Department of Chemistry, The University of New Mexico

Pyridazines. III. The Synthesis of Substituted Pyridazines (1)

Raymond N. Castle (2) and Kenji Kaji

A series of pyridazines and pyridazones have been prepared substituted with alkyl, alkoxyl, halogen, mercapto, substituted mercapto, phenyl, morpholino, piperidino, styryl, substituted styryl and pyridylethenyl groups as potential antitumor agents. The compounds possessing antitumor or tissue culture activity are recorded in Table VI.

Osner, Castle and Aldous (3) reported the synthesis and tissue culture activity of a series of halohydrazinopyridazones. The biological activity of some of these compounds encouraged us to prepare a number of variously substituted pyridazines.

3,4,5-Pyridazinetrithiol (4) was allowed to react with a series of substituted benzyl halides in alkaline solution. The products were 3,4,5-tris(benzylthio)-pyridazines (Table Ia).

In order to prepare bis(benzylthio)chloropyridazines, one mole of 3,4,5-trichloropyridazine (5) (CAUTION - Solutions cause SEVERE blisters) was allowed to react with two moles of the appropriate benzyl halide in alkaline solution. The 4,5-bis-(benzylthio)-3-chloropyridazines thus prepared are recorded in Table Ib. In order to establish that the chlorine atoms in the 4- and 5- positions were replaced by the benzylmercaptide anion, 4,5-dibromo-6-pyridazone (6) (I) (Flow Sheet I) was allowed to react with two moles of benzylmercaptan in dry benzene solution in the presence of sodium amide. 4,5-Bis(benzylthio)-6-pyridazone (II) was obtained. When II was allowed to react with phosphorus oxychloride in the usual manner, 4,5-bis(benzylthio)-3-chloropyridazine (III) was obtained. Compound III was identical with the product obtained from 3,4,5-trichloropyridazine and benzyl mercaptan in alkaline solution, thus the products described in Table Ib are correctly formulated.

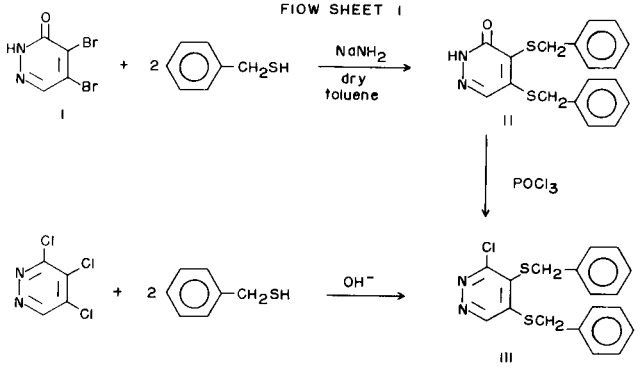
The novel nucleophilic displacement of halogen from 4,5-dichloro-1-phenyl-6-pyridazone (IV) (7) with phosphorus pentasulfide in boiling pyridine solution provided 4,5-dimercapto-1-phenyl-6-pyridazone (VI) (4). When VI was allowed to react with two moles of the appropriate benzyl halide in alkaline (aqueous ethanol) solution, the 4,5-bis(benzylthio)-1-phenyl-6-pyridazones (V) were obtained. (Method B in Table II.) In one instance a compound of type V was prepared by allowing VI to react with the appropriate halide (Route C, Table II) in the presence of sodium amide in an inert hydrocarbon solvent. The same type of 4,5-bis(benzylthio)-1-phenyl-6-pyridazones (V) was obtained from 4,5-dichloro-1-phenyl-6-pyridazone (IV) and the appropriate benzyl mercaptan (Method A, Table II).

In order to obtain pyridazones with alkoxyl, benzylthio and phenyl groups, 4,5-dichloro-1-phenyl-6-pyridazone was allowed to react with either sodium methoxide in absolute methanol solution or with sodium ethoxide in absolute ethanol solution. 5-Chloro-4-methoxy-1-phenyl-6-pyridazone (VIIa) and 5-chloro-4-ethoxy-1-phenyl-6-pyridazone (VIIb) were obtained, respectively. The structural assignments were made on the basis of analogy since it has been found that the halogen atom in the 4- position is more susceptible to nucleophilic displacement than those in the more hindered 5-position (3). These observations are in harmony with the observations of Dury (8). The exceptional reactivity of the 4-halogen atom can be explained if one considers it to be an activated vinylogous chloride such as those described by Benson and Pohland (9). When VIIa or VIIb was allowed to react with benzyl, *p*-chlorobenzyl or 3,4-dichlorobenzyl mercaptan in anhydrous benzene solution in the presence of sodium amide, six new compounds were obtained, VIIIa-VIIIf (Flow Sheet II). Likewise, VIIIe (Flow Sheet III) was obtained from 5-mercapto-4-methoxy-1-phenyl-6-pyridazone (IX) (10) by allowing IX to react with benzyl chloride in alkaline solution.

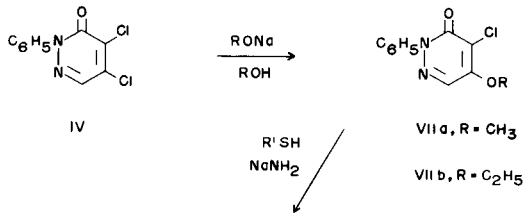
4,5-Dichloro-6-pyridazone (XI) (7) gave 5-chloro-4-piperidino-6-pyridazone (XII) and 5-chloro-4-morpholino-6-pyridazone (XIII) when allowed to react with piperidine and morpholine, respectively. By allowing 4,5-dibromo-6-pyridazone (I) to react with morpholine, 5-bromo-4-morpholino-6-pyridazone (XV) was obtained (Flow Sheet IV). The structures of XII, XIII and XIV were assigned by analogy (3,8,9). Compounds XII and XIII have recently been reported by Bourdais (11).

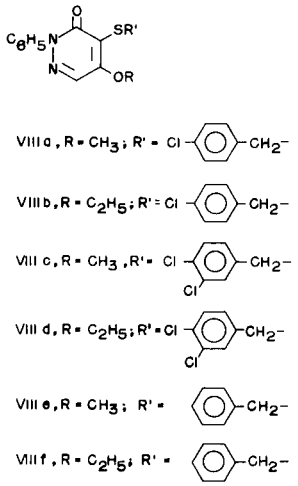
Either 5-bromo- (XV) or 5-chloro-4-morpholino-6-pyridazone (XIII) gave 5-benzylthio-4-morpholino-6-pyridazone (XVI) when allowed to react with benzyl mercaptan in anhydrous benzene solution in the presence of sodium amide. Furthermore 4,5-dichloro-1-phenyl-6-pyridazone (IV) when allowed to react with morpholine gave 5-chloro-4-morpholino-1-phenyl-6-pyridazone (XVII) which was allowed to react with benzyl or *p*-chlorobenzyl mercaptan in anhydrous benzene solution in the presence of sodium amide to give 5-benzylthio- (XVIIIa) and 5-(*p*-chlorobenzylthio)-4-morpholino-1-phenyl-6-pyridazone (XVIIIb), respectively. Likewise with piperidine, 4,5-dichloro-1-phenyl-6-pyridazone (IV) gave 5-chloro-4-piperidino-1-phenyl-6-pyridazone (XIX) which with benzyl or *p*-chlorobenzyl mercaptan in anhydrous benzene solution in the presence of sodium amide gave 5-benzylthio- (XXa) and 5-(*p*-chloro-

FLOW SHEET I

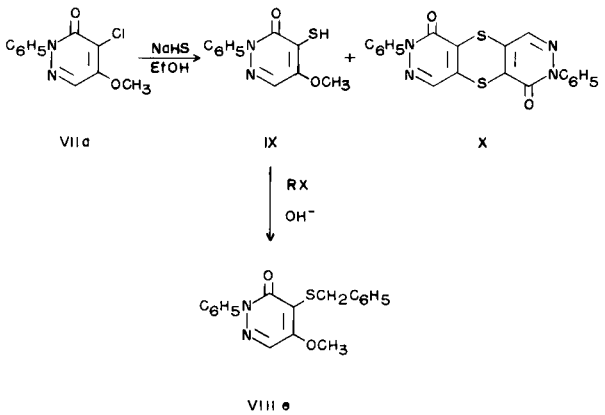


FLOW SHEET II

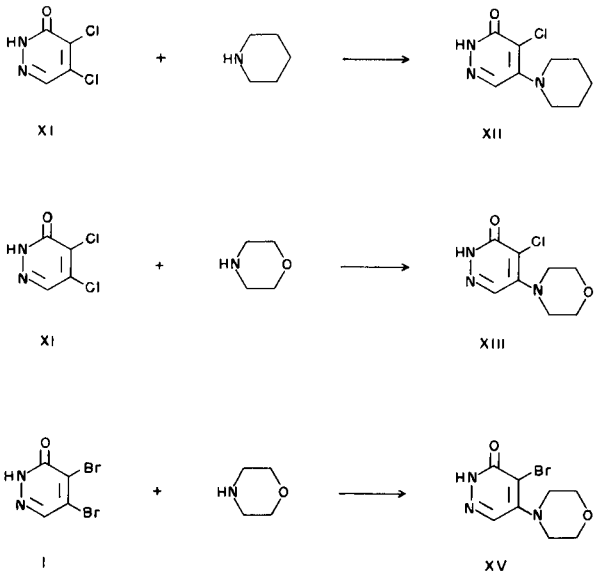




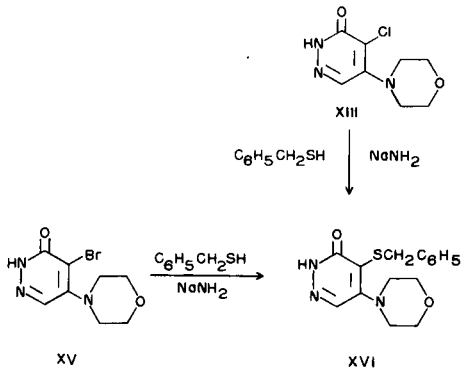
FLOW SHEET III

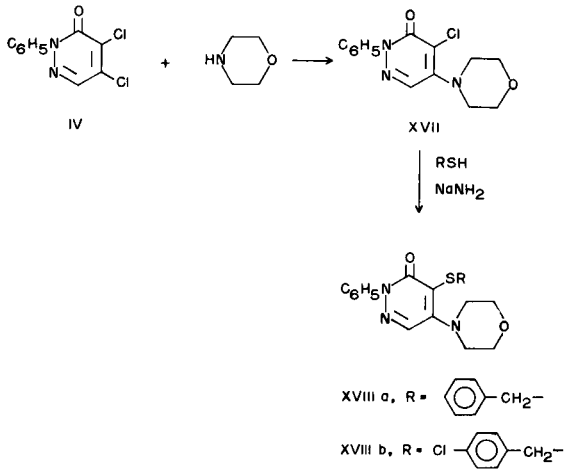


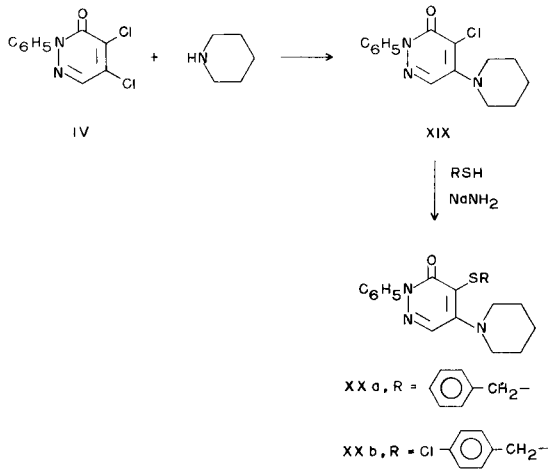
FLOW SHEET IV



FLOW SHEET V







benzylthio)-4-piperidino-1-phenyl-6-pyridazone (XXb), respectively (Flow Sheet V). The structures of these compounds have been assigned by analogy (3, 8, 9).

6-Methyl-3-pyridazinethiol (12) (XXI) was allowed to react with benzyl chloride and a series of substituted benzyl halides in alkaline solution to give compounds XXIIa-XXIIh respectively (Table III). 3-Chloro-6-ethoxypyridazine (XXIII) (13, 14a), when allowed to react with thiourea followed by reaction with sodium hydroxide solution gave 6-ethoxy-3-pyridazinethiol (XXIV) which reacted smoothly with benzyl chloride or with a series of substituted benzyl halides in alkaline solution to give compounds (XXVa-XXVe) (Table IV). In a similar manner 3-chloro-6-*n*-propoxypyridazine (XXVI) (14a-14b) when allowed to react with thiourea and then with sodium hydroxide solution gave 6-*n*-propoxy-3-pyridazinethiol (XXVII) which also gave a series of compounds when allowed to react with benzyl chloride or substituted benzyl halides in alkaline solution. The compounds (XXVIIIa-XXVIIIc) are recorded in Table IV.

3,6-Dimethylpyridazine (XXIX) (15) was allowed to react with benzaldehyde, substituted benzaldehydes and two of the three isomeric pyridinecarboxaldehydes in the presence of anhydrous zinc chloride to give the corresponding 3,6-bis(styryl)pyridazines (XXXa-XXXd) and the 3,6-bis(pyridylethenyl)pyridazines (XXXe-XXXf) respectively (Table V).

These compounds have been screened for antitumor and tissue culture activity according to the CCNSC screening protocol (16). The activity of a compound is considered to be statistically significant if the T/C is 0.53 or less in S-180 or CA-755. In the LE-1210 system, the activity is considered statistically significant if the T/C is 1.25 or more. In the cell culture system (KB cells), the activity of the compound is considered to be statistically significant if the ED_{50} in 4 x 10^0 μg/ml. or less. The slope is simply the difference in response for a one-log difference in dose, the response being the ratio of growth of the test sample to that of the untreated control. The compounds that are active are shown in Table VI and activity is marked with an asterisk.

EXPERIMENTAL (17)

Typical Procedure, Table Ia.

Benzyl chloride (5.06 g., 0.04 mole) was added to the sodium mercaptide solution prepared by dissolving 0.88 g. (0.005 mole) of 3,4,5-pyridazinetrithiol (4) in a mixture of 40 ml. of 5% sodium hydroxide solution, 30 ml. of 28% aqueous ammonia and 40 ml. of ethanol with stirring at room temperature. A solid began to separate during the addition and stirring was continued overnight at room temperature. The solid was collected, washed with a small amount of ethanol and then with water, dried and purified by recrystallization from benzene-cyclohexane. The analytical specimen was recrystallized from cyclohexane, m.p. 157°.

Typical Procedure, Table Ib.

A solution of 1.84 g. (0.01 mole) of 3,4,5-trichloropyridazine (5) (CAUTION - Solutions cause SEVERE blisters.) in 20 ml. of ethanol was added gradually with stirring at room temperature to the sodium mercaptide solution prepared by dissolving 2.48 g. (0.02 mole) of benzyl mercaptan in a mixture of 20 ml. of 5% sodium hydroxide solution, 15 ml. of 28% aqueous ammonia and 30 ml. of ethanol. A solid began to separate during the addition at the reaction temperature (the temperature rose to 36° spontaneously). The suspension was stirred for 6 hours at room temperature, collected, dried and recrystallized from benzene-cyclohexane. There was obtained a 78% yield of colorless needles, m.p. 113-114°. The compound was assigned the structure 4,5-bis(benzylthio)-3-chloropyridazine (Table Ib) and this was established by the synthesis of III described below.

4,5-Bis(benzylthio)-6-pyridazone (II).

4,5-Dibromo-6-pyridazone (I) (6) (5.08 g., 0.02 mole) was added to the sodium benzyl mercaptide suspension previously prepared by heating 9.94 g. (0.08 mole) of benzyl mercaptan with 3.50 g. (0.09 mole) of powdered sodium amide in 100 ml. of dry toluene under reflux over a period of 30 minutes. The reaction mixture was refluxed an additional 5 hours, then concentrated almost to dryness under reduced pressure, water was added and the mixture was filtered in order to collect the insoluble solid. The solid was suspended in 200 ml. of water and acidified with glacial acetic acid. The crude product was collected and recrystallized from ethanol to give 4.30 g. (63%) of 4,5-bis(benzylthio)-6-pyridazone, m.p. 166-167°. The analytical specimen was recrystallized from ethanol, m.p. 167°.

Anal. Calcd. for $C_{18}H_{16}N_2OS_2$: C, 63.49; H, 4.74; N, 8.23. Found: C, 62.95; H, 4.31; N, 8.63.

4,5-Bis(benzylthio)-3-chloropyridazine (III).

A mixture of 0.68 g. (0.002 mole) of II and 1 ml. (*ca.* 0.011 mole) of phosphorus oxychloride was heated about 5 minutes. The reaction mixture was poured onto crushed ice and the precipitated solid was extracted with ether. The ethereal extract was washed with 5% sodium hydroxide solution, then with saturated sodium chloride solution and dried over anhydrous sodium sulfate. A pale yellow solid (0.30 g., 42%) was obtained, m.p. 105-112°. The analytical specimen was prepared by recrystallization from cyclohexane, m.p. 113-114°. This compound was identical in all respects with that obtained from trichloropyridazine (Table Ib) from mixed melting point and infrared spectra.

Anal. Calcd. for $C_{18}H_{15}ClN_2S_2$: C, 60.23; H, 4.21; N, 7.81. Found: C, 60.07; H, 4.06; N, 8.05.

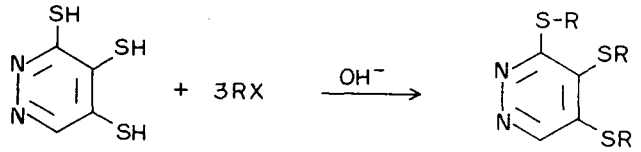
4,5-Dimercapto-1-phenyl-6-pyridazone (VI).

To a mixture of 24.0 g. (0.1 mole) of 4,5-dichloro-1-phenyl-6-pyridazone (IV) (7) and 133.4 g. (0.6 mole) of powdered phosphorus pentasulfide (commercial grade) was added 1 l. of dry pyridine (Eastman Kodak No. 214). It was necessary to cool the flask externally with cold water. The reaction mixture was then heated under reflux for 16 hours. The excess pyridine was removed by distillation under reduced pressure and the viscous residue was poured on crushed ice. The resulting suspension was heated on a steam bath until the evolution of hydrogen sulfide had ceased (about 2 hours). The red solution was filtered to remove a small amount of undissolved material, then acidified to *p*H 1-1.5 with hydrochloric acid. The precipitated solid was collected, dried and recrystallized from benzene-cyclohexane giving 18.5 g. (78%) of crude 4,5-dimercapto-1-phenyl-6-pyridazone (VI), m.p. 109°. The analytical specimen was recrystallized from cyclohexane, m.p. 110°. The product was soluble in 10% sodium hydroxide solution, in ethanol and in benzene.

Anal. Calcd. for $C_{10}H_8N_2OS_2$: C, 50.82; H, 3.41; N, 11.86. Found: C, 50.33; H, 3.15; N, 11.47.

TABLE Ia

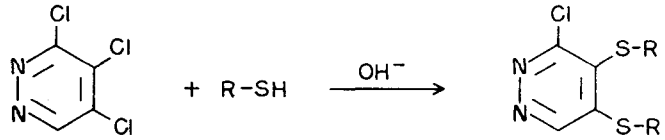
3,4,5-Tris(benzylthio)pyridazines



R	X	m.p.°	Yield %	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
p-Chlorobenzyl	Cl	164	85	Cyclohexane	$C_{25}H_{19}Cl_3N_2S_3$	54.58	54.46	3.48	3.24	5.09	5.15
o-Chlorobenzyl	Cl	123.5	80	Cyclohexane	$C_{25}H_{19}Cl_3N_2S_3$	54.58	54.58	3.48	3.24	5.09	5.28
2,4-Dichlorobenzyl	Cl	167	91	Cyclohexane	$C_{25}H_{16}Cl_6N_2S_3$	45.96	45.93	2.47	2.34	4.29	4.56
3,4-Dichlorobenzyl	Cl	173	90	Cyclohexane	$C_{25}H_{16}Cl_6N_2S_3$	45.96	45.96	2.47	2.30	4.29	4.57
p-Bromobenzyl	Br	170	78	Benzene-Cyclohexane	$C_{25}H_{19}Br_3N_2S_3$	43.94	43.82	2.80	2.72	4.09	4.26
p-Iodobenzyl	Br	179.5	85	Benzene-Cyclohexane	$C_{25}H_{19}I_3N_2S_3$	36.42	36.60	2.33	2.23	3.39	3.58
o-Fluorobenzyl	Br	124	92	Cyclohexane	$C_{25}H_{19}F_3N_2S_3$	59.98	60.02	3.83	3.82		
m-Fluorobenzyl	Br	149.5	94	Cyclohexane	$C_{25}H_{19}F_3N_2S_3$	59.98	59.75	3.83	3.67	5.60	5.93
p-Fluorobenzyl	Br	153	85	Cyclohexane	$C_{25}H_{19}F_3N_2S_3$	59.98	60.27	3.83	3.70	5.60	5.69

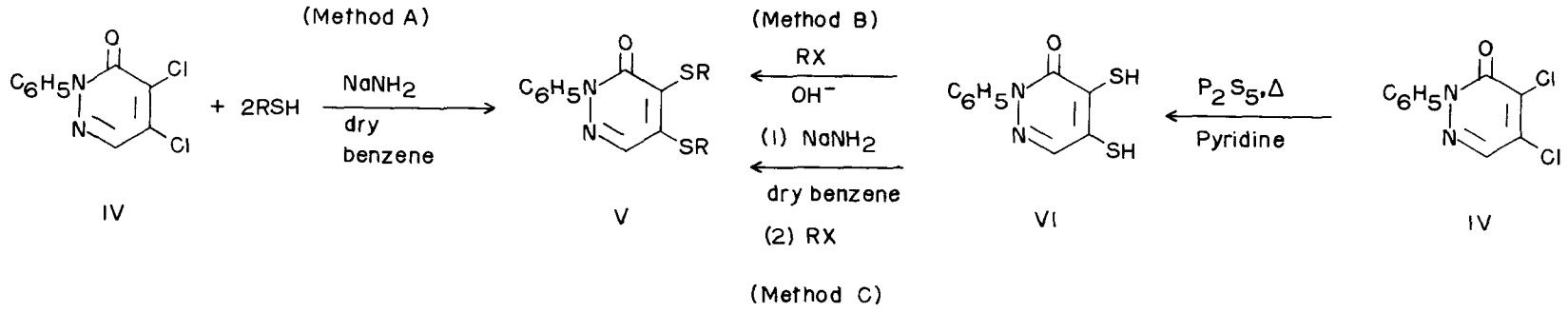
TABLE Ib

4,5-Bis(benzylthio)-3-chloropyridazines



R	m.p.°	Yield %	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Benzyl	113-114	78	Benzene-Cyclohexane	$C_{18}H_{15}ClN_2S_2$	60.23	60.25	4.21	3.86	7.81	7.94
p-Chlorobenzyl	120-121	70	Benzene-Cyclohexane	$C_{18}H_{13}Cl_3N_2S_2$	50.53	50.23	3.06	2.84	6.55	6.73
o-Chlorobenzyl	135-136	84	Benzene-Cyclohexane	$C_{18}H_{13}Cl_3N_2S_2$	50.53	50.69	3.06	2.86		
3,4-Dichlorobenzyl	130-131	71	Benzene-Cyclohexane	$C_{18}H_{11}Cl_5N_2S_2$	43.52	43.59	2.23	2.18		

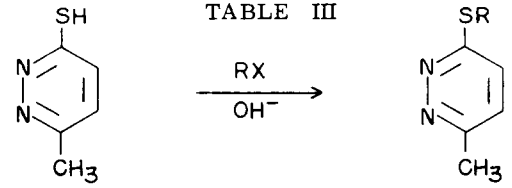
TABLE II



R	X	m.p.°	Method	Yield % (a)	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Benzyl	Cl	163-164	A, B, C	91 (b)	Benzene-Cyclohexane	$C_{24}H_{20}N_2OS_2$	69.19	69.40	4.84	4.42	6.72	7.22
p-Bromobenzyl	Br	170	B	98	Benzene-Cyclohexane	$C_{24}H_{18}Br_2N_2OS_2$	50.18	50.78	3.16	2.95		
o-Chlorobenzyl	I	128-129	A, B	84 (c)	Cyclohexane	$C_{24}H_{18}Cl_2N_2OS_2$	59.38	59.34	3.74	3.53	5.77	5.93
p-Chlorobenzyl	I	167-169	A, B	80 (d)	Benzene-Cyclohexane	$C_{24}H_{18}Cl_2N_2OS_2$	59.38	59.70	3.74	3.57		
o-Fluorobenzyl	Br	132	B	89	Benzene-Cyclohexane	$C_{24}H_{18}F_2N_2OS_2$	63.69	63.67	4.01	3.77		
m-Fluorobenzyl	Br	137	B	84	Benzene-Cyclohexane	$C_{24}H_{18}F_2N_2OS_2$	63.69	63.57	4.01	3.72		
p-Fluorobenzyl	Br	131	B	97	Benzene-Cyclohexane	$C_{24}H_{18}F_2N_2OS_2$	63.69	63.46	4.01	3.87		
2,4-Dichlorobenzyl	I	145	B	90	Cyclohexane	$C_{24}H_{16}Cl_4N_2OS_2$	51.99	51.85	2.91	2.71	5.05	5.42
3,4-Dichlorobenzyl	I	195-197	A, B	90	Cyclohexane	$C_{24}H_{16}Cl_4N_2OS_2$	51.99	52.06	2.91	2.78		

(a) Yields are recorded on material of high quality, but not necessarily of analytical quality. Usually there was not more than 1-2 degrees difference in melting point of this product and that of the analytical specimen. (b) By Method B; Method A, 72%; Method C, 71%. (d) By Method B; Method A, 82%. (d) By Method A; Method B, 79%.

TABLE III

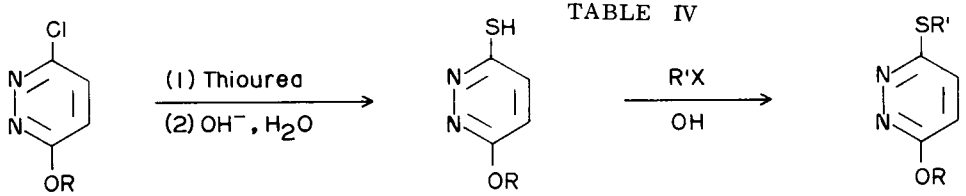


XXI XXII

Compound Number	R	X	m.p.°	Yield % (a)	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XXIIa	Benzyl	Cl	93	79	Cyclohexane	$C_{12}H_{12}N_2S$	66.62	66.29	5.59	5.27	12.96	12.84
XXIIb	*p*-Chlorobenzyl	I	97	85	Cyclohexane	$C_{12}H_{11}ClN_2S$	57.48	57.69	4.42	4.19	11.18	10.96
XXIIc	*o*-Chlorobenzyl	I	64	56	Petroleum ether	$C_{12}H_{11}ClN_2S$	57.48	57.12	4.42	4.12	11.18	11.43
XXIId	2,4-Dichlorobenzyl	I	89	74	Cyclohexane	$C_{12}H_{10}Cl_2N_2S$	50.53	50.31	3.53	3.42	9.82	9.96
XXIIe	3,4-Dichlorobenzyl	I	91	60	Cyclohexane	$C_{12}H_{10}Cl_2N_2S$	50.53	50.23	3.53	3.34	9.82	9.95
XXIIf	*o*-Fluorobenzyl	Br	80	94	Cyclohexane	$C_{12}H_{11}FN_2S$	61.51	61.82	4.73	4.50	11.96	12.12
XXIIg	*m*-Fluorobenzyl	Br	67	94	Cyclohexane	$C_{12}H_{11}FN_2S$	61.51	61.50	4.73	4.52	11.96	12.06
XXIIh	*p*-Fluorobenzyl	Br	107	86	Cyclohexane	$C_{12}H_{11}FN_2S$	61.51	61.57	4.73	4.88	11.96	12.09

(a) Yields are recorded on material of high quality, but not necessarily of analytical quality. Usually there was not more than 1-2 degrees difference in melting point of this product and that of the analytical specimen.

TABLE IV

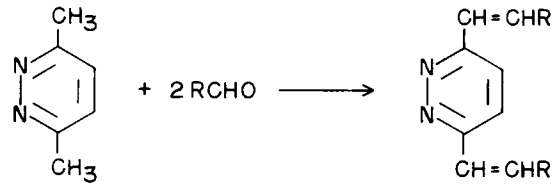


XXIII (R = C_2H_5) XXIV (R = C_2H_5) XXVa (R = C_2H_5)
XXIII (R = n-C_3H_7) XXVII (R = n-C_3H_7) XXVIIIa (R = n-C_3H_7)

Compound Number	R	R'	X	m.p.°	Yield % (a)	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XXVa	C_2H_5	Benzyl	Cl	96-97	94	Cyclohexane	$C_{13}H_{14}N_2OS$	63.38	63.15	5.73	5.47	11.37	11.61
XXVb	C_2H_5	*m*-Fluorobenzyl	Br	88	92	Benzene-Cyclohexane	$C_{13}H_{13}FN_2OS$	59.07	59.63	4.96	4.88	10.60	11.04
XXVc	C_2H_5	*o*-Fluorobenzyl	Br	59	76	Benzene-Cyclohexane	$C_{13}H_{13}FN_2OS$	59.07	59.10	4.96	4.60	10.60	10.84
XXVd	C_2H_5	*p*-Fluorobenzyl	Br	116	92	Benzene-Cyclohexane	$C_{13}H_{13}FN_2OS$	59.07	59.25	4.96	4.64	10.60	11.02
XXVe	C_2H_5	*p*-Bromobenzyl	Br	117	98	Cyclohexane	$C_{13}H_{13}BrN_2OS$	48.01	48.24	4.03	3.98		
XXVIIIa	C_3H_7 (*n*)	Benzyl	Cl	70	91	Benzene-Cyclohexane	$C_{14}H_{16}N_2OS$	64.57	65.00	6.19	5.89	10.76	10.98
XXVIIIb	C_3H_7 (*n*)	*p*-Fluorobenzyl	Br	90	99	Cyclohexane	$C_{14}H_{15}FN_2OS$	60.41	60.59	5.43	5.30	10.07	10.14
XXVIIIc	C_3H_7 (*n*)	*m*-Fluorobenzyl	Br	56	92	Cyclohexane	$C_{14}H_{15}FN_2OS$	60.41	60.70	5.43	5.19	10.07	10.55

(a) Yields are recorded on material of high quality, but not necessarily of analytical quality. Usually there was not more than 1-2 degrees difference in melting point of this product and that of the analytical specimen.

TABLE V



XXIX

Compound Number	R	m.p.°	Yield %(a)	Recrystallization Solvent	Formula	C Calcd.	C Found	H Calcd.	H Found
XXXa	Phenyl	230	74	Ethanol	$C_{20}H_{16}N_2$	84.48	84.14	5.67	5.10
XXXb	*o*-Fluorophenyl	201-202	53	Ethanol	$C_{20}H_{14}F_2N_2$	74.98	74.58	4.41	4.10
XXXc	*m*-Fluorophenyl	195	62	Ethanol	$C_{20}H_{14}F_2N_2$	74.98	74.50	4.41	4.18
XXXd	*p*-Fluorophenyl	247-248	41	Ethanol	$C_{20}H_{14}F_2N_2$	74.98	74.66	4.41	4.23
XXXe	2-Pyridyl	280	42	Ethanol	$C_{18}H_{14}N_4$	75.50	74.98	4.93	4.73
XXXf	3-Pyridyl	260-261	42	Ethanol	$C_{18}H_{14}N_4$	75.50	74.90	4.93	4.83

(a) Yields are recorded on material of high quality, but not necessarily of analytical quality. Usually there was not more than 1-2 degrees difference in melting point of this product and that of the analytical specimen.

TABLE VI

Antitumor and Cell Culture Activity

	SA-180	CA-755	LE-1210	Slope	ED_{50} in $\mu g/ml.$
3-(3-Fluorobenzylthio)-6-*n*-propoxypyridazine				-0.10	2.3×10^{0}*
6-*n*-Propoxy-3-pyridazinethiol	0.94		1.99*	-0.24	4.7×10^{-1}*
3,6-Bisstyrylpyridazine	0.36*			-0.88	2.6×10^{1}
3,6-Bis-(2-fluorostyryl)pyridazine		1.24		-0.57	1.2×10^{0}*
3-Chloro-4,5-bis-(3,4-dichlorobenzylthio)pyridazine	0.35*	0.86	0.86	-0.97	2.3×10^{1}
3-(2,4-Dichlorobenzylthio)-6-methylpyridazine	0.91	1.06	0.98	-0.45	3.7×10^{0}*
3-Chloro-4,5-bis-(2-chlorobenzylthio)pyridazine	0.53*	1.10	0.96	-0.97	2.0×10^{1}
5-(3,4-Dichlorobenzylthio)-4-methoxy-1-phenyl-6-pyridazone	0.50*	0.86	0.95	-1.06	2.3×10^{1}
3,4,5-Tris-(4-iodobenzylthio)pyridazine	0.36*				1.0×10^{2}
3,4,5-Tris-(2,4-dichlorobenzylthio)pyridazine	0.39*	0.90	1.01		1.0×10^{2}
3,4,5-Tris-(3,4-dichlorobenzylthio)pyridazine	0.48*	0.94	1.02		1.0×10^{2}

* Statistically significant activity.

Table II, Method A.

4,5-Dichloro-1-phenyl-6-pyridazone (IV) (7) (1.20 g., 0.005 mole) was added to a sodium benzyl mercaptide suspension prepared by heating 1.37 g. (0.011 mole) of benzyl mercaptan with 0.47 g. (0.012 mole) of powdered sodium amide in 20 ml. of dry benzene under reflux during 1 hour. The reaction mixture was heated under reflux for an additional 5.5 hours. The solid was removed by filtration and washed thoroughly with benzene. The benzene washings were added to the filtrate and the solution was concentrated under reduced pressure to dryness. The residual solid was recrystallized from benzene-cyclohexane to give 1.50 g. (72%) of 4,5-bis(benzylmercapto-1-phenyl-pyridazone (V), m.p. 160-164°. The yellow crystals were recrystallized from benzene-cyclohexane in order to prepare the analytical sample, m.p. 164°. This compound did not depress the melting point of compound V when prepared by the other two methods.

Anal. Calcd. for $C_{24}H_{20}N_2OS_2$: C, 69.19; H, 4.84. Found: C, 69.12; H, 4.57.

Table II, Method B.

Benzyl chloride (1.52 g., 0.01 mole) in 10 ml. of ethanol was added portionwise with stirring at room temperature to 1.27 g. (0.0054 mole) of 4,5-dimercapto-1-phenyl-6-pyridazone (VI) dissolved in a mixture of 20 ml. of 5% sodium hydroxide solution and 15 ml. of 28% aqueous ammonia. Yellow crystals of product began to separate during the addition. Stirring was continued for 18 hours at room temperature. The solid was collected, washed with water, dried and recrystallized from benzene-cyclohexane to give 2.10 g. (91%) of 4,5-bis(benzylmercapto)-1-phenyl-6-pyridazone, m.p. 154°. Recrystallization from benzene-cyclohexane gave yellow crystals, m.p. 164°, identical with the product described under Method A.

Table II, Method C.

Benzyl chloride (1.52 g., 0.012 mole) was added to a suspension of sodium benzyl mercaptide previously prepared by heating 1.27 g. (0.005 mole) of 4,5-dimercapto-1-phenyl-6-pyridazone with 0.59 g. (0.015 mole) of powdered sodium amide in 40 ml. of anhydrous benzene during 30 minutes under reflux. Then the mixture was heated for 5 hours under reflux. The solid was removed from the cold reaction mixture, washed several times with small portions of dry benzene and the washings were combined with the filtrate. The filtrate was concentrated to about 10 ml. and about 20 ml. of cyclohexane was added to precipitate the 4,5-bis(benzylmercapto)-1-phenyl-6-pyridazone (V), m.p. 157° (yield 71%). Purification was effected by recrystallization from benzene-cyclohexane, m.p. 163°. This product did not depress the melting point of V as prepared by either Method A or B.

5-Chloro-4-methoxy-1-phenyl-6-pyridazone (VIIa).

4,5-Dichloro-1-phenyl-6-pyridazone (IV) (7) (12.0 g., 0.05 mole) was added to a sodium methoxide solution prepared from 1.15 g. (0.05 gram atom) of sodium in 160 ml. of absolute methanol. The reaction mixture was heated under reflux for 4.5 hours. The colorless crystals which separated from the cold reaction mixture were collected and dried, yield 10.0 g. (85%), m.p. 160-165°. The analytical sample, separated as colorless needles upon recrystallization from methanol, m.p. 165°.

Anal. Calcd. for $C_{11}H_9ClN_2O_2$: C, 55.82; H, 3.83; N, 11.83. Found: C, 55.52; H, 3.47; N, 11.57.

5-Chloro-4-ethoxy-1-phenyl-6-pyridazone (VIIb).

Compound IV (12.0 g., 0.05 mole) was added to a sodium ethoxide solution. The procedure for VIIa was followed except that ethanol was used in place of methanol. There was obtained 12.2 g. (98%) of VIIb m.p. 136°, which after recrystallization from ethanol had a melting point of 141°.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.18. Found: C, 57.65; H, 4.17; N, 11.65.

5-(*p*-Chlorobenzylthio)-4-methoxy-1-phenyl-6-pyridazone (VIIIa).

5-Chloro-4-methoxy-1-phenyl-6-pyridazone (VIIa) (1.18 g., 0.005 mole) was added to sodium *p*-chlorobenzyl mercaptide suspension previously prepared by heating 0.96 g. (0.006 mole) of *p*-chlorobenzyl mercaptan with 0.27 g. (0.007 mole) of powdered sodium amide in 20 ml. of dry benzene under reflux for 30 minutes. The reaction mixture was heated for 5 hours, cooled and the solid was filtered and washed well with benzene. The filtrate and washings were combined, concentrated under reduced pressure to dryness and the residue was recrystallized from cyclohexane to give 1.30 g. (73%) of VIIIa, m.p. 114-116°. The analytical sample was prepared by recrystallization from cyclohexane, colorless needles, m.p. 116°.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_2S$: C, 60.24; H, 4.23. Found: C, 60.41; H, 4.11.

5-(*p*-Chlorobenzylthio)-4-ethoxy-1-phenyl-6-pyridazone (VIIIb).

This compound was prepared from VIIb (1.25 g., 0.005 mole), 0.85 g. (0.006 mole) of *p*-chlorobenzyl mercaptan and 0.27 g. (0.007 mole) of sodium amide as described for VIIIa above. The yield of VIIIb, m.p. 75-81°, was 86%. The analytical sample prepared by recrystallization from cyclohexane melted at 87°.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_2S$: C, 61.20; H, 4.60. Found: C, 61.29; H, 4.45.

5-(3,4-Dichlorobenzylthio)-4-methoxy-1-phenyl-6-pyridazone (VIIIc).

This compound was prepared from VIIa (1.18 g., 0.005 mole) 1.16 g. (0.005 mole) of 3,4-dichlorobenzyl mercaptan and 0.27 g. (0.007 mole) of sodium amide as described for VIIIa above. The yield of VIIIc, m.p. 118°, was 92%. The analytical specimen recrystallized from cyclohexane, m.p. 118°.

Anal. Calcd. for $C_{18}H_{14}Cl_2N_2O_2S$: C, 54.97; H, 3.59. Found: C, 55.34; H, 3.57.

5-(3,4-Dichlorobenzylthio)-4-ethoxy-1-phenyl-6-pyridazone (VIIId).

This compound was prepared from VIIb (1.25 g., 0.005 mole) 1.16 g. (0.006 mole) of 3,4-dichlorobenzyl mercaptan and 0.27 g. (0.007 mole) of sodium amide as described for VIIIa above. The yield of VIIId, m.p. 91-92°, was 88%. The analytical sample recrystallized from cyclohexane, m.p. 92°.

Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_2S$: C, 56.02; H, 3.95. Found: C, 56.06; H, 3.84.

5-Benzylthio-4-methoxy-1-phenyl-6-pyridazone (VIIIe).

This compound was prepared from VIIa (1.18 g., 0.005 mole), 0.85 g. (0.006 mole) of benzyl mercaptan and 0.27 g. (0.007 mole) of sodium amide as described for VIIIa above. The yield of VIIIe, m.p. 108-112°, was 37%. The analytical specimen was recrystallized from cyclohexane, m.p. 115°.

Anal. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.55; H, 4.74; N, 8.74.

Compound VIIIe was also prepared from IX and benzyl chloride as follows.

Benzyl chloride (0.51 g., 0.004 mole) was added to 0.70 g. (0.003 mole) of 5-mercapto-4-methoxy-1-phenyl-6-pyridazone (IX) dissolved in a mixture of 10 ml. of 5% sodium hydroxide solution, 8 ml. of 28% aqueous ammonia and 20 ml. of ethanol at room temperature. The reaction mixture was stirred for 6 hours at room temperature. The solid which separated was collected and recrystallized from benzene-cyclohexane to give 0.60 g. (62%) of VIIIe, m.p. 111-112°. The analytical sample separated from cyclohexane as colorless needles, m.p. 114-115°. This compound did not depress the melting point of VIIIe prepared from VIIa and benzyl mercaptan.

Anal. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.85; H, 4.85; N, 9.04.

5-Benzylthio-4-ethoxy-1-phenyl-6-pyridazone (VIIIf).

This compound was prepared from VIIb (1.25 g., 0.005 mole), 0.85 g. (0.006 mole) of benzyl mercaptan and 0.27 g. (0.007 mole) of sodium amide as described for VIIIa above. The yield of VIIIf, m.p. 93-95°, was quantitative. The analytical sample separated as colorless needles upon recrystallization from cyclohexane, m.p. 98°.

Anal. Calcd. for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36. Found: C, 67.44; H, 5.11.

5-Mercapto-4-methoxy-1-phenyl-6-pyridazone (IX) and 2,7-Diphenyldipyridazo[4,5-b:4,5-e]-1,4-dithiin-1,6-dione (X).

5-Chloro-4-methoxy-1-phenyl-6-pyridazone (VIIa) (1.18 g., 0.005 mole) was added to 0.56 g. (0.01 mole) of sodium hydrosulfide in 50 ml. of ethanol and the mixture was heated under reflux for 5 hours. Ethanol was removed from the reaction mixture by distillation under reduced pressure. The solid residue was digested with warm water and an insoluble residue was separated by filtration from the alkaline filtrate. This residue was washed repeatedly with water and with ethanol, yield, 0.2 g. (20%). This compound was difficultly soluble in any solvent, m.p. >350°, reddish plates. This compound was assigned structure X and was reported by Castle and Kaji (10).

Anal. Calcd. for $C_{20}H_{12}N_4O_2S_2$: C, 59.38; H, 2.99; N, 13.86; S, 15.86. Found: C, 59.25; H, 2.86; N, 13.77; S, 15.91.

The aqueous alkaline filtrate from which X had been separated was acidified with glacial acetic acid. The crystalline solid which separated melted at 128-133°, 0.60 g. (51%). The analytical sample was prepared by recrystallization from benzene-cyclohexane, colorless plates, m.p. 137-138°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96; S, 13.69. Found: C, 56.40; H, 3.95; N, 12.24; S, 13.70.

5-Chloro-4-piperidino-6-pyridazone (XII).

4,5-Dichloro-6-pyridazone (XI) (7) (16.5 g., 0.1 mole) and 17.0 g. (0.2 mole) of piperidine dissolved in 300 ml. of absolute ethanol were heated under reflux for 3 hours. Colorless crystals separated from the cooled reaction mixture, yield 21.3 g. (quantitative), m.p. 171-173°. The analytical specimen was recrystallized from ethanol, m.p. 192° (lit. (11) 186-187°).

Anal. Calcd. for $C_9H_{12}ClN_3O$: C, 50.59; H, 5.66; N, 19.67. Found: C, 50.33; H, 5.30; N, 19.43.

5-Chloro-4-morpholino-6-pyridazone (XIII).

Compound XI (16.5 g., 0.1 mole) and 17.4 g. (0.2 mole) of morpholine dissolved in 300 ml. of absolute ethanol were heated for 3 hours. Colorless crystals of XIII separated from the reaction mixture upon cooling, 17.3 g. (80%), m.p. 235°. The analytical sample from ethanol melted at 236° (lit. (11) 229°).

Anal. Calcd. for $C_8H_{10}ClN_3O_2$: C, 44.56; H, 4.67. Found: C, 44.58; H, 4.41.

5-Bromo-4-morpholino-6-pyridazone (XV).

4,5-Dibromo-6-pyridazone (I) (12.7 g., 0.05 mole) and 8.72 g. (0.1 mole) of morpholine in 200 ml. of absolute ethanol were heated for 3 hours. A yield of 21.3 g. (82%) of XV separated on cooling, m.p. 151-157°. The analytical sample crystallized in colorless leaflets from ethanol, m.p. 157°.

Anal. Calcd. for $C_8H_{10}BrN_3O_2$: C, 36.93; H, 3.88; N, 16.16. Found: C, 36.79; H, 3.56; N, 15.82.

5-Benzylthio-4-morpholino-6-pyridazone (XVI).

(a) From 5-Bromo-4-morpholino-6-pyridazone (XV).

Compound XV (1.30 g., 0.005 mole) was added to a sodium benzyl mercaptide solution previously prepared by heating 1.24 g. (0.01 mole) of benzyl mercaptan with 0.59 g. (0.015 mole) of sodium amide in 50 ml. of dry toluene. The reaction mixture was heated under reflux for 10 hours. A solid residue was removed by filtration and washed thoroughly with toluene. The washings and the filtrate were combined and concentrated under reduced pressure nearly to dryness. The residue was recrystallized from ethanol to give 0.76 g. (50%) of XV, m.p. 201°. The analytical sample prepared by recrystallization from ethanol melted at 201°.

Anal. Calcd. for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.65; N, 13.85. Found: C, 59.45; H, 5.57; N, 13.70.

(b) XVI From 5-Chloro-4-morpholino-6-pyridazone (XIII).

Compound XVI was prepared from XIII in a manner identical to that described under (a) above, yield 0.80 g. (53%), m.p. 201°, mixed melting point with XVI as prepared under (a), 201°.

5-Chloro-4-morpholino-1-phenyl-6-pyridazone (XVII).

4,5-Dichloro-1-phenyl-6-pyridazone (IV) (12.0 g., 0.05 mole) and 8.70 g. (0.1 mole) of morpholine in 200 ml. of absolute ethanol were heated for 3 hours. Colorless crystals, 13.8 g. (95%), m.p. 176-177° separated from the cold reaction mixture. The analytical sample obtained by recrystallization from ethanol melted at 177°.

Anal. Calcd. for $C_{14}H_{14}ClN_3O_2$: C, 57.63; H, 4.84; N, 14.41. Found: C, 57.69; H, 4.76; N, 14.70.

5-Benzylthio-4-morpholino-1-phenyl-6-pyridazone (XVIIIa).

5-Chloro-4-morpholino-1-phenyl-6-pyridazone (XVII) (1.46 g., 0.005 mole), benzyl mercaptan (0.85 g., 0.006 mole) and sodium amide (0.27 g., 0.007 mole) in 20 ml. of dry benzene was heated for 5 hours and the product worked up in the usual fashion. The residue was recrystallized from benzene-cyclohexane to give 1.3 g. (69%) of XVIIIa, m.p. 114°. The analytical sample was recrystallized from cyclohexane, m.p. 114°.

Anal. Calcd. for $C_{21}H_{21}N_3O_2S$: C, 66.46; H, 5.58; N, 11.07. Found: C, 66.35; H, 5.50; N, 11.54.

5-(*p*-Chlorobenzylthio)-4-morpholino-1-phenyl-6-pyridazone (XVIIIb).

From 1.46 g. (0.005 mole) of XVII, 0.96 g. (0.006 mole) of *p*-chlorobenzyl mercaptan and 0.27 g. (0.007 mole) of sodium amide in 20 ml. of dry benzene, 1.70 g. (82%) of XVIIIb, m.p. 120°, was obtained. The analytical specimen from cyclohexane had a melting point of 125°.

Anal. Calcd. for $C_{21}H_{20}ClN_3O_2S$: C, 60.93; H, 4.88. Found: C, 60.94; H, 4.54.

5-Chloro-4-piperidino-1-phenyl-6-pyridazone (XIX).

Compound IV (4.80 g., 0.02 mole) and 3.40 g. (0.04 mole) of piperidine in 80 ml. of ethanol in a manner similar to the preparation of XVII gave 5.5 g. (95%) of XIX, m.p. 155-157°. The analytical sample from absolute ethanol melted at 157°.

Anal. Calcd. for $C_{15}H_{16}ClN_3O$: C, 62.17; H, 5.57; N, 14.50. Found: C, 62.13; H, 5.64; N, 14.75.

5-Benzylthio-4-piperidino-1-phenyl-6-pyridazone (XXa).

Compound XIX (1.45 g., 0.005 mole), 0.85 g. (0.006 mole) of benzyl mercaptan and 0.27 g. (0.007 mole) of sodium amide in 20 ml. of dry benzene in a manner similar to the preparation of VIIIa gave 1.2 g. (64%) of XXa, m.p. 138°. The analytical sample from benzene-cyclohexane melted at 138°.

Anal. Calcd. for $C_{22}H_{23}N_3OS$: C, 69.99; H, 6.14; N, 11.13. Found: C, 70.02; H, 6.02; N, 11.46.

5-(*p*-Chlorobenzylthio)-4-piperidino-1-phenyl-6-pyridazone (XXb).

Compound XIX (1.45 g., 0.005 mole), 0.85 g. (0.006 mole) of benzyl mercaptan and 0.27 g. (0.007 mole) of sodium amide in 20 ml. of dry benzene in a manner similar to the preparation of VIIIa gave 1.60 g. (78%) of XXb, m.p. 164° after recrystallization from benzene-cyclohexane. The analytical sample recrystallized from the same solvent couple melted at 164°.

Anal. Calcd. for $C_{22}H_{22}ClN_3OS$: C, 64.14; H, 5.38. Found: C, 64.06; H, 5.26.

Typical Procedure, Table III.

3-Benzylthio-6-methylpyridazine (XXIIa).

Benzyl chloride (2.57 g., 0.02 mole) in 20 ml. of ethanol was added to the mercaptide solution prepared by dissolving 1.26 g. (0.01 mole) of 6-methyl-3-pyridazinethiol (XXI) (11) in a mixture of 20 ml. of 5% sodium hydroxide solution, 15 ml. of 28% aqueous ammonia and 20 ml. of ethanol. The reaction mixture was stirred at room temperature for 6 hours. The solid which separated was collected, washed with water and dried in air to give 1.70 g. (79%) of XXIIa, m.p. 91-93°. An analytical specimen prepared by recrystallization from cyclohexane melted at 93°.

6-Ethoxy-3-pyridazinethiol (XXIV).

3-Chloro-6-ethoxypyridazine (13, 14a) (7.93 g., 0.05 mole) was added to a solution of 4.60 g. (0.06 mole) of thiourea in 60 ml. of ethanol. The reaction mixture was heated under reflux for 40 minutes. The excess ethanol was removed by distillation under reduced pressure and to the remaining solution was added 5 g. of sodium carbonate dissolved in 40 ml. of water. A yellow solid separated which was collected, washed with water and recrystallized from ethanol to give 7.0 g. (92%) of XXIV, m.p. 190°. The analytical sample recrystallized from ethanol as long yellow needles, m.p. 190°.

Anal. Calcd. for $C_6H_8N_2OS$: C, 46.14; H, 5.16; N, 17.94. Found: C, 46.22; H, 5.02; N, 18.19.

6-*n*-Propoxy-3-pyridazinethiol (XXVII).

3-Chloro-6-*n*-propoxypyridazine (14a,b) (8.63 g., 0.05 mole) and 4.06 g. (0.06 mole) of thiourea in 60 ml. of ethanol were heated for 2 hours. The reaction mixture was treated as described above for the preparation of XXIV. Compound XXVII was obtained in 65% yield (5.50 g.), m.p. 165°. The analytical specimen separated from ethanol in yellow needles, m.p. 165°.

Anal. Calcd. for $C_7H_{10}N_2OS$: C, 49.39; H, 5.92; N, 16.45. Found: C, 49.55; H, 5.80; N, 16.35.

Typical Procedure, Table IV, Compounds XXVa-e and XXVIIIa-c.

3-Benzylthio-6-ethoxypyridazine.

Benzyl chloride (2.53 g., 0.02 mole) in 20 ml. of ethanol was added to the mercaptide solution prepared by dissolving 1.56 g. (0.01 mole) of XXIV in a mixture of 20 ml. of 5% sodium hydroxide solution, 15 ml. of 28% aqueous ammonia and 20 ml. of ethanol. The reaction mixture was stirred for 12 hours at room temperature. The solid which separated was collected, washed with water and dried in air to give 2.30 g. (94%) of crude XXVa, m.p. 93-95°. The analytical sample separated from cyclohexane in colorless crystals, m.p. 96-97°.

Typical Procedure, Table V, Compounds XXXa and XXXe.

A mixture containing 1.08 g. (0.01 mole) of 3,6-dimethylpyridazine (14a) (XXIX), 22.38 g. (0.219 mole) of benzaldehyde and 1.36 g. (0.01 mole) of anhydrous zinc chloride was heated at 150° for 4 hours. The cooled reaction mixture was treated with a mixture of 10 ml. of benzene and 10 ml. of 2 *N* hydrochloric acid and warmed on the steam bath for 5 minutes. The crude 3,6-bisstyrylpyridazine hydrochloride which separated was collected, washed with water and dried in air. The hydrochloride was converted into the free base by shaking with dilute sodium hydroxide solution. The product crystallized from ethanol in fine pale yellow needles, m.p. 228°, and weighed 2.10 g. (74%). The analytical sample was prepared by recrystallization from ethanol, m.p. 230°. Compound XXXf was prepared in a similar fashion except that the zinc chloride was omitted.

Typical Procedure, Table V, Compounds XXXb, XXXc and XXXd.

Compound XXIX (1.08 g., 0.01 mole) and 2.98 g. (0.024 mole) of *m*-fluorobenzaldehyde were dissolved in 10.2 g. (0.1 mole) of acetic anhydride and the mixture was heated under reflux for 15 hours. The reaction mixture solidified upon cooling. The excess acetic anhydride was removed under reduced pressure and the solid residue collected and washed with an ethanol-benzene mixture. The product amounted to 2.00 g. (62%), m.p. 192-195°. The analytical sample separated from ethanol in golden yellow plates, m.p. 195°.

Acknowledgment.

This investigation was supported by Public Health Service Research Grant No. CA-02653 from the National Cancer Institute. The authors are grateful to Miss Yoko Tokushige for the analytical data reported.

REFERENCES

(1) For Pyridazines, II., see W. D. Guither, D. G. Clark and R. N. Castle, *J. Heterocyclic Chem.*, 2, 67 (1965).

(2) To whom inquiries concerning this paper should be directed.

(3) W. M. Osner, R. N. Castle and D. L. Aldous, *J. Pharm. Sci.*, 52, 539 (1963).

(4) R. N. Castle and K. Kaji, *Tetrahedron Letters*, 393 (1962).

(5) T. Kuraishi, *Pharm. Bull.* (Tokyo), 4, 497 (1956).

(6) C. Grundmann, *Chem. Ber.*, 81, 1 (1948).

(7) D. T. Mowry, *J. Am. Chem. Soc.*, 75, 1909 (1953).

(8) K. Dury, *Angew. Chem. Intern. Ed.*, 4, 292 (1965).

(9) W. R. Benson and A. E. Pohland, *J. Org. Chem.*, 29, 385 (1964).

(10) R. N. Castle and K. Kaji, *Naturwissenschaften*, 51, 38 (1964).

(11) J. Bourdais, *Bull. Soc. Chim. France*, 2124 (1964).

(12) M. Kumagai, *J. Chem. Soc. Japan*, 81, 1605 (1960).

(13) T. Itai and H. Igeta, *J. Pharm. Soc. Japan*, 74, 1195 (1954).

(14a) N. Takahayashi, *ibid.*, 75, 778 (1955). (b) P. Coad and R. A. Coad, *J. Med. Chem.*, 8, 129 (1965).

(15) J. Levisalles, *Bull. Soc. Chim. France*, 997 (1957).

(16) The authors are indebted to Dr. Joseph Leiter, Cancer Chemotherapy National Service Center, Bethesda, Maryland for these screening data.

(17) All melting points are uncorrected.

Received October 28, 1965 Albuquerque, New Mexico 87106