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116. Yoshihiro Nitta, Toshio Miyamoto, Toshiyuki Nebashi, and Fumio Yoneda : Pyrimidine Derivatives. III.*1 The Preparation and Bacteriostatic Activity of Benzamidopyrimidines.

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A number of studies with a view to finding medicine on the benzanilide derivatives have been reported, especially the antibacterial and anthelmintic activities of salicylanilide derivatives have been extensively studied.[1~7] Some of the salicylhaloanilide and halosalicylhaloanilide series were found to have strong antibacterial and antifungal activities. Moreover, certain benzanilide derivatives such as 3,4,5-trimethoxybenzanilide series[8] were found to possess nonhypnotic sedative action. Some investigations of benzamide derivatives, of which aniline part was replaced by heterocyclic amines have partially been attempted, but no systematical works on the syntheses and biological actions of heterocyclic benzamide derivatives have been done.

It is, therefore, of considerable interest to investigate the effect of heterocyclic amines on the bacteriostatic activity of benzamide derivatives, which can be obtained by benzoylation of the heterocyclic amines. In the present paper, 4-amino-2,6-dimethoxypyrimidine and its related compounds, the former being constitutional part in the molecule of sulfadimethoxine used as one of long-acting sulfa drugs, were selected for this purpose as heterocyclic amines.

Reaction of aminopyrimidines with benzoyl chlorides substituted with methyl, methoxy, chloro, bromo, and nitro groups in dry pyridine gave the corresponding benzamidopyrimidines in good yields. Although benzoylation with salicyloyl chloride failed, the desired salicylamidopyrimidines were obtained from reaction between aminopyrimidines and phenyl salicylate in α-methylnaphthalene at 200~210°. The compounds were converted into 3,5-dibromosalicylamidopyrimidines by bromination with bromine. Chemical proof of the structures of the compounds was obtained by decomposition with sulfuric acid to give 3,5-dibromosalicylic acid. Aminopyrimidines also reacted with

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*1 Part II : This Bulletin, **13**, 568 (1965).

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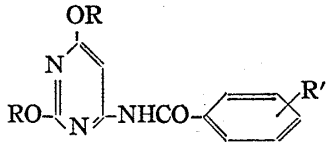
1) R.G. Taborsky, *et al.* : J. Pharm. Sci., **48**, 503 (1959).
2) R.G. Taborsky, R.J. Starkey : *Ibid.*, **51**, 1152 (1962).
3) *Idem* : *Ibid.*, **52**, 542 (1963).
4) H. Lemaire, C.H. Schramm, A. Cahn : *Ibid.*, **50**, 831 (1961).
5) R. Kimura, *et al.* : This Bulletin, **10**, 1226 (1962).
6) H. Schönenberger, *et al.* : Arzneimittel-Forsch., **12**, 1162 (1962).
7) R. Gönnert, E. Schraufstätter : *Ibid.*, **10**, 881 (1960).
8) *a*) U.S. Pat. 2870145 (1959); U.S. Pat. 2870146 (1959) (C.A., **53**, 10264). *b*) L. Vargha, *et al.* : Biochem. Pharm., **11**, 639 (1962). *c*) E. Kasztreiner, J. Borsy, L. Vargha : *Ibid.*, **11**, 667 (1962).

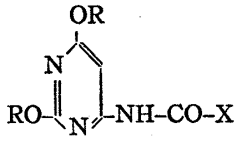
TABLE I. 4-Benzamido-2,6-dialkoxypyrimidines



No.	R	R′	m.p. (°C)	Crystn. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	CH_3	H	139	MeOH–H_2O	$C_{13}H_{13}O_3N_3$	60.22	5.05	16.21	60.31	5.15	16.05
II	〃	2-Cl	126	EtOH–H_2O	$C_{13}H_{12}O_3N_3Cl$	53.16	4.12	14.38	53.35	4.14	14.20
III	〃	4-Cl	154～155	EtOH	$C_{13}H_{12}O_3N_3Cl$	53.16	4.12	14.38	53.47	4.15	14.25
IV	〃	2,4-Cl_2	144～145	MeOH–H_2O	$C_{13}H_{11}O_3N_3Cl_2$	47.58	3.38	12.81	47.63	3.43	12.68
V	〃	3,4-Cl_2	158	〃	$C_{13}H_{11}O_3N_3Cl_2$	47.58	3.38	12.81	47.45	3.34	12.89
VI	〃	3-Br·H_2O	93	EtOH–H_2O	$C_{13}H_{14}O_4N_3Br$	43.84	3.97	11.80	43.83	3.73	11.52
VII	〃	4-Br	150～151	MeOH–H_2O	$C_{13}H_{12}O_3N_3Br$	46.17	3.58	12.43	46.27	3.63	12.69
VIII	〃	2-CH_3	127～128	EtOH–H_2O	$C_{14}H_{15}O_3N_3$	61.53	5.53	15.38	61.92	5.74	15.43
IX	〃	3-CH_3	122	〃	$C_{14}H_{15}O_3N_3$	61.53	5.53	15.38	61.34	5.55	15.44
X	〃	4-CH_3	137	MeOH–H_2O	$C_{14}H_{15}O_3N_3$	61.53	5.53	15.38	61.34	5.30	15.59
XI	〃	3-NO_2	185～186	MeOH	$C_{13}H_{12}O_5N_4$	51.31	3.98	18.42	—	—	18.27
XII	〃	4-NO_2	184	〃	$C_{13}H_{12}O_5N_4$	51.31	3.98	18.42	51.15	4.16	18.27
XIII	〃	4-OCH_3	142～143	MeOH–H_2O	$C_{14}H_{15}O_4N_3$	58.12	5.23	14.53	57.93	5.07	14.25
XIV	〃	3,4-$(OCH_3)_2$	167	MeOH	$C_{15}H_{17}O_5N_3$	56.42	5.37	13.16	56.61	5.42	13.15
XV	〃	3,4,5-$(OCH_3)_3$	107	MeOH–H_2O	$C_{16}H_{19}O_6N_3$	55.01	5.48	12.03	54.94	5.64	12.19
XVI	〃	3-NO_2-4-Cl	160～162	MeOH	$C_{13}H_{11}O_5N_4Cl$	46.10	3.27	16.54	46.04	3.47	16.69
XVII	〃	2-OH	204	MeOH–H_2O	$C_{13}H_{13}O_4N_3$	56.72	4.76	15.27	57.04	4.77	15.53
XVIII	C_2H_5	H·H_2O	76	EtOH–H_2O	$C_{15}H_{19}O_4N_3$	59.00	6.27	13.76	59.47	6.61	13.85
XIX	〃	2-Cl	98	〃	$C_{15}H_{16}O_3N_3Cl$	55.99	5.01	13.06	56.15	4.82	12.65
XX	〃	4-Cl	120	〃	$C_{15}H_{16}O_3N_3Cl$	55.99	5.01	13.06	56.33	4.88	12.57
XXI	〃	2,4-Cl_2	115～116	〃	$C_{15}H_{15}O_3N_3Cl_2$	50.58	4.24	11.80	50.41	4.19	11.78
XXII	〃	3,4-Cl_2	140～141	〃	$C_{15}H_{15}O_3N_3Cl_2$	50.58	4.24	11.80	50.74	4.48	11.71
XXIII	〃	4-Br	128～129	MeOH–H_2O	$C_{15}H_{16}O_3N_3Br$	49.20	4.40	11.47	49.23	4.36	11.25
XXIV	〃	2-CH_3	107～108	EtOH–H_2O	$C_{16}H_{19}O_3N_3$	63.77	6.36	13.95	63.61	6.54	13.87
XXV	〃	3-CH_3	95～96	〃	$C_{16}H_{19}O_3N_3$	63.77	6.36	13.95	63.74	6.50	13.93
XXVI	〃	4-CH_3	128	MeOH–H_2O	$C_{16}H_{19}O_3N_3$	63.77	6.36	13.95	63.88	6.45	14.05
XXVII	〃	3-NO_2	113～114	〃	$C_{15}H_{16}O_5N_4$	54.21	4.85	16.86	54.49	4.62	16.68
XXVIII	〃	4-NO_2	159	MeOH	$C_{15}H_{16}O_5N_4$	54.21	4.85	16.86	54.43	4.94	17.00
XXIX	〃	4-OCH_3	116	MeOH–H_2O	$C_{16}H_{19}O_4N_3$	60.55	6.04	13.24	60.87	5.67	12.96
XXX	〃	3-NO_2-4-Cl	151	MeOH	$C_{15}H_{15}O_5N_4Cl$	49.12	4.12	15.28	49.11	3.98	14.99

XXXI	C_2H_5	2-OH	178	MeOH-H_2O	$C_{15}H_{17}O_4N_3$	59.39	5.65	13.86	59.68	5.69	13.70
XXXII	〃	2-OH-3,5-Br_2	166	EtOH-H_2O	$C_{15}H_{15}O_4N_3Br_2$	39.07	3.28	9.11	39.60	3.35	8.80
XXXIII	C_3H_7	4-Cl	84	MeOH-H_2O	$C_{17}H_{20}O_3N_3Cl$	58.37	5.76	12.01	58.50	5.42	11.93
XXXIV	〃	3,4-Cl_2	86	〃	$C_{17}H_{19}O_3N_3Cl_2$	53.14	5.06	10.94	53.15	4.98	11.00
XXXV	〃	4-Br	79	〃	$C_{17}H_{20}O_3N_3Br$	51.79	5.11	10.66	51.76	5.42	10.47
XXXVI	iso-C_3H_7	4-Cl	102	〃	$C_{17}H_{20}O_3N_3Cl$	58.37	5.76	12.01	58.34	5.67	11.88
XXXVII	〃	2,4-Cl_2	120	〃	$C_{17}H_{19}O_3N_3Cl_2$	53.14	4.98	10.94	53.41	5.21	11.20
XXXVIII	〃	3,4-Cl_2	111	〃	$C_{17}H_{19}O_3N_3Cl_2$	53.14	4.98	10.94	53.17	5.01	10.75
XXXIX	〃	4-Br	145	〃	$C_{17}H_{20}O_3N_3Br$	51.79	5.11	10.66	52.03	5.24	10.44
XL	〃	4-CH_3	96	〃	$C_{18}H_{23}O_3N_3$	65.63	7.04	12.76	65.92	7.19	12.64
XLI	C_4H_9	4-Cl	71	〃	$C_{19}H_{24}O_3N_3Cl$	60.39	6.40	11.12	60.09	6.47	11.20
XLII	〃	3,4-Cl_2	89	〃	$C_{19}H_{23}O_3N_3Cl_2$	55.35	5.62	10.19	55.53	5.72	9.89
XLIII	〃	4-Br	80	〃	$C_{19}H_{24}O_3N_3Br$	54.04	5.73	9.95	54.18	5.89	9.73
XLIV	iso-C_4H_9	4-Cl	114	〃	$C_{19}H_{24}O_3N_3Cl$	60.39	6.40	11.12	60.00	6.45	11.01
XLV	〃	3,4-Cl_2	122	〃	$C_{19}H_{23}O_3N_3Cl$	55.35	5.62	10.19	55.51	5.81	10.18
XLVI	〃	4-Br	101	〃	$C_{19}H_{24}O_3N_3Br$	54.04	5.73	9.95	54.16	5.85	9.57

TABLE II. Nicotinamido- and Isonicotinamidopyrimidines



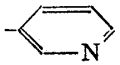
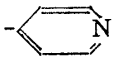
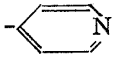
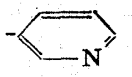
No.	R	X′	m.p. (C°)	Crystn. solvent	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XLVII	CH_3		176	EtOH-H_2O	$C_{12}H_{12}O_3N_4$	55.38	4.65	21.53	55.63	4.75	21.54
XLVIII	C_2H_5	〃	175	〃	$C_{14}H_{16}O_3N_4$	58.32	5.59	19.44	58.65	5.41	19.24
XLIX	C_3H_7	〃	104	MeOH-H_2O	$C_{16}H_{20}O_3N_4$	60.74	6.37	17.71	60.91	6.21	17.70
L	iso-C_3H_7	〃	130	〃	$C_{16}H_{20}O_3N_4$	60.74	6.37	17.71	60.66	6.17	17.80
LI	iso-C_4H_9	〃	119	iso-Pr_2O	$C_{18}H_{24}O_3N_4$	62.77	7.02	16.27	62.48	6.97	16.34
LII	CH_3		213	MeOH-H_2O	$C_{12}H_{12}O_3N_4$	55.38	4.65	21.53	55.24	4.73	21.52
LIII	C_2H_5	〃	164	〃	$C_{14}H_{16}O_3N_4$	58.32	5.59	19.44	58.29	5.47	19.65
LIV	C_3H_7	〃	116	〃	$C_{16}H_{20}O_3N_4$	60.74	6.37	17.71	60.84	6.24	17.74
LV	iso-C_3H_7	〃·H_2O	99	〃	$C_{16}H_{22}O_4N_4$	57.47	6.63	16.76	57.76	6.68	17.01
LVI	iso-C_4H_9		152	〃	$C_{18}H_{24}O_3N_4$	62.77	7.02	16.27	62.91	6.77	16.60

Table III. Antibacterial Activity of 4-Benzamido-2,6-dialkoxypyrimidines

No.	R	R′	Minimum inhibitory concentration (mcg./ml.) *Staph. aureus* 209P	*Shig. flexneri* 2a	*Pr. vulgaris* P-1	*M. tuberculosis* H37Rv	*T. mentagrophytes* T-1
I	CH_3	H	>80	—	—	>5	—
II	〃	2-Cl	20	20	—	>10	—
III	〃	4-Cl	5～10	5	—	>5	—
IV	〃	2,4-Cl_2	10	>20	—	>20	—
V	〃	3,4-Cl_2	>1.25	>1.25	>1.25	>1.25	>1.25
VI	〃	3-Br·H_2O	20	>10	—	>20	—
VII	〃	4-Br	5	>5	>5	>10	>10
VIII	〃	2-CH_3	20	>20	—	>20	>20
IX	〃	3-CH_3	10～20	>20	—	>20	>20
X	〃	4-CH_3	>20	>20	—	>20	>20
XI	〃	3-NO_2	20	>20	—	>5	—
XII	〃	4-NO_2	>80	—	—	>5	—
XIII	〃	4-OCH_3	>20	>20	—	>20	—
XIV	〃	3,4-$(OCH_3)_2$	>80	>80	—	>10	—
XV	〃	3,4,5-$(OCH_3)_3$	>20	20	—	>20	—
XVI	〃	3-NO_2-4-Cl	>2.5	>2.5	—	>1.25	—
XVII	〃	2-OH	>20	>20	>20	—	>20
XIX	C_2H_5	2-Cl	10	10	>20	—	>20
XX	〃	4-Cl	2.5～5	>5	>5	>5	>5
XXI	〃	2,4-Cl_2	2.5～5	>5	>5	—	>5
XXII	〃	3,4-Cl_2	1.25	>2.5	>2.5	—	>2.5
XXIII	〃	4-Br	2.5～5	>5	>5	>2.5	>5
XXIV	〃	2-CH_3	10～20	>10	—	>10	>10
XXV	〃	3-CH_3	10	>20	—	>20	>20
XXVI	〃	4-CH_3	5	>5	—	>5	>20
XXVII	〃	3-NO_2	>5	>5	>5	—	>5
XXVIII	〃	4-NO_2	>80	—	>10	—	—
XXIX	〃	4-OCH_3	10	20	—	>20	—
XXX	〃	3-NO_2-4-Cl	>5	>5	—	>5	—
XXXI	〃	2-OH	>2.5	>2.5	>2.5	—	>10
XXXII	〃	2-OH-3,5-Br_2	2.5	>20	—	—	5～10
XXXIII	C_3H_7	4-Cl	0.6～1.25	>2.5	>2.5	>2.5	>5
XXXIV	〃	3,4-Cl_2	>2.5	>2.5	>2.5	>5	>2.5
XXXV	〃	4-Br	>2.5	>2.5	>2.5	>5	>2.5
XXXVI	iso-C_3H_7	4-Cl	>5	>5	>5	>2.5	>5
XXXVII	〃	2,4-Cl_2	>2.5	>2.5	>2.5	>5	>2.5
XXXVIII	〃	3,4-Cl_2	>2.5	>2.5	>2.5	>5	>2.5
XXXIX	〃	4-Br	>2.5	>2.5	>2.5	>5	>2.5
XLI	C_4H_9	4-Cl	>2.5	>2.5	>2.5	>5	>2.5
XLII	〃	3,4-Cl_2	>2.5	>2.5	>2.5	>5	>2.5
XLIII	〃	4-Br	>2.5	>2.5	>2.5	>5	>2.5
XLIV	iso-C_4H_9	4-Cl	>2.5	>2.5	>2.5	>5	>2.5
XLV	〃	3,4-Cl_2	>2.5	>2.5	>2.5	>5	>2.5
XLVI	〃	4-Br	>2.5	>2.5	>2.5	>5	>2.5
	Sulfadimethoxine		1.25～2.5	2.5	10～20	—	—
	Isoniazid		—	—	—	0.1～0.2	
	Bithionol		—	—	—	—	0.5

Table IV. Antibacterial Activity of Nicotinamido- and Isonicotinamidopyrimidines

No.	R	X	Minimum inhibitory concentration (mcg./ml.) *Staph. aureus* 209P	*Shig. flexneri* 2a	*Pr. vulgaris* P-1	*M. tuberculosis* H37Rv	*T. mentagrophytes* T-1
XLVII	CH_3		80	>80	—	>5	—
XLVIII	C_2H_5	〃	>20	>20	>20	—	>20
XLIX	C_3H_7	〃	>10	>10	>10	>20	>20
L	iso-C_3H_7	〃	>10	>10	>10	>20	>20
LI	iso-C_4H_9	〃	>5	>5	>5	>5	>5
LII	CH_3		80	>80	—	>10	—
LIII	C_2H_5	〃	>10	>10	>20	—	>20
LIV	C_3H_7	〃	>10	>10	>10	>20	>20
LV	iso-C_3H_7	〃	>10	>10	>10	>20	>20
LVI	iso-C_4H_9	〃	>5	>5	>5	>5	>5

nicotinoyl chloride or isonicotinoyl chloride to give the corresponding nicotinamido- or isonicotinamidopyrimidines.

Aminopyrimidines, such as 2,6-dimethoxy-, 2,6-diethoxy-, 2,6-dipropoxy-, 2,6-diisopropoxy-, 2,6-dibutoxy-, and 2,6-diisobutoxy-4-aminopyrimidines, used as starting materials in this study, were obtained by alkoxylation of 2,6-dichloro-4-aminopyrimidine with the corresponding sodium alkoxide. New benzamido-, nicotinamido-, and isonicotinamidopyrimidine derivatives were also prepared and shown in Table I and II.

The antibacterial activities of these new compounds against *Staphylococcus aureus* 209P, *Shigella flexneri* 2a, *Proteus vulgaris* P-1, *Mycobacterium tuberculosis* H37Rv, and *Trichophyton mentagrophytes* T-1 were tested *in vitro*. The results were listed in Table III and IV. Throughout this paper, the figures given under activity refer to the minimum inhibitory concentration.

As can be seen from these data, many of these compounds clearly show activity against *Staphylococcus aureus* 209P. Some of them have slight activity against *Shigella flexneri* 2a and all of them are inactive against *Proteus vulgaris* P-1, *Mycobacterium tuberculosis* H37Rv and *Trichophyton mentagrophytes* T-1. In the course of the screening program in *Staphylococcus aureus* 209P, the relationship of bacteriostatic activity and the chemical structure is summarized as far as have been found out.

1) Introduction of halogens into the phenyl part of benzamidopyrimidines, increased the activities, especially that of chlorine at the 4- or 3,4-positions. Generally speaking, 2,6-diethoxypyrimidine was the most effective as pyrimidine moiety. But, in the case of 4-chlorobenzamide series, the maximum activity was reached by the amide of 2,6-dipropoxypyrimidine, not by that of 2,6-diethoxypyrimidine. Pyrimidine moiety having alkoxy groups higher than propoxy decreased the antibacterial activities along with solubility.

2) According to the publication[5,6] on the relationship of bacteriostatic activity with the chemical structure of benzanilides, only salicyloyl derivatives which have a hydroxy group at the *ortho* position show drastic activities and others have little or no effect on activities. Nevertheless, salicyloyl derivatives in this series are not always more effective than others.

3) Benzamidopyrimidines, which were effective for *Staphylococcus aureus* 209P, also showed activity in the preliminary tests against sulfanilamide resistant strain and the detailed data will be reported elsewhere. Accordingly, it is considered that their mode

of antibacterial action differs from that of sulfanilamides, although these compounds resemble structurally sulfanilamides.

Experimental*3

4-(4-Chlorobenzamido)-2,6-dimethoxypyrimidine (III)——To a solution of 1.55 g. of 4-amino-2,6-dimethoxypyrimidine in 5 ml. of dry pyridine was added dropwise with stirring and cooling an equimolar quantity of 4-chlorobenzoyl chloride. Reaction occurred in a moment when the solution was stirred vigorously at room temperature. The reaction mixture was cooled and poured into H_2O. The precipitate was collected by filtration, washed well with H_2O and dried. The crude product was recrystallized from EtOH to give 2.7 g. of colorless needles, m.p. 154~155°.

4-(2-Hydroxybenzamido)-2,6-diethoxypyrimidine (XXXI)——A mixture of 3.66 g. of 4-amino-2,6-diethoxypyrimidine, 4.8 g. of phenylsalicylate and 8 ml. of α-methylnaphthalene was heated at 200~210° for 1.5 hr. α-Methylnaphthalene and PhOH were removed by distillation under reduced pressure. The product was washed with ligroin and dried. After recrystallization from MeOH-H_2O, the pure compound was obtained as colorless needles, m.p. 178°. Yield, 1.8 g.

4-(2-Hydroxy-3,5-dibromobenzamido)-2,6-diethoxypyrimidine (XXXII)——A solution of 3.03 g. of 4-(2-hydroxybenzamido)-2,6-diethoxypyrimidine in 168 ml. of tetrahydrofuran and 112 ml. of AcOH was stirred at 15~25° during the dropwise addition of 3.20 g. of Br_2 in 10 ml. of AcOH. After the addition, stirring was continued for 5 hr. Reaction mixture was poured into 500 ml. of ice-water with stirring to give precipitate, which was collected and washed with H_2O. The precipitate was dissolved in hot AcOH and the solution was cooled to crystallize compound A, m.p. 235°, and the filtrate was diluted with H_2O to give precipitate, which crystallized from AcOH-H_2O as colorless needles (compound B), m.p. 166°. Compound A and B were refluxed for 15 min. in conc. H_2SO_4 to give 3,5-dibromosalicylic acid respectively. Accordingly, it was established that compound A was 4-(2-hydroxy-3,5-dibromobenzamido)-5-bromo-2,6-diethoxypyrimidine and compound B was 4-(2-hydroxy-3,5-dibromobenzamido)-2,6-diethoxy pyrimidine.

4-Nicotinamido-2,6-dimethoxypyrimidine (XLVII)——To a solution of 1.55 g. of 4-amino-2,6-dimethoxypyrimidine in 5 ml. of dry pyridine was added 1.78 g. of nicotinoyl chloride hydrochloride with stirring. The solution was warmed at 60° for 5 min. After cooling, the reaction mixture was poured into 50 ml. of H_2O and the precipitate was collected, washed with H_2O and dried. Recrystallization from MeOH-H_2O gave 2.3 g. of pure 4-nicotinamido-2,6-dimethoxypyrimidine as fine needles, m.p. 176°.

Antibacterial Activity——Test organism : *Staphylococcus aureus* 209P, *Shigella flexneri* 2a, *Proteus vulgaris* P-1, *Mycobacterium tuberculosis* H37Rv and *Trichophyton mentagrophytes* T-1.
Culture media : Casamino acids medium was used for *Staph. aureus* 209P, *Shig. flexneri* 2a and *Pr. vulgaris* P-1. Kirchner's medium was used for *M. tuberculosis* H37Rv. Sabouraud's medium (1% glucose) was used for *T. mentagrophytes* T-1. The test compounds were dissolved in the medium above mentioned and diluted by the two fold serial dilution method and inoculated with the organisms.
Incubation : Casamino acids medium was incubated at 37° for 24 hr., Kirchner's medium was incubated at 37° for 21 days and Sabouraud's medium was incubated at 27° for 7 days. Then the minimum inhibitory concentration of test samples was estimated by comparison with sulfadimethoxine, isoniazid and bithionol.

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Summary

The preparation of a number of 4-benzamido-, 4-nicotinamido-, and 4-isonicotinamido-2,6-dialkoxypyrimidines was described. Some of these new compounds showed strong antibacterial activities *in vitro*, and the structure-activity relationship was discussed.

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*3 All melting points were not corrected.