[Chem. Pharm. Bull. 11 (11) 1382 ~ 1388]

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216. Kaname Takagi and Takeo Ueda: Syntheses of Pyrimidinylhydrazones of 4-Biphenylylglyoxal.

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Moffet[1] reported that some of aliphatic and aromatic glyoxal derivatives were effective on the PR-8 strain of influenza A virus and Newcastle disease virus in embryonated eggs. After that, Cavallini, *et al.*[2] synthesized 4-biphenylylglyoxal and the related compounds, and Magrassi[3] claimed that some of these compounds exerted protective effect on the PR-8 strain in mice. Takahashi, one member of our group prepared the similar derivatives of 4-biphenylylglyoxal ot those of Magrassi, and Toyoshima, the other members reexamined the effect of these compounds on the virus *in ovo* and in mice.

However, their effects were not reconfirmed by our group in chorioallantoic membrane culture and mice experiments.

It is of interest that ketoxal group might be associated with antiinfluenzal activity in *in ovo* experiments, though it did not show any effect in mice experiments.

Underwood[4] reported that compounds having ketoxal group for instance, 2-oxo-3-ethoxy-butyraldehyde exerted an *in ovo* effect on the PR-8 strain, but did not show any effect in mice, because this agent might readily combine with metabolites. It, however, is probable that *in vivo* antiinfluenzal agent might be obtained by combining ketoxal compounds with suitable partial structure, which keeps the whole molecule free from metabolites. The work of Magrassi appears quite perspective to approach the such active ketoxl compounds *in vivo* by the above conception, though he did not obtain any significantly effective agent among 4-biphenylylglyoxal derivatives.

On the other hand, Dijeck[5] and Vanderhaeghe, *et al.*,[6] reported that some of hydrazinopyrimidine derivatives, particularly some condensation products of hydrazinopyrimidine with aldehydes and ketones showed inhibitory effect on the development of pathogenic microbes.

Taking the above findings into consideration, the authors conceived an idea to synthesize new condensation products of hydrazinopyrimidine derivatives with 4-biphenylylglyoxal for the purpose of finding antimicrobial agents.

This paper describes the syntheses of 2-hydrazino-4-alkoxy-6-methylpyrimidine, 2-hydrazino-4-alkylthio-6-methylpyrimidine, 2-alkylthio-4-hydrazino-6-methylpyrimidine and their condensation products with 4-biphenylylglyoxal.

Syntheses of 2-Hydrazino-4-alkoxy (and 4-alkylthio)-6-methylpyrimidine

Of compounds of 2-hydrazino-4-alkoxy-6-methylpyrimidine, 4-methoxy derivative was synthesized by Shirakawa,[7] and 4-ethoxy and 4-isopropoxy derivatives by Vanderhaeghe.[8]

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1) R.B. Moffet, B.D. Tiffany, J.B. Wright: J. Am. Chem. Soc., **79**, 1682 (1957); *Ibid.*, **79**, 1687 (1957).
2) G. Cavallini, E. Massarani: J. Med. Pharm. Chem., **1**, 365 (1959); *Ibid.*, **2**, 99 (1960) (C.A., **54**, 18425 (1960)).
3) F. Magrassi, P. Altucci, G. Lorenzutti, U. Sapio: *Ibid.*, **1**, 601 (1959) (C.A., **54**, 16654 (1960)).
4) G.E. Underwood: Proc. Soc. exp Biol. and Med., **100**, 312 (1959); Journ. Immunol., **78**, 104 (1957).
5) P.T. van Dijeck, M. Claesen: Antibiotics and Chemotherapy, **9**, 523 (1959) (C.A., **54**, 9086 (1960)).
6) H. Vanderhaeghe, M. Claesen: Bull. Soc. Chim. Belg., **68**, 47 (1959) (C.A., **56**, 10146 (1962)); Belg. Pat., No., 561091 (1957).
7) K. Shirakawa: Yakugaku Zasshi, **73**, 598 (1953).
8) H. Vanderhaeghe, M. Claesen: Bull. Soc. Chim. Belg., **68**, 30 (1959) (C.A. **56**, 10145 (1962)).

From these findings, there were considered the two synthetic processes, to obtain 2-hydrazino-4-alkoxy-6-methylpyrimidine.

The one is a synthetic method employing guanidine and ethyl acetoacetate as the starting materials, as illustrated in Chart 1, while the other, a synthetic method using urea and ethyl acetoacetate as the starting materials as shown in Chart 2.

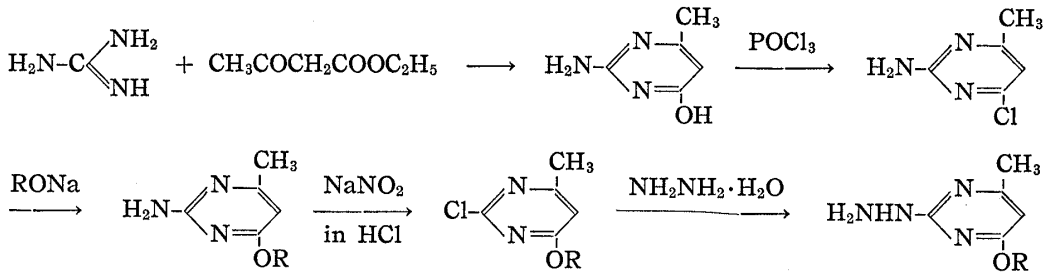


Chart 1.

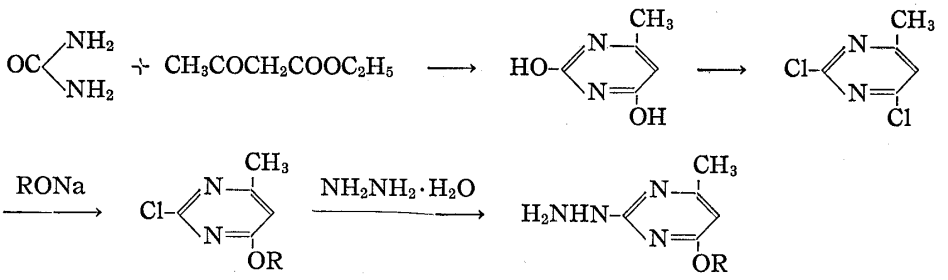


Chart 2.

In the latter method, the reaction of the first step was found to afford 6-methyl-2,4-pyrimidinediol in a poor yield and the reaction of the third step may be difficult to bear the product of selectively partial alkoxylation.

Consequently, by the former method, 2-amino-4-chloro-6-methylpyrimidine,[9] which had been prepared through 2-amino-6-methyl-4-pyrimidinol from the reaction between guanidine and ethyl acetoacetate, was converted to 2-amino-4-alkoxy-6-methylpyrimidine by the alkoxylation with sodium alkoxide in alcoholic solution, and the objective compound was obtained by the chlorination of 2-amino-4-alkoxy-6-methylpyrimidine in cold concentrated hydrochloric acid solution with sodium nitrite and the hydrazination of the resulting chlorinated product with 50 per cent hydrazine hydrate in the presence of potassium carbonate.

Next, the syntheses of derivatives of 2-hydrazino-4-alkylthio-6-methylpyrimidine were undertaken. No compound of this series has ever been revealed in literature.

The synthetic process of these compounds was conceived from the analogy to that of 2-hydrazino-4-alkoxy-6-methylpyrimidine. Employing 2-amino-4-chloro-6-methylpyrimidine as the starting material, it was reacted with sodium hydrosulfide to produce 2-amino-6-methyl-4-pyrimidinethiol, which was converted to 2-amino-4-alkylthio-6-methylpyrimidine by the alkoxylation with either alkyl iodide or alkyl bromide.

2-Hydrazino-4-alkylthio-6-methylpyrimidine was obtained by the chlorination of 2-amino-4-alkylthio-6-methylpyrimidine in concentrated hydrochloric acid solution with sodium nitrite and the hydrazination of the resulting product, 2-chloro-4-alkylthio-6-methylpyrimidine with 50 per cent hydrazine hydrate in the presence of potassium carbonate. The synthetic process of 2-hydrazino-4-alkylthio-6-methylpyrimidine is illustrated in Chart 3.

9) S. Gabriel: Chem. Ber., 32, 2924 (1899).

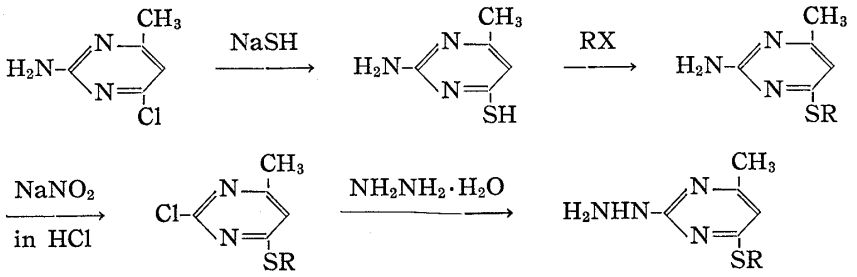
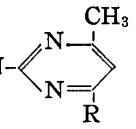


Chart 3.

In this method, it was found that the reaction of the last step should be conducted under the milder condition, since alkylthio group was apt to the hydrazination with hydrazine hydrate.

Vanderhaeghe[8] found that the reaction of 2-methylthio-4-methoxypyrimidine derivatives with hydrazine hydrate afforded mainly 4-hydrazino products. This finding suggests that 4-methoxy group is more reactive with hydrazine hydrate than 2-methylthio group in the reaction. In fact, the authors found that 2,4-dihydrazino compounds were sometimes produced as the side products in the reaction of 2-chloro-4-alkylthio-6-methylpyrimidine with hydrazine hydrate. This fact suggests that 2-chlorine atom might become more reactive under the anionoid influence of hydrazine than 4-methylthio group. The compounds of the two series synthesized are listed in Table I.

Table I. 

R	m.p. (°C)	Recrystn. solvent	Mol. formula	N (%) Calcd.	N (%) Found
HO[a]	235	ethanol–water	$C_5H_8ON_4$	39.98	39.88
CH_3O	112~114	ethanol	$C_6H_{10}ON_4$	36.34	36.29
C_2H_5O	70~ 73	ether	$C_7H_{12}ON_4$	33.31	33.27
C_3H_7O	70~ 71	petr. benzin	$C_8H_{14}ON_4$	30.75	30.81
iso-C_3H_7O	50~ 51	〃	$C_8H_{14}ON_4$	30.75	30.61
C_4H_9O	44~ 45 (129~131/mm. Hg)	distillation	$C_9H_{16}ON_4$	28.55	28.67
CH_3S	120~122	ether	$C_6H_{10}N_4S$	32.91	32.85
C_2H_5S	96~ 97	〃	$C_7H_{12}N_4S$	30.45	30.56
C_3H_7S	64~ 65	petr. benzin	$C_8H_{14}N_4S$	28.25	28.12
iso-C_3H_7S	62~ 65	〃	$C_8H_{14}N_4S$	28.25	28.06
C_4H_9S	52~ 54 (155~158/7 mm. Hg)	distillation	$C_9H_{16}N_4S$	26.39	26.20

a) see Chart 4.

Synthesis of 2-Alkylthio-4-hydrazino-6-methylpyrimidine

Of compounds of this series, 2-methylthio- and 2-ethylthio derivatives were already reported. Vanderhaeghe[8] and Vystrčil[10] reported that 2-methylthio- and 2-ethylthio-4-hydrazino-6-methylpyrimidine were synthesized by the hydrazination of 2-methylthio- and 2-ethylthio-4-chloro-6-methylpyrimidine with hydrazine hydrate, and Vanderhaeghe[8] also synthesized the same products by the hydrazination of 2-methylthio- and 2-ethylthio-4-methoxy-6-methylpyrimidine with hydrazine hydrate.

For the introduction of hydrazino group into pyrimidine ring, a substituent group of chloro, methoxy or methylthio is reacted with hydrazine. In pyrimidine ring, 4-position seems to be more active than 2-position, and chlorine atom more reactive on

10) A. Vystrčil: Chem. Listy., **45**, 407 (1951) (C. A. **46**, 7567 (1952)).

hydrazine than any of the other two. According to this assumption, it may be inferred that 2-alkylthio-4-chloro-6-methylpyrimidine is preferable as the preceding product to the objective compounds. Thus, 2-alkylthio-6-methyl-4-pyrimidinol as the starting material was chlorinated with phosphoryl oxychloride to bear 2-alkylthio-4-chloro-6-methylpyrimidine in a good yield. The latter was converted to 2-alkylthio-4-hydrazino-6-methylpyrimidine by reacting with hydrazine hydrate in alcoholic solution.

At the same time, 2-methylthio-6-methyl-4-pyrimidinol was converted into 2-hydrazino-6-methyl-4-pyrimidinol by heating with 50 per cent hydrazine hydrate, according to the method of Shirakawa[11] (see Table I).

The synthetic process is shown in Chart 4, and the compounds synthesized are listed in Table II.

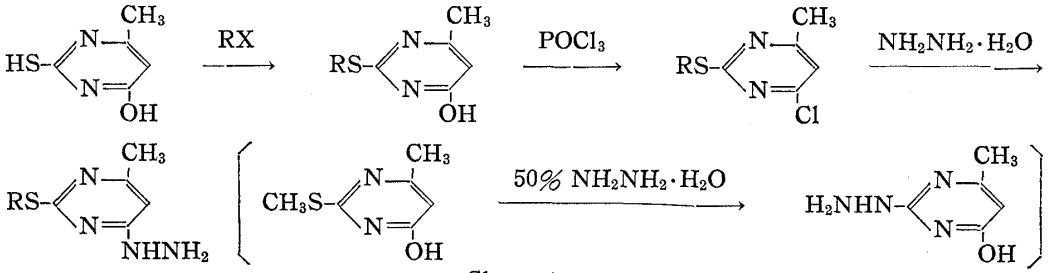
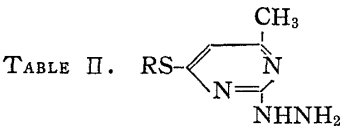


Chart 4.

Table II. 

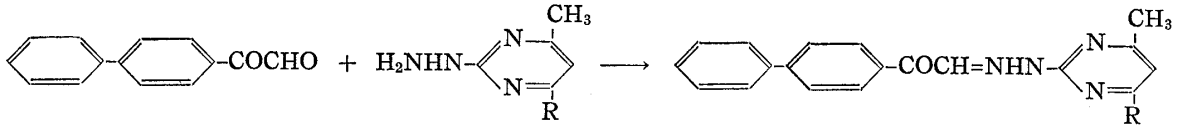
R	m.p. (°C)	Recrystn. solvent	Mol. formula	N) %) Calcd.	Found
CH_3	139~140	ether	$C_6H_{10}N_4S$	32.91	33.09
C_2H_5	95~ 96	〃	$C_7H_{12}N_4S$	30.45	30.62
C_3H_7	104~105	petr. benzin	$C_8H_{14}N_4S$	28.25	28.09
iso-C_3H_7	103~104	〃	$C_8H_{14}N_4S$	28.25	28.44
C_4H_9	76~ 78	〃	$C_9H_{16}N_4S$	26.39	26.24

Syntheses of Pyrimidinylhydrazones of 4-Biphenylylglyoxal

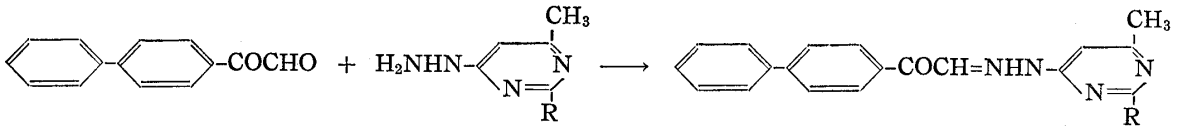
Since compounds of 2-hydrazino-4-alkoxy-6-methylpyrimidine, 2-hydrazino-4-alkylthio-6-methylpyrimidine, and 2-alkylthio-4-hydrazino-6-methylpyrimidine were obtained as described above, the syntheses of their condensation products with 4-biphenylylglyoxal were successively undertaken. No compound of this type has ever been reported. It, however, was shown by Vanderhaeghe[6] that the reaction of some substituted hydrazinopyrimidines with specific aldehydes or ketones afforded condensation products. This report suggested that this reaction would be held true of that between 4-biphenylylglyoxal and the hydrazinopyrimidines. Thus, attempts were made to condense 4-biphenylylglyoxal with each of 2-hydrazino-4-alkoxy-6-methylpyrimidine, 2-hydrazino-4-alkylthio-6-methylpyrimidine, and 2-alkylthio-4-hydrazino-6-methylpyrimidine in ethanolic or ethanolic aqueous solution in the presence of hydrochloric acid. As the results obtained, the objective compounds of the three series were found to result in comparatively good yields by this reaction, as anticipated above.

4-Biphenylylglyoxal as the intermediate was prepared by the oxidation of 4-phenylacetophenone with selenium dioxide in dioxane, according to the method of Musante, *et al.*[12]

11) K. Shirakawa: Yakugaku Zasshi, **73**, 635 (1953); *Ibid.*, **73**, 159 (1953).
12) C. Musante, V. Parrini: Gazz. Chim. Ital., **80**, 868 (1952) (C. A., **46**, 4502 (1952)).



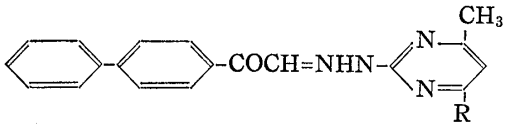
R=hydroxy, alkoxy, alkylthio group.



R=alkylthio group

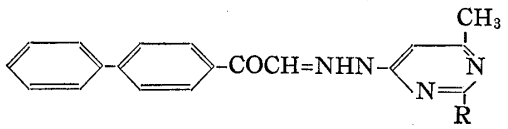
Chart 5.

Table III.



R	m.p. (°C)	Recrystn. solvent	Mol. formula	N (%) Calcd.	N (%) Found
OH	257~258	ethanol	$C_{19}H_{16}O_2N_4$	16.86	16.88
CH_3O	238~240	〃	$C_{20}H_{18}O_2N_4$	16.18	16.35
C_2H_5O	188~189	〃	$C_{21}H_{20}O_2N_4$	15.55	15.41
C_3H_7O	170~172	ethanol-water	$C_{22}H_{22}O_2N_4$	14.96	15.06
iso-C_3H_7O	104~106	〃	$C_{22}H_{22}O_2N_4$	14.96	15.12
C_4H_9O	167~169	ethanol	$C_{23}H_{24}O_2N_4$	14.42	14.28
CH_3S	182~184	acetone	$C_{20}H_{18}ON_4S$	15.46	15.23
C_2H_5S	170~171	acetone-ethanol	$C_{21}H_{20}ON_4S$	14.88	14.76
C_3H_7S	153~155	ethanol	$C_{22}H_{22}ON_4S$	14.36	14.45
iso-C_3H_7S	105~106	〃	$C_{22}H_{22}ON_4S$	14.36	14.18
C_4H_9S	147~149	〃	$C_{23}H_{24}ON_4S$	13.85	13.97

Table IV.



R	m.p. (°C)	Recrystn. solvent	Mol. formula	N (%) Calcd.	N (%) Found
CH_3S	223~225	ethanol-water	$C_{20}H_{18}ON_4S$	15.46	15.28
C_2H_5S	144~145	ethanol	$C_{21}H_{20}ON_4S$	14.88	15.01
C_3H_7S	138~139	acetone-ethanol	$C_{22}H_{22}ON_4S$	14.36	14.24
iso-C_3H_7S	110~113	ethanol	$C_{22}H_{22}ON_4S$	14.36	14.17
C_4H_9S	129~130	〃	$C_{23}H_{24}ON_4S$	13.85	13.93

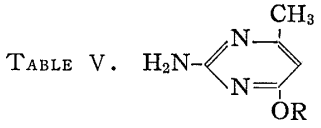
These synthetic processes are shown in Chart 5 and the hydrazones are listed in Table III and IV.

The antimicrobial activity of the compounds synthesized will be reported in another report in the near future.

Experimental

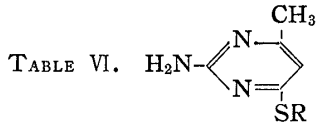
General Method for 2-Amino-4-alkoxy-6-methylpyrimidine——A mixture of 0.04 mole of 2-amino-4-chloro-6-methylpyrimidine and a solution of RONa prepared from 1 g. of Na and 40 ml. of ROH, was refluxed for 4 hr. After removal of the solvent, the precipitate was collected, and recrystallized from EtOH-H_2O. 4-Butoxy derivative was purified by distillation *in vacuo*.

The data for the compounds are listed in Table V.

Table V. 

R	m.p. (°C)	Yield (%)	Mol. formula	N (%) Calcd.	N (%) Found
CH_3	156~157	80	$C_6H_9ON_3$	30.22	30.71
C_2H_5	99~100	80	$C_7H_{11}ON_3$	27.45	27.49
C_3H_7	61~ 62	63	$C_8H_{13}ON_3$	25.15	25.21
iso-C_3H_7	67~ 68	75	$C_8H_{13}ON_3$	25.15	25.08
C_4H_9	120~122/4 mm. Hg	70	$C_9H_{15}ON_3$	—	—

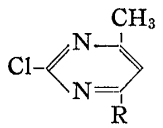
General Method for 2-Amino-4-alkylthio-6-methylpyrimidine——A mixture of EtONa prepared from 1.2 g. of Na in 50 ml. of abs. EtOH, 0.05 mole of 2-amino-6-methyl-4-pyrimidinethiol, and 0.07 mole of alkylhalide was refluxed for 3 hr. After removal of the solvent, H_2O was added and the precipitate was recrystallized from EtOH. The data for the compounds are listed in Table VI.

Table VI. 

R	m.p. (°C)	Yield (%)	Mol. formula	N (%) Calcd.	N (%) Found
CH_3	145~147	75	$C_6H_9N_3S$	27.07	27.02
C_2H_5	123~125	73	$C_7H_{11}N_3S$	24.85	24.75
C_3H_7	107	72	$C_8H_{13}N_3S$	22.95	22.86
iso-C_3H_7	108~109	85	$C_8H_{13}N_3S$	22.95	23.06
C_4H_9	71~ 73	75	$C_9H_{15}N_3S$	21.32	21.19

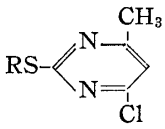
General Method for 2-Chloro-4-alkoxy (and 4-alkylthio)-6-methylpyrimidine——A solution of 20 ml. of conc. HCl was cooled to 0°, and 0.03 mole of 2-amino-4-alkoxy (or 4-alkylthio)-6-methylpyrimidine was added portionwise with stirring.

The solution was then cooled to −15° and a cold solution of 4.5 g. of $NaNO_2$ dissolved in 10 ml. of H_2O was added dropwise below −10°. The solution was stirred for 1 hr. and then alkalized with 30% NaOH solution, the reaction temperature not being allowed to rise above 0°. The cold solution was extracted with Et_2O. Removal of the solvent after drying, the oily residue was distilled *in vacuo*. The data for the compounds obtained are listed in Table VII.

Table VII. 

R	b.p. (°C)/mm. Hg	Yield (%)	Mol. formula
CH_3O	99~100/5	26	$C_6H_7ON_2Cl$
C_2H_5O	80~ 81/4	23	$C_7H_9ON_2Cl$
C_3H_7O	81~ 83/2	25	$C_8H_{11}ON_2Cl$
iso-C_3H_7O	77~ 79/3	26.5	$C_8H_{11}ON_2Cl$
C_4H_9O	98~ 99/4	26	$C_9H_{13}ON_2Cl$
CH_3S	107~110/6	25	$C_6H_7N_2ClS$
C_2H_5S	96~ 97/3	30	$C_7H_9N_2ClS$
C_3H_7S	103~105/2	30	$C_8H_{11}N_2ClS$
iso-C_3H_7S	110~111/5	20	$C_8H_{11}N_2ClS$
C_4H_9S	124~127/4	28	$C_9H_{13}N_2ClS$

General Method for 2-Alkylthio-4-chloro-6-methylpyrimidine——A mixture of 0.03 mole of 2-alkylthio-6-methyl-4-pyrimidinol, which prepared from 2-mercapto-6-methyl-4-pyrimidinol and alkyl halide in MeONa solution, and 20 ml. of $POCl_3$ was refluxed in an oil bath for 2 hr. After distillation of excess $POCl_3$ *in vacuo*, the residue was poured into ice H_2O, and the mixture was extracted with Et_2O. Removal of the Et_2O after drying, the residual oil was distilled under diminished pressure. The data for the compounds are listed in Table VIII.

Table VIII. RS- 

R	b.p. (°C)/mm. Hg	Yield (%)	Mol. formula
CH_3	147/32	70	$C_6H_7N_2ClS$
C_2H_5	89～ 90/0.5	64	$C_7H_9N_2ClS$
C_3H_7	106～107/0.5	50	$C_8H_{11}N_2ClS$
iso-C_3H_7	102～104/0.5	50	$C_8H_{11}N_2ClS$
C_4H_9	102～105/0.3	60	$C_9H_{13}N_2ClS$

General Method for 2-Hydrazino-4-alkoxy (and 4-alkylthio)-6-methylpyrimidine——A mixture of 0.01 mole of 2-chloro-4-alkoxy (or 4-alkylthio)-6-methylpyrimidine, 1.3 g. of 50% hydrazine hydrate and 1 g. of K_2CO_3 in 10 ml. EtOH was refluxed for 30 min. After removal of EtOH, the residual oily product was cooled in ice box. The crude product solidified was collected, washed with H_2O, and recrystallized from appropriate solvent. The derivatives not solidified were distilled under diminished pressure (see Table I).

General Method for 2-Alkylthio-4-hydrazino-6-methylpyrimidine——To a solution of 0.01 mole of 2-alkylthio-4-chloro-6-methylpyrimidine dissolved in 10 ml. EtOH, 1.5 g. of hydrazine hydrate was added. The reaction mixture was refluxed for 15 min. After removal of the solvent, the crude prduct that separated, was washed with H_2O, and recrystallized from appropriate solvent (see Table II).

2-Hydrazino-6-methyl-4-pyrimidinol——According to the method of Shirakawa,[11] this compound was prepared by heating 2 g. of 2-methylthio-6-methyl-4-pyrimidinol with 2 g. of 50% hydrazine hydrate for 1 hr., m.p. 235°(see Table I).

General Method for Pyrimidinylhydrazones of 4-Biphenylylglyoxal——A mixture of equimolar amounts of hydrazinopyrimidine derivatives and 4-biphenylylglyoxal, in EtOH containing a few drop of conc. HCl was refluxed for 5 hr. and the reaction mixture was evaporated under reduced pressure. The crystals separated were filtered and recrystallized from appropriate solvent to obtain yellow needles. Yield : ca. 80% (see Table III and IV).

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Summary

To search for antimicrobial agent, 2-hydrazino-4-alkoxy-6-methylpyrimidine, 2-hydrazino-4-alkylthio-6-methylpyrimidine, and 2-alkylthio-4-hydrazino-6-methylpyrimidine were synthesized by the hydrazination of the corresponding 2-chloro- and 4-chloropyrimidine with hydrazine hydrate, and it was found that chlorine atom at 2-position or 4-position in pyrimidine ring, is more reactive on hydrazine than alkylthio and alkoxy group at 4- or 2-position. These hydrazinopyrimidines of the three series were converted into pyrimidinylhydrazones of 4-biphenylylglyoxal by the condensation with 4-biphenylylglyoxal.

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