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.

(Received May 4, 1961)

UDC 547.852.2.07

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.

(*Pharmaceutical Institute, Keio University**2)

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).

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

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

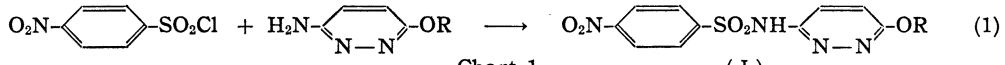


Chart 1. (I)

(2) 3-(*p*-Nitrophenylsulfonamido)-6-halopyridazine could not be synthesized by the reaction between *p*-nitrobenzenesulfonyl chloride and 3-amino-6-halopyridazine under any reaction condition. This result quite coincided with the fact that *p*-nitrobenzenesulfonyl chloride is less reactive than *p*-acetaminobenzenesulfonyl chloride or *p*-tolylsulfonyl chloride.

(3) 3-(*p*-Nitrophenylsulfonamido)-6-halopyridazine could not be obtained by fusion of *p*-nitrophenylsulamide with 3,6-dihalopyrifondazine in the presence of anhydrous potassium carbonate under any reaction condition. The failure of this reaction may be accounted by such two reasons as the unreactivity of *p*-nitrophenylsulfonamide and the thermal decomposition of starting materials. Therefore, it may be said that 3-(*p*-nitrophenylsulfonamido)-6-alkoxypyridazine is not obtainable through 3-(*p*-nitrophenylsulfonamido)-6-halopyridazine at any rate.

(4) The reduction of 3-(*p*-nitrophenylsulfonamido)-6-alkoxypyridazine easily afforded 3-sulfanilyl-6-alkoxypyridazine in good yield, as shown in Chart 2.

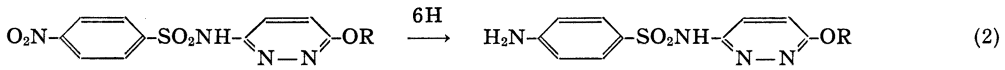
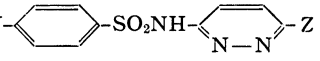
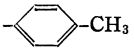
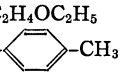
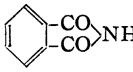


Chart 2. (II)

Table I. General Formula 

Compd. No.	Y	Z	m.p. (°C)	Appearance	Solvent	Formula	Analysis Calcd. N%	Analysis Found N%
1	CH_3-	-Cl	152	White needles	MeOH	$C_{11}H_{10}N_3O_2SCl$	14.81	14.63
2	〃	-Br	142	〃	〃	$C_{11}H_{10}N_3O_2SBr$	12.80	12.92
3	〃	$-OCH_3$	119	〃	〃	$C_{12}H_{13}N_3O_3S$	15.08	15.34
4	〃	$-OC_2H_5$	141	〃	〃	$C_{13}H_{15}N_3O_3S$	14.33	14.05
5	〃	-O-*n*-C_3H_7	150	〃	〃	$C_{14}H_{17}N_3O_3S$	13.68	13.60
6	〃	-O-*n*-C_4H_9	144	〃	〃	$C_{15}H_{19}N_3O_3S$	13.08	12.96
7	〃	-O-*n*-C_5H_{11}	109	White fine needles	70% MeOH	$C_{16}H_{21}N_3O_3S$	12.53	12.48
8	〃	-O-*n*-C_6H_{13}	110	〃	〃	$C_{17}H_{23}N_3O_3S$	12.03	12.22
9	〃	-O-*n*-$C_{10}H_{21}$	125	White fine powder	Benzene +Et_2O	$C_{21}H_{31}N_3O_3S$	10.36	10.58
10	〃	$-OC_2H_4OC_2H_5$	108	White needles	MeOH	$C_{15}H_{19}N_3O_4S$	12.46	12.44
11	〃		164	White prisms	〃	$C_{18}H_{17}N_4O_3S$	11.83	12.01
12	NO_2-	$-OCH_3$	165	Slight yellow needles	〃	$C_{11}H_{10}N_4O_5S$	18.06	18.26
13	〃	$-OC_2H_5$	146	〃	EtOH	$C_{12}H_{12}N_4O_5S$	17.28	17.09
14	〃	-O-*n*-C_3H_7	173	〃	〃	$C_{13}H_{14}N_4O_5S$	16.56	16.41
15	〃	-O-*n*-C_4H_9	159	〃	〃	$C_{14}H_{16}N_4O_5S$	15.82	16.01
16	〃	-O-*n*-C_5H_{11}	133	White needles	〃	$C_{15}H_{18}N_4O_5S$	15.30	15.12
17	〃	-O-*n*-C_6H_{13}	119	〃	〃	$C_{16}H_{20}N_4O_5S$	14.73	14.59
18	〃	$-OC_2H_4OC_2H_5$	151	〃	〃	$C_{14}H_{16}N_4O_6S$	15.21	15.19
19	〃		191	Slight yellow prisms	MeOH	$C_{17}H_{14}N_4O_5S$	14.50	14.67
20	H_2N-CH_2-	-Cl	~280 decomp.	White needles	50% EtOH	$C_{11}H_{11}N_4O_2SCl$	18.42	18.52
21	〃	$-OCH_3$	231 decomp.	〃	〃	$C_{12}H_{14}N_4O_3S$	19.05	19.21
22		-Cl	222 decomp.	White powder	Me_2CO	$C_{19}H_{13}N_4O_4SCl$	13.30	13.53
23	〃	$-OCH_3$	216 decomp.	〃	〃	$C_{20}H_{16}N_4O_5S$	13.20	13.29

Thus, the combination of Reaction 1 with Reaction 2 was found useful for the synthesis of 3-sulfanilyl-6-alkoxypyridazine. The compounds synthesized according to this method are shown in Table I.

Synthesis of 6-Substituted 3-(*p*-Tolylsulfonamido)pyridazine——As reported by Ueda *et al.*,[2] *p*-alkylphenylsulfonamide and its N_1-substitutes are of interest as antiviral compounds. Accordingly, compounds of 6-substituted 3-(*p*-tolylsulfonamido)pyridazine were taken up in order to find antiviral effects. Compounds of this series were obtained, in good yields, by condensing *p*-tolylsulfonyl chloride with 3-amino-6-alkoxypyridazine or 3-amino-6-halopyridazine in anhydrous pyridine. The resulting 3-(*p*-tolylsulfonamido)-6-halopyridazine was easily converted to the corresponding 6-alkoxy derivatives by reacting with sodium alkoxide in alcoholic solution, as shown in Chart 3. The compounds obtained are also listed in Table I.

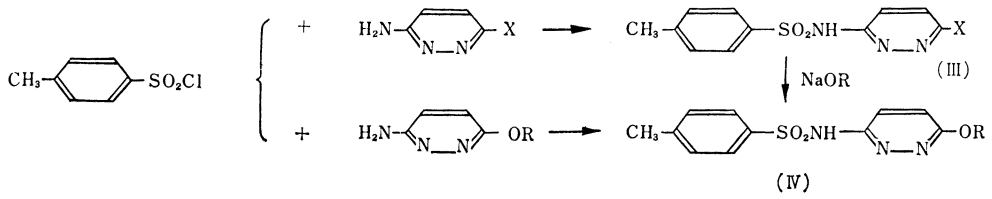


Chart 3.

Synthesis of 6-Substituted 3-(*p*-Aminomethylphenylsulfonamido)pyridazine——Homosulfamine is well known as an excellent sulfa drug having a special antibacterial spectrum. So 6-substituted 3-(*p*-aminomethylphenylsulonamido)pyridazine was taken up to find new antibacterial compounds. According to the modification of Kusami's method[3] for the synthesis of Homosulfamine, compounds of this type were successfully synthesized by reacting potassium phthalimide with benzyl chloride, chlorosulfonating the resulting compound with chlorosulfonic acid and then condensing *p*-(phthalimidomethyl)benzenesulfonyl chloride with 6-substituted 3-aminopyridazine, followed by the hydrolysis of the product with hydrazine hydrate, as shown in Chart 4. The compounds thus obtained are listed in Table I.

Compounds of 6-substituted 3-(*p*-nitrophenylsulfonamido)pyridazine, 6-substituted 3-(*p*-tolylsulfonamido)pyridazine and 6-substituted 3-(*p*-aminomethylphenylsulfonamido)-

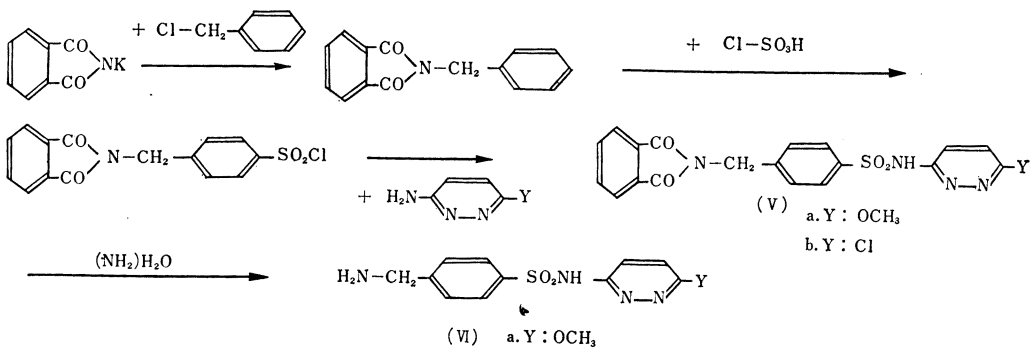


Chart 4.

2) T. Ueda, S. Toyoshima, T. Tsuji: Keio Journal of Medicine, 8, 54 (1959).
3) Kusami, Yamaguchi: Yakugaku Zasshi, **64**, 240 (1944).

pyridazine were screened as to their antibacterial activity, using several kinds of *Staphylococcus aureus* and *Escherichia coli*.

However, all of them were found uneffective against the bacteria. Problems on the antiviral and antiprotozoan activity still remain. The result of this work will be published in the near future.

Experimental

General Method for Synthesis of 3-(*p*-Nitrophenylsulfonamido)-6-alkoxypyridazine (I)——To an ice cooled solution of 0.01 mole of 3-amino-6-alkoxypyridazine in 10 cc. of dehyd. pyridine, 0.01 mole of *p*-nitrophnylsulfonyl chloride was added all at once. After shaking at room temperature for 1 hr. the reaction mixture was heated on a steam bath at 60° for 30 min., and then pyridine was evaporated under a reduced pressure. The tarry residue was triturated with 15 cc. of ice water and acidified with 10% HCl to pH. 4~5. The precipitated crude product was collected and recrystallized from appropriate solvent. Yield, 68~86%.

General Method for Synthesis of 3-(*p*-Tolylsulfonamido)-6-alkoxypyridazine (IV)—— i) 3-Amino-6-alkoxypyridazine (0.01 mole) was reacted with *p*-tolylsulfonyl chloride in dehyd. pyridine in the same manner as described for (I). Yield, 75~85%.

ii) Sodium metal (0.025 mole) was dissolved in 20 cc. of dehyd. R-OH (wherein R stands for Me, Et, But, etc.). To this solution was added 2.5 g. of 3-(*p*-tolylsulfonamido)-6-chloropyridazine and heated in an autoclave at 120~130° for 8 hr. The reaction mixture was filtered and acidified with AcOH and then evaporated to dryness on a steam bath. The residue was dissolved in dil. NH_4OH, chilled and acidified with dil. AcOH. The crude product was collected and recrystallized from MeOH. Yield, 46~70%.

3-(*p*-tolylsulfonamido)-6-methoxy, -6-ethoxy, and -6-butoxypyridazine were obtained by this method and they were identified by measurement of their melting points, which were undepressed on admixture with authentic samples synthesized through the method i).

General Method for Synthesis of 3-(*p*-Tolylsulfonamido)-6-halopyridazine (III)——To a suspension of 0.01 mole of 3-amino-6-halopyridazine in 10 cc. of dehyd. pyridine was added 0.011 mole of *p*-tolylulfonyl chloride slowly with stirring at 40~50°. The reaction mixture was kept at 60° for 30 min. and pyridine was distilled off under a diminished pressure. The resulting tarry product was triturated with 10 cc. of ice water and acidified with 10% HCl to pH 4~5. The precipitate was filtered off and recystallized from MeOH. The yield was 70~83%.

General Method for Synthesis of 3-Sulfanilyl-6-alkoxypyridazine (II) From (I)——3-(*p*-Nitrophenylsulfonamido)-6-alkoxypyridazine (I) (0.01 mole) was hydrogenated over 0.5 g. of 10% Pd-C for about 5 hr. in 60 cc. of 50% aq. AcOH. It smoothly absorbed a calculated amount of H_2 (0.03 mole). After removal of the catalyst, the filtrate was evaporated under a reduced pressure and the residue was puri fied by recrystallization from MeOH.

3-Sulfanilyl-6-methoxypyridazine : The yield of the crude product was 88%. Recrystallized from MeOH, m.p. 180~181°, whichwas undepressed on admixture with the authentic sample synthesized through another route.*[1]

3-Sulfanilyl-6-ethoxypyridazine : The yield of the crude product was 83%, which was recrystallized from MeOH, to m.p. 181~183°, undepressed on admixture with the authentic sample synthesized through another route.*[1]

3-(*p*-Phthalylimidomethylphenylsulfonamido)-6-methoxypyridazine (Va)——To a solution of 1.25 g. (0.01 mole) of 3-amino-6-methoxypyridazine in 10 cc. of dehyd. pyridine was added a solution of 3.7 g. of *p*-phthalylimidomethylbenzensulfonyl chloride in 10 cc. of dehyd. pyridine all at once, and after shaking for 1 hr. at room temperature, the reaction mixture was kept at 60~80° for 30 min. Pyridine was distilled off under reduced pressure and the resulting oil was added to 20 cc. of water and acidified with dil. HCl, giving white precipitate, which was collected and dried. Yield, 2.8 g. Recrystallized form Me_2CO to afford white fine powder.

3-(*p*-Phthalylimidomethylphenylsulfonamido)-6-chloropyridazine (Vb)——3-Amino-6-chloropyridazine (1.3 g; 0.01 mole) was treated in the same manner as above. The yield was 2.6 g. Recrystallized from Me_2CO to afford white fine powder. Positive to Beilstein test.

3-(*p*-Aminomethylphenylsulfonamido)-6-methoxypyridazine (VIa)——A solution of 2.1 g. of 3-(*p*-phthalylimidomethylphenylsulfonamido)-6-methoxypyridazine (Va) in 20 cc. of 10% Na_2CO_3 solution was heated on a steam bath with 0.3 g. of 85% hydrazine hydrate for 3 hr. After the most part of water was removed from the reaction mixture, the residue was acidified with 5% HCl and heated again on a steam bath for 1 hr. The resulting white precipitate*[3] was filtered off and the filtrate

*[3] This was supposed to be 1,4-dihydroxyphthalazine.

was concentrated *in vacuo* and neutralized with NH_4OH to pH. 7~7.5, there was obtained white fine crystals. Yield, 1.0 g. Purified from dil. EtOH, forming white needles.

3-(*p*-Aminomethylphenylsulfonamido)-6-chloropyridazine(VIb)——3-(*p*-Phthalylimidomethylphenylsulfonamido)-6-chloropyridazine (V b) (2.1 g.; 0.01 mole) was hydrolyzed with 0.3 g. of 85% hydrazine hydrate in the same manner as described for (VIa), affording 1.1 g. of (VIb), recrystallized from dil. EtOH to form white needles.

Summary

In order to find antimicrobial agents, compounds of 6-substituted 3-(*p*-nitrophenylsulfonamido)pyridazine, 6-substituted 3-(*p*-tolylsulfonamido)pyridazine and 6-substituted 3-(*p*-aminomethylphenylsulfonamido)pyridazine were synthesized and screened as to their activities on *Staph. aureus* and *E. coli*, but any of them was found uneffective.

(Received May 4, 1961)

UDC 547.852.2.07

97. Tatsuya Horie (Ishida) and Takeo Ueda : Studies on Pyridazine Derivatives. III.*1 Improved Synthetic Method of 3-Sulfanilyl-6-alkoxypyridazine.

(*Pharmaceutical Institute, Keio University**2)

Although some synthetic methods have been submitted[1] for the purpose of the preparation of 3-sulfanilyl-6-alkoxypyridazine as shown in Chart 1 and Chart 2, questions still remain to decide what method should be selected for its industrial production.

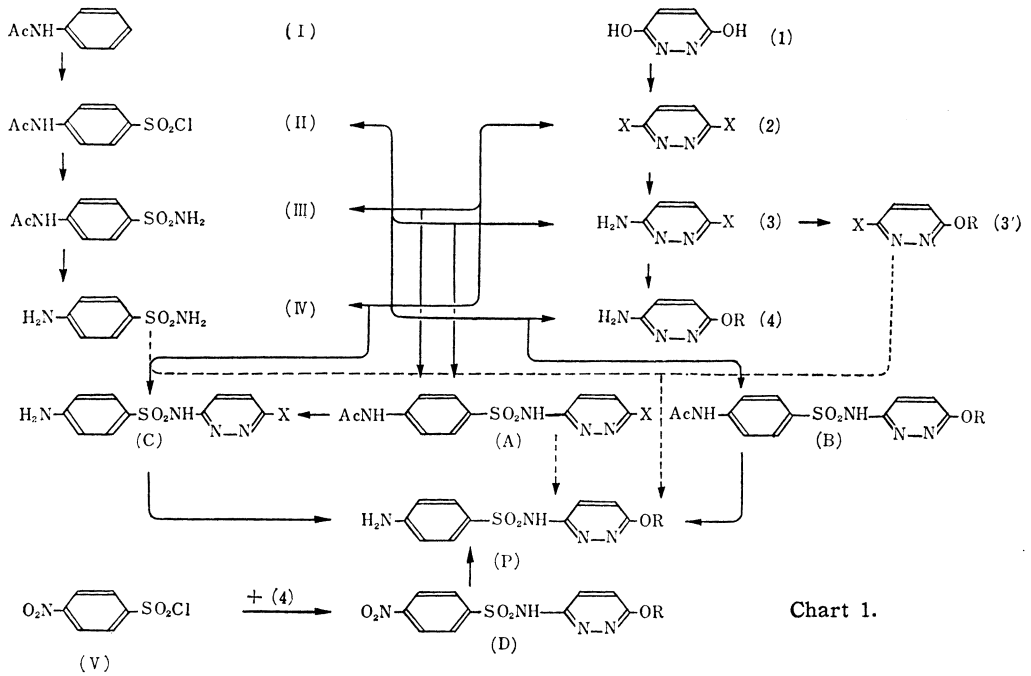


Chart 1.

*1 Part II: This Bulletin, **10**, 591 (1912).

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

1) Part I: This Bulletin, **10**, 580 (1962).