30～60 min. After distillation of the solvent under reduced pressure, 10% HCl solution was added onto the residue. Crude solid was crystallized from EtOH. Recrystallization gave colorless needles.

III) General Procedure for the Synthesis N-(6-Alkoxy-3-pyridazinyl)-5-nitro-2-furamide——0.0044 mole of 3-amino-6-alkoxypyridazine[7] was dissolved in a mixture of 10 cc. of Me_2CO and 10 cc. of pyridine and placed in an ice-water to cool. To this solution, 0.004 mole of 5-nitro-2-furoyl chloride in 5 cc. of Me_2CO was slowly added. Then the mixture was refluxed on a water-bath for 30 min. After distillation of the solvent under reduced pressure, 10% HCl solution was added onto the residue. Crude solid was crystallized from EtOH. Recrystallization gave colorless grains.

The author expresses his deepest thanks to Prof. Takeo Ueda for kind guidance throughout the course of this work.

Summary

Compounds of N-[4-(*p*-alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide (I), N-(5-alkyl-1,3,4-thiadiazolyl)-5-nitro-2-furamide (II), and N-(6-alkoxy-3-pyridazinyl)-5-nitro-2-furamide (III) were synthesized to observe their antibacterial and antifungal activity. On the bacteria, ethyl derivative among the compounds of (I) series and, methyl and ethyl derivatives of (III) series were observed to have effects nearly equal to that of nitrofuran.

Antifungal activity of the compounds of three series were more or less effective on both *Trichophyton asteroides* and *Aspergillus fumigatus*, but uneffective on the other fungi.

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95. Tatsuya Horie(Ishida), Kiyokatsu Kinjo, and Takeo Ueda : Studies on Pyridazine Derivatives. I.*1 Synthesis and Antimicrobial Activity of 6-Substituted 3-Aminopyridazine and its Sulfonamido Derivatives.

(*Pharmaceutical Institute, Keio University**2)

As pyridazine is related structurally to pyrimidine, it is of interest to utilize pyridazine ring as an antagonistic group against naturally occuring substances containing pyrimidine ring, in connection of finding new antimicrobial agents.

In fact, attempts were made by many workers[1~5] to introduce pyridazine ring into the structures of sulfa drugs, since Anderson[6] had reported the synthesis and antibacterial activity of 3-sulfanilylamidopyridazine. Above all, it should be noted that 3-sulfanilylamido-6-methoxypyridazine was confirmed to be valuable by Nichole[7,8] as

*1 Papers were read at the Annual Meeting of Pharm. Soc. of Japan, No. 78 (1958) and 80 (1960).

*2 Shinano-machi, Shinjuku-ku, Tokyo (堀江達也, 金城清勝, 上田武雄).

1) P.S. Winnek and R.O. Roblin : C.A. **40**, 604 (1946).
2) W.G. Overend and L.F. Wiggins : J. Chem. Soc., **1947**, 239. *Idem: Ibid.*, **1947**, 549.
3) C. Grundman : Chem. Ber., **81**, 1 (1948).
4) R.F. Hormer, H. Gregory, W.G. Overend and L.F. Wiggins : J. Chem. Soc., **1948**, 2195.
5) H. Gregory, W.G. Overend and L.F. Wiggins : *Ibid.*, **1948**, 2199.
6) G.W. Anderson, H.E. Faith, H.W. Marson, P.S. Winnek and R.O. Roblin : J. Am. Chem. Soc., **64**, 2902, (1942).
7) R. Nichole : Proc. Soc. Exper. Biol. Med., **92**, 637 (1957).
8) R. Nichole : J. Lab. Clin. Med., **49**, 4101 (1957).

a long acting sulfa drug. In this compound, it may be emphasized that pyridazine ring and methoxy group might be associated with generation of specialantimicrobial activity. Therefore, pyridazine derivatives are of interest for finding new antimicrobial agents.

In parallel with those works, the authors have investigated pyridazine derivatives since several years ago, to find antimicrobial agents, synthesized a number of 6-substituted 3-aminopyridazine and its sulfonamido derivatives, having various substituent groups at 6-position of pyridazine ring such as hydroxy, alkoxy, aralkyloxy, aryloxy, mercapto, alkylthio and arylthio, and tested as to their activity on various bacteria. This paper is concerned with the synthesis of 6-substituted 3-aminopyridazine and its sulfonamido derivatives and their antibacterial activity.

Synthesis of 6-Substituted 3-Aminopyridazine

3-Amino-6-halopyridazine was taken up by the most important intermediate for the synthesis of the desired pyridazine derivatives. The synthetic method of 3-amino-6-halopyridazine from 3,6-dihalopyridazinethrough 3,6-pyridazinediol has been reported in recent papers,[9~11] but any of 3-amino-6-alkoxy-,[12] 3-amino-6-alkylthio,[13] 3-amino-6-hydroxy, and 3-amino-6-pyridazinethiol had not been revealed in any literature until the authors' reports were announced.*[1]

According to the usual method to convert halogen atom to alkoxy group, 3-amino-6-alkoxypyridazine was obtained by reacti ng 3-amino-6-halopyridazine with various kinds of metal alcoholates at 120~140°, for 5~8 hours in an autoclave, as shown in Chart 1.

X : chlorine or bromine atom Met : sodium or potassium

Chart 1.

The product was also found to be synthesized by ammonolysing 3-bromo-6-alkoxypyridazine[13] with liquid ammonia or saturated methanolic ammonia in the presence of small amount of copper powder as catalyst, as shown in Chart 2.[14]

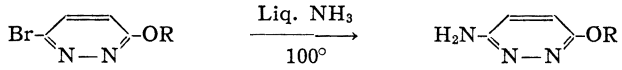


Chart 2.

This product, however, was found unattainable by the reaction of 3-chloro-6-alkoxypyridazine[15,16] with liquid ammonia or with ammonia in methanol under any drastic condition, but 3-chloro-6-pyridazinol was detected in comparatively better yield, as shown in Chart 3.

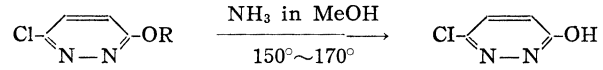


Chart 3.

9) R.H. Mizzoni and P.E. Spoerri : J. Am. Chem. Soc., **73**, 1873 (1951).
10) E.A. Stoch, R.P. Brundage and L.T. Fletcher : *Ibid.* **76**, 3225 (1954).
11) J.H. Clark, J.P. English, G.R. Janson, H.W. Marson, M.M. Rogers and W.E. Taft : J. Am. Chem. Soc., **80**, 980, (1958), 3-Amino-5-methoxypyridazine and some 3-sulfanilyl-6-alkoxypyridazine were reported here, when the authors had announced about them in Annual Meeting of Pharm. Soc. of Japan, No. 78 (1958).
12) Berg. Pat. 579, 291 by H.G. Morren, (C.A., **54**, 9968, h, 1960). Several of 3-amino-6-alkyl pyridazinethiol and 3-amino-6-pyridazinethiol were revealed here, after the authors had studied and reported about them in the Annual Meeting of Pharm. Soc. of Japan, No. 80 (1960).
13) J. Druey, K.Meier and K. Eichemberger : Helv. Chim. Acta., **37**, 121 (1954).
14) T. Ueda, E. Morii, T. Wachi and T. Ishida : Japan Pat. 266,339.
15) T. Itai and H. Igeta : Yakugaku Zasshi, **74**, 1195 (1954).
16) R. Takabayashi : *Ibid.*, **75**, 778 (1955).

These results coincided with the tendency that the bromine atom attached to 6-position of pyridazine ring is more reactive than the chlorine, just as usually observed in nucleophilic substitution against halogen atom. Moreover, some compounds of 3-amino-6-alkoxypyridazine were found obtainable through an indirect route after the hydrolysis of their acetamido derivatives.

3-Amino-6-alkylthiopyridazine was synthesized by reacting 3-amino-6-halopyridazine with metal mercaptide in dioxane solution at 120~130°, as illustrated in Chart 3.

Chart 4.

Next, the synthesis of 3-amino-6-pyridazinol was undertaken, which had not been revealed in any literature. The alkaline hydrolysis of 3-amino-6-halopyridazine did not afford any product under any reaction condition. However, this compound was obtained by solvolysing 3-amino-6-halopyridazine with glaicial acetic acid and anhydrous potassium acetate for about 2 hours under reflux and hydrolysing resulted 3-amino-6-acetoxypyridazine with 10% hydrochloric acid under boiling, as shown in Chart 5.

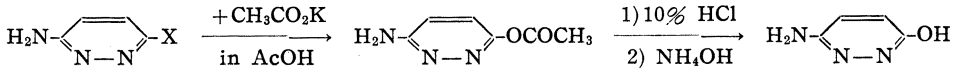
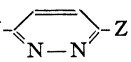


Chart 5.

Table Ia. General Formula 

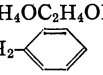
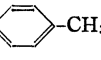
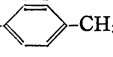
Compd. No.	X	Form	m.p. (°C)	Appearance	Solvent
1	-Cl	Free base	215 (decomp.)	White Prisms	MeOH
2	-Br	〃	210 (〃)	Slight yellow prisms	〃
3	-OH	〃	227	White prisms	EtOH
		HCl salt	246	Slight yellow prisms	MeOH
4	$-OCH_3$	Free base	106	Slight brown prisms	EtOAc
5	$-OC_2H_5$	〃	169	White needles	〃
6	$-O-n-C_3H_7$	〃	113	White prisms	〃
		HCl salt	185	White needles	$EtOH+Et_2O$
7	$-O-n-C_4H_9$	Free base	128	White prisms	Me_2CO
		HCl salt	167	White needles	$EtOH+Et_2O$
8	$-O-n-C_5H_{11}$	Free base	126	White prisms	Me_2CO
		HCl salt	159	White needles	EtOH
9	$-O-iso-C_5H_{11}$	Free base	102	White prisms	EtOAc
		HCl salt	184	White needles	EtOH
10	$-O-n-C_6H_{13}$	Free base	~50	White fine prisms	EtOAc
		HCl salt	164	White powder	$EtOH+Et_2O$
11	$-O-n-C_8H_{17}$	Free base	oil	Slight brown oil	EtOH
		HCl salt	168	White needles	〃
12	$-O-n-C_{10}H_{21}$	Free base	70	White powder	EtOAc
13	$-OC_2H_4OH$	Free base	141 (120° wet)	White prisms	EtOH
		Mono hydrate			
14	$-OC_2H_4OC_2H_5$	Free base	89	〃	〃
15	$-OC_2H_4OC_2H_4OH$	〃	113	〃	〃
16		〃	117	White needles	EtOAc
		Acetate	190	〃	EtOH
17		Free base	160	White prisms	EtOH
18	-SH	〃	~268° (decomp.)	Yellow prisms	Re-ppt.
19	$-SCH_3$	〃	116	Slight yellow neldles	$CHCl_3$
20	$-SC_2H_5$	〃	53	〃	〃
21	$-SC_4H_9$	〃	85	White needles	〃
22		〃	138	White prisms	EtOH
23		〃	149	〃	〃

Table Ib. Analytical Data of Compounds shown in Table Ia

Compd. No.	Form	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	Free base	$C_4H_4N_3Cl$		(known)[13]				
2	〃	$C_4H_4N_3Br$		〃				
3	HCl salt	$C_4H_6N_3OCl$	32.52	4.06	28.47	32.83	4.26	28.46
4	Free base	$C_5H_7N_3O$	48.00	5.60	33.60	48.29	5.76	33.47
5	〃	$C_6H_9N_3O$	51.79	6.47	30.21	51.81	6.44	30.30
6	HCl salt	$C_7H_{12}N_3OCl$	44.32	6.33	22.16	44.39	6.57	22.24
7	Free base mono-hydrate	$C_8H_{15}N_3O_2$	51.90	8.10	22.70	51.88	7.85	22.81
8	HCl salt	$C_9H_{16}N_3OCl$	49.65	7.35	19.31	49.68	7.48	19.53
9	〃	$C_9H_{16}N_3OCl$	49.65	7.35	19.31	49.39	7.54	19.44
10	〃	$C_{10}H_{18}N_3OCl$	—	—	18.14	—	—	18.30
11	〃	$C_{12}H_{22}N_3OCl$	55.06	8.41	16.06	55.35	8.59	16.13
12	Free base	$C_{14}H_{25}N_3O$	66.89	10.03	16.72	66.67	10.30	16.94
13	Free base mono-hydrate	$C_6H_{11}N_3O_4$	41.61	5.20	24.27	41.48	5.60	24.24
14	Free base	$C_8H_{13}N_3O_2$	52.46	7.12	22.94	52.19	6.86	23.06
15	〃	$C_8H_{13}N_3O_3$	48.24	6.53	21.10	48.12	6.66	20.99
16	〃	$C_{11}H_{11}N_3O$	—	—	20.88	—	—	20.69
	Acetate	$C_{13}H_{13}N_3O_2$	—	—	17.28	—	—	17.11
17	Free base	$C_{11}H_{11}N_3O$	—	—	20.88	—	—	
18	〃	$C_4H_5N_3S$	37.79	3.94	33.07	37.39	4.19	32.95
19	〃	$C_5H_7N_3S$	42.62	4.96	29.78	42.68	5.08	29.38
20	〃	$C_6H_9N_3S$	46.45	5.80	27.09	46.55	5.61	26.89
21	〃	$C_8H_{13}N_3S$	—	—	22.95	—	—	22.88
22	〃	$C_{10}H_9N_3S$	—	—	21.70	—	—	21.58
23	〃	$C_{11}H_{11}N_3S$	—	—	19.34	—	—	18.98

On the other hand, 3-amino-6-pyridazinethiol was obtained by reacting 3-amino-6-halopyridazine with sodium bisulfide in aqueous ethanolic solution at 110~120° in an autoclave, according to the analogous method to that of 3-amino-6-alkylthiopyridazine, as shown in Chart 6.

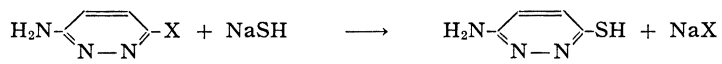


Chart 6.

The compounds synthesized above are shown in Table I.

Synthesis of Sulfonamido Derivatives from 6-Substituted 3-Aminopyridazine

Taking the usual synthetic methods of sulfa drugs into consideration, sulfonamido derivatives of various types from 6-substituted 3-aminopyridazine were synthesized through various routes as shown in Chart 8.

According to the usual method of known sulfa drugs, 3-sulfanilyl-6-halo-, 3-sulfanilyl-6-alkoxy- and 3-sulfanilyl-6-alkylthio-pyridazine were obtained by condensing *p*-acetamidobenzenesulfonyl chloride with each of corresponding aminopyridazines and hydrolysing the resulting acetamido products with aqueous sodium hydroxide solution, as shown in Process A. Hereupon, in the reaction between 3-amino-6-chloropyridazine and *p*-acetamidobenzenesulfonyl chloride, small amount of bis-sulfonamido products were found to be produced in some reaction conditions, which were easily converted to 3-(*p*-acetamidophenylsulfonamido)-6-chloropyridazine by the treatment with sodium hydroxide in ethanolic solution.

Another synthetic method of the new sulfanilamides was conceived through 3-(*p*-nitrophenylsulfonamido)-6-halopyridazine as shown by Process B. However, the exprimental results showed that 3-(*p*-nitrophenylsulfonamido)-6-halopyridazine could not be obtained by the reaction between *p*-nitrobenzenesulfonyl chloride and 3-amino-6-halopy-

ridazine under any reaction condition. Therefore, attempts were made to search the synthetic method through another route.

The authors succeeded in finding the method to produce a number of 6-substituted 3-sulfanilylpyridazine, using 3-sulfanilyl-6-halopyridazine, as shown in Process C, and Process D. Hereupon 3-sulfanilylamido-6-halopyridazine was synthesized by either the fusing reaction[18,17,18] between 3,6-dihalopyridazine and sulfanilamide in the presence of potassium carbonate or hydrolysis of 3-(*p*-acetamidophenylsulfonamido)-6-halopyridazine,

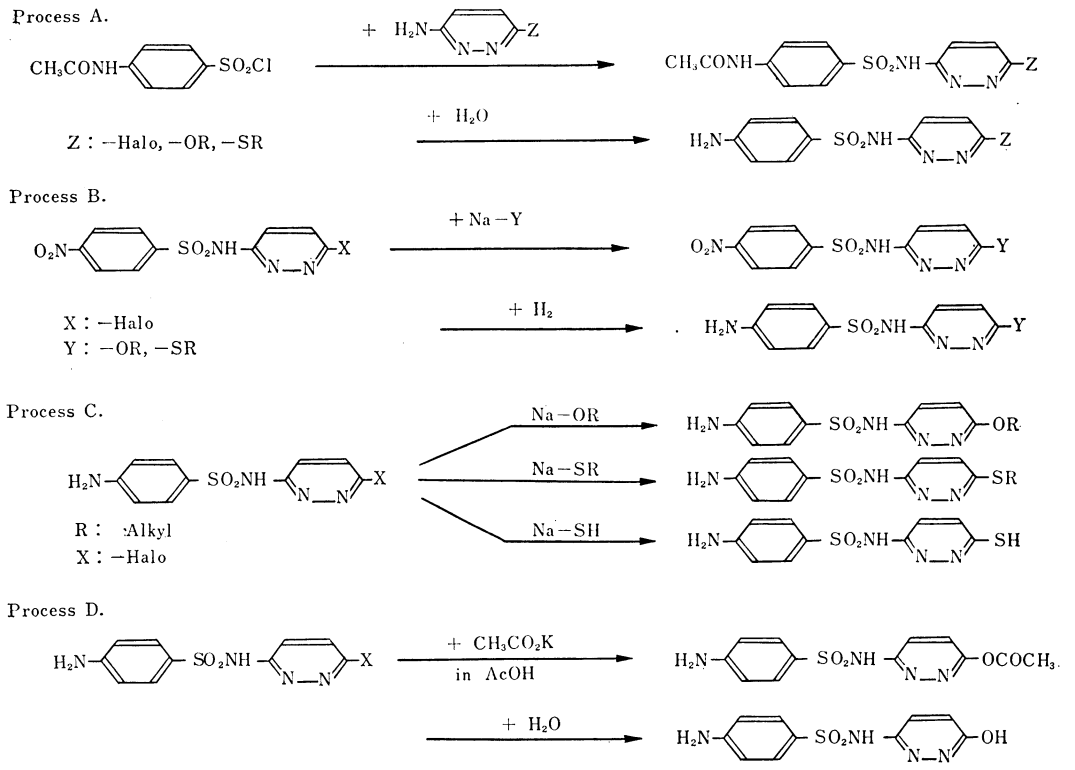
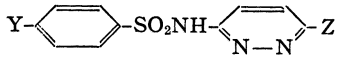


Chart 7.

which was prepared by condensing 3-amino-6-halopyridazine with *p*-acetamidobenzenesulfonyl chloride in anhydrous pyridine or by fusing 3,6-dihalopyridazine with *p*-acetamidobenzenesulfonamide in the presence of potassium carbonate, as shown in Chart 9. This intermediate was converted to desired sulfonamido derivatives by reacting with each of metal alkoxide,[11,19] metal mercaptide and sodium bisulfide, as shown in Process C. However, 3-sulfanilyl-6-pyridazinol was obtained through another route by solvolyzing with glacial acetic acid and potassium acetate, and hydrolyzing the resulted 6-acetoxy derivative with 10% hydrochloric acid, as shown in Process D.

The compounds thus synthesized are shown in Table II, and were tested for their antibacterial activity. It is of interest to find that what route is the best for making 6-substituted 3-sulfanilylpyridazine industrially. The work on this problem will be discussed in the near future.

17) J. Druey : Japan Pat. 31-3123.
18) M. M. Rogers and J. P. English : U. S. Pat. 2,712,011.
19) T. Ueda, E. Morii, T. Wachi, T. Ishida : Japan Pat. 267,845.

Table IIa. General Formula 

Compd. No.	Y	Z	m.p. (°C)	Appearance	Solvent
24	H_2N-	-Cl	195 (decomp.)	Slight yellow pr.	MeOH
25	〃	-Br	200 (〃)	〃	〃
26	〃	-OH	257 (〃)	Slight yel. powder	〃
27	〃	-$OCOCH_3$	210 (〃)	White powder	〃
28	〃	-OCH_3	181	Slight yellow pr.	〃
29	〃	-O-C_2H_5	183	〃	〃
30	〃	-O-iso-C_3H_7	184	〃	〃
31	〃	-O-*n*-C_4H_9	167	Faint yellow pr.	70% EtOH
32	〃	-O-*n*-C_6H_{13}	139	White needles	EtOH + Benzene
33	〃	-O-*n*-C_8H_{17}	133	〃	〃
34	〃	-SH	285 (decomp.)	Yellow powder	NH_3 in MeOH + dil. HCl
35	〃	-SCH_3	198	Slight yellow pr.	MeOH
36	〃	-SC_2H_5	166	〃	dil. MeOH
37	〃	-S-*n*-C_3H_7	168	〃	〃
38	〃	-S-*n*-C_4H_9	140	Faint yellow pr.	〃
39	〃	-S-*n*-C_5H_{10}	151	White prisms	〃
40	〃	-S-*n*-C_6H_{13}	143	〃	〃
41	AcHN-	-Cl	225 (decomp.)	Faint yellow pow.	NH_3 in dil. MeOH + AcOH
42	〃	-Br	194 (〃)	〃	〃
43	〃	-$OCOCH_3$	265 (〃)	White powder	〃
44	〃	-OCH_3	222 (〃)	White needles	〃
45	〃	-OC_2H_5	200 (〃)	〃	〃
46	〃	-O-*n*-C_4H_9	185 (〃)	〃	〃
47	〃	-SCH_3	224	White prisms	MeOH
48	〃	-SC_2H_5	195	〃	〃
49	〃	-SC_4H_9	148	White needles	〃

Table IIb. Analytical Data of Compounds shown in Table IIa

Compd. No.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
24	$C_{10}H_9N_4SO_2Cl$		(known)[13]				
25	$C_{10}H_9N_4SO_2Br$		〃				
26	$C_{10}H_{10}N_4SO_3$	—	—	21.05	—	—	21.13
27	$C_{12}H_{12}N_4SO_4$	—	—	18.18	—	—	18.30
28	$C_{11}H_{12}N_4SO_3$	47.14	4.28	20.00	47.28	4.14	19.86
29	$C_{12}H_{14}N_4SO_3$	49.09	4.76	19.04	49.16	4.78	18.84
30	$C_{13}H_{16}N_4SO_3$	50.06	5.19	18.18	50.31	5.26	18.13
31	$C_{14}H_{18}N_4SO_3$	52.17	5.59	17.39	52.26	5.64	17.48
32	$C_{16}H_{22}N_4SO_3$	54.85	6.28	16.60	54.97	6.49	16.08
33	$C_{18}H_{26}N_4SO_3$	—	—	14.00	—	—	14.31
34	$C_{10}H_{10}N_4S_2O_2$	—	—	19.84	—	—	19.72
35	$C_{11}H_{12}N_4S_2O_2$	44.58	4.05	18.91	44.71	4.18	18.87
36	$C_{12}H_{14}N_4S_2O_2$	—	—	18.05	—	—	17.85
37	$C_{13}H_{16}N_4S_2O_2$	—	—	17.27	—	—	17.49
38	$C_{14}H_{18}N_4S_2O_2$	—	—	16.56	—	—	16.52
39	$C_{15}H_{20}N_4S_2O_2$	—	—	15.90	—	—	16.09
40	$C_{16}H_{22}N_4S_2O_2$	—	—	15.29	—	—	15.43
41	$C_{12}H_{11}N_4SO_3Cl$	44.14	3.37	17.15	44.18	3.66	17.19
42	$C_{12}H_{11}N_4SO_3Br$	—	—	15.09	—	—	14.87
43	$C_{14}H_{14}N_4SO_5$	—	—	15.99	—	—	15.70
44	$C_{13}H_{14}N_4SO_4$	48.45	4.34	17.39	48.26	4.53	17.49
45	$C_{14}H_{16}N_4SO_4$	—	—	16.66	—	—	16.80
46	$C_{16}H_{20}N_4SO_4$	—	—	15.32	—	—	15.44
47	$C_{13}H_{14}N_4S_2O_3$	—	—	16.57	—	—	16.29
48	$C_{14}H_{16}N_4S_2O_3$	—	—	15.90	—	—	16.18
49	$C_{16}H_{20}N_4S_2O_3$	—	—	14.73	—	—	14.77

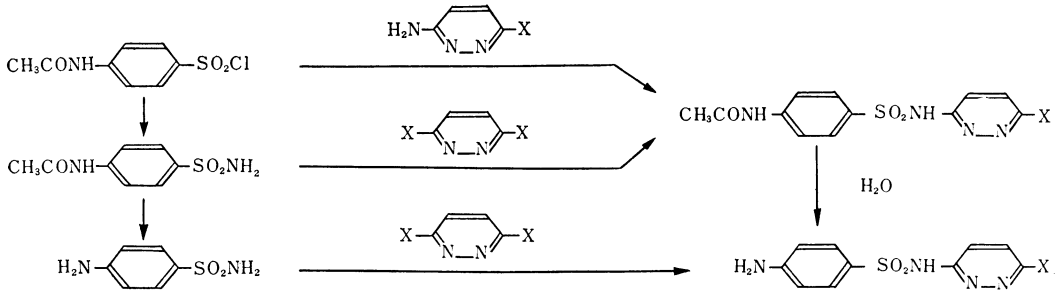
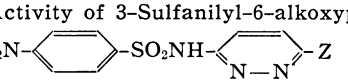


Chart 8.

Antibacterial Activity of 3-Sulfanilyl-6-alkoxypyridazine and 3-Sulfanilyl-6-alkylthiopyridazine

The compounds of 3-sulfanilyl-6-alkoxypyridazine and 3-sulfanilyl-6-alkylthiopyridazine were tested as to their antibacterial spectra, using various bacteria. The experimental procedures and results are shown in Table III and Table IV.

TABLE III. The Antibacterial Activity of 3-Sulfanilyl-6-alkoxypyridazine

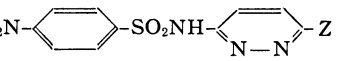
General Formula 

Strains / Drugs (Z) mole/cc.	*S. typhi* 901	*S. paratyphi* A. 1015	*S. paratyphi* B. 8006	*Sh. sonnei* SATO	*S. enteritidis* No. 11	*E. coli* K. 12
-OH	10^{-4}	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$
$-OCH_3$	10^{-5}	2×10^{-5}	10^{-4}	2×10^{-4}	2×10^{-4}	2×10^{-4}
$-OC_2H_5$	2×10^{-5}	2×10^{-5}	2×10^{-5}	2×10^{-5}	2×10^{-5}	2×10^{-5}
-O-iso-C_3H_7	10^{-4}	2×10^{-4}	10^{-4}	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$
-O-*n*-C_4H_9	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$
-O-*n*-C_6H_{13}	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$
-Cl	2×10^{-6}	4×10^{-6}	2×10^{-5}	2×10^{-6}	2×10^{-5}	2×10^{-5}
-Br	4×10^{-6}	10^{-5}	10^{-5}	4×10^{-5}	2×10^{-5}	4×10^{-6}

The medium employed, contained			
KH_2PO_4	0.3%	Agar agar	1.5%
K_2HPO_4	0.7	Glucose	0.5
$MgSO_4\cdot7H_2O$	0.01	Casamino acid	2
$(NH_4)_2SO_4$	0.2	Nicotinic acid	0.01
		Vitamine B_1	0.01

at pH. 7.0. Serial concentrations of the compounds were made in the media. The agar plates were inoculated with one loop of $1:10^{-5}$ concentration of a bacterial suspension of one day old culture, incubated at 37°. The readings of growth were made after 2 days.

TABLE IV. The Antibacterial Activity of 3-Sulfanilyl-6-alkylthiopyridazine

General Formula 

Strains / Drugs (Z) mole/cc.	*E. coli* C. 14	*E. coli* K. 12	*Sh. sonnei* 2a 66	*Sh. sonnei* 1196	*S. tiphi* PB	*Staph. aureus* TERASHIMA	*Myco. tuber* H_{37} RV
-SH	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>2\times10^{-4}$	$>4\times10^{-4}$
$-SCH_3$	5×10^{-5}	5×10^{-5}	5×10^{-5}	5×10^{-5}	2×10^{-4}	10^{-4}	4×10^{-4}
$-SC_2H_5$	5×10^{-5}	5×10^{-5}	10^{-4}	5×10^{-5}	$>2\times10^{-4}$	5×10^{-5}	4×10^{-4}
-S-*n*-C_3H_7	2×10^{-4}	2.5×10^{-5}	2×10^{-4}	10^{-4}	$>2\times10^{-4}$	2.5×10^{-5}	$>4\times10^{-4}$
-S-*n*-C_4H_9	4×10^{-4}	5×10^{-5}	4×10^{-4}	4×10^{-4}	$>4\times10^{-4}$	5×10^{-5}	4×10^{-4}
-S-*n*-C_5H_{11}	$>4\times10^{-4}$	5×10^{-5}	$>4\times10^{-4}$	$>4\times10^{-4}$	$>4\times10^{-4}$	10^{-4}	4×10^{-4}
-S-*n*-C_6H_{13}	$>4\times10^{-4}$	2×10^{-4}	$>4\times10^{-4}$	$>4\times10^{-4}$	$>4\times10^{-4}$	4×10^{-4}	
$-OCH_3$ control	2.5×10^{-5}	2.5×10^{-5}	5×10^{-5}	2.5×10^{-5}	2×10^{-4}	5×10^{-5}	

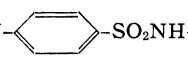
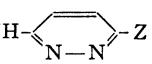
The Müller Hinton's medium was used in this test. The other procedures were the same as that described in Table III. However, in the antituberculous test, the tubes were inoculated with 0.1 cc. of 1:2 concentration of a suspension of two weeks old culture of *Mycobacterium tuberculosis* H_{37} RV in Dubos, incubated at 37°. The readings of growth were made after 7 days.

As shown in Table III, it was made clear that 6-hydroxy derivatives were inactive on the bacteria, both 6-methoxy and 6-ethoxy derivatives exerted activity on all of the bacteria, nearly equal to that of Sulfadiazine or Sulfathiazole. 6-Isopropoxy, 6-butoxy and 6-hexyloxy derivatives showed rather weaker activity that than 6-methoxy derivative, herein indicating a tendency that the longer alkyl chain of alkoxy group, the weaker the activity was, and 6-chloro and 6-bromo derivatives rather active than either 6-methoxy or 6-ethoxy derivative.

However, as emphasized by Nicholes,[7,8] it should be considered that 3-sulfanilyl-6-methoxypyridazine has a long acting antibacterial effect, that is a characteristic property maintaining its higher concentration in blood for a longer duration, on account of its difficult excretability from host body. Regarding this point, Kinjo and Kamata*[3] reconfirmed that 3-sulfanilyl-6-methoxypyridazine showed the longest effect among 3-sulfanilyl-6-ethoxypyridazine, 3-sulfanilyl-6-(2-hydroxyethoxy)pyridazine and 3-sulfanilyl-6-chloropyridazine, determining their concentration in blood of rats for 24 hours. From these findings, it may be said that 3-sulfanilyl-6-methoxypyridazine was the most excellent in balance of antibacterial effect and duration of effect, and the others were inferior to the former on point of duration of antibacterial effect.

From Table IV, it may be said that 6-methylthio and 6-ethylthio derivatives showed *in vitro* activity nearly equal to that of 3-sulfanilyl-6-methoxyridazine as the control among compounds of 3-sulfanilyl-6-alkylthiopyridazine. However, 3-sulfanilyl-6-pyridazinethiol was found inactive on the bacteria, in contrast with the above two effective compounds. All of the derivatives having alkylthio group higher than propylthio-

Table V. Toxicity of 3-Sulfanilyl-6-alkylthiopyridazine on F. L. Cells and its Antiviral Activity

General Formula H_2N-  -SO_2NH-  -Z

Drugs (Z)	Max. non-toxic doses upon F. L. cells. (mole)	Antiviral effect		Drugs (Z)	Max. non-toxic doses upon F. L. cells. (mole)	Antiviral effect	
		Polio.	Adeno.			Polio.	Adeno.
-SH	10^{-4}	0/2[a)]	0/2	-S-*n*-C_4H_9	10^{-4}	0/2	0/2
-SCH_3	10^{-4}	0/2	0/2	-S-*n*-C_5H_{11}	10^{-5}	0/2	0/2
-SC_2H_5	10^{-4}	0/2	0/2	-S-*n*-C_6H_{13}	10^{-6}	0/2	0/2
-S-*n*-C_3H_7	10^{-4}	0/2	0/2				

a) The numerator represents the number of tubes having CPE (−), and the denominator, the number of total tubes used.

Experimental Procedure:

Host cells: F. L. strain of human amnion cells was employed.

Viral materials: Type-1 (Mahoney strain) of polio virus and Type-1 (Adenoid-71 strain) of adeno virus were employed.

Growth medium: Y. L. A. medium added with 5% beef serum or with 5% horse serum. The former was used for polio experiments, the latter for adeno-experiments.

(1) Determination of max. non-toxic concentration of tested compounds on host cells.
10 fold-dilutions of each tested compound were added into tubes, in which the mono layer cell sheet of F. L. cells had been already established, and then these tubes were incubated at 37° for 4 days. After the daily microscopic observation, the max. non-toxic concentration of the compound was determined.

(2) Determination of the viral inhibitory property of tested compounds.
Each of tested compounds was added into tubes, in which the monolayer cell sheet of F. L. cells had been already established, and immediately later $10 \times TCD_{50}$ of adeno type-1 virus ($TCD_{50}=10^{-3.5}$/cc) or $100 \times TCD_{50}$ of polio type-1 ($TCD_{50}=10^{-6.5}$/cc.) was inoculated into these tubes, then these tubes were incubated at 37° for 7 days. Through the daily microscopic observation for the appearance of CPE (cytopathogenic effect), the inhibitory effect of tested compounds on the viral growth was determined.

*[3] Anounced in the Annual Meeting of Pharm. Soc. of Japan, No. 79 (1959).

were, also, inferior to the above compounds. Moreover, of these higher carbon chain derivatives, their activity was observed to decrease by lengthening carbon chain of alkylthio group.

Inhibitory Activity of 3-Sulfanilyl-6-alkylthiopyridazine on Growth of F. L. Cells

The compounds of 3-sulfanilyl-6-alkylthiopyridazine were tested as to their antiviral activity in tissue culture of F. L. cells, using type-1 strain of adeno virus and Mahoney strain of polio virus. The experimental procedures are described in Table V. The result showed that any of the compounds did not exert significant inhibitory activity on the virus. However, it is of interest that the compounds of this series were found to have inhibitory activity on the growth of F. L. cells, which may be considered as one kind of tumor cells, especially hexylthio derivative in concentration of 10^{-6} mole, as shown in Table V.

As described above, the authors made clear the synthesis of 3-sulfanilyl-6-alkoxypyridazine, 3-sulfanilyl-6-alkylthiopyridazine and their intermediates, and examined as to their activity on several kinds of bacteria and viruses. As the results obtained, the relationship between antibacterial activity and structure of compounds of 3-sulfanilyl-6-alkoxypyridazine and 3-sulfanilyl-6-alkylthiopyridazine series were confirmed.

Experimental

(I) Synthesis of 6-Substituted 3-Aminopyridazine

General Method for Synthesis of 3-Amino-6-alkoxypyridazine——To a solution of 0.12 mole of metallic Na in 100 cc. of absolute R-OH (wherein R stands for CH_3–, C_2H_5–, ……, $C_{10}H_{21}$–, HO-C_2H_4–, C_6H_5-CH_2–, etc.) was added 0.1 mole of 3-amino-6-halopyridazine and heated at 120~130° for 6~10 hr. When b.p. of R-OH is lower than 140°, an autoclave was used as the reaction vessel. After the reaction mixture was cooled, precipitated salt (sodium halide) was filtered off and excess of sodium alkoxide (RONa) in the filtrate was neutralized with 10% HCl and then the solution was made alkaline with NH_4OH again. The resulting solution was evaporated to dryness under reduced pressure at the temperature below 140°. The residual oily product was extracted with Me_2CO and the extract was dried over anhydrous K_2CO_3, treated with active charcoal and then the solvent was removed to obtain the crude product, purified by recrystallization from Me_2CO or AcOEt. Hydrochloride: Above obtained crude product was dissolved into alcoholic HCl. After treating with active charcoal, the solution was poured into dry Et_2O. The resulting precipitate was collected and recrystallized from abs. EtOH or EtOH-Et_2O. Yield, (crude) 63~85%.

3-Amino-6-methoxypyridazine[14] by Ammonolysis of 3-Bromo-6-methoxypyridazine——Four grams of 3-bromo-6-methoxypyridazine, 1 cc. of water and 0.2 g. of Cu powder were put into an autoclave, in which 40 cc. of liquid NH_3 was compressed and heated at 100° for 10 hr. (max. press. showed 4.5 atom ospheric pressure). After the reaction vessel was cooled, NH_3 was evaporated and the residue was extracted with Me_2CO to remove off insoluble salts and Cu powder. The extract was treated with charcoal and dried over anhydrous K_2CO_3. When the solvent was removed, there obtained brown oily product. This was recrystallized from AcOEt to form faint brown prisms of m.p. 104~106°. Yield, 1.6 g. No depression of m.p. was observed when mixed with authentic sample synthesized through another route.

3-Chloro-6-methoxypyridazine was also treated under similar condition as above or rather drastic condition, but only the starting material was recovered in good yield.

3-Chloro-6-pyridazinol from 3-Chloro-6-methoxypyridazine——Four grams of 3-chloro-6-methoxypyridazine and 0.1 g. of Cu powder were added to 120 cc. of methanolic ammonia (saturated at 0°) and heated in an autoclave at 150~170° for 24 hr. The reaction mixture was filtered and the filtrate was concentrated to dryness. The residue was extracted with benzene. When benzene was removed, there obtained 2.8 g. of white crystals, which were dried in a desiccator overnight. Recrystallized from benzene to form white needles of m.p. 137~140°, positive to Beilstein test. No depression of m.p. was observed when mixed with authentic sample of 3-chloro-6-pyridazinol, synthesized by the Druey's method.[13]

3-Bromo-6-methoxypyridazine was treated under similar condition as above, 0.8 g. of 3-amino-6-methoxypyridazine and small quantity of starting material was recovered.

General Method for the Synthesis of 3-Amino-6-alkylthiopyridazine——i) To a solution of 0.036 mole of sodium mercaptate (RSNa wherein R stands for CH_3–, C_2H_5–, ……, C_4H_9–.) in 40 cc. of dioxane

was added 0.03 mole of pulverized 3-amino-6-halopyridazine and heated in an autoclave at 120~140° for 8 hr. After cooling, the reaction mixture was made slightly acidic with AcOH and concentrated *in vacuo* and then made alkaline with NH_4OH and evaporated to dryness. The residue was repeatedly extracted with Me_2CO to remove off insoluble salts. After the extract was dried over anhydrous K_2CO_3, the solvent was removed to obtain brown oily product, recrystllize from $CHCl_3$ or Me_2CO. Yield, (crude) ca. 75%.

ii) To a solution of 1.25 g. of metallic Na in 50 cc. of abs. EtOH were added 0.05 mole of R-SH (wherein R stands for phenyl or tolyl) and 6.5 g. of 3-amino-6-chloropyridazine, and heated in an autoclave at 130~140° for 8 hr. After cooling, the precipitate was collected and washed with water to remove off accompanied NaCl. When recrystallized from EtOH, white prisms obtained. Yield, ca. 80%

3-Amino-6-pyridazinol——3.9 g. of 3-amino-6-chloropyridazine and 3.3 g. of freshly fused anhydrous AcOK were added to 30 cc. of glacial AcOH and heated on a oil bath under reflux for 3 hr. Gradually KCl was precipitated. After cooling, the reaction mixture was filtered and AcOH was removed *in vacuo* to form white powder, collected and washed with water. When this was recrystallized from EtOH, there obtaind white fine powder, m.p. 264~265°(decomp.). Yield, 3.5 g. This intermediate was supposed to be 3-amino-6-acetoxypyridazine. 3.5 g. of this 6-acetoxy derivative was boiled with 20 cc. of 10% HCl under reflux for 1 hr. After the reaction mixture was treated with charcoal, concentrated to dryness *in vacuo*. The residue was purified from MeOH to obtain 2.8 g. of white prisms. Yield, 63%. Free base : above obtained hydrochloride was dissolved into NH_4OH and concentrated to dryness. The resulting solid mass was extracted with Me_2CO and evaporated to dryness to obtain white crystals which were recrystallized from EtOH.

3-Amino-6-pyridazinethiol——Ten grams of 3-amino-6-chloropyridazine, 25 cc. of 25% NaSH aqueous solution and 25 cc. of EtOH were put into an autoclave and heated at 120~130° for 8 hr. After cooling, yellow precipitate was filtered and washed with water. This crude material was suspended in 50% MeOH and 10% NaOH was added until the material was nearly dissolved. The solution was treated with charcoal and filtered, then slightly acidified with 10% HCl, to obtain 8.1 g. of yellow prisms. Yield, 87%; m.p. 280~285°(decomp.).

(II) Synthesis of Sulfonamido Derivatives from 6-Substituted 3-Aminopyridazine

General Method for the Synthesis of 3-(*p*-Acetamidophenylsulfonamido)-6-halopyridazine——i) To a solution of 0.02 mole of 3-amino-6-halopyridazine in 30 cc. of dry pyridine was added 0.022 mole of acetylsulfanyl chloride (m.p. 147~149°) (portionwise) keeping the reaction temperature between 40~50° under agitation. When the addition was over, the reaction temperature was raised to 60°, and continued the agitation for 2 hr. more. The reaction mixture was left standing overnight, and pyridine was removed under reduced pressure. When the residual oily product was poured into hot water and neutralized to pH 4.0~5.0 with 10% HCl, there was obtained yellow precipitate which was filtered before cooling. The crude product was purified by dissolving in dil. NH_4OH, followed by charcoal treatment, and precipitation by pouring of the filtrate into dil. AcOH or recrystallization from dil. MeOH. Yield, 85~90%.

ii) 0.01 mole of 3,6-dihalopyridazine, 0.01 mole of N_4-acetylsulfanylamide and 0.01 mole of anhydrous K_2CO_3 were ground together and the solid mixture was heated in an oil bath in a round bottom flask. When the bath temperature had reached about 170°, the contents melted to a slush and the evolution of CO_2 was observed. After keeping at the temperature 170~180° for 1 hr., the reaction mixture was cooled and about 20 cc. of water was added to dissolve the resulting solid mass. The solution was stirred with active charcoal, filtered and brought to pH 4.0~5.0 with 10% HCl. The crude product which precipitated was purified as similar method as described above i). Yield, 68~81%.

3-[Bis(N-acetylsulfanilyl)amino]-6-chloropyridazine——When the procedure i) was applied in industrial scale, a trace of bissulfonamido derivative was detected. After the completion of reaction as described above, pyridine was removed *in vacuo*, and the oily residue was dissolved in dil. NH_4OH. A trace of insoluble matter was obtained, which was purified from large ammount of Me_2CO with charcoal treatment to form colorless fine prisms, which were insoluble in 28% NH_4OH, 10% HCl, H_2O, MeOH, EtOH, and slightly soluble in Me_2CO. Decomposed at over 300°, (The color bigins to change et abnot 220° from brown to black). *Anal.* Calcd. for $C_{20}H_{18}N_3O_6S_2Cl$: N, 13.37. Found: N, 13.08.

iii) 50 mg. of bis compound above obtained was suspended in a mixture of 2 cc. of 10% NaOH and 2 cc. of EtOH and refluxed for 1 hr. on a steam bath. The resulting solution was filtered and acidified with AcOH to precipitate white needles of m.p. 218~222°(decomp.), which were purified from MeOH, then the melting point was raised to 224~225°(decomp.). No depression of m.p. was ob served when mixed with authentic sample.

General Method for the Synthesis of 3-Sulfanilyl-6-halopyridazine——i) 0.01 mole of 3-(*p*-acetamidophenylsulfonamido)-6-halopyridazine was dissolved into a mixture of 10 cc. of 10% NaOH (corresponds to 0.025 mole) and 10 cc. of EtOH and heated on a steam bath for 3 hr. under reflux. The reaction mixture was evaporated, treated with charcoal, and the filtrate was acidified with

AcOH while hot. The yellow prisms were collected and purified from MeOH or by dissolving in dil. NH_4OH and reprecipitated with dil. AcOH. Yield, ca. 90%.

ii)[13,17,18] 0.02 mole of 3,6-dihalopyridazine, 0.02 mole of sulfanylamide and 0.03 mole of anhydrous K_2CO_3 were treated by the similar procedure as described for 3-(*p*-acetamidophenylsulfonamido)-6-halopyridazine ii). A vigorous evolution of CO_2 was observed when the temperature had reached 140~150°. Yield : ca. 65~85%.

General Method for the Synthesis of 3-(*p*-Acetamidophenylsulfonamido)-6-alkoxypyridazine——0.01 mole of 3-amino-6-alkoxypyridazine was dissolved in 10 cc. of dry pyridine and 0.011 mole of acetylsulfanilyl chloride was added into the solution. The reaction was completed at room temperature for 1 hr. under agitation. After the resulting solution was maintained at 80° on a steam bath for 0.5 hr., the pyridine was distilled off under reduced pressure and the residual oily material was added to 15 cc. of hot water, and acidified with 10% HCl to deposit a crystalline precipitate. This was filtered off and washed with water and then recrystallized from MeOH. Yield, ca. 90%.

General Method for the Synthesis of 3-Sulfanilyl-6-alkoxypyridazine——i) To a mixed solution of 10 cc. of 10% NaOH and 10 cc. of EtOH was added 0.01 mole of 3-(*p*-acetamidophenylsulfonamido)-6-alkoxypyridazine and boiled on a steam bath for 2 hr. under reflux. EtOH was removed from the reaction mixture and acidified with dil. AcOH to pH. about 4~5. The resulting crude product was purified from MeOH or dilute MeOH. Yield, 75~85%. Most of the compounds of this series had a faint yellow color.

ii)[11,19] 0.02 mole of 3-sulfanilyl-6-halopyridazine obtained as above was added to a solution consisting of ca. 20~50 cc. of abs. R-OH (wherein R stands for CH_3–, C_2H_5–, ……, $C_{10}H_{21}$– etc.) and 0.048 mole of metallic Na and reacted in an autoclave at a temperature of 120~140° for 6~8 hr. with stirring. After cooling, NaCl precipitated was filtered off and R-OH was distilled off from the filtrate, and thereafter the residue was added into water and acidified with AcOH to deposit a precipitate of light yellow crystals. This was filtered and purified from MeOH or dil. MeOH. Yield of the crude product, 60~90%.

General Method for Synthesis of 3-(*p*-Acetamidophenylsulfonamido)-6-alkylthiopyridazine——It was prepared by condensing 3-amino-6-alkylthiopyridazine obtained above with acetylsulfanyl chloride in dry pyridine under similar conditions as described for 3-(*p*-acetamidophenylsulfonamido)-6-alkoxypyridazine.

General Method for the Synthesis of 3-Sulfanilyl-6-alkylthiopyridazine——i) It was prepared from 3-(*p*-acetamidophenylsulfonamido)-6-alkylthiopyridazine by hydrolysis with dil. NaOH (containing 2.5 equiv. mole of NaOH) according to the procedure similar to that described for 3-sulfanilyl-6-alkoxypyridazine. Yield, 76~88%.

ii) To a solution of 0.46 mole of Na metal in about 100 cc. of MeOH was added 0.02 mole of 3-sulfanilyl-6-halopyridazine and the solution was concentrated to dryness. Here obtained Na salt of 3-sulfanilyl-6-halopyridazine was suspended in a solution of 0.025 mole of sodium mercaptate (RS-Na wherein R represent CH_3–, C_2H_5–, ……, C_6H_{13}–, etc.) in 100 cc. of dioxane and heated in an autoclave at a temperature 125~145° for 8~10 hr. The reaction mixture was chilled and added to 50 cc. of water to dissolve the precipitated matter. After the treatment with active charcoal, the filtrate was concentrated to dryness *in vacuo* and the resulting solid mass was stirred with ca. 50 cc. of water containing few drops of AcOH. The crude product was filtered, washed with water and purified from MeOH or aqueous MeOH with charcoal treatment. Yield, 55~82%.

3-Sulfanilyl-6-acetoxypyridazine——2.8 g. of 3-sulfanilyl-6-halopyridazine and 1.2 g. of freshly fused K_2CO_3 were refluxed with 30 cc. of glacial AcOH for 3 hr. After cooling, the reaction mixture was filtered and AcOH was removed under reduced pressure to give white precipitate, which was filtered and washed with water, then recrystallized from MeOH. Yield of the crude product was 2.6 g., m.p. 210° (decomp.).

3-(*p*-Acetamidophenylsulfonamido)-6-acetoxypyridazine——i) Using the same method as described above for 3-sulfanilyl-6-acetoxypyridazine, it was prepared from 3-(*p*-acetamidophenylsulfonamido)-6-halopyridazine by reaction with anhydrous K_2CO_3 in glacial AcOH. m.p. 240~260° (gradually decomposed), purified from MeOH. Yield : 78% as crude product.

ii) 1.5 g. of 3-amino-6-acetoxypyridazine was reacted with 2.5 g. of acetylsulfanyl chloride by usual manner in 20 cc. of dry pyridine to obtain 0.6 g. of the pure product after recrystallization from MeOH, m.p. 260° (decomp.).

3-Sulfanilyl-6-pyridazinol——i) 3.0 g. of 3-sulfanilyl-6-acetoxypyridazine above obtained was refluxed with 10 cc. of 10% HCl and 10 cc. of EtOH for 1.5 hr. on a steam bath. After the removal of the solvent, the residue was added to dil. NH_4OH to make it into solution, then acidified with AcOH to pH 4.0~5.0, and there obtained slightly yellow precipitate which purified from 75% MeOH. Yield, 1.7 g. (67%).

ii) This was also prepared from 3-(*p*-acetamidophenylsulfonamido)-6-acetoxypyridazine by hydrolysis with dil. HCl in the same manner as described above.

3-Sulfanilyl-6-pyridazinethiol——7.0 g. of 3-sulfanilyl-6-chloropyridazine, 125 cc. of 2*N*-NaSH solution in 90% EtOH and 20 cc. of EtOH solution containing 0.58 g. of Na metal were mixed together and heated in an autoclave at 120~130° for 10 hr. After cooling, precipitated NaCl was filtered off and the filtrate was acidified slightly with 10% HCl. When the solvent was removed, there obtained yellow precipitate, which was purified by dissolving into the mixture of dil. NH_4OH and MeOH, followed by charcoal treatment, and precipitation by acidifying the filtrate with AcOH to pH 4.0~5.0. Yield, 5.0 g. (70%), m.p. 233°(decomp.).

Summary

To find more improved sulfonamide drugs, 3-sulfanilyl-6-hydroxy-, 3-sulfanilyl-6-mercapto-, 3-sulfanilyl-6-alkoxy- and 3-sulfanilyl-6-alkylthio-pyridazine and their intermediates, 3-amino-6-hydroxy-, 3-amino-6-mercapto-, 3-amino-6-alkoxy- and 3-amino-6-alkylthio-pyridazine were synthesized. Few synthetic procedures *via* different routes were examined as to the synthesises of 3-sulfanilyl-6-alkoxy-, 3-sulfanilyl-6-alkylthio- and 3-amino-6-methoxy-pyridazine.

Activities of the compounds of 6-substituted-3-sulfanilyl-pyridazine on some kinds of bacteria and viruses were examined and among them,3-sulfanilyl-6-methoxy-, 3-sulfanilyl-6-ethoxy and 3-sulfanilyl-6-methylthiopyridazine were found to exert remarkable antibacterial effects.

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96. Tatsuya Horie(Ishida) and Takeo Ueda : Studies on Pyridazine Derivatives. II.*1 Synthesis of 6-Substituted 3-(*p*-Nitrophenyl)-, 3-(*p*-Tolyl)- and 3-(*p*-Aminomethylphenyl)sulfonamidopyridazines.

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As described in the preceding paper,*1 various compounds of 6-substituted 3-sulfanilylpyridazine were synthesized and their antimicrobial activity was examined by the authors. As the sequence of those studies, the authors conceived an idea to make antimicrobial agents by introducing nitro, methyl, and aminomethyl groups at para position of benzene ring of 6-substituted 3-phenylsulfonamidopyridazine. Because, it was taken by the authors into consideration that compounds having special antimicrobial spectra have been synthesized by replacing amino group of sulfa drugs with these substituent groups.

This paper describes the syntheses of 6-substituted 3-(*p*-nitrophenyl)-, 3-(*p*-tolyl)- and 3-(*p*-aminomethylphenyl)sulfonamidopyridazines.

Synthesis of 6-Substituted 3-(*p*-Nitrophenyl)sulfonamidopyridazine——To obtain 6-substituted 3-(*p*-nitrophenylsulfonamido)pyridazine, the following routes were considered, referring to the synthesis of 2-(*p*-nitrophenylsulfonamido)pyridine.[1]

(1) 3-(*p*-Nitrophenylsulfonamido)-6-alkoxypyridazine was obtained in good yield, by condensing *p*-nitrobenzenesulfonyl chloride with 3-amino-6-alkoxypyridazine in anhydrous pyridine, as shown in Chart 1.

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*1 Part I. This Bulletin, **10**, 580 (1961).

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1) O. Northey : "Sulfonamide" p. 14.