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Pyrido[2,3-*d*]pyrimidine Antibacterial Agents. II.[1] Piromidic Acid and Related Compounds

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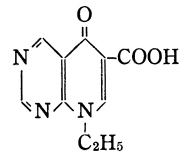
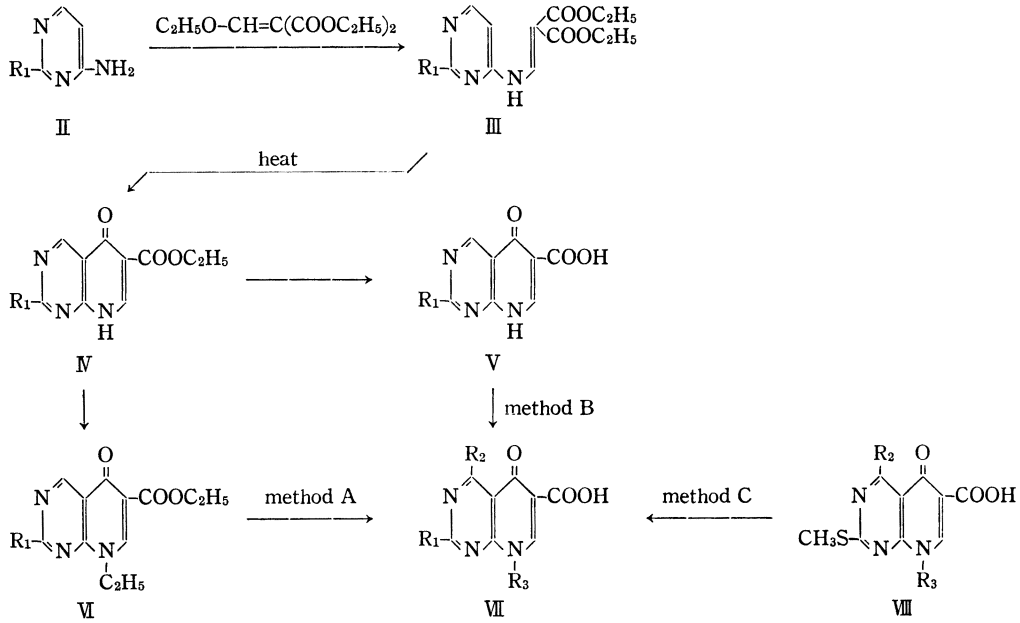
A series of 8-alkyl-2-amino(or substituted-amino)-5,8-dihydro-5-oxopyrido[2,3-*d*]-pyrimidine-6-carboxylic acids and related compounds were synthesized and evaluated as antibacterial agents. The most active compounds *in vitro* against *Escherichia coli* and *Staphylococcus aureus* were 8-ethyl-5,8-dihydro-2-dimethylamino-5-oxopyrido [2,3-*d*]-pyrimidine-6-carboxylic acid (VIIa) and 8-ethyl-5,8-dihydro-5-oxo-2-pyrrolidinopyrido-[2,3-*d*]pyrimidine-6-carboxylic acid, piromidic acid, (VIIb). Structure-activity relationships are discussed.

In our previous paper,[1] the preparation and antibacterial activities of some 8-alkyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acids were reported and it was found that the presence of the electron-releasing group such as methylthio and methoxy at the position 2 of 8-ethyl-5,8-dihydro-5-oxopyrido-[2,3-*d*]pyrimidine-6-carboxylic acid (I) caused a significant enhancement of its *in vitro* activity. As an extension of our study, the analogs having an electron-releasing substituted-amino group at the position 2, of which the activity might be expected to enhance, were prepared.



I



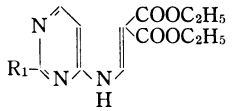
II III IV V VI VII VIII

Chart 1

1) Part I: S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1482 (1971).
2) Location: *Enoki-cho 33-94, Suita, Osaka.*

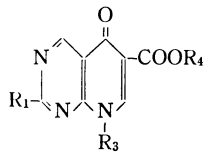
8-Ethyl(or methyl)-2-substituted-amino-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acids (VIIa—d) were obtained in the same method as described previously[1] (Chart 1). Thus, 2-substituted-amino-4-aminopyrimidines (II) were subjected to condensation with diethyl ethoxymethylenemalonate to give diethyl N-(2-substituted-amino-4-pyrimidinyl)-aminomethylenemalonates (III), which underwent subsequently the thermal cyclization on heating with diphenyl ether to yield ethyl 2-substituted-amino-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IV) in good yields. From IV, the corresponding acids (V) and 8-ethyl esters (VI) were derived, respectively, by alkaline hydrolysis and by ethylation. Finally the 8-ethyl acids (VIIa—c) were obtained from either hydrolysis of VI or alkylation of V. 8-Methyl acid (VIId) was prepared by alkylation of Vc.

Table I. Diethyl N-(2-Substituted-amino-4-pyrimidinyl)-aminomethylenemalonates



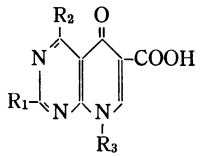
Compd.	R_1	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	$N(CH_3)_2$	64—65	EtOH	90	$C_{14}H_{20}O_4N_4$	54.53	6.54	18.17	54.83	6.79	18.17
IIIb	N□	93—94	hexane	82	$C_{16}H_{22}O_4N_4$	57.47	6.63	16.76	57.22	6.54	16.47
IIIc	N O	93—94	EtOH	79	$C_{16}H_{22}O_5N_4$	54.84	6.33	15.99	54.79	6.37	16.19

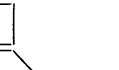
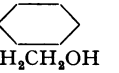
Table II. Ethyl 5,8-Dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylates and Their Acids



Compd.	R_1	R_3	R_4	mp(°C)	Recrystn. solvent	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVa	$N(CH_3)_2$	H	C_2H_5	290—293	CH_3CN	94	$C_{12}H_{14}O_3N_4$	54.95	5.38	21.37	54.92	5.56	21.68
IVb	N□	H	C_2H_5	295—299	EtOH	67	$C_{14}H_{16}O_3N_4$	58.32	5.59	19.44	58.72	5.61	19.73
IVc	N O	H	C_2H_5	270—272	MeOH–$CHCl_3$	53	$C_{14}H_{16}O_4N_4$	55.25	5.30	18.41	55.16	5.13	18.69
Va	$N(CH_3)_2$	H	H	300—303	CH_3CN	90	$C_{10}H_{10}O_3N_4$	51.28	4.30	23.92	51.22	4.51	24.19
Vb	N□	H	H	221—225	DMF–EtOH	88	$C_{12}H_{12}O_3N_4$	55.38	4.65	21.53	55.21	4.78	21.72
Vc	N O	H	H	286—289	DMF	86	$C_{12}H_{12}O_4N_4$	52.17	4.38	20.28	51.99	4.54	20.26
VIa	$N(CH_3)_2$	C_2H_5	C_2H_5	159—161	EtOH	79	$C_{14}H_{18}O_3N_4$	57.92	6.25	19.30	57.52	6.36	19.44
VIb	N□	C_2H_5	C_2H_5	197—198	EtOH	87	$C_{16}H_{20}O_3N_4$	60.74	6.37	17.71	60.81	6.25	17.82
VIc	N O	C_2H_5	C_2H_5	201—203	EtOH	72	$C_{16}H_{20}O_4N_4$	57.82	6.07	16.86	57.74	6.16	16.73

TABLE III. 8-Alkyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic Acids



Compd.	R_1	R_2	R_3	mp (°C)	Recrystn. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIa	$N(CH_3)_2$	H	C_2H_5	288—291	DMF	77, 80[b], 92[c]	$C_{12}H_{14}O_3N_4$	54.95	5.38	21.37	54.86	5.29	21.39
VIIb		H	C_2H_5	314—316	EtOH–$CHCl_3$	68, 82[b], 90[c]	$C_{14}H_{16}O_3N_4$	58.32	5.59	19.44	58.17	5.47	19.65
VIIc		H	C_2H_5	264—266	DMF	75, 79[b], 89[c]	$C_{14}H_{16}O_4N_4$	55.25	5.30	18.41	55.16	5.34	18.63
VIId		H	CH_3	297—299	DMF	76, 71[b]	$C_{13}H_{14}O_3N_4$	56.93	5.15	20.43	57.01	5.29	20.61
VIIe		H	C_2H_5	267—270	MeOH–$CHCl_3$	66	$C_{15}H_{18}O_3N_4$	59.59	6.00	18.53	59.65	5.99	18.67
VIIf	$N(CH_3)_2$	H	CH_3	324—326	MeOH–$CHCl_3$	76	$C_{11}H_{12}O_3N_4$	53.22	4.87	22.57	52.95	5.03	22.32
VIIg	$N(CH_3)_2$	H	n-C_3H_7	261—262	MeOH–$CHCl_3$	66	$C_{13}H_{16}O_3N_4$	56.51	5.84	20.28	56.37	5.76	20.39
VIIh	$N(CH_3)_2$	H	iso-C_3H_7	251—253	EtOH	72	$C_{13}H_{16}O_3N_4$	56.51	5.84	20.28	56.21	5.71	20.46
VIIi	$N(CH_3)_2$	H	n-C_4H_9	205—207	EtOH	71	$C_{14}H_{18}O_3N_4$	57.92	6.25	19.30	58.21	6.18	19.57
VIIj	$N(CH_3)_2$	OH	C_2H_5	324—325	DMF	81	$C_{12}H_{14}O_4N_4$	51.79	5.07	20.14	51.91	5.25	20.08
VIIk	$N(CH_3)_2$	Cl	C_2H_5	250—252	acetone	27[d]	$C_{12}H_{13}O_3N_4Cl$[f]	48.57	4.42	18.88	48.53	4.59	18.62
VIIl	$N(C_2H_5)_2$	H	C_2H_5	220—222	EtOH	89[c]	$C_{14}H_{18}O_3N_4$	57.92	6.25	19.30	58.02	6.38	19.16
VIIm	$N(n$-$C_3H_7)$	H	C_2H_5	168—170	EtOH–hexane	57[c]	$C_{16}H_{22}O_3N_4$	60.36	6.97	17.60	60.20	7.01	17.69
VIIn	NH_2	H	C_2H_5	291—293	EtOH	87	$C_{10}H_{10}O_3N_4$	51.28	4.30	23.92	51.25	4.37	23.97
VIIo	$NHNH_2$	H	C_2H_5	259—261	MeOH	57	$C_{10}H_{11}O_3N_5$	48.19	4.45	28.10	48.30	4.61	27.94
VIIp	$NHCH_3$	H	C_2H_5	274—276	MeOH–$CHCl_3$	85	$C_{11}H_{12}O_3N_4$	53.22	4.87	22.57	53.51	4.88	22.84
VIIq	NHC_2H_5	H	C_2H_5	269—272	MeOH–$CHCl_3$	72	$C_{12}H_{14}O_3N_4$	54.95	5.38	21.37	54.55	5.57	21.34
VIIr	NHC_3H_7(iso)	H	C_2H_5	233—235	MeOH	68	$C_{13}H_{16}O_3N_4$	56.51	5.84	20.28	56.11	5.97	20.52
VIIs	$NHC_4H_9(n)$	H	C_2H_5	192—194	EtOH	65	$C_{14}H_{18}O_3N_4$	57.92	6.25	19.30	57.96	6.42	19.64
VIIt	$NHC_6H_{13}(n)$	H	C_2H_5	164—166	EtOH	67	$C_{16}H_{22}O_3N_4$	60.36	6.97	17.60	59.96	6.84	17.76
VIIu	NH– 	H	C_2H_5	209—211	EtOH	42	$C_{16}H_{20}O_3N_4$	60.74	6.37	17.71	60.34	6.44	17.75
VIIv	$NHCH_2CH_2OH$	H	C_2H_5	268—270	MeOH	54	$C_{12}H_{14}O_4N_4$	51.79	5.07	20.14	51.99	5.38	20.38
VIIw	$NH(CH_2)_3N(CH_3)_2$	H	C_2H_5	165—167	acetone	75	$C_{15}H_{21}O_3N_5$	56.41	6.63	21.93	56.13	6.50	22.13
VIIx	$NH(CH_2)_3N(C_2H_5)_2$	H	C_2H_5	160—162	acetone	67	$C_{17}H_{25}O_3N_5$	58.77	7.25	20.16	58.63	7.32	20.56

a) Yields are by method C unless otherwise stated. *b*) Yields are by method B. *c*) Yields are by method A. *d*) Yield is of chlorination of VIIj.
e) Yields are of the reactions of IX wih amines. *f*) Calcd. for Cl; 11.95. Found: 11.92

Since in our previous study[1] 2-methylthio group of 8-alkyl-2-methylthio-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acids (VIII) had been found to be susceptible to the nucleophilic displacement, the 8-alkyl acids (VII) except VIIk—m were prepared alternatively on treating the corresponding VIII with an appropriate amine. In the case of VIII with diethylamine and di-*n*-propylamine, however, the attempted substitution reaction was unsuccessful, always resulting in a recovery of the starting VIII. Then the amines were allowed to react with 2-chloro-8-ethyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine (IX) to give 2-diethylamino (VIIl) and 2-di-*n*-propylamino (VIIm) derivatives, respectively, in good yields (Chart 2).

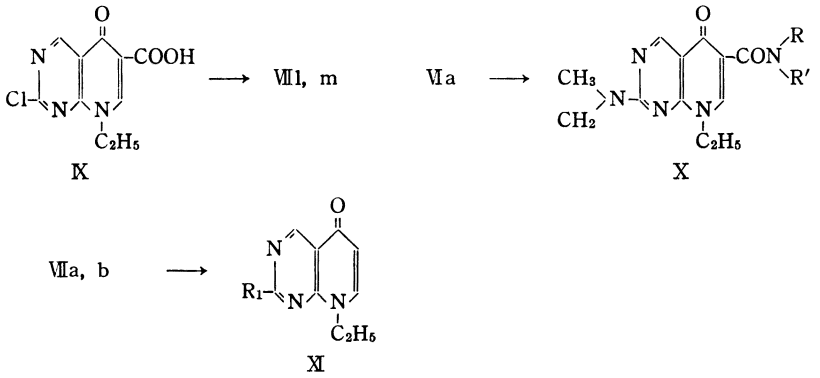


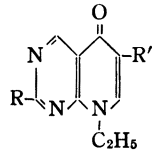
Chart 2

4-Chloro derivatives (VIIk) was obtained by treatment of the corresponding 4-hydroxy acid (VIIj) with phosphorus oxychloride.

Carboxamides (X) were prepared on treating the ester (VIa) with an appropriate amine.

On heating above the melting point, the 6-carboxylic acids (VIIa and VIIb) easily underwent decarboxylation to afford 2-dimethylamino- and 2-pyrrolidino-8-ethyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidines (XIa and XIb), respectively.

TABLE IV. 8-Ethyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidines and -6-carboxamides



Compd.	R	R′	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Xa	$N(CH_3)_2$	$CONH_2$	274—276	EtOH	55	$C_{12}H_{15}O_2N_5$	55.16	5.79	26.81	55.00	5.88	26.91
Xb	$N(CH_3)_2$	$CONHCH_3$	241—243	EtOH	54	$C_{13}H_{17}O_2N_5$	56.71	6.22	25.44	56.92	6.26	25.14
Xc	$N(CH_3)_2$	$CONHCH_2CH_2OH$	247—253	EtOH	35	$C_{14}H_{19}O_3N_5$	55.07	6.27	22.94	55.27	6.35	22.66
Xd	$N(CH_3)_2$	$CONHNH_2$	226—228	EtOH	81	$C_{12}H_{16}O_2N_6$	52.16	5.84	30.42	52.33	5.81	30.54
Xe	$N(CH_3)_2$		189—190	pyridine	51	$C_{16}H_{21}O_3N_5$	57.99	6.39	21.14	57.82	6.62	20.89
XIa	$N(CH_3)_2$	H	154—156	acetone	80	$C_{11}H_{14}ON_4$	60.53	6.47	25.67	60.43	6.59	25.55
XIb		H	208—213	C_6H_6	90	$C_{13}H_{16}ON_4$	63.91	6.60	22.94	64.18	6.66	23.05

These compounds were screened *in vitro* against *Staphylococcus aureus* and *Escherichia coli* by the serial tube dilution method[3] and the minimum inhibitory concentrations were summarized in Table V.

The introduction of a substituent to the position 2 of I significantly affected *in vitro* antibacterial activity. Thus, amino (VIIn) and hydrozino (VIIo) groups reduced the activity against *Escherichia coli*, although the activity of VIIo against *Staphylococcus aureus* increased slightly. The primary lower-alkylamino groups such as methylamino (VIIp), ethylamino (VIIq) and iso-propylamino (VIIr) enhanced the activity against *Escherichia coli* to some extent. On the contrary, the higher-alkylamino groups such as *n*-butylamino (VIIs) and *n*-hexylamino (VIIt), and the cycloalkylamino group such as cyclohexylamino (VIIu) reduced the activity against *Escherichia coli*, while the activity of VIIt against *Staphylocossus aureus* exceptionally increased. The hydrophylic groups such as hydroxyethylamino (VIIv), dimethylaminopropylamino (VIIw) and diethylaminopropylamino (VIIx) also resulted in the decrease of the activity. The secondary lower-alkylamino group such as dimethylamino (VIIa), and the secondary cycloamino groups such as pyrrolidino (VIIb), piperidino (VIIe) and morpholino (VIIc) markedly increased the activity against both *Escherichia coli* and *Staphylococcus aureus*.

The replacement of the ethyl goup at the position 8 of VIIa with methyl (VIIf), *n*-propyl (VIIg), isopropyl (VIIh), or *n*-butyl (VIIi) group and of the ethyl group of VIIb with methyl (VIId) group caused the decrease of the activity to various extent.

The introduction of hydroxy (VIIj) or chloro (VIIk) group to the position 4 of VIIa also resulted in the decrease of the activity.

All of the 8-unsubstituted acids (V), the ethyl esters (VI), the carboxamides (X) and the decarboxylated derivatives (XI) did not show the activity.

TABLE V. *In vitro* Antibacterial Activity (Minim. Inhib. Conc., μg/ml)

Compd.	*Staphylococcus aureus*	*Escherichia coli*	Compd.	*Staphylococcus aureus*	*Escherichia coli*
I	>100	30	VIIm	30	> 30
Va	>100	>100	VIIn	>100	100
Vb	>100	>100	VIIo	30	100
Vc	>100	>100	VIIp	>100	10
VIa	>100	>100	VIIq	>100	10
VIb	>100	>100	VIIr	>100	10
VIc	>100	>100	VIIs	>100	>100
VIIa	10	1	VIIt	30	>100
VIIb	10	1	VIIu	>100	100
VIIc	30	3	VIIv	>100	100
VIId	30	3	VIIw	>100	>100
VIIe	30	10	VIIx	>100	>100
VIIf	100	10	Xa	>100	>100
VIIg	30	3	Xb	>100	>100
VIIh	100	10	Xc	>100	>100
VIIi	>100	>100	Xd	>100	>100
VIIj	> 30	10	Xe	>100	>100
VIIk	> 30	> 30	XIa	>100	>100
VIIl	> 30	30	XIb	>100	>100

It would seem that, in accord with the conclusion in the previous paper, the 5-oxo, 6-carboxy and 8-alkyl functions are prerequisite for *in vitro* antibacterial activity and, further-

3) K. Fujimoto, *Chemotherapy*, **15**, 228 (1967).

more, the replacement with the secondary amino group at the position 2 significantly enhances the activity, which is likely to be the more active when the substituent is small.

In this series of compounds, VIIa and VIIb were the most active. The latter, under the generic name of piromidic acid, is undergoing clinical evaluation after further studies[4] as a chemotherapeutic agent.

Experimental[5]

Pyrrolidino- and Morpholinoamidine Sulfates——To an aqueous solution (30 ml) of methylisothiourea sulfate (14 g) was added dropwise pyrrolidine (10 g). The mixture was kept at room temperature for 30 min with stirring and then heated at 90° for 1 hr. On cooling and addition of MeOH (15 ml) the solid was obtained, and washed with MeOH to give 13.2 g (81%) of pyrrolidinoamidine sulfate, mp >300°. *Anal.* Calcd. for $C_{10}H_{24}O_4N_6S$: C, 37.02; H, 7.46; N, 25.91; S, 9.88. Found: C, 37.04; H, 7.60; N, 26.10; S, 9.76.

Morpholinoamidine sulfate, mp >300°, was prepared in the same treatment of methylisothiourea sulfate with morpholine in 85% yield. *Anal.* Calcd. for $C_{10}H_{24}O_6N_6S$: C, 33.70; H, 6.79; N, 23.58; S, 9.00. Found: C, 33.76; H, 7.02; N, 23.74; S, 9.03.

4-Hydroxy-2-pyrrolidino- and -2-morpholinopyrimidines——To a solution of malic acid (9.6 g) in concd. H_2SO_4 (87 g) was added pyrrolidinoamidine sulfate (11.6 g) at 3—7°. The mixture was kept at 30—33° for 3 hr and allowed to stand overnight at room temperature. After heating at 60—70° for 3 hr and pouring onto crushed ice, the solution was adjusted to pH 8—9 with NH_4OH. The resulting precipitate was collected and recrystallized from water to give 10 g (85%) of 4-hydroxy-2-pyrrolidinopyridine, mp 235—237°. *Anal.* Calcd. for $C_8H_{11}ON_3$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.32; H, 6.62; N, 25.74.

4-Hydroxy-2-morpholinopyrimidine was prepared in the same treatment of morpholinoamidine sulfate with malic acid in 67% yield, mp 181—183° (recyrstn. from H_2O) (lit.[6] mp 169—170°).

4-Chloro-2-pyrrolidino- and -2-morpholinopyrimidines——A mxiture of 4-hydroxy-2-pyrrolidinopyrimidine (21.8 g) and $POCl_3$ (40 ml) was refluxed for 2 hr and then an excess of $POCl_3$ was evaporated under reduced pressure. The mixture was poured onto crushed ice and adjusted to pH 9—10 with NH_4OH. The resulting solid was collected, washed with water and recrystallized from dil. EtOH to yield 23 g (95%) of 4-chloro-2-pyrrolidinopyrimidine, mp 71—72°. *Anal.* Calcd. for $C_8H_{10}N_3Cl$: C, 52.32; H, 5.49; N, 22.88; Cl, 19.31. Found: C, 52.47; H, 5.52; N, 22.84; Cl, 19.17.

4-Chloro-2-morpholinopyrimidine was obtained by chlorination of 4-hydroxy-2-morpholinopyrimidine in 90% yield in the same method as described above, mp 75—76° (recrystn. from dil. EtOH). *Anal.* Calcd. for $C_8H_{10}ON_3Cl$: C, 48.13; H, 5.05; N, 21.05; Cl, 17.76. Found: C, 48.22; H, 4.85; N, 20.75; Cl, 17.79.

4-Amino-2-dimethylaminopyrimidine (IIa)——IIa was prepared according to the literature.[7]

4-Amino-2-pyrrolidino- and -2-morpholinopyrimidines (IIb and IIc)——A mixture of 4-chloro-2-pyrrolidinopyrimidine (20 g) and 8% NH_3–EtOH (400 ml) was heated at 185—195° for 5 hr in an autoclave. After evaporation of EtOH under reduced pressure the residue was suspended in water and the suspension adjusted to pH 8 with aqueous 20% NaOH. The resulting precipitate was collected and recrystallized from dil. EtOH to give 12.6 g (70%) of IIb, mp 162—163°. *Anal.* Calcd. for $C_8H_{12}N_4$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.75; H, 7.27; N, 34.52.

IIc was prepared in the same treatment of 4-chloro-2-morpholinopyrimidine in 78% yield, mp 171—173° (recrystn. from dil. EtOH). *Anal.* Calcd. for $C_8H_{12}ON_4$: C, 53.32; H, 6.71; N, 31.09. Found: C, 53.52; H, 6.69; N, 31.36.

Diethyl N-(2-Substituted-amino-4-pyrimidinyl)aminomethylenemalonates (III), Ethyl 2-Substituted-amino-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylates (IV), 2-Substituted-amino-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic Acids (V), and Ethyl 8-Ethyl-2-substituted-amino-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylates (VI)——Each of the compounds was prepared according to the procedures as described in our previous paper.[1] The results were listed in Table I and II.

8-Alkyl-2-substituted-amino-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic Acids (VII)——Method A: Hydrolysis of VI: A suspension of VI (0.01 mole) in aqueous 7% NaOH (30 ml) was heated at 100° until it became clear. After cooling the alkaline solution was acidified with AcOH, and the precipitates were collected, washed with water and recrystallized to yield VII.

4) M. Shimizu, S. Nakamura, and Y. Takase, "Antimicrobial Agents and Chemotherapy-1970," 1970, p 117. M. Shimizu, Y. Sekine, H. Higuchi, H. Suzuki, S. Nakamura, and K. Nakamura, *ibid.*, 1970, p 123.

5) Melting points were taken in open capillary tubes and uncorrected. Yields are of purified product and not maximal.

6) Burroughs Wellcome & Co., Inc., Brit. Patent, 990857 (1965)[*C.A.*, **63**, 4310 (1965)].

7) Y. Nitta, K. Okui, and K. Ito, Janpn. Patent, 13878 (1965) [*C.A.*, **63**, 13285 (1965)].

Method B: Alkylation of V with Diethyl or Dimethyl Sulfate: V was treated with Et_2SO_4 in the same manner as described previously.[1] Treatment of Vc with Me_2SO_4, followed by working up as usual gave similarly VIId.

Method C: Substitution Reactions of 8-Alkyl-5,8-dihydro-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic Acids (VIII)[1] with Amines: A mixture of VIII (1 mmole) and an appropriate amine (1.5 mmoles) in absolute EtOH (20 ml) was heated at 95—105° for 5—7 hr in a sealed tube. The solvent was evaporated and the crystalline residue was recrystallized from an appropriate solvent to yield VIIa—j and VIIn—x. See Table III.

4-Chloro-8-ethyl-2-dimethylamino-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (VIIk)——A mixture of VIIj (0.02 mole) and $POCl_3$ (9 ml) was refluxed for 3 hr, an excess of $POCl_3$ was removed by evaporation under reduced pressure, and the residue was poured onto crushed ice. The solution was neutralized with NH_4OH and extracted several times with $CHCl_3$. The extracts were combined, washed with water and dried over Na_2SO_4. The solid, after evaporation of the solvent, was recrystallized (Table III).

2-Diethylamino- and 2-Di-*n*-propylamino-8-ethyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic Acids (VIIl and VIIm)——A solution of 2-chloro-8-ethyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid (IX)[1] (0.01 mole) and dialkylamine (0.05 mole) in DMF (100 ml) was heated at 120—130° for 3 hr. After evaporation of the solvent and an excess of the amine, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and concentrated to dryness. The solid was recrystallized (Table III).

8-Ethyl-5,8-dihydro-2-dimethylamino-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxamides (X)——A mixture of VIa (0.01 mole) and an appropriate amine (0.02 mole) (NH_4OH, 30% CH_3NH_2, aminoethanol, 80% $NH_2NH_2 \cdot H_2O$ or morpholine) in absolute EtOH (30 ml) was heated at 160° for 5—6 hr in a sealed tube. The separated crystalline product was collected and recrystallized to give X (Table IV).

2-Dimethylamino- and 2-Pyrrolidino-8-ethyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidines (XI)——Each of VIIa and VIIb was heated above the melting point until the evolution of CO_2 ceased (it took about 20 min). The product was extracted with hot EtOH and the extracts were concentrated to dryness under reduced pressure. The resulting residue was recrystallized to give the corresponding XIa and XIb (Table IV).

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