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Synthesis of Compounds Related to Antitumor Agents. III.[1] On the Additions of Acyl Halide, Dialkyl Acetylenedicarboxylate and N-Substituted Maleimides to 2,4-Diamino-5-hydroxy-6-methylpyrimidine[2]

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2,4-Diamino-5-hydroxy-6-methylpyrimidine (I) was reacted with acyl halides to give pyrimido[5,4-*b*][1,4]oxazin-6(8H)-ones (IIIa,b). Dialkyl acetylenedicarboxylate was made addition with I to afford alkoxycarbonylmethylene-pyrimido[5,4-*b*][1,4]oxazines (VI,VII). The configuration of this compound was assumed to be *cis* from the evidence of building pyridazino or furano ring. Similarly, with maleimide, the adduct (XIV) was obtained and converted to pyrimido[5,4-*b*][1,4]oxazines (XV,XXIa—f).

In the previous paper,[4] we reported on the synthesis of oxazolo[4,5-*d*]pyrimidine derivatives. In this paper we wish to report the reaction of 2,4-diamino-5-hydroxy-6-methylpyrimidine (I) with acyl halide, dialkyl acetylenedicarboxylate and N-substituted maleimides to give pyrimido[5,4-*b*][1,4]oxazines.

Although we have obtained pyrimido[5,4-*b*][1,4]oxazin-7(8H)-ones (IIa, b)[4] by the Schotten-Baumann reaction of I with ethyl bromoacetate or α-bromopropionate, the reaction of the sodium salt of I with chloroacetyl chloride or α-bromopropionyl bromide provided

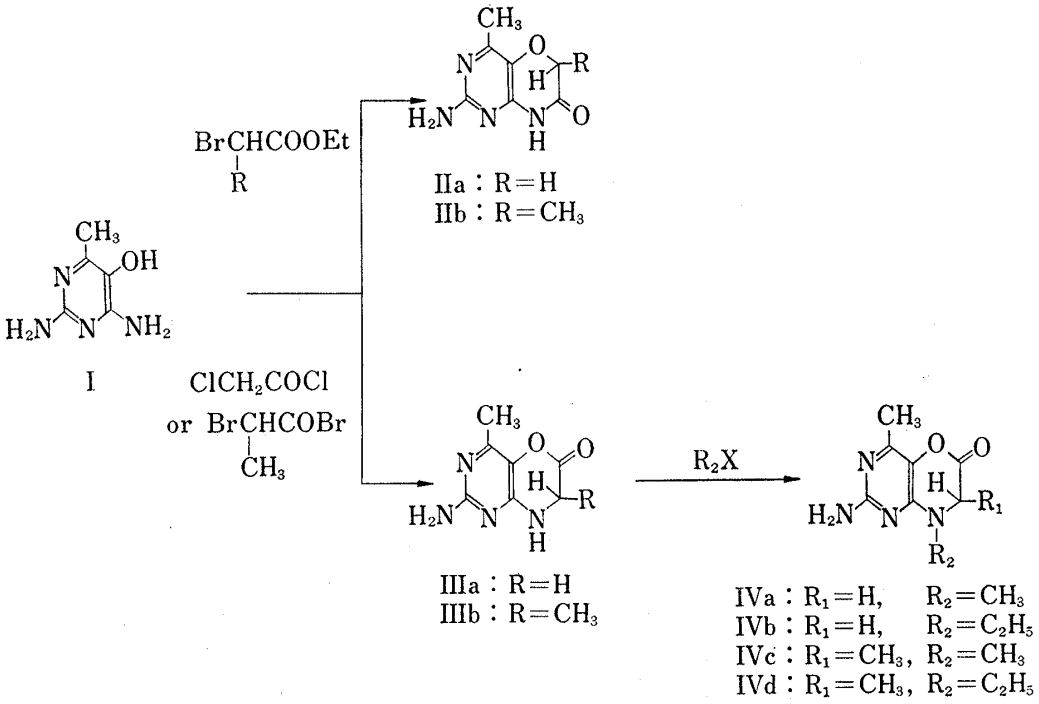


Chart 1

1) Part II: I. Ito, N. Oda, and T. Kato, *Chem. Pharm. Bull.* (Tokyo), **23**, 2105 (1975).
2) A part of this paper was presented at the Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April 1974.
3) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
4) N. Oda, Y. Kanie, and I. Ito, *Yakugaku Zasshi*, **93**, 817 (1973).

pyrimido[5,4-*b*][1,4]oxazin-6(8H)-ones (IIIa, b), which correspond to the structural isomer of IIa, b. In the nuclear magnetic resonance (NMR) spectra, IIa and IIIa revealed their methylene signals at δ 4.95 and 4.50. Methine signals of IIb and IIIb were observed at δ 5.45 and 5.00. The signals of the 6-ones (IIIa, b) were shifted to higher fields than those of the 7-ones (IIa, b). Compounds (IIIa, b) were alkylated with alkyl halides in the presence of sodium alcoholate to yield 8-alkyl pyrimido[5,4-*b*][1,4]oxazin-6-ones (IVa—d) (Chart 1).

Treatment of I with dimethyl acetylenedicarboxylate in ethanol provided yellow crystals (VIII) of a formula $C_{10}H_{10}O_4N_4$. The NMR spectrum revealed an ester methyl signal at δ 4.05, an olefinic proton at δ 6.60. The infrared (IR) spectrum showed α,β-unsaturated carbonyl at 1695 cm^{-1}, an amide carbonyl at 1630 cm^{-1} and an ester at 1250 cm^{-1}. Thus the compound (VIII) was assigned 2-amino-6-methoxycarbonylmethylene-4-methyl-6H-pyrimido[5,4-*b*][1,4]-oxazin-7(8H)-one (VIII). When diethyl acetylenedicarboxylate was used, instead of the dimethyl ester, two compounds were obtained: the major product was 2-amino-6-ethoxycarbonylmethylene-4-methylpyrimido[5,4-*b*][1,4]oxazin-7(8H)-one (VII) and the minor product was diethyl 1-(2,4-diamino-6-methylpyrimidin-5-yl)oxyethylene-1,2-dicarboxylate (VI). NMR spectrum of VI showed two ethylesters protons at δ 1.52 (6H, triplet) and δ 4.78 (4H, quartet), and the IR spectrum showed an ester carbonyl at 1760 cm^{-1}. Refluxing of VI in ethanol gave a cyclized compound (VII). The isolating of VI suggests the reaction mechanism of VI to VII as follows: diethyl acetylenedicarboxylate reacts initially with the hydroxyl group of I, and subsequently with 4-amino group. Similarly dialkyl 1-(2,4-diacetamido-6-methylpyrimidin-5-yl)oxyethylene-1,2-dicarboxylates (Xa, b) were obtained by the reaction of 2,4-diacetamido-6-methylpyrimidine (IX)[4] with dialkyl acetylenedicarboxylate but no cyclized compound

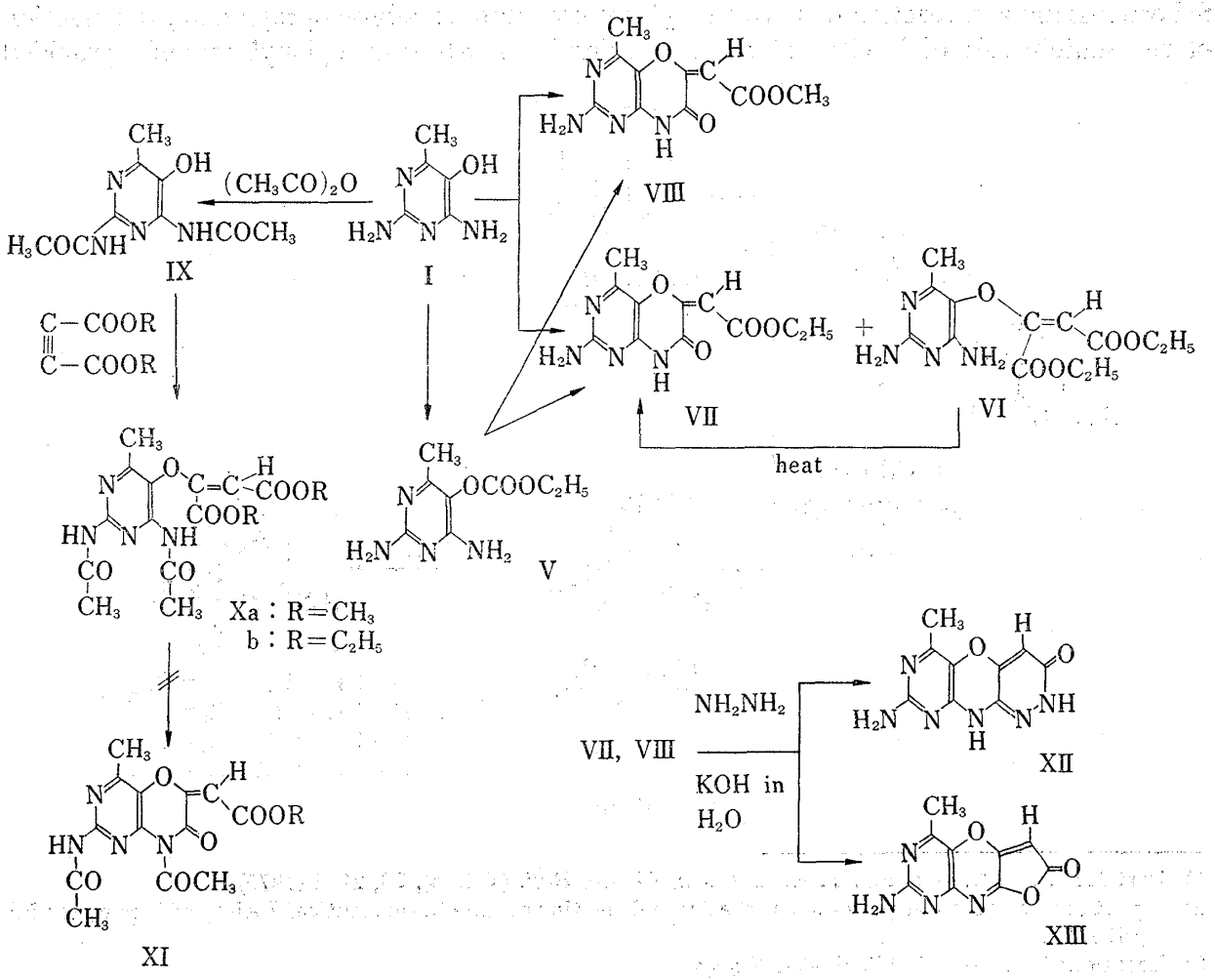


Chart 2

(XI) was obtained. Attempts were made in vain to cyclize Xa,b using organic bases: treatment with sodium alcoholate resulted in hydrolysis of Xa, b to I, and treatment with trialkylamine or pyridine resulted in recovery of the starting materials (Xa, b). This series of reactions with dialkyl acetylenedicarboxylate occurs only in protonic solvents, suggesting that the reaction is originated by solvolysis with solvent used (Chart 2).

Configurational assignments for olefinic proton of VII and VIII might more readily be explained by the consideration of the stability of intermediates (VIa, b) (Chart 3). The intermediate (VIa) in which the bulky groups such as pyrimidine and ethoxycarbonyl are separated, is more likely existed. Then VIa cyclizes to *cis* compound (VIIa).

Further evidence for the assignment was given by the fact that VII and VIII were easily cyclized to afford 5 or 6 membered condensed ring compounds: cyclization of VII and VIII with hydrazine hydrate afforded pyridazino[4,3-*e*]pyrimido[4,5-*b*]oxazine (XII), and with potassium hydroxide afforded furano[3,2-*e*]pyrimido[4,5-*b*]oxazine (XIII). Ultraviolet (UV) and NMR spectral studies offered the evidences for the cyclic nature. Compounds (XII and XIII) exhibited absorption maxima at 345 and 338 mμ respectively, showing bathochromic shifts from 312 mμ in VII and VIII, which indicate the formation of the new condensed rings. Compounds (XII and XIII) revealed their olefinic protons at δ 8.12 and 8.00 respectively, indicating the shielding effects of pyridazino ring for the former, and that of the 5 membered lactone for the latter.

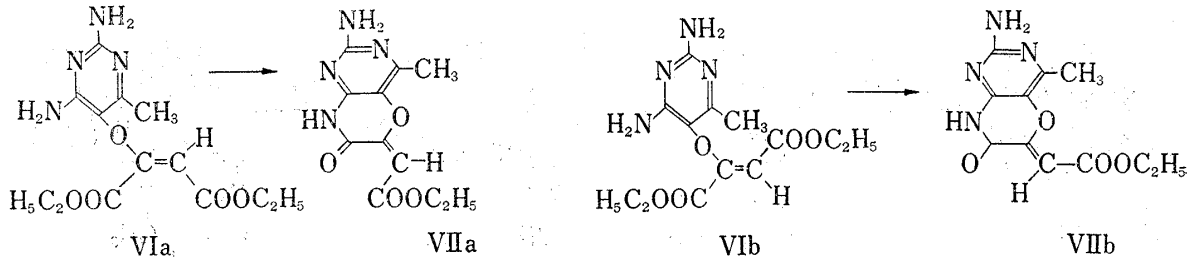


Chart 3

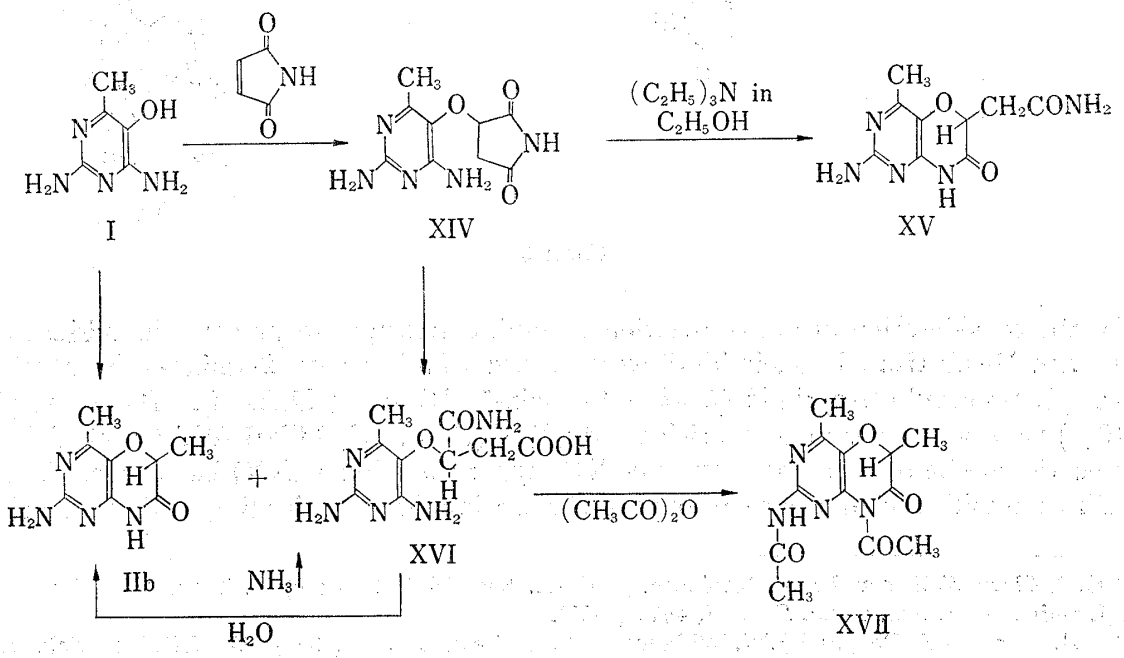


Chart 4

The reaction of I and maleimide in alcohol gave α-(2,4-diamino-6-methylpyrimidin-5-yl)-oxysuccinimide (XIV) in a good yield (90%). The band at 1720 cm^{-1} in its IR spectrum lay in the region associated with known maleimide carbonyl frequencies.[5] The adduct (XIV) was refluxed in ethanol in the presence of triethylamine to give a cyclized product, 2-amino-6-carbamoylmethyl-4-methyl-6H-pyrimido[5,4-*b*][1,4]oxazin-7(8H)-one (XV) which had the absorptions at 1690 and 1660 cm^{-1} in the IR spectrum. This carbonyl absorption was substantially lower than that of the corresponding maleimide (XIV), and fall in the region associated with amide carbonyl indicating that the 5 membered succinimide ring no longer existed. NMR spectrum (CF_3COOD) revealed a methine signal at δ 5.40, which was similar to that of IIb.

Hydrolysis of XIV in refluxing water gave β-carbamoyl-β-(2,4-diamino-6-methylpyrimidin-5-yl)oxyethyl carboxylic acid (XVI) and IIb. Cyclization of XVI to IIb was carried out in a boiling water, passing through NH_3 gas.

Treatment of XVI with sodium acetate in acetic acid-80% ethanol (1 : 1) gave 2-acetamido-8-acetyl-4,6-dimethyl-6H-pyrimido[5,4-*b*][1,4]oxazin-7-one (XVII), which was also synthesized by the alternative route. Refluxing of XIV in acetic anhydride for a few minutes afforded IX and maleimide. Compound (IX) was derived to β-carbamoyl-β-(2,4-diacetamido-6-methyl-pyrimidin-5-yl)oxyethyl carboxylic acid (XIX) in a similar manner as for XVI, and XIX was treated with 28% NH_4OH to give XVII (Chart 5).

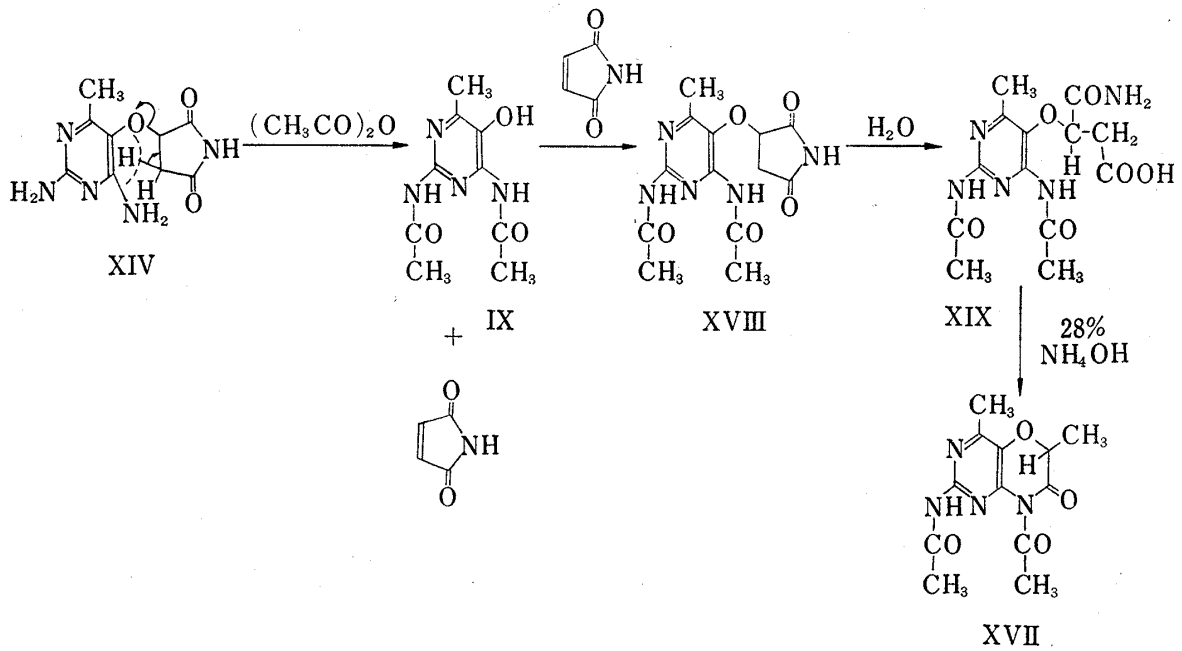


Chart 5

In the consideration of above mentioned results, attempts to prepare the adduct (XX) using I and N-substituted maleimides[6] were unsuccessful but gave 2-amino-6-(N-substituted carbamoyl)-4-methyl-6H-pyrimido[5,4-*b*][1,4]oxazin-7(8H)-ones (XXIa—f). But those yields (8—10%) were very poor in comparision with XIV (75%). G,D.Clark-Walker, *et al.*,[5] have reported the mechanism of ring closure of XIV-type: the adduct (XX) has become involved in cyclization with the adjacent carbonyl of the succinimide ring, leading to the formation of

5) *a*) G.D. Clark-Walker and H.C. Robinson, *J. Chem. Soc.*, **1961**, 2810; *b*) K. Tsou, A.M. Barnett, and R.J. Seligman, *J. Am. Chem. Soc.*, **77**, 4613 (1955).
6) *a*) C.H. Hund, A.S. Roe, and J.W. Williams, *J. Org. Chem.*, **2**, 314 (1937); *b*) W.R. Roderick, *J. Am. Chem. Soc.*, **79**, 1710 (1957); *c*) D.H. Marrian, *J. Chem. Soc.*, **1949**, 1515.

XXIa—f. Thus steric hindrance between the N-substituted group and hydroxyl group of XXII, which was assumed as the intermediate of XXIa—f, may cause poor yields XXIa—f (Chart 6).

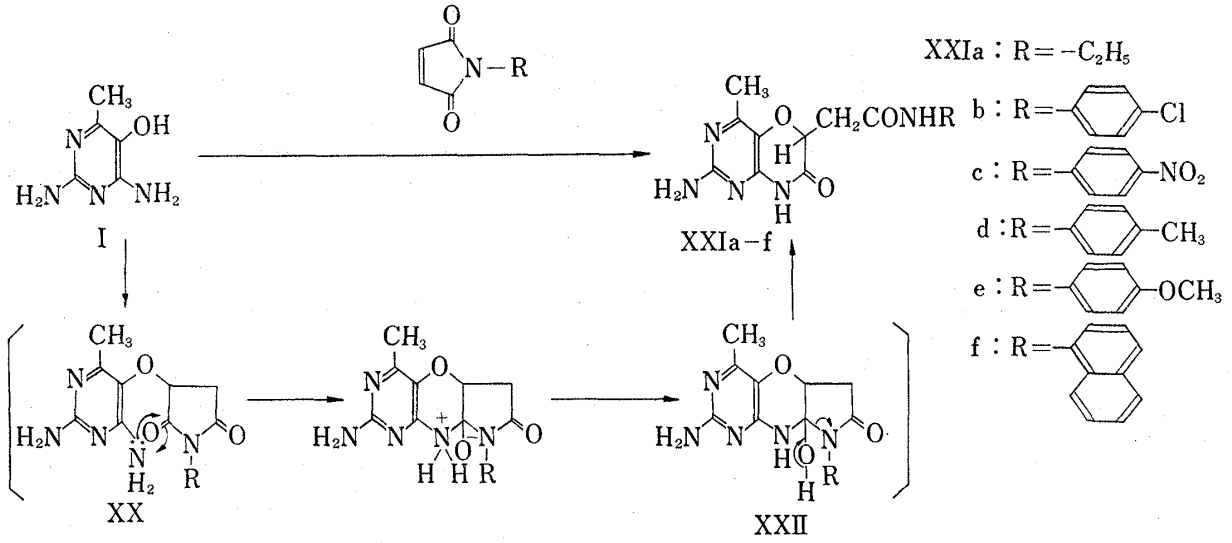


Chart 6

Considering of these facts, it seems that 5-hydroxyl group of I is more reactive than 4-amino group in the additions of acyl halide, dialkyl acetylenedicarboxylate and N-substituted maleimides.

Experimental

All melting points were measured on a Yanagimoto Melting Point Apparatus and are uncorrected. IR spectra were taken on a JASCO infrared spectrophotometer IR-S. UV spectra were measured on a Hitachi EPS-3T spectrophotometer. NMR spectra were run on a JEOL JNM-MH-60 spectrometer and a JEOL JNM-MH-100 spectrometer using tetramethylsilane as an internal standard.

2-Amino-4-methyl-7H-pyrimido[5,4-*b*][1,4]oxazin-6(8H)-one (IIIa)——i) To a solution of 0.1 g of NaOH in 10 ml of H_2O was added 0.745 g (0.005 mol) of I and then 1.13 g of chloroacetyl chloride. The mixture was stirred for 30 min at room temperature. The precipitated crystals were collected, washed with 20 ml of saturated $NaHCO_3$ and recrystallized from dry dimethyl formamide (DMF) to afford 0.42 g(47%) of colorless needles, mp>300°.

ii) To a solution of 2 g of K_2CO_3 in 20 ml of acetone was added 0.745 g (0.005 mol) of I and then 1.13 g of chloroacetyl chloride under stirring at 5—10°. The mixture was stirred for 1 hr at room temperature and treated in the same manner as above method i) to yield 0.29 g (32%) of the product. *Anal.* Calcd. for $C_7H_8O_2N_4$: C, 46.67; H, 4.48; N, 31.10. Found: C, 46.88; H, 4.65; N, 30.88. IRν_{max}^{KBr} cm^{-1}: 1705(lactone), NMR (CF_3COOD) δ: 2.45(3H, singlet, $-CH_3$), 4.50(2H, singlet, $-CH_2-$).

2-Amino-4,7-dimethyl-7H-pyrimido[5,4-*b*][1,4]oxazin-6(8H)-one (IIIb)——i) To a solution of 0.2 g of NaOH in 20 ml of H_2O was added 0.745 g (0.005 mol) of I and then 1.5 g of α-bromopropionyl bromide. The mixture was stirred for 30 min at room temperature. The precipitated crystals were collected and washed with hot EtOH. Recrystallization of the product from dry DMF afforded 0.5 g (51%) of colorless needles, mp>300°.

ii) To a solution of 2 g of K_2CO_3 in 20 ml of acetone was added 0.745 g of I and then 1.1 g of α-bromopropionyl bromide under cooling. The mixture was stirred for 1 hr at room temperature. The precipitated crystals were collected and washed with H_2O. Recrystallization of the product from dry DMF afforded 0.35 g (36%) of colorless needles. *Anal.* Calcd. for $C_8H_{10}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.28; H, 5.04; N, 28.85. NMR (CF_3COOD) δ: 1.83 (3H, doublet, J=7 cps, $\overset{H}{\dashv}C\underline{H}_3$), 5.20(1H, quartet, J=7 cps, $\overset{H}{\dashv}\underline{H}CH_3$).

2-Amino-8-alkyl-4-methyl-7H-pyrimido[5,4-*b*][1,4]oxazin-6-ones (IVa—d)——In a general procedure 0.001 mol of IIIa or IIIb was added into 6 ml of absolute EtOH containing 69 mg(0.003 atom) of metallic sodium. After the addition of 0.003 mol of alkyl halide the mixture was refluxed for 20 hr. The solvent was evaporated *in vacuo* and the residue was triturated with H_2O. Recrystallization of the products from EtOH afforded compounds shown in Table I.

Table I. 2-Amino-8-alkyl-4-methyl-7H-pyrimido[5,4-*b*][1,4]oxazin-6-ones (IVa—d)

IV	mp (°C)	Appearance	Yield (%)	Formula	Analyss (%) Calcd. C	H	N	Found C	H	N
a	235.5	colorless needles	23	$C_8H_{10}O_2N_4$	49.48	5.19	28.85	49.80	5.32	30.02
b	280	colorless needles	32	$C_9H_{12}O_2N_4$	51.92	5.81	26.91	51.99	6.02	26.72
c	199—200	colorless prisms	30	$C_9H_{12}O_2N_4$	51.92	5.81	26.91	52.02	6.03	26.88
d	245	colorless prisms	35	$C_{10}H_{14}O_2N_4$	54.04	6.35	25.21	54.31	6.30	25.49

2-Amino-6-ethoxycarbonylmethylene-4-methylpyrimido[5,4-*b*][1,4]oxazin-7(8H)-one (VII) and Diethyl 1-(2,4-diamino-6-methylpyrimidin-5-yl)oxyethylene-1,2-dicarboxylate (VI)——i) A suspension of 0.298 g (0.002 mol) of I in 5 ml of EtOH was heated to solve then 0.3 g of diethyl acetylenedicarboxylate was added under stirring. After cooling, the precipitated crystals were collected and washed with ether. Recrystallization of the product from dry DMF afforded VII as yellow plates, mp>300°, 0.51 g (97%). *Anal.* Calcd. for $C_{11}H_{12}O_4N_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.76; H, 4.56; N, 21.22. IRν_{max}^{KBr} cm^{-1}: 1695 (α,β-unsaturated carbonyl), 1635 (amide carbonyl), 1250 (ester). NMR (CF_3COOD) δ: 1.58 (3H, triplet, J=7 cps, -$CH_2\underline{CH_3}$), 4.70 (2H, quartet, J=7 cps, -$\underline{CH_2}CH_3$), 6.89 (1H, singlet, olefinic H).

ii) A mixture of 0.298 g of I, 0.3 g of diethyl acetylenedicarboxylate and 10 ml of EtOH was stirred for 2 hr at room temperature. After evaporation of the solvent *in vacuo*, the residue was extracted with hot EtOH. The unsolved residue was recrystallized from dry DMF to afford VII as yellow plates, 0.4 g (77%). The alcoholic extracts were evaporated to dryness and recrystallized from EtOH to afford VI, 60 mg (9.7%), colorless prisms, mp 192°. *Anal.* Calcd. for $C_{18}H_{18}O_5N_4$: C, 50.31; H, 5.85; N, 18.06. Found: C, 50.12; H, 5.88; N, 18.00. IRν_{max}^{KBr} cm^{-1}: 1765 (ester carbonyl), 1710 (α,β-unsaturated carbonyl). NMR ($CDCl_3$:$(CD_3)_2$-SO=1:3) δ: 1.52 (6H, triplet, J=7 cps, 2×-$CH_2\underline{CH_3}$), 4.78 (4H, quartet, J=7 cps, 2×-$\underline{CH_2}CH_3$), 6.10 (1H, singlet, olefinic H).

iii) Cyclization of VI: A mixture of 0.155 g (0.0005 mol) of VI and 6 ml of absolute EtOH was refluxed for 24 hr. After cooling, the precipitated crystals were collected and recrystallized from dry DMF to afford yellow plates, mp>300°, 0.062 g (47%). This product was found to be identified with above VII by its IR spectrum.

2-Amino-6-methoxycarbonylmethylene-4-methylpyrimido[5,4-*b*][1,4]-oxazin-7(8H)-one (VIII)——A mixture of 0.298 g of I, 0.3 g of dimethyl acetylenedicarboxylate and 10 ml of EtOH was stirred at room temperature for 30 min. The reaction was exothermic and the mixture quickly turned to yellow. The precipitated crystals were collected and recrystallized from dry DMF to afford 0.49 g (98%) of yellow plates, mp>300°. *Anal.* Calcd. for $C_{10}H_{10}O_4N_4$: C, 48.00; H, 4.02; N, 22.39. Found: C, 47.88; H, 4.28; N, 22.53. IRν_{max}^{KBr} cm^{-1}: 1695 (α,β-unsaturated carbonyl), 1635 (amide carbonyl). NMR (CF_3COOD) δ: 4.05 (3H, singlet, -OCH_3), 6.60 (1H, singlet, olefinic H).

Reaction of V[4] with Dialkyl Acetylenedicarboxylate——A mixture of 0.106 g (0.0005 mol) of V[4], 0.1 g of dialkyl acetylenedicarboxylate and 20 ml of absolute EtOH was stirred for 4 hr at room temperature. The precipitated crystals were collected and recrystallized from dry DMF, yield, VII, 33 mg (12.5%), VIII 35 mg (14%). The products were found to be identified with VII and VIII by their mp and IR spectra.

8-Amino-6-methyl-2H,3H,10H-pyridazino[4,3-*e*]pyrimido[4,5-*b*]-oxazin-3-one (XII)——A mixture of 0.001 mol of VII or VIII, 2 ml of hydrazine hydrate and 5 ml of EtOH was refluxed for 1 hr. After cooling, the precipitated crystals were collected and recrystallized from EtOH–H_2O (1:1) to afford 85 mg (37%) of pale yellow amorphous powder, mp>300°. *Anal.* Calcd. for $C_9H_8O_2N_6$: C, 46.55; H, 3.47; N, 36.20. Found: C, 46.81; H, 3.62; N, 35.91. IRν_{max}^{KBr} cm^{-1}: 1640 (amide carbonyl). UVλ_{max}^{EtOH} mμ (logε): 345 (4.02). NMR ($CDCl_3$:$(CD_3)_2SO$=1:5) δ: 5.80 (4H, broad singlet, NH_2, 2×NH, exchanged with deuterium oxide), 8.12 (1H, singlet, aromatic H).

7-Amino-5-methyl-2H-furano[3,2-*e*]pyrimido[4,5-*b*]oxazin-2-one (XIII)——A mixture of 0.001 mol of VII or VIII, 0.5 g of KOH and 8 ml of EtOH was refluxed for 20 min. After evaporation of the solvent in vacuo, H_2O was added and filtered. The filtrate was acidified with 10% HCl. The deposited crystals were collected and recrystallized from EtOH–H_2O (1:2) to afford 0.1 g (46%) of colorless prisms, mp>300°. *Anal.* Calcd. for $C_9H_6O_3N_4$: C, 49.28; H, 2.77; N, 25.68. Found: C, 49.28; H, 3.00; N, 25.43. IRν_{max}^{KBr} cm^{-1}: 1760 (lactone). UVν_{max}^{EtOH} mμ (logε): 338 (3.82). NMR ($CDCl_3$:$(CD_3)_2SO$=1:4) δ: 8.00 (1H, singlet, olefinic H).

Dialkyl 1-(2,4-Diacetamido-6-methylpyrimidin-5-yl)oxyethylene-1,2-dicarboxylate (Xa,b)——A mixture of 0.075 g (0.0003 mol) of IX, 0.2 ml of dialkyl acetylenedicarboxylate and 2 ml of EtOH was refluxed for 40 min. After cooling, the deposited crystals were collected and recrystallized from EtOH. Dimethyl ester (Xa); yield, 62 mg (56%), colorless needles, mp 168—168.5°. *Anal.* Calcd. for $C_{15}H_{18}O_7N_4$: C, 49.18; H, 4.95;

N, 15.29. Found: C, 49.00; H, 4.94; N, 15.20. Diethyl ester (Xb); yield, 53 mg (45%), colorless needles, mp 178°. *Anal.* Calcd. for $C_{17}H_{22}O_7N_4$: C, 51.77; H, 5.62; N, 14.21. Found: C, 51.80; H, 5.60; N, 13.99.

α-(2,4-Diamino-6-methylpyrimidin-5-yl)oxysuccinimide (XIV)——A mixture of 0.298 g of I, 0.2 g of maleimide and 10 ml of EtOH was refluxed for a few minutes. After cooled, the deposited crystals were collected and recrystallized from EtOH. Yield 0.43 g (90%), yellow needles, mp 185—186° (decomp). *Anal.* Calcd. for $C_9H_{11}O_3N_5$: C, 45.57; H, 4.67; N, 29.52. Found: C, 45.73; H, 4.67; N, 29.59. IRν_{max}^{KBr} cm^{-1}: 1720 (5 membered amide carbonyl).

2-Amino-6-carbamoylmethyl-4-methyl-6H-pyrimido[5,4-*b*][1,4]oxazin-7(8H)-one (XV)——A mixture of 0.474 g (0.002 mol) of XIV, 0.2 ml of triethylamine and 12 ml of EtOH was refluxed for 30 min. The reaction mixture was turned to red and the crystals were deposited. After cooled, the deposited crystals were collected and recrystallized from dry DMF. Yield 0.36 g (75%), colorless needles, mp>300°. IRν_{max}^{KBr} cm^{-1}: 1690, 1660 (amide carbonyl). NMR (CF_3COOD) δ: 3.50 (2H, doublet, J=5 cps, -CH_2), 5.40 (1H, triplet, J=5 cps, >CH). *Anal.* Calcd. for $C_9H_{11}O_3N_5$: C, 45.57; Y, 4.67; N, 29.52. Found: C, 45.50; H, 4.80; N, 29.32.

β-Carbamoyl-β-(2,4-diamino-6-methylpyrimidin-5-yl)oxyethyl Carboxylic Acid (XVI) and 2-Amino-4,6-dimethyl-6H-pyrimido[5,4-*b*][1,4]oxazin-7(8H)-one (IIb)[4]——A mixture of 0.474 g (0.002 mol) of XIV and 10 ml of H_2O was boiled on a water bath for 5 min. The deposited crystals (IIb) were collected. The filtrate was cooled and the deposited crystals were washed with ethanol and ether successively. Yield 0.41 g (80%), mp 215—216°. IRν_{max}^{KBr} cm^{-1}: 1690 (shoulder) (-COOH). 1670 (amide carbonyl). *Anal.* Calcd. for $C_9H_{13}O_4N_5$: C, 42.35; H, 5.13; N, 27.44. Found: C, 42.02; H, 4.93; N, 27.52. XVI was boiled in water for 30 min to give IIb almost quantitatively.

Reaction of XIV in Acetic Anhydride——A mixture of 0.5 g of XIV and 10 ml of acetic anhydride was refluxed for 30 min. After evaporation of the solvent *in vacuo*, H_2O was added to the residue and the deposited crystals were collected. The crystals were recrystallized from EtOH to give IX. The filtrate was extracted with $CHCl_3$ and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give maleimide. IX and maleimide were identified with those authentic samples by IR spectra, mps and mixed melting point determinations.

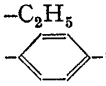
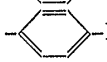
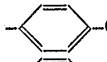
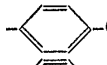
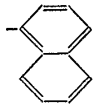
α-(2,4-Diacetamido-6-methylpyrimidin-5-yl)oxysuccinimide (XVIII)——This compound was prepared from IX in the same manner as for XIV and recrystallized from EtOH–AcOEt (2:1). Colorless prisms, mp 203—204°. *Anal.* Calcd. for $C_{13}H_{15}O_5N_5$: C, 48.60; H, 4.71; N, 21.80. Found: C, 48.33; H, 5.00; N, 21.71.

β-Carbamoyl-β-(2,4-diacetamido-6-methylpyrimidin-5-yl)oxyethyl Carboxylic Acid (XIX)——This compound was prepared from XVIII in the same manner as for XVI and recrystallized from H_2O. Colorless prisms, mp 200° (decomp.). *Anal.* Calcd. for $C_{13}H_{17}O_6N_5$: C, 46.02: H, 5.05; N, 20.64. Found: C, 45.88; H, 5.21; N, 20.33.

2-Acetamido-8-acetyl-4,6-dimethyl-6H-pyrimido[5,4-*b*][1,4]oxazin-7-one (XVII)——i) A mixture of 0.51 g (0.002 mol) of XVI, 0.5 g of sodium acetate, 10 ml of 80% EtOH and 10 ml of acetic acid was heated on a water bath at 80—90° for 2 hr. After cooled, the deposited crystals were washed with cold water and recrystallized from EtOH. Colorless prisms, yield 0.17 g (30%), mp 238—239°.

ii) A mixture of 0.339 g (0.001 mol) of XIX and 8 ml of 28% NH_4OH was boiled on a water bath for 1.5 hr. After cooled, the deposited crystals were collected and recrystallized from EtOH. Yield 0.11 g (32%). *Anal.* Calcd. for $C_{12}H_{14}O_4N_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 52.03; H, 5.40; N, 20.33. NMR

Table II. 2-Amino-6-(N-substituted carbamoylmethyl)-4-methyl-6H-pyrimido[5,4-*b*][1,4]oxazin-7(8H)-ones (XXIa—f)

XXI	R	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	$-C_2H_5$	10	$C_{11}H_{15}O_3N_5$	49.81	5.70	26.40	49.75	5.53	26.32
b		8	$C_{15}H_{14}O_3N_5Cl$	51.81	4.06	20.14	51.88	4.33	19.88
c		8	$C_{15}H_{14}O_5N_6$	50.28	3.94	23.45	50.46	4.01	23.09
d		9	$C_{16}H_{17}O_3N_5$	58.71	5.23	21.39	58.99	5.30	21.03
e		8	$C_{16}H_{17}O_4N_5$	55.97	4.99	20.40	55.88	4.70	20.31
f		8	$C_{19}H_{17}O_3N_5$	62.80	4.72	19.27	62.49	4.53	18.99

($CDCl_3$:$(CD_3)_2SO$=1:3) δ: 1.71 (3H, doublet, J=7 cps, $\overset{H}{\underset{}{+}}$ $C\underline{H}_3$), 2.15, 2.20, 2.25 (3×3H, each singlet), 5.05 (1H, quartet, J=7 cps, $\underset{H}{\overset{}{+}}$ CH_3).

General Procedure of 2-Amino-6-(N-substituted carbamoyl methyl)-4-methyl-6H-pyrimido[5,4-*b*][1,4]-oxazin 7(8H)-ones (XXIa—f)——A mixture of 0.298 g of I, 0.002 mol of N-substituted maleimide,[6] 0.3 ml of triethylamine and 10 ml of EtOH was refluxed for 2 hr. After cooled, the deposited crystals were collected and recrystallized from dry DMF. Each of XXIa—f was not melt below 300° and was colorless needles. The properties of the compounds are summarized in Table II.

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