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Synthesis of Compounds related to Antitumor Agents. IV.[1] On the Reaction of Aromatic Carboxylates with 2,4-Diamino-5-hydroxy-6-methylpyrimidine

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Attempts to prepare oxazolo[4,5-*d*]pyrimidines by the reaction of 2,4-diamino-5-hydroxy-6-methylpyrimidine (I) with aromatic carboxylates. The products were carbinolamines which were converted to oxazolo[4,5-*d*]pyrimidines. Also, the application of the Salol reaction of I gave 5-amino-2-(2,4-diamino-6-methylpyrimidin-5-yl)oxy-2-*o*-hydroxyphenyl-7-methyl-3H-oxazolo[4,5-*d*]pyrimidine (XI) which was an unusual product in this reaction.

In the course of our research for some new nucleoside derivatives related to antitumor agents, the reactivity of 2,4-diamino-5-hydroxy-6-methylpyrimidine (I) was reported previously. In continuation of this work, this paper deals with the synthesis of oxazolo[4,5-*d*]-pyrimidines by the reaction of I with aromatic carboxylates.

Treatment of I with benzoic anhydride in pyridine at room temperature gave a mixture of IIa,[3] 5-amino-2-hydroxy-7-methyl-2-phenyl-3H-oxazolo[4,5-*d*]pyrimidine (IIIa) and 2-amino-4-benzamido-5-benzoyloxy-6-methylpyrimidine (IV), in a ratio of 4:2:1. IIIa was also obtained by refluxing IIa in ethanol. The disappearance of the ester carbonyl band in the infrared (IR) spectrum of IIIa and bathocromic shift to 340 mμ from 282 mμ of IIa in the ultraviolet (UV) spectrum substantiated the conclusion that intramolecular cyclization to IIIa has taken place. The IR spectrum of IV showed characteristic absorption of ester carbonyl and amido carbonyl at 1755 and 1680 cm^{-1}, respectively, and was assigned the structure of IV.

When the reaction of I with benzoic anhydride was carried out in refluxing pyridine, 5-amino-3-benzoyl-2-hydroxy-7-methyl-2-phenyl-oxazolo[4,5-*d*]pyrimidine (V) was obtained besides IIa, IIIa and IV. Compound (IV) was also converted into the isomeric compound (V) by refluxing in pyridine (Chart 1).

Some 5-amino-2-hydroxy-2-substituted phenyl-7-methyl-3H-oxazolo[4,5-*d*]pyrimidine derivatives (IIIa—h) were obtained by using of the corresponding benzoyl compounds (IIa—h) (Table I), or from I and the corresponding phenyl benzoates[4] (Table II).

The studies of carbinolamines as to benzoxazol, benzimidazole and benzthiazole derivatives have been widely investigated, notably by R.J. Morgan, *et al.*,[5] but not isolated to be stable. Then, IIIa—h were converted to 5-amino-7-methyl-2-substituted phenyl-oxazolo-[4,5-*d*]pyrimidines (VIIa—f) by two methods. The direct method that IIIa—h were heated in dimethyl sulfoxide (DMSO) at 100—110° in the presence of triethyl amine gave generally

1) *a*) Part III: I. Ito, T. Kato, and N. Oda, *Chem. Pharm. Bull.* (Tokyo), **24**, 1189 (1976); *b*) A part of this paper was presented at Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, April 1975.
2) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
3) N. Oda, Y. Kanie, and I. Ito, *Yakugaku Zasshi*, **93**, 817 (1973).
4) C.F.H. Allen, C.J. Kibler, D.M. McLachlin, and C.V. Wilson, "Organic Syntheses," Coll. Vol. III, ed by A.H. Blatt, John Wiley and Sons, Inc., New York, 1955, p. 29; E. Kopetshni and L. Karezag, *Chem. Ber.*, **47**, 235 (1914).
5) K.J. Morgan and A.M. Turner, *Tetrahedron*, **22**, 1175 (1966); *idem, ibid.*, **25**, 915 (1969).

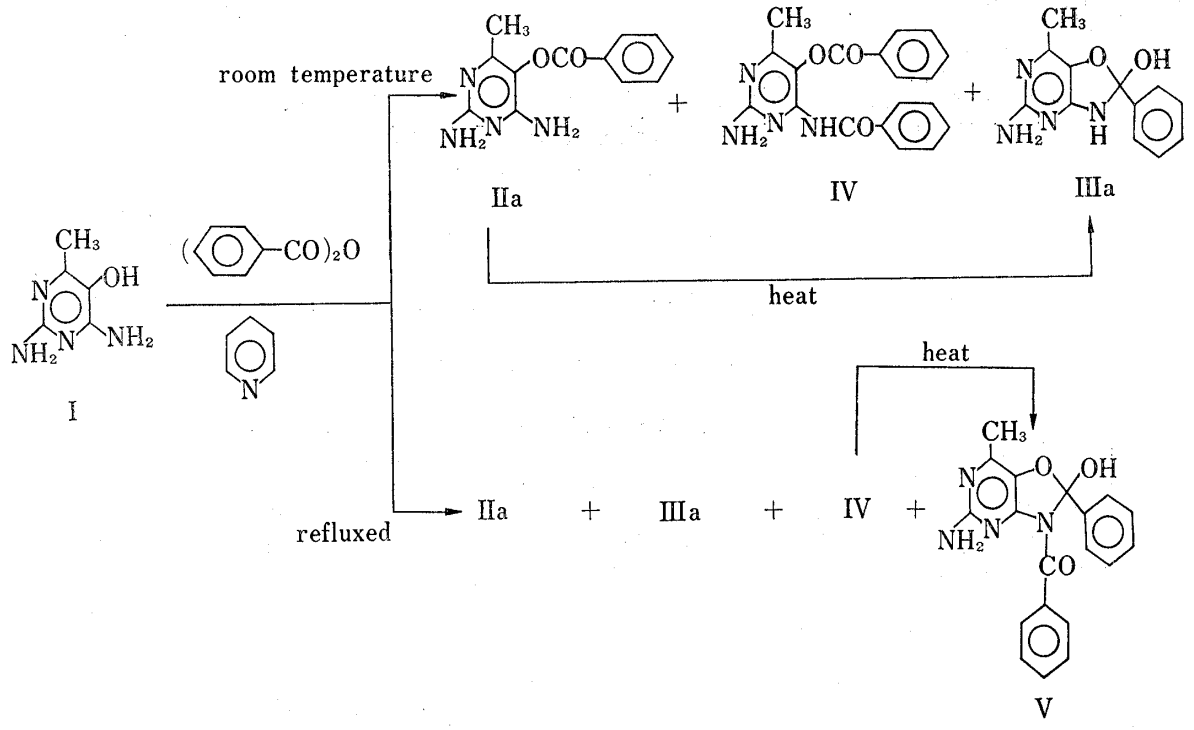
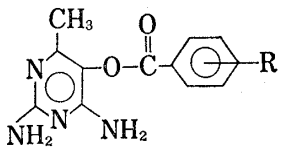


Chart 1

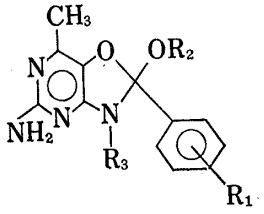
TABLE I. 2,4-Diamino-5-substituted benzoyloxy-6-methylpyrimidines (IIa—h)



Compd. No.	R	mp[a] (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR spectra ν_{max}^{KBr} cm^{-1} (C=O)	UV spectra λ_{max}^{EtOH} mμ (log ε)
a	H	189—190	55	$C_{12}H_{12}O_2N_4$	59.01 (59.35)	4.95 (4.83)	22.94 (22.73)	1740	280 (4.09)
b	*o*-OH	179—180	33	$C_{12}H_{12}O_3N_4$	55.38 (55.30)	4.65 (4.78)	21.53 (21.33)	1690 1680	320 (4.08)
c	*p*-OH	195—197	50	$C_{12}H_{12}O_3N_4$	55.38 (55.67)	4.65 (4.58)	21.53 (21.80)	1735	282 (4.16)
d	*o*-CH_3	223—225	53	$C_{13}H_{14}O_2N_4$	60.45 (60.77)	5.46 (5.38)	21.69 (22.00)	1745	281 (4.17)
e	*m*-CH_3	183—185	45	$C_{13}H_{14}O_2N_4$	60.45 (60.72)	5.46 (5.33)	21.69 (21.88)	1750	280 (4.17)
f	*p*-CH_3	206	58	$C_{13}H_{14}O_2N_4$	60.45 (60.56)	5.46 (5.47)	21.69 (21.76)	1743	280 (4.07)
g	*o*-NO_2	234—237	55	$C_{12}H_{11}O_4N_5$	49.48 (49.55)	4.50 (4.69)	24.04 (22.88)	1755	281 (4.10)
h	*o*-Cl	218—220	50	$C_{12}H_{11}O_2N_4Cl$	51.72 (51.86)	3.98 (3.78)	20.10 (19.87)	1740	280 (4.08)

a) Each of IIa—h was colorless needles.

TABLE II. 5-Amino-2-hydroxy-7-methyl-2-phenyl-3H-oxazolo[4,5-*d*]pyrimidine and Related Compounds (IIIa—h, VIa—f and IXa—e)



Compd. No.	R_1	R_2	R_3	mp (°C)	Yield (%)	Appearance[a] (recrystn. solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N
IIIa	H	H	H	172—174	66[b]	P.Y.N. (EtOH)	$C_{12}H_{12}O_2N_4$	59.01 (58.80)	4.95 (4.87)	22.94 (22.85)
IIIb	*o*-OH	H	H	165—167	35[b]	P.Y.N. (EtOH–AcOEt)	$C_{12}H_{12}O_3N_4$	55.38 (55.03)	4.65 (4.34)	21.53 (21.38)
IIIc	*p*-OH	H	H	161—162	50[b]	P.Y.N. (MeOH)	$C_{12}H_{12}O_3N_4$	55.38 (55.65)	4.65 (4.70)	21.53 (21.88)
IIId	*o*-CH_3	H	H	178—179	55[b]	P.Y.N. (benzene)	$C_{13}H_{14}O_2N_4$	60.45 (60.77)	5.46 (5.38)	21.69 (21.65)
IIIe	*m*-CH_3	H	H	145—146	62[b]	P.Y.N. (isopropyl alcohol)	$C_{13}H_{14}O_2N_4$	60.45 (60.38)	5.46 (5.33)	21.69 (21.29)
IIIf	*p*-CH_3	H	H	168—170	65[b]	P.Y.N. (isopropyl alcohol)	$C_{13}H_{14}O_2N_4$	60.45 (60.55)	5.46 (5.54)	21.69 (21.80)
IIIg	*o*-NO_2	H	H	198—200	54[b]	P.Y.N. (MeOH)	$C_{12}H_{11}O_4N_5$	49.48 (49.81)	4.50 (4.75)	24.04 (24.13)
IIIh	*o*-Cl	H	H	166	55[b]	P.Y.N. (MeOH)	$C_{12}H_{11}O_2N_4Cl$	51.72 (52.02)	3.98 (4.03)	20.10 (20.32)
VIa	H	CH_3	H	245—246 (decomp.)	35	Y.P. (MeOH)	$C_{13}H_{14}O_2N_4$	60.45 (60.33)	5.46 (5.21)	21.69 (21.30)
VIb	*o*-CH_3	CH_3	H	300<	54	Y.N. (MeOH)	$C_{14}H_{16}O_2N_4$	61.75 (61.86)	5.92 (6.00)	20.58 (20.37)
VIc	*m*-CH_3	CH_3	H	225< (decomp.)	54	Y.P. (MeOH)	$C_{14}H_{16}O_2N_4$	61.75 (61.77)	5.92 (5.90)	20.58 (20.13)
VId	*p*-CH_3	CH_3	H	238—240	48	Y.P. (MeOH)	$C_{14}H_{16}O_2N_4$	61.75 (61.69)	5.92 (5.80)	20.58 (20.18)
VIe	*o*-NO_2	CH_3	H	240< (decomp.)	40	Y.N. (MeOH)	$C_{13}H_{13}O_4N_5$	51.49 (51.38)	4.32 (4.30)	23.09 (22.71)
VIf	*p*-Cl	CH_3	H	200—203	43	Y.P. (MeOH)	$C_{13}H_{13}O_2N_4Cl$	53.34 (53.12)	4.48 (4.38)	19.14 (18.83)
IXa	H	$COCH_3$	$COCH_3$	219—220	23	C.P. (MeOH)	$C_{16}H_{16}O_4N_4$	58.53 (58.40)	4.91 (4.78)	17.06 (16.87)
IXb	*o*-CH_3	$COCH_3$	$COCH_3$	233 (decomp.)	30	C.N. (MeOH)	$C_{17}H_{18}O_4N_4$	59.64 (59.89)	5.30 (5.47)	16.37 (16.04)
IXc	*p*-CH_3	$COCH_3$	$COCH_3$	201—204	26	C.N. (EtOH)	$C_{17}H_{18}O_4N_4$	59.64 (59.68)	5.30 (5.39)	16.37 (16.22)
IXd	*o*-NO_2	$COCH_3$	$COCH_3$	190—193	25	C.P. (benzene)	$C_{16}H_{15}O_6N_5$	51.48 (51.09)	4.05 (4.38)	18.76 (18.29)
IXe	*o*-Cl	$COCH_3$	$COCH_3$	232—235	22	C.P. (MeOH)	$C_{16}H_{15}O_4N_4Cl$	52.97 (52.67)	4.17 (4.29)	15.44 (15.04)

a) P.Y.N.: pale yellow needles, Y.P.: yellow plates, Y.N.: yellow needles, C.P.: colorless plates, C. N.: colorless needles

b) reaction yield of I and the corresponding phenyl benzoates

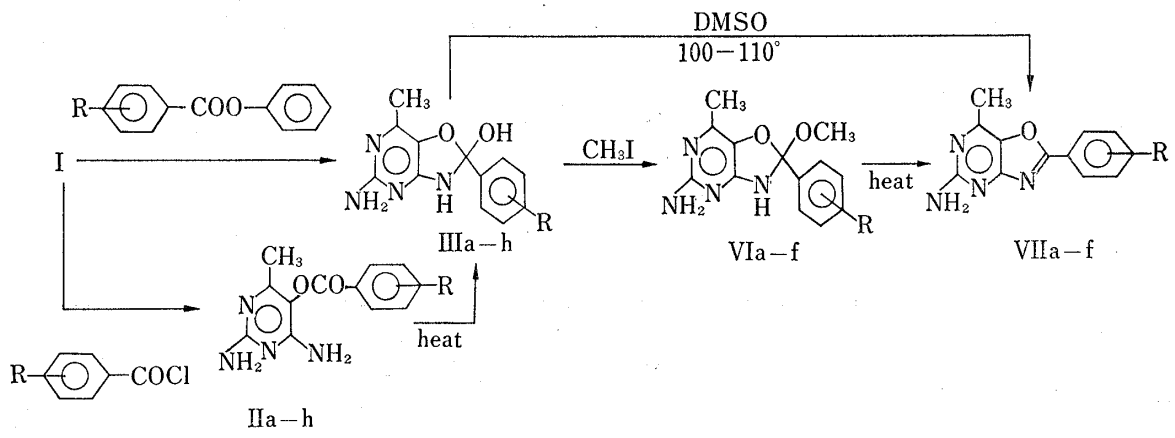
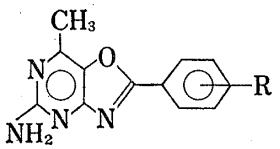


Chart 2

TABLE III. 5-Amino-7-methyl-2-substituted phenyl-oxazolo[4,5-*d*]pyrimidines (VIIa—f)



Compd. No.	R	mp (°C)	Yield[a] (%)	Appearance	Formula	Analysis (%) Calcd. (Found) C	H	N
a	H	270<	25	yellow needles	$C_{12}H_{10}ON_4$	63.71 (63.51)	4.46 (4.33)	24.76 (24.56)
b	*o*-OH	280< (decomp.)	20	pink needles	$C_{13}H_{12}ON_4$	64.99 (64.71)	5.03 (4.86)	23.32 (23.01)
c	*m*-OH	260—265	27	yellow prisms	$C_{13}H_{12}ON_4$	64.99 (64.70)	5.03 (5.09)	23.32 (23.06)
d	*p*-OH	300<	25	red needles	$C_{13}H_{12}ON_4$	64.99 (64.87)	5.03 (5.23)	
e	*o*-NO_2	300<	20	red needles	$C_{12}H_9O_3N_5$	53.14 (53.22)	3.34 (3.58)	
f	*o*-Cl	300<	22	pink needles	$C_{12}H_9ON_4Cl$	55.29 (55.48)	3.48 (3.34)	

a) reaction yield by heating of VIa-f and ethanol

low yields. However, the indirect method that IIIa—h were methylated to the corresponding 5-amino-2-methoxy-7-methyl-2-substituted phenyl-3H-oxazolo[4,5-*d*]pyrimidines (VIa—f) gave good yields (Chart 2) (Table III).

Attempts to prepare VIIa—f starting IIa—h with polyphosphoric acid, phosphorous oxychloride, acetic anhydride or Phillips reagent,[6] were unsuccessful.

Heating IIIa—h in DMSO at 140—150° for 30 minutes gave IIa—h and VIIIa—h. Similarly, heating VIIIa—h in dowtherm at 160—170° for 20 minutes gave IIIa—h and VIIIa—h, and heating IIa—h in dimethylformamide (DMF) at 140—150° for 20 minutes gave IIIa—h and VIIIa—h. Compounds (VIIIa—h) were cyclized to IIIa—h in formic acid or acetic acid at room temperature (Table IV).

Therefore, the hydroxyl protons of carbinolamines (IIIa—h) seem to be labile and the ring cleavage might give rise (Chart 3).

6) M.A. Phillips, *J. Chem. Soc.*, **1928**, 2393.

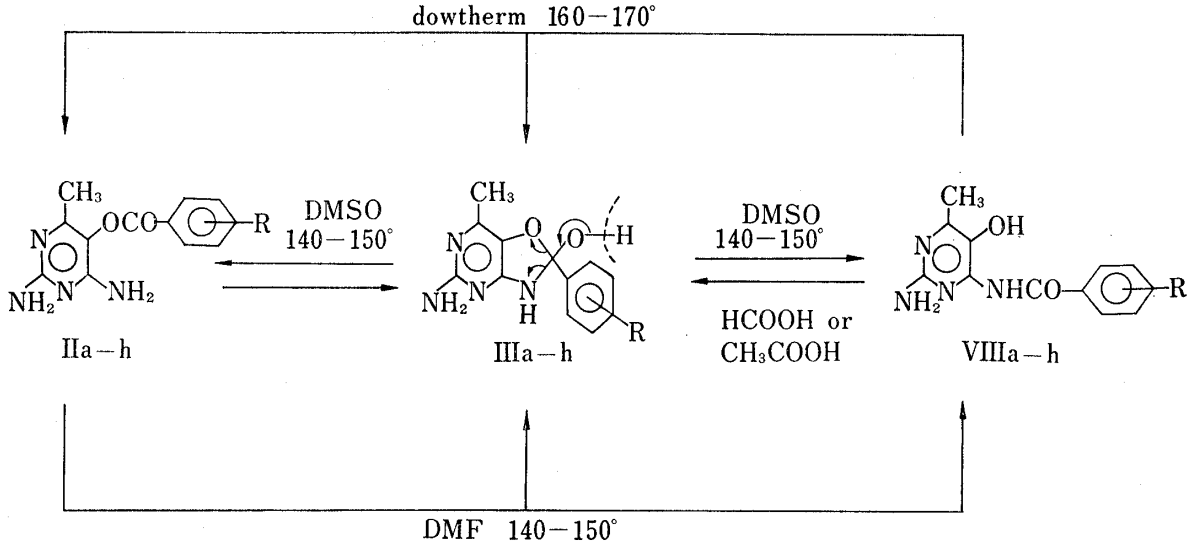
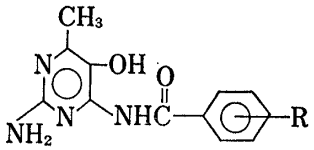


Chart 3

TABLE IV. 2-Amino-4-substituted benzamido-5-hydroxy-6-methylpyrimidines (VIIIa—h)



Compd. No.	R	mp (°C)	Appearance	Formula	Analysis (%) Calcd. (Found) C	H	N
a	H	201—203	colorless needles	$C_{12}H_{12}O_2N_4$	59.01 (58.88)	4.95 (5.03)	22.94 (22.76)
b	*o*-OH	195 (decomp.)	colorless needles	$C_{12}H_{12}O_3N_4$	55.38 (55.31)	4.65 (4.36)	21.53 (21.76)
c	*p*-OH	210—213	colorless needles	$C_{12}H_{12}O_3N_4$	55.38 (55.46)	4.65 (4.79)	21.53 (21.17)
d	*o*-CH_3	207—209 (decomp.)	colorless plates	$C_{13}H_{14}O_2N_4$	60.45 (60.22)	5.46 (5.38)	21.69 (21.47)
e	*m*-CH_3	193—194	colorless plates	$C_{13}H_{14}O_2N_4$	60.45 (60.38)	5.46 (5.27)	21.69 (21.39)
f	*p*-CH_3	225—228	colorless prisms	$C_{13}H_{14}O_2N_4$	60.45 (60.31)	5.46 (5.49)	21.69 (21.50)
g	*o*-NO_2	235 (decomp.)	colorless prisms	$C_{12}H_{11}O_4N_5$	49.48 (48.99)	4.50 (4.53)	24.04 (23.76)
h	*o*-Cl	187—189	colorless needles	$C_{12}H_{11}O_2N_4Cl$	51.72 (51.77)	3.98 (4.09)	20.10 (20.33)

Treatment of carbinol amines (IIIa, d, f, g and h) with acetyl chloride in the presence of potassium carbonate gave diacetyl compounds, 2-acetoxy-3-acetyl-5-amino-7-methyl-2-substituted phenyl-oxazolo[4,5-*d*]pyrimidines (IXa—e) (Table II). These IR spectra exhibited characteristic absorption peaks of primary amino group at 3210—3150 cm^{-1}. Compounds (IIIa, d and g) were allowed to react with acid dichlorides such as malonyl chloride[7] and succinyl chloride to give the tricyclic compounds, 6-amino-8-methyl-9′-substituted phenyl-3H-[1,3]oxazino[2,3-*b*]oxazolopyrimidine-2,4-diones (Xa, c and e) and 7-amino-9-methyl-10′-

7) R. Black, H. Shaw, and T. Kennedy, *J. Chem. Soc.*, **1931**, 276.

substituted phenyl-3H,4H-[1,3]oxazepino[2,3-*b*]oxazolopyrimidine-2,5-diones (Xb, d and f) (Table V). The nuclear magnetic resonance (NMR) spectra of Xa, c and e showed signals at δ 4.10—4.25 as a singlet, and those of Xb, d and f revealed at δ 4.15—4.35 as a multiplet (Chart 4).

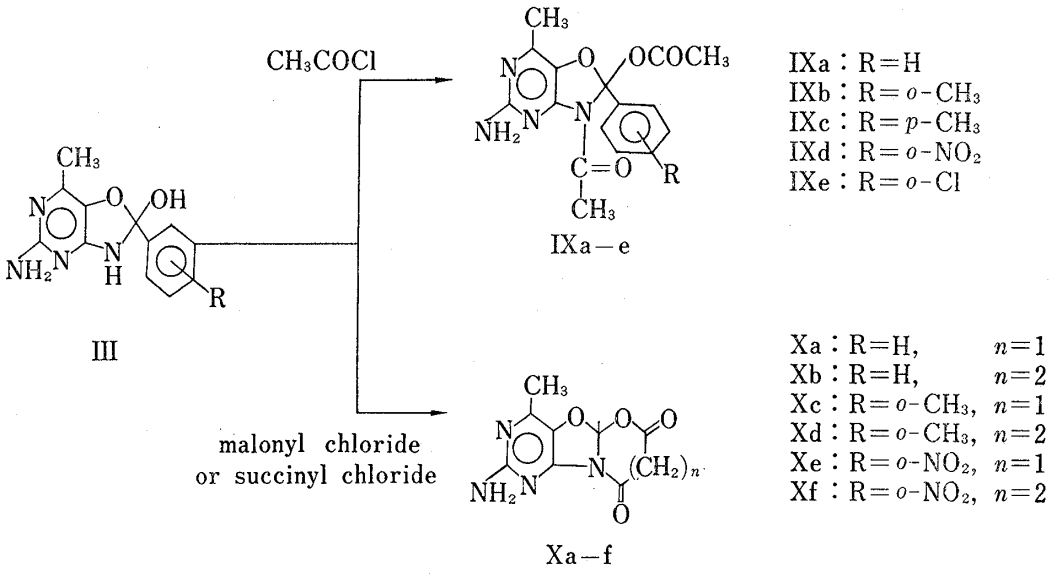
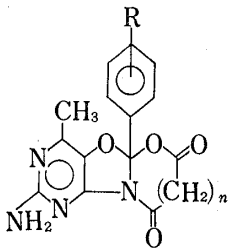


Chart 4

TABLE V. 6-Amino-8-methyl-9′-substituted phenyl-3H-[1,3-]oxazino[2,3-*b*]oxazolopyrimidine-2,4-diones (Xa, c and e) and 7-Amino-9-methyl-10′-substituted phenyl-3H,4H-[1,3]-oxazepino[2,3-*b*]oxazolopyrimidine-2,5-diones(Xb, d and f)



Compd. No.	R	*n*	mp (°C)	Appearance	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
a	H	1	199—202	pale yellow needles	10	MeOH	$C_{15}H_{12}O_4N_4$	57.69 (57.88)	3.87 (4.00)	17.94 (17.66)
b	H	2	233—235	colorless plates	12	isopropyl alcohol	$C_{16}H_{14}O_4N_4$	58.89 (58.97)	4.32 (4.57)	17.17 (17.26)
c	*o*-CH_3	1	243—245	pale yellow needles	10	MeOH	$C_{16}H_{14}O_4N_4$	58.89 (58.90)	4.32 (4.55)	17.17 (16.87)
d	*o*-CH_3	2	210—212	colorless plates	15	EtOH	$C_{17}H_{16}O_4N_4$	60.00 (59.68)	4.74 (4.56)	16.46 (16.24)
e	*o*-NO_2	1	213—215	colorless plates	13	benzene–AcOEt	$C_{15}H_{11}O_6N_5$	50.43 (50.04)	3.10 (3.27)	19.60 (19.65)
f	*o*-NO_2	2	209—212	colorless plates	10	MeOH	$C_{16}H_{13}O_6N_5$	51.76 (51.51)	3.53 (3.22)	18.86 (18.53)

The above experimental results prompted us to study the salol reaction[8] of I. Treatment of I with phenyl salicylate (salol) in ethanol afforded the mixture of IIIb and 5-amino-2-(2,4-diamino-6-methylpyrimidin-5-yl)oxy-2-*o*-hydroxyphenyl-7-methyl-3H-oxazolo[4,5-*d*]pyrimidine (XI) which was an unusual product in Salol reaction. The structure of XI was confirmed by an alternative synthesis from IIIb and thionyl chloride, followed by the reaction with I. The NMR of XI showed two signals at δ 2.18 and δ 2.68 which are assignable to the methyl protons of pyrimidine rings. A broad singlet at δ 4.40—6.20 erased on D_2O-exchange is attributable to the three primary amino protons, a secondary amino proton and a hydroxyl proton.

The mechanism of the abnormal reaction which formed IIIb and XI seems to proceed shown in Chart 5. In the compound (IIb), the intramolecular nucleophilic attack by the amino group on the carbonyl carbon would lead to the carbinolamine (IIIb). On the other hand, the intermolecular nucleophilic attack by the active hydroxyl group of I on the carbonyl carbon of IIb would form a labile compound (XI'), which might give XI by the elimination of water.

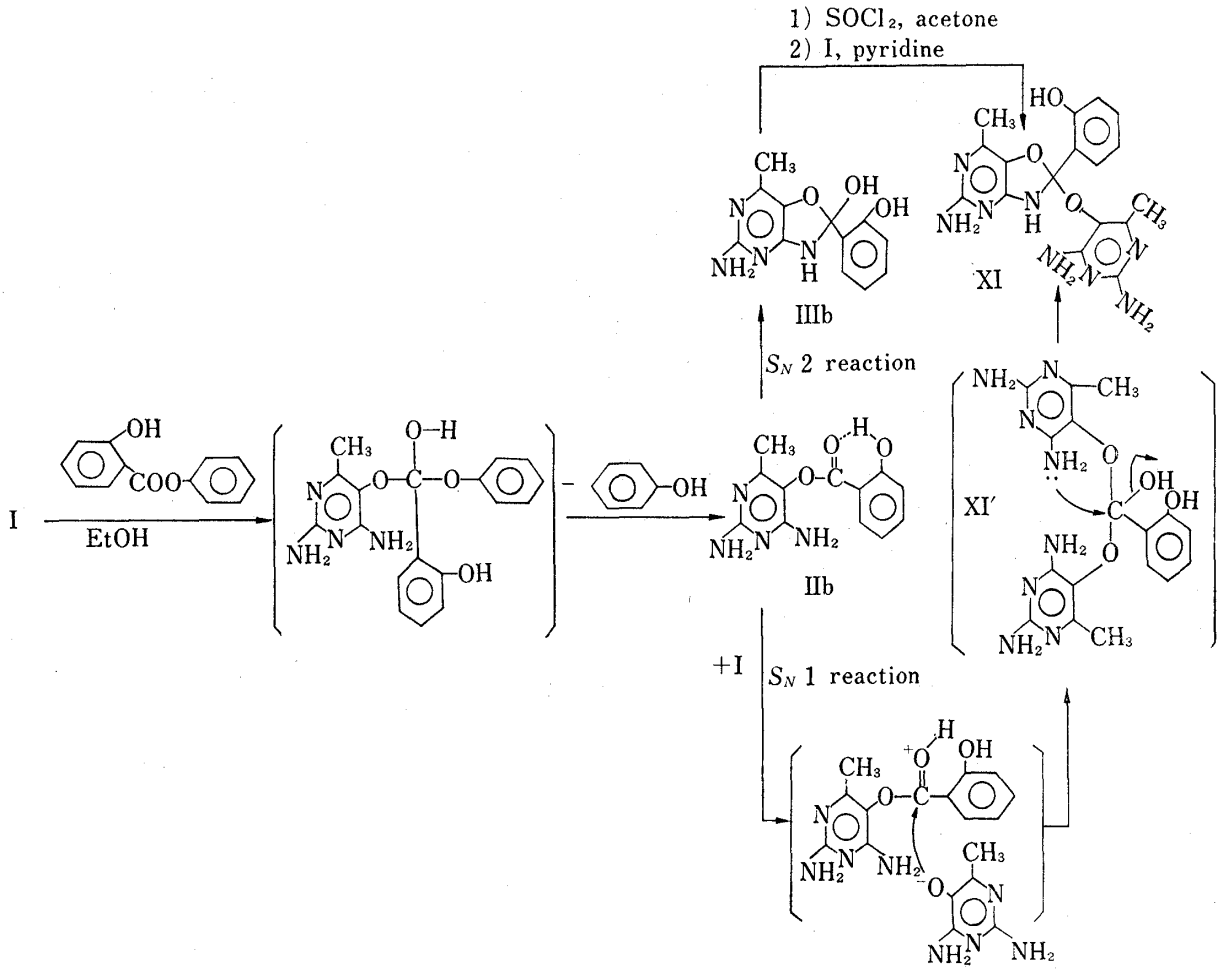


Chart 5

Experimental

All melting points were measured on a Yanagimoto Melting Points Apparatus and are uncorrected. IR spectra were taken on a JASCO infrared spectrophotometer IR-S. UV spectra were measured on a Hitachi

8) M. Schöpff, *Ber.*, **25**, 2740 (1892); I. Goldberg, *Chem. Ber.*, **39**, 1691 (1906); A. Seemer and F.G. Shepard, *J. Chem. Soc.*, **1909**, 95; *idem*, *ibid.*, **1909**, 441; J. Loevenich and A. Loeser, *Chem. Ber.*, **60**, 322 (1927); W.A. Bonner, *J. Am. Chem. Soc.*, **68**, 2745 (1946); J.A. Vanallan, *J. Am. Chem. Soc.*, **69**, 2913 (1947).

EPS-3T spectrophotometer. NMR spectra were run on a JEOL JNM-MH-100 spectrometer using tetramethylsilane as an internal standard.

Reaction of I with Benzoic Anhydride——i) A mixture of 0.745 g (0.005 mol) of I, 1.13 g (0.005 mol) of benzoic anhydride and 20 ml of pyridine was stirred for 20 min at room temperature. The deposited crystals (IIa), mp 189—190° (lit.[3] 180—183°), 0.49 g (40%) were collected. The filtrate was evaporated under reduced pressure below 40° to dryness and the residues were recrystallized from EtOH repeatedly. Compound (IIIa) was obtained as yellow needles, mp 172—174°, 0.24 g (20%). Compound (IV) was obtained as colorless needles, mp 157—159°, 0.17 g (10%). *Anal.* Calcd. for $C_{19}H_{16}O_3N_4$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.40; H, 4.81; N, 15.88. IR ν_{max}^{KBr} cm^{-1}: 1680 (amido carbonyl).

ii) A mixture of 0.745 g (0.005 mol) of I, 1.13 g (0.005 mol) of benzoic anhydride and 20 ml of pyridine was refluxed for 10 min at 110—120° on an oil bath. After cooled, the deposited crystals (IIa), 0.24 g (20%), were collected and washed with EtOH. The filtrate and washing were evaporated to dryness and the residues were recrystallized from EtOH–AcOEt (1: 1) repeatedly. Compound(IIIa), 0.27 g (22%) and IV, 0.21 g (12%) were obtained. Compound (V) was obtained as pale yellow needles, mp 153—154°, 0.17 g (10%). *Anal.* Calcd. for $C_{19}H_{16}O_3N_4$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.33; H, 4.90; N 15.73. IR ν_{max}^{KBr} cm^{-1}: 1685 (amido carbonyl). UV λ_{max}^{EtOH} $m\mu$ (log ε): 308 (4.02).

Cyclization of IIa to IIIa——A mixture of 0.49 g (0.002 mol) of IIa and 20 ml of EtOH was refluxed for 3 hr. After cooled, the deposited crystals were collected and recrystallized from EtOH to give 0.39 g (80%) of IIIa. This product was found to be identified with above IIIa by its IR spectrum and melting point.

Cyclization of IV to V——A mixture of 0.7 g (0.002 mol) of IV and 20 ml of pyridine was refluxed for 3 hr. After evaporation of the solvent, the residues were recrystallized from EtOH–AcOEt (1: 1) to give 0.42 g (60%) of V. This product was found to be identified with above V by its IR spectrum and melting point.

General Procedure of 2,4-Diamino-5-substituted benzoyloxy-6-methylpyrimidines (IIa—h)——To a suspension of 0.745 g (0.005 mol) of I and 20 ml of pyridine was added 0.005 mol of corresponding benzoyl chlorides, prepared from corresponding benzoic acid and thionyl chloride, under cooling and the mixture was stirred for 1 hr at room temperature. To the mixture was added 10 ml of $CHCl_3$ and 5 ml of 10% HCl and the deposited crystals were collected. These compounds were added to 10 ml of saturated $NaHCO_3$ solution and the mixture was stirred for 2 hr at room temperature. The deposited crystals were collected and recrystallized from EOtH–AcOEt (2: 1). The properties of the compounds obtained are summarized in Table I.

General Procedure of 5-Amino-2-hydroxy-7-methyl-2-substituted phenyl-3H-oxazolo[4,5-*d*]pyrimidines (IIIa—h)——i) A mixture of 0.745 g (0.005 mol) of I, 20 ml of pyridine and corresponding phenyl benzoates[9] was refluxed for 1 hr on an oil bath at 110—120°. After evaporation of the solvent, the residues were washed with ether and the deposited crystals were recrystallized from EtOH–AcOEt (1: 1).

ii) A mixture of 0.002 mol of benzoyl compounds (IIa—h) and 10 ml of EtOH was refluxed for 3 hr. After evaporation of the solvent, the residues were recrystallized from EtOH–AcOEt (1: 1). The properties of the compounds obtained are summarized in Table II.

General Procedure of 5-Amino-2-methoxy-7-methyl-2-substituted phenyl-3H-oxazolo[4,5-*d*]pyrimidines (VIa—f)——A mixture of 0.002 mol of IIIa—h, 0.57 g (0.004 mol) of CH_3I, 1 g of potassium carbonate, 15 ml of acetone and 5 ml of EtOH was stirred for 20 hr at room temperature. After evaporation of the solvent, 10 ml of water was added to the residues and the unsoluble crystals were collected. It was recrystallized from MeOH. The properties of the compounds obtained are summarized in Table II.

General Procedure of 5-Amino-7-methyl-2-substituted phenyl-oxazolo[4,5-*d*]pyrimidines (VIIa—f)——i) A mixture of 0.002 mol of IIIa—h, 0.5 ml of triethylamine and 10 ml of DMSO was heated at 110—120° for 2 hr on an oil bath. After cooled, 10 ml of water was added to the residues and the mixture was stirred for 20 hr at room temperature. The deposited crystals were collected and recrystallized from MeOH.

ii) A mixture of 0.002 mol of VIa—f and 20 ml of EtOH was refluxed for 10 hr. After cooled, the deposited crystals were collected and recrystallized from MeOH. The properties of the compounds obtained are summarized in Table III.

Reaction of IIIa—h in DMSO——A mixture of 0.002 mol of IIIa—h and 5 ml of DMSO was heated at 140—150° for 30 min on an oil bath. After evaporation of the solvent *in vacuo*, the residual oil was crystallized from ether and the deposited crystals were recrystallized from EtOH repeatedly to give a small amount of IIa—h and VIIIa—h.

Reaction of VIIIa—h in Dowtherm——A mixture of 0.002 mol of VIIIa—h and 5 ml of dowtherm was heated at 160—170° for 20 min on an oil bath. After evaporation of the solvent *in vacuo*, the residual oil was crystallized from ether and the deposited crystals were recrystallized from EtOH repeatedly to give a small amount of IIa—h and IIIa—h.

Reaction of IIa—h in DMF——A mixture of 0.002 mol of IIa—h and 10 ml of DMF was heated at 140—150° for 20 min on an oil bath. After evaporation of the solvent *in vacuo*, the residual oil was crystallized from ether and the deposited crystals were recrystallized from MeOH repeatedly to give a small amount of IIIa—h and VIIIa—h. The properties of the compounds (VIIIa—h) obtained are summarized in Table IV.

9) *c.f.*, K. Nakazawa, S. Matsuura, and S. Baba, *Yakugaku Zasshi*, **74**, 498 (1954).

Cyclization of VIIIa—h to IIIa—h——A mixture of 0.002 mol of VIIIa—h and 10 ml of 99% formic acid or acetic acid was stirred for 5 hr at room temperature. After evaporation of the solvent, the residues were recrystallized from EtOH.

These products were found to be identified with above IIIa—h by these IR spectra and melting points, respectively.

General Procedure of 5-Amino-2-acetoxy-3-acetyl-7-methyl-oxazolo[4,5-*d*]pyrimidines (IXa—e)——A mixture of 0.002 mol of IIIa, d, f or g, 0.002 mol of acetyl chloride, 1 g of potassium carbonate and 25 ml of acetone was stirred for 20 hr at room temperature. After evaporation of the solvent, 10 ml of water was added to the residues and unsoluble crystals were collected. These products were purified with the solvent shown in Table II. The properties of the compounds obtained are summarized in Table II.

General Procedure of 6-Amino-8-methyl-9′-substituted phenyl-3H-[1,3]oxazino[2,3-*b*]oxazolopyrimidine-2,4-diones (Xa, c, and e) and 7-Amino-9-methyl-10′-substituted phenyl-3H,4H-[1,3]oxazepino[2,3-*b*]oxazolopyrimidine-2,5-diones (Xb, d, and f)——A mixture of 0.002 mol of IIIa, d, or g, 0.002 mol of malonyl chloride or succinyl chloride, 1 g of potassium carbonate and 25 ml of acetone was stirred for 18 hr at room temperature. After evaporation of the solvent, 10 ml of water was added to the residues and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$ and evaporated to dryness. The residues were recrystallized from the solvent shown in Table V. The properties of the compounds obtained are summarized in Table V.

Reaction of I with Salol——A mixture of 0.45 g of I, 0.5 g of salol and 10 ml of EtOH was refluxed for a few minutes on a water bath. After cooled, the deposited crystals were collected and recrystallized from EtOH to give 0.25 g of IIIb and 0.31 g of 5-amino-2-(2,4-diamino-6-methylpyrimidin-5-yl)oxy-2-*o*-hydroxyphenyl-7-methyl-3H-oxazolo[4,5-*d*]pyrimidine (XI). The structure of IIIb was identified with above IIIb by its IR spectrum and melting point. Compound (XI) was obtained as yellow prisms, mp 152—153°. *Anal.* Calcd. for $C_{17}H_{18}O_3N_4$: C, 53.40; H, 4.74; N, 29.30. Found: C, 53.08; H, 4.87; N, 29.33. NMR (DMSO-d_6) δ: 2.18, 2.68 (3H, 3H, each singlet, $2\times CH_3$), 4.40—6.20 (8H, broad singlet, $3\times NH_2$, OH, >NH, exchanged with deuterium oxide), 6.95—7.98 (4H, multiplet, benzene ring protons). UV λ_{max}^{EtOH} mμ (log ε): 302 (4.85), 340 (4.38). Compound (XI) was synthesized in an alternative route: a mixture of 0.3 g of IIIb, 3 ml of thionyl chloride and 20 ml of acetone was refluxed for 1 hr. After evaporation of the solvent and the excess of thionyl chloride, the residual oil was dissolved in 10 ml of pyridine and I was added to the solution. The mixture was heated at 40—50° for 2 hr and pyridine was evaporated *in vacuo* below 40°. To the residues was added 5 ml of water and the deposited crystals were collected. It was recrystallized from EtOH. This product was found to be identified with above XI by its IR spectrum and melting point.

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