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1. Kuniyoshi Tanaka, Einosuke Omura, Toshio Sugawa, Yasushi Sanno, Yasuo Ando, Kin-ichi Imai, and Minoru Kawashima: Studies on Nucleic Acid Antagonists. I. Syntheses of 5-Phenylazopyrimidines.

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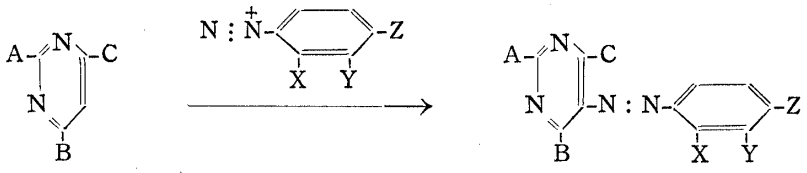
Research of anti-cancer agents, especially those belonging to the category of antimetabolite, seems desirable to be based on intrinsic biological difference between cancerous and normal cells. Taking advantage of the knowledge obtained by many years' studies on the biochemistry of cancer, several researchers have made an attempt to suppress the growth of malignant tumors by inhibiting the nucleic acid metabolism which is supposed to take part in abnormally rapid multiplication of tumor cells. As a result of studies conducted from this point of view, some anti-folic acid substances, such as aminopterine and amethopterine, and anti-purine substances, such as 8-azaguanine and 6-mercaptopurine, were found to show inhibitory effect against several kinds of tumor in experimental animals, and some of them are already in clinical use.

The authors have so far synthesized various kinds of pyrimidine derivatives expecting their antagonistic activity upon nucleic acid metabolism and found that 5-phenylazopyrimidines inhibit not only the multiplication of *Lactobacillus* and *Tetrahymena in vitro* but also the growth of some transplantable tumors in experimental animals. The present paper deals with the synthetic method, and physical and chemical properties of these compounds.

As to the synthesis of 5-phenylazopyrimidine derivatives it was demonstrated by Todd and his co-workers[1] that azo-coupling in the pyrimidine ring always takes place at the 5-position when at least two of its 2-, 4-, and 6-positions are substituted with any of hydroxyl, amino, and mercapto groups (Method-I).



According to this method, coupling of 6-methyluracil, 2,4-diamino-6-hydroxypyrimidine, 2,4-diamino-6-methylpyrimidine, and 2,4,6-triaminopyrimidine with benzenediazonium salt and its derivatives was effected respectively to produce 24 compounds among the 5-phenylazoprimidines listed in Table I (Py-37, 40, 41, 61, 62, 63, 64, 69, 71, 72, 73, 74, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 90, 91).

For the synthesis of compounds to which this method-I could not be applied for lack of

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1) B. Lythgoe, A. R. Todd, A. Topham: J. Chem. Soc., **1944**, 315.

structural requisites mentioned above, the following method was chosen: Acetylacetone or ethyl acetoacetate was subjected to coupling with benzenediazonium salts and the resulting compound was allowed to condense with guanidine or acetamidine (Method-II). 2-Amino-4,6-dimethyl-5-phenylazopyrimidine[2] (Py-26) and its five derivatives (Py-65, 66, 67, 68, 70), and 2,4-dimethyl-6-hydroxy-5-phenylazopyrimidine[3] (Py-58) were synthesized by this method.

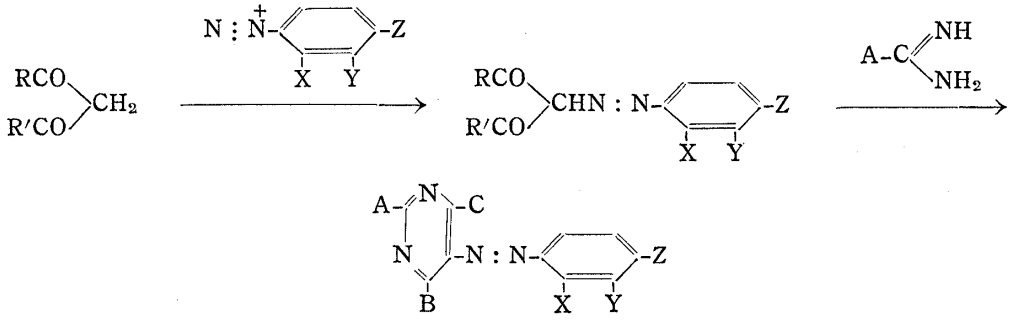
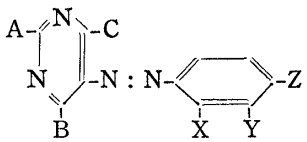


TABLE I. Substituents in 5-Phenylazopyrimidines



Compd. No.	A	B	C	X	Y	Z
Py-26	NH_2	CH_3	CH_3	H	H	H
37	OH	OH	CH_3	H	H	H
40	NH_2	NH_2	OH	H	H	H
41	NH_2	NH_2	NH_2	H	H	H
58	CH_3	CH_3	OH	H	H	H
61	NH_2	NH_2	NH_2	H	H	Cl
62	NH_2	NH_2	NH_2	Cl	H	H
63	NH_2	NH_2	NH_2	H	NO_2	H
64	NH_2	NH_2	NH_2	H	H	SO_3H
65	NH_2	CH_3	CH_3	H	H	Cl
66	NH_2	CH_3	CH_3	Cl	H	H
67	NH_2	CH_3	CH_3	H	NO_2	H
68	NH_2	CH_3	CH_3	H	H	SO_3H
69	NH_2	NH_2	NH_2	Cl	H	Cl
70	NH_2	CH_3	CH_3	Cl	H	Cl
71	NH_2	NH_2	OH	H	H	SO_3H
72	NH_2	NH_2	NH_2	H	H	SO_2NH_2
73	NH_2	NH_2	OH	H	H	SO_2NH_2
74	NH_2	NH_2	NH_2	H	H	COOH
77	NH_2	NH_2	CH_3	H	H	H
78	NH_2	NH_2	CH_3	H	H	SO_3H
79	NH_2	NH_2	OH	H	H	PO_3H_2
80	NH_2	NH_2	NH_2	H	H	PO_3H_2
81	NH_2	NH_2	NH_2	H	H	AsO_3H_2
82	NH_2	NH_2	NH_2	SO_3H	H	H
83	NH_2	NH_2	NH_2	H	PO_3H_2	H
84	NH_2	NH_2	NH_2	H	H	NO_2
85	NN_2	NH_2	NH_2	H	H	$-(CH_2)_3COOH$
86	NH_2	NH_2	NH_2	H	H	$-CONH-CHCOOH$ $\lvert$ CH_2CH_2COOH
90	NH_2	NH_2	NH_2	H	H	F
91	NH_2	NH_2	NH_2	H	F	H

2) R. Hull, B. J. Lovell, H. T. Openshaw, A. R. Todd: J. Chem. Soc. **1947**, 41; F. L. Rose: *Ibid.*, **1952**, 3448.
3) H. Andersag, K. Westphal: Ber., **70**, 2035(1937).

To prove the introduction of phenylazo group into 5-position of the pyrimidine ring by these reactions, the products were converted to the corresponding 5-aminopyrimidines by catalytic reduction; for example, 4-(2,4,6-triamino-5-pyrimidinylazo)benzenesulfonic acid (Py-64) was hydrogenated over palladium-carbon and 2,4,5,6-tetraaminopyrimidine was isolated as the product in the form of its sulfate.

The 5-phenylazopyrimidines thus obtained are yellow, orange, or red crystalline substances showing a high melting point and insoluble in most common organic solvents, but fairly soluble in pyridine, dimethylformamide, and glacial acetic acid. They were therefore purified by recrystallization from these solvents or by reprecipitation from their alkaline solutions with a dilute acid.

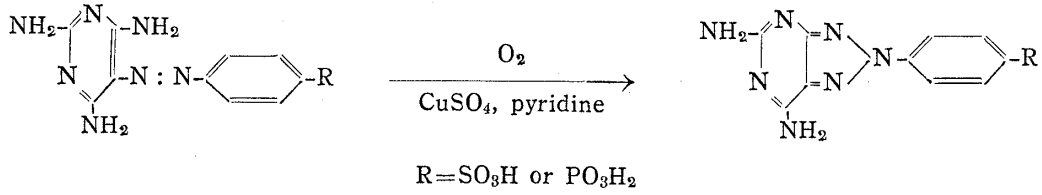
The color of these compounds apparently depends on the kind of substituents in the pyrimidine ring, while the substituents in the benzene ring seem less influential to the color. For example, 2-amino-4,6-dimethyl- or 2,4-dimethyl-6-hydroxy-5-phenylazopyrimidine (Py-26 or 58) and their derivatives having various substituents in the benzene ring are red or reddish orange. The color of these compounds, however, becomes lighter by replacement of the methyl groups in the pyrimidine ring by hydroxyl or amino group. For example, 2,4-diamino-6-methyl-5-phenylazopyrimidine (Py-77), 2,4-dihydroxy-6-methyl-5-phenylazopyrimidine (Py-37), and 2,4-diamino-6-hydroxy-5-phenylazopyrimidine (Py-40) are yellowish orange and 2,4,6-triamino-5-phenylazopyrimidine (Py-41) is yellow. A relationship similar to that between color and structure mentioned above was also observed between the absorption spectrum and structure of the compounds. The absorption spectrum of Py-26 resembled those of 2-amino-4,6-dimethyl-5-(4-chlorophenylazo) pyrimidine (Py-65) and 4-(2-amino-4,6-dimethyl-5-pyrimidinylazo) benzenesulfonic acid (Py-68) whose substituents were the same in the pyrimidine ring but different in the benzene ring. Similarly Py-41 showed resemblance in absorption spectrum to 2,4,6-triamino-5-(3-nitrophenylazo) pyrimidine (Py-63) and 4-(2,4,6-triamino-5-pyrimidinylazo)benzenesulfonic acid (Py-64) (Table II).

TABLE II. Ultraviolet Absorption of 5-Phenylazopyrimidines

Compd. No.	0.01*N* HCl		0.01*N* NaOH	
	λ_{max}	ε	λ_{max}	ε
Py-26	324 mμ	21200	328 mμ	10100
	430	870	435	1500
65	330	26400	350	17400
	430	1600	440	2080
68	327	29000	347	21200
	435	1320	445	2280
Py-41	360	19500	248	13800
			372	22000
63	362	19600	258	16600
			378	20400
64	369	26000	250	17050
			384	27200

It has been manifested by Benson, Hartzel, and their colaborators[4,5] that 5-phenylazopyrimidines suffer ring-closure by oxidation to give 2*H*-*v*-triazolo[*d*]pyrimidine derivatives, and this fact was proved to be true of the new compounds synthesized in the present series of experiments. For instance, 4-(2,4,6-triamino-5-pyrimidinylazo)benzene-sulfonic acid (Py-64) and -phosphonic acid (Py-80) were respectively converted to 4-(5,7-diamino-2-triazolo-[*d*]pyrimidinyl)benzene-sulfonic acid and -phosphonic acid by air-oxidation in the presence of copper sulfate and pyridine.

4) F. R. Benson, L. W. Hartzel, W. L. Savell: J. Am. Chem. Soc., **72**, 1816(1950).
5) L. W. Hartzel, F. R. Benson: *Ibid.*, **76**, 2263(1954).



R=SO_3H or PO_3H_2

The authors express their gratitude to Prof. M. Ishidate and Prof. T. Yoshida of the University of Tokyo for their kind instruction. They are also grateful to Dr. S. Kuwada, Director of this Laboratories, and Dr. S. Tatsuoka, head of the Department, for their continued guidance and encouragement. They are indebted to Messrs. H. Kamio and T. Shima for the absorption spectra and their thanks are also due to members in charge of elementary analyses.

Experimental

Of the 31 kinds of 5-phenylazopyrimidine derivatives mentioned above, Py-26,[2] 37,[6] 40,[4] 41,[5] 58,[3] 71,[5] 74,[5] and 86[5] are known compounds and were synthesized by the methods given in the literature. Of the remaining 23 derivatives, Py-61, 62, 69, and 84 have recently been reported by Timmis, *et al.*,[7] and the following 19 derivatives are new compounds.

2,4,6-Triamino-5-(3-nitrophenylazo)pyrimidine (Py-63)—A solution of 1.3 g. of *m*-nitroaniline in 8 cc. of HCl and 15 cc. of water was diazotized by addition of a solution of 1.5 g. of $NaNO_2$ in 10 cc. of water with ice-cooling and stirring. The reaction mixture was added to a suspension of 2.1 g. of 2,4,6-triaminopyrimidine sulfate in 15 cc. of 30% NaOH solution with ice-cooling and stirring, whereupon an orange-yellow precipitate separated out. After standing over night, the product was filtered and recrystallized from glacial AcOH in yellow crystalline powder, m.p. 283°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_8$: C, 43.76; H, 3.67; N, 40.87. Found: C, 43.76; H, 3.46; N, 40.92.

4-(2,4,6-Triamino-5-pyrimidinylazo)benzenesulfonic Acid (Py-64)—To a solution of 0.8 g. of 2,4,6-triaminopyrimidine sulfate in 200 cc. of water, a solution of 1 g. of *p*-diazobenzenesulfonic acid (freshly prepared from sulfanilic acid) in 200 cc. of water was added dropwise at room temperature with stirring, and the mixture was stirred for additional 2 hrs. After standing over night, the resulting yellow precipitate was filtered, washed with water, and dried (1.3 g.). For purification, the product was treated with a hot solution of 0.7 g. of $NaHCO_3$ in 200 cc. of water with warming, insoluble substance was filtered off, and glacial AcOH was added to the warm filtrate. After cool, the resulting precipitate was filtered, washed with water, and dried to give 1.1 g. of light yellow fine needles, m.p. 332°(decomp.). *Anal.* Calcd. for $C_{10}H_{11}O_3N_7S$: C, 38.81; H, 3.59; N, 31.71. Found: C, 38.73; H, 3.79; N, 31.67.

4-(2,4-Diamino-6-methyl-5-pyrimidinylazo)benzenesulfonic Acid (Py-78)—A portion of 2.2 g. of 2,4-diamino-6-methylpyrimidine was allowed to react with *p*-diazobenzenesulfonic acid in the same way as above. The purified product was obtained as yellow crystalline powder, m.p. 322°(decomp.)(2.4 g.). *Anal.* Calcd. for $C_{11}H_{12}O_3N_6S \cdot H_2O$: C, 40.48; H, 4.32; N, 25.76. Found: C, 40.46; H, 4.36; N, 25.33.

2-(2,4,6-Triamino-5-pyrimidinylazo)benzenesulfonic Acid (Py-82)—To a solution of 1 g. of 2,4,6-triaminopyrimidine sulfate and 2 g. of anhyd. NaOAc in 200 cc. of water, a solution of *o*-diazobenesulfonic acid (prepared from 1 g. of *o*-aminobenzenesulfonic acid by the usual method) in 50 cc. of water was added dropwise with stirring. After standing overnight, the resulting yellow precipitate was filtered, dissolved in 1% $NaHCO_3$ solution with warming, and reprecipitated by addition of glacial AcOH to give 0.65 g. of yellowish orange fine needles, m.p. 330°(decomp.). *Anal.* Calcd. for $C_{10}H_{11}O_3N_7S$: C, 38.81; H, 3.59. Found: C, 38.94; H, 4.01.

4-(2,4,6-Triamino-5-pyrimidinylazo)benzenesulfonamide (Py-72)—To a solution of 1.7 g. of sulfanilamide in 5 cc. of conc. HCl and 17 cc. of water, an aqueous solution of 0.69 g. of $NaNO_2$ was added dropwise with stirring. The diazotized amine solution was added dropwise to a solution of 2.4 g. of 2,4,6-triaminopyrimidine sulfate in 500 cc. of water, followed by a solution of 8 g. of anhyd. NaOAc in 40 cc. of water. After standing over night, the resulting yellow precipitate was filtered and washed with water. To purify the product, it was dissolved in a solution of 1.1 g. of KOH in 60 cc. of water without warming and reprecipitated by acidification of the filtrate with AcOH. The purified product came as a yellow crystalline powder, m.p. 327°(decomp.) (2.8 g.). *Anal.* Calcd. for $C_{10}H_{12}O_2N_8S$: C, 38.96; H, 3.93; S, 10.40. Found: C, 38.89; H, 3.86; S, 10.17.

4-(2,4-Diamino-6-hydroxy-5-pyrimidinylazo)benzenesulfonamide (Py-73)—This compound was produced from 1.7 g. of sulfanilamide and 1.9 g. of 2,4-diamino-6-hydroxypyrimidine sulfate in the same

6) M. Polonovski, M. Pesson: Bull. soc. chim. France, **1948**, 688.
7) G. M. Timmis, D. G. I. Felton, H. O. J. Collier, P. L. Huskinson: J. Pharm. Pharmacol., **9**, 46(1957).

manner as above. Yellow crystalline powder, m.p. 318~320°(decomp.) (2.7 g.). *Anal.* Calcd. for $C_{10}H_{11}O_3N_7S$: C, 38.81; H, 3.59; N, 31.71. Found: C, 38.62; H, 3.72; N, 31.75.

4-(2,4-Diamino-6-hydroxy-5-pyrimidinylazo)benzenephosphonic Acid (Py-79)—To a solution of 1 g. of *p*-aminobenzenephosphonic acid (phosphanilic acid)[8] in 15 cc. of 20% HCl, an aqueous solution of 0.4 g. of $NaNO_2$ was added dropwise at 0° to 5°. On the other hand, 6 g. of anhyd. NaOAc was added to a suspension of 1.1 g. of 2,4-diamino-6-hydroxypyrimidine sulfate in 100 cc. of water, and the above diazotized solution was added slowly with ice-cooling and stirring. The reaction mixture was left standing over night at room temperature and the resulting orange-colored precipitate was filtered and washed with water. The precipitate was dissolved in 2% $NaHCO_3$ solution with warming and the filtered solution was acidified with AcOH to deposit an orange-colored powder, m.p. >300°(1.5 g.). *Anal.* Calcd. for $C_{10}H_{11}O_4N_6P$: P, 9.99. Found: P, 9.95.

4-(2,4,6-Triamino-5-pyrimidinylazo)benzenephosphonic Acid (Py-80)—This compound was prepared from 1 g. of *p*-aminobenzenephosphonic acid[8] and 1.3 g. of 2,4,6-triaminopyrimidine sulfate, and purified in the same way as above. The product is a yellow powder, m.p. 310~312°(decomp.)(1.1 g.). *Anal.* Calcd. for $C_{10}H_{12}O_3N_7P$: P, 10.02. Found: P, 10.14.

3-(2,4,6-Triamino-5-pyrimidinylazo)benzenephosphonic Acid (Py-83)—A portion of 1.5 g. of *m*-aminobenzenephosphonic acid[8] was diazotized and reacted with 1.9 g. of 2,4,6-triaminopyrimidine sulfate as in the above cases. The product was purified to give 1.6 g. of a yellow crystalline powder, m.p. 310° (decomp.). *Anal.* Calcd. for $C_{10}H_{12}O_3N_7P$: P, 10.02. Found: P, 10.20.

4-(2,4,6-Triamino-5-pyrimidinylazo)benzenearsonic Acid (Py-81)—To a solution of 1 g. of *p*-aminobenzenearsonic acid[9] (prepared from *p*-nitrobenzenearsonic acid[10] by catalytic reduction) in 2.5 cc. of HCl and 15 cc. of water, an aqueous solution of 0.3 g. of $NaNO_2$ was added at 0°, when a white precipitate separated out. The reaction mixture was then added dropwise into a solution of 1 g. of 2,4,6-triaminopyrimidine sulfate and 4 g. of anhyd. NaOAc in 100 cc. of water with ice-cooling and stirring, and after the mixture was stirred for additional 2 hrs. and allowed to stand over night, the resulting yellow precipitate was collected. The precipitate was dissolved in 5% $NaHCO_3$ solution with warming and reprecipitated by addition of glacial AcOH. Yellow crystalline powder, m.p. 313°(decomp.) (0.45 g.).

4-[4-(2,4,6-Triamino-5-pyrimidinylazo)phenyl]butyric Acid (Py-85)—A solution of 0.9 g. of 4-(4-aminophenyl)butyric acid[11] in 5 cc. of conc. HCl and 20 cc. of water was diazotized by addition of an aqueous solution of 0.35 g. of $NaNO_2$ with ice-cooling. The reaction mixture was added to a solution of 1.1 g. of 2,4,6-triaminopyrimidine sulfate and 6 g. of anhyd. NaOAc in 150 cc. of water and the resulting yellow precipitate was collected. The precipitate was dissolved in 2% $NaHCO_3$ solution with warming and reprecipitated by addition of glacial AcOH as a yellow powder, m.p. 308°(decomp.) (0.9 g.). *Anal.* Calcd. for $C_{14}H_{17}O_2N_7 \cdot \frac{1}{2}H_2O$: C, 51.85; H, 5.59; N, 30.17. Found: C, 51.74; H, 5.58; N, 29.83.

2,4-Diamino-6-methyl-5-phenylazopyrimidine (Py-77)—To a suspension of 2.5 g. of 2,4-diamino-6-methylpyrimidine in 50 cc. of 2*N* NaOH, a benzenediazonium chloride solution (prepared from 2 g. of aniline by the usual method) was added dropwise with ice-cooling and stirring, whereupon a brown precipitate separated. After the mixture was stirred further for 2 hrs. and then neutralized with AcOH, the precipitate was filtered and recrystallized from EtOH to orange-yellow crystalline powder, m.p. 224~226° (decomp.). *Anal.* Calcd. for $C_{11}H_{12}N_6$: C, 57.91; H, 5.30. Found: C, 58.24; H, 5.79.

2,4,6-Triamino-5-(4-fluorophenylazo)pyrimidine (Py-90)—A solution of 1.4 g. of *p*-fluoroaniline[12,13] (prepared from 1-nitro-4-fluorobenzene by catalytic reduction) in 5 cc. of conc. HCl and 15 cc. of water was diazotized by addition of an aqueous solution of 0.9 g. of $NaNO_2$ and 4 g. of anhyd. NaOAc. The mixture was added dropwise to a solution of 2.9 g. of 2,4,6-triaminopyrimidine sulfate and the resulting yellow crystalline powder was filtered, m.p. 278~280°(decomp.).

2,4,6-Triamino-5-(3-fluorophenylazo)pyrimidine (Py-91)—This compound was prepared from 2.2 g. of *m*-fluoroaniline[12,13] (prepared from 1-nitro-3-fluorobenzene by catalytic reduction) and 4.4 g. of 2,4,6-triaminopyrimidine sulfate. The crude product was extracted with MeOH in a Soxhlet apparatus and yellow needles, m.p. 290~292°(decomp.), were obtained from the extract.

2-Amino-4,6-dimethyl-5-(4-chlorophenylazo)pyrimidine (Py-65)—A solution of 5.1 g. of *p*-chloroaniline in 12 cc. of conc. HCl and 25 cc. of water was diazotized by the customary method and the resulting solution was added to an aqueous solution of 4 g. of acetylacetone and 21 g. of anhyd. NaOAc, whereupon *p*-chlorophenylazoacetylacetone separated out as a yellow precipitate. The precipitate was filtered and recrystallized from EtOH to yellow needles, m.p. 135~136° (7.5 g.). An amount of 3 g. of this product and 2.1 g. of guanidine hydrochloride were added to a mixture of 48 cc. of 10*N* NaOH and 11 cc. of MeOH, and the whole was stirred for 18 hrs. at 50°. After cool, the resulting precipitate was

8) G. O. Doak, L. D. Freedman: J. Am. Chem. Soc., **74**, 753(1952).
9) L. Vanino: "Handbuch der Präparativen Chemie," **II**, 724(1937).
10) G. O. Doak, L. D. Freedman: J. Am. Chem. Soc., **73**, 5656(1951).
11) J. van der Scheer: *Ibid.*, **56**, 744(1934).
12) G. Schiemann, R. Pillarsky: Ber., **62**, 3035(1929).
13) G. M. Bennett, G. L. Brooks, S. Glasstone: J. Chem. Soc., **1935**, 1821.

filtered, washed successively with MeOH and water, and recrystallized from glacial AcOH in orange-red needles, m.p. 211~212° (1.5 g.). *Anal.* Calcd. for $C_{12}H_{12}N_5Cl$: C, 55.05; H, 4.63. Found: C, 55.15; H, 4.76.

2-Amino-4,6-dimethyl-5-(2-chlorophenylazo)pyrimidine (Py-66)—A portion of 5.1 g. of *o*-chloroaniline was treated with 4 g. of acetylacetone in the same way as above to give 8 g. of *o*-chlorophenylazoacetylacetone as long yellow needles, m.p. 124°. An amount of 3 g. of the needles was reacted with 3 g. of guanidine hydrochloride and the product was recrystallized from glacial AcOH into reddish orange needles, m.p. 246~247° (2.6 g.) *Anal.* Calcd. for $C_{12}H_{12}N_5Cl$: C, 55.05; H, 4.63; N, 26.77. Found: C, 55.48; H, 4.86; N, 26.76.

2-Amino-4,6-dimethyl-5-(3-nitrophenylazo)pyrimidine (Py-67) — *m*-Nitrophenylazoacetylacetone, yellow needles, m.p. 137~140°, was prepared from 3.5 g. of *m*-nitroaniline and 2.5 g. of acetylacetone in the same manner as above. A portion of 1.5 g. of the needles was reacted with 1 g. of guanidine hydrochloride and the product was recrystallized from glacial AcOH into orange needles, m.p. 262~263° (0.3 g.). *Anal.* Calcd. for $C_{12}H_{12}O_2N_6$: C, 52.93; H, 4.44; N, 30.87. Found: C, 53.13; H, 4.68; N, 30.84.

2-Amino-4,6-dimethyl-5-(2,4-dichlorophenylazo)pyrimidine (Py-70) — 2,4-Dichlorophenylazoacetylacetone (3.7 g.) was produced as yellow needles, m.p. 181~182°, from 3.2 g. of 2,4-dichloroaniline and 2 g. of acetylacetone as above. The product obtained by the reaction of 3.4 g. of the above needles and 2.1 g. of guanidine hydrochloride was recrystallized from glacial AcOH to 5 g. of orange needles, m.p. 278°. *Anal.* Calcd. for $C_{12}H_{11}N_5Cl_2$: C, 48.64; H, 3.74; N, 23.66; Cl, 23.95. Found: C, 48.76; H, 3.92; N, 23.83; Cl, 24.18.

4-(2-Amino-4,6-dimethyl-5-pyrimidinylazo)benzenesulfonic Acid (Py-68)—*p*-Sulfophenylazoacetylacetone was prepared from 2.1 g. of sulfanilic acid and 0.7 g. of acetylacetone, and reacted with guanidine hydrochloride in a solution of NaOH in hydr. MeOH. The resulting orange-yellow sodium salt was filtered, washed with Et_2O, and dried. From its aqueous solution orange-red needles, m.p. >360°, separated on addition of glacial AcOH. *Anal.* Calcd. for $C_{12}H_{13}O_3N_5S$: C, 46.89; H, 4.27; N, 22.80. Found: C, 47.22; H, 4.38; N, 22.99.

Reductive Cleavage of the Azo-linkage of 4-(2,4,6-Triamino-5-pyrimidinylazo)benzenesulfonic Acid (Py-64)—A solution of 0.5 g. of Py-64 in 20 cc. of 5% $NaHCO_3$ solution was shaken in H_2 atmosphere with Pd-C prepared from 1 cc. of 2% $PdCl_2$ solution, when 116% of the theoretical amount of hydrogen was absorbed in 1 hr. The catalyst was filtered off and the filtrate, after being concentrated, was acidified with dil. H_2SO_4 whereupon a white precipitate deposited, which was recrystallized from 2% H_2SO_4 in colorless fine needles, m.p. >360°. The infrared spectrum of the product was in agreement with that of 2,4,5,6-tetraaminopyrimidine sulfate prepared by other methods.

Oxidative Ring-closure of Py-64: Formation of 4-(5,7-Diamino-*v*-triazolo[*d*]pyrimidin-2-yl)-benzenesulfonic Acid—A portion of 3.1 g. of Py-64 was heated under reflux and bubbling with air for 3 hrs. in a mixture of 7.5 g. of $CuSO_4$, 15 cc. of water, and 15 cc. of pyridine. After cool, the resulting crystals were filtered and again heated in the same conditions as above for 3 hrs. The reaction mixture was poured into water and the solution was acidified with HCl, when a white precipitate separated out. The precipitate was filtered, dissolved in an aqueous solution of $NaHCO_3$ with warming, and reprecipitated by addition of glacial AcOH. The product (1 g.) is colorless crystalline powder, m.p. >360°. *Anal.* Calcd. for $C_{10}H_9O_3N_7S$: C, 39.08; H, 2.95; N, 31.91. Found: C, 38.89; H, 3.01; N, 31.73.

Oxidative Ring-closure of Py-80: Formation of 4-(5,7-Diamino-*v*-triazolo[*d*]pyrimidin-2-yl)-benzenephosphonic Acid—A portion of 1.5 g. of Py-80 was treated in the same way as above to give 0.65 g. of faintly yellow crystalline powder, m.p. >360°. *Anal.* Calcd. for $C_{10}H_{10}O_3N_7P$: N, 31.92; P, 10.09. Found: N, 31.61; P, 10.29.

Summary

Expecting an antagonistic activity upon nucleic acid metabolism, several kinds of pyrimidine derivatives were synthesized, of which 5-phenylazopyrimidines were found to have growth-inhibitory activity against some microörganisms. With consideration for their biological activities, 31 kinds of 5-phenylazopyrimidine derivatives were synthesized by either of two methods according to the kind of substituents to be introduced into the pyrimidine ring; benzenediazonium salts were coupled with pyrimidine derivatives at the 5-position in one method, and phenylazo-β-dicarbonyl compounds were condensed with guanidine or acetamidine in the other.

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