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Synthetic Antibacterials. II.[1] Synthesis of Pyrido[2,3-*d*]pyrimidine Derivatives. (1)

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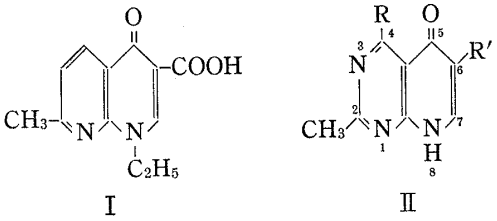
The condensation of 4-substituted 6-amino-2-methylpyrimidines with diethyl ethoxymethylenemalonate, followed by thermal cyclization in Dowtherm A, yielded the corresponding 4-substituted 2-methyl-5-hydroxypyrido[2,3-*d*]pyrimidine-6-carboxylates. These latter compounds served as starting materaials for several transformation reactions.

The discovery of the interesting antibacterial activity of nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) (I)[3] suggested that other similarly substituted polyaza hetrocyclic compounds might also have useful antibacterial properties. Our interest was first directed to the pyrido[2,3-*d*]pyrimidine ring system which is a potential pteridine antagonist as well as an azalogous system of nalidixic acid (I). The pyrido [2,3-*d*]pyrimidine ring system has recently been reviewed.[4] This paper reports the synthesis of 2-methyl-5-hydroxypyrido[2,3-*d*]pyrimidine derivatives (II), in which various substituents have been introduced in the 4 position.



I II

Chart 1

Gould–Jacobs reaction was extended to the synthesis of these compounds, consisting of the condensation of an appropriate 6-aminopyrimidine with diethyl ethoxymethylenemalonate (EMME), followed by thermal cyclization. Although this electrophilic cyclization is extremely useful in the synthesis of quinoline[5] and sometimes has been used successfully in the preparation of naphthyridine derivatives,[6] the application to the synthesis of pyrido-[2,3-*d*]pyrimidine has not as yet done.[7]

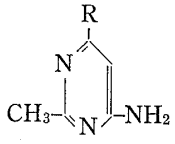
The starting materials for our work in this paper are 4-amino-6-hydroxy-2-methylpyrimidine (III),[8] several 4-substituted 6-amino-2-methylpyrimidines derived from III, and 4,6-

1) Part I: S. Nishigaki, F. Yoneda, H. Matsumoto and K. Morinaga, *J. Med. Chem.*, **12**, 39 (1969).
2) Location: *a*) *Shinanomachi, Shinjuku-ku, Tokyo*; *b*) *Ebara, Shinagawa-ku, Tokyo*.
3) G.Y. Lesher, E.J. Froelich, M.D. Gruett, J.H. Bailey and R.P. Brundage, *J. Med. Pharm. Chem.*, **5**, 1063 (1963).
4) W. J. Irwin and D. G. Wibberley, in "Advances in Hetrocyclic Chemistry," Vol. 10, ed. by A. R. Katritzky and A.J. Boulton, Academic Press, New York, 1969, p. 149.
5) R.C. Elderfield in "Hetrocyclic Compounds," Vol. 4, ed. by R.C. Elderfield, John Wiley and Sons, Inc., New York, 1952, p. 1.
6) M.J. Weiss in "Hetrocyclic Compounds," Vol. 7, ed. by R.C. Elderfield, John Wiley and Sons, Inc., New York, 1961, p. 198.
7) During the preparation of the present paper, a patent by G.Y. Lesher appeared (U.S. Patent 3320257 (1967)), in which the same procedure was applied to the preparation of two compounds, ethyl 2-methyl-5-hydroxypyrido[2,3-*d*]pyrimidine-6-carboxylate and ethyl 2,4-dimethyl-5-hydroxypyrido[2,3-*d*]pyrimidine-6-carboxylate.
8) A. Maggiolo, A.P. Phillips and G.H. Hitchings, *J. Am. Chem. Soc.*, **73**, 106 (1951).

diamino-2-methylpyrimidine. 6-Amino-4-chloro-2-methylpyrimidine (IV),[9] which was prepared by the chlorination of III with phosphorous oxychloride, reacted readily with sodium alkoxides, secondary amines, anilines and hydrazines to give the corresponding pyrimidine derivatives possessing alkoxy-, *sec*-amino-, anilino- and hydrazino-group on the 4-position. Refluxing of IV with phenol in dimethylformamide in the presence of potassium carbonate yielded a mixture of 4-phenoxy and 4-dimethylamino derivatives. The formation of the latter may be an example of the dimethylamination of active chloro compounds using dimethylformamide.[10]

The synthesis of 4,6-diamino-2-methylpyrimidine (IX) from malondiamidine and ethyl acetate was repeated following the direction of Todd, *et al.*[11] IX was also synthesized from malondiiminoether and acetamidine, where the amination of malondiiminoether with ammonia could be omitted. The pyrimidines that were prepared are listed in Table I.

Table I. 6-Amino-2-methylpyrimidines



No.	R	Method	Yield (%)	mp (°C)	Recryst. solvt.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
III	OH	lit. 8	90.0	296[a]	EtOH	$C_5H_7ON_3$	—	—	—	—	—	—
IV	Cl	lit. 9	85.5	189[b]	$CHCl_3$	$C_5H_6N_3Cl$	—	—	—	—	—	—
V	H	lit. 9	88.6	205[c]	$CHCl_3$	$C_5H_7N_3$	—	—	—	—	—	—
VI	OCH_3	*d*)	74.9	163—165	benzene	$C_6H_9ON_3$	51.78	6.52	30.20	51.55	6.55	30.34
VII	OC_2H_5	*d*)	90.0	123[e]	EtOH	$C_7H_{11}ON_3$	—	—	—	—	—	—
VIII	OC_6H_5	*f*)	57.4	177—179	benzene	$C_{11}H_{11}ON_3$	65.67	5.51	20.88	65.73	5.49	20.56
IX	NH_2	lit. 11	45.8	295—297[g]	H_2O	$C_5H_8N_4$	48.37	6.50	45.13	48.14	6.59	44.40
X	$N(CH_3)_2$	*f*)	18.4	189—191[h]	benzene	$C_7H_{12}N_4$	55.24	7.95	36.82	55.53	7.88	36.65
XI		*i*)	100.0	210—211[j]	benzene	$C_{10}H_{16}N_4$	62.47	8.39	—	62.45	8.11	—
XII		*i*)	62.5	203—205[k]	benzene	$C_9H_{14}ON_4$	55.65	7.27	—	56.01	7.03	—
XIII		*i*)	89.2	252—253	EtOH	$C_9H_{14}N_4$	60.65	7.92	31.44	60.27	7.78	31.06
XIV	NHC_6H_5	lit. 8	70.7	193—195[l]	EtOAc	$C_{11}H_{12}N_4$	—	—	—	—	—	—
XV	$NHC_6H_4Cl(p)$	lit. 8	74.0	188—191[m]	EtOAc	$C_{11}H_{11}N_4Cl$	56.28	4.72	23.87	56.36	4.89	24.21
XVI	$NHNH_2$	*i*)	86.5	240—242	MeOH	$C_5H_9N_5$	43.15	6.52	50.33	43.07	6.60	49.94

a) lit.[8] mp 295—297° *b*) lit.[9] mp 191° *c*) lit.[9] mp 205° *d*) prepared by alkoxylation of IV with sodium alkoxides *e*) F. Craveri and G. Zoni, *Boll. Sci. Fac. Chim. Ind. Bologna*, **16**, 132 (1958), mp 122° *f*) prepared by the reaction of IV with phenol in DMF in the presence of K_2CO_3 *g*) lit.[11] mp 296—297° *h*) F. Craveri, G. Zoni, *Boll. Sci. Fac. Chim. Ind. Bologna*, **16**, 126 (1958), mp 185° *i*) prepared by amination of IV with appropriate amines *j*) F. Craveri and G. Zoni, *Boll. Sci. Fac. Chim. Ind. Bologna*, **16**, 126 (1958), mp 206° *k*) F. Craveri and G. Zoni, *Boll. Sci. Fac. Chim. Ind. Bologna*, **16**, 126 (1958), mp 211° *l*) lit.[8] mp 192—193° *m*) lit.[8] mp 190—191°

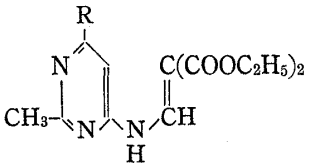
The condensation of 6-amino-4-hydroxy-2-methylpyrimidine with EMME yielded diethyl 4-hydroxy-2-methyl-6-pyrimidinyl aminomethylenemalonate (XVII), which was cyclized to ethyl 2-methyl-4,5-dihydroxypyrido[2,3-*d*]pyrimidine-6-carboxylate (XXIX) by heating in Dowtherm A (a mixture of 73.5% of diphenyl ether and 26.5% of diphenyl) in 60% yield.

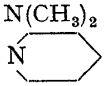
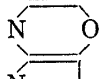
9) Z. Földi, G.v. Fodar, I. Demjen, H. Szeker and J. Halmos, *Chem. Ber.*, **75**, 755 (1947).
10) N.D. Heindel and P.D. Kennewell, *Chem. Commun.*, **1969**, 38.
11) G.W. Kenner, B. Lythgoe, A.R. Todd and A. Topham, *J. Chem. Soc.*, **1943**, 574.

In contrast to the result of this ring closure, it was reported that no product was obtained on the condensation of 6-amino-4-hydroxy-2-methylpyrimidine with 1,3-dicarboxyl compounds.[12]

4-Substituted 6-amino-2-methylpyrimidine derivatives substituted with an electron-donating group such as secondary amino, alkoxy or phenoxy reacted smoothly to give the corresponding 6-pyrimidinylaminomethylenemalonates, which were converted similarly into the pyrido[2,3-*d*]pyrimidines in good yields. These compounds can be prepared directly by heating an appropriate 6-aminopyrimidine and EMME in Dowtherm A, however, the yields were in general worse except on using 4-anilino compounds as starting materials.[13] It may

Table II. Diethyl 6-Pyrimidinylaminomethylenemalonates



No.	R	Reaction condition Temp. (°C)	Time (min)	Yield (%)	mp (°C)
XVII	OH	160—180	120	70.0	206—208
XVIII	H	110—120	45	57.1	99—101[a]
XIX	OCH_3	130—140	30	63.1	89— 91
XX	OC_2H_5	140	90	65.5	63— 65
XXI	OC_6H_5	135—140	30	68.0	135—140
XXII	NH_2	90 (in EtOH)	180	20.7	206—208
XXIII	$N(CH_3)_2$	115—125	30	85.0	148—150
XXIV		110	30	80.7	128—129
XXV		110—120	30	74.5	145—146
XXVI		170	30	34.5	115—117
XXVII	NHC_6H_5	120	60	84.4	145—146
XXVIII	NHC_6H_4–Cl(p)	140—150	30	85.3	183—185

No.	Recryst. solvt.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XVII	benzene	$C_{13}H_{17}O_5N_3$	52.87	5.80	14.23	52.73	5.89	13.93
XVIII	ether	$C_{13}H_{17}O_4N_3$	55.90	6.14	15.05	55.83	6.16	14.89
XIX	ether–petr.ether	$C_{14}H_{19}O_5N_3$	54.36	6.19	13.59	54.42	6.23	13.19
XX	petr.ether	$C_{15}H_{21}O_5N_3$	55.72	6.55	13.00	55.93	6.47	12.91
XXI	petr.ether	$C_{19}H_{21}O_5N_3$	61.44	5.70	11.32	61.72	5.63	11.63
XXII	benzene	$C_{13}H_{18}O_4N_4$	53.04	6.16	19.04	53.11	6.30	19.08
XXIII	EtOH	$C_{15}H_{22}O_4N_4$	55.88	6.88	17.38	55.93	7.01	16.99
XXIV	EtOH	$C_{18}H_{26}O_4N_4$	59.65	7.23	—	59.54	7.07	—
XXV	EtOH	$C_{17}H_{24}O_5N_4$	56.03	6.64	15.38	55.78	6.42	15.45
XXVI	EtOH	$C_{17}H_{24}O_4N_4$	58.60	6.94	16.09	58.87	7.16	16.09
XXVII	benzene–EtOAc	$C_{19}H_{22}O_4N_4$	61.61	5.99	—	61.39	6.04	—
XXVIII	benzene–EtOAc	$C_{19}H_{21}O_4N_4Cl$	56.36	5.23	—	56.69	4.97	—

a) lit.[7] mp 103.8—104.5°

12) R.K. Robins and G.H. Hitchings, *J. Am. Chem. Soc.*, **80**, 3449 (1958).
13) This electrophilic thermal cyclization could be performed without solvent or using a polar solvent such as sulfolane, however, giving no satisfactory yields.

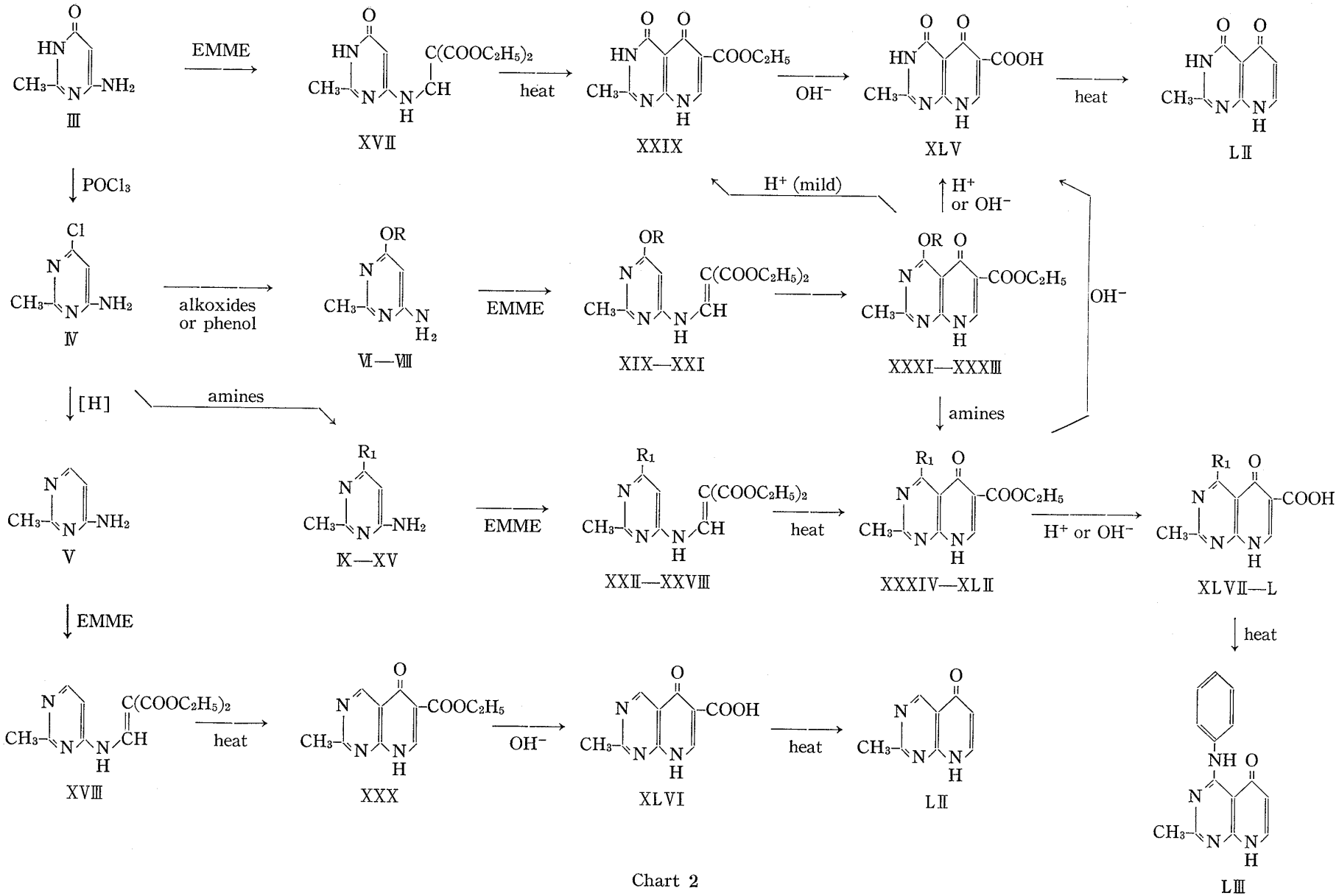
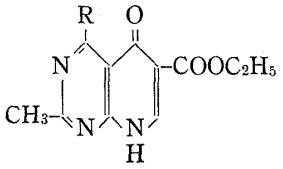


Chart 2

be noteworthy that considerable amounts of 4-ethoxypyrido[2,3-*d*]pyrimidine derivative (XXXII) as a byproduct were formed during the cyclization reaction of the pyrimidinylamino-methylenemalonate possessing a secondary amino group at 4 position. Especially, in the case

Table III. Ethyl 5-Hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylates



No.	R	Method[a]	Reaction condition Temp(°C)	Time(min)	Yield (%)	mp (°C)
XXIX	OH	A	250	60	59.4	284—285
		D[b]				
XXX	H	A	250	15	10.0	288—292[c]
XXXI	OCH_3	A	250	4	45.5	261
XXXII	OC_2H_5	A	250	15	92.0	236—237
XXXIII	OC_6H_5	A	250	10	52.0	252—253
XXXIV	NH_2	B	120 (in DMF)	90	41.0	>300
XXXV	$N(CH_3)_2$	A	250	15	14.7	199—200
XXXVI		A	250	25	43.5	241—242
XXXVII		A	250	20	74.7	250—252
		B	100 (in EtOH)	90	80.5	
XXXVIII		A	250	5	95.8	249—250
		B	100 (in EtOH)	60	70.0	
XXXIX	NHC_6H_5	A	250	10	97.0	275—277
		C	250	40	98.8	
XL	$NHC_6H_4Cl(p)$	A	250	10	95.1	296
		C	250	40	92.0	
XLI	$NHNH_2$	B	120 (in EtOH)	30	94.0	>300
XLII	$NHNHC_6H_5$	B	120 (in EtOH)	60	88.0	267—270

No.	Recryst. solvent	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXIX	acetone	$C_{11}H_{11}O_4N_3$	53.01	4.45	16.86	53.34	4.16	16.48
XXX	EtOAc	$C_{11}H_{11}O_3N_3$	56.65	4.75	—	56.66	4.74	—
XXXI	EtOH	$C_{12}H_{13}O_4N_3$	54.75	4.98	15.96	54.63	5.07	16.07
XXXII	EtOH	$C_{13}H_{15}O_4N_3$	56.31	5.45	—	56.29	5.43	—
XXXIII	EtOH	$C_{17}H_{15}O_4N_3$	62.76	4.65	12.92	62.68	4.71	12.69
XXXIV	DMF	$C_{11}H_{12}O_3N_4$	53.22	4.87	22.57	53.39	4.92	23.36
XXXV	EtOH	$C_{13}H_{16}O_3N_4$	56.51	5.84	20.28	56.63	5.69	20.04
XXXVI	EtOH	$C_{16}H_{20}O_3N_4$	60.74	6.37	17.71	60.82	6.48	17.42
XXXVII	EtOH	$C_{15}H_{18}O_4N_4$	56.59	5.70	17.60	56.45	5.69	17.72
XXXVIII	EtOH	$C_{15}H_{18}O_3N_4$	59.59	6.00	18.53	59.45	6.09	18.58
XXXIX	EtOH–EtOAc	$C_{17}H_{16}O_3N_4$	62.95	4.97	17.28	62.66	4.99	17.17
XL	AcOH	$C_{17}H_{15}O_3N_4Cl$	56.97	4.21	15.62	57.21	4.46	15.91
XLI	DMF	$C_{11}H_{13}O_3N_5$	50.18	4.98	26.61	50.13	4.88	26.58
XLII	EtOH	$C_{17}H_{17}O_3N_5$	60.17	5.05	20.64	50.65	5.14	20.27

a) See Experimental. *b*) acid hydrolysis of XXXII under mild conditions *c*) lit.[7] mp 282—284°

of diethyl 2-methyl-4-dimethylamino-6-pyrimidinyl aminomethylenemalonate (XXIII), compound XXXII was the major product rather than 4-dimethylaminopyrido[2,3-*d*]pyrimidine derivative (XXXV). This result shows apparently that the secondary amino group undergoes solvolysis to ethoxy group by the ethanol which occurs in the cyclization reaction described above.

The cyclization reaction would be effected by the nature of the substituent in the 4-position of the pyrimidine moiety and probably the stability of the intermediate aminomethylenemalonates. For instance, difficulty was experienced in the cyclization of diethyl 2-methyl-6-pyrimidinyl aminomethylenemalonate (XVIII) and only 10% yield of ethyl 2-methyl-5-hydroxypyrido[2,3-*d*]pyrimidine-6-carboxylate (XXX) was recognized. While 4,6-diamino-2-methylpyrimidine (IX) condensed with EMME to give corresponding aminomethylenemalonate (XXII), numerous efforts to cyclize the latter into pyrido[2,3-*d*]pyrimidine were unsuccessful.

Some representative nuclear magnetic resonance (NMR) spectra for pyrido[2,3-*d*]pyrimidines are given in Table V and from these data the possibility was eliminated that the condensation might have occurred through the nitrogen of pyrimidine ring to give a pyrido-[1,2-*c*]pyrimidine derivatives.

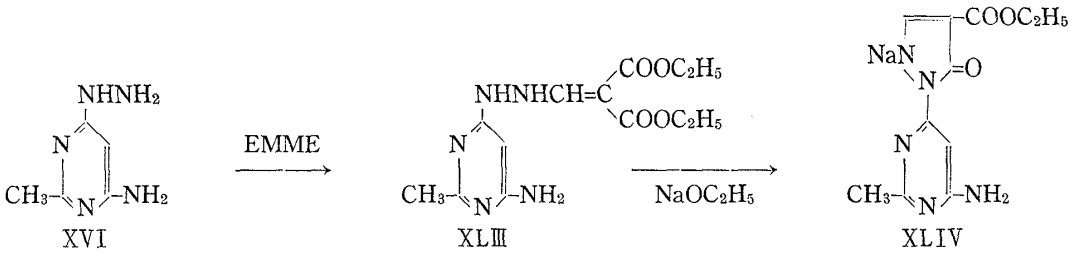


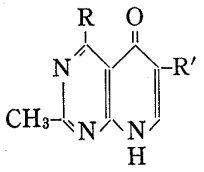
Chart 3

The condensation of 6-amino-4-hydrazino-2-methylpyrimidine (XVI) and EMME led to the exclusive formation of the diethyl 4-(6-amino-2-methylpyrimidinyl)hydrazinomethylenemalonate (XLIII), which was readily cyclized to pyrimidinylpyrazole (XLIV) on treatment with sodium ethoxide. The NMR (DMSO-d_6) of XLIII showed a doublet (J=12 cps) at 10.22 ppm (N_2 H of hydrazino), a broad singlet at 9.30 ppm (N_1 H of hydrazino), a doublet (J=12 cps) at 7.95 ppm (vinyl), a broad singlet at 6.58 ppm (NH_2), a singlet (C_5 H of pyrimidine), a fused quartet at 4.17 ppm (CH_2 of ethyl), a singlet at 2.22 ppm (CH_3) and a triplet at 1.24 ppm (CH_3 of ethyl) (ratio 1:1:1:2:1:4:3:6). The NMR (DMSO-d_6) of XLIV showed a singlet at 7.52 ppm (C_3 H of pyrazole), a singlet at 7.12 ppm (C_5 H of pyrimidine), a broad singlet at 6.60 ppm (NH_2), a quartet at 4.08 ppm (CH_2 of ethyl), a singlet at 2.33 ppm (CH_3) and a triplet at 1.22 ppm (CH_3 of ethyl) (ratio 1:1:2:2:3:3).

Pyrido[2,3-*d*]pyrimidines bearing amino substituents in the 4-position were also prepared in good yields by heating of 4-alkoxy- or 4-phenoxypyrido[2,3-*d*]pyrimidines with amines. This amination offers a convenient synthetic method of 4-amino- or 4-hydrazinopyrido[2,3-*d*]-pyrimidines, which could not be obtained by the cyclization reaction from 4,6-diaminopyrimidine or 6-amino-4-hydrazinopyrimidine and EMME.

The ethyl pyrido[2,3-*d*]pyrimidine-6-carboxylates prepared here were subjected to alkaline and acid hydrolyses. Treatment of the 4-alkoxy, 4-phenoxy, 4-*sec*-amino derivatives with boiling 10% NaOH or KOH solution of 50% aqueous ethanol converted the esters to the corresponding acids and at the same time hydrolyzed the 4-substituents to yield 4,5-dihydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylic acid (LXV). The latter was identical with the product obtained by the alkaline hydrolysis of ethyl 4,5-dihydroxy-2-methylpyrido[2,3-*d*]-pyrimidine-6-carboxylate (XXIX). Alkaline hydrolysis of the 4-anilino and 4-hydrazino compounds has no effect on the 4-substituents and yields the corresponding acids. Acid

Table IV. 5-Hydroxy-2-methylpyrido[2,3-*d*]pyrimidines



No.	R	R	Yield (%)	mp (°C)
XLV	OH	COOH	91.0 96.3[a]	315
XLVI	H	COOH	92.0	272[b]
XLVII	NHC_6H_5	COOH	70.0	>300
XLVIII	NHC_6H_4Cl(p)	COOH	83.0	>300
XLIX	$NHNH_2$	COOH	42.0	>300
L	$NHNHC_6H_5$	COOH	90.0	255
LI	OH	H	35.0	291 (decomp.)
LII	H	H	41.7	280—283 (decomp.)
LIII	NHC_6H_5	H	70.0	>300

No.	Recryst. solvt.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XLV	DMF	$C_9H_7O_4N_3$	46.96	3.50	18.26	47.27	3.89	18.07
XLVI	AcOH	$C_9H_7O_3N_3$	52.68	3.44	20.48	52.56	3.62	20.09
XLVII	AcOH	$C_{15}H_{12}O_3N_4$	60.80	4.08	18.91	60.50	3.92	18.68
XLVIII	DMF	$C_{15}H_{11}O_3N_4Cl$	54.47	3.32	16.94	54.50	3.40	16.81
XLIX	DMF	$C_9H_9O_3N_5$	45.96	3.86	29.78	46.26	4.02	29.43
L	acetone	$C_{15}H_{13}O_3N_5$	57.87	4.21	22.50	57.61	4.32	22.21
LI	EtOH	$C_8H_7O_2N_3$	54.23	3.98	23.72	54.32	3.79	23.48
LII	acetone	$C_8H_7ON_3$	59.62	4.38	26.07	59.67	4.40	25.83
LIII	EtOH	$C_{14}H_{12}ON_4$	66.65	4.79	22.21	66.90	5.09	21.89

a) hydrolysis of XXXVII by 10% KOH in 50% EtOH *b*) lit.[7] mp 275°

Table V. NMR Spectra

Compound No.	δ, ppm (*J*, cps)[a] 2-Methyl	C_7H	$COOC_2H_5$		Others[b]
XXX	2.68 s	8.45 s	1.26 t (7)	4.21 q (7)	9.22 s (C_4 H)
XXXII	2.29 s	8.07 s	1.24 t (7)	4.15 q (7)	1.24 t (7) and 4.15 q (7) (4-ethoxy)
XXXIII	2.32 s	8.27 s	1.25 t (7)	4.17 q (7)	7.28 m (4-phenyl)
XXXVII	2.43 s	8.28 s	1.31 t (7)	4.22 q (7)	3.68 br s (CH_2 of 4-morpholino)
XXXVIII	2.38 s	8.15 s	1.27 t (7)	4.18 q (7)	3.43 br s (CH_2 of 4-pyrrolidino)
XLVI	2.64 s	8.82 s			10.86 s (C_4 H)
LII	2.74 s	7.97 d (8)			6.20 d (8) (C_6 H) 9.24 s (C_4 H)

a) all spectra in DMSO-d_6. TMS=0. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad
b) NH proton could not be observed in all compounds. *c*) 8H

hydrolysis using hydrochloric acid gives the almost same results with alkaline hydrolysis. However, during the acid hydrolysis of ethyl 4-ethoxy-5-hydroxy-2-methylpyrido[2,3-*d*]-pyrimidine-6-carboxylate (XXXII) to XLV, the intermediate, compound XXIX, could be obtained under mild condition described in the Experimental.

The acids were decarboxylated in refluxing quinoline with or without copper chromite catalyst[14] to give the desired products. The pyrimidinylaminomethylenemalonates and pyrido[2,3-*d*]pyrimidines prepared by these methods are listed in Table II, III and IV.

The antibacterial structure-activity relationships of the compounds described herein will be reported together with those of related pyrido[2,3-*d*]pyrimidine derivatives in the next paper of this series.

Experimental[15]

Preparation of Diethyl 6-Pyrimidinylaminomethylenemalonates (XVII—XXVIII). General Procedure——A mixture of 6-aminopyrimidine and equimolar diethyl ethoxymethylenemalonate (EMME) was heated under the conditions described in Table II. After cooling, the solidified mass was recrystallized from a suitable solvent.

Preparation of Ethyl Pyrido[2,3-*d*]pyrimidine-6-carboxylates (XXIX—XLII). General Procedure——Method A: Diethyl 6-pyrimidinylaminomethylenemalonate was added into 5—15 portions of refluxing Dowtherm A and heated at 250°. After cooling, the reaction mixture was diluted with petroleum ether or *n*-pentane, the precipitates were collected by filtration, washed with benzene and then petroleum ether, dried and recrystallized.

Method B: Ethyl 4-lower-alkoxy- or 4-phenoxypyrido[2,3-*d*]pyrimidine-6-carboxylate was refluxed with amines or hydrazines in EtOH or DMF. Evaporation of the solvent and recrystallization of the residue from an appropriate solvent gave the corresponding 4-amino- or 4-hydrazino pyrido[2,3-*d*]pyrimidines.

Method C (Direct Method): A mixture of 1 mole of 6-aminopyrimidine and 1.1 mole of EMME was heated in 15 portions of Dowtherm A for 40 min at 250° and treated by the method similar to method A.

Preparation of Pyrido[2,3-*d*]pyrimidine-6-carboxylic Acids (XLV—L). General Procedure——Ethyl pyrido[2,3-*d*]pyrimidine-6-carboxylate was refluxed in 10% NaOH or KOH in 50% EtOH on steam bath. The reaction mixture was evaporated, dissolved in H_2O, and neutralized with acetic acid. The precipitates were collected, washed with H_2O, dried and recrystallized.

6-Amino-2-methyl-4-phenoxypyrimidine (VIII) and 6-Amino-4-dimethylamino-2-methylpyrimidine (X)——A mixture of 7.2 g (0.005 mole) of 6-amino-4-chloro-2-methylpyrimidine, 4.7 g (0.05 mole) of phenol, 6.9 g of K_2CO_3 and 50 ml of DMF was refluxed for 5 hr. After the removal of excess of DMF, the resulting black brown mud was solidified by addition of H_2O and filtered to give 5.8 g (57.4%) of 6-amino-2-methyl-4-phenoxypyrimidine. Recrystallization from benzene gave colorless scales, mp 177—179°.

The filtrate was extracted with chloroform, the solvent was removed, excess of ether was added and then allowed to stand at room temperature to give 1.4 g (18.4%) of pale brown prisms. Recrystallization from benzene gave colorless prisms of 6-amino-4-dimethylamino-2-methylpyrimidine, mp 189—191°.

4,6-Diamino-2-methylpyrimidine (IX)——To 4.0 ml of EtOH containing 0.23 g (0.01 g atom) of Na were added 0.95 g (0.01 mole) of acetamidine hydrochloride and shaked for a few minutes, and the precipitated NaCl was removed. On the other hand, 2.31 g (0.01 mole) of malondiiminoether dihydrochloride was added into 8.0 ml of EtOH containing 0.46 g (0.02 g atom) of Na and shaked, the separated precipitates were removed by filtration. This filtrate was poured into the free acetamidine in EtOH obtained above, and refluxed for 15 min. After cooling, the crystals which separated were collected to give 0.15 g (12.1%) of IX in a high state of purity.

6-Amino-2-methyl-4-pyrrolidinopyrimidine (XIII)——A mixture of 3.0 g (0.021 mole) of IV and 4.5 g (0.0063 mole) of pyrrolidine was heated for 2 hr at 140°. The reaction product was dissolved in 30 ml of 2N HCl and neutralized with 5% aqueous NH_3. The precipitates were collected by filtration, washed with H_2O and dried. Recrystallization from EtOH gave 3.3 g (89.2%) of colorless plates, mp 252—253°.

6-Amino-4-hydrazino-2-methylpyrimidine (XVI)——A mixture of 10.5 g (0.0075 mole) of IV and 15 g (0.3 mole) of hydrazine hydrate (80%) was heated for 10 min at 120°. After cooling, the solid product was isolated by filtration, washed with a little cold H_2O, dried and recrystallized from MeOH to give 9.0 g (86.5%) of white powder, mp 240—242°.

Ethyl 4-Dimethylamino-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate (XXXV)——Into 12 g of refluxing Dowtherm A was added 1.2 g (0.0037 mole) of diethyl 2-methyl-4-dimethylamino-6-pyrimidinyl-

14) H. Adkins, E.E. Burgoyme and H.J. Schneider, *J. Am. Chem. Soc.*, 72, 2626 (1950).
15) Melting points were determined on a Yanagimoto micro melting point apparatus and were not corrected. NMR spectra were determined on a JNM-C-60 spectrometer.

aminomethylenemalonate (XXIII) and heated at 250° for 15 min. The reaction mixture was cooled, the separated precipitates were collected by filtration and washed with benzene and then with *n*-pentane to give 0.57 g of pale yellow powder, mp 160—180°. This crude product was treated by Al_2O_3-column (eluate: benzene–ethyl acetate) to give 0.15 g (14.7%) of XXXV, mp 184—190° and 0.35 g (34.3%) of ethyl 4-ethoxy-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate (XXXII).

Ethyl 5-Hydroxy-2-methyl-4-piperidinopyrido[2,3-*d*]pyrimidine-6-carboxylate (XXXVI)——Into 30 g of refluxing Dowtherm A was added 2.5 g (0.007 mole) of diethyl 2-methyl-4-piperidino-6-pyrimidinylaminomethylenemalonate (XXIV) and heated at 250° for 15 min. After cooling, the reaction mixture was diluted with petroleum ether and the precipitates which separated were filtered. Acetone was added to the crude product, the insoluble material was filtered off and the solvent evaporated. The residue was dissolved in benzene, filtered and the insoluble part was recrystallized from EtOH to give 0.02 g of ethyl 4-ethoxy-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate (XXXII). Evaporation of benzene from the filtrate and recrystallization of the residue from EtOH gave 1 g (43.5%) of pale yellow needles of XXXVI, mp 241—242°.

Ethyl 4-Hydrazino-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate (XLI)——A mixture of 0.55 g (0.002 mole) of ethyl 4-ethoxy-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate (XXXII) and 0.15 g (0.0024 mole) of hydrazine hydrate (80%) in 20 ml of EtOH was refluxed for 30 min at 120°. After cooling, the separated products were collected by filtration, washed with EtOH and recrystallized from DMF to give 0.47 g (90%) of pale yellow powder, mp>300°.

Diethyl 4-Amino-2-methyl-6-pyrimidinylhydrazinomethylenemalonate (XLIII)——A mixture of 1.4 g (0.01 mole) of 6-amino-4-hydrazino-2-methylpyrimidine and 2.4 g (0.011 mole) of EMME in 50 ml of anhydrous EtOH was refluxed for 1 hr at 100°. After evaporation of EtOH, the residue was recrystallized from EtOAc to give 2.6 g (83.3%) of colorless sandy crystals, mp 190—193°. *Anal.* Calcd. for $C_{13}H_{19}O_4N_5$: C, 50.48; H, 6.19; N, 22.64. Found: C, 50.51; H, 6.08; N, 22.63.

Ethyl 1-(4-Amino-2-methyl-6-pyrimidinyl)-5-hydroxypyrazole-4-carboxylate (XLIV)——In 5 ml of 10% NaOH in 50% EtOH was added 0.1 g (0.0003 mole) of XLIII and refluxed for 10 min. After cooling, the precipitates were collected by filtration, washed with H_2O and dried to give white powder. Recrystallization from DMF yielded white powder of Na salt of XLIV, mp >300°. *Anal.* Calcd. for $C_{11}H_{12}O_3N_5Na$: C, 46.31; H, 4.24; N, 24.55. Found: C, 46.70; H, 4.31; N, 24.28.

4,5-Dihydroxy-2-methylpyrido[2,3*d*]-pyrimidine-6-carboxylic Acid (XLV)——Half gram (0.0015 mole) of ethyl 5-hydroxy-2-methyl-4-morpholinopyrido[2,3-*d*]pyrimidine-6-carboxylate (XXXVII) was heated under reflux in 5 ml of 10% KOH in 50% EtOH for 2 hr. After cooling, the reaction mixture was neutralized with AcOH to separate white powder, which was filtered and recrystallized from DMF to give 0.46 g (96.3%) of colorless crystals, mp >300°.

Acid Hydrolysis of Ethyl 4-Ethoxy-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine (XXXII)——To a mixture of 0.5 ml of conc. HCl and 1.5 ml of glacial AcOH was added 0.1 g of XXXII and heated for 45 min at 100°. The pale yellow crystals which separated were collected by filtration, washed with H_2O and dried. Recrystallization from DMF gave XLV in quantitative yield.

When the same reaction was performed under milder conditions (10 min, 80°) and after cooling neutralized with aqueous NH_3, ethyl 4,5-dihydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate (XXIX) was precipitated. Filtration and recrystallization from EtOH gave pale yellow crystals of XXIX, mp 284—285°.

4,5-Dihydroxy-2-methylpyrido[2,3-*d*]pyrimidine (LI)——A mixture of 0.7 g (0.0012 mole) of 4,5-dihydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylic acid (XLV) and 0.14 g of copper chromite catalyst[14] in 45 ml of distilled quinoline was stirred for 8 hr at 210—220°. From the resulting black brown mixture, insoluble materials was filtrated off, diluted with petroleum benzene, and the precipitates were collected by filtration to give 0.4 g of brown powder. Extraction with hot EtOH and treatment with charcoal gave 0.2 g (35%) of pale brown powder, mp 289—291°. Recrystallization from EtOH gave pale yellow powder, mp 291° (decomp.).

5-Hydroxy-2-methylpyrido[2,3-*d*]pyrimidine (LII)——In 3 ml of distilled quinoline, 0.15 g (0.0007 mole) of 5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylic acid (XLVI) was heated for 2.5 hr at 220—240°. To the resulting black brown mixture, petroleum benzene was added to separate 50 mg (41.7%) of brown powder, mp 260—270°. Recrystallization from acetone-EtOH gave colorless needles, mp 280—283°.

4-Anilino-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine (LIII).——Half gram (0.0017 mole) of 4-anilino-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylic acid (XLVII) was heated for 3 hr in 10 ml of distilled quinoline at 210—220°. After cooling, white needles were precipitated, filtered and washed with ether to give 0.3 g (70%) of LIII, mp >300°. Recrystallization from EtOH with the treatment of charcoal gave colorless needles, mp >300°.