubstituted 1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones is conveniently performed by photochemical cyclization. Functionalization of the former compounds leading to the formation of 1,4-disubstituted and 1,3,4-trisubstituted 1*H*-pyrazolo[3,4-*d*]pyridazines is smoothly effected through pertinent nucleophilic substitutions.

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Studies on the synthesis of pyrazolo[3,4-*d*]pyridazine system, which is of biological and medicinal interest [1], have been increasingly developed by several groups of investigators since the presentation of 3-(β-DL-*erythro*-furanosyl)-4,7-dihydroxy-1*H*-pyrazolo[3,4-*d*]pyridazine (*C*-nucleotide) [2,3]. The majority of the usual synthetic approaches to obtain pyrazolo[3,4-*d*]pyridazines has utilized pyrazoles or pyrazolones with appropriate *ortho* functional groups, capable of forming the pyridazine rings, as starting material [4-9]. To our knowledge, however, there has not yet been any paper concerned with the synthetic route from pyridazines as starting materials except one report [10], in which 2-methyl-6-phenylpyridazin-3(2*H*)-one reacted in a 1,3-dipolar cycloaddition mode with 2-diazopropane to afford a pyrazolo[3,4-*d*]pyridazine derivative. Recently photochemical cyclization has been abundantly utilized for the synthesis of some condensed heterocycles [11]. We would here like to report a convenient synthesis of pyrazolo[3,4-*d*]pyridazines by photochemical cyclization to pyrazolo[3,4-*d*]-4(5*H*)-ones, which is comparable to the approach by ring contraction of pyridazino[4,5-*e*][1,3,4]-thiadiazin-8(7*H*)-ones [12], with subsequent functionalizations.

2-Substituted 5-(1-alkyl-2-alkylidenehydrazino)-4-chloro-3(2*H*)-pyridazinones **5**, the promising intermediates leading to formation of pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones **6**, were readily prepared from the corresponding 2-substituted 4,5-dichloro-3(2*H*)-pyridazinones **1** [13] by successive hydrazination, hydrazone formation and alkylation or methylhydrazination followed by hydrazone formation. 4-Chloro-5-hydrazino-2-methyl-3(2*H*)-pyridazinone (**2a**) [14] was reacted with benzaldehyde in ethanol under reflux for 2 hours to afford 5-benzylidenehydrazino-4-chloro-2-methyl-3(2*H*)-pyridazinone (**3a**) in 92% yield. Additional hydrazones **3b-h** were similarly prepared from other 2-substituted 4-chloro-5-hydrazino-3(2*H*)-pyridazinones **2b-d** [14,15] and appropriate aldehydes in good yields (Table 1). Alkylation of the hydrazones **3a-h** was carried out in dimethylformamide in the presence of anhydrous potassium carbonate with methyl iodide at room temperature or with benzyl chloride at 70° to yield the corresponding 2-substituted 5-(1-alkyl-2-alkylidenehydrazino)-3-(2*H*)-pyridazinones **5a-r**. Some of them, **5e-h** and **5p-r**, were also obtained from the 5-(1-methylhydrazino)-3(2*H*)-pyridazinone derivatives **4a,b** by interaction with aldehydes (Tables 2 and 3).

Table 1

Melting Points, Yields and Analytical Data for Compounds **3a-h**

Compound No.	R	R^2	Mp °C	Yield %	Molecular Formula	Analyses Calcd./(Found) C	H	N
3a	CH_3	C_6H_5	261-263	92	$C_{12}H_{11}ClN_4O$	54.87	4.22	21.33
						(54.98	4.22	21.43)
3b	CH_3	H	213-214	67	$C_6H_7ClN_4O$	38.62	3.78	30.02
						(38.71	3.71	29.91)
3c	C_6H_5	C_6H_5	200-202	77	$C_{17}H_{13}ClN_4O$	62.87	4.03	17.25
						(62.89	4.01	17.21)
3d	$PhCH_2$	C_6H_5	206-208	89	$C_{18}H_{15}ClN_4O$	63.81	4.46	16.54
						(63.61	4.27	16.77)
3e	$PhCH_2$	2-CH_3O-C_6H_4	216-218	51	$C_{19}H_{17}ClN_4O_2$	61.88	4.65	15.19
						(61.67	4.55	15.24)
3f	H	H	235-237	64	$C_5H_5ClN_4O$	34.80	2.29	32.47
						(34.97	2.41	32.59)
3g	H	CH_3	246-248	89	$C_6H_7ClN_4O$	38.62	3.78	30.02
						(38.53	3.73	30.06)
3h	H	C_6H_5	>300 [a]	90	$C_{11}H_9ClN_4O$	53.13	3.65	22.53
						(52.96	3.55	22.56)

[a] Lit mp 304° dec [15].

Scheme 1

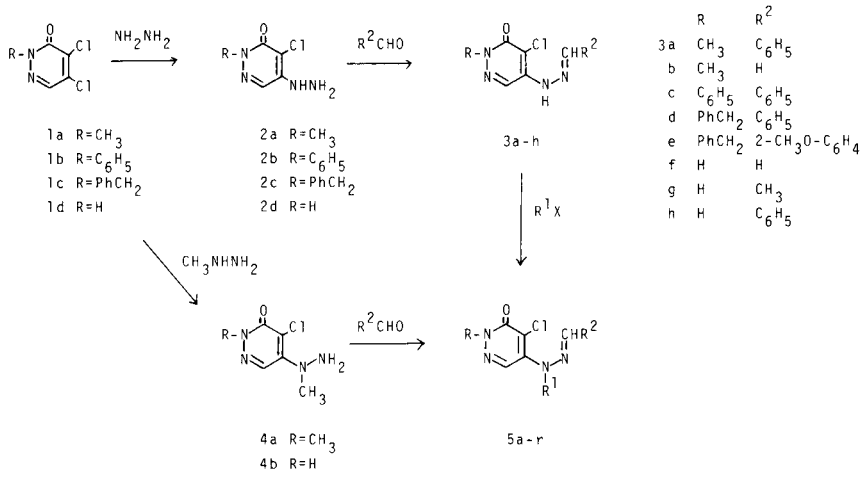


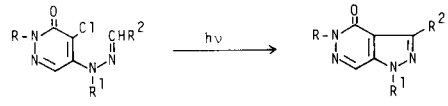
Table 2

Substituents (R, R^1 and R^2) for Compounds **5a-r** and **6a-r**

Compound **5** and **6**	R	R^1	R^2
a	CH_3	CH_3	C_6H_5
b	CH_3	CH_3	H
c	CH_3	$PhCH_3$	C_6H_5
d	CH_3	$PhCH_3$	H
e	CH_3	CH_3	4-Cl-C_6H_4
f	CH_3	CH_3	4-Br-C_6H_4
g	CH_3	CH_3	4-CH_3O-C_6H_4
h	CH_3	CH_3	2-CH_3O-C_6H_4
i	C_6H_5	CH_3	C_6H_5
j	C_6H_5	$PhCH_2$	C_6H_5
k	$PhCH_2$	CH_3	C_6H_5
l	$PhCH_2$	$PhCH_2$	2-CH_3O-C_6H_4
m	$PhCH_2$	$PhCH_2$	H
n	$PhCH_2$	$PhCH_2$	CH_3
o	$PhCH_2$	$PhCH_2$	C_6H_5
p	H	CH_3	H
q	H	CH_3	CH_3
r	H	CH_3	C_6H_5

The photochemical cyclization of 2-unsubstituted and 2-substituted 5-(1-alkyl-2-alkylidenehydrazino)-4-chloro-3(2*H*)-pyridazinones **5a-r** to 1,3-disubstituted and 1,3,5-trisubstituted 1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones **6a-r** was performed as follows: A solution of **5a** (1 mmole) in benzene (200 ml) was irradiated with a 100 W high-pressure mercury lamp surrounded by a water-cooled Pyrex filter at room temperature for 4 hours to afford **6a** in 86% yield. Of other alkylidenehydrazino derivatives **5b-r**, the photochemical reaction proceeded smoothly in benzene or acetone with a 100 W high-pressure mercury lamp, though a 400 W high-pressure one was employed in the case of the reactants **5p**, **5q** and **5r** (Tables 2 and 4).

Scheme 2



The pyrazole or benzopyrazole ring has been known to undergo a photochemical isomerization leading to the corresponding imidazole or benzimidazole [16,17], however, the compound **6a** was found unsusceptible to the phototransposition even on the prolonged irradiation with a 100 W high-pressure or a 30 W low-pressure mercury lamp. In this connection, 1,5-dimethyl-2-phenylimidazo[4,5-*d*]pyridazin-4(5*H*)-one (**9**) was prepared, together with formation of its isomer **9'**, by methylation of 5-methyl-2-phenylimidazo[4,5-*d*]pyridazin-4(5*H*)-one (**8**), obtained by starting with 4,5-diamino-2-methyl-3(2*H*)-pyridazinone (**7**) [18] according to the method of Martin and Castle [19].

Functionalization of 1-methyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**6p**) and 1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**6r**) leading to the formation of 1-methyl-1*H*pyrazolo[3,4-*d*]pyridazine (**11a**), 1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**11b**), 1,4-disubstituted 1*H*-pyrazolo[3,4-*d*]pyridazines **10a,12a,13a,b,f,h** and 1,3,4-trisubstituted 1*H*-pyrazolo[3,4-*d*]pyridazines **10b,12b,13c,d,e,g** was smoothly effected as follows: Reaction of the compounds **6p** and **6r** with phosphorus oxychloride gave 4-chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyridazine **10a**) and the corresponding 3-phenyl derivative **10b** in respective yields of 48% and 57%. Catalytic hydrogenolysis of **10a** and **10b** with palladium on charcoal in methanol afforded the dechlorinated products **11a** and **11b** in 52%

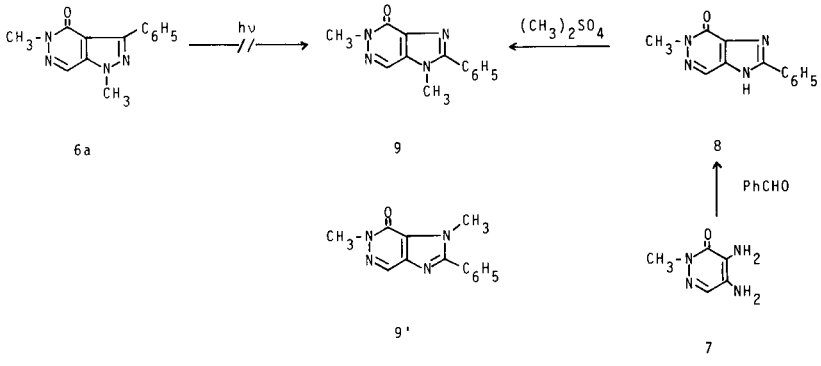
Table 3

Physical and Spectral Data for Compounds **5a-r**

Compound No.	Yield %	Mp [a] °C	Method [b]	Starting Material	Molecular Formula	Analyses Calcd./(Found) C	H	N	IR cm^{-1} [c] ν C=O	^{1}H-NMR [d] δ ppm
5a	89	119-120	A	**3a**	$C_{13}H_{13}ClN_4O$	56.42 (56.39)	4.47 4.68	20.25 20.32)	1650	3.58 (3H, s), 3.84 (3H, s), 7.30-7.90 (5H, m), 7.75 (1H, s), 8.33 (1H, s)
5b	89	137-138	A	**3b**	$C_7H_9ClN_4O$	41.91 (41.78	4.52 4.50	27.93 27.87)	1635	3.35 (3H, s), 3.75 (3H, s), 6.40 (1H, d) [e], 6.65 (1H, d) [e], 8.08 (1H, s)
5c	90	167-168	A	**3a**	$C_{19}H_{17}ClN_4O$	64.68 (64.59	4.86 4.87	15.88 15.89)	1640	3.85 (3H, s), 5.31 (2H, s), 7.15-7.75 (10H, m), 8.42 (1H, s)
5d	63	118-119	A	**3b**	$C_{13}H_{13}ClN_4O$	56.43 (56.49	4.74 4.61	20.25 20.31)	1630	3.78 (3H, s), 4.90 (2H, s), 6.38 (2H, s), 7.27 (5H, s), 8.11 (1H, s)
5e	84	212-214	B	**4a**	$C_{13}H_{12}Cl_2N_4O$	50.18 (50.22	3.89 3.81	18.01 18.10)	1625	3.54 (3H, s), 3.74 (3H, s), 7.25-7.74 (4H, m), 7.89 (1H, s), 8.20 (1H, s)
5f	87	191-193	B	**4a**	$C_{13}H_{12}BrClN_4O$	43.91 (44.01	3.40 3.31	15.75 15.84)	1630	3.64 (3H, s), 3.91 (3H, s), 7.61 (4H, s), 7.82 (1H, s), 8.14 (1H, s)
5g	85	131-133	B	**4a**	$C_{14}H_{13}ClN_4O_2$	54.82 (54.89	4.93 5.04	18.26 18.18)	1645	3.49 (3H, s), 3.74 (3H, s), 3.80 (3H, s) 6.76-7.59 (4H, m), 8.18 (1H, s), 8.21 (1H, s)
5h	89	145-147	B	**4a**	$C_{14}H_{13}ClN_4O_2$	54.82 (54.90	4.93 4.93	18.26 18.30)	1620	3.57 (3H, s), 3.79 (3H, s), 3.90 (3H, s), 7.33-7.97 (4H, m), 8.07 (1H, s), 8.28 (1H, s)
5i	90	181-182	A	**3c**	$C_{18}H_{13}ClN_4O$	63.81 (63.59	4.46 4.53	16.53 16.49)	1650	3.63 (3H, s), 7.30-7.82 (11H, m), 8.53 (1H, s)
5j	88	148-149	A	**3c**	$C_{24}H_{19}ClN_4O$	69.48 (69.27	4.62 4.62	13.50 13.42)	1640	5.37 (2H, s), 7.35-7.96 (16H, m), 8.64 (1H, s)
5k	89	160-162	A	**3d**	$C_{19}H_{17}ClN_4O$	64.68 (64.79	4.86 4.75	15.88 16.04)	1640	3.52 (3H, s), 5.33 (2H, s), 7.40 (5H, s), 7.70 (1H, s), 7.00-7.80 (5H, m), 8.35 (1H, s)
5l	80	127-129	A	**3e**	$C_{26}H_{23}ClN_4O_2$	68.04 (68.06	5.05 5.04	12.21 12.23)	1630	3.55 (3H, s), 5.18 (2H, s), 5.30 (2H, s), 6.65-7.85 (14H, m), 8.26 (1H, s)
5m	56	114-115	C	**3f**	$C_{19}H_{17}ClN_4O$	64.68 (64.43	4.86 4.79	15.88 15.83)	1630	5.09 (2H, s), 5.33 (2H, s), 6.40 (2H, s), 7.29-7.52 (10H, m), 8.26 (1H, s)
5n	61	116-117	C	**3g**	$C_{20}H_{19}ClN_4O$	65.48 (65.54	5.22 5.26	15.27 15.29)	1630	1.90 (3H, d) [f], 5.10 (2H, s), 5.37 (2H, s), 6.49 (1H, q) [f], 7.22-7.50 (10H, m), 8.36 (1H, s)
5o	59	100-102	C	**3h**	$C_{25}H_{21}ClN_4O$	70.01 (70.21	4.93 4.95	13.06 13.02)	1630	5.32 (2H, s), 5.42 (2H, s), 7.20-7.75 (15H, m), 7.61 (1H, s), 8.52 (1H, s)
5p	90	243-245	B	**4b**	$C_6H_7ClN_4O$	38.62 (38.45	3.78 3.73	30.03 30.27)	1655	3.67 (3H, s), 7.98 (2H, s), 8.88 (1H, s)
5q	83	205-206	B	**4b**	$C_7H_9ClN_4O$	41.91 (41.97	4.52 4.50	27.93 27.98)	1640	2.23 (3H, d) [g], 3.62 (3H, s), 7.65 (1H, q) [g], 8.76 (1H, s)
5r	89	199-200	B	**4b**	$C_{12}H_{11}ClN_4O$	54.89 (54.94	4.22 4.17	21.33 21.58)	1630	3.81 (3H, s), 7.30-7.95 (5H, m), 8.13 (1H, s), 9.10 (1H, s)

[a] All compounds were recrystallized from ethanol. [b] Method A: alkylation of **3a-e**; Method B: hydrazonation of **4a-b**; Method C: dibenzylation of **3f,g,h**. [c] Potassium bromide disks. [d] All compounds were measured in deuteriochloroform except **5e** (in DMSO-d_6) and **5f,p,q,r** (in trifluoroacetic acid). [e] J = 10.5 Hz. [f] J = 5.0 Hz. [g] J = 5.5 Hz.

Scheme 3



and 51% yields, respectively. The 4-thiol derivatives **12a** and **12b** were prepared by the reaction of **6p** and **6r** with phosphorus pentasulfide in a boiling pyridine solution [20] in respective yields of 76% and 78%. The 4-chloro-derivative **10a** and **10b** were easily reacted with several nucleophilic reagents (sodium alkoxides, amines and sodium benzylmercaptide) to yield the corresponding 4-alkoxy, 4-amino 4-benzylthio-1*H*-pyrazolo[3,4-*d*]pyridazine deriva-

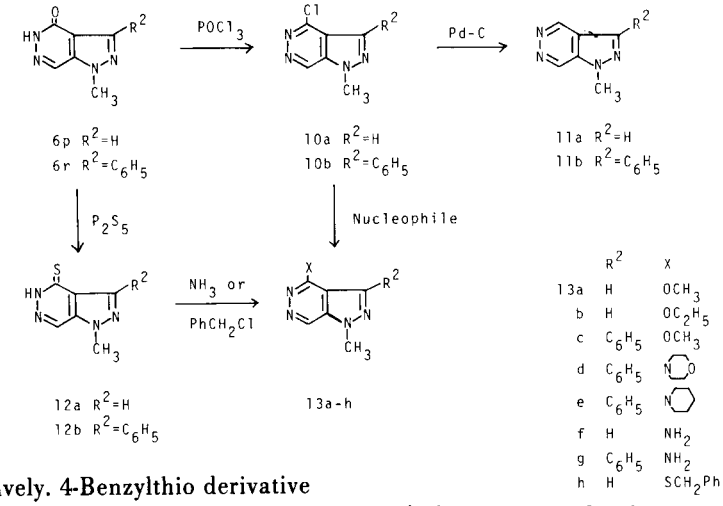
Table 4

Physical and Spectral Data for Compounds **6a-r**

Compound No.	Yield %	Mp [a] °C	Reaction Solvent	Molecular Formula	Analyses Calcd./(Found) C	H	N	IR cm^{-1} [c] ν C=O	^{1}H-NMR [d] δ ppm
6a	85	142-143	B	$C_{13}H_{12}N_4O$	64.99	5.03	23.32	1660	3.85 (3H, s), 4.00 (3H, s), 7.40-7.65 (3H, m),
					(65.12	5.01	23.27)		8.05 (1H, s), 8.30-8.60 (2H, m)
6b	86	208-210	A	$C_7H_8N_4O$	51.21	4.91	34.13	1650	3.82 (3H, s), 4.12 (3H, s), 8.19 (2H, s)
					(51.47	4.97	34.18)		
6c	84	135-137	B	$C_{19}H_{16}N_4O$	72.13	5.10	17.71	1645	3.87 (3H, s), 5.60 (2H, s), 7.30-7.80 (3H, m),
					(72.27	5.12	17.78)		8.00 (1H, s), 8.20-8.60 (2H, m)
6d	69	140-141	B	$C_{13}H_{12}N_4O$	64.98	5.03	23.32	1645	3.77 (3H, s), 5.53 (2H, s), 7.29 (5H, s), 7.94
					(65.02	5.21	23.11)		(1H, s), 8.20 (1H, s)
6e	55	220-222	A	$C_{13}H_{11}ClN_4O$	56.84	4.04	20.39	1640	3.72 (3H, s), 4.14 (3H, s), 7.40-7.61 (2H, m),
					(56.83	4.02	20.42)		8.36-8.52 (2H, m), 8.55 (1H, s)
6f	76	236-238	A	$C_{13}H_{11}BrN_4O$	48.92	3.47	17.55	15.35	3.99 (3H, s), 4.19 (3H, s), 7.67 (4H, s),
					(49.03	3.47	17.49)		8.59 (1H, s)
6g	52	199-201	A	$C_{14}H_{14}N_4O_2$	62.21	5.22	20.73	1650	3.80 (6H, s), 3.98 (3H, s), 6.81-7.02
					(62.12	5.31	20.79)		(2H, m), 7.91 (1H, s), 8.15-8.34 (2H, m)
6h	48	163-164	A	$C_{14}H_{14}N_4O_2$	62.21	5.22	20.73	1655	3.82 (3H, s), 3.97 (3H, s), 6.83-7.00 (3H, m),
					(62.30	5.18	20.68)		7.66-7.85 (1H, m), 8.11 (1H, s)
6i	76	199-200	A	$C_{18}H_{14}N_4O$	71.51	4.67	18.53	1675	4.09 (3H, s), 7.32-7.75 (8H, m), 8.22
					(71.59	4.61	18.75)		(1H, s) 8.30-8.55 (2H, m)
6j	79	175-176	A	$C_{24}H_{18}N_4O$	76.14	4.79	14.81	1660	5.63 (2H, s), 7.40 (5H, s), 7.30-7.70
					(75.86	4.75	14.95)		(8H, m), 8.10 (1H, s), 8.34-8.60 (2H, m)
6k	88	137-139	B	$C_{19}H_{16}N_4O$	72.14	5.10	17.71	1650	4.05 (3H, s), 5.46 (2H, s), 7.42 (5H, s) 7.27-7.70
					(72.07	5.04	17.89)		(3H, m), 8.11 (1H, s), 8.28-8.50 (2H, m)
6l	90	204-206	B	$C_{26}H_{22}N_4O_2$	73.67	5.25	13.08	1650	3.74 (3H, s), 5.30 (2H, s), 5.51 (2H, s),
					(73.92	5.25	13.26)		6.84-7.58 (14H, m), 7.87 (1H, s)
6m	68	155-156	B	$C_{19}H_{16}N_4O$	72.15	5.05	17.59	1635	5.37 (2H, s), 5.52 (2H, s), 7.18-7.48 (10H, m),
					(72.14	5.10	17.71)		7.94 (1H, s), 8.21 (1H, s)
6n	80	123-124	B	$C_{20}H_{18}N_4O$	72.76	5.53	16.68	1655	2.68 (3H, s), 5.38 (2H, s), 5.41 (2H, s), 7.20-
					(72.71	5.49	16.96)		7.49 (10H, m), 7.95 (1H, s)
6o	87	145-147	B	$C_{25}H_{20}N_4O$	76.51	5.14	14.28	1640	5.42 (2H, s), 5.56 (2H, s), 7.26-7.68 (13H, m),
					(76.47	5.15	14.39)		7.90 (1H, s), 8.30-8.58 (2H, m)
6p	77	244-245	A	$C_6H_6N_4O$	48.00	4.03	37.32	1660	4.45 (3H, s), 8.75 (1H, s), 8.92 (1H, s)
					(47.83	3.89	37.23)		
6q	84	199-200	A	$C_7H_8N_4O$	52.21	4.91	34.13	1665	2.90 (3H, s), 4.30 (3H, s), 8.79 (1H, s)
					(52.10	5.11	34.02)		8.76 (1H, s)
6r	80	285-286	A	$C_{12}H_{10}N_4O$	63.70	4.46	24.77	1640	4.42 (3H, s), 7.60-8.10 (5H, m), 8.85 (1H, s)
					(63.58	4.48	25.02)		

[a] All compounds were recrystallized from ethanol. [b] Reaction solvent, A: acetone; B: benzene. Source of light, **6a-6o**: a 100 W high-pressure mercury lamp; **6p-6r**: a 400 W high-pressure mercury lamp. [c] Potassium bromide disks. [d] All compounds were measured in deuteriochloroform except **6e** (in DMSO-d_6) and **6f,p,q,r** (in trifluoroacetic acid).

Scheme 4



tives **13a-e** and **13h**, respectively. 4-Benzylthio derivative **13h** was also prepared by S-alkylation of **12a** with benzyl chloride in a potassium hydroxide solution in 71% yield. Furthermore, amination of **12a** and **12b** with aqueous ammonia in a pressure bottle were also smoothly effected to give 4-amino derivatives **13f** and **13g** in 57% and 85% yields, respectively.

EXPERIMENTAL

Melting points were determined with a Yanagimoto melting point apparatus and were uncorrected. The ir spectra were recorded on a JASCO IRA-I spectrophotometer. The ^{1}H-nmr spectra were taken at 60 MHz with a Hitachi R-20 spectrometer in the indicated solvents. Chemical shifts are reported in δ ppm from tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad.

4-Chloro-5-hydrazino-2-methyl-3(2*H*)-pyridazinone (**2a**) and 4-Chloro-5-hydrazino-2-phenyl-3(2*H*)-pyridazinone (**2b**).

These compounds were prepared by the method of Reicheneder and Dury [14].

2-Benzyl-4-chloro-5-hydrazino-3(2*H*)-pyridazine (**2c**).

Compound **1c** [13] (2.55 g, 10 mmoles) was dissolved in 70 ml of boiling methanol. To this solution 80% hydrazine hydrate (1.60 g, 40 mmoles) was added portionwise and the whole was allowed to reflux for 3 hours. The precipitated solid after cooling was collected and recrystallized from ethanol to give 1.63 g (65%) of compound **2c** as reddish-brown needles, mp 159-161°; ir (potassium bromide): ν cm^{-1} 3360, 3320, 3265 (NH,NH_2), 1620 (C=O); ^{1}H-nmr (dimethylsulfoxide-d_6): δ 5.19 (2H, s, CH_2), 6.28 (2H, br, NH_2), 7.26 (5H, s, C_6H_5), 7.89 (1H, br, NH), 8.18 (1H, s, H-6).

Anal. Calcd. for $C_{11}H_{11}ClN_4O$: C, 52.70; H, 4.42; N, 22.35. Found: C, 52.71; H, 4.21; N, 22.60.

4-Chloro-5-hydrazino-3(2*H*)-pyridazinone (**2d**).

This compound was prepared by the method of Castle [15].

2-Substituted 5-alkylidenehydrazino-4-chloro-3(2*H*)-pyridazinones **3a-h**.

General Procedure.

A suspension of 2-substitued 4-chloro-5-hydrazino-3(2*H*)-pyridazinones **2a-d** (10 mmoles) and appropriate aldehydes (12 mmoles) in ethanol (100 ml) was heated under reflux for 2 hours, then cooled. The resulting precipitate was collected and recrystallized from ethanol to yield **3a-h**. The results are summarized in Table 1.

4-Chloro-2-methyl-5-(1-methylhydrazino)-3(2*H*)-pyridazinone (**4a**).

Methylhydrazine (2.76 g, 60 mmoles) was added dropwise to the suspension of compound **1a** (3.58 g, 20 mmoles) in methanol (20 ml) with stirring. The stirring was continued for 10 hours at room temperature and the separated product was collected by filtration. Recrystallization from ethanol gave 2.19 g (58%) of **4a** as pale yellow needles, mp 131-133°; ir (potassium bromide): ν cm^{-1} 3285, 3190 (NH_2), 1660 (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.45 (3H, s, CH_3), 3.73 (3H, s, CH_3), 4.02 (2H, br, NH_2), 8.20 (1H, s, H-6).

Anal. Calcd. for $C_6H_9ClN_4O$: C, 38.21; H, 4.81; N, 29.70. Found: C, 38.08; H, 5.02; N, 29.92.

4-Chloro-5-(1-methylhydrazino)-3(2*H*)-pyridazinone (**4b**).

Compound **4b** was prepared in a similar manner as for compound **4a**; thus compound **1d** (3.30 g, 20 mmoles) and methylhdyrazine (2.76 g, 60 mmoles) in methanol (80 ml) gave **4b** in a yield of 2.98 g (85%) as pale yellow needles, mp 174-175°; ir (potassium bromide): ν cm^{-1} 3310, 3200 (NH_2), 1615 (C=O); ^{1}H-nmr (dimethylsulfoxide-d_6): δ 3.39 (3H, s, CH_3), 4.45 (2H, br, NH_2), 8.17 (1H, s, H-6).

Anal. Calcd. for $C_5H_7ClN_4O$: C, 34.40; H, 4.04; N, 32.09. Found: C, 34.21; H, 3.92; N, 32.21.

2-Substituted 5-(1-Alkyl-2-alkylidenehydrazino)-4-chloro-3(2*H*)-pyridazinones **5a-r**. General Procedure.

Method A for Compounds **5a-d** and **5i-l**.

Anhydrous potassium carbonate (830 mg, 6 mmoles) was added to a solution of 2-substituted 5-alkylidenehydrazino-4-chloro-3(2*H*)-pyridazinones **3a-e** (3 mmoles) and alkyl halide (3.5 mmoles of methyl iodide or benzyl chloride) in dimethylformamide (50 ml), and the whole was stirred at room temperature for 4 hours in the case of methylation or heated at 70° for 3 hours in the case of benzylation. The reaction mixture was poured into 150 ml of cold water and extracted with methylene chloride. The residue obtained by concentrating the solvent was recrystallized from ethanol to give the compounds **5a-d** and **5i-l**, respectively. The results are summarized in Table 3.

Method B for Compounds **5e-h** and **5p-r**.

A suspension of compound **4a** or **4b** (10 mmoles) and the appropriate aldehydes (12 mmoles) in ethanol (50 ml) was heated under reflux for 2 hours, then cooled. The resulting precipitate was collected and recrystallized from ethanol to give the compounds **5e-h** and **5p-r**. The results are summarized in Table 3.

Method C for Compounds **5m-o**.

Anhydrous potassium carbonate (830 mg, 6 mmoles) was added to a solution of compound **3f**, **3g** or **3h** (3 mmoles) and benzyl chloride (890 mg, 7 mmoles) in dimethylformamide (50 ml), and the whole was heated at 70° for 3 hours. The reaction mixture was treated in a similar manner as method A to give the dibenzylated compounds **5m-o**. The results are summarized in Table 3.

Photochemical Cyclization of Compound **5**. General Procedure.

A solution of **5a-r** (1 mmole) in benzene or acetone (200 ml) was irradiated with a 100 W high-pressure mercury lamp surrounded by a water-cooled Pyrex filter at room temperature. Irradiation was continued for 4-8 hours until the disappearance of the starting material while the reaction was followed by silica gel thin-layer chromatography. The residue obtained upon removal of the solvent was recrystallized from ethanol to give compounds **6a-r**. A 400 W high-pressure mercury lamp was employed in the case of compounds **5p**, **5q** and **5r**. The results are summarized in Table 4.

5-Methyl-2-phenylimidazo[4,5-*d*]pyridazin-4(5*H*)-one (**8**).

A mixture of compound **7** [18] (280 mg, 2 mmoles) and benzaldehyde (265 mg, 2.5 mmoles) in 5 ml of nitrobenzene was heated in an oil bath at 180° for 3 hours, then cooled. The resulting precipitate was collected and recrystallized from ethanol to give 294 mg (65%) of compound **8** as colorless scales, mp >300°; ir (potassium bromide): ν cm^{-1} 3230 (NH), 1640 (C=O); ^{1} H-nmr (trifluoroacetic acid): δ 3.97 (3H, s, CH_3), 7.25-8.05 (3H, m, *meta* and *para*-H in C_6H_5), 8.15-8.40 (2H, m, *ortho*-H in C_6H_5), 8.69 (1H, s, H-7).

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.79; H, 4.31; N, 24.91.

Methylation of Compound **8**.

A solution of compound **8** (226 mg, 1 mole) and dimethyl sulfate (252 mg, 2 mmoles) in 2*N* sodium hydroxide solution was heated at 100° for 2 hours. The reaction mixture was extracted with methylene chloride and dried over anhydrous magnesium sulfate. The residue obtained upon removal of methylene choride was chromatographed on silica gel with chloroform as an eluant to afford two compounds, 1,5- and 3,5-dimethyl-2-phenylimidazo[4,5-*d*]pyridazin-4(5*H*)-ones **9** and **9′**. The structural assignment of the two products, **9** and **9′**, is tentative.

The product which eluted first was recrystallized from cyclohexane to give 104 mg (43%) of colorless needles, mp 122-124°; ir (potassium bromide): ν cm^{-1} 1655 (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.91 (3H, s, CH_3), 4.24 (3H, s, CH_3), 7.56-8.00 (5H, m, C_6H_5), 8.37 (1H, s, H-7).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H. 5.03; N, 23.32. Found: C, 65.18; H, 4.92; N, 23.48.

The product which eluted second was recrystallized from ethanol to give 38 mg (16%) of colorless prisms, mp 276-277°; ir (potassium bromide): ν cm^{-1} 1660 (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.99 (3H, s, CH_3), 4.08 (3H, s, CH_3), 7.74-7.98 (5H, m, C_6H_5), 8.24 (1H, s, H-7).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.05; H. 5.10; N, 23.39.

4-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**10a**).

Compound **6p** (0.75 g, 5 mmoles) was gently refluxed with 20 ml of phosphorus oxychloride for 10 minutes. The residue obtained upon removal of the excess of phosphorus oxychloride was poured into 50 ml of ice water. The solid which separated was collected by filtration and washed with water. Recrystallization from ethanol gave 0.40 (48%) of the product **10a** as colorless needles, mp 201-204°; ir (potassium bromide): ν cm^{-1} 3020, 1540, 1480, 1320, 1280, 1215, 1140; ^{1}H-nmr (deuteriochloroform): δ 4.28 (3H, s, CH_3), 8.13 (1H, s, H-3), 9.37 (1H, s, H-7).

Anal. Calcd. for $C_6H_5ClN_4$: C, 43.27; H, 1.82; N, 33.64. Found: C, 43.11; H, 2.01; N, 23.52.

4-Chloro-1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**10b**).

Compound **10b** was prepared by the same method as compound **10a**; thus compound **6r** (1.13 g, 5 mmoles) in 20 ml of phosphorus oxychloride yielded 0.70 g (57%) of **10b** as colorless needles (from ethanol), mp 127-129°; ir (potassium bromide): ν cm^{-1} 3040, 1575, 1445, 1260, 1135: ^{1}H-nmr (deuteriochloroform): δ 4.25 (3H, s, CH_3), 7.27-7.83 (5H, m, C_6H_5), 9.39 (1H, s, H-7).

Anal. Calcd. for $C_{12}H_9ClN_4$: C, 58.91; H, 3.71; N, 22.90. Found: C, 58.80; H, 3.62; N, 22.89.

1-Methyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**11a**).

A solution of compound **10a** (0.3 g, 1.78 mmoles) and potassium hydroxide (0.14 g, 2.5 mmoles) in methanol (60 ml) was reduced catalytically using a palladium catalyst (5% palladium on carbon, 100 mg) at atmospheric pressure and room temperature. After the uptake of an equimolar amount of hydrogen, the catalyst was filtered off and the solvent was removed under reduced pressure. The product was treated with water and extracted with methylene chloride, which was dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from ethanol to give colorless needles of **11a** (126 mg, 53% yield), mp 216-218°; ir (potassium bromide): ν cm^{-1} 3060, 1590, 1495, 1270; 1200, 1120; ^{1}H-nmr (deuteriochloroform): δ 4.23 (3H, s, CH_3), 8.15 (1H, s, H-3), 9.46 (2H, s, H-4 and H-7).

Anal. Calcd. for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.89; H, 4.40; N, 41.91.

1-Methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**11b**).

Compound **10b** (0.3 g, 1.23 mmoles) was allowed to reduce catalytically with palladium on carbon (100 mg) and potassium hydroxide (0.10 g, 1.78 mmoles) in methanol (80 ml) by the same method as compound **11a** to give 132 mg (51%) of **11b** as colorless needles (from benzene), mp 167-169°; ir (potassium bromide): ν cm^{-1} 3010, 1500, 1450, 1260, 1175, 1010; ^{1}H-nmr (deuteriochloroform): δ 4.26 (3H, s, CH_3), 7.40-7.58 (3H, m, *meta* and *para*-H in C_6H_5), 7.84-8.00 (2H, m, *ortho*-H in C_6H_5), 9.43 (1H, d, ring-H, J = 1.5 Hz), 9.65 (1H, d, ring-H, J = 1.5 Hz).

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.72; H, 4.58; N, 26.71.

1-Methyl-1*H*-pyrazolo[3,4-*d*]pyridazine-4(5*H*)-thione (**12a**).

Compound **6p** (1.8 g, 12 mmoles) was dissolved in 80 ml of dry pyridine and the mixture was heated under reflux with stirring. Phosphorus pentasulfide (8.0 g, 36 mmoles) was added slowly to the boiling solution and the whole was heated in an oil bath at 140° for 10 hours. The excess pyridine was evaporated under reduced pressure and 200 ml of ice water was added to the residue. The mixture was heated on a steam bath for one hour, then cooled. The resulting pale yellow compound **12a** (1.51 g, 76%) was collected and washed with water. Purification was accomplished by acid-base precipitation, mp 274-275°; ir (potassium bromide): ν cm^{-1} 3240 (NH), 1220 (C=S); ^{1}H-nmr (trifluoroacetic acid): δ 4.47 (3H, s, CH_3), 8.85 (1H, s, H-3), 9.25 (1H, s, H-7).

Anal. Calcd. for $C_6H_6N_4S$: C, 43.36; H. 3.64; N, 33.71. Found: C, 43.23; H, 3.43; N, 33.85.

1-Methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine-4(5*H*)-thione (**12b**).

Compound **6r** (2.26 g, 10 mmoles) was allowed to react with phosphorus pentasulfide (6.88 g, 30 mmoles) in dry pyridine (80 ml) in a similar manner as compound **12a** to give 1.79 g (78%) of pale brown product **12b**, mp 251-253°; ir (potassium bromide): ν cm^{-1} 3190 (NH), 1210 (C=S); ^{1}H-nmr (trifluoroacetic acid); δ 4.52 (3H, s, CH_3), 7.74 (5H, s, C_6H_5), 9.47 (1H, s, H-7).

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.48; H, 4.16; N, 23.12. Found: C, 59.38; H, 4.15; N, 23.16.

4-Methoxy-1-methyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**13a**).

Compound **10a** (0.2 g, 1.2 mmoles) was added to a sodium methoxide solution prepared by dissolving metallic sodium (0.03 g, 1.4 matoms) in anhydrous methanol (10 ml), and the reaction mixture was refluxed for 5 hours. The solvent was evaporated under reduced pressure and the residue was extracted with ether. The resulting product after removing ether was recrystallized from benzene-ether to give 0.068 g (35%) of **13a** as colorless needles, mp 153-155°; ir (potassium bromide): ν cm^{-1} 2940, 1590, 1450, 1365, 1270; ^{1}H-nmr (deuteriochloroform): δ 4.19 (3H, s, CH_3), 4.27 (3H, s, CH_3), 8.05 (1H, s, H-3), 9.12 (1H, s, H-7).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.01; N, 5.08; N, 34.21.

4-Ethoxy-1-methyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**13b**).

Compound **10a** (0.3 g, 1.8 mmoles) was allowed to react with sodium ethoxide prepared by dissolving metallic sodium (0.06 g, 2.7 matoms) in anhydrous ethanol (10 ml) in a similar manner as compound **13a** to yield 0.21 g (67%) of **13b** as colorless needles (from ethanol), mp 111-112°; ir (potassium bromide): ν cm^{-1} 2990, 1590, 1570, 1405, 1335, 1260, 1030; ^{1}H-nmr (deuteriochloroform): δ 1.53 (3H, t, OCH_2CH_3, J = 7.5 Hz), 4.19 (1H, s, NCH_3), 4.77 (2H, q, OCH_2CH_3, J = 7.5 Hz), 8.07 (1H, s, H-3), 9.12 (1H, s, H-7).

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 54.05; H, 5.83; N, 31.29.

4-Methoxy-1-methyl-3-phenyl-1*H*-pyridazino[3,4-*d*]pyridazine (**13c**).

Compound **10b** (0.3 g, 1.2 mmoles) was allowed to react with sodium methoxide prepared by dissolving metallic sodium (0.042 g, 1.8 matoms) in anhydrous methanol (10 ml) similarly as compound **13a** to give 0.18 g (60%) of **13c** as colorless needles (from cyclohexane), mp 139-141°; ir (potassium bromide): ν cm^{-1} 2985, 1580, 1560, 1410, 1365, 1255, 1040; ^{1}H-nmr (deuteriochloroform): δ 4.16 (3H, s, CH_3), 4.24 (3H, s, CH_3), 7.22-7.54 (3H, m, *meta* and *para*-H in C_6H_5), 7.88-8.05 (2H, m, *ortho*-H in C_6H_5), 9.05 (1H, s, H-7).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.08; H, 5.18; N, 23.09.

1-Methyl-4-morpholino-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**13d**).

A solution of **10b** (0.3 g, 1.2 mmoles) and morpholine (0.26 g, 2.9 mmoles) in ethanol was refluxed for 20 hours. The reaction mixture was evaporated under reduced pressure. The residue was extracted with ether and dried over anhydrous magnesium sulfate. The solid obtained upon removal of ether was recrystallized from cyclohexane to give 0.21 g (59%) of **13d** as colorless needles, mp 158-160°; ^{1}H-nmr (deuteriochloroform): δ 3.15-372 (8H, m, morpholino-H), 4.18 (3H, s, CH_3), 7.25-7.55 (3H, m, *meta* and *para*-H in C_6H_5), 7.65-7.85 (2H, m, *ortho*-H in C_6H_5), 9.08 (1H, s, H-7); ir (potassium bromide): ν cm^{-1} 2840, 1540, 1415, 1365, 1250, 1110.

Anal. Calcd. for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.27; H, 5.70; N, 23.74.

1-Methyl-3-phenyl-4-piperidino-1*H*-pyrazolo[3,4-*d*]pyridazine (**13e**).

Compound **10b** (0.2 g, 0.8 mmoles) was reacted with piperidine (0.16 g, 1.9 mmoles) in ethanol (5 ml) in a similar way as compound **13d** to give 0.17 g (71%) of **13e** as colorles needles (from cyclohexane), mp 163-165°; ^{1}H-nmr (deuteriochloroform): δ 1.46 (6H, br, piperidino-H), 3.30 (4H, br, piperidino-H), 4.13 (3H, s, CH_3), 7.23-7.52 (3H, m, *meta* and *para*-H in C_6H_5), 7.60-7.83 (2H, m, *ortho*-H in C_6H_5), 8.97 (1H, s, H-7); ir (potassium bromide): ν cm^{-1} 3040, 2920, 2800, 1535, 1410, 1365, 1245.

Anal. Calcd. for $C_{17}H_{19}N_5$: C, 69.60; H, 6.53; N, 23.88. Found: C, 69.49; H, 6.72; N, 24.02.

4-Amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**13f**).

A suspension of compound **12a** (1.0 g, 6 mmoles) with 20 ml of aqueous ammonia in a stainless steel pressure bottle was heated at 120° for 5 hours. The resulting product after cooling was collected and recrystallized from ethanol to give 0.56 g (57%) of compound **13f** as colorless needles, mp 289-290°; ir (potassium bromide): ν cm^{-1} 3230, 3120 (NH_2); ^{1}H-nmr (trifluoroacetic acid): δ 4.50 (3H, s, CH_3), 9.00 (1H, s, ring-H), 9.05 (1H, s, ring-H).

Anal. Calcd. for $C_6H_7N_5$: C, 48.32; H, 4.73; N, 46.95. Found: C, 48.21; H, 4.57; N, 47.00.

4-Amino-1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**13g**).

Compound **12b** (0.96 g, 3.9 mmoles) was reacted with 20 ml of aqueous ammonia by the same method as compound **13f** to yield 0.76 g (85%) of compound **13g** as colorless plates (from ethanol), mp 250-251°; ir (potassium bromide): ν cm^{-1} 3460, 3200 (NH_2); ^{1}H-nmr (trifluoroacetic acid): δ 4.50 (3H, s, CH_3), 7.80 (5H, s, C_6H_5), 9.15 (1H, s, H-7).

Anal. Calcd. for $C_{12}H_{11}N_5$: C, 63.97; H, 4.92; N, 31.09. Found: C, 64.05; H, 4.80; N, 31.21.

4-Benzylthio-1-methyl-1*H*-pyrazolo[3,4-*d*]pyridazine (**13h**).

Method A.

Sodium benzylmercaptide (0.32 g, 2.2 mmoles) was added to a solution of compound **10a** (0.3 g, 1.8 mmoles) in anhydrous ethanol (10 ml). The mixture was allowed to stir for 3.5 hours at room temperature and evaporated under reduced pressure. The residue was extracted with ether and dried over anhydrous magnesium sulfate. The resulting product obtained upon removal of ether was recrystallized from ethanol to give 0.36 g (78%) of **13h** as colorless needles, mp 103-104°; ir (potassium bromide): ν cm^{-1} 1540, 1440, 1390, 1295, 1200, ^{1}H-nmr (deuteriochloroform): δ 4.12 (3H, s, CH_3), 4.72 (2H, s, CH_2), 7.08-7.55 (5H, m, C_6H_5), 7.98 (1H, s, H-3), 9.17 (1H, s, H-7).

Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92, H, 4.72; N, 21.86. Found: C, 60.89; H, 4.72; N, 21.92.

Method B.

Compound **12a** (0.83 g, 5 mmoles) was dissolved in 5.5 ml of 1*N* potassium hydroxide solution. Benzyl chloride (0.70 g, 5.5 mmoles) was added dropwise to the solution with stirring. The stirring was continued for 3 hours. The separated solid was collected and recrystallized from ethanol to yield 0.91 g (71%) of **13h**, mp 103-104°, which was identical with the product prepared *via* method A by a comparison of the melting point, thin-layer chromatography (silica gel), ir and ^{1}H-nmr spectra.

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